Cardiovascular disease in older people with diabetes in Southeast Asia

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- Sydney Health Partners Geriatric Medicine Clinical Academic Group

Candidate Statement of Originality

This is to certify that the content of this thesis is my own work. This thesis has not been submitted for any other degree or purpose.

I certify that the intellectual content of this thesis is the product of my own work, and that all assistance received in preparing this thesis and all sources have been acknowledged.

Wei Jin Wong

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Publications and Conference Presentations Arising from This Thesis

This thesis provides evidence on the burden of comorbidities and the management of cardiovascular disease in older people with type 2 diabetes in the Southeast Asian region. As of June 2025, my PhD studies have resulted in 5 publications (3 as peer-reviewed papers, 2 as preprints). Two other chapters have been submitted to peer-reviewed journals. I am the first author of each of these papers.

In addition, my PhD studies have yielded 1 conference presentation and 2 awards.

Published papers from this thesis:

Wong WJ, Nguyen TV, Farooq I, Zhang Y, Harrison C, Tan KM, Harris K, Woodward M, TN Nguyen. 'Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease - an observational study.' Australasian Journal on Ageing, 2025; 44(2): e70045. Doi: https://doi.org/10.1111/ajag.70045

Wong WJ, Nguyen TV, Ahmad F, Vu HTT, Koh AS, Tan KM, Zhang Y, Harrison C, Woodward M, Nguyen TN. 'Hypertension in adults with diabetes in Southeast Asia: A systematic review.' The Journal of Clinical Hypertension, 2025; 27(1): e14936. Doi: https://doi.org/10.1111/jch.14936

Wong WJ, Tan KM, Harrison C, Ng CC, Lim WC, Nguyen TN. 'Diabetes, frailty, and burden of comorbidities among older Malaysians with stroke.' International Journal of Diabetes in Developing Countries, 2024. Doi: https://doi.org/10.1007/s13410-024-01389-3

Wong WJ, Nguyen TV, Nguyen VT, Ngo TTK, Nguyen TN. 'Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam.' (Pre-print). medRxiv 2025 doi: 10.1101/2025.05.28.25328459

Wong WJ, Yau MS, Tan KM, Nguyen TN. 'Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia.' (Pre-print). medRxiv 2025 doi: https://doi.org/10.1101/2025.05.05.25326965

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Wong WJ, Nguyen TV, Truong DN, Zhang Y, Harrison C, Woodward M, Nguyen TN. 'Comorbidities, geriatric syndromes, and glycaemic control among older patients with diabetes: a multi-centre study in Vietnam.'

Wong WJ, Tan KM, Zhang Y, Harrison C, Woodward M, Nguyen TN. 'Exploring evidence of SGLT2 inhibitors use in Southeast Asia: A systematic review.'

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Awards and support schemes that I received during my PhD studies:

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Other publications:

In addition to the studies in my PhD thesis, with the support of my supervisors, during my PhD candidature I have developed some national and international collaboration with various colleagues, including researchers and clinicians from Malaysia, Vietnam, Australia (Westmead Applied Research Centre, Sydney Health Partners Musculoskeletal Clinical Academic Group and Sydney Health Partners Geriatric Medicine Clinical Academic Group). Through these collaboration work, I have developed further skills in quantitative and qualitative research, evidence synthesis, economic evaluations, and project management. I have contributed to the following papers in the field of cardiovascular research:

Wong WJ, Nguyen TN, Fortin M, Harrison C. Prevalence and patterns of comorbidities in older people with type 2 diabetes in Australian primary care settings.' Australasian Journal on Ageing, 2024; 43(2): 306-313. Doi: https://doi.org/10.1111/ajag.13282

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Nguyen TV, Nguyen HTK, **Wong WJ**, Ahmad F, Nguyen TN. 'The prescription of beta-blockers in older patients with heart failure with reduced ejection fraction: an observational study in Vietnam.' Scientific Reports, 2024; 14, 12923. Doi: https://doi.org/10.1038/s41598-024-63479-w

Kuan WC, Sim R, **Wong WJ**, Dujaili J, Kasim S, Lee KKC, Teoh SL. 'Economic evaluations of guideline-directed medical therapies for heart failure with reduced ejection fraction: a systematic review.' Value in Health, 2023; 26 (10): 1558-1576. Doi: https://doi.org/10.1016/j.jval.2023.05.011

Authorship Attribution Statements

The following statements endorse Wei Jin Wong's (WJW) roles in the studies that comprise the foundation of his PhD thesis. Studies that are part of this thesis were conducted in consultation with his supervisors, and in collaboration with external collaborators. Wei Jin's responsibilities and contributions are outlined below.

Study/Chapter	**WJW's Responsibilities and Contributions**	**Papers**
Chapter 3: An observational study in Vietnam to examine comorbidities, geriatric syndromes, and glycemic control among older patients with diabetes	Conceptualized the study with primary supervisor. Analyzed the data, created graphic and table presentations. Discussed findings with supervisors and co-investigators. Drafted the manuscript. Incorporated feedback from supervisors and co-investigators into the final manuscript.	**Wong WJ**, Nguyen TV, Truong DN, Zhang Y, Harrison C, Woodward M, Nguyen TN. 'Comorbidities, geriatric syndromes, and glycaemic control among older patients with diabetes: a multi-centre study in Vietnam.'2025 (submitted)
Chapter 4: An observational study in Malaysia exploring diabetes, frailty, and burden of comorbidities among older	Conceptualized the study with primary supervisor. Analyzed the data, created graphic and table presentations. Discussed findings with supervisors and co-investigators. Drafted the manuscript. Incorporated feedback from supervisors and co-investigators into the final manuscript.	**Wong WJ**, Tan KM, Harrison C, Ng CC, Lim WC, Nguyen TN. 'Diabetes, frailty, and burden of comorbidities among older Malaysians with stroke.' International Journal of Diabetes in Developing Countries, 2024; pp.1-9. Doi: 10.1007/s13410-024-01389-3

Malaysians with stroke		
Chapter 5: A systematic review of hypertension in adults with diabetes in Southeast Asia	Conceptualized the study with primary supervisor. Established search strategy. Performed literature search and abstract screening. Extracted data and created table presentations. Discussed and interpreted findings with primary supervisor. Drafted the manuscript. Incorporated supervisors' and co-authors' feedback into final manuscript.	**Wong WJ**, Nguyen TV, Ahmad F, Vu HTT, Koh AS, Tan KM, Zhang Y, Harrison C, Woodward M, Nguyen TN. 'Hypertension in adults with diabetes in Southeast Asia: A systematic review.' The Journal of Clinical Hypertension, 2025; 27(1): e14936. Doi: 10.1111/jch.14936
Chapter 6: An observational study in Vietnam examining the prevalence of forgetfulness to take antihypertensive medications and its relationship with blood pressure control.	Conceptualized the study with primary supervisor. Analyzed the data, created graphic and table presentations. Discussed findings with primary supervisor and co-investigators. Drafted the manuscript. Incorporated feedback from supervisors and co-investigators into the final manuscript.	**Wong WJ**, Nguyen TV, Nguyen VT, Ngo TTK, Nguyen TN. 'Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam.' (Pre-print). medRxiv 2025.05.28.25328459, 2025. Doi: 10.1101/2025.05.28.25328459

Chapter 7: An observational study in Malaysia assessing the impact of frailty on statin prescriptions among older stroke survivors.	Conceptualized the study with primary supervisor. Analyzed the data, created graphic and table presentations. Discussed findings with supervisors and co-investigators. Drafted the manuscript. Incorporated feedback from supervisors and co-investigators into the final manuscript.	**Wong WJ**, Yau MS, Tan KM, Nguyen TN. 'Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia.' (Pre-print). medRxiv 2025.05.05.25326965, 2025. Doi: 10.1101/2025.05.05.25326965
Chapter 8: An observational study in Vietnam examining the prevalence of frailty and its relationship with prescriptions of secondary prevention medications in older people.	Conceptualized the study with primary supervisor. Analyzed the data, created graphic and table presentations. Discussed findings with supervisors and co-investigators. Drafted the manuscript. Incorporated feedback from supervisors and co-investigators into the final manuscript.	**Wong WJ**, Nguyen TV, Farooq I, Zhang Y, Harrison C, Tan KM, Harris K, Woodward M, TN Nguyen. 'Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease - an observational study.' Australasian Journal on Ageing, 2025; 44(2): e70045. Doi: https://doi.org/10.1111/ajag.70045
Chapter 9: A systematic review on the use of SGLT2	Conceptualized the study with primary supervisor. Established search strategy.	**Wong WJ**, Tan KM, Zhang Y, Harrison C, Woodward M, Nguyen TN. 'Exploring evidence of SGLT2 inhibitors use in

inhibitors in Southeast Asia.	Performed literature search and abstract screening. Extracted data and created table presentations. Discussed and interpreted findings with primary supervisor. Drafted the manuscript. Incorporated supervisors' and co-authors' feedback into final manuscript.	Southeast Asia: A systematic review.' 2025 (submitted)

I, Wei Jin Wong, attest that the above authorship attribution statements are correct.

Wei Jin Wong

As the principal supervisor of the candidature upon which this thesis is based, I can confirm that the above authorship attribution statements are correct.

Dr Tu Nguyen

Generative Artificial Intelligence (AI) use statement

During the preparation of the thesis, the author used ChatGPT for the purposes of text enhancement. The use of this generative AI tool includes spelling corrections, minor sentence restructuring, and clarity enhancement. The author confirms that where text was modified by generative AI, the content was reviewed for possible errors, inaccuracies, and bias. The author takes full responsibility for the submitted thesis, confirms the work is their own, and has used generative AI in accordance with University guidelines and policies.

Abstract

Background. Countries in the Southeast Asia are experiencing rapid population aging, which is accompanied by an increased prevalence of cardiometabolic diseases. Older adults with type 2 diabetes are at a heightened risk of cardiovascular disease and mortality due to cardiovascular disease. Established evidence from clinical trials suggests that appropriate control of blood glucose, blood pressure, dyslipidaemia, and cardiovascular secondary prevention treatment can improve the event-free survival rate in people with diabetes. However, there is limited evidence regarding the management of cardiovascular risk factors and cardiovascular diseases in older and frail populations in the region. Furthermore, treatment access and patient experiences, as well as health outcomes, may differ significantly among low- and middle-income countries compared to high-income countries. The disparity is even more concerning given the limited healthcare resources in many of the Southeast Asian countries. Considering these challenges, there is a pressing need for more research to better understand the burden of comorbidities and geriatric syndromes among older adults with diabetes, which could affect treatment decision and patient outcomes, and to explore the management of cardiovascular risk factors and diseases in older adults with diabetes in this region, which will help inform future practice, policies, and patient management strategies.

Aims. This thesis has two major aims: (1) To examine the prevalence of comorbidities and common geriatric syndromes in older people with type 2 diabetes in Southeast Asia, and (2) To examine the management of cardiovascular risk factors and cardiovascular diseases in older people with type 2 diabetes in this region.

Methods. The thesis comprises of 7 studies, including 2 systematic reviews and 5 observational studies conducted in two middle-income countries in Southeast Asia (Malaysia and Vietnam).

Results.

Aim 1: Examine the prevalence of comorbidities and common geriatric syndromes in older people with type 2 diabetes in Southeast Asia	
	Description
Study 1	This is an observational study to examine the prevalence of comorbidities, geriatric syndromes, and their association with glycemic control among older patients with diabetes in Vietnam. The study revealed a high prevalence of poor

	glycaemic control and high burden of comorbidities, frailty, and polypharmacy among the participants. Participants with polypharmacy, frailty, or in the first year of diabetes had increased odds of poor glycaemic control. These findings highlight the need for further studies on optimizing polypharmacy, frailty and managing long-term diabetes.
Study 2	This is an observational study in Malaysia to examine the prevalence of type 2 diabetes in older patients with stroke, and the burden of comorbidities among patients with diabetes and frailty compared to those without these conditions. This study was published as "**Wong WJ**, Tan KM, Harrison C, Ng CC, Lim WC, Nguyen TN. Diabetes, frailty and burden of comorbidities among older Malaysians with stroke. International Journal of Diabetes in Developing Countries. (2024) https://doi.org/10.1007/s13410-024-01389-3". The study found a high prevalence of frailty and diabetes among older patients with stroke. While the frail and diabetic group had the highest overall burden of comorbidities, the non-frail and diabetic group had the most significant cardiovascular disease burden. These findings underscore the urgent need for integrated and personalized management approaches to enhance the overall well-being and quality of life for older stroke survivors with diabetes.
Aim 2: Examine the management of cardiovascular risk in older people with type 2 diabetes in Southeast Asia	
Study 3	This is a systematic review to quantify the prevalence of hypertension and blood pressure control in adults with diabetes in Southeast Asia. This study was published as "**Wong WJ**, Nguyen TV, Ahmad F, Vu HTT, Koh AS, Tan KM, Zhang Y, Harrison C., Woodward M, Nguyen TN. Hypertension in Adults with Diabetes in Southeast Asia: A Systematic Review. The Journal of Clinical Hypertension (2025), 27: e14936. https://doi.org/10.1111/jch.14936". This review showed that blood pressure control in adults with diabetes remains a significant challenge in the Southeast Asian region and there is a gap in the evidence of medication adherence to antihypertensive medications in this region.

Study 4	From the gap identified in the systematic review above, an observational study was conducted to examine the prevalence of forgetfulness to take antihypertensive medications and its relationship with poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam. This study was published as "**Wong WJ**, Nguyen TV, Nguyen V, Ngo TTK, Nguyen TN. Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam. (Preprint). medRxiv 2025 doi:10.1101/2025.05.28.25328459." The study found that approximately one-third of the participants forgot to take antihypertensive medicines sometimes, and forgetfulness was also associated with increased odds of poor BP control. The study also revealed that hypertension duration and disability in activities of daily living were significantly associated with forgetfulness. These findings suggest the need for future studies focusing on interventions on forgetfulness to improve medication adherence for this population. Further support is particularly needed for older adults with disability and for those newly diagnosed with hypertension.
Study 5	This is an observational study to assess the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia. This study was published as "**Wong WJ**, Yau MS, Tan KM, Nguyen T. Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia. (Preprint). medRxiv 2025 doi: 10.1101/2025.05.05.25326965" The study found that frailty was associated with reduced odds of receiving statins in the study population. The differences in the relationship between frailty and statin prescriptions among participants with and without diabetes may suggest a personalized approach in secondary prevention for older patients after strokes. Future studies are needed to understand prescribers' perspectives, aiding in the development of personalized healthcare for older individuals.
Study 6	This is an observational study to examine the prevalence of frailty and its relationship with the prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease in Vietnam. This study was

	published as "**Wong WJ**, Nguyen TV, Farooq I, Zhang Y, Harrison C, Tan KM, Harris K, Woodward M, Nguyen TN. Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease—An observational study in Vietnam. Australasian Journal on Ageing (2025); 44:e70045. doi:10.1111/ajag.70045". The study found that frailty was present in 59% of the participants, who were older patients with coronary heart disease and diabetes, and increased Clinical Frailty Scale was associated with reduced prescriptions of beta-blockers, ACEIs/ARBs and all four types of secondary prevention medications. These findings suggest that future research should explore the link between frailty and the prescriptions of secondary prevention medicines in a larger, more diverse population.
Study 7	This is a systematic review to examine the utilization of sodium glucose cotransporter 2 (SGLT2) inhibitors in Southeast Asia. The benefits of SGLT2 inhibitors are increasingly recognized, not only in the management of diabetes but also in cardiovascular and renal conditions. However, evidence regarding SGLT2 inhibitor use in Southeast Asian populations is limited and is yet to be summarized. This review showed that SGLT2 inhibitor treatment may offer promising benefits for patients with type 2 diabetes, heart failure and chronic kidney disease in the region. While the clinical efficacy of these agents appears to be comparable to Western populations, region-specific factors such as genetic variations, healthcare infrastructure, cost, and cultural considerations must be addressed to optimize their use. Further research is needed to understand the availability and affordability, as well as the safety of SGLT2 inhibitors, taking into consideration the effect of ageing and frailty in this region.

Conclusion.

This thesis highlighted the complexities faced by older people with diabetes living in the Southeast Asian region. The suboptimal management of modifiable risk factors for cardiovascular disease such as blood pressure, glycemic levels, and prescriptions of cardiovascular secondary prevention medicines, highlights the heterogeneity in care received. Future longitudinal studies should investigate the reasons behind these disparities and their impact on mortality and quality of life. More efforts are needed to optimize the prevention and management of cardiovascular disease among older adults with type 2 diabetes in the region. The potential benefits of SGLT2 inhibitors and its increasing availability in the region may have the potential to significantly impact the treatment of diabetes and its related comorbidities in Southeast Asia.

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List of Abbreviations and Acronyms

Abbreviation/acronym	Meaning
ACE	Angiotensin-Converting Enzyme
ANOVA	Analysis of Variance
ARB	Angiotensin Receptor Blocker
ASCVD	Atherosclerotic Cardiovascular Disease
BEACH program	Bettering the Evaluation and Care of Health program
BP	Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
CCI	Charlson Comorbidity Index
CCF	Congestive Cardiac Failure
CFS	Clinical Frailty Scale
CGA	Comprehensive Geriatric Assessment
CI	Confidence Interval
CKD	Chronic Kidney Disease
COVID-19	Coronavirus disease
CrCl	Creatinine Clearance
CVD	Cardiovascular Disease
DALY	Disability-Adjusted Life Year
DAPA	Dapagliflozin
DAPA-HF Trial	Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure trial
DBP	Diastolic blood pressure
DELIVER Trial	Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure
DM	Diabetes Mellitus
DPP4i	Dipeptidyl Peptidase-4 inhibitors
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EMPEROR Trial	Empagliflozin Outcome Trial in Patients with Chronic Heart Failure
ESRD/ ESKD	End-Stage Renal Disease/ End-Stage Kidney Disease

GLP1RA	Glucagon-like Peptide-1 Receptor Agonist
GORD	Gastro-Oesophageal Reflux Disease
GP	General Practitioner
HbA1c	Glycated hemoglobin
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
hHF	hospitalization for Heart Failure
HR	Hazard Ratio
IBM	International Business Machines Corporation
ICER	Incremental Cost-Effectiveness Ratio
IHD	Ischemic Heart Disease
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire Clinical Summary Score
KT	Kidney Transplantation
LS	Least Squares
LVEF	Left Ventricular Ejection Fraction
LY	Life-Years
MDPI	Multidisciplinary Digital Publishing Institute
MET	Metformin
mm Hg	Millimeters of mercury, unit of blood pressure measurement
MoH	Ministry of Health
NHLBI	National Heart, Lung and Blood Institute
NY	New York
NYHA	New York Heart Association
PHP	Philippine Peso
PLOS	Public Library of Science
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PVD	Peripheral Vascular Disease
QALY	Quality-Adjusted Life Year

RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RM	Ringgit Malaysia
RR	Relative Risk
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SGD	Singapore Dollars
SGLT2 inhibitors	Sodium glucose co-transporter 2 inhibitors
SoC	Standard of Care
SPSS	Statistical Package for the Social Sciences
ST	Standard Treatment
SULPHONYL	Sulphonylurea
THB	Thai Baht
TIA	Transient Ischemic Attack
T2DM/ T2D	Type 2 Diabetes Mellitus/Type 2 Diabetes
UHC	Universal Health Coverage
UK	United Kingdom
USA	United States of America
USD	United States Dollars
UTI	Urinary Tract Infections

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I would like to first acknowledge and to say thank you to God as He has indeed been the provider and help through this. A verse from the Book of Proverbs 3:5-6 reads, 'Trust in the LORD with all your heart, and do not lean on your own understanding. In all your ways acknowledge him, and he will make straight your paths.' These words have certainly been my guiding light.

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Finally, in all things, God works for the good of those who love Him, I certainly never dreamt that doing this was even possible. I am grateful for the opportunity to have done so, and the lessons learnt. To whoever that reads this, my encouragement to you is to always ‘keep on keeping on’, to not fear seasons of uncertainty as in staying the course, you may eventually be surprised as growth happens when we are outside of our comfort zone.

Chapter 1
Introduction

1.1 Diabetes

Type 2 diabetes mellitus (T2DM) is a chronic medical condition characterized by elevated blood glucose levels, and is resulted from a combination of resistance to insulin action, inadequate insulin secretion, and inappropriate glucagon secretion.[1] Poor control of type 2 diabetes is associated with an increased risk of microvascular (such as diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy) and macrovascular complications (such as coronary heart disease, cerebrovascular disease, and peripheral artery disease).[1,2] The management of type 2 diabetes requires multifactorial non-pharmacological and pharmacological treatments aiming to prevent or delay its complications through the management of blood glucose levels, cardiovascular risk factors, and comorbidities.[2] Patients with type 2 diabetes are at increased risk of developing cardiovascular disease (CVD), and cardiovascular complications are the leading cause of morbidity and mortality in this population.[1,3] The global prevalence of diabetes in adults was estimated to be around 10.5% (536.6 million people) in 2021, and rising to 12.2% in 2045.[4] Furthermore, studies have report a high proportion of undiagnosed diabetes mellitus globally, with the majority of cases occurring in low-to-middle-income countries.[5]

1.2 Cardiovascular disease in individuals with type 2 diabetes

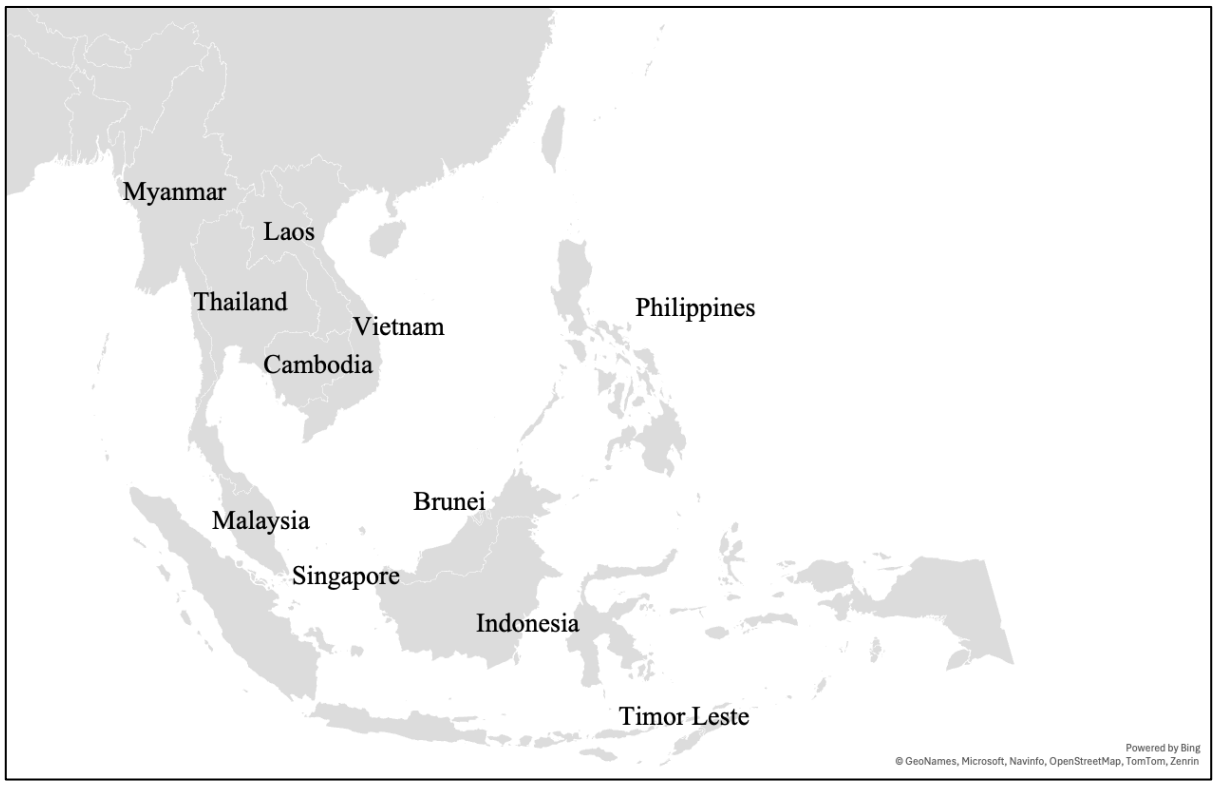
Cardiovascular diseases such as coronary heart disease, stroke, peripheral arterial disease, cardiomyopathy, and congestive heart failure are common in patients with diabetes and contribute to over two-thirds of mortality among patients with type 2 diabetes mellitus.[6,7] Patients with diabetes have twice the risk of incident myocardial infarction and stroke as that of the general population.[8] This represents a great societal cost, with major loss of life expectancy and quality of life.[9,10] The 2023 Guidelines for the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC) recommended that managing patients with diabetes and CVD requires an interdisciplinary approach, involving clinicians from different disciplines and areas of expertise to support shared decision-making and implement a personalized treatment strategy to reduce each patient's disease burden.[3] Established evidence from clinical trials suggests that appropriate control of blood glucose, blood pressure, dyslipidemia, and cardiovascular secondary prevention treatment can

improve the event-free survival rate in people with diabetes.[3] The ultimate common goal in managing CVD in patients with diabetes is to improve their prognosis and health-related quality of life.[3]

1.3 Southeast Asia

Globally, approximately 1 in 11 adults has diabetes mellitus, with 90% having type 2 diabetes, and Asia is the primary hub of this global diabetes epidemic.[1] There is a growing prevalence of diabetes in the Southeast Asia region.[11] In Southeast Asian countries, the population is aging rapidly, with the prevalence of diabetes among older adults (aged 65 years and above) projected to more than double from 35.5 million in 2019 to nearly 80 million by 2045.[12] Southeast Asia consists of 11 countries, namely (in alphabetical order): Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste and Vietnam (See Figure 1). Collectively, they form an en bloc group known as ASEAN (Association of Southeast Asian Nations), an intergovernmental organization of the various countries. Timor-Leste was the latest country to apply for membership and is in the process of becoming the 11th member of ASEAN. In comparison with other parts of Asia, the region has been less visible in global health[13] but has become an emerging focus area in recent years.[14] The region is home to almost 700 million people, just under 10% of the global population. The Southeast Asian countries vary in economic development and growth, as well as regional collaboration in health. According to the World Bank country classification, the economic background ranges from high-income countries (such as Brunei and Singapore) to upper-middle income countries (Malaysia and Thailand), and low- to middle-income countries (including Cambodia, Indonesia, Laos, Myanmar, the Philippines, Timor-Leste, and Vietnam). The region is one of the most culturally diverse regions, with many different languages and ethnic groups residing here. Countries in the region are classified in the World Health Organization (WHO) South-East Asia Region (SEARO) (including Myanmar, Thailand and Timor-Leste), and the Western Pacific Region (WPRO) (including Brunei, Cambodia, Laos, Malaysia, Philippines, Singapore, and Vietnam). Indonesia was recently reassigned from SEARO to WPRO at the recent 78th session of the World Health Assembly on 23rd May 2025.

Figure 1: Map of countries in Southeast Asia



The increased prevalence of diabetes in this region can be attributed to several factors, including rapid urbanization, sedentary lifestyles, changing dietary habits and an aging population.[4] The rapid economic development experienced in certain countries in the region has led to advancements in healthcare, contributing to a growing population of older people. Due to age-related physiological changes such as reduced insulin sensitivity and impaired glucose metabolism, older adults are more susceptible to developing diabetes. Consequently, as the region's population continues to age, the overall burden of diabetes is expected to increase together. For example, the prevalence of diabetes in Malaysia has been reported to increase with age, about 11% among individuals aged 30-39 and over 40% in those aged 60 years and above. Similarly, the number of adults with obesity in Indonesia has doubled over the last two decades and the country is listed among the top 10 countries with the highest number of adults living with diabetes.[15] Vietnam has also reported an increase in the prevalence of prediabetes and undiagnosed diabetes.[16] With most countries in the region classified as low-to-middle-income countries, the growing older population, along with the increasing prevalence of diabetes and cardiovascular diseases places additional pressure on healthcare systems that are often under-resourced. Furthermore, rapid urbanization has contributed to shifts in dietary behaviours and reductions in physical activity, while inadequate access to

healthcare and screening services affects early detection. As a result, the prevalence of prediabetes and undiagnosed diabetes continues to rise, particularly in urbanized areas where sedentary lifestyles and high-calorie diets are increasingly prevalent.

1.4 Older adults with diabetes and cardiovascular disease

The demographic shift towards an aging population in the Southeast Asia has significant implications for the management of diabetes and CVD. Age is a known irreversible risk factor for both diabetes and cardiovascular disease. Older adults with type 2 diabetes are at a heightened risk of cardiovascular disease and mortality due to cardiovascular disease. In a systematic review examining the prevalence of CVD among adults with T2DM conducted by Einarson at al[17], CVD was reported to affect over one-third of all persons with T2DM, accounting for approximately 50% of all deaths, with coronary heart disease and stroke being the major contributors. Einarson at al.[17] further described age as a significant risk factor, noting that the prevalence of CVD was higher among older adults compared to younger adults. However, the authors acknowledged that there were few studies that quantified the effect of age on CVD prevalence among people with T2DM.

For older persons with diabetes and CVD, disease management becomes increasingly complex due to the presence of geriatric syndromes such as frailty and polypharmacy. These geriatric syndromes have been reported to significantly influence health outcomes.[18] Frailty, in particularly, has been associated with increased hospitalization and poorer prognosis[19], yet its impact on the delivery and appropriateness of care remains under-explored in older adults in Southeast Asia. For instance, in the management of CVD, it is unclear how frailty influences decisions around prescription of medicines such as secondary prevention medications. Additionally, clinical trials that inform current guidelines have historically excluded or underrepresented older adults, particularly those with complex health profiles.[20] As a result, clinical decision-making often relies on extrapolated data which may not fully consider the risks, benefits and priorities relevant to the older populations. Furthermore, treatment access and patient experiences, as well as health outcomes, may differ significantly among low- and middle-income countries compared to high-income countries. The disparity is even more concerning given the limited healthcare resources in many of the Southeast Asian countries.

A significant proportion of individuals with T2DM, particularly older adults, often present with multiple comorbidities.[21] There is a growing awareness among clinicians treating patients with

T2DM of the need to be mindful of comorbidities, ensuring that diabetes management plans are patient-centered and holistic.[21] The presence and type of comorbidities can also influence glycemic targets and choices of pharmacological agents. Comorbidities were reported to be associated with increased complexity of care and significantly influenced the functional status of older adults with T2DM.[22] The International Geriatric Diabetes Society has further emphasized the need for deeper understanding of comorbidities to enhance the quality of care provided and more efficient utilization of healthcare resources.[23] Similarly, Diabetes UK in a research prioritization initiative highlighted the importance of improving care for older adults with diabetes, particularly on improving understanding on their characteristics to better support patient-centered care.[24]

Considering these challenges, there exists an urgent need for more research to better understand the burden of comorbidities and geriatric syndromes among older adults with type 2 diabetes in Southeast Asia. This can help improve diabetes care, support better treatment decisions and improve patient outcomes. A greater understanding of the connections between diabetes, cardiovascular disease and other comorbidities could lead to more effective treatments, highlighting the necessity for more multidisciplinary research.[25] There is also a pressing need to understand the management of cardiovascular risk factors and CVD in older adults with diabetes in this region. This understanding can help inform future practice, policies, and patient-centred management strategies. Gaining insights into these gaps is particularly important for the LMICs in this region, where resource constraints demand more targeted, data-driven approaches to ensure that care for older adults with diabetes is both effective and equitable.

Therefore, this thesis has two major aims: (1) To examine the prevalence of comorbidities and common geriatric syndromes such as frailty and polypharmacy in older people with type 2 diabetes in Southeast Asia, and (2) To examine the management of cardiovascular risk factors and CVD among older people with type 2 diabetes in this region.

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Chapter 2
Methodology

This chapter outlines the methodological approaches undertaken for the whole thesis. Detailed methods for each study are presented in the relevant publications in chapters 3-9.

This thesis comprises of 7 studies, including 2 systematic reviews and 5 observational studies conducted in two middle-income countries in Southeast Asia (Malaysia and Vietnam).

Table 1. A summary of the methodology of the 7 studies in my thesis

Aim 1: Examine the prevalence of comorbidities and common geriatric syndromes in older people with type 2 diabetes in Southeast Asia	
Description	
Study 1	**Comorbidities, geriatric syndromes, and glycaemic control among older patients with diabetes: a multi-centre study in Vietnam.** Research questions: What are the prevalences of comorbidities and geriatric syndromes in older adults with type 2 diabetes in Vietnam, and how do they relate to glycaemic control? Study design: Cross sectional analysis of a prospective observational study. Study population: Adults aged ≥ 60 years with type 2 diabetes that attended outpatient cardio-metabolic clinics of Thong Nhat Hospital and Gia Dinh Hospital in Ho Chi Minh City, Vietnam from November 2022 to June 2023.
Study 2	**Diabetes, frailty and burden of comorbidities among older Malaysians with stroke.** Research questions: What is the prevalence of diabetes in older patients with stroke?

	What are the differences of comorbidities among patients with diabetes and frailty versus those without these conditions? Study design: Cross-sectional analysis of a retrospective observational study. Study population: Adults aged ≥ 65 years with acute stroke who were admitted to the Geriatric Medicine Unit at Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia from January 2016 to January 2020.
Aim 2: Examine the management of cardiovascular risk in older people with type 2 diabetes in Southeast Asia	
Description	
Study 3	**Hypertension in adults with diabetes in Southeast Asia: A systematic review.** Main research questions: What is the prevalence of hypertension among adults with type 2 diabetes in Southeast Asia? What are the blood pressure control rates among adults with type 2 diabetes in Southeast Asia? Study design: Systematic review. Study population: Adults with type 2 diabetes and hypertension living in Southeast Asian countries.
Study 4	**Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam.** Research questions: What is the prevalence of forgetfulness in taking prescribed antihypertensive medications among older adults with type 2 diabetes and hypertension in Vietnam, and how does it relate to blood pressure control? Study design: Cross-sectional analysis of a prospective observational study.

	Study population: Adults ≥ 60 years old with hypertension that attended outpatient cardio-metabolic clinics of Thong Nhat Hospital and University Medical Centre in Ho Chi Minh City, Vietnam from June 2023 to June 2024.
Study 5	**Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia.** Research questions: How does frailty influence the prescription of statins among older stroke survivors with and without type 2 diabetes in Malaysia? Study design: Cross-sectional analysis of a retrospective observational study. Study population: Adults aged ≥ 65 years with ischaemic stroke who were admitted to the Geriatric Medicine Unit at Universiti Malaya Medical Centre, Kuala Lumpur, Malaysia from January 2016 to January 2020.
Study 6	**Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease - An observational study in Vietnam.** Research questions: What is the association between frailty and the prescription of secondary prevention medications in older adults with diabetes and coronary heart disease in Vietnam? Study design: Cross-sectional analysis of a prospective observational study. Study population: Adults aged ≥ 60 years with type 2 diabetes and coronary heart disease that attended the cardiovascular outpatient clinics of Thong Nhat Hospital in Ho Chi Minh City from November 2022 to June 2023.
Study 7	**Exploring evidence of SGLT2 inhibitors use in Southeast Asia: A systematic review.** Research questions:

	What evidence exists from research regarding the use of SGLT2 inhibitors among people living in Southeast Asian countries? Study design: Systematic review. Study population: Southeast Asian populations who received SGLT2 inhibitors.

Chapter 3

Comorbidities, geriatric syndromes, and glycaemic control among older patients with diabetes: a multi-centre study in Vietnam

Comorbidities, geriatric syndromes, and glycaemic control among older patients with diabetes: a multi-centre study in Vietnam

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Abstract

Aim. This study aimed to examine the burden of comorbidities and common geriatric syndromes in older adults with type 2 diabetes mellitus in Vietnam and their relationship with poor glycaemic control.

Methods. This is a cross-sectional study of patients aged 60 years or older diagnosed with type 2 diabetes who visited the cardio-metabolic clinics of two urban hospitals in Ho Chi Minh City, Vietnam, between November 2022 and June 2023. Poor glycaemic control was defined as HbA1c ⩾7.0%. Comorbidity severity was assessed using the Charlson Comorbidity Index (CCI). Frailty was defined using Fried's criteria. Polypharmacy was defined as the use of five or more medications daily. Multiple-adjusted logistic regression models were applied to identify the factors associated with poor glycaemic control.

Results. There were 576 participants. They had a mean age of 71.9 (SD 7.6) years, 46% were female, 30% were frail, 77% had polypharmacy. The mean duration of diabetes was 10.9 years (SD 7.4). The mean CCI was 2.5 (SD 1.1), and 34% of the participants had a CCI ≥3. The most common comorbidities were dyslipidaemia (98%), hypertension (96%), followed by chronic kidney disease (17%), and peripheral artery disease (11%). The prevalence of poor glycaemic control (HbA1c ≥ 7%) was 47%. The factors significantly associated with poor glycaemic control were polypharmacy, frailty, and long duration of diabetes.

Conclusion. There was a high prevalence of comorbidity, frailty, and polypharmacy among the participants; all were related to poor glycaemic control. Optimizing polypharmacy, frailty and comorbidity is essential in managing long-term diabetes.

Keywords. Diabetes, glucose control, frailty, polypharmacy, geriatric syndromes, comorbidity, Vietnam.

Introduction

Globally, the prevalence of diabetes among people aged 65 years and older is approximately 20%.[1] It is anticipated that, by 2045, approximately 75% of adults with type 2 diabetes mellitus (T2DM) will be living in low- and middle-income countries (LMICs).[2,3] Countries around the world are undergoing an epidemiological transition, as populations age. This trend is particularly pronounced in LMICs, where the growth rate of older populations is expected to surpass high-income countries by 2050.[4] As diabetes can increase the risk of other chronic health conditions, such as cardiovascular and kidney diseases, it continues to be a significant public health challenge. Effective glycaemic control becomes essential for preventing acute complication and reducing risks of long-term micro- and macro-vascular outcomes. However, achieving and maintaining glycaemic control is a challenge due to a variety of influencing factors. Glycaemic control among individuals with T2DM in LMICs have previously been reported as suboptimal.[5]

Older adults often have complex health needs that can make their diabetes care more challenging. [6] [7] For example, there is an increased risk of hypoglycemia from commonly used medicines like metformin and sulfonylureas due to reduced kidney function that happens with aging. In severe stages of reduced kidney function, these medicines are sometimes contraindicated limiting management options for older adults. The current management of T2DM focuses mainly on controlling blood glucose levels assessed by haemoglobin A1c (HbA1c) levels. The American Diabetes Association Standards of Care in Diabetes 2025 [8] highlights the need for individualized goals in older adults due to the heterogeneity in health status, functional abilities, and cognitive function in this population. For the general adult population, it recommended HbA1c targets of < 6.5% when achievable without significant hypoglycaemia, or under 7.0% for most individuals at high risk of hypoglycaemia. For older adults with T2DM and intermediate or complex health (such as frailty, cognitive or functional impairments, severe coexisting conditions), a more relaxed target (HbA1c < 8.0%) was recommended. The International Geriatric Diabetes Society further highlights how care provides for older adults with diabetes should respond to changes associated with aging, such as increasing frailty, cognitive impairment and comorbidities which may affect glycaemic management.[6]

In Vietnam, the prevalence of T2DM has been steadily increasing.[9] Recent reports indicate a rising prevalence of prediabetes and undiagnosed T2DM, with older age as one of the associated factors.[10] Studies have also reported that the rate of poor glycaemic control in Vietnam ranged from 33% - 82%.[11] Poor glycaemic control is more frequently observed in older adults with T2DM, who often experience multiple geriatric conditions, such as frailty, multimorbidity and polypharmacy.[12,13] However, there is a lack of studies that focus on these issues in older adults with T2DM in Vietnam, and specifically how these geriatric conditions affect diabetes management in this population.

This study aimed to examine the burden of comorbidities and common geriatric syndromes (frailty, polypharmacy) in older adults with type 2 diabetes in Vietnam and their relationship with poor glycaemic control.

Methods

Study design and population

A cross-sectional analysis was conducted, using data from a cohort study of frailty in older patients with type 2 diabetes in Vietnam. Details of this study were published elsewhere. Briefly, a total of 644 older patients aged 60 years or older diagnosed with type 2 diabetes who visited the cardio-metabolic clinics of Thong Nhat Hospital and Gia Dinh Hospital in Ho Chi Minh City from November 2022 to June 2023 were recruited. Among these 644 participants, those with a measurement of glycated haemoglobin (HbA1c) (n=576) were included in the current study.

Data collection

Data were collected from patient interviews and medical records. Information obtained included demographic characteristics, height, weight, medical history, duration of having diabetes (in years), number of medications used, and number of comorbidities. Body mass index (BMI) was calculated from measured weight and height and classified into four groups: underweight (BMI < 18.5 kg/m^2), ideal (BMI 18.5–22.9 kg/m^2), overweight (BMI 23.0–24.9 kg/m^2), and obese (BMI ≥ 25.0 kg/m^2). Comorbidities were assessed using the Charlson Comorbidity Index (CCI), which estimates the 10-year risk of death associated with a combination of comorbidities. Comorbidity strength was categorized as mild (CCI 1-2), moderate (CCI 3-4), and severe (CCI ≥ 5).[14] Frailty was defined by Fried's frailty criteria, which include five components (unintentional weight loss, weakness, exhaustion, slowness and low physical activity).[15] Participants with three or more of these five components were identified as being frail, those with one or two components as prefrail, and those with none as robust. Polypharmacy was defined as the use of five or more medications daily.[16]

HbA1c values were obtained from the latest measurement recorded within the past three months in the medical records. Poor glycaemic control was defined as HbA1c ≥7.0%.[8]

The studies were approved by the Ethics Committee of the University of Medicine and Pharmacy at Ho Chi Minh City (Reference Number 934/DHYD-HDDD, dated 24/11/2022). Informed consent was obtained from all participants.

Statistical analysis

Participant characteristics are presented as mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. Comparisons among groups were conducted using chi-square tests or Fisher's exact tests for binary variables, and Student's t-tests or One-Way ANOVA for continuous variables.

Logistic regression models were applied to identify the factors associated with poor glycaemic control. Unadjusted odds ratios (OR) and adjusted ORs and their 95% confidence intervals (CIs) were calculated for the predefined variables. Besides three main variables of interest (frailty, polypharmacy, and the Charlson Comorbidity Index), we also included socio-demographic factors (age, sex, marital status, educational level), lifestyle factor (smoking), duration of diabetes, and cardiovascular risk factors/cardiovascular disease (hypertension, dyslipidaemia,

obesity, heart failure, coronary heart disease, stroke, peripheral artery disease, chronic kidney disease). P values <0.05 were considered statistically significant. All variables were examined for interaction and multicollinearity. Data were analysed in SPSS Statistics 29.0.

Results

Characteristics of the participants:

The 576 participants had a mean age of 71.9 (SD 7.6) years, 46% were female, 96% were retired, and 74% were married. Regarding educational level, 9% had low education (completed primary school or less), 47% completed high school, 36% attended college or university, and 9% obtained higher education. In terms of diabetes duration, 36% of the participants had diabetes for more than 10 years, followed by 6-10 years (32%), 1-5 years (28%) and < 1 year (4%).

Prevalence of comorbidities, polypharmacy, and frailty:

The most common cardiovascular comorbidities were dyslipidaemia (98%), hypertension (96%), chronic kidney disease (17%), peripheral artery disease (11%), coronary heart disease (2%), ischemic stroke (2%) and heart failure (1%), with no significant differences among participants with good and poor glycaemic control (Table 1).

Regarding the overall comorbidity burden, more than a third (34%) of all participants had moderate to severe comorbidity (28% reporting CCI of 3-4 and 6% reporting a CCI of ≥ 5), while 66% reporting a CCI of 1-2, and there was no significant differences among participants with good and poor glycaemic control.

The prevalence of polypharmacy was 77% in all participants, 70% in those with good glycaemic control vs. 84% in those with poor glycaemic control (p<0.001).

The prevalence of frailty and pre-frailty was 30% and 46% in all participants; 27% and 44% in those with good glycaemic control vs. 33% and 48% in those with poor glycaemic control, respectively (p=0.011)

Mean levels of HbA1c by duration of diabetes, the severity of comorbidities, polypharmacy, and frailty:

The prevalence of poor glycaemic control (HbA1c ≥ 7%) was 47%.

The distribution of HbA1c levels among the study participants is presented in Figure 1. Overall, the mean HbA1c level was 7.3%, SD 1.5.

HbA1c level was highest among participants that were diagnosed with diabetes for less than 1 year (7.8%, SD 1.9), followed by those with more than 10 years of diabetes (7.5%, SD 1.4), 6-10 years (7.4%, SD 1.6), and lowest among those with 1-5 years of diabetes (7.0%, SD 1.4), p=0.004.

The mean HbA1c level was significantly higher in participants with polypharmacy compared to those without polypharmacy (7.4%, SD 1.4 vs. 7.1%, SD 1.6, p=0.018).

There were no significant differences by frailty (7.1%, SD 1.2 in robust, 7.3%, SD 1.6 in prefrail, and 7.5%, SD 1.5 in frail participants, p=0.074), and by comorbidity severity (7.3%, SD 1.4 in those with CCI 1-2, 7.5%, SD 1.7 in those with CCI 3-4, and 7.1%, SD 1.3 in those with CCI ≥5, p=0.182).

The factors associated with poor glycaemic control in logistic regression analysis:

The unadjusted and adjusted ORs of factors associated with poor glycaemic control are presented in Table 2. In the adjusted model, the odds of having poor glycaemic control were twice as high in participants with polypharmacy compared to those without polypharmacy (adjusted OR 2.18, 95% CI 1.38 – 3.42). Compared to robust participants, the adjusted ORs for poor glycaemic control were 1.75 (95% CI 1.10 – 2.76) in pre-frail participants, and 2.03 (95% CI 1.11 – 3.72) in frail participants. Compared to participants with a diabetes duration from 1 – 5 years, the odds of poor glycaemic control were 2.46 (95% CI 0.97 – 6.21) in those that had diabetes for less than 1 year, 1.68 (95% CI 1.06 – 2.66) in those that had diabetes from 6 to 10 years, and 2.23 (95% CI 1.39 – 3.56) in those that had diabetes for more than 10 years.

Discussion

In our study, nearly half of the study participants had poor glycaemic control. Previous studies in Vietnam and other countries in the Southeast Asia also reported a very high prevalence of poor glycaemic control among adults with T2DM. In a study of 189 patients with T2DM at an urban hospital in Hanoi, Vietnam from 2018 to 2019, 70% of the study participants (mean age 62.4 years, SD 7.6) had uncontrolled glycaemic levels (defined as HbA1c level ≥ 6.5%).[11] In a study of 557 T2DM patients recruited from seven clinics in Malaysia (mean age 56.0, SD 9.1), 77% had poor glycaemic control (HbA1c ≥ 6.5%), with a mean HbA1c level for all participants of 8.0%, SD 2.0) .[17] Another study of 385 patients with T2DM in 1 general and 17 community hospitals in Thailand (mean age 59.8 years, SD 9.1) found that 80% of the participants had poor glycaemic control (HbA1c ≥ 7%).[18] In a recent review of the prevalence and management of hypertension in adults with diabetes in Southeast Asian countries, out of the 51 studies that reported the percentages of participants achieving target glucose control, 46 studies found that more than 50% of the participants had poor glucose control.[19]

The two most common comorbidities in this study were dyslipidaemia and hypertension, which was similar to another study that reported hypertension as the most common comorbidity in older adults with diabetes presenting at primary care in Australia.[20] Of note, more than one third of our study participants were classified as having moderate or severe comorbidity. We did not find any significant difference in the prevalence of the cardiovascular risk factors and comorbidities between participants with good and poor glycaemic control in our study. There are growing number of studies discussing the impact of comorbidities on overall management and progression of T2DM.[21] The increasing awareness of comorbidities can help assess the risk and benefits of intensifying, maintaining or de-intensifying glucose control treatments in older people with diabetes.[22] Older people with diabetes face a wide range of medical conditions, functional and cognitive impairment.[23] Additional variation in psychosocial environment and access to resources further complicates diabetes management for older adults.[24] Recognizing this variability is crucial for providing effective and person-centred care for them.

Our study found that duration of diabetes, frailty, and polypharmacy were significantly associated with poor glycaemic control among the participants. The mean HbA1c level was highest in participants with diabetes for less than 1 year. This was different when compared to a study in Malaysia[17] which reported that, for each 1-year increase in duration of diabetes, there was a 5% reduction in the odds of achieving target glycaemic control. This could be due to the mean age of study population in Malaysia being much younger (59.8 years) than in our study (71.9 years). Our finding may suggest further support is needed for older patients with newly diagnosed T2DM. Due to age-related changes and impact, such as cognitive impairment, retirement, and mobility issues, older adults may have difficulties navigating through a diagnosis of diabetes and its treatment when compared to younger population.

The increased odds of having HbA1c ≥ 7.0% among prefrail and frail participants could reflect the cautious approach of the physicians when treating older patients with frailty. In fact, the American Diabetes Association Standards of Care in Diabetes recommended a more relaxed target (HbA1c < 8.0%) for older adults with T2DM and frailty.[8] The impact of frailty on glycaemic control in our study participants highlights the value of frailty assessment in diabetes. Strain et al. proposed that frailty, rather than age, can influence the prognosis for older adults with diabetes and hence, should be an important factor for setting treatment goals and individualizing care.[25]

The high prevalence of polypharmacy across all participants in our study, regardless of whether they had good or poor glycaemic control highlights further opportunities for improvement. Lipska et al. concluded from four large randomized clinical trials that more aggressive attempts to manage glycaemic levels using multiple pharmacological agents are often associated with reduced benefits and increased potential harms in older adult adults with type 2 diabetes.[13] Complex medical regimens have been reported to negatively impact patient medication adherence.[26] The International Geriatric Diabetes Society recently recommended that healthcare providers should consider simpler and safer medication regimens for older adults with diabetes.[6] Therefore, exploring strategies to simplify treatment plans and reduce polypharmacy could be helpful in improving glycaemic control in older adults with diabetes and multiple comorbidities.

Strengths and limitations

The strengths of this study lie in its high-quality, multi-centre data and clinical relevance, making it valuable for understanding the impact of common geriatric syndromes, like frailty and polypharmacy, on glycaemic control. However, due to the cross-sectional nature of the study, we could not clarify whether frailty or polypharmacy precedes poor glycaemic control or vice versa. Future longitudinal studies could provide helpful information on this topic. Although this study reported on the association of polypharmacy and glycaemic control, information on type of medicines and adherence were not collected. Future studies could also explore the use of oral antihyperglycaemic agents and insulin together with levels of treatment adherence and its association with glycaemic control. The study participants were recruited from two major hospitals in Ho Chi Minh City, an urban city in Vietnam. Therefore, the

findings should be interpreted within this context and may not be generalisable to other regions, such as rural areas.

Conclusion

There was a high prevalence of poor glycaemic control and high burden of comorbidity, frailty, and polypharmacy among the participants. Diabetes duration, frailty, and polypharmacy were factors significantly associated with glycaemic control among the participants of this study. The study findings highlight the importance of considering geriatric related issues as part of the comprehensive diabetes management and underscore the need for further research on optimizing polypharmacy, frailty and developing personalized treatment plans in managing long-term diabetes.

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Table 1 Participant characteristics

Characteristic	All participants (N = 576)	Participants with HbA1c < 7% (n=306)	Participants with HbA1c ≥ 7% (n=270)	p-value
Age, years	71.9 (7.6)	72.1 (7.4)	71.7 (7.9)	0.232
Age group				
< 75	383 (67)	204 (67)	179 (66)	0.925
≥ 75	193 (34)	102 (33)	91 (34)	
Sex				
Male	309 (54)	165 (54)	144 (53)	0.888
Female	267 (46)	141 (46)	126 (47)	
Working status				
Working	24 (4)	13 (4)	11 (4)	0.917
Retired	552 (96)	293 (96)	259 (96)	
Marital status				
Married	426 (74)	226 (74)	200 (74)	0.679
Never married	16 (3)	7 (2)	9 (3)	
Divorced/separated	7 (1)	5 (2)	2 (1)	
Widowed	127 (22)	68 (22)	59 (22)	
Education				
Primary school or less	49 (9)	26 (9)	23 (9)	0.056
High school	269 (47)	158 (52)	111 (41)	
College/University	206 (36)	100 (33)	106 (39)	
Higher education	52 (9)	22 (7)	30 (11)	
Body mass index				
Underweight	15 (3)	10 (3)	5 (2)	0.722
Normal	309 (54)	160 (53)	149 (55)	
Overweight	153 (27)	82 (27)	71 (26)	
Obese	96 (17)	51 (17)	45 (17)	
Smoking (yes vs. no)	166 (29)	88 (29)	78 (29)	0.972
Duration of diabetes (years)	10.9 (7.4)	9.7 (7.1)	12.3 (7.6)	<0.001
<1 year	23 (4)	12 (4)	11 (4)	<0.001
1 – 5 years	161 (28)	107 (35)	54 (20)	
6 – 10 years	186 (32)	96 (31)	90 (33)	
>10 years	206 (36)	91 (30)	115 (43)	
Total number of medications	5.5 (1.4)	5.3 (1.4)	5.8 (1.3)	<0.001
Polypharmacy	441 (77)	215 (70)	226 (84)	<0.001
Frailty				
Robust	141 (25)	90 (29)	51 (19)	0.011
Pre-frail	265 (46)	135 (44)	130 (48)	
Frail	170 (30)	81 (27)	89 (33)	
Charlson Comorbidity Index (CCI)	2.5 (1.1)	2.4 (1.2)	2.5 (1.1)	0.463

Comorbidity severity				
CCI 1 – 2 (mild)	379 (66)	204 (67)	175 (65)	0.715
CCI 3 – 4 (moderate)	160 (28)	81 (27)	79 (29)	
CCI ≥ 5 (severe)	37 (6)	21 (7)	16 (6)	
Cardiovascular risk factors and comorbidities				
Dyslipidaemia	564 (98)	302 (99)	262 (97)	0.242
Hypertension	551 (96)	291 (95)	260 (96)	0.481
Chronic kidney disease	96 (17)	50 (16)	46 (17)	0.823
Peripheral artery disease	65 (11)	34 (11)	31 (12)	0.889
Coronary heart disease	10 (2)	7 (2)	3 (1)	0.349
Ischemic stroke	9 (2)	7 (2)	2 (1)	0.135
Heart failure	8 (1)	5 (2)	3 (1)	0.729

Continuous data are presented as mean (standard deviation). Categorical data are shown as n (%). CCI: Charlson Comorbidity Index, HbA1c: Glycated hemoglobin

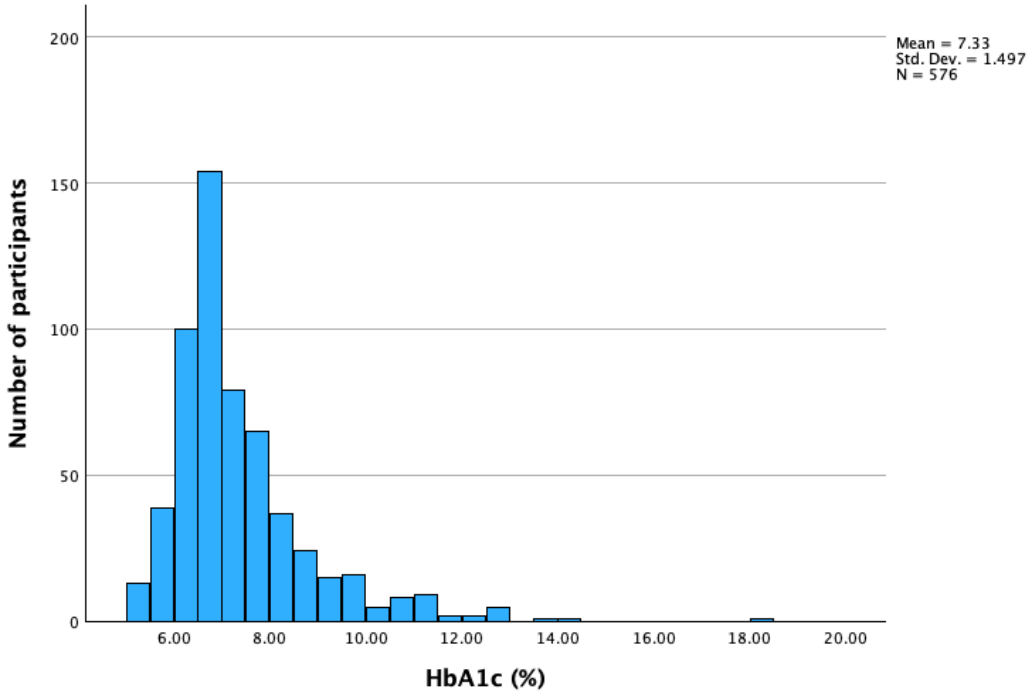

Figure 1. The distribution of HbA1c among the study participants

Table 2. Factors associated with poor glycaemic control

Variables	Unadjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age ≥ 75 vs. <75	1.02 (0.72 – 1.44)	0.925	0.79 (0.48 – 1.31)	0.361
Female vs. male	1.02 (0.74 – 1.42)	0.880	0.98 (0.63 – 1.51)	0.919
Retired vs. working	1.05 (0.46 – 2.37)	0.917	1.05 (0.44 – 2.53)	0.914
Married vs. never married/ divorced/ separated/ widowed	1.01 (0.70 – 1.47)	0.953	1.11 (0.67 – 1.85)	0.677
Primary school or less vs. higher education	1.00 (0.56 -1.80)	0.993	1.16 (0.59 – 2.25)	0.667
Obesity (BMI ≥ 25.0 vs <25.0)	1.00 (0.65 – 1.55)	0.998	1.06 (0.66 – 1.69)	0.813
Smoking (yes vs. no)	1.01 (0.70 – 1.44)	0.972	0.96 (0.60 – 1.55)	0.868
Duration of having diabetes		**<0.001**		**0.006**
1 – 5 years (reference group)	1		1	
< 1 year	1.82 (0.75 – 4.38)	0.184	2.46 (0.97 – 6.21)	0.057
6 – 10 years	**1.86 (1.20 – 2.87)**	**0.005**	**1.68 (1.06 – 2.66)**	**0.027**
>10 years	**2.50 (1.63 – 3.84)**	**<0.001**	**2.23 (1.39 – 3.56)**	**<0.001**
Polypharmacy	**2.17 (1.45 – 3.26)**	**<0.001**	**2.18 (1.38 – 3.42)**	**<0.001**
Comorbidity severity		0.715		0.785
CCI 1 – 2 (mild, reference group)	1		1	
CCI 3 – 4 (moderate)	1.14 (0.79 – 1.65)	0.497	1.21 (0.71 – 2.08)	0.487
CCI ≥ 5 (severe)	0.89 (0.45 – 1.76)	0.733	1.23 (0.41 – 3.70)	0.708
Frailty		**0.012**		**0.033**
Robust (reference group)	1		1	
Pre-frail	**1.70 (1.12 – 2.59)**	**0.013**	**1.75 (1.10 – 2.76)**	**0.017**
Frail	**1.94 (1.23 – 3.06)**	**0.004**	**2.03 (1.11 – 3.72)**	**0.021**
Dyslipidaemia	0.43 (0.13 – 1.46)	0.177	0.32 (0.10 – 1.21)	0.094
Hypertension	1.34 (0.59 – 3.04)	0.483	0.97 (0.37 – 2.49)	0.941
Chronic kidney disease	1.05 (0.68 – 1.63)	0.823	0.79 (0.39 – 1.61)	0.509
Peripheral artery disease	1.04 (0.62 – 1.74)	0.889	0.87 (0.47 – 1.64)	0.677
Coronary heart disease	0.48 (0.12 – 1.88)	0.291	0.33 (0.08 – 1.43)	0.138
Ischemic stroke	0.32 (0.07 – 1.55)	0.156	0.26 (0.05 – 1.45)	0.126
Heart failure	0.68 (0.16 – 2.86)	0.595	0.71 (0.15 – 3.40)	0.672

BMI: Body Mass Index, CCI: Charlson Comorbidity Index, ORs: Odds Ratios

Chapter 4

Diabetes, frailty, and burden of comorbidities among older Malaysians with stroke

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ORIGINAL ARTICLE

Diabetes, frailty and burden of comorbidities among older Malaysians with stroke

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Abstract

Background Stroke is a global health challenge. The increasing prevalence of diabetes and the ageing population further add to the complexities of stroke care.

Objective This study aims to (1) describe the prevalence of diabetes in older patients with stroke and (2) compare the burden of comorbidities among patients with diabetes and frailty compared to those without these conditions.

Methods This was a cross-sectional study in older patients aged ≥ 65 years with stroke. Comorbidities were assessed using the Charlson Comorbidity Index (CCI). Frailty assessments were done using the Clinical Frailty Scale. Participants were classified into four groups: Group 1, frail and diabetic; Group 2, non-frail and diabetic; Group 3, frail and non-diabetic; and Group 4, non-frail and non-diabetic.

Results There were 384 participants (mean age 81.11 ± 6.37). Diabetes was present in 45.1%. The mean CCI was highest for the frail and diabetic group (6.97 ± 1.97), followed by non-frail and diabetic (6.00 ± 2.02), frail and non-diabetic (5.49 ± 1.79) and non-frail and non-diabetic (4.74 ± 1.68), $p < 0.001$. The non-frail and diabetic group had a significantly higher prevalence of hypertension (96.9%) and ischaemic heart disease (34.4%) compared to the other three groups.

Conclusions There was a high prevalence of diabetes among older patients with stroke. While the frail and diabetic group had the highest overall burden of comorbidities, the non-frail and diabetic group had the most significant cardiovascular disease burden. These findings highlight the urgent need for integrated and personalized management approaches to enhance the overall well-being and quality of life for older stroke survivors with diabetes.

Keywords Stroke · Older person · Diabetes · Frailty · Cardiovascular disease

Introduction

Stroke continues to be a major contributor to mortality and disability [1]. Due to the nature of the disease, stroke patients experience loss of brain function that affects motor and cognitive function resulting in disabilities. Recent advancements have allowed improved care resulting in a growing number of stroke survivors [2]. These stroke survivors may regain some motor capability depending on recovery [3]. Factors influencing the prognosis of stroke recovery include age, stroke severity, subtypes of stroke and comorbidities like diabetes [4, 5].

The prevalence of diabetes has increased considerably over recent decades [6–8]. This has implications when considering management and prevention strategies for stroke. The high prevalence of diabetes among stroke in-patients specifically can increase complexities and healthcare utilization. Some studies have reported how diabetes influences

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mortality and recurrent stroke, although this is usually limited to the younger population [9, 10].

With most studies focusing on patients aged less than 65 years [11], there is currently limited data on in-hospital and long-term outcomes for older stroke patients with diabetes. This is partly contributed by the age limit set in some clinical trials [12]. With the growing number of older people and the fact that age is an irreversible risk factor for stroke, studies in this specific age group are needed to help guide future care, especially when age-specific prevalence rates of diabetes are noted to be growing faster in the older population (≥ 65 years of age) when compared to those younger [13]. Research prioritization exercises have also highlighted the lack of evidence to guide care for older people with diabetes and the need for more studies to explore how it relates to other comorbidities [14, 15]. The additional influence of frailty on health outcomes for an older person [12, 16] further increases the complexity but also shows the necessity for further studies.

Like many other regions, stroke and diabetes are growing public health concerns in Malaysia [17]. Malaysia has one of the highest rates of diabetes in the Western Pacific region [18]. For broader stroke management strategies, this is critical as the prevalence of diabetes in hospitalized patients with strokes in Malaysia has been reported to be highest among Southeast Asian and East Asian countries [8]. Stroke is also the second major cause of premature mortality among older adults in Malaysia [19]. The growth of the older population has overtaken the younger population, and it is estimated that the older population will make up almost 20% of the population by 2040 [20]. The continuous rise of diabetes and the growing ageing population in Malaysia further add to challenges for broader stroke management [21]. In 2016, more than 40% of hospital admissions for stroke in Malaysia were those 65 years and older [17]. In this study of Malaysian older patients hospitalized with strokes, we aimed to (1) describe the *prevalence of diabetes* and (2) compare the *burden of comorbidities and cardiovascular risk factors among patients with diabetes and frailty compared to those without these conditions.*

Materials and methods

Study design

This study was a cross-sectional, secondary analysis using data from an observational study on the prevalence of pre-stroke frailty and its impact on outcomes in older patients hospitalized with strokes in Malaysia. Details of this study were published in 2023 [22]. In brief, patients from Universiti Malaya Medical Centre, a teaching hospital in Kuala Lumpur, Malaysia, were included for analysis. The study period was from January 2016 to January 2020. Older patients aged ≥ 65 years admitted to the Geriatric Medicine Unit with acute stroke were eligible for the study. Patients underwent a Comprehensive Geriatric Assessment (CGA) at the point of admission where medical history and functional abilities before their stroke were recorded. Ethics approval was obtained from the Medical Research Ethics Committee of the University Hospital (MEC No: 201312–0636).

Variable definitions

Comorbidities were assessed using the Charlson Comorbidity Index (CCI). The CCI is a widely used index and is considered to be the gold standard measure in predicting patient survivability in patients with multiple comorbidities in clinical research [23].

Participants' history of cardiovascular disease was collected using a predefined list of eight conditions, namely hypertension, previous stroke/transient ischaemic attack, dyslipidaemia, chronic kidney disease (eGFR < 60mL/min), atrial fibrillation, ischaemic heart disease, congestive heart failure and peripheral vascular disease.

Participants' frailty status before their admission with stroke was assessed using the Clinical Frailty Scale (CFS) version 2. The CFS is a 9-point scale that can be used to summarize the level of frailty in an older person [24–26]. The CFS score ranges from 1 to 9, and a score of 4 or greater indicates a frailty status [25, 27]. Briefly, scoring was as follows: 1, very fit; 2, well; 3, managing well; 4, living with very mild frailty; 5, living with mild frailty; 6, living with moderate frailty; 7, living with severe frailty; 8, living with very severe frailty; 9, terminally ill. For this study, the frail category includes CFS 4–8 and the non-frail category includes CFS 1–3. CFS 9 was excluded as it describes patients with limited life expectancy.

Sample size justification

The sample size was estimated for the first aim of this study (to examine the prevalence of diabetes among older adults with stroke), using a single population proportion formula: $n = Z^2_{1-\alpha/2} \times [p \times (1-p)/d^2]$, with n = the required sample size, $Z_{1-\alpha/2} = 1.96$ (with $\alpha = 0.05$ and 95% confidence interval), p = prevalence of diabetes in older patients with stroke and d = precision (assumed as 0.05). Our literature search found that the prevalence of diabetes ranged from 17 to 53% in adults with strokes in studies conducted in Malaysia and other countries in the Southeast Asian region [4, 28–33]. Therefore, we estimated that the prevalence of diabetes in older adults with stroke in this study would be around 40 to 55% and the sample size for our study was calculated to be at least 380 participants.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics version 26.0 (IBM Corp, Armonk, NY, USA). Comparisons

between participants with and without diabetes were conducted using independent samples *t*-test for continuous variables and chi-square tests or Fisher's exact tests for categorical variables. p value < 0.05 was deemed significant.

Participants were also classified into four groups according to their frailty status and whether they had diabetes or not: Group 1, frail and diabetic; Group 2, non-frail and diabetic; Group 3, frail and non-diabetic; and Group 4, non-frail and non-diabetic. Comparisons among these four groups were assessed using chi-square tests or Fisher's exact tests for categorical variables and ANOVA test for continuous variables. Two-tailed p values < 0.05 were deemed statistically significant.

Results

A total of 384 participants were included in our study. They had a mean age of 81.11 (SD 6.373), and 57% were female. A diagnosis of diabetes was recorded in 45.1% of the participants (173/384) (Table 1).

The distribution of the Clinical Frailty Scale score in participants with and without diabetes is presented in Fig. 2. Using the cut-off point of 4, the prevalence of frailty was 75.3% in all participants, 81.3% in those with diabetes and 70.5% in those without diabetes ($p = 0.015$).

The burden of comorbidities among 384 participants

The mean Charlson Comorbidity Index was 5.97 ± 2.05 in all participants. Compared to participants without diabetes, participants with diabetes had a higher Charlson Comorbidity Index (6.82 ± 2.02 versus 5.28 ± 1.80, $p < 0.001$).

Among 384 participants with strokes, 139 (36%) were classified into Group 1, frail and diabetic; 32 (8%) were classified into Group 2, non-frail and diabetic; 148 (39%) were classified into Group 3, frail and non-diabetic; and 62 (16%) were classified into Group 4, non-frail and non-diabetic. When comparing the four groups of frailty-diabetes, participants with diabetes and frailty had the highest comorbidity burden, as shown with the highest Charlson Comorbidity Index mean score in Fig. 3. The mean CCI for the frail and diabetic group was 6.97 ± 1.97, followed by non-frail and diabetic, 6.00 ± 2.02; frail and non-diabetic, 5.49 ± 1.79; and non-frail and non-diabetic, 4.74 ± 1.68 ($p < 0.001$).

Table 1 Study participants, characteristics

Variables	All participants ($N = 384$)	Participants without diabetes ($N = 211$)	Participants with diabetes ($N = 173$)	p values
Age (mean)	81.11 ± 6.373	81.95 ± 6.182	80.09 ± 6.471	0.004
Sex				
Male	165 (43.0%)	91 (43.1%)	74 (42.8%)	0.945
Female	219 (57.0%)	120 (56.9%)	99 (57.2%)	
Ethnicity				
Malay	86 (22.4%)	44 (20.9%)	42 (24.3%)	0.103
Chinese	210 (54.7%)	126 (59.7%)	84 (48.6%)	
Indian	82 (21.4%)	37 (17.5%)	45 (26.0%)	
Others	6 (1.6%)	4 (1.9%)	2 (1.2%)	
Residence status				
Home	346 (91.5%)	193 (92.8%)	153 (90.0%)	0.333
Nursing home	32 (8.5%)	15 (7.2%)	17 (10.0%)	
Smoking	24 (6.3%)	16 (7.6%)	8(4.7%)	0.251
Polypharmacy (≥ 5 medicines)	150 (39.4%)	55 (26.2%)	95 (55.6%)	< 0.001
Stoke subtype				
Total/partial anterior circulatory ischaemic	67 (17.4%)	37 (17.5%)	30 (17.3%)	0.217
Posterior circulatory ischaemic	20 (5.2%)	11 (5.2%)	9 (5.2%)	
Lacunar ischaemic	249 (64.8%)	130 (61.6%)	119 (68.8%)	
Haemorrhagic	48 (12.5%)	33 (15.6%)	15 (8.7%)	

Compared to participants without diabetes, those with diabetes were younger (mean age 80.09 ± 6.47 compared to 81.95 ± 6.18, respectively, $p = 0.004$). The age distribution of the participants is presented in Fig. 1

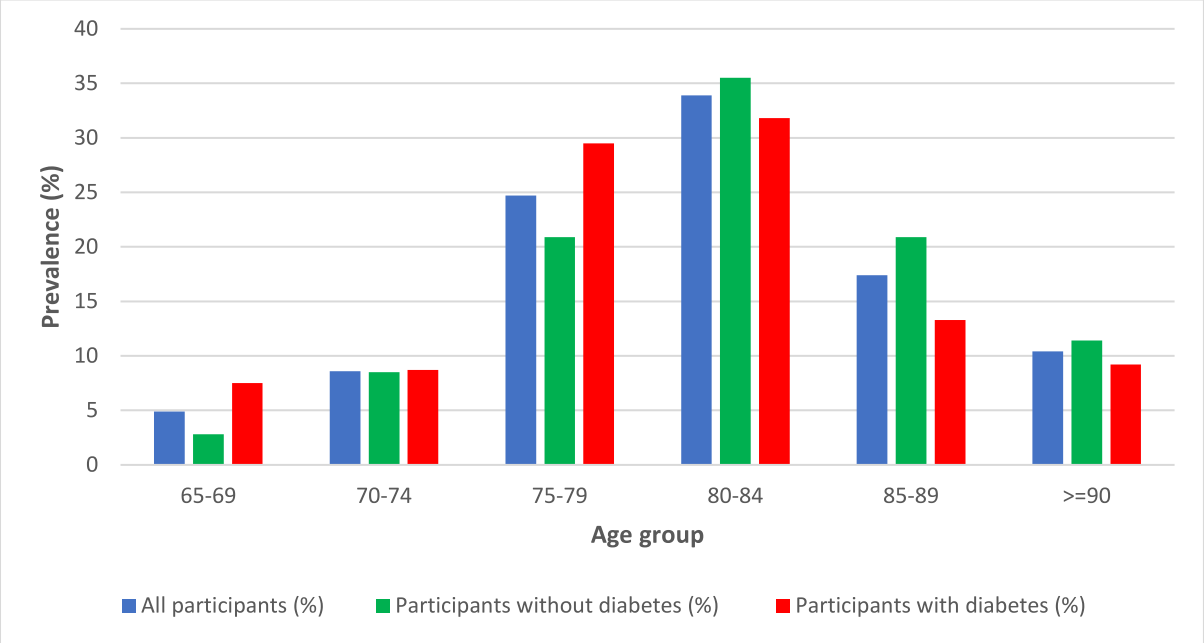

Fig. 1 Age distribution among participants with and without diabetes

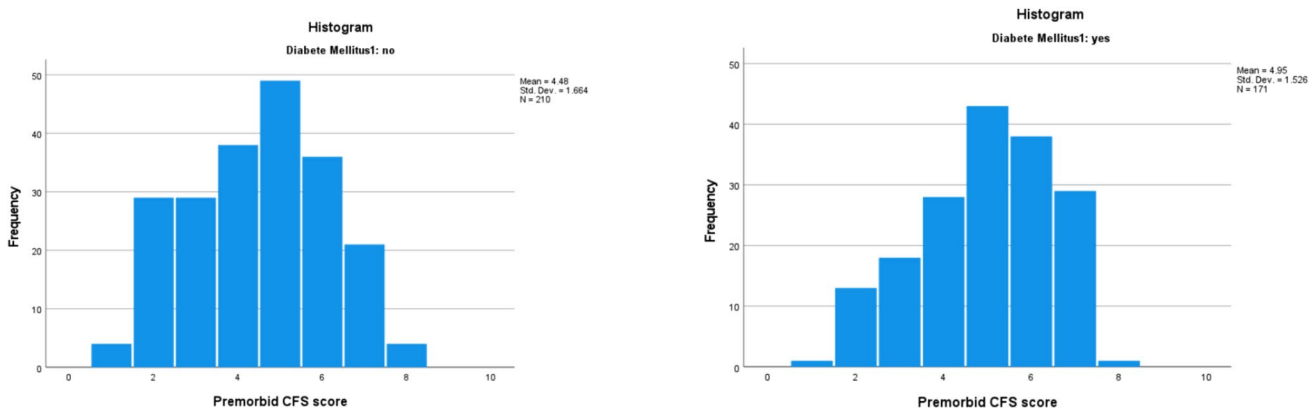

Fig. 2 The distribution of the Clinical Frailty Scale in participants with and without diabetes

The burden of cardiovascular disease and risk factors

Among the history of cardiovascular diseases and risk factors, the most prevalent was hypertension (81.8%), followed by previous stroke/TIA (48.2%), dyslipidaemia (39.8%), chronic kidney disease (39.3%), atrial fibrillation (21.9%), ischaemic heart disease (20.4%), heart failure (3.6%) and peripheral vascular disease (2.9%).

Participants with diabetes had a significantly higher prevalence of hypertension (90.8% versus 74.4%, $p<0.001$), ischaemic heart disease (27.2% versus 14.8%, $p=0.003$), congestive heart failure (5.8% versus 1.9%, $p=0.043$) and chronic kidney disease (45.1% versus 34.6%, $p=0.036$).

The cardiovascular risk factors and disease burden across the four groups of frailty-diabetes are presented in Fig. 4. Across the four groups, hypertension was the most prevalent. The non-frail and diabetic group had a significantly higher prevalence of hypertension (96.9%) and ischaemic heart disease (34.4%) compared to the other three groups. There was no significant difference in other cardiovascular diseases and risk factors among the four groups.

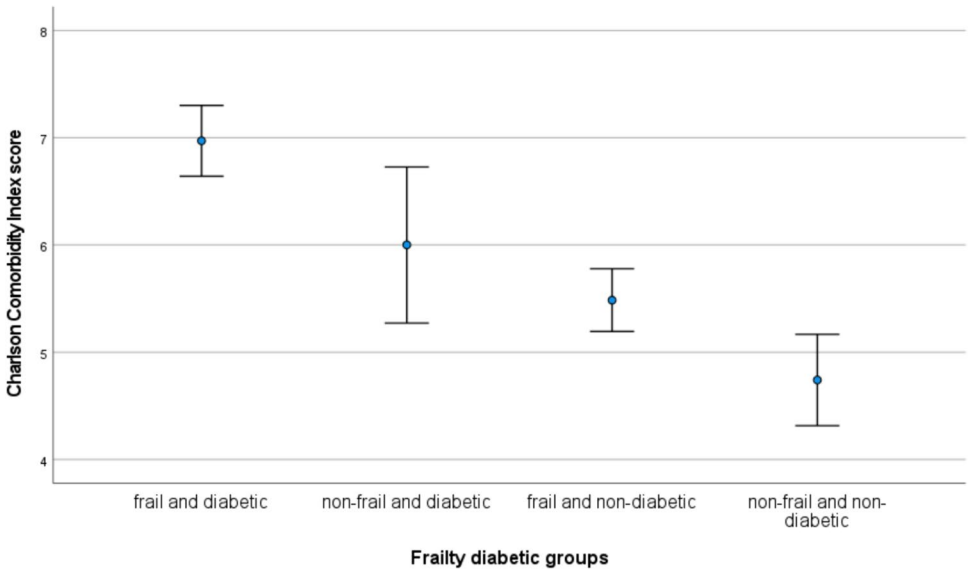

Fig. 3 The mean Charlson Comorbidity Index score among the four groups of frailty-diabetes

Discussion

In this study in 384 older Malaysian admitted to hospital due to strokes, we found a high prevalence of diabetes (45.1%) among patients with strokes. Patients with diabetes had a higher burden of frailty, higher Charlson Comorbidity Index score, cardiovascular risk factors such as hypertension and CKD and disease burden such as IHD and heart failure, and were at a younger age at the time of stroke. More than one-third (36%) of the patients had both diabetes and frailty.

The prevalence of diabetes in stroke inpatients in our study was higher compared to other countries in the Southeast Asian region. The mean age of our study participants is 81 years of age. As such, the results of our analysis provide an evidence base for the older old population with participants in similar studies having a mean age ranging from 57 to 68 years [4, 28–32]. Analysis from the National Neurology Registry for Acute Stroke in Malaysia showed estimates of diabetes prevalence ranged from 24.9 to 53.3% depending on first or recurrent stroke across ischaemic and haemorrhagic stroke [33]. Studies in neighbouring countries such as Thailand, Indonesia and Singapore have reported a prevalence ranging from 17.1 to 38.5% [4, 28, 29]. Similar studies in other countries such as Ethiopia, Pakistan and China have also reported a prevalence ranging from 8.1 to 35.46% [30–32]. In a study of 208 stroke patients in a hospital in the city of Yogyakarta, Indonesia, the prevalence of diabetes was found to be 34.1% with common comorbidities including hypertension, dyslipidaemia and cardiac diseases like atrial fibrillation [4]. In another analysis of 9766 patients across 3 hospitals in Singapore, the prevalence of diabetes in stroke inpatients was found to be 38.5% [28]. With diabetes influencing stroke prevalence and outcomes, countries like Malaysia, Indonesia and Singapore face similar challenges in managing the growing impact of non-communicable diseases like diabetes.

Older people in Malaysia were more than ten times more likely to have diabetes compared to younger people [18]. There is growing evidence of the association of diabetes with frailty in the older population [34]. In a study among community-dwelling older adults in Malaysia, the prevalence of frailty was found to be 18.3% and the top 2 comorbidities associated were diabetes and hypertension [35]. With the growing population of older people in Malaysia, there is a need to have routine frailty assessments when providing care for older persons with diabetes. Evidence-based interventions can be tailored to the different frailty groups.

Research on the role of frailty in stroke outcomes is still growing. In a study of 433 individuals with ischaemic stroke, the 28-day mortality was noted to be higher in frail participants compared to non-frail participants [36]. A separate study also reported higher 1-year mortality in frail participants [22]. In another study of 530 patients in China, it was found that frailty was an independent risk factor for 1-year all-cause mortality among older stroke patients [37]. A systematic review and meta-analysis described how the prevalence of frailty in acute stroke ranged from 2.2 to 54%, with outcomes inconsistently reported [38]. Studies that met inclusion criteria appeared to be mainly from higher-income countries although the methodology was designed to be inclusive and global [38]. Age being an irreversible risk factor for stroke highlights the need for studies in the older population, especially in low- to middle-income countries such as Malaysia.

In patients with diabetes, frailty was found to be associated with an increased risk of all-cause mortality, cardiovascular-related mortality, major adverse cardiovascular events and hypoglycaemia [39]. It does highlight the need for frailty

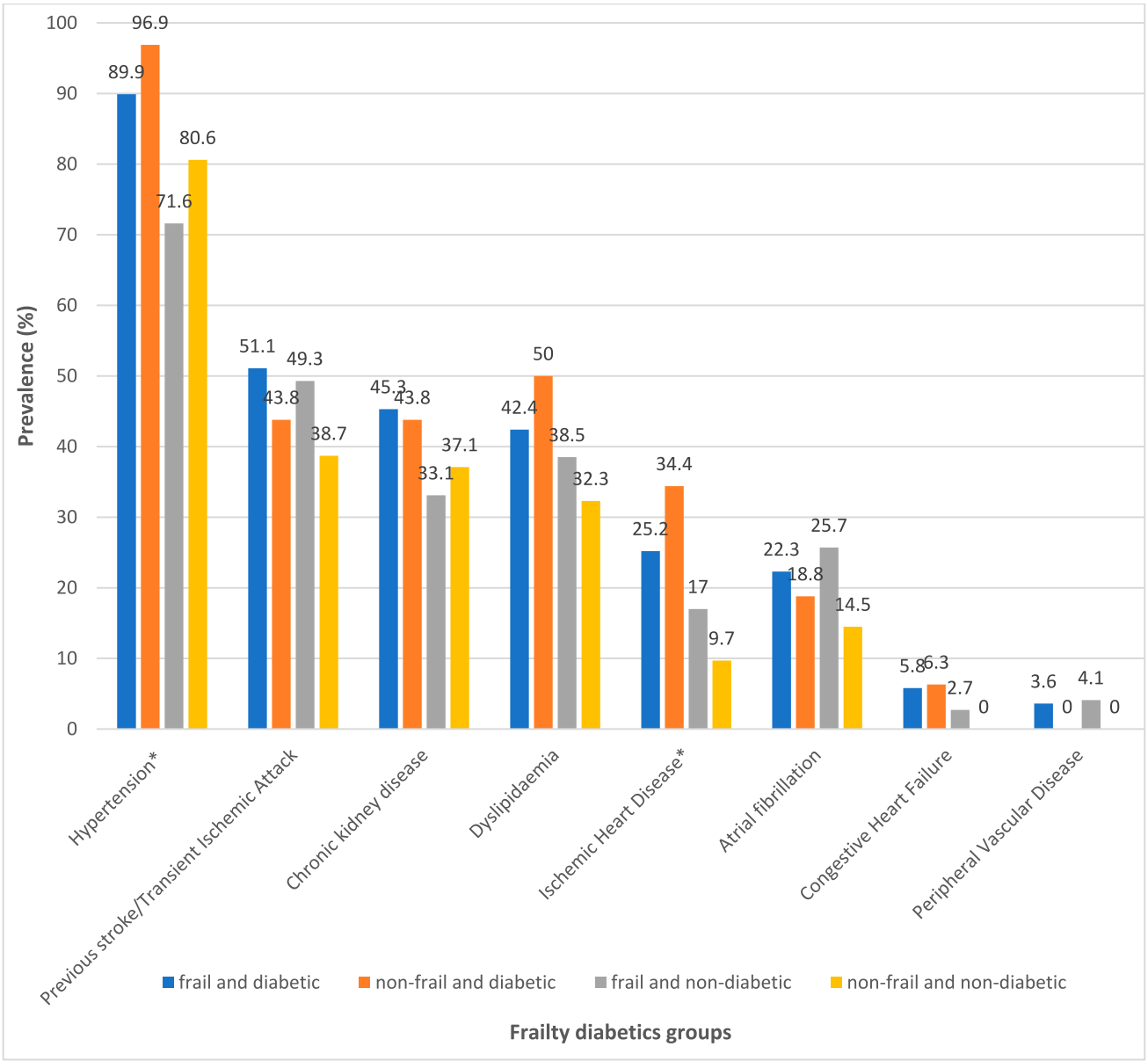

Fig. 4 Cardiovascular risk factor and cardiovascular disease burden across the four frailty-diabetes groups (*p value < 0.05)

assessment and management to be incorporated into routine diabetes care. The results of our analysis demonstrate a significant association between diabetes and increased frailty among older people with stroke. This aligns with previous studies that have further described the link between diabetes and frailty [40]. The presence of diabetes appears to influence frailty potentially due to metabolic and inflammatory interactions which may exacerbate age-related decline in physiological reserves. The accelerated pace of muscle wastage, decreased physical function and heightened vulnerability to stressors in individuals with diabetes could contribute to the increased likelihood of a stroke attack.

Our findings highlight the compounded cardiovascular disease burden in older stroke survivors, especially among patients in the non-frail and diabetic group. This is also similar to another study in an Egyptian population [41]. The synergistic relationship between diabetes and cardiovascular disease burden has been extensively documented with diabetes serving as a significant risk factor for the development and progression of cardiovascular complications. In the context of stroke survivors, diabetes may also exacerbate underlying vascular damage, leading to greater impairment in vascular integrity and contributing to recurrent cardiovascular events. The increased prevalence of comorbidities such as hypertension, IHD, CCF, PVD, dyslipidaemia,

cerebrovascular disease (including TIA) and chronic kidney disease observed in individuals with diabetes could further contribute to the amplified cardiovascular disease burden observed in our study population.

Clinical implications

Implications of our findings underscore the need for tailored interventions and management strategies for older stroke survivors with diabetes. Furthermore, the goals of treatment differ in people with varying levels of frailty, with many not tolerating the usual targets of treatment at the higher frailty levels. The integration of multidisciplinary approaches, encompassing medical management, lifestyle modifications and rehabilitative interventions, becomes imperative in addressing the intertwined challenges of frailty and cardiovascular disease burden. Optimizing appropriate glycaemic control and managing cardiovascular risk factors through appropriate pharmacological and lifestyle interventions could help reduce the adverse outcomes associated with diabetes in this population. This is more relevant as control rates for diabetes in the older population in Malaysia were reported to be low (21.8%) [42] in comparison with neighbouring countries like Thailand reporting higher rates (26.4%) [43].

Moreover, the findings emphasize the importance of early identification and screening for diabetes and frailty in the older population. Timely diagnosis and management of diabetes could potentially mitigate the progression of frailty and help reduce the impact of stroke. Routine comprehensive geriatric assessment that incorporates frailty assessment and cardiovascular risk assessment should be further encouraged even in non-routine settings. This can aid in identifying high-risk individuals who may benefit from early targeted interventions.

Strengths and limitations

Our study findings provide insights into the complex interplay between diabetes, frailty and comorbidities, particularly cardiovascular health, further shedding light on the multifaceted challenges in this vulnerable population. It also highlights the critical need for diabetes management particularly with the high prevalence of diabetes reported in Malaysia. Our study was conducted in a very old population in Malaysia and contributed to the evidence on the epidemiology of stroke, diabetes and comorbidities in low- and middle-income countries.

However, our study was a single-site study and results may not be generalizable to other health settings. The cross-sectional design prevents any establishment of a causal relationship between diabetes, frailty and cardiovascular disease burden. Future prospective studies with larger sample sizes and longitudinal follow-up can help to elucidate the temporal relationships and mechanisms underlying the observed associations. Although our study did not explore the influence of diabetes on the likelihood of stroke, it does describe the higher prevalence of frailty and cardiovascular comorbidities burden in those with diabetes. The results of our analysis do provide an opportunity for this area to be further explored and its influence on the management of post-stroke outcomes.

Conclusion

There was a high prevalence of diabetes among older patients with stroke. While the frail and diabetic group had the highest overall burden of comorbidities, the non-frail and diabetic group had the most significant cardiovascular disease burden. These findings underscore the urgent need for integrated and personalized management approaches to enhance the overall well-being and quality of life for older stroke survivors with diabetes.

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Data Availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Research involving human participants This study was a retrospective analysis of medical records of patients.

Informed consent Project was approved by the Medical Research Ethics Committee of the hospital (MEC no: 201312–0636).

Conflict of interest The authors declare no competing interests.

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Chapter 5

Hypertension in adults with diabetes in Southeast Asia: A systematic review

The Journal of Clinical Hypertension

WILEY

REVIEW OPEN ACCESS

Hypertension in Adults With Diabetes in Southeast Asia: A Systematic Review

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ABSTRACT

Diabetes is one of the most pressing health issues in the Southeast Asian region, and hypertension has been commonly reported as a comorbidity in adults with diabetes. This systematic review aimed to synthesize evidence on the prevalence and management of hypertension in adults with diabetes in Southeast Asian countries. A literature search was conducted in Ovid MEDLINE and Embase Classic + Embase from database inception until March 15, 2024. Studies were included if (1) they were conducted in Southeast Asian countries, (2) the study populations were adults with diabetes, and (3) there was information related to hypertension or blood pressure (BP) in the study results. Of the 7486 abstracts found, 90 studies qualified for this review. Most studies reported a hypertension prevalence of 70% or higher (ranging from 29.4% to 93.4%). Despite this high prevalence, a substantial proportion of these populations did not receive adequate BP control, with most studies indicating a control rate of less than 40%. There was limited evidence on the prescription of antihypertensive therapies and medication adherence. There was a lack of studies from 4 of the 11 countries in the region. This review highlights that BP control in adults with diabetes remains a significant challenge in Southeast Asia. Given the ongoing epidemiological transition, and the increasing older population in this region who are likely to accumulate multiple chronic conditions complicating medication strategies, this review highlights the urgent need to improve BP management in those with diabetes.

1 | Background

The region of Southeast Asia is a rapidly growing and developing part of the world. Geographically, it consists of 11 countries situated south of Mainland China, east of the Indian subcontinent and north of Australia. The 11 countries are (in alphabetical order) Brunei, Cambodia, Indonesia, Lao People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor Leste, and Vietnam. The region has a wide diversity in socio-cultural backgrounds and contributes to approximately 9% of the world's global population [1]. Five member countries in the region are ranked among the top 30 most populous countries globally—Indonesia at number 4 (with 274 million people), the Philippines at 13 (with 118 million people), Vietnam at 16 (with 99 million

[Correction added on January 29, 2025, after first online publication: The affiliations of the second author, Tan Van Nguyen, have been corrected in this version.]

people), Thailand at 20 (with 72 million people), and Myanmar at 27 (with 55 million people). Alongside population growth, these countries are undergoing significant demographic changes and are not immune to the global epidemiological transition. Increasing economic development in some low- and middle-income countries has been proposed as a contributing factor to the rising prevalence of diseases like diabetes and cardiovascular disease. The longer life expectancy and increasing older population have strained healthcare resources in these countries. They share common challenges linked to the ongoing epidemiological transition and a shift in the disease burden from communicable to non-communicable diseases [1]. The Southeast Asia region is expected to see an increase in morbidity and mortality associated with cardio-metabolic diseases in the coming decades [2]. As a response, a multidisciplinary expert panel has called for Southeast Asia specific clinical pathways for regional approaches to the growing epidemic of non-communicable diseases [3].

One of the most pressing health issues in this region is the rising incidence of type 2 diabetes, which has become a significant public health concern [4]. The prevalence of type 2 diabetes in this region is estimated to be around 9%, with outcomes generally poorer compared to Caucasian populations [5–7]. It is expected that by 2025, the major prevalence of diabetes will not be in North America or Europe but in the Asia Pacific region [8], of which Southeast Asia is a part. This will further add pressure on already burdened health systems in the region.

Hypertension has been commonly reported as a comorbidity in adults with type 2 diabetes [9]. This is concerning as it can increase the risks of complications associated with diabetes, leading to reduced kidney function and contributing to cardiovascular disease. Therefore, blood pressure (BP) control remains a crucial aspect of managing patients with diabetes, not only in preventing vascular complications related to diabetes but also in managing overall cardiovascular risk. Predictive modeling has shown that aggressive management of both diabetes and hypertension can reduce cardiovascular events [10]. As such, it is critical to manage both conditions effectively in these populations [11].

In this review, we aimed to synthesize the evidence from research related to the prevalence of hypertension and its management in adults with diabetes in Southeast Asian populations.

2 | Methods

2.1 | Search Strategy and Information Sources

A literature search was done in the following databases from database inception until March 15, 2024: Ovid MEDLINE (from 1946), Embase Classic + Embase (from 1947). Articles written in languages apart from English were excluded. Search results were managed using Covidence (Table S1).

Keywords and Medical Subject Headings terms were: diabetes, diabetes mellitus, BP, hypertension, with the combination of countries, and populations: Malaysia, Malaysian, Indonesia, Indonesian, Singapore, Singaporean, Vietnam, Vietnamese, Thailand, Thai, Brunei, Laos, Timor Leste, Cambodia, Cambodian, Myanmar, Burma, Philippines, Filippino, Southeast Asia.

2.2 | Eligibility (Inclusion) Criteria

Studies were included if (1) they were conducted in Southeast Asian countries, (2) the study populations were adults with diabetes, and (3) there was information related to hypertension or BP in the study results.

2.3 | Exclusion Criteria

Case reports, abstracts, reviews, non-English text, study protocols for randomized control trials, studies that looked at diaspora (e.g., Filipino Americans, Vietnamese living in European countries), and studies that included multiple countries outside Southeast Asia and did not provide specific results for Southeast Asian countries, were excluded.

2.4 | Study Selection and Data Extraction

Full texts were retrieved and assessed. All references selected for retrieval from the databases were managed by Covidence. Duplicated references were excluded. Study titles and abstracts were screened independently by two members of the research team (W.J.W. and F.A.), based on the inclusion and exclusion criteria. The full texts of qualified publications were read and selected for the final decision to include after discussion between W.J.W., F.A., and T.N.N. Any disagreement was solved by discussion between these three reviewers. The included studies were then managed into an Excel file listing the year of publication, first author name, title, and journal (Table S2).

2.5 | Quality Assessment

Quality assessment of the included studies was evaluated using the National Heart, Lung, Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort, Cross-Sectional Studies, and Controlled Intervention Studies. The quality assessment tool consists of 14 items for evaluation in each study design. Items were scored accordingly—Y-Yes, N-No, or O-Others (CD-Cannot determine, NA-Not applicable, NR-Not reported). Studies were then classified as "good," "fair," or "poor."

2.6 | Data Analysis

We extracted information on the country, published year, study sample size, study design, and the study findings into tables. The results of this review were narratively summarized in accordance with the review objective. This review followed the PRISMA guidelines (Figure 1).

3 | Results

A total of 7486 abstracts (5452 from Embase & 2034 from Medline) were screened and reviewed, and 90 articles were included in this review [12–103] (Figure 1). Of the 90 articles, 88 were observational studies, 1 was a randomized controlled trial, and 1 was a quasi-experimental controlled study. These 90 studies were

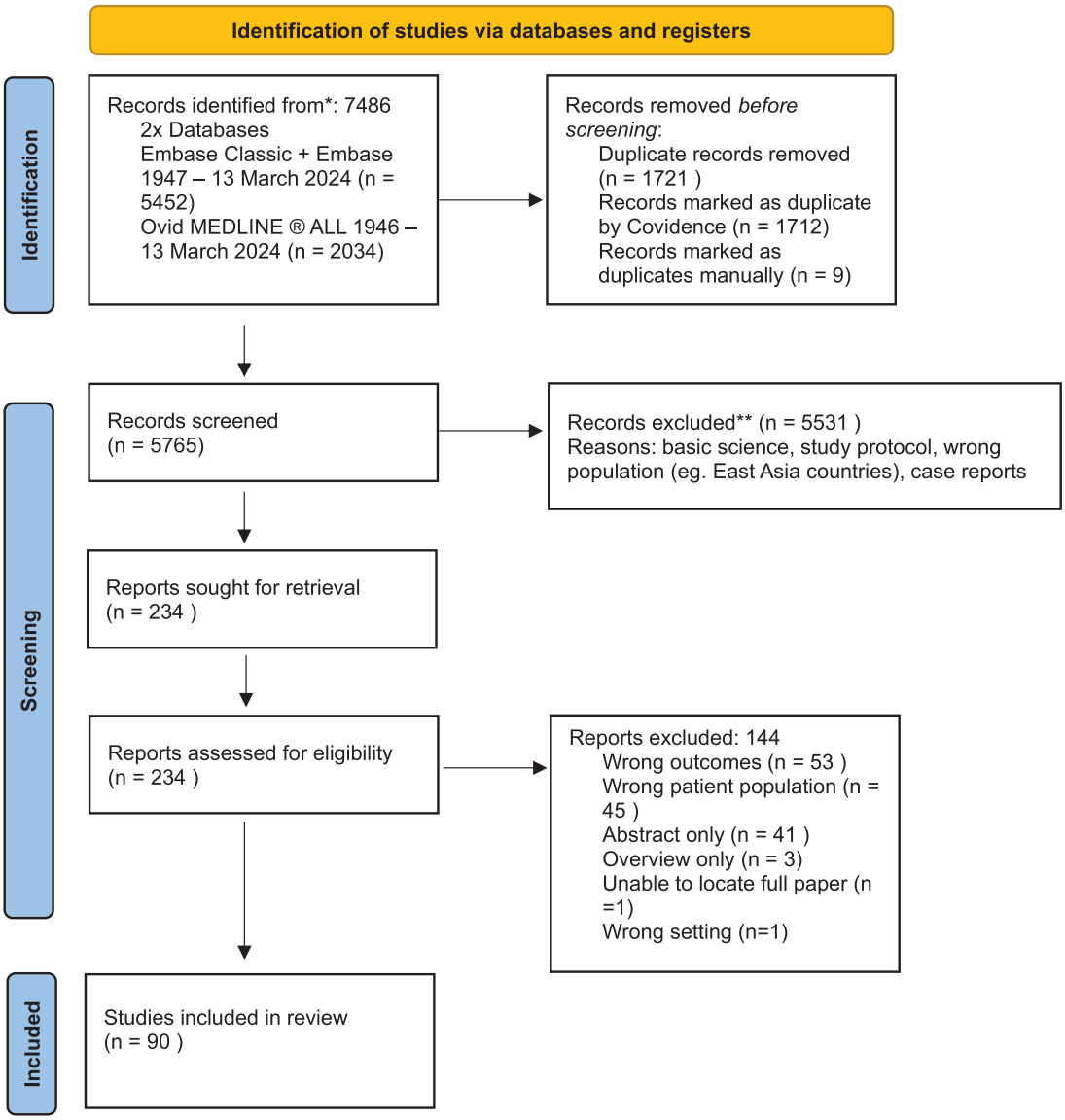

FIGURE 1 | PRISMA flowchart.

from 7 Southeast Asian countries (Figure 2), including: Malaysia (39 articles) [12–51], Thailand (24 articles) [52–75], Singapore (10 articles) [76–86], Indonesia (6 articles) [87–92], Cambodia (5 articles) [93–97], Vietnam (3 articles) [98–100], and Philippines (3 articles) [101–103]. The mean age of the participants in these studies ranged from 50.3 to 72.6 years (Table 1). Most studies were conducted in the general adult population, and only six studies were exclusively devoted to an older demographic, specifically including participants aged 60 or older [40, 41, 58, 65, 82, 99].

3.1 | Quality Assessment/Risk of Bias Analysis

The 88 observational studies were evaluated using the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The remaining studies were evaluated using the NHLBI Quality Assessment of Controlled Intervention Studies. Of the 90 included studies, 75 studies were classified as "good," and 15 were classified as "fair" (Table S3).

We summarized the findings into four main themes for adults with diabetes: (1) Prevalence of hypertension (Table 1); (2) BP control rate (Table 2); (3) Percentage of patients with diabetes who received antihypertensive medicines (Table 3); and (4) Adherence to antihypertensive medicines. We also provided information on glucose control in Table S4.

3.2 | Prevalence of Hypertension in People With Diabetes

Among the 90 studies included in this review, data on the prevalence of hypertension in adults with diabetes was obtained from 55 studies [12, 13, 15, 18, 19, 21, 22, 24, 25, 28, 29, 31, 33, 36, 39–45, 47–51, 55–61, 63, 64, 66, 67, 69, 70, 74, 75, 78, 79, 81, 84, 88, 89, 91, 92, 94, 95, 97, 98, 100–103]. Among the included 90 studies, 85 studies reported using office BP measurements and 5 studies used out-of-office BP measurements (Table S4). Most studies reported a hypertension prevalence of 70% or higher (ranging from 29.4% to 93.4%). Malaysia contributed the most

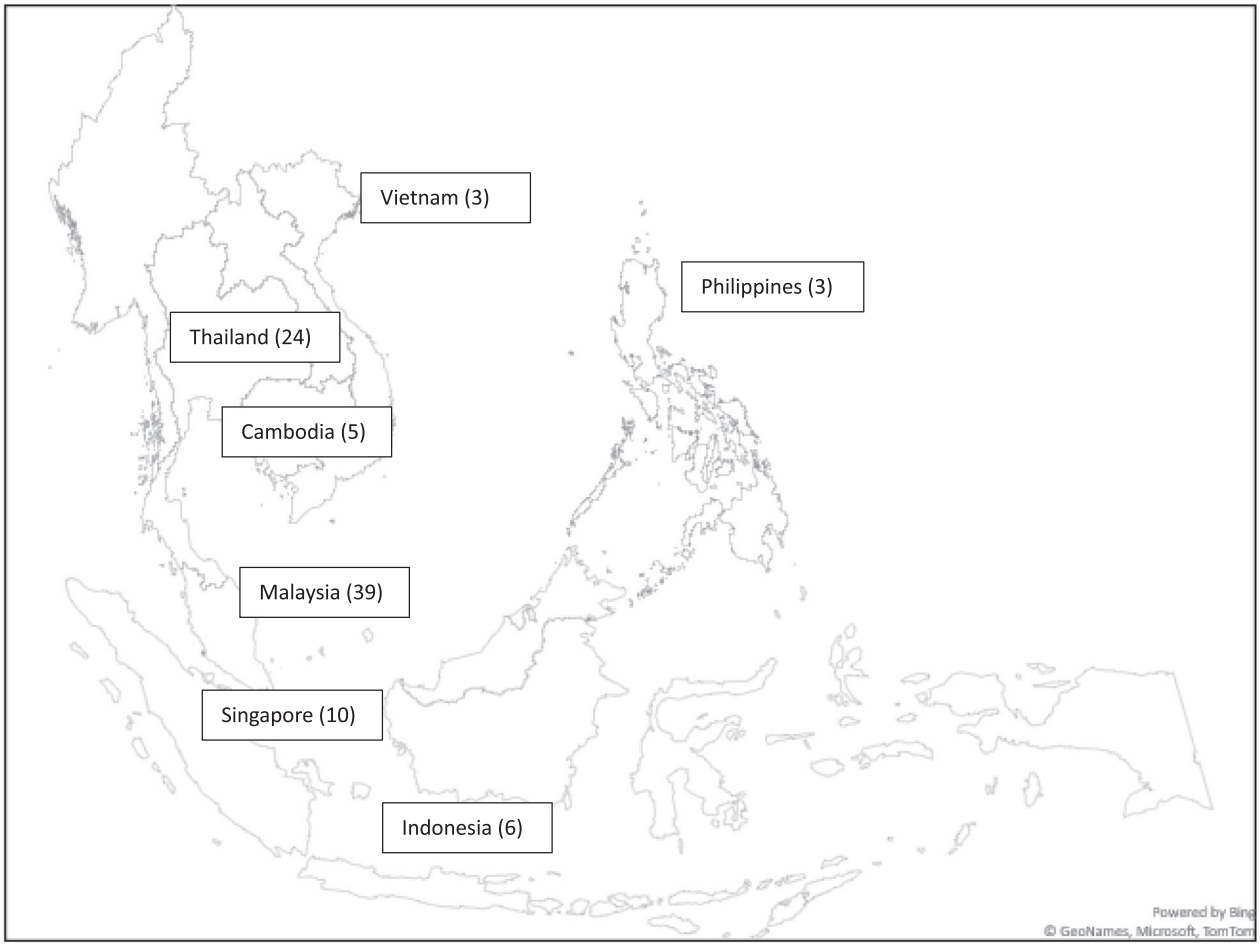

FIGURE 2 | Number of studies per country in Southeast Asia.

studies (25 studies), followed by Thailand (15 studies). Among the 25 studies in Malaysia, the reported prevalence of hypertension was > 70% in most of the studies (90.4%–93.4% in 4 studies, 80.3%–87.9% in 8 studies, 72.9%–79.1% in 8 studies, 57.4%–67.7% in 3 studies, and 32.4%–36.9% in 2 studies) [12, 13, 15, 18, 19, 21, 22, 24, 25, 28, 29, 31, 33, 36, 39–45, 47–51]. Similarly, there was also a very high prevalence of hypertension among adults with diabetes in Thailand: 80.5%–89.3% (4 studies), 70.2%–78.2% (6 studies), 63.4%–69.95% (3 studies), and 55.35%–57.3% (2 studies) [55–61, 63, 64, 66, 67, 69, 70, 74, 75].

In other Southeast Asian countries, the prevalence of hypertension ranged from 29.4% to 58.8% in Cambodia (3 studies) [94, 95, 97], 43.9%–68.1% in Indonesia (4 studies) [88, 89, 91, 92], 42%–73.5% in Philippines (3 studies)[101–103], 59.4%–92.4% in Singapore (3 studies)[78, 81, 84], and 35.6%–78.4% in Vietnam (2 studies) [98, 100].

3.3 | BP Control Rate in People With Diabetes

Among the 90 studies included in this review, information on BP control rate was obtained from 46 studies [14, 16, 17, 20, 23–27, 29–32, 34–37, 40, 41, 45–47, 51, 52, 54, 56, 58, 62, 63, 65, 66, 68, 69, 71–73, 76, 77, 80–82, 85, 90, 93, 96, 99].

The percentage of study participants achieving BP control varied across the countries, with most studies indicating a control rate of less than 40%. Among the 23 studies in Malaysia, most of the studies reported a BP control rate of 22% to 39% (15 studies), while several studies reported a much lower rate (3.1%–8% in 2 studies, and 15%–19.9% in 3 studies), or higher (43.4% –47.2% in 3 studies) [14, 16, 17, 20, 23–27, 29–32, 34–37, 40, 41, 45–47, 51]. Among the six studies in Singapore, BP control rate was 12.7%–13.4% in 2 studies, 22.5%–26.2% in 2 studies, and 42.7%–69.9% in 2 studies [76, 77, 80–82, 85]. Among the 13 studies in Thailand, BP control rate was 6.2% in 1 study, 14.9%–18% in 2 studies, 28.4%–39.7% in 5 studies, 47.1%–53.1% in 3 studies, 65.5%–75.4% in 2 studies [52, 54, 56, 58, 62, 63, 65, 66, 68, 69, 71–73]. In other countries, the control rate was 12.3%–58.4% in Cambodia (2 studies) [93, 96], 9.2% in Indonesia (1 study) [90], and 37.2% in Vietnam (1 study) [99].

Regarding the cut-off to define controlled BP, the majority of studies (35 out of 46) employed a cut-off of 130/80 mmHg [14, 16, 17, 20, 23–27, 29, 30, 32, 34–37, 40, 41, 45, 47, 52, 54, 56, 62, 63, 66, 71–73, 77, 80–82, 85, 90]. The remaining 11 studies used a cut-off of 140/80–90 mmHg or a varying cut-off based on patient age [31, 46, 51, 58, 65, 68, 69, 76, 93, 96, 99]. For example, one study in Malaysia defined controlled hypertension as BP < 140/80 mmHg for patients with both diabetes and hypertension, and BP < 150/90 mmHg for those aged 80 years and above [46]. Another study in Thailand set a BP target of < 140/90 mmHg for

TABLE 1 | A summary of the studies providing the prevalence of hypertension in people with diabetes.

	Author and year	Country	Sample size	Study design	Age (years), mean (or an alternative when not stated)	Prevalence of hypertension
1	Hernandez et al. 2021 [95]	Cambodia	9139	Observational, retrospective	55.7	58.2%
2	Wagner et al. 2017 [97]	Cambodia	13 997	Observational, cross-sectional	—	58.7%
3	King et al. 2005 [94]	Cambodia	2246	Cross-sectional	50.3 (Siemreap) 55.3 (Kampong Chan)	29.4% (Siemreap) 58.8% (Kampong Chan)
4	Soeatmadji et al. 2023 [92]	Indonesia	221	Observational, prospective	55.6	43.9%
5	Sitorus et al. 2022 [91]	Indonesia	144	Cross-sectional	30.6% > 60 years old	68.1%
6	Mutika et al. 2021 [89]	Indonesia	170	Cross-sectional	86% > 45 years old	57%
7	Fajriansyah et al. 2020 [88]	Indonesia	220	Randomized controlled trial	57.7	62.7%
8	Husin et al. 2023 [28]	Malaysia	6719	Quasi-experimental controlled study	59.9	78.2%
9	Shaharuddin et al. 2023 [42]	Malaysia	495	Cross-sectional	52.2	78.3%
10	Sim et al. 2023 [43]	Malaysia	1985	Observational, retrospective	56.9	72.9%
11	Wan et al. 2023 [51]	Malaysia	288 913	Observational retrospective	58.7	81.6%
12	Lee et al. 2022 [31]	Malaysia	425	Cross-sectional	66.8% aged ≥ 60	90.4%
13	Ab Rahman et al. 2022 [12]	Malaysia	2696	Observational retrospective	60.4	85.8%
14	Wan et al. 2022 [47]	Malaysia	18 312	Observational, retrospective	49.4% aged ≥ 60	83.5%
15	Chee et al. 2021 [19]	Malaysia	301	Cross-sectional	61	77.1%
16	Chew et al. 2021 [21]	Malaysia	552	Observational, retrospective	59.9	78.3%
17	Keng et al. 2021 [29]	Malaysia	260	Cross-sectional	58.7	87.9%
18	Wan et al. 2021 [50]	Malaysia	18 341	Observational, retrospective	59.3	83.5%
19	Wan et al. 2021 [48]	Malaysia	17 592	Observational, retrospective	59.1	83%
20	Rahim et al. 2020 [39]	Malaysia	33	Cross-sectional	57.9	63.6%
21	Wan et al. 2020 [49]	Malaysia	7646	Observational, retrospective	58.1	80.4%
22	Lim et al. 2019 [33]	Malaysia	2960	Cross-sectional	60	79.1%
23	Syed Soffian et al. 2019 [44]	Malaysia	23 557	Cross-sectional	26.5% aged ≥ 60	75.8%
24	Sazlina et al. 2015 [41]	Malaysia	21 336	Cross-sectional	67.8	36.9%
25	Sazlina et al. 2014 [40]	Malaysia	10 363	Cross-sectional	71.3	32.4%
26	Abougalambou et al. 2013 [13]	Malaysia	1077	Observational, prospective	22.5% aged ≥ 65	92.7%
27	Chew et al. 2012 [24]	Malaysia	70 889	Cross-sectional	52.3	57.4%
28	Chew et al. 2011 [25]	Malaysia	212	Cross-sectional	62.7	77.3%

(Continues)

TABLE 1 | (Continued)

	Author and year	Country	Sample size	Study design	Age (years), mean (or an alternative when not stated)	Prevalence of hypertension
29	Mafauzy et al. 2011 [36]	Malaysia	1670	Cross-sectional	57.5	80.3%
30	Abougalambou 2010 [15]	Malaysia	1077	Prospective, cross-sectional	58.3	92.7%
31	Tan et al. 2008 [45]	Malaysia	196	Cross-sectional	60	93.4%
32	Chan et al. 2005 [18]	Malaysia	517	Cross-sectional	57.9	67.7%
33	Giron et al. 2022 [101]	Philippines	405	Cross-sectional	—	73.5%
34	Jimeno et al. 2012 [102]	Philippines	770	Cross-sectional	61.6	68.4%
35	Sy et al. 2009 [103]	Philippines	172	Cross-sectional	50.8	42%
36	Sun et al. 2021 [84]	Singapore	189 520	Observational, retrospective	64.2	92.4%
37	Luo et al. 2018 [81]	Singapore	943	Cross-sectional	56.5	59.4%
38	Lee and Tang 2015 [78]	Singapore	786	Cross-sectional	63.95	83.1%
39	Lertsakulbunlue et al. 2023 [60]	Thailand	84 602	Cross-sectional	58.4 (2014), 58.8 (2015), 59.3 (2018)	73.4% (2014) 75.7% (2015) 75.3% (2018)
40	Puangpet et al. 2022 [63]	Thailand	488	Cross-sectional	63.9	80.5%
41	Euswas et al. 2021 [55]	Thailand	104 472	Cross-sectional	61.1 (2014), 61.5 (2015), 62.3 (2018)	76.2% (2014) 78.2% (2015) 78.1% (2018)
42	Sakboonyarat et al. 2021 [66]	Thailand	186 010	Cross-sectional	61.1	74.4%
43	Zaman et al. 2021 [75]	Thailand	4050	Cross-sectional	56.7% aged ≥ 60	57.3%
44	Kaewput et al. 2020 [57]	Thailand	8464	Observational, retrospective	69.3	89.3%
45	Nata et al. 2020 [61]	Thailand	30 377	Cross-sectional	61.2	76.8%
46	Vonok et al. 2019 [74]	Thailand	24 992	Cross-sectional	59.9	70.2%
47	Kaewput et al. 2019 [58]	Thailand	54 295	Cross-sectional	72.6	83.5%
48	Sakboonyarat and Rangsin 2018 [67]	Thailand	25 902	Cross-sectional	60.6	70.9%
49	Sieng et al. 2017 [69]	Thailand	26 860	Cross-sectional	59.6 (specialized diabetes clinic), 68.3% (general medical clinic)	65.5% (specialized diabetes clinic) 74.3% (general medical clinic)
50	Hurst et al. 2015 [56]	Thailand	55 797	Cross-sectional	61.6	55.35%
51	Sieng et al. 2015 [70]	Thailand	26 869	Cross-sectional	60	69.95%

(Continues)

TABLE 1 | (Continued)

	Author and year	Country	Sample size	Study design	Age (years), mean (or an alternative when not stated)	Prevalence of hypertension
52	Leelawattana et al. 2006 [59]	Thailand	9284	Cross-sectional	65.6 (long-DM), 58.2 (short-DM)	85% (long-DM) 80% (short-DM)
53	Rawdaree et al. 2006 [64]	Thailand	9419	Cross-sectional	59.4	63.4%
54	Sahl et al. 2023 [98]	Vietnam	806	Cross-sectional	74.8% ≥ aged 60	35.6%
55	Nguyen KT et al. 2020 [100]	Vietnam	1631	Cross-sectional	62.7	78.4%

adults younger than 60 years, while a goal of < 150/90 mmHg was used for those 60 years and older [68].

3.4 | Percentage of Patients With Diabetes Who Received Antihypertensive Medicines

Among the 90 studies included in this review, information on the percentage of patients with diabetes who received antihypertensive medicines was obtained from 15 studies [14, 24, 34–36, 52, 53, 58, 60, 62, 72, 83, 86, 90, 102]. A study from Indonesia reported that 52% of the participants received antihypertensive medicines [90]. In Malaysia (5 studies) [14, 24, 34–36], this ranged from 32.4% to 94.2%. A study in the Philippines reported that 64.4% of the participants received antihypertensive medicines [102]. In Singapore (2 studies) [83, 86], the uptake ranged from 78.9% to 97.2% while in Thailand (6 studies) [52, 53, 58, 60, 62, 72], the uptake ranged from 21.8% to 84%.

There was limited information on the types of antihypertensive medications used in these studies. One study in older adults (aged 65 or above) in Thailand reported that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) were the most commonly used (63.8%) [58]. One study in Malaysia reported that 68.9% were on 2 antihypertensives or more (31.3% on 2, 17.9% on 3, and 19.7% on more than 3 antihypertensives) [14]. Another study in Singapore reported that 43.1% of the participants were on ≥ 2 types of antihypertensives [86].

3.5 | Adherence to Antihypertensive Medicine in People With Diabetes

Among the 90 studies included in this review, information on adherence to antihypertensive medicine in patients with diabetes was obtained from only one study in Indonesia [87], where, of 571 participants with type 2 diabetes, 45.5% reported being non-adherent to antihypertensives. This study also highlighted that older age was associated with non-adherence to antihypertensives: adjusted odds ratios for non-adherence were 2.37 (95% CI 1.11–5.07) in patients aged 50–59, 5.65 (95% CI 2.68–11.92) in the age group 60–69, and 4.14 (95% CI 1.74–9.82) in patients aged 70 or older (with patients aged 49 or younger as the reference group).

3.6 | Glucose Control

Out of the 90 studies included, 17 studies did not provide information on glucose control (HbA1c or plasma glucose levels), 51 studies reported the percentages of participants achieving target glucose control, while the remaining 22 studies reported mean or median values of HbA1c and/or plasma glucose levels. Of the 51 studies reporting the percentages of participants with target glucose control, 46 studies reported that less than 50% of the study populations achieved target glucose control, and the remaining 5 studies reported 51%–75% of the study participants achieving targeted glucose control (Table S4).

TABLE 2 | A summary of studies reporting BP control in people with diabetes.

	Author and year	Country	Sample size	Study design	Age (years), mean (or an alternative when not stated)	BP control rate	Cut off (SBP/DBP mmHg)
1	Taniguchi et al. 2017 [96]	Cambodia	2230	Observational, retrospective	54.5 (median)	58.4%	140/90
2	Isaakidis et al. 2011 [93]	Cambodia	2858	Observational, prospective	57 (median)	12.3%	140/90 (non-diabetics), 130/80 (diabetics)
3	Soegondo et al. 2009 [90]	Indonesia	770	Cross-sectional	57	9.2%	130/80
4	Lim et al. 2024 [32]	Malaysia	5094	Cross-sectional	59	22.8%	130/80
5	Wan et al. 2023 [51]	Malaysia	288 913	Observational retrospective	58.7	35.8% achieved < 140/80, 24.3% achieved < 130/80	130–140/80
6	Wan et al. 2022 [47]	Malaysia	18 312	Observational retrospective	59.3	22.2%	130/80
7	Lee et al. 2022 [31]	Malaysia	425	Cross-sectional	66.8% > 60	43.5%	140/80
8	Keng et al. 2021 [29]	Malaysia	214	Cross-sectional	58.7	30.9%	130/80
9	Teh et al. 2020 [46]	Malaysia	13 784	Cross-sectional	61	35.2%	140/80 (for diabetic hypertensive patients) 150/90 (for patients aged 80 years and above)
10	Hieng 2017 [27]	Malaysia	233	Cross-sectional	55.9	36.4%	130/80
11	Mahmood et al. 2016 [37]	Malaysia	706	Cross-sectional	58.7	31.7%	130/80
12	Cheong et al. 2015 [20]	Malaysia	1107	Cross-sectional	56.9	24.3%	130/80
13	Sazlina et al. 2015 [41]	Malaysia	21 336	Cross-sectional	67.78	19.9%	130/80
14	Sazlina et al. 2014 [40]	Malaysia	10 363	Cross-sectional	71.28	21.9%	130/80
15	Chew et al. 2013 [23]	Malaysia	70 889	Cross-sectional	68.1 (≥ 60 years), 50.2 (≤ 60 years)	21.8%	130/80
16	Ahmad et al. 2013 [16]	Malaysia	520	Cross-sectional	61.28	43.4%	130/80
17	Lee et al. 2013 [30]	Malaysia	70 092	Cross-sectional	58.3	21.3% (Malay) 25% (Chinese) 30% (Indian)	130/80
18	Chew et al. 2012 [24]	Malaysia	70 889	Cross-sectional	58.3	23.5%	130/80

(Continues)

TABLE 2 | (Continued)

	Author and year	Country	Sample size	Study design	Age (years), mean (or an alternative when not stated)	BP control rate	Cut off (SBP/DBP mmHg)
19	Abougalambou et al. 2011 [14]	Malaysia	1077	Observational, prospective	22.5% > 65	47.2%	130/80
20	Chew et al. 2011 [25]	Malaysia	212	Cross-sectional	62.7	24.5%	130/80
21	Mafauzy et al. 2011 [36]	Malaysia	1670	Cross-sectional	57.5	39.1%	130/80
22	Tan et al. 2008 [45]	Malaysia	196	Cross-sectional	60	32%	130/80
23	Mafauzy 2006 [35]	Malaysia	1099	Cross-sectional	55.8	15%	130/80
24	Chan 2005 [17]	Malaysia	517	Cross-sectional	56.7	3.1%	130/80
25	Mafauzy 2005 [34]	Malaysia	438	Cross-sectional	54.1	17.5%	130/80
26	Eid et al. 2004 [26]	Malaysia	211	Cross-sectional	53.7	8%	130/80
27	Feng et al. 2021 [76]	Singapore	209 930	Cross-sectional	51.7% ≥ 65 in 2013 and 56.2% in 2019	69.9% in 2013 decreased to 62.5% in 2019 (decrease by 7.4%)	140/90
28	Liu et al. 2020 [80]	Singapore	2189	Cross-sectional	60.6	12.7%	130/80
29	Luo et al. 2018 [81]	Singapore	943	Cross-sectional	56.5	42.7%	130/80
30	Huang et al. 2010 [77]	Singapore	3280	Cross-sectional	62.5	13.4%	130/80
31	Malhotra et al. 2010 [82]	Singapore	4494	Cross-sectional	33.5% 60–64, 42.7% 65–74, 23.8% ≥ 75	22.5%	130/80
32	Toh et al. 2007 [85]	Singapore	575	Cross-sectional	55.9% aged ≥ 65	26.2%	130/80
33	Puangpet et al. 2022 [63]	Thailand	488	Cross-sectional	63.9	39.1%	130/80
34	Sakboonyarat et al. 2022 [65]	Thailand	98	Observational, prospective	69.2	53.1%	140/90
35	Sakboonyarat et al. 2021 [66]	Thailand	186 010	Cross-sectional	61.1	29.8%–39.7%	130/80
36	Sakboonyarat et al. 2019 [68]	Thailand	65 667	Cross-sectional	63.9	75.4%	140/90–< 60 years 150/90–> 60 years
37	Kaewput et al. 2019 [58]	Thailand	54 295	Cross-sectional	72.6	65.5%	140/90
38	Sieng and Hurst 2017 [69]	Thailand	26 860	Cross-sectional	59.6 (specialized clinics), 60.4 (general medical clinics)	53% (specialized clinics), 48.6% (general medical clinics)	140/80
39	Changsirikulchai et al. 2016 [54]	Thailand	1254	Cross-sectional	68.2	47.1%	130/80

(Continues)

TABLE 2 | (Continued)

	Author and year	Country	Sample size	Study design	Age (years), mean (or an alternative when not stated)	BP control rate	Cut off (SBP/DBP mmHg)
40	Hurst et al. 2015 [56]	Thailand	55 797	Cross-sectional	61.6	32.8%	130/80
41	Sudchada et al. 2012 [72]	Thailand	714	Cross-sectional	58.4 (Males), 60 (Females)	28.4%	130/80
42	Tiptaradol 2012 [73]	Thailand	3996	Cross-sectional	55.8	6.2%	130/80
43	Sriwijitkamol et al. 2011 [71]	Thailand	722	Observational, retrospective	64.5	31%	130/80
44	Aekplakorn et al. 2007 [52]	Thailand	37 138	Cross-sectional	—	14.9%	130/80
45	Ngarmukos et al. 2006 [62]	Thailand	4875	Cross-sectional	58.9 (without nephropathy, 61.8 (with nephropathy)	18%	130/80
46	Cam et al. 2021 [99]	Vietnam	390	Cross-sectional	—	37.2%	140/90

Abbreviation: BP, blood pressure.

4 | Discussion

This review showed that the prevalence of hypertension in people with diabetes in Southeast Asia was often high and a large proportion of people with diabetes fail to receive adequate BP control. There was limited evidence on the prescription of anti-hypertensive therapies and medication adherence in the region.

Our study found that the high prevalence of hypertension in people with diabetes in Southeast Asia was comparable with other regions and countries worldwide, reporting a prevalence of > 50%. In an analysis using the UK Biobank data (a large prospective study of residents in the United Kingdom), Sun et al. reported that 85.1% of patients with type 2 diabetes (mean age 56.2 years) had hypertension [104]. In a separate analysis, Mohamed et al. found that uncontrolled hypertension in diabetic patients in sub-Saharan Africa ranged from 54% to 85% [105]. A secondary analysis of the Framingham cohort study reported that the prevalence of hypertension in adults with new-onset diabetes ranged between 56% (using 140/90 mmHg as a cut-off) and 58% (using 130/8 mmHg as a cut-off) [106]. Similarly, Tatsumi & Ohkubo reported approximately 50% of diabetic patients in Japan have hypertension [107]. Collectively, these findings, along with our analysis highlight the persistent global challenges in managing patients with diabetes. For the Southeast Asian region, this is even more important with the burden of cardiovascular disease expected to rise by 85.4% from 2025 to 2050 [108].

Although most of the studies included in this review reported a hypertension prevalence of 70% or higher, the range of this prevalence varied widely, from 29.4% to 93.4%. Differences in study settings, locations, and participant age may contribute to this wide range. Studies based on urban clinics/hospitals and electronic medical records tend to report a higher prevalence of hypertension in adults with diabetes. For example, Lee and colleagues [31] reported that 90.4% of participants with type 2 diabetes had hypertension. The participants in this study were patients who presented at two primary care government clinics in urban areas in Malaysia, and majority were 60 years or older (67%) [31]. A separate study in Singapore using the Singapore Health Services Diabetes Registry database found the prevalence of hypertension to be 92.4% [84]. This study was based on data from electronic medical records from SingHealth consisting of four hospitals, five national centers, eight primary care clinics, and three intermediate long-term-care community hospitals [84]. On the other hand, studies in rural and community settings tend to report a much lower prevalence of hypertension. For instance, in a study conducted by King and colleagues in Cambodia [94], the prevalence of hypertension was 29.4% in adults living in Siamreap (classified as rural) compared to 58.8% in adults living in Kampong Chan (classified as semi-urban). In a separate analysis by Sahl et al. looking at rural areas in Vietnam, hypertension prevalence among individuals with type 2 diabetes was found to be 35.6% [98]. These findings may suggest the potential of undetected cases in rural/semi-urban areas. The relationship between rurality and the prevalence of non-communicable diseases like diabetes and hypertension is complex. Rural populations may experience different patterns of hypertension compared to urban populations due to a possible lack of resources or awareness. For patients with diabetes and hypertension living

TABLE 3 | Percentage of people with diabetes who received antihypertensive medicines.

	Author and year	Country	Sample size	Study design	Age (years), mean (unless specified otherwise)	Percentage with antihypertensive treatment
1	Soegondo et al. 2009 [90]	Indonesia	770	Cross-sectional	57	52%
2	Chew et al. 2012 [24]	Malaysia	70 889	Cross-sectional	52.3	58.2%
3	Abougalambou et al. 2011 [14]	Malaysia	1077	Observational, prospective	22.5% > 65	94.2% (25.3% on monotherapy, 31.3% on 2 medications, 17.9% on 3 medications, 19.7% on more than 3 medications)
4	Mafauzy et al. 2011 [36]	Malaysia	1670	Cross-sectional	57.5	75%
5	Mafauzy 2006 [35]	Malaysia	1099	Cross-sectional	55.8	75.9%
6	Mafauzy 2005 [34]	Malaysia	438	Cross-sectional	54.1	32.4%
7	Jimeno et al. 2012 [102]	Philippines	724	Cross-sectional	61.6	64.4%
8	Seng 2023 [83]	Singapore	83 721	Observational, retrospective	65.3	78.9%
9	Wu et al. 2006 [86]	Singapore	388	Cross-sectional	58.3	97.2% (56.9% on monotherapy, 43.1% on ≥ 2 drugs)
10	Lertsakulbunlue 2023 [60]	Thailand	84 602	Cross-sectional	58.4 (2014), 58.8 (2015), 59.3 (2018)	71.5% (2014), 72.9% (2015), 72.6% (2018)
11	Kaewput et al. 2019 [58]	Thailand	54 295	Cross-sectional	72.6	63.8% of elderly with T2DM patients with HTN received ACE-I/ARB
12	Sudchada 2012 [72]	Thailand	714	Cross-sectional	59.3	21.8%
13	Aekplakorn et al. 2007 [52]	Thailand	37 138	Cross-sectional	—	82.2%
14	Ngarmukos et al. 2006 [62]	Thailand	4875	Cross-sectional	58.9 (without nephropathy), 61.8 (with nephropathy)	84%
15	Aekplakorn et al. 2003 [53]	Thailand	5105	Cross-sectional	54 (newly diagnosed diabetes), 58.6 (known diabetes)	67%

Abbreviation: ARB, angiotensin receptor blocker.

in rural areas, the lack of health access and support may also put these patients at a disadvantage to those living in urban areas.

Despite the high prevalence of hypertension, a substantial proportion of these populations did not receive adequate BP control, with most studies reporting a control rate of less than 40%, and diabetic patients who were older were more likely to have uncontrolled BP [109]. Additionally, the majority of the studies included in this review reported that fewer than 50% of the study populations achieved targeted glucose control, indicating a dual burden of poor glucose and BP control in these populations. As both hypertension and diabetes prevalence rise alongside increasing lifespans in the region, substantial work remains. In one of the included studies on the Malaysian population, the investigators identified age ≥ 60 as an independent risk factor for diabetes-related complications, even with good control of cardiovascular risk factors [23]. Furthermore, participants in that study were able to achieve glycemic and lipid control but failed to meet the BP targets [23]. Another study in Singapore highlighted the influence of socioeconomic status on patients with diabetes and uncontrolled hypertension [110]. Additionally, high systolic BP was identified as the leading contributor to disability-adjusted life years (DALYs) at 56.9% in Southeast Asia [111].

In this review, the majority of studies focused on adults aged 18 or older. Most studies used the same target BP for all age groups, either 140/90 or 130/80 mmHg. Only six studies exclusively focused on older adults (aged 60 years and above) [40, 41, 58, 65, 82, 99]. The optimal BP target in older adults remains controversial due to the scarcity of studies in this population. Some researchers have suggested that stricter BP control may be worthwhile to improve outcomes in patients aged 75 years or more with diabetes [112]. Other studies have suggested that in people aged 80 or older with diabetes, the BP target should be less than 140–150/90 mmHg and antihypertensive treatment should be tailored to prevent sudden changes in BP [9]. For instance, the Japanese hypertension guidelines recommend a target of < 140/90 mmHg for those aged 65–74 and < 150/90 mmHg for those aged over 75, and if stable and tolerated, a target of < 130/80 mmHg can be cautiously considered [113]. A separate systematic review of nine studies found significant differences in hypertension guidelines across Southeast Asia, Europe, and the United States. Southeast Asian and European guidelines classify hypertension onset at BP 140/90 mmHg, whereas American guidelines classify it at BP 130/90 mm [114], to reduce the burden of hypertension-related diseases on health systems [115]. In Southeast Asian countries, the population is aging rapidly, with the prevalence of diabetes among older adults (aged 65 years and above) projected to more than double from 35.5 million in 2019 to nearly 80 million by 2045 [116]. Given the varying BP targets across different population groups and settings, future studies focusing on older populations should consider these differences. The additional influence of frailty status in older adults further highlights the opportunities and challenges associated with targeted BP management for this population [117, 118].

The use of antihypertensive medicines remains a crucial component of management for adults with diabetes. However, in some Southeast Asian countries, the availability and access to these medicines continue to be an issue [119]. It was reported that where antihypertensives were available and affordable, patients were more likely to use them or have their BP controlled [120]. Besides medicine availability, there are other challenges that can affect BP control. One of the issues identified is the lack of adherence to antihypertensive medicines [87], which may be because of forgetfulness and lack of knowledge [87]. Sakboonyarat and colleagues described the use of an innovative, low-cost model using a network of homecare providers to help promote BP control among older Thai patients [65]. This program highlighted medication non-adherence as a problem but showed that the intervention group experienced improved adherence [65]. In a separate randomized controlled trial in Indonesia, the study investigators further described an innovative, low-cost pharmacist-led intervention to help patients with type 2 diabetes improve adherence to antihypertensive medicines [121]. Given that the majority of Southeast Asian countries are classified as low- to middle-income, prioritizing the costs of future and further interventions to improve BP control is essential. Efforts have also been made to explore the use of technology, such as telemonitoring, which has been studied in a multi-ethnic Asian population [122]. These integrated approaches, combining increasing access to medications, innovative low-cost interventions, and technology, hold promise in improving BP control among people with diabetes in Southeast Asia. Most member states in the region are classified as low- to middle-income countries, making the allocation and utilization of health resources crucial in such resource-constrained settings. The recent COVID-19 pandemic highlighted the inadequacies of some health systems to manage systemic shocks, with repercussions extending beyond healthcare to negatively impact economies and development. The pandemic underscored the importance of preventive care in addressing population-level health challenges. In resource-limited areas, collaboration becomes crucial in managing population-level health challenges. Region-specific management strategies can help mitigate the impact of these health issues.

4.1 | Strength and Limitations

Our study sought to provide evidence on the prevalence and management of hypertension in populations with type 2 diabetes across Southeast Asian countries. The literature search was meticulously conducted, yet it was limited to studies published in English. Therefore, studies only published in other languages or unpublished would have been missed, potentially leading to a bias in the data collated. There may be potential discrepancies among the reviewers in the processes of study selection and data extraction. However, we have followed the review protocol and have regular communications to minimize these discrepancies. There was also a lack of evidence on this topic from 4 out of the 11 countries in the region, including Brunei, Lao People's Democratic Republic, Myanmar, and Timor Leste—highlighting a substantial gap in the existing literature on the research topic from these countries. Nevertheless, a key strength of this review was the systematic and extensive search conducted across multiple large databases such as MEDLINE and Embase, ensuring a broad and representative collection of studies. The inclusion criteria and methodologies employed were designed to minimize bias and maximize the relevance and quality of the evidence gathered.

5 | Conclusion

This review highlights that BP control in adults with diabetes remains a significant challenge in the Southeast Asian region and there is a lack of studies examining medication adherence, particularly in older people with diabetes. More studies focusing on older populations are required, especially in the context of providing age-specific recommendations for BP targets and factors influencing medication adherence in these populations. Our work underscores the need for more inclusive and comprehensive research efforts to address hypertension in populations with type 2 diabetes, particularly in Southeast Asian countries. Longitudinal studies are essential to understand the long-term impact of uncontrolled hypertension on cardiovascular events and survival rates in the region.

Author Contribution

T.N.N. and W.J.W. conceptualized the study, designed the study protocol, conducted the literature search, and performed the data extraction and analysis. W.J.W., F.A., and T.N.N. conducted the abstract screening and study selection. W.J.W. drafted the paper with critical inputs and supervision from T.N.N. All authors (W.J.W., T.V.N., F.A., H.T.T.V., A.S.K., K.M.T., Y.Z., C.H., M.W., T.N.N.) contributed to the interpretation of the results and critically revised the manuscript. All authors accept responsibility to submit for publication and gave approval for the final version to be published.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Online Supplemental Tables

Online Supplemental Table 1 – Search strategy

Database:
Embase Classic+Embase <1947 to 2024, March 15>
Ovid MEDLINE(R) ALL <1946 to March 15, 2024>

#	Query	Results from 15 Mar 2024
1	malaysia.mp. or Malaysia/	68,893
2	Malaysia/ or malaysian.mp.	58,117
3	indonesia.mp. or Indonesia/	62,215
4	Indonesia/ or indonesian.mp.	50,801
5	Singapore/ or singapore.mp.	64,769
6	Singapore/ or singaporean.mp.	47,034
7	vietnam.mp. or Vietnam/	54,292
8	vietnamese.mp.	17,519
9	Thailand.mp. or Thailand/	101,206
10	Thai.mp.	45,961
11	brunei.mp. or Brunei/	1,675
12	Laos.mp. or Laos/	7,846
13	Timor leste.mp. or Timor-Leste/	1,571
14	cambodia.mp. or Cambodia/	13,726
15	Cambodian.mp.	4,246
16	Myanmar.mp. or Myanmar/	13,024
17	Burma.mp. or Myanmar/	9,953
18	Phillipines.mp. or Philippines/	25,619
19	Philippines/ or filipino.mp.	32,293
20	southeast asia.mp. or Asia, Southeastern/	42,969
21	Asia, Southeastern/ or south east* asia.mp.	30,309
22	Asia, Southeastern/ or southeast* asia.mp.	45,168
23	Asia, Southeastern/ or Asean.mp.	21,727
24	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	449,602
25	diabetes.mp. or Diabetes Mellitus/	2,245,602
26	blood pressure.mp. or Blood Pressure/	1,317,103
27	Hypertension/ or hypertension.mp.	1,800,543
28	26 or 27	2,608,578
29	24 and 25 and 28	7,486

Online Supplemental Table 2 – List of the included articles (90 papers)

The number of included studies from 7 Southeast Asian countries: Cambodia (5), Indonesia (6), Malaysia (39), Philippines (3), Singapore (10), Thailand (24), and Vietnam (3).

No.	Year of publication	First author name	Title	Journal	Country/ Population
Cambodia (5)					
1	2021	Nazaneen Nikpour Hernandez	An innovative model for management of cardiovascular disease risk factors in the low resource setting of Cambodia	Health Policy and Planning	Cambodia
2	2018	Dawn Taniguchi	Evaluation of a multi-faceted diabetes care program including community-based peer educators in Takeo province, Cambodia, 2007-2013	PLoS One	Cambodia
3	2017	Julie Wagner	Diabetes and cardiometabolic risk factors in Cambodia: results from two screening studies	Journal of Diabetes	Cambodia
4	2011	P Isaakidis	Treatment of hypertension in rural Cambodia: results from a 6-year programme	Journal of Human Hypertension	Cambodia
5	2005	Hilary King	Diabetes and associated disorders in Cambodia: two epidemiological surveys	The Lancet	Cambodia
Indonesia (6)					
1	2023	Djoko Wahono Soeatmadji	Clinicodemographic profile and outcomes of type 2 diabetes mellitus in the Indonesian cohort of DISCOVER: a 3-year prospective cohort study	Journal of the ASEAN Federation of Endocrine Societies	Indonesia
2	2022	Nikson Sitorus	Association between blood pressure and quality of life of	Open Access Macedonian Journal of	Indonesia

			patients with diabetes mellitus type 2 in the Bogor City Indonesia	Medical Sciences	
3	2021	Winnie Tunggal Mutika	Characteristics of patients with type 2 diabetes mellitus	Indian Journal of Public Health Research & Development	Indonesia
4	2020	Fajriansyah	Impact of pharmacist counseling on health-related quality of life of patients with type 2 diabetes mellitus: a cluster randomized controlled study	Journal of Diabetes & Metabolic Disorders	Indonesia
5	2020	Sofa D. Alfian	Modifiable Factors associated with non-adherence to antihypertensive or antihyperlipidemic drugs are dissimilar: a multicenter study among patients with diabetes in Indonesia	Journal of General Internal Medicine	Indonesia
6	2009	Sidartawan Soegondo	Prevalence and risk factors for microalbuminuria in a cross-sectional study of type-2 diabetic patients in Indonesia: a subset of DEMAND study	Medical Journal of Indonesia	Indonesia
Malaysia (39)					
1	2024	Lim Lee-Ling	Real world evaluation of care for type 2 diabetes in Malaysia: a cross-sectional analysis of the treatment adherence to guideline evaluation in type 2 diabetes (TARGET-T2D) study	PLoS One	Malaysia
2	2023	Masliyana Husin	The effectiveness of enhanced primary healthcare (EnPHC) interventions on type 2 diabetes management in Malaysia: difference-	Primary Care Diabetes	Malaysia

			in-differences (DID) analysis		
3	2023	Ruth Sim	Impact of Covid-19 lockdown on glycemic, weight, blood pressure control and medication adherence in patients with type 2 diabetes	Patient Preference and Adherence	Malaysia
4	2023	Wan Kim Sui	Baseline treatments and metabolic control of 288,913 type 2 diabetes patients in a 10-year retrospective cohort in Malaysia	Scientific Reports	Malaysia
5	2022	Lee Ping Yein	The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor	Malaysian Family Physician	Malaysia
6	2022	Norazida Ab Rahman	Medication Regimen Complexity and medication burden among patients with Type 2 diabetes mellitus: a retrospective analysis	Frontiers in Pharmacology	Malaysia
7	2022	Shazwani Shaharuddin	Investigating the prevalence of diabetic complications in overweight/obese patients: a study in a tertiary hospital in Malaysia	International Journal of Diabetes in Developing Countries	Malaysia
8	2022	Wan Kim Sui	Five-year LDL-cholesterol trend and its predictors among type 2 diabetes patients in an upper-middle-income country: a retrospective open cohort study	PeerJ – Life and Environment	Malaysia
9	2021	Chee Kok Han	Prevalence and predictors of left ventricular diastolic dysfunction in	Frontiers in Cardiovascular medicine	Malaysia

			Malaysian patients with type 2 diabetes mellitus without prior known cardiovascular disease		
10	2021	Chew Boon How	Is therapeutic inertia present in hyperglycaemia, hypertension and hypercholesterolaemia management among adults with type 2 diabetes in three health clinics in Malaysia? A retrospective cohort study	BMC Primary care	Malaysia
11	2021	Wan Kim Sui	Changes in body mass index, glycosylated hemoglobin A1C, blood pressure and LDL-cholesterol among type 2 diabetes patients in Malaysia: A population-based longitudinal study	Journal of Diabetes	Malaysia
12	2021	Wan Kim Sui	Predictors of glycosylated haemoglobin A1C trend among type 2 diabetes patients in a multi-ethnic country	Scientific Reports	Malaysia
13	2021	Zhi Yi Keng	Rate of achievement of therapeutic outcomes and factors associated with control of non-communicable diseases in rural east Malaysia: implications for policy and practice	Scientific Reports	Malaysia
14	2020	Fairuz Fadzilah Rahim	Prevalence and factors associated with prediabetes and diabetes in fishing communities in Penang, Malaysia: a cross-sectional study	PLoS One	Malaysia

15	2020	Wan Kim Sui	Clinical inertia in type 2 diabetes management in a middle-income country: a retrospective cohort study	PLoS One	Malaysia
16	2020	Xin Rou Teh	Quality of hypertension management in public primary care clinics in Malaysia: An update	PLoS One	Malaysia
17	2019	Sharifah Saffinas Syed Soffian	Management and glycemic control of patients with type 2 diabetes mellitus at primary care level in Kedah, Malaysia: A statewide evaluation	PLoS One	Malaysia
18	2019	Yvonne Mei Fong Lim	Clinic and patient variation in intermediate clinical outcomes for type 2 diabetes: a multilevel analysis	BMC Primary Care	Malaysia
19	2017	Yung Chun Hieng	An internal audit of diabetes care for type 2 diabetic patients in a public hospital diabetes clinic in Malaysia	Malaysian Journal of Medical Sciences	Malaysia
20	2016	M.I. Mahmood	Glycaemic control and associated factors among patients with diabetes at public health clinics in Johor, Malaysia	Public Health	Malaysia
21	2015	Cheong Ai Theng	Blood pressure control among hypertensive patients with and without diabetes mellitus in six public primary care clinics in Malaysia	Asia-Pacific Journal of Public Health	Malaysia
22	2015	Shariff-Ghazali Sazlina	Predictors of poor glycaemic control in older patients with type 2 diabetes mellitus	Singapore Medical Journal	Malaysia

23	2014	Shariff-Ghazali Sazlina	Control of glycemia and other cardiovascular disease risk factors in older adults with type 2 diabetes mellitus: Data from the Adult Diabetes Control and Management	Geriatrics & Gerontology International	Malaysia
24	2013	Chew Boon How	Age≥ 60 years was an independent risk factor for diabetes-related complications despite good control of cardiovascular risk factors in patients with type 2 diabetes mellitus	Experimental Gerontology	Malaysia
25	2013	Nafees Ahmad	Guidelines adherence and hypertension control at a tertiary hospital in Malaysia	Journal of Evaluation in Clinical Practice	Malaysia
26	2013	Ping Yein Lee	Does ethnicity contribute to the control of cardiovascular risk factors among patients with Type 2 Diabetes?	Asia-Pacific Journal of Public Health	Malaysia
27	2013	Salwa Selim Ibrahim Abougalambou	A study evaluating prevalence of hypertension and risk factors affecting on blood pressure control among type 2 diabetes patients attending teaching hospital in Malaysia	Diabetes & Metabolic Syndrome: Clinical Research & Reviews	Malaysia
28	2012	Chew Boon How	Determinants of uncontrolled hypertension in adult type 2 diabetes mellitus: an analysis of the Malaysian diabetes registry 2009	Cardiovascular Diabetology	Malaysia
29	2011	Chew Boon How	Quality of care for adult type 2 diabetes mellitus at a university primary care centre in Malaysia	International Journal of Collaborative Research on Internal	Malaysia

				Medicine & Public Health	
30	2011	Mafauzy Mohamed	The status of diabetes control in Malaysia: Results of DiabCare 2008	Medical Journal of Malaysia	Malaysia
31	2011	Maskon Oteh	Institutional hypertension control in Malaysia: a multicenter study focusing on gender and cardiovascular risk factor profile difference	Hypertension Research	Malaysia
32	2011	Salwa Selim Ibrahim Abougalambou	Prevalence of hypertension, control of blood pressure and treatment in hypertensive with type 2 diabetes in Hospital University Sains Malaysia	Diabetes & Metabolic Syndrome: Clinical Research & Reviews	Malaysia
33	2010	Salwa Selim Ibrahim Abougalambou	Current clinical status and complications among type 2 diabetic patients in Universiti Sains Malaysia hospital	International Journal of Diabetes Mellitus	Malaysia
34	2008	Florence Tan	Standard of care for type 2 diabetic patients in a public hospital general medical clinic: report of a self-audit	Medical Journal of Malaysia	Malaysia
35	2006	Mafauzy Mohamed	Diabetes control and complications in public hospitals in Malaysia	Medical Journal of Malaysia	Malaysia
36	2005	Chan Giin Cherng	Type 2 diabetes mellitus with hypertension at primary healthcare level in Malaysia: are they managed according to guidelines	Singapore Medical Journal	Malaysia
37	2005	Chan Giin Cherng	Management of type 2 diabetes mellitus: is it in accordance with the guidelines?	Medical Journal of Malaysia	Malaysia

38	2005	Mafauzy Mohamed	Diabetes control and complications in private primary healthcare in Malaysia	Medical Journal of Malaysia	Malaysia
39	2004	M Eid	Non-achievement of clinical targets in patients with type 2 diabetes mellitus	Medical Journal of Malaysia	Malaysia
Philippines (3)					
1	2022	Maria Stella Giron	Prevalence of diabetes among community-living older persons in the Philippines: The FITforFrail Study	Journal of the ASEAN Federation of Endocrine Societies	Philippines
2	2012	Cecilia Jimeno	DiabCare 2008: Survey on glycaemic control and the status of diabetes care and complications among patients with type 2 diabetes mellitus in the Philippines	Philippine Journal of Internal Medicine	Philippines
3	2009	Heustein Sy	Complications and cardiovascular risk factors among newly-diagnosed type 2 diabetics in Manila	Philippine Journal of Internal Medicine	Philippines
Singapore (10)					
1	2023	Loraine Liping Seng	Real-world systolic and diastolic blood pressure levels and cardiovascular mortality in patients with type 2 diabetes – results from a large registry cohort in Asia	Journal of the American Heart Association	Singapore
2	2021	Liang Feng	Trends in cardiovascular risk factors and treatment goals in patients with diabetes in Singapore-analysis of the SingHealth Diabetes Registry	PLoS One	Singapore
3	2021	Xingzhi Sun	Effective treatment recommendations for type 2 diabetes management using reinforcement learning: treatment	Journal of Medical Internet Research	Singapore

			recommendation model development and validation		
4	2020	Lei Liu	Hypertension, blood pressure control and diabetic retinopathy in a large population-based study	PLoS One	Singapore
5	2018	Miyang Luo	Diabetes management in a primary care network (PCN) of private general practitioners in Singapore: An observational study	Medicine	Singapore
6	2015	Lee Eng Sing	The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore	Singapore Medical Journal	Singapore
7	2010	Olivia S. Huang	Glycemic and Blood pressure control in an Asian Malay Population with Diabetes and Diabetic Retinopathy	JAMA Ophthalmology	Singapore
8	2010	Rahul Malhotra	Prevalence, awareness, treatment and control of hypertension in the elderly population of Singapore	Hypertension Research	Singapore
9	2007	Matthias PHS Toh	Measuring the Quality of Care of Diabetic Patients at the Specialist Outpatient Clinics in Public Hospitals in Singapore	Annals Academy of Medicine	Singapore
10	2006	Akira Y T Wu	Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore	Singapore Medical Journal	Singapore
Thailand (24)					
1	2023	Sethapong Lertsakulbunlue	Trends in predicted 10-year risk for cardiovascular diseases among patients with type 2	BMC Cardiovascular Disorders	Thailand

			diabetes in Thailand, from 2014 to 2018		
2	2022	Boonsub Sakboonyarat	Model development to improve primary care services using an innovative network of homecare providers (WinCare) to promote blood pressure control among elderly patients with noncommunicable diseases in Thailand: a prospective cohort study	BMC Primary Care	Thailand
3	2022	Thanapat Puangpet	Control and complications of diabetes in urban primary care units in Thailand: a cross-sectional study	BMC Primary Care	Thailand
4	2021	Boonsub Sakboonyarat	National trends in the prevalence of glycemic control among patients with type 2 diabetes receiving continuous care in Thailand from 2011 to 2018	Scientific Reports	Thailand
5	2021	Nathakamol Euswas	National trends in the prevalence of diabetic retinopathy among Thai patients with type 2 diabetes and its associated factors from 2014 to 2018	PLoS One	Thailand
6	2021	Sojib bin Zaman	The burden of chronic kidney disease among people with diabetes by insurance schemes: Findings from a primary referral hospital in Thailand	Diabetes Epidemiology and Management	Thailand
7	2020	Naowanit Nata	Impaired glomerular filtration rate in type 2 diabetes mellitus subjects: a nationwide cross-sectional study in Thailand	Journal of Diabetes Research	Thailand

8	2020	Wisit Kaewput	Rate of kidney function decline and factors predicting progression of kidney disease in type 2 diabetes mellitus patients with reduced kidney function: a nationwide retrospective cohort study	Therapeutic Apheresis and dialysis	Thailand
9	2019	Boonsub Sakboonyarat	Prevalence and associated factors of uncontrolled hypertension among hypertensive patients: a nation-wide survey in Thailand	BMC Research Notes	Thailand
10	2019	Lampung Vonok	Influence of antiplatelet therapy on cardiovascular disease prevention among type 2 diabetic patients in Thailand	Journal of Clinical and Diagnostic Research	Thailand
11	2019	Wisit Kaewput	Temporal trends in optimal diabetic care and complications of elderly type 2 diabetes patients in Thailand: a nationwide study	Journal of Evidence-Based Medicine	Thailand
12	2018	Boonsub Sakboonyarat	Prevalence and associated factors of ischemic heart disease (IHD) among patients with diabetes mellitus: a nation-wide, cross-sectional survey	BMC Cardiovascular Disorders	Thailand
13	2017	Sokha Sieng	A combination of process of care and clinical target among type 2 diabetes mellitus patients in general medical clinics and specialist diabetes clinics at hospital level	BMC Health Services Research	Thailand
14	2016	Siribha Changsirikulchai	National survey: evaluation of cardiovascular risk	Nephrology	Thailand

			factors in Thai patients with type 2 diabetes and chronic kidney disease after the development of cardiovascular disease		
15	2015	Cameron Hurst	The association between hypertension comorbidity and microvascular complications in type 2 diabetes patients: a nationwide cross-sectional study in Thailand	Diabetes & Metabolism Journal	Thailand
16	2015	Sokha Sieng	Comparison of HbA1c, blood pressure, and cholesterol (ABC) control in type 2 diabetes attending general medical clinics and specialist diabetes clinics in Thailand	Diabetes Research and Clinical Practice	Thailand
17	2012	Patcharaporn Sudchada	Diabetes and cardiovascular risk factor controls in Thai type 2 diabetes with no history of cardiovascular complications; situation and compliance to diabetes management guideline in Thailand	Journal of Diabetes and its complications	Thailand
18	2012	Sriwat Tiptaradol	Prevalence, awareness, treatment and control of coexistence of diabetes and hypertension in Thai population	International Journal of Hypertension	Thailand
19	2011	Apiradee Sriwijitkamol	Attainment of American Diabetes Association Clinical Practice Recommendations in 722 Thai Type 2 diabetes patients	Journal of the Medical Association of Thailand	Thailand

20	2007	Wichai Aekplakorn	Prevalence and management of diabetes and associated risk factors by regions of Thailand: Third National Health Examination Survey 2004	American Diabetes Association	Thailand
21	2006	Chardpraorn Ngarmukos	Thailand Diabetes Registry Project: Prevalence, characteristics and treatment of patients with diabetic nephropathy	Journal of the Medical Association of Thailand	Thailand
22	2006	Petch Rawdaree	Thailand Diabetes Registry Project: Clinical status and long term vascular complications in diabetic patients	Journal of the Medical Association of Thailand	Thailand
23	2006	Rattana Leelawattana	Thailand Diabetes Registry Project: Prevalence of vascular complications in long-standing type 2 diabetes	Journal of the Medical Association of Thailand	Thailand
24	2003	Wichai Aekplakorn	The prevalence and management of diabetes in Thai Adults: The international collaborative study of cardiovascular disease in Asia	Diabetes Care	Thailand
Vietnam (3)					
1	2023	Amalie Sophie Sahl	Diabetes-related distress and the association to hypertension and cardiovascular disease among individuals living with type 2 diabetes in rural areas in Vietnam	medRxiv	Vietnam
2	2021	TD Cam	Adherence to blood pressure control and association with comorbidities in	Genetics and Molecular Research	Vietnam

			elderly Vietnamese patients		
3	2020	Khue Thy Nguyen	A cross-sectional study to evaluate diabetes management, control and complications in 1631 patients with type 2 diabetes mellitus in Vietnam (DiabCare Asia)	International Journal of Diabetes in Developing Countries	Vietnam

Online Supplemental Table 3 – Quality assessment of the 90 studies included in this review

No.	Year of publication	First author name	Title	Study design	Quality rating
Cambodia (5)					
1	2021	Nazaneen Nikpour Hernandez	An innovative model for management of cardiovascular disease risk factors in the low resource setting of Cambodia	Observational, retrospective	Good
2	2018	Dawn Taniguchi	Evaluation of a multi-faceted diabetes care program including community-based peer educators in Takeo province, Cambodia, 2007-2013	Observational, retrospective	Good
3	2017	Julie Wagner	Diabetes and cardiometabolic risk factors in Cambodia: results from two screening studies	Observational, cross-sectional	Good
4	2011	P Isaakidis	Treatment of hypertension in rural Cambodia: results from a 6-year programme	Observational, prospective	Good
5	2005	Hilary King	Diabetes and associated disorders in Cambodia: two epidemiological surveys	Cross-sectional	Good
Indonesia (6)					
1	2023	Djoko Wahono Soeatmadji	Clinicodemographic profile and outcomes of type 2 diabetes mellitus in the Indonesian cohort of DISCOVER: a 3-year prospective cohort study	Observational, prospective	Good
2	2022	Nikson Sitorus	Association between blood pressure and quality of life of patients with diabetes mellitus type 2 in the Bogor City Indonesia	Cross-sectional	Fair
3	2021	Winnie Tunggal Mutika	Characteristics of patients with type 2 diabetes mellitus	Cross-sectional	Fair
4	2020	Fajriansyah	Impact of pharmacist counseling on health-related quality of life of patients with type 2 diabetes mellitus: a cluster randomized controlled study	Randomized controlled trial	Good
5	2020	Sofa D. Alfian	Modifiable Factors associated with non-adherence to antihypertensive or antihyperlipidemic drugs are dissimilar: a multicenter study among patients with diabetes in Indonesia	Cross-sectional	Good

6	2009	Sidartawan Soegondo	Prevalence and risk factors for microalbuminuria in a cross-sectional study of type-2 diabetic patients in Indonesia: a subset of DEMAND study	Cross-sectional	Fair
Malaysia (39)					
1	2024	Lim Lee-Ling	Real world evaluation of care for type 2 diabetes in Malaysia: a cross-sectional analysis of the treatment adherence to guideline evaluation in type 2 diabetes (TARGET-T2D) study	Cross-sectional	Good
2	2023	Masliyana Husin	The effectiveness of enhanced primary healthcare (EnPHC) interventions on type 2 diabetes management in Malaysia: difference-in-differences (DID) analysis	Quasi-experimental controlled study	Good
3	2023	Ruth Sim	Impact of Covid-19 lockdown on glycemic, weight, blood pressure control and medication adherence in patients with type 2 diabetes	Observational retrospective	Good
4	2023	Wan Kim Sui	Baseline treatments and metabolic control of 288,913 type 2 diabetes patients in a 10-year retrospective cohort in Malaysia	Observational retrospective	Good
5	2022	Lee Ping Yein	The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor	Cross-sectional	Good
6	2022	Norazida Ab Rahman	Medication Regimen Complexity and medication burden among patients with Type 2 diabetes mellitus: a retrospective analysis	Observational retrospective	Good
7	2022	Shazwani Shaharuddin	Investigating the prevalence of diabetic complications in overweight/obese patients: a study in a tertiary hospital in Malaysia	Cross-sectional	Good
8	2022	Wan Kim Sui	Five-year LDL-cholesterol trend and its predictors among type 2 diabetes patients in an upper-middle-income country: a retrospective open cohort study	Observational, retrospective	Good
9	2021	Chee Kok Han	Prevalence and predictors of left ventricular diastolic dysfunction in Malaysian patients with type 2 diabetes mellitus without prior known cardiovascular disease	Cross-sectional	Good
10	2021	Chew Boon How	Is therapeutic inertia present in hyperglycaemia, hypertension and hypercholesterolaemia management among adults with	Observational, retrospective	Good

			type 2 diabetes in three health clinics in Malaysia? A retrospective cohort study		
11	2021	Wan Kim Sui	Changes in body mass index, glycosylated hemoglobin A1C, blood pressure and LDL-cholesterol among type 2 diabetes patients in Malaysia: A population-based longitudinal study	Observational, retrospective	Good
12	2021	Wan Kim Sui	Predictors of glycosylated haemoglobin A1C trend among type 2 diabetes patients in a multi-ethnic country	Observational, retrospective	Good
13	2021	Zhi Yi Keng	Rate of achievement of therapeutic outcomes and factors associated with control of non-communicable diseases in rural east Malaysia: implications for policy and practice	Cross-sectional	Good
14	2020	Fairuz Fadzilah Rahim	Prevalence and factors associated with prediabetes and diabetes in fishing communities in Penang, Malaysia: a cross-sectional study	Cross-sectional	Good
15	2020	Wan Kim Sui	Clinical inertia in type 2 diabetes management in a middle-income country: a retrospective cohort study	Observational, retrospective	Good
16	2020	Xin Rou Teh	Quality of hypertension management in public primary care clinics in Malaysia: An update	Cross-sectional	Good
17	2019	Sharifah Saffinas Syed Soffian	Management and glycemic control of patients with type 2 diabetes mellitus at primary care level in Kedah, Malaysia: A statewide evaluation	Cross-sectional	Good
18	2019	Yvonne Mei Fong Lim	Clinic and patient variation in intermediate clinical outcomes for type 2 diabetes: a multilevel analysis	Cross-sectional	Good
19	2017	Yung Chun Hieng	An internal audit of diabetes care for type 2 diabetic patients in a public hospital diabetes clinic in Malaysia	Cross-sectional	Fair
20	2016	M.I. Mahmood	Glycaemic control and associated factors among patients with diabetes at public health clinics in Johor, Malaysia	Cross-sectional	Good
21	2015	Cheong Ai Theng	Blood pressure control among hypertensive patients with and without diabetes mellitus in six public primary care clinics in Malaysia	Cross-sectional	Good
22	2015	Shariff-Ghazali Sazlina	Predictors of poor glycaemic control in older patients with type 2 diabetes mellitus	Cross-sectional	Good

23	2014	Shariff-Ghazali Sazlina	Control of glycemia and other cardiovascular disease risk factors in older adults with type 2 diabetes mellitus: Data from the Adult Diabetes Control and Management	Cross-sectional	Good
24	2013	Chew Boon How	Age≥ 60 years was an independent risk factor for diabetes-related complications despite good control of cardiovascular risk factors in patients with type 2 diabetes mellitus	Cross-sectional	Good
25	2013	Nafees Ahmad	Guidelines adherence and hypertension control at a tertiary hospital in Malaysia	Cross-sectional	Good
26	2013	Ping Yein Lee	Does ethnicity contribute to the control of cardiovascular risk factors among patients with Type 2 Diabetes?	Cross-sectional	Good
27	2013	Salwa Selim Ibrahim Abougalambou	A study evaluating prevalence of hypertension and risk factors affecting on blood pressure control among type 2 diabetes patients attending teaching hospital in Malaysia	Observational, prospective	Good
28	2012	Chew Boon How	Determinants of uncontrolled hypertension in adult type 2 diabetes mellitus: an analysis of the Malaysian diabetes registry 2009	Cross-sectional	Good
29	2011	Chew Boon How	Quality of care for adult type 2 diabetes mellitus at a university primary care centre in Malaysia	Cross-sectional	Good
30	2011	Mafauzy Mohamed	The status of diabetes control in Malaysia: Results of DiabCare 2008	Cross-sectional	Good
31	2011	Maskon Oteh	Institutional hypertension control in Malaysia: a multicenter study focusing on gender and cardiovascular risk factor profile difference	Cross-sectional	Good
32	2011	Salwa Selim Ibrahim Abougalambou	Prevalence of hypertension, control of blood pressure and treatment in hypertensive with type 2 diabetes in Hospital University Sains Malaysia	Observational, prospective	Good
33	2010	Salwa Selim Ibrahim Abougalambou	Current clinical status and complications among type 2 diabetic patients in Universiti Sains Malaysia hospital	Prospective, cross-sectional	Good
34	2008	Florence Tan	Standard of care for type 2 diabetic patients in a public hospital general medical clinic: report of a self-audit	Cross-sectional	Fair
35	2006	Mafauzy Mohamed	Diabetes control and complications in public hospitals in Malaysia	Cross-sectional	Fair

36	2005	Chan Giin Cherng	Type 2 diabetes mellitus with hypertension at primary healthcare level in Malaysia: are they managed according to guidelines	Cross-sectional	Fair
37	2005	Chan Giin Cherng	Management of type 2 diabetes mellitus: is it in accordance with the guidelines?	Cross-sectional	Fair
38	2005	Mafauzy Mohamed	Diabetes control and complications in private primary healthcare in Malaysia	Cross-sectional	Fair
39	2004	M Eid	Non-achievement of clinical targets in patients with type 2 diabetes mellitus	Cross-sectional	Fair
Philippines (3)					
1	2022	Maria Stella Giron	Prevalence of diabetes among community-living older persons in the Philippines: The FITforFrail Study	Cross-sectional	Good
2	2012	Cecilia Jimeno	DiabCare 2008: Survey on glycaemic control and the status of diabetes care and complications among patients with type 2 diabetes mellitus in the Philippines	Cross-sectional	Good
3	2009	Heustein Sy	Complications and cardiovascular risk factors among newly-diagnosed type 2 diabetics in Manila	Cross-sectional	Fair
Singapore (10)					
1	2023	Loraine Liping Seng	Real-world systolic and diastolic blood pressure levels and cardiovascular mortality in patients with type 2 diabetes – results from a large registry cohort in Asia	Observational, retrospective	Good
2	2021	Liang Feng	Trends in cardiovascular risk factors and treatment goals in patients with diabetes in Singapore-analysis of the SingHealth Diabetes Registry	Cross-sectional	Good
3	2021	Xingzhi Sun	Effective treatment recommendations for type 2 diabetes management using reinforcement learning: treatment recommendation model development and validation	Observational, retrospective	Good
4	2020	Lei Liu	Hypertension, blood pressure control and diabetic retinopathy in a large population-based study	Cross-sectional	Good
5	2018	Miyang Luo	Diabetes management in a primary care network (PCN) of private general practitioners in Singapore: An observational study	Cross-sectional	Good

6	2015	Lee Eng Sing	The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore	Cross-sectional	Fair
7	2010	Olivia S. Huang	Glycemic and Blood pressure control in an Asian Malay Population with Diabetes and Diabetic Retinopathy	Cross-sectional	Good
8	2010	Rahul Malhotra	Prevalence, awareness, treatment and control of hypertension in the elderly population of Singapore	Cross-sectional	Good
9	2007	Matthias PHS Toh	Measuring the Quality of Care of Diabetic Patients at the Specialist Outpatient Clinics in Public Hospitals in Singapore	Cross-sectional	Good
10	2006	Akira Y T Wu	Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore	Cross-sectional	Fair
Thailand (24)					
1	2023	Sethapong Lertsakulbunlue	Trends in predicted 10-year risk for cardiovascular diseases among patients with type 2 diabetes in Thailand, from 2014 to 2018	Cross-sectional	Good
2	2022	Boonsub Sakboonyarat	Model development to improve primary care services using an innovative network of homecare providers (WinCare) to promote blood pressure control among elderly patients with noncommunicable diseases in Thailand: a prospective cohort study	Observational, prospective	Good
3	2022	Thanapat Puangpet	Control and complications of diabetes in urban primary care units in Thailand: a cross-sectional study	Cross-sectional	Good
4	2021	Boonsub Sakboonyarat	National trends in the prevalence of glycemic control among patients with type 2 diabetes receiving continuous care in Thailand from 2011 to 2018	Cross-sectional	Good
5	2021	Nathakamol Euswas	National trends in the prevalence of diabetic retinopathy among Thai patients with type 2 diabetes and its associated factors from 2014 to 2018	Cross-sectional	Good
6	2021	Sojib bin Zaman	The burden of chronic kidney disease among people with diabetes by insurance schemes: Findings from a primary referral hospital in Thailand	Cross-sectional	Good
7	2020	Naowanit Nata	Impaired glomerular filtration rate in type 2 diabetes mellitus subjects: a nationwide cross-sectional study in Thailand	Cross-sectional	Good

8	2020	Wisit Kaewput	Rate of kidney function decline and factors predicting progression of kidney disease in type 2 diabetes mellitus patients with reduced kidney function: a nationwide retrospective cohort study	Observational, retrospective	Good
9	2019	Boonsub Sakboonyarat	Prevalence and associated factors of uncontrolled hypertension among hypertensive patients: a nation-wide survey in Thailand	Cross-sectional	Good
10	2019	Lampung Vonok	Influence of antiplatelet therapy on cardiovascular disease prevention among type 2 diabetic patients in Thailand	Cross-sectional	Fair
11	2019	Wisit Kaewput	Temporal trends in optimal diabetic care and complications of elderly type 2 diabetes patients in Thailand: a nationwide study	Cross-sectional	Good
12	2018	Boonsub Sakboonyarat	Prevalence and associated factors of ischemic heart disease (IHD) among patients with diabetes mellitus: a nation-wide, cross-sectional survey	Cross-sectional	Good
13	2017	Sokha Sieng	A combination of process of care and clinical target among type 2 diabetes mellitus patients in general medical clinics and specialist diabetes clinics at hospital level	Cross-sectional	Good
14	2016	Siribha Changsirikulchai	National survey: evaluation of cardiovascular risk factors in Thai patients with type 2 diabetes and chronic kidney disease after the development of cardiovascular disease	Cross-sectional	Good
15	2015	Cameron Hurst	The association between hypertension comorbidity and microvascular complications in type 2 diabetes patients: a nationwide cross-sectional study in Thailand	Cross-sectional	Good
16	2015	Sokha Sieng	Comparison of HbA1c, blood pressure, and cholesterol (ABC) control in type 2 diabetes attending general medical clinics and specialist diabetes clinics in Thailand	Cross-sectional	Good
17	2012	Patcharaporn Sudchada	Diabetes and cardiovascular risk factor controls in Thai type 2 diabetes with no history of cardiovascular complications; situation and compliance to diabetes management guideline in Thailand	Cross-sectional	Good
18	2012	Sriwat Tiptaradol	Prevalence, awareness, treatment and control of coexistence of diabetes and hypertension in Thai population	Cross-sectional	Good
19	2011	Apiradee Sriwijitkamol	Attainment of American Diabetes Association Clinical Practice Recommendations in 722 Thai Type 2 diabetes patients	Observational, retrospective	Fair

20	2007	Wichai Aekplakorn	Prevalence and management of diabetes and associated risk factors by regions of Thailand: Third National Health Examination Survey 2004	Cross-sectional	Good
21	2006	Chardpraorn Ngarmukos	Thailand Diabetes Registry Project: Prevalence, characteristics and treatment of patients with diabetic nephropathy	Cross-sectional	Good
22	2006	Petch Rawdaree	Thailand Diabetes Registry Project: Clinical status and long term vascular complications in diabetic patients	Cross-sectional	Good
23	2006	Rattana Leelawattana	Thailand Diabetes Registry Project: Prevalence of vascular complications in long-standing type 2 diabetes	Cross-sectional	Good
24	2003	Wichai Aekplakorn	The prevalence and management of diabetes in Thai Adults: The international collaborative study of cardiovascular disease in Asia	Cross-sectional	Good
Vietnam (3)					
1	2023	Amalie Sophie Sahl	Diabetes-related distress and the association to hypertension and cardiovascular disease among individuals living with type 2 diabetes in rural areas in Vietnam	Cross-sectional	Good
2	2021	TD Cam	Adherence to blood pressure control and association with comorbidities in elderly Vietnamese patients	Cross-sectional	Good
3	2020	Khue Thy Nguyen	A cross-sectional study to evaluate diabetes management, control and complications in 1631 patients with type 2 diabetes mellitus in Vietnam (DiabCare Asia)	Cross-sectional	Good

Online Supplemental Table 4

Studies reporting use of office vs out-of-office blood pressure reading and % HbA1c control rates

No.	Year of publication	First author name	Title	Journal	Country/ Population	Definition of prevalence of hypertension: Office blood pressure Or Out-of-office blood pressure	Data related to glucose control
Cambodia (5)							
1	2021	Nazaneen Nikpour Hernandez	An innovative model for management of cardiovascular disease risk factors in the low resource setting of Cambodia	Health Policy and Planning	Cambodia	Office BP (laboratory result + Doctor's follow up) HTN defined: syst BP ≥ 140mmHg & dias BP ≥ 90mmHg	40% achieved HbA1c<7.0%
2	2018	Dawn Taniguchi	Evaluation of a multi-faceted diabetes care program including community-based peer educators in Takeo province, Cambodia, 2007-2013	PLoS One	Cambodia	Out of office (Screened at home by visits from peer educators) Elevated BP defined: syst BP ≥ 140mmHg OR dias BP ≥ 90mmgHg	24.1% achieved HbA1c <7.0%
3	2017	Julie Wagner	Diabetes and cardiometabolic risk factors in Cambodia: results from two screening studies	Journal of Diabetes	Cambodia	Office (screening at mobile clinics) HTN defined as SBP ≥140 and/or DBP ≥90mmgHg	No data

4	2011	P Isaakidis	Treatment of hypertension in rural Cambodia: results from a 6-year programme	Journal of Human Hypertension	Cambodia	Office screening (at clinic) HTN defined SBP≥140mmHg and/or DBP ≥90mmHg on at least two separate visits	Median HbA1c = 11.4% % of HbA1c <7.0% not reported
5	2005	Hilary King	Diabetes and associated disorders in Cambodia: two epidemiological surveys	The Lancet	Cambodia	Out of office (village or community health centre) HTN, SBP ≥140mmHg and/or DBP ≥90mmHg, or being on antihypertensive	No data on HbA1c Mean 2-h blood glucose: 5.5 -8.2 (mmol/L)
Indonesia (6)							
1	2023	Djoko Wahono Soeatmadji	Clinicodemographic profile and outcomes of type 2 diabetes mellitus in the Indonesian cohort of DISCOVER: a 3-year prospective cohort study	Journal of the ASEAN Federation of Endocrine Societies	Indonesia	Office (medical records reviewed, laboratory results were noted during initial clinical visit)	Mean HbA1c 9.2± 2% at baseline and 8.0 ±1.8 at follow-up % of HbA1c <7.0% not reported
2	2022	Nikson Sitorus	Association between blood pressure and quality of life of patients with diabetes mellitus type 2 in the Bogor City Indonesia	Open Access Macedonian Journal of Medical Sciences	Indonesia	Out-of-office (interviews done in respondents house)	No data

3	2021	Winnie Tunggal Mutika	Characteristics of patients with type 2 diabetes mellitus	Indian Journal of Public Health Research & Development	Indonesia	Office (data from medical records)	No data
4	2020	Fajriansyah	Impact of pharmacist counseling on health-related quality of life of patients with type 2 diabetes mellitus: a cluster randomized controlled study	Journal of Diabetes & Metabolic Disorders	Indonesia	Office (medical records and interviews at primary healthcare centers)	Mean HbA1c: 8.45 – 8.9% % of HbA1c <7.0% not reported
5	2020	Sofa D. Alfian	Modifiable Factors associated with non-adherence to antihypertensive or antihyperlipidemic drugs are dissimilar: a multicenter study among patients with diabetes in Indonesia	Journal of General Internal Medicine	Indonesia	Office (medical records)	No data
6	2009	Sidartawan Soegondo	Prevalence and risk factors for microalbuminuria in a cross-sectional study of type-2 diabetic patients in Indonesia: a subset of DEMAND study	Medical Journal of Indonesia	Indonesia	Office (screening at primary care settings)	Only 15% had HbA1c recorded 6.1% achieved HbA1c <7% (or 40% if out of those that had HbA1c recorded)

Malaysia (39)							
1	2024	Lim Lee-Ling	Real world evaluation of care for type 2 diabetes in Malaysia: a cross-sectional analysis of the treatment adherence to guideline evaluation in type 2 diabetes (TARGET-T2D) study	PLoS One	Malaysia	Office (hospital-based screening)	29.7% achieved HbA1c<7% 65% achieved HbA1c < 8.5%
2	2023	Masliyana Husin	The effectiveness of enhanced primary healthcare (EnPHC) interventions on type 2 diabetes management in Malaysia: difference-in-differences (DID) analysis	Primary Care Diabetes	Malaysia	Office (medical records)	33-35% achieved HbA1c <7%
3	2023	Ruth Sim	Impact of Covid-19 lockdown on glycemic, weight, blood pressure control and medication adherence in patients with type 2 diabetes	Patient Preference and Adherence	Malaysia	Office (hospital medical records)	Mean HbA1c = 8.09% % of HbA1c <7.0% not reported
4	2023	Wan Kim Sui	Baseline treatments and metabolic control of 288,913 type 2 diabetes patients in a	Scientific Reports	Malaysia	Office (registry dataset and clinical audit. Sources: hospital and health clinic settings)	31.9% achieved HbA1c ≤6.5% 40.9% achieved HbA1c <7% =

			10-year retrospective cohort in Malaysia				31.2% achieved HbA1c >8.5% Mean HbA1c = 7.96%±2.11
5	2022	Lee Ping Yein	The proportion of undiagnosed diabetic peripheral neuropathy and its associated factors among patients with T2DM attending urban health clinics in Selangor	Malaysian Family Physician	Malaysia	Office (medical records and interview at urban health clinics)	23.3% achieved HbA1c <6.49% 76.7% achieved HbA1c > 6.5%
6	2022	Norazida Ab Rahman	Medication Regimen Complexity and medication burden among patients with Type 2 diabetes mellitus: a retrospective analysis	Frontiers in Pharmacology	Malaysia	Office (medical records)	34.5% achieved HbA1c ≤ 7.0%
7	2022	Shazwani Shaharuddin	Investigating the prevalence of diabetic complications in overweight/obese patients: a study in a tertiary hospital in Malaysia	International Journal of Diabetes in Developing Countries	Malaysia	Office (diabetic clinic and clinical notes)	Mean HbA1c = 10.5% % of HbA1c <7.0% not reported
8	2022	Wan Kim Sui	Five-year LDL-cholesterol trend and its predictors among	PeerJ – Life and Environment	Malaysia	Office (public primary care clinics)	42% achieved HbA1c < 7%

			type 2 diabetes patients in an upper-middle-income country: a retrospective open cohort study				Mean HbA1c = 7.88% ± 2.03
9	2021	Chee Kok Han	Prevalence and predictors of left ventricular diastolic dysfunction in Malaysian patients with type 2 diabetes mellitus without prior known cardiovascular disease	Frontiers in Cardiovascular medicine	Malaysia	Office (diabetic outpatient clinic at tertiary healthcare center)	20.27% achieved HbA1c <7.0% 33.89% achieved HbA1c 7-8% 45.84% achieved HbA1c > 8% Mean HbA1c = 8.3%
10	2021	Chew Boon How	Is therapeutic inertia present in hyperglycaemia, hypertension and hypercholesterolaemia management among adults with type 2 diabetes in three health clinics in Malaysia? A retrospective cohort study	BMC Primary care	Malaysia	Office (medical records at health clinics)	26.3% achieved HbA1c < 7.0% Mean HbA1c = 8%
11	2021	Wan Kim Sui	Changes in body mass index, glycosylated hemoglobin A1C,	Journal of Diabetes	Malaysia	Office (registry: public health clinics)	29.6% achieved HbA1c ≤ 6.5%

			blood pressure and LDL-cholesterol among type 2 diabetes patients in Malaysia: A population-based longitudinal study				43.1% achieved HbA1c < 7.0% 63.5% achieved HbA1c ≤ 8.0% Mean HbA1c = 7.88% ± 2.03
12	2021	Wan Kim Sui	Predictors of glycosylated haemoglobin A1C trend among type 2 diabetes patients in a multi-ethnic country	Scientific Reports	Malaysia	Office (registry database – public healthcare facilities)	38.6% - 42.6% achieved HbA1c<7.0%
13	2021	Zhi Yi Keng	Rate of achievement of therapeutic outcomes and factors associated with control of non-communicable diseases in rural east Malaysia: implications for policy and practice	Scientific Reports	Malaysia	Office (diabetes registry record)	43.0% achieved HbA1c ≤ 6.5% Mean HbA1c = 7.7%
14	2020	Fairuz Fadzilah Rahim	Prevalence and factors associated with prediabetes and diabetes in fishing communities in Penang, Malaysia: a cross-sectional study	PLoS One	Malaysia	Out-of-office (screening at mosque, a place for religious and community gatherings)	No data

15	2020	Wan Kim Sui	Clinical inertia in type 2 diabetes management in a middle-income country: a retrospective cohort study	PLoS One	Malaysia	Office (diabetes registry record – public health clinics)	Mean HbA1c = 8.1% ± 1.6 % of HbA1c <7.0% not reported
16	2020	Xin Rou Teh	Quality of hypertension management in public primary care clinics in Malaysia: An update	PLoS One	Malaysia	Office (public primary care clinics)	No data
17	2019	Sharifah Saffinas Syed Soffian	Management and glycemic control of patients with type 2 diabetes mellitus at primary care level in Kedah, Malaysia: A statewide evaluation	PLoS One	Malaysia	Office (public health clinics)	15.6% achieved HbA1c <6.5% Mean HbA1c = 8.4% ± 2.23
18	2019	Yvonne Mei Fong Lim	Clinic and patient variation in intermediate clinical outcomes for type 2 diabetes: a multilevel analysis	BMC Primary Care	Malaysia	Office (public clinics)	75% achieved HbA1c < 7% Mean HbA1c = 8.4% ± 2.2
19	2017	Yung Chun Hieng	An internal audit of diabetes care for type 2 diabetic patients in a public hospital diabetes clinic in Malaysia	Malaysian Journal of Medical Sciences	Malaysia	Office (diabetes clinic)	6.7% achieved HbA1c < 6.5% Mean HbA1c = 9.2% ± 1.91

20	2016	M.I. Mahmood	Glycaemic control and associated factors among patients with diabetes at public health clinics in Johor, Malaysia	Public Health	Malaysia	Office (health clinics)	32% achieved HbA1c ≤ 6.5%
21	2015	Cheong Ai Theng	Blood pressure control among hypertensive patients with and without diabetes mellitus in six public primary care clinics in Malaysia	Asia-Pacific Journal of Public Health	Malaysia	Office (Primary care clinics -medical records)	No data
22	2015	Shariff-Ghazali Sazlina	Predictors of poor glycaemic control in older patients with type 2 diabetes mellitus	Singapore Medical Journal	Malaysia	Office (Public primary healthcare clinics and hospitals)	61.6% achieved HbA1c < 8.0%
23	2014	Shariff-Ghazali Sazlina	Control of glycemia and other cardiovascular disease risk factors in older adults with type 2 diabetes mellitus: Data from the Adult Diabetes Control and Management	Geriatrics & Gerontology International	Malaysia	Office (Registry from public primary healthcare clinics and hospitals)	41.7% achieved HbA1c < 7.0%
24	2013	Chew Boon How	Age≥ 60 years was an independent risk factor for diabetes-related complications despite good control	Experimental Gerontology	Malaysia	Office (registry from health clinics and hospitals)	14.5% - 22.6% achieved HbA1c ≤ 6.5%

			of cardiovascular risk factors in patients with type 2 diabetes mellitus				
25	2013	Nafees Ahmad	Guidelines adherence and hypertension control at a tertiary hospital in Malaysia	Journal of Evaluation in Clinical Practice	Malaysia	Office (medical records)	No data
26	2013	Ping Yein Lee	Does ethnicity contribute to the control of cardiovascular risk factors among patients with Type 2 Diabetes?	Asia-Pacific Journal of Public Health	Malaysia	Office (primary health care clinics and hospitals)	28.7% - 39.3% achieved HbA1c < 6.5%
27	2013	Salwa Selim Ibrahim Abougalambou	A study evaluating prevalence of hypertension and risk factors affecting on blood pressure control among type 2 diabetes patients attending teaching hospital in Malaysia	Diabetes & Metabolic Syndrome: Clinical Research & Reviews	Malaysia	Office (outpatient clinic)	23.4% achieved HbA1c < 7%
28	2012	Chew Boon How	Determinants of uncontrolled hypertension in adult type 2 diabetes mellitus: an analysis of the Malaysian diabetes registry 2009	Cardiovascular Diabetology	Malaysia	Office (Registry – health clinics and hospitals)	46.1% achieved HbA1c ≤ 6.5%
29	2011	Chew Boon How	Quality of care for adult type 2 diabetes mellitus at a	International Journal of Collaborative	Malaysia	Office (University primary care clinic –	23.6% achieved HbA1c < 7%

			university primary care centre in Malaysia	Research on Internal Medicine & Public Health		collected from case records)	
30	2011	Mafauzy Mohamed	The status of diabetes control in Malaysia: Results of DiabCare 2008	Medical Journal of Malaysia	Malaysia	Office (general hospitals, and clinics)	22% achieved HbA1c < 7 %
31	2011	Maskon Oteh	Institutional hypertension control in Malaysia: a multicenter study focusing on gender and cardiovascular risk factor profile difference	Hypertension Research	Malaysia	Office (tertiary referral centers)	No data
32	2011	Salwa Selim Ibrahim Abougalambou	Prevalence of hypertension, control of blood pressure and treatment in hypertensive with type 2 diabetes in Hospital University Sains Malaysia	Diabetes & Metabolic Syndrome: Clinical Research & Reviews	Malaysia	Office (outpatient diabetic clinic)	23.4% achieved HbA1c <7%
33	2010	Salwa Selim Ibrahim Abougalambou	Current clinical status and complications among type 2 diabetic patients in Universiti Sains Malaysia hospital	International Journal of Diabetes Mellitus	Malaysia	Office (outpatient diabetic clinic medical records)	23.4% achieved HbA1c ≤ 7%
34	2008	Florence Tan	Standard of care for type 2 diabetic patients in a public	Medical Journal of Malaysia	Malaysia	Office (outpatient clinic – clinic cards,	26% achieved HbA1c ≤ 7%

			hospital general medical clinic: report of a self-audit			prescriptions and laboratory results)	
35	2006	Mafauzy Mohamed	Diabetes control and complications in public hospitals in Malaysia	Medical Journal of Malaysia	Malaysia	Office (public hospitals)	Mean HbA1c = 7.8%± 2.2 % of HbA1c <7.0% not reported
36	2005	Chan Giin Cherng	Type 2 diabetes mellitus with hypertension at primary healthcare level in Malaysia: are they managed according to guidelines	Singapore Medical Journal	Malaysia	Office (health clinics)	No data
37	2005	Chan Giin Cherng	Management of type 2 diabetes mellitus: is it in accordance with the guidelines?	Medical Journal of Malaysia	Malaysia	Office (medical records)	17.2% achieved HbA1c < 7%
38	2005	Mafauzy Mohamed	Diabetes control and complications in private primary healthcare in Malaysia	Medical Journal of Malaysia	Malaysia	Office (clinics)	20% achieved HbA1c < 7%
39	2004	M Eid	Non-achievement of clinical targets in patients with type 2 diabetes mellitus	Medical Journal of Malaysia	Malaysia	Office (outpatient diabetes clinics)	28% achieved HbA1c < 7 %
Philippines (3)							
1	2022	Maria Stella Giron	Prevalence of diabetes among community-living older persons in	Journal of the ASEAN Federation of	Philippines	Office	No data

			the Philippines: The FITforFrail Study	Endocrine Societies			
2	2012	Cecilia Jimeno	DiabCare 2008: Survey on glycaemic control and the status of diabetes care and complications among patients with type 2 diabetes mellitus in the Philippines	Philippine Journal of Internal Medicine	Philippines	Office (patient interview and review of medical records)	15% achieved HbA1c < 7.0%
3	2009	Heustein Sy	Complications and cardiovascular risk factors among newly-diagnosed type 2 diabetics in Manila	Philippine Journal of Internal Medicine	Philippines	Office (health centers)	Mean HbA1c = 8.6% ± 2.7 % of HbA1c <7.0% not reported
Singapore (10)							
1	2023	Loraine Liping Seng	Real-world systolic and diastolic blood pressure levels and cardiovascular mortality in patients with type 2 diabetes – results from a large registry cohort in Asia	Journal of the American Heart Association	Singapore	Office (Multi-institutional registry: primary care and hospital based care)	77.3% achieved HbA1c ≤ 8% Mean HbA1c = 7.4% ± 1.6
2	2021	Liang Feng	Trends in cardiovascular risk factors and treatment goals in patients with diabetes in Singapore-analysis of the SingHealth Diabetes Registry	PLoS One	Singapore	Office (Multi-institutional registry)	39.3% - 51.8% achieved HbA1c <7.0%

3	2021	Xingzhi Sun	Effective treatment recommendations for type 2 diabetes management using reinforcement learning: treatment recommendation model development and validation	Journal of Medical Internet Research	Singapore	Office (diabetes registry – electronic medical records data)	67.7%-72.6% achieved HbA1c <7%
4	2020	Lei Liu	Hypertension, blood pressure control and diabetic retinopathy in a large population-based study	PLoS One	Singapore	Office (study clinic)	Mean HbA1c = 8.2% ± 2 % of HbA1c <7.0% not reported
5	2018	Miyang Luo	Diabetes management in a primary care network (PCN) of private general practitioners in Singapore: An observational study	Medicine	Singapore	Office (GP clinics – manual and electronic records)	31.6% achieved HbA1c <7%
6	2015	Lee Eng Sing	The prevalence of albuminuria among diabetic patients in a primary care setting in Singapore	Singapore Medical Journal	Singapore	Office (primary care clinics)	Mean HbA1c = 7.2% ± 1.0 % of HbA1c <7.0% not reported
7	2010	Olivia S. Huang	Glycemic and Blood pressure control in an Asian Malay Population with	JAMA Ophthalmology	Singapore	Office (Clinics)	26.9% achieved HbA1c <7%

			Diabetes and Diabetic Retinopathy				
8	2010	Rahul Malhotra	Prevalence, awareness, treatment and control of hypertension in the elderly population of Singapore	Hypertension Research	Singapore	Out-of-office (interview at residence)	No data
9	2007	Matthias PHS Toh	Measuring the Quality of Care of Diabetic Patients at the Specialist Outpatient Clinics in Public Hospitals in Singapore	Annals Academy of Medicine	Singapore	Office (review of medical records)	51.2% achieved HbA1c ≤ 7.0%
10	2006	Akira Y T Wu	Microalbuminuria prevalence study in hypertensive patients with type 2 diabetes mellitus in Singapore	Singapore Medical Journal	Singapore	Office (diabetes clinics and general practices)	Mean HbA1c = 7.9% % of HbA1c <7.0% not reported
Thailand (24)							
1	2023	Sethapong Lertsakulbunlue	Trends in predicted 10-year risk for cardiovascular diseases among patients with type 2 diabetes in Thailand, from 2014 to 2018	BMC Cardiovascular Disorders	Thailand	Office (hospital medical records)	Median HbA1c = 7.6% % of HbA1c <7.0% not reported
2	2022	Boonsub Sakboonyarat	Model development to improve primary care services using an innovative network of	BMC Primary Care	Thailand	Office (interviews conducted at primary care unit)	No data

			homecare providers (WinCare) to promote blood pressure control among elderly patients with noncommunicable diseases in Thailand: a prospective cohort study				
3	2022	Thanapat Puangpet	Control and complications of diabetes in urban primary care units in Thailand: a cross-sectional study	BMC Primary Care	Thailand	Office (primary care units)	41.2% of women and 44.4% of men achieved HbA1c < 7%
4	2021	Boonsub Sakboonyarat	National trends in the prevalence of glycemic control among patients with type 2 diabetes receiving continuous care in Thailand from 2011 to 2018	Scientific Reports	Thailand	Office (public hospitals – data collection at clinic and medical records)	34.8% achieved HbA1c <7%
5	2021	Nathakamol Euswas	National trends in the prevalence of diabetic retinopathy among Thai patients with type 2 diabetes and its associated factors from 2014 to 2018	PLoS One	Thailand	Office (Hospital medical records)	Mean HbA1c = 7.9 %– 8% % of HbA1c <7.0% not reported

6	2021	Sojib bin Zaman	The burden of chronic kidney disease among people with diabetes by insurance schemes: Findings from a primary referral hospital in Thailand	Diabetes Epidemiology and Management	Thailand	Office (clinical registry from a primary referral hospital)	No data
7	2020	Naowanit Nata	Impaired glomerular filtration rate in type 2 diabetes mellitus subjects: a nationwide cross-sectional study in Thailand	Journal of Diabetes Research	Thailand	Office (medical and personal data from participating hospitals)	31.3% achieved HbA1c<7%
8	2020	Wisit Kaewput	Rate of kidney function decline and factors predicting progression of kidney disease in type 2 diabetes mellitus patients with reduced kidney function: a nationwide retrospective cohort study	Therapeutic Apheresis and dialysis	Thailand	Office (medical records)	Mean HbA1c: 7.8% ± 2.0 % of HbA1c <7.0% not reported
9	2019	Boonsub Sakboonyarat	Prevalence and associated factors of uncontrolled hypertension among hypertensive patients: a nation-wide survey in Thailand	BMC Research Notes	Thailand	Office (medical records)	No data

10	2019	Lampung Vonok	Influence of antiplatelet therapy on cardiovascular disease prevention among type 2 diabetic patients in Thailand	Journal of Clinical and Diagnostic Research	Thailand	Office (survey at diabetic & hypertension clinic)	28.3% achieved HbA1c ≤ 7%
11	2019	Wisit Kaewput	Temporal trends in optimal diabetic care and complications of elderly type 2 diabetes patients in Thailand: a nationwide study	Journal of Evidence-Based Medicine	Thailand	Office (Public hospitals)	56.7% achieved HbA1c < 7%
12	2018	Boonsub Sakboonyarat	Prevalence and associated factors of ischemic heart disease (IHD) among patients with diabetes mellitus: a nation-wide, cross-sectional survey	BMC Cardiovascular Disorders	Thailand	Office (public hospitals, private hospitals and clinics)	Mean HbA1c = 8.0% ± 2.2 % of HbA1c <7.0% not reported
13	2017	Sokha Sieng	A combination of process of care and clinical target among type 2 diabetes mellitus patients in general medical clinics and specialist diabetes clinics at hospital level	BMC Health Services Research	Thailand	Office (medical records from hospitals)	33.8% - 36.9% achieved HbA1c < 7%
14	2016	Siribha Changsirikulchai	National survey: evaluation of cardiovascular risk factors in Thai	Nephrology	Thailand	Office (Hospital medical records)	39.2% achieved HbA1c < 7%

			patients with type 2 diabetes and chronic kidney disease after the development of cardiovascular disease				
15	2015	Cameron Hurst	The association between hypertension comorbidity and microvascular complications in type 2 diabetes patients: a nationwide cross-sectional study in Thailand	Diabetes & Metabolism Journal	Thailand	Office (hospital medical records)	28.4% - 36.3% achieved HbA1c < 7 %
16	2015	Sokha Sieng	Comparison of HbA1c, blood pressure, and cholesterol (ABC) control in type 2 diabetes attending general medical clinics and specialist diabetes clinics in Thailand	Diabetes Research and Clinical Practice	Thailand	Office (hospital medical records)	34.58% achieved HbA1c <7.0%
17	2012	Patcharaporn Sudchada	Diabetes and cardiovascular risk factor controls in Thai type 2 diabetes with no history of cardiovascular complications; situation and compliance to	Journal of Diabetes and its complications	Thailand	Office (outpatient medical records and electronic hospital database)	28.2% achieved HbA1c < 6.5%

			diabetes management guideline in Thailand				
18	2012	Sriwat Tiptaradol	Prevalence, awareness, treatment and control of coexistence of diabetes and hypertension in Thai population	International Journal of Hypertension	Thailand	Out of office (multistage probability sampling design)	No data on HbA1c Mean fasting plasma glucose (mg/dL) = 172.8 -185.1
19	2011	Apiradee Sriwijitkamol	Attainment of American Diabetes Association Clinical Practice Recommendations in 722 Thai Type 2 diabetes patients	Journal of the Medical Association of Thailand	Thailand	Office (hospital medical records)	49% achieved HbA1c < 7 % 26.4% achieved HbA1c < 6.5%
20	2007	Wichai Aekplakorn	Prevalence and management of diabetes and associated risk factors by regions of Thailand: Third National Health Examination Survey 2004	American Diabetes Association	Thailand	Out of office (multistage probability sampling design)	No data on HbA1c Fasting plasma glucose <7.8mmol/l : 35.8% - 44.6%
21	2006	Chardpraorn Ngarmukos	Thailand Diabetes Registry Project: Prevalence, characteristics and treatment of patients with diabetic nephropathy	Journal of the Medical Association of Thailand	Thailand	Office (hospital-based diabetic registry)	7% achieved HbA1c < 7 %

22	2006	Petch Rawdaree	Thailand Diabetes Registry Project: Clinical status and long term vascular complications in diabetic patients	Journal of the Medical Association of Thailand	Thailand	Office (medical institutes)	30.7% achieved HbA1c < 7 % Mean HbA1c = 8.2% ± 1.9
23	2006	Rattana Leelawattana	Thailand Diabetes Registry Project: Prevalence of vascular complications in long-standing type 2 diabetes	Journal of the Medical Association of Thailand	Thailand	Office (diabetes clinics)	Mean HbA1c = 8.0 – 8.5% % of HbA1c <7.0% not reported
24	2003	Wichai Aekplakorn	The prevalence and management of diabetes in Thai Adults: The international collaborative study of cardiovascular disease in Asia	Diabetes Care	Thailand	Out of office (household)	No data on HbA1c Mean fasting plasma glucose = 101.0 ± 1.5 mg/dl
Vietnam (3)							
1	2023	Amalie Sophie Sahl	Diabetes-related distress and the association to hypertension and cardiovascular disease among individuals living with type 2 diabetes in rural areas in Vietnam	medRxiv	Vietnam	Out-of-office (interviews done in participants homes)	No data

2	2021	TD Cam	Adherence to blood pressure control and association with comorbidities in elderly Vietnamese patients	Genetics and Molecular Research	Vietnam	Office (Hospital)	No data
3	2020	Khue Thy Nguyen	A cross-sectional study to evaluate diabetes management, control and complications in 1631 patients with type 2 diabetes mellitus in Vietnam (DiabCare Asia)	International Journal of Diabetes in Developing Countries	Vietnam	Office (diabetes clinics/units and central hospitals)	36.1% achieved HbA1c < 7.0% Mean HbA1c: 7.9% ± 1.8

Chapter 6

Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam

Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam

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Abstract

Background. Poor adherence to antihypertensive medications is very common in older adults. One of the leading causes of poor adherence is forgetfulness, which can be particularly challenging to manage because it is often unintentional. A better understanding of the impact of forgetfulness can help in developing targeted interventions to improve BP control.

Aim. This study aimed to (1) examine the prevalence of forgetfulness to take antihypertensive medications and its associated factors in older adults with type 2 diabetes and hypertension in Vietnam, and (2) investigate the relationship between forgetfulness to take antihypertensive medications and poor blood pressure (BP) control in this population.

Methods. This observational study was conducted at the outpatient clinics of two major hospitals in Vietnam from June 2023 to June 2024. Forgetfulness was assessed using the question: "Do you sometimes forget to take your prescribed antihypertensive medications?", with the answer of "Yes" or "No". Poor BP control was defined as mean systolic BP ≥140 mmHg or a mean diastolic BP ≥90 mmHg. Logistic regression analysis was conducted to examine the associated factors for forgetfulness and the relationship between forgetfulness and poor BP control. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Results. There were 448 participants. They had a mean age of 73.5 years (SD 7.2), 32.1% were female. The prevalence of forgetfulness to take antihypertensives was 29.5%, highest among participants in the first 5 years of hypertension (43.8%), followed by those with >15 years (28.0%), 11-15 years (25.2%), and 6-10 years (23.9%) (p=0.009). Logistic regression analysis revealed that hypertension duration and disability in activities of daily living were significantly associated with forgetfulness. Forgetfulness increased the odds of poor BP control, with an adjusted OR of 1.64 (95%CI 1.03 -2.56).

Conclusion. In this study, there was a high prevalence of forgetfulness to take antihypertensive medications, and forgetfulness was associated with increased odds of poor BP control. These findings suggest the need for future studies focusing on interventions on forgetfulness to improve medication adherence for this population. Further support is particularly needed for older adults with disability and for those newly diagnosed with hypertension.

Keywords. Hypertension, high blood pressure, antihypertensive medications, blood pressure control, diabetes, medication adherence, Vietnam.

Introduction

Hypertension remains a significant public health issue globally.[1] It is the leading cause of stroke and coronary heart disease in older adults .[2] The global prevalence of hypertension is rising, mainly due to a growing ageing population, increased exposure to lifestyle-related risk factors such as smoking, poor diets and a lack of physical activity.[3] Blood pressure (BP) lowering treatment can reduce stroke by about 35% to 40%, myocardial infarction by about 15% to 25%, and dementia by about 10-30%.[4,5] Nevertheless, poor BP control is still a major concern, as evidenced by a global control rate of approximately 20%.[6]

Hypertension is often reported as a comorbidity in older adults with type 2 diabetes. In older people with diabetes, the heterogeneity in comorbidity, frailty, functional disability, polypharmacy, and cognitive impairment makes the treatment of hypertension challenging. In persons with hypertension, evaluation of adherence to antihypertensive treatment is considered to be an integral part of overall patient assessment.[7] However, poor adherence to BP lowering medications is very common among older adults.[7-9] Poor adherence to medications can result in worse health outcomes and greater healthcare costs. Therefore, it is important to understand the reasons for non-adherence. One of the leading causes of non-adherence is forgetfulness[10], which can be particularly challenging to manage because it is often unintentional.[11] A better understanding of the impact of forgetfulness can help in developing targeted interventions to improve BP control.

Globally, notable disparities have been reported to exist between high-income countries (HICs) and low-to-middle-income countries (LMICs) in hypertension care.[1] The age-

standardized prevalence of hypertension has been reported to be higher in LMICs than in HICs, and approximately three-quarters of individuals with hypertension are living in LMICs.[12] Additionally, lower levels of awareness, treatment and control rates of hypertension have been reported in LMICs when compared against HICs.[12] Furthermore, antihypertensive medication nonadherence has been reported to be more prevalent in LMICs and non-Western countries.[13]

Vietnam is experiencing an increasing prevalence of hypertension and diabetes,[14] both of which are major risk factors for cardiovascular diseases. Cardiovascular disease remains the leading cause of mortality in Vietnam.[15] Additionally, the country is facing a growing older population, which adds further strain on the healthcare system.[15] High BP has also been reported to be one of the top modifiable risk factors for all-cause dementia, particularly vascular cognitive impairment.[16] The BP control rate among adults with hypertension and diabetes in Vietnam was reported to be less than 40%.[17] Therefore, implementing effective strategies to improve BP control becomes increasingly important.

This study aimed to (1) examine the prevalence of forgetfulness to take antihypertensive medications and factors associated with forgetfulness in older adults with type 2 diabetes and hypertension in Vietnam, and (2) investigate the relationship between forgetfulness to take antihypertensive medications and poor BP control in this population.

Methods

Study population

We used data from an observational study on frailty in older adults with hypertension in Vietnam from June 2023 to June 2024. Community-dwelling adults aged 60 years or older with hypertension attending the outpatient cardio-metabolic clinics of two major hospitals in Vietnam (Thong Nhat Hospital in Ho Chi Minh City and University Medical Centre of Ho

Chi Minh City) during the study period were recruited. Further details of the study were described elsewhere.[18] The study was approved by the Ethics Committees of the University of Medicine and Pharmacy at Ho Chi Minh City (Reference Number 627/HDDD-DHYD, date 26/06/2023). Informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki. For the purposes of this analysis, only patients with diabetes were included.

Data collection and variable definitions

Data were collected from patient interviews and medical records. Information obtained included demographic characteristics, lifestyles (regular exercise, smoking, alcohol consumption), height, weight, medical history, duration of having hypertension, medications used, and comorbidities. Body mass index (BMI) was calculated from measured weight and height. Smoking was defined as previous or current smoking. Polypharmacy was defined as using 5 or more medications daily.[19] Frailty was assessed using a Clinical Frailty Scale (CFS).[20] Participants were also assessed for disability in activities of daily living (ADLs), including six activities that are fundamental for independent life at home (bathing, using the toilet, transferring, dressing, eating and continence).[21]

Participants' forgetfulness to take antihypertensive medications was assessed using one question: "Do you sometimes forget to take your prescribed antihypertensive medications?", with the answer of "Yes" or "No".[22]

Mean systolic BP and diastolic BP were calculated from the BP measurements obtained in patients' medical records in the past 6 months. Poor BP control was defined as a mean systolic BP ≥ 140 mmHg or a mean diastolic BP ≥ 90 mmHg. We also conducted sensitivity analysis with the cut points of systolic BP ≥ 130 mmHg or diastolic BP ≥ 80 mmHg. These BP targets were chosen to align with the 2022 Vietnamese Society of Hypertension

Guidelines, and the 2024 European Society of Cardiology (ESC) Guidelines for the management of elevated blood pressure and hypertension.[23,24] The 2024 European Society of Cardiology (ESC) recommends a target of systolic BP of 120 to 129 mmHg, if tolerated in patients with hypertension and diabetes.[24] The 2022 Vietnamese Society of Hypertension guidelines highlighted that the management of hypertension can be complicated by pathologies associated with aging such as functional and cognitive impairment, and frailty.[23] According to the 2022 Vietnamese Society of Hypertension guidelines, for hypertensive patients with type 2 diabetes from 16–69 years old, the BP target of <130/80 mmHg is recommended, and for hypertensive patients with type 2 diabetes aged 70 years or older, the target of systolic BP should be <140 mmHg (lower accepted if tolerated).[23]

Statistical analysis

The participant characteristics are presented as mean and standard deviation (SD) for continuous variables, or frequencies and percentages for categorical variables. Comparisons between groups were conducted using Chi-square tests or Fisher's exact tests for categorical variables, and Student’s t-tests for continuous variables.

Logistic regression analysis was conducted to examine the associated factors for forgetfulness. Univariable logistic regression were conducted for all potential variables that can be associated with forgetfulness, variables with p-values <0.05 were selected to include in the multivariable analysis, and the final model contained only variables with p-values <0.05. Results are presented as odds ratios (ORs) and 95% confidence intervals (CIs).

Logistic regression analysis was also applied to examine the relationship between forgetfulness to take antihypertensive medications and poor BP control. Forgetfulness was the predictive variable of interest, and poor BP control was the outcome variable, adjusted for predefined variables such as age, sex, marital status, education, lifestyles (smoking, alcohol

consumption, exercise), duration of having hypertension, the CFS score, and number of antihypertensive medications.

P values <0.05 were considered statistically significant. Data were analyzed using IBM SPSS Statistics 29.0.1.0.

Results

Participant characteristics

A total of 448 participants with diabetes and hypertension were included in this study. They had a mean age of 73.5 (SD 7.2) years and 32.1% were female. The percentage of participants who had forgetfulness to take medications was 29.5% (132/448). Figure 1 presents the prevalence of forgetfulness by duration of hypertension. The prevalence of forgetfulness was highest among participants in the first 5 years of hypertension (43.8%), followed by those with >15 years of hypertension (28.0%), 11-15 years (25.2%), and 6-10 years (23.9%) (p=0.009).

Table 1 presents participant characteristics. There was a high prevalence of polypharmacy (98%). Regarding hypertension duration, 31.9% of the participants had hypertension for ≥ 15 years, 23.0% for 11-15 years, 25.2% for 6-10 years, and 19.9% for 1-5 years. Amongst the study cohort, 1.3% had disability in ≥ 3 activities of daily living. The most common comorbidities were coronary heart disease (54.9%), chronic kidney disease (26.8%), osteoarthritis (17%), heart failure (9.4%), stroke (8.9%), cognitive impairment (6.9%), atrial fibrillation (6.0%), osteoporosis (2.2%), and chronic obstructive and pulmonary disease (1.6%).

There were significant differences in the prevalence of disability, cognitive impairment, and the duration of hypertension among participants who did not forget to take antihypertensives compared to those who forgot. The prevalence of disability in ≥ 3 ADLs was 3.8% in

participants who forgot to take antihypertensives vs 0.3% in those who did not forget (p= 0.010). The prevalence of cognitive impairment was 10.6% in participants who forgot to take antihypertensives vs 5.4% in those who did not forget (p= 0.047). The percentage of participants that were in their first 5 years of hypertension diagnosis was significantly higher in those who forget to take medications vs those who did not forget (29.5% vs. 15.8%, p=0.009)

Details of antihypertensive medications are presented in Table 2. Almost half (47.3%) of the participants were taking ≥ 3 antihypertensive medications. The most common antihypertensive medications used were renin-angiotensin-system (RAS) inhibitors (90.8%), followed by beta blockers (71.9%), calcium channel blockers (CCBs) (65.6%), thiazide (10.7%), mineralocorticoid receptor antagonist (MRA) (4.7%) and loop diuretics (2.0%). There were no significant differences in the number, or the types of antihypertensive medications used among the two groups.

Factors associated with forgetfulness

Table 3 present the ORs of factors associated with forgetfulness. The final model showed that hypertension duration and disability in ≥3 ADLs were significantly associated with forgetfulness. Compared to participants with hypertension for ≥15 years, participants with a hypertension duration of 1-5 years had increased odds of forgetfulness, with an adjusted OR of 2.13 (95% CI 1.22 – 3.74). Disability in ≥3 ADLs was also associated with increased odds of forgetfulness, with an adjusted OR of 14.80 (95% CI 1.7-128.69).

The relationship between forgetfulness and poor BP control

The prevalence of poor BP control (≥140/90 mmHg) was 27.5% in all participants, 34.1% in those who forgot to take medications compared to those who did not (24.7%), p = 0.042. Forgetfulness was associated with an increased odds of poor BP control (adjusted OR 1.64,

95%CI 1.03 – 2.56). A similar trend was also observed with the BP≥130/80 mmHg cut-off (adjusted OR 1.20, 95% CI 0.79 – 1.84).

Discussion

In our study, approximately one third of the study participants reported forgetting to take their antihypertensive medications sometimes. This finding was slightly higher than the prevalence of 25% reported in a study in Greece[22], which explored forgetfulness to take medications in patients with hypertension and dyslipidemia. Another study in Vietnam[25] that assessed medication adherence among older people with coronary heart disease found that 23.6% of participants were non-adherent. A study on adherence to antihypertensive medications in Ethiopia revealed that age was significantly associated with level of adherence, young participants were more adherent compared to older participants.[26] This trend was also reported in another study in Lebanon[27] that found that older adults with hypertension were more likely to exhibit non-adherence to antihypertensive medication. The higher prevalence of medication forgetfulness in our study could be due to the older study population and highlights the importance of improving medication adherence among older adults with hypertension and diabetes.

Our study showed that the odds of forgetfulness to take antihypertensives was significantly higher in the first 5 years of being diagnosed with hypertension, and in participants with disability in ≥ 3 ADLs. This was similar to another study in Bangladesh reporting that people with newly diagnosed hypertension had higher rates of poor medication adherence (17.6%) compared to those having hypertension >5 years (15.5%).[28] These findings suggest more support is needed for people with newly diagnosed hypertension or during the first 5 years of diagnosis, including access to relevant resources to manage their medications.. Ongoing

patient education and medication counselling can be helpful to encourage adherence to treatment plans and to proactively support patients in managing their medications. Older adults may experience age-related changes that contribute to disabilities in ADLs. In some cases, medication side effects may exacerbate these challenges. For older adults, it is important to identify disabilities in ADLs, and to recognize whether issues such as visual impairment or decreased grip strength (which can make it difficult to open medicine bottles) are barriers to medication adherence. Involving caregivers in the medication use process for these patients is essential, as their support can make a significant difference in medication management. When considering future studies aimed at reducing forgetfulness in taking antihypertensive medications among older people, particular considerations should be given for these factors and how they can be managed to help improve overall medication adherence.

Our study showed that forgetfulness to adhere to antihypertensive medication increased the odds of poor BP control among the study participants. A scientific statement from the American Heart Association recently reported how medication nonadherence is one of the main contributors to national prevalence of poor BP control.[29] A meta-analysis of 27 million patients with hypertension from 68 countries identified that patients with antihypertensive medication nonadherence had increased odds of having suboptimal BP control, complications from hypertension, all-cause hospitalization and all-cause of mortality.[13] Another systematic review and meta-analysis of 12 cohort studies also concluded that poor adherence to antihypertensives significantly increases overall and cardiovascular mortality risk.[30]

Effective hypertension management among Vietnamese adults continues to be a significant public health challenge. Some of the reasons for this include varying health literacy levels, less than optimal medication adherence and unfavourable lifestyle practices.[31] A systematic review and meta-analysis reported the pooled prevalence of measured hypertension in Vietnam was 21.1%.[32] Additionally, a higher prevalence of hypertension has been reported

among older adults, with further variations amongst those living in urban compared to those living in rural and regional areas.[32] This shows the complexity for population level management and the need for contextualized approaches. Forgetfulness to take medications could also be due to the use of multiple medications or complex medication regimens. A possible strategy for reducing forgetfulness is the use of fixed-dose combinations. A recent review on hypertension therapy using fixed-dose polypills highlighted the high adherence (>95%) reported in the included studies.[33] A recent global survey (with participants from Vietnam) amongst medical doctors who prescribed antihypertensive medicines to patients with hypertension reported that fixed dose combination antihypertensives were valuable for patients with large pill burden or who struggled with adherence.[34] With the majority of the study participants in this study reporting using >1 antihypertensive medication (91.1%), the use of fixed-dose combinations or polypills as a strategy to reduce forgetfulness can be explored further in future studies.

Strength and limitations

To the best of our knowledge, this was the first study in Vietnam to examine forgetfulness to take antihypertensive medications, a common factor that can lead to poor medication adherence to antihypertensives in older people. Our findings provide valuable information for targeted interventions to improve adherence in this population. Due to the cross-sectional nature of the study, we were unable to explore impact of forgetfulness and poor BP control on disease progression and mortality. Participants in this study were recruited from two major hospitals in Ho Chi Minh City, a populous city. Older adults living in regional and rural areas may have different demographics and patient experience. Therefore, the findings may not be generalisable, and it is important to interpret the results within their specific context.

Conclusion

In this study, there was a high prevalence of forgetfulness to take antihypertensive medications, and forgetfulness was associated with poor BP control in older patients with type 2 diabetes and hypertension. These findings suggest the need for future studies focusing on interventions on forgetfulness to improve medication adherence for this population. Further support is particularly needed for older adults with disability and for those newly diagnosed with hypertension.

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Table 1. Participant characteristics

Variables	All participants (n=448)	Forgetfulness to take medications		p
		No (n=316)	Yes (n=132)	
Age (years)	73.5 (7.2)	73.6 (7.1)	73.3 (7.3)	0.628
Sex				
Female	144 (32.1)	107 (33.9)	37 (28.0)	0.228
Male	304 (67.9)	209 (66.1)	95 (72.0)	
Low education (yes vs. no)	96 (21.4)	68 (21.5)	28 (21.2)	0.942
Married (yes vs. no)	426 (95.1)	299 (94.6)	127 (96.2)	0.477
Smoking (yes vs. no)	43 (9.6)	29 (9.2)	14 (10.6)	0.640
Regular exercise (yes vs. no)	208 (46.4)	142 (44.9)	66 (50.0)	0.327
Frequent use of alcohol drinks (yes	11 (2.5)	7 (2.2)	4 (3.0)	0.738

vs. no)				
Hypertension duration				
1 – 5 years	89 (19.9)	50 (15.8)	39 (29.5)	0.009
6 – 10 years	113 (25.2)	86 (27.2)	27 (20.5)	
11 – 15 years	103 (23.0)	77 (24.4)	26 (19.7)	
≥ 15 years	143 (31.9)	103 (32.6)	40 (30.3)	
Body mass index (kg/m^2)				
<18.50	11 (2.5)	11 (3.5)	0 (0)	0.057
18.50-24.99	306 (68.3)	209 (66.1)	97 (73.5)	
≥ 25.0	131 (29.2)	96 (30.4)	35 (26.5)	
CFS score	3.5 (0.9)	3.4 (0.8)	3.5 (1.0)	0.600
Frailty (yes vs. no)	136 (30.4)	93 (29.4)	43 (32.6)	0.509
Polypharmacy (yes vs. no)	438 (98.0)	311 (98.7)	127 (96.2)	0.132
ADL score	5.9 (0.6)	5.9 (0.4)	5.8 (0.8)	0.200
Disability in ≥ 3 ADLs (yes vs. no)	6 (1.3)	1 (0.3)	5 (3.8)	0.010
Hospitalization in the past 12 months (yes vs. no)	175 (39.1)	122 (38.6)	53 (40.2)	0.760
Falls in the past 12 months (yes vs. no)	36 (8.0)	26 (8.2)	10 (7.6)	0.817
Coronary heart disease (yes vs. no)	246 (54.9)	174 (55.1)	72 (54.5)	0.920
Chronic kidney disease (yes vs. no)	120 (26.8)	84 (26.6)	36 (27.3)	0.880
Osteoarthritis (yes vs. no)	76 (17.0)	49 (15.5)	27 (20.5)	0.203
Heart failure (yes vs. no)	42 (9.4)	29 (9.2)	13 (9.8)	0.824
Stroke (yes vs. no)	40 (8.9)	30 (9.5)	10 (7.6)	0.516

Cognitive impairment (yes vs. no)	31 (6.9)	17 (5.4)	14 (10.6)	0.047
Atrial fibrillation (yes vs. no)	27 (6.0)	16 (5.1)	11 (8.3)	0.185
Osteoporosis (yes vs. no)	10 (2.2)	7 (2.2)	3 (2.3)	0.970
Chronic obstructive pulmonary disease (yes vs. no)	7 (1.6)	4 (1.3)	3 (2.3)	0.679
LDL-Cholesterol (mmol/L)	2.1 (0.9)	2.0 (0.9)	2.2 (1.0)	0.215
LDL-Cholesterol ≥ 2.60 mmol/L	115 (25.7)	73 (23.1)	42 (31.8)	0.054
HbA1c levels (%)	7.3 (1.5)	7.3 (1.4)	7.4 (1.7)	0.574
HbA1c ≥ 7.0 %	223 (50.2)	158 (50.3)	65 (50.0)	0.951

Continuous data are presented as mean and standard deviation. Categorical data are shown as n (%). CFS = Clinical Frailty Scale, ADL = Activities of Daily Living, LDL = Low-Density Lipoprotein, HbA1c = glycated haemoglobin

Table 2. Details of antihypertensive pharmacological treatment

Variables	All participants (n=448)	Forgetfulness to take medications		p
		No (n=316)	Yes (n=132)	
Number of antihypertensive medications				
1	40 (8.9)	30 (9.5)	10 (7.6)	0.708
2	196 (43.8)	135 (42.7)	61 (46.2)	
≥ 3	212 (47.3)	151 (47.8)	61 (46.2)	
Types of antihypertensive medications				

RAS inhibitors	407 (90.8)	287 (90.8)	120 (90.9)	0.977
Beta-blockers	322 (71.9)	230 (72.8)	92 (69.7)	0.508
CCBs	294 (65.6)	205 (64.9)	89 (67.4)	0.604
Thiazide	48 (10.7)	35 (11.1)	13 (9.8)	0.702
MRA	21 (4.7)	13 (4.1)	8 (6.1)	0.374
Loop diuretics	9 (2.0)	5 (1.6)	4 (3.0)	0.459

Data are shown as n (%).

RAS = Renin-Angiotensin-System, CCBs = Calcium Channel Blockers, MRA = Mineralocorticoid Receptor Antagonist

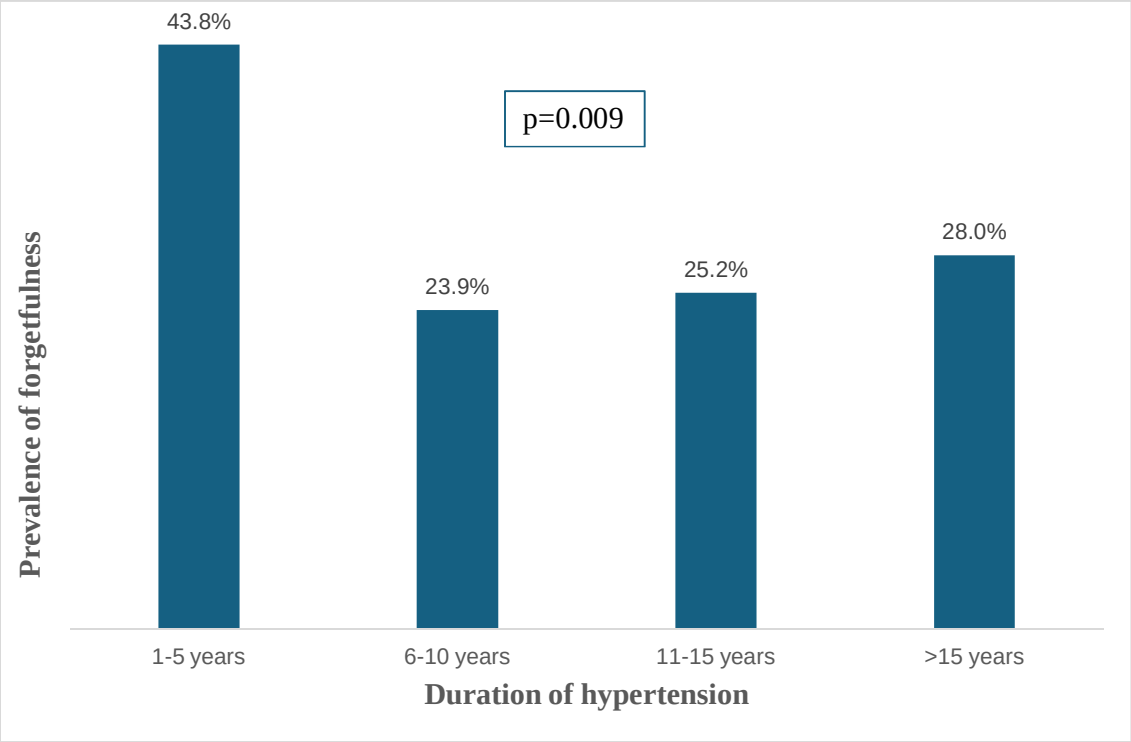

Figure 1. Prevalence of forgetfulness by duration of hypertension

Table 3. Unadjusted and adjusted odds ratios for forgetfulness

	Unadjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Age (years)	0.99 (0.97 – 1.02)	0.627	-	
Female vs. male	0.76 (0.49 – 1.19)	0.229	-	

Low education (yes vs. no)	0.98 (0.60 – 1.61)	0.942	-	
Married (yes vs. no)	1.44 (0.52 – 4.00)	0.479	-	
Smoking (yes vs. no)	1.17 (0.60 – 2.30)	0.640	-	
Regular exercise (yes vs. no)	1.23 (0.82 – 1.84)	0.328	-	
Frequent use of alcohol drinks (yes vs. no)	1.38 (0.40 – 4.79)	0.613	-	
CFS score	1.06 (0.85 – 1.33)	0.599	-	
Frailty (yes vs. no)	1.16 (0.75 – 1.79)	0.509	-	
Hypertension duration		0.011		0.006
1 – 5 years	2.01 (1.15 – 3.50)	0.014	2.13 (1.22 – 3.74)	0.008
6 – 10 years	0.81 (0.46 – 1.42)	0.461	0.84 (0.47 – 1.48)	0.537
11 – 15 years	0.87 (0.49 – 1.55)	0.634	0.87 (0.48 – 1.56)	0.639
≥ 15 years (reference group)	1		1	
Obesity (BMI ≥ 25.0 kg/m^2)	0.78 (0.49 – 1.23)	0.280	-	
Polypharmacy (yes vs. no)	0.33 (0.09 – 1.24)	0.099	-	
Number of antihypertensive medications		0.708	-	
1 (reference group)	1		-	
2	1.36 (0.62 – 2.95)	0.443	-	
3 or more	1.21 (0.56 – 2.63)	0.627	-	
ADL score	0.77 (0.55 – 1.08)	0.127	-	
Disability in ≥ 3 ADLs (yes vs. no)	12.04 (1.44 – 107.20)	0.022	14.80 (1.70 – 128.69)	0.015
Hospitalization in the past 12 months (yes vs. no)	1.07 (0.70 – 1.62)	0.760	-	
Falls in the past 12 months (yes vs. no)	0.91 (0.43 – 1.95)	0.817	-	

Coronary heart disease (yes vs. no)	0.98 (0.65 – 1.47)	0.920	-	
Heart failure (yes vs. no)	1.08 (0.54 – 2.15)	0.824	-	
Stroke (yes vs. no)	0.78 (0.37 – 1.65)	0.517	-	
Atrial fibrillation (yes vs. no)	1.71 (0.77 – 3.78)	0.189	-	
Chronic kidney disease (yes vs. no)	1.04 (0.66 – 1.64)	0.880	-	
Osteoarthritis (yes vs. no)	1.40 (0.83 – 2.36)	0.205	-	
Osteoporosis (yes vs. no)	1.03 (0.26 – 4.03)	0.970	-	
Chronic obstructive pulmonary disease (yes vs. no)	1.81 (0.40 – 8.22)	0.440	-	
Cognitive impairment (yes vs. no)	2.09 (1.00 – 4.37)	0.051	-	
LDL-Cholesterol ≥ 2.60 mmol/L	1.55 (0.99 – 2.43)	0.055	-	
HbA1c ≥ 7.0 %	0.99 (0.65 – 1.49)	0.951	-	

Variables with p-values <0.05 on univariable analyses were selected to include in the multivariable analysis, and the final model contained only variables with p-values <0.05

Table 4. Associations between forgetfulness to take medications with poor blood pressure control

	BP ≥ 140/90 mmHg		BP ≥ 130/80 mmHg	
	Odds ratios (95%CI)	p-value	Odds ratios (95%CI)	p-value

Unadjusted	1.58 (1.02 – 2.45)	0.043	1.15 (0.76 – 1.74)	0.515
Adjusted	1.64 (1.03 – 2.56)	0.036	1.20 (0.79 – 1.84)	0.398

Adjusted for age, sex, education, marital status, lifestyles (smoking, alcohol consumption, regular exercise), hypertension duration, the Clinical Frailty Scale, number of antihypertensive medications

Chapter 7

Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia

Title: Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia

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Impact statement:

- This study shows that increasing frailty was significantly associated with reduced odds of receiving statins among older stroke survivors.
- It also highlights the impact that comorbidities like diabetes may have in influencing treatment choices. Further studies are needed to help develop personalized strategies for cardiovascular prevention in older adults.

Keywords: Statin, Frailty, Diabetes, Stroke

Introduction

Stroke continues to be a leading source of mortality and morbidity worldwide, with the bulk of the global burden in lower-income and lower-middle-income countries.[1] There are two main types of stroke, ischemic stroke and hemorrhagic stroke. With age being an irreversible risk factor for stroke, older persons are more vulnerable to stroke and its long-term effects. For older stroke survivors, managing cardiovascular risk factors such as hyperlipidaemia is a crucial strategy in reducing the likelihood of subsequent cardiovascular events and further complications. Strategies can include non-pharmacological steps like lifestyle interventions and pharmacological options such as the use of lipid lowering therapies like statins. Statins, also known as hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, are primarily used for their lipid-lowering effects and cardiovascular benefits. Statins are recommended by the American Heart Association and American Stroke Association[2] for the prevention of recurrent stroke in patients post ischemic strokes.

Frailty is a condition characterized by decreased physiological reserve and increased vulnerability to adverse health effects.[3] Frailty has also been linked to a higher incidence of future cardiovascular events.[4] A study of 15753 participants with type 2 diabetes from the UK Biobank showed that both pre-frailty and frailty were associated with a higher risk of cardiovascular events, including strokes.[5] Therefore, the presence of frailty in patients with diabetes could significantly increase the risk of recurrent strokes. As such, the impact of frailty on cardiovascular diseases including stroke is an important research area.[6] However, for older stroke survivors with frailty, this continues to be an under-explored area. With reports of increasing prevalence of frailty among older people, its importance and influence are growing, particularly in how it impacts care. Frailty may influence clinical decisions, including the prescriptions of medicines like statins.

Malaysia is a country in the Southeast Asia that is undergoing an epidemiological transition.[7] The increasing number of older population, and with it frailty, presents many challenges for the healthcare system. Furthermore, the prevalence of type 2 diabetes in older adults in Malaysia is

high.[8] People with diabetes have an increased risk of stroke and post-stroke complications. For stroke care, the combination of a growing number of older people, together with the reported high prevalence of poorly controlled cardiovascular risk factors like blood pressure control in people with diabetes[9] further highlights the magnitude of the challenge at hand. There is a need to better understand how these influence strategies like statin prescription as part of stroke care for the older person. Statins have been reported to be underutilized for secondary prevention and there is limited data on the relationship of frailty and the use of lipid lowering therapies in this population.[4] The benefit of statin prescription depends on sufficient life expectancy to realize the long-term risk reduction they confer.[10] In clinical practice, some clinicians may consider predicted life expectancy against the estimated 'time-to-benefit- from statins when deciding to initiate therapy leading to variation in practice.[11] This becomes relevant in frail older adults where reduced physiological reserve may affect both the benefits and harms of treatment. Hence, understanding how frailty influences statin prescription can help optimize cardiovascular care in an aging population. The interaction between frailty and diabetes in the context of statin use also remains unexplored. To help improve stroke care for older persons, it underscores the need for further incorporation of geriatric-related issues like frailty and how it relates to other risk factors like diabetes. By examining these factors, this study seeks to enhance understanding of how frailty and diabetes influence clinical decision making such as prescribing habits.

Aim

This study aimed to examine the association of frailty and the prescriptions of statins in older participants with stroke, and compare statin prescription rates and the impact of frailty on the prescriptions of statins between participants with and without type 2 diabetes.

Ethics approval

Ethics approval was obtained from the Medical Research Ethics Committee of the University Hospital (MEC No: 201312 – 0636).

Methods

Data source and setting

We used data from an observational study on the prevalence of pre-stroke frailty and its impact on outcomes in 384 older patients (aged 65 years or over) in Malaysia from 2016 to 2020. This database also had data on frailty status of the patient post-stroke and prior to discharge from hospital. Further details of the study was described elsewhere.[12] For the purposes of this analysis, only patients with ischaemic stroke (n=336) were included.

Participants

Participants' characteristics such as the socio-demographics, comorbidities including diabetes, and post-stroke function, were obtained from electronic medical records. All cases of diabetes in this study were type 2 diabetes. Disability at discharge was defined with a Modified Rankin Scale (MRS) of 3 or above. Frailty was defined according to the Clinical Frailty Scale (CFS) version 2.0. The CFS v2.0 score ranges from 1-9 and a cut-point of 4 was applied to define frailty.[13]

Outcomes

Information on prescribed medications was obtained from the hospital electronic discharge summary system by a trained research assistant. Information collected included number of medicines, name of medicine together with dose, frequency and route. Statin use was defined as the prescriptions of any statin medication. In this study, the types of statins that were prescribed included atorvastatin, rosuvastatin, and simvastatin. Polypharmacy was defined as the presence, on prescriptions at hospital discharge, of five or more medications.[14]

Statistical analysis

Continuous variables are presented as mean and standard deviation (SD), and categorical variables as frequency and percentage. Comparisons between participants with and without diabetes were assessed using the Chi-square test or Fisher's exact test for categorical variables and Student's t-test

or Mann-Whitney test for continuous variables. Two-tailed p-values < 0.05 were considered statistically significant.

To examine the relationship between frailty and the prescription of statins, odds ratios (ORs) were estimated from logistic regression models, unadjusted and adjusted for pre-defined covariates that may affect statin prescriptions, including age, sex, comorbidity burden (the Charlson Comorbidity Index), dyslipidemia, history of previous stroke, polypharmacy, and disability at discharge (MRS ≥3) . Frailty was treated as a continuous variable (CFS score). Results are presented as ORs and 95% confidence intervals (CIs) for all participants, and for those with and without diabetes.

Analysis of the data was performed using SPSS 29.0.

Results

A total of 282 participants with data of frailty assessment and medication prescriptions upon discharge were included (150 without diabetes, 132 with diabetes). They had a mean age of 80.8 (SD 6.3) years and 57.4% were female. Table 1 presents the participant general characteristics, stratified by diabetes. The mean CFS score was 6.1 (SD 1.1) in all participants, 6.0 (SD 1.1) in participants without diabetes, and 6.2 (SD 1.0) in participants with diabetes (p=0.099). The percentages of frailty (defined with a CFS ≥4) were 97.2% in all participants, 96.0% in those without diabetes vs 98.5% in those with diabetes (p=0.290).

In terms of comorbidities, the mean Charlson Comorbidity Index was 5.9 (SD 1.9) in all participants, 5.2 (SD 1.7) in participants without diabetes, and 6.7 (SD 1.9) in participants with diabetes (p<0.001). Participants with diabetes had higher prevalence of hypertension (91.7% vs 74.7% in those without diabetes, p<0.001) and coronary artery disease (26.5% vs 11.3% in those without diabetes, p=0.001). Polypharmacy was more common in participants with diabetes (56.1% vs 27.3% in those without diabetes, p <0.001). Participants with diabetes had a significant longer hospitalization, with a mean length of stay of 20.7 days (SD 27.1) vs 14.9 days (SD 11.4) in those without diabetes (p=0.018).

Table 2 presents the prescriptions of statins and other cardiovascular medicines in the participants. Overall, statin was the most commonly prescribed medication at discharge (69.0%), followed by antiplatelets (65.5%), calcium channel blockers (38.4%), angiotensin converting enzyme inhibitors/angiotensin receptor blockers (19.6%) and beta-blockers (18.9%) (Figure 1). There was no significant difference on statin prescription rates between participants with and without diabetes (71.0% vs. 67.3%, respectively, p=0.508).

The unadjusted and adjusted odds ratios of frailty and other covariates on statin prescriptions in all participants, without diabetes and with diabetes are presented in Table 3.

On the adjusted models, increased CFS score was significantly associated with reduced odds of receiving statins in all participants (adjusted OR 0.64, 95% CI 0.46 -0.88), and in participants without diabetes (adjusted OR 0.54, 95% CI 0.33 – 0.89), but not in participants with diabetes (adjusted OR 0.73, 95%CI 0.46 – 1.17).

Among the covariates, factors that were significantly associated with statin prescriptions in participants with diabetes included dyslipidemia (adjusted OR 3.22, 95%CI 1.20 – 8.69), disability at discharge (adjusted OR 65.40, 95%CI 4.40 – 971.73), and polypharmacy (adjusted OR 2.90, 95%CI 1.19 – 7.09). In participants without diabetes, the only covariate that was significantly associated with statin prescriptions were age (adjusted OR 0.93, 95%CI 0.87 – 0.99 for each year increase in age).

Discussion

In our study, only 69.0% of the participants were prescribed statins and frailty was observed to reduce the likelihood of receiving statins in older adults with ischemic stroke. The impact of frailty on the reduced prescription of statins was significant in participants without diabetes compared to those with diabetes.

Our findings are in line with previous studies on statins in patients with strokes. Several studies have reported the underuse of statins in patients post strokes. A study in Finland found that statin was not used by more than 25% of ischemic stroke patients within 90 days after hospital discharge, with women and older patients using statins less frequently.[15] Another study of 220 older adults with atherosclerotic cardiovascular disease in a tertiary hospital in Saudia Arabia[16] also reported an under-prescription of statins, with only 59.5% on the therapy. Compared to our study, participants in the Saudi Arabia study were slightly younger (mean age 75 $\pm$ 7) and investigators did not include patients with diabetes and further explore impact of frailty.

There are several reasons that may explain the reduced prescription of statins in older patients, particularly in those with frailty. Frail older adults have an inherent risk of polypharmacy.[17] In our study, polypharmacy was present in more than a third of the study population. As polypharmacy may also sometimes influence adherence and increase the risk of drug-drug interactions, prescribers may prioritize certain medicines over others depending on risk-benefit ratios. This could be done as well to help simplify patients' medication management plan and improve overall treatment adherence. In addition, there has been some controversy on the use of statins in older people. In older individuals, changes in liver and kidney function can alter drug metabolism and clearance, increasing the risk of adverse effects of statins, such as myopathy, myalgias, muscle weakness, injuries, and cognitive dysfunction.[18] This could increase the risk of falls[19], especially in frail older adults who are already at high fall risk. There was also some concern about the potential increased risk of haemorrhagic stroke with statin use.[20] Even so, two meta-analyses published in 2022 and 2024 reported no increase in the risk of haemorrhagic stroke associated with statins.[21,22] However, the investigators of these meta-analyses did not take frailty into account in their analyses. In a study of 1665 older Australian men in the Concord Health and Ageing in Men Project[23], Gnjidic and colleagues found a lack of independent association between the use of statins and institutionalisation or mortality in older and frail men. In a study examining new statin use among older veterans in USA, Orkaby and colleagues also found no significant difference in mortality

outcomes between frail and non-frail individuals.[24] These studies suggest that frailty should not be considered as a "contraindication" for statin use in frail adults.

The absence of a significant association between frailty and statin prescriptions among participants with diabetes may result from the small sample size. However, it may also suggest a difference in prescription patterns among stroke patients with and without diabetes. In our study, among participants without diabetes, age and frailty were the only factors that were associated with statin prescriptions: advanced age and higher levels of frailty reduced the odds of receiving statins. In contrast, these two factors did not significantly affect statin prescriptions among participants with diabetes, while factors such as dyslipidemia and the consequences of strokes (as reflected by disability at discharge) may have a stronger influence on clinicians' decisions of prescribing. Diabetes is a risk factor for cardiovascular events, hence post-stroke older patients with diabetes require careful management compared to those without this condition. There has been evidence that the lack of statins early after ischemic stroke was associated with increased probability of poor health outcomes.[15] Whether this is true for frail older adults is yet to be seen. Further studies are needed to understand the perspectives of clinicians in prescribing statins for stroke prevention in older individuals with frailty and diabetes post ischemic strokes. This understanding can ultimately guide more tailored and effective management strategies for this vulnerable group.

Strength and limitation

To the best of our knowledge, our study is the first to show the influence of frailty on statin prescription and the potential interaction between frailty and diabetes in older Malaysians with ischemic stroke. However, this study has some limitations. Data of serum cholesterol levels and medication use prior to admission were not obtained. Additionally, there was no information available regarding factors that could be contraindications for statin use, such as abnormal liver function or a previous history of adverse effects. Due to the cross-sectional nature of study, we were unable to explore the impact of these interactions on adverse outcomes such as re-hospitalization or

mortality. The study was conducted at a single tertiary hospital and findings may not be representative of all older patients with stroke in Malaysia.

Conclusion

This study in older Malaysians post ischemic stroke showed that frailty was associated with reduced odds of receiving statins. The differences in the relationship between frailty and statin prescription among participants with and without diabetes may suggest a personalized approach in secondary prevention for older patients after strokes. Future studies should include longitudinal outcomes to help clarify the usefulness of statin in secondary prevention post ischemic stroke, particularly among frail older adults with diabetes. Prescribers' perspectives could also be sought to better understand risk-benefit consideration, aiding in the development of personalized healthcare for older individuals.

Author contributions

Wei Jin Wong and Tu Nguyen conceived the study and all authors contributed to the study design. Kit Mun Tan and Mei Shin Yau acquired the data. Wei Jin Wong and Tu Nguyen analyzed the data. All authors interpreted the data. Wei Jin Wong drafted the manuscript. All authors critically revised the manuscript. The final version was approved by all authors.

Conflict of interest

None to declare

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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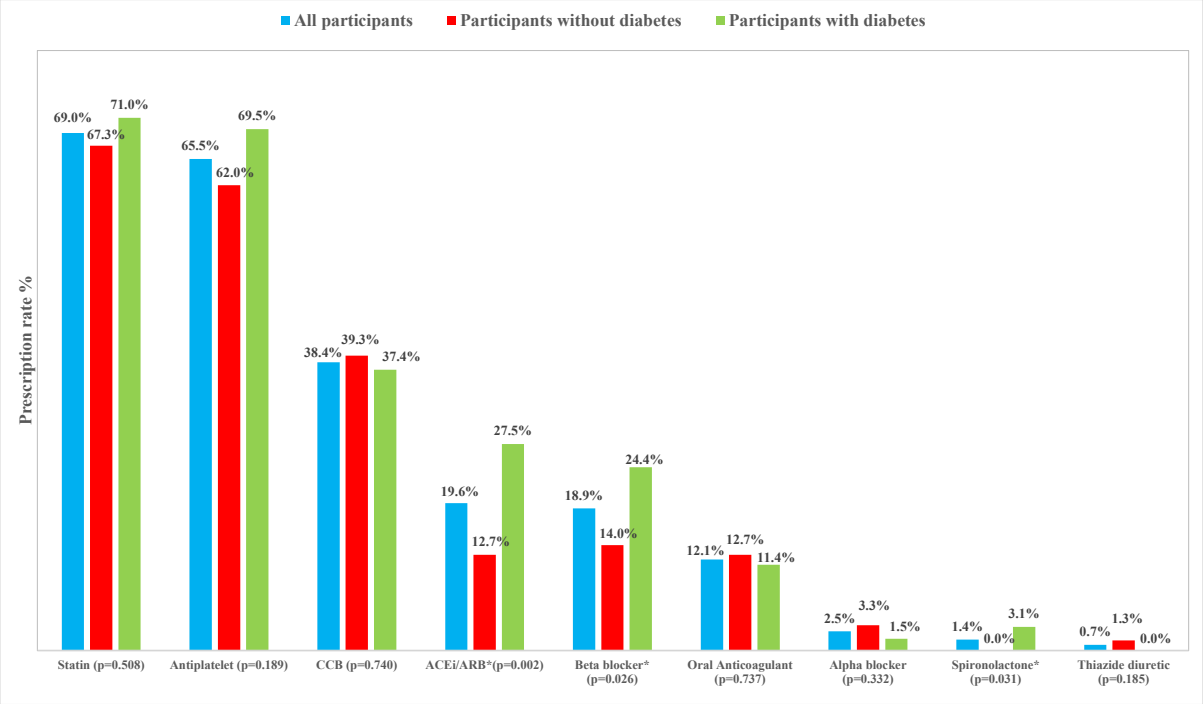
Figure 1. Prescription rates of cardiovascular medications among the participants



*p < 0.05

Table 1. Patient Characteristics.

Variables	All participants (N = 282)	Participants without diabetes (N = 150)	Participants with diabetes (N = 132)	P-value
Age (Mean)	80.8 ± 6.3	81.4 ± 6.1	80.1 ± 6.4	0.082
Ethnicity				
Malay	64 (22.7%)	34 (22.7%)	30 (22.7%)	0.338
Chinese	146 (51.8%)	84 (56.0%)	62 (47.0%)	
Indian	68 (24.1%)	30 (20.0%)	38 (28.8%)	
Others	4 (1.4%)	2 (1.3%)	2 (1.5%)	
Female	162 (57.4%)	87 (58.0%)	75 (56.8%)	0.841
Male	120 (42.6%)	63 (42.0%)	57 (43.2%)	
Smoking	18 (6.5%)	11 (7.3%)	7 (5.4%)	0.518
Polypharmacy	115 (40.8%)	41 (27.3%)	74 (56.1%)	<0.001
Predischarge CFS score	6.1 ± 1.1	6.0 ± 1.1	6.2 ± 1.0	0.099
Predischarge CFS score ≥4	274 (97.2%)	144 (96.0%)	130 (98.5%)	0.290
Charlson Comorbidity Index	5.9 ± 1.9	5.2 ± 1.7	6.7 ± 1.9	<0.001
History of Stroke	100 (35.7%)	48 (32.4%)	52 (39.4%)	0.225
Hypertension	233 (82.6%)	112 (74.7%)	121 (91.7%)	<0.001
Dyslipidemia	121 (42.9%)	63 (42.0%)	58 (43.9%)	0.743
AF	61 (21.6%)	31 (20.7%)	30 (22.7%)	0.675
CCF	10 (3.5%)	3 (2.0%)	7 (5.3%)	0.135
CAD	52 (18.4%)	17 (11.3%)	35 (26.5%)	0.001
PVD	7 (2.5%)	3 (2.0%)	4 (3.0%)	0.579
CKD (GFR <60mL/min)	107 (37.9%)	55 (36.7%)	52 (39.4%)	0.638
Disability at discharge (MRS ≥ 3)	261 (92.6%)	135 (90.0%)	126 (95.5%)	0.082

Length of stay (days)	17.6 ± 20.5	14.9 ± 11.4	20.7 ± 27.1	0.018
Discharge Nursing Home	33 (11.7%)	14 (9.3%)	19 (14.4%)	0.187

Data are shown as n (%) for categorical variables and mean with standard deviation for continuous variables. AF: Atrial Fibrillation, CCF: Congestive Cardiac Failure, CAD: Coronary Artery Disease, PVD: Peripheral Vascular Disease, CKD: Chronic Kidney Disease, MRS: Modified Rankin Scale

Table 2. Prescription rate of cardiovascular medicines in participants with and without diabetes.

Medications	All participants (N=282)	Participants without diabetes (N= 150)	Participants with diabetes (N= 132)	p-value
Statin	194 (69.0%)	101 (67.3%)	93 (71.0%)	0.508
Antiplatelets	184 (65.5%)	93 (62.0%)	91 (69.5%)	0.189
CCB (non-DHP & DHP)	108 (38.4%)	59 (39.3%)	49 (37.4%)	0.740
ACEI/ARB	55 (19.6%)	19 (12.7%)	36 (27.5%)	0.002
Beta blocker	53 (18.9%)	21 (14.0%)	32 (24.4%)	0.026
Oral anticoagulants	34 (12.1%)	19 (12.7%)	15 (11.4%)	0.737
Alpha blocker	7 (2.5%)	5 (3.3%)	2 (1.5%)	0.332
Spironolactone	4 (1.4%)	0 (0%)	4 (3.1%)	0.031
Thiazide	2 (0.7%)	2 (1.3%)	0 (0%)	0.185

ACEI: Angiotensin Converting Enzyme Inhibitor, ARB: Angiotensin Receptor Blocker, CCB: calcium channel blocker, DHP: dihydropyridines, Antiplatelet: aspirin, clopidogrel, Oral anticoagulants: warfarin, dabigatran, apixaban, rivaroxaban

Table 3. Unadjusted and adjusted odds ratios of frailty and other covariates on statin prescriptions in all participants, without diabetes and with diabetes

Variables	All participants				Participants without diabetes				Participants with diabetes			
	Unadjusted ORs (95%CI)	**p**	**Adjusted ORs (95%CI)**	**p**	**Unadjusted ORs (95%CI)**	**p**	**Adjusted ORs (95%CI)**	**p**	**Unadjusted ORs (95%CI)**	**p**	**Adjusted ORs (95%CI)**	**p**
CFS score	0.78 (0.61 – 1.02)	0.065	0.64 (0.46 – 0.88)	**0.006**	0.68 (0.47 – 0.96)	0.030	0.54 (0.33 – 0.89)	**0.016**	0.94 (0.63 – 1.40)	0.746	0.73 (0.46 -1.17)	0.193
Age	0.97 (0.93 – 1.01)	0.164	0.97 (0.93 – 1.02)	0.242	0.95 (0.89 - 1.00)	0.057	0.93 (0.87 – 0.99)	**0.046**	1.00 (0.95 – 1.06)	0.927	1.02 (0.95 – 1.10)	0.530
Male (vs. female)	0.81 (0.49 – 1.34)	0.410	0.68 (0.39 – 1.17)	0.166	0.84 (0.42-1.67)	0.617	0.51 (0.23 – 1.12)	0.092	0.77 (0.36 – 1.64)	0.495	0.82 (0.35 -1.90)	0.639
Charlson comorbidity index	1.03 (0.90 – 1.17)	0.707	0.98 (0.83 – 1.16)	0.813	0.93 (0.77 – 1.14)	0.493	0.98 (0.76 – 1.26)	0.877	1.10 (0.89 – 1.35)	0.376	0.88 (0.67 – 1.17)	0.381
Dyslipidemia	1.77 (1.04 – 2.99)	0.034	1.86 (1.04- 3.32)	**0.036**	1.38 (0.69 – 2.79)	0.364	1.76 (0.77 -4.03)	0.181	2.40 (1.07 – 5.40)	0.034	3.22 (1.20 – 8.69)	**0.021**

History of stroke	1.07 (0.63 – 1.81)	0.814	0.99 (0.55 – 1.79)	0.980	1.13 (0.54 – 2.37)	0.739	1.20 (0.51 – 2.83)	0.669	0.97 (0.45 – 2.10)	0.935	0.96 (0.39 – 2.35)	0.924
Disability at discharge (MRS ≥ 3)	1.22 (0.47 – 3.17)	0.686	3.75 (1.06 – 13.22)	**0.040**	0.48 (0.13-1.8)	0.279	2.22 (0.37 -13.26)	0.381	10.82 (1.17-100.29)	0.036	65.40 (4.40 – 971.73)	**0.002**
Polypharmacy	1.71 (1.01 - 2.92)	0.047	1.86 (1.03 – 3.34)	**0.039**	1.24 (0.57 – 2.71)	0.587	1.68 (0.69 – 4.11)	0.255	2.28 (1.06 – 4.91)	0.036	2.90 (1.19 – 7.09)	**0.019**

Chapter 8

Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease – An observational study in Vietnam

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RESEARCH ARTICLE

Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease—An observational study in Vietnam

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Abstract

Objectives: This study sought to quantify the prevalence of frailty among type 2 diabetes (T2D) patients with coronary heart disease (CHD) and examine the relationship between frailty and the prescription of secondary prevention medications.

Methods: A prospective observational study was conducted at a tertiary hospital in Vietnam from November 2022 to June 2023. Patients aged 60 years or above with T2D and CHD were included for analysis. Multivariable logistic regression was applied to examine the association between frailty and the prescription of secondary prevention medications: antiplatelets, statins, beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEIs/ARBs). Frailty was measured using the Clinical Frailty Scale (CFS) version 2.0.

Results: There were 274 participants included in this analysis. Participants had a median age of 72.0 years, 28% were female and 59% were frail. The prescription rates of cardiovascular medicines for frail versus non-frail participants were as follows: antiplatelets (66% vs. 94%, $p < .001$), statins (96% vs. 92%, $p = .21$), beta-blockers (81% vs. 88%, $p = .13$), ACEIs/ARBs (75% vs. 81%, $p = .22$) and for all four types (42% vs. 64%, $p < .001$). In the multiple adjusted regression models, increased CFS score was associated with reduced prescriptions of beta-blockers, ACEIs/ARBs and all four types of medications.

Conclusions: Frailty was common among older Vietnamese patients with CHD and diabetes, and significantly affected the prescription of secondary prevention medicines. Future research should explore the link between frailty and secondary prevention medicines in a larger, more diverse population.

KEYWORDS

cardiovascular disease, frailty, prescriptions, secondary prevention, Vietnam

1 | INTRODUCTION

Coronary heart disease (CHD) is one of the main causes of death and disability in high-income countries, especially in older people.[1] In lower-income countries, there is an increasing prevalence of CHD with the increasing life span and prevalence of lifestyle risk factors in the region.[2] One of the challenges with CHD is the influence of modifiable and non-modifiable risk factors that can contribute to it. Non-modifiable risk factors include age, sex and family history. Modifiable risk factors, including high blood pressure, dyslipidaemia, diabetes and smoking, can be managed through non-pharmacological strategies like lifestyle changes or through pharmacological agents, with proven benefits.[3] Individuals with diabetes are also more likely to experience CHD than those without diabetes.[1,4] In patients with a diagnosis of CHD, secondary prevention is a key strategy to reduce the risk of cardiac events and mortality.[1] Antiplatelets, statins, beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are recommended as secondary prevention medications for patients with CHD.[3]

The increasing prevalence of frailty among older adults has been shown to complicate outcomes and present additional challenges.[5] Frailty-related variations in pharmacokinetics and pharmacodynamics can impact the effectiveness and safety of cardiovascular medications, potentially influencing prescribers' decisions.[6,7] To help close knowledge gaps in cardiovascular care for older adults, recommendations have been proposed for research in specific areas, such as the appropriate use of medications in older patients.[8] Furthermore, recent calls have also been made to consider frailty status when providing care for older people.[7,9]

Like its neighbouring countries in Southeast Asia, Vietnam is experiencing a growing population of older people together with a growing economy. Additionally, recent studies have also highlighted the growing prevalence of diabetes.[10] In Vietnam, there have been several studies on frailty in older people in clinical settings and in the community. The prevalence of frailty is quite high in older patients in Vietnam, particularly in those with cardiovascular disease.[11–17] The prevalence of frailty in Vietnam ranges from 11% to 22% in the community, while in hospitals estimates range from 19% to 55%.[11–19] However, there is limited evidence about frailty in older Vietnamese people with diabetes, and there have been no studies examining the association between frailty and the prescriptions of cardiovascular medicines in this population. The aim of this study was to quantify the prevalence of frailty and to examine the association between frailty and the prescription of secondary prevention medications for cardiovascular disease among patients with both diabetes and CHD in Vietnam.

Practice impact

This study showed that frailty significantly affected the prescription of secondary prevention medicines, especially beta-blockers and ACEIs/ARBs. Future longitudinal studies would be useful in exploring how frailty can be optimised to improve cardiovascular care for older persons.

2 | METHODS

This study was a secondary analysis based on a primary study investigating medication adherence in older patients with chronic CHD in Vietnam. In brief, this prospective observational study was conducted at the cardiovascular outpatient clinics of Thong Nhat Hospital, a tertiary hospital in Ho Chi Minh City from November 2022 to June 2023. A total of 643 consecutive patients aged 60 years or above with chronic CHD who visited the clinics during the study period were recruited. From the study dataset, participants with type 2 diabetes were included in this analysis.

Based on previously published studies in Vietnam,[15] we assumed that the prescription rates of each type of secondary prevention medication (antiplatelets, statins, beta-blockers and ACEIs/ARBs) in older patients with CHD would be around 60%–70% and there would be about a 20% difference between the frail and non-frail. Therefore, we estimated that a sample size of at least 186 participants (93 frail and 93 non-frail) would enable the detection of a significant difference in the prescription rates between frail and non-frail (at 80% power, 5% significance level).

2.1 | Variable definitions

Frailty was defined according to the Clinical Frailty Scale (CFS) version 2.0. The CFS score ranges from 1 to 9, with a score of 4 or above indicating the presence of frailty.[20]

Information on secondary prevention medications for cardiovascular disease was obtained from the hospital discharge summary and categorised into: antiplatelets (aspirin, clopidogrel, ticagrelor and prasugrel), statins (atorvastatin, rosuvastatin and simvastatin), beta-blockers (bisoprolol, metoprolol and nebivolol) and ACEIs/ARBs (captopril, imidapril, lisinopril, perindopril, candesartan, losartan, irbesartan, telmisartan and valsartan).

Polypharmacy was defined as the presence, on prescriptions at hospital discharge, of five or more medications.

Age and sex were as recorded in medical records. Body mass index (BMI, kg/m^2) was calculated from measured weight (kg) and height (m) and was classified into four groups: underweight (BMI < 18.5 kg/m^2), normal (BMI 18.5–22.9 kg/m^2), overweight (BMI 23–24.9 kg/m^2) and obese (BMI ≥ 25.0 kg/m^2). Smoking status was categorised based on self-report as non-smoking or smoking. Low educational status was defined as having completed only primary school or being illiterate.

Information on the history of cardiovascular conditions other than CHD (hypertension, dyslipidaemia, heart failure, atrial fibrillation, ischemic stroke, peripheral artery disease, chronic kidney disease, percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery [CABG]) was obtained from medical records.

2.2 | Statistical analysis

Continuous variables are presented as mean (standard deviation), and categorical variables as frequency and percentage. Comparisons between frail and non-frail participants were assessed using the χ^2 test or Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney test for continuous variables. Two-tailed *p*-values <.05 were considered statistically significant.

To examine the relationship between frailty and the prescription of secondary prevention medications, odds ratios (ORs) were estimated from logistic regression models, unadjusted and adjusted for pre-specified covariates chosen based on clinical judgement, including age, sex, socioeconomic conditions (education level, living alone and having public health insurance) and total number of medications used. Frailty was treated as a continuous variable (CFS score) in the models. Models involved antiplatelets, and all four types of secondary prevention medications were also adjusted for anticoagulant use, as patients who are on oral anticoagulants usually do not receive antiplatelets. Five separate models were fitted for (1) antiplatelets, (2) statins, (3) beta-blockers, (4) angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEIs/ARBs) and (5) all four types of these prevention medications. Data analysis was performed using SPSS 27.0 and R 4.4.1.

2.3 | Ethics approval

The study was approved by the Ethics Committees of the University of Medicine and Pharmacy at Ho Chi Minh City (reference number: 936/HDDD-DHYD; date: 24 November 2022). Informed consent was obtained from all participants. This study was compiled in accordance with the Declaration of Helsinki.

3 | RESULTS

A total of 274 participants with diabetes and CHD were included in this analysis. They had a median age of 72.0 years, and 28% were female. Most participants were retired (95%), had public health insurance (97%), and 11% were living alone. More than half of the participants had above normal BMI—overweight (29%) or obese (31%), 97% had a history of hypertension, 95% had dyslipidaemia, and 67% received revascularisation therapy previously (64% PCI and 3% CABG). The prevalence of polypharmacy was very high (97%).

The prevalence of frailty was 59% (161/274). The distribution of the CFS score is presented in Figure 1. Frail participants were older compared to non-frail participants (median age 75.0 vs. 68.0 years, $p < .001$) (Table 1). There was a higher percentage of low educational status (21% vs. 10%), sedentary lifestyle (85% vs. 53%) and history of PCI (79% vs. 54%) in frail participants compared to the non-frail group. The prevalence of atrial fibrillation was significantly higher in frail participants (37%) compared to the non-frail (8%), $p < .001$. The percentages of participants using oral anticoagulants for stroke prevention associated with atrial fibrillation were significantly higher in the frail group (34%) compared to the non-frail group (5%), $p < .001$.

3.1 | Prescription rates of secondary prevention medications for cardiovascular disease

Overall, 51% of the participants were prescribed all four types of secondary prevention medication, and the prescription rate was significantly lower in the frail group (42%) compared to the non-frail group (64%), $p < .001$ (Table 2). Among the four types of secondary prevention medication, there was no significant difference in the prescription rate of statins (96% in the frail group vs. 92.0% in the non-frail group, $p = .21$), beta-blockers (81% in the frail group vs. 88% in the non-frail group, $p = .13$) or ACEIs/ARBs (75% in the frail group vs. 81% in the non-frail group, $p = .22$), but the prescription of antiplatelets was lower in frail participants (66% in the frail group vs. 94% in the non-frail group, $p < .001$).

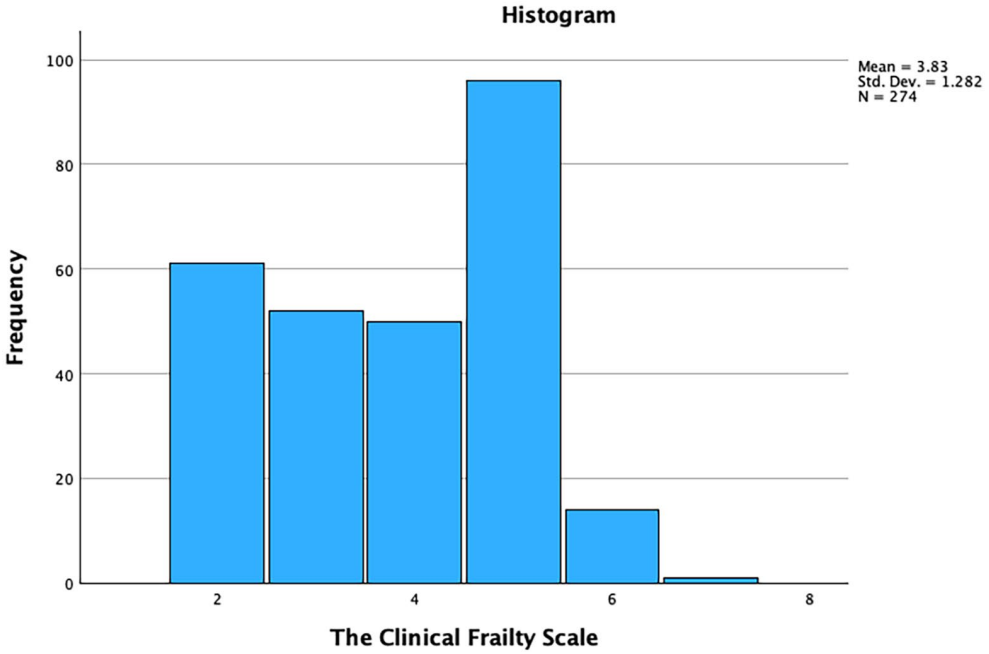

FIGURE 1 Distribution of the Clinical Frailty Scale (CFS).

3.2 | The association between the CFS score and the prescription of secondary prevention medications for cardiovascular disease

The relationship between CFS score and the prescription of secondary prevention medications is presented in Table 3. In the unadjusted models, for every 1 point increase in the CFS, we saw an OR of .54 (95% CI: .42–.71) for antiplatelets, .75 (95% CI: .58–.98) for beta-blockers, .90 (95% CI: .72–1.12) for ACEIs/ARBs, 1.14 (95% CI: .77–1.69) for statins and .74 (95% CI: .61–.90) for all 4 types of prevention medications. In the adjusted models, increased CFS score was still significantly associated with reduced prescriptions of beta-blockers, ACEIs/ARBs and all four types of medications (Table 3).

4 | DISCUSSION

In this study, more than half of older participants with diabetes and CHD had frailty (59%). Frailty reduced the likelihood of prescription of all four types of cardiovascular secondary prevention medications, and particularly of beta-blockers and ACEIs/ARBs.

The prevalence of frailty in our study is higher compared to other studies in the general population. This could be explained by differences in the study populations and the frailty definition used. The CFS has been shown to identify a higher prevalence of frailty compared to other frailty definitions.[21,22] Globally, Collard et al. reported that the overall prevalence of frailty in community-dwelling adults was 11%.[23] In a study involving 17 Asian countries (China, Hong Kong, Taiwan, India, Indonesia, Japan, Lebanon, Malaysia, Nepal, Singapore, South Korea, Sri Lanka, Thailand, Turkey, Vietnam, Saudi Arabia, Iran), the prevalence of frailty in the general population was reported to be 21%, with a range from 6% to 46%.[24] In European populations, a meta-analysis of 62 studies from 22 European countries showed that the prevalence of frailty was 18%, ranging from 12% in community-based studies to 45% in non-community-based studies.[25] A separate meta-analysis, including 31,343 adults in the United States, Switzerland, Sweden, Brazil, Taiwan, Italy, United Kingdom, Spain, France and Canada, found that frailty and pre-frailty were associated with an increased risk of any type of cardiovascular disease and higher risk of cardiovascular mortality.[26] These studies highlight the growing prevalence of frailty and its impact on cardiovascular outcomes globally. Frailty and cardiovascular disease share similar underlying pathophysiological conditions, and this may sometimes confound the association between them.[27] In another study of two prospective cohorts, the China Health and Retirement Longitudinal Study and the English Longitudinal Study of Ageing, frailty was associated with an increased risk of cardiovascular disease and all-cause mortality in patients with pre-diabetes and diabetes.[28]

Our finding of the relationship between frailty and prescription of secondary prevention medications aligns

TABLE 1 Participants characteristics by frailty status.

Characteristic	All participants ($n=274$)	Non-frail participants ($n=113$)	Frail participants ($n=161$)	p-Value (frail vs. non-frail)
Age (median and range)	72.0 (60–93)	68.0 (60–90)	75.0 (60–93)	<.001
CFS score	3.8 (1.3)	2.5 (.5)	4.8 (.6)	<.001
Sex				
Female	76 (28)	13 (12)	63 (39)	<.001
Male	198 (72)	100 (89)	98 (61)	
Working status				
Retired	261 (95)	105 (93)	156 (97)	.13
Working	13 (5)	8 (7)	5 (3)	
Carer				
None (living alone)	31 (11)	15 (13)	16 (10)	.007
Spouse	196 (72)	89 (79)	107 (67)	
Children	39 (14)	6 (5)	33 (21)	
Other	8 (3)	3 (3)	5 (3)	
Having public health insurance	267 (97)	112 (99)	155 (96)	.25
Education				
Illiterate	4 (2)	0 (.0)	4 (3)	.004
Primary school	39 (15)	11 (10)	28 (18)	
Secondary school	8 (3)	2 (2)	6 (4)	
High school	89 (34)	32 (29)	57 (37)	
Higher education	125 (47)	67 (60)	58 (38)	
Body mass index				
Underweight	6 (2)	2 (2)	4 (3)	.90
Normal	105 (38)	45 (40)	60 (37)	
Overweight	78 (29)	30 (27)	48 (30)	
Obese	85 (31.0%)	36 (32)	49 (30)	
Smoking				
Non-smoking	135 (49)	34 (30)	101 (63)	<.001
Current smoking	28 (10)	17 (15)	11 (7)	
Ex-smoking	111 (41)	62 (55)	49 (30)	
Alcohol consumption	17 (6)	6 (5)	11 (7)	.61
Sedentary lifestyle	197 (72)	60 (53)	137 (85)	<.001
Total number of medications	7.3 (1.8)	7.2 (1.6)	7.4 (1.9)	.58
Polypharmacy (using ≥5 medications)	267 (97)	112 (99)	155 (96)	.25
Cardiovascular history				
Hypertension	266 (97)	111 (98)	155 (96)	.48
Dyslipidaemia	259 (95)	110 (97)	149 (93)	.1
Peripheral artery disease	77 (28)	34 (31)	43 (27)	.50
Atrial fibrillation	68 (25)	9 (8)	59 (37)	<.001
Heart failure	52 (19)	22 (20)	30 (19)	.86
Chronic kidney disease	30 (11)	8 (7)	22 (14)	.09
Ischemic stroke	20 (7)	7 (6)	13 (8)	.56
PCI	176 (64)	89 (79)	87 (54)	<.001
CABG	8 (3)	3 (3)	5 (3)	>.99

Note: Continuous data are presented as mean (standard deviation). Categorical data are shown as *n* (%).

Abbreviations: CABG, coronary artery bypass graft surgery; CFS, Clinical Frailty Scale; PCI, percutaneous coronary intervention.

TABLE 2 Prescriptions of secondary prevention medicines by frailty status.

Medication types	All participants ($n=274$), n (%)	Non-frail ($n=113$), n (%)	Frail ($n=161$), n (%)	p
Antiplatelets	212 (77)	106 (94)	106 (66)	<.001
Statins	258 (94)	104 (92)	154 (96)	.21
Beta-blockers	229 (84)	99 (88)	130 (81)	.13
ACEIs/ARBs	213 (78)	92 (81)	121 (75)	.22
All four types (antiplatelets, statins, beta-blockers, ACEIs/ARBs)	140 (51)	72 (64)	68 (42)	<.001

Abbreviations: ACEI, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

TABLE 3 Relationship between the CFS score and the prescription of secondary prevention medications.

	Unadjusted model		Adjusted model 1		Adjusted model 2	
Secondary prevention medications	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Antiplatelets	.54 (.42–.71)	<.001	.57 (.43–.76)	<.001	.79 (.46–1.36)	.39
Statins	1.14 (.77–1.69)	.51	1.19 (.75–1.89)	.45	1.33 (.79–2.25)	.29
Beta-blockers	.75 (.58–.98)	.04	.72 (.53–.96)	.03	.68 (.50–.93)	.02
ACEIs/ARBs	.90 (.72–1.12)	.34	.74 (.57–.97)	.03	.71 (.55–.95)	.02
All four types	.74 (.61–.90)	.002	.68 (.54–.84)	<.001	.76 (.59–.98)	.04

Note: Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, socio-economic conditions (low education, living alone and public health insurance), total number of medications used. Models involved antiplatelets and all four types of secondary prevention medications were also adjusted for anticoagulant use.

Abbreviation: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers.

with published studies worldwide. A systematic review of 16 cohort studies (145,668 participants) examining the prescribing of cardioprotective medicines post-myocardial infarction found that in most studies, the prescription rates of antiplatelets, lipid-lowering therapies, ACEIs/ARBs and beta-blockers postmyocardial infarction were lower in the frail patients compared to non-frail patients.[29] In Vietnam, increasing frailty prevalence with poorer health outcomes has been reported in patients with cardiovascular disease and diabetes.[15,16] In a study of 324 older participants with acute coronary syndrome in Vietnam, frailty was present in 48% of the study sample and was significantly associated with a higher risk of arrhythmia, in-hospital mortality, 30-day mortality and 30-day readmission.[15] In another Vietnamese study by Pham and colleagues, in older patients with acute coronary syndrome, the prevalence of frailty was found to be 33%.[30] However, there is very limited evidence about the relationship between frailty and the use of secondary prevention medications in older Vietnamese patients, particularly in those with diabetes and CHD. A novel aspect of our study is in its distinct contribution to the body of evidence regarding the prescription of secondary prevention medications in older patients with diabetes and CHD in Vietnam. Our study provides important insights into the local epidemiology and clinical practices. The high prescription rates of prevention medicines in this cohort of older patients with diabetes and CHD (including those with frailty) may reflect adherence to cardiovascular prevention guidelines among clinicians and the translation of evidence into clinical practice. However, the reduced likelihood of being prescribed all four types of preventive medication with increased CFS scores does highlight the potential impact of frailty. Clinicians may assume that frail patients have functional limitations and are less likely to benefit from intensive management of cardiovascular risk factors. Older patients with frailty may have biological changes that could amplify the side effects of medicines like beta-blockers and ACEIs/ARBs. A separate study by Zullo et al. found the use of beta-blockers was associated with increased risk of hypotension and breathlessness in frail older adults.[31] Furthermore, prescribing practices may be influenced by concerns that frail patients might struggle to adhere to complex medication regimens. To manage polypharmacy, medications that are perceived as having a better risk-to-benefit profile could be prioritised over others, especially when frailty is present. However, with growing studies on the reversibility of frailty, future research could investigate

the appropriate combination of preventive medications to improve the use of secondary prevention medications for this population.

The inclusion of frailty screening could be further investigated as a tool to help optimise care for this population. Several studies have explored the incorporation of frailty screening into cardiovascular care.[32] For settings with limited resources, how this is implemented is an opportune area for future research. Our study provides further evidence for the Vietnamese population, and the results of our analysis can be used as a reference for future studies.

This study has some limitations. Since it is a secondary epidemiological analysis, there may be some unmeasured confounding variables, such as income. The inability to control for these confounders can introduce bias and affect the validity of the findings. Information on newer cardioprotective medications, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, was not collected. In addition, the study was conducted at a single site, so the findings may not be generalisable nationally. Differences in hospital resources, patient demographics and clinical practices may influence the observed patterns of medication prescribing, thereby potentially limiting the external validity of the results. Therefore, the findings should be interpreted with caution when considering their application to different health-care systems or policy contexts.

Future multicentred studies would provide a more comprehensive understanding of the relationship between frailty and cardiovascular secondary prevention medication prescribing patterns in older patients with diabetes in Vietnam, thereby improving the generalisability of the findings. Future studies should also explore clinicians' perspectives on how frailty is perceived and influences the decision to prescribe medicines.

5 | CONCLUSIONS

This study found a high prevalence of frailty among older patients with diabetes and CHD. We found that frailty independently affected the prescription of cardiovascular secondary prevention medications in this Vietnamese population. Future research should focus on longitudinally assessing the relationship between frailty and cardiovascular medications in a more diverse and larger population of older patients with diabetes.

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CONFLICT OF INTEREST STATEMENT

Tu Nguyen is an Associate Editor of the Australasian Journal on Ageing. The remaining authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed in the present study are available from the corresponding author on reasonable request.

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Chapter 9

Exploring evidence of SGLT2 inhibitors use in Southeast Asia: A systematic review

Exploring evidence of SGLT2 inhibitors use in Southeast Asia: a systematic review

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Abstract

Background. The benefits of sodium glucose cotransporter 2 (SGLT2) inhibitors are increasingly recognized, not only in the management of diabetes but also in cardiovascular and renal conditions. However, evidence regarding SGLT2 inhibitor use in Southeast Asian populations remains limited and has yet to be systematically reviewed.

Methods. A systematic literature search was conducted in Ovid Medline, Cochrane Central Register of Controlled Trials and Embase from database inception until 21 October 2024. Studies were included if they were conducted in adults living in Southeast Asian countries and contained information on the use of SGLT2 inhibitors.

Results. A total of 23 studies were included. These studies were conducted in only 5 out of 11 countries in the region (Malaysia, Philippines, Singapore, Thailand and Vietnam). Among these 23 studies, 12 were conducted in patients with type 2 diabetes, 7 in patients with heart failure, and 4 in patients with chronic kidney disease. Thirteen studies focused on economic evaluations. Limited evidence from these 5 countries suggests that SGLT2 inhibitors appear to be safe, effective, and are likely to be cost-effective and cost-saving.

Conclusions. Published evidence in Southeast Asian countries showed that SGLT2 inhibitor treatment may offer promising benefits for patients with type 2 diabetes, heart failure and chronic kidney disease. Further research is needed to understand the availability and affordability, as well as the safety, of SGLT2 inhibitors, taking into consideration the effect of ageing and frailty in this region. In addition, key region-specific factors, such as genetic variations, healthcare infrastructure, and cultural considerations remain to be addressed.

Introduction

Sodium glucose cotransporter 2 (SGLT2) inhibitors have become an important, effective choice of therapy for the treatment and management of diabetes.[1,2] These medications work by blocking the reabsorption of glucose and sodium in the renal proximal convoluted tubule, which promotes their excretion and helps manage blood glucose levels effectively.[1] SGLT2 inhibitors were first introduced to clinical practice about a decade ago, beginning with canagliflozin, which received approval from the U.S. Food and Drug Administration in 2013 for the treatment of type 2 diabetes. In 2014, dapagliflozin and empagliflozin were approved, followed by sotagliflozin and bexagliflozin in 2023.[1,2] Beyond its role in glycemic management, SGLT2 inhibitors have also demonstrated significant cardiovascular and renal benefits.[3-5] These benefits include a reduction in major adverse cardiovascular events (MACE), hospitalization for heart failure (HF) and delay in progression of chronic kidney disease (CKD) among patients with type 2 diabetes.[6] In 2019, the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) trial showed that the risk of worsening HF or death from cardiovascular causes was lower among participants who received dapagliflozin treatment compared to placebo.[7] Published in 2022, the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction (DELIVER) trial reported that dapagliflozin reduced the risk of worsening HF or cardiovascular death in patients with HF and a mildly reduced or preserved ejection fraction.[8] The DELIVER Investigators noted the necessity for further research in other populations, such as ethnically diverse groups.[8] Similar findings in patients with HF were also reported with another SGLT2 inhibitor, empagliflozin, in the EMPEROR-Preserved trial.[9] Additionally, SGLT2 inhibitors have also been associated with potential improvements of hepatic steatosis and/or fibrosis in patients with non-alcoholic fatty liver disease.[10] Along with its glycemic benefits, these additional therapeutic effects make

SGLT2 inhibitors an important treatment of choice for diabetes and its associated comorbidities.

While the clinical efficacy and safety of SGLT2 inhibitors have been well-established in Western populations, their use in Southeast Asia warrants further investigation due to the region's unique demographic, genetic, environmental, and healthcare characteristics. The Southeast Asia region is experiencing an increasing burden of type 2 diabetes, driven by rapid urbanization, changes in dietary habits, and decreasing physical activity.[11] With Asia being recognized as the epicentre of the global type 2 diabetes mellitus epidemic, the prevalence of diabetes is particularly evident in Southeast Asia.[12] For example, Indonesia was ranked fifth globally in terms of number of people living with diabetes, with an estimated 19.5 million people in 2021.[13] Type 2 diabetes was also found to have a greater impact as a comorbidity in patients in the Southeast Asia when compared to those in Western countries. For example, Banks et al. reported that diabetes was 3 times more prevalent in Singaporean patients with HF compared to their Swedish counterparts, and more strongly associated with poor outcomes.[14] Southeast Asia also has a high burden of CKD[15] and one of the highest rates of end-stage renal disease (ESRD) in the world.[12] Countries in the Southeast Asia region are also experiencing an ongoing epidemiological transition with a growing population of older people.[16] In older people, the presence of geriatric conditions, such as frailty, multimorbidity, malnutrition, polypharmacy, and disability, can significantly complicate the management of diabetes.[17,18] Concurrently, the region also faces significant healthcare disparities, including varying access to modern medications and healthcare services, especially in rural and lower-income settings.[16]

As identified by O'Hara et al.[19], further exploration is needed regarding the access to, and use of, SGLT2 inhibitors in low- to middle-income countries and underserved populations. Data

examining the use of SGLT2 inhibitors are limited in Southeast Asia. Lifestyle, cultural, social factors and biological traits may influence the uptake and effect of SGLT2 inhibitors. Thus, there is a need for population-specific evaluations in the use of medicines. A recent expert panel statement from Asia-Pacific countries[20] highlighted the low utilization of SGLT2 inhibitors in many countries, despite the growing evidence of their usefulness, particularly in resource-limited settings. Therefore, this paper seeks to review the existing data on the use of SGLT2 inhibitors in Southeast Asian countries in order to provide an update on how SGLT2 inhibitors are currently used in the region.

Methods

A systematic electronic literature search was conducted in the following databases from inception until 21 October 2024: (1) Ovid Medline, (2) Cochrane Central register of controlled trials, and (3) Embase. This review followed the PRISMA guidelines.[21]

The term used for search was 'sodium-glucose transporter 2 inhibitors', which was then combined with the names of the Southeast Asian countries. For this review, Southeast Asian countries that were included follows the regional grouping in the Association of Southeast Asian Nations (ASEAN). The 11 included countries were (in alphabetical order) Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor Leste and Vietnam.

Details of the search strategy are as below:

#1 (Sodium-Glucose Transporter 2 inhibitors) OR (Sodium glucose co-transporter type 2 inhibitor) OR (Sodium glucose cotransporter 2 inhibitor) OR (Sodium dependent glucose cotransporter 2 inhibitor) OR (SGLT-2 inhibitors) OR (Gliflozins) OR (Gliflozin) OR (Canagliflozin) OR (Empagliflozin) OR (Ertugliflozin) OR (Sotagliflozin) OR (Dapagliflozin) OR (Ipragliflozin) OR (Lusegliflozin) OR (Tofogliflozin)

#2 (Brunei) OR (Burma) OR (Burmese) OR (Cambodia) OR (Cambodian) OR (Indonesia) OR (Indonesian) OR (Laos) OR (Malaysia) OR (Malaysian) OR (Myanmar) OR (Philippines) OR (Filipino) OR (Singapore) OR (Singaporean) OR (Southeast Asia) OR (Thailand) OR (Thai) OR (Timor Leste) OR (Vietnam) OR (Vietnamese)

#3 Search: #1 AND #2

Studies were included if (1) they were conducted in countries in Southeast Asia and (2) explored the use of SGLT2 inhibitors. The exclusion criteria were animal studies, abstract only, case reports, and systematic reviews. Multi-country studies that included Southeast Asian countries as part of their study sites were also excluded if they did not provide results for a specific country in Southeast Asia.

Results from the search were managed using Covidence®. Study titles and abstracts were screened independently by two members of the research team, based on the inclusion and exclusion criteria. The full texts of qualified publications were read and selected for the final decision to include after discussion among these two reviewers. Any disagreement was solved by discussion with the third member of the team.

We extracted information on the study design, country/countries where participants were recruited, the type of SGLT2 inhibitors, study populations (sample size, age, the main disease of interest), study aims and findings. For studies conducted in older adults (aged 60 years or above), we also searched for data related to frailty, an important geriatric syndrome that can affect the safety and efficacy of SGLT2 inhibitors.[22] The results of this review were summarized narratively.

Results

Description of the included studies

A total of 23 eligible studies were included in this review, following the screening of 288 publication records (Figure 1). There were 8 from Thailand[23-30], 7 from Malaysia[31-37], 6 from Singapore[38-43], 1 from Philippines[44] and 1 study[45] that was conducted in three Southeast Asian countries (Malaysia, Thailand and Vietnam). Among the included studies, 12 studies were conducted in patients with type 2 diabetes[23-27,31-33,38-41], 7 studies in patients with heart failure[28,29,34-36,42,44], and 4 studies in patients with chronic kidney disease[30,37,43,45]. The types of SGLT2 inhibitors that were used in these studies were canagliflozin, dapagliflozin and empagliflozin (Table 1). In terms of study designs, 9 were observational studies[25-27,32,38-41,43], 1 was a randomized controlled trial[33] and 13 were economic evaluation studies[23,24,28-31,34-37,42,44,45]. The sample sizes of these observational studies ranged from 57[40] to 67,556[38] (with 3 studies[32,40,41] having less than 100 participants). In terms of age, 5 studies[23,28-30,36] were conducted in older adults (aged 60 years or above), while the remaining studies were in adult populations. Among the 5 studies conducted in older adults, there was no data related to frailty.

Economic evaluations

Among the 13 studies that focused on the economic evaluation of SGLT2 inhibitors, 6 studies[31,34,36,37,42,45] were cost-effectiveness analyses, 5 studies[24,28-30,44] were cost-utility analyses, 1 study[23] was a combination of cost-utility and budget impact analysis and 1 study[35] was a budget impact analysis. Overall, 3 studies[23,24,30] adopted a societal perspective as part of their evaluation, while the remaining 10 studies[28,29,31,34-37,42,44,45] utilizing the perspectives of the healthcare systems or providers. Of these 13 studies, 12 studies [23,24,28-31,34,36,37,42,44,45] adopted a discount rate of 3% (in accordance with current practices [46] for economic evaluation). The remaining study was a budget impact analysis[35] that was conducted without discounting as per guidelines.[47] Discount rates are sometimes applied in economic evaluation as costs and

benefits of health interventions may occur at different time points and valued differently.[48] Economic evaluations usually consider a discount rate of 3-6%.[49]

SGLT2 inhibitors were demonstrated to be cost-effective or cost-saving in 11 out of the 13 studies,[28-31,34-37,42,44,45] while 2 studies [23,24] conducted in Thailand suggested that it would not be cost-effective in the Thai context. Deerochanawong et al.[24] conducted an economic evaluation of add-on dapagliflozin in patients with type 2 diabetes and high cardiovascular risk, and found that this was not cost-effective. Similarly, Kongmalai et al.[23] evaluated the addition of SGLT2 inhibitors to standard of care for treating patients with type 2 diabetes and HF and found it to be not cost-effective. Kongmalai et al. proposed a price reduction for SGLT2 inhibitors by 55.6% to make these medications cost-effective.[23] The potential reason for the inconsistent findings of these 2 studies compared to the other 11 studies could be due to the methodology. The societal perspective was applied in these 2 studies, while the healthcare system perspective was adopted in other studies. However, the third study (also conducted in Thailand) that considered a societal perspective showed that the addition of dapagliflozin was cost saving.[30] Vareesangthip conducted a cost-utility analysis of dapagliflozin as an add-on to current therapy in patients with or without T2DM who had an eGFR of 25-75mL/min per 1.73m^2 of body surface area and a urinary albumin-to-creatinine ratio of 200-5000mg/g.[30] In this instance, the benefit of dapagliflozin was slowing the progression of CKD and decreasing the possibility of the need for dialysis and kidney transplantation which offset the costs associated with dapagliflozin therapy.[30]

Safety and efficacy of SGLT2 inhibitors

Of the 23 included studies, 10 studies[25-27,32,33,38-41,43] (9 observational studies and 1 randomized controlled trial) aimed to examine the safety and efficacy of SGLT2 inhibitors in the Southeast Asian populations.

The common side effects of SGLT2 inhibitors reported in these studies were genitourinary infections, like urinary tract infections, hypoglycemia and potential dehydration. Uitrakul and colleagues conducted a study in 853 patients with type 2 diabetes in Thailand and found that the incidence of urinary tract infection was significantly higher in those who used SGLT2 inhibitors than non-users (33.5% vs 11.7%).[26] Regarding dehydration and hypoglycemia, most studies concluded that the risks of these side effects were not increased in SGLT2 inhibitor users compared to non-users, even during fasting periods.[32,33] SGLT2 inhibitor use was also not associated with increased risk of diabetic ketoacidosis during Ramadan fasting.[32,41]

The only randomized controlled trial in this review aimed to assess whether switching from sulfonylurea to a dapagliflozin in the fasting month of Ramadan resulted in a reduction in hypoglycemia.[33] The study reported that fewer patients exhibited hypoglycemia in the dapagliflozin group than in the sulfonylurea group.[33]

Regarding the clinical benefits, a study in Singapore reported an association between ≥ 3 years of SGLT2 inhibitor use and improved cognitive scores.[39] Two studies in Singapore and Thailand reported that the use of SGLT2 inhibitors was more effective than non-use in reducing HbA1c, body weight and systolic blood pressure in patients with type 2 diabetes.[27,40] Similar findings were reported in another study in Singapore where SGLT2 inhibitor initiation was associated with significantly ($p<0.001$) lower mean HbA1c than those initiated on DPP4-inhibitors, although the difference (7.54% vs 7.68%) was modest.[38] SGLT2 inhibitor initiation was also associated with fewer hospitalizations and deaths up to one-year post-initiation.[38] A

study of 4,446 patients with type 2 diabetes in Singapore [43] found that SGLT2 inhibitors demonstrated protective effects on chronic kidney disease progression, with the hazard ratio (HR) and 95% confidence interval (CI) for developing end stage kidney disease of 0.33 (0.17 - 0.65), compared to non-use of SGLT2 inhibitors.

Discussion

We have conducted the first systematic review of studies examining the use of SLGT2 inhibitors among adults living in Southeast Asian countries. Our findings indicate that evidence related to the use of SGLT2 inhibitors is still limited in this region. Previous studies have focused on the cost-effectiveness, efficacy and safety of SLGT2 inhibitors. There were no studies that examined the availability of these medications in the region. Limited evidence, from just 5 out of 11 countries in the region (Malaysia, Philippines, Singapore, Thailand and Vietnam), suggests that SGLT2 inhibitors appear to be safe, effective, and are likely to be cost-effective but inconsistent findings exist across populations. The lack of robust evidence underscores a significant gap in our understanding of access to SGLT2 inhibitors in the region.

Although evidence suggests that the cardiovascular and renal benefits of SGLT2 inhibitors observed in global trials may be generalizable to Southeast Asian populations[50], further local studies are necessary to confirm these findings. There has been evidence of the influence of racial, ethnic and regional groups on the effect of SGTL2 inhibitors. A 2024 meta-analysis of 7 trials comparing SGLT2 inhibitors vs placebo reported consistent benefits observed among White and Asian populations, and a lack of benefits in Black and other populations: HRs for major adverse cardiovascular events were 0.92 (95% CI 0.86 – 0.98) among White participants, 0.69 (95% CI 0.53 – 0.92) among Asian participants, 1.11 (95% CI 0.82 – 1.51) among Black participants, and 0.83 (95% CI 0.52 – 1.35) among other race.[51] A 2025 meta-analysis of 14

randomized controlled trials of 94,445 participants demonstrated that SGLT2 inhibitors showed consistent efficacy on the studied outcomes (composite of cardiovascular death or heart failure hospitalization, composite of cardiovascular disease and chronic kidney disease progression, major adverse cardiovascular events, cardiovascular death, all-cause death) across three pre-specified racial groups of Asian, Black and White, except for heart failure hospitalization. [52] The efficacy of SGLT2 inhibitors on heart failure hospitalization was more pronounced in Black and Asian patients compared to White patients.[52]. However, there were no studies from Southeast Asian countries in these meta-analyses.

This review revealed that there have been limited studies on SGLT2 inhibitors in older adults in Southeast Asia, and there has been no evidence on the use of this drug class in those with frailty. Further studies are needed to provide region-specific data on the safety and efficacy of SGLT2 inhibitors in these populations. Evidence from the literature so far has shown that SGLT2 inhibitors are effective and safe in frail patients compared to non-frail patients. Post-hoc analyses from major trials on SGLT2 inhibitors, such as the DAPA-HF [53], DELIVER [54], EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) [55], DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) [56], the CANVAS program and the CREDENCE trial, [22] showed that the benefit of these medications was consistent across the spectrum of frailty, with no significant difference in safety. However, most of the trial participants were recruited from more developed countries, limiting generalizability to the local settings in many low- and middle-income countries in the Southeast Asia. This uncertainty can be a challenge for local clinicians to make evidence-informed decisions accounting for the genetic, environmental and healthcare differences.

To address these gaps, targeted local clinical trials and more observational studies are needed to further evaluate both the therapeutic benefits and safety profiles of SGLT2 inhibitors, especially in older populations in Southeast Asia. This can include pharmacokinetic and pharmacodynamic analyses, as variations in metabolism and body composition may influence drug response. Furthermore, regionally adapted clinical guidelines and prescribed education are important to support cautious and individualized use. Without this, the growing population of older adults with diabetes in Southeast Asia may be underserved, potentially missing out on meaningful reductions in cardiovascular and renal morbidity, and further exacerbating health inequities.

Preliminary findings showed that SGLT2 inhibitors seem to be cost-effective for patients in the region. Economic evaluation of new and useful medicines likes SGLT2 inhibitors are important, particularly in areas of limited resources that are sometimes faced by low- to middle-income countries. Despite the clear clinical benefits of SGLT2 inhibitors, several barriers hinder their widespread adoption in Southeast Asia. One of the most significant challenges is the cost of these medications[19], which limits patient access. The upcoming availability of generic SGLT2 inhibitors may help reduce access barriers by providing a more affordable cost. For example, generic versions of dapagliflozin and empagliflozin were recently made available in Malaysia. Another challenge is the uneven healthcare infrastructure across Southeast Asia. Access to healthcare and medications varies greatly between urban and rural areas, with rural populations often experiencing limited access to essential healthcare services, including regular monitoring of renal function, a crucial consideration when using SGLT2 inhibitors. Inadequate healthcare infrastructure, coupled with a lack of healthcare worker education regarding the newer pharmacological treatments[20], may contribute to underutilization or suboptimal use of SGLT2 inhibitors in clinical practice.

In economic evaluations in healthcare, analysis is conducted from a viewpoint or perspective. Examples of these perspectives can include patient, healthcare provider, health system or societal. There are variations in methodological approaches and applications of the different perspectives. The societal approach is the broadest perspective and includes all healthcare related costs and potentially other indirect costs as well.[57] There is no one-size-fits-all as to which perspective should be used as it has its merits, depending on the intended use of the analysis and who is it for (eg. policymaker, context).[57] For Thailand, the Thai Health Technology Assessment guidelines recommend using a societal perspective for economic evaluations.[58] With the increasing prevalence of diabetes and its impact in Thailand and the broader Southeast Asian region[13], policymakers can further explore innovative ways for financing to further help improve access to SGLT2 inhibitors.

Despite existing challenges, there are substantial opportunities to increase the use of SGLT2 inhibitors in Southeast Asia. As economic development continues in many countries in the region, access to healthcare and modern medications is expected to improve. Increased investment in healthcare infrastructure, particularly in rural and underserved areas, could facilitate better management of diabetes and related comorbidities, improving access to SGLT2 inhibitors. Furthermore, as the prevalence of T2DM, chronic kidney disease, and cardiovascular disease continues to rise in Southeast Asia[59] there is an urgent need for effective interventions that target both glycemic control and cardiovascular risk reduction. Additionally, the potential usefulness of SGLT inhibitors for improvement of non-alcoholic fatty liver disease provides another opportunity given that the region is experiencing an increasing trend of obesity.[60] Countries in the Southeast Asian region have been reported to have some of the

fastest growing rates of obesity and metabolic syndrome globally[61] as such, the increased use of SGLT2 inhibitors offers much possibilities.

SGLT2 inhibitors, with their demonstrated efficacy in reducing cardiovascular morbidity and mortality, may become an integral part of the therapeutic arm in managing T2DM and heart failure in this region. Enhanced awareness campaigns for healthcare providers and patients about the benefits of SGLT2 inhibitors could promote their use. Finally, future clinical trials specifically designed to assess the effectiveness and safety of SGLT2 inhibitors with a substantial number of participants in Southeast Asian countries are essential. These studies would provide more granular data on ethnic-specific responses to SGLT2 inhibitors, helping to refine treatment guidelines and inform clinical practice in the region.

Strengths and limitations

To the best of our knowledge, this is the first systematic review to summarize the evidence of research on SGLT2 inhibitors among adults living in Southeast Asian countries. The literature search conducted across three large databases, ensured a comprehensive collection of studies. The inclusion criteria and methodologies applied were designed to minimize bias and maximize the relevance of the studies obtained. However, our study has several limitations. The literature search was limited to studies published in English, omitting studies published in local languages. There may be inconsistencies among the reviewers during the study selection and data extraction phases. To address this, we have adhered strictly to the review protocol and maintained regular communications and cross-checks among team members to reduce any potential discrepancies.

Conclusion

This study highlighted the need for further studies on the use of SGLT2 inhibitors in Southeast Asian population. Limited evidence suggests that SGLT2 inhibitor treatment may offer promising benefits for patients with type 2 diabetes, heart failure and chronic kidney disease in the region. Further research is needed to understand the availability and affordability, as well as the safety of SGLT2 inhibitors, taking into consideration the effect of ageing and frailty in this region. In addition, region-specific factors such as genetic variations, healthcare infrastructure, cost, and cultural considerations should be addressed to optimize their use. With ongoing research, improved healthcare delivery, and greater access to medications, SGLT2 inhibitors have the potential to significantly impact the treatment of T2DM and related comorbidities in Southeast Asia.

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Figure 1. PRISMA flowchart

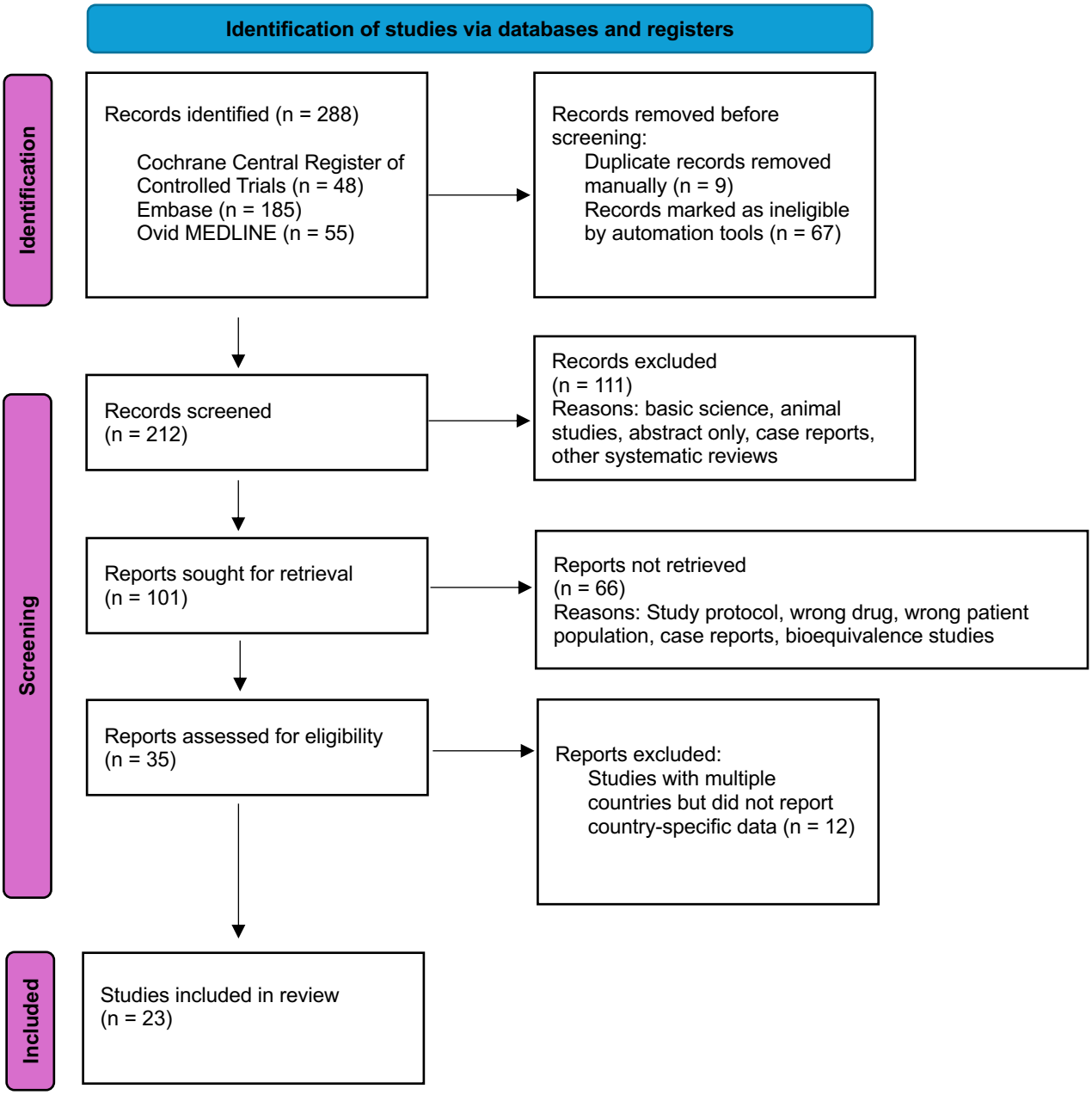

Table 1. Summary of the 23 studies included in this review

No	Author (Last surname), Year, Title	Study designs	Southeast Asian Countries involved	Types of SGLT2 inhibitors involved	Study Population (sample size and mean/median age)	Aim & Findings
Type 2 diabetes (12 studies)						
1	Kongmalai, 2024[23] Cost-Utility and Budget Impact Analysis of Adding SGLT-2 Inhibitors to Standard Treatment in Type 2 Diabetes Patients with Heart Failure: Utilizing National Database Insights from Thailand	Cost-utility and Budget Impact analysis Societal perspective	Thailand	Canagliflozin, Dapagliflozin, Empagliflozin,	Adult T2DM patients who had previously been diagnosed with HF and exhibited a range of baseline New York Heart Association (NYHA) and left ventricular ejection fraction (LVEF) values. Patients entered the model at 60 years old.	Aim: To evaluate the cost-utility of adding SGLT2i to the standard treatment for T2DM-HF patients in Thailand Findings: Canagliflozin produced the greatest gain in QALYs, with an increase of 1.21 years, followed by dapagliflozin (0.54 years) and empagliflozin (0.06 years). On average, SGLT2 inhibitors resulted in a 0.41-year gain in QALYs. Canagliflozin also had the highest additional treatment cost at US$5,600, compared to dapagliflozin at US$3,547 and empagliflozin at US$2,694. The ICERs were US$4,632 for canagliflozin, US$6,430 for dapagliflozin, US$48,952 for empagliflozin, and US$8,480 for SGLT2i overall, per QALY gained. These values exceed Thailand's willingness-to-pay threshold of US$4,564 per QALY, indicating that SGLT2i treatments are not cost-effective in this setting. Threshold analysis suggests that to meet cost-effectiveness criteria, the prices of

						canagliflozin, dapagliflozin, empagliflozin, and SGLT2i overall would need to be reduced by 2.3%, 38.2%, 90.2%, and 55.6%, respectively. A budget impact analysis projected a five-year cost of US$15.6 million for treating type 2 diabetes patients with heart failure. Overall, adding canagliflozin, dapagliflozin, empagliflozin, or any SGLT2i to standard care was likely to not be considered cost-effective for these patients in the Thai healthcare context.
2	Deerochanawong, 2021[24] Cost–Utility Analysis of Dapagliflozin as an Add-On to Standard Treatment for Patients with Type 2 Diabetes and High Risk of Cardiovascular Disease in Thailand	Cost-utility analysis Societal perspective (direct medical and non-medical costs). Indirect costs was not taken into consideration	Thailand	Dapagliflozin	Aged ≥40 years, T2DM, HbA1c in range of 6.5%-12%, CrCl≥60mL/min, have multiple risk factors or established ASCVD	Aim: To analyze the cost–utility of adding dapagliflozin to the standard treatment for treating patients with type 2 diabetes and high cardiovascular risk in a Thai context Findings: The addition of dapagliflozin increased the treatment cost from USD 8,707 to USD 14,455, while improving QALYs from 9.28 to 9.58. This resulted in an ICER of USD 18,988 per QALY. Compared to standard care, patients receiving dapagliflozin experienced greater clinical benefits, including fewer hospitalizations for heart failure and reduced incidence of macroalbuminuria. However, it was not considered cost-effective when assessed against the local cost-effectiveness threshold of 160,000 THB (approximately USD 5,310) per QALY.

3	Sim, 2023[31] Cost-effectiveness of glucose-lowering therapies as add-on to standard care for people with type 2 diabetes in Malaysia	Cost-effectiveness study Healthcare payer's perspective Model was developed for 4 treatments: Standard care, DPP4i, SGLT2i and GLP1RA	Malaysia	SGLT2 inhibitors	Adults with T2DM Patients entered the model at 53 years old. Mean age could not be obtained from the paper	Aim: To evaluate the cost-effectiveness of various glucose-lowering therapies as add-on to standard care for people with T2DM. Findings: The cost of treating an individual with T2DM ranged from RM 12,494 to RM 41,250, with QALY gains varying between 6.155 and 6.731, depending on the treatment option. Using a willingness-to-pay threshold of RM 29,080 per QALY, SGLT2i emerged as the most cost-effective glucose-lowering therapy when used as an add-on to standard care over a patient's lifetime. This approach yielded a net monetary benefit of RM 176,173 and an ICER of RM 12,279 per QALY gained. Compared to standard care alone, SGLT2i provided an additional 0.577 QALYs and 0.809 LYs. Among available treatments, SGLT2i had the highest likelihood of being cost-effective in the Malaysian context.
4	Goh, 2023[32] Effect of empagliflozin in patients with type 2 diabetes during Ramadan on volume status, ketonaemia, and hypoglycaemia	Prospective cohort	Malaysia	Empagliflozin	Adult Muslims with T2DM N: 98 participants Median age: 48 (Empagliflozin), 51.5 (Control)	Aim: To investigate the effects of empagliflozin use in fasting T2DM patients during Ramadan. Findings: The baseline measurement for body size, blood pressure and kidney function were comparable between the two groups, empagliflozin and control. No significant changes in blood pressure, body weight, urea, creatinine, eGFR or hemoglobin levels in either group. There was no significant difference

						observed in blood ketone levels (empagliflozin vs control, 0.17 ± 0.247 mmol/L vs 0.13 ± 0.082 mmol/L, p = 0.304) or the incidence of hypoglycemia (empagliflozin vs control, 19.1% vs 16%, p = 0.684).
5	Wan Seman, 2016[33] Switching from sulphonylurea to a sodium-glucose cotransporter2 inhibitor in the fasting month of Ramadan is associated with a reduction in hypoglycaemia	Randomized, open-label, two-arm parallel-group study	Malaysia	Dapagliflozin	Adults with T2DM N: 110 patients Mean age DAPA + MET group: 53±9.1 SULPHONYL + MET group: 56±9.1	Aim: To assess the risk of hypoglycaemia associated with the use of dapagliflozin compared with that of sulphonylurea in patients with T2DM who fast during Ramadan. Findings: A small percentage of patients in the dapagliflozin group experienced hypoglycaemia compared to those in the sulphonylurea group: 6.9% (4 patients) versus 28.8% (15 patients), p = 0.002. The risk of hypoglycaemia in the fourth week of Ramadan was significantly lower in the dapagliflozin group, with a relative risk (RR) of 0.24 (95% CI: 0.09–0.68; p = 0.002). There were no significant differences between the groups in terms of postural hypotension (13.8% vs 3.8%; p = 0.210) or urinary tract infections (10.3% vs 3.8%; p = 0.277). In combination with metformin, dapagliflozin was associated with a lower risk of hypoglycaemia than sulphonylurea.
6	Goh, 2022[38] Real-world evaluation of	Retrospective cohort	Singapore	Canagliflozin, Dapagliflozin, Empagliflozin	T2DM patients N: 67,556 patients	Aim: To compare the effects of SGLT2 inhibitors with DPP4 inhibitors on patient outcomes in an ethnically diverse Asian population using real-world evidence

	sodium-glucose co-transporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors for managing type 2 diabetes mellitus: a retrospective multi-ethnic cohort study				Mean age: 56.3±10.2 – 62.9±11.6	and further translate such differences into any potential healthcare cost savings. Findings: Patients who started treatment with SGLT2i were more likely to reach their glycaemic control targets compared to those on DPP4i (RR 1.09; 95% CI 1.04–1.14), a finding that was significant only among patients of Chinese ethnicity. There was no increased risk of diabetic ketoacidosis observed in those using SGLT2i. SGLT2i were also linked to a lower risk of hypoglycaemia (RR 0.69; 95% CI 0.59–0.82) and urinary tract infections (RR 0.52; 95% CI 0.43–0.63), although the reduction in hypoglycaemia was not statistically significant in Malay patients. Compared to DPP4i, SGLT2i were associated with a 12% reduction in hospitalisations for any cause and a 34% decrease in all-cause mortality, potentially leading to over $50 million in healthcare savings over a 10-year period.
7	Low, 2022[39] Association between use of sodium-glucose co-transrporter-2 (SGLT2) inhibitors and cognitive function in a longitudinal study	Prospective cohort	Singapore	SGLT2 inhibitors (Canagliflozin, dapagliflozin, empagliflozin)	Adults with T2DM N: 476 patients Mean age: 60.6±7.4	Aim: Explore association between SGLT2i and longitudinal changes in cognitive function in adults with T2DM and assessed the cognitive domains which were impacted by SGLT2i Findings: Among the 138 patients (29.0%) using SGLT2 inhibitors, 84 (17.7%) had been on the medication for less than 3 years, while 54 (11.3%) had used it for 3 years or more. In the unadjusted analysis,

	of patients with type 2 diabetes					SGLT2i use was significantly linked to improved language scores on the RBANS cognitive test (coefficient 0.60; 95% CI 0.10–1.11; p = 0.019). This positive association remained significant after adjusting for potential confounders (coefficient 0.74; 95% CI 0.12–1.36; p = 0.019). In the fully adjusted model, SGLT2i use for 3 years or longer was associated with improvements in overall RBANS scores (coefficient 0.54; 95% CI 0.13–0.95; p = 0.010) and specifically in the language domain (coefficient 1.12; 95% CI 0.27–1.97; p = 0.010).
8	Shao, 2018[40] Short-term outcomes of patients with Type 2 diabetes mellitus treated with canagliflozin compared with sitagliptin in a real-world setting	Retrospective cohort	Singapore	Canagliflozin	Adults with T2DM N: 57 patients Mean age: 46.4±12.1	Aim: To evaluate the effectiveness and safety of canagliflozin as compared to sitagliptin in a real-world setting Findings: A total of 57 patients were included in the study (22 received canagliflozin 300 mg and 35 received sitagliptin 100 mg). Baseline characteristics were comparable between the two groups, with an overall mean HbA1c of 9.4% ± 1.4%. Treatment with canagliflozin 300 mg resulted in significantly greater reductions in HbA1c (LS mean change: −1.6% vs. −0.4%; p < 0.001), body weight (−3.0 kg vs. 0.2 kg; p < 0.001), and systolic blood pressure (−9.7 mmHg vs. 0.4 mmHg; p < 0.001) compared to sitagliptin 100 mg. Around half of the patients taking canagliflozin (10 out of 22) experienced mild side effects related to osmotic diuresis, though these did not lead to treatment discontinuation.

9	Shao, 2018[41] The effect of Ramadan fasting and continuing sodium-glucose co-transporter-2 (SGLT2) inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes	Prospective cohort	Singapore	Canagliflozin, Empagliflozin	Adult T2DM patients observing Ramadan fasting N: 68 Mean age: 52.2±11.1	Aim: The effect of Ramadan fasting and continuing sodium-glucose co-transporter-2 (SGLT2) inhibitor use on ketonemia, blood pressure and renal function in Muslim patients with type 2 diabetes. Findings: A total of 68 patients with comparable baseline characteristics were enrolled in the study: 35 in the study group (on stable dose of SGLT2i) and 33 in the control group (not on SGLT2i during study period). During Ramadan fasting, both groups showed similar changes in various health parameters. There were no significant differences in weight loss (LS mean change: −1.8 kg vs. −1.1 kg; p = 0.205), estimated glomerular filtration rate (eGFR) (−6.0 vs. −4.2 ml/min/1.73 m²; p = 0.399), sitting systolic blood pressure (−8.1 vs. −10.4 mmHg; p = 0.569), sitting diastolic blood pressure (−3.7 vs. −3.5 mmHg; p = 0.934), or plasma β-hydroxybutyrate levels (−0.01 vs. −0.02 mmol/L; p = 0.649) between the groups. Ramadan fasting was associated with significant changes in weight, BP and eGFR regardless whether patients were on SGLT2 inhibitor treatment. Continued use of SGLT2 inhibitors during Ramadan did not increase ketonemia, nor increase risk of eGFR deterioration and hypoglycaemia.
10	Chanawong, 2023[25]	Retrospective cohort	Thailand	Dapagliflozin, Empagliflozin	Patients with T2DM who have been prescribed	Aim: To evaluate the renoprotective effects of SGLT2 inhibitors compared with DPP4 inhibitors by

	Renoprotective Effect of Thai Patients with Type 2 Diabetes Mellitus Treated with SGLT-2 Inhibitors versus DPP-4 Inhibitors: A Real-World Observational Study				either DPP4i or SGLT2i N: 1079 patients (388 in the SGLT2i group and 691 in the DPP4i group) Median age: 64 – 66	comparing the changes in eGFR levels and the glucose-lowering effects Findings: A total of 388 patients were treated with SGLT2 inhibitors and 691 with DPP4 inhibitors. After 18 months of treatment, both groups showed a significant decline in estimated glomerular filtration rate (eGFR) compared to baseline. However, the reduction in eGFR was less pronounced in patients who started with a baseline eGFR below 60 mL/min/1.73 m^2, compared to those with higher baseline eGFR levels (≥60 mL/min/1.73 m^2). Additionally, both groups experienced significant decreases in fasting blood glucose and haemoglobin A1c levels from baseline. Patients with eGFR <60 mL/min/1.73 m^2 who used SGLT2 inhibitors demonstrated a smaller decline in eGFR than those who used DPP4 inhibitors despite no statistical significance.
11	Uitrakul, 2022[26] The Incidence and Risk Factors of Urinary Tract Infection in Patients with Type 2 Diabetes Mellitus Using SGLT2 Inhibitors: A	Retrospective cohort	Thailand	Dapagliflozin, Empagliflozin	Patients with T2DM N: 853 participants Mean age (95% CI): 55.7 (53.8 – 57.2) - 65.2 (64.1 - 67.3)	Aim: To investigate the overall incidence of UTI related to SGLT2 inhibitors in Thai patients with type 2 diabetes mellitus, as well as its potential risk factors. Findings: The overall incidence of urinary tract infections (UTIs) was higher in the SGLT2 inhibitor group (33.49%) compared to the non-SGLT2 inhibitor group (11.72%). There was no significant difference in UTI rates between patients treated with

	Real-World Observational Study					dapagliflozin (34.00%) and those on empagliflozin (33.03%). Patients using SGLT2 inhibitors had a 3.7 times greater risk of developing a UTI compared to those not on these medications (95% CI: 2.60–5.29). Additionally, gender, age, and occupation were identified as significant risk factors for UTI in this study.
12	Sriphrapradang, 2020[27] Effectiveness and safety of sodium-glucose co-transporter-2 inhibitors in Thai adults with type 2 diabetes mellitus: a real-world study	Retrospective observational cohort	Thailand	Canagliflozin, Dapagliflozin, Empagliflozin	Adults with T2DM N: 1159 patients Mean age: 61.1±10.9	Aim: To assess the real-life clinical effectiveness, safety, tolerability and cardio-renal outcomes of SGLT2 inhibitors in Thai participants with T2DM. Findings: Among 1,159 participants (52.6% women; average age 61.1 ± 10.9 years; mean BMI 28.7 ± 5.2 kg/m²), 65.1% were treated with dapagliflozin, 34.3% with empagliflozin, and 0.6% with canagliflozin. The median duration of SGLT2 inhibitor use was 15 months (interquartile range: 8–23 months). Pre-existing conditions included coronary artery disease (16.5%), stroke (6.4%), heart failure (4.9%), and peripheral arterial disease (1.6%). Average HbA1c levels dropped by 0.7% (95% CI: −1.0 to −0.4) from a baseline of 8.3 ± 1.5%. After 24 months, there were significant reductions in body weight (by 2.5 kg), systolic blood pressure (by 3.5 mmHg), and diastolic blood pressure (by 2.4 mmHg). The median annual decline in eGFR was −1.3 ml/min/1.73 m². Reported side effects included pollakiuria (7.2%), genital tract infections (2.8%), urinary tract infections (2.2%), and hypoglycemia (0.9%). No

						cases of diabetic ketoacidosis were observed during the study period.
Heart failure (7 studies)						
13	Tan, 2024[34] Cost-effectiveness of empagliflozin in the treatment of Malaysian patients with chronic heart failure and preserved or mildly reduced ejection fraction	Cost-effectiveness Healthcare system perspective	Malaysia	Empagliflozin	HF patients with EF>40% Aged ≥ 18 years	Aim: To perform a cost-utility analysis (CUA) of add-on empagliflozin to SoC versus SoC alone in EF>40% patients from the perspective of Malaysian healthcare system, and to analyse the economic value when it is prescribed for HF patients irrespective of their ejection fraction by taking into consideration the findings of the early analysis for HFrEF Findings: In the base-case analysis, the incremental cost-effectiveness ratio (ICER) for treating heart failure (HF) patients with an ejection fraction (EF) greater than 40% was RM 40,454 per QALY gained. Given a cost-effectiveness threshold of RM 47,439 per QALY, empagliflozin was considered cost-effective in 57% of simulations. The model's results were particularly sensitive to factors such as empagliflozin's effectiveness in reducing HF-related hospitalizations, cardiovascular mortality, and its price. For the overall HF population, the ICER was lower, at RM 29,463 per QALY gained. These findings suggest that empagliflozin is likely a cost-effective treatment for HF patients with EF >40% from the perspective of the Malaysian healthcare system.

14	Tan, 2024[35] Budget Impact Analysis of Dapagliflozin in Treating Patients With Heart Failure With Reduced Ejection Fraction From the Perspective of Malaysian Public Healthcare System	Budget Impact Analysis Healthcare system perspective	Malaysia	Dapagliflozin	Malaysian HF patients who would be diagnosed and treated in MOH facilities No mean age reported	Aim: To explore the budgetary impact of adding dapagliflozin to the SoC compared to SoC alone for treatment of HFrEF from the MOH's perspective. Findings: The base-case analysis projected that over a five-year period, incorporating dapagliflozin into treatment for heart failure with reduced ejection fraction (HFrEF) would lead to total cost savings of RM 2.6 million (approximately USD 0.6 million or EUR 0.5 million), amounting to a 0.3% reduction in overall costs. These savings were mainly due to decreased spending on hospitalizations for heart failure (hHF). Additionally, dapagliflozin was estimated to prevent 731 hHF events and 366 cardiovascular deaths. Sensitivity and scenario analyses indicated that the results were most influenced by assumptions related to loop diuretic usage and the price of dapagliflozin. While the first four years were projected to yield cost savings or break even, a projected 2.5% annual increase in dapagliflozin use could lead to additional costs for the Ministry of Health starting in the fifth year. Overall, adding dapagliflozin to standard care has the potential to reduce heart failure hospitalizations, cardiovascular deaths, and renal complications, offering both clinical benefits for HFrEF patients and cost savings for the Malaysian healthcare system.

15	Ong, 2023[36] Cost-effectiveness of adding empagliflozin to the standard of care for patients with heart failure with reduced ejection fraction from the perspective of healthcare system in Malaysia	Cost-effectiveness Ministry of Health perspective	Malaysia	Empagliflozin	Heart failure with reduced EF Starting age of 60 years	Aim: To determine the cost-effectiveness of adding empagliflozin to the standard of care versus SoC alone for the treatment of patients with heart failure (HF) with reduced ejection fraction (HFrEF) Findings: Compared to standard care (SoC) alone, adding empagliflozin to SoC for treating heart failure with reduced ejection fraction (HFrEF) was associated with higher costs (RM 25,333 vs. RM 21,675) but also provided greater health benefits (3.64 vs. 3.46 QALYs), resulting in an incremental cost-effectiveness ratio (ICER) of RM 20,400 per QALY based on the KCCQ-CSS model. A scenario analysis using NYHA classifications yielded a higher ICER of RM 36,682 per QALY. Deterministic sensitivity analysis confirmed the model's reliability and identified the cost of empagliflozin as the key factor influencing cost-effectiveness. When government medication procurement prices were applied, the ICER dropped significantly to RM 6,621 per QALY. Overall, the results suggest that empagliflozin is likely to be a cost-effective option from the perspective of the Ministry of Health.
16	Mendoza, 2021[44] Cost-utility analysis of add-on dapagliflozin in heart failure	Cost-utility Healthcare provider's perspective	Philippines	Dapagliflozin	HF patients with New York Heart Association class II, III, and IV whose ejection	Aim: To determine the cost-effectiveness of dapagliflozin in addition to standard therapy versus standard therapy alone among patients with HFrEF using the public healthcare provider's perspective in the Philippines.

	with reduced ejection fraction in the Philippines				fraction was ≤40% Starting age of 55 years	Findings: The incremental cost-effectiveness ratio (ICER) for adding dapagliflozin to standard therapy in patients with heart failure with reduced ejection fraction (HFrEF) was PHP177,868 (US$3,434) at the current price of PHP44.00 per 10 mg tablet, and PHP160,983 (US$3,108) at a potentially negotiated price of PHP40.00. Both ICERs fall below the cost-effectiveness threshold, which corresponds to the Philippines' 2019 per capita GDP of PHP180,500 (US$3,485), indicating cost-effectiveness. For HFrEF patients with diabetes, the ICERs were even lower: PHP132,582 (US$2,560) and PHP120,249 (US$2,321), respectively, using the same price assumptions. These findings suggest that dapagliflozin is likely a cost-effective treatment option in this context.
17	Varghese, 2023[42] Cost-Effectiveness of Empagliflozin on Top of Standard of Care for Heart Failure With Reduced Ejection Fraction in Singapore	Cost-effectiveness Healthcare perspective	Singapore	Empagliflozin	Heart failure with reduced EF No Mean age reported	Aim: To estimate the cost-effectiveness of empagliflozin + SoC versus SoC in patients with HF with reduced ejection fraction Findings: The combination of empagliflozin with standard care (SoC) was found to be highly cost-effective compared to SoC alone, with an incremental cost-effectiveness ratio (ICER) of less than SGD$ 8,000 per quality-adjusted life year (QALY) gained. The base-case findings were supported by consistent results across various scenario and sensitivity

						analyses, confirming the robustness of the model. When health states were defined using Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) quartiles, the ICER dropped further to SGD$ 4,625 per QALY. These outcomes suggest that empagliflozin is likely a cost-effective option for treating patients with heart failure with reduced ejection fraction (HFrEF).
18	Krittayaphong 2022[28] Cost-Utility Analysis of Combination Empagliflozin and Standard Treatment Versus Standard Treatment Alone in Thai Heart Failure Patients with Reduced or Preserved Ejection Fraction	Cost-utility analysis Healthcare system perspective	Thailand	Empagliflozin	Heart failure with reduced or preserved EF Starting age of 60 years	Aim: Cost-utility analysis of combination empagliflozin and standard treatment (ST) versus ST alone in Thai HF patients with HFrEF or HFpEF Findings: In patients with heart failure with reduced ejection fraction (HFrEF), adding empagliflozin resulted in a gain of 0.26 life years and 0.20 quality-adjusted life years (QALYs) at an additional cost of 409.82 USD compared to standard treatment alone, with an ICER of 69,218 THB per QALY (approximately 2,065 USD per QALY gained). For patients with heart failure with preserved ejection fraction (HFpEF), empagliflozin added 0.07 life years and 0.05 QALYs at an extra cost of 622.49 USD, resulting in an ICER of 395,826 THB per QALY (about 11,809 USD per QALY gained). These findings suggest that empagliflozin is likely a cost-effective add-on therapy for HFrEF patients but not for those with HFpEF.

19	Krittayaphong 2021[29] Cost-utility analysis of add-on dapagliflozin treatment in heart failure with reduced ejection fraction	Cost-utility analysis Healthcare system perspective	Thailand	Dapagliflozin	HFrEF patients with left ventricular ejection fraction (LVEF) ≤40%, and New York Heart Association (NYHA) class II–IV with an average age of 65 years. Starting age of 65 years	Aim: To determine the cost-utility of add-on dapagliflozin treatment for HFrEF Findings: The addition of dapagliflozin to standard therapy increased costs from 17,442 THB (559 USD) to 54,405 THB (1,745 USD), while improving quality-adjusted life years (QALYs) from 6.33 to 6.92, resulting in an incremental cost-effectiveness ratio (ICER) of 62,090 THB/QALY (1,991 USD/QALY). Sensitivity analyses showed that adding dapagliflozin was cost-effective in 87% of cases at a willingness-to-pay threshold of 160,000 THB/QALY (5,131 USD/QALY). The ICER was higher for patients without diabetes compared to those with diabetes (68,304 vs. 47,613 THB/QALY or 2,191 vs. 1,527 USD/QALY). Overall, dapagliflozin is likely to be a cost-effective treatment option for patients with heart failure with reduced ejection fraction (HFrEF).
Chronic kidney disease (4 studies)						
20	Lim, 2024[37] Cost-effectiveness analysis of dapagliflozin for people with chronic kidney disease in Malaysia	Cost-effectiveness Healthcare perspective	Malaysia	Dapagliflozin	CKD No mean age reported	Aim: Assessed the cost effectiveness of the introduction of dapagliflozin in addition to SoC versus SoC Findings: Dapagliflozin combined with standard care (SoC) was found to be the dominant treatment compared to SoC alone, with costs of RM 81,814 versus RM 85,464 (USD 19,762 vs. USD 20,644). Adding dapagliflozin for patients with chronic kidney

						disease (CKD) increased life expectancy by 0.46 years and quality-adjusted life years (QALYs) by 0.41 compared to SoC alone (10.01 vs. 9.55 years and 8.76 vs. 8.35 QALYs). This corresponds to a saving of RM 8,894 (USD 2,148) per QALY gained. The benefits stemmed from delaying CKD progression, which reduced the costs associated with dialysis and kidney transplantation. These findings remained consistent despite variations in disease management costs and patient subgroups and fell below the willingness-to-pay threshold of RM 46,000 per QALY. Overall, dapagliflozin is likely to be cost-saving, though confirmation through real-world data is recommended.
21	Vareesangthip 2022[30] Cost–Utility Analysis of Dapagliflozin as an Add-on to Standard of Care for Patients with Chronic Kidney Disease in Thailand	Cost-utility analysis Societal perspective (direct medical and non-medical costs were included)	Thailand	Dapagliflozin	CKD Starting age of 60 years	Aim: To evaluate the cost–utility of dapagliflozin in addition to SoC compared with SoC alone Findings: Adding dapagliflozin to standard care (SoC) was estimated to increase life expectancy by 0.34 years and quality-adjusted life years (QALYs) by 0.30 compared to SoC alone (7.13 vs. 6.78 years and 5.10 vs. 4.80 QALYs). The total cost was lower with dapagliflozin treatment than with SoC alone (648,413 THB vs. 689,284 THB or 20,947.64 USD vs. 22,268.01 USD). The cost savings were primarily due to reduced expenses related to dialysis and kidney transplantation. Overall, dapagliflozin is likely to be cost-saving by delaying the progression of chronic kidney disease to dialysis.

22	Varghese, 2024[45] Cost-effectiveness of add-on empagliflozin versus standard of care in management of CKD in Malaysia, Thailand and Vietnam – findings from a modelling study assessing an EMPA-KIDNEY eligible population, using CKD progression model	Cost-effectiveness (modelling) Multiple countries (3x) Healthcare perspective	Malaysia, Thailand, Vietnam	Empagliflozin	CKD No mean age reported	Aim: To assess the economic value of empagliflozin in patients with CKD in Malaysia, Thailand and Vietnam Findings: Adding empagliflozin to standard care (SoC) was found to be cost-saving in Malaysia and Thailand, and cost-effective in Vietnam, with an ICER of 77,838,407 Vietnam Dong per QALY. This is below the willingness-to-pay threshold of 96,890,026 Vietnam Dong per QALY. Most of the cost savings over a patient's lifetime came from preventing or delaying the need for dialysis or kidney transplantation, with these savings nearly double the additional treatment expenses. The findings were consistent regardless of diabetes status and across a wide range of albuminuria levels. Overall, empagliflozin is expected to be cost-saving in Malaysia and Thailand and cost-effective in Vietnam.
23	Liu, 2022[43] A real-world study on SGLT2 inhibitors and diabetic kidney disease progression	Retrospective cohort	Singapore	Canagliflozin, Dapagliflozin, Empagliflozin	Patients with diabetic kidney disease N: 4,446 patients Mean age: 60.6± 13.5	Aim: To evaluate the renal outcomes of CKD patients with or without SGLT2 inhibitor use in a multi-ethnic Asian population. Findings: This was an analysis of 4,446 participants, of whom 1,598 were treated with SGLT2 inhibitors. The use of SGLT2is was associated with a significant

						reduction in the progression of chronic kidney disease (CKD), with a hazard ratio (HR) of 0.60 (95% confidence interval [CI] 0.49–0.74). For patients with an eGFR of ≥45 mL/min/1.73 m², the HR was 0.60 (95% CI 0.47–0.76), and for those with eGFR between 15–44 mL/min/1.73 m², the HR was 0.43 (95% CI 0.23–0.66). Additionally, the risk of developing end-stage kidney disease (ESKD) was reduced in the entire cohort [HR 0.33 (95% CI 0.17–0.65)] and particularly in patients with eGFR 15–44 mL/min/1.73 m² [HR 0.24 (95% CI 0.09–0.66)]. Among the SGLT2 inhibitors, empagliflozin demonstrated a consistent reduction in renal risk across CKD stages 1 through 4, compared to canagliflozin and dapagliflozin.

ASCVD: Atherosclerotic Cardiovascular Disease; BP: Blood pressure; CKD: Chronic Kidney Disease; CI: Confidence Interval; CrCl: Creatinine Clearance; CV: Cardiovascular; DAPA: Dapagliflozin; DPP4i: Dipeptidyl Peptidase-4 inhibitor; EF: Ejection Fraction; eGFR: estimated Glomerular Filtration Rate; ESKD: End-Stage Kidney Disease; GLP-1RA: Glucagon-like peptide-1 receptor agonist; HbA1c: Hemoglobin A1c; HF: Heart Failure; HFpEF: Heart Failure with Preserved Ejection Fraction; HFrEF: Heart Failure with Reduced Ejection Fraction; hHF: hospitalization for Heart Failure; HR: Hazard ratio; ICER: Incremental Cost-Effectiveness Ratio; KCCQ-CSS: Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; KT: Kidney Transplantation; LVEF: Left Ventricular Ejection Fraction; LY: Life-years; LS: Least Squares; MDPI: Multidisciplinary Digital Publishing Institute; MET: Metformin; MoH: Ministry of Health; NYHA: New York Heart Association; PHP: Philippine Pesp; PLOS: Public Library of Science; QALY: Quality-Adjusted Life Year; RBANS: Repeatable Battery for the Assessment of Neuropsychological Status; RM: Ringgit Malaysia; RR: Relative risk; SoC: Standard of Care; SGD$: Singapore Dollars; SGLT2i: Sodium Glucose Co-Transporter 2 inhibitor; SULPHONYL: Sulphonylurea; ST: Standard Treatment; THB: Thai Baht; T2DM: Type 2 Diabetes Mellitus; USD: United States Dollars; UTI: Urinary Tract Infections

Chapter 10
Discussion & Conclusion

The thesis highlights some of the complexities in the management of cardiovascular risk factors and cardiovascular disease in older people with type 2 diabetes living in the Southeast Asian region. Although numerous cost-effective interventions for prevention and management of cardiovascular diseases are available, a substantial proportion of the global population remains without access to them. The Universal Health Coverage (UHC) index provides a standardized measure of the extent to which populations can access essential health services and is widely used to monitor progress toward universal health coverage. Recent analyses indicate that, despite global improvements in the UHC effective coverage index, many countries in Southeast Asia continue to score lower than Western countries.[1] Using hypertension as an example, there are significant disparities across access to basic diagnostic services such as blood pressure screening, as well as the availability and affordability of appropriate treatment options.[2] Inconsistencies in diagnostic and treatment access can influence both the onset and progression of disease-related complications, thereby increasing the likelihood of developing additional comorbidities over time.

10.1 Comorbidities, frailty, and polypharmacy in older adults with type 2 diabetes

The studies presented in Chapter 3 and Chapter 4 of this thesis provide the local evidence on comorbidities among older people with type 2 diabetes living in 2 different countries in the Southeast Asian region. Chapter 3 revealed a high prevalence of poor glycaemic control and high prevalence of comorbidities, frailty, and polypharmacy among older adults with diabetes in Vietnam. Participants with polypharmacy, frailty, or in the first year of diabetes had increased odds of poor glycaemic control. These findings highlight the need for further studies on optimizing polypharmacy, frailty and managing long-term diabetes. Chapter 4 found a high prevalence of frailty and diabetes among older patients with stroke in Malaysia. While frail and diabetic participants had the highest overall burden of comorbidities, non-frail and diabetic participants had the most significant cardiovascular disease burden. Individuals who were non-frail, despite having greater physiological reserve, still faced a significant cardiovascular risk in the present of diabetes, requiring focused cardiovascular risk management. On the other hand, in individuals affected by both frailty and diabetes, frailty may worsen the effects of diabetes by hindering the body's ability to regulate metabolic and inflammatory stressors,

resulting in a broader spectrum of health issues. Aging, poor glycaemic control, polypharmacy, and other socioeconomic factors may contribute to the accumulation of comorbidities in this group. These findings underscore the urgent need for integrated and personalized management approaches to enhance the overall well-being and quality of life for older stroke survivors with diabetes.

Table 1 summarizes the prevalence of polypharmacy and frailty reported in older individuals with diabetes in the studies in this thesis. The prevalence of frailty was around 30% in general older adults with diabetes, higher (at 60%) in those with diabetes and coronary heart disease, and highest among those with diabetes and stroke (up to 98.5%). The Clinical Frailty Scale was the most commonly used tool for frailty assessment in these studies. The prevalence of frailty in our study populations highlights the potential role frailty has in CVD management for older adults with diabetes. The high prevalence of polypharmacy reported in our studies highlights another challenge that older adults with diabetes face.

Table 1: Summary of prevalence of polypharmacy and frailty in older people with diabetes from studies in this thesis

Study	**Polypharmacy (%)**	**Frailty (%)**
Comorbidities, geriatric syndromes, and glycaemic control among older patients with diabetes: a multi-centre study in Vietnam (Chapter 3)	76.6%	29.5% Pre-frail: 46.0%
Diabetes, frailty and burden of comorbidities among older Malaysians with stroke (Chapter 4)	55.6%	81.3%
Forgetfulness to take antihypertensive medications and poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam (Chapter 6)	98	30.4%

Assessing the impact of frailty on statin prescriptions among older stroke survivors with and without diabetes in Malaysia (Chapter 7)	56.1%	98.5%
Frailty and prescriptions of secondary prevention medications in older people with diabetes and coronary heart disease—An observational study in Vietnam (Chapter 8)	97%	59%

10.2 The impact of frailty on the prescriptions of cardiovascular secondary prevention medications

Frailty is a multifaced age-related condition influenced by various physiological, social and environmental factors.[3,4] With the growing population of older people, frailty assessments can be used as a guide to identify older adults who are at higher risk of adverse health outcomes and optimize their care. In clinical settings, the management of older adults with frailty is complex due to the limited evidence supporting various treatment options, both at the individual and health system level.[4] The growing awareness of frailty has led to its inclusion in recent studies.[5] However, the impact of frailty on the prescriptions of different classes of medications is underexplored among Southeast Asian populations.

In Chapter 7, frailty was associated with reduced odds of receiving statins in among older stroke survivors in Malaysia. The prevalence of frailty in stroke patients with diabetes was very high, at 98.5%, and there was a difference in the relationship between frailty and statin prescriptions among participants with and without diabetes. On the adjusted models, increased Clinical Frailty Scale was significantly associated with reduced odds of receiving statins in all participants (adjusted OR 0.64, 95% CI 0.46 - 0.88), and in participants without diabetes (adjusted OR 0.54, 95% CI 0.33 – 0.89), but not in participants with diabetes (adjusted OR 0.73, 95%CI 0.46 – 1.17). The absence of a significant association between frailty and statin prescriptions among participants with diabetes may result from the small sample size. However, it may also suggest a difference in prescription patterns among stroke patients with

and without diabetes. In this study, while advanced age and higher levels of frailty reduced the odds of receiving statins among participants without diabetes, these two factors did not significantly affect statin prescriptions among participants with diabetes. In participants with diabetes, factors such as dyslipidaemia and the severity of strokes may have a stronger influence on clinicians' decisions of prescribing. Diabetes is a risk factor for cardiovascular events, hence post-stroke older patients with diabetes require careful management compared to those without this condition. The differences in the relationship between frailty and statin prescriptions among participants with and without diabetes may suggest a personalized approach in secondary prevention for older patients after strokes. Future studies are needed to understand prescribers' perspectives, aiding in the development of personalized healthcare for older individuals.

In Chapter 8, frailty was present in 59% of the participants, who were older patients with coronary heart disease and diabetes in Vietnam, and increased Clinical Frailty Scale was associated with reduced prescriptions of beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEIs/ARBs) and all four types of secondary prevention medications (antiplatelets, statins, beta-blockers, ACEIs/ARBs). The study findings highlight the potential impact of frailty on cardiovascular secondary prevention for older adults with diabetes. Older patients with frailty may have biological changes that could amplify the side effects of medicines like beta-blockers and ACEIs/ARBs, hence influencing clinicians' decisions in prescribing these medications. Furthermore, prescribing practices may be influenced by concerns that frail patients might struggle to adhere to treatment due to the complex medication regimens and polypharmacy. These findings suggest that future research should explore the link between frailty and the prescriptions of secondary prevention medicines in a larger, more diverse population.

These two studies show the potential influence of frailty in the prescription of secondary prevention medications for CVD. Therefore, it is crucial to adopt a personalized approach and a multidisciplinary care approach in managing CVD for older adults with diabetes. Effective care involving collaborations among geriatricians, cardiologists, endocrinologists, general practitioners, pharmacists, allied health and nursing staff is needed to ensure comprehensive support for these patients. Chapter 3 particularly highlighted a prevalence of pre-frail of 46.0% using the Fried's Frailty Phenotype approach. Individuals with pre-frailty may exhibit some signs of overall decline or progression to frailty and hence provides an opportunity for early

intervention to help reduce further progression.[6,7] It is crucial to implement early intervention such as physical exercise, nutrition, review of polypharmacy and social assessment to prevent frailty in pre-frail older adults with diabetes.[7,8]

10.3 Cardiovascular risk factor management for older adults with diabetes: blood pressure control

Chapter 5 showed that the prevalence of hypertension in people with diabetes in Southeast Asia was high. Despite the high prevalence of hypertension, a substantial proportion of these populations did not receive adequate blood pressure control, with most studies reporting a control rate of less than 40%, and diabetic patients who were older were more likely to have uncontrolled blood pressure. Additionally, most of the studies included in this review reported that less than 50% of the study populations achieved targeted glucose control, indicating a dual burden of poor glucose and blood pressure control in these populations. As the prevalence of both hypertension and diabetes continues to rise in the region, driven by factors such as aging populations, lifestyle changes, and increasing lifespans, substantial work remains to address the growing burden of these two conditions. This review also highlighted that there has been limited evidence on the prescription of antihypertensive therapies and medication adherence in the region.

From the gap identified in the systematic review above, the study in Chapter 6 was designed to examine the prevalence of forgetfulness to take antihypertensive medications and its relationship with poor blood pressure control in older adults with type 2 diabetes and hypertension in Vietnam. This study found that approximately one-third of the participants reported forgetting to take antihypertensive medicines sometimes, and forgetfulness was associated with increased odds of poor BP control (adjusted OR 1.64, 95% CI 1.03 - 2.56). The study also revealed that hypertension duration and disability in activities of daily living were significantly associated with forgetfulness. These findings suggest the need for future studies focusing on interventions on forgetfulness to improve medication adherence for this population. Further support is particularly needed for older adults with disability and for those newly diagnosed with hypertension.

Individuals diagnosed with diabetes have an increased risk of developing CVD.[9] The prevalence of diabetes increases with age,[10] therefore, for older persons with diabetes, it is essential for adequate cardiovascular risk factor management. Noale et. al summarized that

cardiovascular-related morbidity is not necessarily a consequence of aging but due to specific, often modifiable risk factors. Therefore, the management of cardiovascular risk factors continues to be an important part of prevention strategies to prolong life, improve quality of life and reduce morbidity for individuals with diabetes.[11]

10.4 The adoption of novel pharmacological treatment: SGLT2 inhibitors

Chapter 9 showed that there is limited evidence on the use of SGLT2 inhibitors in this region. The studies included in this review have focused on the cost-effectiveness, efficacy and safety of SLGT2 inhibitors. There were no studies that examined the availability of these medications in the region. Limited evidence, from just five out of eleven countries in the region (Malaysia, Philippines, Singapore, Thailand and Vietnam), suggests that SGLT2 inhibitors appear to be safe and effective, and are likely to be cost-effective but inconsistent findings exist across populations. The lack of robust evidence underscores a significant gap in our understanding of the access to SGLT2 inhibitors in the region. While the clinical efficacy of these agents appears to be comparable to Western populations, region-specific factors such as genetic variations, healthcare infrastructure, cost, and cultural considerations must be addressed to optimize their use. Further research is needed to understand the availability and affordability, as well as the safety of SGLT2 inhibitors, taking into consideration the effect of ageing and frailty in this region. SGLT2 inhibitors may offer promising benefits for patients with type 2 diabetes, heart failure and chronic kidney disease in the region.

10.5 Strengths and Limitations

Details of strengths and limitations of each study in this thesis are presented in Chapters 3-9. The two systematic reviews in this thesis were the first reviews of these issues in the Southeast Asia. The observational studies presented in this thesis offer insights into the prevalence of comorbidities and geriatric syndromes in older adults with diabetes in the region, as well as into how frailty influenced the prescriptions of cardiovascular secondary prevention medications for this population. The findings from these studies can serve as a valuable reference for future research in the region.

Some other limitations of this thesis include a lack of observational studies from other countries in the region. The observational studies in this thesis were conducted in only two countries (Malaysia and Vietnam), which restricts the ability to generalize findings across the broader region. Other countries may have different healthcare systems, socioeconomic conditions,

access to medical resources, cultural practices, and demographic characteristics that could influence the outcomes studied in these studies. Future studies should aim to include a wider range of countries in the region to achieve a more representative sample. This could involve multi-country collaborations or utilizing international health databases. In addition, conducting comparative analyses across countries with different healthcare systems or socioeconomic conditions could offer deeper insights into how these factors influence the outcomes being studied.

Regarding comorbidities and geriatric syndromes, this thesis only examined frailty and polypharmacy. Other geriatric syndromes such as falls, cognitive impairment, and disability in activities of daily living in older persons were not examined. By focusing solely on frailty and polypharmacy, the thesis may overlook the potential interaction between frailty, polypharmacy and other geriatric syndromes. Neglecting this broader perspective could lead to an incomplete understanding of how these geriatric syndromes exacerbate each other and affect the management of CVD in older adults with diabetes.

There is also a limited scope of cardiovascular risk factors and CVD in this thesis. The thesis only examined blood pressure control and glycemic control. Other important cardiovascular risk factors such as dyslipidemia, smoking, obesity, or sedentary lifestyles were not examined in this thesis. Among the cardiovascular disease, this thesis only examined secondary prevention strategies to prevent recurrent cardiovascular events among older adults with diabetes who were diagnosed with coronary heart disease or stroke. The secondary prevention treatment for older adults with diabetes and other common CVD such as heart failure, peripheral artery disease, or atrial fibrillation was not examined in this thesis.

These limitations point to significant gaps in the scope of the research, which can impact the generalizability and comprehensiveness of the findings. The narrow focus on specific geriatric syndromes and cardiovascular conditions, combined with the limited geographic scope, suggests that the thesis may not fully capture the complexity of health challenges in the studied population.

10.6 Future Directions

From a global health perspective, there is a pressing need for further studies that incorporates the assessments of frailty and polypharmacy for older adults with diabetes in the Southeast

Asian region. With the region's growing older population and constrained healthcare resources, understanding the influence of geriatric syndromes like frailty and polypharmacy represents an important area for exploration and research. Further research is needed to investigate the prevalence of other important geriatric syndromes such as falls, cognitive impairment, and disability in activities of daily living in older persons with diabetes and how they affect the management of CVD. Additionally, more studies should explore the secondary prevention treatment of other common CVD in older adults with diabetes, such as heart failure, peripheral artery disease, or atrial fibrillation.

Future research should also focus on longitudinal studies to examine how prescriptions of secondary prevention medications affect clinical outcomes. Investigating the effects of reversing frailty and reducing polypharmacy among older adults with diabetes could provide valuable insights, particularly regarding outcomes related to cardiovascular disease. Finally, it is crucial to conduct more studies aimed at improving blood pressure control for individuals with diabetes in this region.

10.7 Conclusion

In conclusion, this thesis revealed a high prevalence of comorbidities, frailty, and polypharmacy among older adults with types 2 diabetes. The suboptimal management of modifiable risk factors for cardiovascular disease such as blood pressure, glycaemic levels, and prescriptions of cardiovascular secondary prevention medicines, highlights the heterogeneity in care received. Future longitudinal studies should investigate the reasons behind these disparities and their impact on mortality and quality of life. The current phenomenon of rapid ageing being experienced by populations in Southeast Asia countries highlights the need also for incorporation of geriatric specific factors when providing care for older adults with diabetes, and particularly for those with diabetes and CVD. In developing a personalized approach, factors like frailty, comorbidities, polypharmacy, and socioeconomic background should be considered. More efforts are needed to optimize the prevention and management of cardiovascular disease among older adults with type 2 diabetes in the region. The potential benefits of SGLT2 inhibitors and its increasing availability in the region may have the potential to significantly impact the treatment of diabetes and its related comorbidities in Southeast Asia. However, existing local evidence is still limited and highlights the need for more local studies in the region.

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Appendices

Relevant published papers authored by me that are related to the thesis topic but not included as a chapter:

Appendix 1
Wong WJ, Nguyen TN, Fortin M, Harrison C. Prevalence and patterns of comorbidities in older people with type 2 diabetes in Australian primary care settings.' Australasian Journal on Ageing, 2024; 43(2): 306-313. Doi: https://doi.org/10.1111/ajag.13282

Appendix 2
Addressing comorbid conditions in older people with type 2 diabetes'. 29 April 2024 on InSight+ (by The Medical Journal of Australia), accessed at https://insightplus.mja.com.au/2024/16/addressing-comorbid-conditions-in-older-people-with-type-2-diabetes/

Appendix 3
Nguyen TV, Nguyen HTT, Truong DN, Nguyen VQ, Nguyen HQ, Nguyen HQ, Ngo TTK, Amsalu E, **Wong WJ**, Nguyen TN. 'Medication adherence and hospitalizations in older patients with coronary heart disease in Vietnam.' British Journal of Clinical Pharmacology, 2025; 1-9. Doi: https://doi.org/10.1111/bcp.16405

Appendix 1

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RESEARCH ARTICLE

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Prevalence and patterns of comorbidities in older people with type 2 diabetes in Australian primary care settings

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Abstract

Objective: The aim of this study was to identify the prevalence and patterns of comorbidity in community-dwelling older people with type 2 diabetes mellitus (T2DM) attending general practice settings in Australia.

Methods: This study involved a cross-sectional analysis using the Bettering the Evaluation and Care of Health (BEACH) sub-study data. In a series of sub-studies, a representative sample of general practitioners was asked to record all diagnosed chronic conditions for patients at 40 consecutive encounters using structured paper-based recording forms. The dataset was analysed with descriptive analyses, and exploratory factor analyses were applied to examine comorbidity patterns.

Results: Of the 14,042 patients aged 65 years or older, 2688 had a diagnosis of T2DM (19%). Of the 2688 patients with T2DM, hypertension was present in 67% (95% CI: 64.6–70.0), followed by arthritis 52% (95% CI: 48.8–54.8), hyperlipidaemia 45% (95% CI: 41.8–47.9), ischemic heart disease, 23% (95% CI: 20.7–24.9), depression 16% (95% CI: 48.8–54.8), atrial fibrillation 10% (95% CI: 8.9–11.6), congestive heart failure 7% (95% CI: 6.0–8.1), stroke/cerebrovascular accident 7% (95% CI: 5.4–8.2) and peripheral vascular disease 5% (95% CI: 4.4–6.2). We identified two comorbidity patterns among older people with T2DM. The first were psychological and musculoskeletal conditions and the second were cardiovascular conditions and chronic renal failure.

Conclusions: The prevalence of cardiovascular and non-cardiovascular comorbidities in community-dwelling older people with T2DM was high. Adequate primary care strategies should be in place to support the long-term care for this population.

KEYWORDS

comorbidities, geriatric medicine, older person, primary care, type 2 diabetes mellitus

1 | INTRODUCTION

The national prevalence of type 2 diabetes mellitus (T2DM) in Australia is estimated to be about 5%[1] with studies indicating this has increased over the past few decades.[2]

The prevalence of T2DM increases with age, to about 5% in those aged 45–54 years, 10% in those aged 55–64 years and almost 20% in those 65 years and above.[3] The increasing prevalence in the older population underscores the reason why T2DM remains a national public health priority.[4,5]

For older persons with T2DM, the provision of targeted care can help improve treatment outcomes.[6] When developing targeted management strategies, it is helpful to take into account risk factors that contribute to the complexity of care and affect progression. Age[4] and comorbidities[7] are among the reported factors that can influence the treatment and management of those with T2DM. As comorbidities can increase the burden of illness for a patient, understanding the type and prevalence of comorbidities can help in the development of targeted care, both at the patient and population levels.[6]

The impact of comorbidities in people with T2DM remains underexplored. There have been increasing calls for a better understanding of the prevalence of comorbidities and how it affects overall health outcomes in people with T2DM.[8] Although T2DM has been commonly associated with cardiovascular-related comorbidities, much less is known about its association with non-cardiovascular-related comorbidities. The International Geriatric Diabetes Society has called for a better understanding of comorbidities to help improve how care is provided, thus supporting more efficient use of health resources.[9] In a research prioritisation exercise, Diabetes UK have also identified care for older people with diabetes as an area for further research, specifically in improving understanding of the characteristics of older people with diabetes to support patient-centred care.[10] It recommends the use of existing or new datasets to help better characterise the population of older people with diabetes.[10] In Australia, general practitioners (GPs) form the backbone of the health-care system as the main providers of primary care. In 2019–20, about 95% of all older people in Australia visited a GP at least once.[11] GP data can provide an ideal snapshot of active T2DM cases and help inform management strategies and cost implications.

In this study, we used a representative sample of older patients at Australian GP encounters to: (1) estimate the prevalence of different comorbidities in older patients at encounters with diagnosed T2DM and (2) identify comorbidity patterns in older patients at encounters with T2DM.

Practice Impact

The number of comorbidities in older people with type 2 diabetes mellitus (T2DM) in Australia is high and varied. Our exploratory factor analyses show two patterns of comorbidities—(1) psychological, musculoskeletal conditions and gastro-oesophageal reflux disease and (2) cardiovascular conditions together with chronic renal failure. Health systems must be adequately supported to provide the necessary services required.

2 | METHODS

For this study, we analysed data from a series of sub-studies from the Bettering the Evaluation And Care of Health (BEACH) program. The BEACH program was a continuous, national cross-sectional study of GP clinical activity in Australia from April 1998 to March 2016.[1] It involved GPs recording patient encounters on structured paper-based recording sheets, and the data were then coded by trained clinical coders. Each year, an ever-changing, random sample of about 1000 GPs took part in recording information on patient encounters for 100 consecutive consenting patients. For this sub-study, a random sample of 1800 participating GPs was asked to record all diagnosed chronic conditions in each of 30 consecutive patients over 15 separate 5-week recording periods between 27 November 2012 and 28 March 2016. Our analysis examined those patients aged 65 years or older.

The recording sheets contained a list of comorbidities with corresponding check boxes and GPs were invited to tick accordingly, together with an option for free text if needed. There were 27 different comorbidities listed (including T2DM) for ease of recording. The list of comorbidities was based on common presentations at GP clinics.

2.1 | Statistical analysis

Analysis of the data was performed using SAS (version 9.4). Continuous variables are presented as means with 95% confidence intervals, and categorical variables as frequencies and percentages with 95% confidence intervals. The BEACH study has a single-stage cluster design with the GP (as the unit of sampling) having a cluster of patient encounters around them (the unit of inference). Descriptive statistics were provided at the patient encounter level (unadjusted) and for the general population who have diagnosed T2DM. All descriptive analyses adjusted for the cluster using 'surveymeans' procedure in SAS (version 9.4) to produce robust 95% confidence intervals. The importance of measuring patient encounter prevalence is that it reflects the complexity of a GP's day-to-day workload (e.g. the comorbidities of patients sitting in front of them). Adjusting the results to estimate population prevalence allows for comparison with international findings in countries with different primary care systems.

Further description on the method of adjustment has been described extensively elsewhere.[1] Briefly, it adjusts for the number of times a patient has seen a GP in the previous 12 months. This considers the fact that

frequent attenders seeing GP's will have a higher chance of being included in our sample. It then adjusts for the proportion of people in each age–sex group who did not see a GP at least once. This is so as it is assumed, in the Australian context, that this group of people did not have a current diagnosed chronic condition being managed. Since the method of estimating general population prevalence assumes that patients with diagnosed T2DM would see a GP at least once in a year, the estimate for patients who attend at least once is the same as those people with diagnosed T2DM living within the wider population. We report the adjusted prevalence estimates as the population level.

To identify comorbidity patterns in community-dwelling older adults with T2DM, we conducted an exploratory factor analysis of the 11 comorbidities. Only comorbidity types with a prevalence greater than 2% were included in this analysis. The number of factors to be extracted was decided based on the cumulative proportion of variance explained greater than 1. Oblimin rotation was applied as the factors were expected to be correlated. The minimum loading for an item to be linked to a factor was 0.30. In cases where one item was loaded into two factors, the one with higher loading value was chosen.

We analysed all chronic conditions recorded (both the listed conditions and those entered in free text) when calculating the overall number of comorbidities. The comorbidities reported in the prevalence table and used in the exploratory factor analyses were based on the 27 listed comorbidities.

The BEACH program received ethics approval by the Human Research Ethics Committee of the University of Sydney (Ref: 2012/130).

3 | RESULTS

Of the 1800 GPs who agreed to participate, 1449 GPs returned the recording sheets with completed information on 43,501 patients at the sampled encounters. After reducing our sample to older patients, we found that 1400 GPs recorded all chronic conditions for 14,042 patients aged 65 and above at the sampled encounters. Of these, 19% (2688) of older patients at encounters were reported as having diagnosed T2DM.

Patient characteristics of those in our sample of encounters are shown in Table 1. Male patients were more likely to have a T2DM diagnosis, with 22% of male patients at encounters reported to have T2DM compared with 17% of female patients. The majority of the patients in the dataset were 65–84 years old, and patients in this age group had higher prevalence of T2DM compared to those 85 years old and above. Patients with a non-English-speaking background were more likely to have T2DM (31% compared to 18% for those with an English-speaking background). Indigenous patients at encounters were more likely to have a T2DM diagnosis compared with those from a non-indigenous background. Patients at encounters with a health-care card were more likely to have a diagnosis of T2DM compared to those with no health-care card. GP characteristics were not associated with differences in the prevalence of T2DM.

Figure 1 shows that majority of older patients with a T2DM diagnosis had at least one comorbidity, with 95% of the population reporting to have one or more comorbidities, while almost two-thirds (68%) had three or more comorbidities.

Table 2 shows the prevalence of specific comorbidities among older patients with T2DM. As shown below, the majority of the top five comorbidities were risk factors for cardiovascular disease, with hypertension reported in almost two-thirds (67%) of patients within the general population, followed by arthritis-related comorbidities at 52%, hyperlipidaemia (45%), ischemic heart disease (23%) and obesity (20%).

For the exploratory factor analyses, the three sub-types of arthritis were grouped together and comorbidities with a prevalence less than 2% among patients at encounters were excluded. This meant that hyperthyroidism and type 1 diabetes were excluded. Cross-loading among the factors did not happen. Exploratory factor analyses identified two patterns of comorbidities, as shown in Table 3, the first being psychological, musculoskeletal conditions and gastro-oesophageal reflux disease (GORD) and the second being cardiovascular conditions together with chronic renal failure.

4 | DISCUSSION

Our analysis of 2688 older patients with type 2 diabetes shows that the majority of patients in this group have at least one comorbidity. The number of older patients with one or more comorbidity in our study was also noted to be higher than the 60% that was reported in a review.[6] This could be due to our analysis considering all diagnosed chronic conditions as opposed to a predefined list, which has been shown to provide a more accurate estimate.[12]

The most prevalent comorbidities were varied, ranging from cardiovascular disease (e.g. ischemic heart disease and stroke), endocrinology (e.g. thyroid disorders) and mental health (e.g. depression and anxiety). Hypertension was the most common comorbidity reported in our study, consistent with findings from other studies.[7,13] The high number of reported cardiovascular-related comorbidities in our study was consistent with

TABLE 1 Prevalence of type 2 diabetes among patients aged 65+ at encounters.

	Number of patient encounters ($n = 14,042$)	Number of patients at encounters with T2DM ($n = 2688$)	Prevalence of T2DM at GP encounters (percentages and 95% confidence intervals)
Patient sex (missing)	(77)	(16)	
Male	5767	1275	22% (20.9–23.3)
Female	8198	1397	17% (16.1–18.0)
Patient age (missing)	(0)	(0)	
65–84	11,475	2323	20% (19.4–21.1)
85+	2567	365	14% (12.8–15.6)
Socioeconomic status (missing)	(251)	(40)	
Most advantaged	7844	1391	18% (16.8–18.7)
Most disadvantaged	5947	1257	21% (20.0–22.3)
Commonwealth health-care card (missing)	(668)	(103)	
Yes	10,490	2184	21% (19.9–21.7)
No	2884	401	14% (12.6–15.3)
Language background (missing)	(778)	(115)	
Non-English-speaking	1118	341	31% (27.7–33.4)
English-speaking	12,146	2232	18% (17.6–19.2)
Indigenous background (missing)	(779)	(117)	
Indigenous	96	42	44% (31.3–56.2)
Non-indigenous	13,167	2529	19% (18.4–20.0)
GP practice location (missing)	(1647)	(320)	
Major city	8235	1570	19% (18.1–20.1)
Inner regional	2776	512	18% (16.8–20.1)
Outer regional/remote	1384	286	21% (18.1–23.3)
GP sex (missing)	(0)	(0)	
Male	8872	1702	19% (18.2–20.2)
Female	5170	986	19% (17.8–20.3)
GP age group (missing)	(60)	(15)	
<45	2625	509	19% (17.7–21.1)
45–54	3663	743	20% (18.8–21.8)
55+	7694	1421	19% (17.4–19.5)
Country of GP graduation (missing)	(34)	(12)	
Overseas	4143	840	20% (18.9–21.7)
Australia	9865	1836	19% (17.7–19.6)
Total	14,042	2688	19% (18.4–19.9)

other studies, both locally in Australia[14,15] and internationally.[7,13] Cardiovascular-related conditions continue to represent a large portion of comorbidity patterns in older people with T2DM[16,17] and a large contributor to mortality rates.[18,19] For older people with T2DM, ongoing efforts in managing cardiovascular risk factors need to be sustained, if not further strengthened.

Our study showed two patterns of multimorbidity that included 'psychological, musculoskeletal and GORD' and 'cardiovascular conditions and chronic renal failure'. As

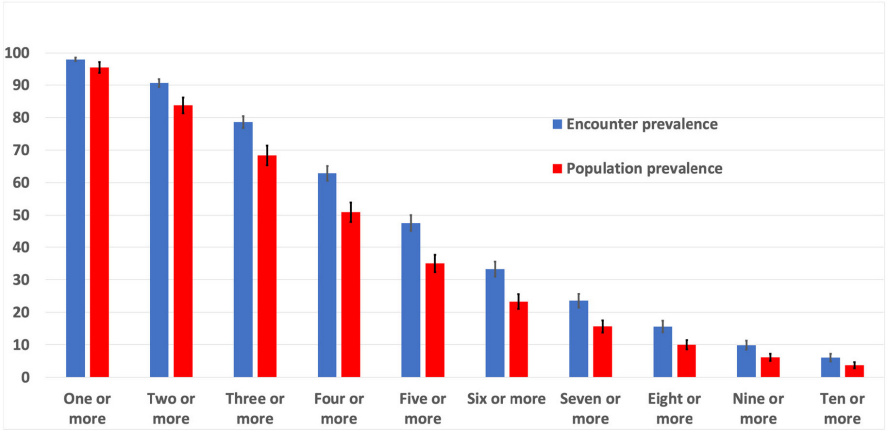

FIGURE 1 Number of comorbidities among older patients with type 2 diabetes.

expected, patterns of cardiometabolic-related comorbidities are associated with T2DM and this has been extensively reported.[20] In contrast, there are fewer studies on non-cardiovascular-related comorbidities in older people with T2DM in the literature, and when reported, they usually had lower prevalence compared to cardiovascular comorbidities.[7,8,13] In our study, comorbidities that formed the cluster 'psychological, musculoskeletal, and GORD' include depression, insomnia, anxiety, arthritis, chronic back pain and gastro-oesophageal reflux disease.

Non-cardiovascular comorbidities can also complicate the management of T2DM as they may require additional medications, lifestyle modifications and specialised health-care interventions. Neglecting these comorbidities can affect achieving glycaemic target range, increase risk of complications and decrease quality of life.[7,8]

Symptoms of psychological conditions like depression and anxiety can include lower energy, loss of appetite and sleep disturbances. These symptoms are sometimes present in people living with T2DM, particularly in those with glycaemic levels outside the target range.[21] For older persons with T2DM, this is concerning as differentiating symptoms related to T2DM or psychological conditions can then be challenging.[21] It highlights the importance of specific screening for psychological conditions together with adequate monitoring of treatment effectiveness.

Patients with musculoskeletal conditions like arthritis can experience chronic pain, limited mobility and functional impairment, which can significantly affect quality of life.[22] Moreover, older patients are at an increased risk of falls and fractures.[6] Managing diabetes and musculoskeletal conditions together can then be challenging, as pain and immobility may interfere with physical activity and exercise, which are critical components of diabetes management. In a study in 67,132 patients with diabetes in the United States, the authors found that higher HbA1c levels were associated with the presence of chronic back pain, possibly due to the impact of diabetes on neuropathic pathways.[23] Considering the limited evidence to support patient care in diabetes and musculoskeletal conditions, a comprehensive approach is then needed, one that includes regular screening, tailored exercise program and pain management strategies to help minimise the impact of musculoskeletal conditions in older people with diabetes.

People with diabetes are prone to experiencing gastrointestinal disorders, as reported in a meta-analysis, and this condition can be exacerbated in older people due to ageing-related changes in the digestive system.[24] Medications commonly used for diabetes management like metformin and sulfonylureas are also associated with gastrointestinal-related side effects.[17] This could affect taking diabetes medicines or alternatively, introduce unnecessary further therapy to manage gastrointestinal-related symptoms. As there are various reasons that could affect gastrointestinal side effects for older people with diabetes, regular monitoring and thorough history taking is needed to better identify whether gastro-related side effects are due to medications used or other pathophysiological reasons related to diabetes.

4.1 | The important role of primary care in the management of type 2 diabetes

The high number of older people with T2DM with varied comorbidities in our study highlights the complexity of patients that are attending primary care. This is consistent with another study in Australia that shows how more than 50% of overall patients with T2DM attending GPs are aged 60 years and above.[25] Self-managing T2DM alone already requires much time and effort. The additional comorbidities an older person with T2DM may have then further adds to the resources needed for management. GPs can

TABLE 2 Prevalence of specific comorbidities among patients aged 65+ with type 2 diabetes.

Comorbidity	Prevalence % (95% CI) $n = 2688$	
	Among population	At encounters
Hypertension	67 (64.6–70.0)	71 (69.5–73.3)
Any arthritis	52 (48.8–54.8)	59 (57.1–61.7)
Osteoarthritis	50 (46.5–52.5)	57 (54.8–59.4)
Other arthritis	3 (1.8–3.3)	3 (2.4–3.9)
Rheumatoid arthritis	2 (1.0–2.6)	2 (1.6–2.7)
Hyperlipidaemia	45 (41.8–47.9)	48 (45.9–50.8)
Ischemic heart disease	23 (20.7–24.9)	28 (26.4–30.1)
Obesity	20 (18.3–22.6)	23 (21.4–25.1)
Gastro-oesophageal reflux disease	18 (15.9–19.7)	23 (20.6–24.3)
Depression	16 (13.8–17.3)	20 (17.8–21.1)
Chronic back pain	13 (11.2–14.6)	17 (14.8–18.2)
Malignant neoplasm	12 (10.0–13.4)	14 (12.2–15.0)
Atrial fibrillation	10 (8.9–11.6)	14 (12.8–15.5)
Chronic obstructive pulmonary disease	9 (8.0–10.7)	12 (10.8–13.4)
Anxiety	9 (7.9–10.7)	12 (10.1–12.9)
Osteoporosis	9 (7.8–10.6)	12 (10.6–13.5)
Chronic renal failure	9 (7.3–9.8)	12 (10.8–13.6)
Congestive heart failure	7 (6.0–8.1)	10 (9.0–11.4)
Stroke/cerebrovascular accident	7 (5.4–8.2)	8 (6.7–8.8)
Hypothyroidism	7 (5.5–7.6)	8 (6.7–8.9)
Asthma	7 (5.5–7.5)	9 (7.7–9.9)
Peripheral vascular disease	5 (4.4–6.2)	8 (6.5–8.7)
Dementia	5 (4.3–6.2)	7 (5.5–7.7)
Sleep apnoea	5 (3.9–5.7)	6 (5.4–7.3)
Glaucoma	4 (3.0–4.7)	5 (3.6–5.3)
Insomnia	4 (3.0–4.7)	6 (4.7–6.7)
Hyperthyroidism	1 (0.5–1.2)	1 (0.6–1.4)
Type 1 diabetes	0 (0.1–0.5)	0 (0.1–0.6)

play an important role as 'gatekeepers' due to their ease of access and ability to conduct screening, diagnosis and intervention. Additionally, the varied comorbidities show the care that is needed from other health-care providers and not just solely from the GP.[26] The majority of patient encounters in our study were recorded by GPs practising in major city areas, which is representative of the proportion at the national level. We did not analyse further on the impact of geographical locations and continuity and access of treatment as this was not the scope of the study, but this can be explored further in future studies to provide insights on how primary care providers are innovating.

The fact that prevalence of cardiovascular-related and non-cardiovascular-related comorbidities continues to be high in older people with diabetes highlights the ongoing need for adequate management strategies. People with T2DM may sometimes consult GPs for these other comorbidities and mention diabetes as a concern and thus not be viewed as a priority.[26] As having glycaemic levels within the target range have an added benefit of managing cardiovascular risk factors and influencing progression of other non-cardiovascular-related comorbidities, primary care providers should continue to be well supported to help facilitate this.

4.2 | Implications for research and practice

The results of this analysis underline the high prevalence and type of comorbidities among older patients with T2DM. Providing care for older person continues to be a challenge as health-care systems are often configured around a single condition. With the number of older people with multiple comorbidities expected to increase further,[27] health systems should take the necessary steps in preparation to provide better care. Organisational adaptations are needed as we grow and develop mature health-care systems for targeted approaches, especially in settings with scarce resources. The ever-evolving challenges faced by older person living with diabetes, particularly in managing the multiple comorbidities, involves understanding specific social factors that contribute to its increasing prevalence.[27] This also calls for localised interventions considering the unique nature of different sociodemographic groups and geographical locations. Even with the growth of evidence-based strategies, implementation appears to still be uneven, with the lack of contextualisation identified as one of the barriers to this.[28] Furthermore, there are few care pathways that are guided by the unique comorbidity patterns faced by those with T2DM.[29] Hence, further understanding of prevalence can provide a basis for improved implementation.

4.3 | Strengths

To our knowledge, this study is the first estimation of prevalence and patterns of comorbidities in older people with T2DM using Australian general practice data. Published studies thus far tend to include patients from a younger population and the results of our analysis adds to the broader literature by reporting prevalence for older people. The BEACH methodology ensured the robustness of data and the benefits of involving GPs in the data collection. GPs were able to record the diagnosed chronic

TABLE 3 Factor loading matrix of the comorbidities with Oblimin rotation.

	Comorbidities loading into each factor ($n = 2688$)			
	Factor 1—psychological, musculoskeletal and GORD		Factor 2—cardiovascular conditions and chronic renal failure	
Type of comorbidity	Among population	At encounters	Among population	At encounters
Depression	0.52	0.49	—	—
Insomnia	0.41	0.41	—	—
Anxiety	0.49	0.48	—	—
Arthritis	0.36	0.33	—	—
Chronic back pain	0.33	0.35	—	—
Gastro-oesophageal reflux disease (GORD)	0.30	0.31	—	—
Ischemic heart disease	—	—	0.40	0.41
Congestive heart failure	—	—	0.43	0.46
Chronic renal failure	—	—	0.32	0.31
Peripheral vascular disease	—	—	0.31	0.32
Atrial fibrillation	—	—	0.34	0.35

Note: The minimum loading for an item to be linked to a factor was 0.3.

conditions by: using their knowledge of the patient; accessing the patient's medical records; and acting as an expert interviewer. This is a more robust method than relying on patient self-report or medical record review alone. The BEACH dataset has been shown to be representative of all patients at GP encounters.[30]

4.4 | Limitations

The dataset is cross-sectional and not able to provide information on the association with health outcomes. Although studies involving care and management of people with multiple comorbidities are growing, more longitudinal studies are needed to better understand the type and nature and extent of influence the different types of comorbidities can have on patient management and health outcomes. We did not compare the number and pattern of comorbidities in a younger and older population and this could be considered for future studies.

5 | CONCLUSIONS

Our study found that most older people with T2DM have three or more additional chronic conditions, which can influence their management and health outcomes. The patterns of comorbidities revealed through our study are useful for developing holistic and individualised treatment plans, and addressing potential drug interactions and contraindications. Overall, a comprehensive understanding of these comorbidities is essential to optimise the care and outcomes for older people with diabetes. With diabetes and associated comorbidities contributing to the growth of non-communicable diseases in Australia, the next stage of focus would be on the development of specific and targeted approaches considering the different cultural and socioeconomic features unique to the affected population. By focusing on older people in an Australian primary care setting, it reminds us that patients from different demographics have unique comorbidity patterns and effort needs to be sustained or further amplified in designing health-care systems which are equitable for all.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest declared.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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Appendix 2

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Addressing comorbid conditions in older people with type 2 diabetes

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As diabetes care continues to grow and evolve, understanding of comorbidity patterns can help inform the design of future health services.

Although there have been considerable improvements in diabetes care in Australia in recent years, the prevalence of significant comorbid conditions in older people with diabetes can add to the complexity of care needed.

The prevalence of diabetes (type 1, type 2 and other diabetes, excluding gestational diabetes) in Australia is estimated to be around 5%. In 2021, diabetes contributed to 11.2% of all deaths in Australia and was among the ten leading causes of death. Mortality rates for diabetes have also been reported to be higher in people aged 85 years and over compared with younger populations.

The prevalence of diabetes increases with age, with about 20% of Australians aged 80–84 years living with diabetes.

The prevalence of diabetes increases with age (Halfpoint / Shutterstock).

In a recent research prioritisation exercise, Diabetes UK identified certain areas of focus to improve the care of older people. Among them was a better understanding of characteristics such as comorbid conditions of older people with diabetes.

In a 2020 review, a panel of multidisciplinary experts who were part of the International Geriatric Diabetes workshop highlighted the lack of inclusion of older people in diabetes research compared with younger population. Recommendations were made also for the development and establishment of patient classification systems based on comorbidity patterns. This would help guide treatment allocation and better use of limited health care resources.

Older people with diabetes have varied backgrounds and medical profiles, and a better understanding of comorbidity patterns can help in the development of targeted care.

The patterns of comorbid conditions in older people

For our analysis, we focused on older people aged over 65 years with type 2 diabetes mellitus where all of their comorbid conditions were recorded by the general practitioner. We conducted descriptive analyses and explanatory factor analyses to identify comorbidity patterns of older people with type 2 diabetes mellitus.

We found that 19% of patients aged 65 years or older at GP encounters had a diagnosis of type 2 diabetes mellitus. Patients aged 65–84 years had a higher type 2 diabetes mellitus prevalence than those aged 85 years or over (20% *v* 14%). Patients from a non-English speaking background were more

likely to have type 2 diabetes mellitus (31%) compared with those from an English-speaking background (18%). The majority of patients with type 2 diabetes mellitus (95%) had at least one comorbid condition, and almost two-thirds (68%) had three or more comorbid conditions.

We identified a high prevalence of cardiovascular-related comorbid conditions such as hypertension (71%), hyperlipidaemia (48%) and ischaemic heart disease (28%) in our dataset. We also identified two distinct patterns of comorbid conditions among older people with type 2 diabetes mellitus: a pattern that associates psychological and musculoskeletal conditions, and another pattern linking cardiovascular conditions with chronic renal failure. The psychological and musculoskeletal conditions frequently occurring together comprised depression, insomnia, anxiety, arthritis, chronic back pain and gastro-oesophageal reflux disease. The cardiovascular conditions that co-occurred together included ischaemic heart disease, congestive heart failure, peripheral vascular disease, atrial fibrillation and chronic renal failure.

Our study had some limitations, including the cross-sectional design. We were not able to explore the influence and impact of comorbid conditions over time. Future longitudinal studies examining the impact of comorbid conditions among older people with type 2 diabetes mellitus could address this.

The challenges of mental health and linguistic diversity

The presence of non-cardiovascular-related comorbid conditions highlights the heterogeneity of older people with type 2 diabetes mellitus.

Older people with type 2 diabetes mellitus are not exempt from the ongoing mental health crisis. A recent report from Bartholomaeus and colleagues showed an increasing rate of utilisation by older Australians of primary care mental health services from 2009 to 2019. If we consider mental health and its implications for diabetes, there is growing evidence of an association between mental disorders such as depression and anxiety, poor glycaemic control, diabetes-related complications and mortality. The Royal Australian College of General Practitioners (RACGP) have resources on mental health and type 2 diabetes mellitus that could be used accordingly.

In our study sample, the prevalence of type 2 diabetes mellitus was much higher in people with non-English speaking background (31%) compared with people with English-speaking background (18%). A recent review on access to health services among culturally and linguistically diverse populations in Australia highlighted the different challenges, one of them being inadequate interpreter services and its link to low levels of health literacy. However, another study reported that some GPs felt that an interpreter was not needed due to the GPs being multilingual. In managing type 2 diabetes mellitus, patients may require other health services apart from their GPs, and considerations should be made to ensure more members of the health care team have the necessary communication support.

As diabetes care continues to grow and evolve, understanding of comorbidity patterns can help inform the design of future health services. Our analysis of patients attending GPs in our studied population showed many older patients with type 2 diabetes mellitus (two-thirds) have several comorbid

conditions. This shows the continuing need to strengthen primary health care in Australia, led by GPs, ensuring continuity of care. Given their complex needs, it is essential to maintain continuity of care beyond their GPs to prevent the fragmentation of treatment for older patients with diabetes.

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Appendix 3

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ORIGINAL ARTICLE

Medication adherence and hospitalizations in older patients with coronary heart disease in Vietnam

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Abstract

Aims: This study aimed to assess medication adherence among older people with coronary heart disease and its relationship with hospitalizations.

Methods: This is a prospective cohort study conducted at the outpatient clinics of a major hospital in Vietnam from November 2022 to June 2023. Consecutive older patients with coronary heart disease were recruited and followed for 6 months. Medication adherence was defined using the five-item Medication Adherence Report Scale (MARS-5). Multivariable logistic regression models were applied to examine the impact of medication adherence on hospitalization due to cardiovascular disease (CVD) and all-cause hospitalization.

Results: There were 643 participants, mean age 73 ± 8 years, 74.3% were male. Overall, 76.4% (491/643) were classified as 'adherent'. Over 6 months follow-up, 23.3% of the participants were admitted to hospital and of these hospitalizations, 9.2% were due to CVD. The CVD-related hospitalization rate was significantly higher in the non-adherent group compared to the adherent group (13.8% *vs*. 7.7%, $P = 0.023$, respectively). In logistic regression models, medication adherence was associated with significantly reduced odds of CVD-related hospitalization (adjusted odds ratio [OR] 0.48, 95% confidence interval [CI] 0.27–0.86). Medication adherence was also associated with a trend of reduced all-cause hospitalization (adjusted OR 0.75, 95% CI 0.49–1.15).

Conclusions: This study showed a positive relationship between medication adherence and reduced risk of CVD-related hospitalization in older people with coronary heart disease. Healthcare providers should consider incorporating adherence assessment into the long-term care for older patients with coronary heart disease.

KEYWORDS

coronary heart disease, frailty, MARS-5, medication adherence, multimorbidity, Vietnam

The authors confirm that the PI for this paper is Tan Van Nguyen (T.V.N.) and that he had direct clinical responsibility for patients.

1 | INTRODUCTION

Coronary heart disease is the leading cause of mortality globally.[1] The prevalence of coronary heart disease increases with ageing.[2] The management of coronary heart disease aims to reduce cardiovascular events and mortality, control symptoms and improve quality of life.[1] The treatment of coronary heart disease is complex and generally includes a combination of optimizing risk factors, pharmacotherapy and percutaneous or surgical revascularization if indicated. Pharmacological management includes anti-anginal medications (such as nitrates, beta blockers, calcium channel blockers), and cardioprotective medications (such as antiplatelets, statins, angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers).[1] These medications have been shown to reduce cardiovascular events in patients with coronary heart disease.[1] In older people with coronary heart disease, medication adherence is critical to manage this condition. However, poor medication adherence continues to be a significant health challenge worldwide and many studies have shown that medication adherence rates in older patients lie around 30% to 50%.[3,4] Poor medication adherence can lead to worsening symptoms, increased risk of acute coronary syndromes and strokes, increased hospitalizations and reduced overall quality of life.[3,5–7] Poor or suboptimal medication adherence may also lead to unnecessary therapeutic intensification, whether dose increase or addition of new agents. This can further increase the risk of potential harm from polypharmacy. The risk is further amplified for older persons due to the biological changes associated with ageing.

In Vietnam, the population is ageing, and coronary heart disease is among the leading causes of mortality in this population.[8–11] There have been several studies on medication adherence in patients with cardiovascular disease (CVD) in Vietnamese adults. In a study of 175 patients (mean age 61) hospitalized due to acute myocardial infarction, the adherence rate to antiplatelet therapy among the participants was quite high at 1 month after discharge (90.3%), then declining by 6 months (88.0%), 12 months (75.4%) and more than 12 months (46.3%).[12] A study conducted on 1038 patients with chronic CVD (mean age 63) published in 2022 showed that only 59.3% of the participants were adherent to their cardiovascular medications.[13] Another study in 177 patients (median age 63) reported an adherence rate to oral anticoagulants of 37.7%.[14] A study among people living in rural areas in Vietnam with hypertension (aged 35–64) showed that only 49.8% of the participants were adherent to antihypertensive medications.[15] However, there is limited evidence on medication adherence in older people with coronary heart disease.

Therefore, the primary aims of this study were to assess adherence to cardiovascular medications in people aged 60 years or older with coronary heart disease, and to examine the relationship between medication adherence and CVD-related hospitalization in this population. The secondary aim was to examine the relationship between medication adherence and all-cause hospitalization.

What is already known about this subject

- Several studies on medication adherence among Vietnamese adults with cardiovascular disease found that adherence rates were suboptimal, ranging from 38% to 59%.
- However, there is limited evidence regarding medication adherence in older adults with coronary heart disease.

What this study adds

- This was the first study to examine medication adherence in older people with chronic coronary syndrome in Vietnam.
- Our study also reported the relationship of medication adherence with CVD-related hospitalizations, an outcome that is not routinely reported in studies on medication adherence.

2 | METHODS

2.1 | Study design and population

This prospective, observational study was conducted at the outpatient clinics of Thong Nhat Hospital in Ho Chi Minh City from November 2022 to June 2023. Consecutive patients aged ≥60 years diagnosed with coronary heart disease who visited the clinics during the study period were recruited. Coronary heart disease was defined if a patient had any of these criteria more than 3 months before participating in this study: (1) a history of acute coronary syndrome, or (2) significant stenosis on percutaneous coronary angiogram or computerized tomography coronary angiogram (≥50% for left main coronary artery, ≥70% for other coronary arteries), or (3) percutaneous coronary interventions (PCI) or coronary artery bypass graft surgery (CABG). Exclusion criteria included (1) having dementia or having a mental illness that can affect their ability to answer the study questionnaires, (2) not being able to provide consent, and (3) having a life expectancy of <6 months.

The study was approved by the Ethics Committees of the University of Medicine and Pharmacy at Ho Chi Minh City (Reference Number 936/HDDD-DHYD, date 24/11/2022). Informed consent was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki.

2.2 | Data collection

Data were collected from patient interviews and medical records. Information obtained included demographic characteristics, height,

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weight, medical history, blood test results and comorbidities. Frailty was assessed using the Clinical Frail Scale (CFS).[16,17] The CFS score ranges from 1 to 9, and a score of 4 or greater indicates a frailty status.[16,18] Polypharmacy was defined as using five or more medications on a daily basis. Cardiovascular multimorbidity (CVD multimorbidity) was defined as having any of the following conditions in addition to coronary heart disease: heart failure, stroke, atrial fibrillation, peripheral artery disease, chronic kidney disease and diabetes.

2.2.1 | Assessment of medication adherence

Participants' medication adherence was assessed using the five-item Medication Adherence Report Scale, MARS-5 (© Professor Rob Horne).[19,20] We used the Vietnamese version of the MARS-5 which was approved by Professor Rob Horne. The MARS-5 questionnaire comprised five components: (1) I forget to take my medicines, (2) I alter the dose, (3) I stop taking them for a while, (4) I decide to miss out a dose, (5) I take less than instructed. The first statement indicates unintentional non-adherence, and the other four statements indicate intentional non-adherence. The participants answered these five statements on a 5-point Likert scale (1, always; 2, often; 3, sometimes; 4, rarely; 5, never). MARS-5 total scores range from 5 to 25, and higher scores indicate better medication adherence. In line with previous studies, we used a cut-off value of 23 to define adherence: non-adherence was defined as MARS-5 scores ≤23 and adherence was defined as MARS-5 scores 24–25.[19,20]

2.2.2 | Outcome variables

The primary outcome was CVD-related hospitalization. The secondary outcome was all-cause hospitalization. All participants were followed up for 6 months after being included in the study. Hospitalization information was obtained by making phone calls to the phone numbers provided by participants or their caregivers after 6 months. The causes of hospitalization were documented and classified as CVD-related hospitalization or all-cause hospitalization.

2.3 | Sample size estimation

Based on the local data, we estimated that the rate of CVD-related hospitalization in older patients with chronic coronary heart disease in 6 months would be around 10%. Therefore, we estimated that at least 640 patients with coronary heart disease would be needed in this study to detect a difference in the CVD-related hospitalization rates between patients who were adherent to medication compared to those who were non-adherent (assuming a relative difference of 40% in CVD-related hospitalization rates between the two groups, with a power of 80%, one-sided test, alpha = 0.05, and allowing for 10%–12% dropout during follow-up).

2.4 | Statistical analysis

Study population characteristics are presented as mean and standard deviation (SD) for continuous variables, or frequencies and percentages for categorical variables. Comparisons in general characteristics and hospitalization rates between the adherent and non-adherent groups were conducted using chi-square tests or Fisher's exact test for categorical variables, and Student's *t*-tests for continuous variables. Multivariable logistic regression models were applied to examine the impact of medication adherence on CVD-related hospitalization and all-cause hospitalization. The following covariates were hypothesized to possibly have an impact on hospitalization in older people with coronary heart disease and were therefore included in the adjusted logistic regression models: age, sex, history of PCI/CABG, frailty and CVD multimorbidity. Age (in years) and frailty (the CFS score) were treated as continuous variables, and all other variables were categorical. *P*-values <0.05 were considered statistically significant. Data were analysed using SPSS Statistics 27.0. and R 4.3.1 (IBM, Cary, NC, USA).

3 | RESULTS

A total of 643 participants were included in this study. They had a mean age of 73.1 ± 8.3 years, 25.7% were female and 74.3% were male. Table 1 presents the participant characteristics. A majority of participants (49.0%) had completed higher education. Most of the participants were retired, and 4.4% of them were still working. The mean CFS score was 3.9, and 60.3% of the participants were classified as being frail. Polypharmacy was present in 89.6% of the participants (with a mean total number of medications of 6.7), and 65.8% had a history of PCI/CABG. Hypertension and dyslipidaemia were present in 96.9% and 95.3% of the participants, respectively. Among the cardiometabolic comorbidities, diabetes mellitus was the most prevalent (42.6%), followed by atrial fibrillation (30.1%), heart failure (15.6%), chronic kidney disease (8.0%), and ischaemic stroke (5.6%). Regarding carers, 10.6% of the participants did not have any carer, 70.6% had support from their spouse, 17.0% from their children, and 1.8% from other relatives or professional carers.

Compared to the non-adherent group, the adherent group was older (mean age 73.5 years in the adherentgroup *vs.* 72.0 years in the non-adherent group). The proportion of females was higher in the adherent group (28.1% *vs.* 17.8% in the non-adherent group, $P = 0.011$). The proportion having support from children was significantly higher in the adherent group compared to the non-adherent group (19.8% *vs.* 7.9%, $P = 0.006$, respectively). There was no significant difference in the prevalence of cardiovascular risk factors and cardiovascular comorbidities between the two groups, except for atrial fibrillation, which was more prevalent in the adherent group (32.8% *vs.* 22.4% in the non-adherent group, $P = 0.015$).

TABLE 1 Participant characteristics.

Characteristics	All participants ($n = 643$)	Non-adherence group ($n = 152$)	Adherence group ($n = 491$)	*P*-value
Age	73.1 ± 8.3	72.0 ± 7.7	73.5 ± 8.4	0.064
Age group				
60–69	255 (39.6%)	71 (46.7%)	184 (37.5%)	
70–79	237 (36.9%)	52 (34.2%)	185 (37.7%)	0.104
≥80	151 (23.5%)	29 (19.1%)	122 (24.8%)	
Sex				
Female	165 (25.7%)	27 (17.8%)	138 (28.1%)	0.011
Male	478 (74.3%)	125 (82.2%)	353 (71.9%)	
Working status				
Retired	615 (95.6%)	144 (94.7%)	471 (95.9%)	0.530
Working	28 (4.4%)	8 (5.3%)	20 (4.1%)	
Carer				
None	68 (10.6%)	20 (13.2%)	48 (9.8%)	0.006
Spouse	454 (70.6%)	118 (77.6%)	336 (68.4%)	
Children	109 (17.0%)	12 (7.9%)	97 (19.8%)	
Other	12 (1.8%)	2 (1.3%)	10 (2.0%)	
Public health insurance				
Yes	632 (98.3%)	150 (98.7%)	482 (98.2%)	0.667
No	11 (1.7%)	2 (1.3%)	9 (1.8%)	
Education (missing 31)				
Illiterate	16 (2.5%)	7 (4.7%)	9 (1.9%)	0.184
Primary school/secondary school	110 (18.1%)	22 (14.8%)	88 (19.0%)	
High school	186 (30.4%)	43 (28.9%)	143 (30.9%)	
Higher education	300 (49.0%)	77 (51.7%)	223 (48.2%)	
Body mass index				
Underweight	36 (5.6%)	7 (4.6%)	29 (5.9%)	0.291
Normal	223 (34.7%)	46 (30.3%)	177 (36.0%)	
Overweight	189 (29.4%)	44 (28.9%)	145 (29.5%)	
Obese	195 (30.3%)	55 (36.2%)	140 (28.5%)	
Smoking				
Non-smoking	327 (50.9%)	67 (44.1%)	260 (53.0%)	0.066
Current smoking	70 (10.9%)	23 (15.1%)	47 (9.6%)	
Ex-smoking	246 (32.2%)	62 (40.8%)	184 (37.5%)	
Frailty (CFS ≥4)	388 (60.3%)	92 (60.5%)	296 (60.3%)	0.958
CFS score	3.9 ± 1.3	3.8 ± 1.2	3.9 ± 1.3	0.721
Total number of medications	6.7 ± 1.8	7.2 ± 4.7	6.7 ± 3.0	0.132
Polypharmacy (using ≥5 medications)	576 (89.6%)	141 (92.8%)	435 (88.6%)	0.142
Medical history				
PCI	413 (64.3%)	102 (67.1%)	311 (63.3%)	0.397
CABG	10 (1.5%)	2 (1.3%)	8 (1.6%)	0.785
Hypertension	623 (96.9%)	150 (98.7%)	473 (96.3%)	0.145
Dyslipidaemia	613 (95.3%)	144 (94.7%)	469 (95.5%)	0.689
Diabetes	274 (42.6%)	58 (38.2%)	216 (44.0%)	0.204
Atrial fibrillation	195 (30.1%)	34 (22.4%)	161 (32.8%)	0.015
Peripheral artery disease	164 (25.7%)	45 (29.8%)	119 (24.4%)	0.183
Heart failure	100 (15.6%)	26 (17.1%)	74 (15.1%)	0.545

TABLE 1 (Continued)

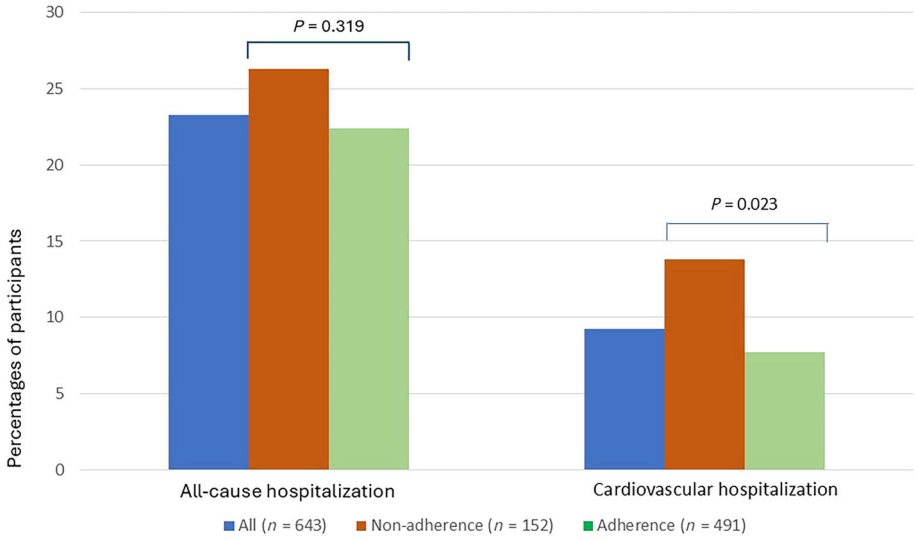
Characteristics	All participants ($n = 643$)	Non-adherence group ($n = 152$)	Adherence group ($n = 491$)	*P*-value
Chronic kidney disease	52 (8.0%)	11 (7.2%)	41 (8.4%)	0.660
Ischaemic stroke	36 (5.6%)	9 (5.9%)	27 (5.5%)	0.843
Cardiovascular multimorbidity	511 (79.5%)	113 (74.3%)	398 (81.1%)	0.073

Note: Continuous data are presented as mean ± standard deviation. Categorical data are shown as *n* (%).
Abbreviations: CABG, coronary artery bypass graft surgery; CFS, Clinical Frailty Scale; PCI, percutaneous coronary intervention.

TABLE 2 Distribution of the five-item Medication Adherence Report Scale (MARS-5) scores and its individual components.

		Always = 1 (*n*, %)	Often = 2 (*n*, %)	Sometimes = 3 (*n*, %)	Rarely = 4 (*n*, %)	Never = 5 (*n*, %)	Mean ± SD
Item 1	I forget to take my medicines	0	12 (1.9%)	117 (18.2%)	37 (5.8%)	477 (74.2%)	4.52 ± 0.85
Item 2	I alter the dose	0	3 (0.5%)	9 (1.4%)	6 (0.9%)	625 (97.2%)	4.95 ± 0.32
Item 3	I stop taking them for a while	0	4 (0.6%)	8 (1.2%)	6 (0.9%)	625 (97.2%)	4.95 ± 0.34
Item 4	I decide to miss out a dose	0	5 (0.8%)	10 (1.6%)	8 (1.2%)	620 (96.4%)	4.93 ± 0.38
Item 5	I take less than instructed	0	4 (0.6%)	15 (2.3%)	15 (2.3%)	609 (94.7%)	4.91 ± 0.41

FIGURE 1 Hospitalization rates after 6 months.



3.1 | Medication adherence

The distribution of the MARS-5 scores and the individual components are presented in Table 2. Among the five components of the MARS-5, most of the participants answered 'sometimes' to item 1 'I forget to take my medicines'. Overall, 76.4% (491/643) were classified into the adherent group, and 23.6% (152/643) of the participants were classified into the non-adherent group.

3.2 | Hospitalization

Over 6 months of follow-up, 23.3% of the participants were admitted to hospital (22.4% in the adherent group compared to 26.3% in the non-adherent group, $P = 0.319$). Of these, 9.2% were due to CVD. The CVD-related hospitalization rate was significantly higher in the non-adherent group than in the adherent group (13.8% *vs.* 7.7%, $P = 0.023$, respectively) (Figure 1).

3.3 | The relationship between adherence and hospitalization

In logistic models, medication adherence was associated with significantly reduced likelihood of CVD-related hospitalization (adjusted OR 0.48, 95% CI 0.27–0.86). A history of PCI/CABG was also associated with reduced CVD-related hospitalization (adjusted OR 0.53, 95% CI 0.29–0.94) (Figure 2).

Medication adherence was also associated with a trend of reduced all-cause hospitalization, but the difference was not

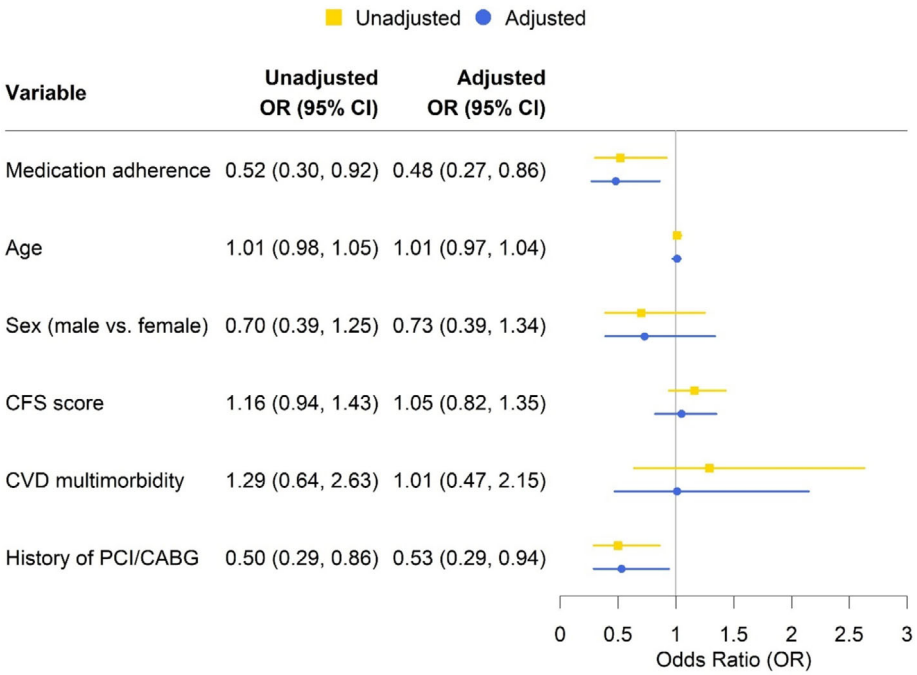


FIGURE 2 Predictor factors for cardiovascular related hospitalization. CABG, coronary artery bypass graft surgery; CFS, Clinical Frailty Scale; CVD, cardiovascular disease; PCI, percutaneous coronary interventions.

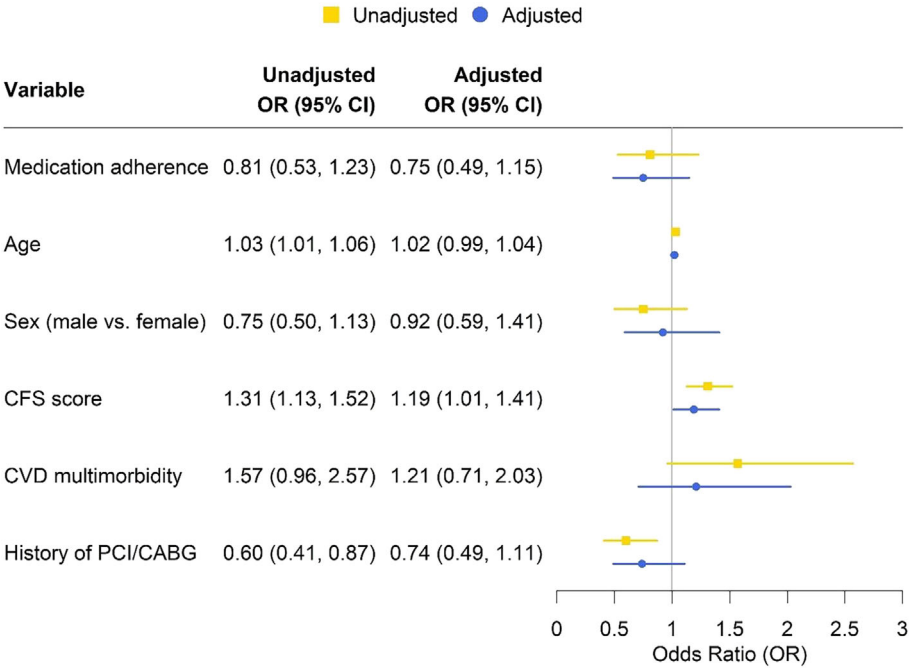


FIGURE 3 Predictor factors for all-cause hospitalization.
CABG, coronary artery bypass graft surgery; CFS, Clinical Frailty Scale; CVD, cardiovascular disease; PCI, percutaneous coronary interventions.

statistically significant (adjusted OR 0.75, 95% CI 0.49–1.15). In the adjusted model, frailty was the only independent predictor for all-cause hospitalization (adjusted OR 1.19, 95% CI 1.01–1.41 for every 1-point increase in the CFS score) (Figure 3).

4 | DISCUSSION

Our study evaluated medication adherence in older people with coronary heart disease. The study contributes to the limited existing evidence on medication adherence in Vietnamese people by providing insights for the older population. Our analysis showed that a high proportion of older participants with chronic coronary heart disease in the study reported being adherent to their medications. We found an association between medication adherence and reduced CVD-related hospitalization.

Information on medication adherence is important as it contributes to patient health. Published studies on medication adherence in the Vietnamese population showed varying levels of adherence, depending on the patient cohorts, clinical settings and the instruments

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used to measure and define adherence.[12–15] While most previous studies on medication adherence in Vietnam recruited younger participants (age ranged from 53 to 63),[12–15] the results of our study provide insights into medication adherence among an older population cohort. Vietnam is going through an epidemiological transition, with a growing number of older people. The older population typically requires increased utilization of healthcare resources due to their more significant health needs. Therefore, the findings of our study can provide valuable guidance for developing health policies and plans at a population level, particularly in settings where resources are limited.

Our results showed that medication adherence was associated with reduced CVD-related hospitalizations, but not all-cause hospitalizations. The risk of CVD-related hospitalization was reduced by half in the adherent group compared to the non-adherent group in our study. This finding is in line with observations from studies worldwide. In a systematic review on the impact of medication adherence on coronary heart disease costs and outcomes conducted by Bitton and colleagues, the authors found that high adherence was significantly associated with reduced coronary artery disease-related events, mortality, readmissions and annual costs for secondary prevention of coronary artery disease.[21] CVDs continue to be a significant source of burden of disease on health systems in low- to middle-income countries like Vietnam.[22] The observed reduction in CVD-related hospitalization among older patients with coronary heart disease who adhered to their cardiovascular medications is likely due to the effectiveness of these medications in managing their heart condition. By controlling key risk factors and reducing symptoms, these medications can prevent CVD events which lead to hospitalizations. The discrepancy in the relationship between medication adherence and CVD-related hospitalization compared to all-cause hospitalization can have several explanations. Firstly, the study was powered to detect differences in CVD-related hospitalizations in individuals who adhered to cardiovascular medications compared to those who did not, rather than all-cause hospitalizations. In addition, in this study the focus on medication adherence specifically referred to cardiovascular medications. Given that the study population are patients with coronary heart disease, it is logical that adherence to cardiovascular medications would reduce their risk of CVD-related hospitalizations, but not necessarily reduce hospitalizations due to other causes such as infection, injuries or non-CVD chronic diseases. Further studies in Vietnam are needed to explore the impact of medication adherence on all-cause hospitalizations in this population. The growing impact of CVD on health systems shows the need for more steps to be taken to help manage this. Pharmacotherapies continue to play essential roles in managing coronary heart disease in older people and as such, medication adherence should be an integral part of broader management strategies. Importantly, medication adherence is a modifiable behavioural risk factor that can be targeted for intervention. There is a pressing need for innovative and evidence-based strategies to enhance medication adherence in older patients with coronary heart disease in Vietnam. In our study, there was a significant prevalence of non-intentional non-adherence (due to forgetfulness). This finding indicates a need for further intervention studies incorporating strategies such as sending reminders to those who forget their pills, using pillboxes, or maintaining a calendar of medication use to improve adherence. Association of medication adherence with major adverse cardiovascular events also has implications for healthcare costs, which is a major challenge for policymakers in resource limited settings. As the management of CVD involves high utilization of healthcare resources, focusing on medication adherence as a modifiable patient factor becomes a possible focus point when planning cost-effective strategies for managing CVD.

Exploring factors for non-adherence could also potentially reduce unnecessary hospital readmission rates. Considering the broader level impact of medication adherence, more studies should be done to explore factors influencing medication adherence in Vietnam, particularly in the older population. Older patients with coronary heart disease are more likely to experience multiple chronic conditions and polypharmacy, making it challenging to adhere to complex medication regimens. In addition, physiological changes associated with ageing, such as cognitive decline and physical limitations, can also impact medication adherence in older individuals, especially those living in low- and middle-income countries.[23,24] Patients in low- and middle-income countries have added barriers compared to patients in high-income or developed countries. Examples of these barriers may include limited access to medicines, varying educational backgrounds affecting health literacy levels, and resources to support medication adherence. A recent systematic review of factors that can influence medication adherence of adults with chronic diseases found that socioeconomic status and social support might have a positive impact on adherence.[25] In patients taking long-term medicines for CVD prevention, their perception of health goals may affect medication adherence.[26] In low- and middle-income countries, poor medication adherence has also been influenced by a lack of knowledge, negative beliefs and negative attitudes.[24] Simplified regimens, like the use of single-pill combinations, might be of particular interest in such settings, as recently demonstrated for arterial hypertension in Africa.[27,28] As young and old patients may have different perceptions of health goals, further studies could be done to explore specific reasons for non-adherence in older patients with coronary heart disease. Further studies could also be conducted to explore the relationship of educational background, its impact on health literacy and its relationship with factors experienced by the older population such as frailty and polypharmacy.

To the best of our knowledge, this was the first study to examine medication adherence in older people with chronic coronary syndrome in Vietnam. Additionally, our study was conducted at Thong Nhat Hospital, one of the largest hospitals in Vietnam with specialized services for older patients, which enabled the collection of data for older people with complex medication management plans. Our study also reported the relationship with hospitalization rates, an outcome that is not routinely reported in studies on medication adherence. With the growing population of older people coupled with the growing burden of CVDs, factors that can influence hospitalization rates should be considered for healthcare planning.

However, our study has several limitations. The study was conducted on older patients attending outpatient clinics from one hospital, so it may not accurately reflect all older people with coronary heart disease in Vietnam. There was a high proportion of achieving higher education among our study participants, which may explain the high proportion of medication adherence observed in this study. In addition, the high medication adherence rate observed might have been influenced by patients' awareness of being part of a study. Our follow-up duration was only 6 months, and we did not re-assess medication adherence at the end of follow-up. Further studies with larger sample sizes and longer follow-up periods are needed to understand the impact of medication adherence on adverse outcomes and quality of life in older patients with coronary heart disease.

5 | CONCLUSION

This study showed a positive relationship between medication adherence and reduced risk of CVD-related hospitalization in older people with coronary heart disease. Our study highlights the important role of medication adherence in improving health outcomes for older people with coronary heart disease. There is a need to better understand the reasons why patients are non-adherent to their medicines, particularly in different contexts and specific populations. Contextualized strategies would be useful to help improve adherence and potentially reduce unnecessary hospitalization rates. Healthcare providers should consider incorporating adherence assessment into the long-term care for older patients with coronary heart disease.

AUTHOR CONTRIBUTIONS

Tan Van Nguyen is the principal investigator (PI) and oversaw the study. Tan Van Nguyen and Tu Ngoc Nguyen led the study concept and study design and wrote the first draft of the manuscript. Tan Van Nguyen, Hang Thi Thuy Nguyen, Dung Ngoc Truong, Viet Quoc Nguyen, Huy Quang Nguyen and Huy Quoc Nguyen led ethics application, recruitment and data acquisition. All authors were involved in analysis and interpretation of data and revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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