THE UNIVERSITY OF SYDNEY

Analysing, Predicting, and Improving Outcomes for Kidney Transplant Recipients

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A thesis submitted to fulfil the requirements of the degree of Doctor of Philosophy

Faculty of Medicine and Health

The University of Sydney

June 2025

Authorship attribution

I carried out work presented in this thesis under the supervision of Professor Steve Chadban (Sydney Medical School, the University of Sydney) and co-supervised by Dr Tracey Ying (Sydney Medical School, the University of Sydney).

For all chapters that have been published or submitted, I made substantial contributions to the study design, data acquisition, analysis, and interpretation. I wrote the manuscripts for submission, coordinated the submission and revision processes, and compiled the thesis.

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BS designed the study together with her supervisors, acquired the data, performed the analysis, interpreted the results, drafted the manuscript and figures, and oversaw the manuscript revision. The dataset was provided by the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry and Clinical Study Data Request (CSDR).

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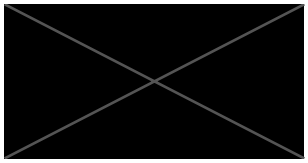

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Attesting authorship statement

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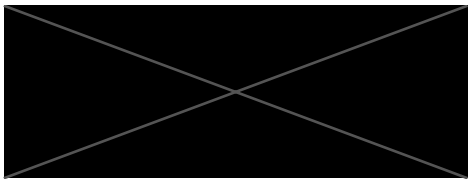

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Statement of originality

This thesis is submitted to the University of Sydney in fulfilment of the requirements for the degree of Doctor of Philosophy.

I certify that, to the best of my knowledge, this intellectual content of this thesis is the product of my own work. It has not been submitted, either in whole or in part, for any degree or qualification at this or any other institution. All sources of assistance and support have been appropriately acknowledged.

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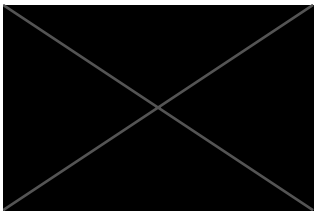

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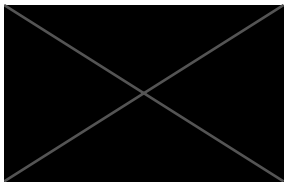

Date: 8/8/2025

Ethical Clearance

Chapter 2: ethical approval was obtained from the Human Research Ethics Committee, the University of Sydney. (Project No. 2019/922)

Chapter 3: ethical approval was obtained from the Human Research Ethics Committee, the University of Sydney. (Project No. 2020/798)

Chapter 4: ethical approval was obtained from the Ethics Review Committee of the Sydney Local Health District, Royal Prince Alfred Hospital Zone. (Protocol No: X21-0020 & 2020/ETH02670)

Chapter 5: ethical approval was obtained from the Human Research Ethics Committee, the University of Sydney. (Project No. 2024/HE001003)

Chapter 6: ethical approval was not required for this systematic review.

Abstract

Background: Kidney failure is a growing global health burden. Kidney transplantation offers the best treatment for eligible patients, however long-term outcomes remain suboptimal due to chronic rejection and premature death, particularly from cardiovascular disease, infection, and cancer. As the transplant population becomes older, more obese and more comorbid, understanding how these factors influence outcome is important to inform clinical decision making and patient expectations. Clinical registries and non-inferiority trials are increasingly relied upon to support transplant research and guide policy. Their reliability and validity are critical to ensuring high quality evidence in the field.

Methods: This thesis is presented as a thesis by publication and applies a range of research methods to address key challenges in kidney transplantation research. The overarching aim is to evaluate the reliability of registry data, assess the impact of evolving transplant population characteristics on outcomes, and critically appraise the quality of evidence generated by non-inferiority trials. Chapter 2 evaluates the validity of the Australian and New Zealand Dialysis and Transplant (ANZDATA) Registry data by performing deterministic linkage with a rigorously monitored clinical trial dataset (A2309), using kappa statistics to assess agreement across key variables. Chapter 3, 4 and 5 utilised data from ANZDATA registry. In chapter 3, a retrospective matched cohort study is described where kidney recipients aged 70 and over were matched to a wait-listed maintenance dialysis patient by age, diabetes and time on dialysis. A stratified Cox regression model was used to compare survival within the pair. Chapter 4 examines post-transplant outcomes in obese versus non-

obese recipients using a paired-donor design, where recipients of kidneys from the same deceased donor are compared to control for confounding by donor factors. Conditional Poisson regression was used to evaluate the relative risk of delayed graft function, and stratified cox regression was used to compare time to graft failure and time to death. Chapter 5 investigates the association between obesity and cancer incidence and mortality using multivariable piecewise exponential model in kidney recipients, with obesity status and transplant status modelled as a time-varying covariates. Chapter 6 is a systematic review of non-inferiority trials in kidney transplantation, assessing trial design and reporting using a 20-point scoring system adapted from Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Results: All 95 participants in the A2309 clinical trial were successfully linked to the ANZDATA Registry. Agreement was excellent for death, graft failure, and key baseline characteristics including age, sex, primary kidney disease, and donor details, while agreement for ethnicity, graft function, and acute rejection was moderate to good. In the matched analysis of kidney transplant recipients aged ≥70 years and waitlisted dialysis patients, transplantation was associated with higher early post-transplant mortality but significantly lower mortality beyond 9 months (HR 0.40, 95% CI 0.23-0.70, p=0.001), demonstrating a clear survival benefit in older candidates. Among 1,522 deceased donor transplant pairs, obesity was associated with a 26% higher risk of delayed graft function (95% CI 1.11-1.44, p<0.001), 25% higher risk of death-censored graft failure (95% CI 1.05-1.49, p=0.012), and 32% higher risk of all-cause mortality (95% CI 1.15-1.56, p=0.001). A dose-response relationship was observed, with higher degrees of obesity associated with progressively increased risks of delayed graft function and graft failure. In a cohort of 65,712

patients initiating treatment for kidney failure, obesity was associated with a lower incidence of cancer (aHR 0.93, 95% CI 0.88–0.99, p=0.02) and cancer-related mortality (aHR 0.72, 95% CI 0.65–0.79, p<0.001) compared to non-obese patients. The lower cancer incidence observed in obese patients was driven by reduced risks of colorectal, lip and oral cavity, cervical, prostate, lung and bladder cancers, and multiple myeloma, whereas breast and uterine cancer risks were elevated. Obesity was also associated with improved survival from oesophageal, colorectal, lip and oral cavity, prostate, and lung cancers, as well as lymphoma and multiple myeloma. The systematic review of 44 non-inferiority trials in kidney transplantation identified substantial deficiencies in trial design and reporting, including inadequate justification of non-inferiority margins, inappropriate use of risk measures, poor handling of missing data, and frequent misinterpretation of results. Trial quality did not improve over time and showed no association with journal impact factor.

Conclusion: This thesis demonstrates the value of leveraging clinical registries to address key challenges in kidney transplantation. The ANZDATA registry provides reliable data for evaluating patient and graft outcomes, although continued validation and standardisation remain essential. Transplantation provides a survival benefit in selected elderly patients despite early risks, while obesity presents a complex profile, associated with inferior graft outcomes but lower cancer incidence and cancer-related mortality. The major deficiencies in non-inferiority trial design and reporting highlight an urgent need for stricter editorial standards, better trialist awareness, and stronger guideline adherence to improve the quality of evidence in our field.

Acknowledgement

I would like to thank my primary supervisor, Professor Steve Chadban. Steve's boundless energy and enthusiasm for research have been a constant source of inspiration. I am deeply grateful for his generosity with his time, knowledge, encouragement and support. He can cut through complex problems with clarity and optimism. Often when I'm just convinced there is no way forward, he somehow sees three. His belief in me and in the value of this work has shaped not only this thesis but also how I see myself as a researcher. I always leave our meetings feeling recharged and excited about the next step. His wisdom will continue to inspire me for many years to come.

I am equally honoured and privileged to have Dr Tracey Ying as my co-supervisor. Tracey has gone above and beyond what is expected of a supervisor, always providing thoughtful advice with patience, clarity, and kindness. I have been greatly influenced by her remarkable responsiveness, organisational skills, and agility. Her ability to act fast, think ahead, and manage complex problems with calm and efficiency has shaped the way I approach my own work.

I would also like to acknowledge the generous financial support of the Dr Pamela Guha Postgraduate Research Scholarship, and the Australian Government Research Training Program Offset Scholarship, which enabled me to complete this research.

Thank you to my wonderful husband Jack for always standing firmly behind every decision I make. Your willingness to take on more than your fair share of parenting responsibilities, especially on countless weekends and late nights, allowed me to pursue this work wholeheartedly. A special thank you to my daughter Ellie and my son Miles, who unknowingly contributed to this thesis by taking just enough naps. Their giggles, chaos, and cuddles reminded me daily of the joy beyond deadlines.

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Publications arising from this thesis

This thesis is submitted as thesis by publications. Chapter 3 and 4 of the thesis have been published. Chapter 2, 5 and 6 are currently being submitted for publication.

Chapter 3

Shi B, Ying T, Chadban SJ. Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: a matched-pair analysis. *Am J Transplant*. Published online 2023. doi:10.1016/j.ajt.2023.07.006

Chapter 4

Shi B, Ying T, Xu J, Wyburn K, Laurence J, Chadban SJ. Obesity is Associated With Delayed Graft Function in Kidney Transplant Recipients: A Paired Kidney Analysis. *Transpl Int*. 2023;36:11107. doi:10.3389/ti.2023.11107

Other publications not forming part of this thesis:

Shah KK, Robledo K, **Shi B,** Gill J, Ying T, Wyld M, Morton R. Impact of Suspensions and Reactivations from Waitlist on Quality of Life in Canadian-Australasian Randomised Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease (CARSK). *J Am Soc Nephrol*. 2023;34(11S):341-342. doi:10.1681/asn.20233411s1341d

Singer J, Tunbridge MJ, **Shi B,** Perkins G, Chai C, Salehi T, Sim B, Kireta S, Johnson J, Akerman A, Milogiannakis V, Aggarwal A, Turville S, Hissaria P, Ying T, Wu H, Grubor-Bauk B, Coates T, Chadban S. Dietary Inulin to Improve SARS-CoV-2 Vaccine Response in Kidney Transplant Recipients: The RIVASTIM-Inulin Randomised Controlled Trial. *Vaccines*. 2024;12(6):608. doi:10.3390/vaccines12060608

Perkins G, Tunbridge MJ, Singer J, Chai C, **Shi B,** Ying T, Chadban S, Coates T. Outcomes of the RIVASTIM: Rapamycin randomized controlled trial of immunosuppression modification to improve vaccine responses in kidney transplant recipients. *Transplantation*. 2024;108(9S). doi:10.1097/01.tp.0001066352.10840.01

Perkins G, Tunbridge MJ, Chai CS, Hope CM, Yeow AEL, Salehi T, Singer J, **Shi B,** Masavuli MG, Mekonnen ZA, Garcia-Valtanen P, Kireta S, Johnston JK, Drogemuller CJ, Sim BZ, Spencer SM, Sallustio BC, Comerford I, Bouras G, Weiskopf D, Sette A, Aggarwal A, Milogiannakis V, Akerman A, Turville S, Hurtado PR, Ying T, Hissaria P, Barry SC, Chadban SJ, Grubor-Bauk B, Coates PT. mTOR Inhibitors and Vaccine Response in Kidney Transplant Recipients*. J Am Soc Nephrol*. Published online 2025. doi:10.1681/asn.0000000716

Conference proceedings arising from this thesis

Oral Presentations

Bree S. Outcome of kidney transplantation in the elderly compared with dialysis. American Transplant Congress. Boston USA, June 6, 2022 *(Young Investigator Award)*

Bree S. Obesity is associated with delayed graft function in kidney transplant recipients. The Transplantation Society of Australia and New Zealand 40th Annual Scientific Meeting. Adelaide, June 20, 2022 *(Early Career Researchers Award)*

Bree S. Outcome of kidney transplantation in the elderly compared with dialysis. The Transplantation Society of Australia and New Zealand 40th Annual Scientific Meeting. Adelaide, June 20, 2022 *(Early Career Researchers Award)*

Bree S. Design and reporting quality of non-inferiority trials in kidney transplantation: a systematic review. The Transplantation Society of Australia and New Zealand 40th Annual Scientific Meeting. Canberra, June 23, 2025

Poster Presentations

Bree S. Obesity is associated with delayed graft function in kidney transplant recipients. American Transplant Congress. Boston USA, June 6-8, 2022

Bree S. Validity of kidney transplant outcomes in the ANZDATA Registry: a comparison with clinical trial data. The Transplantation Society of Australia and New Zealand 40th Annual Scientific Meeting. Canberra, June 22-24, 2025

Awards arising from this thesis

Young Investigator Award: American Transplant Congress, Boston USA 2022

Early Career Research Award x 2: The Transplantation Society of Australia and New Zealand, Adelaide 2022

The Pamela Guha Postgraduate Research Scholarship: University of Sydney 2020

The Australian Government Research Training Program Offset Scholarship: University of Sydney 2020

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CHAPTER 1

Introduction

Introduction

Kidney failure, also known as Stage 5 Chronic Kidney Disease defined by estimated glomerular filtration rate (eGFR) < 15ml/min/1.73m^2, is a growing public health challenge, with its prevalence more than doubling in the United States between 2000 and 2019, and showing similar trend globally.[1,2] Kidney failure is associated with reduced quality and length of life, and has been upgraded as a fast growing cause of premature mortality by the Global Burden of Disease Study.[3] Beyond mortality, kidney failure imposes a significant burden on patients, their carers, health care systems, societies and our environment .[4] Kidney failure typically requires kidney replacement therapy (KRT) to prevent death, however up to 50% of Australians with kidney failure do not receive KRT, opting instead for supportive care.[5] KRT is provided for the remainder, either through dialysis or kidney transplantation.

Kidney transplantation is recognised as the most effective treatment for eligible patients with kidney failure, offering superior survival, improved quality of life, and lower long-term healthcare costs compared with maintenance dialysis. [6–9] Kidney recipients have been reported to experience a 48 to 82% reduction in long-term mortality compared to waitlisted dialysis patients[6] , with the magnitude of survival benefit increasing over time[7]. Despite improvements in systems of care and significant advances in immunosuppressive therapy over recent decades, long-term survival continues to be challenged by chronic graft rejection and premature mortality from cardiovascular disease, infection and cancer. Consequently, 2% of kidney transplant recipients experience graft failure and a further 2% die with a functioning graft per annum[10,11] Ten-year graft survival in Australia and New Zealand for recipients of a first deceased donor kidney transplant is just over 50%.[12] Failure

to improve long-term outcomes may be attributable to a combination of recipient characteristics, in particular progressive increases in age, frailty and multi-morbidity of recipients, and donor and graft-related factors including increases in donor age and marginality. Increasing rates of post-transplant complications such as delayed graft function, post-transplant diabetes, acute rejection, and infection are also likely contributory. Outcomes vary substantially across patient populations, and persistent disparities continue to adversely affect access to and quality of care for individuals with kidney failure. Optimising long-term transplant outcomes requires a deeper understanding of factors influencing graft and patient survival. Sustaining long-term graft function and reducing premature mortality remain key priorities in kidney transplantation.[12,13]

Clinical registries capture longitudinal patient data that is critically important for measuring and reporting outcomes and improving patient care. Well-managed registries serve as powerful tools for driving clinical improvement and informing health service planning, often at a relatively lower cost compared to clinical trials.[14,15] The Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry has routinely collected data on all patients with kidney failure receiving KRT in Australia and New Zealand since 1963.[16] The Registry has been extensively used for transplant research, outcome assessment, quality improvement, treatment comparisons, documentation of stock and flow, and policy development. Over the past five years, the ANZDATA Registry data supported over 200 research projects in the field of kidney transplantation.[17] Given its widespread use in shaping clinical practice and informing research, the reliability and accuracy of ANZDATA Registry data are of utmost importance. Chapter 2 will evaluate the validity of ANZDATA Registry data by comparison to

rigorously monitored clinical data captured from the same patients for a clinical trial as gold standard.

The rising prevalence of kidney failure has been largely driven by an increasing number of older patients receiving KRT. The incidence of kidney failure peaks in the 70 to 79 age group.[18] The number of patients aged 65 and above waiting for a kidney transplant has more than tripled since 2000 in the United States. [19] Older kidney transplant recipients face both a higher burden and greater intensity of perioperative and long-term complications including infectious morbidity and mortality, cardiovascular events, metabolic complications, cancer and frailty.[20] As compared to younger KTRs, older patients are more likely to experience death with function, but less likely to incur graft failure.[21] There remains uncertainty regarding the survival advantage of transplantation in patients over 70 years. Chapter 3 will use a novel matched pair analysis to assess the impact of kidney transplantation on survival among waitlisted individuals in this age group.

The population with kidney failure has not only become older over time but has also become increasingly obese, driven by lifestyle changes characterised by reduced physical activity and higher daily calory intake. In the United States, more than 50% of kidney recipients have a body mass index (BMI) greater than 30 kg/m2, highlighting the need to better understand this population and the impact of obesity on dialysis and transplant outcomes.[22] Obese patients are less likely to receive a kidney transplant and more likely to be bypassed when an organ becomes available.[23,24] Existing studies have reported conflicting transplant outcomes for obese recipients.[25–28] However, these findings may have been limited by unmeasured confounding factors, particularly donor-related characteristics,

which are challenging to fully adjust for in conventional analyses. To address these limitations, Chapter 4 will compare outcomes between obese and non-obese recipients who received kidneys from the same deceased donor.

In the general population, obesity is a well-established risk factor for developing cancer overall, and for specific cancers including but not limited to renal cell carcinoma, breast, female genital tract cancers, gallbladder, esophageal, thyroid and liver cancers, and leukaemia, accounting for about 6% of all cancer cases.[29,30] Some of these cancers also occur more frequently among kidney transplant recipients, largely due to the prolonged use of immunosuppressive therapy to minimise graft rejection.[31–33] However, whether obesity further modifies this risk in the transplant population remains unclear. Paradoxically, two studies reported a 30-40% reduction in the overall cancer risk among obese kidney transplant recipients, suggesting a complex and poorly understood interaction.[34,35] The risk of specific cancer subtypes associated with obesity after transplantation remains unknown. Chapter 5 will utilise population-level data to examine the relationship between obesity and cancer incidence in kidney transplant recipients, with a particular focus on identifying obesity-associated cancer subtypes in this population.

No trial over the past four decades has demonstrated superiority over standard-of-care immunosuppression, which already yields excellent patient and graft survival. However, novel agents offer potential secondary benefits, including reduced risk of long-term kidney toxicity and metabolic complications, simple administration, and potentially lower price. As a result, non-inferiority trials, which aim to determine whether a new treatment is not unacceptably worse than an existing therapy by a pre-specified margin, are frequently

adopted. non-inferiority trials are inherently more complex than superiority trials and have been widely criticised in other medical fields for methodological shortcomings, including inappropriate margin selection, inadequate power, and misinterpretation of results.[36–41] Despite their widespread use in transplantation, the quality and validity of non-inferiority trials in this field remain unknown. Chapter 6 will systematically evaluate the design and reporting quality of non-inferiority trials in kidney transplantation while assessing their adherence to existing guidelines.

Data source

In this thesis, we obtained data from the ANZDATA Registry, a clinical quality registry that collects comprehensive longitudinal data on all patients who receive KRT in Australia and New Zealand.[16] This valuable database enabled us to investigate associations between key risk factors, including older age and obesity, and both short and long-term post-transplant outcomes. In addition, using clinical trial data as gold standard, we assessed the quality of data reported by ANZDATA.

Thesis structure

This thesis is structured as two published peer-reviewed publications and three submitted manuscripts. Each chapter is presented as a stand-alone study, with its own literature review contained within the introduction and discussion sections. Rather than providing a separate literature review, this introduction serves to provide context for the research

undertaken, outlining the relevance and contributions of the studies within the field of kidney transplantation.

Overarching purpose and specific objectives by chapter

The overarching purpose of this thesis is to improve long-term outcomes in kidney transplantation by addressing key knowledge gaps in high-risk populations and evaluating the methods and tools that underpin transplant research. This thesis examines the validity of registry data, explores associations between recipient characteristics and outcomes, and critically appraises the quality of non-inferiority trials, a complex clinical trial design that is increasingly used in transplantation research. The objectives of each chapter are as follows.

Chapter 2 - Validity of Kidney Transplant Outcomes in the ANZDATA Registry: A Comparison with Clinical Trial Data

Clinical registries play an important role in monitoring patient care, guiding health service planning, and research. The ANZDATA Registry, which routinely collects data on patients receiving kidney replacement therapy across Australia and New Zealand, is widely used to support clinical practice guidelines and policy making. However, the data collected has rarely been audited and the reliability of its dataset remains unknown. This chapter aims to assess the validity of key transplant-related variables captured by the ANZDATA Registry by comparing them with data collected in a rigorously monitored, FDA-regulated, multicentre, randomized controlled clinical trial (A2309).[42] Using deterministic linkage, patients enrolled

in both datasets were matched, and key variables were compared using kappa and weighted kappa statistics.

Chapter 3 - Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: a matched-pair analysis

The proportion of older adults with end-stage kidney disease has increased substantially, with prevalence in this age group tripling over recent decades.[19] Elderly recipients experience increased risks of infection, cardiovascular events, cancer, metabolic complications, delayed wound healing and post-operative recovery, cognitive impairment and frailty, often resulting in prolonged hospital stay and elevated mortality risks.[43] As the number of older candidates continues to rise in the context of persistent organ shortages, optimising allocation becomes an increasingly prominent issue. The objective of this study is to determine whether kidney transplantation offers a survival advantage over remaining on dialysis among patients aged ≥70 years. This chapter used a matched-pair design to compare survival between kidney transplant recipients and waitlisted dialysis patients, matched on two major risk factors: 1) dialysis duration, and 2) diabetes as the cause of kidney failure. Only dialysis patients who had completed transplant evaluation and were actively waitlisted were included, ensuring comparability. By controlling for age, primary kidney disease, and dialysis duration, the study aimed to provide robust, population-based evidence to inform transplant eligibility decisions and transplant candidate education for elderly patients.

Chapter 4 - Obesity is associated with delayed graft function in kidney transplant recipients: a paired kidney analysis

Obesity is increasingly common among patients evaluated for kidney transplantation, affecting nearly 40% of this population.[44] Obese kidney transplant recipients are at greater risks of post-transplant diabetes, heart failure, atrial fibrillation, and cardiovascular death.[45,46] In addition, obesity has been associated with higher rates of surgical complications, leading to longer hospital stays and increased healthcare costs.[25] Despite these risks, long-term graft and patient outcomes among obese recipients remain uncertain, with conflicting evidence regarding graft and patient survival. This chapter aims to evaluate the association between obesity and transplant outcomes, including delayed graft function, graft survival, and patient survival. To address potential confounding from donor-related factors, a matched-pair design was used to compare obese and non-obese recipients who received kidneys from the same donor.

Chapter 5 - The impact of obesity on cancer incidence among dialysis patients and kidney transplant recipients

Obesity is a well-established risk factor for various types of cancer in the general population, including cancers of the breast, thyroid, endometrium, colon, kidney, pancreas, and liver. [30] Patients with kidney failure experience markedly higher cancer incidence and mortality than the general population,[47] with cancer death being a leading cause of death post-transplant.[11] Obesity is highly prevalent among patients receiving KRT, however the relationship between obesity and cancer risk among this population has rarely been

explored. This chapter aims to evaluate the association between obesity and cancer incidence and mortality in dialysis and transplant populations. I used a piecewise exponential model incorporating the competing risk of non-cancer deaths, with obesity status and transplant status as time-varying covariates.

Chapter 6 - Design and reporting quality of non-inferiority trials in kidney transplantation: a systematic review

Non-inferiority trials are designed to assess whether a new therapy is no worse than the current standard-of-care within a clinically acceptable margin.[48] Compared to superiority trials, designing and reporting non-inferiority studies are more complex, and flaws in trial conduct or reporting can lead to false and misleading conclusions. In kidney transplantation, non-inferiority trials have been extensively used for evaluating novel therapies. However, the quality of those trials has not been systematically reviewed. This chapter aims to critically examine the design and reporting of non-inferiority trials in kidney transplantation, using the Consolidated Standards of Reporting Trials (CONSORT) extension statements 2010 for non-inferiority trials as the primary framework for assessing reporting quality.[49]

References

1. Kuehn, B. M. (2022). End-stage Kidney Disease Doubles. *JAMA*, *327*(16), 1540–1540. https://doi.org/10.1001/jama.2022.5342

2. Chapter 2: Prevalence of Renal Replacement Therapy for End Stage Kidney Disease. Retrieved March 30, 2025, from https://www.anzdata.org.au/wp-content/uploads/2020/09/c02_prevalence_2019_ar_2020_v1.0_20201111.pdf

3. Cockwell, P., & Fisher, L.-A. (2020). The global burden of chronic kidney disease. *The Lancet*, *395*(10225), 662–664. https://doi.org/10.1016/s0140-6736(19)32977-0

4. Chadban, S., Arıcı, M., Power, A., Wu, M.-S., Mennini, F. S., Álvarez, J. J. A., Sanchez, J. J. G., Barone, S., Card-Gowers, J., Martin, A., & Retat, L. (2024). Projecting the economic burden of chronic kidney disease at the patient level (Inside CKD): a microsimulation modelling study. *EClinicalMedicine*, *72*, 102615. https://doi.org/10.1016/j.eclinm.2024.102615

5. Sparke, C., Moon, L., Green, F., Mathew, T., Cass, A., Chadban, S., Chapman, J., Hoy, W., & McDonald, S. (2013). Estimating the Total Incidence of Kidney Failure in Australia Including Individuals Who Are Not Treated by Dialysis or Transplantation. *American Journal of Kidney Diseases*, *61*(3), 413–419. https://doi.org/10.1053/j.ajkd.2012.10.012

6. Wolfe, R. A., Ashby, V. B., Milford, E. L., Ojo, A. O., Ettenger, R. E., Agodoa, L. Y. C., Held, P. J., & Port, F. K. (1999). Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. *The*

New England Journal of Medicine, *341*, 1725–1730. https://doi.org/10.1056/nejm199912023412303

7. Tonelli, M., Wiebe, N., Knoll, G., Bello, A., Browne, S., Jadhav, D., Klarenbach, S., & Gill, J. (2011). Systematic Review: Kidney Transplantation Compared With Dialysis in Clinically Relevant Outcomes. *American Journal of Transplantation*, *11*(10), 2093–2109. https://doi.org/10.1111/j.1600-6143.2011.03686.x

8. Yang, F., Liao, M., Wang, P., Yang, Z., & Liu, Y. (2021). The Cost-Effectiveness of Kidney Replacement Therapy Modalities: A Systematic Review of Full Economic Evaluations. *Applied Health Economics and Health Policy*, *19*(2), 163–180. https://doi.org/10.1007/s40258-020-00614-4

9. Laupacis, A., Keown, P., Pus, N., Krueger, H., Ferguson, B., Wong, C., & Muirhead, N. (1996). A study of the quality of life and cost-utility of renal transplantation. *Kidney International*, *50*(1), 235–242. https://doi.org/10.1038/ki.1996.307

10. Clayton, P. A., McDonald, S. P., Russ, G. R., & Chadban, S. J. (2019). Long-Term Outcomes after Acute Rejection in Kidney Transplant Recipients: An ANZDATA Analysis. *Journal of the American Society of Nephrology*, *30*(9), 1697–1707. https://doi.org/10.1681/asn.2018111101

11. Ying, T., Shi, B., Kelly, P. J., Pilmore, H., Clayton, P. A., & Chadban, S. J. (2020). Death after Kidney Transplantation: An Analysis by Era and Time Post-Transplant. *Journal of the American Society of Nephrology*, *31*(12), 2887–2899. https://doi.org/10.1681/asn.2020050566

12. Hariharan, S., Israni, A. K., & Danovitch, G. (2021). Long-Term Survival after Kidney Transplantation. *New England Journal of Medicine*, *385*(8), 729–743. https://doi.org/10.1056/nejmra2014530

13. Wang, J. H., Skeans, M. A., & Israni, A. K. (2016). Current Status of Kidney Transplant Outcomes: Dying to Survive. *Advances in Chronic Kidney Disease*, *23*(5), 281–286. https://doi.org/10.1053/j.ackd.2016.07.001

14. Larsson, S., Lawyer, P., Garellick, G., Lindahl, B., & Lundström, M. (2017). Use of 13 Disease Registries In 5 Countries Demonstrates The Potential To Use Outcome Data To Improve Health Care's Value. *Health Affairs*, *31*(1), 220–227. https://doi.org/10.1377/hlthaff.2011.0762

15. Lee, P., Chin, K., Liew, D., Stub, D., Brennan, A. L., Lefkovits, J., & Zomer, E. (2019). Economic evaluation of clinical quality registries: a systematic review. *BMJ Open*, *9*(12), e030984. https://doi.org/10.1136/bmjopen-2019-030984

16. McDonald, S. P. (2015). Australia and New Zealand Dialysis and Transplant Registry. *Kidney International Supplements*, *5*(1), 39–44. https://doi.org/10.1038/kisup.2015.8

17. The ANZDATA Registry. *ANZDATA: Current Projects 2019-2023*. Retrieved April 15, 2024, from https://www.anzdata.org.au/anzdata/data-requests/data-projects/

18. Wiggins, J., & Patel, S. (2009). *The Coming Pandemic of CKD/ESKD and the Aging Population*. https://www.asn-online.org/education/distancelearning/curricula/geriatrics/

19. United States Renal Data System. (2021). *2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. https://adr.usrds.org/2021/end-stage-renal-disease/7-transplantation

20. Knoll, G. A. (2013). Kidney Transplantation in the Older Adult. *American Journal of Kidney Diseases*, *61*(5), 790–797. https://doi.org/10.1053/j.ajkd.2012.08.049

21. Lim, W. H., Chang, S., Chadban, S., Campbell, S., Dent, H., Russ, G. R., & McDonald, S. P. (2010). Donor–recipient age matching improves years of graft function in deceased-donor kidney transplantation. *Nephrology Dialysis Transplantation*, *25*(9), 3082–3089. https://doi.org/10.1093/ndt/gfq127

22. Sureshkumar, K. K., Chopra, B., Josephson, M. A., Shah, P. B., & McGill, R. L. (2021). Recipient Obesity and Kidney Transplant Outcomes: A Mate-Kidney Analysis. *American Journal of Kidney Diseases*, *78*(4), 501-510.e1. https://doi.org/10.1053/j.ajkd.2021.02.332

23. Segev, D. L., Simpkins, C. E., Thompson, R. E., Locke, J. E., Warren, D. S., & Montgomery, R. A. (2008). Obesity Impacts Access to Kidney Transplantation. *Journal of the American Society of Nephrology*, *19*(2), 349–355. https://doi.org/10.1681/asn.2007050610

24. McDonald, S., & Ladhani, M. (2021). Obesity in dialysis patients – What is the problem? *Obesity Research & Clinical Practice*, *15*(5), 413–414. https://doi.org/10.1016/j.orcp.2021.09.005

25. Lafranca, J. A., IJermans, J. N., Betjes, M. G., & Dor, F. J. (2015). Body mass index and outcome in renal transplant recipients: a systematic review and meta-analysis. *BMC Medicine*, *13*(1), 111. https://doi.org/10.1186/s12916-015-0340-5

26. Hill, C. J., Courtney, A. E., Cardwell, C. R., Maxwell, A. P., Lucarelli, G., Veroux, M., Furriel, F., Cannon, R. M., Hoogeveen, E. K., Doshi, M., & McCaughan, J. A. (2015). Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis. *Nephrology Dialysis Transplantation*, *30*(8), 1403–1411. https://doi.org/10.1093/ndt/gfv214

27. Ahmadi, S.-F., Zahmatkesh, G., Streja, E., Molnar, M. Z., Rhee, C. M., Kovesdy, C. P., Gillen, D. L., Steiner, S., & Kalantar-Zadeh, K. (2014). Body Mass Index and Mortality in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis. *American Journal of Nephrology*, *40*(4), 315–324. https://doi.org/10.1159/000367812

28. Nicoletto, B. B., Fonseca, N. K. O., Manfro, R. C., Gonçalves, L. F. S., Leitão, C. B., & Souza, G. C. (2014). Effects of Obesity on Kidney Transplantation Outcomes. *Transplantation*, *98*(2), 167–176. https://doi.org/10.1097/tp.0000000000000028

29. Pati, S., Irfan, W., Jameel, A., Ahmed, S., & Shahid, R. K. (2023). Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers*, *15*(2), 485. https://doi.org/10.3390/cancers15020485

30. Bhaskaran, K., Douglas, I., Forbes, H., dos-Santos-Silva, I., Leon, D. A., & Smeeth, L. (2014). Body-mass index and risk of 22 specific cancers: a population-based cohort study

of 5·24 million UK adults. *The Lancet*, *384*(9945), 755–765. https://doi.org/10.1016/s0140-6736(14)60892-8

31. Vajdic, C. M., McDonald, S. P., McCredie, M. R. E., Leeuwen, M. T. van, Stewart, J. H., Law, M., Chapman, J. R., Webster, A. C., Kaldor, J. M., & Grulich, A. E. (2006). Cancer Incidence Before and After Kidney Transplantation. *JAMA*, *296*(23), 2823–2831. https://doi.org/10.1001/jama.296.23.2823

32. Stewart, J. H., Vajdic, C. M., Leeuwen, M. T. van, Amin, J., Webster, A. C., Chapman, J. R., McDonald, S. P., Grulich, A. E., & McCredie, M. R. E. (2009). The pattern of excess cancer in dialysis and transplantation. *Nephrology Dialysis Transplantation*, *24*(10), 3225–3231. https://doi.org/10.1093/ndt/gfp331

33. Yanik, E. L., Clarke, C. A., Snyder, J. J., Pfeiffer, R. M., & Engels, E. A. (2016). Variation in Cancer Incidence among Patients with ESRD during Kidney Function and Nonfunction Intervals. *Journal of the American Society of Nephrology*, *27*(5), 1495–1504. https://doi.org/10.1681/asn.2015040373

34. Foucher, Y., Lorent, M., Albano, L., Roux, S., Pernin, V., Quintrec, M. L., Legendre, C., Buron, F., Morelon, E., Girerd, S., Ladrière, M., Glotz, D., Lefaucher, C., Kerleau, C., Dantal, J., Branchereau, J., Giral, M., Blancho, G., Branchereau, J., … Serre, J.-E. (2021). Renal transplantation outcomes in obese patients: a French cohort-based study. *BMC Nephrology*, *22*(1), 79. https://doi.org/10.1186/s12882-021-02278-1

35. McCloskey, O. M., Devine, P. A., Courtney, A. E., & McCaughan, J. A. (2018). Is big bad or bearable? Long-term renal transplant outcomes in obese recipients. *QJM: An*

International Journal of Medicine, *111*(6), 365–371. https://doi.org/10.1093/qjmed/hcx258

36. Gyawali, B., Tessema, F. A., Jung, E. H., & Kesselheim, A. S. (2019). Assessing the Justification, Funding, Success, and Survival Outcomes of Randomized Noninferiority Trials of Cancer Drugs. *JAMA Network Open*, *2*(8), e199570. https://doi.org/10.1001/jamanetworkopen.2019.9570

37. Parsyan, A., Marini, W., Fazelzad, R., Moher, D., & McCready, D. (2020). Current Issues in Conduct and Reporting of Noninferiority Randomized Controlled Trials in Surgical Management of Cancer Patients. *Annals of Surgical Oncology*, 1–9. https://doi.org/10.1245/s10434-020-08575-7

38. Hernandez, A. V., Pasupuleti, V., Deshpande, A., Thota, P., Collins, J. A., & Vidal, J. E. (2013). Deficient Reporting and Interpretation of Non-Inferiority Randomized Clinical Trials in HIV Patients: A Systematic Review. *PLoS ONE*, *8*(5), e63272. https://doi.org/10.1371/journal.pone.0063272

39. Arifin, A. J., Tan, V. S., Yan, M., Warner, A., Boldt, R. G., Chen, H., Rodrigues, G. B., Palma, D. A., & Louie, A. V. (2023). Ensuring Superior Reporting of Radiation Therapy Noninferiority Trials: A Systematic Review. *Advances in Radiation Oncology*, *8*(3), 101178. https://doi.org/10.1016/j.adro.2023.101178

40. Aupiais, C., Zohar, S., Taverny, G., Roux, E. L., Boulkedid, R., & Alberti, C. (2018). Exploring how non-inferiority and equivalence are assessed in paediatrics: a systematic

review. *Archives of Disease in Childhood*, *103*(11), 1067. https://doi.org/10.1136/archdischild-2018-314874

41. Komorowski, A. S., Lo, C. K. L., Kapoor, A. K., Smieja, M., Loeb, M., Mertz, D., & Bai, A. D. (2023). More Than a Decade Since the Latest CONSORT Non-inferiority Trials Extension: Do Infectious Diseases Trials Do Enough? *Clinical Infectious Diseases*, *78*(2), 324–329. https://doi.org/10.1093/cid/ciad574

42. Tedesco Silva Jr., H. T. S., Cibrik, D., Johnston, T., Lackova, E., Mange, K., Panis, C., Walker, R., Wang, Z., Zibari, G., & Kim, Y. S. (2010). Everolimus Plus Reduced-Exposure CsA versus Mycophenolic Acid Plus Standard-Exposure CsA in Renal-Transplant Recipients. *American Journal of Transplantation*, *10*(6), 1401–1413. https://doi.org/10.1111/j.1600-6143.2010.03129.x

43. Hernández, D., Alonso-Titos, J., Armas-Padrón, A. M., Ruiz-Esteban, P., Cabello, M., López, V., Fuentes, L., Jironda, C., Ros, S., Jiménez, T., Gutiérrez, E., Sola, E., Frutos, M. A., González-Molina, M., & Torres, A. (2018). Mortality in Elderly Waiting-List Patients Versus Age-Matched Kidney Transplant Recipients: Where is the Risk? *Kidney and Blood Pressure Research*, *43*(1), 256–275. https://doi.org/10.1159/000487684

44. Wakam, G. K., Sheetz, K. H., Gerhardinger, L., Montgomery, J. R., & Waits, S. A. (2021). Population-based Trends in Obesity and Kidney Transplantation Among Patients With End-stage Kidney Disease. *Transplantation Direct*, *7*(12), e787. https://doi.org/10.1097/txd.0000000000001163

45. Parikh, C. R., Klem, P., Wong, C., Yalavarthy, R., & Chan, L. (2003). Obesity as an independent predictor of posttransplant diabetes mellitus. *Transplantation Proceedings*, *35*(8), 2922–2926. https://doi.org/10.1016/j.transproceed.2003.10.074

46. Young, J. B., Neumayer, H.-H., & Gordon, R. D. (2010). Pretransplant cardiovascular evaluation and posttransplant cardiovascular risk. *Kidney International*, *78*(118), S1–S7. https://doi.org/10.1038/ki.2010.209

47. Engels, E. A., Pfeiffer, R. M., Fraumeni, J. F., Kasiske, B. L., Israni, A. K., Snyder, J. J., Wolfe, R. A., Goodrich, N. P., Bayakly, A. R., Clarke, C. A., Copeland, G., Finch, J. L., Fleissner, M. L., Goodman, M. T., Kahn, A., Koch, L., Lynch, C. F., Madeleine, M. M., Pawlish, K., … Lin, M. (2011). Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients. *JAMA*, *306*(17), 1891–1901. https://doi.org/10.1001/jama.2011.1592

48. Kaji, A. H., & Lewis, R. J. (2015). Noninferiority Trials: Is a New Treatment Almost as Effective as Another? *JAMA*, *313*(23), 2371–2372. https://doi.org/10.1001/jama.2015.6645

49. Piaggio, G., Elbourne, D. R., Pocock, S. J., Evans, S. J. W., Altman, D. G., & Group, for the C. (2012). Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA*, *308*(24), 2594. https://doi.org/10.1001/jama.2012.87802

CHAPTER 2

Validity of kidney transplant outcomes in the ANZDATA Registry: a comparison with clinical trial data

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Author contribution:

BS designed the study together with her supervisors, acquired the data, performed the analysis, interpreted the results, drafted the manuscript and figures, and oversaw the manuscript revision.

Abstract

Clinical registries capture data that is used to assess quality of clinical care, inform health service planning, and enable health outcomes research. Confidence in data validity is critically important. Here we evaluated the validity of data within the ANZDATA registry by comparison with data for the same patients from the database of a rigorously monitored, prospective, industry sponsored clinical trial. We performed deterministic linkage between the ANZDATA Registry and A2309 trial database. Agreement between the datasets was assessed using kappa statistics for variables including age, sex, donor sex, donor type, ethnicity, primary kidney disease, acute rejection, graft function, graft failure, and death. All 95 A2309 participants from Australia and New Zealand were matched. Agreement for age, sex, donor sex, and donor type was perfect (kappa=1.00). Ethnicity, primary kidney disease, graft function over time and incidence of acute rejection showed moderate-good agreement. Graft failure and death exhibited almost perfect concordance (kappa=0.85 and 1.00, respectively). ANZDATA registry provides reliable data for key transplant outcomes. Subtle differences in nomenclature, definitions and timing may hamper comparisons between registries and other datasets and this could be improved by standardization.

Introduction

Clinical registries systematically collect data which is used primarily to examine the quality of patient care. Well-managed registries have been shown to significantly impact the rate of clinical improvement, often at a lower cost, by providing transparent and accessible data.[1,2] Registry data is also used to inform health services planning and to enable the conduct of research. Such research is of particular importance to Clinical Practice Guideline producers, who make extensive use of registry-based research in generating recommendations for clinical practice.[3]

The Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry is a clinical quality registry that routinely collects data of all patients treated with maintenance kidney replacement therapy in Australia and New Zealand since 1963.[4] The registry is valuable, with economic evaluations estimating that the ANZDATA registry has generated a net benefit of $49 million and a benefit to cost ratio of 7:1 in 2016.[5] The registry supports health service planning, development, and quality activities through quality assurance reports, Key Performance Indicator (KPI) reports and interim data summaries. The extensive longitudinal observational dataset maintained by the ANZDATA registry is a valuable resource for addressing clinical research questions. Between 2019 and 2023, over 200 research projects in kidney transplantation requested data from the registry.[6] Given the degree to which ANZDATA data is utilized to direct and monitor the practice and business of kidney replacement therapy, confidence in the quality and accuracy of data is critically important.

The ANZDATA registry collects data voluntarily which relies on the ongoing contribution of nurses and clinicians. Despite its extensive use, the data collected are rarely audited. Large pharmaceutical

clinical trials are meticulously overseen by the Food & Drug Administration (FDA) to ensure they are designed, conducted, analyzed and reported according to federal law and good clinical practice (GCP) regulations.[7] FDA's regulations and guidance for clinical trials support efficient medical product development while ensuring robust evidence for assessing product safety and efficacy. The A2309 study was a randomized controlled trial evaluating the efficacy and safety of two regimens of everolimus plus reduced-exposure cyclosporine compared to mycophenolic acid (MPA) plus standard exposure cyclosporine in *de novo* kidney-transplant recipients over 24 months.[8] The current study aims to assess the validity of data collected by the ANZDATA registry by comparing it with the A2309 study for all patients common to both databases.

Methods

The ANZDATA Registry collects a wide range of statistics to monitor dialysis and transplant outcomes for all patients treated with kidney replacement therapy in Australia and New Zealand.[4] From the ANZDATA registry, we extracted data on recipient factors, including age at transplant, sex, ethnicity, primary kidney disease, current dialysis, pre-existing diabetes mellitus, body mass index at the time of transplantation, donor age, donor gender, donor type, creatinine levels at 1, 3, 6, and 12 months, date of delayed graft function, date of acute rejection, date and type of graft failure, and date and cause of death.

The A2309 trial was a 24-month, phase IIIb, multicentre, randomized, open-label non-inferiority study of efficacy and safety of two regimens of everolimus plus reduced-exposure cyclosporine (CsA) compared with mycophenolic acid plus standard-exposure CsA. Patients were recruited from 79

centres across sixteen countries between 2006 and 2008. The trial protocol, baseline characteristics, and outcomes have been reported.[8] The eligibility criteria of study participants were summarised in Table 1. Our study included all participants from Australia and New Zealand in the A2309 trial. Deterministic data linkage with ANZDATA was performed using initials, age at transplantation and sex.

Ethnicity in both datasets was re-categorised as Caucasian and non-Caucasian to account for differences in original categorisation. Delayed graft function was not assessed in our study due to a discrepancy in its definition between the ANZDATA registry and the A2309 trial. In the ANZDATA registry, delayed graft function was defined as the need for dialysis within 72 hours of transplantation, a definition used until 2017. In contrast, the A2309 trial defined delayed graft function as needing dialysis within seven days of transplantation.

Agreement between nominal variables in ANZDATA and A2309 was assessed using kappa statistics.[9] Agreement between ordinal variables was assessed using weighted kappa statistic.[10] We then compared agreement statistics against the following commonly cited scale: 0.0-0.20 for poor agreement, 0.21-0.40 for fair agreement, 0.41-0.60 for moderate agreement, 0.61-0.80 for good agreement, and >0.80 for very good agreement.[11,12]

All analyses were performed using Stata Statistical Software: Release 14.2 (StataCorp., College Station, TX)

This study was approved by the Human Research Ethics Committees of the University of Sydney.

Results

Patient and transplant characteristics

The study flow chart is presented in Figure 1. Of the 833 participants in the A2309 study cohort, 95 were from Australia and New Zealand. After conducting deterministic data linkage with the ANZDATA registry, all 95 participants were matched. Five A2309 participants discontinued the study due to withdrawal of consent, and three ANZDATA participants were lost to follow-up.

Baseline demographics and clinical characteristics for A2309 and ANZDATA are compared in Table 2. Agreement between A2309 and ANZDATA was very good for age, sex, donor sex and donor type (kappa=1.00). There was moderate agreement for ethnicity, with 90% of the A2309 sample classified as Caucasian compared to 82% in ANZDATA (kappa=0.53). Agreement in primary kidney disease was good overall, with complete agreement for diabetic and polycystic kidney disease, but moderate agreement only for glomerular disease (32% of the A2309 sample compared 51% in ANZDATA (kappa=0.70)). Agreement on the number of previous transplants, donor sex and donor type was 100%.

Acute rejection, graft failure and death

Nineteen percent of the cohort were reported to have experienced acute rejection in ANZDATA, compared to 23% in A2309. Agreement in the occurrence of acute rejection between ANZDATA and the A2309 study was good overall (agreement 87%, kappa 0.62) (Table 3). In addition to the 14 patients recorded as having acute rejection in both databases, three (4%) additional patients were recorded in A2309 but not in ANZDATA, and four (5%) additional patients were recorded in ANZDATA but not in A2309. Of those "missed" by ANZDATA, two patients died soon after being diagnosed with rejection, and in one case the episode of "Banff IIB acute rejection and renal vein thrombosis" captured by A2309 was classified only as "renal vein thrombosis" in ANZDATA.

As reported in Table 4, ANZDATA reported three graft failure events compared to four in the A2309 study (overall agreement 99%, kappa 0.85). The individual reported as incurring graft loss in 2309 but not ANZDATA subsequently died, and this was captured in both databases. The overall agreement on the causes of graft failure was excellent, and recorded dates of graft loss were within one-week of each other.

Agreement on the occurrence and date of death was perfect between ANZDATA and A2309 (Table 3, 4). Causes of death also showed excellent agreement, with only slight variation in 2 cases, largely attributable to nomenclature: bacterial septicaemia in ANZDATA compared with abdominal sepsis in A2309, and malignant disease in ANZDATA compared with malignant melanoma in A2309 (Table 5).

Graft function

eGFR values at 1, 3, 6 and 12 months post-transplant for both ANZDATA and A2309 are detailed in Table 6. At 1 month post-transplant, there was 97% agreement with a weighted Kappa value of 0.84, indicating very good agreement across eGFR categories. At 3 months (agreement 96%, weighted kappa=0.80), 6 months (agreement 95%, weighted Kappa=0.74), and 12 months post-transplant (agreement 91%, weighted Kappa=0.61), agreement remained very good or good, but declined numerically with increasing time post-transplant. The majority of discrepancies between eGFR categories were minor.

Discussion

In this study, we assessed the validity of data for a cohort of de novo kidney transplant recipients within the ANZDATA registry by comparing demographic and clinical outcomes data with the same data elements stored within the data repository for a large, phase IIIb, multi-centre, randomised controlled study sponsored by Pharma that served as a gold standard. The results demonstrate a high level of concordance in baseline demographics and clinical characteristics between the two datasets. These results are reassuring for the many users of registry data who rely upon data quality and accuracy.

Agreement was very good for baseline variables such as age, sex, primary kidney disease, donor sex, and donor type, indicating reliable data for these key parameters. This is important as baseline parameters are essential components of most quality reports and research projects derived from registry data.

Clinical outcomes are of at least equal importance, being key points of interest to patients, clinicians, planners and researchers. The hard outcomes of patient and graft survival were small in number due to the modest cohort size and follow-up period of only 2 years. However, agreement between the databases was very good. Incidence, cause and timing of death were essentially concordant, with minor differences in nomenclature and timing only. Agreement regarding graft failure events was very good, with only one instance of graft failure not recorded in ANZDATA. This patient subsequently died and their death was recorded. ANZDATA policy defines graft loss as any of patient death, return to dialysis or re-transplantation, and thus the missing graft failure event would have been superseded by the patient's death for reporting purposes. On that basis, hard outcomes for this cohort were reliably reported in ANZDATA. Accuracy and completeness of registry reporting of hard outcomes has recently come into focus with an evaluation of death reporting by USRDS uncovering systematic underreporting for a defined period of time.[13] A change in law as to how state-based death reports may be used was identified as the cause, and measures to overcome this deficiency have been implemented. Confidence that registries capture the hard clinical outcomes of death and graft failure accurately, completely and in a timely fashion is a key factor underpinning data utilization and assessment of this should arguably be done more frequently.[14]

Beyond hard outcomes, kidney function (eGFR) over time and the incidence and type of acute rejection episodes are important events for patients and clinicians, and are also surrogates for longer-term hard outcomes.

Agreement between the databases was good to very good for eGFR captured at specific timepoints post-transplant. As eGFR is typically measured very frequently during the first year after

transplantation, it is common for multiple measurements to be made during each scheduled "window" for collection. eGFR data submitted to the A2309 database was generated by a central trial lab, whereas the lab used to generate eGFR data for ANZDATA is not specified. Day-day variability and inter-lab variability in eGFR is well recognized, and it is therefore likely that variability in results due to differences in labs and sample timing may have detracted from agreement between the datasets.

Good levels of agreement between the databases were evident for acute rejection. Differences in classification likely detracted from agreement: acute rejection was defined in A2309 as biopsy-proven and graded according to Banff criteria; in ANZDATA Banff Criteria were preferred but not required and greater latitude in reporting was permitted. Two patients reported to experience acute rejection in A2309 but not in ANZDATA died soon after their diagnosis. Reporting rejection requires submission of a specific "Rejection Form". It is conceivable that submission of the Rejection Form may be overlooked in the context of patient death, raising the potential for systematic under-reporting, albeit infrequent given the low rates of early recipient death in contemporary transplantation.

Existing studies have looked at data quality in the ANZDATA registry across a variety of variables by using different benchmarks for comparison.[12,15–19] One study found strong agreement for the cause of death between ANZDATA and the National Death Index (NDI), which is consistent with our findings.[17] Another study reported high-level agreement between ANZDATA and the New South Wales Cancer Registry for cancer outcomes with minor differences evident but largely explicable, indicating reliable reporting.[16] Three studies have shown very good data accuracy for diabetes mellitus, which is also consistent with our result of good agreement.[12,15,18] The same studies

demonstrated variable degrees of agreement for other co-morbidities, including coronary artery disease (CAD), chronic lung disease, peripheral vascular disease and cerebrovascular disease, highlighting potential areas for improvement in data collection and reporting. As these comorbidities were not collected in the A2309 study, we were unable to confirm these results. A study focusing on ethnicity data, categorising patients into European, Maori, Pacific, Asian and other, demonstrated a high level of agreement between ANZDATA and hospital-based patient clinical records, whilst our result showed only moderate agreement for ethnicity.[19] This may be in part due to differences in categorization of ethnicity between the A2309 study and ANZDATA.

The strength of our study lies in using a robust clinical trial dataset as the benchmark. Clinical trial data are meticulously collected, rigorously monitored, and held to high standards of accuracy and completeness, making them an optimal benchmark for validating registry data. This approach allows for a more precise and reliable assessment of the registry's data quality. However, there are limitations to consider. Firstly, the study focuses solely on transplant patients who were enrolled in a clinical trial, which may limit the generalisability of the findings. Secondly, while our sample size is robust, the total number of patients was still limited. We are grateful to Novartis for providing access to this cohort of A2309 patients, however our attempts to expand our study to include additional Novartis-sponsored trials involving patients also recorded in ANZDATA proved difficult, time consuming and ultimately futile. As an increasing number of journals now require provision of data access post-publication, it is hoped that access will improve in the future. Thirdly, we only included data entered between 2006-2008, which may not reflect more recent trends or improvements in data quality. Lastly, differences in the definitions used between the two datasets require careful interpretation of the results to avoid potential misinterpretations.

Our findings highlight the reliability of the ANZDATA registry for important baseline characteristics and key transplant outcomes. This supports ongoing use of data from the ANZDATA Registry to support clinical decision-making, health service planning, and clinical research. The identified areas of moderate to poor agreement, such as ethnicity and primary kidney disease, highlight the need for broad agreement on nomenclature and classifications and enhanced data collection and validation processes. Clinicians and policymakers can be confident in the Registry's core data elements, but should be aware of potential discrepancies in certain less critical variables.

In conclusion, this study demonstrates that the ANZDATA registry provides reliable data for patient and transplantation characteristics and the incidence of acute rejection, graft failure, and death outcomes. Future work should focus on both enhancing and demonstrating the accuracy and completeness of registry data through standardization of data definitions and collection methods, supplemented by routine audits. Such efforts will serve to further support the value of data from clinical quality registries in directing clinical practice and underpinning research, ultimately contributing to better patient outcomes and health service efficiency.

References

1. Larsson, S., Lawyer, P., Garellick, G., Lindahl, B., & Lundström, M. (2017). Use of 13 Disease Registries In 5 Countries Demonstrates The Potential To Use Outcome Data To Improve Health Care's Value. *Health Affairs*, *31*(1), 220–227. https://doi.org/10.1377/hlthaff.2011.0762

2. Lee, P., Chin, K., Liew, D., Stub, D., Brennan, A. L., Lefkovits, J., & Zomer, E. (2019). Economic evaluation of clinical quality registries: a systematic review. *BMJ Open*, *9*(12), e030984. https://doi.org/10.1136/bmjopen-2019-030984

3. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group, Rossing, P., Caramori, M. L., Chan, J. C. N., Heerspink, H. J. L., Hurst, C., Khunti, K., Liew, A., Michos, E. D., Navaneethan, S. D., Olowu, W. A., Sadusky, T., Tandon, N., Tuttle, K. R., Wanner, C., Wilkens, K. G., Zoungas, S., & Boer, I. H. de. (2022). KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney International*, *102*(5), S1–S127. https://doi.org/10.1016/j.kint.2022.06.008

4. McDonald, S. P. (2015). Australia and New Zealand Dialysis and Transplant Registry. *Kidney International Supplements*, *5*(1), 39–44. https://doi.org/10.1038/kisup.2015.8

5. Monash University, & Health Outcomes Australia. (2016). *Economic evaluation of clinical quality registries: final report* (Nos. 978-1-925224-65–8). the Australian Commission on Safety and Quality in Health Care.

6. The ANZDATA Registry. (n.d.). *ANZDATA: Current Projects 2019-2023*. Retrieved April 15, 2024, from https://www.anzdata.org.au/anzdata/data-requests/data-projects/

7. U.S. Food & Drug Administration. (n.d.). *Regulations: Good Clinical Practice and Clinical Trials*. Retrieved April 15, 2024, from https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

8. Tedesco Silva Jr., H., Cibrik, D., Johnston, T., Lackova, E., Mange, K., Panis, C., Walker, R., Wang, Z., Zibari, G., & Kim, Y. S. (2010). Everolimus Plus Reduced-Exposure CsA versus Mycophenolic Acid Plus Standard-Exposure CsA in Renal-Transplant Recipients. *American Journal of Transplantation*, *10*(6), 1401–1413. https://doi.org/10.1111/j.1600-6143.2010.03129.x

9. Sim, J., & Wright, C. C. (2005). The Kappa Statistic in Reliability Studies: Use, Interpretation, and Sample Size Requirements. *Physical Therapy*, *85*(3), 257–268. https://doi.org/10.1093/ptj/85.3.257

10. Ranganathan, P., Pramesh, C. S., & Aggarwal, R. (2017). Common pitfalls in statistical analysis: Measures of agreement. *Perspectives in Clinical Research*, *8*(4), 187–191. https://doi.org/10.4103/picr.picr_123_17

11. Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*(1), 159–174.

12. Palamuthusingam, D., Pascoe, E. M., Hawley, C. M., Johnson, D. W., Ratnayake, G., McDonald, S., Boudville, N., Jose, M., & Fahim, M. (2022). Evaluating data quality in the Australian and New Zealand dialysis and transplant registry using administrative hospital

admission datasets and data-linkage. *Health Information Management Journal*, *52*(3), 212–220. https://doi.org/10.1177/18333583221097724

13. Noreen, S. M., Patzer, R. E., Mohan, S., Schold, J. D., Lyden, G. R., Miller, J., Verbeke, S., Stewart, D., Fritz, A. R., McBride, M., & Snyder, J. J. (2024). Augmenting the Unites States transplant registry with external mortality data: A moving target ripe for further improvement. *American Journal of Transplantation*, *24*(2), 190–212. https://doi.org/10.1016/j.ajt.2023.09.002

14. Chadban, S., & Gill, J. S. (2024). How hard are the hard outcomes reported in national transplant registries? *American Journal of Transplantation*, *24*(2), 158–159. https://doi.org/10.1016/j.ajt.2023.10.023

15. Kotwal, S., Webster, A. C., Cass, A., & Gallagher, M. (2016). Comorbidity recording and predictive power of comorbidities in the Australia and New Zealand dialysis and transplant registry compared with administrative data: 2000–2010. *Nephrology*, *21*(11), 930–937. https://doi.org/10.1111/nep.12694

16. Webster, A. C., supramaniam, R., O'Connell, D. L., Chapman, J. R., & Craig, J. C. (2010). Validity of registry data: Agreement between cancer records in an end-stage kidney disease registry (voluntary reporting) and a cancer register (statutory reporting). *Nephrology*, *15*(4), 491–501. https://doi.org/10.1111/j.1440-1797.2010.01297.x

17. Sypek, M. P., Dansie, K. B., Clayton, P., Webster, A. C., & Mcdonald, S. (2019). Comparison of cause of death between Australian and New Zealand Dialysis and

Transplant Registry and the Australian National Death Index. *Nephrology*, *24*(3), 322–329. https://doi.org/10.1111/nep.13250

18. Gray, N. A., Mahadevan, K., Campbell, V. K., Noble, E. P., & Anstey, C. M. (2013). An audit of ANZDATA data quality. *Nephrology*, *18*(10), 665–670. https://doi.org/10.1111/nep.12126

19. Page, M., Wyeth, E. H., Samaranayaka, A., McNoe, B., Walker, R., Schollum, J., Marshall, M., Walker, R., & Derrett, S. (2017). Accuracy of ethnicity data recorded in hospital-based patient clinical records and the Australia and New Zealand Dialysis and Transplant Registry. *The New Zealand Medical Journal*, *130*(1454), 65–71.

Table 1. Eligibility criteria for A2309 study participants

Inclusion criteria
1. Male or female kidney recipients in Australia and New Zealand 2. Age between 18-70 3. Female with a negative pregnancy test
Exclusion criteria
1. No evidence of graft function within 24 hours of transplantation 2. Recipients of kidneys from HLA-identical living related donors 3. Donor organ with a cold ischemia time > 40 hours 4. Received kidney from a non-heart beating donor 5. Donor age > 65 years 6. Platelet count < 100,000/mm^3 at the evaluation before randomization 7. Absolute neutrophil count <1,500/mm^3 at baseline before surgery or white blood cell count < 4,500/mm^3 8. Recipient of dual kidney transplants 9. Recipients of multiple solid organ or tissue transplants or recipients of previous organ or tissue transplant 10. Severe hypercholesterolemia or hypertriglyceridemia 11. Abnormal liver profile 12. Most recent anti-HLA Class I panel reactive antibodies >20% by a Complement Dependent Cytotoxicity-based assay or >50% by a flow cytometry or Enzyme Linked Immunosorbent Assay-based assay 13. Recipient of ABO incompatible transplants or T-cell crossmatch positive transplant

Anti-HLA, anti-Human Leukocyte Antigen.

Table 2. Baseline demographics and clinical characteristics

Characteristics	ANZDATA n (%)	A2309 n (%)	Agreement	Kappa/weighted kappa*
Age at transplant			100%	1.00*
18-34	16 (17)	16 (17)		Very good
35-49	31 (32)	31 (32)		
50-65	42 (44)	42 (44)		
60+	6 (6)	6 (6)		
Male	66 (69)	66 (69)	100%	1.00
				Very good
Caucasian	78 (82)	85 (90)	88%	0.53
				Moderate
Primary kidney disease			79%	0.70
Diabetic kidney disease	8 (8)	8 (8)		Good
Glomerular disease	48 (51)	30 (32)		
Polycystic disease	18 (19)	18 (19)		
Other	21 (22)	39 (41)		
Number of HLA mismatches			91%	0.71*
0	4 (4)	2 (2)		Good
1-2	27 (28)	21 (22)		
3-4	34 (36)	45 (47)		
5-6	30 (32)	27 (28)		
Current dialysis			91%	0.82
None	12 (13)	14 (14)		Very good
Hemodialysis	64 (67)	58 (61)		
Peritoneal dialysis	19 (20)	23 (24)		
Diabetic	9 (9)	14 (15)	93%	0.66
				Good
Body mass index at baseline			93%	0.75*
Underweight	1 (1)	2 (2)		Good
Normal	46 (48)	38 (40)		
Overweight	30 (32)	27 (28)		
Obese	18 (19)	14 (15)		
Missing	0 (0)	14 (15)		
Donor characteristics				
Aged 50 and older	46 (48)	48 (51)	98%	0.96
				Very good
Male	41 (43)	41 (43)	100%	1.00
				Very good
Living donor	49 (52)	49 (52)	100%	1.00
				Very good

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; HLA, human leukocyte antigen.

Table 3. Agreement of acute rejection, graft failure and death between ANZDATA and A2309

Outcome			A2309			Agreement %	Kappa
			No	Yes	Total		
Acute rejection	ANZDATA	No	69	4*(4**)	77	87	0.62
		Yes	4	14	18		Good
		Total	73	22	95		
Graft failure	ANZDATA	No	91	1	92	99	0.85
		Yes	0	3	3		Very good
		Total	91	4	95		
Death	ANZDATA	No	92	0	92	100	1.00
		Yes	0	3	3		Very good
		Total	92	3	95		

*One case was classified as Banff IIB in 2309 but Renal Vein Occlusion in ANZDATA

**4 cases were classified as “rejection” in 2309 were not classified as rejection using Banff criteria

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry.

Table 4. Comparison of date and cause of graft failure between ANZDATA and A2309 study

Graft failure number	Cause of graft failure		Difference in graft failure date (days)
	ANZDATA	A2309	
1	Renal artery thrombosis	Infarcted kidney	0
2	Nil recorded	Acute rejection	-
3	Cortical necrosis (not due to rejection)	Infarcted kidney	3
4	Renal vein thrombosis	Technical - renal vein thrombosis	5

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry.

Table 5. Comparison of date and cause of death between ANZDATA and A2309 study

Death no.	Cause of death		Difference in death date (days)
	ANZDATA	A2309	
1	Cardiac arrest	Cardiac arrest	0
2	Bacterial septicaemia	Abdominal sepsis	0
3	Malignant disease	Malignant melanoma	0

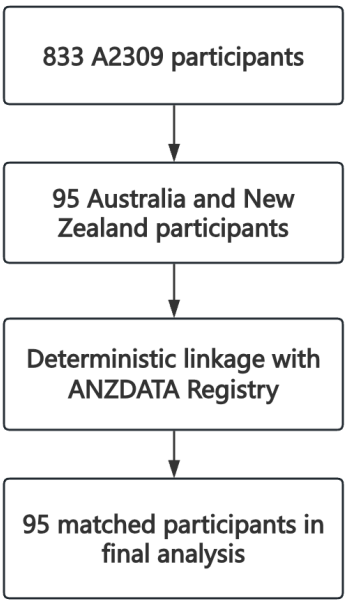
ANZDATA, Australia and New Zealand Dialysis and Transplant Registry.

Table 6. Agreement in graft function at month 1, 3, 6 and 12 post-transplant

eGFR	ANZDATA n (%)	A2309 n (%)	Agreement %	weighted Kappa
1 month post-transplant			97	0.84
<15 ml/min	1 (1)	1 (1)		Very good
15-<30 ml/min	6 (7)	6 (7)		
30-<60 ml/min	51 (56)	48 (52)		
60-<90 ml/min	29 (32)	28 (31)		
≥90 ml/min	4 (4)	8 (9)		
3 months post-transplant			96	0.80
<15 ml/min	0 (0)	0 (0)		Very good
15-<30 ml/min	3 (4)	3 (4)		
30-<60 ml/min	50 (63)	48 (61)		
60-<90 ml/min	25 (32)	26 (33)		
≥90 ml/min	1 (1)	2 (3)		
6 months post-transplant			95	0.74
<15 ml/min	0 (0)	0 (0)		Good
15-<30 ml/min	1 (2)	4 (6)		
30-<60 ml/min	42 (68)	38 (61)		
60-<90 ml/min	19 (31)	17 (27)		
≥90 ml/min	0 (0)	3 (5)		
12 months post-transplant			91	0.61
<15 ml/min	0 (0)	0 (0)		Good
15-<30 ml/min	2 (3)	3 (4)		
30-<60 ml/min	38 (54)	40 (57)		
60-<90 ml/min	27 (39)	22 (31)		
≥90 ml/min	3 (4)	5 (7)		

ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; eGFR, estimated glomerular rate.

Figure 1. Study flowchart



ANZDATA Registry, the Australia and New Zealand Dialysis and Transplant Registry.

CHAPTER 3

Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: a matched-pair analysis

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Publication arising from this chapter:

Shi B, Ying T, Chadban SJ. Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: a matched-pair analysis. *Am J Transplant*. Published online 2023. doi:10.1016/j.ajt.2023.07.006

Author contribution:

BS designed the study together with her supervisors, acquired the data, performed the analysis, interpreted the results, drafted the manuscript and figures, and oversaw journal submission and revisions.

Abstract

Background. Kidney transplantation offers improved survival and quality of life compared to dialysis for most recipients, however benefits for elderly patients (>70) remain uncertain. Methods. Using the Australia and New Zealand Dialysis and Transplant Registry (2009-2019), elderly transplant recipients were matched to a waitlisted dialysis patient by age, cause of ESKD and dialysis duration (paired controls). We censored dialysis patients at the time of transplant. Survival was compared using Stratified Cox regression. Results. Elderly transplant recipients (KTRs) (n=465) were matched to waitlisted pair. Transplant group mortality initially exceeded dialysis, due to excess infection-related deaths (1.9 transplant versus 0.3 dialysis/100 patient-years, p=0.03). Beyond month 9, a progressive survival benefit in favour of transplantation was apparent. Over a median follow-up of 1.7 years, mortality was 38% lower for KTRs (95% CI 0.41-0.94, p=0.02), and 5-year survival was 80% KTRs vs 53% dialysis (P<0.001). Recipients of living and standard criteria donor kidneys acquired immediate survival advantage compared to dialysis whilst recipients of expanded criteria donor kidneys experienced elevated risk of death for the first 17 months. Conclusions. Compared with remaining on dialysis, elderly KTRs incur an increased risk of early post-transplant mortality but thereafter may anticipate progressively superior survival rates.

Introduction

The number of elderly patients with end-stage kidney disease (ESKD) has steadily increased over the past few decades. In Europe, almost half of all patients receiving renal replacement therapy (RRT) were over 65 years of age in 2019 compared to 30% in 1999.[1,2] In the US, the proportion of ESKD patients aged 70 and over that are waitlisted for a kidney transplant has increased from 3% in 1999 to nearly 10% in 2019.[3]

Existing literature has shown that in comparison to younger transplant recipients, the elderly are more susceptible to infections, cardiovascular events, cancer, cognitive impairment, poor functional status and frailty, leading to higher readmission rates, costs and post-transplant mortality.[4] However, existing data suggests selected recipients aged 65 years and older, as compared to remaining on dialysis, experience overall benefits of improved longevity, lower risks of cardiovascular events, and improved quality of life.[5,6]

As both the number of candidates and the shortfall in kidneys available for transplantation continue to rise[7], appropriate kidney allocation is of utter importance. Equipoise exists regarding the survival benefit of kidney transplantation for those over 70 years old compared to remaining on dialysis based on contemporary data. We therefore aimed to determine the impact of transplantation, as compared to remaining on dialysis, on survival

among patients aged 70 or over who were waitlisted for transplantation, using a matched pair design.

Methods

We extracted data from Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The ANZDATA Registry is a clinical quality registry that collects comprehensive data from all patients with ESKD in Australia and New Zealand. Details of the structure and methods of ANZDATA Registry data collection can be found on the Registry website (https://www.anzdata.org.au/anzdata/). We accessed data for all people aged 70 and over receiving renal replacement therapy in Australia and New Zealand. Patients who received a kidney-only transplant between January 1, 2009, and December 31, 2019 were retrospectively matched to a maintenance dialysis patient by age, diabetes as the cause of ESKD and time on dialysis. We included dialysis controls who were actively waitlisted for transplantation at any point during the study follow-up period, while excluding those who were never waitlisted or had their waitlist status removed before matching and were not re-activated thereafter. If subsequently transplanted they were censored at the time of transplantation. The matching was done without replacement. For kidney recipients, follow-up commenced on the date of transplantation. For dialysis controls, follow-up commenced on the date when the duration of dialysis was the same as their transplant pair. Follow-up was until the date of transplantation (for dialysis controls only), loss to follow-up, death or December 31, 2019.

We compared baseline characteristics of paired recipients using Wilcoxon's signed rank test for continuous variables and ordinal categorical variables, Bowker's test for nominal categorical variable, and McNemar's test for dichotomous variables. Survival was compared using Kaplan-Meier curves. Time to death was analyzed using stratified Cox regression modelling, adjusting for confounders. Test of proportional-hazards assumption was performed using Schoenfeld residuals with p-values below the significance level of 0.05 deemed a violation. The potential confounders considered were sex, ethnicity, smoking status, body mass index (BMI), and pre-existing comorbidities, including diabetes, chronic lung disease, cardiovascular disease (any of coronary artery, cerebrovascular or peripheral vascular), non-skin cancer and transplant era (in 5.5-year interval). We calculated all-cause death incident rates and cause-specific death incident rates within and after one year post-transplant by dividing the total number of deaths by the total patient-years at risk within the time period. Death incident rates were reported as per 100 patient-years. We compared the death incident rates by using incident rate ratios. 95% confidence interval was reported. Stratified Cox regression model was used to compare hazards by the following time-periods post-transplant: 0 to <3 months, 3 to <12 months, 1 to <5 years, and $\geq$ 5years. We performed a subgroup analysis according to 3 donor types: (1) living donor (LD), (2) standard criteria donor (SCD) and (3) expanded criteria donor (ECD).

We used stepwise selection methods where variables with a significance level of 0.20 were included in the base multivariable model. We next used backward selection to remove variables that were not significant at the 0.05 level. Variables considered clinically significant

included sex, pre-existing cardiovascular disease, diabetes, chronic lung disease, smoking status and BMI, were also included in the multivariable model. We used a complete case analysis because the number of missing values was less than 5%. All analyses were performed using Stata Statistical Software: Release 14.2 (StataCorp., College Station, TX)

Results

Study cohort

The study flow chart is presented in Figure 1. A total of 19,476 patients aged 70 and over received maintenance dialysis between 2009 and 2019, of whom 465 (2%) received a kidney-only transplant. After the matching criteria were applied, we identified 465 pairs. Follow-up time was 1,617 person-years for the transplant cohort (median 2.9 years, interquartile range 1.2-5.3 years) and 833 person-years for dialysis controls (median 0.9 year, interquartile range 0.4-2.3 years). All dialysis control patients were waitlisted for transplantation for at least part of the study period: seventy percent (n=327) were active on the transplant waiting list in the first year of study follow-up, and 421 (90%) were active after three years. Two of the kidney recipients and three of the dialysis patients were lost to follow-up.

Baseline characteristics were compared between the transplant and dialysis groups in Table 1. Both groups were similar in age, sex, ethnicity, time on renal replacement therapy, body mass index, smoking status, and pre-existing comorbidities, including diabetes, chronic lung disease, cardiovascular disease and non-skin cancer (Table 1). In the transplanted elderly cohort, 41 (9%) received a pre-emptive live donor transplant and were matched to dialysis controls who were starting dialysis.

Overall patient survival

By Kaplan-Meier survival analysis, those transplanted incurred an excess risk of death during the early post-transplant period, reaching parity with controls at 9 months post-transplant (Figure 2A). One-year survival rates were comparable between the two groups (kidney recipients 94% vs remaining on dialysis 95%), however, after the first year a clear and progressive survival advantage in favor of transplantation was evident (Figure 2B). Univariable analysis showed that long-term survival was superior for transplanted elderly recipients, with 5- and 10-year survival of 80% and 53% compared with matched elderly patients remaining on dialysis at 53% and 17% ($p<0.001$, $p<0.001$).

On multivariate analysis, the relative risk of death between the two groups varied over time (Figure 3). The proportion hazards assumption was not violated based on the analysis of Schoenfeld residuals ($p=0.72$). In the early post-transplant period, elderly transplant

recipients incurred a two-fold increase in perioperative mortality compared to remaining on dialysis, although this was not statistically significant (aHR 2.10, 95% CI 0.82-5.39, p=0.12). Transplantation yielded superior survival after 9 months post-transplant that increased over time. At 1-5 years post-transplant, transplant recipients were 60% more likely to survive than those remaining on dialysis (aHR 0.40, 95%CI 0.23-0.70, p=0.001).

Overall, receiving a transplant was a significant protective factor for survival by multivariable modelling (Table 3). Transplant patients were 38% more likely to survive after adjusting for sex, BMI, smoking status and pre-existing comorbidities, including diabetes, cardiovascular disease and chronic lung disease. (aHR 0.62, 95% CI 0.41-0.94, p=0.02).

A sensitivity analysis restricted to those dialysis patients who were not transplanted during the study follow-up demonstrated a more pronounced reduction in risk of death for transplants compared to controls (aHR 0.48, 95% CI 0.32-0.72, p<0.001) (Supplementary Figure 1).

Patient survival by donor type

We compared dialysis patients and kidney recipients categorized by donor type: (1) LD; (2) SCD; and (3) ECD (Figure 4). Patient survival was superior for transplantation versus dialysis for all donor types. Patient survival at 1 and 5 years was 99% and 81% for LD recipients

compared with 96% and 83% for SCD, 93% and 78% for ECD, and 94% and 53% for dialysis patients (p=0.02, p=0.003). Recipients of LD and SCD kidneys acquired an immediate survival advantage over those remaining on dialysis, which was sustained throughout the study. Recipients of ECD kidneys experienced an elevated risk of death compared to remaining on dialysis in the first 17 months post-transplant. From 17 months onward, recipients of all kidney types had better survival than dialysis patients. Using stratified Cox regression model, mortality was 67%, 39% and 12% lower for recipients of LD, SCD and ECD kidney compared to those remaining on dialysis (LD: aHR=0.33, 95% CI 0.12-0.94, p=0.04; SCD: aHR=0.61, 95% CI 0.38-0.99, p=0.04; ECD: aHR=0.88, 95% CI 0.54-1.44, P=0.62).

Cause of death

Overall, the most frequent causes of death in both elderly recipients and dialysis patients were cardiovascular diseases (kidney recipients 1.4 per 100 person-years vs remaining on dialysis 4.7 per 100 person-years) (Table 4). Kidney recipients were 70% less likely to die from cardiovascular death compared to remaining on dialysis (IRR 0.30, 95% CI 0.17-0.52, p<0.001). Elderly kidney recipients incurred a much greater risk of death from infection in the first year post-transplant compared to remaining on dialysis (kidney recipients 1.9 per 100 person-years vs remaining on dialysis 0.3 per 100 person-years, p=0.05). There was no significant difference in the incidence of death from cancer between the groups.

Discussion

In this matched-pair analysis, we evaluated the outcome of kidney recipients aged 70 and over compared with waitlisted maintenance dialysis patients comparable in age, cause of ESKD and dialysis duration, and adjusted for important confounders. We found that elderly recipients incurred an increased risk of death in the first nine months after transplantation, but experienced progressively superior survival rates thereafter. Transplantation was associated with markedly superior survival over 5 years of follow-up. Whilst the excess of early post-transplant mortality was largely attributable to infections, cardiovascular deaths were the most prominent cause of death among both elderly kidney recipients and dialysis patients over the full follow-up period.

Existing literature has clearly demonstrated a survival advantage of kidney transplantation over dialysis for comparable patients aged either 60 or 65 and over.[5,8] The magnitude of benefit appears contingent upon donor characteristics, with living donors and standard criteria deceased donors affording more immediate and overall greater survival benefits than extended criteria donors.[9] Kidney recipients aged 70 and over may incur a greater risk of death than those aged 60 to 69. As the median age of kidney recipients continues to increase over time, the relative benefits of transplanting candidates 70 years and older has become a more relevant question, and in this regard contemporary data are lacking. Our results confirm a long-term survival benefit for LD and SCD compared to remaining on dialysis, with ECD recipients having an early elevated mortality that diminished after 17

months post-transplantation. Heldal et al., using Norwegian Renal Registry data, found no significant survival benefit for transplant recipients aged 70 and over during the period 1990-2005, but suggested improvements over time with a 60% reduction in death during the period 2000 to 2005.[10] Another study using Scientific Registry of Transplant Recipients data showed a 41% reduction in mortality among those aged 70 years or more transplanted between 1990 to 2004 [11]. A third registry study of patients aged 70 and over who started RRT between 2002 and 2013 reported a 60% reduction in risk of death at three years post-transplant, as compared to a matched group who remained on dialysis.[12] Our study adds to this literature by demonstrating a robust survival advantage associated with transplantation of selected elderly recipients compared with maintenance dialysis during the last decade. Utilizing a large, bi-national kidney transplant registry data we used a matched-pair design so that kidney recipients and dialysis patients were comparable at the start of the study follow-up in terms of two critical factors: time on dialysis and diabetes as the cause of ESKD, both of which are known to substantially impact mortality risk.[13,14] In addition, we included only dialysis patients who underwent the same wait listing assessment and were actively waitlisted for a transplant, further enhancing the comparability of the two groups. Our data thereby provides the strongest support to date in favour of transplanting candidates aged 70 years and older.

Although our study has demonstrated a survival advantage for transplantation of patients 70 years and older, only 2% of the 19,476 patients in this age category received a transplant, suggesting that candidates were carefully selected. This is relevant in considering the generalizability of our findings. We were not able to access specific criteria used by

individual units in determining suitability for transplant waitlisting. Candidates evaluated for transplantation in Australia and New Zealand were required to expect an 80% or greater probability of survival to 5 years after transplantation prior to 2018 [15], although this requirement has since been replaced by an expectation that the patient will likely benefit from transplantation. By examining baseline comorbidity data, we found patients with pre-existing cardiovascular disease were at double the risk of death compared to those with no pre-existing cardiovascular disease. Lemoine et al. conducted a risk factor analysis for recipients older than 70 years and reported that death or graft failure in the first year post-transplant was attributable to cardiovascular diseases in 29% of cases, and was associated with arrhythmia and reduced left-ventricular ejection fraction (LVEF).[16] Which pre-transplant factors are most predictive of premature post-transplant mortality for elderly candidates, and whether selection based upon such risk factors can improve post-transplant survival remains to be examined.

We described a high incidence of death from infection during the first year post-transplant among our elderly cohort, consistent with a recent study from France that showed 59% of deaths among kidney recipients older than 70 during the first post-transplant year were attributable to infection.[16] This is specific to the elderly, as cardiovascular deaths are twice as common during the first year across the general transplant population.[17] Older patients are more susceptible to infectious complications of immunosuppressive therapy for reasons including immune senescence, impaired drug elimination and impaired intra cellular signaling pathways.[18–21] Future studies on personalized management of immunosuppression

are needed to determine whether this may reduce infection post-transplant and optimize graft and patient survival for elderly recipients.

The number of elderly patients with ESKD continues to grow disproportionately compared to other age groups.[3] For most transplant centers worldwide, there is no strict upper age limit for kidney transplantation. KDIGO (Kidney Disease: Improving Global Outcomes) clinical practice guidelines recommended not excluding patients from kidney transplantation due to their age alone.[22] However, elderly patients, including those with no formal contraindications, are still less likely to be placed on the transplant waiting list and less likely to receive a transplant once listed than younger patients.[23,24] We have demonstrated that kidney transplantation provided a long-term survival advantage compared to remaining on dialysis for elderly patients. Our findings support increasing access to transplantation for selected patients aged 70 years and older. In the context of a global shortage of kidneys for transplantation, increased access for elderly candidates will exacerbate this problem. Potential solutions, including promotion of living donation and preferential use of older and expanded criteria organs are potential solutions that have been explored in existing studies and should be revisited.[9,25–27]

There are several limitations to our study. In addition to candidate selection criteria for transplant waitlisting, the predominantly white racial mix of our population may limit generalizability. There may be inherent differences between those waitlisted and those transplanted which may also be influenced by center practices. We used registry data for

our analyses, which may be subject to issues of accuracy of data capture, retrospectivity and potential for unmeasured confounders. However, the registry data enabled use of a rigorous, matched pair design that enabled us to control for the major potential confounders of age, dialysis duration, diabetes and eligibility for transplantation. Whilst the outcomes of transplantation versus dialysis would ideally be addressed by conduct of a randomized clinical trial, such a trial is not feasible nor ethical given our current lack of equipoise. Thus, we believe the matched-pair analysis we have used is the most rigorous and best design to address this question.

In conclusion, our study demonstrated a substantial survival advantage of transplantation over ongoing dialysis for candidates aged 70 and over who were waitlisted for kidney transplantation. These results may be used by clinicians to better inform patients of the relative benefits and risks of transplantation. Our data supports providing access to transplantation for such patients, as recommended by current KDIGO guidelines[20], but also identifies death from infection in the first year after transplantation as an important risk that patients and health care providers should be informed of. Further work to determine how to prevent early post-transplant deaths is required.

References

1. Boenink, R., Astley, M. E., Huijben, J. A., Stel, V. S., Kerschbaum, J., Rosenberg-Ots, M., Åsberg, A. A., Lopot, F., Golan, E., Nuez, P. C. de la, Camblor, M. R., Trujillo-Alemán, S., Millan, J. C. R. S., Mingo, P. U., Díaz, J. M., Bouzas-Caamaño, M. E., Artamendi, M., Madre, M. I. A., Pablos, C. S. de, … Kramer, A. (2021). The ERA Registry Annual Report 2019: summary and age comparisons. *Clinical Kidney Journal*, *15*(3), sfab273-. https://doi.org/10.1093/ckj/sfab273

2. ERA-EDTA Registry. (n.d.). *Annual Report 1999*. https://era-edta-reg.org/files/annualreports/AnnRep1999.pdf

3. United States Renal Data System. (2021). *2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. https://adr.usrds.org/2021/end-stage-renal-disease/7-transplantation

4. Hernández, D., Alonso-Titos, J., Armas-Padrón, A. M., Ruiz-Esteban, P., Cabello, M., López, V., Fuentes, L., Jironda, C., Ros, S., Jiménez, T., Gutiérrez, E., Sola, E., Frutos, M. A., González-Molina, M., & Torres, A. (2018). Mortality in Elderly Waiting-List Patients Versus Age-Matched Kidney Transplant Recipients: Where is the Risk? *Kidney and Blood Pressure Research*, *43*(1), 256–275. https://doi.org/10.1159/000487684

5. Wolfe, R. A., Ashby, V. B., Milford, E. L., Ojo, A. O., Ettenger, R. E., Agodoa, L. Y. C., Held, P. J., & Port, F. K. (1999). Comparison of Mortality in All Patients on Dialysis, Patients on Dialysis Awaiting Transplantation, and Recipients of a First Cadaveric Transplant. *The*

New England Journal of Medicine, *341*, 1725–1730. https://doi.org/10.1056/nejm199912023412303

6. Tonelli, M., Wiebe, N., Knoll, G., Bello, A., Browne, S., Jadhav, D., Klarenbach, S., & Gill, J. (2011). Systematic Review: Kidney Transplantation Compared With Dialysis in Clinically Relevant Outcomes. *American Journal of Transplantation*, *11*(10), 2093–2109. https://doi.org/10.1111/j.1600-6143.2011.03686.x

7. McCormick, F., Held, P. J., & Chertow, G. M. (2018). The Terrible Toll of the Kidney Shortage. *Journal of the American Society of Nephrology*, *29*(12), ASN.2018101030. https://doi.org/10.1681/asn.2018101030

8. Chaudhry, D., Chaudhry, A., Peracha, J., & Sharif, A. (2022). Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis. *The BMJ*, *376*, e068769. https://doi.org/10.1136/bmj-2021-068769

9. Gill, J. S., Schaeffner, E., Chadban, S., Dong, J., Rose, C., Johnston, O., & Gill, J. (2013). Quantification of the Early Risk of Death in Elderly Kidney Transplant Recipients. *American Journal of Transplantation*, *13*(2), 427–432. https://doi.org/10.1111/j.1600-6143.2012.04323.x

10. Heldal, K., Hartmann, A., Grootendorst, D. C., Jager, D. J. de, Leivestad, T., Foss, A., & Midtvedt, K. (2010). Benefit of kidney transplantation beyond 70 years of age. *Nephrology Dialysis Transplantation*, *25*(5), 1680–1687. https://doi.org/10.1093/ndt/gfp681

11. Rao, P. S., Merion, R. M., Ashby, V. B., Port, F. K., Wolfe, R. A., & Kayler, L. K. (2007). Renal Transplantation in Elderly Patients Older Than 70 Years of Age: Results From the Scientific Registry of Transplant Recipients. *Transplantation*, *83*(8), 1069–1074. https://doi.org/10.1097/01.tp.0000259621.56861.31

12. Legeai, C., Andrianasolo, R. M., Moranne, O., Snanoudj, R., Hourmant, M., Bauwens, M., Soares, J., Jacquelinet, C., Couchoud, C., & Macher, M. (2018). Benefits of kidney transplantation for a national cohort of patients aged 70 years and older starting renal replacement therapy. *American Journal of Transplantation*, *18*(11), 2695–2707. https://doi.org/10.1111/ajt.15110

13. Chadban, S. J., & Staplin, N. D. (2014). Is it time to increase access to transplantation for those with diabetic end-stage kidney disease? *Kidney International*, *86*(3), 464–466. https://doi.org/10.1038/ki.2014.154

14. Robinson, B. M., Zhang, J., Morgenstern, H., Bradbury, B. D., Ng, L. J., McCullough, K. P., Gillespie, B. W., Hakim, R., Rayner, H., Fort, J., Akizawa, T., Tentori, F., & Pisoni, R. L. (2014). Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney International*, *85*(1), 158–165. https://doi.org/10.1038/ki.2013.252

15. The Transplantation Society of Australia and New Zealand. (2022, October 1). *Clinical Guidelines for Organ Transplantation from Deceased Donors*. https://tsanz.com.au/guidelinesethics-documents/tsanz-clinical-guidelines.htm

16. Lemoine, M., Beauport, D. T., Lobbedez, T., Choukroun, G., Ligny, B. H. de, Hazzan, M., Guerrot, D., & Bertrand, D. (2019). Risk Factors for Early Graft Failure and Death After

Kidney Transplantation in Recipients Older Than 70 Years. *Kidney International Reports*, *4*(5), 656–666. https://doi.org/10.1016/j.ekir.2019.01.014

17. Ying, T., Shi, B., Kelly, P. J., Pilmore, H., Clayton, P. A., & Chadban, S. J. (2020). Death after Kidney Transplantation: An Analysis by Era and Time Post-Transplant. *Journal of the American Society of Nephrology*, *31*(12), 2887–2899. https://doi.org/10.1681/asn.2020050566

18. Krenzien, F., ElKhal, A., Quante, M., Biefer, H. R. C., Hirofumi, U., Gabardi, S., & Tullius, S. G. (2015). A Rationale for Age-Adapted Immunosuppression in Organ Transplantation. *Transplantation*, *99*(11), 2258–2268. https://doi.org/10.1097/tp.0000000000000842

19. Cossart, A. R., Cottrell, W. N., Campbell, S. B., Isbel, N. M., & Staatz, C. E. (2018). Characterizing the pharmacokinetics and pharmacodynamics of immunosuppressant medicines and patient outcomes in elderly renal transplant patients. *Translational Andrology and Urology*, S198–S213. https://doi.org/10.21037/tau.2018.10.16

20. Martins, P. N. A., Pratschke, J., Pascher, A., Fritsche, L., Frei, U., Neuhaus, P., & Tullius, S. G. (2005). Age and Immune Response in Organ Transplantation. *Transplantation*, *79*(2), 127–132. https://doi.org/10.1097/01.tp.0000146258.79425.04

21. Meier-Kriesche, H.-U., Ojo, A. O., Hanson, J. A., & Kaplan, B. (2001). Exponentially increased risk of infectious death in older renal transplant recipients. *Kidney International*, *59*(4), 1539–1543. https://doi.org/10.1046/j.1523-1755.2001.0590041539.x

22. Chadban, S. J., Ahn, C., Axelrod, D. A., Foster, B. J., Kasiske, B. L., Kher, V., Kumar, D., Oberbauer, R., Pascual, J., Pilmore, H. L., Rodrigue, J. R., Segev, D. L., Sheerin, N. S., Tinckam, K. J., Wong, G., & Knoll, G. A. (2020). KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. *Transplantation*, *104*(4S1), S11–S103. https://doi.org/10.1097/tp.0000000000003136

23. Segall, L., Nistor, I., Pascual, J., Mucsi, I., Guirado, L., Higgins, R., Laecke, S. V., Oberbauer, R., Biesen, W. V., Abramowicz, D., Gavrilovici, C., Farrington, K., & Covic, A. (2016). Criteria for and Appropriateness of Renal Transplantation in Elderly Patients With End-Stage Renal Disease. *Transplantation*, *100*(10), e55–e65. https://doi.org/10.1097/tp.0000000000001367

24. Sørensen, S. S. (2015). Rates of renal transplantations in the elderly—data from Europe and the US. *Transplantation Reviews*, *29*(4), 193–196. https://doi.org/10.1016/j.trre.2015.04.005

25. Ojo, A. O., Hanson, J. A., Meier-Kriesche, H.-U., Okechukwu, C. N., Wolfe, R. A., Leichtman, A. B., Agodoa, L. Y., Kaplan, B., & Port, F. K. (2001). Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *Journal of the American Society of Nephrology : JASN*, *12*(3), 589–597. https://doi.org/10.1681/asn.v123589

26. Merion, R. M., Ashby, V. B., Wolfe, R. A., Distant, D. A., Hulbert-Shearon, T. E., Metzger, R. A., Ojo, A. O., & Port, F. K. (2005). Deceased-Donor Characteristics and the Survival Benefit of Kidney Transplantation. *JAMA*, *294*(21), 2726–2733. https://doi.org/10.1001/jama.294.21.2726

27. Jay, C. L., Washburn, K., Dean, P. G., Helmick, R. A., Pugh, J. A., & Stegall, M. D. (2017). Survival Benefit in Older Patients Associated With Earlier Transplant With High KDPI Kidneys. *Transplantation*, *101*(4), 867–872. https://doi.org/10.1097/tp.0000000000001405

Table 1. Demographics and baseline characteristics

Characteristics	Transplant N=465	Dialysis N=465	p-value
Age			0.88
70-74	405 (87)	409 (88)	
75-79	56 (12)	53 (11)	
>80	4 (1)	3 (1)	
Male	316 (68)	310 (67)	0.67
Ethnicity			0.82
Caucasian	267 (57)	255 (55)	
Indigenous[a]	3 (1)	3 (1)	
Asian	54 (12)	64 (14)	
Other	124 (27)	129 (28)	
Not reported	17 (4)	14 (3)	
Time since KRT initiation			1.00
0-1yr	92 (20)	92 (20)	
1-3yr	165 (35)	165 (35)	
3yr+	208 (45)	208 (45)	
Diabetes as primary renal disease	77 (17)	77 (17)	0.84
Dialysis modality			<0.001
Pre-emptive transplant	41 (9)	-	
HD	299 (64)	335 (72)	
PD	125 (27)	130 (28)	
BMI at KRT initiation			0.55
Underweight (<18.5)	4 (1)	5 (1)	
Normal (18.5-<25)	132 (29)	146 (32)	
Overweight (25-<30)	206 (45)	186 (41)	
Obese (30+)	113 (25)	121 (26)	
Smoking status			0.56
Never	230 (51)	220 (49)	
Former	214 (47)	217 (48)	
Current	11 (2)	16 (4)	
Pre-existing comorbidities			
Diabetes	130 (28)	144 (31)	0.31
Chronic lung disease	65 (14)	55 (12)	0.33
Cardiovascular disease	185 (40)	203 (44)	0.23
Non-skin cancer	63 (14)	59 (13)	0.70

KRT, kidney replacement therapy; HD, hemodialysis; PD, peritoneal dialysis; BMI, body mass index.
[a]Indigenous: Aboriginal and Torres Strait Islanders.

Table 2. Recipients and transplantation characteristics

Factor	N=465, n (%)
Previous grafts	
0	450 (97)
1	15 (3)
Donor type	
LD	93 (20)
SCD	181 (39)
ECD	191 (41)
KDPI (N=372)	
<20	35 (9)
20-85	227 (61)
>85	110 (30)
Ischemia time (N=372)	
<12h	195 (42)
12-18h	107 (23)
>=18h	50 (11)
Unknown	20 (4)
Left, right or dual KTx	
Left Kidney	155 (42)
Right kidney	200 (54)
Double/En-bloc kidney	17 (5)
Delayed graft function	118 (25)
Acute rejection within six months	69 (15)
Graft failure	26 (6)
eGFR one month after transplant	
<15 ml/min	23 (5)
15-<30 ml/min	81 (17)
30-<60 ml/min	254 (55)
60-<90 ml/min	78 (17)
≥90 ml/min	5 (1)
Unknown	24 (5)
Number of HLA mismatches	
0	22 (5)
1-2	112 (24)
3-4	155 (33)
5-6	168 (36)
Unknown	8 (2)
CNI at transplant	442 (95)
Antimetabolite at transplant	440 (95)
Prednisolone at transplant	442 (95)
mTOR at transplant	5 (1)

LD, living donor; SCD, standard criteria donor; ECD, expanded criteria donor; KDPI, kidney donor profile index; KTx, kidney transplantation; eGFR, estimated glomerular rate; HLA, human leukocyte antigen; CNI, calcineurin inhibitor; mTOR, mammalian target of rapamycin.

Table 3. Risk factor for patient survival based on multivariable analysis of patient survival with stratified Cox regression model

Covariates	Hazard ratio	95% CI	P-value
Transplant	0.62	(0.41-0.94)	0.02
Male	0.58	(0.30-1.13)	0.11
Pre-existing cardiovascular disease	2.13	(1.18-3.83)	0.012
Pre-existing chronic lung disease	1.15	(0.54-2.45)	0.72
Pre-existing diabetes	1.79	(0.83-3.84)	0.137
Smoking status			0.44
Never	1*		
Former	1.14	(0.66-1.96)	
Current	2.49	(0.57-10.87)	
BMI category			0.087
Normal (<25 kg/m^2)	1*		
Overweight (25 to <30 kg/m^2)	1.89	(0.96-3.72)	
Obese (≥30 kg/m^2)	2.32	(1.06-5.07)	

BMI, body mass index.
*Reference group.

Table 4. Cause of death by time post-transplant

Cause of death	Timing of death	Group	N	P-Y	Incident rate (per 100 P-Y)	Incident Rate Ratio [95% confidence interval]	P-value
All-cause	<1 year	Transplant	21	412	5.1	0.86 [0.44-1.70]	0.64
		Dialysis	19	322	5.9		
	≥1 year	Transplant	60	1205	5.0	0.37 [0.26-0.53]	<0.001
		Dialysis	69	511	13.5		
	Overall	Transplant	81	1617	5.0	0.47 [0.35-0.65]	<0.001
		Dialysis	88	833	10.6		
CV	<1 year	Transplant	9	412	2.2	0.59 [0.22-1.52]	0.23
		Dialysis	12	322	3.7		
	≥1 year	Transplant	14	1205	1.2	0.22 [0.11-0.43]	<0.001
		Dialysis	27	511	5.3		
	Overall	Transplant	23	1617	1.4	0.30 [0.17-0.52]	<0.001
		Dialysis	39	833	4.7		
Infection	<1 year	Transplant	8	412	1.9	6.25 [0.84-277.43]	0.05
		Dialysis	1	322	0.3		
	≥1 year	Transplant	12	1205	1.0	0.64 [0.24-1.79]	0.33
		Dialysis	8	511	1.6		
	Overall	Transplant	20	1617	1.2	1.14 [0.50-2.86]	0.76
		Dialysis	9	833	1.1		
Cancer	<1 year	Transplant	1	412	0.2	0.26 [0.00-3.24]	0.26
		Dialysis	3	322	0.9		
	≥1 year	Transplant	18	1205	1.5	1.53 [0.55-5.26]	0.42
		Dialysis	5	511	1.0		
	Overall	Transplant	19	1617	1.2	1.22 [0.51-3.23]	0.65
		Dialysis	8	833	1.0		
Other	<1 year	Transplant	3	412	0.7	0.78 [0.10-5.83]	0.77
		Dialysis	3	322	0.9		
	≥1 year	Transplant	16	1205	1.3	0.23 [0.12-0.44]	<0.001
		Dialysis	29	511	5.7		
	Overall	Transplant	19	1617	1.2	0.31 [0.16-0.56]	<0.001
		Dialysis	32	833	3.8		

CV, cardiovascular; P-Y, patient-years.

Figure 1. Study flowchart

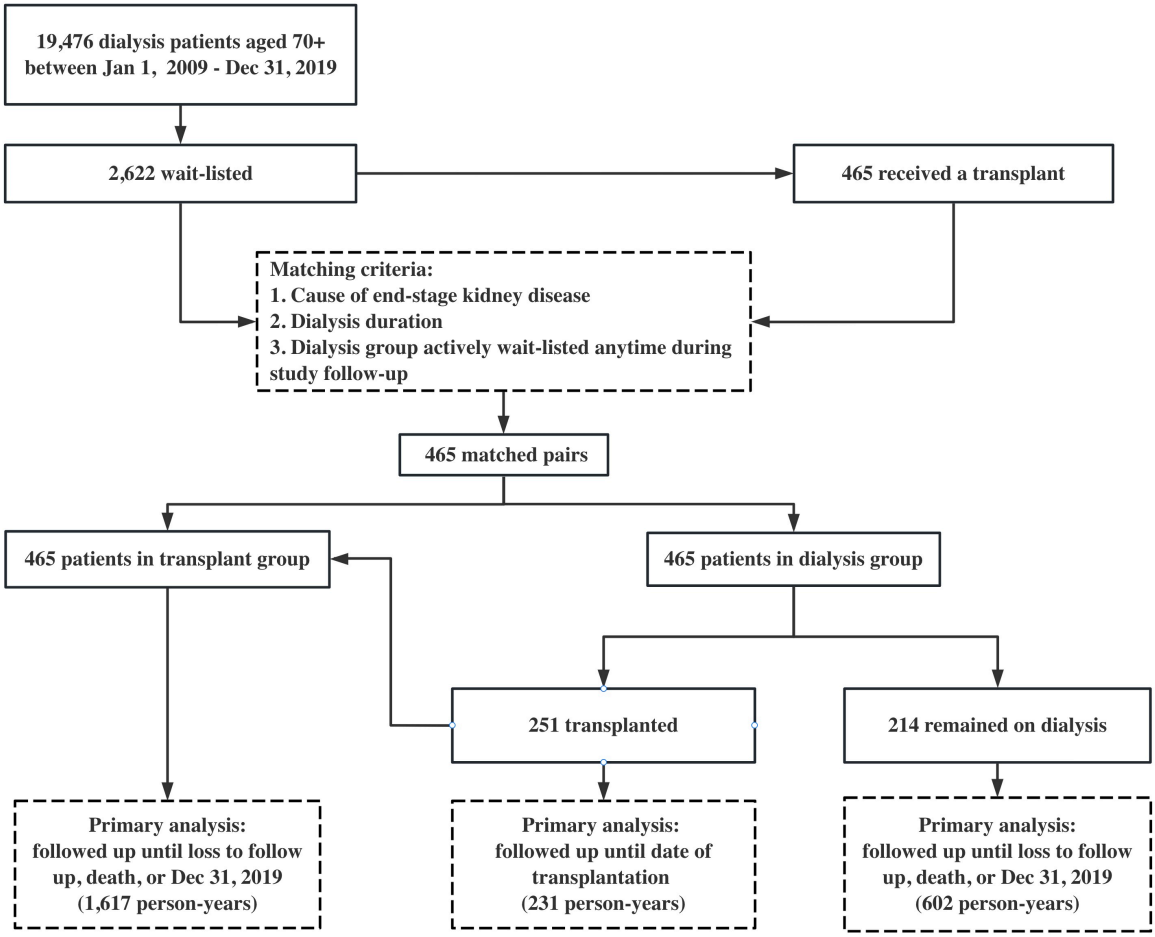


Figure 2. Kaplan-Meier survival curves comparing time to death among elderly dialysis patients versus kidney recipients

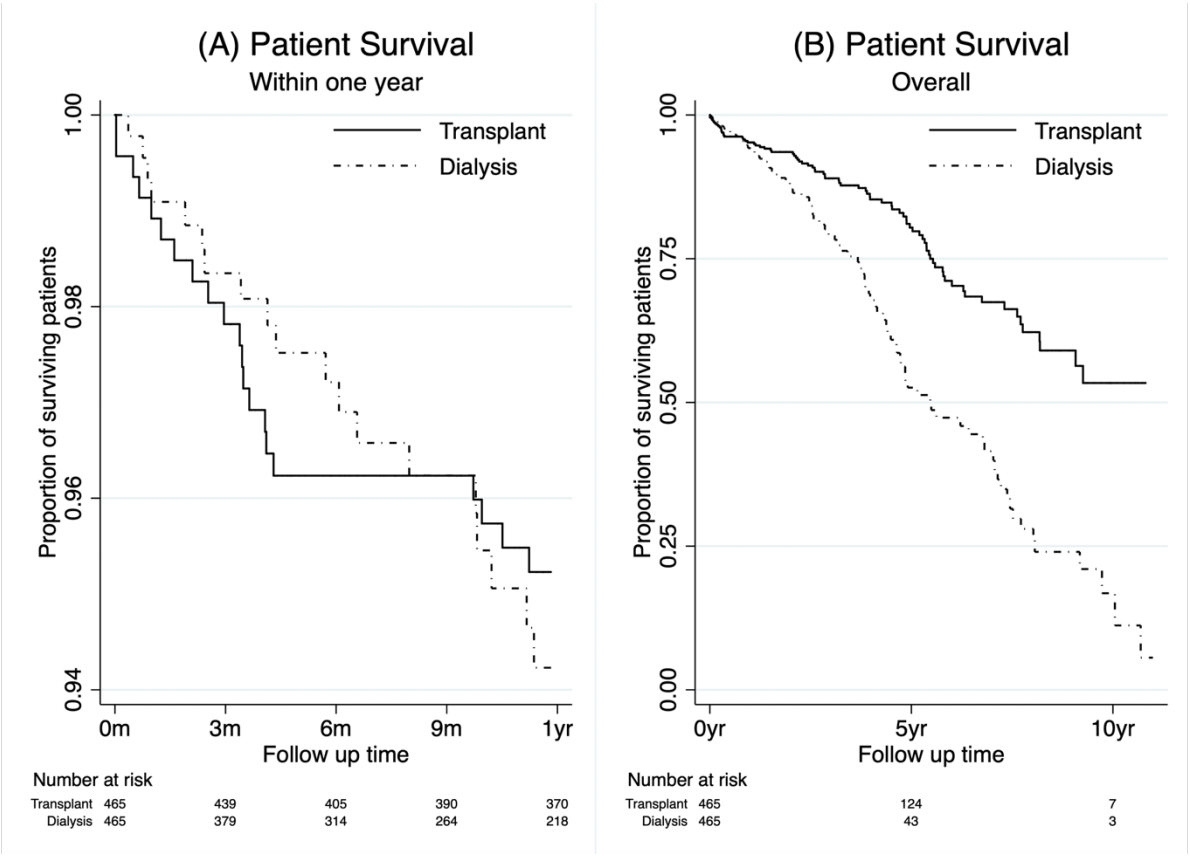
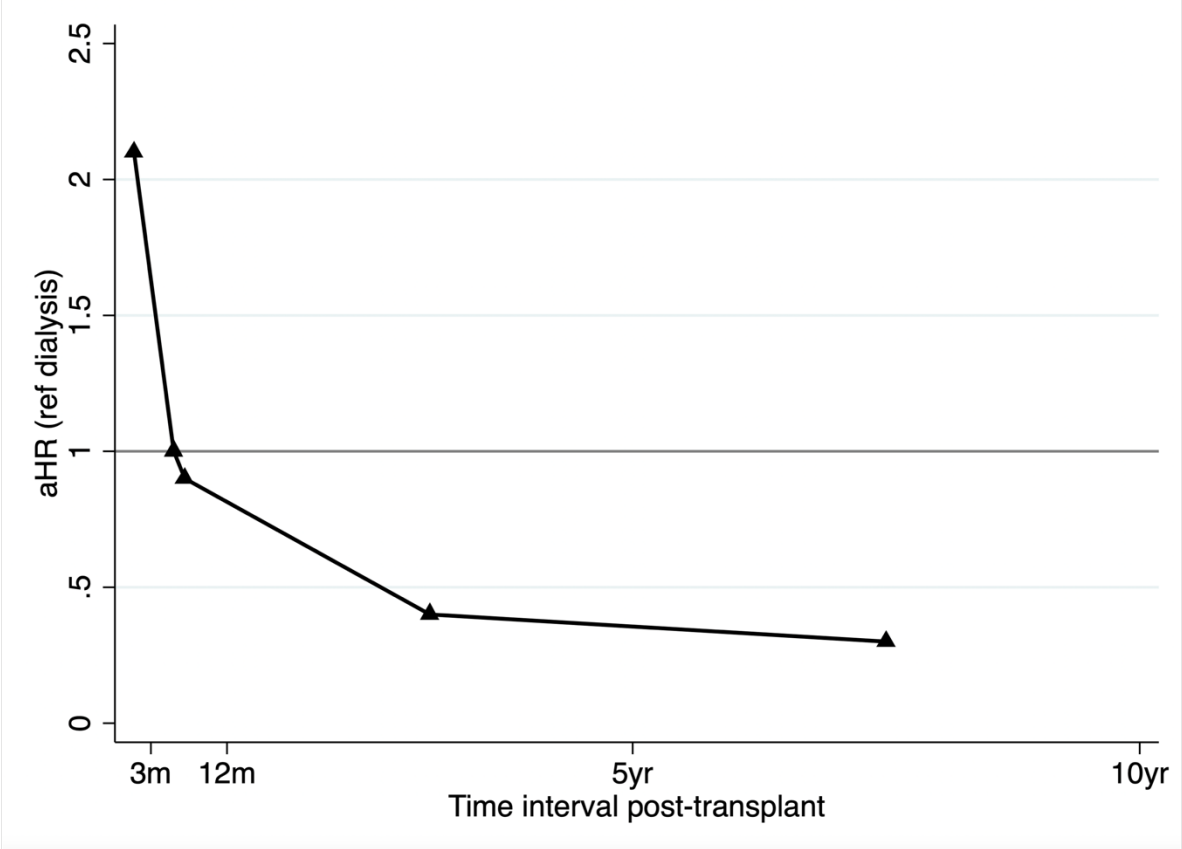
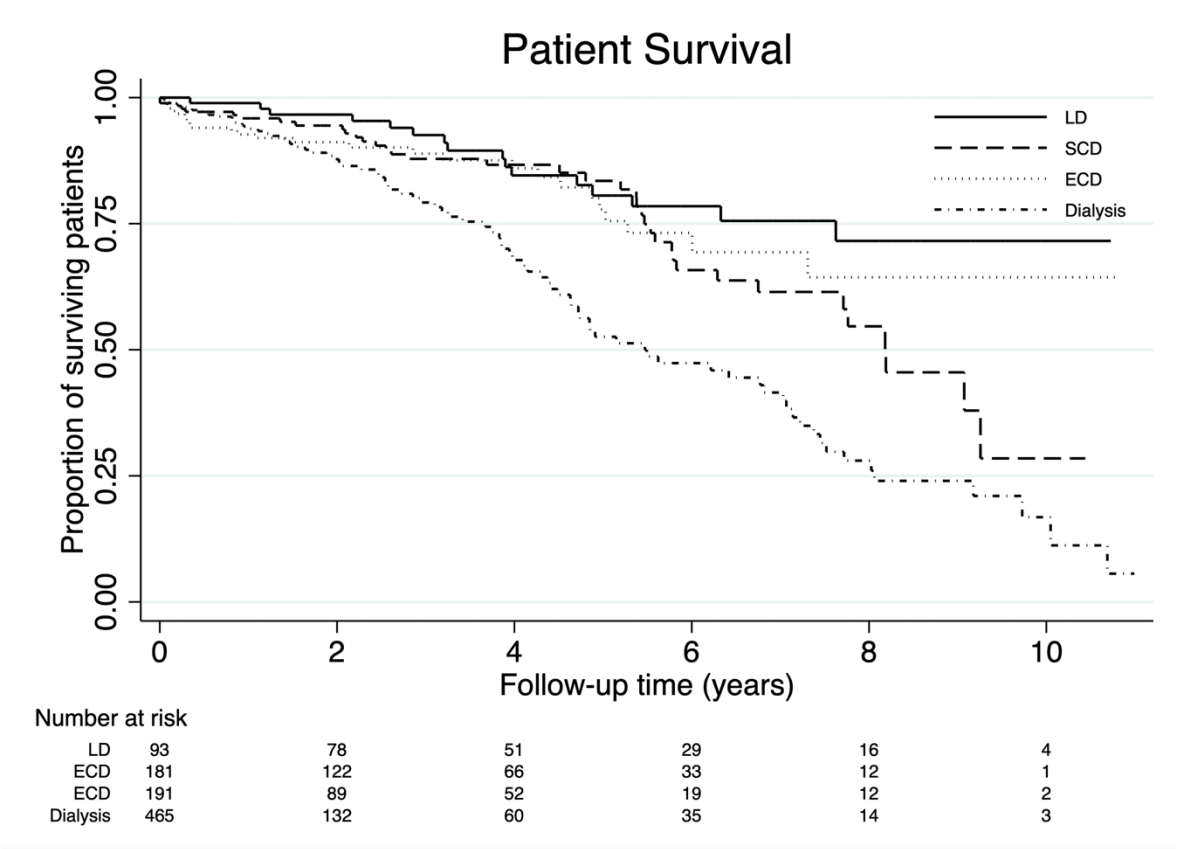


Figure 3. Relative risk of death over time among elderly kidney recipients versus dialysis patients (reference) based on multivariable stratified Cox model



aHR, adjusted hazard ratio.

Figure 4. Kaplan-Meier survival curves comparing time to death among elderly patients receiving a living donor kidney, a standard criteria deceased donor kidney, an expanded criteria deceased donor kidney, or remaining on dialysis.



LD, living donor; SCD, standard criteria donor; ECD, expanded criteria donor.

CHAPTER 4

Obesity is associated with delayed graft function in kidney transplant recipients: a paired kidney analysis

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Publication arising from this chapter:

Shi B, Ying T, Xu J, Wyburn K, Laurence J, Chadban SJ. Obesity is Associated With Delayed Graft Function in Kidney Transplant Recipients: A Paired Kidney Analysis. Transpl Int. 2023;36:11107. doi:10.3389/ti.2023.11107

Author contribution:

BS designed the study together with her supervisors, acquired the data, performed the analysis, interpreted the results, drafted the manuscript and figures, and oversaw journal submission and revisions.

Abstract

Obesity is increasingly prevalent among candidates for kidney transplantation. Existing studies have shown conflicting post-transplant outcomes for obese patients which may relate to confounding bias from donor-related characteristics that were unaccounted for. We used ANZDATA Registry data to compare graft and patient survival between obese (BMI >27.5kg/m2 Asians; > 30kg/m2 non-Asians) and non-obese kidney transplant recipients, while controlling for donor characteristics by comparing recipients of paired kidneys. We selected transplant pairs (2000-2020) where a deceased donor supplied one kidney to an obese candidate and the other to a non-obese candidate. We compared the incidence of delayed graft function (DGF), graft failure and death by multivariable models. We identified 1,522 pairs. Obesity was associated with an increased risk of DGF (aRR=1.26, 95% CI 1.11-1.44, p<0.001). Obese recipients were more likely to experience death-censored graft failure (aHR=1.25, 95% CI 1.05-1.49, p=0.012), and more likely to die with function (aHR=1.32, 95% CI 1.15-1.56, p=0.001), versus non-obese recipients. Long-term patient survival was significantly worse in obese patients with 10- and 15- year survival of 71%, 56% compared to 77%, 63% in non-obese patients. Addressing obesity is an unmet clinical need in kidney transplantation.

Introduction

Over the past four decades, the worldwide prevalence of obesity has tripled. In addition to the associations between obesity and hypertension, type 2 diabetes and coronary artery disease, obesity is clearly associated with premature mortality.[1] Obesity has therefore had a significant impact on community health as well as posing a major economic challenge to global healthcare systems. Obesity is increasingly prevalent in the end-stage kidney disease (ESKD) and kidney transplant populations.[2,3] In the US, the proportion of ESKD patients that were obese between 2008 and 2016 was nearly 40%.[4]

Whilst kidney transplant recipients with high body mass index (BMI) are more like to develop post-transplant diabetes, congestive heart failure, atrial fibrillation, and cardiovascular death,[5–7] transplantation offers a survival benefit for obese recipients compared to remaining on dialysis.[8,9] However, kidney transplant recipients with high BMI are at an increased risk of post-transplant complications, including prolonged wound healing, dehiscence, hernias, surgical site infections, deep vein thrombosis, and reintubation. These issues contribute to a longer hospital stay and higher hospital costs for transplantation in the obese.[10–12]

The long-term graft and patient outcomes of obese recipients compared to non-obese recipients have remained controversial. When compared to non-obese recipients, some reports described an increased risk of graft failure and mortality for obese recipients whilst others have found no significant differences.[12–15] These disparate outcomes, may relate to the confounding bias of non-randomly distributed donor-related characteristics which were

not accounted for.[16–18] Therefore, we sought to investigate the association between obesity and incidence of delayed graft function (DGF), graft survival and patient survival while controlling for donor characteristics by comparing obese and non-obese recipients of kidneys from a common donor, a matched-pair analysis. We hypothesized that obesity would increase the risk of DGF and lead to inferior graft and patient survival.

Methods

We extracted data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The ANZDATA Registry is a clinical quality registry that collects comprehensive data from all patients with ESKD in Australia and New Zealand. Details of the structure and method of ANZDATA Registry data collection can be found on the Registry website (https://www.anzdata.org.au/anzdata/). We included all deceased donor kidney-only transplant pairs between January 1, 2000 and December 31, 2020, where a deceased donor supplied one kidney to an obese recipient and the other to a non-obese recipient. We excluded recipients under the age of 18, recipients of a deceased donor kidney retrieved outside Australia or New Zealand, and recipients of a second or subsequent transplant. We used the World Health Organization (WHO) classification of obesity as BMI greater than 30 kg/m^2 for non-Asians, and greater than 27.5 kg/m^2 for Asians due differences in body habitus compared to the Western population.[19–21] Follow-up was until loss to follow-up, or December 31, 2020. The primary outcome was DGF which was defined as receipt of hemodialysis within 72 hours after transplant prior to 2017, and receipt of hemodialysis within 7 days of transplantation after 2017.[22] This modification to the definition of delayed

graft function was due to a policy change made by ANZDATA in 2017. The secondary outcomes were death and death-censored graft failure.

We compared baseline characteristics of paired recipients using paired t-test or Wilcoxon's signed rank test for continuous variables and McNemar's test for dichotomous variables. We estimated the cumulative incidence of graft failure using Aalen-Johansen estimator to account for death as a competing event. We used Gray's test to compare the cumulative incidence of graft failure in the presence of the competing risk of death. We used Kaplan-Meier curves to compare unadjusted patient survival. We used a logrank test to compare the probability of patient survival at different time points. We estimated the rate ratio of DGF for obese patients compared with non-obese patients, using conditional Poisson regression, adjusting for potential confounders[23–25]. As a sensitivity analysis, we repeated this analysis excluding patients who experienced graft failure within 90 days of transplantation. Time to graft failure and time to death were analyzed using Cox regression stratified by donor.[24,25]

A dose-response analysis was performed to examine the association between the degree of obesity (i.e. class I, class II and class III) and clinical outcomes. Obesity was categorized as class I, class II and class III according to WHO guidelines (Table 3). We estimated the rate ratio of DGF using conditional Poisson regression and hazard ratio of graft failure and death using Cox regression, adjusting for potential confounders.

The potential confounders considered were age at transplantation, sex, ethnicity, cause of kidney disease, duration of dialysis, dialysis modality prior to transplant, human leukocyte

antigen (HLA) mismatch, ischemia time, maximum panel reactive antibodies, donor kidney side, pre-existing comorbidities including diabetes, chronic lung disease, cardiovascular disease (any of coronary artery, cerebrovascular or peripheral vascular), and non-skin cancer, acute rejection within six months of transplantation (for graft failure and death only), DGF (as a categorical variable, for graft failure and death only), and graft failure (as a time-varying covariate, for death only). We used stepwise selection methods where variables with a significance level of 0.20 were considered and included in the base multivariable model. We used backward selection method to remove variables that were not significant at the 0.05 level[26]. We used complete case analysis because the number of missing values was less than 5%. All analyses were performed using Stata Statistical Software: Release 14.2 (StataCorp., College Station, TX) This study was approved by the Ethics Review Committee of the Sydney Local Health District, Royal Prince Alfred Hospital Zone.

Results

Study cohort

Between January 1, 2000, and December 31, 2020, 16,554 patients received their first kidney transplant in Australia and New Zealand. After inclusion and exclusion criteria were applied, 1,522 pairs were identified where a deceased donor supplied one kidney to an obese recipient and the other to a non-obese recipient (Figure 1). Follow-up time was 19,768 person-years in total, with a median follow-up time of 5.3 years (interquartile range

2.5-9.5 years). Nine of the obese recipients and seven of the non-obese recipients were lost to follow-up.

Donor and recipient baseline characteristics are summarized in Tables 1 and 2. Baseline characteristics indicate that obese and non-obese recipients were comparable in terms of sex, time on dialysis, ischemia time, HLA mismatch and maximum panel reactive antibody percentage. The obese group included a higher proportion of recipients aged 50-65 (48% vs. 44%), p<0.001), fewer people of Asian ancestry (12% vs 15%, p<0.001), more Indigenous people (17% vs 11%, p<0.001), more people with pre-existing diabetes (33% vs. 21%, p<0.001) and comorbid cardiovascular disease (33% vs. 27%, p=0.001) and more right-sided kidneys (55% vs 45%, p<0.001).

Outcomes

Delayed graft function

A greater proportion of obese recipients experienced DGF compared to non-obese recipients (39% vs 30%, p<0.001). Conditional Poisson regression demonstrated an increased risk of DGF for obese recipients versus their non-obese pair (aRR=1.27, 95% CI 1.12-1.44, p<0.001), after adjusting for dialysis modality prior to transplant, ischemia time and pre-existing cardiovascular disease and accounting for donor-related factors (Supplemental Table 1).

Sensitivity analysis, excluding those patients who experienced graft failure within 90 days of transplantation, showed similar effect of obesity on DGF to the primary analysis (aRR=1.29, 95% CI 1.12-1.48, p<0.001).

Graft failure

Unadjusted graft failure was more common amongst the obese recipients (Figure 2). Cumulative incidence of graft failure at 5 years was not affected by obesity status (11% obese vs. 10% non-obese), however, obese recipients were found to have a higher incidence of long-term graft failure with 10- and 15-year cumulative incidence of 21% and 30% compared to 18% and 27% in non-obese patients. The Gray's test confirmed a significant difference on the overall incidence of graft failure between obese and non-obese recipients (p=0.044). On multivariable analysis, obesity was confirmed as an independent risk factor for death-censored graft failure. Obesity was associated with a higher risk of death-censored graft failure after adjusting for DGF, donor kidney side, age, ethnicity and HLA mismatch (aHR=1.25, 95% CI 1.05-1.49, p=0.012) (Supplemental Table 2). Recipients who experienced delayed graft function were more likely to experience death-censored graft failure (aHR=1.84, 95% CI 1.39-2.44, p<0.001).

Patient survival

There were 342 (22%) deaths in the obese group compared to 260 (17%) (p<0.001). Death from cardiovascular disease was the most prominent cause of death amongst the obese recipients, with 105 cardiovascular deaths (31%) compared to 65 (25%) among the non-

obese recipients. Obesity was strongly associated with inferior survival in both the short and long-term (p<0.001) (Figure 3). Short and long-term patient survival was significantly worse in obese recipients with 5-, 10- and 15-year survival of 87%, 71% and 56% compared to 91%, 77% and 63% in non-obese patients (p=0.017, p<0.001, p<0.001). In the multivariable model, obesity was found to be strongly associated with worse patient survival. Obese recipients had an increased risk of death compared to non-obese recipients (aHR=1.32, 95% CI 1.15-1.56, p=0.001) (Supplemental Table 3). Significant determinants of death that were included in the final model were graft failure, older age, Indigenous ethnicity, diabetes as primary renal disease, length of time on dialysis and pre-existing cardiovascular disease. Graft failure was adjusted as a time-varying covariate in the model. Recipients with graft failure had a much higher risk of death (aHR=2.84, 95%CI 2.00-4.03, p<0.001)

Degree of obesity and clinical outcomes

We performed a dose-response analysis to examine the association between the degree of obesity and clinical outcomes. The 1,522 obese recipients were classified as 1,173 (77%) class I; 304 (20%) class II and 45 (3%) class III (Table 3). We combined obesity classes II and III due to insufficient patient number in obesity class III.

When comparing with non-obese recipients, class II/III obese recipients had a 1.44 higher rate of DGF whilst class I obese recipients had a 1.20 higher rate. This trend was not statistically significant when comparing class I obese recipients to class II/III obese recipients (Figure 4. aRR 1.20, 95% CI 0.88-1.62, p=0.25). A similar non-significant trend was found for death-censored graft failure and death. Class II/III obese recipients had a 1.67 higher rate of

death-censored graft failure compared to a 1.16 higehr rate for class I obese recipients (aHR 1.45, 95% CI 0.95-2.21, p=0.085). Class II/III obese recipients had a 1.42 higher rate of death compared to a 1.26 higher rate for class I obese recipients (aHR 1.10, 95% CI 0.71-1.71, p=0.66).

Discussion

In this paired analysis, we controlled for unmeasured donor-related characteristics by comparing outcomes of kidneys from the same donor and demonstrated that obese recipients were more likely to experience DGF, death-censored graft failure and death after deceased donor kidney transplantation when comparing with non-obese recipients.

Studies examining impact of obesity on kidney transplant outcomes have shown conflicting results, but may be confounded by unmeasured donor-related characteristics. These may include donor kidney function and proteinuria, pre-renal insults to the donor kidney during terminal illness, use of inotropic medications and nephrotoxin exposure, many of which are not adequately captured nor accounted for in existing studies, The majority of published studies have reported an increased risk of delayed graft function for obese recipients.[12,13,15] However, the impact of DGF on long-term transplant outcomes including graft and patient survival remains contentious. Our results are consistent with two systematic review and meta-analyses which showed an increased risk of graft failure for obese recipients compared to non-obese recipients.[14,15] In terms of overall mortality, two meta-analyses reported an increased risk of death for obese recipients, in line with our results.[12,14] One systematic review and meta-analysis reported no association between obesity and overall

mortality[27], however, this analysis included only six studies that reported hard transplant outcomes. Another systematic review and meta-analysis reported that there was an increased risk of graft failure and death only for studies that included obese patients who were transplanted before 2000, but no association for those transplanted after 2000.[13] This contradicts our study result which included patients transplanted after 2000 only.

We found a trend towards increasing risks of DGF, graft failure and death with increasing degrees of obesity, however, this increase was not statistically significant. The number of recipients with class II/III obesity in our study was small and likely inadequately powered to provide certainty. A recent US registry study reported 27% lower odds of DGF ($p<0.001$) for recipients with BMI >30-35 versus BMI >35 kg/m^2, though no difference in graft or patient survival at a median follow-up of 3.9 years[28].

Our study provides detailed insights from a large, bi-national kidney transplant registry over a 20-year period. We examined a different BMI cut-off for the Asian population that has significant structural variations compared to the western population. Donor-related factors, which could potentially impact outcomes such as DGF, were carefully accounted and unmeasured confounders were evenly matched by the use of a matched-pair analysis. As randomized controlled trials to compare outcomes for obese versus non-obese recipients are not feasible, we believe the paired analysis we have performed provides the most rigorous assessment of the impact of obesity on hard outcomes following kidney transplantation.

Obesity has more than doubled worldwide in the past 20 years. Although our study has demonstrated that obesity was strongly associated with an increased risk of DGF and inferior long-term outcomes, previous work has clearly indicated that transplantation yields superior outcomes compared to remaining on dialysis for the majority of obese candidates for transplantation.[8,9,29] Our findings should be used to inform patients and providers of the increased risks associated with transplantation for obese recipients. Rather than avoiding transplantation for the obese, these data should encourage the pursuit of strategies to improve outcomes, such as weight-loss management prior to transplantation and improvements in peri-operative management to reduce the incidence of DGF and other complications associated with obesity. This poses two key questions: (1) can transplant management be optimized for obese recipients; and (2) can weight loss before or post-transplant improve transplant outcomes for obese candidates. Some studies have reported an "obesity paradox" where a decrease in BMI for dialysis patients was associated with worse graft and patient survival.[30–33] However, in these studies there was no clear indication of whether the weight loss was intentional, or unintentional due to disease progression or comorbidities. The reason behind the paradox remains unknown. Hypotheses include that obese patients may be less prone to protein energy wasting[34], have a better appetite and well-preserved energy stores, have better hemodynamic tolerance, stem cell mobilization, hemodynamic tolerance, and more efficient disposal of lipophilic uremic toxins[35,36]. A healthy lifestyle that is beneficial to the general public has been shown to improve mortality in chronic kidney disease (CKD) patients.[37] Intentional weight loss in the pre-transplant population may reduce the risk of wound infection, DGF, death-censored failure and reduce the length of hospitalization and alleviates the financial burden on transplant programs.[38] Weight-management programs for CKD patients that include a renal-specific diet, regular

exercise combined with anti-obesity medication have been reported to be effective in weight reduction, with improved functional ability, graft function and significantly longer adverse event-free period for the combined outcome of all-cause mortality, myocardial infarction, stroke, and hospitalization for congestive heart failure.[39–41] Another possible intervention is bariatric surgery. A recent study reported a lowering of 7 kg/m^2 in BMI in the long-term and a median of 2.4 years longer life expectancy in the bariatric surgery cohort compared to usual obesity care.[41] However, there is very limited data on the outcomes of bariatric surgery on dialysis and kidney transplant patients. In a retrospective cohort study, researchers demonstrated lower all-cause mortality at 5 years for obese ESKD patients who had undergone bariatric surgery.[43] In another retrospective study, bariatric surgery before or after kidney transplantation was reported to be associated with reduced risk of graft failure and mortality compared to control with no bariatric surgery.[44] More data are required to determine if bariatric surgery does improve long-term outcomes from kidney transplantation.

Several limitations should be noted in considering our analysis. First, it is a retrospective registry study that depends on the quality of data captured. Second, the analysis used BMI as the only indicator for categorizing obesity, which does not differentiate between fat and muscle mass, nor between visceral and subcutaneous fat. Other methods such as waist circumference, waist-to-hip ratio, in-vivo neutron activation analysis (IVNAA), densitometry, deuterium oxide dilution, and dual energy X-ray absorptiometry (DXA) are also available and may enhance specificity. However, such measures are not routinely used in candidate assessment and are not reported to ANZDATA. Third, there may be other potential confounders that are unaccounted for, such as social status, genetic factors,

immunosuppression and drug dosing. Fourth, even though significant confounders were adjusted for in the model, residual confounding is still possible. Five, indication of whether dialysis is required after transplantation may vary between centers resulting in potential center effect for DGF which was not accounted for. Six, there may be a loss of statistical power due to pairing. However, we believe that it is important to utilize a matched pair analysis to minimize bias due to donor-related characteristics, such as donor kidney function, hemodynamic instability during organ procurement, use of vasoactive medications and exposure to nephrotoxins, all of which are captured crudely or not at all in registry data. Finally, the study cohort was predominantly Caucasian. The remaining non-Caucasian patient group was heterogeneous, with 40% and 23% of the Indigenous group being Australian Aboriginal and New Zealand Mauri, and 25% and 23% of the Asian group being Indian and Chinese, respectively. Therefore, the comparison between Caucasian and non-Caucasian patients in our study is different from the same comparison in the US where around 70% of non-Caucasian patients were Black/African American.[45]

In conclusion, our study demonstrates a strong relationship between obesity and post-transplant outcomes after carefully controlling for donor-related factors in a paired kidney analysis. Addressing obesity is an unmet clinical need in kidney transplantation. Transplantation is recommended for many obese candidates as it is acknowledged to yield superior outcomes to dialysis. However, design and evaluation of strategies to: (1) optimize transplant management for obese recipients; and (2) reduce the prevalence of obesity among transplant candidates are required.

References

1. World Health Organization. Obesity and overweight. Published June 9, 2021. Accessed March 23, 2022. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

2. Gore JL, Pham PT, Manovich GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, Singer JS. Obesity and Outcome Following Renal Transplantation. *Am J Transplant*. 2006;6(2):357-363. doi:10.1111/j.1600-6143.2005.01198.x

3. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and trends in overweight and obesity in patients at time of kidney transplantation. *Am J Kidney Dis*. 2003;41(2):480-487. doi:10.1053/ajkd.2003.50059

4. Wakam GK, Sheetz KH, Gerhardinger L, Montgomery JR, Waits SA. Population-based Trends in Obesity and Kidney Transplantation Among Patients With End-stage Kidney Disease. *Transplant Direct*. 2021;7(12):e787. doi:10.1097/txd.0000000000001163

5. Parikh CR, Klem P, Wong C, Yalavarthy R, Chan L. Obesity as an independent predictor of posttransplant diabetes mellitus. *Transplant P*. 2003;35(8):2922-2926. doi:10.1016/j.transproceed.2003.10.074

6. Lentine KL, Schnitzler MA, Abbott KC, et al. De Novo Congestive Heart Failure After Kidney Transplantation: A Common Condition With Poor Prognostic Implications. *Am J Kidney Dis*. 2005;46(4):720-733. doi:10.1053/j.ajkd.2005.06.019

7. Young JB, Neumayer HH, Gordon RD. Pretransplant cardiovascular evaluation and posttransplant cardiovascular risk. *Kidney Int*. 2010;78(118):S1-S7. doi:10.1038/ki.2010.209

8. Gill JS, Lan J, Dong J, et al. The Survival Benefit of Kidney Transplantation in Obese Patients. *Am J Transplant*. 2013;13(8):2083-2090. doi:10.1111/ajt.12331

9. Krishnan N, Higgins R, Short A, et al. Kidney Transplantation Significantly Improves Patient and Graft Survival Irrespective of BMI: A Cohort Study. *Am J Transplant*. 2015;15(9):2378-2386. doi:10.1111/ajt.13363

10. Pham PT, Danovitch GM, Pham PT. Kidney Transplantation in the Obese Transplant Candidates: To Transplant or Not To Transplant? *Semin Dialysis*. 2013;26(5):568-577. doi:10.1111/sdi.12109

11. Zrim S, Furlong T, Grace B, Meade A. Body mass index and postoperative complications in kidney transplant recipients. *Nephrology*. 2012;17(6):582-587. doi:10.1111/j.1440-1797.2012.01621.x

12. Lafranca JA, IJermans JN, Betjes MG, Dor FJ. Body mass index and outcome in renal transplant recipients: a systematic review and meta-analysis. *Bmc Med*. 2015;13(1):111. doi:10.1186/s12916-015-0340-5

13. Nicoletto BB, Fonseca NKO, Manfro RC, Gonçalves LFS, Leitão CB, Souza GC. Effects of Obesity on Kidney Transplantation Outcomes. *Transplantation*. 2014;98(2):167-176. doi:10.1097/tp.0000000000000028

14. Ahmadi SF, Zahmatkesh G, Streja E, et al. Body Mass Index and Mortality in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis. *Am J Nephrol*. 2014;40(4):315-324. doi:10.1159/000367812

15. Hill CJ, Courtney AE, Cardwell CR, et al. Recipient obesity and outcomes after kidney transplantation: a systematic review and meta-analysis. *Nephrol Dial Transpl*. 2015;30(8):1403-1411. doi:10.1093/ndt/gfv214

16. Merion RM, Ashby VB, Wolfe RA, et al. Deceased-Donor Characteristics and the Survival Benefit of Kidney Transplantation. *Jama*. 2005;294(21):2726-2733. doi:10.1001/jama.294.21.2726

17. Massie AB, Luo X, Chow EKH, Alejo JL, Desai NM, Segev DL. Survival Benefit of Primary Deceased Donor Transplantation with High-KDPI Kidneys. *Am J Transplant*. 2014;14(10):2310-2316. doi:10.1111/ajt.12830

18. Summers DM, Johnson RJ, Allen J, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. *Lancet*. 2010;376(9749):1303-1311. doi:10.1016/s0140-6736(10)60827-6

19. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157-163. doi:10.1016/s0140-6736(03)15268-3

20. World Health Organization, International Diabetes Institute, International Association for the Study of Obesity, International Obesity Task Force. *The Asia-Pacific perspective: Redefining obesity and its treatment*. Health Communications Australia. 2000.

21. Low S, Chin MC, Ma S, Heng D, Deurenberg-Yap M. Rationale for redefining obesity in Asians. *Ann Acad Medicine Singap*. 2009;38(1):66-69.

22. Australia and New Zealand Dialysis and Transplant Registry. *ANZDATA Data Dictionary*. Retrieved March 1, 2023, from https://www.anzdata.org.au/anzdata/services/data-management/data-dictionary/

23. Hardin JW, Hilbe JM. *Generalized Linear Models and Extensions Edition*. Stata Press; 2018.

24. Cummings P, McKnight B. Analysis of Matched Cohort Data. *Stata J*. 2004;4(3):274-281. doi:10.1177/1536867x0400400305

25. Cummings P, McKnight B, Greenland S. Matched Cohort Methods for Injury Research. *Epidemiol Rev*. 2003;25(1):43-50. doi:10.1093/epirev/mxg002

26. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Medicine Community Heal*. 2020;8(1):e000262. doi:10.1136/fmch-2019-000262

27. Ladhani M, Craig JC, Irving M, Clayton PA, Wong G. Obesity and the risk of cardiovascular and all-cause mortality in chronic kidney disease: a systematic review and meta-analysis. *Nephrol Dial Transpl*. 2017;32(3):439-449. doi:10.1093/ndt/gfw075

28. Sureshkumar KK, Chopra B, Josephson MA., Shah PB, McGill RL. Recipient Obesity and Kidney Transplant Outcomes: A Mate-Kidney Analysis. *American Journal of Kidney Diseases*. 2021;78(4), 501-510.e1. https://doi.org/10.1053/j.ajkd.2021.02.332

29. Bennett WM, McEvoy KM, Henell KR, Pidikiti S, Douzdjian V, Batiuk T. Kidney transplantation in the morbidly obese: complicated but still better than dialysis. *Clin Transplant*. 2011;25(3):401-405. doi:10.1111/j.1399-0012.2010.01328.x

30. Schold JD, Srinivas TR, Guerra G, et al. A 'Weight-Listing' Paradox for Candidates of Renal Transplantation? *Am J Transplant*. 2007;7(3):550-559. doi:10.1111/j.1600-6143.2006.01629.x

31. Molnar MZ, Streja E, Kovesdy CP, et al. Associations of Body Mass Index and Weight Loss with Mortality in Transplant-Waitlisted Maintenance Hemodialysis Patients. *Am J Transplant*. 2011;11(4):725-736. doi:10.1111/j.1600-6143.2011.03468.x

32. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, et al. Association of Morbid Obesity and Weight Change Over Time With Cardiovascular Survival in Hemodialysis Population. *Am J Kidney Dis*. 2005;46(3):489-500. doi:10.1053/j.ajkd.2005.05.020

33. Kalantar-Zadeh K, Kuwae N, Wu DY, et al. Associations of body fat and its changes over time with quality of life and prospective mortality in hemodialysis patients. *Am J Clin Nutrition*. 2006;83(2):202-210. doi:10.1093/ajcn/83.2.202

34. Glicklich D, Mustafa MR. Obesity in Kidney Transplantation: Impact on Transplant Candidates, Recipients, and Donors. *Cardiol Rev*. 2019;27(2):63-72. doi:10.1097/CRD.0000000000000216

35. Stenvinkel P, Lindholm B. Resolved: being fat is good for dialysis patients: the Godzilla effect: con. *J Am Soc Nephrol*. 2008;19(6):1062-1064.

36. Carrero JJ, Qureshi AR, Axelsson J, et al. Comparison of nutritional and inflammatory markers in dialysis patients with reduced appetite. *Am J Clin Nutrition*. 2007;85(3):695-701. doi:10.1093/ajcn/85.3.695

37. Ricardo AC, Madero M, Yang W, et al. Adherence to a Healthy Lifestyle and All-Cause Mortality in CKD. *Clin J Am Soc Nephro*. 2013;8(4):602-609. doi:10.2215/cjn.00600112

38. Sever MS, Zoccali C. Moderator's view: Pretransplant weight loss in dialysis patients: cum grano salis. *Nephrol Dial Transpl*. 2015;30(11):1810-1813. doi:10.1093/ndt/gfv333

39. Cook SA, MacLaughlin H, Macdougall IC. A structured weight management programme can achieve improved functional ability and significant weight loss in obese patients with chronic kidney disease. *Nephrol Dial Transpl*. 2008;23(1):263-268. doi:10.1093/ndt/gfm511

40. MacLaughlin HL, Cook SA, Kariyawasam D, Roseke M, Niekerk MV, Macdougall IC. Nonrandomized Trial of Weight Loss With Orlistat, Nutrition Education, Diet, and Exercise in Obese Patients With CKD: 2-Year Follow-up. *Am J Kidney Dis*. 2010;55(1):69-76. doi:10.1053/j.ajkd.2009.09.011

41. MacLaughlin HL, Hall WL, Condry J, Sanders T, Macdougall IC. Participation in a Structured Weight Loss Program and All-Cause Mortality and Cardiovascular Morbidity in Obese Patients With Chronic Kidney Disease. *J Renal Nutr*. 2015;25(6):472-479. doi:10.1053/j.jrn.2015.05.001

42. Carlsson L, Sjöholm K, Jacobson P, et al. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. *New Engl J Med*. 2020;383(16):1535-1543. doi:10.1056/nejmoa2002449

43. Sheetz KH, Gerhardinger L, Dimick JB, Waits SA. Bariatric Surgery and Long-term Survival in Patients With Obesity and End-stage Kidney Disease. *Jama Surg*. 2020;155(7):581-588. doi:10.1001/jamasurg.2020.0829

44. Cohen JB, Lim MA, Tewksbury CM, et al. Bariatric surgery before and after kidney transplantation: long-term weight loss and allograft outcomes. *Surg Obes Relat Dis*. 2019;15(6):935-941. doi:10.1016/j.soard.2019.04.002

45. United States Renal Data System. *2021 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States*. Published 2021. Accessed March 23, 2022. https://adr.usrds.org/2021/end-stage-renal-disease/7-transplantation

Table 1. Donor characteristics

Factor	N=1,522 n (%)
Age	
<18	79 (5)
18-34	254 (17)
35-49	426 (28)
50-65	556 (37)
65+	207 (14)
Male	870 (57)
Body mass index (BMI)	
Underweight	47 (3)
Normal	556 (37)
Overweight	534 (35)
Obese	383 (25)
Terminal serum creatinine concentration, µmol/L	96.4 ± 83.2
Diabetes	96 (6)
Hypertension	388 (25)
Neurological determination of death (NDD)	1,167 (77)
Cause of death	
Intracranial hemorrhage	640 (44)
Traumatic brain injury	285 (19)
Cerebral infarct	94 (6)
Cerebral hypoxia/ischemia	380 (26)
Other neurological condition	12 (1)
Non-neurological condition	59 (4)

Table 2. Recipient and transplantation characteristics for obese and non-obese recipients

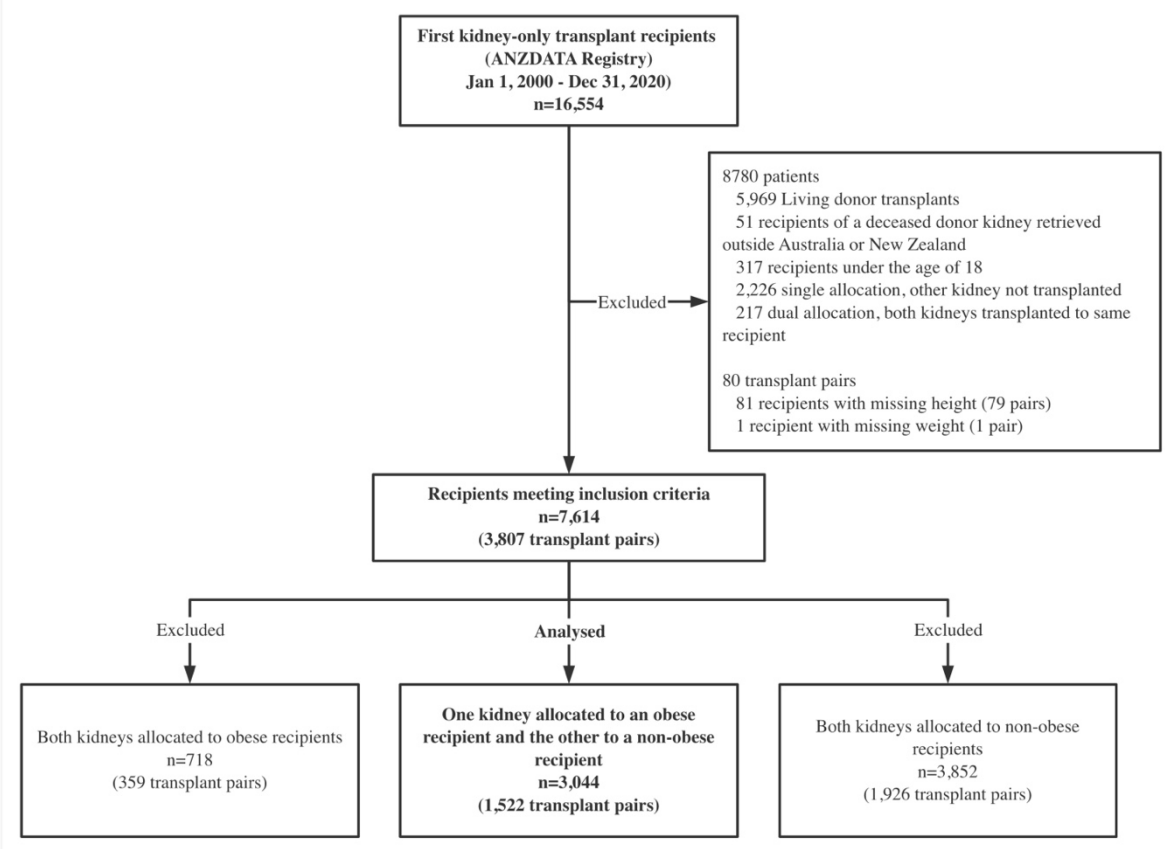
Factor	Obese	Not obese	P-value
	N=1,522	N=1,522	
Age at transplant	n (%)	n (%)	<0.001
18-34	113 (7)	193 (13)	
35-49	430 (28)	414 (27)	
50-65	728 (48)	667 (44)	
65+	251 (16)	248 (16)	
Male	985 (65)	991 (65)	0.82
Ethnicity			<0.001
Caucasian	1,001 (66)	1,006 (66)	
Indigenous	257 (17)	162 (11)	
Asian	185 (12)	232 (15)	
Other	79 (5)	122 (8)	
Primary renal disease			<0.001
GN	575 (38)	628 (41)	
Renovascular	123 (8)	112 (7)	
Diabetes	351 (23)	231 (15)	
Other	473 (31)	551 (36)	
Time since first RRT			0.14
0-1 year	173 (11)	209 (14)	
1-3 years	594 (39)	575 (38)	
Over 3 years	755 (50)	738 (48)	
Dialysis modality prior to transplant			0.008
Pre-emptive transplant	11 (1)	17 (1)	
HD	1,106 (73)	1,030 (68)	
PD	405 (27)	475 (31)	
Ischemia time [mean (sd)]	12.1 (4.9)	12.0 (5.0)	0.52
HLA mismatches			0.58
0	46 (3)	38 (2)	
1-2	408 (27)	427 (28)	
3-4	483 (32)	460 (30)	
5-6	580 (38)	596 (39)	
Maximum panel reactive antibodies			0.50
0	918 (60)	935 (61)	
1-50	491 (32)	465 (31)	
>50	110 (7)	121 (8)	
Pre-existing comorbidities			
Chronic lung disease	130 (9)	124 (8)	0.69
Cardiovascular disease	501 (33)	418 (27)	0.001
Diabetes	504 (33)	316 (21)	<0.001
Right kidney	832 (55)	690 (45)	<0.001

GN, Glomerulonephritis; HD, hemodialysis; PD, peritoneal dialysis; HLA, Human Leukocyte Antigen; RRT, renal replacement therapy

Table 3. Degree of obesity was categorized into obese class I, obese class II, and obese class III according to World Health Organization guidelines

Classification	BMI, kg/m^2, non-Asians	BMI, kg/m^2, Asians	n (%)
Obese class I	30-34.9	27.5-32.4	1,173 (77)
Obese class II	35-39.9	32.5-37.4	304 (20)
Obese class III	40+	37.5+	45 (3)

Figure 1. Study flowchart



ANZDATA, the Australia and New Zealand Dialysis and Transplant registry.

Figure 2. Unadjusted cumulative incidence of graft failure using Aalen-Johansen estimator to account for death as a competing event among obese (BMI >27.5kg/m^2 for Asians; > 30kg/m^2 for non-Asians) and non-obese recipients.

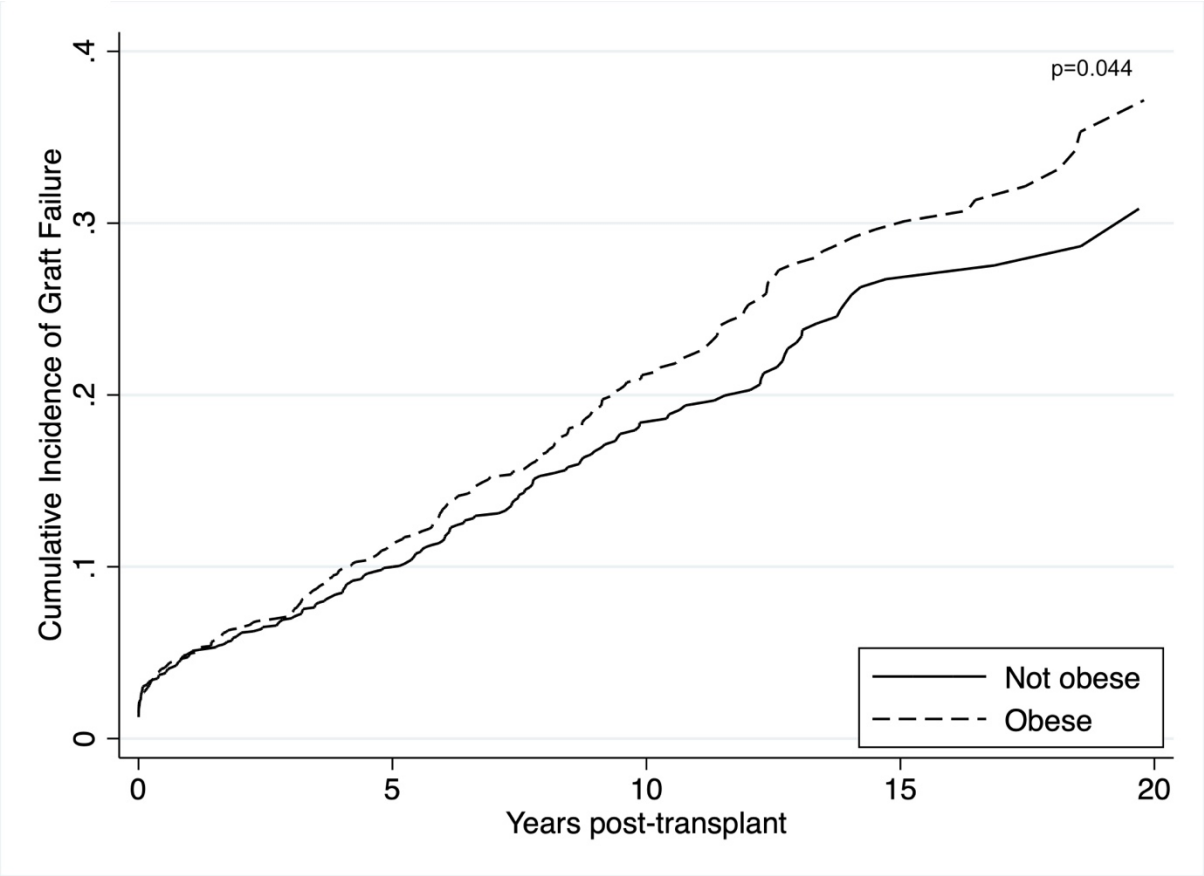


Figure 3. Kaplan-Meier estimates of patient survival after renal transplant among obese (BMI >27.5kg/m^2 for Asians; > 30kg/m^2 for non-Asians) and non-obese recipients.

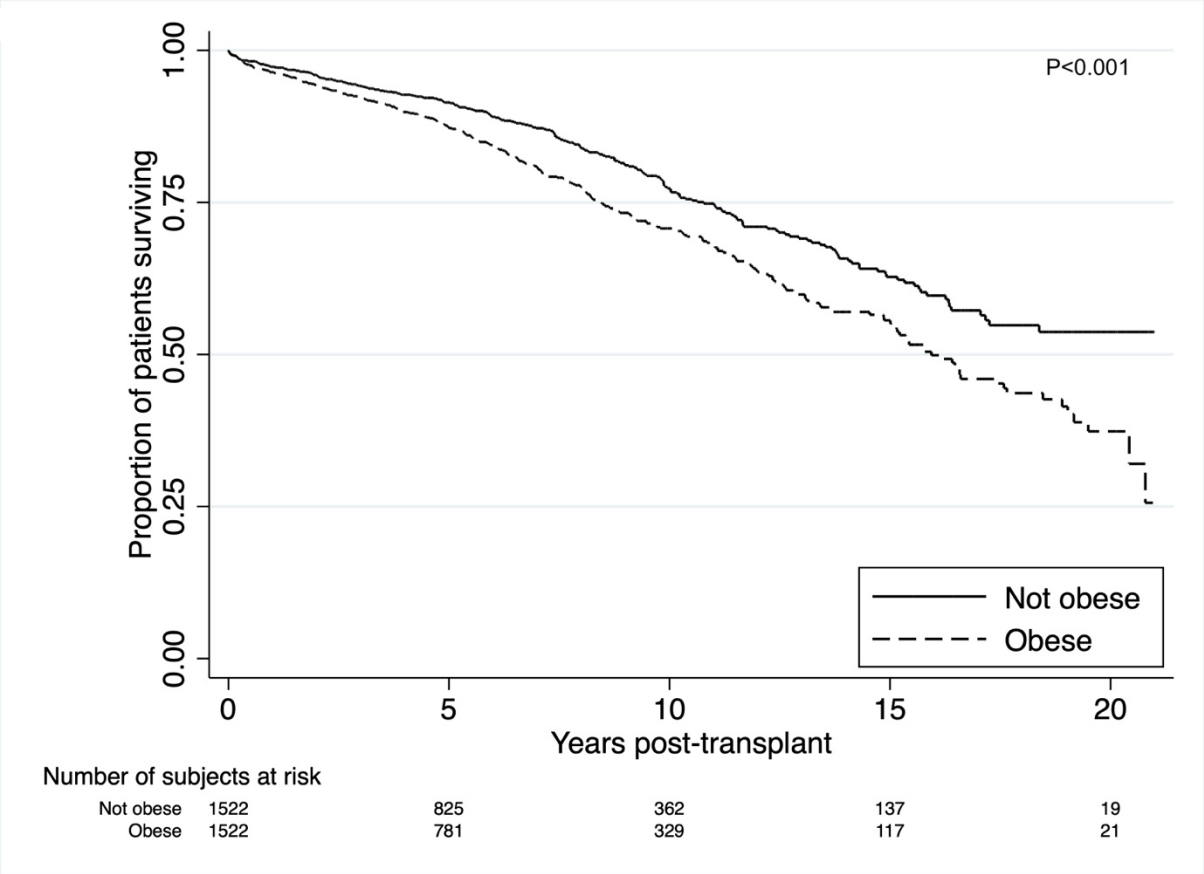
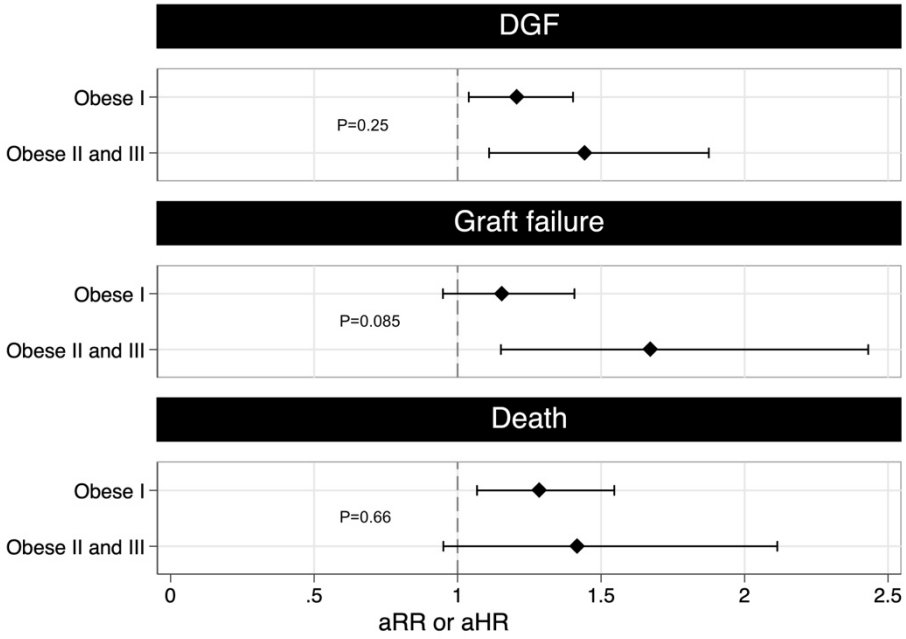


Figure 4. The figure shows the multivariable adjusted risk ratio for DGF and adjusted hazard ratio for graft failure and death grouped by class I obese and class II and III obese.



aHR, adjusted hazard ratio; aRR, adjusted rate ratio; DGF, delayed graft function.

CHAPTER 5

The impact of obesity on cancer incidence among dialysis patients and kidney transplant recipients

Authors:

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Author contribution:

BS designed the study together with her supervisors, acquired the data, performed the analysis, interpreted the results, drafted the manuscript and figures, and oversaw the manuscript revision.

Abstract

Background. Obesity is increasingly prevalent amongst patients with kidney failure (KF). Obesity is an independent risk factor for cancer in the general population, however, the impact of obesity on cancer outcomes in KF is unclear. Methods. We included all patients initiating kidney replacement therapy between 2000 and 2023 from the Australia and New Zealand Dialysis and Transplant Registry. Cancer incidence and mortality were compared between obese (BMI >27.5 kg/m² for Asians, >30 kg/m² for non-Asians) and non-obese patients using a piecewise exponential model. Site-specific cancer risks were assessed using Cox models. Obesity and transplant status were included as time-varying covariates. Results. We followed 65,712 patients, contributing 234,236 patient-years during dialysis or after graft failure, and 123,744 patient-years with a functioning transplant. At baseline, 24,112 (37%) were obese. Obese patients experienced a lower risk of cancer incidence (aHR=0.93, 95% CI 0.88-0.99, p=0.02) and cancer-related mortality (aHR=0.72, 95% CI 0.65-0.79, p<0.001) compared to non-obese patients. The reduced incidence associated with obesity was observed for cancers of the colorectum, lip and oral cavity, cervix, prostate, lung, bladder, and multiple myeloma, while an increased risk was noted for breast and uterine cancers. Obesity was associated with better survival from esophageal, colorectal, lip and oral cavity, prostate, and lung cancers, as well as lymphoma and multiple myeloma. Protection from cancer was largely attributable to reduced risks among the dialysis population. Conclusions. Obesity was associated with a lower cancer incidence and mortality among people receiving kidney replacement therapy. Further studies are warranted to elucidate the mechanisms underlying this reverse epidemiology.

Introduction

Obesity is associated with a substantially elevated risk of cancer within the general population. In the United States, nearly 50% of cancers in individuals under 65 years of age are attributable to overweight and obesity.[1] Extensive research has highlighted that obesity is a major risk factor for various types of cancers, including uterine, endometrial, cervical, thyroid, breast, colorectal, kidney, esophageal, pancreatic, and liver cancers, as well as leukaemia.[2–5] Several of these obesity-associated cancers occur at increased frequency among people receiving kidney replacement therapy (KRT): including thyroid, cervical, kidney, and bladder cancers in dialysis patients; [6–9] and colorectal, esophageal, kidney cancers, and leukaemia in transplant recipients. [8,10–12] Whether obesity is associated with the incidence or outcomes of such types of cancer among patients receiving KRT is not known.

People receiving maintenance dialysis incur a markedly higher incidence and mortality from cancer compared to the general population, likely driven by immune system dysfunction, nutritional inadequacies, impaired DNA repair mechanisms and persistent infections. [7–9,13–16] Cancer is also a leading cause of death following kidney transplantation,[17] with increased risks primarily attributed to immunosuppressive therapy. [8,14,18] Whether cancer risk is elevated for obese KRT patients remains unclear. Paradoxically, some studies suggest that obese kidney transplant recipients may experience lower overall cancer risks compared to their non-obese counterparts.[19,20]

Obesity is highly and increasingly prevalent among people with kidney failure who receive KRT. Obesity is present in over 40% of the prevalent U.S. dialysis population and 30% of prevalent kidney transplant recipients.[21,22] With increased availability of drugs effective in promoting weight loss, understanding the relationships between obesity and outcomes including cancer among people receiving KRT is required.[23] For many transplant centres, obesity may be a barrier to candidate acceptance for transplantation.[24] Obesity and its association with cancer risk may influence transplant candidacy decisions, but also the approach to screening for cancer pre- and post-transplant.

Using population-level data, we aimed to analyse the impact of obesity on cancer incidence and mortality among people receiving KRT We secondarily assessed associations with specific cancer types, and associations within dialysis and kidney transplant populations.

Methods

Data source and study cohort

We extracted data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). ANZDATA is a clinical quality registry that has been collecting longitudinal data on patients receiving KRT for kidney failure in Australia and New Zealand since 1977.[25] The

structure and methodology of ANZDATA Registry data collection are described in detail on the registry's official website (https://www.anzdata.org.au/anzdata/).

We included all adult patients who received their first KRT by dialysis or kidney transplantation in Australia and New Zealand between January 1, 2000 and December 31, 2023. We excluded patients under the age of 18, those with missing height or weight at the start of KRT, patients with a calculated baseline body mass index (BMI) of less than 15 kg/m^2 or greater than 70 kg/m^2, and patients with a history of solid organ or haematological cancer before KRT or missing cancer diagnosis date. Weight was collected in the annual survey by ANZDATA Registry. We classified obesity at all time points based on the World Health Organization (WHO) guidelines, defining it as a BMI greater than 30 kg/m^2 for non-Asians and greater than 27.5 kg/m^2 for Asians, considering differences in body composition between Asian and Western populations.[26–29] Follow up period was from the start of KRT (date of dialysis commencement or date of kidney transplantation, whichever comes first) , until death, loss to follow-up, or December 31, 2023. We conducted a sensitivity analysis where patients with cancer diagnosis within 6 months of starting KRT treatment were excluded.

The ANZDATA Registry captures all incident cancer, cancer-related deaths and deaths due to treatment withdrawal caused by cancer among dialysis patients and kidney transplant recipients. De novo cancer diagnosis, its re-occurrence and contribution to death were collected using ANZDATA Registry Cancer Survey Form (https://www.anzdata.org.au/wp-content/uploads/2020/01/CancerSurveyForm_CA.pdf). Cancers were classified by site and

cell type using codes based on the International Classification of Diseases for Oncology.[30] Previous studies have demonstrated the accuracy and reliability of cancer records within the ANZDATA Registry, showing high concordance with cancer incidence and mortality data from the New South Wales Cancer Registry and the Australian National Death Index.[31,32] For the study, we included all solid organ and haematological cancer diagnosis with nonmelanoma skin cancer diagnosis excluded. For cancer-related death, we included all cancer including nonmelanoma skin cancer.

Statistical analyses

We compared baseline characteristics of obese and non-obese patients using Pearson's chi-square test. We calculate rate of cancer by dividing the total number of first cancer diagnosis by the total patient-years at risk. The nonparametric estimation of cumulative incidence functions of first nonskin cancer diagnosis and cancer death was calculated for obese versus non-obese patients using obesity status at baseline, with nonmelanoma skin cancer-related death and non-cancer death as competing risks.[33,34]

For multivariable survival analysis, we used piecewise exponential model, splitting follow-up period in 5-year intervals and with competing risk of non-cancer deaths. Obesity status and transplant status (functioning vs. on dialysis or graft failed) as time-varying covariates. We used a piecewise exponential model due to its flexibility in incorporating internal time-varying covariates and its ability to accommodate changing hazard rates over time, while

also accounting for the competing risk of non-cancer death.[35–37] We tested the goodness of fit of the model using Cox-Snell residuals.[37] The potential confounders considered were age, gender, ethnicity, cause of kidney disease, modality, smoking status, and pre-existing comorbidities including chronic lung disease, diabetes and cardiovascular disease. We stratified the model by era (2000 to 2011 and 2012 to 2023). We started with a full model that included all potential confounders. Variables with the largest p-values were removed one at a time until all remaining variables had a significance level below 0.05. The excluded variables were then reintroduced individually to assess whether any demonstrated a significant association. First diagnosis of each cancer type and cancer death from each cancer type between obese and non-obese patients were compared using Cox regression model, adjusted for transplant status. We performed subgroup analysis based KRT modality (first starting dialysis censored at the time of kidney transplant vs. first kidney transplantation censored at the time of graft failure), sex (male vs. female) and age (<55 vs. >=55).

We conducted a dose-response analysis to examine the association between the degree of obesity and cancer outcomes. Degree of obesity was categorised according to World Health Organization guidelines. For non-Asians, obesity class I was defined as a BMI of 30.0–34.9 kg/m², class II as 35.0–39.9 kg/m², and class III as ≥40.0 kg/m². For Asians, class I was defined as BMI 27.5–32.4 kg/m², class II as 32.5–37.4 kg/m², and class III as ≥37.5 kg/m².

We used a full-case analysis, as the proportion of missing data was minimal. A two-sided p-value of less than 5% was considered statistically significant. All analyses were performed

using Stata Statistical Software: Release 17.0 (StataCorp., CollegeStation, TX). The study was approved by the Ethics Committee of the University of Sydney (2024/HE001003).

Results

Study cohort

The study flowchart is presented in Figure 1. Between January 1, 2000 and December 31, 2023, a total of 76,314 patients in Australia and New Zealand initiated their first KRT. Among them, 73,653 commenced with dialysis, while 2,661 received a pre-emptive kidney transplant. After exclusion criteria were applied, 65,712 patients were included in the analysis. A total of 16,816 patients received a kidney transplant at some point during the study period. Among them, 751 patients underwent two transplants, and 23 patients received three transplants. Over the study period, patients accrued 357,980 follow-up years (median 3.9 years; interquartile range 1.7-7.6 years). Of these, 234,236 were during dialysis or after graft failure, and 123,744 person-years were with a functioning transplant. A total of 111,720 person-years were accumulated in obese patients and 246,260 person-years in non-obese patients. A total of 530 patients (0.8%) were lost to follow-up after a medium time of 3.0 years.

Baseline characteristics were compared between obese and non-obese patients in Table 1 based on obesity status at study commencement. The obese group included a higher proportion of patients aged 50 and over (78% vs. 73%, p<0.001), fewer males (59% vs. 62%, p<0.001), more Indigenous patients (31% vs. 17%, p<0.001), fewer Asian patients (8% vs. 12%, p<0.001), more patients with diabetic kidney disease (53% vs. 32%, p<0.001) and more patients with pre-existing cardiovascular disease (50% vs. 44%, p<0.001).

Incidence of first cancer diagnosis

During the study period, 5,749 first incidences of cancer were identified, with 1,687 (9%) among obese patients and 4,062 (8%) among non-obese patients. Seventy-three percent of cancer cases were diagnosed during dialysis, while 27% occurred after transplantation with a functioning graft. The overall crude cancer incidence rate was 15.1 per 1,000 person-years for obese patients compared to 16.5 for non-obese patients (Table 3). The difference in cancer incidence rates was more pronounced during dialysis, with rates of 15.9 per 1,000 person-years in obese patients and 19.2 per 1,000 person-years in non-obese patients. In contrast, among patients with a functioning graft, cancer incidence rates were similar between groups (obese: 12.5 per 1,000 person-years; non-obese: 12.3 per 1,000 person-years).

The cumulative incidence of first cancer diagnosis at 5, 10, and 15 years were similar between the two groups (5 years 6% obese vs. 7% non-obese; 10 years 9% obese vs. 10% non-obese; 15 years 11% obese vs. 12% non-obese) (Figure 2A). The multivariable analyses demonstrated a decreased risk of cancer incidence for obese patients compared to non-obese patients (aHR=0.93, 95% CI 0.88-0.99, p=0.02), after adjusting for transplant status, age, sex, ethnicity, primary kidney disease, initial RRT modality, smoking status, chronic lung disease and cardiovascular disease and stratified on era (Table 2). There was no evidence of an association between transplant status and the risk of cancer incidence (aHR=0.96, 95% CI 0.88-1.03, p=0.24). The effect size of obesity was similar in the sensitivity analysis excluding patients with cancer diagnosed within 6 months of starting KRT (aHR=0.92, 95% CI 0.87-0.99, p=0.03).

The five most frequently diagnosed cancers among obese patients were lung cancer (1.63 per 1,000 patient-years), kidney cancer (1.59 per 1,000 patient years), female breast cancer (1.20 per 1,000 patient years), melanoma (1.17 per 1,000 patient years), and colorectal cancer (1.16 per 1,000 patient years). Among non-obese patients, the five most commonly diagnosed first cancers were lung cancer (1.88 per 1,000 patient-years), kidney cancer (1.57 per 1,000 patient-years), prostate cancer (1.51 per 1,000 patient-years), colorectal cancer (1.46 per 1,000 patient-years), and melanoma (1.42 per 1,000 patient-years).

Obese patients showed a lower risk of colorectal cancer (aHR=0.72, 95% CI 0.60-0.89, p=0.002), lip and oral cavity cancer (aHR=0.56, 95% CI 0.36-0.84, P=0.008), multiple

myeloma (aHR=0.68, 95% CI 0.53-0.87, p=0.002), cervical cancer (aHR=0.55, 95% CI 0.32-0.94, p=0.03), prostate cancer (aHR=0.69, 95% CI 0.56-0.84, p<0.001), lung cancer (aHR=0.079, 95% CI 0.67-0.94, p=0.007) and bladder cancer (aHR=0.65, 95% CI 0.49-0.86, p=0.002) (Figure 3A). In contrast, obese patients incurred a higher risk of female breast cancer (aHR=1.41, 95% CI 1.14, 1.76, p=0.002) and uterine cancer (aHR=3.09, 95% CI 1.96-4.89, p<0.001).

Cancer death

There were 37,036 deaths recorded during study follow-up, of which 2,571 were cancer-related deaths. Among these, 605 (3%) occurred in obese patients and 1,966 (4%) in non-obese patients. The majority of the cancer deaths occurred while patients were on dialysis (n=1,884, 73%), whereas 27% occurred after transplantation with a functioning graft (n=687). The overall crude rate of cancer death was lower among obese patients compared to non-obese patients (5.2 vs. 7.6 per 1,000 person-years) (Table 3). During dialysis, the cancer death rate among obese patients was nearly half that of non-obese patients (5.0 vs. 9.2 per 1,000 person-years). In contrast, after kidney transplantation and while the graft was functioning, the cancer death rate was similar between the two groups (obese 5.7 per 1,000 person-years vs. non-obese 5.1 per 1,000 person-years).

The 10-year cumulative incidence of cancer-related deaths were 4% for both obese and non-obese patients (Figure 2B). Multivariable modelling confirmed that obesity was associated with a lower risk of cancer death. After adjusting for transplant status, age, sex, ethnicity, primary kidney disease, initial RRT modality, smoking status, chronic lung disease, and stratified on era, obese patients had a 28% decreased risk of cancer death compared to non-obese patients (aHR 0.72, 95%CI 0.65-0.79, p<0.001) (Table 2). Cancer death risk was not significantly associated with transplant status (aHR, 0.91; 95% CI, 0.81–1.02; p=0.11).

Among obese patients, the most common causes of cancer-related deaths were lung cancer (0.86 per 1,000 patient years), liver cancer (0.76 per 1,000 patient years), colorectal cancer (0.27 per 1,000 patient years), melanoma (0.27 per 1,000 patient years) and multiple myeloma (0.27 per 1,000 patient years). Among non-obese patients, the leading cause of cancer-related deaths were lung cancer (1.36 per 1,000 patient years), colorectal cancer (0.55 per 1,000 patient years), multiple myeloma (0.43 per 1,000 patient years), kidney cancer (0.30 per 1,000 patient years) and lymphoma (0.30 per 1,000 patient years).

Obesity was protective against cancer-related death for several cancer types, including esophageal cancer (aHR=0.42, 95% CI 0.21-0.83, p=0.01), colorectal cancer (aHR=0.45, 95% CI 0.31-0.67, p<0.001), lip and oral cavity cancer (aHR=0.27. 95% CI 0.11-0.70, p=0.007), lymphoma (aHR=0.52, 95% CI 0.31-0.88, p=0.01), multiple myeloma (aHR=0.45, 95% CI 0.30-0.68, p<0.001), prostate cancer (aHR=0.28, 95% CI 0.14-0.54, p<0.001) and lung cancer (aHR=0.58, 95% CI 0.47-0.73, p<0.001).

Stratified analyses

Incidence of first cancer and cancer death following dialysis initiation or first transplantation

The majority of person-years were accrued during the first dialysis and first transplant periods, with 226,202 person-years during first dialysis and 119,642 person-years during first transplant. During first dialysis period (censored at the time of transplant), obesity was significantly associated with a reduced risk of esophageal, colorectal, lip and oral cavity, lymphoma, multiple myeloma, prostate, lung, bladder cancer, and cancer from unknown primary site (Figure S1A). In contrast, obesity was associated with significantly increased risks of breast and uterine cancer. During the first transplant period (censored at the time of graft failure), obesity was significantly associated with a lowered risk of incident cervical, non-melanoma skin and bladder cancer, and a higher risk of liver cancer. Obesity was not protective against cancer mortality post-transplant, and was associated with higher mortality from liver cancer (Figure S1B).

Incidence of first cancer and cancer death by sex

In multivariable analyses, male sex was associated with a higher risk of first cancer diagnosis (aHR, 1.17; 95% CI, 1.11–1.24; p<0.001) and cancer-related death (aHR, 1.25; 95% CI, 1.14–1.36; p<0.001). Among male patients, we observed that obese patients experienced a lower risk of lip and oral cavity cancer, multiple myeloma, prostate cancer, lung cancer, and bladder cancer, and an increased risk of thyroid cancer (Figure S2A). At the same time, obese female patients had a lower risk of colorectal cancer, thyroid cancer, lymphoma, cervical cancer, melanoma and cancer from unknown primary site compared to non-obese female patients.

For cancer-related mortality, the association between obesity and site-specific cancer death was generally similar in males and females (Figure S2B). In both sexes, obese patients had a significantly lower risk of death from colorectal cancer. Additionally, obese females had a reduced risk of death from lymphoma and lung cancer, while obese males showed a lower risk of death from lip and oral cavity cancer, multiple myeloma, prostate cancer, lung cancer and cancer from unknown primary site.

Incidence of first cancer and cancer death by age

After stratifying patients by age at 55 years, we observed similar trends in the association between obesity and cancer incidence and mortality among both age groups. However, a greater number of events occurred among patients aged over 55 years, resulting in more

statistically significant associations and narrower confidence intervals in this group (Figure S3).

Degree of obesity and cancer outcomes

Out of the 24,112 patients who were obese at baseline, 13,280 (55%) were classified as class I, 6,284 (26%) class II, 4,548 (18%) class III.

After adjusting for confounders, class II/III obese patients had a 10% lowered risk of cancer diagnosis compared to non-obese patients (aHR=0.90, 95% CI 0.83-0.99, p=0.03), while obese I patients had a 5% lowered risk (aHR=0.95, 95% CI 0.88-1.01, p=0.11). When looking at cancer types, class II/III obese patients had a greater reduction in risk of colorectal cancer, lip and oral cavity cancer, multiple myeloma, prostate cancer, lung cancer, melanoma and bladder cancer compared to class I obese patients (Figure 4A). However, class II/III obese patients had a greater risk of female reproductive system cancer including breast cancer and uterine cancer.

A similar trend was found for cancer deaths. Overall, class II/III obese patients had a 33% lower risk of cancer death compared to non-obese patients (aHR=0.67, 95% CI 0.57-0.78, p<0.001), while class I obese patients had a 26% lower risk (aHR=0.74, 95% CI 0.66-0.82, p<0.001). Class II/III obese patients experienced greater reductions in risk of colorectal

cancer, lip and oral cavity cancer, lymphoma, prostate cancer, lung cancer and cancer from unknown primary site (Figure 4B).

Discussion

In this population-based study of over 76,000 patients with kidney failure initiating KRT over the past 23 years in Australia and New Zealand, we found that obese patients had significantly lower rates of overall cancer incidence and cancer-related mortality when compared with non-obese patients, an association predominantly observed among dialysis patients. The magnitude and direction of this association varied by cancer type and the degree of obesity. Obesity was generally associated with lower risks of esophageal, colorectal, lip and oral cavity, prostate, lung, and bladder cancers, as well as lymphoma and multiple myeloma, but with increased risks of breast and uterine cancers. Patients with higher degrees of obesity experienced greater reductions in cancer incidence and cancer-related mortality compared to those with lower levels of obesity. When looking at first kidney transplant, censored at graft failure, obesity was not significantly associated with either cancer incidence or cancer death.

An obesity paradox, whereby obesity is associated with prolonged survival, has been widely reported among patients receiving KRT in terms of all-cause mortality[38–43]. Whether protection against cancer is a component of this apparent benefit of obesity in kidney

failure has rarely been explored. One study using data from the LIPRO-VET (Lipid profiles and management in veterans with CKD) study between 2004 and 2006 showed a consistently inverse relationship between BMI categories and cancer mortality in kidney failure patients, even for extremely obese patients[40], a result consistent with our findings. Foucher et al. analyzed 4,691 first kidney-only transplant recipients from the French prospective DIVAT (Données Informatisées et VAlidées en Transplantation) cohort and reported a 27% lower risk of cancer for obese compared to non-obese recipients after adjusting for confounders.[20] Another small study including 328 kidney transplant recipients in Northern Ireland suggested a 42% reduction in risk of cancer incidence per category increase of BMI in 5 kg/m^2 intervals.[19] In our subgroup analysis looking at first kidney transplant recipients, we did not find any evidence that obese recipients experienced a significantly lower risk of cancer or cancer death. This could be due to the following reasons: 1) in this study, the follow up was censored at the time of graft failure, where previous studies followed patients until death or end of follow up period. The treatment received post graft failure could potentially influence the risk of cancer death; 2) Our study used a time-varying obesity status while existing studies used only the BMI at the time of transplant. Transplant recipients are typically required to undergo strict weight management prior to surgery and post-transplant weight gain is found to be common[44]. As opposed to existing studies, we elected to include obesity as a time-dependent variable.

We found that patients with class II/III obesity had a greater reduction in both cancer incidence and cancer mortality compared to class I obese patients, when each group was compared with non-obese patients. Soohoo et al., using BMI categories at study baseline,

reported a similar reduction of cancer mortality among patients with BMI 30-35 and 35-50 compared to those with BMI of 25-30, however small numbers in higher BMI categories may have obscured important differences.[40]

The association between obesity and specific cancer types among kidney failure patients has not been well studied. In the general population, the International Agency for Research on Cancer (IARC) has reported that obesity is associated with an increased risk of several cancers, including those of the oesophagus, colorectum, liver, breast, prostate, kidney, and lymphoma.[45] In our population of KRT patients, this positive association with obesity was confirmed only for breast cancer. In contrast, we observed a significant inverse association between obesity and the risk of esophageal, colorectal, and prostate cancers, as well as a weak protective effect in lymphoma. Another study examining cancer mortality in a cohort of 900,000 U.S. adults found that obese patients had an increased risk of death from colorectal, liver, prostate, breast, cervical, and kidney cancers, as well as lymphoma and multiple myeloma, while a lower risk of death was demonstrated for lung cancer.[46] Of all reported associations, only the inverse relationship between obesity and lung cancer mortality aligned with our findings in the kidney failure population. In contrast to the general population, we also observed lower cancer mortality associated with obesity in oesophageal, colorectal, and prostate cancers, as well as lymphoma and multiple myeloma.

Our study confirms the presence of reverse epidemiology in both cancer incidence and cancer deaths among patients receiving KRT. The underlying mechanisms of this obesity

paradox remain unclear. However, several potential explanations have been proposed. Obese patients often have greater nutritional and fat reserves, better appetites, as well as increased lean body mass, which may provide a physiological advantage during illness and better capacity to withstand side-effects from cancer treatments.[40,47] Patients in lower BMI categories may be malnourished and frail, or have experienced unintentional weight loss due to underlying comorbidities, chronic or acute diseases, or smoking, which could confound the observed associations.[48,49] Other studies have suggested that weight loss in cancer patients may indicate more aggressive tumour or a more advanced stage at diagnosis. [47,50] Weight loss can begin over half a year before cancer is formally diagnosed, and subclinical changes in metabolism may occur two years prior. Weight loss may be a sign of cancer-associated cachexia which involves systemic metabolic dysfunction, and fat and muscle wasting driven by inflammation.[51] Cachexia is an independent risk factor of cancer mortality. Obese individuals may be less susceptible to rapid fat loss and energy imbalance due to their higher baseline adiposity, delaying or reducing the severity of cachexia-related complications.

Obesity is increasingly prevalent among patients initiating dialysis, with over 40% classified as obese in the United States in 2016.[52] Current guidelines, including the 2020 Kidney Disease: Improving Global Outcomes (KDIGO) guideline and the American Society of Transplantation (AST) guideline, recommend weight loss interventions prior to receiving a transplant.[24,53] In practice, obese patients are less likely to be placed on transplant waiting list and, once wait-listed, are more likely to be inactivated due to weight-related concerns compared to non-obese patients.[54,55] Our findings suggest that obesity may be associated

with better cancer-related outcomes, at least whilst on dialysis waiting to receive a transplant, which has important clinical implications for the management of obese candidates for kidney transplantation. Further research is required to determine whether intentional pre-transplant weight loss is beneficial in this context. In addition, we found that non-obese KRT patients had a higher risk of esophagus, colorectal, lip and oral cavity, cervical, prostate, lung and bladder cancer, as well as lymphoma and multiple myeloma, while obese patients were at an increased risk of breast and uterine cancers. More data are required to determine whether targeted cancer screening based on obesity status could improve long-term cancer outcomes in these patient groups.

Our present study is the first in the literature that used a large registry-based cohort over a 20-year period to look at the effect of obesity on both cancer incidence and cancer mortality on patients receiving KRT. We conducted a comprehensive analysis on cancer types. Obesity status and transplant status were fitted as time-varying covariates to adjust for its chronological changes. In addition, we used an ethnicity-specific BMI cutoff for the Asian population, which reflects differences in body composition compared to Western populations.

This study has several limitations. First, as a retrospective registry-based study, its findings are dependent on the accuracy and completeness of the data recorded in the registry. However, previous studies have demonstrated good concordance between registry-reported cancer outcomes and the death registry.[31] Second, BMI is not a perfect measure

of adiposity. One study suggested that central adiposity is a stronger predictor of overall cancer risk.[56] However, measures that better distinguish fat from lean mass such as waist circumference, in vivo neutron activation analysis, and dual-energy X-ray absorptiometry (DXA) are not routinely collected by ANZDATA and therefore could not be incorporated in our analyses. Third, potentially confounders such as socio-economic status, diet, physical activity, genetic factors, workplace exposures and screening behaviours were not accounted for. Fourth, our cohort was predominantly Caucasian which may not be generalisable to other populations.

In conclusion, our study found a 7% lower risk of cancer incidence and a 28% lower risk of cancer deaths among obese patients receiving KRT compared to their non-obese counterparts, findings that were predominantly driven by the dialysis population. Dose-response analyses indicated a greater reduction in cancer risk among patients with higher classes of obesity (Class II/II). Future research is required to elucidate the mechanism underlying this reverse epidemiology and to inform strategies for cancer prevention and management in this high-risk population.

References

1. Massetti, G. M., Dietz, W. H., & Richardson, L. C. (2017). Excessive Weight Gain, Obesity, and Cancer: Opportunities for Clinical Intervention. *JAMA*, *318*(20), 1975. https://doi.org/10.1001/jama.2017.15519

2. Bhaskaran, K., Douglas, I., Forbes, H., dos-Santos-Silva, I., Leon, D. A., & Smeeth, L. (2014). Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *The Lancet*, *384*(9945), 755–765. https://doi.org/10.1016/s0140-6736(14)60892-8

3. Pati, S., Irfan, W., Jameel, A., Ahmed, S., & Shahid, R. K. (2023). Obesity and Cancer: A Current Overview of Epidemiology, Pathogenesis, Outcomes, and Management. *Cancers*, *15*(2), 485. https://doi.org/10.3390/cancers15020485

4. Tzenios, N. (2023). Obesity As a Risk Factor For Cancer. *EPRA International Journal of Multidisciplinary Research (IJMR)*, 101–104. https://doi.org/10.36713/epra12423

5. Kantor, A. F., Hoover, R. N., Kinlen, L. J., Mcmullan, M. R., & Fraumeni, J. F. (1987). Cancer in Patients Receiving Long-Term Dialysis Treatment. *American Journal of Epidemiology*, *126*(3), 370–376. https://doi.org/10.1093/oxfordjournals.aje.a114668

6. Butler, A. M., Olshan, A. F., Kshirsagar, A. V., Edwards, J. K., Nielsen, M. E., Wheeler, S. B., & Brookhart, M. A. (2015). Cancer Incidence Among US Medicare ESRD Patients Receiving Hemodialysis, 1996-2009. *American Journal of Kidney Diseases*, *65*(5), 763–772. https://doi.org/10.1053/j.ajkd.2014.12.013

7. Maisonneuve, P., Agodoa, L., Gellert, R., Stewart, J. H., Buccianti, G., Lowenfels, A. B., Wolf, R. A., Jones, E., Dsiney, A. P., Briggs, D., McCredie, M., & Boyle, P. (1999). Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *The Lancet*, *354*(9173), 93–99. https://doi.org/10.1016/s0140-6736(99)06154-1

8. Vajdic, C. M., McDonald, S. P., McCredie, M. R. E., Leeuwen, M. T. van, Stewart, J. H., Law, M., Chapman, J. R., Webster, A. C., Kaldor, J. M., & Grulich, A. E. (2006). Cancer Incidence Before and After Kidney Transplantation. *JAMA*, *296*(23), 2823–2831. https://doi.org/10.1001/jama.296.23.2823

9. Lin, M. Y., Kuo, M. C., Hung, C. C., Wu, W. J., Chen, L. T., Yu, M. L., Hsu, C.-C., Lee, C.-H., Chen, H.-C., & Hwang, S.-J. (2015). Association of Dialysis with the Risks of Cancers. *PLoS ONE*, *10*(4), e0122856. https://doi.org/10.1371/journal.pone.0122856

10. Stewart, J. H., Vajdic, C. M., Leeuwen, M. T. van, Amin, J., Webster, A. C., Chapman, J. R., McDonald, S. P., Grulich, A. E., & McCredie, M. R. E. (2009). The pattern of excess cancer in dialysis and transplantation. *Nephrology Dialysis Transplantation*, *24*(10), 3225–3231. https://doi.org/10.1093/ndt/gfp331

11. Yanik, E. L., Clarke, C. A., Snyder, J. J., Pfeiffer, R. M., & Engels, E. A. (2016). Variation in Cancer Incidence among Patients with ESRD during Kidney Function and Nonfunction Intervals. *Journal of the American Society of Nephrology*, *27*(5), 1495–1504. https://doi.org/10.1681/asn.2015040373

12. Birkeland, S., L⊘kkegaard, H., & Storm, H. (2000). Cancer risk in patients on dialysis and after renal transplantation. *The Lancet*, *355*(9218), 1886–1887. https://doi.org/10.1016/s0140-6736(00)02298-4

13. Lee, M.-J., Lee, E., Park, B., & Park, I. (2021). Epidemiological characteristics of cancers in patients with end-stage kidney disease: a Korean nationwide study. *Scientific Reports*, *11*(1), 3929. https://doi.org/10.1038/s41598-021-83164-6

14. Engels, E. A., Pfeiffer, R. M., Fraumeni, J. F., Kasiske, B. L., Israni, A. K., Snyder, J. J., Wolfe, R. A., Goodrich, N. P., Bayakly, A. R., Clarke, C. A., Copeland, G., Finch, J. L., Fleissner, M. L., Goodman, M. T., Kahn, A., Koch, L., Lynch, C. F., Madeleine, M. M., Pawlish, K., … Lin, M. (2011). Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients. *JAMA*, *306*(17), 1891–1901. https://doi.org/10.1001/jama.2011.1592

15. Xie, X., Li, F., Xie, L., Yu, Y., Ou, S., & He, R. (2023). Meta-analysis of cancer risk among end stage renal disease undergoing maintenance dialysis. *Open Life Sciences*, *18*(1), 20220553. https://doi.org/10.1515/biol-2022-0553

16. Kitai, Y., Matsubara, T., Funakoshi, T., Horimatsu, T., Muto, M., & Yanagita, M. (2016). Cancer screening and treatment in patients with end-stage renal disease: remaining issues in the field of onco-nephrology. *Renal Replacement Therapy*, *2*(1), 33. https://doi.org/10.1186/s41100-016-0046-y

17. Ying, T., Shi, B., Kelly, P. J., Pilmore, H., Clayton, P. A., & Chadban, S. J. (2020). Death after Kidney Transplantation: An Analysis by Era and Time Post-Transplant. *Journal of the*

American Society of Nephrology, *31*(12), 2887–2899. https://doi.org/10.1681/asn.2020050566

18. Rosales, B. M., Mata, N. D. L., Vajdic, C. M., Kelly, P. J., Wyburn, K., & Webster, A. C. (2020). Cancer mortality in kidney transplant recipients: An Australian and New Zealand population-based cohort study, 1980–2013. *International Journal of Cancer*, *146*(10), 2703–2711. https://doi.org/10.1002/ijc.32585

19. McCloskey, O. M., Devine, P. A., Courtney, A. E., & McCaughan, J. A. (2018). Is big bad or bearable? Long-term renal transplant outcomes in obese recipients. *QJM: An International Journal of Medicine*, *111*(6), 365–371. https://doi.org/10.1093/qjmed/hcx258

20. Foucher, Y., Lorent, M., Albano, L., Roux, S., Pernin, V., Quintrec, M. L., Legendre, C., Buron, F., Morelon, E., Girerd, S., Ladrière, M., Glotz, D., Lefaucher, C., Kerleau, C., Dantal, J., Branchereau, J., Giral, M., Blancho, G., Branchereau, J., … Serre, J.-E. (2021). Renal transplantation outcomes in obese patients: a French cohort-based study. *BMC Nephrology*, *22*(1), 79. https://doi.org/10.1186/s12882-021-02278-1

21. Wakam, G. K., Sheetz, K. H., Gerhardinger, L., Montgomery, J. R., & Waits, S. A. (2021). Population-based Trends in Obesity and Kidney Transplantation Among Patients With End-stage Kidney Disease. *Transplantation Direct*, *7*(12), e787. https://doi.org/10.1097/txd.0000000000001163

22. Camilleri, B., Bridson, J. M., Sharma, A., & Halawa, A. (2016). From chronic kidney disease to kidney transplantation: The impact of obesity and its treatment modalities. *Transplantation Reviews*, *30*(4), 203–211. https://doi.org/10.1016/j.trre.2016.07.006

23. Friedman, A. N., Miskulin, D. C., Rosenberg, I. H., & Levey, A. S. (2003). Demographics and trends in overweight and obesity in patients at time of kidney transplantation. *American Journal of Kidney Diseases*, *41*(2), 480–487. https://doi.org/10.1053/ajkd.2003.50059

24. Chadban, S. J., Ahn, C., Axelrod, D. A., Foster, B. J., Kasiske, B. L., Kher, V., Kumar, D., Oberbauer, R., Pascual, J., Pilmore, H. L., Rodrigue, J. R., Segev, D. L., Sheerin, N. S., Tinckam, K. J., Wong, G., & Knoll, G. A. (2020). KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. *Transplantation*, *104*(4S1), S11–S103. https://doi.org/10.1097/tp.0000000000003136

25. McDonald, S. P. (2015). Australia and New Zealand Dialysis and Transplant Registry. *Kidney International Supplements*, *5*(1), 39–44. https://doi.org/10.1038/kisup.2015.8

26. Low, S., Chin, M. C., Ma, S., Heng, D., & Deurenberg-Yap, M. (2009). Rationale for redefining obesity in Asians. *Annals of the Academy of Medicine, Singapore*, *38*(1), 66–69.

27. WHO expert consultation. (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *The Lancet*, *363*(9403), 157–163. https://doi.org/10.1016/s0140-6736(03)15268-3

28. Deurenberg, P., Deurenberg-Yap, M., & Guricci, S. (2002). Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obesity Reviews*, *3*(3), 141–146. https://doi.org/10.1046/j.1467-789x.2002.00065.x

29. World Health Organization, International Diabetes Institute, International Association for the Study of Obesity, & International Obesity Task Force. (2000). *The Asia-Pacific Perspective Redefining Obesity and its Treatment*. https://iris.who.int/bitstream/handle/10665/206936/0957708211_eng.pdf

30. Trott, P. A. (1977). International Classification of Diseases for Oncology. *Journal of Clinical Pathology*, *30*(8), 782. https://doi.org/10.1136/jcp.30.8.782-c

31. Webster, A. C., Supramaniam, R., O'connell, D. L., Chapman, J. R., & Craig, J. C. (2010). Validity of registry data: Agreement between cancer records in an end-stage kidney disease registry (voluntary reporting) and a cancer register (statutory reporting). *Nephrology*, *15*(4), 491–501. https://doi.org/10.1111/j.1440-1797.2010.01297.x

32. Sypek, M. P., Dansie, K. B., Clayton, P., Webster, A. C., & Mcdonald, S. (2019). Comparison of cause of death between Australian and New Zealand Dialysis and Transplant Registry and the Australian National Death Index. *Nephrology*, *24*(3), 322–329. https://doi.org/10.1111/nep.13250

33. Choudhury, J. B. (2002). Non-parametric confidence interval estimation for competing risks analysis: application to contraceptive data. *Statistics in Medicine*, *21*(8), 1129–1144. https://doi.org/10.1002/sim.1070

34. Everitt, B., & Rabe-Hesketh, S. (2003). *Handbook of Statistical Analyses Using Stata, Third Edition*. https://doi.org/10.1201/noe1584884040.ch9

35. Yeh, C., Le, C., & McHugh, R. (1984). Competing Risk Analysis for Life Table Data with known Observation Times. *Biometrical Journal*, *26*(1), 111–118. https://doi.org/10.1002/bimj.4710260121

36. Laird, N., & Olivier, D. (1981). Covariance Analysis of Censored Survival Data Using Log-Linear Analysis Techniques. *Journal of the American Statistical Association*, *76*(374), 231–240. https://doi.org/10.1080/01621459.1981.10477634

37. Kalbfleisch, J. D., & Prentice, R. L. (2011). The Statistical Analysis of Failure Time Data. *Wiley Series in Probability and Statistics*, 247–277. https://doi.org/10.1002/9781118032985.ch8

38. Park, J., Ahmadi, S.-F., Streja, E., Molnar, M. Z., Flegal, K. M., Gillen, D., Kovesdy, C. P., & Kalantar-Zadeh, K. (2014). Obesity Paradox in End-Stage Kidney Disease Patients. *Progress in Cardiovascular Diseases*, *56*(4), 415–425. https://doi.org/10.1016/j.pcad.2013.10.005

39. Kalantar-Zadeh, K., Abbott, K. C., Salahudeen, A. K., Kilpatrick, R. D., & Horwich, T. B. (2005). Survival advantages of obesity in dialysis patients. *The American Journal of Clinical Nutrition*, *81*(3), 543–554. https://doi.org/10.1093/ajcn/81.3.543

40. Soohoo, M., Streja, E., Hsiung, J.-T., Kovesdy, C. P., Kalantar-Zadeh, K., & Arah, O. A. (2022). Cohort Study and Bias Analysis of the Obesity Paradox Across Stages of Chronic

Kidney Disease. *Journal of Renal Nutrition*, *32*(5), 529–536. https://doi.org/10.1053/j.jrn.2021.10.007

41. Badve, S. V., Paul, S. K., Klein, K., Clayton, P. A., Hawley, C. M., Brown, F. G., Boudville, N., Polkinghorne, K. R., McDonald, S. P., & Johnson, D. W. (2014). The Association between Body Mass Index and Mortality in Incident Dialysis Patients. *PLoS ONE*, *9*(12), e114897. https://doi.org/10.1371/journal.pone.0114897

42. Kovesdy, C. P., Czira, M. E., Rudas, A., Ujszaszi, A., Rosivall, L., Novak, M., Kalantar-Zadeh, K., Molnar, M. Z., & Mucsi, I. (2010). Body Mass Index, Waist Circumference and Mortality in Kidney Transplant Recipients. *American Journal of Transplantation*, *10*(12), 2644–2651. https://doi.org/10.1111/j.1600-6143.2010.03330.x

43. Doshi, M., Streja, E., Rhee, C. M., Park, J., Ravel, V. A., Soohoo, M., Moradi, H., Lau, W. L., Mehrotra, R., Kuttykrishnan, S., Kovesdy, C. P., Kalantar-Zadeh, K., & Chen, J. L. T. (2016). Examining the robustness of the obesity paradox in maintenance hemodialysis patients: a marginal structural model analysis. *Nephrology Dialysis Transplantation*, *31*(8), 1310–1319. https://doi.org/10.1093/ndt/gfv379

44. Hoogeveen, E. K., Aalten, J., Rothman, K. J., Roodnat, J. I., Mallat, M. J. K., Borm, G., Weimar, W., Hoitsma, A. J., & Fijter, J. W. de. (2011). Effect of Obesity on the Outcome of Kidney Transplantation: A 20-Year Follow-Up. *Transplantation*, *91*(8), 869–874. https://doi.org/10.1097/tp.0b013e3182100f3a

45. Wild, C. P., Weiderpass, E., & Stewart, B. W. (2020). *World Cancer Report. Cancer Research for Cancer Prevention*. International Agency for Research on Cancer (IARC).

World Health Organization (WHO). https://www.iarc.who.int/cards_page/world-cancer-report/

46. Calle, E. E., Rodriguez, C., Walker-Thurmond, K., & Thun, M. J. (2003). Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults. *The New England Journal of Medicine*, *348*, 1625–1638. https://doi.org/10.1056/nejmoa021423

47. Shachar, S. S., & Williams, G. R. (2017). The Obesity Paradox in Cancer—Moving Beyond BMI. *Cancer Epidemiology and Prevention Biomarkers*, *26*(1), 13–16. https://doi.org/10.1158/1055-9965.epi-16-0439

48. Johansen, K. L., Kutner, N. G., Young, B., & Chertow, G. M. (2006). Association of body size with health status in patients beginning dialysis 2 3 1–4. *The American Journal of Clinical Nutrition*, *83*(3), 543–549. https://doi.org/10.1093/ajcn.83.3.543

49. Klesges, R. C., Meyers, A. W., Klesges, L. M., & Vasque, M. E. L. (1989). Smoking, Body Weight, and Their Effects on Smoking Behavior: A Comprehensive Review of the Literature. *Psychological Bulletin*, *106*(2), 204–230. https://doi.org/10.1037/0033-2909.106.2.204

50. Kritchevsky, S. B., Wilcosky, T. C., Morris, D. L., Truong, K. N., & Tyroler, H. A. (1991). Changes in plasma lipid and lipoprotein cholesterol and weight prior to the diagnosis of cancer. *Cancer Research*, *51*(12), 3198–3203.

51. Petruzzelli, M., & Wagner, E. F. (2016). Mechanisms of metabolic dysfunction in cancer-associated cachexia. *Genes & Development*, *30*(5), 489–501. https://doi.org/10.1101/gad.276733.115

52. Lavenburg, L.-M. U., Kim, Y., Weinhandl, E. D., Johansen, K. L., & Harhay, M. N. (2022). Trends, Social Context, and Transplant Implications of Obesity Among Incident Dialysis Patients in the United States. *Transplantation*, *106*(11), e488–e498. https://doi.org/10.1097/tp.0000000000004243

53. Kasiske, B. L., Cangro, C. B., Hariharan, S., Hricik, D. E., Kerman, R. H., Roth, D., Rush, D. N., Vazquez, M. A., & Weir, M. R. (2001). The Evaluation of the Renal Transplant Candidates: Clinical Practice Guidelines. *American Journal of Transplantation*, *1*, 1–95. https://doi.org/10.1034/j.1600-6143.2001.0010s2001.x

54. Lee, J. H., McDonald, E. O., & Harhay, M. N. (2021). Obesity Management in Kidney Transplant Candidates: Current Paradigms and Gaps in Knowledge. *Advances in Chronic Kidney Disease*, *28*(6), 528–541. https://doi.org/10.1053/j.ackd.2021.09.009

55. Huang, E., Shye, M., Elashoff, D., Mehrnia, A., & Bunnapradist, S. (2014). Incidence of Conversion to Active Waitlist Status Among Temporarily Inactive Obese Renal Transplant Candidates. *Transplantation*, *98*(2), 177–186. https://doi.org/10.1097/tp.0000000000000037

56. Barberio, A. M., Alareeki, A., Viner, B., Pader, J., Vena, J. E., Arora, P., Friedenreich, C. M., & Brenner, D. R. (2019). Central body fatness is a stronger predictor of cancer risk than

overall body size. *Nature Communications*, *10*(1), 383. https://doi.org/10.1038/s41467-018-08159-w

Table 1. Baseline characteristics comparing patients classified as obese versus non-obese at kidney replacement therapy initiation

Characteristics	Obese n (%)	Not obese n (%)	p-value
Total	24,112 (100)	41,600 (100)	
Age			<0.001
18-34	1,218 (5)	3,974 (10)	
35-49	4,263 (18)	7,211 (17)	
50-65	9,339 (39)	12,150 (29)	
65+	9,292 (39)	18,265 (44)	
Male	14,153 (59)	25,970 (62)	<0.001
Ethnicity			<0.001
Caucasian	14,123 (59)	28,142 (68)	
Indigenous	7,464 (31)	6,949 (17)	
Asian	1,931 (8)	5,116 (12)	
Other	594 (2)	1,393 (3)	
Primary kidney disease			<0.001
Glomerular disease	4,336 (18)	9,950 (24)	
Hypertension/Renovascular	2,391 (10)	6,138 (15)	
Diabetic	12,788 (53)	13,178 (32)	
Other	4,597 (19)	12,334 (30)	
Initial modality			<0.001
Pre-emptive transplant	446 (2)	1,741 (4)	
Haemodialysis	17,955 (74)	27,510 (66)	
Peritoneal dialysis	5,711 (24)	12,349 (30)	
Era			<0.001
2000–2011	8,684 (36)	19,378 (47)	
2012–2023	15,428 (64)	22,222 (53)	
Pre-existing co-morbidities			
Chronic lung disease	3,876 (16)	5,909 (14)	<0.001
Cardiovascular disease	11,949 (50)	18,409 (44)	<0.001
Diabetes	15,967 (66)	17,184 (41)	<0.001
Smoking status			<0.001
Current	11,387 (47)	20,280 (49)	
Former	9,863 (41)	15,206 (37)	
Never	2,682 (11)	5,806 (14)	
Unknown	180 (1)	308 (1)	

Table 2. Multivariable piecewise exponential model on first solid organ or hematological cancer diagnosis and cancer death

Covariates	First solid organ/hematologic cancer diagnosis			Cancer death		
	aHR	95% CI	p-value	aHR	95% CI	p-value
Obese (time-varying)	0.93	(0.88-0.99)	0.02	0.72	(0.65-0.79)	<0.001
Functioning graft (time-varying)	0.96	(0.88-1.03)	0.24	0.91	(0.81-1.02)	0.11
Age			<0.001			<0.001
18-34	Ref			Ref		
35-49	2.13	(1.83-2.49)		3.87	(2.80-5.36)	
50-65	4.31	(3.73-4.98)		10.39	(7.61-14.18)	
65+	6.35	(5.47-7.42)		19.01	(13.86-26.19)	
Male	1.17	(1.11-1.24)	<0.001	1.25	(1.14-1.36)	<0.001
Ethnicity			<0.001			<0.001
Caucasian				Ref		
Indigenous	0.82	(0.76-0.89)		0.90	(0.79-1.01)	
Asian	0.61	(0.55-0.68)		0.49	(0.41-0.59)	
Other	0.69	(0.58-0.81)		0.60	(0.46-0.79)	
Primary kidney disease			<0.001			<0.001
Glomerular disease	Ref			Ref	(1.14-1.41)	
Hypertension/renal vascular disease	0.97	(0.88-1.06)		1.05	(0.92-1.20)	
Diabetic kidney disease	0.86	(0.79-0.92)		1.03	(0.92-1.16)	
Other	1.12	(1.03-1.19)		1.27	(1.14-1.41)	
Initial modality			0.03			0.003
Pre-emptive transplant				Ref		
Haemodialysis	1.05	(0.92-1.21)		1.28	(1.01-1.62)	
Peritoneal dialysis	1.06	(0.89-1.21)		1.11	(0.87-1.42)	
Smoking status			<0.001			<0.001
Never	Ref			Ref		
Former	1.20	(1.13-1.27)		1.37	(1.26-1.50)	
Current	1.38	(1.27-1.51)		1.83	(1.62-2.07)	
Pre-existing lung disease	1.22	(1.13-1.31)	<0.001	1.39	(1.25-1.54)	<0.001
Pre-existing cardiovascular disease	0.91	(0.85-0.96)	0.001	-	-	-

Table 3. Cancer incidence rate and cancer death rate by obesity status

Type of cancer	First cancer diagnosis							Cancer death						
	Total events	Cancer incidence rate per 1,000 person-years						Total events	Cancer death rate per 1,000 person-years					
		Overall		0-5 years		5-15 years			Overall		0-5 years		5-15 years	
		Obese	Non-obese	Obese	Non-obese	Obese	Non-obese		Obese	Non-obese	Obese	Non-obese	Obese	Non-obese
Any nonskin cancer	5,749	15.10	16.49	16.19	17.78	12.99	14.78	2,571	5.20	7.57	4.65	7.05	6.08	8.13
Digestive system														
Esophagus	87	0.17	0.26	0.18	0.29	0.17	0.21	59	0.09	0.19	0.07	0.22	0.11	0.13
Colorectal	511	1.16	1.46	1.25	1.62	1.01	1.30	175	0.27	0.55	0.23	0.53	0.33	0.63
Liver	187	0.60	0.45	0.56	0.47	0.70	0.43	120	0.38	0.29	0.33	0.26	0.50	0.34
Endocrine system														
Thyroid	139	0.40	0.36	0.46	0.36	0.28	0.38	7	0.01	0.02	0.00	0.01	0.03	0.02
Head and neck														
Lip and oral cavity	137	0.22	0.43	0.20	0.29	0.25	0.57	45	0.04	0.15	0.03	0.11	0.08	0.16
Hematologic														
Lymphoma	256	0.55	0.74	0.53	0.71	0.56	0.81	95	0.16	0.30	0.12	0.27	0.22	0.36
Multiple myeloma	314	0.74	0.88	1.00	1.38	0.25	0.23	139	0.24	0.43	0.31	0.65	0.11	0.15
Leukaemia	115	0.38	0.27	0.42	0.31	0.31	0.23	41	0.08	0.12	0.09	0.12	0.06	0.12
Female reproductive system														
Breast	343	1.20	0.79	1.29	0.80	1.07	0.76	53	0.17	0.13	0.16	0.09	0.22	0.16
Uterus	79	0.42	0.12	0.47	0.13	0.34	0.11	15	0.09	0.02	0.07	0.02	0.11	0.01
Cervix	90	0.14	0.29	0.16	0.22	0.11	0.40	8	0.01	0.03	0.00	0.02	0.03	0.02
Male reproductive system														
Prostate	512	1.06	1.51	1.11	1.60	0.95	1.32	81	0.09	0.27	0.08	0.21	0.11	0.38
Respiratory system														
Lung	675	1.63	1.88	1.77	2.05	1.34	1.69	453	0.86	1.36	0.83	1.31	0.86	1.48
Skin														
Melanoma	501	1.17	1.42	1.22	1.49	1.04	1.31	105	0.27	0.28	0.26	0.17	0.28	0.43
Urinary system														
Kidney	588	1.59	1.57	1.58	1.52	1.63	1.62	107	0.24	0.30	0.14	0.20	0.34	0.44
Bladder	275	0.58	0.80	0.76	0.87	0.25	0.72	74	0.16	0.22	0.18	0.20	0.11	0.25
Other														
Unknown primary site	160	0.37	0.45	0.42	0.54	0.25	0.36	347	0.71	1.02	0.72	1.20	0.67	0.78

Figure 1. Study flowchart

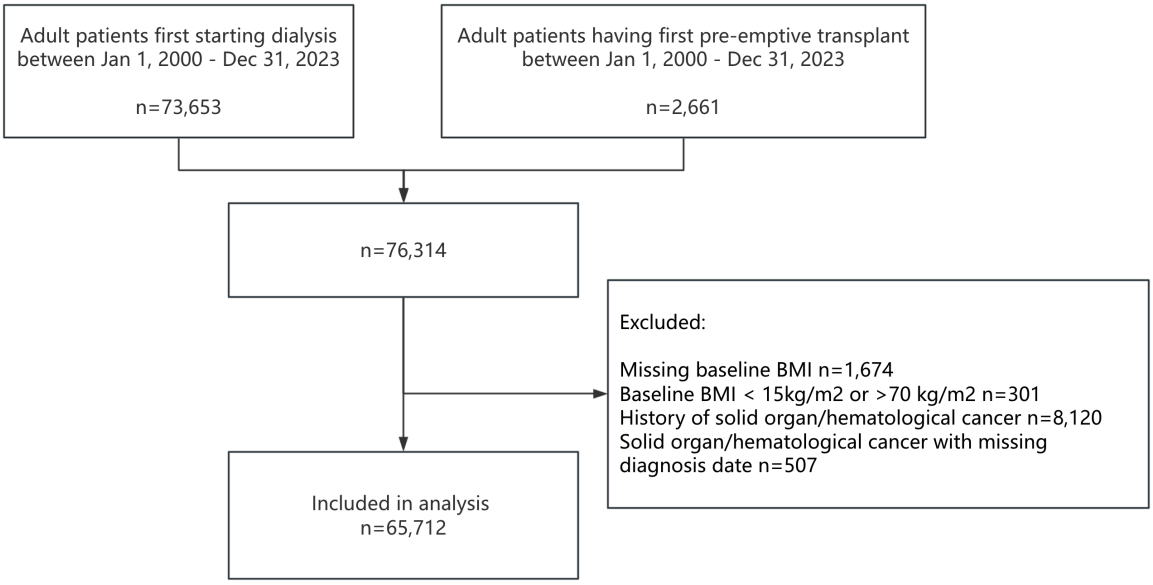


Figure 2. Cumulative incidence function by obesity status in patients initiating kidney replacement therapy

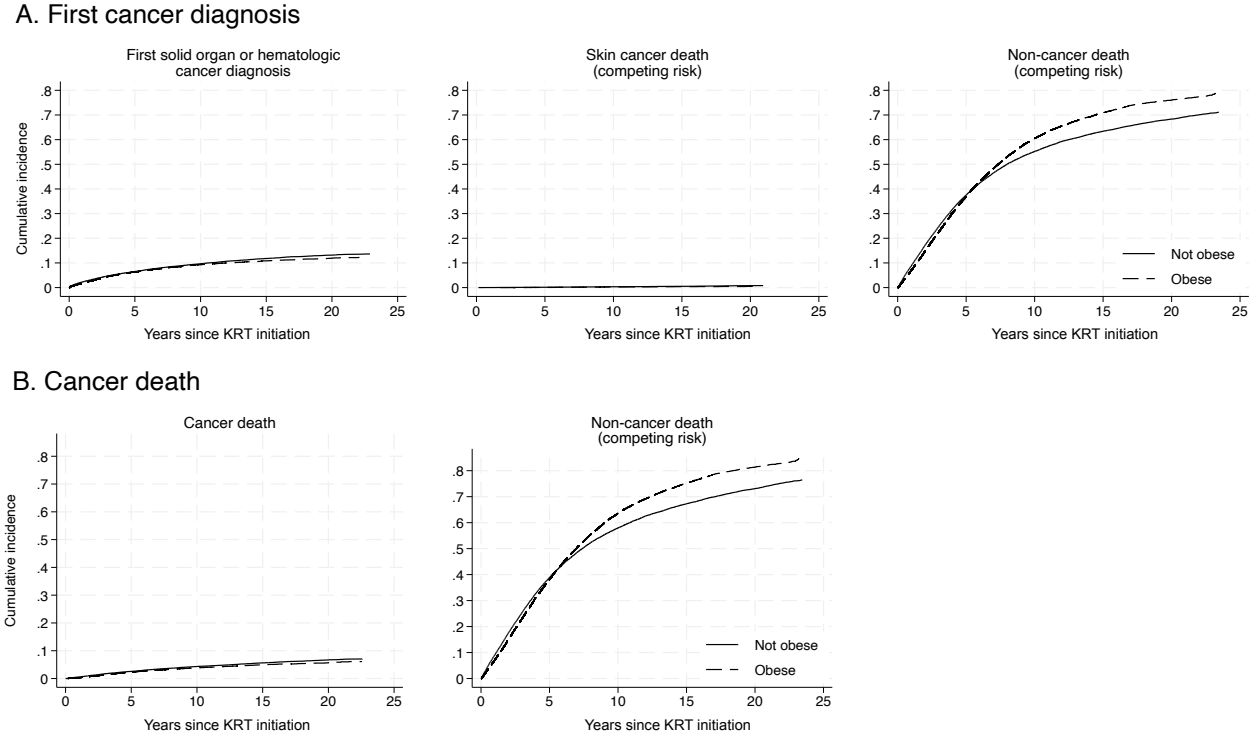
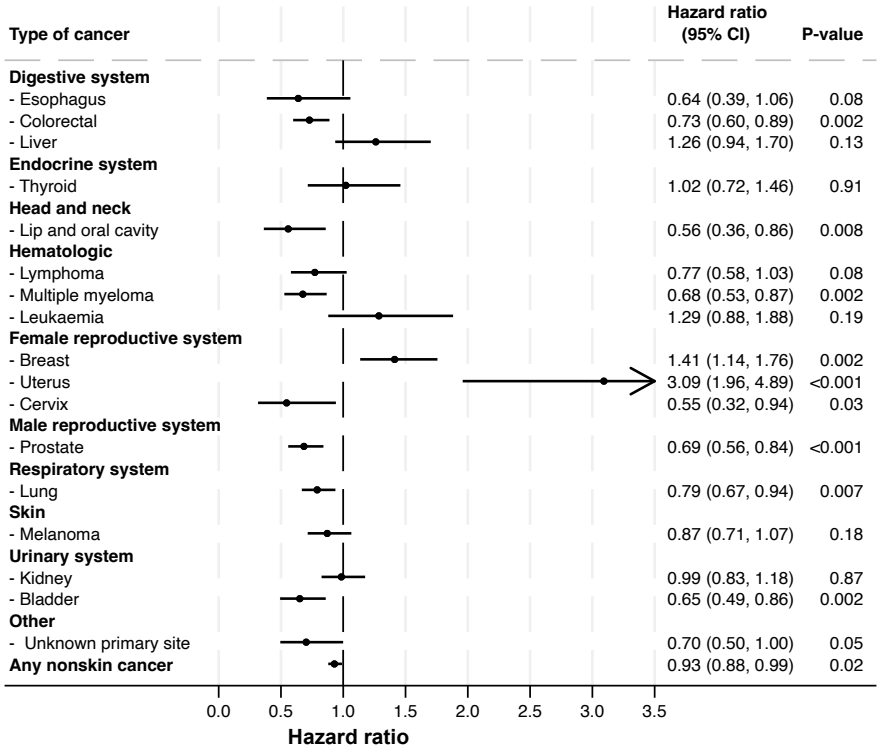


Figure 3. Hazard ratios for cancer incidence and cancer-related death by cancer type.

A. First cancer diagnosis



B. Cancer death

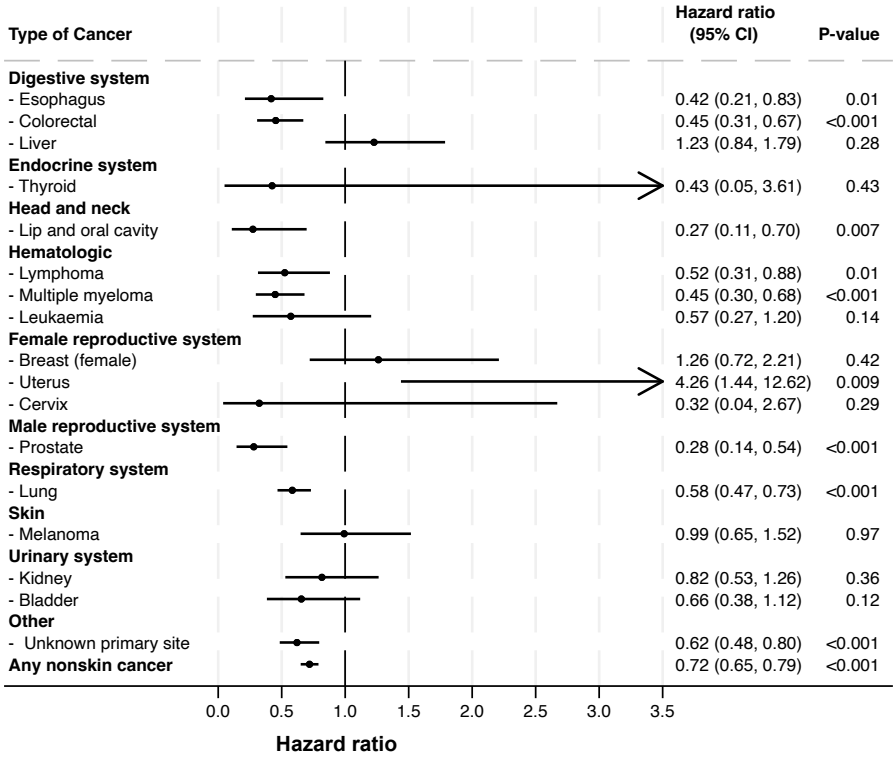
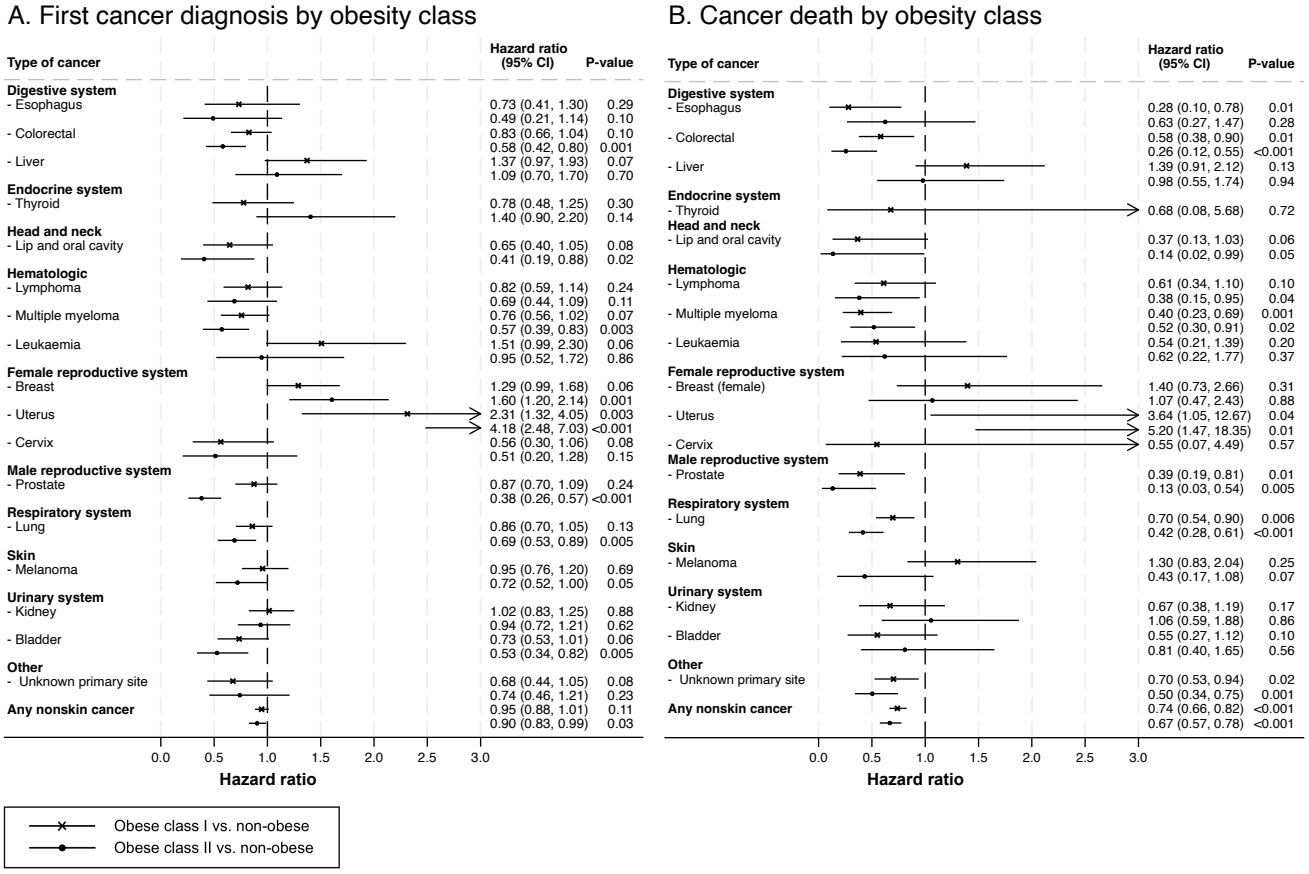


Figure 4. Cancer incidence and cancer-related mortality comparing obese class I and obese class II with non-obese patients



CHAPTER 6

Design and reporting quality of non-inferiority trials in kidney transplantation: a systematic review

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Author contribution:

BS designed the study together with her supervisors, developed data collection form in REDCap, performed the search, selected studies for inclusion, performed the analysis, interpreted the results, drafted the manuscript and figures, and oversaw the manuscript revision.

Abstract

Background. Non-inferiority trials facilitate innovation in kidney transplantation and their use is increasing. We aimed to assess the design and reporting quality of non-inferiority trials in kidney transplantation, specifically assessing adherence to existing guidelines. Methods. We searched MEDLINE, Embase, and CENTRAL for randomized-controlled non-inferiority trials in kidney transplantation published up to February 2025. Two investigators reviewed and extracted data. Adherence to CONSORT, FDA and EMEA guidelines was evaluated. Results. We identified 44 unique trials: 37 (84%) compared a novel immunosuppressive regimen to standard of care and 26 (59%) were industry sponsored. The non-inferiority margin (the worst-case loss in efficacy considered clinically acceptable) was not justified in 31 (70%) studies and poorly justified in 6 (14%). Of 32 studies with a categorical primary outcome, 30 (94%) inappropriately assessed absolute risk reduction, rather than relative risk, leading to inflated tolerance for loss of efficacy in 18 trials. Most studies had high withdrawal and dropout rates, and 37 (84%) did not specify methods for handling missing data. Intention to treat analysis alone was used to determine primary efficacy in 22 (50%) studies, thereby creating bias toward a non-inferiority finding when dropout rates were high. Thirteen studies (30%) provided an incorrect conclusion, most claiming equivalence when non-inferiority had not been adequately demonstrated. Trial quality did not improve over time, and no association was evident between trial quality and journal impact factor. Conclusion. We found major deficiencies in the design, conduct and reporting of non-inferiority trials in kidney transplantation which is compromising the evidence base for novel therapies in this field.

Introduction

Non-inferiority (NI) trials aim to demonstrate that a new treatment is not likely to be worse than standard of care by a predetermined margin (Figure 1).[1] A certain loss of efficacy may be justified due to ancillary benefits of the new treatment such as improved safety profile, lower cost or easier administration.[2] In kidney transplantation NI trial methodology has been relied on to evaluate almost every proposed innovation to standard of care over the past two decades.

The design, execution, and interpretation of NI trials presents unique challenges that differ from those encountered in superiority trials. Poorly designed NI trials can bias towards a false positive conclusion of non-inferiority, potentially leading to adoption of inferior therapies.[3] Several guidelines are available to assist researchers in navigating these complexities. The Consolidated Standards of Reporting Trials (CONSORT) extension statements, particularly those from 2006 and 2010, focus on the reporting of NI trials.[4,5] The U.S. Food and Drug Administration (FDA) guidelines from 2016 provides comprehensive guidance on all aspects of NI trial design.[6] Additionally, the European Medicines Evaluation Agency (EMEA) guidelines from 2000 and 2006 discus the nuances of switching between non-inferiority and superiority designs and provide recommendations on the choice of non-inferiority margins.[7,8] The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 and E10 guidelines offer broader statistical guidance relevant to all clinical trial designs.[9,10]

The quality of design, execution and reporting of NI trials in kidney transplantation has never been systematically assessed despite our reliance on them for testing novel therapies. Here, we aimed to evaluate the design and reporting quality of NI trials in kidney transplantation, focusing on compliance with existing guidelines and identifying areas for improvement.

Methods

We searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to February 2025 using the search combination ("non inferior*" or "noninferior*" or "non-inferior*") and ("kidney transplantation" or "kidney transplant*" or "renal transplant*" or "kidney graft" or "kidney allograft" or "renal allograft" or "renal graft"). We included all published randomised controlled trials involving adult and paediatric kidney-only transplant recipients that use non-inferiority as the primary statistical analysis and were primary publications. We excluded articles that were conference abstracts, pilot studies, and trial protocols.

Two authors (B.S and J.B) independently reviewed and extracted study information according to a standardised form in data management tool REDCap.[11] This included assessment of the compliance with the CONSORT 2010 extension for NI trials, focusing on

methodological and reporting quality of NI trials. In addition, we developed a scoring system to evaluate the quality of reporting based on the CONSORT 2010 extension for NI trials[5] . Recommendations with multiple components were separated so each item addressed a single reporting element. Each item was assigned one point. Two additional items were included, each worth 2 points: 1) consistency between the significance level of the confidence interval and the specified type I error rate, and 2) number of analyses performed on the primary outcome. The total possible score was 20. Studies were classified as having excellent reporting quality if scored 16-20 points, good if 11-15, fair if 6-10, and poor if 0-5. Data was extracted from supplementary materials if they were referenced in the articles. Disagreements not resolved by consensus were adjudicated by a third author (S.C).

Categorical variables are reported as frequencies and proportions. We assessed associations between trial quality and year of publication (before and after the publication of the CONSORT 2010 extension for NI trials), journal impact factor, trial registration, and conclusion declared by authors by using Fisher's exact test. P-value of less than 0.05 was considered statistically significant. All analyses were performed using Stata Statistical Software, Release 18.0.

Results

Study characteristics

We conducted database searches on 14 September, 2020 and 8 February, 2025, and identified 491 records. We excluded 438 records and retrieved and reviewed 53 full articles. We further excluded 9 records after full review as they were not randomised controlled trials, they were conference abstracts, they were not main publications, the transplants were not kidney-only, or they were duplicate records, resulting in the total of 44 articles (Figure 2).

Characteristics of the included studies are summarised in Table 1. Six studies (14%) were published prior to 2010, 16 (36%) between 2010 and 2014, 13 (30%) between 2015 and 2019, and 9 (20%) between 2020 and 2024. The most frequent journal of publication was the American Journal of Transplantation (n=16, 36%). Fifty-nine percent of the trials were sponsored by industry (n=26), with another 5% reporting mixed sponsorship (n=2). Twenty-five trials (57%) were phase III/IV, 38 (86%) were conducted across multiple centres and 18 (41%) were multinational. The most common study design utilised a single intervention arm compared with an active control arm (n=26, 59%).

Thirty-seven (84%) studies evaluated a novel induction or maintenance immunosuppression regimen. The remaining intervention types are detailed in Table 1. Of the trials evaluating an immunosuppressive regimen the most common primary endpoint was a categorical composite of efficacy failure (n=17, 39%), which included biopsy proven acute rejection

(BPAR) along with different combinations of graft loss, death, graft dysfunction (defined by an estimated glomerular filtration rate, eGFR, cutoff) and loss to follow-up.

Quality of study methods

Control arm and analysis set

Details on the quality of study methods and reporting are presented in Table 2. Six trials (14%) used a non-standard treatment and 1 trial (2%) used a novel treatment as the control arm instead of standard-of-care. Just over half the papers (n=23) made some reference to evidence that the chosen active control was the most effective standard of care. Only four trials with medicinal interventions referred to evidence that the dose of their active control was optimal and a further six stated that they used the optimal dose without justification.

Fifty-seven percent of the studies reported results based on a single type of analysis only – either intention-to-treat (ITT) or modified intention-to-treat analysis (n=22) or per-protocol (PP) analysis (n=3). Only 19 (43%) trials reported more than one type of analysis for the primary outcome.

Non-Inferiority Margin

Seventy percent (n=31) of the trials did not provide any justification for the non-inferiority margin. Among those that did, the reported justification included clinical reasoning (n=5), margins used in other similar trials (n=6), pretrial collaboration with a regulatory agency (n=3), and statistical considerations (n=2). Four studies (9%) based their margin on multiple factors. One study reported the margin only in supplementary material[12] and another not at all[13] .

Studies with a continuous primary outcome (n=12) had non-inferiority margins based on difference of the mean or median between groups. Of the studies with a categorical primary outcome (n=32), nearly all (n=30) used absolute risk reduction (ARR) as the non-inferiority margin, while one study used an odds ratio and one did not specify the type of margin used. Close to half of these studies (n=15) used a NI margin of 10% ARR, including studies whose primary outcome was graft and/or patient survival as well as those with an efficacy composite including BPAR.

An ARR non-inferiority margin must be viewed in relation to the predicted and observed event rate in the control group to understand what relative loss of efficacy is proposed to be clinically acceptable. Table 4 shows the calculated relative risk (RR) margins for those studies employing an ARR margin; the calculated RR margins range from 1.2 to 4.3 (mean 1.9). Eighteen of these studies overestimated the primary event rate in the control group by a mean of 31% (range 4 to 80%). Thus, the ARR margin in many cases represents an even

greater relative loss of efficacy compared to the observed control event rate; mean 2.62, range 1.22 to 12.1.

Power and Sample Size Calculation

Fourteen percent of the studies did not report the power (n=6). Sixteen percent of the studies had power below 80% (n=7). The majority of studies had power between 80% to 90% (n=18, 41%).

Twelve studies (27%) did not report the overall Type I error rate used for sample size calculation. Among those studies that reported the Type I error rate, 12 of the studies (28%) did not report whether the Type I error rate was one sided or two sided. Forty-three percent of the studies did not report the confidence interval used for sample size calculation (n=19). Another nine percent reported the confidence interval used but failed to provide information on whether it was two-sided or one-sided (n=4).

When calculating the sample size, 36% of the studies adjusted for loss to follow-up (n=16). None of the studies considered the duration or minimum or maximum period of recruitment and follow-up when determining sample size.

Thirty percent (n=13) of the studies did not report the assumed control arm outcome used for sample size calculation. Fifty-seven percent of the studies did not report the assumed true difference between the treatment and control (n=25). Fourteen percent of the studies did not report whether the sample size calculation took into account the non-inferiority margin (n=6). Only forty-one percent of studies reported sample size calculations that can be reproduced by the reader (n=18).

Missing data and Sensitivity analysis

Two studies had withdrawal and noncompliance rates exceeding 60%, five studies 40-60%, and 24 studies 20-40%. The top reasons for withdrawal and noncompliance include adverse events, unsatisfactory therapeutic effect, administrative problems and withdrawal of consent. Despite the high withdrawal and noncompliance rate, eighty-four percent of the studies did not report use of a method to account for missing data (n=37). The majority of the studies did not include sensitivity analyses (n=27, 61%).

Quality of reporting

Quality of reporting according to the CONSORT 2010 is presented in Table 3.

Title and Introduction

Only 6 studies (14%) explicitly identified themselves as NI trials in the title. Twenty-one studies (48%) did not specify a non-inferiority hypothesis in the introduction, while 20 studies (45%) did not report a rationale for selecting a non-inferiority design.

Reference Treatment and Population

Ninety-three percent of the studies did not report whether their participants were similar to those in prior trials establishing the reference treatment's efficacy (n=41), and fifty-nine percent of the studies failed to provide any evidence that the reference treatment was similar to those used in previous efficacy trials (n=26).

Outcome and Hypothesis

Two studies (5%) did not clearly specify their non-inferiority outcome and primary hypotheses. The majority of studies did not report whether the outcomes were similar to those used in prior trials that had established the treatment efficacy of the current standard of care (n=32, 73%).

Interim Analyses and Stopping Guidelines

Reporting of interim analyses were limited. Only 8 studies (18%) mentioned conducting interim analyses, and 7 studies (17%) clarified the outcomes to which these analyses applied. Six studies (14%) specified whether the interim analyses were related to a non-inferiority hypothesis.

Stopping guidelines were mentioned in 5 studies (11%), with 4 studies (9%) clarifying which outcomes the stopping guidelines applied to and whether they were related to the non-inferiority hypothesis.

Statistical Approach and Interpretation

Nearly half of the studies did not report whether a one-sided or two-sided confidence interval approach was used for the primary outcome, which is critically important for result interpretation in a NI trial (n=20, 45%). Only 5 studies (11%) included a graph showing both the confidence intervals and the non-inferiority margin.

Study conclusion

Sixty-four percent of studies (n=28) declared the intervention was noninferior to control and nine percent (n=4) declared that non-inferiority was not shown (also labelled as 'inconclusive'). Seven percent (n=3) concluded that the intervention was either statistically superior[14] or inferior[15,16] to the control treatment. Twenty percent (n=9) declared none of the above standard conclusions of non-inferiority trial methodology. These non-standard conclusions included 'no difference' or 'no statistically significant difference' (n=6, 13%)[17–22], and that the intervention was 'comparable to' (n=2, 5%)[23,24] or 'not appreciably worse than' (n=1, 2%)[25] control.

The correct conclusion could not be determined based on information provided in the article in nine studies (20%). The conclusion provided was incorrect in thirteen studies (30%); most often a claim of some sort of equivalence when the true result was non-inferiority not shown[17,18,23] or not enough information was provided to determine the true result[20–22,24,26,27] (Figure 3). Seven of these studies[17,18,20–22,26,27] quoted a non-significant p-value from a superiority test to support their claim of equivalence of the intervention to control. Of the remaining four studies with incorrect conclusions, two[28,29] concluded only non-inferiority not shown when in fact the intervention was statistically inferior to the control based on the primary outcome and two[19,25] used other statements of equivalence when a conclusion of non-inferiority was appropriate.

Quality grading of non-interiority trials

According to the quality grading system of NI trials, 9% of the studies had poor quality (n=4), 45% fair quality (n=20), 39% good quality (n=17) and 7% excellent quality (n=3) (Table 3).

We combined poor and fair grading into one category, and good and excellent grading into another category due to the small number in some categories. We found no evidence of better quality grade for studies published after 2012, the year CONSORT 2010 was published, compared to studies published before 2012 (p=0.17). The mean impact factor of journals publishing articles in this review was 9. Fifty-seven percent of the studies published in a journal with an impact factor of 9 or higher classified as "good or excellent" compared to 44 percent in journals with an impact factor lower than 9 (p=0.69). However, studies drawing an incorrect conclusion or not providing sufficient information to determine the conclusion were equally represented between lower and higher impact journals. There is no evidence that declaring non-inferiority was associated with better or worse quality grade (p=0.34). Excluding those with mixed sponsorship, having an industry sponsor was not associated with quality grade (p=0.94). Investigator-led studies were more likely to declare an incorrect conclusion or fail to provide enough information to determine the conclusion (n=10, 63%) compared to industry sponsored studies (n= 6, 23%) (p=0.03).

Discussion

Non-inferiority trials are essential to advance care in kidney transplantation, as established treatments exist and placebo-controlled trials are ethically challenging. No trial in the past 40 years has demonstrated superiority over standard of care in the key primary endpoints of patient and graft survival, however new therapies have potential advantages in side-effect profile, incidence of complications, convenience and cost. NI trials are therefore well suited for this purpose. However, design and interpretation of NI trials is more nuanced than superiority trials. Our systematic review has highlighted major deficiencies in the design, conduct and reporting of NI trials in kidney transplantation which affect the validity and interpretability of the evidence generated. Key concerns include: 1) Failure to justify the choices of active control therapy and acceptable NI margins; 2) Pervasive use of absolute risk reduction NI margins that equate to very high loss of efficacy on the relative scale; 3) inadequate methods to handle missing data and the sole use of ITT analysis to determine primary efficacy, both of which create bias in favour of non-inferiority; and 4) frequent failure to interpret and report results in relation to the non-inferiority hypothesis. We found poor compliance with CONSORT 2010 recommendations and no improvement of quality after the publication of CONSORT 2010.

Selection of the optimal standard of care active control is fundamental to the clinical relevance of NI trial results. This should be based on evidence from previous randomized trials that proved the efficacy of standard of care over placebo.[3,6,30,31] Failure to observe this principle leads to 'biocreep' where newer less effective treatments gradually become accepted.[32,33] In this review 16% of the trials used a non-standard or even novel treatment as active control. Furthermore, only half of studies made any reference to evidence that

their active control was the most effective standard of care. While the components of standard of care immunosuppression in kidney transplant have remained broadly unchanged for over two decades there has been evolution in formulations and dose and variation in practise between centres persists.[34,35] Only four immunosuppression trials in this review made any attempt to justify the doses of their active control.

The investigator-defined NI margin represents the worst-case loss of efficacy that is considered clinically acceptable for a new treatment compared to standard of care. Guidelines suggest the NI margin must be justified based on clinical judgement and where possible statistical reasoning.[3,6,8] Clinical judgement, ideally by expert consensus, is essential to decide what loss of efficacy can be tolerated considering the potential ancillary benefits of the novel therapy.[8,36] The few studies in this review where justification on clinical grounds was attempted did so vaguely and with few details about how this determination was reached. If applying a statistical approach it is essential to know the treatment effect of the active control compared to placebo. Regulatory guidelines recommend that NI margins should not exceed the lower bound of the 95% CI of the active control's effect size.[6,8] This is challenging in kidney transplantation due to lack of placebo-controlled trials testing the effect of each component of standard of care and indeed none of the trials in this review attempted such an analysis to justify their NI margin. Overall, the proportion of studies in this review who neglected to provide any justification at all for the NI margin is striking and more so, the clear lack of clinical judgement that is evident in some choices. For example, the use of the same absolute risk reduction margin of 10% in studies

with primary outcomes of disparate clinical frequencies and importance such as graft survival and BPAR composites.

The near universal use of absolute risk reduction NI margins in kidney transplant NI trials with categorical outcomes fails to account for potential loss of efficacy on the relative scale.[37] As shown in table 4 this results in trials pre-specifying that a novel therapy will be considered non-inferior if it is anywhere from 1.2 to 4.3 times worse than standard of care. This considerably reduces the clinical relevance of declarations of non-inferiority in this evidence base. This issue is accentuated by the frequent overestimation of control group event rates leading to further inflation of the tolerated loss of efficacy relative to standard of care. Overall, generous NI margins in these studies introduce a strong bias toward conclusions of non-inferiority thus risking adoption of inferior therapies and worse patient outcomes.

We found high dropout and nonadherence rates in the trials under review, with 70% of trials exceeding 20%. Unlike in superiority trials, PP analysis is usually the more conservative option in NI trials as ITT analysis will create bias toward a finding of non-inferiority in the setting of frequent protocol breaches where participants are more likely to cross-over to standard of care regimens. Ultimately, both ITT and PP analyses have biases in different contexts and most NI trial guidelines recommend both be performed and the results compared.[1,5,6] Concerningly given the high rates of protocol breaches and drop out, the large majority of trials here (50%) used ITT alone to determine primary efficacy, less than

half reported a PP analysis and 84% did not describe a method of accounting for missing data.

Finally, and perhaps most concerningly, over a quarter of trials in this review failed to report accurate conclusions according to NI trial methodology. As shown in figure 3, the acceptable conclusions from a non-inferiority trial are noninferiority, non-inferiority not shown (inconclusive) and superior or inferior. Nine studies in this review instead concluded with other statements of equivalence such as saying the treatments were comparable or not statistically different (based on a p value > 0.05 from a superiority test). Nine studies claimed non-inferiority or some other type of equivalence when in fact non-inferiority was not shown or not enough information was provided to determine the true outcome.

We are the first study to systematically evaluate the design and reporting of NI trials in kidney transplantation. The deficiencies we have identified in some domains such as justification of the NI margin and use of ITT and PP analysis are similar to those identified in systematic reviews of NI trials in other fields including oncology, cardiology and infectious diseases[38–41] . However, the rate of potentially misleading study conclusions reported here is higher than other studies (30% vs. 6-15%).[38,40,41] The pitfalls of using an absolute risk reduction NI margin have been noted previously across several specialties[37,42] but the degree of inflation of the margin on the relative scale seen here is particularly notable.

In terms of limitations of our systematic review, firstly, trial authors may be constrained by article word limits from presenting a full description and justification of their methods, however, we did extract data from supplementary material where available. Secondly, our analysis was restricted to kidney transplantation, limiting the generalisability of our findings to other fields. Finally, despite a rigorously designed search strategy, it is possible that some studies were not captured and missed.

In conclusion, our findings highlight major deficiencies in the design and reporting of NI trials in kidney transplantation. Despite the availability of guidelines, the quality of NI trials has not improved over time. These flaws can lead to misleading conclusions, potentially endorsing less effective treatments and compromising patient care. Clinical trialists and journal editors alike need to be more aware of the methodological complexities and common pitfalls in the design and reporting of NI trials. Higher journal impact factors were not associated with better study quality, highlighting the need for higher editorial standards in promoting rigorous trial methodology and providing incentives to trialists to improve design quality.

References

1. Rehal, S., Morris, T. P., Fielding, K., Carpenter, J. R., & Phillips, P. P. J. (2016). Non-inferiority trials: are they inferior? A systematic review of reporting in major medical journals. *BMJ Open*, *6*(10), e012594. https://doi.org/10.1136/bmjopen-2016-012594

2. Murthy, V. L., Desai, N. R., Vora, A., & Bhatt, D. L. (2012). Increasing Proportion of Clinical Trials Using Noninferiority End Points. *Clinical Cardiology*, *35*(9), 522–523. https://doi.org/10.1002/clc.22040

3. Mauri, L., & D'Agostino, R. B. (2017). Challenges in the Design and Interpretation of Noninferiority Trials. *New England Journal of Medicine*, *377*(14), 1357–1367. https://doi.org/10.1056/nejmra1510063

4. Piaggio, G., Elbourne, D. R., Altman, D. G., Pocock, S. J., Evans, S. J. (2006). Reporting of Noninferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement. *JAMA*, *295*(10), 1152–1160. https://doi.org/10.1001/jama.295.10.1152

5. Piaggio, G., Elbourne, D. R., Pocock, S. J., Evans, S. J. W., Altman, D. G. (2012). Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT 2010 Statement. *JAMA*, *308*(24), 2594. https://doi.org/10.1001/jama.2012.87802

6. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, & Center for Biologics Evaluation and Research. (2016). *Non-Inferiority Clinical Trials to Establish Effectiveness Guidance for Industry*. https://www.fda.gov/media/78504/download

7. Committee for Proprietary Medicinal Products (CPMP). (2001). Points to consider on switching between superiority and non-inferiority. *British Journal of Clinical Pharmacology*, *52*(3), 223–228. https://doi.org/10.1046/j.1365-2125.2001.01397-3.x

8. Committee for Medicinal Products for Human Use (CHMP). (2006). Guideline on the choice of the non-inferiority margin. *Statistics in Medicine*, *25*(10), 1628–1638. https://doi.org/10.1002/sim.2584

9. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (1998). *Statistical Principles for Clinical Trials E9*. https://database.ich.org/sites/default/files/E9_Guideline.pdf

10. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (2000). *Choice of Control Group and Related Issues in Clinical Trials E10*. https://database.ich.org/sites/default/files/E10_Guideline.pdf

11. Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

12. Gaston, R. S., Kaplan, B., Shah, T., Cibrik, D., Shaw, L. M., Angelis, M., Mulgaonkar, S., Meier-Kriesche, H.-U., Patel, D., & Bloom, R. D. (2009). Fixed- or Controlled-Dose Mycophenolate Mofetil with Standard- or Reduced-Dose Calcineurin Inhibitors: The Opticept Trial. *American Journal of Transplantation*, *9*(7), 1607–1619. https://doi.org/10.1111/j.1600-6143.2009.02668.x

13. Ju, M. K., Huh, K. H., Park, K. T., Kim, S. J., Cho, B. H., Kim, C. D., So, B. J., Kang, C. M., Lee, S., Joo, D. J., & Kim, Y. S. (2013). Mizoribine Versus Mycophenolate Mofetil in Combination Therapy With Tacrolimus for De Novo Kidney Transplantation: Evaluation of Efficacy and Safety. *Transplantation Proceedings*, *45*(4), 1481–1486. https://doi.org/10.1016/j.transproceed.2012.12.028

14. Malinoski, D., Saunders, C., Swain, S., Groat, T., Wood, P. R., Reese, J., Nelson, R., Prinz, J., Kishish, K., Walker, C. V. D., Geraghty, P. J., Broglio, K., & Niemann, C. U. (2023). Hypothermia or Machine Perfusion in Kidney Donors. *New England Journal of Medicine*, *388*(5), 418–426. https://doi.org/10.1056/nejmoa2118265

15. Novoa, P. A., Grinyó, J. M., Ramos, F. J. P., Errasti, P., Franco, A., Aldana, G., Pefaur, J., Marti-Cuadros, A. M., Otero, A. B., Saval, N., & Oppenheimer, F. (2011). De Novo Use of Everolimus With Elimination or Minimization of Cyclosporine in Renal Transplant Recipients. *Transplantation Proceedings*, *43*(9), 3331–3339. https://doi.org/10.1016/j.transproceed.2011.10.032

16. Silva, H., Yang, H., Abouljoud, M., Kuo, P., Wisemandle, K., Bhattacharya, P., Dhadda, S., Holman, J., Fitzsimmons, W., First, M. R., & Group, T. E.-R. D. N. K. S. (2007). One-Year Results with Extended-Release Tacrolimus/MMF, Tacrolimus/MMF and Cyclosporine/MMF in De Novo Kidney Transplant Recipients. *American Journal of Transplantation*, *7*(3), 595–608. https://doi.org/10.1111/j.1600-6143.2007.01661.x

17. Krämer, B. K., Charpentier, B., Bäckman, L., Jr, H. T. S., Mondragon-Ramirez, G., Cassuto-Viguier, E., Mourad, G., Sola, R., Rigotti, P., Mirete, J. O., & Group, for the T. P. R. R. S. (2010). Tacrolimus Once Daily (ADVAGRAF) Versus Twice Daily (PROGRAF) in De Novo

Renal Transplantation: A Randomized Phase III Study. *American Journal of Transplantation*, *10*(12), 2632–2643. https://doi.org/10.1111/j.1600-6143.2010.03256.x

18. Moes, A. D., Hesselink, D. A., Meiracker, A. H. van den, Zietse, R., & Hoorn, E. J. (2017). Chlorthalidone Versus Amlodipine for Hypertension in Kidney Transplant Recipients Treated With Tacrolimus: A Randomized Crossover Trial. *American Journal of Kidney Diseases*, *69*(6), 796–804. https://doi.org/10.1053/j.ajkd.2016.12.017

19. Sabé, N., Oriol, I., Melilli, E., Manonelles, A., Bestard, O., Polo, C., Arcos, I. L., Perelló, M., Garcia, D., Riera, L., Tebé, C., Len, Ò., Moreso, F., Cruzado, J. M., & Carratalà, J. (2019). Antibiotic Treatment Versus No Treatment for Asymptomatic Bacteriuria in Kidney Transplant Recipients: A Multicenter Randomized Trial. *Open Forum Infectious Diseases*, *6*(6), ofz243. https://doi.org/10.1093/ofid/ofz243

20. Sandwijk, M. S. van, Vries, A. P. J. de, Bakker, S. J. L., Berge, I. J. M. ten, Berger, S. P., Bouatou, Y. R., Fijter, J. W. de, Florquin, S., Heide, J. J. H. van der, Idu, M. M., Krikke, C., Pant, K. A. M. I. van der, Reinders, M. E., Ringers, J., Weerd, N. C. van der, Bemelman, F. J., & Sanders, J.-S. S. (2018). Early Steroid Withdrawal Compared With Standard Immunosuppression in Kidney Transplantation - Interim Analysis of the Amsterdam-Leiden-Groningen Randomized Controlled Trial. *Transplantation Direct*, *4*(6), e354. https://doi.org/10.1097/txd.0000000000000794

21. Smith, M. P. W., Cherukuri, A., Newstead, C. G., Lewington, A. J. P., Ahmad, N., Menon, K., Pollard, S. G., Prasad, P., Tibble, S., Giddings, E., & Baker, R. J. (2013). Alemtuzumab Induction in Renal Transplantation Permits Safe Steroid Avoidance with Tacrolimus

Monotherapy. *Transplantation Journal*, *96*(12), 1082–1088. https://doi.org/10.1097/tp.0b013e3182a64db9

22. Bestard, O., Meneghini, M., Crespo, E., Bemelman, F., Koch, M., Volk, H. D., Viklicky, O., Giral, M., Banas, B., Ruiz, J. C., Melilli, E., Hu, L., Duivenvoorden, R. van, Nashan, B., Thaiss, F., Otto, N. M., Bold, G., Stein, M., Sefrin, A., … Grinyó, J. M. (2021). Preformed T cell alloimmunity and HLA eplet mismatch to guide immunosuppression minimization with tacrolimus monotherapy in kidney transplantation: Results of the CELLIMIN trial. *American Journal of Transplantation*, *21*(8), 2833–2845. https://doi.org/10.1111/ajt.16563

23. Vincenti, F., Schena, F. P., Paraskevas, S., Hauser, I. A., Walker, R. G., Grinyo, J., & Group, on behalf of the F. S. (2008). A Randomized, Multicenter Study of Steroid Avoidance, Early Steroid Withdrawal or Standard Steroid Therapy in Kidney Transplant Recipients. *American Journal of Transplantation*, *8*(2), 307–316. https://doi.org/10.1111/j.1600-6143.2007.02057.x

24. Russ, G. R., Tedesco-Silva, H., Kuypers, D. R., Cohney, S., Langer, R. M., Witzke, O., Eris, J., Sommerer, C., Zur-Mühlen, B. von, Woodle, E. S., Gill, J., Ng, J., Klupp, J., Chodoff, L., & Budde, K. (2013). Efficacy of Sotrastaurin Plus Tacrolimus After De Novo Kidney Transplantation: Randomized, Phase II Trial Results. *American Journal of Transplantation*, *13*(7), 1746–1756. https://doi.org/10.1111/ajt.12251

25. Okumi, M., Unagami, K., Furusawa, M., Kakuta, Y., Iizuka, J., Takagi, T., Shirakawa, H., Shimizu, T., Omoto, K., Inui, M., Ishida, H., & Tanabe, K. (2018). Once-daily versus twice-daily tacrolimus for de novo living kidney transplantation patients including ABO/HLA

compatible and incompatible: A randomized trial. *Clinical Transplantation*, *32*(12), e13423. https://doi.org/10.1111/ctr.13423

26. Páez-Vega, A., Gutiérrez-Gutiérrez, B., Agüera, M. L., Facundo, C., Redondo-Pachón, D., Suñer, M., López-Oliva, M. O., Yuste, J. R., Montejo, M., Galeano-Álvarez, C., Millan, J. C. R.-S., Los-Arcos, I., Hernández, D., Fernández-Ruiz, M., Muñoz, P., Valle-Arroyo, J., Cano, A., Rodríguez-Benot, A., Crespo, M., … Bardají, B. (2021). Immunoguided Discontinuation of Prophylaxis for Cytomegalovirus Disease in Kidney Transplant Recipients Treated With Antithymocyte Globulin: A Randomized Clinical Trial. *Clinical Infectious Diseases*, *74*(5), 757–765. https://doi.org/10.1093/cid/ciab574

27. Stevens, R. B., Wrenshall, L. E., Miles, C. D., Farney, A. C., Jie, T., Sandoz, J. P., Rigley, T. H., & Gaber, A. O. (2016). A Double-Blind, Double-Dummy, Flexible-Design Randomized Multicenter Trial: Early Safety of Single- Versus Divided-Dose Rabbit Anti-Thymocyte Globulin Induction in Renal Transplantation. *American Journal of Transplantation*, *16*(6), 1858–1867. https://doi.org/10.1111/ajt.13659

28. Ooms, L. S. S., Minnee, R. C., Dor, F. J. M. F., Kimenai, D. J. A. N., Tran, K. C. K., Hartog, H., Wetering, J. van de, Willemsen, S. P., IJzermans, J. N. M., & Terkivatan, T. (2020). Stenting the ureteroneocystostomy reduces urological complications in kidney transplantation: a noninferiority randomized controlled trial, SPLINT trial. *Transplant International*, *33*(10), 1190–1198. https://doi.org/10.1111/tri.13638

29. Sommerer, C., Suwelack, B., Dragun, D., Schenker, P., Hauser, I. A., Witzke, O., Hugo, C., Kamar, N., Merville, P., Junge, M., Thaiss, F., Nashan, B., Group, A. S., Almartine, E., Dantal, J., Dragun, D., Feldkamp, T., Hauser, I. A., Hazzan, M., … Witzke, O. (2019). An

open-label, randomized trial indicates that everolimus with tacrolimus or cyclosporine is comparable to standard immunosuppression in de novo kidney transplant patients. *Kidney International*, *96*(1), 231–244. https://doi.org/10.1016/j.kint.2019.01.041

30. D'Agostino, R. B., Massaro, J. M., & Sullivan, L. M. (2003). Non-inferiority trials: design concepts and issues – the encounters of academic consultants in statistics. *Statistics in Medicine*, *22*(2), 169–186. https://doi.org/10.1002/sim.1425

31. Treadwell, J. R., Uhl, S., Tipton, K., Shamliyan, T., Viswanathan, M., Berkman, N. D., Sun, X., Coleman, C. I., Elshaug, A. G., Singh, S., Wang, S.-Y., & Ramakrishnan, R. (2012). Assessing equivalence and noninferiority. *Journal of Clinical Epidemiology*, *65*(11), 1144–1149. https://doi.org/10.1016/j.jclinepi.2012.05.001

32. Fleming, T. R. (2008). Current issues in non-inferiority trials. *Statistics in Medicine*, *27*(3), 317–332. https://doi.org/10.1002/sim.2855

33. Schumi, J., & Wittes, J. T. (2011). Through the looking glass: understanding non-inferiority. *Trials*, *12*(1), 106. https://doi.org/10.1186/1745-6215-12-106

34. Axelrod, D. A., Naik, A. S., Schnitzler, M. A., Segev, D. L., Dharnidharka, V. R., Brennan, D. C., Bae, S., Chen, J., Massie, A., & Lentine, K. L. (2016). National Variation in Use of Immunosuppression for Kidney Transplantation: A Call for Evidence-Based Regimen Selection. *American Journal of Transplantation*, *16*(8), 2453–2462. https://doi.org/10.1111/ajt.13758

35. Kaufman, D. B., Shapiro, R., Lucey, M. R., Cherikh, W. S., Bustami, R. T., & Dyke, D. B. (2004). Immunosuppression: practice and trends. *American Journal of Transplantation*, *4*, 38–53. https://doi.org/10.1111/j.1600-6135.2004.00397.x

36. Archdeacon, P., Dixon, C., Belen, O., Albrecht, R., & Meyer, J. (2012). Summary of the US FDA Approval of Belatacept. *American Journal of Transplantation*, *12*(3), 554–562. https://doi.org/10.1111/j.1600-6143.2011.03976.x

37. Pong, S., Urner, M., Fowler, R. A., Mitsakakis, N., Seto, W., Hutchison, J. S., Science, M., & Daneman, N. (2021). Testing for non-inferior mortality: a systematic review of non-inferiority margin sizes and trial characteristics. *BMJ Open*, *11*(4), e044480. https://doi.org/10.1136/bmjopen-2020-044480

38. Bai, A. D., Komorowski, A. S., Lo, C. K. L., Tandon, P., Li, X. X., Mokashi, V., Cvetkovic, A., Kay, V. R., Findlater, A., Liang, L., Loeb, M., & Mertz, D. (2020). Methodological and Reporting Quality of Noninferiority Randomized Controlled Trials Comparing Antibiotic Therapies: A Systematic Review. *Clinical Infectious Diseases*, *73*(7), e1696–e1705. https://doi.org/10.1093/cid/ciaa1353

39. Komorowski, A. S., Bai, A. D., Cvetkovic, A., Mourad, O., Lo, C. K. L., Li, X. X., Mokashi, V., Findlater, A., Duncan, D. B., Fuller, C., Yamamura, D., Mertz, D., & Group, M. I. D. F. R. (2022). Methodological and reporting quality of non-inferiority randomized controlled trials comparing antifungal therapies: a systematic review. *Clinical Microbiology and Infection*, *28*(5), 640–648. https://doi.org/10.1016/j.cmi.2021.11.003

40. Lo, C. K. L., Komorowski, A. S., Hall, C. W., Sandstrom, T. S., Alamer, A. A. M., Mourad, O., Li, X. X., Ohaly, R. A., Benoit, M.-È., Duncan, D. B., Fuller, C. A., Shaw, S., Suresh, M., Smaill, F., Kapoor, A. K., Smieja, M., Mertz, D., Bai, A. D., & Group, for the M. I. D. F. R. (2023). Methodological and Reporting Quality of Noninferiority Randomized Controlled Trials Comparing Antiretroviral Therapies: A Systematic Review. *Clinical Infectious Diseases*, *77*(7), 1023–1031. https://doi.org/10.1093/cid/ciad308

41. Henanff, A. L., Giraudeau, B., Baron, G., & Ravaud, P. (2006). Quality of Reporting of Noninferiority and Equivalence Randomized Trials. *JAMA*, *295*(10), 1147. https://doi.org/10.1001/jama.295.10.1147

42. Greco, A., Spagnolo, M., Laudani, C., Occhipinti, G., Mauro, M. S., Agnello, F., Faro, D. C., Legnazzi, M., Rochira, C., Scalia, L., & Capodanno, D. (2024). Assessment of Noninferiority Margins in Cardiovascular Medicine Trials. *JACC: Advances*, *3*(7), 101021. https://doi.org/10.1016/j.jacadv.2024.101021

Table 1. Characteristics of included studies

	Total N=44
	n (%)
Year of publication	
2005-09	6 (14)
2010-04	16 (36)
2015-19	13 (30)
2020-24	9 (20)
Journal	
American Journal of Transplantation	16 (36)
Transplantation	5 (11)
Transplantation Proceedings	4 (9)
New England Journal of Medicine	2 (5)
Other	17 (39)
Sponsor type	
Investigator-initiated	16 (36)
Industry	26 (59)
Mixed	2 (5)
Trial phase	
Phase I/II	16 (36)
Phase III/IV	25 (57)
Not reported	3 (7)
Number of study arms	
Two	26 (59)
Three	15 (34)
Four	3 (7)
Intervention type	
Drug/medicinal	41 (93)
Immunosuppression	37
Antimicrobial	3
Antihypertensive	1
Surgical/anaesthetic technique	2 (5)
Organ preservation	1 (2)
Number of participants recruited	
0-99	2 (5)
100-499	27 (61)
500-999	13 (30)
1000+	2 (5)
Region of recruitment	
Multinational/transcontinental	18 (41)
Europe	11 (25)
North America	8 (18)
Asia	7 (16)
Number of centres	
Single centre	6 (14)

Multicentre	38 (86)
Primary endpoint type	
Single continuous	12 (27)
eGFR	10
Blood pressure	1
Opiate usage	1
Single binary	12 (27)
Graft survival	1
BPAR	6
Infection	3
Delayed graft function	1
Nephrostomy insertion	1
Composite binary	20 (45)
Composite efficacy failure	17
Graft and patient survival	2
Infusion reaction composite	1
Blinding	
Double blinded	6 (14)
Partially blinded	2 (5)
Unblinded	36 (82)

Table 2. Summary of study methods and reporting

		Total N=44
		n (%)
Control arm	**What has the trial include as control**	
	Standard-of-care	37 (84)
	Non-novel treatment	6 (14)
	Novel treatment	1 (2)
Non-inferiority Margin	**Type of non-inferiority margin**	
	Absolute risk reduction	30 (68)
	Mean/Median difference	12 27)
	Odds ratio	1 (2)
	Not reported	1 (2)
	Justification attempted for non-inferiority margin*	13 (30)
	Clinical bases	5
	Results of previous study or same margin used in similar studies	6
	Reference to regulatory agency guidance/collaboration	3
	Statistical considerations	2
Analysis on primary outcome	**Analysis used to determine primary efficacy**	
	Intention-to-treat/modified intention-to-treat	22 (50)
	Per-protocol	3 (7)
	Intention-to-treat/modified intention-to-treat and per-protocol	17 (39)
	Intention-to-treat/modified intention-to-treat and as treated	1 (2)
	Intention-to-treat/modified intention-to-treat and observed case analysis	1 (2)
	Per-protocol analysis reported	20 (44)
	Per-protocol defined	14
	Number of analyses performed on the primary outcome	
	1	25 (57)
	2	19 (43)
Power and sample size calculation	**Power**	
	60-69%	4 (9)
	70-79%	3 (7)
	80-89%	18 (41)
	90% and over	13 (30)
	Not reported	6 (14)
	Overall Type I error rate used for sample size calculation	
	One-sided, 0.0125	1 (2)
	One-sided, 0.025	11 (25)
	One-sided, 0.05	2 (5)
	Two-sided, 0.05	6 (14)
	Unclear, 0.025	2 (5)
	Unclear, 0.05	10 (23)
	Not reported	12 (27)

	Overall confidence interval used for sample size calculation reported	25 (57)
	Sample size calculation taken into account the non-inferiority margin	38 (86)
	Loss to follow-up been adjusted for when calculating sample size	16 (36)
	Assumed control arm outcome used for sample size calculation specified	31 (70)
	Sample size calculation can be reproduced using the stats reported	18 (41)
Missing data	**Maximum dropout and premature trial discontinuation rates across study arms**	
	0-20%	13 (30)
	20-40%	24 (55)
	40-60%	5 (11)
	60-80%	2 (5)
	Method used to treat missing data	
	Last observation carried forward	2 (5)
	Multiple imputation	5 (11)
	No method used/not reported	37 (84)
	Number of sensitivity analysis performed	
	0	30 (68)
	1	9 (20)
	2	4 (9)
	3	1 (2)
	Sensitivity analysis	
	Patient population	5 (11)
	Adjusting for baseline variables	2 (5)
	Excluding protocol violations	1 (2)
	Missing data	5 (11)
	Other	7 (16)
	Unclear/not reported	27 (61)
Conclusions	**Is the authors' conclusion correct based on the information provided**	
	Yes	28 (64)
	No	13 (30)
	Not enough info provided	3 (7)
	Reported p-value for non-inferiority	8 (18)
	Confidence interval reported	
	One-sided, 95%	1 (2)
	One-sided, 97.5%	1 (2)
	Two-sided, 90%	4 (9)
	Two-sided 95%	27 (61)
	Two-sided 97.5%	2 (5)
	Two-sided, unclear	2 (5)
	No CI reported	7 (16)

*Studies using more than one justification counted multiple times

Table 3. Quality of the studies according to the quality grading of non-inferiority trials

Consort Item No.	Description	Total N=44	Score allocated
		n (%)	
	Title		
1a	Identification as a noninferiority randomized trial in the title	6 (14)	1
	Introduction		
2a	Reported the rationale for using a noninferiority design in the introduction	24 (55)	1
2b	Included hypothesis concerning non-inferiority specified in the introduction	23 (52)	1
2b	Non-inferiority margin specified	38 (86)	2
2b	Justification for the non-inferiority margin		
	Well justified	7 (16)	2
	Poorly justified	6 (14)	1
	Not justified	31 (70)	0
	Methods		
4a	Reported whether participants in the noninferiority trial are similar to those in any trial(s) that established efficacy of the reference treatment	3 (7)	1
5	Reported whether reference treatment in the trial is identical (or very similar) to that in any trial(s) that established efficacy	18 (41)	1
6a	Noninferiority outcome(s) specified (i.e. the primary outcome)	42 (95)	1
6a	Secondary outcomes specified and reported whether hypothesis for the secondary outcome is non-inferiority or superiority	5 (11)	1
6a	Reported whether the outcomes in the trial are identical (or very similar) to that in any trial(s) that established the efficacy of the reference treatment	12 (27)	1
7a	Reported whether the sample size was calculated using a noninferiority criterion	38 (86)	1
7b	Any interim analyses explained and reported to which outcome(s) they are applied and whether related to a non-inferiority hypothesis	6 (14)	1
12a	Reported whether a 1- or 2- sided confidence interval approach was used to compare groups for primary outcome	24 (55)	1
A1*	Consistency of the significance level of the confidence interval and type I error rate		
	Yes	19 (43)	1
	No	2 (5)	0
	Unclear	23 (52)	0
A2*	Number of analyses on the primary outcome		
	One	25 (57)	0

	Two	19 (43)	1
	Results		
17a	For outcomes for which non-inferiority hypothesized the effect size and confidence intervals provided	35 (80)	1
22	Interpret results in relation to the noninferiority hypothesis	29 (66)	2
	Overall quality determined by total scores		
	Excellent (16-20 out of 20)	3 (7)	
	Good (11-15 out of 20)	17 (39)	
	Fair (6-10 out of 20)	20 (45)	
	Poor (0-5 out of 20)	4 (9)	

Figure 1. Possible scenarios in non-inferiority trials

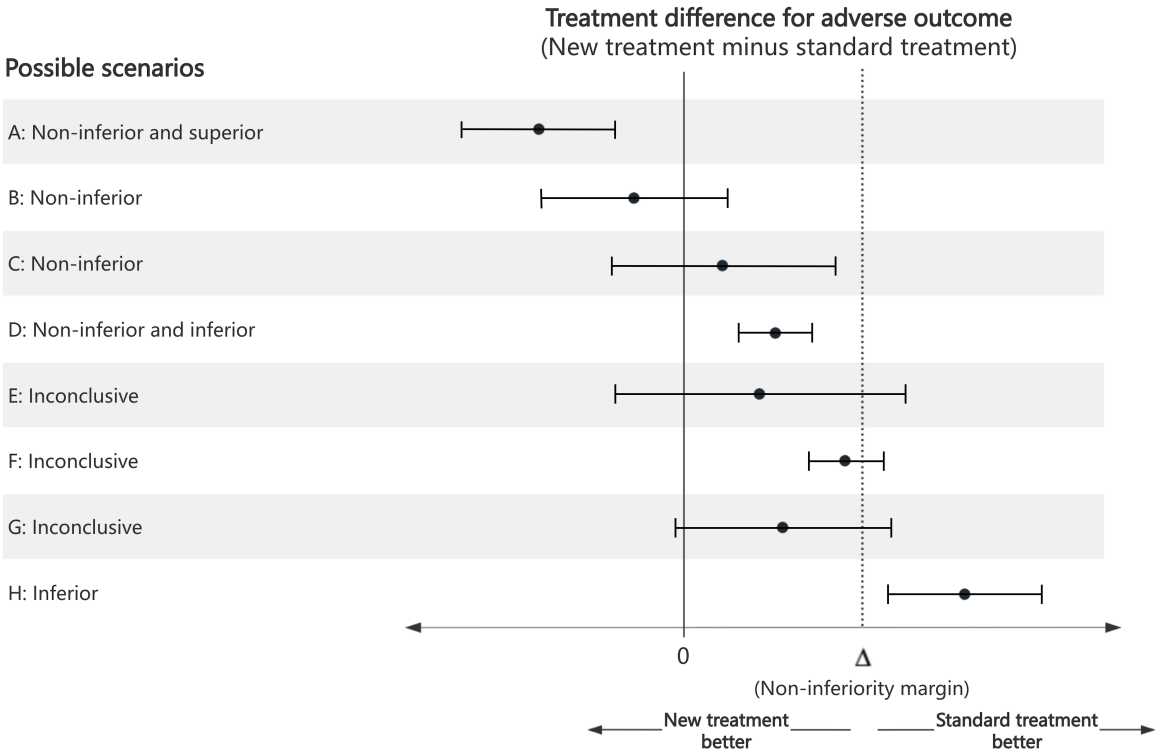


Figure 2. Study flowchart

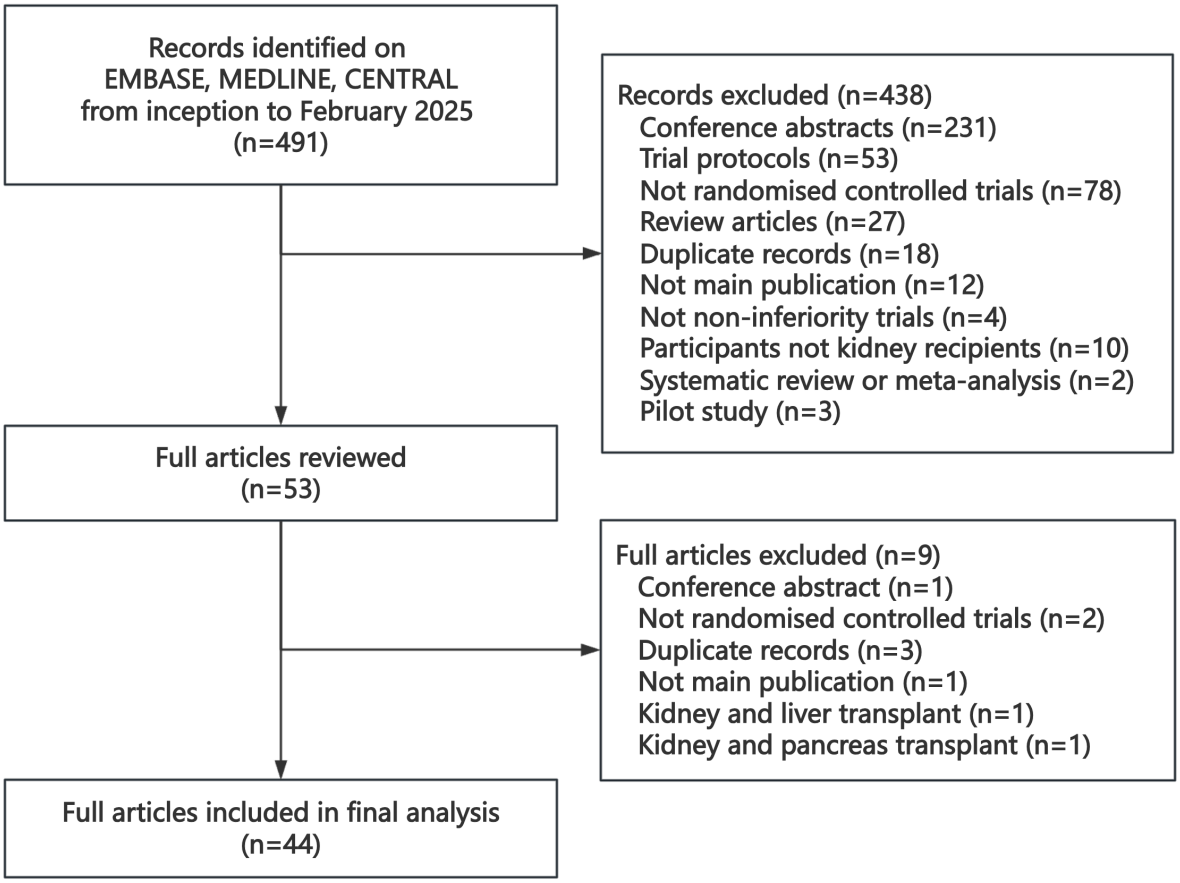
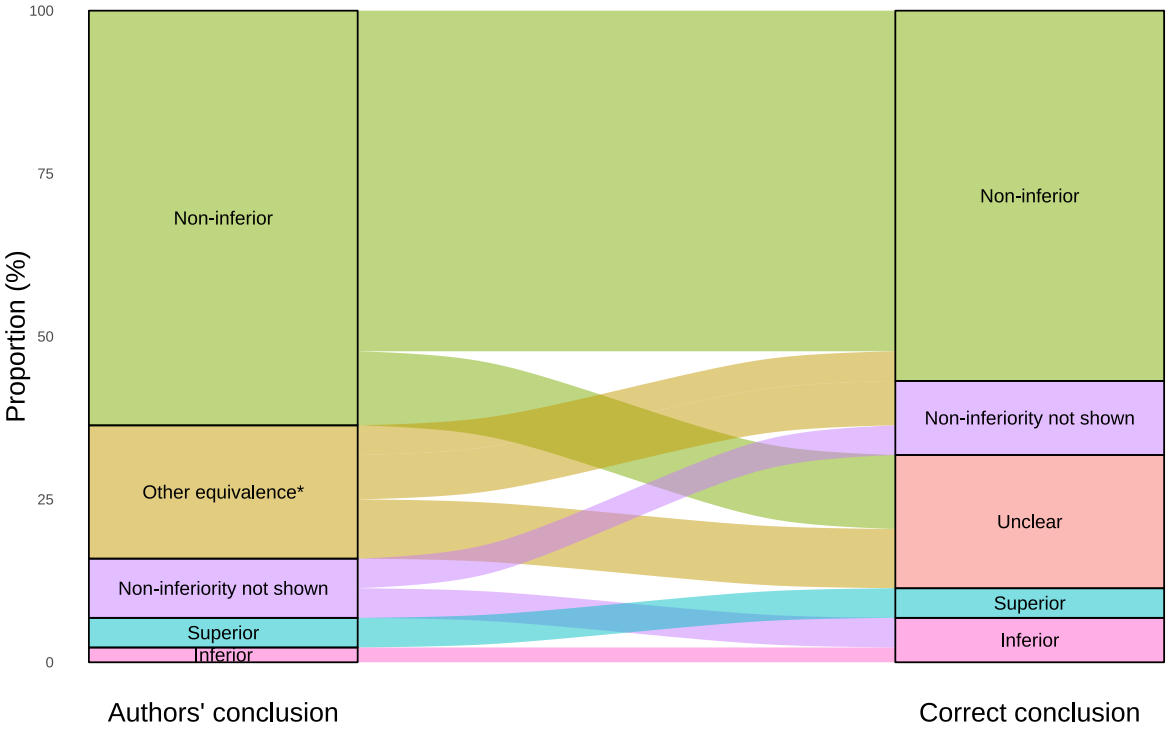


Figure 3. Evaluation of author's conclusions in non-inferiority trials in kidney transplantation



*Other statements of equivalence included "no statistically significant difference", "comparable" and "not appreciably worse".

CHAPTER 7

Discussion and future directions

Discussion and future directions

In this thesis, I have investigated two interrelated areas aimed at improving outcomes for kidney transplant recipients. The first focuses on understanding the evolving demographic and clinical characteristics of the transplant population and their implications for post-transplant outcomes. The second examines the quality and reliability of existing evidence used in kidney transplant research, which is fundamental to contemporary clinical decision-making and policy development. By addressing these aspects, this work provides insights into optimising recipient selection, refining clinical management strategies, and ensuring robust evidence to guide future research in transplantation.

In Chapter 2, I evaluated the accuracy of registry data by comparing demographic characteristics and clinical outcomes of kidney transplant recipients in the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) with those recorded in a large, multinational clinical trial. High levels of agreement were observed for key variables such as age, sex, donor type, graft outcomes, and mortality data, validating the reliability of registry data for research and clinical improvement. The comparison also revealed areas requiring improvement, specifically, moderate discrepancies in reporting of ethnicity and acute rejection. These results emphasise the importance of maintaining robust data definitions, improving classification consistency, and conducting periodic audits to ensure the integrity of registry-based research. As ANZDATA continues to serve as a cornerstone for clinical quality assurance and service provision in Australia and New Zealand, and also as a source of data for analyses that inform global practice and Practice Guidelines[1], assuring and strengthening the completeness and accuracy of its datasets will be crucial.

Chapter 3 addressed the pressing question of whether elderly patients, particularly those aged 70 and over, benefit from kidney transplantation compared to remaining on dialysis. Through a matched-pair design controlling for dialysis duration and diabetic status which are two important determinants of mortality, I demonstrated a clear long-term survival advantage for selected transplant recipients in this age group. Importantly, this benefit became evident after an initial period of increased post-transplant mortality, primarily attributed to infections. These findings reinforce the role of transplantation as a viable treatment for well-selected elderly candidates, consistent with international recommendations that age alone should not be a contraindication to transplantation.[1] However, the elevated early post-transplant mortality risk observed in older recipients underscores the need for tailored perioperative strategies designed to reduce infection risks, and for further research to identify risk markers that can refine candidate selection. These data may also be used to inform elderly transplant candidate expectations. Importantly, the results also define a time point where the expected benefits of kidney transplantation surpass that of remaining on dialysis, thereby providing useful guidance to both clinicians and patient expectations.

Chapter 4 examined the impact of obesity on transplant outcomes using a paired analysis of recipients of kidneys from the same donor. Obese recipients experienced a higher risk of delayed graft function, as well as increased rates of graft failure and death following deceased donor transplantation. By matching on donor characteristics and using a large bi-national registry cohort, this study adds clarity to previously inconsistent findings in the literature on transplant outcomes for obese recipients. Given the growing prevalence of

obesity among transplant candidates and the ethical constraints surrounding randomised studies in this context, the matched-pair methodology presented here offers a robust alternative to evaluate the association. Future research is urgently needed to inform best practices for the management of obese kidney transplant recipients. Key priorities include the development of targeted perioperative strategies to reduce early complications such as delayed graft function, as well as evaluation of structured weight-loss interventions before and after transplantation. Clinical trials and observational studies are required to assess the safety, feasibility, and long-term impact of approaches such as dietary counselling, and bariatric surgery in this high-risk population. Predictive models that incorporate both recipient and donor factors may help to identify obese candidates most likely to benefit from transplantation. This data may also be used to inform expectations of obese transplant candidates prior to transplantation.

In Chapter 5, I explored the relationship between obesity and cancer outcomes in the dialysis and transplant populations. Contrary to expectations based on general population studies, obesity was associated with a lower incidence of cancer and reduced cancer-related death among dialysis patients. This inverse association is consistent with previously identified associations between obesity and survival in the dialysis population, often referred to as reverse epidemiology. Such protection was particularly evident in specific cancer types, including oesophageal, colorectal, lip and oral cavity, prostate, lung, and bladder cancers, as well as lymphoma and multiple myeloma. As is evident for the general population, obesity remained positively associated with breast and uterine cancers. By modelling obesity and transplant status as time-varying covariates and using a competing risks statistical method, the analysis accounted for changes in exposure and competing

causes of death. While the biological mechanisms underlying these findings remain unclear, potential explanations include greater nutritional reserves, delayed onset of cancer-associated cachexia, and surveillance bias. Importantly, these results challenge assumptions that obesity is detrimental in patients with kidney failure and raise questions about the implications of weight loss recommendations in transplant candidates. Further research is needed to determine whether intentional weight loss improves or indeed may be harmful in this population.

Finally, in Chapter 6, I systematically evaluated non-inferiority (NI) trials in kidney transplantation. These trials are critical for assessing novel therapies where superiority over placebo is not ethically and/or pragmatically feasible. Despite the widespread use of NI designs in this field, my review identified substantial shortcomings in trial methodology, including insufficient justification of non-inferiority margins, inconsistent analytic approaches to missing data, and inadequate interpretation of findings within the NI framework. Compliance with established reporting standards, such as the CONSORT 2010 extension, was limited. Concerningly, there was no significant improvement over time, nor was quality associated with journal impact factor. These deficiencies may undermine the credibility of NI trials and risk supporting the approval of less effective therapies. Addressing these issues through stricter editorial review, clearer regulatory guidelines, and improved education to clinicians and trialists is essential for improving the quality and validity of evidence generated through NI trials in kidney transplantation.

Together, the findings presented in this thesis highlight both opportunities and limitations of using large-scale registry data to evaluate clinical outcomes in kidney transplantation.

While the ANZDATA Registry provides a powerful platform for population-based observational research, its credibility and use can be significantly enhanced through systematic data linkage with hospital databases, cancer and death registries and regular audit. The results of my registry analyses presented here underscore the need for more nuanced clinical decision-making tools, particularly for groups with complex risk profiles such as elderly or obese transplant candidates. Developing individualised risk stratification models that incorporate both recipient and donor characteristics may improve transplant eligibility assessment and optimise long-term outcomes. These tools could also help prioritise resources and tailor perioperative strategies to patient-specific risk profiles. Building on the insights gained from this work, my future research will focus on developing and validating such models to support clinical decision-making, inform trial design, inform guideline development, and ultimately improve long-term outcomes for kidney transplant recipients.

Reference

1. Chadban, S. J., Ahn, C., Axelrod, D. A., Foster, B. J., Kasiske, B. L., Kher, V., Kumar, D., Oberbauer, R., Pascual, J., Pilmore, H. L., Rodrigue, J. R., Segev, D. L., Sheerin, N. S., Tinckam, K. J., Wong, G., & Knoll, G. A. (2020). KDIGO Clinical Practice Guideline on the Evaluation and Management of Candidates for Kidney Transplantation. Transplantation, 104(4S1), S11–S103. https://doi.org/10.1097/tp.0000000000003136

APPENDIX A

Publication arising from chapter 3

Shi B, Ying T, Chadban SJ. Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: a matched-pair analysis. *Am J Transplant*. Published online 2023. doi:10.1016/j.ajt.2023.07.006

American Journal of Transplantation 23 (2023) 1551–1560

Contents lists available at ScienceDirect

American Journal of Transplantation

journal homepage: www.amjtransplant.org

Original Article

Survival after kidney transplantation compared with ongoing dialysis for people over 70 years of age: A matched-pair analysis

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ARTICLE INFO

Keywords:
elderly
kidney transplantation
dialysis
patient survival

ABSTRACT

Kidney transplantation offers improved survival and quality of life compared to dialysis for most recipients; however, benefits for elderly patients (>70 years) remain uncertain. Using the Australia and New Zealand Dialysis and Transplant Registry (2009-2019), elderly transplant recipients were matched to a waitlisted dialysis patient by age, cause of end-stage kidney disease, and dialysis duration (paired controls). We censored dialysis patients at the time of transplant. Survival was compared using stratified Cox regression. Elderly transplant recipients (KTRs) (n = 465) were matched to waitlisted pairs. Transplant group mortality initially exceeded dialysis due to excess infection-related deaths (1.9 transplant versus 0.3 dialysis/100 patient-years, $P = .03$). Beyond month 9, a progressive survival benefit in favor of transplantation was apparent. Over a median follow-up of 1.7 years, mortality was 38% lower for KTRs (95% confidence interval 0.41-0.94, $P = .02$), and 5-year survival was 80% KTRs vs 53% dialysis ($P < .001$). Recipients of living and standard criteria donor kidneys acquired immediate survival advantage compared with dialysis, while recipients of expanded criteria donor's kidneys experienced elevated risk of death for the first 17 months. Compared with remaining on dialysis, elderly KTRs incur an increased risk of early posttransplant mortality but thereafter may anticipate progressively superior survival rates.

Abbreviations: aHR, adjusted hazard ratio; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; BMI, body mass index; CI, confidence interval; CV, cardiovascular; ECD, expanded criteria donor; ESKD, end-stage kidney disease; HD, hemodialysis; KTR, kidney transplant recipients; LD, living donor; PD, peritoneal dialysis; RRT, renal replacement therapy; SCD, standard criteria donor.

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https://doi.org/10.1016/j.ajt.2023.07.006
Received 9 March 2023; Received in revised form 28 June 2023; Accepted 10 July 2023
Available online 17 July 2023

1. Introduction

The number of elderly patients with end-stage kidney disease (ESKD) has steadily increased over the past few decades. In Europe, almost half of all patients receiving renal replacement therapy (RRT) were over 65 years of age in 2019 compared with 30% in 1999.[1,2] In the US, the proportion of ESKD patients aged 70 years and over who are waitlisted for a kidney transplant has increased from 3% in 1999 to nearly 10% in 2019.[3]

Existing literature has shown that, in comparison to younger transplant recipients, the elderly are more susceptible to infections, cardiovascular events, cancer, cognitive impairment, poor functional status, and frailty, leading to higher readmission rates, costs, and posttransplant mortality.[4] However, existing data suggest selected recipients aged 65 years and older, as compared with those remaining on dialysis, experience overall benefits of improved longevity, lower risks of cardiovascular events, and improved quality of life.[5,6]

As both the number of candidates and the shortfall in kidneys available for transplantation continue to rise,[7] appropriate kidney allocation is of utter importance. Equipoise exists regarding the survival benefit of kidney transplantation for those over 70 years old compared with those remaining on dialysis based on contemporary data. We therefore aimed to determine the impact of transplantation, as compared with those remaining on dialysis, on survival among patients aged 70 years or older who were waitlisted for transplantation, using a matched-pair design.

2. Materials and Methods

We extracted data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The ANZDATA Registry is a clinical quality registry that collects comprehensive data from all patients with ESKD in Australia and New Zealand. Details of the structure and methods of ANZDATA Registry data collection can be found on the Registry website (https://www.anzdata.org.au/anzdata/). We accessed data for all people aged 70 years or older receiving RRT in Australia and New Zealand. Patients who received a kidney-only transplant between January 1, 2009, and December 31, 2019, were retrospectively matched to a maintenance dialysis patient by age, diabetes as the cause of ESKD, and time on dialysis. We included dialysis controls who were actively waitlisted for transplantation at any point during the study follow-up period, while excluding those who were never waitlisted or had their waitlist status removed before matching and were not reactivated thereafter. If subsequently transplanted, they were censored at the time of transplantation. The matching was done without replacement. For kidney recipients, follow-up commenced on the date of transplantation. For dialysis controls, follow-up commenced on the date when the duration of dialysis was the same as that of their transplant pair. Follow-up was until the date of transplantation (for dialysis controls only), loss to follow-up, death, or December 31, 2019.

We compared baseline characteristics of paired recipients using Wilcoxon's signed rank test for continuous variables and ordinal categorical variables, Bowker's test for nominal categorical variables, and McNemar's test for dichotomous variables. Survival was compared using Kaplan-Meier curves. Time to death was analyzed using stratified Cox regression modeling, adjusting for confounders. Test of proportional-hazards assumption was performed using Schoenfeld residuals, with *P* values below the significance level of 0.05 deemed a violation. The potential confounders considered were sex, ethnicity, smoking status, body mass index (BMI), and preexisting comorbidities, including diabetes, chronic lung disease, cardiovascular disease (any of the coronary arteries, cerebrovascular, or peripheral vascular), nonskin cancer, and transplant era (in a 5.5-year interval). We calculated all-cause death incident rates and cause-specific death incident rates within and after 1-year posttransplant by dividing the total number of deaths by the total patient years at risk within the time period. Death incident rates were reported per 100 patient-years. We compared the death incident rates by using incident rate ratios. 95% confidence interval (CI) was reported. Stratified Cox regression model was used to compare hazards by the following time periods post-transplant: 0 to $<$3 months, 3 to $<$12 months, 1 to $<$5 years, and $\geq$5 years. We performed a subgroup analysis according to 3 donor types: (1) living donor (LD), (2) standard criteria donor (SCD), and (3) expanded criteria donor (ECD).

We used stepwise selection methods where variables with a significance level of 0.20 were included in the base multivariable model. We next used backward selection to remove variables that were not significant at the 0.05 level. Variables considered clinically significant, including sex, preexisting cardiovascular disease, diabetes, chronic lung disease, smoking status, and BMI, were also included in the multivariable model. We used a complete case analysis because the number of missing values was $<$ 5%. All analyses were performed using Stata Statistical Software, Release 14.2 (StataCorp).

3. Results

3.1. Study cohort

The study flow chart is presented in Figure 1. A total of 19,476 patients aged 70 years and older received maintenance dialysis between 2009 and 2019, of whom 465 (2%) received a kidney-only transplant. After the matching criteria were applied, we identified 465 pairs. Follow-up time was 1617 person-years for the transplant cohort (median 2.9 years, interquartile range 1.2-5.3 years) and 833 person-years for dialysis controls (median 0.9 years, interquartile range 0.4-2.3 years). All dialysis control patients were waitlisted for transplantation for at least part of the study period: 70% (n = 327) were active on the transplant waiting list in the first year of study follow-up, and 90% (n = 421) were active after 3 years. Two of the kidney recipients and 3 of the dialysis patients were lost to follow-up.

Baseline characteristics were compared between the transplant and dialysis groups in Table 1. Both groups were similar in age, sex, ethnicity, time on renal replacement therapy, BMI, smoking status, and pre-existing comorbidities, including

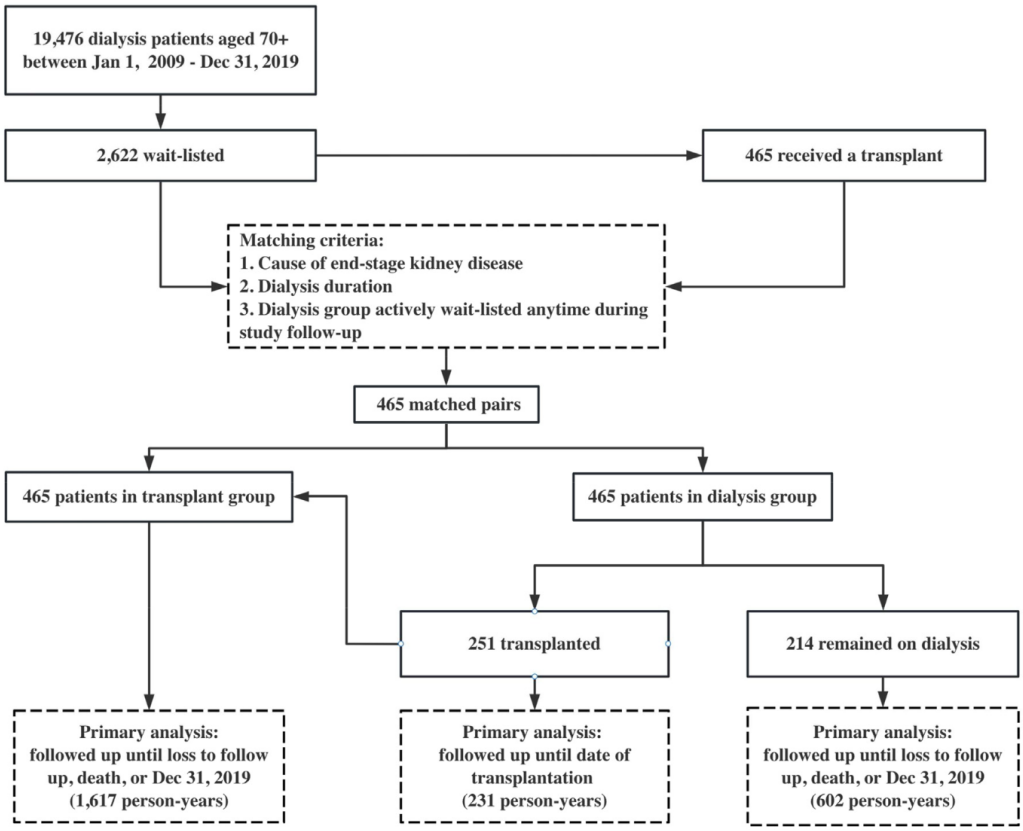

Figure 1. Study design: a matched-pair analysis where elderly recipients aged 70 years and older were matched to a waitlisted dialysis patient by age, cause of end-stage kidney disease, and dialysis duration.

diabetes, chronic lung disease, cardiovascular disease, and nonskin cancer (Table 1). In the transplanted elderly cohort, 41 (9%) received a pre-emptive live donor transplant and were matched to dialysis controls who were starting dialysis (Table 2).

3.2. Overall patient survival

By Kaplan-Meier survival analysis, those transplanted incurred an excess risk of death during the early posttransplant period, reaching parity with controls at 9 months posttransplant (Fig. 2A). One-year survival rates were comparable between the 2 groups (kidney recipients 94% vs remaining on dialysis 95%); however, after the first year, a clear and progressive survival advantage in favor of transplantation was evident (Fig. 2B). Univariable analysis showed that long-term survival was superior for transplanted elderly recipients, with 5- and 10-year survival of 80% and 53% compared with matched elderly patients remaining on dialysis at 53% and 17% ($P < .001$, $P < .001$).

On multivariate analysis, the relative risk of death between the 2 groups varied over time (Fig. 3). The proportional-hazards assumption was not violated based on the analysis of Schoenfeld residuals ($P = .72$). In the early posttransplant period, elderly transplant recipients incurred a 2-fold increase in perioperative mortality compared with those remaining on dialysis, although this was not statistically significant (adjusted hazard ratio [aHR] 2.10, 95% CI 0.82-5.39, $P = .12$). Transplantation yielded superior survival after 9 months posttransplant, which increased over time. At 1 to 5 years posttransplant, transplant recipients were 60% more likely to survive than those remaining on dialysis (aHR: 0.40; 95% CI: 0.23-0.70; $P = .001$).

Overall, receiving a transplant was a significant protective factor for survival by multivariable modeling (Table 3). Transplant patients were 38% more likely to survive after adjusting for sex, BMI, smoking status, and pre-existing comorbidities, including diabetes, cardiovascular disease, and chronic lung disease (aHR 0.62, 95% CI 0.41-0.94, $P = .02$).

A sensitivity analysis restricted to those dialysis patients who were not transplanted during the study follow-up demonstrated a more pronounced reduction in risk of death for transplants compared to controls (aHR 0.48, 95% CI 0.32-0.72, $P < .001$) (Supplementary Fig. S).

3.3. Patient survival by donor type

We compared dialysis patients and kidney recipients categorized by donor type: (1) LD; (2) SCD; and (3) ECD (Fig. 4). Patient survival was superior for transplantation versus dialysis for all donor types. Patient survival at 1 and 5 years was 99% and 81% for LD recipients, compared with 96% and 83% for SCD, 93% and 78% for ECD, and 94% and 53% for dialysis patients

Table 1
Demographics and baseline characteristics.

Characteristics	Transplant N = 465 n (%)	Dialysis N = 465 n (%)	*P* value
Age (y)			.88
70-74	405 (87)	409 (88)	
75-79	56 (12)	53 (11)	
>80	4 (1)	3 (1)	
Male	316 (68)	310 (67)	.67
Ethnicity			.82
Caucasian	267 (57)	255 (55)	
Indigenous[a]	3 (1)	3 (1)	
Asian	54 (12)	64 (14)	
Other	124 (27)	129 (28)	
Not reported	17 (4)	14 (3)	
Time since first RRT			1.00
Preemptive transplant/initiating dialysis	41 (9)	41 (9)	
0-1 y	51 (11)	51 (11)	
1-3 y	165 (35)	165 (35)	
>3 y	208 (45)	208 (45)	
Diabetes as primary renal disease	77 (17)	77 (17)	.84
Dialysis modality			< .001
Preemptive transplant	41 (9)	-	
HD	299 (64)	335 (72)	
PD	125 (27)	130 (28)	
BMI at RRT entry			.55
Underweight (<18.5)	4 (1)	5 (1)	
Normal (18.5-< 25)	132 (29)	146 (32)	
Overweight (25-< 30)	206 (45)	186 (41)	
Obese (30+)	113 (25)	121 (26)	
Smoking status			.56
Never	230 (51)	220 (49)	
Former	214 (47)	217 (48)	
Current	11 (2)	16 (4)	
Preexisting comorbidities			
Diabetes	130 (28)	144 (31)	.31
Chronic lung disease	65 (14)	55 (12)	.33
Cardiovascular disease	185 (40)	203 (44)	.23
Nonskin cancer	63 (14)	59 (13)	.70

Abbreviations: BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; RRT, renal replacement therapy .

[a] Indigenous: Aboriginal and Torres Strait Islanders.

Table 2
Recipients and transplantation characteristics.

Factor	N = 465, n (%)
Previous grafts	
0	450 (97)
1	15 (3)
Donor type	
LD	93 (20)
SCD	181 (39)
ECD	191 (41)
KDPI (N = 372)	
< 20	35 (9)
20-85	227 (61)
> 85	110 (30)
Ischemia time (N = 372)	
< 12 h	195 (42)
12-18 h	107 (23)
≥18 h	50 (11)
Unknown	20 (4)
Left, right or dual KTx	
Left Kidney	155 (42)
Right kidney	200 (54)
Double/En-bloc kidney	17 (5)
Delayed graft function	118 (25)
Acute rejection within 6 mo	69 (15)
Graft failure	26 (6)
eGFR 1 mo after transplant	
< 15 mL/min	23 (5)
15-< 30 mL/min	81 (17)
30-< 60 mL/min	254 (55)
60-< 90 mL/min	78 (17)
≥ 90 mL/min	5 (1)
Unknown	24 (5)
No. of HLA mismatches	
0	22 (5)
1-2	112 (24)
3-4	155 (33)
5-6	168 (36)
Unknown	8 (2)
CNI at transplant	442 (95)
Antimetabolite at transplant	440 (95)
Prednisolone at transplant	442 (95)
mTOR at transplant	5 (1)

(*P* = .02, *P* = .003). Recipients of LD and SCD kidneys acquired an immediate survival advantage over those remaining on dialysis, which was sustained throughout the study. Recipients of ECD kidneys experienced an elevated risk of death compared with those remaining on dialysis in the first 17 months posttransplant. From 17 months onward, recipients of all kidney types had better survival than dialysis patients. Using stratified Cox regression model, mortality was 67%, 39%, and 12% lower for recipients of LD, SCD, and ECD kidneys compared with those remaining on dialysis (LD: aHR = 0.33, 95% CI = 0.12-0.94, *P* = .04; SCD: aHR = 0.61, 95% CI = 0.38-0.99, *P* = .04; ECD: aHR = .88, 95% CI = 0.54-1.44, *P* = .62).

3.4. Cause of death

Overall, the most frequent causes of death in both elderly recipients and dialysis patients were cardiovascular diseases (kidney recipients: 1.4 per 100 person-years versus those remaining on dialysis: 4.7 per 100 person-years) (Table 4). Kidney recipients were 70% less likely to die from cardiovascular death compared with those remaining on dialysis (incidence risk ratio: 0.30; 95% CI: 0.17-0.52; *P* < .001). Elderly kidney recipients incurred a much greater risk of death from infection in the first year posttransplant compared with those remaining on dialysis (kidney recipients: 1.9 per 100 person-years versus those remaining on dialysis: 0.3 per 100 person-years, *P* = .05). There was no significant difference in the incidence of death from cancer between the groups.

4. Discussion

In this matched-pair analysis, we evaluated the outcome of kidney recipients aged 70 years and older compared with waitlisted maintenance dialysis patients comparable in age, cause of ESKD, and dialysis duration and adjusted for important confounders. We found that elderly recipients incurred an increased risk of death in the first 9 months after transplantation but experienced progressively superior survival rates thereafter. Transplantation was associated with markedly superior survival over 5 years of follow-up. Although the excess of early posttransplant mortality was largely attributable to infections, cardiovascular deaths were the most prominent cause of death among both elderly kidney recipients and dialysis patients over the full follow-up period.

Existing literature has clearly demonstrated a survival advantage of kidney transplantation over dialysis for comparable patients aged either 60 or 65 years and older.[5,8] The magnitude of benefit appears contingent upon donor characteristics, with LDs and standard criteria deceased donors affording more immediate and overall greater survival benefits than ECDs.[9] Kidney recipients aged 70 years and older may incur a greater risk of death than those aged 60 to 69 years. As the median age of

Abbreviations: CNI, calcineurin inhibitor; ECD, expanded criteria donor; eGFR, estimated glomerular rate; HLA, human leukocyte antigen; KDPI, kidney donor profile index; KTx, kidney transplantation; LD, living donor; mTOR, mammalian target of rapamycin; SCD, standard criteria donor.

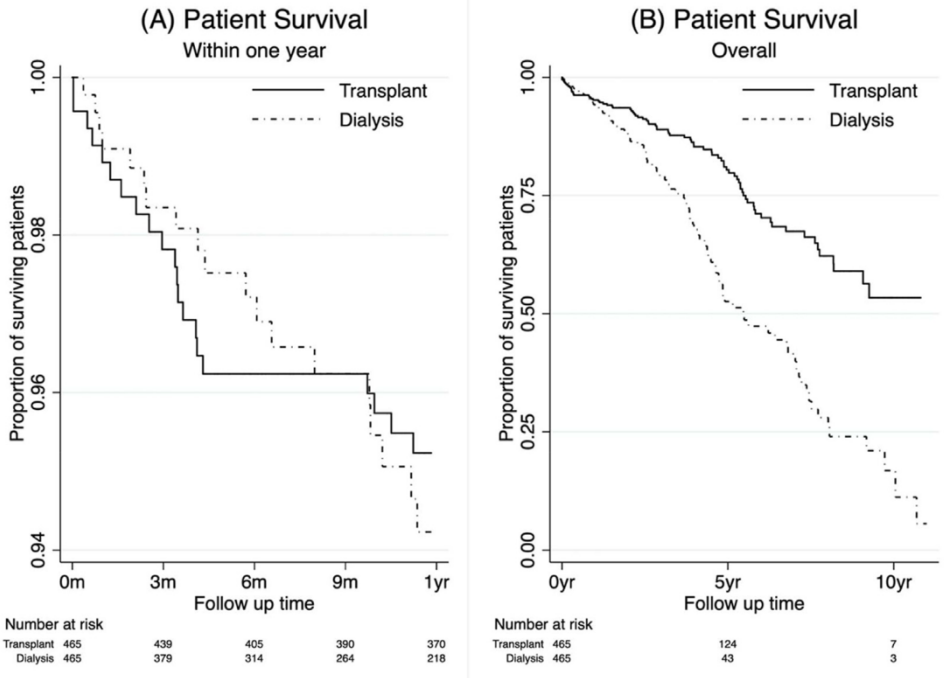

Figure 2. Elderly recipients incurred an increased risk of death in the first 9 months after transplantation but experienced progressively superior survival rates thereafter.

kidney recipients continues to increase over time, the relative benefits of transplanting candidates aged 70 years and older have become a more relevant question, and in this regard, contemporary data are lacking. Our results confirm a long-term survival benefit for LDs and SCDs compared with those remaining on dialysis, with ECD recipients having early elevated mortality that diminished after 17 months posttransplant. Heldal et al[10], using Norwegian Renal Registry data, found no significant survival benefit for transplant recipients aged 70 years and older during the period 1990-2005 but suggested improvements

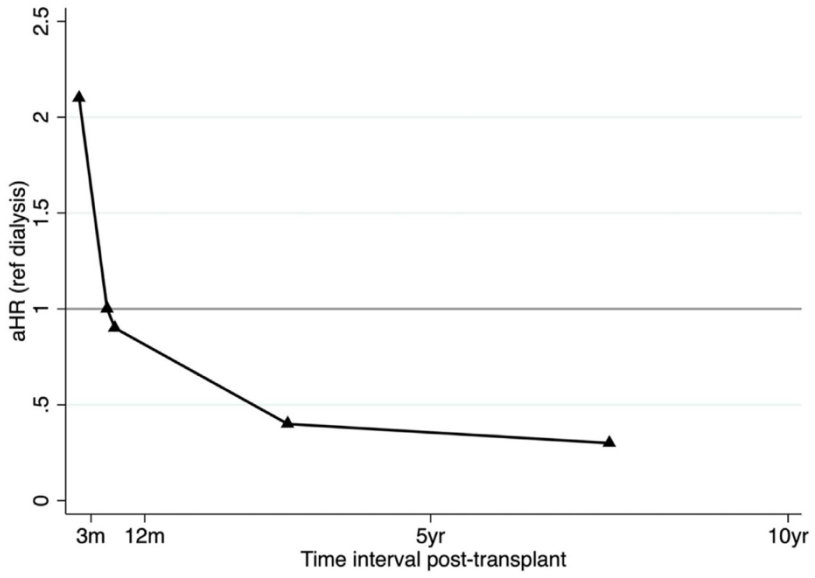

Figure 3. The relative risk of death between the 2 groups varied over time. In the early posttransplant period, elderly transplant recipients incurred a 2-fold increase in perioperative mortality compared with those remaining on dialysis. Transplantation yielded superior survival after 9 months post-transplant, which increased over time. *Abbreviation:* aHR, adjusted hazard ratio.

Table 3
Risk factor for patient survival. Multivariable analysis of patient survival with a stratified Cox regression model.

Covariates	Hazard ratio	95% CI	*P* value
Transplant	0.62	(0.41-0.94)	.02
Male	0.58	(0.30-1.13)	.11
Pre-existing cardiovascular disease	2.13	(1.18-3.83)	.01
Pre-existing chronic lung disease	1.15	(0.54-2.45)	.72
Pre-existing diabetes	1.79	(0.83-3.84)	.14
Smoking status			.44
Never	1[a]		
Former	1.14	(0.66-1.96)	
Current	2.49	(0.57-0.87)	
BMI category			.09
Normal (< 25 kg/m^2)	1[a]		
Overweight (25 to < 30 kg/m^2)	1.89	(0.96-3.72)	
Obese (≥ 30 kg/m^2)	2.32	(1.06-5.07)	

Abbreviations: BMI, body mass index; CI, confidence interval.
[a] Reference group.

over time, with a 60% reduction in death during the period 2000-2005.[10] Another study using Scientific Registry of Transplant Recipients data showed a 41% reduction in mortality among those aged 70 years or more who were transplanted between 1990 and 2004.[11] A third registry study of patients aged 70 years and older who started RRT between 2002 and 2013 reported a 60% reduction in risk of death at 3 years posttransplant compared with a matched group who remained on dialysis.[12] Our study adds to this literature by demonstrating a robust survival advantage associated with transplantation of selected elderly recipients compared with maintenance dialysis during the last decade. Utilizing large, binational kidney transplant registry data, we used a matched-pair design so that kidney recipients and dialysis patients were comparable at the start of the study follow-up in terms of 2 critical factors: time on dialysis and diabetes as the cause of ESKD, both of which are known to substantially impact mortality risk.[13,14] In addition, we included only dialysis patients who underwent the same waitlist assessment and were actively waiting for a transplant, further enhancing the comparability of the 2 groups. Our data thereby provides the strongest support to date in favor of transplant candidates aged 70 years and older.

Although our study has demonstrated a survival advantage for transplantation in patients aged 70 years and older, only 2% of the 19,476 patients in this age category received a transplant, suggesting that candidates were carefully selected. This is relevant when considering the generalizability of our findings. We were not able to access specific criteria used by individual units in determining suitability for transplant waitlisting. Candidates evaluated for transplantation in Australia and New Zealand were required to expect an 80% or greater probability of survival for 5 years after transplantation prior to 2018,[15] although this requirement has since been replaced by an expectation that the patient will likely benefit from transplantation. By examining]baseline comorbidity data, we found patients with pre-existing cardiovascular disease were at double the risk of death compared with those with no pre-existing cardiovascular disease. Lemoine et al[16] conducted a risk factor analysis for recipients older than 70 years and reported that death or graft failure in the first year posttransplant was attributable to cardiovascular diseases in 29% of cases and was associated with arrhythmia and reduced left-ventricular ejection fraction. Which pretransplant factors are most predictive of premature posttransplant mortality for elderly candidates, and whether selection based upon such risk factors can improve posttransplant survival, remains to be examined.

We described a high incidence of death from infection during the first year posttransplant among our elderly cohort, consistent with a recent study from France that showed 59% of deaths among kidney recipients older than 70 years during the first posttransplant year were attributable to infection.[16] This is specific to the elderly, as cardiovascular deaths are twice as common during the first year across the general transplant population.[17] Older patients are more susceptible to infectious complications of immunosuppressive therapy for reasons including immune senescence, impaired drug elimination, and impaired intracellular signaling pathways.[18-21] Future studies on personalized management of immunosuppression are needed to determine whether this may reduce infection posttransplant and optimize graft and patient survival for elderly recipients.

The number of elderly patients with ESKD continues to grow disproportionately compared with other age groups.[3] For most transplant centers worldwide, there is no strict upper age limit for kidney transplantation. Kidney Disease Improving Global Outcomes clinical practice guidelines recommend not excluding patients from kidney transplantation due to their age alone.[22] However, elderly patients, including those with no formal contraindications, are still less likely to be placed on the transplant waiting list and less likely to receive a transplant once listed than younger patients.[23,24] We have demonstrated that kidney transplantation provides a long-term survival advantage compared with those remaining on dialysis for elderly patients. Our findings support increasing access to transplantation for selected patients aged 70 years and older. In the context of a global shortage of kidneys for transplantation, increased access for elderly candidates will exacerbate this problem. Potential solutions, including

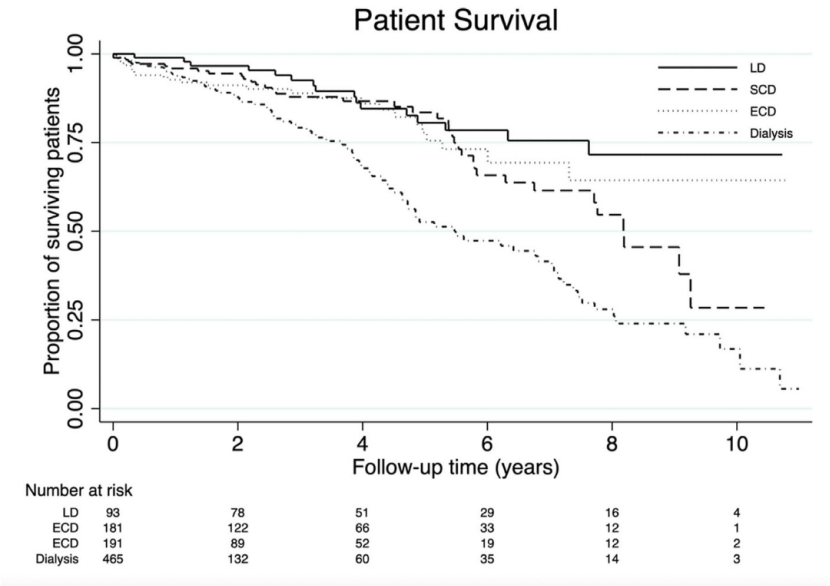

Figure 4. Recipients of living donor (LD) and standard criteria donor (SCD) kidneys acquired an immediate survival advantage compared with dialysis, whereas recipients of expanded criteria donor (ECD) kidneys experienced an elevated risk of death for the first 17 months posttransplant.

Table 4
Cause of death by time posttransplant.

Cause of death	Timing of death	Group	N	P-Y	Incident rate (per 100 P-Y)	Incident rate ratio (95% confidence interval)	*P* value
All-cause	<1 y	Transplant	21	412	5.1	0.86 (0.44-1.70)	.64
		Dialysis	19	322	5.9		
	≥1 y	Transplant	60	1205	5.0	0.37 (0.26-0.53)	< .001
		Dialysis	69	511	13.5		
	Overall	Transplant	81	1617	5.0	0.47 (0.35-0.65)	< .001
		Dialysis	88	833	10.6		
CV	<1 y	Transplant	9	412	2.2	0.59 (0.22-1.52)	.23
		Dialysis	12	322	3.7		
	≥1 y	Transplant	14	1205	1.2	0.22 (0.11-0.43)	< .001
		Dialysis	27	511	5.3		
	Overall	Transplant	23	1617	1.4	0.30 (0.17-0.52)	< .001
		Dialysis	39	833	4.7		
Infection	<1 y	Transplant	8	412	1.9	6.25 (0.84-277.43)	.05
		Dialysis	1	322	0.3		
	≥1 y	Transplant	12	1205	1.0	0.64 (0.24-1.79)	.33
		Dialysis	8	511	1.6		
	Overall	Transplant	20	1617	1.2	1.14 (0.50-2.86)	.76
		Dialysis	9	833	1.1		

(*continued on next page*)

Table 4 (*continued*)

Cause of death	Timing of death	Group	N	P-Y	Incident rate (per 100 P-Y)	Incident rate ratio (95% confidence interval)	*P* value
Cancer	<1 y	Transplant	1	412	0.2	0.26 (0.00-3.24)	.26
		Dialysis	3	322	0.9		
	≥1 y	Transplant	18	1205	1.5	1.53 (0.55-5.26)	.42
		Dialysis	5	511	1.0		
	Overall	Transplant	19	1617	1.2	1.22 (0.51-3.23)	.65
		Dialysis	8	833	1.0		
Other	<1 y	Transplant	3	412	0.7	0.78 (0.10-5.83)	.77
		Dialysis	3	322	0.9		
	≥1 y	Transplant	16	1205	1.3	0.23 (0.12-0.44)	< .001
		Dialysis	29	511	5.7		
	Overall	Transplant	19	1617	1.2	0.31 (0.16-0.56)	< .001
		Dialysis	32	833	3.8		

Abbreviations: CV, cardiovascular; P-Y, patient-years.

promotion of living donation and preferential use of older and expanded criteria organs, have been explored in existing studies and should be revisited.[9,25-27]

There are several limitations to our study. In addition to candidate selection criteria for transplant waitlisting, the predominantly white racial mix of our population may limit generalizability. There may be inherent differences between those waitlisted and those transplanted, which may also be influenced by center practices. We used registry data for our analyses, which may be subject to issues of accuracy of data capture, retrospectively, and potential for unmeasured confounders. However, the registry data enabled use of a rigorous, matched-pair design that enabled us to control for the major potential confounders of age, dialysis duration, diabetes, and eligibility for transplantation. Although the outcomes of transplantation versus dialysis would ideally be addressed by conduct of a randomized clinical trial, such a trial is neither feasible nor ethical given our current lack of expertise. Thus, we believe the matched-pair analysis we have used is the most rigorous and best way to address this question.

In conclusion, our study demonstrated a substantial survival advantage of transplantation over ongoing dialysis for candidates aged 70 years and older who were waitlisted for kidney transplantation. These results may be used by clinicians to better inform patients of the relative benefits and risks of transplantation. Our data support providing access to transplantation for such patients, as recommended by current Kidney Disease Improving Global Outcomes guidelines,[20] but also identifies death from infection in the first year after transplantation as an important risk that patients and health care providers should be informed of. Further work to determine how to prevent early posttransplant deaths is required.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose, as described by the American Journal of Transplantation.

Funding source

Bree Shi was funded by the Pamela Guha Postgraduate Scholarship for her PhD studies.

Data availability statement

The data are not available due to privacy and ethical considerations.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are thankful to the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry for supplying the data reported here.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajt.2023.07.006.

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References

1. Boenink R, Astley ME, Huijben JA, et al. The ERA Registry Annual Report 2019: summary and age comparisons. *Clin Kidney J*. 2022;15(3): 452–472. https://doi.org/10.1093/ckj/sfab273.
2. ERA. *EDTA registry: annual report*; 1999. https://era-edta-reg.org/files/annualreports/AnnRep1999.pdf. Accessed July 1, 2022.
3. United States renal data system. USRDS Annual Data report. Epidemiology of kidney disease in the United States. https://adr.usrds.org/2021/end-stage-renal-disease/7-transplantation; 2021. Accessed July 1, 2022.
4. Hernández D, Alonso-Titos J, Armas-Padrón AM, et al. Mortality in elderly waiting-list patients versus age-matched kidney transplant recipients: where is the risk? *Kidney Blood Press Res*. 2018;43(1): 256–275. https://doi.org/10.1159/000487684.
5. Wolfe RA, Ashby VB, Milford EL, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999;341(23):1725–1730. https://doi.org/10.1056/NEJM199912023412303.
6. Tonelli M, Wiebe N, Knoll G, et al. Systematic review: kidney transplantation compared with dialysis in clinically relevant outcomes. *Am J Transplant*. 2011;11(10):2093–2109. https://doi.org/10.1111/j.1600-6143.2011.03686.x.
7. McCormick F, Held PJ, Chertow GM. The terrible toll of the kidney shortage. *J Am Soc Nephrol. ASN*. 2018;29(12):2775–2776. https://doi.org/10.1681/ASN.2018101030.
8. Chaudhry D, Chaudhry A, Peracha J, Sharif A. Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis. *BMJ*. 2022;376: e068769. https://doi.org/10.1136/bmj-2021-068769.
9. Gill JS, Schaeffner E, Chadban S, et al. Quantification of the early risk of death in elderly kidney transplant recipients. *Am J Transplant*. 2013; 13(2):427–432. https://doi.org/10.1111/j.1600-6143.2012.04323.x.
10. Heldal K, Hartmann A, Grootendorst DC, et al. Benefit of kidney transplantation beyond 70 years of age. *Nephrol Dial Transplant*. 2010; 25(5):1680–1687. https://doi.org/10.1093/ndt/gfp681.
11. Rao PS, Merion RM, Ashby VB, Port FK, Wolfe RA, Kayler LK. Renal transplantation in elderly patients older than 70 years of age: results from the Scientific Registry of Transplant Recipients. *Transplantation*. 2007;83(8):1069–1074. https://doi.org/10.1097/01.tp.0000259621.56861.31.
12. Legeai C, Andrianasolo RM, Moranne O, et al. Benefits of kidney transplantation for a natio[illegible]d older starting renal replacemer[illegible]1): 2695–2707. https://doi.org/10.1111/ajt.15110.
13. Chadban SJ, Staplin ND. Is it time to increase access to transplantation for those with diabetic end-stage kidney disease? *Kidney Int*. 2014; 86(3):464–466. https://doi.org/10.1038/ki.2014.154.
14. Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int*. 2014;85(1): 158–165. https://doi.org/10.1038/ki.2013.252.
15. The Transplantation Society of Australia and New Zealand: clinical guidelines for organ transplantation from deceased donors. https://tsanz.com.au/guidelinesethics-documents/tsanz-clinical-guidelines.htm. Accessed November 21, 2022.
16. Lemoine M, Titeca Beauport D, Lobbedez T, et al. Risk factors for early graft failure and death after kidney transplantation in recipients older than 70 years. *Kidney Int Rep*. 2019;4(5):656–666. https://doi.org/10.1016/j.ekir.2019.01.014.
17. Ying T, Shi B, Kelly PJ, Pilmore H, Clayton PA, Chadban SJ. Death after kidney transplantation: an analysis by era and time post-transplant. *J Am Soc Nephrol*. 2020;31(12):2887–2899. https://doi.org/10.1681/ASN.2020050566.
18. Krenzien F, ElKhal A, Quante M, et al. A rationale for age-adapted immunosuppression in organ transplantation. *Transplantation*. 2015; 99(11):2258–2268. https://doi.org/10.1097/TP.0000000000000842.
19. Cossart AR, Cottrell WN, Campbell SB, Isbel NM, Staatz CE. Characterizing the pharmacokinetics and pharmacodynamics of immunosuppressant medicines and patient outcomes in elderly renal transplant patients. *Transl Androl Urol*. 2019;8(suppl 2):S198–S213. https://doi.org/10.21037/tau.2018.10.16.
20. Martins PNA, Pratschke J, Pascher A, et al. Age and immune response in organ transplantation. *Transplantation*. 2005;79(2):127–132. https://doi.org/10.1097/01.tp.0000146258.79425.04.
21. Meier-Kriesche HU, Ojo AO, Hanson JA, Kaplan B. Exponentially increased risk of infectious death in older renal transplant recipients. *Kidney Int*. 2001;59(4):1539–1543. https://doi.org/10.1046/j.1523-1755.2001.0590041539.x.
22. Chadban SJ, Ahn C, Axelrod DA, et al. KDIGO clinical practice guideline on the evaluation and management of candidates for kidney transplantation. *Transplantation*. 2020;104(4S1) (suppl 1):S11–S103. https://doi.org/10.1097/TP.0000000000003136.
23. Segall L, Nistor I, Pascual J, et al. Criteria for and appropriateness of renal transplantation in elderly patients with end-stage renal disease: a Literature Review and Position Statement on Behalf of the European Renal Association-European Dialysis and Transplant Association Descartes Working Group and European Renal Best Practice. *Transplantation*. 2016;100(10):e55–e65. https://doi.org/10.1097/TP.0000000000001367.
24. Sørensen SS. Rates of renal transplantations in the elderly-data from Europe and the US. *Transplant Rev (Orlando)*. 2015;29(4):193–196. https://doi.org/10.1016/j.trre.2015.04.005.
25. Ojo AO, Hanson JA, Meier-Kriesche HU, et al. Survival in recipients of marginal cadaveric donor kidneys compared with other recipients and wait-listed transplant candidates. *J Am Soc Nephrol*. 2001;12(3): 589–597. https://doi.org/10.1681/ASN.V123589.
26. Merion RM, Ashby VB, Wolfe RA, et al. Deceased-donor characteristics and the survival benefit of kidney transplantation. *JAMA*. 2005;294(21): 2726–2733. https://doi.org/10.1001/jama.294.21.2726.
27. Jay CL, Washburn K, Dean PG, Helmick RA, Pugh JA, Stegall MD. Survival benefit in older patients associated with earlier transplant with high KDPI kidneys. *Transplantation*. 2017;101(4):867–872. https://doi.org/10.1097/TP.0000000000001405.

APPENDIX B

Publication arising from chapter 4

Shi B, Ying T, Xu J, Wyburn K, Laurence J, Chadban SJ. Obesity is Associated With Delayed Graft Function in Kidney Transplant Recipients: A Paired Kidney Analysis. Transpl Int. 2023;36:11107. doi:10.3389/ti.2023.11107

ESOT | Transplant International

ORIGINAL RESEARCH
published: 30 May 2023
doi: 10.3389/ti.2023.11107

Obesity is Associated With Delayed Graft Function in Kidney Transplant Recipients: A Paired Kidney Analysis

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Obesity is increasingly prevalent among candidates for kidney transplantation. Existing studies have shown conflicting post-transplant outcomes for obese patients which may relate to confounding bias from donor-related characteristics that were unaccounted for. We used ANZDATA Registry data to compare graft and patient survival between obese (BMI >27.5 kg/m^2 Asians; >30 kg/m^2 non-Asians) and non-obese kidney transplant recipients, while controlling for donor characteristics by comparing recipients of paired kidneys. We selected transplant pairs (2000–2020) where a deceased donor supplied one kidney to an obese candidate and the other to a non-obese candidate. We compared the incidence of delayed graft function (DGF), graft failure and death by multivariable models. We identified 1,522 pairs. Obesity was associated with an increased risk of DGF (aRR = 1.26, 95% CI 1.11–1.44, $p < 0.001$). Obese recipients were more likely to experience death-censored graft failure (aHR = 1.25, 95% CI 1.05–1.49, $p = 0.012$), and more likely to die with function (aHR = 1.32, 95% CI 1.15–1.56, $p = 0.001$), versus non-obese recipients. Long-term patient survival was significantly worse in obese patients with 10- and 15-year survival of 71% and 56% compared to 77% and 63% in non-obese patients. Addressing obesity is an unmet clinical need in kidney transplantation.

OPEN ACCESS

Keywords: kidney transplantation, patient survival, graft survival, obesity, DGF

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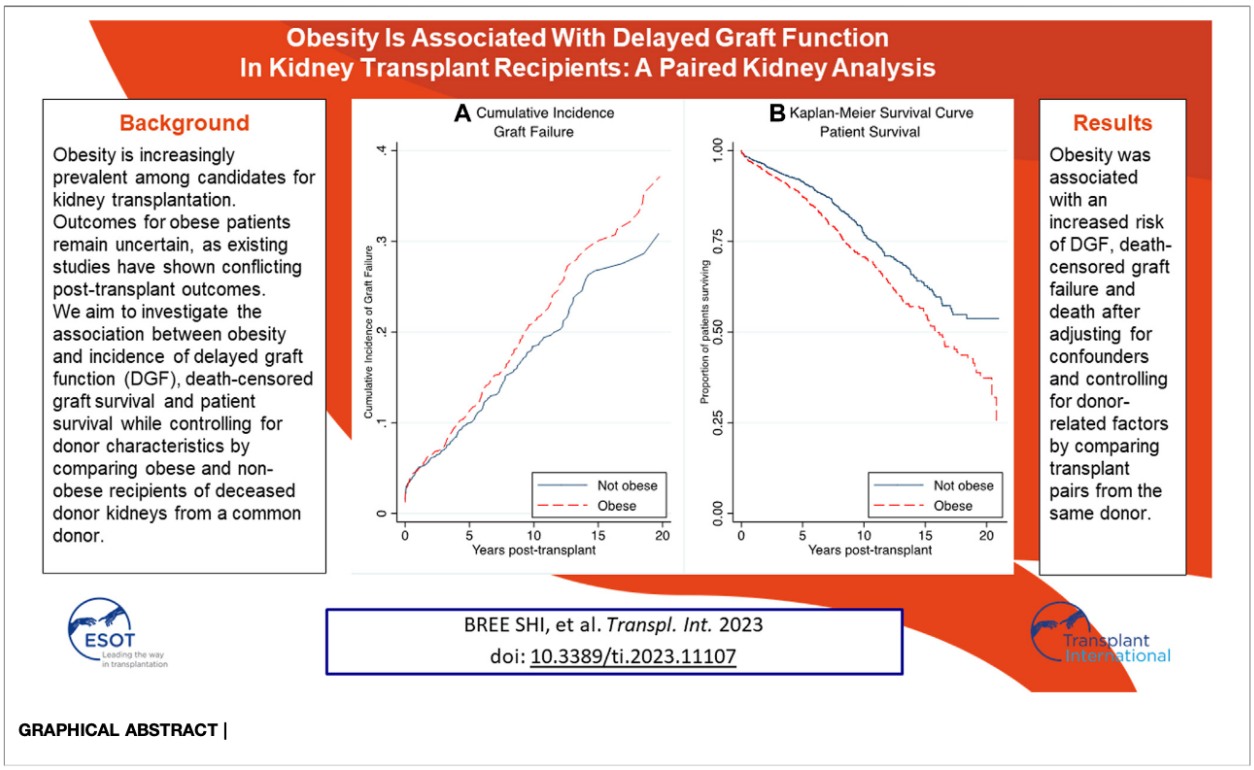
Received: *05 December 2022*
Accepted: *11 May 2023*
Published: *30 May 2023*

Citation:
Shi B, Ying T, Xu J, Wyburn K, Laurence J and Chadban SJ (2023) Obesity is Associated With Delayed Graft Function in Kidney Transplant Recipients: A Paired Kidney Analysis. Transpl Int 36:11107. doi: 10.3389/ti.2023.11107

INTRODUCTION

Over the past four decades, the worldwide prevalence of obesity has tripled. In addition to the associations between obesity and hypertension, type 2 diabetes and coronary artery disease, obesity is clearly associated with premature mortality [1]. Obesity has therefore had a significant impact on community health as well as posing a major economic challenge to global healthcare systems. Obesity is increasingly prevalent in the end-stage kidney disease (ESKD) and kidney transplant populations

Abbreviations: aHR, adjusted hazard ratio; ANZDATA, the Australia and New Zealand Dialysis and Transplant registry; aRR, adjusted rate ratio; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; DGF, delayed graft function; ESKD, end-stage kidney disease; GN, Glomerulonephritis; HD, hemodialysis; HLA, human leukocyte antigen; PD, peritoneal dialysis; RRT, renal replacement therapy; WHO, World Health Organization.



GRAPHICAL ABSTRACT |

[2,3]. In the US, the proportion of ESKD patients that were obese between 2008 and 2016 was nearly 40% [4].

Whilst kidney transplant recipients with high body mass index (BMI) are more like to develop post-transplant diabetes, congestive heart failure, atrial fibrillation, and cardiovascular death [5–7], transplantation offers a survival benefit for obese recipients compared to remaining on dialysis [8,9]. However, kidney transplant recipients with high BMI are at an increased risk of post-transplant complications, including prolonged wound healing, dehiscence, hernias, surgical site infections, deep vein thrombosis, and reintubation. These issues contribute to a longer hospital stay and higher hospital costs for transplantation in the obese [10–12].

The long-term graft and patient outcomes of obese recipients compared to non-obese recipients have remained controversial. When compared to non-obese recipients, some reports described an increased risk of graft failure and mortality for obese recipients whilst others have found no significant differences [12–15]. These disparate outcomes, may relate to the confounding bias of non-randomly distributed donor-related characteristics which were not accounted for [16–18]. Therefore, we sought to investigate the association between obesity and incidence of delayed graft function (DGF), graft survival and patient survival while controlling for donor characteristics by comparing obese and non-obese recipients of kidneys from a common donor, a matched-pair analysis. We hypothesized that obesity would increase the risk of DGF and lead to inferior graft and patient survival.

MATERIALS AND METHODS

We extracted data from the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). The ANZDATA Registry is a clinical quality registry that collects comprehensive data from all patients with ESKD in Australia and New Zealand. Details of the structure and method of ANZDATA Registry data collection can be found on the Registry website (https://www.anzdata.org.au/anzdata/). We included all deceased donor kidney-only transplant pairs between 1 January 2000 and 31 December 2020, where a deceased donor supplied one kidney to an obese recipient and the other to a non-obese recipient. We excluded recipients under the age of 18, recipients of a deceased donor kidney retrieved outside Australia or New Zealand, and recipients of a second or subsequent transplant. We used the World Health Organization (WHO) classification of obesity as BMI greater than 30 kg/m^2 for non-Asians, and greater than 27.5 kg/m^2 for Asians due to differences in body habitus compared to the Western population [19–21]. Follow-up was until loss to follow-up, or 31 December 2020. The primary outcome was DGF which was defined as receipt of hemodialysis within 72 h after transplant prior to 2017, and receipt of hemodialysis within 7 days of transplantation after 2017 [22]. This modification to the definition of delayed graft function was due to a policy change

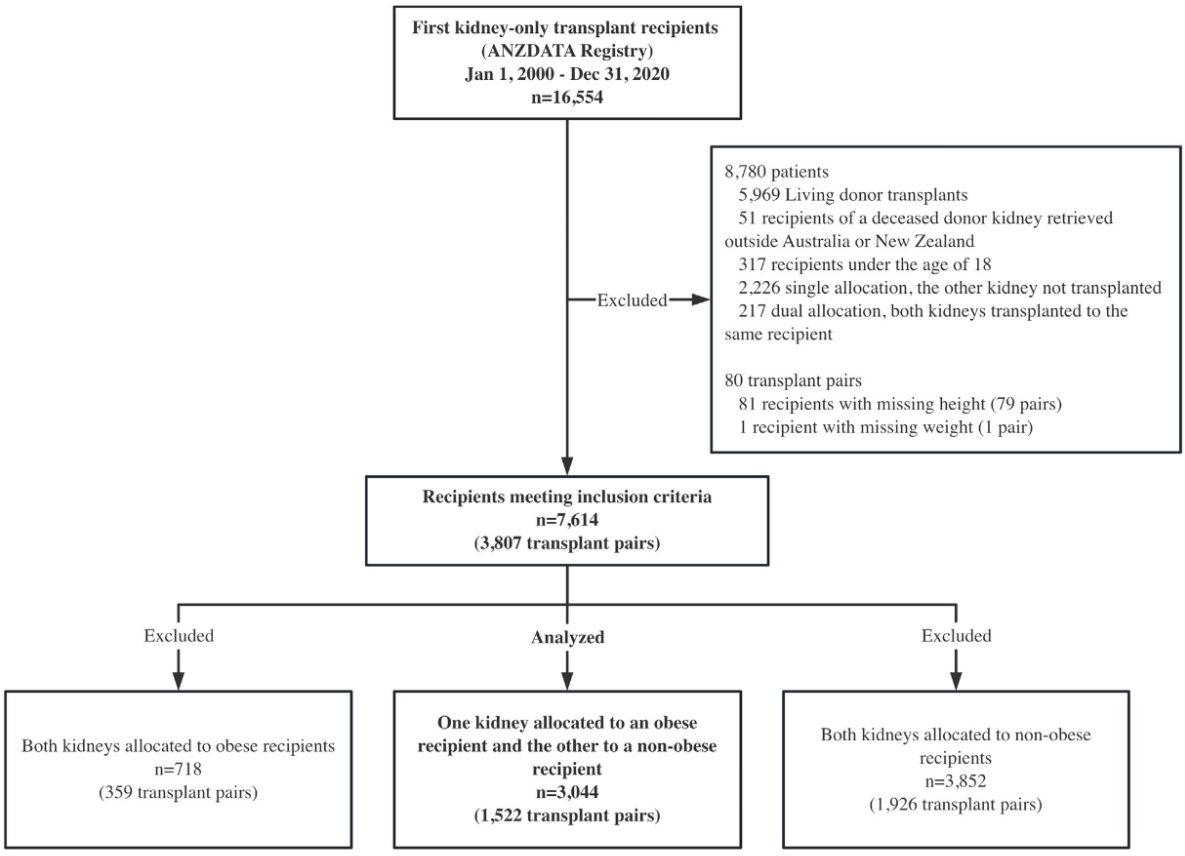


FIGURE 1 | Study design: a paired kidney analysis where one kidney was allocated to an obese recipient and the other to a non-obese recipient. ANZDATA, the Australia and New Zealand Dialysis and Transplant registry.

made by ANZDATA in 2017. The secondary outcomes were death and death-censored graft failure.

We compared baseline characteristics of paired recipients using paired t-test or Wilcoxon's signed rank test for continuous variables and McNemar's test for dichotomous variables. We estimated the cumulative incidence of graft failure using Aalen-Johansen estimator to account for death as a competing event. We used Gray's test to compare the cumulative incidence of graft failure in the presence of the competing risk of death. We used Kaplan-Meier curves to compare unadjusted patient survival. We used a logrank test to compare the probability of patient survival at different time points. We estimated the rate ratio of DGF for obese patients compared with non-obese patients, using conditional Poisson regression, adjusting for potential confounders [23–25]. As a sensitivity analysis, we repeated this analysis excluding patients who experienced graft failure within 90 days of transplantation. Time to graft failure and time to death were analyzed using Cox regression stratified by donor [24,25].

A dose-response analysis was performed to examine the association between the degree of obesity (i.e., class I, class II and class III) and clinical outcomes. Obesity was categorized as class I, class II and class III according to WHO guidelines (**Table 3**). We estimated the rate ratio of DGF using conditional Poisson regression and the hazard ratio of graft failure and death using Cox regression, adjusting for potential confounders.

The potential confounders considered were age at transplantation, sex, ethnicity, cause of kidney disease, duration of dialysis, dialysis modality prior to transplant, human leukocyte antigen (HLA) mismatch, ischemia time, maximum panel reactive antibodies, donor kidney side, pre-existing comorbidities including diabetes, chronic lung disease, cardiovascular disease (any of coronary artery, cerebrovascular or peripheral vascular), and non-skin cancer, acute rejection within 6 months of transplantation (for graft failure and death only), DGF (as a categorical variable, for graft failure and death only), and graft failure

(as a time-varying covariate, for death only). We used stepwise selection methods where variables with a significance level of 0.20 were considered and included in the base multivariable model. We used backward selection method to remove variables that were not significant at the 0.05 level [26]. We used complete case analysis because the number of missing values was less than 5%. All analyses were performed using Stata Statistical Software: Release 14.2 (StataCorp., College Station, TX) This study was approved by the Ethics Review Committee of the Sydney Local Health District, Royal Prince Alfred Hospital Zone.

RESULTS

Study Cohort

Between 1 January 2000, and 31 December 2020, 16,554 patients received their first kidney transplant in Australia and New Zealand. After inclusion and exclusion criteria were applied, 1,522 pairs were identified where a deceased donor supplied one kidney to an obese recipient and the other to a non-obese recipient (**Figure 1**). Follow-up time was 19,768 person-years in total, with a median follow-up time of 5.3 years (interquartile range 2.5–9.5 years). Nine of the obese recipients and seven of the non-obese recipients were lost to follow-up.

Donor and recipient baseline characteristics are summarized in **Tables 1**, **2**. Baseline characteristics indicate that obese and non-obese recipients were comparable in terms of sex, time on dialysis, ischemia time, HLA mismatch and maximum panel reactive antibody percentage. The obese group included a higher proportion of recipients aged 50–65 (48% vs. 44%), $p < 0.001$), fewer people of Asian ancestry (12% vs. 15%, $p < 0.001$), more Indigenous people (17% vs. 11%, $p < 0.001$), more people with pre-existing diabetes (33% vs. 21%, $p < 0.001$) and comorbid cardiovascular disease (33% vs. 27%, $p = 0.001$) and more right-sided kidneys (55% vs. 45%, $p < 0.001$).

TABLE 1 | Donor characteristics.

Factor	N = 1,522 n (%)
Age	
<18	79 (5)
18–34	254 (17)
35–49	426 (28)
50–65	556 (37)
65+	207 (14)
Male	870 (57)
Body mass index (BMI)	
Underweight	47 (3)
Normal	556 (37)
Overweight	534 (35)
Obese	383 (25)
Terminal serum creatinine concentration, μmol/L	96.4 ± 83.2
Diabetes	96 (6)
Hypertension	388 (25)
Neurological determination of death (NDD)	1,167 (77)
Cause of death	
Intracranial hemorrhage	640 (44)
Traumatic brain injury	285 (19)
Cerebral infarct	94 (6)
Cerebral hypoxia/ischemia	380 (26)
Other neurological condition	12 (1)
Non-neurological condition	59 (4)

Outcomes

Delayed Graft Function

A greater proportion of obese recipients experienced DGF compared to non-obese recipients (39% vs. 30%, $p < 0.001$). Conditional Poisson regression demonstrated an increased risk of DGF for obese recipients versus their non-obese pair (aRR = 1.27, 95% CI 1.12–1.44, $p < 0.001$), after adjusting for dialysis modality prior to transplant, ischemia time and pre-existing cardiovascular disease and accounting for donor-related factors (**Supplementary Table S1**).

Sensitivity analysis, excluding those patients who experienced graft failure within 90 days of transplantation, showed a similar effect of obesity on DGF to the primary analysis (aRR = 1.29, 95% CI 1.12–1.48, $p < 0.001$).

Graft Failure

Unadjusted graft failure was more common amongst obese recipients (**Figure 2**). Cumulative incidence of graft failure at 5 years was not affected by obesity status (11% obese vs. 10% non-obese), however, obese recipients were found to have a higher incidence of long-term graft failure with 10- and 15-year cumulative incidence of 21% and 30% compared to 18% and 27% in non-obese patients. The Gray's test confirmed a significant difference on the overall incidence of graft failure between obese and non-obese recipients ($p = 0.044$). On multivariable analysis, obesity was confirmed as an independent risk factor for death-censored graft failure. Obesity was associated with a higher risk of death-censored graft failure after adjusting for DGF, donor kidney side, age, ethnicity and HLA mismatch (aHR = 1.25, 95% CI 1.05–1.49, $p = 0.012$) (**Supplementary Table S2**). Recipients who experienced delayed graft function were more likely to experience death-censored graft failure (aHR = 1.84, 95% CI 1.39–2.44, $p < 0.001$).

Patient Survival

There were 342 (22%) deaths in the obese group compared to 260 (17%) ($p < 0.001$). Death from cardiovascular disease was the most prominent cause of death amongst the obese recipients, with 105 cardiovascular deaths (31%) compared to 65 (25%) among the non-obese recipients. Obesity was strongly associated with inferior survival in both the short and long-term ($p < 0.001$) (**Figure 3**). Short and long-term patient survival was significantly worse in obese recipients with 5-, 10- and 15-year survival of 87%, 71% and 56% compared to 91%, 77% and 63% in non-obese patients ($p = 0.017$, $p < 0.001$, $p < 0.001$). In the multivariable model, obesity was found to be strongly associated with worse patient survival. Obese recipients had an increased risk of death compared to non-obese recipients (aHR = 1.32, 95% CI 1.15–1.56, $p = 0.001$) (**Supplementary Table S3**). Significant determinants of death that were included in the final model were graft failure, older age, Indigenous ethnicity, diabetes as

TABLE 2 | Recipient and transplantation characteristics for obese and non-obese recipients.

Factor	Obese N = 1,522	Not obese N = 1,522	*p*-value
Age at transplant	n (%)	n (%)	<0.001
18–34	113 (7)	193 (13)	
35–49	430 (28)	414 (27)	
50–65	728 (48)	667 (44)	
65+	251 (16)	248 (16)	
Male	985 (65)	991 (65)	0.82
Ethnicity			<0.001
Caucasian	1,001 (66)	1,006 (66)	
Indigenous	257 (17)	162 (11)	
Asian	185 (12)	232 (15)	
Other	79 (5)	122 (8)	
Primary renal disease			<0.001
GN	575 (38)	628 (41)	
Renovascular	123 (8)	112 (7)	
Diabetes	351 (23)	231 (15)	
Other	473 (31)	551 (36)	
Time since first RRT			0.14
0–1 year	173 (11)	209 (14)	
1–3 years	594 (39)	575 (38)	
Over 3 years	755 (50)	738 (48)	
Dialysis modality prior to transplant			0.008
Pre-emptive transplant	11 (1)	17 (1)	
HD	1,106 (73)	1,030 (68)	
PD	405 (27)	475 (31)	
Ischemia time [mean (sd)]	12.1 (4.9)	12.0 (5.0)	0.52
HLA mismatches			0.58
0	46 (3)	38 (2)	
1–2	408 (27)	427 (28)	
3–4	483 (32)	460 (30)	
5–6	580 (38)	596 (39)	
Maximum panel reactive antibodies			0.50
0	918 (60)	935 (61)	
1–50	491 (32)	465 (31)	
>50	110 (7)	121 (8)	
Pre-existing comorbidities			
Chronic lung disease	130 (9)	124 (8)	0.69
Cardiovascular disease	501 (33)	418 (27)	0.001
Diabetes	504 (33)	316 (21)	<0.001
Right kidney	832 (55)	690 (45)	<0.001

GN, Glomerulonephritis; HD, hemodialysis; PD, peritoneal dialysis; HLA, Human Leukocyte Antigen; RRT, renal replacement therapy.

primary renal disease, length of time on dialysis and pre-existing cardiovascular disease. Graft failure was adjusted as a time-varying covariate in the model. Recipients with graft failure had a much higher risk of death (aHR = 2.84, 95% CI 2.00–4.03, $p < 0.001$).

Degree of Obesity and Clinical Outcomes

We performed a dose-response analysis to examine the association between the degree of obesity and clinical outcomes. The 1,522 obese recipients were classified as 1,173 (77%) class I; 304 (20%) class II and 45 (3%) class III (**Table 3**). We combined obesity classes II and III due to insufficient patient numbers in obesity class III.

When comparing with non-obese recipients, class II/III obese recipients had a 1.44 higher rate of DGF whilst class I obese recipients had a 1.20 higher rate. This trend was not statistically significant when comparing class I obese recipients to class II/III obese recipients (**Figure 4**. aRR 1.20, 95% CI 0.88–1.62, $p = 0.25$). A similar non-significant trend was found for death-censored graft failure and death. Class II/III obese recipients had a 1.67 higher rate of death-censored graft failure compared to a 1.16 higher rate for class I obese recipients (aHR 1.45, 95% CI 0.95–2.21, $p = 0.085$). Class II/III obese recipients had a 1.42 higher rate of death compared to a 1.26 higher rate for class I obese recipients (aHR 1.10, 95% CI 0.71–1.71, $p = 0.66$).

DISCUSSION

In this paired analysis, we controlled for unmeasured donor-related characteristics by comparing outcomes of kidneys from the same donor and demonstrated that obese recipients were more likely to experience DGF, death-censored graft failure and death after deceased donor kidney transplantation when comparing with non-obese recipients.

Studies examining the impact of obesity on kidney transplant outcomes have shown conflicting results, but may be confounded by unmeasured donor-related characteristics. These may include donor kidney function and proteinuria, pre-renal insults to the donor kidney during terminal illness, use of inotropic medications and nephrotoxin exposure, many of which are not adequately captured nor accounted for in existing studies, The majority of published studies have reported an increased risk of delayed graft function for obese recipients [12,13,15]. However, the impact of DGF on long-term transplant outcomes including graft and patient survival remains contentious. Our results are consistent with two systematic review and meta-analyses which showed an increased risk of graft failure for obese recipients compared to non-obese recipients [14,15]. In terms of overall mortality, two meta-analyses reported an increased risk of death for obese recipients, in line with our results [12,14]. One

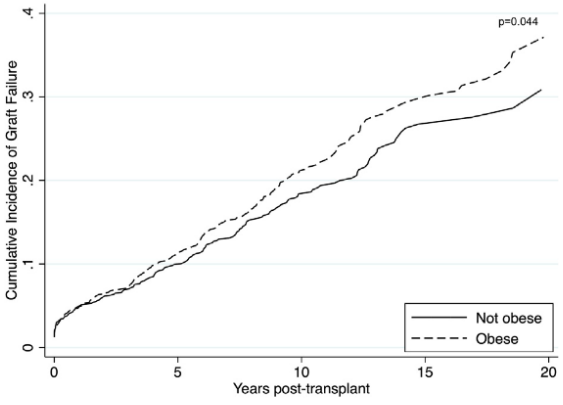


FIGURE 2 | Unadjusted cumulative incidence of graft failure using Aalen-Johansen estimator to account for death as a competing event among obese (BMI >27.5 kg/m^2 for Asians; >30 kg/m^2 for non-Asians) and non-obese recipients. Obese recipients had a higher incidence of graft failure compared to non-obese recipients ($p = 0.044$).

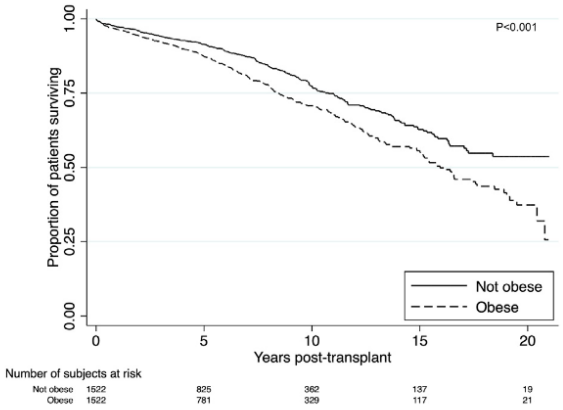


FIGURE 3 | Kaplan-Meier estimates of patient survival after renal transplant among obese (BMI >27.5 kg/m^2 for Asians; >30 kg/m^2 for non-Asians) and non-obese recipients. Unadjusted patient survival was superior for non-obese recipients ($p < 0.001$).

systematic review and meta-analysis reported no association between obesity and overall mortality [27], however, this analysis included only six studies that reported hard transplant outcomes. Another systematic review and meta-analysis reported that there was an increased risk of graft failure and death only for studies that included obese patients who were transplanted before 2000, but no association for those transplanted after 2000 [13]. This contradicts our study result which included patients transplanted after 2000 only.

We found a trend towards increasing risks of DGF, graft failure and death with increasing degrees of obesity, however, this increase was not statistically significant. The number of recipients with class II/III obesity in our study was small and likely inadequately powered to provide certainty. A recent US registry study reported 27% lower odds of DGF ($p < 0.001$) for recipients with BMI >30–35 versus BMI >35 kg/m^2, though no difference in graft or patient survival at a median follow-up of 3.9 years [28].

Our study provides detailed insights from a large, bi-national kidney transplant registry over a 20-year period. We examined a different BMI cut-off for the Asian population that has significant structural variations compared to the Western population. Donor-related factors, which could potentially impact outcomes such as DGF, were carefully accounted and unmeasured confounders were evenly matched by the use of a matched-pair analysis. As randomized controlled trials to compare outcomes for obese versus non-obese recipients are not feasible, we believe the paired analysis we have performed provides the most rigorous assessment of the impact of obesity on hard outcomes following kidney transplantation.

Obesity has more than doubled worldwide in the past 20 years. Although our study has demonstrated that obesity was strongly associated with an increased risk of DGF and inferior long-term outcomes, previous work has clearly indicated that transplantation yields superior outcomes compared to remaining on dialysis for the majority of obese candidates for transplantation [8,9,29]. Our findings should be used to inform patients and providers of the increased risks associated with transplantation for obese recipients. Rather than avoiding transplantation for the obese, these data should encourage the pursuit of strategies to improve outcomes, such as weight-loss management prior to transplantation and improvements in peri-operative management to reduce the incidence of DGF and other complications associated with obesity. This poses two key questions: (1) can transplant management be optimized for obese recipients; and (2) can weight loss before or post-transplant improve transplant outcomes for obese candidates. Some studies have reported an "obesity paradox" where a decrease in BMI for dialysis patients was associated with worse graft and patient survival [30–33]. However, in these studies there was no clear indication of whether the weight loss was intentional, or unintentional due to disease progression or comorbidities. The reason behind the paradox remains unknown. Hypotheses include that obese patients may be less prone to protein energy wasting [34], have a better appetite and well-preserved energy stores, have better hemodynamic tolerance, stem cell mobilization, hemodynamic tolerance, and more efficient disposal of lipophilic uremic toxins [35,36]. A healthy lifestyle that is beneficial to the general public has been shown to improve mortality in chronic kidney disease (CKD) patients [37]. Intentional weight loss in the pre-transplant population may reduce the risk of wound infection, DGF, death-censored failure and reduce the length of hospitalization and alleviates the financial burden on transplant programs [38]. Weight-management programs for CKD patients that include a renal-specific diet, regular exercise combined with anti-obesity medication have been reported to be effective in weight reduction, with improved functional ability, graft function and significantly longer adverse event-free period for the combined outcome of all-cause mortality, myocardial infarction, stroke, and hospitalization for congestive heart failure [39–41]. Another possible intervention is bariatric surgery. A recent study reported a lowering of 7 kg/m^2 in BMI in the long-term and a median of 2.4 years longer life expectancy in the bariatric surgery cohort compared to usual obesity care [42]. However, there is very limited data on the outcomes of bariatric surgery on dialysis and kidney transplant patients. In a retrospective cohort study, researchers demonstrated lower all-cause mortality at 5 years for

TABLE 3 | Degree of obesity was categorized into obese class I, obese class II, and obese class III according to World Health Organization guidelines.

Classification	BMI, kg/m^2, non-Asians	BMI, kg/m^2, Asians	n (%)
Obese class I	30–34.9	27.5–32.4	1,173 (77)
Obese class II	35–39.9	32.5–37.4	304 (20)
Obese class III	40+	37.5+	45 (3)

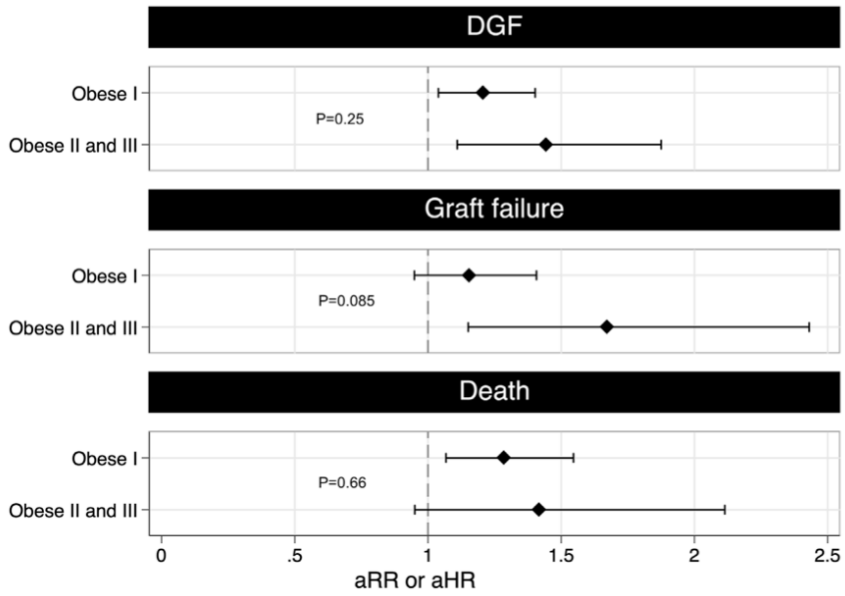


FIGURE 4 | The figure shows the multivariable adjusted risk ratio for DGF and adjusted hazard ratio for graft failure and death grouped by class I obese and class II and III obese. A higher risk of DGF and graft failure was found for greater vs. lesser degrees of obesity, suggesting a possible dose-response relationship (DGF: aRR 1.20, 95% CI 0.88–1.62, $p = 0.25$; graft failure: aHR 1.45, 95% CI 0.95–2.21, $p = 0.085$). The adjusted rate ratio for DGF was estimated using conditional Poisson regression after adjusting for dialysis modality prior to transplant, ischemia time and pre-existing cardiovascular disease. The adjusted hazard ratio for graft failure was estimated using stratified Cox regression after adjusting for DGF, age at transplantation, ethnicity, HLA mismatches and donor kidney side. The adjusted hazard ratio for death was estimated using stratified Cox regression after adjusting for graft failure, age at transplantation, time since first renal replacement therapy, HLA mismatches, pre-existing cardiovascular disease and pre-existing diabetes. aHR, adjusted hazard ratio; aRR, adjusted rate ratio; DGF, delayed graft function; HLA, Human Leukocyte Antigen.

obese ESKD patients who had undergone bariatric surgery [43]. In another retrospective study, bariatric surgery before or after kidney transplantation was reported to be associated with reduced risk of graft failure and mortality compared to control with no bariatric surgery [44]. More data are required to determine if bariatric surgery does improve long-term outcomes from kidney transplantation.

Several limitations should be noted in considering our analysis. First, it is a retrospective registry study that depends on the quality of data captured. Second, the analysis used BMI as the only indicator for categorizing obesity, which does not differentiate between fat and muscle mass, nor between visceral and subcutaneous fat. Other methods such as waist circumference, waist-to-hip ratio, *in vivo* neutron activation analysis (IVNAA), densitometry, deuterium oxide dilution, and dual energy X-ray absorptiometry (DXA) are also available and may enhance specificity. However, such measures are not routinely used in candidate assessment and are not reported to ANZDATA. Third, there may be other potential confounders that are unaccounted for, such as social status, genetic factors, immunosuppression and drug dosing. Fourth, even though significant confounders were adjusted for in the model, residual confounding is still possible. Five, indication of whether dialysis is required after transplantation may vary between centers resulting in potential center effect for DGF which was not accounted for. Six, there may be a loss of statistical power due to pairing. However, we believe that it is important to utilize a matched pair analysis to minimize bias due to donor-related characteristics, such as donor kidney function, hemodynamic instability during organ procurement, use of vasoactive medications and exposure to nephrotoxins, all of which are captured crudely or not at all in registry data. Finally, the study cohort was predominantly Caucasian. The remaining non-Caucasian patient group was heterogeneous, with 40% and 23% of the Indigenous group being Australian Aboriginal and New Zealand Mauri, and 25% and 23% of the Asian group being Indian and Chinese, respectively. Therefore, the comparison between Caucasian and non-Caucasian patients in our study is different from the same comparison in the US where around 70% of non-Caucasian patients were Black/African American [45].

In conclusion, our study demonstrates a relationship between obesity and post-transplant outcomes after carefully controlling for donor-related factors in a paired kidney analysis. Addressing obesity is an unmet clinical need in kidney transplantation. Transplantation is recommended for many obese candidates as it is acknowledged to yield superior outcomes to dialysis. However, design and evaluation of strategies to: (1) optimize transplant management for obese recipients; and (2) reduce the prevalence of obesity among transplant candidates are required.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The data are not available due to privacy and ethical considerations. Requests to access these datasets should be directed to https://anzdata.org.au/.

AUTHOR CONTRIBUTIONS

BS—prepared the study protocol, acquired the data, designed and conducted the statistical analysis, interpreted the results, drafted the manuscript, edited the manuscript and approved the final version of the manuscript. TY—conceived the study, designed the statistical analysis, interpreted the results, edited the manuscript and approved the final version of the manuscript. JX—prepared the study protocol, acquired the data and approved the final version of the manuscript. KW—interpreted the results, edited the manuscript and approved the final version of the manuscript. JL—conceived the study, designed the statistical analysis, interpreted the results, edited the manuscript and approved the final version of the manuscript. SC—conceived the study, designed the statistical analysis, interpreted the results, edited the manuscript and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The data reported here have been supplied by Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2023.11107/full#supplementary-material

REFERENCES

1. World Health Organization. *Obesity and Overweight* (2021). Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (Accessed March 23, 2022).
2. Gore JL, Pham PT, Manovich GM, Wilkinson AH, Rosenthal JT, Lipshutz GS, et al. Obesity and Outcome Following Renal Transplantation. *Am J Transpl* (2006) 6(2):357–63. doi:10.1111/j.1600-6143.2005.01198.x
3. Friedman AN, Miskulin DC, Rosenberg IH, Levey AS. Demographics and Trends in Overweight and Obesity in Patients at Time of Kidney Transplantation. *Am J Kidney Dis* (2003) 41(2):480–7. doi:10.1053/ajkd.2003.50059
4. Wakam GK, Sheetz KH, Gerhardinger L, Montgomery JR, Waits SA. Population-based Trends in Obesity and Kidney Transplantation Among Patients with End-Stage Kidney Disease. *Transpl Direct* (2021) 7(12):e787. doi:10.1097/txd.0000000000001163
5. Parikh CR, Klem P, Wong C, Yalavarthy R, Chan L. Obesity as an Independent Predictor of Posttransplant Diabetes Mellitus. *Transpl P* (2003) 35(8):2922–6. doi:10.1016/j.transproceed.2003.10.074
6. Lentine KL, Schnitzler MA, Abbott KC, Li L, Burroughs TE, Irish W, et al. De Novo Congestive Heart Failure after Kidney Transplantation: A Common Condition with Poor Prognostic Implications. *Am J Kidney Dis* (2005) 46(4):720–33. doi:10.1053/j.ajkd.2005.06.019
7. Young JB, Neumayer HH, Gordon RD. Pretransplant Cardiovascular Evaluation and Posttransplant Cardiovascular Risk. *Kidney Int* (2010) 78(118):S1–S7. doi:10.1038/ki.2010.209
8. Gill JS, Lan J, Dong J, Rose C, Hendren E, Johnston O, et al. The Survival Benefit of Kidney Transplantation in Obese Patients. *Am J Transpl* (2013) 13(8):2083–90. doi:10.1111/ajt.12331
9. Krishnan N, Higgins R, Short A, Zehnder D, Pitcher D, Hudson A, et al. Kidney Transplantation Significantly Improves Patient and Graft Survival Irrespective of BMI: A Cohort Study. *Am J Transpl* (2015) 15(9):2378–86. doi:10.1111/ajt.13363
10. Pham PT, Danovitch GM, Pham PT. Kidney Transplantation in the Obese Transplant Candidates: To Transplant or Not to Transplant? *Semin Dial* (2013) 26(5):568–77. doi:10.1111/sdi.12109
11. Zrim S, Furlong T, Grace B, Meade A. Body Mass index and Postoperative Complications in Kidney Transplant Recipients. *Nephrology* (2012) 17(6):582–7. doi:10.1111/j.1440-1797.2012.01621.x
12. Lafranca JA, Ijermans JN, Betjes MG, Dor FJ. Body Mass index and Outcome in Renal Transplant Recipients: a Systematic Review and Meta-Analysis. *Bmc Med* (2015) 13(1):111. doi:10.1186/s12916-015-0340-5
13. Nicoletto BB, Fonseca NKO, Manfro RC, Gonçalves LFS, Leitão CB, Souza GC. Effects of Obesity on Kidney Transplantation Outcomes: a Systematic Review and Meta-Analysis. *Transplantation* (2014) 98(2):167–76. doi:10.1097/tp.0000000000000028
14. Ahmadi SF, Zahmatkesh G, Streja E, Molnar MZ, Rhee CM, Kovesdy CP, et al. Body Mass Index and Mortality in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis. *Am J Nephrol* (2014) 40(4):315–24. doi:10.1159/000367812
15. Hill CJ, Courtney AE, Cardwell CR, Maxwell AP, Lucarelli G, Veroux M, et al. Recipient Obesity and Outcomes after Kidney Transplantation: a Systematic Review and Meta-Analysis. *Nephrol Dial Transpl* (2015) 30(8):1403–11. doi:10.1093/ndt/gfv214
16. Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, et al. Deceased-Donor Characteristics and the Survival Benefit of Kidney Transplantation. *Jama* (2005) 294(21):2726–33. doi:10.1001/jama.294.21.2726
17. Massie AB, Luo X, Chow EKH, Alejo JL, Desai NM, Segev DL. Survival Benefit of Primary Deceased Donor Transplantation with High-KDPI Kidneys. *Am J Transpl* (2014) 14(10):2310–6. doi:10.1111/ajt.12830
18. Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJ, et al. Analysis of Factors that Affect Outcome after Transplantation of Kidneys Donated after Cardiac Death in the UK: a Cohort Study. *Lancet* (2010) 376(9749):1303–11. doi:10.1016/s0140-6736(10)60827-6
19. WHO Expert Consultation. Appropriate Body-Mass index for Asian Populations and its Implications for Policy and Intervention Strategies. *Lancet* (2004) 363(9403):157–63. doi:10.1016/s0140-6736(03)15268-3
20. World Health Organization, International Diabetes Institute, International Association for the Study of Obesity, International Obesity Task Force. *The Asia-Pacific Perspective: Redefining Obesity and its Treatment*. WHO (2000).
21. Low S, Chin MC, Ma S, Heng D, Deurenberg-Yap M. Rationale for Redefining Obesity in Asians. *Ann Acad Med Singap* (2009) 38(1):66–74. doi:10.47102/annals-acadmedsg.v38n1p66

22. Australia and New Zealand Dialysis and Transplant Registry. *ANZDATA Data Dictionary* (2023). Available at: https://www.anzdata.org.au/anzdata/services/data-management/data-dictionary/ (Retrieved March 1, 2023).
23. Hardin JW, Hilbe JM. *Generalized Linear Models and Extensions Fourth Edition*. College Station: Stata Press (2018).
24. Cummings P, McKnight B. Analysis of Matched Cohort Data. *Stata J* (2004) 4(3):274–81. doi:10.1177/1536867x0400400305
25. Cummings P, McKnight B, Greenland S. Matched Cohort Methods for Injury Research. *Epidemiol Rev* (2003) 25(1):43–50. doi:10.1093/epirev/mxg002
26. Chowdhury MZI, Turin TC. Variable Selection Strategies and its Importance in Clinical Prediction Modelling. *Fam Med Community Heal* (2020) 8(1): e000262. doi:10.1136/fmch-2019-000262
27. Ladhani M, Craig JC, Irving M, Clayton PA, Wong G. Obesity and the Risk of Cardiovascular and All-Cause Mortality in Chronic Kidney Disease: a Systematic Review and Meta-Analysis. *Nephrol Dial Transpl* (2017) 32(3): 439–49. doi:10.1093/ndt/gfw075
28. Sureshkumar KK, Chopra B, Josephson MA, Shah PB, McGill RL. Recipient Obesity and Kidney Transplant Outcomes: A Mate-Kidney Analysis. *Am J Kidney Dis* (2021) 78(4):501–10.e1. doi:10.1053/j.ajkd.2021.02.332
29. Bennett WM, McEvoy KM, Henell KR, Pidikiti S, Douzdjian V, Batiuk T. Kidney Transplantation in the Morbidly Obese: Complicated but Still Better Than Dialysis. *Clin Transpl* (2011) 25(3):401–5. doi:10.1111/j.1399-0012.2010.01328.x
30. Schold JD, Srinivas TR, Guerra G, Reed AI, Johnson RJ, Weiner ID, et al. A 'Weight-Listing' Paradox for Candidates of Renal Transplantation? *Am J Transpl* (2007) 7(3):550–9. doi:10.1111/j.1600-6143.2006.01629.x
31. Molnar MZ, Streja E, Kovesdy CP, Bunnapradist S, Sampaio MS, Jing J, et al. Associations of Body Mass Index and Weight Loss with Mortality in Transplant-Waitlisted Maintenance Hemodialysis Patients. *Am J Transpl* (2011) 11(4):725–36. doi:10.1111/j.1600-6143.2011.03468.x
32. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD, McAllister CJ, Shinaberger CS, Gjertson DW, et al. Association of Morbid Obesity and Weight Change over Time with Cardiovascular Survival in Hemodialysis Population. *Am J Kidney Dis* (2005) 46(3):489–500. doi:10.1053/j.ajkd.2005.05.020
33. Kalantar-Zadeh K, Kuwae N, Wu DY, Shantouf RS, Fouque D, Anker SD, et al. Associations of Body Fat and its Changes over Time with Quality of Life and Prospective Mortality in Hemodialysis Patients. *Am J Clin Nutr* (2006) 83(2): 202–10. doi:10.1093/ajcn/83.2.202
34. Glicklich D, Mustafa MR. Obesity in Kidney Transplantation: Impact on Transplant Candidates, Recipients, and Donors. *Cardiol Rev* (2019) 27(2): 63–72. doi:10.1097/CRD.0000000000000216
35. Stenvinkel P, Lindholm B. Resolved: being fat is good for dialysis patients: the Godzilla effect: con. *J Am Soc Nephrol* (2008) 19(6):1059–64. doi:10.1681/01.asn.0000926896.67402.33
36. Carrero JJ, Qureshi AR, Axelsson J, Avesani CM, Suliman ME, Kato S, et al. Comparison of Nutritional and Inflammatory Markers in Dialysis Patients with Reduced Appetite. *Am J Clin Nutr* (2007) 85(3):695–701. doi:10.1093/ajcn/85.3.695
37. Ricardo AC, Madero M, Yang W, Anderson C, Menezes M, Fischer MJ, et al. Adherence to a Healthy Lifestyle and All-Cause Mortality in CKD. *Clin J Am Soc Nephro* (2013) 8(4):602–9. doi:10.2215/cjn.00600112
38. Sever MS, Zoccali C. Moderator's View: Pretransplant Weight Loss in Dialysis Patients: Cum Grano Salis. *Nephrol Dial Transpl* (2015) 30(11):1810–3. doi:10.1093/ndt/gfv333
39. Cook SA, MacLaughlin H, Macdougall IC. A Structured Weight Management Programme Can Achieve Improved Functional Ability and Significant Weight Loss in Obese Patients with Chronic Kidney Disease. *Nephrol Dial Transpl* (2008) 23(1):263–8. doi:10.1093/ndt/gfm511
40. MacLaughlin HL, Cook SA, Kariyawasam D, Roseke M, Niekerk MV, Macdougall IC. Nonrandomized Trial of Weight Loss with Orlistat, Nutrition Education, Diet, and Exercise in Obese Patients with CKD: 2-Year Follow-Up. *Am J Kidney Dis* (2010) 55(1):69–76. doi:10.1053/j.ajkd.2009.09.011
41. MacLaughlin HL, Hall WL, Condry J, Sanders T, Macdougall IC. Participation in a Structured Weight Loss Program and All-Cause Mortality and Cardiovascular Morbidity in Obese Patients with Chronic Kidney Disease. *J Ren Nutr* (2015) 25(6):472–9. doi:10.1053/j.jrn.2015.05.001
42. Carlsson L, Sjöholm K, Jacobson P, Andersson-Assarsson JC, Svensson PA, Taube M, et al. Life Expectancy after Bariatric Surgery in the Swedish Obese Subjects Study. *New Engl J Med* (2020) 383(16):1535–43. doi:10.1056/nejmoa2002449
43. Sheetz KH, Gerhardinger L, Dimick JB, Waits SA. Bariatric Surgery and Long-Term Survival in Patients with Obesity and End-Stage Kidney Disease. *Jama Surg* (2020) 155(7):581–8. doi:10.1001/jamasurg.2020.0829
44. Cohen JB, Lim MA, Tewksbury CM, Torres-Landa S, Trofe-Clark J, Abt PL, et al. Bariatric Surgery before and after Kidney Transplantation: Long-Term Weight Loss and Allograft Outcomes. *Surg Obes Relat Dis* (2019) 15(6): 935–41. doi:10.1016/j.soard.2019.04.002
45. United States Renal Data System. *USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States* (2021). Available at: https://adr.usrds.org/2021/end-stage-renal-disease/7-transplantation (Accessed March 23, 2022).