Using patient-reported outcomes to improve prognostication in advanced gastro-oesophageal cancer

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy at The University of Sydney

Faculty of Medicine and Health
The University of Sydney
Australia
2025

Statement of originality

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

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

Sayeda Kamrun Naher

Abstract

Advanced gastro-oesophageal cancer is associated with poor prognosis and short, but variable, survival times. The goal of this PhD research was to improve prognostication for individuals with advanced gastro-oesophageal cancer by combining standard clinicopathological information from clinical trials with patient-reported outcomes (PROs).

We identified, organised, and summarised survival data from 44 randomised clinical trials, to provide estimated ranges for best-case, typical, and worst-case scenarios for survival time according to lines and types of treatment. This approach provides clinicians with information that they can use to estimate and explain scenarios for survival time to their patients seeking quantitative information about their prognosis.

In a separate scoping review, we identified, organised, and summarised 7 studies assessing the prognostic value of patient-reported outcomes as predictors of subsequent survival time in advanced gastro-oesophageal cancer. We found that appetite loss, pain, physical functioning, role functioning, social functioning, and global quality of life provided useful prognostic information in this setting.

We then developed and validated a multivariable prognostic model incorporating both PROs and standard clinicopathological features. We developed the model using data from INTEGRATE IIa (n=251) trial and validated it using INTEGRATE (n=152) data, demonstrating their predictive accuracy in an independent cohort. Both were randomised controlled trials of second and subsequent line treatment in advanced gastro-oesophageal cancer. This multivariable model included patient reported measures of appetite loss, constipation, fatigue, and pain and provided prognostic estimates that were more accurate and better

calibrated than those based on only clinicopathological features alone, indicating the importance of considering self-ratings of aspects of health-related quality of life when prognosticating in this setting.

This body of work provides coherent, structured strategies to help oncologists estimate and explain survival time and probabilities to patients with advanced gastro-oesophageal cancer seeking information about their prognosis. This research facilitates a personalised, patient-centred approach to prognostication that should support better-informed shared decision making, communication, survivorship care planning and overall patient care.

Publications Arising from this Thesis

Peer-reviewed journal publications

Chapter 2 of this thesis is published as:

Naher SK, Mercieca-Bebber R, Siu D, Stockler MR, Kiely BE, Grimison P. Estimating survival scenarios in advanced or metastatic gastric and oesophageal adenocarcinoma: a systematic review of randomized-controlled trials. Curr Med Res Opin. 2024 Aug;40(8):1357-1367. doi: 10.1080/03007995.2024.2376129. Epub 2024 Jul 13. PMID: 38961804.

All authors contributed to the study conception and design. Sayeda K. Naher led and conducted the material preparation, data collection, and analysis, with support from Derrick Siu. Sayeda K. Naher drafted the initial version of the manuscript. All authors reviewed, revised, and approved the final manuscript.

Chapter 3 of this thesis is published as:

Naher SK, Mercieca-Bebber R, Siu D, Grimison P, Stockler MR. Prognostic value of patient reported outcomes in advanced gastro-oesophageal cancer: a systematic review. Intern Med J. 2023 Nov;53(11):1946-1955. doi: 10.1111/imj.16209. Epub 2023 Aug 22. PMID: 37605848.

All authors contributed to the study conception and design. Sayeda K. Naher led and conducted the material preparation, data collection, and analysis, with support from Derrick

Siu. Sayeda K. Naher drafted the initial version of the manuscript. All authors reviewed, revised, and approved the final manuscript.

Chapter 4 of this thesis is published as:

Development and Validation of a Prognostic Model incorporating patient reported outcomes for Advanced Gastric and Oesophageal Carcinoma (AGOC) Using Individual Patient Data from Two AGITG Randomised Clinical Trials.

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Sayeda Kamrun Naher, David Espinoza, Peter Grimison, Martin Stockler, Rebecca Mercieca-Bebber, and Katrin Marie Sjoquist contributed to the conception and design of the study. Material preparation, data collection, and analysis were conducted by Sayeda K. Naher and David Espinoza. Data collection for the included trials was supported by Nick Pavlakis, Kohei Shitara, David Goldstein, and Katrin Marie Sjoquist. Sayeda K. Naher drafted the initial manuscript, and all authors provided input on subsequent revisions. All authors reviewed and approved the final version of the manuscript.

Published abstracts and conference presentations

Sayeda Naher, Rebecca Mercieca-Bebber, Derrick Siu, Peter Grimison, Martin Stockler, Belinda Kiely. **Estimating survival scenarios in advanced oesophageal and gastric (AOG) adenocarcinoma treated with systemic therapy: Systematic review of randomised-controlled trials (RCT).** Oral Presentation Abstracts. Asia-Pacific Journal of Clinical Oncology 19:27-40, 2023.

1. Oral abstract and poster, Medical Oncology Group of Australia (MOGA), Annual Scientific Meeting, August 2023 (Perth, Australia).
2. poster presentation, New South Wales (NSW) Cancer Conference September 2023 (Sydney, Australia).

Sayeda Kamrun Naher, Peter S. Grimison, Ho Wai Derrick Siu, Rebecca Mercieca-Bebber, and Martin R. Stockler. **Prognostic value of patient-reported outcomes (PROs) in advanced gastroesophageal cancer (GO): A systematic review.** Journal of Clinical Oncology 2022 40:4_suppl, 251-251.

1. Oral abstract and short video presentation, Australasian Gastro-intestinal Trials Group (AGITG), Annual Scientific Meeting, October 2021 (virtual).
2. Poster and short video presentation, Clinical Oncology Society of Australia (COSA), Annual Scientific Meeting, November 2022(virtual).

3. Poster and short video presentation, American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, January 2022(virtual).

S. Naher, D. Espinoza, P. Grimison, K. Shitara, N. Pavlakis, D. Goldstein, et al. **Development and validation of a prognostic model for advanced gastric and oesophageal carcinoma (AGOC) using individual patient data from two clinical trials**. Journal of Clinical Oncology 2025 Vol. 43 Pages 499-499. DOI: 10.1200/JCO.2025.43.4_suppl.499

1. Poster and short video presentation, American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium, January 2025 (San Francisco, United States of America (USA).

Supervisors statement

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

Professor Martin Stockler

Associate Professor Peter Grimison

Dr Rebecca Mercieca-Bebber

Acknowledgements

I would like to express my deepest gratitude to Dr. Rebecca Mercieca-Bebber, for her immense support throughout my PhD. Over the past four years, I have learned so much thanks to her expert advice, guidance, encouragement, patience, and dedication. Her mentorship and friendship have been invaluable to me.

I am grateful to Professor Martin Stockler, for introducing me to clinical research and encouraging me to pursue it. His guidance, support, passion for research and education, and commitment to excellence have been instrumental in my development.

I am grateful to Associate Professor Peter Grimison, for his invaluable contributions, insightful guidance, and unwavering support throughout the course of my research.

Dr. Mercieca-Bebber, A/Prof Grimison, and Professor Stockler have provided me with tremendous opportunities throughout my PhD, for which I am always grateful.

I am thankful to my fellow PhD students, especially Derrick Siu for his assistance with the systematic review (chapter 2 and 3), A/Prof. Katrin Sjoquist for her continuous feedback and review of the prognostic model developed as part of this thesis (Chapter 4), and David

Espinoza for expert statistical support with model development and validation (Chapter 4).

I also gratefully acknowledge the assistance from two University of Sydney Librarians -Tess Aitken and Jessica Hughes for developing search terms to identify clinical trials in Chapter 2, and for the systematic review presented as Chapter 3.

Special thanks also go to the patients and doctors who participated in the clinical trials and contributed to the studies presented in this thesis.

I appreciate the financial support I received through my NHMRC Clinical Trials Centre PhD Scholarship.

I am deeply grateful to my wonderful parents and brothers for their unconditional love and unwavering belief in me. Their support and encouragement have made everything possible.

To my delightful children, Ethan and Mahina, thank you for the joy you bring to my life.

Finally, to my loving husband, Meraj, I am forever grateful for your patience, kindness, support, and encouragement over the past four years. Your unwavering support has been crucial in making this thesis possible.

Authorship attribution statement

I undertook this PhD at the NHMRC Clinical Trials Centre, University of Sydney under the supervision of Professor Martin Stockler, Associate Professor Peter Grimison, and Dr Rebecca Mercieca-Bebber.

This thesis is presented in a hybrid format combining traditional chapters (Chapters 1 and 5) with original articles submitted for publication in peer-reviewed journals (Chapters 2, 3 and 4). When this thesis was submitted for assessment, Chapters 2 and 3 had been published; and Chapter 4 was submitted and under review.

I, Sayeda K. Naher, was primarily responsible for the development of the research proposals, comprehensive literature review, data collection and analysis, interpretation of findings, and the overall drafting of the thesis.

No content produced by generative AI tools has been used in the preparation of this thesis.

Sayeda Kamrun Naher

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

Professor Martin Stockler

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List of Frequently Used Abbreviations

ALP	Alkaline Phosphatase
BMI	Body mass index
BMJ	British Medical Journal
BSC	Best supportive care
CA	Carbohydrate antigen
CI.	Chemotherapy and immunotherapy combined
CI	Confidence interval
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy- General
FDA	Food and Drug Administration
GO	Gastro-oesophageal
HER	Human epidermal growth factor
HQOL	Health related quality of life
HR	Hazard ratio
IQR	Interquartile range
KM	Kaplan-Meier
LASSO	Least absolute shrinkage and selection operator
LDH	Lactate dehydrogenase
MOS	Medical Outcomes Study
NCI	National Cancer Institute
NLR	Neutrophil-lymphocyte ratio
OS	Overall survival
PFS	Progression free survival

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient reported outcome
PROM	Patient reported outcome measure
PS	Performance status
PT DATA	Patient's Disease and Treatment Assessment
QOL	Quality of life
QLQ-C30	Quality of life questionnaire core30
QLQ- STO 22	Quality of life questionnaire- Stomach (gastric) cancer module
QUIPS	Quality in Prognosis Studies
RCT	Randomised controlled trial
SCC	Squamous cell carcinoma
SF-20	20-Item Short Form Health Survey

Chapter 1

Background

1.1 Overview

This chapter gives context for my thesis on the topic of estimating the survival of people with advanced gastro-oesophageal cancer.

I begin by highlighting some basic concepts regarding the meaning and importance of prognostication in the context of advanced cancer, as well as methods for estimating survival and exploring various survival scenarios. I explain the use and application of patient-reported outcomes (PROs) in oncology practice, with particular focus on their application in prognostication.

Furthermore, I describe current approaches for predicting survival in advanced gastro-oesophageal cancer, specifically adenocarcinoma, hereafter referred to as GO cancer, which is the focus population of this thesis. I also describe existing prognostic models for GO cancer and the importance of developing and validating prognostic models that incorporate PROs.

1.2 What is prognostication?

In medicine, prognosis refers to a forecast of the future outcomes of a specific disease or health condition.[1,2] An official website of the United States (US) government NIH – National Cancer Institute defined prognosis as, "The likely outcome or course of a disease; the chance of recovery or recurrence".[3] It could be the value of an outcome or the probability of a particular outcome, such as death by, or survival beyond, a specified time point.[1] Hippocrates, often regarded as the father of medicine, mentioned prognosis in "The book of Prognostics" and suggested that estimating prognosis is one of the most critical skills that a physician can develop.[4] The Oxford English Dictionary defines prognosis as, "A prediction of the probable course and outcome of a disease or of an individual case of disease; the course or outcome itself."[5] In medicine, outcomes are often specific events, such as death or specified complications, but they may also be disease progression, (changes in) pain, or quality of life. [6] Prognosis encompasses both the anticipated course of the illness and its ultimate outcome. Prognostication is the action of making (estimating) a prognosis. In this thesis, I focus on prognostication primarily in terms of overall survival time from a specified time point, specifically randomisation in a trial, or the start of a specific treatment.

1.3 Importance of prognostication

Overall survival is an important endpoint in oncology clinical trials, particularly in advanced cancers, due to its unambiguous and absolute nature, meaning there is minimal risk of measurement error in reporting overall survival, as compared with other endpoints.[7] It is also an

important outcome for patients, carers and clinicians. Cancer patients, their families and clinicians value accurate information about prognosis as it guides treatment decisions and plans for the future.[8] A study published in the *Journal of Clinical Oncology* found that patients who reported recent conversations with their oncologists about prognosis had a significant improvement in their understanding of the terminal nature of their illness.[9]

A study from Spain reported in 2023 that 52% of 863 participants with advanced cancer wanted information about their prognosis.[10] Another study in US patients with advanced cancer reported that 71% of the 590 participants wanted information about their life expectancy, but only 18% recalled disclosure of their prognosis by a physician. [11]

1.4 How do doctors estimate survival time?

Estimating a patient's survival time is a complex and critical aspect of patient care.[12] In routine clinical practice, clinical trial data provide valuable insights into the effectiveness of treatments and the expected outcomes for people with characteristics similar to those who participated in the trials.[13] However, participants in clinical trials are often highly selected based on specific criteria, including age, stage of disease, performance status, comorbidities, test results, and other factors.[14] Clinical trial participants as a group generally have better outcomes than members of the broader community of all-comers with the same disease and treatment.[14]

As a result, the survival probabilities and times observed in clinical trials may need to be adjusted to account for individual patients treated in routine clinical practice, outside of trials. Medical professionals use various methods to make these personalised adjustments, including clinical

judgment based on their experience and expertise.[15] Adjustments may be required to account for factors such as age, performance status, comorbidities, symptoms, functional status, social support, and other attributes associated with outcomes.

The extent to which this personalisation improves prognostic estimates remains an open question for research.

Ultimately, the goal of estimating survival time is to provide patients and their families with information that helps them make informed decisions about their care, treatment, and plans. By understanding the limitations of clinical trial data and applying appropriate adjustments, doctors may be able to offer patients a clearer picture of what to expect and better support navigating their healthcare journey.

1.5 Kaplan-Meier curves and the description of survival data

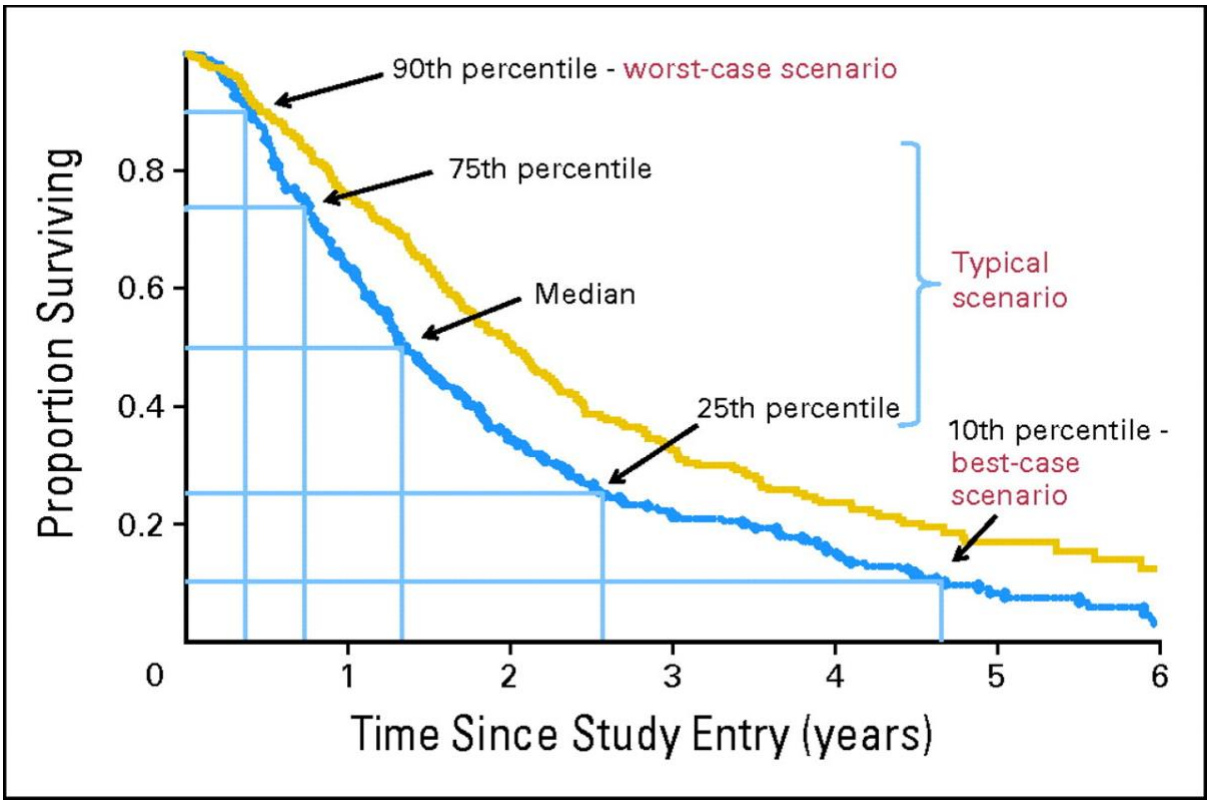
Kaplan-Meier (KM) curves are the most commonly used method to describe survival data in clinical trials and oncology research.[16-19] Published KM curves often form the basis of estimates. So, an understanding of how these are generated is crucial to understanding how survival is estimated for individual patients in clinical practice. The KM method was first reported in 1958 by E. L. Kaplan and Paul Meier in *The Journal of the American Statistical Association (JASA),* one of the premier statistical science journals.[16] They described a non-parametric statistic to estimate the survival function from lifetime data, including censored observations. The method of analysis requires three key data elements: 1) serial time (e.g. interval from randomisation, diagnosis, start of treatment); 2) status at serial time (1=event of interest, e.g. death; 0=censored, e.g. alive); and

3) study group (e.g. experimental, control).[18] The table is then arranged in ascending order by serial time, beginning with the shortest times for each group. KM analysis is typically performed with a statistical program such as SAS, SPSS, SigmaPlot, or R. The method includes a graphical representation (plot) of survival data. The y-axis is the survival probability, and the x-axis represents time. The plot is a step function, where vertical drops occur at time points when deaths occurred, and the depth of the drop represents the ratio of the number of subjects who died at that time point divided by the number followed for at least that long. KM survival curves are often summarised by the median survival time, that is, the length of time within which 50% of subjects have died, and beyond which 50% of subjects have survived. Results of trials and other clinical research studies are usually described by reporting and comparing median survival times. While the median survival time provides a reasonable single-number summary of a complex distribution, it is not an ideal summary statistic for describing survival data to patients and their families. Prognostic explanations should include indicators of variability around the point estimate. An essay written by evolutionary biologist and science writer Stephen Jay Gould highlighted the shortcomings of using the median survival time to describe the outcomes of a group, or to convey a prognosis to an individual, based on his own experience when diagnosed with peritoneal mesothelioma.[20] The median marks the midpoint of a distribution and is a misleading estimate of prognosis, because the outcomes of individuals in a distribution vary widely, and very few individuals have a survival time approximately equal to the median.

1.6 Scenarios for survival time

Above, I discussed estimating survival; however, in the context of communicating estimated survival to patients, the estimate must be communicated along with inherent uncertainty around that estimate. Instead of providing the median overall survival time, which can sometimes be shorter than the mean survival time, especially when there are many long-term survivors, using best-case, worst-case, and typical-case scenarios (a three-scenario strategy) has been recommended. [21] [22,23] This approach offers a more realistic and comprehensive understanding of survival outcomes and is also well understood by patients, family members, and healthcare professionals.[24] Figure 1 illustrates the best, typical and worst-case scenarios from the KM curve.

FIGURE 1. Percentiles and their corresponding scenarios of the Kaplan-Meier OS curve



Providing three scenarios for survival time, instead of a single point estimate of median survival time, is more accurate and conveys both a realistic hope for a survival time that is longer, and a realistic understanding that survival time might be much shorter. This approach was supported by a survey of 500 cancer patients, in which the majority of respondents agreed that explaining three scenarios, rather than a single point-estimate of median survival time, made more sense, was more helpful, was preferable, conveyed hope, reassured them, and was less upsetting.[25]

Explaining three scenarios helps patients grasp the range of possible outcomes, addressing the uncertainty inherent in medical prognosis. It allows patients to understand that their survival is likely to be longer or shorter than the median survival time, giving them a more balanced perspective.[26]

By presenting the best-case scenario, patients can maintain hope for a better-than-average outcome, which may be helpful for emotional well-being. Including a worst-case scenario helps patients and their families prepare for the possibility of a worse-than-average outcome, aiding in more informed decision-making and planning. Overall, the three-scenario approach is a more comprehensive and empathetic communication strategy, that aims to enhance patient understanding.

1.7 Prognostic models

A prognostic model is a structured combination of various predictors used to estimate the risks of a particular outcome for individual patients.[27] Prognostic information plays a supporting role

in the medical field by helping professionals more accurately predict the course of a disease or condition for individual patients, to better inform decisions about patient care and treatment.

Firstly, accurate prognostication supports decision-making about patient management.[27,28] Healthcare providers can use prognostic information to tailor treatment plans according to the expected progression of the disease. For example, in cases where prognosis is poor, providers may focus on palliative care or prioritise interventions that aim to improve the patient's quality of life rather than pursuing aggressive treatments with limited benefit.

Furthermore, prognostic information can inform decisions and policies about healthcare delivery.[29] By providing insights into the expected outcomes according to patient and disease characteristics, these models can enable more efficient allocation of healthcare resources.[30] For instance, identifying patients unlikely to benefit from costly interventions can avoid suffering and expenditure on unhelpful treatments. Hemingway et al. state that valid and reliable evidence about prognosis is necessary for individuals with the disease or health conditions, funders, and policymakers. [31] Estimation of prognosis to model the population burden of disease and evaluate the impact of healthcare performance is also valuable for policymakers.

Prognostic models play a crucial role in the design and analysis of clinical trials that evaluate new therapeutic interventions. By accounting for factors that influence disease progression and treatment response, these models help researchers identify suitable patient populations for inclusion in trials, sample size calculation, stratification, and optimise trial endpoints. This ensures that clinical trials are conducted with greater precision, yielding more meaningful results and advancing medical knowledge, ultimately leading to the development of effective treatments.

Prognostic models are designed to assist doctors in decision-making by offering more objective probability estimates, complementing other essential clinical information. Additionally, they enhance the comprehension of the factors influencing the progression and outcome of patients with a specific disease.[32] Prognostic models can also assist with trial design and planning by facilitating more accurate estimation of event rates, required sample sizes, and timelines for trials.[2,33]

However, there is less attention to prognostic research than to therapeutic or etiological research.[28] Even though questions about prognosis are essential and often asked by patients, research to guide clinicians is limited.[31] Simon and Altman described methodological and statistical problems of prognostic research.[34] They reported several important limitations of prognostic studies, including a lack of a priori hypotheses, unspecified eligibility criteria, inappropriate statistical methods, and failure to account for multiple hypotheses and/or statistical tests. These limitations undermine the reliability and validity of prognostic studies because the absence of a priori hypotheses encourages data-driven rather than evidence-based conclusions, unspecified eligibility criteria reduce generalisability and introduce bias, inappropriate statistical methods can distort findings, and failing to account for multiple hypotheses or statistical tests increases the risk of false-positive results, ultimately compromising the credibility of the research. Prognostic models that address these concerns are lacking in GO cancer.

In a series of four articles in the British Medical Journal (BMJ), Karel Moons and colleagues carefully explained the importance, design, analysis, and reporting of prognostic research.[32] A

key insight from Karel Moons' work was the necessity of further validation of prognostic models. Many more prognostic models are available than have been validated. Validation is essential for application in practice and to ensure generalisability. They also highlighted the relative paucity of prognostic research and suggested that further high-quality research be conducted prior to integrating prognostic models in routine clinical practice.[28]

Traditional prognostic models in oncology have primarily relied on clinicopathologic factors such as tumour stage, histological grade, molecular markers, and patient demographics, which offer valuable insights into disease progression and outcomes.[35] However, integrating patient-reported outcomes (PROs), particularly aspects of health-related quality of life (QOL) has the potential to improve prognostic models by capturing the patient's subjective experience of illness and treatment. PROs for prognostic models can be collected quickly, cheaply, and are non-invasive. By incorporating patient-centred data, prognostic models can provide a more comprehensive view of health status, improving risk assessment and supporting personalised care.[36] Incorporation of PRO may increase patient engagement, inform patient and provider education, shape policy, and potentially enhance service delivery and governance.[37]

1.8 Patient-reported outcomes (PROs) and quality of life (QOL)

The US Food and Drug Administration (FDA, 2009, p. 2) defines a patient-reported outcome (PRO) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else."[38] Symptoms, side effects, mood, functional status, aspects of quality of life (QOL), and overall well-

being are examples of outcomes that can be patient-reported. PROs can be measured in absolute terms (e.g., rating of pain at the present time) or as a change from a previous assessment (e.g., rating of change in pain compared with 24 hours ago).[39] PRO reports are distinct from assessments made by healthcare professionals or other observers as they reflect the patient's own perceptions, feelings, and observations, not those of another individual.

Several groups have developed and operationalised definitions of quality of life in relation to oncology. David Cella, a leading expert in measuring outcomes among cancer patients and assessing quality of life, defined PRO in the book "Patient-Reported Outcomes in Performance Measurement" as information on health care outcomes obtained directly from patients, without alteration or interpretation by clinicians or other health care professionals.[40] The European Organisation for Research and Development of Cancer (EORTC) defined the purpose of quality of life assessment as being: "to summarise the broad-based assessment of the combined impact of disease and treatment and the trade-off between the two."[41] Health-related quality of life (HRQoL) is a comprehensive, multidimensional concept that encompasses disease symptoms, treatment side effects, and functional status across physical, social, and mental health domains.[42] HRQoL outcomes are a significant subset of the broader category of PROs.

By incorporating patients' voices and priorities into healthcare decision-making, PROs contribute to patient-centred care and offer the potential to document and, thence, improve the quality of life of individuals affected by illness.

Measuring aspects of QOL using PROs can be informative in clinical trials evaluating healthcare interventions, and in routine practice when the condition or its treatment can affect quality of

life. De Ligt et al. explained in their review the increasing role of PROs in improving the quality of life of metastatic breast cancer patients.[43] According to this review, PROs can significantly enhance care by improving QOL, survival rates, and patient-provider communication.

The European Society of Medical Oncology (ESMO) has recommended monitoring of PROs as part of routine clinical care due to potential benefits on patient-doctor communication, patient satisfaction, treatment adherence, and symptom control.[44]

1.9 Patient-Reported Outcome Measures (PROMs) and quality of life measurement in oncology

Various psychometric instruments have been used or specifically developed to assess PROs in oncology trials and to monitor symptoms in oncology clinical practice. Patients are asked to respond based on their own experiences and perceptions, including ratings of severity (e.g. symptoms or disabilities), functional assessments (what they can do), ratings of disability (what they can't do), and how they feel about these things (e.g. satisfaction with function, health, etc). Recall periods may be current or span an interval of the last 24 hours, 1 week, 3 weeks, etc.

Standardised, multi-item questionnaires have been designed and validated to capture aspects of health and well-being in populations affected by specific cancers and/or treatments. Examples of instruments intended for people affected by cancer in general include the European Organisation for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30),[45] Functional Assessment of Cancer Therapy- General (FACT-G),[46] Patient's Disease and Treatment Assessment Form (PT DATA Form).[47] The QLQ-C30 and FACT-G may be supplemented by modules

designed for specific cancer types or types of treatments. For example, the EORTC module for gastric cancer (QLQ-STO22) can be added to the QLQ-C30 to assess issues specific to the experience and treatment of gastric (stomach) cancers.[48] PROMs can cover one or multiple domains, and each domain can be evaluated with one or multiple items. PROMs require validation in their populations of intended use.[49] Thorough validation strengthens their credibility and enhances their value in clinical decision-making.[50] Validation ensure applicability or generalisability of a model.[51]

1.10 Prognostic value of PROs in oncology

PROs, including symptoms and aspects of QOL, have been shown to predict overall survival in advanced cancers of many primary types, including breast, colorectal, lung and gynaecological cancers.[52-57]

Many studies have shown that aspects of QOL at baseline are predictive of survival in patients about to start chemotherapy for advanced cancer. For example, in colorectal cancer, baseline global QOL score ($p<0.0001$) measured with the EORTC QLQ-C30 was a significant independent predictor of survival and pain ($P=0.003$) in advanced breast cancer by EORTC QLQ-C30.[55,56] Gotay and colleagues reviewed 39 papers studying the prognostic significance of PROs in cancer. They reported that in 36 of these papers, at least one domain of PRO was significantly associated with survival in multivariable analysis.[58] Scales for Global QOL and for physical functioning were consistently predictive of survival time; appetite loss, fatigue, and pain were also frequently predictive of survival time in multiple cancer types, including breast, gastrointestinal, lung, and

brain. The most commonly assessed PRO domain was overall QOL, measured by EORTC QLQ-C30 in 22 of the 39 included studies. The review also determined that PROs were more strongly predictive of survival than clinician-rated performance status. An explanation offered for this finding was that ratings of performance status are based on clinician perspectives, whereas PROs are rated directly by patients. The fact that patient ratings were stronger predictors of survival than performance status supports the application of PROs in routine clinical practice to improve predictions of survival. Gotay's review was subsequently updated by Mierzynska et al, providing further support for the prognostic significance of PROs. [59] Both these reviews included multiple cancer types, predominantly arising from the breast, prostate and lung. These reviews included a few studies of gastric or gastro-oesophageal cancer. Gotay et al. included one study of gastric cancer; Mierzynska et al. included one study of gastric cancer and three of oesophageal cancer. These reviews showed that social functioning measured by EORTC QLQ-C30 in gastric cancer and fatigue, reflux by EORTC QLQ-C30 STO22, and physical symptoms by Medical Outcomes Study (MOS) 20-Item Short Form Health Survey (SF-20) in oesophageal cancer had prognostic significance.

1.11 Challenges with using PROs for prognostication

There are challenges in operationalising how clinicians can use PRO data to improve the accuracy of their estimates of expected survival time. It is difficult for clinicians to know which domains, PROMs, and questionnaires are the most informative about prognostication. There are also challenges associated with the optimal timing of questionnaire completion in a clinical setting to inform any predictions of survival time. Changing systemic treatment, lines of treatment, and

changes in PROs over time with disease progression and treatment side effects may all impact prognosis. PROs collected before starting a particular treatment, “at baseline”, could serve as a convenient and standardised strategy for supporting prognostication, particularly in an advanced setting.[60] Practical methods to improve prognostication in routine clinical practice would be highly valued by patients, their families, and clinicians.[61]

1.12 Advanced gastro-oesophageal (GO) cancer

The primary focus of my thesis are adenocarcinomas of the stomach and of the gastro-oesophageal junction, which in this thesis are together referred to as gastro-oesophageal (GO) cancer. The stomach, a sac-like organ in the digestive system, receives food from the oesophagus at the gastroesophageal junction.[62] Cancer occurs when the normal process of cell growth and death malfunctions, causing abnormal cells to multiply uncontrollably.[62] Gastro-oesophageal cancers arise from cells of the stomach and gastro-oesophageal junction, the majority of which are adenocarcinomas (90-95%).[62-64]

Advanced GO cancers are a significant challenge in oncology, contributing to the global burden of cancer-related mortality. Gastric cancer is the third leading cause of cancer death worldwide.[65] In Australia, gastric cancer is the 10th leading cause of cancer death.[66]

Advanced gastric cancer (defined as metastatic to distant sites, localised but inoperable, or recurrent after primary surgery) had a median survival of approximately four months when

treated with best supportive care (BSC) in the control groups of randomised controlled trials of chemotherapy.[67] The addition of chemotherapy to BSC in these trials improved median survival by approximately 7 months, to 11 months.[67]

Advanced GO cancer also causes a substantial burden of symptoms. The most common symptoms at diagnosis include anorexia, weight loss, dyspepsia, and abdominal pain. [68] Dysphagia could also be a symptom of cancer at the gastro-oesophageal junction or proximal gastric cancer. [68] All these symptoms severely affect almost every aspect of QOL in this patient group. [21] For example anorexia and weight loss indicate malnutrition, leading to reduced energy levels, impaired ability to perform daily tasks, and a diminished capacity to work.[69] Hence, QOL is an important consideration in this patient group, highlighting the need for comprehensive and patient-centred approaches to care.

1.13 Known prognostic indicators in GO cancer

There are several known prognostic factors for advanced GO cancer, including performance status, presence or absence of primary tumour, presence of liver or peritoneal metastasis, neutrophil to lymphocyte ratio, serum levels of carbohydrate antigen 19-9 (CA19-9). [70-72] Inflammation and nutrition scores have also been shown to have prognostic value.[73]

Koo et al. developed a prognostic model from a sample of more than 1500 patients and validated it in 900 patients with advanced GO cancer who underwent chemotherapy. They reported eight factors associated with poor prognosis: Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2, no gastrectomy, peritoneal metastasis, bone metastasis, lung

metastasis, alkaline phosphatase >120 IU/l, albumin <3.3 g/dL, and total bilirubin >1.2 mg/dL.[74] Narita et al. identified and validated a nomogram using more than 800 participants with advanced gastric cancer who underwent first-line chemotherapy and found that ECOG PS, prior gastrectomy, human epidermal growth factor (HER2) status, serum Alkaline Phosphatase (ALP), and serum lactate dehydrogenase (LDH) were prognostic. [72] Eight factors associated with poor prognosis were identified by multivariable analysis: ECOG performance status ≥2 (2 points), bone metastasis (2 points), no gastrectomy, peritoneal metastasis, lung metastasis, alkaline phosphatase > 120 IU/l, albumin < 3.3 g/dL, and total bilirubin > 1.2 mg/dL (1 point).

A systematic review by Feng et al. identified 101 prognostic models for gastric cancer, 17 of which focused on advanced disease. This review reported 55 predictors that were included more than twice in various models. Among 55 predictors, 10 predictors (age at diagnosis, sex, lymph node involvement, metastasis, invasion depth, TNM stage, tumour size, tumour site, differentiation, and histologic type) were included more than 10 times, supporting their predictive power in gastric cancer.[75] However, none of the prognostic models included in this review included PROs. The prognostic value of extent to which PROs provide prognostic information are predictive of survival survival in this population.

1.14 Prognostic model for GO cancer incorporating PROs.

Despite the existence of many prognostic models, few included or tested the prognostic significance of PROs.[75] Also, the majority of prognostic models have focused on early-stage

disease.[76,77] A systematic review by Boorn et al. examined 47 prediction models for gastro-oesophageal cancer. The majority focused on curative or early-stage settings, with 27 studies in curative settings. Only seven studies addressed advanced or palliative care settings, while 13 studies did not clearly specify the setting.[78] Models by Chua et al. and Fuchs et al. showed baseline global QOL ($p<0.001$), physical functioning($P=0.003$), role functioning($P<0.001$) and anorexia ($p<0.0001$) were independent prognostic factors in advanced gastric cancer. [71,79] Even though prognostic models incorporating PROs exist, their number is limited relative to the number of prognostic models without PROs, and few studies have analysed PROs together with other prognostic indicators. The European Society of Medical Oncology (ESMO) has suggested incorporating PROs in the routine clinical care of cancer patients.[80] Therefore, developing a prognostic model that includes PROs represents an unmet need.

1.15 The validation of prognostic models

Validating a prognostic model typically involves demonstrating that it performs effectively for patients beyond the original dataset used to develop the model.[81] Validation is crucial for prognostic models to corroborate accuracy, usefulness,[82] and reproducibility—the extent to which the model provides similar results in independent datasets.[83] Validation of prognostic models is an important step before implementation in clinical practice. To obtain reliable estimates of performance, models should undergo both internal and external validation. This should include assessments of both discrimination and calibration.[84]

The systematic review mentioned above by Feng et al. identified 101 prognostic models for gastric cancer, 17 of which focused on advanced disease.[75] They reported that 32 external validations were conducted for 20 distinct models, with 22 of these validations reported within the same study as the model development, raising questions about the external validity and reproducibility of 91 of these models. The review did not specify whether the validations were conducted on advanced disease or early-stage disease. Considering that prognostic models may perform differently depending on the stage of cancer, not having accurate information could affect the model's relevance and reliability for clinical use.[85]

The lack of validation of prognostic models in advanced GO cancer settings is an important limitation and gap in knowledge about prognostication in GO cancer.

There is a need to consolidate available information, develop, test and validate prognostic models for advanced GO cancer that incorporate known clinicopathological prognostic factors and pertinent PROs. Such models would benefit doctors, patients, and healthcare communication and potentially improve decision-making by supporting personalised, evidence-based care.

1.16 Summary and overview of the subsequent thesis chapters

This chapter provides a background for the subsequent chapters of this thesis. It provides a summary of how survival is reported in clinical trials and used as a basis for estimating survival in clinical practice, an exploration of existing research regarding prognostic factors, and the use of PRO for prognostication in advanced GO cancer.

Advanced GO cancers present a formidable challenge in clinical practice due to their poor prognosis, characterised by short survival times. There has been a notable shift toward integrating PROs into both routine patient care and clinical trial assessments in cancer populations. Further, there is emerging evidence that PROMs can improve predictions of survival time. Specific PRO domains of prognostic importance are likely to differ by diagnosis and disease stage.

In Chapter 2, I explore whether the use of simple multiples of the median overall survival from KM curves from published randomised clinical trials can also be used to estimate scenarios for survival time in advanced GO cancer. This method has been used in advanced prostate, breast, and lung cancer and may apply to reports of advanced GO cancer trials. This chapter will determine the accuracy and validity of using these scenarios for survival in previously reported GO cancer trials, considering their unique characteristics and challenges.

Chapter 3 aims to shed light on existing research about the complex interplay between PROs and prognostication in advanced GO cancer with a systematic review. By reviewing existing research, this chapter explores how PROs have impacted, enhanced, or supported previous prognostic models, and the extent to which they have provided insights into prognostication in this setting.

Chapter 4 reports the development and validation of a prognostic model in advanced GO cancer that incorporates PROs to provide additional prognostic information above and beyond that offered by established clinical and pathological variables using data from two randomised controlled trials.

Chapter 5 provides summaries the key findings of this thesis, situating them within the broader context of existing literature in the field to highlight their relevance and contribution. It discusses the strengths and limitations of the work reported in this thesis. Finally, it outlines future research directions, providing recommendations to address unanswered questions, refine methods, and explore new areas of investigation to further advance the field.

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Chapter 2

Estimating survival scenarios in advanced or metastatic gastric and oesophageal (GO) adenocarcinoma: a systematic review of randomised-controlled trials (RCT).

2.1 Overview

This chapter presents a published study (refer to Appendix A for the publication). It provides a summary of survival data from clinical trials of advanced or metastatic gastro-oesophageal adenocarcinoma (GO) identified through a systematic search.

The primary goal of this study was to provide oncologists with a straightforward framework for estimating survival times in patients with GO cancer. I applied a calculation method to the systematically identified studies to assess whether the simple multiples of the median overall survival, which have proven effective for estimating worst-case, typical, and best-case survival scenarios in breast and prostate cancer, are also applicable to GO cancer.

Publication details

Naher SK, Mercieca-Bebber R, Siu D, Stockler MR, Kiely BE, Grimison P. Estimating survival scenarios in advanced or metastatic gastric and oesophageal adenocarcinoma: a systematic review of randomised-controlled trials. Curr Med Res Opin. 2024 Aug;40(8):1357-1367. doi: 10.1080/03007995.2024.2376129. Epub 2024 Jul 13. PMID: 38961804.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sayeda K. Naher and Derrick Siu. The first draft of the manuscript was written by Sayeda K Naher, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

2.2 Manuscript

Abstract

Purpose

We aimed to summarise survival data from RCTs in patients with GO adenocarcinoma; estimate and explain worst-, typical- and best-case scenarios of survival time; and determine if simple multiples of median overall survival (mOS) could estimate these percentiles.

Methods

We systematically searched RCTs of systemic therapies for GO adenocarcinoma published from 2000 to 2022. The following key percentiles were extracted from overall survival curves: 90th (worst-case), 75th (lower-typical), 25th (upper-typical), and 10th (best-case). We tested if these percentiles could be estimated by simple multiples of mOS: 0.25 of the median for the 90th percentile, 0.5 for the 75th, 2 for the 25th, and 3 for the 10th.

Results

We identified 44 trials (22,447 participants). For first-line chemotherapy and immunotherapy combined (CI) trials (n=3), worst-to-best case survival time ranged from 4 months to not reached, compared to 3-30 months for other trials (n=27) and 1-23 months for subsequent line (n=14). Simple multiples of mOS accurately estimated the following survival percentiles: 90th (n=3/3 trials), 75th (n=3/3) and 25th (n=2/3) in first-

line CI trials. In other first-line trials, the mOS accurately estimated the 90th survival percentile in n=22/27 trials, 75th percentile in n=26/27, 25th percentile in 27/27 and 10th percentile in 22/27. Simple multiples of the mOS accurately predicted the 90th, 75th, 25^{th,} and 10th survival percentiles in the majority of trials of second and subsequent lines, except for chemotherapy-only and immunotherapy-only trials.

Conclusion

We provide realistic, evidence-based prognostic information as scenarios for survival time, which can inform clinical decision-making. Simple multiples of the mOS accurately estimated the percentiles for most groups.

Introduction

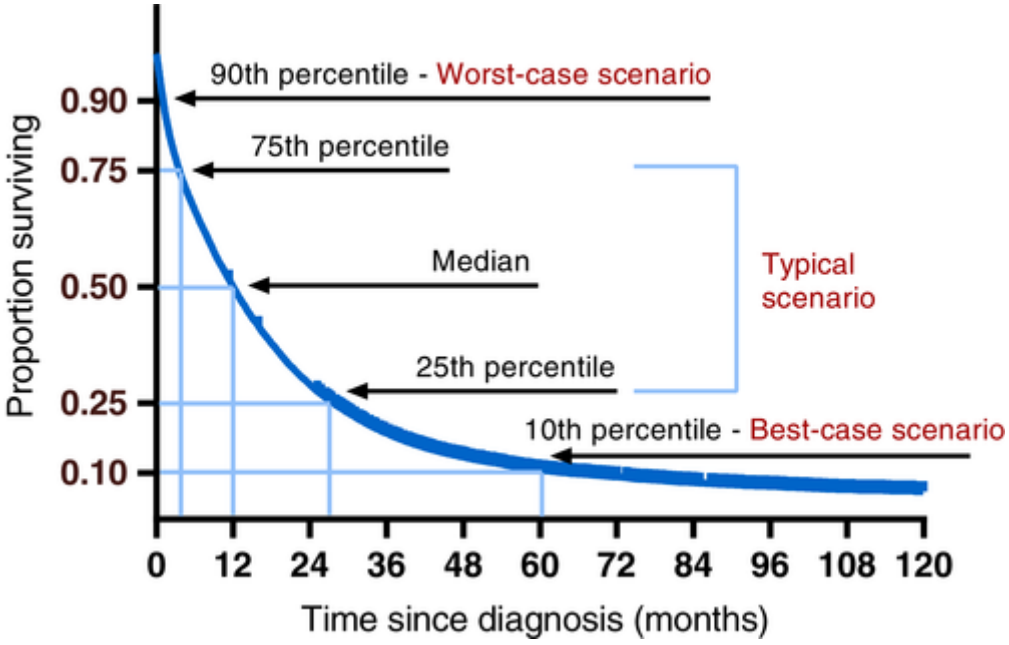
Prognostic information is valued by patients in the metastatic cancer setting. It should communicate to patients in a manner that is meaningful and realistic, while maintaining hope. Surveys of over 500 oncologists in the US showed that the majority of participants believe education about delivering prognostic information is vital and essential.[1] [2] A large observational study of 590 participants with advanced cancer highlighted the importance and misconceptions of prognosis in advanced cancer.[3] More than 70% of patients wanted to know their prognosis; however, only 17% received this information. Prognostic information was associated with better advanced care planning and quality of end-of-life care; however, participants felt that maintaining hope was also essential. A phase 2 trial of 222 patients showed that around 90% of patients and family members found prognostic information formatted as three scenarios (best-case, worst-case, and typical-case) was feasible, acceptable, and helpful. This approach improves their understanding and helps them plan. [4] Another survey of Australian medical oncologists reported that more than half of the oncologists preferred survival discussions to be presented as three case scenarios – best, worst and typical.[5] Therefore, we strongly believe educating and delivering prognostic information in a range of scenarios based on similar patients would be more meaningful than a single point estimate of the median. Our study will provide clinicians with these scenarios and a method to determine these scenarios from any OS curve in advanced GO cancer trials.

A range of typical survival times, as shown in Figure 2.1, can be obtained from the interquartile range of a survival distribution (25^{th} to 75^{th} percentiles) of the median

survival time. Using survival data from trials to estimate best-case (best 10%), worst-case (worst 10%), and typical (middle 50%) survival times may offer a realistic yet optimistic picture of survival outcomes.[6] Overall survival (OS) curves could serve as a useful basis for estimating these scenarios.[7] Our previous work in advanced breast, lung and prostate cancer settings has shown that the survival curves were roughly exponential in shape; therefore, the percentiles of each OS curve could be estimated by simple multiples of its median. [8-11] For instance, the 90th percentile (representing the upper bound for the worst case scenario) was roughly one-quarter of the median OS, the 75th percentile (representing the lower bound for the typical case scenario) was half the median OS, the 25th percentile (representing the upper bound for the typical case scenario) was double the median OS and the 10th percentile (representing the lower bound for the best case scenario) was three times the median OS.

Metastatic gastric and oesophageal cancer (GO) is essentially incurable; therefore, providing prognostic information with a range of possibilities from best case to worst case should help preserve optimism and prepare patients and families for the worst case. The purpose of this study was to identify and summarise survival data from recent randomised trials for GO adenocarcinoma, enabling clinicians to estimate survival time for their patients in this setting. Our second aim was to determine whether simple multiples of the median OS, which were accurate for estimating the bounds of worst-, typical-, and best-case survival in other cancers, were similarly accurate in GO adenocarcinoma.

FIGURE 2.1. Percentiles and their corresponding scenarios of the Kaplan-Meier OS curve



Methods

A systematic literature search of MedlineOVID, Embase, and the Cochrane Central Register of Controlled Trials was conducted in June 2022 without language or data restrictions. We limited our search to studies published after 2000, as prior to this time period might not reflect current treatment practices. We combined terms related to advanced cancers of the stomach or oesophagus with randomised clinical trials (Appendix 2.1). Our search was developed in collaboration with two academic librarians.

We included phase III trials with at least 100 participants per arm that reported at least one Kaplan-Meier (KM) curve for OS. We excluded human epidermal growth factor

receptor 2(HER2) positive adenocarcinoma, as treatment and prognosis are different. Two reviewers screened articles, selected trials, and extracted published information about the trials and their results. For eligible trials, we recorded year of publication, research location, research period, patients' median age, proportion of males, percentage of gastric cancer, treatment arm, treatment received, median overall survival, and number of KM curves.

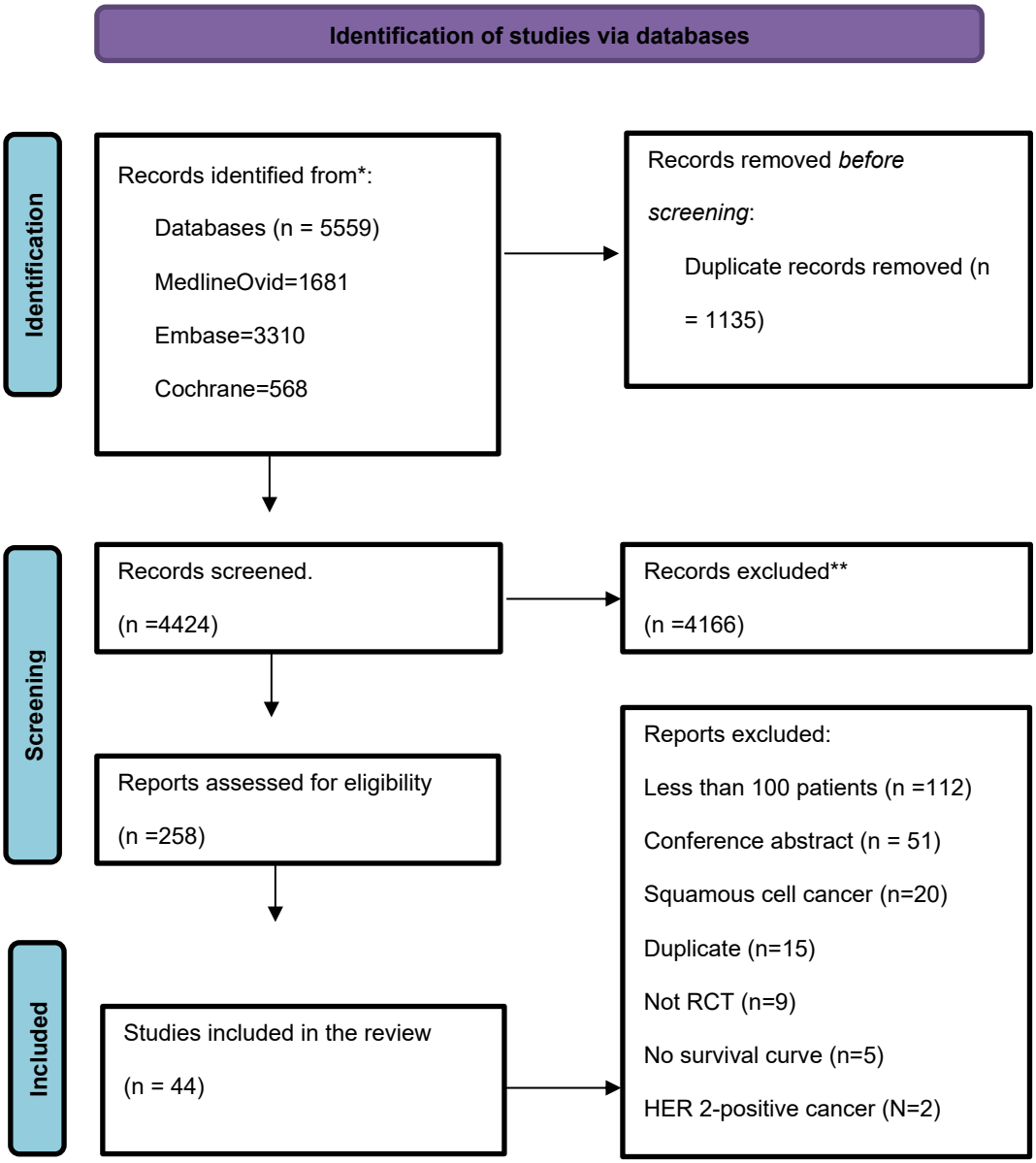
Using methods developed by Kiely et al. [9,11,12], we analysed the survival curves from these trials to calculate the typical (25th to 75th percentiles), best-case (10th percentile) and worst-case (90th percentile) scenarios for survival time as per Figure 2.1.

Each OS curve was independently traced by two authors by using "WebPlotDigitizer" a web-based tool to extract data from plots, images, and maps.[13] Survival curves for each treatment group in each trial were analysed to determine the following key percentiles (relevant scenario): 10th (best-case), 25th (upper-typical), 75th (lower-typical) and 90th (worst-case; Figure:2.1). Discrepancies were resolved by consensus and repeated measurement.

From our prior work on breast, lung and prostate cancers [8-10,14] we hypothesised that if the median of the OS curve is multiplied by four simple multiples, then percentiles could be estimated as representative scenarios as follows: 0.25 or ¼ for the 90th percentile (worst-case), 0.5 or ½ for the 75th (lower-typical), 2 for the 25th percentile (upper-typical) and 3 for the 10th percentile (best-case). We decided a priori that an estimate would be deemed accurate if it was within 0.75 -1.33 times the actual value, consistent with the criteria of Christakis and Lamont. [15]

Statistical software package RS Studio 4.1.1 was used for this data analysis.

FIGURE 2.2: PRISMA Flow chart for studies



Results

Our search strategy identified 5559 studies, 1135 duplicates were removed, leaving 4424 records to be screened. A total of 258 studies were assessed for full-text eligibility, and 44 studies (22,447 participants) were eligible and included as outlined in Figure 2.2.

Among the 44 eligible trials, 30 were in the first-line treatment setting[16-45] (n=16,457 participants), and 14[46-59] were in the second or subsequent line setting (n=5,990 participants). The majority of trials (21/44, 48%) were conducted in multiple countries involving more than 15 to 20 countries across the globe (15 studies in first line and 6 in second and subsequent line). The remaining studies were primarily conducted in Asian countries (18, 41%). A total of six studies in the first line and two subsequent lines, trials were conducted in Japan, and three first-line trials were conducted in China

Characteristics of the included trials

Among the first line setting trials (n=30), 24 were published between 2011 and 2022, and 6 were published between 2006 and 2010. The majority of participants were male (70%), half of the participants had Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (49%), and the median age was 58 years, with a range of 18 to 94 years. Around 80% had gastric adenocarcinoma. Regarding chemotherapy, a majority of the trials used fluoropyrimidine[16-24,26,29-32,34-43,45] (n=25, 83%), and platinum[16-26,29-31,34-37,41-43,45] (n=23, 77%) followed by S-1[17,25,27,28,32,33,43,44] (n=8, 27%). Targeted therapies included rilotumab,[19] cetuximab,[29] bevacizumab,[34,37]

onartuzumab,[35] andecaliximab,[36] and panitumumab,[41] while immunotherapies included nivolumab,[23,24] pembrolizumab[39] and avelumab.[31]

Among the 14-second (n=11) and subsequent line (n=3) trials, 8 trials were published between 2016 and 2022, 6 trials between 2011 and 2015. Majority of patients were male (73%) and had gastric adenocarcinoma (84%), and more than half the participants (54%) had ECOG performance status of 2. One trial used chemotherapy (paclitaxel) with vascular endothelial growth factor inhibitor (anti-VEGF, ramucirumab).[59] 11 trials used chemotherapy alone (paclitaxel, S1, trifluridine/tipiracil),[46,47,50-56,58,59] three used immunotherapy alone (avelumab, nivolumab and pembrolizumab),[47,48,57] one trial used anti-VEGF alone (ramucirumab)[49] , and four trials included a best supportive care arm.[48,49,53,56]

Table 2.1 summarises the characteristics of the included trials and participants.

Table 2.1: Characteristics of the trials, treatment groups, and participants

	No of trials	%
Year of publication		
2006-2010	6	14
2011-2015	16	36
2016-2022	22	50
Research location		
Global	21	48
Asian	18	41
Non-Asian	4	9
Not reported	1	2
First line treatment types	30	68
Chemotherapy + anti-VEGF*	1	2
Chemotherapy alone	11	25
Immunotherapy alone	3	7
Anti-VEGF alone	1	2
Best supportive care	4	9
Participant characteristics	Median	Range
Patients per trial	446	202-1581
Age (years)	62	18-94
Male (%)	71	51-82
Gastric cancer (%)	80	32-100
ECOG performance status 0 or 1^ (%)	43	Oct-80

*VEGF (Vascular Endothelial Growth Factor)

^ECOG (Eastern Cooperative Oncology Group). Note five trials did not report ECOG.

Survival duration

The range of survival among various trials were as below.

Among the first-line chemotherapy and immunotherapy combined trials (CI) (n=3 trials), survival of worst to median to best case ranged from 4 months to 15 months to not reached. For other first-line trials (n=27), survival ranged from 4 to 11 to 30 months. For subsequent line trials of chemotherapy and anti-VEGF therapy (n=1), survival ranged from 3 to 10 to 23 months, for chemotherapy alone (n=11) 2 to 7 to 21 months, immunotherapy alone (n=3) 1 to 6 to 22 months, anti-VEGF alone (n=1) 1 to 5 to 17 months and best supportive care (n=4) 1 to 4 to 13 months.

Eight studies were published after 2016 in second- and subsequent-line trials. For these studies, survival ranged from 2 to 7 to 19 months.

Table 2.2 summarises survival scenarios by treatment line and type.

Table 2.2: Survival scenarios for gastric and oesophageal adenocarcinoma according to different treatment groups and lines

Treatment line and regimen	Number of KM curves	Number of participants	Survival scenario in months (mean)				
			90th worst	75th lower typical	50th median	25th upper typical	10th best
First line		16,457					
Chemotherapy + immunotherapy[21,22,37]	3	1,408	4.4	7.7	14.5	24.8	Not reached
Chemotherapy with or without other therapy[14–20,23,25–36,38–43,58]	59	15,049	3.6	6.4	11	19	30
Subsequent line		5,990					
Chemotherapy + anti-VEGF[57]	1	330	3	5	9.5	15.2	22.5
Chemotherapy[44,48–50,52–56,59]	14	4,044	2.4	4.2	7.4	12.8	21.3
Immunotherapy[45,46,55,59]	3	711	1.4	2.8	6.4	13.6	22.1
Anti-VEGF alone[47]	1	238	1.3	2.4	5.1	9.8	17.3
Best supportive care[46,47,51,54]	4	667	1.1	2	3.9	7.9	13.1

Abbreviations: VEGF, Vascular Endothelial Growth Factor; KM, Kaplan Meier overall survival curve.

Accuracy of simple multiples of median overall survival in the first-line treatment setting

Simple multiples of mOS were accurate in predicting worst-case (90th percentile) and lower typical (75th percentile) in all three CI trials (Table 2.3). However, best-case scenarios were not reached due to the length of the follow-up period. Therefore, the best-case survival estimates could not accurately be calculated. The remaining of the other first line trials multiplication were accurate, as evident in Table 2.3.

Table 2.3: Number and percentages of trials where multiplication of survival scenarios were accurate.

Treatment line and regimen	Number of trials	Survival scenarios			
		90th worst	75th lower typical	25th upper typical	10th best
First line					
Chemotherapy + immunotherapy[21,22,37]	3	3 (100%)	3 (100%)	2 (67%)	Not reached
Chemotherapy with or without other therapy[14–20,23,25–36,38–43,58]	27	22 (81%)	26 (96%)	27 (100%)	22(81%)
Subsequent line					
Chemotherapy + anti-VEGF[57]	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Chemotherapy[44,48–50,52–56,59]	11	7 (64%)	11 (100%)	11 (100%)	11 (100%)
Immunotherapy[45,46,55,59]	3	2 (67%)	3 (100%)	3 (100%)	2 (67%)
Anti-VEGF alone[47]	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Best supportive care[46,47,51,54]	4	4 (100%)	4 (100%)	4 (100%)	4 (100%)

Abbreviation: VEGF, Vascular Endothelial Growth Factor.

Accuracy of simple multiples of median overall survival in the second and subsequent line treatment settings

Among subsequent line treatment trials, mOS could be used to accurately estimate survival percentiles in most cases (Table 2.3). Of note, in the chemotherapy alone trial, survival estimates were accurate in the majority group, apart from the worst-case scenario, which was 64% (n=7/11). Also, in immunotherapy, only trials' best-case and worst-case scenarios were accurate in 67%(n=2/3).

Discussion

We provide realistic, evidence-based prognostic information as scenarios for survival time, which can inform clinical decision-making. This review provides important insights into survival time in advanced GO adenocarcinoma. In first-line chemotherapy and immunotherapy combined trials, survival ranged from the worst case of 4 months, median 15 months, and the best case of not reached due to an insufficient follow-up period. In second and subsequent line trials, survival in the worst case could be as low as one month to three months, and in the best case, it could be 17 months to 23 months. We also provide survival estimates for second- and subsequent-line trials with best supportive care, where participants did not receive any active treatment. Survival was as short as one month (worst-case) and as high as 13 months (best-case). This data is of particular value for clinicians discussing survival scenarios in cases where the patient decides on best supportive care without further treatment. Therefore, this review would serve a valuable purpose of informing discussions about survival in various treatment settings in advanced GO cancer.

We found that simple multiples of the mOS accurately estimated the percentiles for most groups. For most trials, we could estimate the best survival time (10% participants living longest) by multiplying the median survival time by 3. Similarly, the worst survival time (the 10% of participants with the shortest survival time) can be computed by multiplying the median OS by 0.25. As per our previous work [8-11] , the method of using simple multiples of an OS curve's median to approximate its range of various survival

times held true in this population. Therefore, our hypothesis of a simple multiple of an OS curve's median (0.25 for worst case, 0.5 to 2 for average case and 3 for best case) could arguably be utilised in metastatic or advanced gastric and oesophageal adenocarcinoma and other advanced cancer settings. For example, the median OS from the CheckMate 649[23] trial, which is a first-line chemotherapy and immunotherapy combined trial, reported a median overall survival of 14.4 months. The three survival scenarios can be calculated as a best case scenario of more than 42 months (3 multiplied by 14), a typical case scenario of 7 to 28 months (half to double of 14) and a worst case scenario of less than 5 months (one-quarter of 14)." Based on our results, it might still be possible to provide an estimate by multiplying the median survival by 3 to estimate the best-case survival scenario. However, longer follow-up data is needed before such estimates could reliably be applied to chemotherapy and immunotherapy combined trials, as it has not been reached in the trial. Unlike chemotherapy and other conventional drugs, the response to immunotherapy is often highly variable and can lead to long-tailed survival distributions. In chemotherapy, survival curves tend to follow more predictable patterns with a relatively uniform decline over time. However, immunotherapy trials have reported survival curves with plateaus and delayed separations, reflecting censoring, durable responses and long-term survival in some patients. These distinct characteristics make it difficult to apply traditional statistical models and assumptions. The variability and unpredictable nature of immunotherapy responses require more sophisticated and perhaps individualised approaches to scenario prediction.

The strengths of our study include a robust search strategy, a comprehensive summary of contemporary clinical trials in advanced GO cancer and an easily adaptable formula for use in real-world practice.

A limitation of our survival estimates is that they are derived from randomised trials which typically enrol patients with better prognosis than the general population. Population-based studies of patients with similar diagnoses and treatments provide the ideal source for estimating survival.[60] However, limited survival data is available outside of clinical trials and clinical trials offer valuable prognosis information. Therefore, in the absence of such data, our methods can be applied to trial data to derive informative survival estimates. We excluded patients with HER2-positive gastric cancer as the prognosis differs from non-HER2 [61,62]amplified cancer. It is not a direct comparison of different treatments; therefore, studies like this cannot confirm the contribution or survival benefit of any specific therapy, or the most effective therapy.

Further studies could help to determine how well clinical trial data correlate with everyday practice and survival among non-trial participants. Additionally, further studies with HER2-amplified cancer could add survival estimates in patients with HER2-positive cancers.

This review has important clinical implications. Questions about life expectancy and prognosis are common; however, there is significant variability in the sharing of this information.[63] There is abundant literature regarding the importance and ways of communicating prognosis information in advanced cancer[60,64-66] ; however, methods

to estimate life expectancy reliably have previously been lacking. This review, along with our previous reviews of breast, lung, and prostate cancers, [5,8-10] could serve the purpose of efficiently estimating various survival scenarios. Clinician could provide survival information in best, average and worst-case scenarios in advanced GO adenocarcinoma based on this review.

Several studies used baseline patient characteristics, pathological and clinical variables to establish a prognostic model for advanced GO cancer.[67,68] Overall, while these studies have laid the groundwork for prognostic modelling, their limitations due to heterogeneity suggest a need for further refinement. Future research should focus on developing more universally applicable models, possibly through the integration of larger, more diverse patient datasets and the use of advanced statistical techniques to account for variability in clinical practice

Conclusions

We provide prognostic information based on data from randomised trials for GO adenocarcinoma, presented as best-case, worst-case, and typical-case scenarios for survival time. This approach ensures information that is evidence-based, realistic, and allows both preparation for the worst and hoping for the best. Simple multiples of the mOS accurately estimated the percentiles for the majority of treatment groups and settings for advanced GO adenocarcinoma.

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Chapter 3

Prognostic value of patient-reported outcomes in advanced gastro-oesophageal cancer: a systematic review.

3.1 Overview

This chapter presents a published work (refer to Appendix B for the publication). It offers a summary of patient-reported outcomes (PROs) associated with overall survival in gastro-oesophageal (GO) cancer.

The primary goal of this study was to identify and summarise studies that have assessed the prognostic value of PROs in advanced GO cancer. It found that in adenocarcinoma, OS was associated with global quality of life (QOL), physical functioning, role functioning, social functioning, and pain. Multivariable analyses emphasised the importance of patient-reported physical function, social functioning, mobility, appetite loss, and pain in predicting survival for GO cancer.

Publication details

Naher SK, Mercieca-Bebber R, Siu D, Grimison P, Stockler MR. Prognostic value of patient-reported outcomes in advanced gastro-oesophageal cancer: a systematic review. Intern Med J. 2023 Nov;53(11):1946-1955. doi: 10.1111/imj.16209. Epub 2023 Aug 22. PMID: 37605848.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sayeda K Naher, Derrick Siu. The first draft of the manuscript was written by Sayeda K Naher, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

3.2 Manuscript

Abstract

Background

To summarise the prognostic value of patient-reported outcomes (PROs) in advanced gastro-oesophageal (GO) cancer.

Methods

We systematically searched multiple databases using search terms related to advanced GO cancer, PRO, and prognosis. Studies examining the relationship between baseline PROs and prognosis were included. Two reviewers independently screened articles and extracted data on study design, survival and associations between PROs and survival, in both univariable and multivariable analyses. QUIPS was used for quality assessment.

Results

From 3004 studies screened, 7 studies were eligible, comprising PRO data from 2,761 of 3,408 (81%) participants. Median survival times ranged from 4.5 to 9.5 months. Among participants with oesophageal squamous cell cancer (SCC), physical functioning, social functioning and fatigue (QLQ-C30) were associated with overall survival in one univariable analysis. Among three studies of participants with adenocarcinoma, univariable analyses revealed associations between overall survival (OS) and global quality of life (QOL), physical functioning, role

functioning, social functioning; two studies showed an association with pain. There was an association of emotional functioning, fatigue, lack of mobility, lack of self-care, and appetite loss/anorexia and OS in one study.

One multivariable analysis among participants with oesophageal SCC showed that physical and social functioning were associated with OS. Among participants with adenocarcinoma, multivariable analyses showed associations between OS and physical functioning/lack of mobility, appetite loss/anorexia (3 studies), global QOL, role functioning/lack of self-care, pain (2 studies), and social functioning (1 study).

Conclusions

Physical functioning, role functioning, social functioning, pain, anorexia, and global QOL were associated with OS in advanced GO cancer.

Introduction

Gastric cancer is the fourth leading cause of cancer-related death and the fifth most common cancer globally.[1] Oesophageal cancer ranks seventh in global incidence and sixth in global mortality.[1] Together they accounted for an estimated 1,313,000 deaths in 2020 (796,000 for gastric cancer and 544,000 for oesophageal cancer). Advanced (metastatic or inoperable) gastric and oesophageal (GO) cancers have a poor prognosis, with reported median overall survival times of three to five months,[2] which can be improved by an average of approximately seven months with chemotherapy.[3,4] Along with poor survival, most patients also suffer from high symptom burden,[5] making quality of life (QOL) paramount for decision making.[6,7] Estimates of expected survival time can help patients affected by advanced cancer and their families prioritise their remaining time together, make important treatment decisions, and plan for future care. Previous reviews and surveys have confirmed that patients affected by cancer are very keen to know about their prognosis.[8,9] In advanced GO cancer, nomograms for assessing prognosis have been developed using clinical and biochemical variables like performance status, liver metastasis, peritoneal metastasis, neutrophil to lymphocyte ratio, etc.[10-13] The incorporation of PROs into these prognostication models appears limited.

The US Food and Drug Administration (FDA, 2009, p. 2) defines a patient-reported outcome (PRO) as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else".[14] Disease symptoms, treatment side effects, mood, and measures of QOL and overall well-

being may be patient-reported. A recent systematic review showed physical functioning and global QOL had prognostic value in multiple primary cancer types, including breast, lung, and prostate cancers.[15,16] However, there were only three studies on advanced GO cancer in this review, and no contemporary systematic reviews have focused on advanced GO cancer.

We hypothesised that particular PROs might be useful prognostic indicators in advanced GO cancer. We conducted this systematic review to evaluate and describe the relationship between PROs and overall survival in advanced GO cancer.

Methods

Search Strategy and Selection Criteria

We followed the Cochrane methodology for prognostic studies described by Riely and colleagues [17] and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines to ensure complete and transparent reporting. [18,19]

A systematic literature search of MedlineOVID, Embase, PubMed, and the Cochrane Central Register of Controlled Trials was performed from inception to March 2021, without any language or data restrictions. We combined terms related to advanced cancers of the stomach or oesophagus with prognostic and PRO terms (Appendix 3.1). Our search was developed in collaboration with two academic librarians.

Study eligibility criteria

Studies were included if they met the following criteria:

1. Participants had unresectable, metastatic, or recurrent cancers of the oesophagus, stomach, and/or gastroesophageal junction;

2. Reported overall survival (OS);
3. Reported baseline PROs;
4. Participants received systemic therapy (chemotherapy, targeted therapy and /or immunotherapy);
5. Minimum 50 participants;
6. Reported at least one univariable/multivariable analysis examining the relationship between baseline PROs and OS.

We did not limit by language. We excluded reviews, commentary, editorials, and conference abstracts.

Study screening

All abstracts were screened by two authors (SKN, DS) independently according to the selection criteria detailed above. Full-text papers were then checked using the same eligibility criteria. We used "COVIDENCE",[20] an online tool for systematic reviews, for study screening.

Data collection process

Data was extracted into a predefined data extraction form (Appendix 3.2) independently by two authors (SKN, DS). Any disagreements were resolved with discussion and adjudication by a third author (RMB). We extracted data regarding: first author, year of publication, research location, research period, study design, participant age, gender, cancer type, treatment received, line of treatment, PRO instrument/s used, number of participants, number of participants with PRO data, modelling method to assess prognostic factors, pre-defined clinical and laboratory variables with known potential prognostic significance (weight loss, performance status, anaemia, hypoalbuminemia, presence of peritoneal or liver metastasis,

ascites, neutrophil to lymphocyte ratio), and prognostic relationships of key PROs (PROs included-global QOL, physical functioning, role functioning, social functioning, emotional functioning, pain, appetite loss/anorexia, dysphagia, fatigue) which have known or potential prognostic value in cancer patients based on prior studies.[15,16]

Study risk of bias assessment

Two authors (SKN, DS) used the QUIPS checklist to assess study quality. This tool was developed for use in prognostic studies.[21] It assesses six domains as high, moderate and low risk of bias: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. Any disagreements were resolved with discussion from a third author (RMB).

Synthesis method

Overall survival (OS) was our primary endpoint. OS was typically calculated from the date of study entry until death from any cause or censored at last follow-up. We calculated the number of studies examining the relationship between prognosis (overall survival) and clinical variables: weight loss, performance status, anaemia, hypoalbuminemia, presence of peritoneal or liver metastases, ascites, and neutrophil-to-lymphocyte ratio. In all the included studies, initial univariable analyses examined the relationship between survival and individual factors, and multivariable analyses examined the independent effects of multiple prognostic factors including PROs, disease, and clinical variables. We did not obtain individual patient data. We documented the relationship of overall survival expressed in those studies as hazard ratio (HR), with 95% confidence interval (CI) and p-value for each univariable and multivariable analysis, for the following PROs: global QOL, physical functioning, role functioning, social

functioning, emotional functioning, pain, appetite loss/anorexia, dysphagia, and fatigue. These PROs were selected a priori as being important to the clinical population and having prognostic relevance in other cancer settings.[15,16]

Results

Of 3,004 identified records, 2346 study titles and abstracts were screened, after removal of 658 duplicates. 126 studies were assessed for full-text eligibility, and 7 studies met the inclusion criteria[22-28] as outlined in Figure 3.1.

Figure 3.1: PRISMA Flow chart for studies

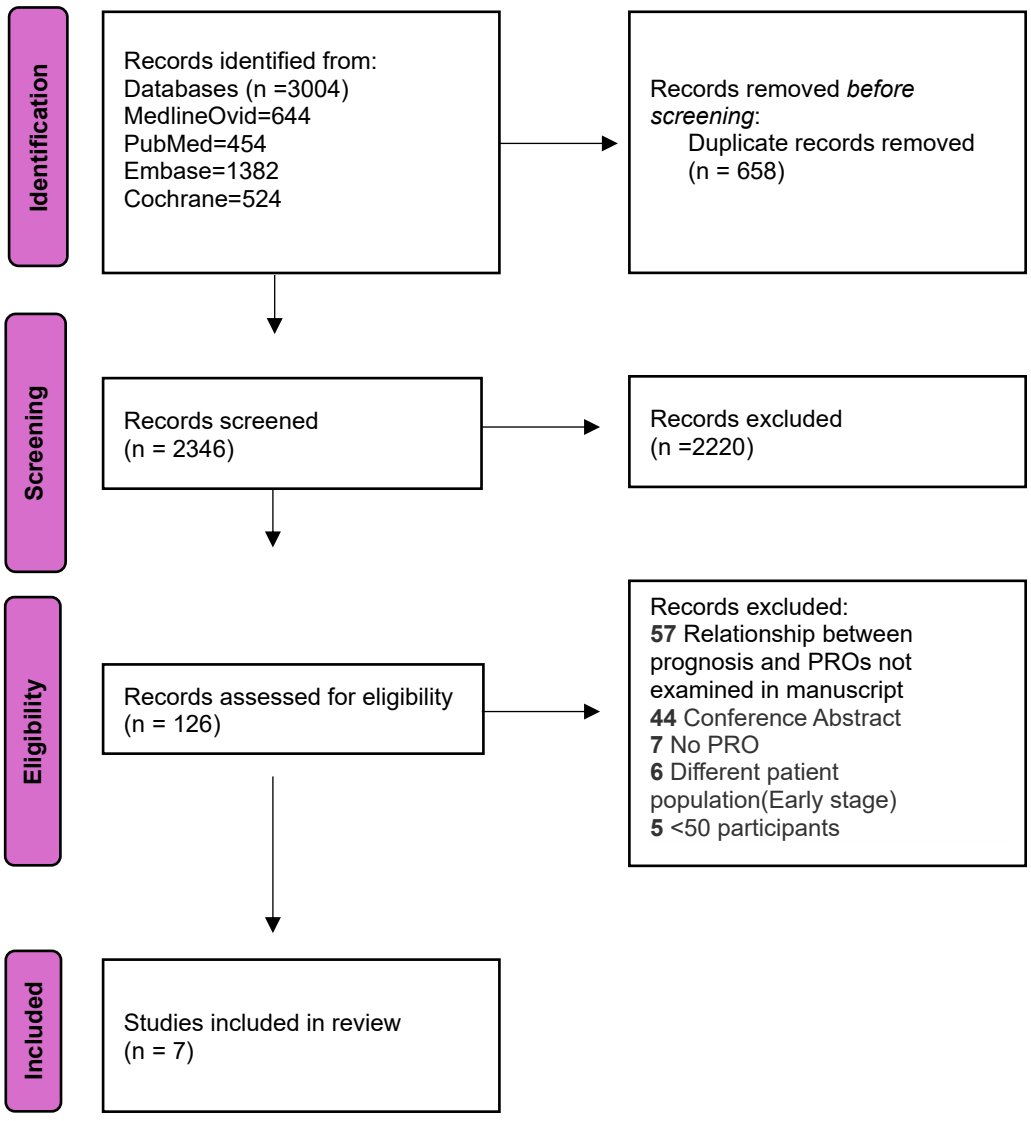

Table 3.1: Key features of the included studies

Study reference	Study design	Research location	No. of patients	Participants with baseline PRO data (%)	PRO measures used	Median survival (months)	Line of treatment	Type of treatment
SCC								
Conroy *et al.*[26]	RCT	Europe	71	59 (83%)	EORTC QLQ-C30	6.8	1st	Chemotherapy
Adenocarcinoma/ mixed†								
Chua *et al.*[25]	Pooled analysis of RCT	UK	1080	817 (76%)	EORTC QLQ-C30	7.9	1st	Chemotherapy
Park *et al.*[29]	Pooled analysis of RCT	Korea	254	164 (65%)	EORTC QLQ-C30	9.5	1st	Chemotherapy
Fuchs *et al.*[27]	Pooled analysis of RCT	Multicentre	1020	953 (93%)	EORTC QLQ-C30	6.9	2nd	Chemotherapy + targeted therapy
Martin *et al.*[28]	RCT	Multicentre	147	136 (93%)	EORTC QLQ-C30, QLQ-STO22, EQ-5D, PTDATA	5.1	2nd	Targeted therapy
Abdel-Rahman[23]	Pooled analysis of RCT	Multicentre	654	525 (80%)	EQ-5D-3L(41)	NR	1st	Chemotherapy
Abraham *et al.*[24]	Cohort	UK	182	107 (59%)	FAACT A/CS	8.8	1st	NR

EORTC, European Organisation for Research and Treatment of Cancer; FAACT A/CS, Functional Assessment of Anorexia Cachexia Therapy Anorexia/ Cachexia Subscale; NR, not reported; PRO, patient-reported outcome; PTDATA, Patient Disease and Treatment Assessment; QLQ-30, 30-item Quality of Life Core Questionnaire; RCT, randomised controlled trial; SCC, squamous cell carcinoma; UK, United Kingdom.
†Gastric adenocarcinoma, oesophageal adenocarcinoma, gastro-oesophageal junction adenocarcinoma and adenosquamous.

Table 3.1 describes the characteristics of the included studies. All studies were conducted between 1992 and 2017. Four studies were pooled analyses of RCTs.[22,24,26,28] Additionally, there were two randomised controlled trials (RCTs)[25,27] and one cohort study.[23] Apart from one study on oesophageal squamous cell carcinoma (SCC)[25] the other studies included gastric, gastro-oesophageal, and oesophageal adenocarcinoma. Chemotherapy included a taxane in 4 studies,[22,24,26,28] a platinum in 4 studies, [22,24,25,28] fluoropyrimidines in 3 studies,[22,24,28] and another chemotherapy in 2 studies (vinorelbine, irinotecan).[25,28] Two studies used targeted therapy, one with regorafenib,[27] the other with ramucirumab.[26] One study did not report type

of treatment.[23] None of the studies included immunotherapy. Five studies were conducted in the first-line setting, [22-25,28] and two in the second-line setting. [26,27]

Five different PRO instruments were used across the seven included studies (Table 1): five studies used the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30),[24-28] two studies used the EQ-5D-3L.[22,27] The Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale (FAACT A/CS),[23] the EORTC gastric cancer module STO22, and the Patient Disease and Treatment Assessment (PTDATA)[27] were used in one study. All studies used Cox proportional hazard regression to assess univariable and multivariable relationships between PROs and survival.

Risk of bias

Four studies had low risk of bias in five or more domains; however, three studies had moderate risk of bias (Appendix 3.3).

PRO with prognostic significance

In a univariable analysis for oesophageal SCC, physical functioning, social functioning and fatigue (QLQ-C30) were associated with OS.[25] For adenocarcinoma, physical functioning,[24,26,28] global QOL,[24,26,28] role functioning,[24,26,28] and social functioning[24,26,28] (QLQ-C30) were significant in three studies. Pain was significant in two studies[22,26] (QLQ-C30 n=2, EQ-5D-3L). Fatigue,[26], appetite loss,[23,26] and emotional functioning [26](QLQ-C30) were significant in one study. Abdel Rahman[22] used EQ-5D and showed that lack of mobility (p=<0.001) and lack of

self-care (p=0.017) were significant. Table 3.2 shows the univariable relationship of the PROs and prognosis.

Table 3.2: Univariable relationship of the PROs and prognosis

Study reference	PRO measure used HR (CI) *P* value	Global QOL	Physical functioning	Role functioning	Social functioning	Emotional functioning	Pain	Appetite loss/ anorexia	Fatigue
SCC									
Conroy *et al.*[26]	EORTC QLQ-C30	NR	*P* = 0.02	NR	NR	NR	NR	NR	*P* = 0.01
Adenocarcinoma/mixed†									
Chua *et al.*[25]	EORTC QLQ-C30	0.52 (0.45–0.60) *P* < 0.001	0.67 (0.57–0.78) *P* < 0.001	0.62 (0.54–0.73) *P* < 0.001	0.74 (0.64–0.83) *P* = 0.0001	NS	NA	NA	NA
Park *et al.*[29]	EORTC QLQ-C30	0.51 (0.33–0.80) *P* = 0.003	0.64 (0.41–0.99) *P* = 0.04	0.61 (0.40–0.94) *P* = 0.027	0.44 (0.26–0.73) *P* = 0.001	NS	NS	NS	NS
Fuchs *et al.*[27]	EORTC QLQ-C30	0.67 (0.58–0.78) *P* < 0.001	0.63 (0.55–0.74) *P* < 0.001	0.65 (0.56–0.75) *P* < 0.001	0.72 (0.62–0.83) *P* < 0.001	0.77 (0.66–0.87) *P* < 0.001	1.48 (1.27–1.73) *P* < 0.001	1.88 (1.61–2.19) *P* < 0.001	1.68 (1.42–1.98) *P* < 0.001
Abdel-Rahman[23]	EQ -5D-3L	NA	*P* < 0.001 (lack of mobility)	*P* < 0.017 (lack of self-care)	NA	NA	*P* < 0.001	NA	NA
Abraham *et al.*[24]	FAACT AC/S	NA	NA	NA	NA	NA	NA	0.67 (0.55–0.81) *P* < 0.0001	NA

†Gastric adenocarcinoma, oesophageal adenocarcinoma, gastro-oesophageal junction adenocarcinoma and adenosquamous.

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FAACT A/CS, Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale; HR, hazard ratio; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; PTDATA, Patient Disease and Treatment Assessment; QLQ-C30, 30-item Quality of Life Core Questionnaire; QOL, quality of life; RCT, randomised controlled trial; SCC, squamous cell carcinoma; UK, United Kingdom.

Martin et al 2018[27] did not report univariable data.

Table 3.3 illustrates the significant PRO domains with prognostic value in multivariable analysis. In multivariable analyses of patients with oesophageal SCC, physical and social functioning were prognostic factors.[25] Among patients with adenocarcinoma, physical functioning/lack of mobility was a significant prognostic factor in three studies,[22,24,27] appetite loss/anorexia in three studies, [23,26,27] role functioning,[24] lack of self-care,[22] global QOL in two studies,[22,24] pain in two studies,[22,27] and social functioning in one study.[28]

Table 3.3: Multivariable relationship of the PROs, clinical and laboratory variables and prognosis

Study reference	Global QOL HR (CI) *P* value	Physical functioning	Role functioning	Social functioning	Pain	Appetite loss/ anorexia	Other clinical and laboratory variables
SCC							
Conroy *et al.*[26]	NR	$P = 0.03$	NR	$P = 0.03$	NR	NR	NA
Adenocarcinoma/mixed†							
Chua *et al.*[25]	0.57 (0.45–0.72) $P < 0.001$	0.76 (0.60–0.97) $P = 0.003$	0.69 (0.54–0.88) $P < 0.001$	NS	NS	NS	Performance status ($P \leq 0.0001$), liver metastasis ($P \leq 0.0001$), peritoneal metastasis ($P = 0.007$) and alkaline phosphatase >100 U/L ($P \leq 0.0001$) were significant and haemoglobin <11 g/L
Park[29]	NR	NR	NR	0.36 (0.21–0.62) $P < 0.001$	NR	NR	Age ($P = 0.04$), bone metastasis($P = 0.02$) and low haemoglobin ($P = 0.04$)
Fuchs *et al.*[27]	NR	NR	NR	NR	NR	1.50 (1.20–1.86) $P < 0.0001$	Presence of primary tumour ($P = 0.001$), poor/ unknown tumour differentiation ($P = 0.0005$), time to progression since prior therapy ($P = 0.0002$), performance status ($P = 0.0001$), presence of peritoneal metastasis ($P \leq 0.0001$), high ALP level ($P = 0.003$), low lymphocyte level ($P = 0.001$), high LDH level (0.001), low albumin level ($P = 0.0006$), high AST level (0.001), high neutrophil level ($P \leq 0.0001$) and low sodium level ($P \leq 0.0001$)
Martin *et al.*[28]	NS	0.66 (0.45–0.98) $P = 0.04$	NS	NS	0.60 (0.40–0.89) $P = 0.01$	0.57 (0.36–0.90) $P = 0.02$	NA
Abdel-Rahman[23]	0.41 (0.24–0.69) $P = 0.001$	$P < 0.001$ (lack of mobility)	$P = 0.04$ (lack of self-care)	NA	$P < 0.001$	NA	Performance status ($P = 0.03$)
Abraham *et al.*[24]	NA	NA	NA	NA	NA	0.70 (0.53–0.94) $P = 0.01$	BMI ($P = 0.02$)

†Gastric adenocarcinoma, oesophageal adenocarcinoma, gastro-oesophageal junction adenocarcinoma and adenosquamous.
BMI, body mass index; CI, confidence interval; HR, hazard ratio; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; QOL, quality of life; SCC, squamous cell carcinoma.

Overall, longer overall survival was associated with better global QOL and better physical, role, emotional and social functioning. Conversely, shorter overall survival was associated with worse pain, appetite loss/anorexia, and fatigue. Park et al.[28] showed that patients with good social functioning, compared to patients with poor social functioning, were more likely to survive for one year (45.3% vs 18.3% respectively). In Abraham et al.,[23]adenocarcinoma patients with less anorexia (higher FAACT-A/CS scores of >37) lived longer (19.3 months) than those with more anorexia (lower FAACT-A/CS scores of ≤37) (6.7 months). Fuchs et al[26]

showed patients with more appetite loss had almost two-fold (HR, 1.50; 95% CI, 1.20 to 1.86) worse prognosis.

Multiple clinical and laboratory variables were assessed. Chua et al[24] assessed 16 clinical and laboratory variables in an univariable model; among them, the multivariable model showed performance status(p=<0.0001), liver metastasis (p=<0.0001), peritoneal metastasis (p=0.007), alkaline phosphatase >100U/L (p=<0.0001), were significant. and haemoglobin <11g/L was borderline significant (p=0.011). Park et al[28] evaluated 14 clinical and laboratory variables in an univariable model, and three were significant in a multivariable model: age (p=0.04), bone metastasis (p=0.02), and low haemoglobin(p=0.04). Fuchs et al[26] include 41 baseline factors (18 clinical, 22 laboratory parameters and geographical region) in the univariable model. The multivariable model showed – presence of primary tumour (p=0.001), poor/unknown tumour differentiation (p=0.0005), time to progression since prior therapy (p=0.0002), performance status (p=0.0001), presence of peritoneal metastasis (p=<0.0001), high ALP level(p=0.003), low lymphocyte level (p=0.001), high LDH level (0.001), low albumin level (p=0.0006), high AST level (0.001), high neutrophil level (p=<0.0001), and low sodium level (p=<0.0001) were significant. Martin et al.[27]did not report any clinical or laboratory variables; however, the multivariable model with PROs was adjusted for ECOG status, number of metastatic sites, baseline vascular endothelial growth factor and neutrophil and lymphocyte ratio. Abdul Rahman[22] evaluated 15 clinical and laboratory variables in an univariable model; among them, the multivariable model showed performance status (p=0.03) was significant. Abraham et al[23] assessed 7 clinical variables (gender, age, O'Rourke Dysphagia score, treatment, performance status, total number of metastasis, and BMI) in the

univariable model, and BMI (p=0.02) in untreated patients was significant in the multivariable analysis.

Among the included studies, several clinical and laboratory variables were also found to have prognostic significance: weight loss in three studies,[23,26,28]ECOG performance status in six studies,[22-24,26-28]anaemia in three studies,[24,26,28]hypoalbuminemia in three[24,26,28]studies, presence of peritoneal or liver metastases in five studies[23,24,26-28] neutrophil and lymphocyte ratio in one[27]study. None of the studies assessed the prognostic significance of ascites.

Discussion

This comprehensive systematic review provides contemporary evidence of the prognostic value of PROs in advanced GO cancer. Multiple PRO domains were independently associated with survival and remained significant when considered with other clinical and demographic variables. Among patients with oesophageal SCC, physical functioning, social functioning and fatigue were predictive of survival in one univariable analysis, and physical and social functioning retained prognostic significance in a multivariable analysis of the same sample. Among patients with adenocarcinoma, physical functioning, role functioning, social functioning, global QOL, pain, and appetite loss/anorexia had prognostic significance in univariable and multivariable analyses. Overall, at least one or more PROs were significant in each of the studies included. Multiple clinical and laboratory variables, including low performance status, low BMI, low haemoglobin, and the presence of peritoneal and liver metastasis, also showed prognostic significance in multivariable analyses, along with PROs.

Our findings are in line with the findings of the systematic reviews by Gotay et al.[15] , who provided evidence of the prognostic value of PROs in multiple cancers. In that review, among 39 clinical trials of various cancers, 36 studies showed that at least one PRO had prognostic significance in multivariable analysis. Subsequently, another systematic review by Mierzynska et al.[16] showed that physical functioning and global quality of life were associated with survival in cancers of multiple primary types, including breast, lung, and prostate. Another systematic review by Trajkovic-Vidakovic M et al[29] included 44 studies in the palliative care setting for advanced cancer. The study found that confusion, anorexia, fatigue, cachexia, weight loss, dyspnoea and dysphagia were independently associated with survival in multivariable analyses in 30-56% of the studies. However, all these studies included multiple primary tumour types, with limited discussion specific to the unique clinical context of GO cancers. There is limited information to guide prognostication in advanced GO cancer. A systematic review and meta-analysis by van den Boorn et al.[30] identified a paucity of data in advanced GO cancer. Among 45 studies of prediction models, only 7 studies were in the advanced setting, 25 were in the curative setting, and in 13 the setting was unclear/mixed. Furthermore, none of the prediction models included PROs. A recent systematic review by Kleef et al. [5] showed a weak correlation (r = 0.27) between overall survival and global health status in GO cancer. However, their primary aim was to determine the most common patient-reported issues and longitudinal trajectory of QOL.

Our review is the first to focus directly on the relationship between survival and PRO in advanced GO cancer. Furthermore, our data on PROs included in multivariable models of prognosis, along with clinical and demographic patient characteristics, may offer more confidence in the estimates provided by univariable prognostic models. Specifically, physical

functioning, role functioning, social functioning, global QOL, pain, and appetite loss/anorexia had prognostic significance in both univariable and multivariable analyses.

Strengths of our study include a comprehensive search strategy, which was developed in conjunction with two academic librarians. Study screening, data extraction and quality assessment were completed by two independent reviewers, with a third reviewer to resolve discrepancies. We included studies of chemotherapy and targeted therapies in first-line and subsequent settings. Our findings were consistent across studies, including differing populations, interventions, and PRO measures.

Our study had some limitations. Despite some heterogeneity of PRO instruments and methods used across the studies, the majority of the evaluated studies used the EORTC QLQ-C30 instrument. None of the studies reported a priori hypotheses for analysis of the PRO and other prognostic factors. We did not have access to individual patient data. Treatment with immunotherapy has become standard practice in advanced GO cancer following the improvements in survival reported in the Keynote 062 trial of pembrolizumab [31] and the Checkmate 649 trial of nivolumab.[32] Future studies should examine the association between PROs and overall survival in patients with advanced GO cancer treated with immune checkpoint inhibitors. Most studies in our review used data from clinical trials, which only include participants who meet strict eligibility criteria. These data may not apply to participants who are not eligible for clinical trials, particularly those with different symptoms and comorbidities.[33,34]

Monitoring of PROs may have a role in the routine clinical management of patients with advanced GO cancers. Basch et al. [35] have already established clinical benefits of electronic monitoring of PROs in a RCT of 766 participants with a range of advanced cancers. The European Society for Medical Oncology (ESMO) has recently recommended symptom monitoring with PROMs in routine clinical care during systemic cancer treatment, following multiple RCTs that have confirmed benefits in communication, satisfaction, treatment adherence, symptom control, reduced emergency room and hospital admissions, and survival.[36-39] Our study findings suggest that PRO data could offer additional benefit in more accurately predicting the length of survival of advanced GO patients when assessed before therapy, when interpreted in the context of other known prognostic clinical and demographic factors. Further prospective research is required to determine whether the specific PRO domains identified in this review as prognostically significant can be used to improve the quality, accuracy, and utility of prognostic information in practice and research.

Conclusions

In conclusion, our review indicates that multiple PRO domains were associated with survival in advanced GO cancer. Baseline PRO assessment might be used to improve the accuracy of prognostication, assist in communication about prognosis with patients and carers, and be used to stratify randomisation in clinical trials.

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Chapter 4

Development and Validation of a Prognostic Model incorporating patient-reported outcomes for Advanced Gastric and Oesophageal Carcinoma (AGOC) Using Individual Patient Data from Two AGITG Randomised Clinical Trials

4.1 Overview

This chapter presents a published work (refer to Appendix C). It offers a validated prognostic model incorporating patient-reported outcomes (PROs) in gastro-oesophageal (GO) cancer.

This study developed a prognostic model and nomogram for advanced GO cancer, incorporating clinicopathological variables and PROs to improve survival prediction. The model was developed using a randomised clinical trial sample, in a two-stage process, using the least absolute shrinkage and selection operator (LASSO) regression. The model was then validated in a second clinical trial sample. The final model with PROs and clinicopathological variables demonstrated high predictive accuracy for estimating the survival of patients with advanced GO cancer.

Publication details

Naher, S.K., Espinoza, D., Grimison, P. *et al.* Development and validation of a prognostic model incorporating patient-reported outcomes for advanced gastric and oesophageal carcinoma (AGOC) using individual patient data from two AGITG randomised clinical trials. *Gastric Cancer* (2025). https://doi.org/10.1007/s10120-025-01654-2

Author Contributions

Sayeda Kamrun Naher, David Espinoza, Peter Grimison, Martin Stockler, Rebecca Mercieca-Bebber, and Katrin Marie Sjoquist contributed to the conception and design of the study. Sayeda K. Naher and David Espinoza conducted material preparation, data collection, and analysis. Data collection for the included trials was supported by Nick Pavlakis, Kohei Shitara, David Goldstein, and Katrin Marie Sjoquist. Sayeda K. Naher drafted the initial manuscript, and all authors provided input on subsequent revisions. All authors reviewed and approved the final version of the manuscript.

4.2 Manuscript

Abstract

Background

We developed and validated a prognostic model incorporating readily accessible clinicopathological data and specific patient-reported outcomes (PROs).

Methods

We used data from two randomised trials comparing regorafenib to placebo: AGITG INTEGRATE IIa (n=251) for model development and AGITG INTEGRATE (n=152) for validation. Candidate variables were chosen from systematic literature review and expert consultation. Significant prognostic factors in the multivariable model were identified using univariable Cox proportional hazards models with a p-value of <0.1. Multivariable Cox proportional hazards models were developed using clinicopathological and PRO variables, with model selection refined using the least absolute shrinkage and selection operator (LASSO). The model's discrimination and calibration were assessed using concordance indices (C-statistics) and calibration plots.

Results

Univariable analysis identified nine clinicopathological variables and 4 PRO domains that were prognostic for overall survival: body mass index (BMI), ECOG performance status, number of metastatic sites, liver involvement, treatment with regorafenib, neutrophil-lymphocyte ratio (NLR), LDH, albumin, CA 19-9, appetite loss, constipation, fatigue, and pain. The initial multivariable model (M1) incorporated geographic region (Asia vs non-Asia), performance status, number of metastatic sites, treatment with regorafenib, NLR, BMI, LDH, CA 19-9, and albumin. The preferred multivariable model (M2), including the abovementioned variables plus the 4 PROs, demonstrated superior discriminative ability with higher C-statistic values than models without PROs. Plots supported the model's calibration.

Conclusions

Incorporating PROs into prognostic models for AGOC improved the accuracy of survival predictions. Further research is needed to validate its use in routine clinical practice.

Introduction

Advanced (metastatic or inoperable or unresectable) gastric and oesophageal carcinoma (AGOC) is common and has a poor prognosis, with the fifth-highest incidence and fourth-highest mortality rates globally.[1] Predicting future survival time is an important and difficult problem for doctors, patients, and carers. The range and complexity of factors influencing prognosis contribute to this difficulty.[2] Patients with advanced cancer who discussed prognosis and life expectancy with their oncologists developed a better understanding of the nature of their illness.[3]

Nomograms for estimating prognosis in AGOC have been developed using clinicopathological variables, including performance status, presence of liver metastasis, peritoneal metastasis, and neutrophil-to-lymphocyte ratio (NLR).[4-8] The majority of previous models were developed in the setting of first-line chemotherapy.[4,5] Other studies assessed a limited number of variables.[8,9] The applicability of these models to patients receiving second- and subsequent-line systemic therapy is unclear.

Patient-reported outcomes (PROs) collected at baseline have shown prognostic value in other types of advanced cancer. [10,11] A systematic review by Mierzynska et al. reported on the prognostic value of baseline PRO scores across 41 studies and 15 cancer types.[11] The domains most frequently associated with survival included physical functioning (17 studies) and global health status and quality of life (15 studies).[11] Among these studies, Park 2008 reported that patient-reported social functioning, assessed at baseline with the QLQ-C30, was prognostic in

advanced gastric cancer in a model including bone metastases, haemoglobin, and age.[12] Our systematic review identified multiple PRO domains that were prognostic in gastric cancer.[13] Despite broad, growing evidence about the value of PROs in predicting survival, there has been limited development and validation of prognostic models for AGOC that incorporate PROs.[14,15]

The AGITG INTEGRATE and INTEGRATE IIa are randomised trials of regorafenib in AGOC.[16,17] These trials showed that regorafenib, a multitargeted oral tyrosine kinase inhibitor (TKI), improved progression-free and overall survival in AGOC after prior systemic therapies had failed or were poorly tolerated. Both trials included participants with ECOG performance status 0-1 who had previously received at least 2 lines of systemic therapy.

We sought to improve prognostication by developing and validating a model and nomogram using readily available clinicopathological variables plus a focused set of PROs, using individual patient data from these two clinical trials.

Methods

We used INTEGRATE IIa (n=251, NCT02773524) for model development and INTEGRATE (n=152, ANZCTR 12612000239864) for validation. Both were randomised controlled trials in similar participants and clinical settings.

Model and Nomogram Development

Candidate variables

We identified potential prognostic variables by reviewing the literature and consulting oncologists, quality-of-life (QOL) experts, statisticians, and members of the INTEGRATE Trial Management Committees.[13]

Variables tested in univariable analyses included geographical region, Eastern Cooperative Oncology Group (ECOG) performance status, prior therapy lines, neutrophil to lymphocyte ratio (NLR), serum albumin concentration, body mass index(BMI), primary disease site, number of metastatic sites, tumour location; serum concentrations of carbohydrate antigen (CA) 19-9 and lactate dehydrogenase (LDH); previous resection of primary (gastrectomy), age, sex at birth, treatment with regorafenib versus (vs) placebo and the following PRO assessed at baseline with the EORTC QLQ-C30 and QLQ-STO22 (appetite loss, pain, fatigue, lack of mobility, lack of energy, leg swelling, constipation) (See Appendix A).

Prognostic factors included in the multivariable model were identified through univariable Cox proportional hazards models, using a p-value threshold of <0.1. Multivariable models were developed using the least absolute shrinkage and selection operator (LASSO). A 10% missing value threshold was set; variables exceeding this were planned for imputation to prevent sample size reduction. However, as no variable had missing data exceeding the 10% threshold, imputation was not necessary. Standardisation was applied to albumin, LDH, and CA 19-9 to ensure comparability.

Cox proportional hazards regression was used for all time-to-event analyses. The proportional hazards assumption was assessed, and this showed strong evidence that the variable for gastrectomy violated this assumption ($p<0.001$). We therefore stratified all multivariable analyses by gastrectomy status (yes/no).

Geographical region (Asia vs. non-Asia: Australia, USA, Canada, NZ) was included in the multivariable models because it was prognostic in a previous analysis of the INTEGRATE trial, even though it was not prognostic in our current univariable analysis.[20]

Three models were developed from the multivariable analyses, all stratified by gastrectomy status. The first model (M1) included only clinicopathological variables. The second model (M2) expanded on M1 by adding PROs from EORTC QLQ-C30. The third model (M3) expanded M2 by including selected variables from the QLQ-STO22. A nomogram was developed for M2, including the variables selected by the LASSO.

The rationale for selecting Model M2 was that the QLQ-C30 is a widely used and readily available generic patient-reported outcome measure (PROM), which includes identified, important PRO domains, with minimal respondent and administrator burden. The rationale for testing Model M3 was its inclusion of a subscale from the QLQ-STO22 specifically assessing pain 'in the stomach area' and pain associated 'with eating', rather than the generic pain subscale from the QLQ-C30.

Validation of the model

Internal validation of the models was assessed in terms of discrimination and calibration. Discrimination was assessed with the concordance index (C-index), which assesses the model's ability to distinguish between individuals who did and did not experience the event of interest (death).[21,22] Confidence intervals for the C-index were calculated using bootstrap resampling from the construction data set (1000 bootstrap samples per model).

External validation was assessed using data from the INTEGRATE trial; this data was not used for model development. Calibration assesses the accuracy of the model's predicted probabilities of outcomes by comparing them with the actual observed outcomes.[23] Calibration was assessed visually by plotting observed versus predicted probabilities of overall survival at 6 months. The effects of model recalibration were assessed using re-estimation of the intercept and re-estimation of both the intercept and the slope.

Analyses were performed using SAS version 9.4 and R version 4.3.2.[18,19]

Results

Descriptive Statistics

The baseline characteristics of the 403 participants in INTEGRATE and INTEGRATE IIa are summarised in Table 1. Approximately half the participants were recruited in Asia. The median age was 63 years, 77% were male, and the primary site was the stomach in 69%. The median overall survival time was 6 months, with a range from 2 to 30 months.

Baseline PROs indicated a significant symptom burden, with appetite loss reported in 61%, constipation in 42%, fatigue in 66%, and pain in 46%.

Table 4.1: Baseline characteristics of the participants

Characteristics	INTEGRATE N (%)	INTEGRATE IIa N (%)	Both groups N (%)
Region			
Asia	54 (36%)	157 (63%)	211 (52%)
Rest of world	98 (65%)	94 (38%)	192 (48%)
Age -Median (IQR)	62(54 to 68)	64 (57 to 71)	63 (56 to 70)
Sex - Male	120 (79%)	190 (76%)	310 (77%)
Primary site			
GOJ	58 (38%)	69 (28%)	127 (32%)
Stomach	94 (62%)	182 (73%)	276 (69%)
ECOG			
0	62 (41%)	93 (37%)	155 (39%)
1	90 (59%)	158 (63%)	248 (62%)
Prognosis (months) - Median (range)	6 (3 to 18)	4 (2 to 30)	6 (2 to 30)
BMI - Median (IQR)	23 (21 to 27)	22 (19 to 25)	22(20 to 26)
Prior lines of treatment			
1-2	152 (100%)	149 (59%)	301 (75%)
3+		101 (40%)	101 (25%)
Number of metastatic Sites 4+	35 (23%)	52 (21%)	87 (22%)
Liver metastasis	75 (49%)	128 (51%)	203 (50%)
Peritoneal metastasis	47 (31%)	74 (30%)	121 (30%)
Gastrectomy	52 (34%)	99 (39%)	151 (38%)
NLR- Median (IQR)	3 (2 to 6)	3 (2 to 5)	3 (2 to 5)
LDH- Median (IQR)	241 (187 to 396)	231 (177 to 355)	234 (178 to 374)
Albumin - Median (IQR)	37 (35 to 43)	37 (32 to 40)	37 (33 to 41)
Ca 19.9- Median (IQR)	53 (12 to 309)	53 (13 to 544)	53 (13 to 467)
PRO domain score, 0-100 scale (EORTC QLQ-C30)			
Appetite loss			
30+	91 (60%)	157 (63%)	248 (62%)

Characteristics	INTEGRATE N (%)	INTEGRATE IIa N (%)	Both groups N (%)
<30	45 (30%)	83 (33%)	128 (32%)
Constipation			
30+	62 (41%)	107 (43%)	169 (42%)
<30	74 (49%)	132 (53%)	206 (51%)
Fatigue			
30+	97 (64%)	170 (68%)	267 (66%)
<30	39 (26%)	70 (28%)	109 (27%)
Pain			
30+	61 (40%)	123 (49%)	184 (46%)
<30	75 (49%)	117 (47%)	192 (48%)
Pain (STO22)			
30+	54 (36%)	106 (42%)	160 (40%)
<30	82 (54%)	133 (53%)	215 (53%)

IQR, interquartile range; GOJ, gastro-oesophageal junction; ECOG, eastern cooperative oncology group; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; CA, carbohydrate antigen; PRO, patient reported outcome; EORTC QLQ, European Organisation for Research and Treatment of Cancer quality of life questionnaire. The possible scores for these scales range from 0 (none at all) to 100 (worst possible).

Univariable and multivariable model

In the development dataset, 9 of 15 clinicopathological variables collected at baseline met the prespecified threshold ($p < 0.1$) in univariable analysis for potential inclusion in the multivariable model. These factors included ECOG performance status (1 vs 0) ($p = 0.02$), BMI ($p = 0.08$), number of metastatic sites ($p<0.001$), liver involvement ($p=0.04$), treatment with regorafenib vs placebo ($p = 0.005$), NLR ($p<0.001$), LDH ($p<0.001$), albumin ($p<0.001$), and CA 19-9 ($p<0.001$). Univariable and multivariable analyses are summarised in Table 2. Baseline PROs that met the univariable analysis threshold for inclusion in the multivariable model

included appetite loss (p<0.001), constipation (p<0.001), fatigue (p<0.001), and pain (p<0.001) from the QLQ-C30, and stomach pain (p<0.001) from the QLQ-STO22.

Table 4.2: Univariable and multivariable analyses of associations between baseline characteristics and overall survival time

Variable	Class	Univariable		M1 - Multivariable		M2 - Multivariable		M3 - Multivariable	
		Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Region	Rest of world vs Asia	1.17 (0.89-1.53)	0.26	1.58 (1.15-2.18)	0.005	1.68 (1.20-2.35)	0.0026	1.59 (1.14-2.22)	0.006
Age	10-year increase	0.92 (0.82-1.03)	0.26						
Sex		0.89 (0.66-1.21)	0.47						
Primary Site	Stomach vs GOJ	0.86 (0.64-1.15)	0.32						
ECOG performance status	1 vs 0	1.38 (1.05-1.80)	0.02	1.16 (0.87-1.54)	0.31	1.04 (0.76-1.40)	0.82	1.06 (0.78-1.42)	0.72
BMI	10-unit increase	0.75 (0.55-1.03)	0.08	0.53 (0.38-0.75)	0.0004	0.57 (0.39-0.84)	0.004	0.59 (0.41-0.85)	0.005
Prior lines of treatment	2-unit increase	1.09 (0.88-1.35)	0.42						
Number of metastatic sites	4+ vs 1	2.19 (1.44-3.33)	<.001	2.61 (1.66-4.12)	<.0001	2.20 (1.39-3.48)	0.001	2.07 (1.29-3.31)	0.001
Liver metastasis	yes vs no	0.76 (0.59-0.99)	0.04						
Peritoneal Metastasis	yes vs no	1.19 (0.89-1.58)	0.24						
Treatment	Rego vs Placebo	0.67 (0.51-0.89)	0.005	0.73 (0.54-0.97)	0.03	0.77 (0.57-1.04)	0.09	0.75 (0.55-1.00)	0.05
NLR	6-unit increase	1.26 (1.11-1.44)	<.001	1.26 (1.07-1.47)	0.004	1.21 (1.02-1.43)	0.03	1.25 (1.05-1.48)	0.011
LDH	250-unit increase	1.42 (1.20-1.68)	<.001	1.40 (1.17-1.67)	<.001	1.51 (1.26-1.82)	<.0001	1.49 (1.24-1.78)	<.0001
Albumin	10-unit increase	0.68 (0.56-0.83)	<.001	0.73 (0.60-0.89)	0.002	0.80 (0.65-1.00)	0.05	0.80 (0.64-0.99)	0.04
Ca 19.9	200-unit increase	1.01 (1.00-1.01)	<.001	1.01 (1-1.01)	<.0001	1.01 (1-1.01)	0.0006	1.01 (1-1.01)	0.0003
Appetite loss	33-unit increase	1.43 (1.25-1.64)	<.001			1.21 (1.01-1.45)	0.03	1.22 (1.02-1.46)	0.03
Constipation	33-unit increase	1.31 (1.13-1.53)	<.001			1.07 (0.89-1.27)	0.48		
Fatigue	33-unit increase	1.50 (1.26-1.80)	<.001			1.07 (0.81-1.42)	0.63	1.08 (0.84-1.40)	0.53
Pain	33-unit increase	1.43 (1.24-1.64)	<.001			1.18 (0.97-1.44)	0.10		
Pain (STO22)	33-unit increase	1.70 (1.37-2.10)	<.001					1.38 (1.07-1.79)	0.013

GOJ, gastro-oesophageal junction; NLR, neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; CA, carbohydrate antigen.

Three multivariable models were constructed from the multivariable analysis, all stratified by gastrectomy status. The first model (M1) included clinicopathological factors such as region, ECOG status, number of metastatic sites (extent of cancer), BMI, treatment, NLR, LDH, albumin, and CA 19-9. The second model (M2) expanded on M1 by adding PROs from EORTC QLQ-C30, specifically fatigue, pain, appetite loss, and constipation. The third model (M3) used the item on stomach pain from the QLQ-STO22, along with the subscales for fatigue and appetite loss from the QLQ-C30, to model M1. Liver involvement was excluded from the LASSO-based multivariable models.

These multivariable analyses(M2) demonstrated several clinicopathological and PRO factors that were prognostic for overall survival in models accounting for the effects of other variables. Survival times were shorter for participants from the rest of the world than from Asia (HR 1.68, 95% CI: 1.20-2.35, p=0.0026). Shorter survival times were also associated with number of metastatic sites (HR = 2.20, 95% CI: 1.39-3.48, p=0.001), higher NLR (HR = 1.21, 95% CI: 1.02-1.43, p=0.03), higher LDH (HR = 1.51, 95% CI: 1.26-1.82, p<0.0001), and higher CA 19-9 (HR = 1.01, 95% CI: 1-1.01, p=0.0006). Longer survival times were associated with higher BMI (HR = 0.57, 95% CI: 0.39-0.84, p = 0.004) and higher serum albumin (HR = 0.80, 95% CI: 0.65-1.00, p = 0.05). Performance status, liver metastasis, and lines of previous therapy were not significant in multivariable models.

Among the PRO, appetite loss was associated with shorter survival in both univariable and multivariable analysis (HR = 1.21, 95% CI: 1.01-1.45, p=0.03), whereas constipation, fatigue, and pain were significant in univariable models (p<0.001), but not in the multivariable model (p>0.10). The pain subscale from the QLQ-STO22 had slightly greater prognostic significance than the pain scale from the QLQ-C30.

Overall, factors such as region, number of metastatic sites, treatment, NLR, LDH, albumin, and appetite loss consistently showed significant associations with survival, while other factors like age, sex, and primary site show little to no impact.

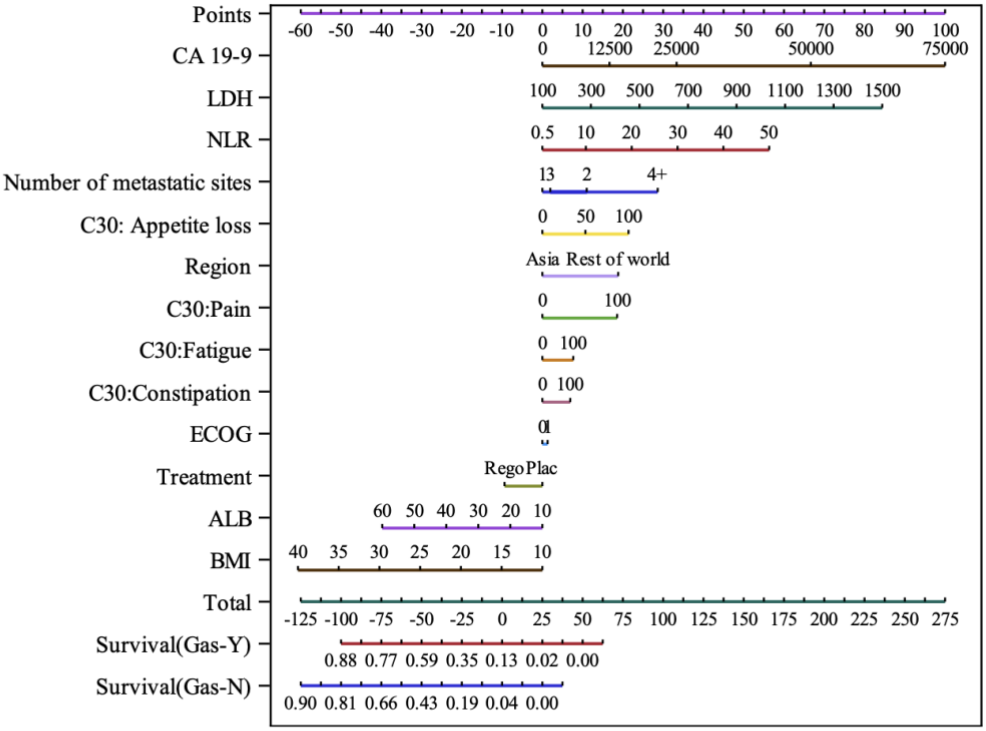
Model Performance

The performance of these multivariable models was assessed using the C-statistic (see Table 3). M2 and M3 exhibited higher C-statistics than M1, indicating improved prediction by including PROs. M2, which incorporated the PRO indicators from EORTC QLQ-C30, but not the QLQ-STO22, was chosen as the final model based on its higher C-statistics in both the gastrectomy and non-gastrectomy strata and the benefit of using PRO domains from one, rather than two, separate PRO measures.

Table 4.3: Model's C-Statistic + Bootstrap 95% Cis

Model	Gastrectomy	C -statistic	95% CI	
M1	No	0.695	0.660	0.732
	Yes	0.664	0.619	0.714
M2	No	0.723	0.686	0.759
	Yes	0.692	0.645	0.750
M3	No	0.721	0.685	0.756
	Yes	0.685	0.633	0.743

Figure 4.1: Nomograms for Model 2 prognostic model



CA, carbohydrate antigen; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio;

C30, EORTC QLQ-C30; ECOG, eastern cooperative oncology group; Rego, regorafenib; Plac, placebo; ALB, albumin; BMI, body mass index; Gas, gastrectomy; Y, yes; N, no.

*The more points the lower the estimated probability of survival at 6 months.

The nomogram based on Model 2 illustrates the extent to which the various predictor variables affect the probability of overall survival at 6 months. For example, in this dataset,

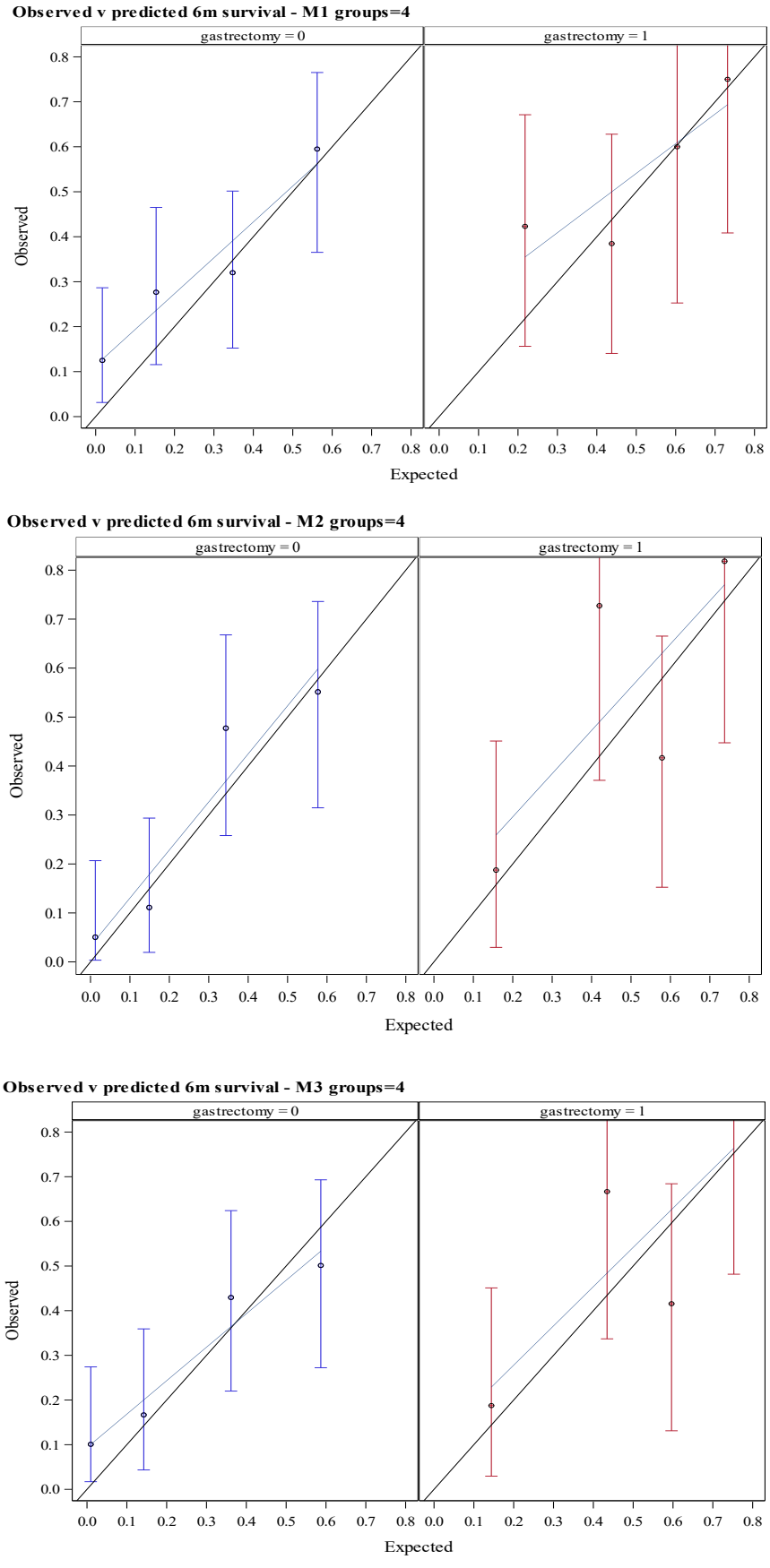
having 4 or more metastatic sites was associated with a much lower probability of survival at 6 months than having 3 or fewer metastatic sites, whereas having an ECOG performance status of 0 versus 1 had relatively little effect. Appetite loss and pain had larger effects on the probability of survival than fatigue and constipation.

Validation of the model

Calibration

The model's predictions of 6-month survival were well-calibrated for participants with and without prior gastrectomy, as indicated by calibration curves close to the 45-degree reference line, reflecting perfect calibration (Figure 2). Panel B, showing the calibration of M2, indicates the improvement resulting from inclusion of the PRO for fatigue, pain, and constipation to M1 shown in Panel A. Use of the QLQ-STO22 items for stomach pain in M3 did not improve calibration compared with use of the generic items for pain M2 from the QLQ-C30. There was a tendency for the lowest predicted survival probabilities to underestimate the observed survival probability in all the models.

Figure 4.2: Calibration plot for observed vs predicted(expected) probability of survival at 6 months in the validation cohort (INTEGRATE trial)



Discussion

This study advances prognostic modelling for overall survival in AGOC patients by incorporating a broader set of clinicopathological variables and PROs from the EORTC QLQ-C30 and QLQ-STO22, enhancing both accuracy and clinical applicability. Our model M2 incorporates additional clinicopathological variables and patient-reported outcomes including fatigue, alongside known predictors of survival such as pain, appetite loss, and constipation.[20] We selected candidate PROs a priori, based on prior literature and expert consultation, and conducted robust univariable testing before including variables in our multivariable analyses.

Our methodological approach builds on previous work by using a more comprehensive and robust multivariable modelling strategy, with models incorporating PROs demonstrating superior predictive performance, reflected in improved C-statistics from 0.695 in M1 to 0.723 in M2 with the inclusion of patient-reported pain, appetite loss, and constipation. The incorporation of these additional variables provided more individualised and accurate estimates of survival probability at 6 months.

Sensitivity analyses demonstrated good calibration with only minor variations observed across different scenarios and support the use of model M2.

A prognostic model that included baseline clinicopathological variables and selected PRO from the QLQ-C30 provided clinically useful estimates of overall survival. These variables can feasibly be collected in routine clinical practice, using a readily accessible, simple, PRO measure. The use of standardised and widely-accepted measures (like the EORTC QLQ-C30)

facilitates implementation with minimal additional training for healthcare providers.[26] Standardised PROs can enhance consistency and comparability across different clinical settings. Patients and clinicians should benefit from improved understanding of their prognosis and be better equipped to make decisions regarding their future treatment and care.[27] Model M2 could also be used as a stratification factor in future randomised trials.

Our analyses demonstrated that pain ratings focused on abdominal pain and/or pain related to eating (as captured by the QLQ-STO22, Model M3) offered greater prognostic value than general pain ratings from the QLQ-C30 (Model M2). However, the overall performance of Model M3 was not significantly better than that of Model M2. Additionally, the benefit of using the pain score from the QLQ-C30 over the abdominal pain score of the QLQ-STO22 is reduced responder- and administrator- burden, and easier, streamlined administration of a single, readily accessible instrument (QLQ-C30). These findings warrant further investigation in additional datasets.

Our study has important strengths. We used Cox proportional hazards models with the LASSO method for variable selection. This approach strengthens the model's reliability, reduces the risk of overfitting, and identifies independent prognostic factors more effectively than previous methods.[28,29] Variable selection involved both univariable screening and multivariable modelling to account for potential confounders. INTEGRATE IIa and INTEGRATE included participants from Asia, Australia, and Canada, resulting in a more diverse study population than studies conducted in a single region. We used validated translations of the EORTC PROs in non-English speaking participants.

This study also has limitations. Firstly, the models were built and validated with data from clinical trial populations, which may not be representative of the broader, more

heterogeneous population treated outside of clinical trials. [30] Trial participants often differ in demographics, comorbidities, and disease severity, which may limit the model's generalizability to routine clinical practice. Future studies should test the model's external validity by applying it in routine clinical settings. Our sample sizes were moderate, and further validation in larger, independent data sets is also warranted.[31] While the model showed good predictive accuracy across our 2 study cohorts, its performance might differ in a broader, more diverse population. All participants were receiving second or subsequent lines of treatment and had an ECOG performance status of 0-1. The applicability of our model to patients with ECOG performance status worse than 1 or having first-line treatment remains an open question for further research.

We did not perform decision curve analysis (DCA) or net reclassification improvement (NRI) in this study; alternative methods for assessing model performance and clinical utility in terms of reclassification were used. These approaches provide additional insights if the proposed application of a model is to categorise participants to directly influence decision-making. Future studies of models designed to influence decision making should incorporate DCA and NRI.

Future research should explore the applicability of our model in routine clinical settings to validate its utility and impact further. A web-based tool would facilitate its use and allow real-time validation in clinical practice settings.[32] Future research could assess the integration of this model in an Electronic Health Record to enhance data collection, accessibility, and data-driven decision-making.[33] Training programs for clinicians could facilitate their adoption and implementation with the aim of improving doctor-patient communication and care.[34]

In conclusion, we developed and validated a nomogram to predict the probability of survival at 6 months in AGOC patients being treated with second or subsequent line anti-cancer treatments. By incorporating clinicopathological and patient-reported variables that are simple to collect and often collected routinely, the model enhanced prognostic accuracy and supports a more personalised approach. Implementation of this nomogram in clinical practice could improve patient care and decision-making, by contributing to more frequent and accurate discussions of prognosis, and better stratification in clinical trials.

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Chapter 5

Discussion

5.1 Overview

The overarching goal of my PhD studies was to improve prognostication for people with advanced gastro-oesophageal adenocarcinoma (GO cancer) using data from clinical trials and related research. Advanced GO cancers include adenocarcinomas arising from the stomach or gastro-oesophageal junction, that are either metastatic to distant sites, or localised but inoperable, or recurrent after primary surgery. Specifically, I aimed to:

1. Assess the validity of using simple multiples of the median overall survival from Kaplan-Meier curves in advanced GO cancer trials to estimate scenarios for survival time, based on methods applied in other advanced solid tumours.
2. Explore the role of patient-reported outcomes (PROs) in prognostication for advanced GO cancers through a systematic review.
3. Develop and validate a prognostic model for advanced GO cancers that incorporates PROs with clinicopathological variables using individual participant data from two randomised trials.

This Discussion chapter summarises the main findings of each research chapter, implications for research and practice, strengths and limitations of the work as a whole and recommendations for future research.

5.2 Chapter 2 - Summary of key findings

In Chapter 2, I reported a systematic review of recent clinical trials of treatments for advanced GO cancer to identify, summarise, and analyse survival data across a range of treatments. These trials were categorised by treatment type and treatment line. A total of 44 studies with 22,447 participants were included. 30 trials investigated first-line treatments, while 14 trials focused on second-line or subsequent therapies.

Median overall survival times among the 44 trials varied by line of treatment. The mean of the median overall survival was approximately 15 months among the 3 trials of chemotherapy combined with immunotherapy as first-line treatment, versus 11 months among the 27 trials of other first-line treatments, and ranged from 4 to 10 months in 14 trials of second- or subsequent-line treatments.

This systematic review highlighted significant variability in overall survival times across different treatment regimens and lines of therapy. This variability arises from differences in treatments, tumour biology, patient characteristics, prior treatments, molecular markers, and healthcare access.[1] The range of survival estimates highlighted the complexity of effective prognostication, which required the incorporation of multiple prognostic variables to personalise predictions of enhanced survival time and guide informed treatment decisions.

In Chapter 2, I also successfully applied a simple method to estimate ranges for typical-case, best-case, and worst-case scenarios for survival time, as previously established in breast, lung, prostate, and other cancers. This method used simple multiples of the median from a given survival curve, e.g. from a clinical trial, to estimate survival times at other specified percentiles of the same survival curve.[2]

5.3 Overview of Survival Estimation Method and its accuracy in GO cancer

This review described a percentile-based approach to summarising and describing survival data from clinical trials. The 90th percentile was used to define an upper boundary for the worst-case scenario, and was estimated by one-quarter of the median overall survival time (mOS). The 75th percentile marked the lower bound of a range for the typical-case scenario, estimated as half the median OS. The 25th percentile represented the upper bound of the range for the typical-case scenario, twice the median OS. The 10th percentile indicated a lower bound for the best-case scenario, estimated as three times the median OS.

In first-line trials of chemotherapy with immunotherapy, simple multiples of the mOS accurately predicted the 75th and 90th percentiles of the respective survival curves. Reliable estimates of the 10^{th} percentiles were infrequent because of short follow-up times. Trials of other first-line regimens demonstrated good accuracy across all percentiles. In trials of subsequent-line treatments, simple multiples of the mOS generally provided accurate estimates of all 3 scenarios for survival time. The least accurate predictions based on simple multiples of the median were of the worst-case scenario in trials of chemotherapy alone, which were accurate in 64% (7/11) survival curves. The best- and worst-case scenarios in trials of immunotherapy were accurate in 2 out of 3 cases (67%).

5.4 Chapter 2 - Clinical Implications

This approach for estimating and describing scenarios for survival time based on simple multiples of the median survival time offers a practical and immediately applicable approach for clinicians in everyday practice. By using this approach, healthcare providers can formulate and explain 3 scenarios for survival time, rather than just a median survival time, based on that patient's proposed treatment regimen. This approach had previously been shown to be applicable in breast, prostate and lung cancers.[3-5] My systematic review has established its applicability in advanced gastro-oesophageal cancer. This approach enables more effective communication with patients by providing a structured way to estimate and present ranges of survival times with probabilities that correspond to the scenarios sought by patients, as reported in previous surveys.[4]

Enhanced Communication and Realistic Expectations

The approach allows clinicians to offer patients a range of survival scenarios, including an optimistic best-case scenario, a realistic worst-case scenario, and a most likely typical scenario. This approach helps bridge the gap between complex data and patient understanding. By presenting survival estimates in terms of multiple ranges rather than single-number summaries, clinicians can more accurately and honestly convey the inherent uncertainty of prognosis. This should help reduce misunderstandings and provide a clearer picture of potential outcomes that is both more realistic and more hopeful.[6,7]

Empowering Informed Decision-Making

When patients are presented with a range of scenarios for survival time, they should be better equipped to make informed decisions about their treatment. Understanding the range of possible trajectories of their disease should help patients better weigh the benefits and risks of various treatment options in the context of their personal goals and values.[8] For instance, it may help patients choose between a more aggressive treatment that offers the prospect of longer survival but at the cost of more severe side effects, versus a more conservative approach with less severe side effects but the prospect of shorter survival time.[9,10] A patient who values immediate quality of life more highly than the possibility of longer length of life may opt for the treatment plan that minimises side effects, even if it results in shorter survival.[11] Using scenarios for survival time to explain prognosis should help clinicians tailor their recommendations to each individual patient's specific priorities and goals.[12]

In summary, estimating and explaining 3 scenarios for survival time based on the median survival time from a pertinent clinical trial provided a practical method for formulating and explaining possible outcomes of treatment in routine clinical practice, helping to set more realistic expectations and facilitating informed, shared decision-making. This should empower patients by offering a clearer understanding of their prognosis and help clinicians tailor discussions and treatment plans to align with each patient's personal goals and preferences. This approach should also enhance patient-clinician relationships and support more personalised and effective cancer care.

5.5 Chapter 3 - Summary of key findings

Chapter 3 presented a systematic review of contemporary studies aimed at identifying the prognostic significance of PRO domains in advanced gastro-oesophageal cancer. A total of seven studies included PROs, comprising 2,761 of 3,408 trial participants (81%).

Five different PRO instruments were used in the seven studies included in this analysis. The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) was used in 5 studies, and the EQ-5D-3L was used in 2 studies. The Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale (FAACT A/CS), the EORTC gastric cancer module (STO22), and the Patient Disease and Treatment Assessment (PTDATA) Form were each used in one study. All studies used Cox proportional hazards regression to evaluate both univariable and multivariable relationships between PROs and survival time.

The following PRO domains were associated with survival time in advanced gastro-oesophageal cancer:

- **Global QOL**: A pivotal study by Chau et al. reported a hazard ratio for overall survival of 0.57 (p<.0.001) for global QOL (EORTC QLQ-C30), indicating that higher global QOL was associated with longer survival. [19]

- **Physical Functioning**: Three studies demonstrated that better physical functioning, as measured by either the EORTC QLQ-C30 or EQ-5D-3L, was associated with longer survival. [19-21]

- **Role Functioning**: One study showed that better role functioning, as measured by the EORTC QLQ-C30, was associated with longer survival (HR 0.69, $p < 0.001$).[19]

- **Pain**: Two studies showed that pain, measured with either the EORTC QLQ-C30 or the EQ-5D-3L, was associated with shorter survival.[20,21]

- **Appetite Loss/Anorexia**: three studies showed that appetite loss, measured with either the EQ-5D-3L or FACT AC/S, was associated with shorter survival.[21-23] For example, median survival in participants with more severe anorexia/cachexia (FAACT-A/CS score 37 or lower) was 7 months, compared with 19 months in those with less severe anorexia/cachexia (score of 37 or lower).[23]

Other Significant Clinical and Laboratory Variables

In addition to PROs, several clinicopathological variables included in these studies demonstrated prognostic significance, as outlined below. These included ratings of Eastern Cooperative Oncology Group physical functional performance status (ECOG PS), sites of disease, and results of laboratory tests.

Chau et al. reported that the presence of poor performance status (ECOG PS 2-4), liver metastases, peritoneal metastases, or serum alkaline phosphatase ≥ 100 U/L were prognostic

in a study of over 1000 participants.[19] Similarly Fuchs et al. identified 12 clinical and laboratory factors that were associated with shorter survival: peritoneal metastases, ECOG PS of 1 (versus 0), the presence of a primary tumour, time to progression since prior therapy <6 months, poor/unknown tumour differentiation, low serum albumin concentration, low serum sodium concentration, low blood lymphocyte count, high blood neutrophil count, high serum aspartate aminotransferase (AST), high serum alkaline phosphatase (ALP), and high lactate dehydrogenase (LDH).[22] Although these models incorporated PROs and clinicopathological variables, they lacked a priori specification of PRO domains and used older statistical methods. I sought to develop a more robust model addressing these limitations.

5.6 Chapter 3 - Clinical Implications

This review highlighted that PROs provide important prognostic information in GO cancer. Previous studies had highlighted the prognostic value of PROs in multiple cancers.[24,25] A study published in December 2024 showed PROs had prognostic significance in metastatic melanoma.[26] Another study by Lim et al. analysed data from 46 clinical trials using the EORTC QLQ-C30 across 17 cancer types, including gastric cancer. Their stratified multivariable model revealed that physical functioning, pain, and appetite loss were independent predictors of survival time.[27]

PROs reflect patients' perspectives on their health, quality of life, symptoms, and functional status, providing a more holistic view of their condition. [28,29] Additionally, incorporating PROs

enables a more personalised prognosis by considering each patient's individual situation and experiences, rather than relying exclusively on clinical and pathological factors. Eliciting, valuing, and incorporating information about PRO could improve patient-doctor communication.[30]

Incorporating PROs into prognostication makes survival predictions more accurate, more patient-centred, and more useful for clinicians by better supporting decision-making and reflecting the importance of how patients are feeling and doing when assessing their health and prognosis.

5.7 Chapter 3: Findings of this thesis in context

Significance of PROs as prognostic factors in other cancers

Patient-reported outcomes had been shown to provide prognostic information across many cancer types, including platinum-resistant ovarian cancer, lung cancer, colorectal cancer, breast cancer, and melanoma. [25,31-36] Systematic reviews have also confirmed this in multiple cancer types.[25,37] Our systematic review, reported in Chapter 3 of this thesis, found that physical functioning, role functioning, social functioning, global quality of life, pain, and appetite loss/anorexia were prognostic in advanced gastro-oesophageal cancer, with the majority of studies using the EORTC QLQ-C30. These findings have advanced the field by highlighting the prognostic significance of patient-reported outcomes in advanced gastro-oesophageal cancer. By incorporating patient perspectives into survival predictions, clinicians can provide a more accurate and holistic assessment of prognosis.[38] Incorporating PROs in

prognostication should help personalise care, integrate quality-of-life assessment into clinical practice, and emphasise the importance of PRO in research.[39,40]

5.8 What justifies the need for another model?

The incorporation of PROs in prognostic models for GO cancers was previously limited. The prognostic value of PROs in gastro-oesophageal cancer was assessed in only 7 of 3,000 studies of prognosis identified by our search, and each had notable limitations. All studies evaluated PROs in analyses that were exploratory and post-hoc rather than specified a priori. This highlighted a significant gap in incorporating PROs alongside clinicopathological variables in prognostic research for GO cancers.

The statistical techniques used in these previous studies were not ideally suited to PRO data**.** All studies employed Cox regression modelling with conventional methods for variable selection, which are prone to problems with multicollinearity. Multicollinearity is a major problem in regression modelling of PROs, because domains of HRQL are often highly intercorrelated.[41] Use of the least absolute shrinkage and selection operator (LASSO) as the method for variable selection in the multivariable Cox model reduces the total number of variables included, thereby reducing the probability of overfitting and multicollinearity and enhancing clinical applicability.[42-44]

The development of a prognostic model that incorporates PROS with clinicopathological variables using current statistical methods, such as LASSO, would fill an important gap. The model developed, evaluated, and reported in Chapter 4 addressed these limitations by selecting key PROs identified in previous research a priori and using LASSO to improve rigour and accuracy.

5.9 Chapter 4 - Summary of key findings

Chapter 4 focused on the development and validation of a prognostic model that incorporated PROs alongside conventional clinicopathological prognostic factors in advanced gastro-oesophageal cancer, to address the limitations identified by our systematic review. This model was developed using individual participant data from the INTEGRATE IIa clinical trial (N = 251) and validated using individual participant data from the INTEGRATE clinical trial (N = 152). The goal was to enhance survival prediction by incorporating both traditional clinicopathological variables and specific PROs using optimal statistical methods.

Three prognostic models were developed using data from INTEGRATE IIa, employing multivariable analysis stratified by gastrectomy status, and are referred to as models M1, M2, and M3. M1 included only traditional clinicopathological factors such as geographical region, ECOG performance status, body mass index (BMI), assigned treatment with regorafenib, blood neutrophil-lymphocyte ratio (NLR), serum lactate dehydrogenase concentration (LDH), serum albumin concentration, and serum concentration of Carbohydrate Antigen 19-9 (CA19-

9). M2 expanded M1 by adding PROs from the EORTC QLQ-C30, specifically fatigue, pain, appetite loss, and constipation, which had been identified a priori based on previous research and discussion with experts. M3 expanded M1 by adding stomach pain from the EORTC QLQ-STO22 instead of pain from QLQ-C30, along with fatigue and appetite loss from the QLQ-C30.

The final multivariable model included the following variables associated with shorter survival time: randomly assigned treatment with placebo rather than regorafenib, a higher number of metastatic sites, elevated NLR, elevated LDH, low serum albumin, and elevated CA 19-9.

Enhanced Model Performance with PROs

The incorporation of PROs in M2 and M3, including fatigue, pain, appetite loss, and constipation, as measured by the QLQ-C30, improved the predictive accuracy of the survival model as demonstrated by improved performance metrics, including higher AIC and C-statistics, compared with models using only traditional clinicopathological factors (M1). This indicates that these PROs provided additional prognostic information above and beyond that offered by established clinicopathological variables.

Validation

The three models (M1, M2, M3) developed using data from INTEGRATE IIa were validated using data from INTEGRATE, supporting their predictive accuracy in a separate dataset. All three models demonstrated good calibration for the probability of survival at 6 months, with

calibration plots approximating the 45-degree reference line for perfect calibration.[45] All 3 models (M1, M2, and M3) performed similarly in the separate validation dataset, supporting the conclusion that incorporating PROs contributed to improved additional useful prognostic information above and beyond that provided by established clinicopathological variables.

5.10 Chapter 4 - Clinical Implications

The nomogram based on model M2, which includes PRO items from the QLQ-C30, advances prognostication by incorporating items for an extensively validated and widely used PROM, together with established and widely used clinicopathological variables. Inclusion of participants from Asia, Oceania, and other regions increased diversity, enhanced generalisability, and broadened insights from previous studies.

Enhanced Predictive Accuracy

Adding PROs to traditional clinicopathological data increased the accuracy of the prognostic model. For example, in M2, the hazard ratio for overall survival associated with loss of appetite was 1.21, p=0.034, indicating a 21% increase in the hazard of death for a 33-unit increase in the 0 to 100 score for appetite loss, in a model that already accounted for a range of other independently significant prognostic factors. This means that the hazard of death for an individual with severe appetite loss is 1.77 times that of an individual with no appetite loss. Similarly, the hazard ratio for pain was 1.18, indicating that the hazard of death in an individual with severe pain is 1.64 times that of an individual with no pain. Because hazard ratios are multiplicative, the hazard of death in an individual with both severe pain and severe appetite loss would be 2.9 times that of an individual with neither of these symptoms. This

translates into a predicted survival time that is 66% shorter. These hazard ratios indicated substantial prognostic significance beyond what is provided by established factors.

Enhanced Patient Engagement

Eliciting and incorporating PROs in prognostication could promote patient engagement by emphasising the importance of the patient's experience and attitudes. This involvement can lead to a greater sense of ownership and encourage more active participation in healthcare decisions. It might also reassure patients that how they are feeling and doing is being taken seriously.

In summary, the developed model offered a practical and advanced tool for predicting survival, incorporating both PRO and clinicopathological data. This approach enhanced predictive accuracy, supports patient-centred care, might improve communication between patients and clinicians, and should facilitate better-informed and personalised decisions. By considering attributes rated by both clinicians and patients, the model provided a more comprehensive and empathetic approach to healthcare, which should facilitate greater patient involvement, satisfaction, and perhaps better outcomes.

5.11 Chapter 4: Findings of this thesis in context

Estimating prognosis in advanced gastro-oesophageal cancer is challenging because survival times are often short and subject to substantial biological and clinical variability.[46] Previous prognostic models relied primarily on clinicopathological variables, and few incorporated

PROs. Systematic reviews indicated that incorporating PROs could enhance the predictive accuracy of prognostic models.[47,48] The prognostic model developed and validated in this thesis included both clinicopathological variables and PRO using rigorous, current methods (LASSO).

Prognostic models for other cancers have also incorporated PROs. For example, a prognostic model in prostate cancer incorporating patient-reported pain enhanced the accuracy of survival predictions.[49] In advanced lung cancer, physical function, fatigue, and appetite loss emerged as predictors of overall survival.[50] The model reported in Chapter 4 of this thesis, which included a range of clinicopathological variables and PROs, has advanced the field by showing that PROs, like appetite loss, pain, and fatigue, can provide valuable prognostic information, above and beyond that of traditional clinicopathological factors, in advanced GO cancer.

Nomograms have been used in other cancer types; for example, data from more than 22,000 participants were used to build a nomogram in colorectal cancer for progression-free survival and overall survival.[51] In nasopharyngeal carcinoma, competing risk nomograms were developed using big-data, intelligence platform-based analysis.[52]

5.12 Strengths

The study of survival times in RCT of systemic therapy in advanced GO cancer, reported in Chapter 2, provided a comprehensive, systematic summary of contemporary clinical trials in this area, along with an approach for estimating best-case, typical-case, and worst-case

scenarios for survival based on the median overall survival times from pertinent clinical trials that can be applied to patients seen in routine clinical practice with suitable adjustments for patients with important differences from those included in clinical trials.

The systematic review of PROs as prognostic factors in advanced GO cancer, reported in Chapter 3, provided updated evidence on the prognostic value of PROs in this setting.

The strengths of both studies were a comprehensive search strategy developed with academic librarians; study screening, data extraction, and quality assessment were each conducted independently by two reviewers, with a third reviewer resolving conflicts. These methods enhanced the reliability and accuracy of the findings.

A strength of all three projects in this thesis was the use of a patient-focused approach aiming to incorporate PROs into prognostication. This should enhance clinicians' appreciation that patients' ratings of how they are feeling and doing, in other words, PROs, can improve prognostication and are therefore beneficial for patient-doctor communication and shared decision-making. This addressed a critical gap that many previous prognostic models have overlooked by focusing only on clinicopathological variables.[53]

A key strength of the model developed, evaluated, and validated in Chapter 4 was the use of LASSO to incorporate PROs with clinicopathological variables in a single, multivariable model. This enhanced the model's reliability and accuracy by reducing the risk of overfitting and collinearity, identifying independent prognostic factors more effectively and parsimoniously than previous methods.[42,43] This increased the rigour and reliability of variable selection. Additionally, the comprehensive scoping and assessment of variables before including them in the selection pool enhanced the model's reliability and accuracy. These methodological

strengths should improve the accuracy and reliability of prognostic assessments based on this model.

Another key strength of the study in Chapter 4 was the inclusion of a diverse cohort from the INTEGRATE IIa trial, comprising participants from Asia, Oceania, and other regions. The study recruited participants from seven countries, stratified by region: Asia (Japan, Taiwan, Korea) versus non-Asia (Australia, New Zealand, the United States, and Canada). This multinational representation enhanced both the applicability and generalisability of our findings compared to previous studies.[54]

Finally, validation of the model in a separate trial (INTEGRATE) supported the model's accuracy and robustness. Validation supported our confidence applying the model in other data sets, and supported our choice of PROs. The applicability of the model in routine clinical practice remains an open question worthy of further research.[55]

In summary, the strengths of this thesis were its rigorous evaluation and incorporation of PROs into prognostication based on comprehensive scoping using systematic reviews, rigorous statistical methods, and data from high-quality clinical trials. These contributions advance the field of oncology by refining and improving prognostic tools that could be applied in routine practice to enhance patient-centred care. By incorporating PROs in prognostication, the work in this thesis provides a more holistic picture that could lead to greater patient engagement and decision-making that is better-informed and more shared.[56]

5.13 Limitations

The research included in this thesis addresses the challenges of predicting survival in advanced GO cancer, but it is important to acknowledge several limitations.

Clinical trials, such as those from which survival curves were derived in Chapter 2 of this thesis, and for the prognostic model developed in Chapter 4, often involve highly selected patient populations with stringent eligibility criteria. For example, most trials were restricted to participants with an ECOG performance status of 0 or 1, whereas the broader population of people diagnosed with GO cancer may have an ECOG of 0-4. Tight eligibility criteria can limit the generalisability of findings from clinical trials to the broader population of patients treated outside of clinical trials, many of whom would not meet these strict criteria, have different (likely worse) baseline characteristics, and may have different outcomes.[57,58] Strict exclusion criteria in RCTs may inadvertently exclude those from vulnerable populations. This can result in trial participants representing a healthier subset of the broader population seen in routine clinical practice outside of trials. Excluding such patients from trials can lead to insufficient information about the health outcomes of these groups, making it difficult for these individuals to make informed treatment decisions, potentially affecting their outcomes. However, there is no reason to hypothesise that the associations of PROs with survival time observed in our studies would be less apparent or less important in patients treated outside of clinical trials. If anything, we hypothesise that these effects would be more apparent in a more diverse population with greater variability.

Another limitation of the work in this thesis (Chapter 2) was the short follow-up time for included clinical trials, particularly those of immunotherapy, which was generally too short to accurately assess survival times for the longest-living participants. As a result, it proved difficult to evaluate the accuracy of 'best-case scenarios for survival time', defined by the 10th

percentiles of Kaplan Meier survival distributions. Immunotherapy trials in other cancers, particularly metastatic melanoma, for example, support the conclusion that many trials are reported with insufficient follow-up to accurately estimate long term outcomes, particularly 25th and 10th percentiles, highlighting the need for longer-term follow-up.[16]

The majority of trials in the systematic review reported in Chapter 3 collected PROs only from English-speaking participants and excluded those from other linguistic backgrounds or with insufficient English-language skills.[59] There remains a significant need for improved cancer care and clinical trial representation for patients from culturally and linguistically diverse backgrounds (CALD).[60,61] Current research leaves unanswered questions about the extent to which PROs are prognostic in CALD populations. However, we see no reason to hypothesise that PRO would be less important in people from CALD backgrounds. We hypothesise that PROs would be at least as helpful, perhaps more so, in people from CALD backgrounds. This remains an important open question for further research.

5.14 Future directions for research and practice

Future research requires prospective studies evaluating the accuracy and practical benefits of using prognostic models incorporating PROs in advanced GO cancer in diverse settings.

Future studies are needed to corroborate the extent to which PRO data improve the accuracy of survival predictions in advanced GO cancer. For instance, researchers could enrol a cohort of patients with advanced GO cancer, and initially estimate survival times using traditional prognostic factors. The study could then randomly assign clinicians to estimate prognosis

using standard methods versus a PRO-based prognostic model, allowing a direct comparison of the accuracy of survival estimates generated by each approach. We hypothesise that in a broader population, the addition of PROs to prognostic models would yield larger improvements in prognostic accuracy than in the INTEGRATE trials.

Greater evidence supporting the prognostic significance of PROs could lead to broader adoption of these methods, potentially improving prognostication, patient-engagement, patient-clinician communication, shared decision-making, treatment selection, and perhaps even clinical outcomes. Such studies hold promise for advancing personalised medicine and improving the quality of care for patients with advanced gastroesophageal cancer. Our results also support the use of PRO to determine eligibility and/or stratification in clinical trials.

Widespread adoption of PROs in cancer care faces several challenges, which could be overcome by using standardised PRO instruments, integrating them with electronic health records, and training clinicians to utilise PRO data.[63] A survey conducted by Maharaj et al. across Australian and New Zealand healthcare facilities revealed considerable variability in the use of PROs. Larger metropolitan centres have increasingly adopted PROs, although often using different PROMs with limited standardisation of methods.[64] Many centres are yet to incorporate PROs into routine clinical practice. Addressing these challenges is crucial for fully realising the potential of PROs to improve patient care.

Future research could explore the broader implications of accurate prognostication, including its role in guiding treatment pathways, facilitating timely palliative care, supporting patient goal setting, and improving decision-making and quality of life. Furthermore, research could explore the use of PROs, which could give patients further insight into their own goals of care.

Another potential area for future research is the utility of a web-based prognostic nomogram for routine clinical practice, providing estimates of median, best-case, and worst-case outcomes for GO cancer based on clinicopathological, PROs, and treatment information.

Further research is also needed to improve the description and prediction of survival outcomes in trials of immunotherapy. A substantial body of literature has emerged on innovative statistical methods designed to enhance the interpretation of survival data and curves.[65,66] Some anti-cancer treatments, such as immunotherapies, may result in long-term survival in a subset of treated patients. Median survival times and multiples of the median suitable for trials of cytotoxic chemotherapy may not be as applicable to trials of immunotherapy. Studies addressing these questions require longer follow-up than is often available in trials of immunotherapy.

5.15 Conclusions

My study of survival curves from relevant randomised trials found that estimates derived from simple multiples of the median were generally accurate in defining the boundaries of worst-case and lower-typical scenarios for survival time in advanced GO cancer. However, many recent trials—particularly those of immunotherapy—had insufficient follow-up to estimate boundaries for upper-typical or best-case scenarios reliably.

My scoping review of PRO as prognostic factors in advanced GO cancer identified appetite loss, pain, physical functioning, role functioning, social functioning and global quality of life as

providing important prognostic information. However, many of these studies did not account for, or adjust for, established clinicopathological prognostic factors and used suboptimal statistical methods.

The multivariable model I developed using data from INTEGRATE IIa, and validated with data from INTEGRATE, indicated that incorporating specific PROs—particularly appetite loss, fatigue, and pain—provided useful prognostic information above and beyond that offered by traditional clinicopathological variables.

My research has contributed a novel prognostic approach and model incorporating PROs with established clinicopathological variables, which improved prognostic accuracy and provided a more holistic assessment for patient care. By validating this model, my work demonstrated the potential to offer more accurate and personalised predictions of survival time, which could enhance the ability of oncologists to estimate and communicate prognosis, better meeting the needs and preferences of their patients and significant others.

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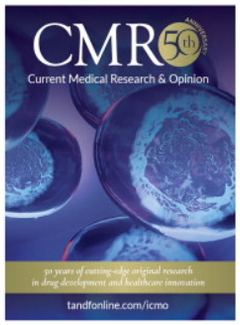
Appendices

A. Publication 1



Current Medical Research and Opinion

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icmo20

Estimating survival scenarios in advanced or metastatic gastric and oesophageal adenocarcinoma: a systematic review of randomized-controlled trials

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To cite this article: Sayeda K. Naher, Rebecca Mercieca-Bebber, Derrick Siu, Martin R. Stockler, Belinda E. Kiely & Peter Grimison (13 Jul 2024): Estimating survival scenarios in advanced or metastatic gastric and oesophageal adenocarcinoma: a systematic review of randomized-controlled trials, Current Medical Research and Opinion, DOI: 10.1080/03007995.2024.2376129

To link to this article: https://doi.org/10.1080/03007995.2024.2376129

CURRENT MEDICAL RESEARCH AND OPINION
https://doi.org/10.1080/03007995.2024.2376129
Article ST-0187/2376129

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REVIEW ARTICLE

Estimating survival scenarios in advanced or metastatic gastric and oesophageal adenocarcinoma: a systematic review of randomized-controlled trials

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ABSTRACT

Background: We aimed to summarize survival data from RCTs in patients with GO adenocarcinoma; estimate and explain worst-, typical-, and best-case-scenarios of survival time; and determine if simple multiples of median overall survival (mOS) could estimate these percentiles.

Methods: We systematically searched RCTs of systemic therapies for GO adenocarcinoma published 2000–2022. The following key percentiles were extracted from overall survival curves: 90th (worst-case), 75th (lower-typical), 25th (upper-typical), and 10th (best-case). We tested if these percentiles could be estimated by simple multiples of mOS: 0.25 of the median for the 90th percentile, 0.5 for the 75th, 2 for the 25th, and 3 for the 10th.

Results: We identified 44 trials (22,447 participants). For first line chemotherapy and immunotherapy combined (CI) trials ($n = 3$) worst-to-best case survival time ranged from 4 months to not reached, compared to 3–30 months for other trials ($n = 27$) and 1–23 months for subsequent lines ($n = 14$). Simple multiples of mOS accurately estimated the following survival percentiles: 90th ($n = 3/3$ trials), 75th ($n = 3/3$), and 25th ($n = 2/3$) in first line CI trials. In other first line trials, the mOS accurately estimated the 90th survival percentile in $n = 22/27$ trials, 75th percentile in $n = 26/27$, 25th percentile in 27/27 trials, and 10th percentile in 22/27 trials. Simple multiples of the mOS accurately predicted the 90th, 75th, 25th, and 10th survival percentiles in the majority of trials of second and subsequent lines apart from chemotherapy and immunotherapy only trials.

Conclusion: We provide realistic, evidence-based prognostic information as scenarios for survival time which can inform clinical decision-making. Simple multiples of the mOS accurately estimated the percentiles for most groups.

ARTICLE HISTORY
Received 20 February 2024
Revised 24 June 2024
Accepted 1 July 2024

KEYWORDS
Prognosis; gastric adenocarcinoma; advanced; metastatic; communication

Introduction

Prognostic information is valued by patients in the metastatic cancer setting. It should communicate to patients in a manner that is meaningful and realistic, while maintaining hope. Surveys of over 500 oncologists in the US showed that the majority of participants believe education about delivering prognostic information is vital and essential[1,2]. A large observational study of 590 participants with advanced cancer highlighted the importance and misconception of prognosis in advanced cancer[3]. More than 70% of patients wanted to know about their prognosis however only 17% were provided with this information. Prognostic information was associated with better advanced care planning, and quality of end-of-life care, however participants felt that maintaining hope was also essential. A phase 2 trial of 222 patients showed that around 90% of patients and family members found prognostic information formatted as three scenarios (best-case, worst-case, and typical-case) was feasible, acceptable, and helpful. This approach improves their understanding and aided in making plans[4]. Another survey of Australian medical oncologists reported that more than half of the oncologists preferred survival discussions to be presented as three case scenarios – best, worse, and typical[5]. Therefore, we strongly believe educating and delivering prognostic information in a range of scenarios based on similar patients would be more meaningful rather than a single point estimate of the median. Our study will provide clinicians with these scenarios and method to determine these scenarios from any OS curve in advanced GO cancer trials.

A range of typical survival times as shown in Figure 1 can be obtained from the interquartile range of a survival distribution (25th to 75th percentiles) of the median survival time. Using survival data from trials to estimate best case (best 10%), worst case (worst 10%), and typical (middle 50%) survival times may offer a realistic yet optimistic picture of survival outcomes[6]. Overall survival (OS) curves could serve as a useful basis for estimating these scenarios[7]. Our previous work in advanced breast, lung and

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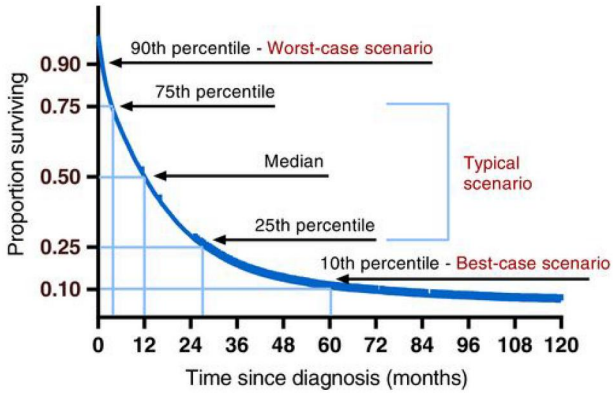

Figure 1. Percentiles and their corresponding scenarios of Kaplan-Meier OS curve.

prostate cancer settings has shown that the survival curves were roughly exponential in shape, therefore the percentiles of each OS curve could be estimated by simple multiplies of its median[8–11]. For instance, the 90th percentile (representing the upper bound for the worst case scenario) was roughly one-quarter of the median OS, the 75th percentile (representing the lower bound for the typical case scenario) was half the median OS, the 25th percentile (representing the upper bound for the typical case scenario) was double the median OS and the 10th percentile (representing the lower bound for the best case scenario) was three times the median OS.

Metastatic gastric and esophageal cancer (GO) is essentially incurable, therefore providing prognostic information with a range of possibilities from best case to worst case should help preserve optimism and prepare patients and families for the worst case. The purpose of this study was to find and summarize survival data from recent, randomized trials for GO adenocarcinoma to enable clinicians to estimate survival time for their patients in this situation. Our second aim was to determine if the simple multiples of the median OS that were accurate for estimating the bounds of worst-case, typical-case, and best-case scenarios for survival in other cancers were accurate in GO adenocarcinoma.

Methods

A systematic literature search of MedlineOVID, Embase, and Cochrane Central Register of Controlled Trials was performed in June 2022 without any language or data restrictions. We limited our search to studies published after 2000 as prior to this time period might not reflect current treatment practices. We combined terms related to advanced cancers of the stomach or esophagus with randomized clinical trials (Appendix A). Our search was developed in collaboration with two academic librarians.

We included phase III trials with at least 100 participants per arm, that reported at least one Kaplan-Meier (KM) curve for OS. We excluded human epidermal growth factor receptor 2 (HER 2) positive adenocarcinoma as the treatment and prognosis is different. Two reviewers screened articles, selected trials, and extracted published information about the trials and their results. For eligible trials, we recorded year of publication, research location, research period, patients' median age, proportion of male, percentage of gastric cancer, treatment arm, treatment received, median overall survival, and number of KM curves.

Using methods developed by Kiely et al.[8,9,11], we analyzed the survival curves from these trials to calculate the typical (25th to 75th percentiles), best-case (10th percentile), and worst-case (90th percentile) scenarios for survival time as per Figure 1.

Each OS curve was independently traced by two authors by using "WebPlotDigitizer", a web-based tool to extract data from plots, images, and maps[12]. Survival curves for each treatment group in each trial were analyzed to determine the following key percentiles (relevant scenario): 10th (best-case), 25th (upper-typical), 75th (lower-typical), and 90th (worst-case; Figure 1). Discrepancies were resolved by consensus and repeated measurement.

From our prior work on breast, lung, and prostate cancers[8–10] we hypothesized that if the median of the OS curve is multiplied by four simple multiples, then percentiles could be estimated as representative scenarios as follows: 0.25 for the 90th percentile (worst-case), 0.5 for the 75th (lower-typical), 2 for the 25th percentile (upper-typical), and 3 for the 10th percentile (best-case). We decided a priori that an estimate would be deemed accurate if it was within 0.75–1.33 times the actual value, consistent with criteria of Christakis and Lamont[13].

Statistical software package RS studio 4.1.1 was used for this data analysis.

Results

Our search strategy identified 5,559 studies, 1,135 duplicates were removed, leaving 4,424 records to be screened. A total of 258 studies were assessed for full-text eligibility and 44 studies (22,447 participants) were eligible and included as outlined in Figure 2.

Among the 44 eligible trials, 30 were in the first line treatment setting[14–43] ($n = 16,457$ participants), and 14[44–57] in the second or subsequent line setting ($n = 5,990$ participants). The majority of trials (21/44, 48%) were conducted in multiple countries involving more than 15–20 countries across the globe (15 studies in the first line and six in the second and subsequent lines). The remaining studies were primarily conducted in Asian countries (18, 41%). A total of six studies in the first line, and two subsequent line trials were conducted in Japan, and three first line trials were conducted in China.

Characteristics of the included trials

Among the first line setting trials ($n = 30$), 24 were published between 2011 and 2022, and six were published between 2006 and 2010. The majority of participants were male (70%), half of the participants had Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 (49%), the median age was 58 years with a range of 18–94 years. Around 80%

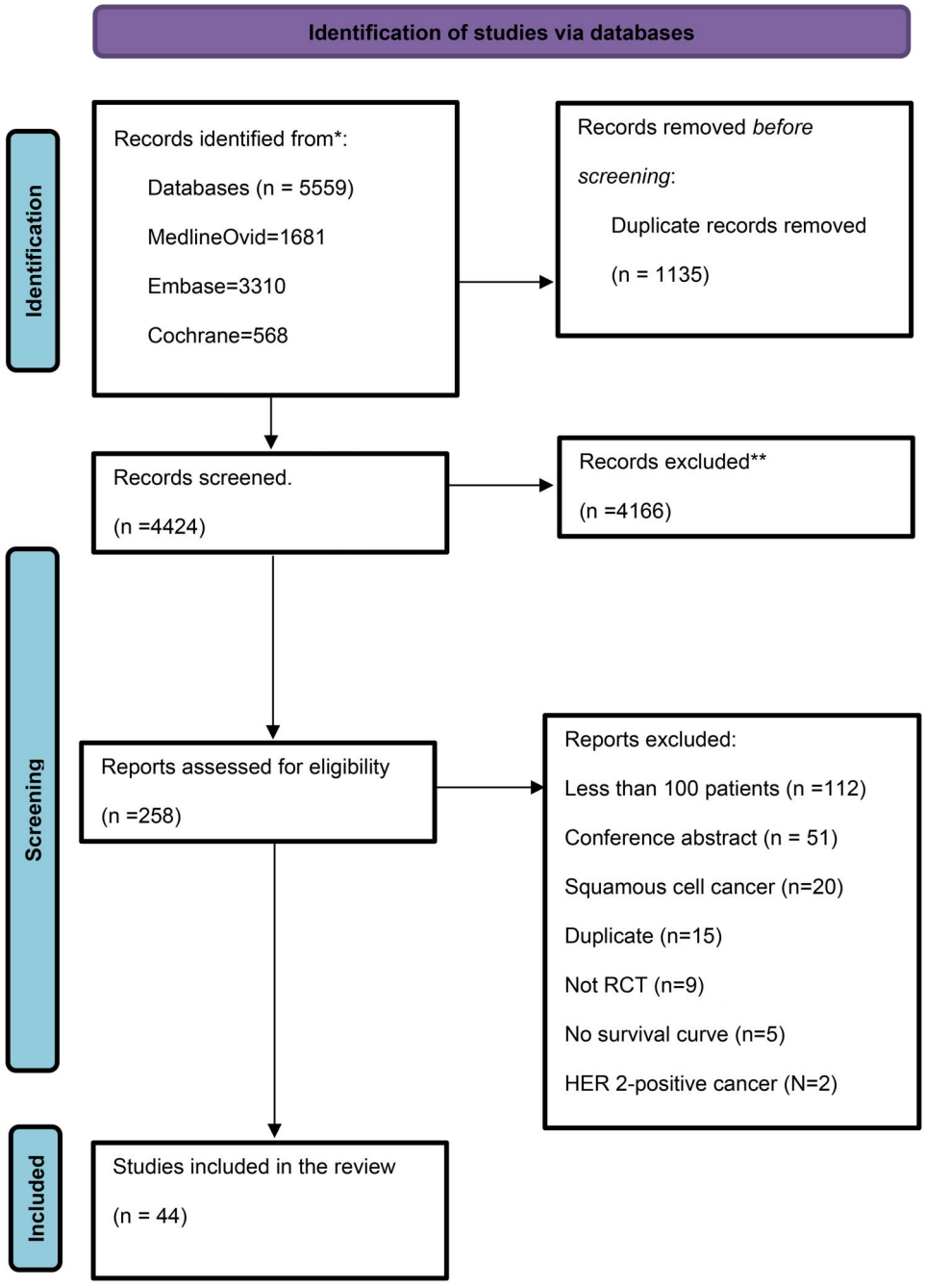

Figure 2. PRISMA flow chart for studies.

had gastric adenocarcinoma. Regarding chemotherapy, a majority of the trials used fluoropyrimidine[14–22,24,27–30,32–41,43] ($n = 25$, 83%), and platinum[14–24,27–29,32–35,39–41,43] ($n = 23$, 77%) followed by S-1[15,23,25,26,30,31,41,42] ($n = 8$, 27%). Targeted therapies included rilotumab[17], cetuximab[27], bevacizumab[32,35], onartuzumab[33], andecaliximab[34], and panitumumab[39], while immunotherapies included nivolumab[21,22], pembrolizumab[37], and avelumab[29].

Among the 14 second ($n = 11$) and subsequent line ($n = 3$) trials, eight trials were published between 2016 and 2022, with six trials between 2011 and 2015. The majority of patients were male (73%) and had gastric adenocarcinoma (84%), and more than half the participants (54%) had an ECOG performance status of 2. One trial used chemotherapy (paclitaxel) with vascular endothelial growth factor inhibitor (anti-VEGF, ramucirumab)[57]. Eleven trials used chemotherapy alone (paclitaxel, S1, trifluridine/tipiracil)[44,45,48–54,56,57], three used immunotherapy alone (avelumab, nivolumab, and pembrolizumab)[45,46,55], one trial used anti-VEGF alone (ramucirumab)[47], and four trials included a best supportive care arm[46,47,51,54].

Table 1 summarizes the characteristics of the included trials and participants.

Survival duration

The range of survival among various trials were as below.

Table 1. Characteristics of the trials, treatment groups, and participants.

	No of trials	%
Year of publication		
2006–2010	6	14
2011–2015	16	36
2016–2022	22	50
Research location		
Global	21	48
Asian	18	41
Non-Asian	4	9
Not reported	1	2
First line treatment types	30	68
Chemotherapy + anti-VEGF	1	2
Chemotherapy alone	11	25
Immunotherapy alone	3	7
Anti-VEGF alone	1	2
Best supportive care	4	9
Participant characteristics	Median	Range
Patients per trial	446	202–1,581
Age (years)	62	18–94
Male (%)	71	51–82
Gastric cancer (%)	80	32–100
ECOG performance status 0 or 1 (%)	43	10–80

Abbreviations: VEGF, Vascular Endothelial Growth Factor; ECOG, Eastern Cooperative Oncology Group.
Note, five trials did not report ECOG.

Among the first line chemotherapy and immunotherapy combined trials (CI) ($n = 3$ trials) survival of worst to median to best case ranged from 4 months to 15 months to not reached. For other first line trials ($n = 27$) survival ranged from 4 to 11 to 30 months. For subsequent line trials of chemotherapy and anti-VEGF therapy ($n = 1$), survival ranged from 3 to 10 to 23 months, for chemotherapy alone ($n = 11$) 2 to 7 to 21 months, immunotherapy alone ($n = 3$) 1 to 6 to 22 months, anti-VEGF alone ($n = 1$) 1 to 5 to 17 months, and best supportive care ($n = 4$) 1 to 4 to 13 months.

Eight studies were published after 2016 in second and subsequent line trials. For these studies survival ranged from 2 to 7 to 19 months.

Table 2 summarizes survival scenarios by treatment line and type.

Accuracy of simple multiples of median overall survival in the first line treatment setting

Simple multiples of mOS were accurate in predicting worst-case (90th percentile) and lower typical (75th percentile) in all three CI trials (Table 3). However best-case scenarios were not reached due to the length of the follow-up period. Therefore, the best-case survival estimates could not accurately be calculated. The remaining of the other first line trials multiplications were accurate, as evident in Table 3.

Accuracy of simple multiples of median overall survival in the second and subsequent line treatment settings

Among subsequent line treatment trials, mOS could be used to accurately estimate survival percentiles in most cases (Table 3). Of note, in chemotherapy alone trial survival estimates were accurate in the majority group apart from the worst-case scenario which was 64% ($n = 7/11$). Also, in immunotherapy only trials, best-case and worst-case scenarios were accurate in 67% ($n = 2/3$).

Table 3 summarizes the number and percentages of trials where simple multiplication of mOS were accurate.

Discussion

We provide realistic, evidence-based prognostic information as scenarios for survival time which can inform clinical decision-making. This review contributes important information on survival time in advanced GO adenocarcinoma. In first line chemotherapy and immunotherapy combined trials, survival ranged from worst case of 4 months, median 15 months, and best case of not reached due to an insufficient follow-up period. In second and subsequent line trials, survival in worst case could be as low as 1–3 months and best-case could be 17–23 months. We also provide survival estimates with best supportive care in second and subsequent line trials where participants did not receive any active treatment. Survival was as short as 1 month (worst-case) and as high as 13 months (best-case). This data is of particular value for clinicians discussing survival scenarios in cases where the patient decides on best supportive care without further treatment. Therefore, this review would serve a valuable purpose of informing discussions about survival in various treatment settings in advanced GO cancer.

We found that simple multiples of the mOS accurately estimated the percentiles for most groups. For most trials we could estimate best survival time (10% participants living longest) by multiplying median survival time by 3. Similarly, worst survival time (10% participants living the shortest amount of time) could be computed by multiplying the median OS by 0.25. As per our previous work[8–11] the method of using simple multiples of an OS curve's median to approximate its range of various survival time held true in this population. Therefore, our hypothesis of a simple multiple of an OS curve's median (0.25 for worst case, 0.5–2 for average case and 3 for best case) could arguably be utilized in metastatic or advanced gastric and osophageal adenocarcinoma and other advanced cancer settings. For example, the median OS from the CheckMate 649[21] trial, which is a first line chemotherapy and immunotherapy combined trial, reported a median overall survival of 14.4 months. The three survival scenarios can be calculated as a best case scenario of more than 42 months (3 multiplied by 14), a typical case scenario of 7–28 months (half to double of 14) and a worst case scenario of less than 5 months (one-quarter of 14). Based on our results, it might still be possible to provide an estimate by multiplying the median survival by 3 to estimate the best-case survival scenario. However longer follow-up data is needed before such estimates could reliably be applied to chemotherapy and immunotherapy combined trials. Unlike chemotherapy and other conventional drugs, the response to immunotherapy is often highly variable and can lead to long-tail survival distributions. In chemotherapy, survival curves tend to follow more predictable patterns with a relatively uniform decline over time. However, immunotherapy trials have reported survival curves with plateaus and

Table 2. Survival scenarios for gastric and esophageal adenocarcinoma according to different treatment groups and lines.

Treatment line and regimen	Number of KM curves	Number of participants	Survival scenario in months (mean)				
			90th worst	75th lower typical	50th median	25th upper typical	10th best
First line		16,457					
Chemotherapy + immunotherapy[21,22,37]	3	1,408	4.4	7.7	14.5	24.8	Not reached
Chemotherapy with or without other therapy[14–20,23,25–36,38–43,58]	59	15,049	3.6	6.4	11	19	30
Subsequent line		5,990					
Chemotherapy + anti-VEGF[57]	1	330	3	5	9.5	15.2	22.5
Chemotherapy[44,48–50,52–56,59]	14	4,044	2.4	4.2	7.4	12.8	21.3
Immunotherapy[45,46,55,59]	3	711	1.4	2.8	6.4	13.6	22.1
Anti-VEGF alone[47]	1	238	1.3	2.4	5.1	9.8	17.3
Best supportive care[46,47,51,54]	4	667	1.1	2	3.9	7.9	13.1

Abbreviations: VEGF, Vascular Endothelial Growth Factor; KM, Kaplan Meier overall survival curve.

Table 3. Number and percentages of trials where multiplication of survival scenarios were accurate.

Treatment line and regimen	Number of trials	Survival scenarios			
		90th worst	75th lower typical	25th upper typical	10th best
First line					
Chemotherapy + immunotherapy[21,22,37]	3	3 (100%)	3 (100%)	2 (67%)	Not reached
Chemotherapy with or without other therapy[14–20,23,25–36,38–43,58]	27	22 (81%)	26 (96%)	27 (100%)	22(81%)
Subsequent line					
Chemotherapy + anti-VEGF[57]	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Chemotherapy[44,48–50,52–56,59]	11	7 (64%)	11 (100%)	11 (100%)	11 (100%)
Immunotherapy[45,46,55,59]	3	2 (67%)	3 (100%)	3 (100%)	2 (67%)
Anti-VEGF alone[47]	1	1 (100%)	1 (100%)	1 (100%)	1 (100%)
Best supportive care[46,47,51,54]	4	4 (100%)	4 (100%)	4 (100%)	4 (100%)

Abbreviation: VEGF, Vascular Endothelial Growth Factor.

delayed separations, reflecting censoring, durable responses, and long-term survival in some patients. These distinct characteristics make it difficult to apply traditional statistical models and assumptions. The variability and unpredictable nature of immunotherapy responses require more sophisticated and perhaps individualized approaches to scenario prediction.

The strengths of our study include a robust search strategy, a comprehensive summary of contemporary clinical trials in advanced GO cancer, and an easily adaptable formula for use in real world practice.

A limitation of our survival estimates is that they are derived from randomized trials which typically enrol patients with better prognosis than the general population. Population-based studies of patients with similar diagnoses, using similar treatments, provide the ideal source for estimating survival[60]. However, limited survival data is available outside of clinical trials and clinical trials offer valuable prognosis information. Therefore, in the absence of such data, our methods can be applied to trial data to derive informative survival estimates. We excluded patients with HER2 positive gastric cancer as the prognosis differs from non-HER2[61,62] amplified cancer. It is not a direct comparison of different treatment; therefore, studies like this are not able to confirm the contribution or survival benefit from any specific therapy or the most effective therapy.

Further studies could help to determine how well clinical trial data correlate with everyday practice and survival among non-trial participants. Additionally further studies with HER 2 amplified cancer could add survival estimates in patients with HER 2 positive cancers.

This review has important clinical implications. Questions about life expectancy and prognosis are common; however, there is significant variability in the sharing of this information[63]. There is abundant literature regarding the importance and ways of communicating prognosis information in advanced cancer[60,64–66]; however, methods to estimate life expectancy reliably have previously been lacking. This review, along with our previous reviews in breast, lung, and prostate cancers[5,8–10], could serve this purpose of efficiently estimating various survival scenarios. Clinicians could provide survival information in best, average, and worst-case scenarios in advanced GO adenocarcinoma based on this review.

Several studies used baseline patient characteristics, pathological and clinical variables for establishing a prognostic model for advanced GO cancer[58,59]. Overall, while these studies have laid the groundwork for prognostic modeling, their limitations in terms of heterogeneity suggest a need for further refinement. Future research should focus on developing more universally applicable models, possibly through the integration of larger, more diverse patient datasets and the use of advanced statistical techniques to account for variability in clinical practice.

Conclusions

We provide prognostic information based on data from randomized trials for GO adenocarcinoma presented as best

case, worst case, and typical case scenarios for survival time. This approach ensures information that is evidence-based; realistic; and allows both preparation for the worst, and hoping for the best. Simple multiples of the mOS accurately estimated the percentiles for the majority of treatment groups and settings for advanced GO adenocarcinoma.

Transparency

Declaration of funding

This study is a part of Sayeda K. Naher's PhD project, for which she is supported by a NHMRC CTC University of Sydney post graduate research scholarship. Rebecca Mercieca-Bebber is supported by a NHMRC CTC Early Career Fellowship (APP1138100).

Declaration of financial/other relationships

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Sayeda K. Naher, Derrick Siu. The first draft of the manuscript was written by Sayeda K. Naher and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Authors acknowledge the assistance from two University of Sydney Librarians – Tess Aitken and Jessica Hughes for developing search terms.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the CONTACT on reasonable request.

Previous presentation

Medical Oncology Group of Australia (MOGA) Annual Scientific Meeting (ASM) August 2023 – oral and poster presentation. NSW Cancer Conference September 2023 – poster presentation.

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Appendices

Search terms

EMBASE Searches	Results	Type	Actions
	1	exp stomach Neoplasms/	181,512
	2	exp stomach Neoplasms/	181,512
	3	stomach cancer.tw.	8,400
	4	(stomach tumor or stomach tumo?r*).tw.	659
	5	stomach carcinoma.tw.	737
	6	stomach malignan*.tw.	70
	7	exp gastric Neoplasms/	0
	8	gastric cancer.tw.	100,109
	9	(gastric tumor or gastric tumo?r*).tw.	6,157
	10	gastric carcinoma.tw.	18,211
	11	gastric malignan*.tw.	1,624
	12	exp esophageal Neoplasms/	99,387
	13	esophageal carcinoma.tw.	8,940
	14	esophageal* malignan*.tw.	836
	15	o*sophag* cancer*.tw.	6,069
	16	o*sophag* tumo?r*.tw.	564
	17	(esophagogastric tumor or esophagogastric tumo?r*).tw.	38
	18	(gastroesophag* tumor or gastroesophag* tumo*?r*).tw.	76
	19	gastroesophag* cancer.tw.	774
	20	oesophagogastric cancer.tw.	332
	21	or/1–20	278,192
	22	advanced.tw.	766,854
	23	metastatic.tw.	414,865
	24	metastasis.tw.	385,021
	25	inoperable.tw.	25,122
	26	palliative.tw.	118,161
	27	recurrent.tw.	483,668
	28	unresectable.tw.	36,992
	29	or/22–28	1,899,327
	30	21 and 29	77,619
	31	clinical trial.tw.	255,025
	32	exp clinical trial/	1,720,455
	33	phase II trial.tw.	21,859
	34	phase III trial.tw.	14,201
	35	randomized controlled trial.pt.	0
	36	controlled clinical trial.pt.	0
	37	randomized.ab.	816,700
	38	or/31–37	2,161,846
	39	21 and 29 and 38	11,304
	40	overall survival.tw.	368,084
	41	OS.mp.	238,859
	42	Survival Analysis/	36,255
	43	kaplan meier survival curve.tw.	2,683
	44	kaplan meier curve.tw.	4,763
	45	or/40–44	482,723
	46	39 and 45	4,235

Cochrane registry of controlled clinical trials

# ▲	Searches	Results	Type
	1	exp stomach Neoplasms/	2,898
	2	exp stomach Neoplasms/	2,898
	3	stomach cancer.tw.	390
	4	(stomach tumor or stomach tumo?r*).tw.	19
	5	stomach carcinoma.tw.	35
	6	stomach malignan*.tw.	26
	7	exp gastric Neoplasms/	2,898
	8	gastric cancer.tw.	6,545
	9	(gastric tumor or gastric tumo?r*).tw.	141
	10	gastric carcinoma.tw.	638
	11	gastric malignan*.tw.	44
	12	exp esophageal Neoplasms/	1,824
	13	esophageal carcinoma.tw.	682
	14	esophageal* malignan*.tw.	16
	15	o*sophag* cancer*.tw.	531
	16	o*sophag* tumo?r*.tw.	23
	17	(esophagogastric tumor or esophagogastric tumo?r*).tw.	3
	18	(gastroesophag* tumor or gastroesophag* tumo*?r*).tw.	2
	19	gastroesophag* cancer.tw.	96
	20	oesophagogastric cancer.tw.	57
	21	or/1–20	10,338
	22	advanced.tw.	63,294
	23	metastatic.tw.	31,475
	24	metastasis.tw.	9,740
	25	inoperable.tw.	2,670
	26	palliative.tw.	6,494
	27	recurrent.tw.	33,500
	28	unresectable.tw.	6,196
	29	or/22–28	123,424
	30	21 and 29	4,635
	31	clinical trial.tw.	160,511
	32	exp clinical trial/	144
	33	phase II trial.tw.	8,600
	34	phase III trial.tw.	9,972
	35	randomized controlled trial.pt.	558,222
	36	controlled clinical trial.pt.	93,200
	37	randomized.ab.	635,571
	38	or/31–37	1,055,605
	39	21 and 29 and 38	2,768
	40	overall survival.tw.	45,161
	41	OS.mp.	28,025
	42	Survival Analysis/	8,438
	43	kaplan meier survival curve.tw.	128
	44	kaplan meier curve.tw.	237
	45	or/40–44	59,192
	46	39 and 45	1,333

Medline Ovid

# ▲	Searches	Results	Type
	1	exp stomach Neoplasms/	105,986
	2	exp stomach Neoplasms/	105,986
	3	stomach cancer.tw.	6,959
	4	(stomach tumor or stomach tumo?r*).tw.	534
	5	stomach carcinoma.tw.	632
	6	stomach malignan*.tw.	29
	7	exp gastric Neoplasms/	105,986
	8	gastric cancer.tw.	71,089
	9	(gastric tumor or gastric tumo?r*).tw.	4,229
	10	gastric carcinoma.tw.	12,944
	11	gastric malignan*.tw.	1,038
	12	exp esophageal Neoplasms/	56,357
	13	esophageal carcinoma.tw.	6,290
	14	esophageal* malignan*.tw.	498
	15	o*sophag* cancer*.tw.	3,799
	16	o*sophag* tumo?r*.tw.	338
	17	(esophagogastric tumor or esophagogastric tumo?r*).tw.	24
	18	(gastroesophag* tumor or gastroesophag* tumo*?r*).tw.	47
	19	gastroesophag* cancer.tw.	438
	20	oesophagogastric cancer.tw.	184
	21	or/1–20	181,119
	22	advanced.tw.	502,240
	23	metastatic.tw.	258,197
	24	metastasis.tw.	267,837
	25	inoperable.tw.	14,032
	26	palliative.tw.	71,158
	27	recurrent.tw.	315,779
	28	unresectable.tw.	21,752
	29	or/22–28	1,253,022
	30	21 and 29	47,853
	31	clinical trial.tw.	171,016
	32	exp clinical trial/	942,837
	33	phase II trial.tw.	11,329
	34	phase III trial.tw.	6,947
	35	randomized controlled trial.pt.	569,941
	36	controlled clinical trial.pt.	94,895
	37	randomized.ab.	563,663
	38	or/31–37	1,291,381
	39	21 and 29 and 38	5,128
	40	overall survival.tw.	207,924
	41	OS.mp.	124,544
	42	Survival Analysis/	144,967
	43	kaplan meier survival curve.tw.	1,541
	44	kaplan meier curve.tw.	2,349
	45	or/40–44	376,471
	46	39 and 45	2,114

B. Publication 2

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doi:10.1111/imj.16209

REVIEW

Prognostic value of patient reported outcomes in advanced gastro-oesophageal cancer: a systematic review

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Key words
patient-reported outcomes, overall survival, gastro-oesophageal cancer, advanced.

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Received 9 January 2023; accepted 26 July 2023.

Abstract

To summarise the prognostic value of patient-reported outcomes (PROs) in advanced gastro-oesophageal (GO) cancer. We systematically searched multiple databases using search terms related to advanced GO cancer, PRO and prognosis. Studies examining the relationship between baseline PROs and prognosis were included. Two reviewers independently screened articles and extracted data on study design, survival and associations between PROs and survival, in both univariable and multivariable analyses. QUIPS was used for quality assessment. From 3004 studies screened, seven studies were eligible, comprising PRO data from 2761 of 3408 (81%) participants. Median survival times ranged from 4.5 to 9.5 months. Among participants with oesophageal squamous cell carcinoma (SCC), physical functioning, social functioning and fatigue (QLQ-C30) were associated with overall survival (OS) in one univariable analysis. Among three studies of participants with adenocarcinoma, univariable analyses revealed associations between OS and global quality of life (QOL), physical functioning, role functioning and social functioning; two studies showed association with pain. There was an association between emotional functioning, fatigue, lack of mobility, lack of self-care, appetite loss/anorexia and OS in one study. One multivariable analysis among participants with oesophageal SCC showed physical and social functioning was associated with OS. Among participants with adenocarcinoma, multivariable analyses showed associations between OS and physical functioning/lack of mobility, appetite loss/anorexia (three studies), global QOL, role functioning/lack of self-care, pain (two studies) and social functioning (one study). Physical functioning, role functioning, social functioning, pain, anorexia and global QOL were associated with OS in advanced GO cancer.

Introduction

Gastric cancer is the fourth leading cause of cancer-related death and fifth most common cancer globally.[1] Oesophageal cancer ranks seventh in global incidence and sixth in global mortality.[1] Taken together, they accounted for an estimated 1 313 000 deaths in 2020 (796 000 for gastric cancer and 544 000 for oesophageal cancer). Advanced (metastatic or inoperable) gastric and oesophageal (GO) cancers have a poor prognosis, with reported median overall survival (OS) times of 3–5 months,[2] which can be improved by an average of approximately 7 months with chemotherapy[2,3] and around 13 months with combined immunotherapy and chemotherapy.[4,5] Along with poor survival, most patients also suffer from high symptom burden,[6] making quality of life (QOL) paramount for decision-making.[7,8] Estimates of expected survival time can help patients affected by advanced cancer and their families prioritise their remaining time together, make important treatment decisions and plan for future care. Previous reviews and surveys confirmed that patients affected by cancer are very keen to know about their prognosis.[9,10] In advanced GO cancer, nomograms for assessing prognosis have been developed using clinical and biochemical variables like performance status, liver metastasis, peritoneal metastasis, neutrophil-to-lymphocyte ratio and so on.[11–14] Incorporation of patient-reported outcomes (PROs) in these prognostication models appears limited.

Conflict of interest: None.

The US Food and Drug Administration (FDA, p. 2) defines a PRO as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'.[15] Disease symptoms, treatment side effects, mood, measures of QOL and overall well-being may be patient-reported. A recent systematic review showed physical functioning and global QOL had prognostic value in multiple primary cancer types, including breast, lung and prostate cancers.[16,17] However, there were only three studies on advanced GO cancer in this review, and no contemporary systematic reviews have focused on advanced GO cancer.

We hypothesised that particular PROs might be useful prognostic indicators in advanced GO cancer. We conducted this systematic review to evaluate and describe the relationship between PROs and OS in advanced GO cancer.

Methods

Search strategy and selection criteria

We followed the Cochrane methodology for prognostic studies described by Riely *et al.*[18] and adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines to ensure complete and transparent reporting.[19,20]

A systematic literature search of MedlineOVID, Embase, PubMed and Cochrane Central Register of Controlled Trials was performed from inception to March 2021 without any language or data restrictions. We combined terms related to advanced cancers of the stomach or oesophagus with prognostic and PRO terms (Appendix A). Our search was developed in collaboration with two academic librarians. As studies with a smaller sample size might not be sufficiently powered to detect a difference, we decided *a priori* to exclude studies with less than 50 participants.

Study eligibility criteria

Studies were included if they met the following criteria:

1 Participants had unresectable, metastatic or recurrent cancers of the oesophagus, stomach and/or gastroesophageal junction;
2 Reported OS;
3 Reported baseline PROs;
4 Participants received systemic therapy (chemotherapy, targeted therapy and/or immunotherapy);
5 Minimum 50 participants;
6 Reported at least one univariable/multivariable analysis examining the relationship between baseline PROs and OS.

We did not limit by language. We excluded reviews, commentary, editorials and conference abstracts.

Study screening

All abstracts were screened by two authors (SKN and DS) independently according to the selection criteria detailed above. Full-text papers were then checked using the same eligibility criteria. We used 'COVIDENCE',[21] an online tool for systematic reviews, for study screening.

Data collection process

Data were extracted into a predefined data extraction form (Appendix B) independently by two authors (SKN and DS). Any disagreements were resolved with discussion and adjudication by a third author (RMB). We extracted data regarding first author, year of publication, research location, research period, study design, participant age, gender, cancer type, treatment received, line of treatment, PRO instrument/s used, number of participants, number of participants with PRO data, modelling method to assess prognostic factors, predefined clinical and laboratory variables with known potential prognostic significance (weight loss, performance status, anaemia, hypoalbuminaemia, presence of peritoneal or liver metastasis, ascites and neutrophil-to-lymphocyte ratio), and prognostic relationships of key PROs (PROs included-global QOL, physical functioning, role functioning, social functioning, emotional functioning, pain, appetite loss/anorexia, dysphagia and fatigue) which have known or potential prognostic value in cancer patients based on prior studies.[16,17]

Study risk of bias assessment

Two authors (SKN and DS) used the QUIPS checklist to assess study quality. This tool was developed for use in prognostic studies.[22] It assesses six domains as high, moderate and low risk of bias: study participation, study attrition, prognostic factor measurement, outcome measurement, adjustment for other prognostic factors, and statistical analysis and reporting. Any disagreements were resolved with discussion from a third author (RMB).

Synthesis method

OS was our primary end-point. OS was typically calculated from the date of study entry until death from any cause or censored at the last follow-up. We calculated the number of studies examining the relationship between prognosis (OS) and clinical variables of weight loss, performance status, anaemia, hypoalbuminaemia,

presence of peritoneal or liver metastases, ascites and neutrophil-to-lymphocyte ratio. In all the included studies, initial univariable analyses examined the relationship between survival and individual factors, and multivariable analyses examined the independent effects of multiple prognostic factors, including PROs, disease and clinical variables. We did not obtain individual patient data. We documented the relationship of OS expressed in those studies as hazard ratio (HR), with 95% confidence interval (CI) and *P* value for each univariable and multivariable analysis, for the following PROs: global QOL, physical functioning, role functioning, social functioning, emotional functioning, pain, appetite loss/anorexia, dysphagia and fatigue. These PROs were selected *a priori* as being important to the clinical population and having prognostic relevance in other cancer settings.[16,17]

Results

Of 3004 identified records, 2346 study titles and abstracts were screened, after removal of 658 duplicates. One hundred twenty-six studies were assessed for full-text eligibility and seven studies met inclusion criteria[23–29] as outlined in Figure 1.

Table 1 describes the characteristics of the included studies. All studies were conducted between 1992 and 2017. Four studies were pooled analyses of randomised controlled trials (RCTs).[23,25,27,29] Additionally, there were two RCTs[26,28] and one cohort study.[24] Apart from one study with oesophageal squamous cell carcinoma (SCC),[26] the other studies included gastric, GO and oesophageal adenocarcinoma. Chemotherapy included a taxane in four studies,[23,25,27,29] a platinum in four studies,[23,25,26,29] fluoropyrimidines in three studies[23,25,29] and another chemotherapy in two studies (vinorelbine and irinotecan).[26,29] Two studies used targeted therapy, one with regorafenib,[28] the other with ramucirumab.[27] One study did not report type of treatment.[24] None of the studies included immunotherapy. Five studies were conducted in the first line setting,[23–26,29] and two in the second line setting.[27,28] None of the studies reported the use of stents. Three studies reported prior surgery,[23,26,29] two studies reported chemotherapy or radiotherapy,[23,26] four studies did not report prior adjuvant treatment.[24,25,27,28]

Five different PRO instruments were used across the seven included studies (Table 1): five studies used the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30),[25–29] two studies used the EQ-5D-3L.[23,28] The Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale (FAACT A/CS),[24] the EORTC gastric cancer module STO22 and the Patient Disease and Treatment Assessment (PTDATA)[28] were used in one study. All of these multi-item measures are patient-reported and have been validated in cancer populations. The response scales differ for each measure; for example, the EORTC QLQ-C30 has a 4-point response scale and asks about the past week. The FAACT A/CS has a 5-point response scale based on the past week. The EQ-5D-3L includes five dimensions, each with three levels of severity and participants respond based on their current state of health. It also includes a 0–100 visual analogue scale with two extreme points.

All studies used Cox proportional hazard regression to assess univariable and multivariable relationships between PROs and survival. For all the included studies, PROs were collected before starting any systemic treatment for metastatic disease during study enrolment, including a cohort study by Abraham *et al.*[24]

Risk of bias

Four studies had low risk of bias in five or more domains; however, three studies had moderate risk of bias (Appendix C).

PRO with prognostic significance

In a univariable analysis for oesophageal SCC, physical functioning, social functioning and fatigue (QLQ-C30) were associated with OS.[26] Table 2 describes these univariable relationships. For adenocarcinoma, physical functioning,[25,27,29] global QOL,[25,27,29] role functioning[25,27,29] and social functioning[25,27,29] (QLQ-C30) were significant in three studies. Pain was significant in two studies[23,27] (QLQ-C30 $n = 2$, EQ-5D-3L). Fatigue,[27] appetite loss[24,27] and emotional functioning[27](QLQ-C30) were significant in one study. Abdel Rahman[23] used EQ-5D and showed lack of mobility ($P \leq 0.001$) and lack of self-care ($P = 0.017$) was significant. Martin *et al.*[28] did not report univariable data.

Table 3 illustrates the significant PRO domains with prognostic value in multivariable analysis. In multivariable analysis for patients with oesophageal SCC, physical and social functioning had prognostic significance.[26] Among patients with adenocarcinoma, physical functioning/lack of mobility was a significant prognostic factor in three studies,[23,25,28] appetite loss/anorexia in three studies,[24,27,28] role functioning,[25] lack of self-care,[23] global QOL in two studies,[23,25] pain in two studies[23,28] and social functioning in one study.[29]

Overall, longer OS was associated with better global QOL and better physical, role, emotional and social functioning. Conversely, shorter OS was associated with worse pain, appetite loss/anorexia and fatigue. Park *et*

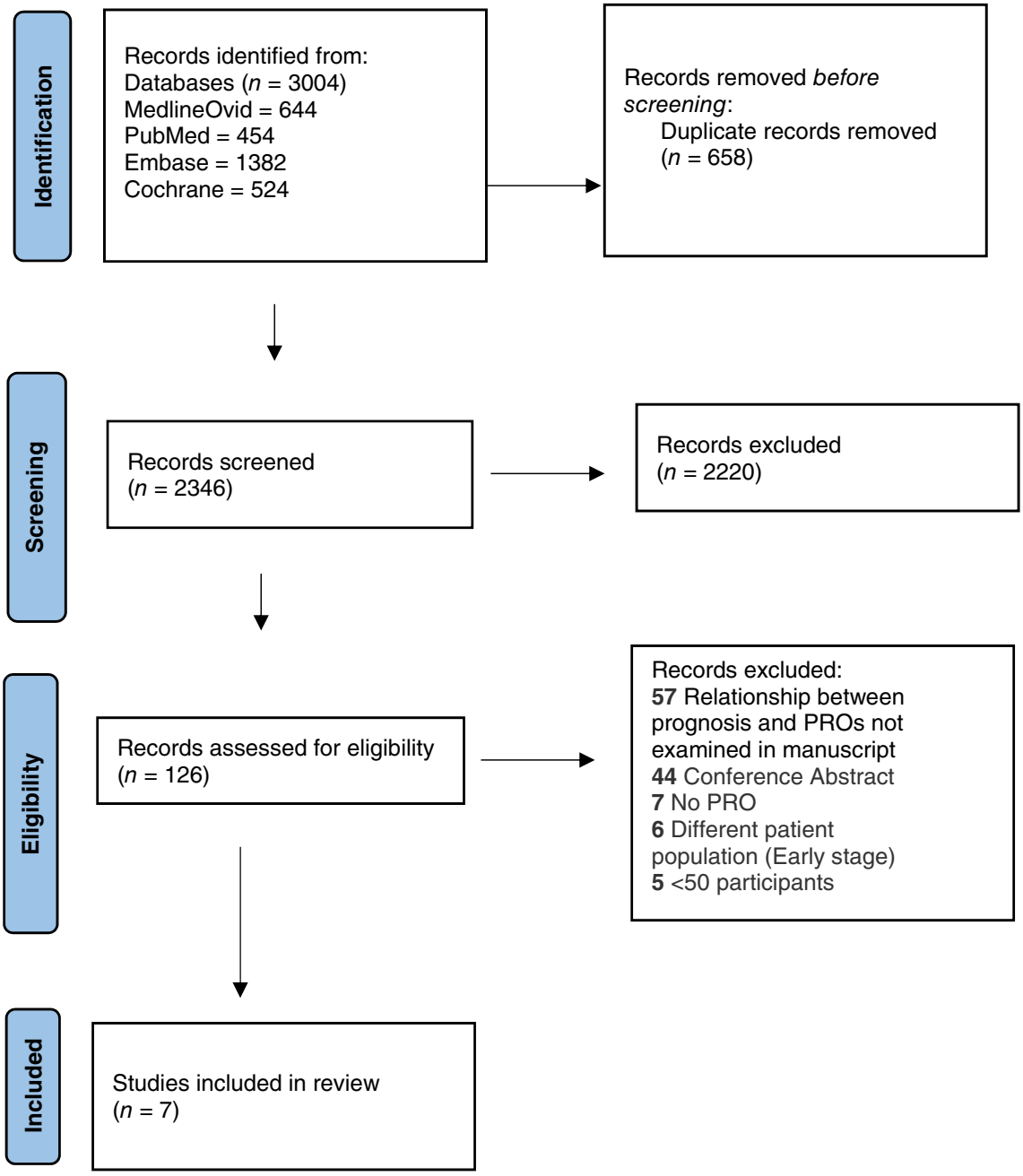

Figure 1 PRISMA flow chart for studies. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; PRO, patient-reported outcome.

al.[29] showed patients with good social functioning compared to patients with poor social functioning were more likely to survive for 1 year (45.3% vs 18.3% respectively). In Abraham *et al.*,[24] adenocarcinoma patients with less anorexia (higher FAACT-A/CS scores of >37) lived longer (19.3 months) than patients with more anorexia (lower FAACT-A/CS scores of ≤37) (6.7 months). Fuchs *et al.*[27] showed patients with more appetite loss had almost twofold (hazard ratio (HR), 1.50; 95% confidence interval (CI), 1.20–1.86) worse prognosis.

Multiple clinical and laboratory variables were assessed. Chua *et al.*[25] assessed 16 clinical and laboratory variables in a univariable model; among them the

Table 1 Key features of the included studies

Study reference	Study design	Research location	No. of patients	Participants with baseline PRO data (%)	PRO measures used	Median survival (months)	Line of treatment	Type of treatment
SCC								
Conroy *et al.*[26]	RCT	Europe	71	59 (83%)	EORTC QLQ-C30	6.8	1st	Chemotherapy
Adenocarcinoma/ mixed†								
Chua *et al.*[25]	Pooled analysis of RCT	UK	1080	817 (76%)	EORTC QLQ-C30	7.9	1st	Chemotherapy
Park *et al.*[29]	Pooled analysis of RCT	Korea	254	164 (65%)	EORTC QLQ-C30	9.5	1st	Chemotherapy
Fuchs *et al.*[27]	Pooled analysis of RCT	Multicentre	1020	953 (93%)	EORTC QLQ-C30	6.9	2nd	Chemotherapy + targeted therapy
Martin *et al.*[28]	RCT	Multicentre	147	136 (93%)	EORTC QLQ-C30, QLQ-STO22, EQ-5D, PTDATA	5.1	2nd	Targeted therapy
Abdel-Rahman[23]	Pooled analysis of RCT	Multicentre	654	525 (80%)	EQ-5D-3L(41)	NR	1st	Chemotherapy
Abraham *et al.*[24]	Cohort	UK	182	107 (59%)	FAACT A/CS	8.8	1st	NR

EORTC, European Organisation for Research and Treatment of Cancer; FAACT A/CS, Functional Assessment of Anorexia Cachexia Therapy Anorexia/ Cachexia Subscale; NR, not reported; PRO, patient-reported outcome; PTDATA, Patient Disease and Treatment Assessment; QLQ-30, 30-item Quality of Life Core Questionnaire; RCT, randomised controlled trial; SCC, squamous cell carcinoma; UK, United Kingdom.
†Gastric adenocarcinoma, oesophageal adenocarcinoma, gastro-oesophageal junction adenocarcinoma and adenosquamous.

multivariable model showed performance status ($P \leq 0.0001$), liver metastasis ($P \leq 0.0001$), peritoneal metastasis ($P = 0.007$) and alkaline phosphatase >100 U/L ($P \leq 0.0001$) were significant, and haemoglobin <11 g/L was borderline significant ($P = 0.011$). Park *et al.*[29] evaluated 14 clinical and laboratory variables in a univariable model and three were significant in a multivariable model – age ($P = 0.04$), bone metastasis ($P = 0.02$) and low haemoglobin ($P = 0.04$). Fuchs *et al.*[27] included 41 baseline factors (18 clinical, 22 laboratory parameters and geographical region) in a univariable model. The multivariable model showed presence of primary tumour ($P = 0.001$), poor/unknown tumour differentiation ($P = 0.0005$), time to progression since prior therapy ($P = 0.0002$), performance status ($P = 0.0001$), presence of peritoneal metastasis ($P \leq 0.0001$), high ALP level ($P = 0.003$), low lymphocyte level ($P = 0.001$), high LDH level ($P = 0.001$), low albumin level ($P = 0.0006$), high AST level ($P = 0.001$), high neutrophil level ($P \leq 0.0001$) and low sodium level ($P \leq 0.0001$) were significant. Martin *et al.*[28] did not report any clinical or laboratory variables; however, the multivariable model with PROs was adjusted for ECOG status, number of metastatic sites, baseline vascular endothelial growth factor and neutrophil and lymphocyte ratio. Abdul Rahman[23] evaluated 15 clinical and laboratory variables in a univariable model; among them the multivariable model showed performance status ($P = 0.03$) was significant. Abraham *et al.*[24] assessed seven clinical variables (gender, age, O'Rourke Dysphagia score, treatment, performance status, total number of metastasis, and body mass index (BMI)) in a univariable model and BMI ($P = 0.02$) in untreated patients was significant in multivariable analysis.

Among the included studies, several clinical and laboratory variables were also found to have prognostic significance: weight loss in three studies,[24,27,29] ECOG performance status in six studies,[23–25,27–29] anaemia in three studies,[25,27,29] hypoalbuminaemia in three studies,[25,27,29] presence of peritoneal or liver metastases in five studies[24,25,27–29] and neutrophil and lymphocyte ratio in one study.[28] None of the studies assessed the prognostic significance of ascites.

Discussion

This comprehensive systematic review provides contemporary evidence of the prognostic value of PROs in advanced GO cancer. Multiple PRO domains were associated with survival, independently and when

Table 2 Univariable relationship of the PROs and prognosis

Study reference	PRO measure used HR (CI) *P* value	Global QOL	Physical functioning	Role functioning	Social functioning	Emotional functioning	Pain	Appetite loss/ anorexia	Fatigue
SCC									
Conroy *et al.*[26]	EORTC QLQ-C30	NR	$P = 0.02$	NR	NR	NR	NR	NR	$P = 0.01$
Adenocarcinoma/mixed†									
Chua *et al.*[25]	EORTC QLQ-C30	0.52 (0.45–0.60) $P < 0.001$	0.67 (0.57–0.78) $P < 0.001$	0.62 (0.54–0.73) $P < 0.001$	0.74 (0.64–0.83) $P = 0.0001$	NS	NA	NA	NA
Park *et al.*[29]	EORTC QLQ-C30	0.51 (0.33–0.80) $P = 0.003$	0.64 (0.41–0.99) $P = 0.04$	0.61 (0.40–0.94) $P = 0.027$	0.44 (0.26–0.73) $P = 0.001$	NS	NS	NS	NS
Fuchs *et al.*[27]	EORTC QLQ-C30	0.67 (0.58–0.78) $P < 0.001$	0.63 (0.55–0.74) $P < 0.001$	0.65 (0.56–0.75) $P < 0.001$	0.72 (0.62–0.83) $P < 0.001$	0.77 (0.66–0.87) $P < 0.001$	1.48 (1.27–1.73) $P < 0.001$	1.88 (1.61–2.19) $P < 0.001$	1.68 (1.42–1.98) $P < 0.001$
Abdel-Rahman[23]	EQ -5D-3L	NA	$P < 0.001$ (lack of mobility)	$P < 0.017$ (lack of self-care)	NA	NA	$P < 0.001$	NA	NA
Abraham *et al.*[24]	FAACT AC/S	NA	NA	NA	NA	NA	NA	0.67 (0.55–0.81) $P < 0.0001$	NA

†Gastric adenocarcinoma, oesophageal adenocarcinoma, gastro-oesophageal junction adenocarcinoma and adenosquamous.

CI, confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; FAACT A/CS, Functional Assessment of Anorexia Cachexia Therapy Anorexia/Cachexia Subscale; HR, hazard ratio; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; PTDATA, Patient Disease and Treatment Assessment; QLQ-C30, 30-item Quality of Life Core Questionnaire; QOL, quality of life; RCT, randomised controlled trial; SCC, squamous cell carcinoma; UK, United Kingdom.

Table 3 Multivariable relationship of the PROs, clinical and laboratory variables and prognosis

Study reference	Global QOL HR (CI) *P* value	Physical functioning	Role functioning	Social functioning	Pain	Appetite loss/ anorexia	Other clinical and laboratory variables
SCC							
Conroy *et al.*[26]	NR	$P = 0.03$	NR	$P = 0.03$	NR	NR	NA
Adenocarcinoma/mixed†							
Chua *et al.*[25]	0.57 (0.45–0.72) $P < 0.001$	0.76 (0.60–0.97) $P = 0.003$	0.69 (0.54–0.88) $P < 0.001$	NS	NS	NS	Performance status ($P \leq 0.0001$), liver metastasis ($P \leq 0.0001$), peritoneal metastasis ($P = 0.007$) and alkaline phosphatase >100 U/L ($P \leq 0.0001$) were significant and haemoglobin <11 g/L
Park[29]	NR	NR	NR	0.36 (0.21–0.62) $P < 0.001$	NR	NR	Age ($P = 0.04$), bone metastasis($P = 0.02$) and low haemoglobin ($P = 0.04$)
Fuchs *et al.*[27]	NR	NR	NR	NR	NR	1.50 (1.20–1.86) $P < 0.0001$	Presence of primary tumour ($P = 0.001$), poor/ unknown tumour differentiation ($P = 0.0005$), time to progression since prior therapy ($P = 0.0002$), performance status ($P = 0.0001$), presence of peritoneal metastasis ($P \leq 0.0001$), high ALP level ($P = 0.003$), low lymphocyte level ($P = 0.001$), high LDH level (0.001), low albumin level ($P = 0.0006$), high AST level (0.001), high neutrophil level ($P \leq 0.0001$) and low sodium level ($P \leq 0.0001$)
Martin *et al.*[28]	NS	0.66 (0.45–0.98) $P = 0.04$	NS	NS	0.60 (0.40–0.89) $P = 0.01$	0.57 (0.36–0.90) $P = 0.02$	NA
Abdel-Rahman[23]	0.41 (0.24–0.69) $P = 0.001$	$P < 0.001$ (lack of mobility)	$P = 0.04$ (lack of self-care)	NA	$P < 0.001$	NA	Performance status ($P = 0.03$)
Abraham *et al.*[24]	NA	NA	NA	NA	NA	0.70 (0.53–0.94) $P = 0.01$	BMI ($P = 0.02$)

†Gastric adenocarcinoma, oesophageal adenocarcinoma, gastro-oesophageal junction adenocarcinoma and adenosquamous.

BMI, body mass index; CI, confidence interval; HR, hazard ratio; NA, not assessed; NR, not reported; NS, not significant; PRO, patient-reported outcome; QOL, quality of life; SCC, squamous cell carcinoma.

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considered with other clinical and demographic variables. Among patients with oesophageal SCC, physical functioning, social functioning and fatigue were predictive of survival in one univariable analysis, and physical and social functioning retained prognostic significance in a multivariable analysis of the same sample. Among patients with adenocarcinoma, physical functioning, role functioning, social functioning, global QOL, pain and appetite loss/anorexia had prognostic significance in univariable and multivariable analyses. Overall at least one or more PROs were significant in each of the studies included. Multiple clinical and laboratory variables, including low-performance status, low BMI, low haemoglobin, presence of peritoneal and liver metastasis, also showed prognostic significance in multivariable analyses, along with PROs.

Our findings are in line with the findings of the systematic reviews by Gotay *et al.*,[16] who provided evidence of the prognostic value of PROs in multiple cancers. In that review, among 39 clinical trials of various cancers, 36 studies showed at least one PRO had prognostic significance in multivariable analyses. Subsequently, another systematic review by Mierzynska *et al.*[17] showed physical functioning and global QOL were associated with survival in cancers of multiple primary types, including breast, lung and prostate. Another systematic review by Trajkovic-Vidakovic *et al.*[30] included 44 studies in the palliative care setting of advanced cancer. The study found that confusion, anorexia, fatigue, cachexia, weight loss, dyspnoea and dysphagia were independently associated with survival in multivariable analyses in 30–56% of the studies. However, all these studies included multiple primary cancer types, with limited specific discussion within the unique clinical context of GO cancers. There is limited information to guide prognostication in advanced GO cancer. A systematic review and meta-analysis by van den Boorn *et al.*[31] identified paucity of data in advanced GO cancer. Among 45 studies of prediction models, only seven studies were in the advanced setting, 25 were in the curative setting, and in 13 studies the setting was unclear/mixed. Furthermore, none of the prediction models included PROs. A recent systematic review by Kleef *et al.*[6] showed a weak correlation ($r = 0.27$) between OS and global health status in GO cancer. However, their primary aim was to determine the most common patient-reported issues and longitudinal trajectory of QOL.

Our review is the first to focus directly on the relationship between survival and PRO in advanced GO cancer. Furthermore, our data on PROs included in multivariable models of prognosis, along with clinical and demographic patient characteristics, may offer more confidence in the estimates provided by univariable prognostic models. Specifically, physical functioning, role functioning, social functioning, global QOL, pain and appetite loss/anorexia had prognostic significance in both univariable and multivariable analyses.

Strengths of our study include a comprehensive search strategy which was developed in conjunction with two academic librarians. Study screening, data extraction and quality assessment were completed by two independent reviewers with a third reviewer to resolve discrepancies. We included studies of chemotherapy and targeted therapies in the first line and subsequent settings. Our findings were consistent across studies, including differing populations, interventions and PRO measures.

Our study had some limitations. Despite some heterogeneity of PRO instruments and methods used across the studies, the majority of the evaluated studies used the EORTC QLQ-C30 instrument. None of the studies reported *a priori* hypotheses for analysis of the PRO and other prognostic factors. We did not have access to individual patient data. Treatment with immunotherapy has become standard practice in advanced GO cancer following the improvements in survival reported in the Keynote 062 trial of pembrolizumab[4] and the Checkmate 649 trial of nivolumab.[5] Future studies should examine associations between PRO and OS in patients with advanced GO cancer being treated with immune checkpoint inhibitors. Most studies in our review used data from clinical trials, only including participants who met strict eligibility criteria. These data may not be applicable to participants who would not be eligible for clinical trials, in particular those with differing symptoms and comorbidities.[32,33]

Monitoring of PROs may have a role in the routine clinical management of patients with advanced GO cancers. Basch *et al.*[34] have already established the clinical benefits of electronic monitoring of PROs in an RCT of 766 participants with a range of advanced cancers. The European Society for Medical Oncology[35] has recently recommended symptom monitoring with PROMs in routine clinical care during systematic cancer treatment after multiple RCTs have confirmed benefits on communication, satisfaction, treatment adherence, symptom control, reduction of emergency room and hospital admissions and survival.[36–38] Our study findings suggest that PRO data could offer additional benefit in more accurately predicting the length of survival of advanced GO cancer patients when assessed prior to therapy, when interpreted in the context of other known prognostic clinical and demographic factors as described by Yang *et al.*[39] in a large retrospective cohort study of more than 13 000 participants from US NCI's Surveillance, Epidemiology, and End Results registries.[39] It showed age and gender are significant prognostic factors.

Further prospective research is required to determine whether the specific PRO domains identified in this review as having prognostic significance can be used to improve the quality, accuracy and utility of prognostic information in practice and research. We are proposing to develop a prognostic model based on the findings of this review incorporating specific PRO symptoms and clinicians' estimates of survival along with known predictor variables, such as performance status, liver metastasis and peritoneal metastasis. We plan to test its performance in a contemporary clinical trial dataset. If validated, the prognostic model could be used to inform patients and their carers about their life expectancy, assist in decision-making and better stratify participants in clinical trials.

Conclusions

In conclusion, our review indicates that multiple PRO domains were associated with survival in advanced GO cancer. Baseline PRO assessment might be used to improve the accuracy of prognostication, assist in communication about prognosis with patients and carers and be used to stratify randomisation in clinical trials.

Acknowledgements

This study is a part of Sayeda K. Naher's PhD project, for which she is supported by an NHMRC CTC University of Sydney Postgraduate Research Scholarship. Rebecca Mercieca-Bebber is supported by an NHMRC CTC Early Career Fellowship (APP1138100).

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix A. Supporting Information.
Appendix B. Supporting Information.
Appendix C. Supporting Information.

C. Publication 3

Gastric Cancer
https://doi.org/10.1007/s10120-025-01654-2

ORIGINAL ARTICLE

Development and validation of a prognostic model incorporating patient reported outcomes for advanced gastric and esophageal carcinoma (AGOC) using individual patient data from two AGITG randomized clinical trials

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Received: 13 June 2025 / Accepted: 21 August 2025

Abstract

Background We developed and validated a prognostic model incorporating readily accessible clinicopathological data and specific patient-reported outcomes (PROs).

Methods We used data from two randomized trials comparing regorafenib to placebo: AGITG INTEGRATE IIa ($n=251$) for model development and AGITG INTEGRATE ($n=152$) for validation. Candidate variables were chosen from a systematic literature review and expert consultation. Significant prognostic factors in the multivariable model were identified using univariable Cox proportional hazards models with a p-value of <0.1. Multivariable Cox proportional hazards models were developed using clinicopathological and PRO variables, with model selection refined using least absolute shrinkage and selection operator (LASSO). The model's discrimination and calibration were assessed using concordance indices (C-statistics) and calibration plots.

Results Univariable analysis identified 9 clinicopathological variables and 4 PRO domains that were prognostic for overall survival: body mass index (BMI), ECOG performance status, number of metastatic sites, liver involvement, treatment with regorafenib, neutrophil–lymphocyte ratio (NLR), LDH, albumin, CA 19–9, appetite loss, constipation, fatigue, and pain. The initial multivariable model (M1) incorporated geographic region (Asia vs non-Asia), performance status, number of metastatic sites, treatment with regorafenib, NLR, BMI, LDH, CA 19–9, and albumin. The preferred multivariable model (M2), including the abovementioned variables plus the 4 PROs, demonstrated superior discriminative ability with higher C-statistic values than models without PROs. Plots supported the model's calibration.

Conclusions Incorporating PROs into prognostic models for AGOC improved the accuracy of survival predictions. Further research is needed to validate its use in routine clinical practice.

Keywords Gastric cancer · Prognostic model · Patient reported outcomes · Validation

Introduction

Advanced (metastatic or inoperable or unresectable) gastric and esophageal carcinoma (AGOC) is common and has a poor prognosis with the fifth-highest incidence and fourth-highest mortality rates globally [1]. Predicting future

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ASCO Gastrointestinal Cancers Symposium (GI) 2025 - mini oral and poster presentation.

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Published online: 16 September 2025

survival time is an important and difficult problem for doctors, patients, and carers. The range and complexity of factors influencing prognosis contribute to this difficulty [2]. Patients with advanced cancer who discussed prognosis and life expectancy with their oncologists developed a better understanding of the nature of their illness [3].

Nomograms for estimating prognosis in AGOC have been developed using clinicopathological variables including performance status, presence of liver metastasis, peritoneal metastasis, and neutrophil to lymphocyte ratio (NLR) [4–7]. The majority of previous models were developed in the setting of first-line chemotherapy [4, 5]. Other studies assessed a limited number of variables [6, 7]. The applicability of these models to patients having second and subsequent line systemic therapy is unclear.

Patient-reported outcomes (PROs) collected at baseline have shown prognostic value in other types of advanced cancer [8, 9]. A systematic review by Mierzynska et al. reported on the prognostic value of various baseline PRO scores in 41 studies across 15 cancer types [9]. The domains most frequently associated with survival included physical functioning (17 studies) and global health status and quality of life (15 studies) [9]. Among these studies, Park 2008 reported that patient-reported social functioning, assessed at baseline with the QLQ-C30, was prognostic in advanced gastric cancer in a model including bone metastases, hemoglobin, and age [10]. Our systematic review identified multiple domains of PRO that were prognostic in gastric cancer [11]. Despite broad, growing evidence about the value of PROs in predicting survival, there has been limited development and validation of prognostic models for AGOC that incorporate PROs. [12, 13].

The AGITG INTEGRATE and INTEGRATE IIa are randomized trials of regorafenib in AGOC [14, 15]. These trials showed that regorafenib, a multi-targeted, oral tyrosine kinase inhibitor (TKI), improved progression-free survival and overall survival in AGOC after previous systemic therapies had failed or were poorly tolerated. Both trials included participants with ECOG performance status 0–1 previously treated with at least two lines of systemic therapy.

We sought to improve prognostication by developing and validating a model and nomogram using readily available clinicopathological variables plus a focused set of PROs, using individual patient data from these two clinical trials.

Methods

We used INTEGRATE IIa ($n = 251$, NCT02773524) for model development and INTEGRATE ($n = 152$, ANZCTR 12612000239864) for validation. Both were randomized controlled trials in similar participants and clinical settings.

Model and nomogram development - candidate variables

We identified potential prognostic variables by reviewing the literature and consulting with oncologists, quality of life (QOL) experts, statisticians, and members of INTEGRATE Trial Management Committees [11].

Variables tested in univariable analyses included geographical region, Eastern Cooperative Oncology Group (ECOG) performance status, prior therapy lines, neutrophil to lymphocyte ratio (NLR), serum albumin concentration, body mass index(BMI), primary disease site, number of metastatic sites, tumor location; serum concentrations of carbohydrate antigen (CA) 19–9 and lactate dehydrogenase (LDH); previous resection of primary (gastrectomy), age, sex at birth, treatment with regorafenib versus (vs) placebo and the following PRO assessed at baseline with the EORTC QLQ-C30 and QLQ-STO22 (appetite loss, pain, fatigue, lack of mobility, lack of energy, leg swelling, constipation) (See Appendix A).

Prognostic factors included in the multivariable model were identified through univariable Cox proportional hazards models, using a p-value threshold of < 0.1. Multivariable models were developed using the least absolute shrinkage and selection operator (LASSO). A 10% missing value threshold was set; variables exceeding this were planned for imputation to prevent sample size reduction. However, as no variable had missing data exceeding the 10% threshold, imputation was not necessary. Standardization was applied to albumin, LDH, and CA 19–9 to ensure comparability.

Cox proportional hazards regression was used for all time-to-event analyses. The proportional hazards assumption was assessed, and this showed strong evidence that the variable for gastrectomy violated this assumption ($p < 0.001$). We therefore stratified all multivariable analyses by gastrectomy (yes versus no).

Geographical region (Asia vs. non-Asia: Australia, USA, Canada, NZ) was included in the multivariable models because it was prognostic in a previous analysis of the INTEGRATE trial, even though it was not prognostic in our current univariable analysis [18].

Three models were developed from the multivariable analyses, all stratified by gastrectomy status. The first model (M1) included only clinicopathological variables. The second model (M2) expanded on M1 by adding PROs from EORTC QLQ-C30. The third model (M3) expanded M2 by including selected variables from the QLQ-STO22. A nomogram was developed for M2, including the variables selected by the LASSO.

The rationale for selecting Model M2 was that the QLQ-C30 is a widely used and readily available generic

patient-reported outcome measure (PROM), which includes identified, important PRO domains, with minimal respondent and administrator burden. The rationale for testing Model M3 was its inclusion of a subscale from the QLQ-STO22 specifically assessing pain 'in the stomach area' and pain associated 'with eating', rather than the generic pain subscale from the QLQ-C30.

Validation of the model

Internal validation of the models was assessed in terms of discrimination and calibration. Discrimination was assessed with the concordance index (C-index), which assesses the model's ability to distinguish between individuals who did and did not experience the event of interest (death) [19, 20]. Confidence intervals for the C-index were calculated using bootstrap-resampling from the construction data set (1000 bootstrap samples per model).

External validation was assessed using data from the INTEGRATE trial; this data was not used for model development. Calibration assesses the accuracy of the model's predicted probabilities of outcomes by comparing them with the actual observed outcomes [21]. Calibration was assessed visually using plots of observed versus predicted probabilities of overall survival at 6 months. The effects of model recalibration were assessed using re-estimation of intercept and re-estimation of both the intercept and the slope.

Analyses were performed using SAS version 9.4 and R version 4.3.2. [16, 17].

Results

Descriptive statistics

The baseline characteristics of the 403 participants in INTEGRATE and INTEGRATE IIa are summarized in Table 1. Approximately half the participants were recruited in Asia. The median age was 63 years, 77% were male, and the primary site was stomach in 69%. The median overall survival time was 6 months, with a range from 2 to 30 months.

Baseline PROs indicated a significant symptom burden, with appetite loss reported in 61%, constipation in 42%, fatigue in 66%, and pain in 46%.

Univariable and multivariable model

In the development dataset, 9 of 15 clinicopathological variables collected at baseline met the pre-specified threshold in univariable analysis ($p \leq 0.1$) for potential inclusion in the multivariable model. These factors included ECOG performance status (1 vs 0) ($p = 0.02$), BMI ($p = 0.08$), number of metastatic sites ($p < 0.001$), liver involvement ($p = 0.04$), treatment with regorafenib vs placebo ($p = 0.005$), NLR ($p < 0.001$), LDH ($p < 0.001$), albumin ($p < 0.001$), and CA 19–9 ($p < 0.001$). Univariable and multivariable analyses are summarized in Table 2.

Baseline PROs that met the univariable analysis threshold for inclusion in the multivariable model included appetite loss ($p < 0.001$), constipation ($p < 0.001$), fatigue ($p < 0.001$), and pain ($p < 0.001$) from the QLQ-C30, and stomach pain ($p < 0.001$) from the QLQ-STO22.

Three multivariable models were constructed from the multivariable analysis, all stratified by gastrectomy status. The first model (M1) included clinicopathological factors such as region, ECOG status, number of metastatic sites (extent of cancer), BMI, treatment, NLR, LDH, albumin, and CA 19–9. The second model (M2) expanded on M1 by adding PROs from EORTC QLQ-C30, specifically fatigue, pain, appetite loss, and constipation. The third model (M3) used the item on stomach pain from the QLQ-STO22, along with the subscales for fatigue and appetite loss from the QLQ-C30, to model M1. Liver involvement was excluded from multivariable models based on the LASSO.

These multivariable analyses (M2) demonstrated several clinicopathological and PRO factors that were prognostic for overall survival in models accounting for the effects of other variables. Survival times were shorter for participants from the rest of the world than from Asia (HR 1.68, 95% CI 1.20–2.35, $p = 0.0026$). Shorter survival times were also associated with number of metastatic sites (HR = 2.20, 95% CI 1.39–3.48, $p = 0.001$), higher NLR (HR = 1.21, 95% CI 1.02–1.43, $p = 0.03$), higher LDH (HR = 1.51, 95% CI 1.26–1.82, $p < 0.0001$), and higher CA 19–9 (HR = 1.01, 95% CI 1–1.01, $p = 0.0006$). Longer survival times were associated with higher BMI (HR 0.57, 95% CI 0.39–0.84, $p = 0.004$), and higher serum albumin (HR = 0.80, 95% CI 0.65–1.00, $p = 0.05$). Performance status, liver metastasis, and lines of previous therapy were not significant in multivariable models.

Among the PRO, appetite loss was associated with shorter survival in both univariable and multivariable analysis (HR = 1.21, 95% CI 1.01–1.45, $p = 0.03$), whereas constipation, fatigue, and pain were significant in univariable models ($p < 0.001$), but not in the multivariable model ($p > 0.10$). The subscale for pain from the QLQ-STO22 had slightly increased prognostic significance than the pain scale from the QLQ-C30.

Overall, factors such as region, number of metastatic sites, treatment, NLR, LDH, albumin, and appetite loss consistently showed significant associations with survival, while other factors like age, sex, and primary site show little to no impact.

Table 1 Baseline characteristics of the participants

Characteristics	Integrate N (%)	Integrate IIa N (%)	Both groups N (%)
Region			
Asia	54 (36%)	157 (63%)	211 (52%)
Rest of world	98 (65%)	94 (38%)	192 (48%)
Age -Median (IQR)	62(54–68)	64 (57–71)	63 (56–70)
Sex—Male	120 (79%)	190 (76%)	310 (77%)
Primary site			
GOJ	58 (38%)	69 (28%)	127 (32%)
Stomach	94 (62%)	182 (73%)	276 (69%)
ECOG			
0	62 (41%)	93 (37%)	155 (39%)
1	90 (59%)	158 (63%)	248 (62%)
Prognosis (months)- Median (range)	6 (3–18)	4 (2–30)	6 (2–30)
BMI—Median (IQR)	23 (21–27)	22 (19–25)	22(20–26)
Prior lines of treatment			
1–2	152 (100%)	149 (59%)	301 (75%)
3 +		101 (40%)	101 (25%)
Number of metastatic	35 (23%)	52 (21%)	87 (22%)
Sites	75 (49%)	128 (51%)	203 (50%)
4 +			
Liver metastasis			
Peritoneal metastasis	47 (31%)	74 (30%)	121 (30%)
Gastrectomy	52 (34%)	99 (39%)	151 (38%)
NLR- Median (IQR)	3 (2–6)	3 (2–5)	3 (2–5)
LDH- Median (IQR)	241 (187–396)	231 (177–355)	234 (178–374)
Albumin—Median (IQR)	37 (35–43)	37 (32–40)	37 (33–41)
Ca 19–9- Median (IQR)	53 (12–309)	53 (13–544)	53 (13–467)
PRO domain score, 0–100 scale (EORTC QLQ-C30)			
Appetite loss			
30 +	91 (60%)	157 (63%)	248 (62%)
< 30	45 (30%)	83 (33%)	128 (32%)
Constipation			
30 +	62 (41%)	107 (43%)	169 (42%)
< 30	74 (49%)	132 (53%)	206 (51%)
Fatigue			
30 +	97 (64%)	170 (68%)	267 (66%)
< 30	39 (26%)	70 (28%)	109 (27%)
Pain			
30 +	61 (40%)	123 (49%)	184 (46%)
< 30	75 (49%)	117 (47%)	192 (48%)
Pain (STO22)			
30 +	54 (36%)	106 (42%)	160 (40%)
< 30	82 (54%)	133 (53%)	215 (53%)

IQR interquartile range, *GOJ* gastro-esophageal junction, *ECOG* eastern cooperative oncology group, *BMI* body mass index, *NLR* neutrophil to lymphocyte ratio, *LDH* lactate dehydrogenase, *CA* carbohydrate antigen, *PRO* patient reported outcome, *EORTC QLQ* European Organisation for Research and Treatment of Cancer quality of life questionnaire. The possible scores for these scales ranges from 0 (none at all) to a 100 (worst possible).

Model performance

The performance of these multivariable models was assessed using the C-statistic (see Table 3). M2 and M3 exhibited higher C-statistics than M1, indicating improved prediction by including PROs. M2, which incorporated the PRO indicators from EORTC QLQ-C30, but not the QLQ-STO22, was chosen as the final model on the basis of its higher

Table 2 Univariable and multivariable analyses of associations between baseline characteristics and overall survival time

Variable	Class	Univariable		M1—Multivariable		M2—Multivariable		M3—Multivariable	
		Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Region	Rest of world vs Asia	1.17 (0.89–1.53)	0.26	1.58 (1.15–2.18)	0.005	1.68 (1.20–2.35)	0.0026	1.59 (1.14–2.22)	0.006
Age	10-year increase	0.92 (0.82–1.03)	0.26						
Sex		0.89 (0.66–1.21)	0.47						
Primary Site	Stomach vs GOJ	0.86 (0.64–1.15)	0.32						
ECOG performance status	1 vs 0	1.38 (1.05–1.80)	0.02	1.16 (0.87–1.54)	0.31	1.04 (0.76–1.40)	0.82	1.06 (0.78–1.42)	0.72
BMI	10-unit increase	0.75 (0.55–1.03)	0.08	0.53 (0.38–0.75)	0.0004	0.57 (0.39–0.84)	0.004	0.59 (0.41–0.85)	0.005
Prior lines of treatment	2-unit increase	1.09 (0.88–1.35)	0.42						
Number of metastatic sites	4 + vs 1	2.19 (1.44–3.33)	< 0.001	2.61 (1.66–4.12)	< 0.0001	2.20 (1.39–3.48)	0.001	2.07 (1.29–3.31)	0.001
Liver metastasis	Yes vs no	0.76 (0.59–0.99)	0.04						
Peritoneal Metastasis	Yes vs no	1.19 (0.89–1.58)	0.24						
Treatment	Rego vs Placebo	0.67 (0.51–0.89)	0.005	0.73 (0.54–0.97)	0.03	0.77 (0.57–1.04)	0.09	0.75 (0.55–1.00)	0.05
NLR	6-unit increase	1.26 (1.11–1.44)	< 0.001	1.26 (1.07–1.47)	0.004	1.21 (1.02–1.43)	0.03	1.25 (1.05–1.48)	0.011
LDH	250-unit increase	1.42 (1.20–1.68)	< 0.001	1.40 (1.17–1.67)	< 0.001	1.51 (1.26–1.82)	< 0.0001	1.49 (1.24–1.78)	< 0.0001
Albumin	10-unit increase	0.68 (0.56–0.83)	< 0.001	0.73 (0.60–0.89)	0.002	0.80 (0.65–1.00)	0.05	0.80 (0.64–0.99)	0.04
CA 19–9	200-unit increase	1.01 (1.00–1.01)	< 0.001	1.01 (1–1.01)	< 0.0001	1.01 (1–1.01)	0.0006	1.01 (1–1.01)	0.0003
Appetite loss	33-unit increase	1.43 (1.25–1.64)	< 0.001			1.21 (1.01–1.45)	0.03	1.22 (1.02–1.46)	0.03
Constipation	33-unit increase	1.31 (1.13–1.53)	< 0.001			1.07 (0.89–1.27)	0.48		
Fatigue	33-unit increase	1.50 (1.26–1.80)	< 0.001			1.07 (0.81–1.42)	0.63	1.08 (0.84–1.40)	0.53
Pain	33-unit increase	1.43 (1.24–1.64)	< 0.001			1.18 (0.97–1.44)	0.10		
Pain (STO22)	33-unit increase	1.70 (1.37–2.10)	< 0.001					1.38 (1.07–1.79)	0.013

Table 3 Model's *C*-Statistic + Bootstrap 95% CIs

Model	Gastrectomy	*C* -statistic	95% CI	
M1	No	0.695	0.660	0.732
	Yes	0.664	0.619	0.714
M2	No	0.723	0.686	0.759
	Yes	0.692	0.645	0.750
M3	No	0.721	0.685	0.756
	Yes	0.685	0.633	0.743

C-statistics in both the gastrectomy and non-gastrectomy strata and the benefit of using PRO domains from one, rather than two, separate PRO measures.

The nomogram (Fig. 1) based on Model-2 illustrates the extent to which the various predictor variables affect the probability of overall survival at 6 months. For example, in this dataset, the 4 or more metastatic sites were associated with a much lower probability of survival at 6 months than 3 or fewer metastatic sites, whereas having an ECOG

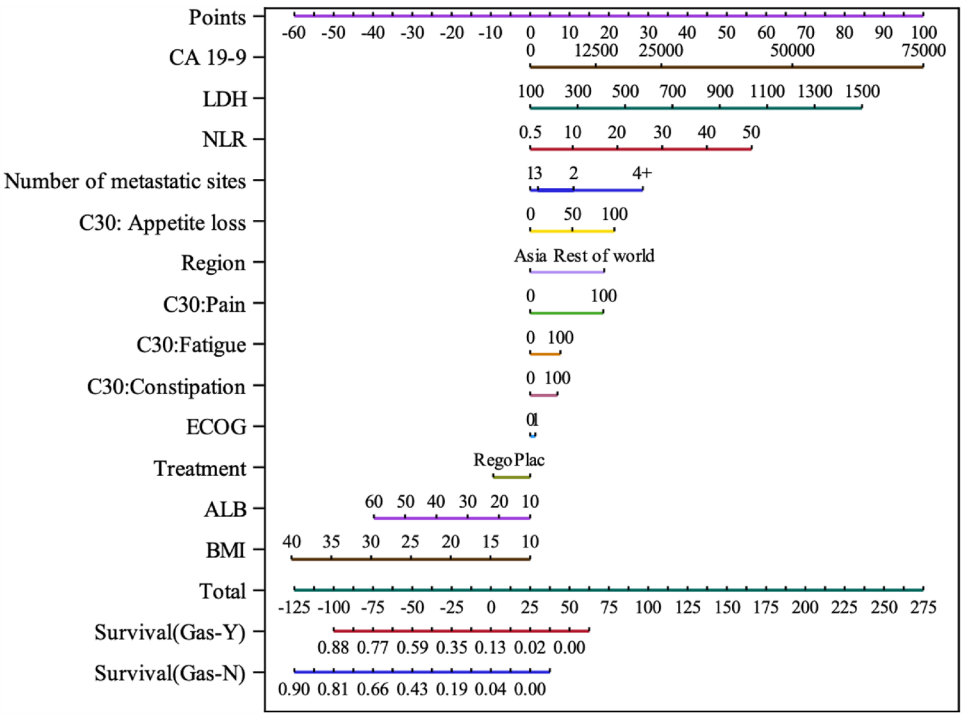

Fig. 1 Nomogram for predicted probability of survival at 6 months. *CA* carbohydrate antigen, *LDH* lactate dehydrogenase, *NLR* neutrophil to lymphocyte ratio, *C30* EORTC QLQ-C30, *ECOG* eastern cooperative oncology group, *Rego* regorafenib, Plac placebo, *ALB* albumin, *BMI* body mass index, *Gas* gastrectomy, *Y* yes, *N* no. *The more points the lower the estimated probability of survival at 6 months

performance status 0 versus 1 had relatively little effect. Appetite loss and pain had larger effects on the probability of survival than fatigue and constipation.

Validation of the model

Calibration

The model's predictions of 6-month survival were well-calibrated for participants with and without prior gastrectomy, as indicated by the calibration curves being close to the 45-degree reference line reflecting perfect calibration (Fig. 2). Panel B, showing the calibration of M2, indicates the improvement resulting from the inclusion of the PRO for fatigue, pain, and constipation to M1 shown in Panel A. Use of the QLQ-STO22 items for stomach pain in M3 did not improve calibration compared with the use of the generic items for pain in M2 from the QLQ-C30. There was a tendency for the lowest predicted survival probabilities to underestimate the observed survival probability in all the models.

Discussion

This study advances prognostic modeling for overall survival in AGOC patients by incorporating a broader set of clinicopathological variables and PROs from the EORTC QLQ-C30 and QLQ-STO22, enhancing both accuracy and clinical applicability. Our model M2 incorporates additional clinicopathological variables and patient-reported outcomes including fatigue, alongside known predictors of survival such as pain, appetite loss, and constipation [18]. We selected candidate PROs a priori, based on prior literature and expert consultation, in addition to robust univariable testing ahead of including variables in our multivariable analyses.

Our methodological approach builds on previous work by using a more comprehensive and robust multivariable modeling strategy, with our models that incorporated PROs demonstrating superior predictive performance, reflected by improved C-statistics from 0.695 in M1 to 0.723 in M2 with the inclusion of patient-reported pain, appetite loss, and constipation. The incorporation of these additional variables provided more individualized and accurate estimates of survival probability at 6 months.

Sensitivity analyses demonstrated good calibration with only minor variations observed across different scenarios, and support the use of model M2.

A prognostic model that included baseline clinicopathological variables and selected PRO from the QLQ-C30 provided clinically useful estimates of overall survival. These variables can feasibly be collected in routine clinical practice, using a readily accessible, simple, low-burden, PRO measure. The use of standardized and widely accepted measures (like the EORTC QLQ-C30) facilitates implementation with minimal additional training for healthcare providers [22]. Standardized PROs can enhance consistency and comparability across different clinical settings. Patients and clinicians should benefit from improved

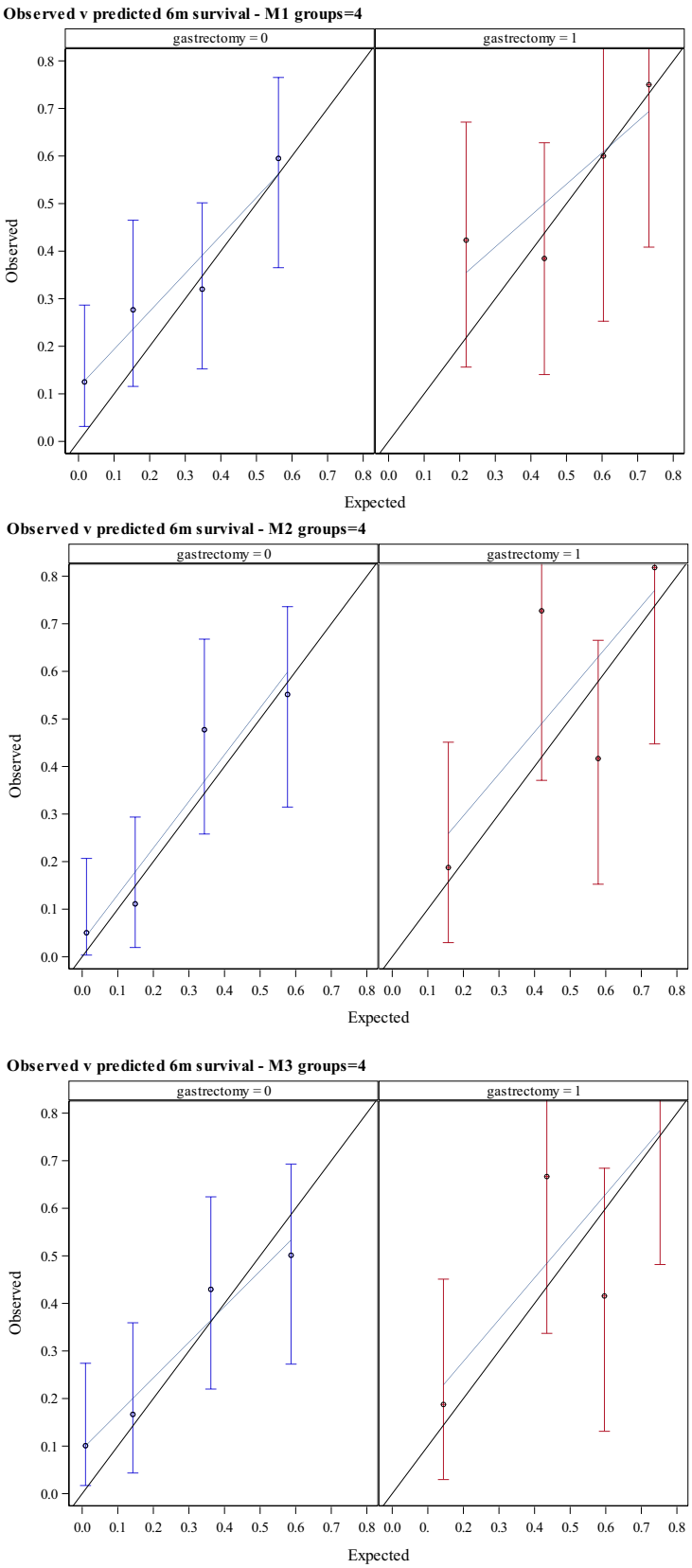

Fig. 2 Calibration plot for observed vs predicted 6 months survival in INTEGRATE I trial population

understanding of their prognosis and be better equipped to make decisions regarding their future treatment and care [23]. Model M2 could also be used as a stratification factor in future randomized trials.

Our analyses demonstrated that pain ratings focused on abdominal pain and/or pain related to eating (as captured by the QLQ-STO22, Model M3) offered greater prognostic value than general pain ratings from the QLQ-C30 (Model M2). However, the overall performance of Model M3 was not significantly better than that of Model M2. Additionally, the benefit of using the pain score from the QLQ-C30 over the abdominal pain score of the QLQ-STO22 is reduced responder- and administrator-burden, and easier, streamlined administration of a single, readily accessible instrument (QLQ-C30). These findings warrant further investigation in additional datasets.

Our study has important strengths. We used Cox proportional hazards models with the LASSO method for variable selection. This approach strengthens the model's reliability, reduces the risk of overfitting, and identifies independent prognostic factors more effectively than previous methods [24, 25]. Variable selection involved both univariable screening and multivariable modeling to account for potential confounders. INTEGRATE IIa and INTEGRATE included participants from Asia, Australia, and Canada resulting in a more diverse study population than studies performed in only one region. We used validated translations of the EORTC PROs in non-English speaking participants.

This study also has limitations. Firstly, the models were built and validated with data from clinical trial populations, which may not be representative of the broader, more heterogeneous population treated outside of clinical trials. [26] Trial participants often differ in terms of demographics, comorbidities, and disease severity, which could limit the model's generalizability to routine clinical practice. Future studies should test the model's external validity by applying it in routine clinical settings. Our sample sizes were moderate, and further validation in larger, independent data sets is also warranted [27]. While the model showed good predictive accuracy within our 2 study cohorts, its performance might differ in a broader or more diverse population. All participants were receiving second or subsequent lines of treatment and had an ECOG performance status of 0–1. The applicability of our model to patients with ECOG performance status worse than 1 or having first-line treatment remains as open questions for further research.

We did not perform a decision curve analysis (DCA) and net reclassification improvement (NRI) in this study; alternative methods for assessing model performance and clinical utility in terms of reclassification. These approaches provide additional insights if the proposed application of a model is to categorize participants to directly influence decision making. Future studies of models designed to influence decision making should incorporate DCA and NRI.

Future research should explore the applicability of our model in routine clinical settings to further validate its utility and impact. A web-based tool would facilitate its use and allow real-time validation in clinical practice settings [28]. Future research could assess the integration of this model in an Electronic Health Record to enhance data collection, accessibility, and data-driven decision-making [29]. Training programs for clinicians could facilitate its adoption and implementation with the aim of improving doctor–patient communication and care [30].

In conclusion, we developed and validated a nomogram to predict the probability of survival at 6 months in AGOC being treated with second or subsequent line anticancer treatments. By incorporating clinicopathological and patient-reported variables that are simple to collect, and often collected routinely, the model enhanced prognostic accuracy and supports a more personalized approach. Implementation of this nomogram in clinical practice could improve patient care and decision-making by contributing to more frequent and accurate discussions of prognosis, and better stratification in clinical trials.

GOJ gastro-esophageal junction, *NLR* neutrophil to lymphocyte ratio, *LDH* lactate dehydrogenase, *CA* carbohydrate antigen.

Appendix 1

See Tables 4 and 5

EORTC QLQ-C 30 and STO22 scoring range

1 = not at all

2 = a little

3 = quite a bit

4 = very much.

EORTC scoring

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems. Symptom scales / items and Global health status/QoL: Score = {(RS − 1) range} Å ~ 100.

Author contributions Sayeda Kamrun Naher, David Espinoza, Peter Grimison, Martin Stockler, Rebecca Mercieca- Bebber, and Katrin Marie Sjoquist contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sayeda

Table 4 Baseline clinicopathological prognostic factors

Variable	Continuous	Categorical	Range	Coding for analysis
Performance status (ECOG)		Yes	0—5	0 = 0 1 = 1 2 = other if any
Number of prior lines of therapy		Yes	1–2 vs 3 +	0 = 1–2 1 = 3 – 3 +
Neutrophil: lymphocyte ratio	Yes		Disease and contest specific could differ in trial. Might need to be normalized and transformed	
Albumin	Yes		Might need to be normalized and transformed	
BMI	Yes			
Primary disease site		Yes	GOJ vs stomach	0 = Gastro-esophageal junction 1 = Stomach
Region		Yes	Asian vs rest of world	0 = Asia 1 = rest of world
Extent of cancer *(number of metastatic sites)	yes			0 = 1–2 1 = 3–4 2 = 5 + (could redistribute after analysis)
Tumor location (liver)		Yes	Liver vs other	0 = liver 1 = other
Tumor location (Peritoneal/other)		Yes	Peritoneal vs other	0 = peritoneal 1 = other
Baseline tumor markers 19.9 and LDH	Yes		Normal range 0–37 U/ml	
Gastrectomy/ primary resection		Yes	Yes/no	0 = yes 1 = no
Sex		Yes	Male/female	0 = male 1 = female
Age	Yes			

*Extent of cancer was taken from target lesion that might not represent true extent

Table 5 Overview of baseline prognostic factors, detailing both continuous and categorical variables, their respective ranges, and coding schemes for analysis. Baseline patient reported outcomes (PROs) tested for possible prognostic significance

Variable	PROM and item number	Continuous range
Appetite loss	QLQ-C30 item 13	Transformed scale score 0–100 (higher = worse)
Appetite loss	STO22 item 34	Transformed scale score 0–100 (higher = worse)
Pain	QLQ-C30 item 9,19	Transformed scale score 0–100 (higher = worse)
Pain	STO22 item 35, 36	Transformed scale score 0–100 (higher = worse)
Fatigue	QLQ-C30 item 10,12,18	Transformed scale score 0–100 (higher = worse)
Constipation	QLQ-C30 item 16	Transformed scale score 0–100 (higher = worse)
Clinicians' survival estimates		In weeks

K Naher and David Espinoza. The collection of data in the trials used was contributed to by Nick Pavlakis, Kohei Shitara, David Goldstein, and Katrin Marie Sjoquist. The first draft of the manuscript was written by Sayeda K Naher and all authors commented on subsequent versions of the manuscript. All authors read and approved the final manuscript.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions. This study is a part of Sayeda K. Naher's PhD project, for which she is supported by a NHMRC CTC University of Sydney post graduate research scholarship. Rebecca Mercieca-Bebber is supported by a NHMRC Early Career Fellowship (APP1138100). Funding through unrestricted grants and drug for the studies was provided by Bayer. INTEGRATE and INTEGRATE IIa are Investigator Sponsored Collaborative Studies led by the Australasian Gastro-Intestinal Trials Group (AGITG) and coordinated by the NHMRC Clinical Trials Centre, University of Sydney.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest Nick Pavlakis: Honoraria—BeiGene, Bayer, Takeda, and Pierre Fabre; Consulting or Advisory Role—Roche, Boehringer Ingelheim, AstraZeneca, Merck KGaA, Merck Serono, Amgen, Merck Sharp & Dohme, Novartis, Pfizer, Takeda, Bristol Myers Squibb, BeiGene, Gilead Sciences, and Janssen Oncology; Research Funding—Bayer (Inst), Pfizer (Inst), and Roche (Inst). Kohei Shitara: Honoraria—Bristol Myers Squibb, Janssen, AstraZeneca, Lilly, Ono Pharmaceutical, and Astellas Pharma; Consulting or Advisory Role—Bristol Myers Squibb, Takeda, Ono Pharmaceutical, MSD, Novartis, Daiichi Sankyo, Amgen, Astellas Pharma, Guardant Health, Bayer, Zymeworks, AstraZeneca, and ALX Oncology; Research Funding—MSD (Inst), Daiichi Sankyo (Inst), Taiho Pharmaceutical (Inst), Chugai Pharma (Inst), Ono Pharmaceutical (Inst), Astellas Pharma (Inst), Eisai (Inst), Amgen (Inst), and PRA Health Sciences (Inst). Katrin Sjoquist: Honoraria—BMS, Merck, MSD, Servier, Novotech (Inst), Astellas Pharma, Lisata (Inst), and Bayer (Inst); Research Funding—Bayer (Inst); Other Relationship—Novotech. List of where and when the study has been presented: ASCO Gastrointestinal Cancers Symposium (GI) 2025—mini oral and poster presentation.

Ethical approval The trials were approved by HRECs prior to initiation/patient recruitment. For INTEGRATE IIa—ClinicalTrials.gov identifier: NCT04879368. For INTEGRATE trial- clinical trial registration: ANZCTR 12612000239864.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent was obtained from all patients.

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Other appendices

Appendix 2.1

Search terms

EMBASE

Searches	Results	Type	Actions
1	exp stomach Neoplasms/	181512
2	exp stomach Neoplasms/	181512
3	stomach cancer.tw.	8400
4	(stomach tumor or stomach tumo?r*).tw.	659
5	stomach carcinoma.tw.	737
6	stomach malignan*.tw.	70
7	exp gastric Neoplasms/	0
8	gastric cancer.tw.	100109
9	(gastric tumor or gastric tumo?r*).tw.	6157
10	gastric carcinoma.tw.	18211
11	gastric malignan*.tw.	1624
12	exp esophageal Neoplasms/	99387
13	esophageal carcinoma.tw.	8940
14	esophageal* malignan*.tw.	836
15	o*sophag* cancer*.tw.	6069
16	o*sophag* tumo?r*.tw.	564
17	(esophagogastric tumor or esophagogastric tumo?r*).tw.	38
18	(gastroesophag* tumor or gastroesophag* tumo*?r*).tw.	76

19	gastroesophag* cancer.tw.	774
20	oesophagogastric cancer.tw.	332
21	or/1-20	278192
22	advanced.tw.	766854
23	metastatic.tw.	414865
24	metastasis.tw.	385021
25	inoperable.tw.	25122
26	palliative.tw.	118161
27	recurrent.tw.	483668
28	unresectable.tw.	36992
29	or/22-28	1899327
30	21 and 29	77619
31	clinical trial.tw.	255025
32	exp clinical trial/	1720455
33	phase II trial.tw.	21859
34	phase III trial.tw.	14201
35	randomized controlled trial.pt.	0
36	controlled clinical trial.pt.	0
37	randomized.ab.	816700
38	or/31-37	2161846
39	21 and 29 and 38	11304
40	overall survival.tw.	368084
41	OS.mp.	238859
42	Survival Analysis/	36255

43	kaplan meier survival curve.tw.	2683
44	kaplan meier curve.tw.	4763
45	or/40-44	482723
46	39 and 45	4235

Cochrane registry of controlled clinical trials

# ▲	Searches	Results	Type
1	exp stomach Neoplasms/		2898
2	exp stomach Neoplasms/		2898
3	stomach cancer.tw.		390
4	(stomach tumor or stomach tumo?r*).tw.		19
5	stomach carcinoma.tw.		35
6	stomach malignan*.tw.		26
7	exp gastric Neoplasms/		2898
8	gastric cancer.tw.		6545
9	(gastric tumor or gastric tumo?r*).tw.		141
10	gastric carcinoma.tw.		638
11	gastric malignan*.tw.		44
12	exp esophageal Neoplasms/		1824
13	esophageal carcinoma.tw.		682
14	esophageal* malignan*.tw.		16
15	o*sophag* cancer*.tw.		531
16	o*sophag* tumo?r*.tw.		23
17	(esophagogastric tumor or esophagogastric tumo?r*).tw.		3
18	(gastroesophag* tumor or gastroesophag* tumo*?r*).tw.		2

19	gastroesophag* cancer.tw.	96
20	oesophagogastric cancer.tw.	57
21	or/1-20	10338
22	advanced.tw.	63294
23	metastatic.tw.	31475
24	metastasis.tw.	9740
25	inoperable.tw.	2670
26	palliative.tw.	6494
27	recurrent.tw.	33500
28	unresectable.tw.	6196
29	or/22-28	123424
30	21 and 29	4635
31	clinical trial.tw.	160511
32	exp clinical trial/	144
33	phase II trial.tw.	8600
34	phase III trial.tw.	9972
35	randomized controlled trial.pt.	558222
36	controlled clinical trial.pt.	93200
37	randomized.ab.	635571
38	or/31-37	1055605
39	21 and 29 and 38	2768
40	overall survival.tw.	45161
41	OS.mp.	28025

	42	Survival Analysis/	8438
	43	kaplan meier survival curve.tw.	128
	44	kaplan meier curve.tw.	237
	45	or/40-44	59192
	46	39 and 45	1333

Medline Ovid

# ▲	Searches	Results	Type
1	exp stomach Neoplasms/	105986	
2	exp stomach Neoplasms/	105986	
3	stomach cancer.tw.	6959	
4	(stomach tumor or stomach tumo?r*).tw.	534	
5	stomach carcinoma.tw.	632	
6	stomach malignan*.tw.	29	
7	exp gastric Neoplasms/	105986	
8	gastric cancer.tw.	71089	
9	(gastric tumor or gastric tumo?r*).tw.	4229	
10	gastric carcinoma.tw.	12944	
11	gastric malignan*.tw.	1038	
12	exp esophageal Neoplasms/	56357	
13	esophageal carcinoma.tw.	6290	
14	esophageal* malignan*.tw.	498	
15	o*sophag* cancer*.tw.	3799	

16	o*sophag* tumo?r*.tw.	338
17	(esophagogastric tumor or esophagogastric tumo?r*).tw.	24
18	(gastroesophag* tumor or gastroesophag* tumo*?r*).tw.	47
19	gastroesophag* cancer.tw.	438
20	oesophagogastric cancer.tw.	184
21	or/1-20	181119
22	advanced.tw.	502240
23	metastatic.tw.	258197
24	metastasis.tw.	267837
25	inoperable.tw.	14032
26	palliative.tw.	71158
27	recurrent.tw.	315779
28	unresectable.tw.	21752
29	or/22-28	1253022
30	21 and 29	47853
31	clinical trial.tw.	171016
32	exp clinical trial/	942837
33	phase II trial.tw.	11329
34	phase III trial.tw.	6947
35	randomized controlled trial.pt.	569941
36	controlled clinical trial.pt.	94895
37	randomized.ab.	563663

38	or/31-37	1291381
39	21 and 29 and 38	5128
40	overall survival.tw.	207924
41	OS.mp.	124544
42	Survival Analysis/	144967
43	kaplan meier survival curve.tw.	1541
44	kaplan meier curve.tw.	2349
45	or/40-44	376471
46	39 and 45	2114

Appendix 3.1 – 3.3

Appendix 3.1

Search term used

Medline Ovid/Embase/ Cochrane Central Register of Controlled Trial

# ▲	Searches
1	patient reported outcome measures/
2	Quality of Life/
3	(patient adj1 rated).tw.
4	patient-reported outcome*.tw.
5	(patient adj1 report*).tw.
6	quality of life.tw.
7	self-rated.tw.
8	self-report*.tw.
9	QL.tw.
10	QOL.tw.
11	HRQL.tw.
12	HRQOL.tw.
13	PROM.tw.
14	PRO.tw.
15	health status/
16	health status.tw.
17	(patient adj2 rating*).tw.
18	or/1-17
19	advanced.tw.
20	metastatic.tw.

21 metastasis.tw.

22 inoperable.tw.

23 palliative.tw.

24 recurrent.tw.

25 unresctable.tw.

26 or/19-25

27 exp stomach Neoplasms/

28 stomach cancer.tw.

29 (stomach tumor or stomach tumo?r*).tw.

30 stomach carcinoma.tw.

31 stomach malignan*.tw.

32 exp gastric Neoplasms/

33 gastric cancer.tw.

34 (gastric tumor or gastric tumo?r*).tw.

35 gastric carcinoma.tw.

36 gastric malignan*.tw.

37 exp esophageal Neoplasms/

38 esophageal carcinoma.tw.

39 esophageal* malignan*.tw.

40 o*sophag* cancer*.tw.

41 o*sophag* tumo?r*.tw.

42 (esophagogastric tumor or esophagogastrictumo?r*).tw.

43 (gastroesophag* tumor or gastroesophag* tumo*?r*).tw.

44 gastroesophag* cancer.tw.

45 esophagogastric cancer.tw.

46 or/27-45

47 prognosis.tw.

48 predict* survival.tw.

49 estimat* survival.tw.

50 length of life.tw.

51 life duration.tw.

52 overall survival.tw.

53 OS.tw.

54 prognostication.tw.

55 exp mortality/

56 or/47-55

57 18 and 26 and 46 and 56

PubMed

(((quality of life[MeSH Terms]) OR (patient reported outcome[MeSH Terms])) OR (health status[MeSH Terms])and (((prognosis[MeSH Terms]) OR (overall survival[MeSH Terms])) OR (length of life[MeSH Terms])) OR (prognostic factor[MeSH Terms]) and (((((((advanced gastric cancer[MeSH Terms]) OR (metastatic gastric cancer[MeSH Terms])) OR (advanced stomach cancer[MeSH Terms])) OR (metastatic stomach cancer[MeSH Terms])) OR (advanced gastroesophageal cancer[MeSH Terms])) OR (metastatic gastroesophageal cancer[MeSH Terms])) OR (advanced esophageal cancer[MeSH Terms])) OR (metastatic esophageal cancer[MeSH Terms])) AND (((quality of life[MeSH Terms]) OR (patient reported outcome[MeSH Terms])) OR (health status[MeSH Terms]))

Appendix 3.2

Data extraction list

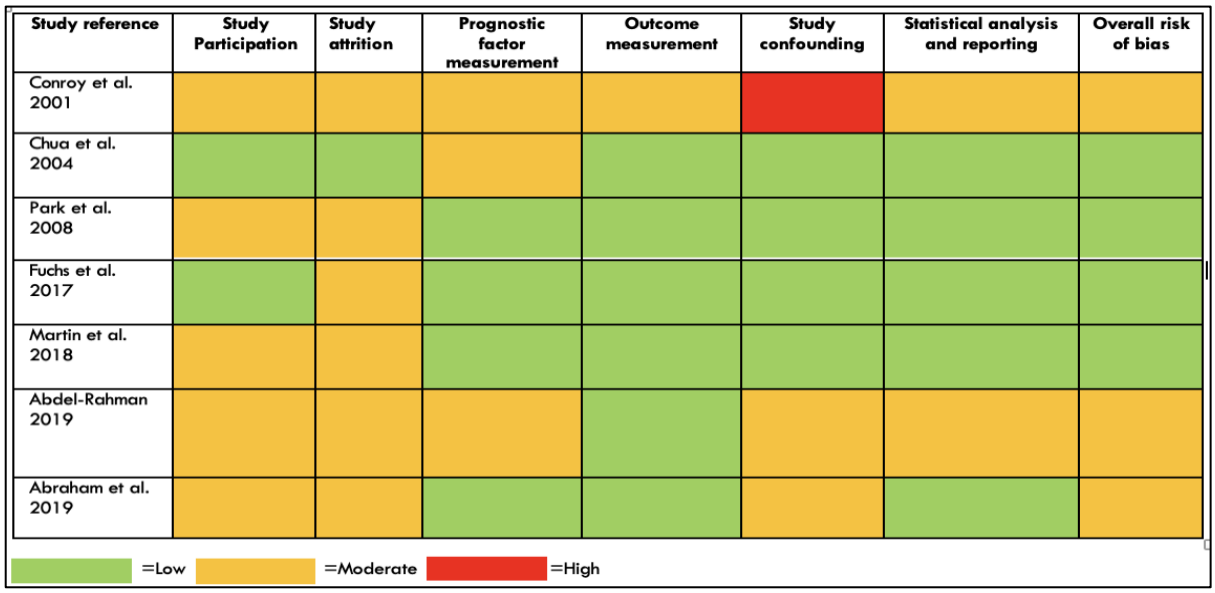
Citation, year
Initial reviewer
Research location (# of centres)
Research period
Start Date
End date
Study design, RCT
Cohort study
cross sectional
pooled analysis of RCT
other
patients' characteristics,
age in years given as Mean (SD) [Range] unless indicated otherwise
Gender
Cancer type, Gastric
Oesophageous
oesophgogastric
Histology, adenocarcinoma
squamous
adenosquamous
Treatment (Tx) received, chemotherapy,
Taxane
Fluropyrimidine
Platinum

Other chemo
targated therapy, Regorafinib
Ramucirumab
other
immunotherapy, nivolumab
Pembrolizumab
other
Line of treatment
1st Line
2nd line
other
PRO instrument used. EQ-5D-3L
QLQ-C30
QLQ-OES
FACT -G
Other
No of participants
Number of patients with PRO data
% of total patients with PRO data completion
Modelling method to assess prognostic factor, cox regression
cox proportional hazard
linear regression
other
Prognostic factors studied for analysis of OS, Clinical variable, weight loss
Poor performance/ECOG status
Anaemia
Hypoalbumenemia
presence of peritoneal mets
presence of liver mets
Ascitis
Neutrophil/lymphocyte ratio
other
PRO Items used on univariate analysis for OS, Global QOL (HR/Odds ratio)
Physical functioning
Role functioning
Social functioning
Emotional functioning
Pain
Appetite loss
Dysphagia
Fatigue
other
PRO Items used on multivariate analysis for OS, Global QOL (HR/Odds ratio)
Physical functioning
Role functioning
Emotional functioning
Social functioning
Pain
Appetite loss
Dysphagia
Fatigue

other
name of PROs with prognostic significance (P<0.05)
Median survival (months)
comments

Appendix 3.3

Figure 2: Risk of bias of primary studies



Appendix 4.1

Table with baseline clinicopathological prognostic factors:

Variable	Continuous	Categorical	Range	Coding for analysis
Performance status (ECOG)		Yes	0 - 5	0=0 1=1 2=other if any
Number of prior lines of therapy		Yes	1-2 vs 3+	0=1-2 1=3 – 3+
Neutrophil: lymphocyte ratio	Yes		disease and contest specific could differ in trial. Might need to be normalised and transformed	
Albumin	Yes		Might need to be normalised and transformed	
BMI	Yes			
Primary disease site		yes	GOJ vs stomach	0= Gastro-oesophageal junction 1= Stomach
Region		yes	Asian vs rest of world	0= Asia 1=rest of world
Extent of cancer *(number of metastatic sites)	yes			0=1-2 1=3-4 2=5+ (could redistribute after analysis)
Tumour location (liver)		yes	Liver vs other	0=liver 1=other
Tumour location (Peritoneal/other)		yes	Peritoneal vs other	0=peritoneal 1=other
Baseline tumour markers 19.9 and LDH	Yes		Normal range 0-37 U/ml	
Gastrectomy/ primary resection		yes	yes/no	0=yes 1=no
sex		yes	Male/female	0=male 1=female
Age	yes			

*Extent of cancer was taken from target lesion that might not represent true extent.

This table provides an overview of baseline prognostic factors, detailing both continuous and categorical variables, their respective ranges, and coding schemes for analysis.
Baseline patient reported outcomes (PROs) tested for possible prognostic significance:

Variable	PROM and item number	Continuous range
Appetite loss	QLQ-C30 item 13	Transformed scale score 0-100 (higher= worse)
Appetite loss	STO22 item 34	Transformed scale score 0-100 (higher= worse)
pain	QLQ-C30 item 9,19	Transformed scale score 0-100 (higher= worse)
pain	STO22 item 35, 36	Transformed scale score 0-100 (higher= worse)
fatigue	QLQ-C30 item 10,12,18	Transformed scale score 0-100 (higher= worse)
constipation	QLQ-C30 item 16	Transformed scale score 0-100 (higher= worse)
Clinicians' survival estimates		In weeks.

EORTC QLQ-C 30 and **STO22** scoring range
1= not at all
2= a little
3= quite a bit
4= very much

EORTC scoring.
All of the scales and single-item measures range in score from 0 to 100. A high scale score
represents a higher response level.

Thus, a high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL,

but a high score for a symptom scale / item represents a high level of symptomatology / problems.

Symptom scales / items and Global health status / QoL:
Score = $\{(RS - 1)$ range$\}$ Å~100