

POSTOPERATIVE MORTALITY FOR ELDERLY PATIENTS UNDERGOING ELECTIVE COLORECTAL SURGERY: A SYSTEMATIC REVIEW

Thesis: Master of Clinical Science

Joanna Rae Sutherland
School of Translational Science
The Joanna Briggs Institute
University of Adelaide
October 2014

Table of contents

Abstract	3
Author's Statement	4
Forward	5
Introduction-Colorectal Surgery: structure, process and outcome	8
Data and Evidence Synthesis.....	13
Methodology-Controversies and Challenges	19
The Systematic Review Protocol	22
Search Results	26
Review Findings	36
Discussion	49
Conclusions.....	54
Appendices.....	56
Appendix I PubMed search strategy	56
Appendix II MASTARI critical appraisal instruments	57
Appendix III Data extraction instrument	59
Appendix IV Studies selected for critical appraisal	61
Appendix V Details of included studies.....	63
Appendix VI Excluded studies	69
Appendix VII Detailed data from included studies.....	70
Bibliography.....	72

ABSTRACT

Despite good evidence that reporting surgical outcomes is of value to patients, clinicians, hospitals and funders, it may be difficult for stakeholders to access the outcome data they need. The aim of this systematic review was to meet the gap in the published literature, and provide a pooled estimate for the 30 day all-cause postoperative mortality for elderly patients in highly developed countries undergoing elective colorectal surgery.

This review considered studies that included patients aged 65 years and over from highly developed countries, presenting for elective colorectal surgical resection, reported via published and unpublished studies performed between 1998 and 2013. A meta-analysis of proportions was undertaken, using a fixed effects model, in order to reduce the likelihood of giving undue weight to smaller studies. Twenty four studies were included after assessment.

The 30 day postoperative mortality rates for all studies ranged from 0.57 to 11.3%. The overall pooled mortality rate for all included patients in all studies aged 65 years and over was 5.34% (95% Confidence Intervals 5.26-5.41%). Mortality rates generally increased with increasing age. There was a noticeable difference between national-level reported mortality rates, and those reported from academic centres, and from regional and non-academic centres. In studies where a qualitative outcome assessment was reported, all eleven assessments were positively framed (as “safe”, “favourable”, or described procedures with a “small” mortality). No study referred to “unsafe” or “unfavourable” outcomes.

The implications of this systematic review for future research regarding outcomes after elective colorectal surgery in elderly patients are that more studies are needed, in order to answer the following questions:

1. How can health systems best report adverse outcomes after surgery?
2. What postoperative outcomes are of greatest importance to patients?
3. How can qualitative outcomes be incorporated with quantitative outcomes (such as mortality/survival) to produce meaningful metrics for patients?
4. How can appropriate outcome data be best incorporated into patient-level risk prediction scores for surgery?
5. How can outcome data be incorporated into shared decision-making processes for surgery, and how can patient risk- tolerance be assessed?

AUTHOR'S STATEMENT

This thesis "Postoperative mortality for elderly patients undergoing elective colorectal surgery: A systematic review" is entirely original work by the author Joanna Rae Sutherland. I certify that this work contains no material that has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by any other person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any other university or other tertiary institution without the prior approval of the University of Adelaide, and, where applicable, any other partner institution responsible for the joint award of this degree.

I give consent to this copy of my thesis, when deposited in the University library, being made available for loan or photocopying, subject to the provisions of the Copyright Act 1968.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library search, and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

Joanna Rae Sutherland

October 14, 2014

*“Where is the wisdom we have lost in knowledge?
Where is the knowledge we have lost in information?”
T.S.Eliot, from The Rock: 1934*

Chapter 1: Forward

The World Health Organization (WHO)¹ and the Institute of Medicine (IOM)² have defined the quality of healthcare in terms of six variables:

- Safety
- Effectiveness
- Patient-centeredness
- Equity
- Accessibility, and
- Efficiency

The quality of surgical care may be assessed by structural, process or outcome measures.³ Thirty day postoperative mortality is a valid and widely used outcome measure,^{4,5} reflecting procedural safety. Public reporting of surgical outcome measures tends to lead to improvement in outcomes, and hence safety.⁶ Surgical outcome reporting is likely to enhance patient-centeredness of healthcare systems by providing the information patients and clinicians need to support shared decision-making for surgery.^{7,8} Outcome reporting may also increase the equity⁹ and efficiency¹⁰ of healthcare institutions and systems, by enabling the identification and support of institutions with “poor track records”.¹¹

Despite good evidence that reporting surgical outcomes is of value to patients, clinicians, hospitals and funders, it may be difficult for stakeholders to access the outcome data they need. Only one developed nation (New Zealand) currently collects and publically reports postoperative mortality data for an entire system of care.¹² In the United Kingdom (UK), particularly since the Bristol Royal Infirmary inquiry into paediatric cardiac surgery deaths, there has been an increase in public access to surgical mortality data, most recently via the My Hospital Guide and “Dr Foster Intelligence”.¹³ This website was set up in order “to empower patients and improve transparency in healthcare”. In the United States (US), the National Surgical Quality Improvement Program (NSQIP) provides feedback to individual participating hospitals regarding their standardised postoperative mortality rates for selected procedures, but the data is not publically available.⁴ The Australian and New Zealand Audit of Surgical Mortality (ANZASM) is a voluntary audit which is primarily an educational tool for participating surgeons.¹⁴ The outcome data from the ANZASM audit is thus unavailable in detail to policy makers, healthcare funders, hospitals, clinicians other than surgeons, patients and their carers.

Colorectal surgery is surgery undertaken on the large intestine, including the right (ascending) colon, the transverse colon, the left (descending) colon (including the sigmoid colon) and the rectum. Colorectal surgery can be carried out as a planned, non-urgent (“elective”) procedure, or as an immediate life-saving procedure (“emergency”). In the published data, 30 day all-

cause postoperative mortality is often aggregated for those patients undergoing emergency and elective surgery, and for heterogeneous patient groups (with respect to age, intercurrent medical conditions, and disease indication for surgery). Consequently it may be difficult to predict outcomes for planned surgery, as distinct from emergency life-saving surgery, or for surgery performed on older patients compared with that performed on younger patients. Where available, large population reports for pooled age groups from the United States,¹⁵ New Zealand,¹² England¹⁶ and Denmark¹⁷ demonstrate 30 day postoperative mortality after elective colorectal surgery of between 1.9% and 6.2%, and a positive correlation between increasing age and postoperative mortality in all of these studies. The precise mortality risk for elective colorectal surgery in older patients remains poorly defined.

The aim of this systematic review was to find the best available research evidence and provide a pooled estimate for 30 day all-cause postoperative mortality for elderly patients in highly developed countries undergoing elective colorectal surgery. By restricting the study to highly developed countries, variation in outcome between countries due to healthcare system factors which are resource-sensitive (particularly technology, workforce and training factors) could be minimised. Providing this estimate of postoperative mortality after elective colorectal surgery in elderly patients is likely to enhance decision-making from many perspectives, including:

Public policy makers

As populations age, there will be an increase in the burden of colorectal cancers.¹⁸ Many countries, including Australia, have instituted national bowel cancer screening programmes,¹⁹ to target the increasing rates of colorectal cancer. Such programmes are effective at saving lives, as cancer or pre-cancerous lesions detected through screening can be treated with elective surgery.²⁰ As these screening programmes are extended to older patients, it is important to know all outcomes from all interventions (including surgery) which result from screening.²¹

Healthcare funders

In most developed nations, surgery accounts for a considerable proportion of the healthcare budget. Currently, in developed nations (with the exception of New Zealand) there is no routine country- or system-wide collection of post-surgical outcomes, such as postoperative mortality. Thus there is very little information available to assess the value of this spending, and to inform prioritisation and funding decisions for surgical services.

Hospitals and clinicians

There has been much debate in the United Kingdom about national and regional variations in surgical outcomes, and the necessity to more closely align patient need (based on risk of poor postoperative outcome) with appropriate postoperative resources.²² Outcome data is influenced by patient, surgical and institutional factors, and these must be acknowledged when attempting to pool or compare results from different centres or countries. Although it is recognised that such risk adjustment can be challenging, more transparent outcome data, such as the results of this systematic review, may be useful for benchmarking (of hospital

networks, units and departments, and/or individual clinicians), for quality improvement purposes, and also for hospital level resourcing and prioritisation decisions.

Patients and carers

Availability of 30 day all-cause postoperative mortality data is likely to be of significant interest to patients and their families, particularly when making decisions regarding elective surgery. Decision-making under conditions of uncertainty, especially when considering the risks and benefits of the proposed treatment, requires complex trade-offs. For truly informed consent, the potential range of outcomes should be individualised as much as possible. Increasingly, risk prediction scores are used for this purpose. The background to these risk prediction scores is described as useful "...as surgical culture moves more towards outcome measures and providing the patient (as the end user of the service) with as much information as possible to make fully informed consent".²³ However, creation of valid risk prediction scores first requires the availability of relevant population-wide prevalence data informing outcomes.

Older patients

Most of the published data clearly demonstrates an increase in adverse outcomes, including mortality, from all elective surgery with advancing patient age.^{4,12,24,25} With an ageing population, and with improved anaesthesia-related safety,²⁶ patients are increasingly referred for surgery that was unavailable to previous generations of older citizens. Pooled age estimates for surgical survival may present an unrealistic risk assessment for older patients.

Colorectal surgery is increasingly offered to, and performed for older patients. This systematic review aimed to provide an estimate of 30 day all-cause postoperative mortality, which is currently neither widely collected nor reported for the population of interest (older patients having elective colorectal surgical resection). Worldwide, it is expected that the funds allocated to elective surgery will be aligned with postoperative outcomes (and incorporate mortality as an outcome of interest), in order to demonstrate value for money.²⁷ Currently, surgical outcome data may be available to individual surgeons (for their own quality assurance purposes), but in Australia, as for many other developed nations, this data is not made widely available to clinicians (other than surgeons), hospitals, healthcare funders, nor to patients. The results presented in the systematic review which follows improve the availability of information to support individuals and institutions to arrive at more informed healthcare decisions.

Chapter 2: Introduction-Colorectal Surgery: Structure, Process and Outcome

This chapter includes an outline of quality metrics used for colorectal surgery, and the tension between quality measures for individual surgeons, versus teams responsible for surgical care for patients. Reasons for differences in outcome measures between countries and between institutions are discussed.

Colorectal surgery has been acknowledged as a subset of surgery with a relatively high mortality rate.^{22, 28} Public reporting has not occurred in Australia for outcomes of colorectal surgery. Review of the relevant medical literature for colorectal surgery outcomes reveals that explicit postoperative mortality rates are often difficult to identify and/or interpret, as data may be presented as relative risk or odds ratio (compared with a reference group). Despite the knowledge that elderly patients as a group tend to be sicker than younger patients, there is good evidence that age alone is a prognostic factor for postoperative mortality.^{22,24,28-31} In 2009, Bentrem et al³² analysed US data from the National Surgical Quality Improvement Project (NSQIP) which included 17 268 patients from 121 hospitals undergoing colorectal surgery. These authors concluded that despite the higher levels of comorbidity found in elderly patients, mortality rates after colorectal surgery were independently associated with increased age, and that risks of cardiac, pulmonary and renal complications were also elevated in elderly patients.

Historically, surgery has been portrayed as an individual effort, and surgeons have self-selected as the “archetypal hero” (p990).³³ More recently however, surgery has been considered a structured, multi-disciplinary process. For colorectal surgery, the contributions of numerous team members are required for optimal patient outcomes.³⁴ Almoudaris³⁵ has acknowledged the importance of shared outcome measures for hospital-based clinicians and teams caring for patients having colorectal surgery. There is considerable debate about the most appropriate outcome measures to use. One outcome measure which is increasingly recommended as an international standard is 30 day postoperative mortality.³⁶ Other early postoperative mortality adverse outcome metrics include 60day and 90 day postoperative mortality, however these are less commonly measured and reported than 30 day postoperative mortality. In New Zealand, the public reporting of 30 day postoperative mortality occurs by procedure, and for an entire system of care.¹² For Australia, public reporting of 30 day postoperative mortality has been a feature in Victoria since 2002 for cardiac surgery in public hospitals,³⁷ and has recently commenced in New South Wales (Australia)³⁸ for fractured neck of femur.

Published reports considering postoperative outcomes after colorectal surgery have often included heterogeneous patient groups with regard to age, reasons for surgery and comorbidities. Most reports often fail to distinguish between elective and emergency surgery outcomes. The postoperative mortality rate for emergency colorectal surgery has long been acknowledged as significantly higher than for elective (planned) surgery.³⁹⁻⁴¹ Most of the data informing postoperative mortality for colorectal surgery comes from patients having surgery for cancer. One large systematic review⁴² published in 2000 considered postoperative

complications (including mortality) for elderly patients presenting for colorectal cancer surgery. This review demonstrated increases in postoperative morbidity and mortality with increasing age. However, the studies included in the review were for patients having both emergency and elective surgery, and the review reported mortality rates for elderly patients (aged over 65 years, combined emergency and elective surgery) as a proportion of mortality occurring in the reference group (patients under 65 years). For pooled elective and emergency surgery, and for the group of “young old” (patients aged between 65-74 years), compared with patients younger than 65 years, this review demonstrated a relative mortality risk of 1.8. Absolute mortality rates confined to elderly patients only having elective colorectal surgery were not explicitly reported in this review.

Long term outcomes of colorectal surgery (but not usually short term survival, reflected by 30 day postoperative mortality) may be affected by cancer stage and grade.⁴³ Apart from malignant tumours, indications for colorectal resection can also include benign neoplasms (non-cancerous growths), diverticular disease (a non-cancerous bowel condition which can result in ‘diverticulae’ or pouches of bowel, which may rupture, or become infected), ischaemic bowel disease (where there is inadequate blood flow to the bowel), volvulus (twisting of the bowel), and other reasons. Site of resection may affect short term mortality (left versus right colon, or rectum).⁴⁴ There are many other factors which can potentially influence postoperative mortality for colorectal surgery. These factors include the presence of comorbid medical conditions,²⁹ the management of postoperative complications⁴⁵ and the institution providing care.⁶ Higher blood transfusion rates are independently associated with increased 30 day mortality after non-cardiac surgery,⁴⁶⁻⁴⁸ and transfusion triggers or practices may vary between institutions.

There have been numerous innovations and improvements in the management of patients presenting for colorectal surgery in recent years. Survival improvements for patients with rectal cancer have been attributed to the role of the multidisciplinary team,³⁴ allowing timely referral for appropriate multimodal therapy. Since the 1990s, particularly for rectal cancer surgery, the increasing concentration of specialised surgery in high-volume centres, performance of surgery by specialised colorectal surgeons⁴⁹ and the more widespread application of evidence-based guidelines⁵⁰ have resulted in improved long term survival. In the Netherlands, improved referral for chemotherapy for patients treated for colon cancer in University hospitals has been attributed to the availability of multidisciplinary team care.⁵¹ Enhanced recovery (“fast track”) programmes for patients having colorectal surgery have become increasingly popular since the 1990s. In a meta-analysis of randomized controlled trials, Zhuang⁵² found that although enhanced recovery programmes (compared with traditional care) are associated with reduced length of hospital stay and reduced total complication rates after elective colorectal surgery, there was no demonstrated reduction in 30 day postoperative mortality. However most of these studies pertain to population-based patient groups (all ages), and do not specifically address outcomes for elderly patients.

Technical aspects of surgery have also been shown to affect outcomes after colorectal surgery. One example is the performance of total mesorectal excision (TME) for rectal cancer, originally described by Heald⁵³ in 1986, and subsequently adopted as a standard of care, due

to reduction in local cancer recurrence rates and improvements in long term outcomes. However, the benefit of TME for elderly patients, particularly on short term postoperative mortality, has not been demonstrated.⁵⁴ The use of laparoscopic (“minimally invasive”) surgical techniques have also increased in popularity since the 1990s; however although some smaller studies have suggested a reduction in early postoperative mortality rates, in a systematic review of laparoscopic compared with open colorectal surgery in elderly patients, Grailey⁵⁵ found no reduction in postoperative mortality. In an earlier review investigating the short term benefits of laparoscopic surgery for colorectal resection, Schwenk et al⁵⁶ found no benefit of laparoscopic surgery in reducing early postoperative mortality, but noted that of 25 studies included in the review, only six reported postoperative deaths. Other authors have reported the benefits of the combined effect of laparoscopic surgery and enhanced recovery programmes,⁵⁷ but none have demonstrated any effect on short term mortality after surgery. No reduction in postoperative mortality has been demonstrated for the use of any particular energy source instruments in laparoscopic colectomy,⁵⁸ nor for innovations such as robotic surgery.⁵⁹ Other advances which may lead to improvement in some patient outcomes include the use of metallic stents for obstructing colorectal lesions, which may reduce the requirement for urgent colorectal surgery.⁶⁰ The evidence for the techniques described in relation to postoperative mortality is limited, however for most of the described techniques the outcomes for elderly patients have not been specifically determined.

In summary, there is a large degree of clinical heterogeneity in reviews which examine postoperative mortality after colorectal surgery, and for most of the evidence, mortality rates for elderly patients, and for elderly patients presenting for elective surgery, are difficult to identify. There are also other sources of heterogeneity, particularly related to differences in mortality rates reported between institutions, and between countries.

North American authors including Finlayson⁶¹ have commented on the significant discrepancy between population-based postoperative mortality (including the postoperative mortality for colorectal surgery in elderly patients), and the published mortality rates reported from single institutions. Reasons for this discrepancy have been suggested as selection bias (single centres who publish results tend only to operate on lower risk patients, particularly if results are from clinical trials, which tend to exclude higher risk patients), performance discrepancy (the possibility that academic centres, in particular, may have better postoperative survival rates than other centres) or publication bias (reduced likelihood of publishing results with higher than perceived average mortality rates). In one large series examining outcomes for colorectal surgery in the United Kingdom (UK), Faiz et al,⁶² in a survey of English hospital results, noted that between individual hospital groups (trusts), adjusted mortality rates after elective colorectal surgery in elderly patients was from between 0 and 14.5%. The reasons proposed by these authors include potentially different availability and utilisation of risk stratification, geriatric services and intensive care between institutions. Further, Faiz emphasises the need to monitor institutional outcomes in order to identify units with “consistently poor track records of treating high risk patient groups such as the elderly” (p784). Morris et al from the UK¹⁶ also identified a number of trusts where 30 day postoperative mortality after colorectal surgery consistently laid outside statistically predetermined limits over

the time period 1998-2006 (indicating outlying postoperative mortality). All these institutions were district general hospitals, rather than academic or tertiary referral institutions. Mathews⁶³ has pointed out that evidence from smaller institutions, particularly from tertiary and quaternary specialised referral centres, has often been used to advocate for “major operations in elderly patients”, but that such “highly favourable” reports should be interpreted with caution because of the probable presence of publication bias, and the uncertainty of extrapolating such results to less experienced centres and surgeons.

Notwithstanding the variability between results from national studies, and those from some individual centres, several authors have commented on the apparent differences in outcomes after colorectal surgery between the UK and other countries.^{16,64} Different outcomes may be explained by differences between healthcare systems (potentially reflecting different levels of service provision, or unmet need), different patient risk profiles, or differences in structures of care, especially related to postoperative high dependency and intensive care. Most series report higher levels of postoperative mortality after colorectal (and other) surgery in the UK than in the USA or elsewhere in Europe.

Other factors which may influence the outcomes after colorectal surgery between institutions are the effects of caseload and specialisation. Archampong⁶⁵ in a comprehensive systematic review confirmed the association between high surgeon and high hospital caseload (in unadjusted studies) and improved postoperative outcome, for all colorectal, colon and rectal cancer patients. Cohen⁶⁶ has acknowledged the influence of hospitals on surgical outcomes, and recommended that surgeons use their hospital-specific mortality risk in discussion with patients, potentially to adjust patients' individual probability risk of postoperative mortality. In a large study of over 22,000 patients, Billingsley⁶⁷ noted the association with high surgeon and hospital caseload, and reduced postoperative mortality after surgery for colon cancer, and concluded that the effect was largely due to improved systems of care in high caseload hospitals which produced better outcomes. Conversely, Oliphant⁴⁹ analysed the results for patients in the west of Scotland having surgery for colorectal cancer, and observed that between 1992 and 2004 an increase in postoperative deaths occurred in those patients receiving care from non-specialist surgeons. His conclusion was that increasing surgical subspecialisation was a significant factor in improved patient outcomes, but was unable to specify which features of specialist care were responsible for the improvement. Jestin et al,⁶⁸ in a survey of general (university) hospitals and district hospitals in Sweden, have suggested that variability in clinical guideline compliance for the care of patients having elective surgery for colorectal cancer may be explained by differences in hospital structure.

Given the improvements in care described previously, for patients having colorectal surgery over recent years, it is expected that there will have been improvements in outcomes, as reflected by reductions in 30 day postoperative mortality. In general, this hypothesis is supported by the available outcome data for large series in the UK and Europe.^{16,17,62,69} Jafari et al⁷⁰ most recently demonstrated that in the USA, over the period 2001-2010, in-hospital mortality rates for patients having resections for colorectal cancer have improved, with particular improvements in outcome for elderly patients. This study was a retrospective review, derived from the USA National Inpatient Sample, and presented mortality rates for combined

elective and emergency surgery. Identifiable outcome data showing mortality rates for older patients having elective colorectal surgery is not available in this review. However, it confirmed persistently higher postoperative morbidity and mortality rates for elderly patients, and also confirmed the paucity of available data regarding “national surgical trends and specific rates of mortality” in the elderly population.

Like other highly developed nations, Australia’s population is ageing, and the number of older people is projected to increase sharply. Under one projection, the number of people in Australia aged between 65 and 84 years will grow from 2.4 million (in 2007) to 4 million (in 2022), and to 6.4 million by 2056.⁷¹ We know also that approximately 50% of all cancers and 70% of cancer deaths occur in older people.⁷² Most colorectal surgery in highly developed nations is performed for cancer. However, despite the current and likely increasing burden of elderly patients presenting for colorectal resection, it is difficult to access data from large series, or systems of care, which reflect outcomes (including mortality) for elderly patients after colorectal surgery. Much of the outcome data comes from smaller series, from individual institutions, and largely from younger patients who tend to be over-represented in clinical trials.⁷³ For Australia, as for other highly developed nations, a contemporary estimate of postoperative mortality for colorectal surgery is lacking. In order to better understand the spending requirements, and to enable planning and prioritisation decisions, good understanding of postoperative mortality rates is essential. This information is also required for developing countries, as the burden of surgery increases. Weiser et al⁷⁴ have identified surgical safety as a priority for developing nations, and a “substantial global health concern”. Postoperative mortality rates reflect the overall safety of a surgical procedure. For colorectal surgery, better data informing the postoperative mortality for elderly patients undergoing elective colorectal surgery will potentially impact pre-, intra- and postoperative clinical decision-making. The data is also required to inform system-level and policy decisions which may impact public policy (such as funding of colorectal screening programmes) and organisational decisions around hospital planning and networking of cancer and/or surgical services.

Having discussed the variation in colorectal surgery postoperative outcome measures, in the following chapter, the collection of data in a systematic review is discussed, in order to answer clinical questions such as the prevalence of postoperative adverse outcomes.

Chapter 3: Data and Evidence Synthesis

In this chapter, the process of data collection and analysis via the systematic review process is discussed. Healthcare professionals are likely to be confronted with large amounts of published information, and often discover apparently conflicting results for a variety of clinical problems. Hence it is necessary to identify the best ways to integrate large volumes of information, in order to answer the questions which arise in modern healthcare. The questions are many and varied- the simplest questions may be about the best way to diagnose a problem, or the best medication to treat a clinical condition. More complex questions may concern the best way to organise processes or systems of care, or how to organise funding to achieve the best health outcomes for a population.

A systematic review is a transparent process of data collection and analysis, which aims to answer a pre-determined question. Of importance, the question is specific, and the data which is used in the review meets pre-determined eligibility criteria. The Cochrane Collaboration is arguably the most easily recognised international organisation which conducts systematic reviews of randomised controlled trials of healthcare interventions. The Cochrane Collaboration⁷⁵ in its on-line reviewer's handbook defines the systematic review as characterised by:

- a clearly stated set of objectives with pre-defined eligibility criteria for studies
- an explicit, reproducible methodology
- a systematic search that attempts to identify all studies that would meet the eligibility criteria
- an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias, and
- a systematic presentation, and synthesis, of the characteristics and findings of the included studies.

The Joanna Briggs Institute promotes evidence-based healthcare as an iterative process, and encourages evidence synthesis via the systematic review.⁷⁶ The Joanna Briggs approach encourages (where appropriate) the inclusion of more diverse forms of evidence, as well as the results of randomised controlled trials. This approach allows for the inclusion of qualitative evidence, the findings of economic analyses, expert opinion and textual analyses. The subject of the systematic review presented in this thesis is purely quantitative. Therefore the structure of the systematic review is best assessed against the criteria described by the Cochrane Collaboration.

The evidence collated during systematic reviews can, on occasion, be aggregated via a meta-analysis. The process of meta-analysis therefore aims to improve the precision and accuracy of estimates, and increase the generalisability of results from single trials or studies.

Most researchers attribute the term "meta-analysis" to Gene Glass from the University of Colorado. Glass described meta-analysis as "the statistical analysis of a large collection of analysis results from individual studies, for the purpose of integrating the findings"(p3).⁷⁷ An educational researcher, Glass framed this recommendation as a moral necessity, as the

volume of educational research was large and increasing, and there was a pressing need to extract useful knowledge from the “abundance of information” available, rather than spend resources “adding a new experiment or survey to the pile” (p4). This same issue of information abundance has been apparent to health and medical researchers, and the same imperative prevails- to distil knowledge from information. Further, as Glass emphasises, this imperative “is particularly true of those questions that are more properly referred to as outcome evaluation than analytic research” (p3). The systematic review described in the following chapters addresses the evaluation of the frequency of an adverse outcome (death) for older patients undergoing elective colorectal surgery. The challenge is to find the relevant information, and to distil knowledge from the available information.

Originally, the technique of meta-analysis in health research was taken to mean the analysis of quantitative results, by mathematically combining data from similar trials.⁷⁸ Typically, more sophisticated meta-analysis involved identification of common causes and associations, and via meta-regression, and used the combined data from individual trials to strengthen the evidence for causation or association with greater precision than was possible from individual studies alone. More recently, the field of evidence synthesis has been expanded to include “the amalgamation of both qualitative and quantitative data sources”, and also to include techniques to identify and incorporate heterogeneous data, and to quantify the degree of uncertainty which results from the synthesis and therefore underpinning any conclusions (p11).⁷⁹ The underlying philosophy of evidence synthesis is that combining results from many sources can produce more powerful (and less uncertain) conclusions. The science of evidence synthesis has developed in order to address heterogeneity between clinical trial populations, and more recently to address and manage disparate data sources (chiefly quantitative and qualitative). Athanasiou and Darzi⁷⁹ refer to integrative synthesis and interpretative synthesis, and the distinction between knowledge support and decision support. Integrative synthesis usually implies the process of combining variable data in order to produce meaningful conclusions and recommendations. This process has traditionally been applied to quantitative data. Interpretive synthesis is more commonly applied to qualitative data, and involves defining an underpinning theoretical construct. The systematic review described in the following chapters will involve both integrative synthesis (of quantitative data) and some descriptive synthesis. The aim of the systematic review described here is to more closely define one outcome (thirty day postoperative mortality) which will assist knowledge support and decision support for patients, clinicians and policy makers who are involved in the field of elective colorectal surgery for elderly patients.

The principal challenges in the processes of meta-analysis and of evidence synthesis have been identified as

- Ensuring a systematic and complete search, including identification of publication bias
- Identifying and managing bias and heterogeneity of data, and
- Minimising and expressing uncertainty.

In the rest of this chapter, these challenges will be discussed in further detail. In the following

chapter the methodology used in this systematic review will be described, and more specifically, how these challenges have been managed.

Having clearly defined the research question, an essential part of high quality systematic review process is to outline the protocol for the review. The aim of a pre-determined protocol is to reduce bias in the search process. The following elements of the search process should be pre-defined as part of a published protocol. Any deviation from the published protocol should be declared and explained in the final published review.

Systematic searching

Having pre-defined the search question, the next decision to be made by the systematic reviewers is which databases are to be searched, and subsequently, whether there are other repositories of relevant information apart from large and well-known databases. The Cochrane Collaboration recommends at a minimum to search CENTRAL (The Cochrane Central Register of Controlled Trials), MEDLINE and EMBASE as the three most important bibliographic databases.⁷⁵ However the Cochrane Collaboration (formed in the 1990s) tends to concentrate on the systematic review of randomised controlled trials, and has not to date been heavily involved in the review or incorporation of other forms of evidence. The Joanna Briggs Institute (JBI) model of evidence-based healthcare advocates for the incorporation of a more pluralist evidence base. In Section 1 of their treatise, Pearson et al⁸⁰ argue that an inclusive approach to evidence synthesis should allow for the inclusion of evidence arising from “quantitative research, qualitative research, opinion and discourse, and economic analysis” (p10). Further, Pearson et al acknowledge (p30) that in order for clinical wisdom to be appropriately informed by evidence, the “feasibility, appropriateness and meaningfulness” of practices and interventions must be considered, along with their effectiveness (the “FAME” scale). Feasibility refers to the practicality, or workability of solutions in the “real world” of clinical practice. Appropriateness takes into account the context of the evidence base, and for the particular patient or group of patients under consideration. Meaningfulness also provides a contextual nuance, and accounts for cultural and linguistic diversity between and within patient populations. Hence simply relying on effectiveness data to inform a systematic review question may not produce an evidence base which is suitable for all patients or patient groups. Incorporation of disparate, non-traditional evidence often requires searching databases, and via search engines, which are not traditionally considered “academic” (e.g. Google scholar, the OpenSIGLE repository, government reports, newsletters, academic theses etc).

At a minimum, a two-step search process is recommended.⁸¹ Generally, the first phase involves a limited “first pass” review of the literature using identified key words typically in a very large database (such as PubMed). The results of this first phase search will allow for refinement of search terms, identification of synonyms, and general feasibility of the search process. The second phase of the search process involves the identified databases. A third phase may involve hand searching of references of relevant articles (so-called “pearling”), and contacting relevant organisations or experts to seek out additional data. In a review of systematic reviews of laparoscopic and open colorectal surgery, Martel et al⁸² found that selective referencing, incomplete searching and failure to identify relevant trials were

significant problems.

Searches can be limited by specifying the type of article to be included (e.g. restricting the search to include only randomised controlled clinical trials), the ages of the patients to be included, or the dates of publication. The traditional dichotomy in performing the search is a “trade-off” between sensitivity and specificity- that is, ensuring a complete search risks resulting in a large number of irrelevant results, but any curtailment of the search by attempting to reduce irrelevant papers risks missing important data. The ideal search process maximises the “signal” and minimises the “noise”.

Publication bias

Publication bias refers to the likelihood that results of objective clinical trials are less likely to be published if the results are statistically non-significant,⁸³ or if the results do not conform to the perceived interests of sponsors or funders.⁸⁴ Time lag bias is a form of publication bias, and refers to the delay in publication of studies with negative results. English language bias is another form of publication bias, with Egger’s findings⁸⁵ supporting the hypothesis that negative findings may be published in the language of origin, whereas positive findings are more likely to be published in English.

The systematic review presented in the following pages is unique in that it does not attempt to compare the results from different surgical approaches, nor does it look to compare outcomes from surgery to outcomes from other, non-surgical interventions. Instead, there is an attempt to quantify and integrate the evidence of harm (death at 30 days postoperatively) resulting from a commonly performed surgical intervention (elective colorectal surgical resection, in a sub group of elderly patients, in highly developed nations). Athanasiou and Darzi⁷⁹ state that the “outcomes of a surgical procedure principally depend on the level of experience of a clinician” (p56). This statement conflicts with the opinions of other authors. Almoudaris³⁵ refers to the importance of perioperative care processes impacting postoperative mortality rates in patients having colorectal surgery. Obias³⁴ discusses the important role of the multidisciplinary team in the management of patients with rectal cancer. In a large North American study, Ghaferi⁴⁵ has demonstrated for vascular and general surgery (not including colorectal surgery) that the outcomes of individual patients appear to be related to the ability of the hospital to rescue the patient from postoperative complications (rather than the frequency of complications *per se*). Notwithstanding these disagreements about the relative importance of differences in outcomes due to the skills of clinicians, or the role of teams and of hospitals, Athanasiou and Darzi⁷⁹ (both surgeons) confirm that surgeons or centres with poorer outcomes are less likely to report or publish their results.

Data bias and quality assessment

For many systematic reviews which compare the effects of different treatments, bias relating to the data in included trials can be challenging. However, the systematic review which follows does not compare different forms of treatment; hence common sources of bias (detection bias, performance bias, attrition bias) are not considered relevant or important here. Publication bias has been discussed. Selection bias (as it applies to this systematic review) will be

considered under comments on heterogeneity. The remaining main sources of bias which may be problematic here are forms of reporting bias, including citation bias and duplication bias.⁷⁹ Citation bias refers to selectivity in quoting research in published reports, and can introduce bias into systematic reviews as the final phase of literature searching often includes (as here) a hand search of quoted articles or “pearling” from primary search results. Duplication bias refers to the repeated inclusion of individual trials, if they are reported in disparate journal articles (or other publications). The next chapter will describe how these forms of bias have been addressed in this review.

The quality assessment of included trials is an important feature of a well-conducted systematic review. For quantitative reviews, generally involving randomised controlled trials, such appraisal generally requires an assessment of trial design, particularly assessment of bias attributable to randomisation, sampling and blinding problems. For observational studies, quality assessment focuses on judgements around the validity and reliability of results- for example, whether bias has been minimised in terms of treatment and control groups (for case-control studies), whether the trial population is representative of the population in general, whether confounding factors have been recognised and managed, and whether follow-up is complete and appropriate.

Heterogeneity

Heterogeneity in systematic reviews refers to the diversity of material which comprises the review. Heterogeneity can be clinical and/or statistical. Clinical heterogeneity is always present between trials for any systematic review. This occurs because trial populations are never identical- there will always be clinical differences which may arise for example from different ages of trial populations, differences in the extent of comorbidities, and different models of care. Fletcher⁸⁶ asserts that assessment of clinical heterogeneity must be qualitative- there is no valid or feasible test or method of calculation. Hence combining trials with clinical heterogeneity will be a matter of judgement. However all sources of clinical heterogeneity should be acknowledged. Clinical heterogeneity will be closely addressed in this systematic review. Where possible, mortality rates for heterogeneous clinical sub groups will be reported.

Statistical heterogeneity reflects the degree to which differences between trial results reflect true differences, or may have arisen by chance. The traditional test applied to measure heterogeneity (Cochran’s Q) reflects the degree to which each study’s computed estimate varies from the pooled estimate, and with a weighting reflecting the size of the study.⁸⁷ However the power of Cochran’s test is acknowledged to be poor when the number of studies in a review is small, and conversely the test is excessively powerful when the number of studies is large. Higgins et al⁸⁸ developed a statistical test (I^2) which reflects the degree of consistency between trial results as a percentage (range=0-100). The advantage of Higgins I^2 is that it can be applied across meta-analyses of different sizes, and can be applied to subgroups within one analysis. However Higgins et al stress that quantification of statistical heterogeneity is less important than qualitative assessment of clinical and methodological heterogeneity when considering variability of trial results.

Rigor and Reliability

Although the aim of a systematic review is to identify all evidence relevant to a research question, and by combining studies, strengthen any recommendations arising from primary research, concern about the reliability of recommendations may persist. The best means of managing this concern in the conduct of systematic reviews is to ensure transparency in reporting of search methods and results of appraisal of included (and excluded) articles.

The best way to maximise transparency and avoid bias in a systematic review is to publish a protocol prior to commencement of the review. The protocol should include a clearly defined research question, the search strategy, inclusion criteria, critical appraisal criteria, data extraction and synthesis methodology. Any deviation from the published protocol should be clearly explained in the subsequent published review.

Since 1996, there has been international consensus around the process and reporting of meta-analyses.⁸⁹ The QUOROM statement was updated in 2005 as the PRISMA statement, which consists of a 27 item checklist.⁹⁰ The MOOSE statement was developed in 1997 to assist reporting for observational studies in epidemiology.⁹¹ The PRISMA statement and checklist are thought to be useful not only for assessment of randomized controlled trials, but also for interventional research, and for evaluation of systematic reviews. The PRISMA statement recommends that authors of systematic reviews include a diagram (usually referred to as a "PRISMA" diagram) which clearly describes their search strategy, and numbers of articles identified, screened, retrieved, eligible and included in the final analysis.

Appropriate management of trial results requires transparency of bias assessment and reporting (particularly the criteria and process used in critical appraisal of retrieved articles). Detection of publication bias is best managed graphically via a funnel (bias assessment) plot.⁹² Critical appraisal criteria should be made clear, and a summary of included trials with scoring against criteria should be included as part of the review. Any checklist or tools used as part of critical appraisal should be included in the review.⁸⁰ A minimum of two independent reviewers should perform the critical appraisal process. Double data entry, ideally with two independent reviewers should also be employed.⁸⁰

Heterogeneity should be formally assessed, and, where appropriate, test values reported. If meta-analysis is undertaken, there should be a formal assessment and justification for combining studies. Many authors prefer narrative assessment and summary over meta-analysis, because of the risk of error and inappropriate conclusions if an inappropriate quantitative approach is undertaken.⁹³⁻⁹⁵

The question to be answered in the systematic review which follows is "what is the 30 day all-cause postoperative mortality for elderly patients in highly developed countries undergoing elective colorectal surgery?" The main challenges for this reviewer are around ensuring a complete search, managing clinical heterogeneity and also expressing uncertainty of results. The following chapter will outline the proposed methodology to be used in this review, and how these challenges will be managed.

Chapter 4: Methodology- Controversies and Challenges

In this chapter the potentially challenging or controversial methodological aspects underlying the approach to systematic review and meta-analysis used in this thesis will be outlined. Also described will be some detail as to how these challenges can be overcome, in order to produce information which is of value to healthcare policy makers, funders, clinicians, patients and their carers.

Mortality estimates

The first challenge for the review topic is the precise meaning of mortality. In one sense, mortality is an immutable concept, and one arm of a dichotomous outcome (the patient died, or did not). A positivist view of surgery, and attendant complications might consider the postoperative mortality rate from any procedure as a “fixed effect”, with the patient’s own risk factors as the main determinants influencing their likelihood of death.

Alternatively, the mortality rate from a particular procedure reflects a vast number of underlying assumptions and behaviours, and can be interpreted as reflecting a “random effect”. Under this framework, the perceived mortality rate from a certain procedure will in itself influence the uptake of the procedure. As standards improve, and surgery is perceived as safer, surgical options are offered to patients who historically would have been considered “too risky” (often older, or less “fit” patients, i.e. patients with greater levels of comorbidity). This phenomenon has been well described in the non-medical literature as the Peltzman effect.⁹⁶ It is also referred to as “risk compensation”- that is, humans have a subconscious level of risk tolerance, and will alter their behaviour so that “risky” activities result in more or less the same rate of bad outcomes, despite the regulatory framework intended to improve outcomes. The inverse is the “reverse Peltzman effect”- i.e. perceived high risk surgery will be less likely to be offered to (or accepted by) older or more risky patients with higher levels of comorbidities. Peltzman’s original description involved road safety and regulation- as the perceived risk of an activity (e.g. driving on a highway) is reduced (by regulations covering motor vehicle safety standards, and by making the highway safer), driver risk-taking behaviour increases, leading to an overall risk homeostasis,⁹⁷ or relatively constant highway mortality rate.

Thus, the perceived postoperative mortality rate will influence the uptake of surgery by patients generally, and also by older patients in particular (as it is well known that postoperative mortality increases with age). The postoperative mortality rate, rather than being a fixed or random effect of a procedure, may simply represent the mortality rate which the community acknowledges or tolerates for a given procedure.

Mortality rates are also affected by other “externalities”. In particular, the effect of collecting and publically reporting surgical outcome data has been shown to influence mortality.⁹⁸ Otherwise known as the “Hawthorne effect”, this phenomenon has been attributed to behaviour changes enacted by individuals who are aware that they are being observed. It has been documented for hand hygiene compliance⁹⁹, antibiotic prescribing¹⁰⁰ and elective cardiac surgery.¹⁰¹

Search process

Another challenge in the review which follows is to define the extent of the search. Ideally, a limited search will result in a small number of relevant articles. The wider the search, the greater the likely number of irrelevant articles. It is likely that much outcome data for older patients may be included in outcome studies for patients of all ages, hence it will not be appropriate to limit the search by patient age. Similarly, outcomes for patients having elective surgery may be extractable from studies which also include patients having emergency surgery, so it will not be appropriate to limit the search to elective surgery only (even though these are the only results relevant to the search question). Hence it is likely that a wide search will be required, with a large number of potentially relevant articles identified on first pass, which will need to be examined in full.

It is also well recognized that raw mortality data is often not published directly by authors.⁷⁹ If potentially useful data is identified (reported as odds ratios, or likelihood ratios), it may be necessary to contact authors directly. Author contact may also be required if potentially useful results are identified within datasets which include emergency patients, or patients outside the specified age range.

If any pooling of mortality results is to occur, it will be important that the size of included trials and datasets are large enough so that smaller trials do not skew the pooled result. Here, Hanley's "rule of three" is instructive.¹⁰² This rule states that if n = the adverse event occurrence rate (in this case, postoperative mortality rate), then the upper limit of the 95% confidence interval of the probability of an adverse event is $3/n$. For our patient group, it is likely that postoperative mortality may be 2%, therefore a minimum sample size of 150 is required in order to meet Hanley's criteria.

Datasets

Some data may be available from administrative databases. In contrast to clinical databases, administrative databases are often developed without fine granularity of clinical detail which allows for sophisticated risk adjustment.¹⁰³ The most attractive feature of administrative datasets, such as the NSQIP⁴ data, are their large size, with a wealth of contained data. It has been noted that (at least in the USA, and probably in Australia in the future) administrative datasets are increasingly required to contain significant clinical details regarding quality and safety reporting (e.g. appropriate antibiotic administration and thromboprophylaxis), so there is an expectation that the value of clinical and administrative datasets will coalesce. Finlayson and Birkmeyer¹⁰⁴ have emphasised the value of large administrative datasets to represent the "real world", in contrast to smaller series from academic centres which may exhibit selection bias (or potentially for other reasons may not reflect outcomes in other centres). However, these authors emphasise that diagnostic coding is often of poor quality and validity, and therefore administrative datasets may be unable to provide the information on patient comorbidities required for risk adjustment of outcome data.

The above notwithstanding, the systematic review which follows examines a non-ambiguous outcome (30 day postoperative mortality), which is unlikely to be beset by the "pitfalls of

administrative data”.¹⁰⁴

The most obvious issue with a pooled assessment of outcome data are the clinical heterogeneity of the samples, the inability to adjust for comorbidities, and therefore the likelihood of confounders. The justification for pooling data is that the pooled sample will more likely represent the population, and therefore the outcomes are more realistic than outcomes reported from single institutions.

Bayesian and frequentist risk assessment

The systematic review which follows intends to assess the prevalence of 30 day all-cause postoperative mortality after elective colorectal surgery in older patients from highly developed countries. It therefore takes a “frequentist” approach to a population-based measure. Frequentist measures have been criticised as being too simplistic, and not accounting for individual patient differences in risk prediction. Clearly the frequency incidence of a complication (such as postoperative mortality) is not the same as the likelihood that such an outcome will occur for every patient. A Bayesian model allows for modification of frequentist paradigms, and enables the identification of subsets of patients with greater or lesser risks or particular outcomes. In an era of “personalised medicine” Bayesian approaches to postoperative risk prediction have a certain appeal.¹⁰⁵ These models require a modification of a population-level risk assessment (the “prior probability”) using patient-derived data, to produce a final risk prediction measure (the “posterior” probability). However, as Deveraux¹⁰⁶ has noted, in order to calculate a Bayesian risk index, contemporary complication rates for individual surgeries are required, and “it is unknown whether contemporary complication rates at one institution are generalisable to another” (p 631). The example Deveraux uses is the Detsky index to predict postoperative cardiac mortality.¹⁰⁷ It is anticipated that the results of this systematic review, by providing a proxy for population-based outcome measures for one surgery type (elective colorectal surgery, in elderly patients), will enable better use of Bayesian models to predict individual patient risk of postoperative mortality.

In this chapter, the challenges of defining and retrieving data for postoperative mortality have been outlined. The following chapter describes in detail the protocol for the systematic review which follows, and describes the means by which these challenges were managed.

Chapter 5: The Systematic Review Protocol

The protocol for the systematic review which follows was detailed in advance, and published in the Joanna Briggs Library.¹⁰⁸

OBJECTIVE

The objective of this review was to provide an estimate of the prevalence of all-cause 30 day postoperative mortality for older patients in highly developed countries undergoing elective colorectal surgery.

INCLUSION CRITERIA

Types of participants

This review considered studies that included patients aged 65 years and over from highly developed countries, presenting for elective colorectal surgical resection. For the purposes of this review, highly developed countries included only countries with a very high Human Development Index (HDI).¹⁰⁹ The HDI is a composite measure of health, education and income. A country is defined as having a very high HDI if its HDI lies in the top quartile. The United Nations (UN) report (2013) includes 47 nations which have a very high HDI. Taiwan is not recognised by the UN, however its high self-assessed HDI ranks it within the top quartile,¹¹⁰ and therefore results from Taiwan were eligible to be included in the review. Studies including patients from countries without a very high HDI were excluded, on the grounds that these countries are not considered "highly developed".

Types of interventions

Studies including patients having colorectal resection with or without anastomosis (joining of the ends of resected bowel) were included. Studies including patients having exploratory or diverting procedures (for example, patients who at surgery are found to have widespread disease which is unsuitable for operation) were excluded from this review.

Types of outcomes

This review considered studies which included the following outcome measure: rates of 30 day all-cause postoperative mortality (that is, patients dying from any cause within the first 30 days after surgery). Studies which reported rates of 30 day all-cause postoperative mortality together with in-hospital mortality (that is, patients dying within their hospital admission, irrespective of timing in relation to operative surgery) were included in this review.

Types of studies

This review considered experimental, analytical and descriptive epidemiological study designs including randomised controlled trials (RCTs), prospective and retrospective cohort studies, case series and cross sectional studies. As the mortality rate (estimate of risk) could be as low as 2% (1:50 cases), only studies with a minimum sample size of 150 were considered. This sample size requirement accords with Hanley's "rule of three".¹⁰² This rule is helpful when considering the confidence intervals of the probabilities for adverse outcomes, and states that if $n =$ adverse event occurrence rate, the upper limit of the 95% confidence interval of the

probability of an adverse event is $3/n$. Hanley's "rule of three" is therefore applied to determine minimum sample size for included studies, in order to minimize the potential for small samples to skew event rate estimates, should a pooled rate be achievable. The use of this approach, acknowledging Hanley's rule, is consistent with the work of Bainbridge et al¹¹¹ who performed a similar meta-analysis of perioperative and anaesthetic-related mortality.

SEARCH STRATEGY

The search strategy aimed to find both published and unpublished studies performed between 1998 and 2013. A three-step search strategy was used. An initial limited search of PubMed was undertaken, followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all relevant keywords and index terms was then undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles were hand searched for additional studies. Only studies published in English were considered for inclusion in this review, as it was assumed that publications from highly developed nations are almost exclusively published or available in English. Studies published after 1998 were considered for inclusion in this review, in order to provide a mortality estimate which accurately reflects the improvements in surgical care (particularly laparoscopic approaches, and enhanced recovery pathways) which have been introduced in highly developed nations since the 1990s.

Keywords

Initial keywords used were: colorectal surgery, mortality, death, fatal outcome

Databases

The databases searched were: PubMed, Embase, Scopus, Web of Science, CINAHL, The Cochrane Central Register of Controlled Trials and the website of The Cochrane Colorectal Cancer Group.

The search for unpublished studies and grey literature included: Google scholar, The Grey Literature Report (The New York Academy of Medicine) and the World Health Organization.

For the search strategy used in PubMed, see Appendix I.

As the results for the population of interest (older patients presenting for elective surgery) may have been included in larger studies or surveys of pooled emergency and elective patients, and/or studies of adults of all ages, there were no limitations applied to the search with regard to age, or type of surgery (i.e. elective surgery). A search limited to older patients and/or elective surgery could have led to an oversight of relevant and extractable data. Where combined data was presented for both elective and emergency patients, and/or for patients aged under and over the age of 65 years, the corresponding author was contacted to request extraction of the relevant data for the population of interest. If the data could not be separated, the study/report was not included in the review.

ASSESSMENT OF METHODOLOGICAL QUALITY

Articles and reports which met the inclusion criteria were critically appraised by two independent reviewers using the relevant Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument (JBI-MAStARI) tool, which uses domain-based evaluation (see Appendix II). Where necessary, authors were contacted to confirm that patients in the published studies met the inclusion criteria for this review. Any disagreements which arose between the reviewers were resolved with discussion, or with a third reviewer.

DATA COLLECTION

Data was extracted from papers included in the review using a modification of the standardised data extraction tool from JBI-MAStARI (see Appendix III). The data extracted included the number of patients included in the study, the number of patients dying within 30 days of elective colorectal surgery, specific details of the study type, the dates covered by the interventions, the setting and model of care, the indication for, as well as the precise intervention(s), the population age range, gender and level of comorbidity, experience of surgeons involved, and whether the study or report included any qualitative assessment of the safety or acceptability of the surgical outcome.

DATA SYNTHESIS

Outcomes for the population of interest were identified, and outcome rates over time were analysed. A meta-analysis of proportions was undertaken for the reported mortality rate for all included studies. Pooled mortality rates were calculated using the StatsDirect software (as described below). Sub-group analysis was undertaken for mortality rates for age groups from 70 years and over, from 75 years and over, and from 79 years and over. Outcome data was reported separately for countries and regions. Outcome data was analysed according to the population studied (academic and non-academic centres, and also for whole systems of care). Outcomes were reported separately for laparoscopic colorectal surgery and open surgery, for cancer surgery and non-cancer surgery, for colonic surgery and rectal surgery, for surgery where specialist colorectal surgeons were involved and those where non-specialist colorectal surgeons were involved, and for “fast track” or enhanced recovery models of care and conventional postoperative care. Any qualitative assessment of the safety or acceptability of surgical outcome was reported.

As the review question did not conform to the standard intervention/control paradigm, the JBI MAStARI software was not suitable for use. Statistical analysis was performed with StatsDirect statistical software <http://www.statsdirect.com/> (England StatsDirect Ltd. 2013). Heterogeneity was assessed using I^2 , which reflects the variability between studies which cannot be attributed to chance alone.¹¹² Values of I^2 greater than 50% were attributed to significant heterogeneity between studies.⁸⁸ As data was collected over a number of years in most cases, the date assigned to the results from each study was the median year of collection. Cochran Q was also calculated as an assessment of heterogeneity. A meta-analysis of proportions was undertaken, using a fixed effects model, in order to reduce the likelihood of giving undue weight to smaller studies.¹¹³ StatsDirect transforms proportions

using the Freeman-Tukey double arcsine method, and then performs an inverse variance weighted effects meta-analysis via the der Simonian and Laird method. Where pooling of data was not possible, findings were presented in narrative form, and, where appropriate, figures were used to assist in data presentation.

Chapter 6: Search Results

This chapter describes the results of the search outlined in the systematic review protocol described in the previous chapter. The number of studies discovered, retrieved and analysed will be presented. In Chapter 7, the specific results of the included studies will be presented.

The result of the search process is summarized in Figure 1. A total of 12,581 studies were identified by the search strategy, and were screened to match the inclusion criteria according to title and abstract. Eighty-five duplicates were deleted. Twelve thousand one hundred and fifty-nine studies were discarded as not meeting inclusion criteria. Three hundred and thirty seven articles were retrieved in full text and examined in detail. Seventeen studies met the inclusion criteria with extractable data identified. A further 143 studies were identified which potentially met the inclusion criteria, and the corresponding authors were contacted in order to request further data. Eight authors subsequently provided data from their published work (included in nine articles), which was confirmed to have satisfied the original inclusion criteria. Reasons for exclusion of retrieved articles are outlined in Figure 2.

Figure 1 PRISMA diagram

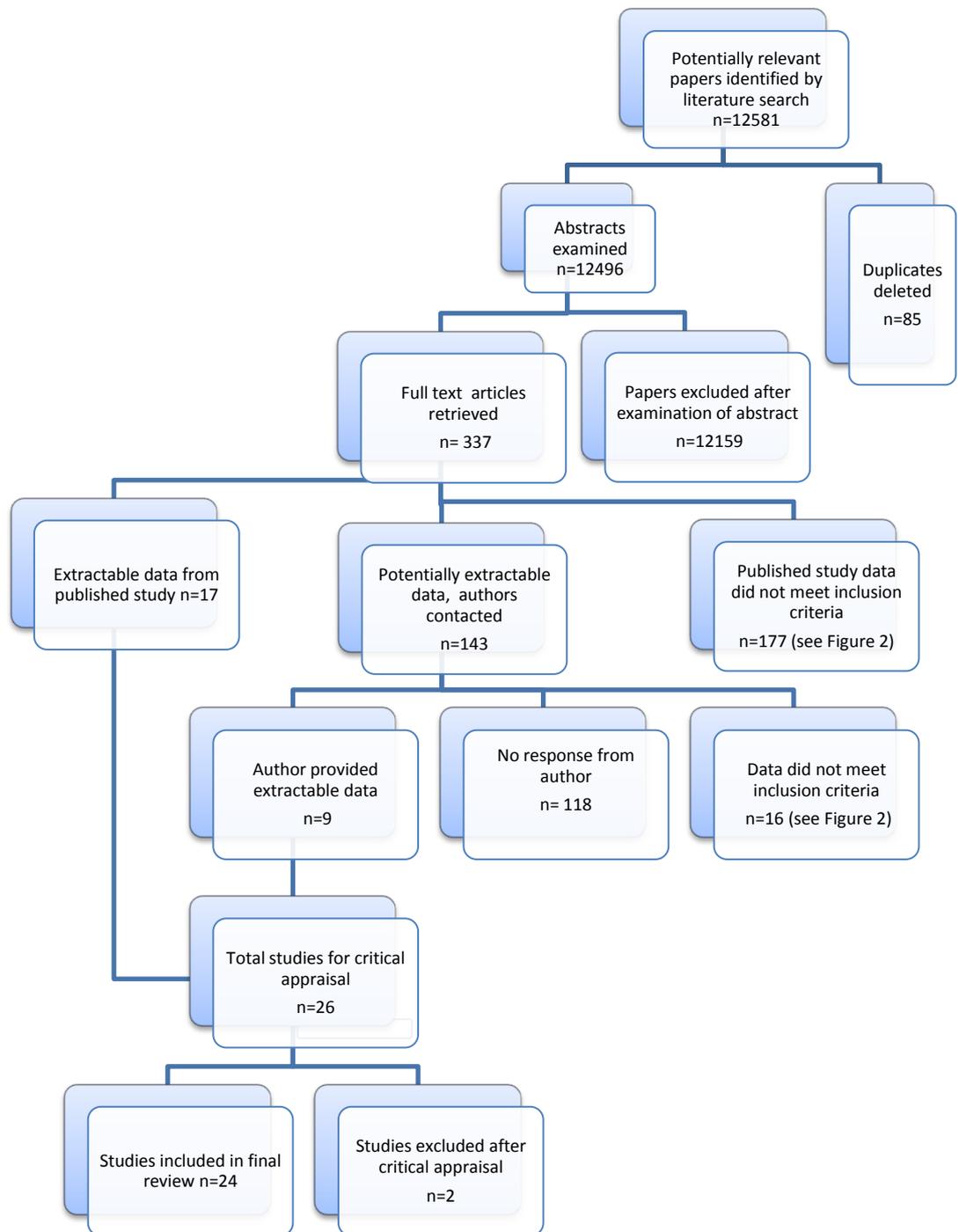
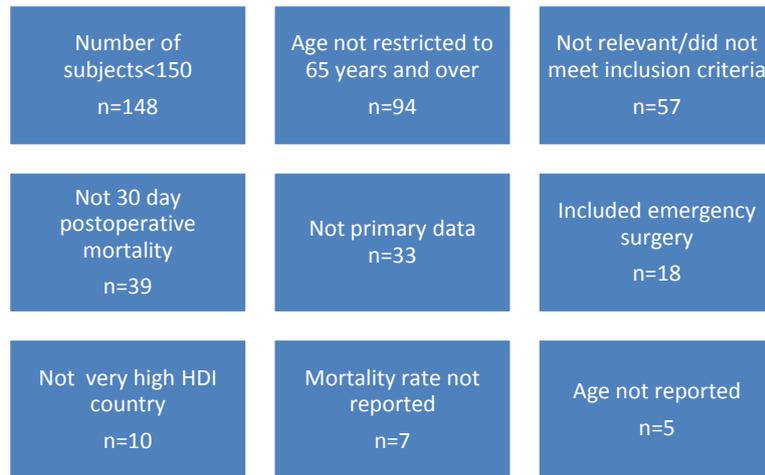


Figure 2 Reasons for exclusion of retrieved articles (n=177†)



†Some articles were excluded on the basis of more than one criterion. Articles which were not relevant, or did not meet inclusion criteria, included studies considering the effect of bowel preparation or of different surgical techniques.

Methodological quality

Instruments used for critical appraisal are found at Appendix II. Twenty six studies were assessed by the two reviewers for methodological quality. These studies are listed in Appendix IV. There were no disagreements between the two reviewers regarding the results of the critical appraisal of methodological quality. Results of critical appraisal are listed in Table 1. Twenty four studies were included after assessment. Details of included studies are presented in Appendix V, and details of the studies excluded after methodological appraisal are presented in Appendix VI, together with the reasons for exclusion. The excluded studies were Law¹¹⁴ (data from these patients appeared in another study by the same author-included in this review) and Kristjansson¹¹⁵ (an observational study with a large number of excluded, yet apparently eligible patients, hence the possibility of selection bias). The one RCT included¹¹⁶ was assessed as being of high quality, although as the mortality results for each arm were aggregated for the purpose of this systematic review, many of the assessment domains were considered irrelevant (e.g. allocation concealment, and blinding to treatment allocation for outcome assessment). The methodology of the remainder of the included studies was assessed as being of high quality, with appropriate patient sampling, clearly defined inclusion criteria, adequate follow-up and transparent and reliable outcome measurement and analysis.

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

Table1: Results of Critical Appraisal

Number of studies included and excluded

Number of studies included	Number of studies excluded
24	2

Randomized Control Trial / Pseudo-randomized Trial

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Frasson M et al, 2008	Y	N	N/A	Y	N/A	N/A	N/A	Y	Y	Y
%	100.00	0.00	N/A	100.00	N/A	N/A	N/A	100.00	100.00	100.00

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

Comparable Cohort / Case Control Studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Keane C et al, 2012	Y	U	U	N/A	Y	Y	N/A	Y	Y
Feroci F et al, 2013	N	N	Y	Y	Y	Y	U	Y	Y
Lian L et al, 2010	Y	Y	Y	U	Y	Y	N/A	Y	Y
Puig-La Calle J et al, 2000	Y	U	N/A	N/A	Y	Y	Y	Y	Y
%	75.00	25.00	66.67	50.00	100.00	100.00	50.00	100.00	100.00

Descriptive / Case Series Studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Cerdaen C et al, 2011	Y	Y	N/A	Y	N/A	Y	Y	Y	Y
Finlayson E et al, 2001	Y	Y	N/A	Y	N/A	Y	Y	Y	Y
Hendry P et al, 2009	N/A	Y	N/A	Y	N/A	Y	N/A	Y	Y
Jullumstro E et al, 2012	Y	Y	N/A	Y	N/A	Y	N/A	Y	Y
Kennedy G et al, 2011	Y	Y	N/A	Y	N/A	Y	N/A	Y	Y
Kolfschoten N et al, 2013	Y	Y	N/A	Y	N/A	Y	N/A	Y	Y
POMRC, 2012	N/A	Y	N/A	Y	N/A	Y	N/A	Y	Y
Faiz O et al, 2011	Y	Y	Y	Y	N/A	Y	N/A	Y	Y
Law W L et al, 2011	U	U	N/A	Y	N/A	Y	U	Y	Y
Kurian A et al, 2010	Y	Y	N/A	Y	Y	Y	N/A	Y	Y
Heriot A et al, 2006	U	Y	U	Y	N/A	Y	N/A	Y	Y
Jullumstro E et al, 2011	Y	Y	N/A	Y	N/A	Y	N/A	Y	Y
Morris E et al, 2011	Y	Y	N/A	Y	Y	Y	N/A	Y	Y
Pinto R et al, 2011	N/A	Y	N/A	Y	Y	Y	Y	Y	Y
Rothwell L et al, 2006	N/A	Y	N/A	Y	Y	Y	Y	Y	Y

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Rumstadt B et al, 2009	U	Y	Y	Y	N/A	Y	N/A	Y	Y
Tan W S et al, 2012	N/A	Y	Y	Y	Y	Y	N/A	Y	Y
Tan E et al, 2007	N/A	Y	N/A	Y	N/A	Y	Y	Y	Y
Wu C et al, 2006	Y	Y	Y	Y	Y	Y	N/A	Y	Y
%	76.92	94.74	80.00	100.00	100.00	100.00	83.33	100.00	100.00

Description of studies

Appendix VII lists included studies, relevant data and conclusions.

Twenty three studies were observational studies,^{12,16,61,62,117-135} and one was a RCT.¹¹⁶ Seventeen studies^{62,117-119,122,123,125,126,128-135} were published in clinical surgical journals, four^{16,61,121,127} in general medical journals, and three^{12,120,124} in other journals or formats (a government report, journals of anaesthesia or medical education).

The timeframe for data collection in all included studies covered the years 1980-2011. Of the 24 included papers, seven were published between 1998 and 2008,^{61,116-121} and the remaining 17^{12,16,62,122-135} were published after 2008. Of those 17 studies published since 2008, 13 were published between 2011 and 2013,^{12,16,62,126-135} and included data from surgery occurring between 1980 and 2011. The number of patients in each study ranged from 150 to 133,148. The total number of patients in all the included studies was 319,741.

Patient populations in the studies were from the USA,^{61,117,120,124,125,130,131} UK,^{16,62,118,121} other Europe,^{116,123,127,129,130,134,135} Australasia,^{12,119,126,132,133} and one multi-centre study¹²² (included UK and other Europe).

Patients

Numbers: The total number of patients in all studies was 319,741. The total number of deaths in all studies was 17,685.

Ages: Of the included studies, ten presented pooled data from patients aged 65 years and over.^{12,16,61,119,120,128-130,132,134} Four studies were restricted to patients aged 70 years and over,^{116,123,133,135} four included data only from patients aged 75 years and over,^{62,117,121,126} and 6 included data only from patients aged 80 years and over.^{118,122,124,125,127,131} Five studies allowed further data extraction for mortality rates for different age sub-groups over 65 years (from 70 years and over, 75 years and over, and 79 years and over).^{12,61,62,123,134}

Gender: Twenty two studies reported male/female ratios for included patients.^{12,16,62,116,117,118-127,129-135}

Comorbidities: Eleven of the included studies referred to specific comorbidities for included patients.^{116-119,122,123,130,131,133-135} Seven studies reported levels of obesity or body mass index.^{116,125,130,131,133-135} Nineteen of the included studies reported a preoperative physical status score.^{12,16,62,116,118-125,128,130-135} The most common descriptor used was the American Society of Anesthetists (ASA) status.¹³⁶ This descriptor reports physical status from Class 1 through to 5, with ASA Class 1 being no systemic disease, and ASA 4 being severe systemic disease which is an "eminent threat to life", and ASA Class 5 being a brain-dead patient for organ donation. Sixteen studies referred to the ASA score of included patients^{12,116,118,119,121-125,128,130-133,135} and four studies^{12,62,120,135} used the Charlson descriptor.¹³⁷ The Charlson descriptor is a validated comorbidity index which is used to risk adjust mortality data in longitudinal studies. Kofschoten¹³⁵ used both ASA and Charlson scores. Hendry¹²² used a postoperative mortality risk prediction score. The score used was the P-POSSUM mortality equation.¹³⁸ In 12 studies, extractable details of patient preoperative physical status were provided.^{62,116,118,121,123-125,128,130,131,133,134} Two studies excluded patients with comorbidities.^{116,134}

Pathology: Fourteen studies included patients with colorectal cancer only.^{16,61,62,117-119,121,126-130,134,135} Of the studies including only patients with cancer, four studies^{61,126,128,130} included patients with colon cancer only, two studies^{117,129} included patients with rectal cancer only, and eight studies^{16,62,118,119,121,127,134,135} included patients with colorectal cancer. Nine studies included patients with benign and malignant colorectal disease.^{12,116,122-125,131,133} In one study, the specific pathologic reasons for surgery were not specified.¹²⁰ For studies which included patients with cancer only, ten of the 14 studies reported tumour stage.^{16,117-119,121,127-129,134,135}

Anatomical site of surgery: Studies and reports contained patients having colonic, rectal and colorectal surgery. Fourteen studies^{12,16,116,118,119,121,122,124,127,131-135} contained patients having colorectal surgery, eight studies^{61,62,120,123,125,126,128,130} contained patients having colonic surgery only, and two studies^{117,129} contained patients having rectal surgery only. The studies of patients having rectal surgery only included patients with cancer.

Demographics: Two studies reported indices of deprivation^{12,16}, and three studies^{12,120,130} included race or ethnicity.

Time to outcome

All studies reported 30 day postoperative mortality. Seven of the included studies assessed combined 30 day and in-hospital postoperative mortality.^{12,61,62,119,128,129,133,135}

Settings

Of the 24 included studies, nine^{12,16,61,62,118,120,121,130,135} included national level data (from USA, UK, England, New Zealand and Netherlands), nine^{116,117,119,122,125,126,131-133} were from academic institutions, one study¹²³ reported data from a mixed group of hospitals, two studies^{124,127} reported data from unspecified institutions, two studies^{128,129} were from regional hospitals, and one study¹³⁴ was from a tertiary non-academic centre.

Interventions and surgeons

Twelve studies^{62,116,123-126,130-135} included patients having either laparoscopic or open surgery, and eight of these studies^{116,124-126,132-135} directly compared outcomes for laparoscopic versus open colorectal resection. All of the studies comparing outcomes of laparoscopic and open surgery had been published after 2008. Of the 13 publications between 2011 and 2013, seven addressed differences in outcomes between patients having open and laparoscopic colorectal surgery.

Other included studies considered the effect of day-of-surgery admission on outcomes,¹¹⁹ the effect of epidural analgesia,¹²⁰ and the effect of enhanced recovery programmes^{122,123,132} on postoperative outcome.

Six of the studies^{116,119,126,129,133,134} reported results of interventions performed by specialist colorectal surgeons (including trainees), three studies^{124,128,132} included combined data from general and colorectal surgeons, and in 15 studies^{12,16,61,62,117,118,120-123,125,127,130,131,135} the surgeons' qualifications were not specified.

Models of care, other treatments

Four studies^{122,123,132,134} included a protocol-driven enhanced recovery or "fast track" postoperative care model, and in a further three studies^{116,129,133} postoperative care was protocol-driven, but the

precise protocol was not described. In 17 studies^{12,16,61,62,117-121,124-128,130,131,135} the model of care was not specified. Two studies reported the preoperative radiotherapy and transfusion rate.^{117,130}

Qualitative assessment of surgical safety

Eleven studies offered a qualitative assessment of the safety of elective colorectal surgery for elderly patients.^{117,122-125,127,128,131,133-135}

In this chapter, the features of included studies have been outlined, including methodological quality, settings and patients, models of care and qualitative assessments of safety. The following chapter presents quantitative and qualitative assessment of results from the included studies.

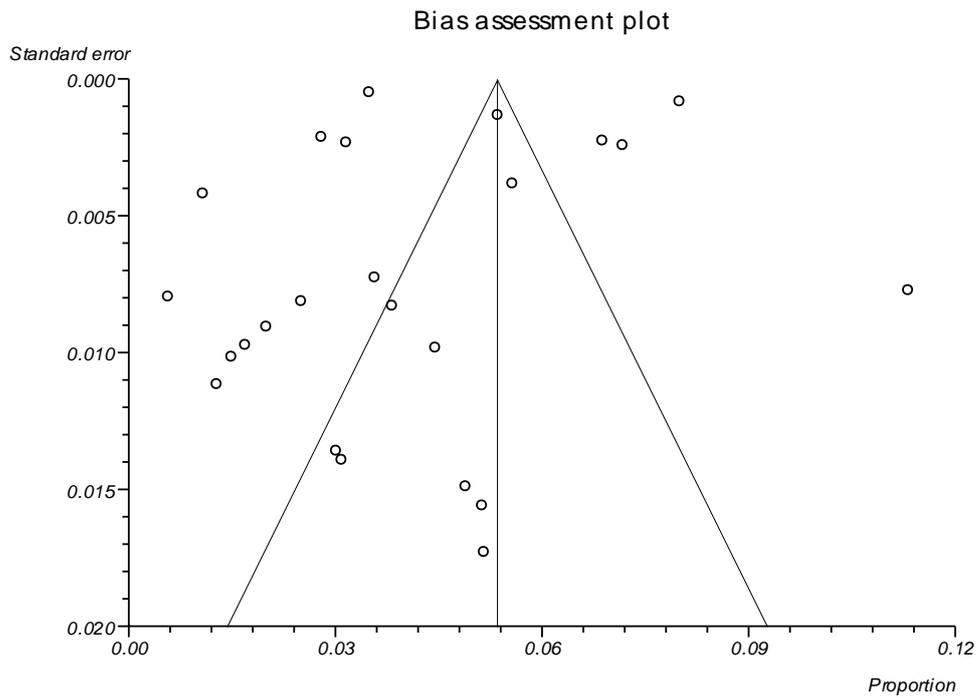
Chapter 7: Review Findings

In this chapter, the findings of the review (as specified in advance in the published protocol)¹⁰⁸ will be detailed. The main outcome of interest is the pooled mortality rate (using appropriate statistical modelling). Other outcomes include any relationship of mortality rate with age, comorbidities, pathology, anatomical site of surgery, geographical location, type of institution, type of surgery, qualifications of surgeon and model of care. If any qualitative assessment of outcomes (“safety”) is made, this will be reported and analysed across studies. Reporting conforms to previously published guidelines.^{90,91}

Assessment of heterogeneity

There was significant statistical heterogeneity detected across studies for 30 day postoperative mortality ($I^2 > 99\%$). Despite the detected heterogeneity, it was felt that a meta-analysis of proportions would provide a clinically relevant estimation of current mortality rates for the surgery and populations under consideration. Given the degree of statistical and clinical heterogeneity, it was determined that other than pooled event rate reporting for the total population, no further statistical analysis was possible. Event rates are reported in narrative form. Significant reporting bias was detected (see Figure 3, Bias Assessment Plot), with a preponderance of reports of lower mortality rates. The assumption that there is an underlying “fixed” mortality rate across all studies appears untenable, however for the following reasoning, the random effects model was considered inappropriate. In order to avoid undue weight from smaller studies (which were disproportionately from academic centres, and which tended to report lower than average, or national, mortality rates), it was determined that a fixed effects model would provide a more realistic pooled mortality rate than a random effects model.¹³⁹

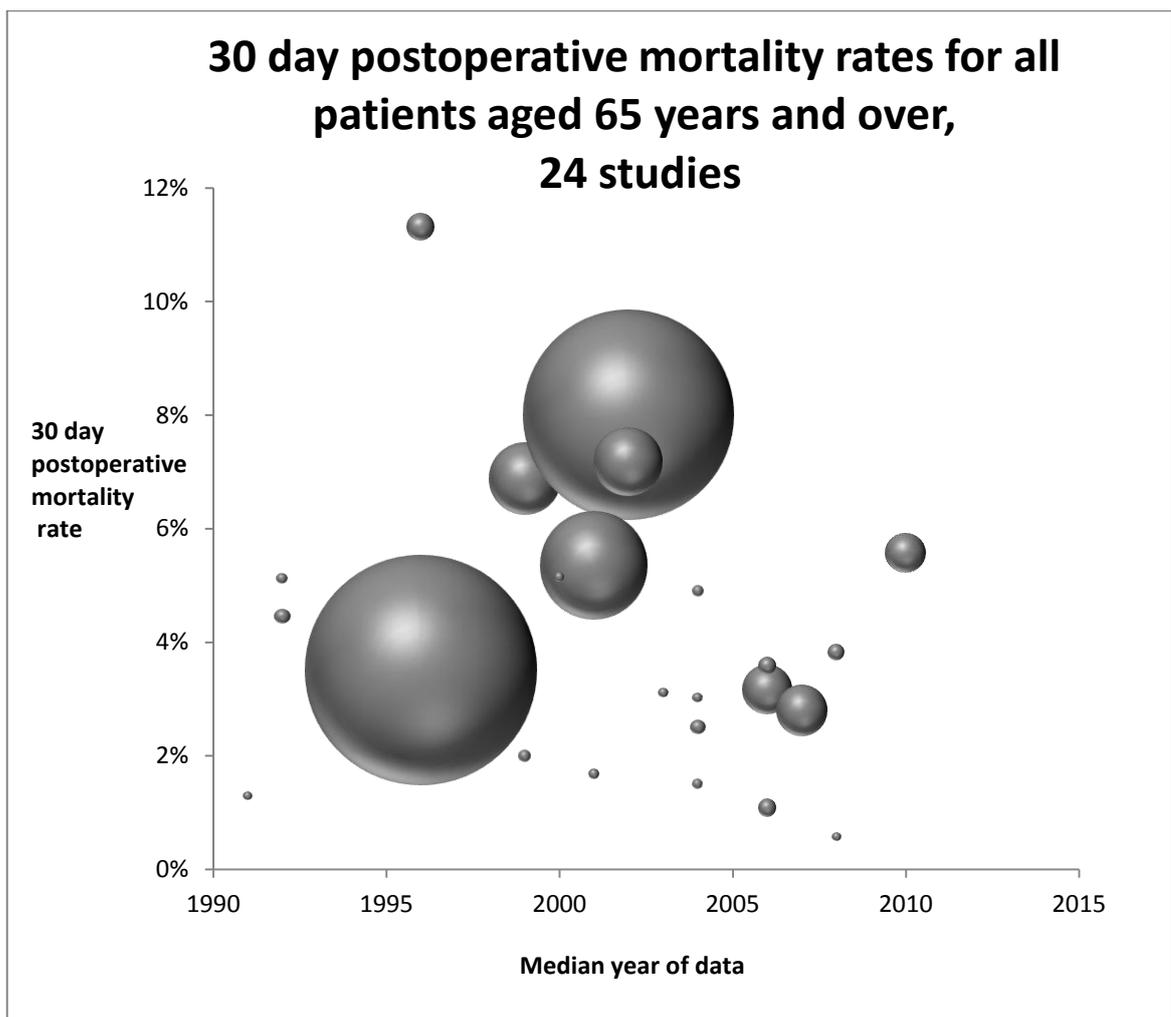
Figure 3 Bias Assessment (Stats Direct)



Mortality rates

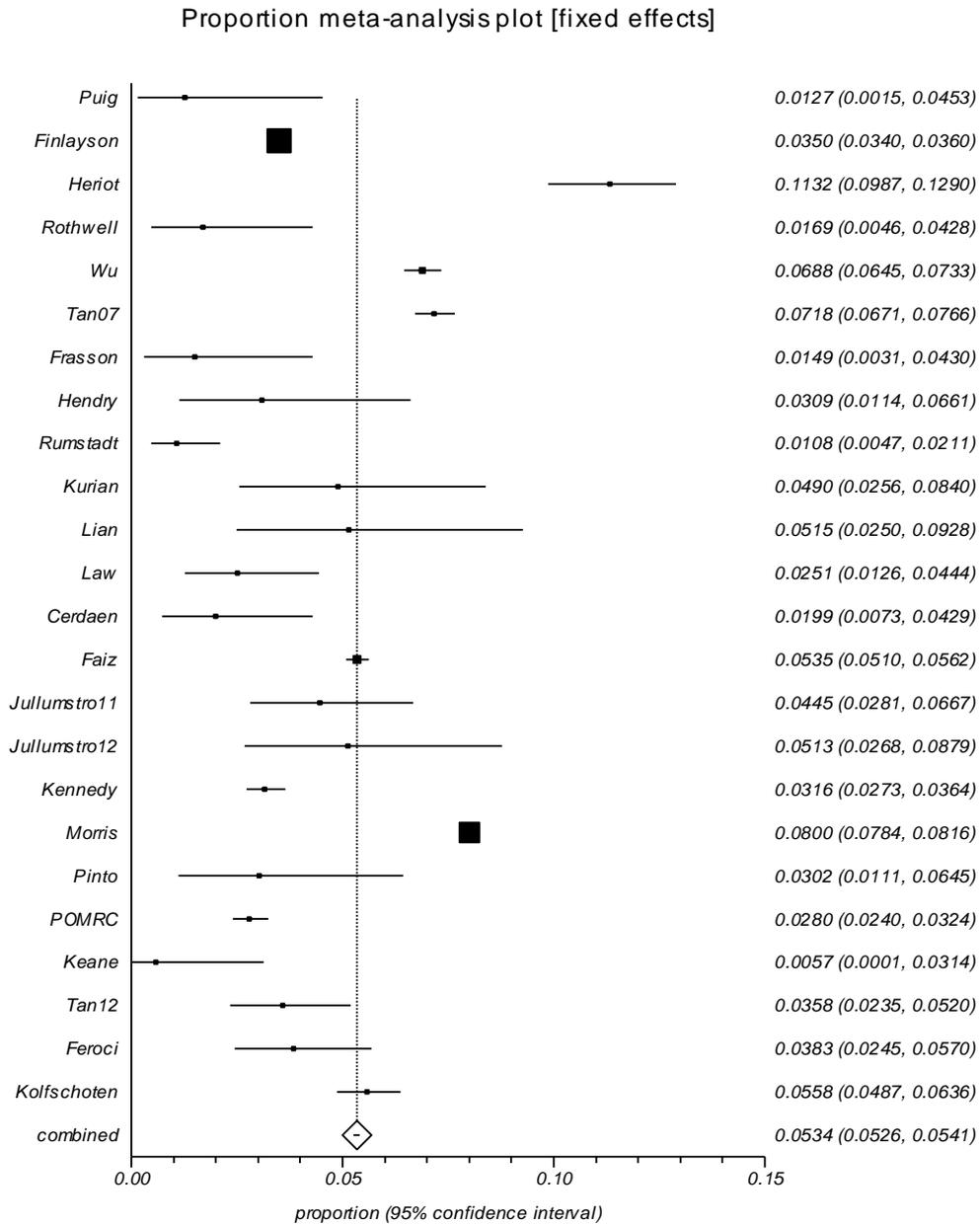
The 30 day postoperative mortality rates for all studies ranged from 0.57 to 11.3% (see Figure 4). The overall pooled mortality rate for all included patients in all studies aged 65 years and over was 5.34% (95% C.I. 5.26-5.41%) (see Figure 5). Mortality rates generally increased with increasing age.

Figure 4



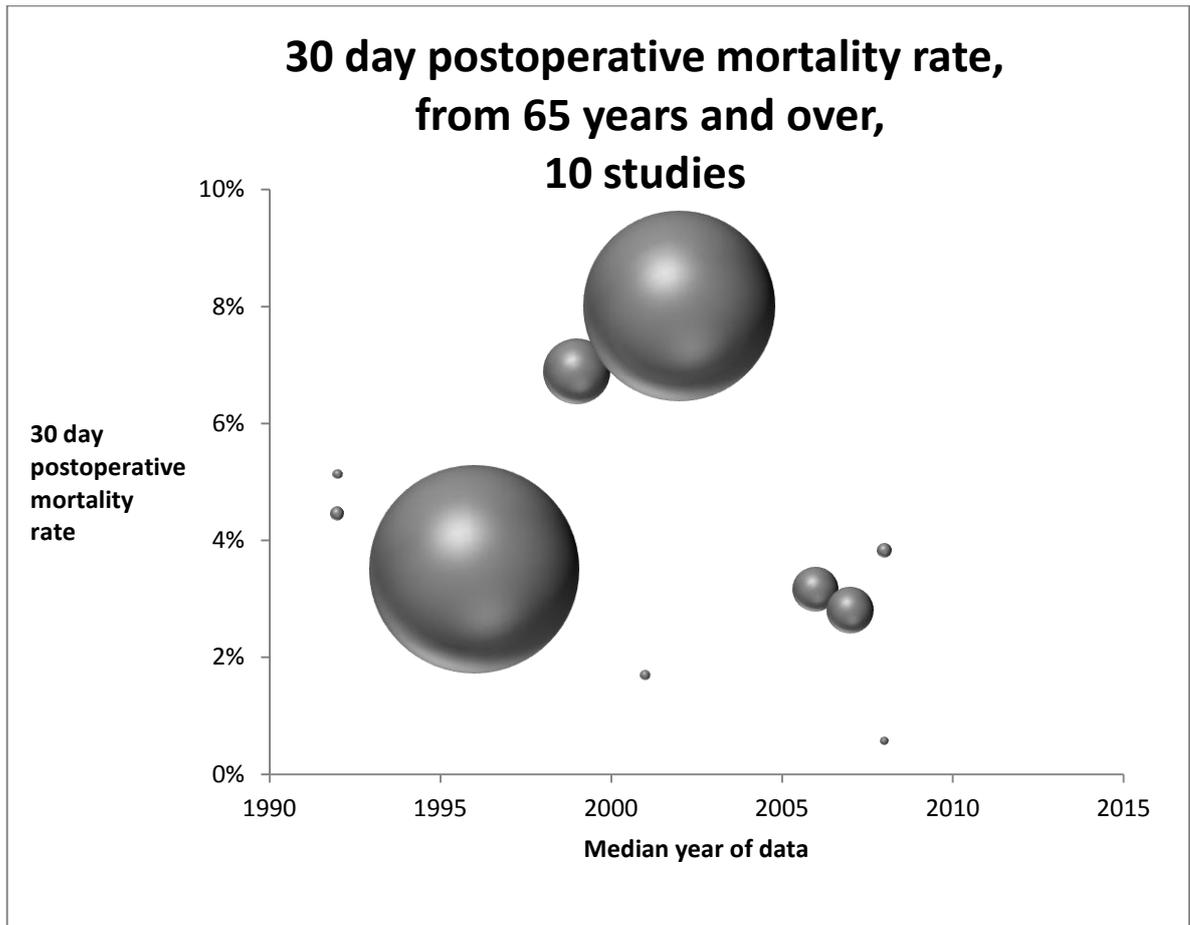
Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Figure 5



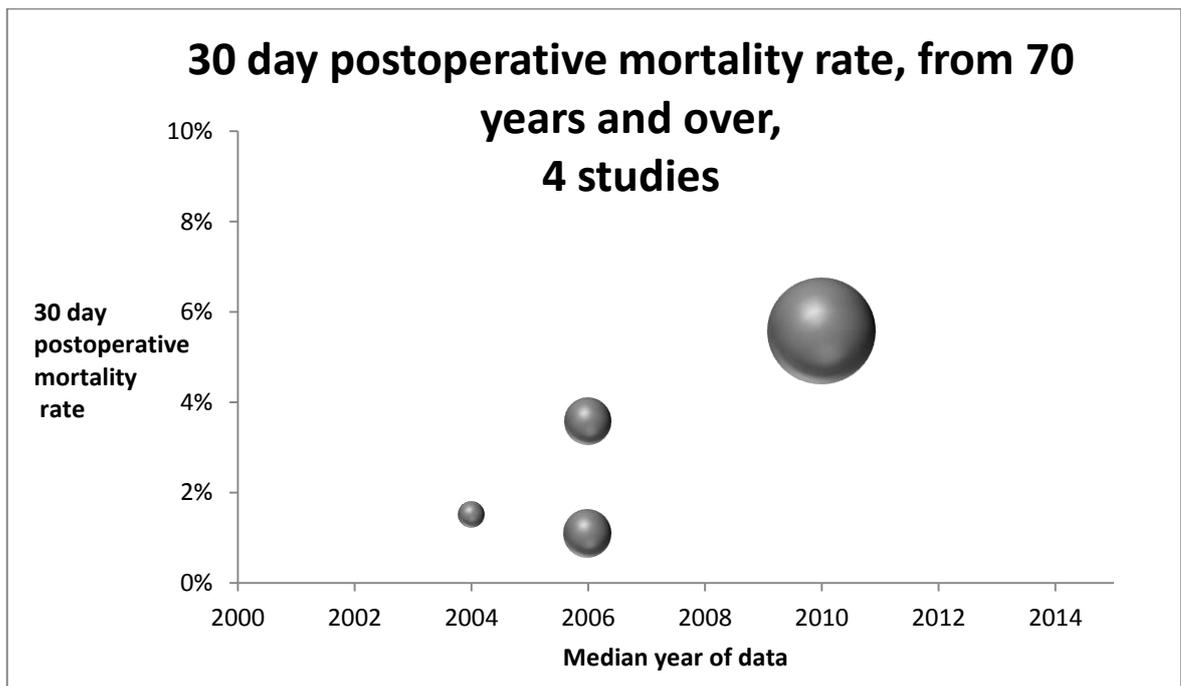
For the ten studies including patients aged from 65 years and over, mortality rates ranged from 0.57 to 8.00% (see Figure 6). For patients aged from 70 years and over, mortality rates ranged from 1.08 to 5.57% (see Figure 7). For patients aged from 75 years and over, mortality rates ranged from 1.3 to 7.18% (see Figure 8). For patients aged from 79 years and over, mortality rates ranged from 1.99 to 11.3% (see Figure 9).

Figure 6



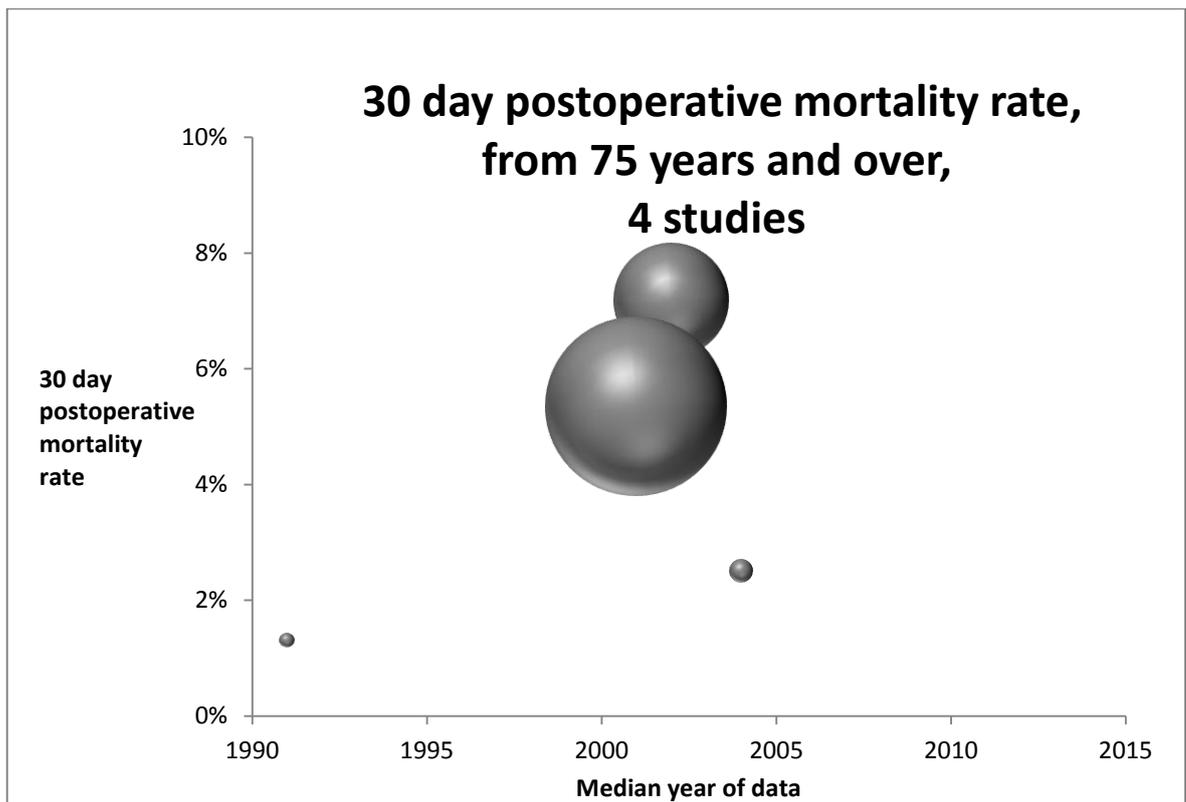
Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Figure 7



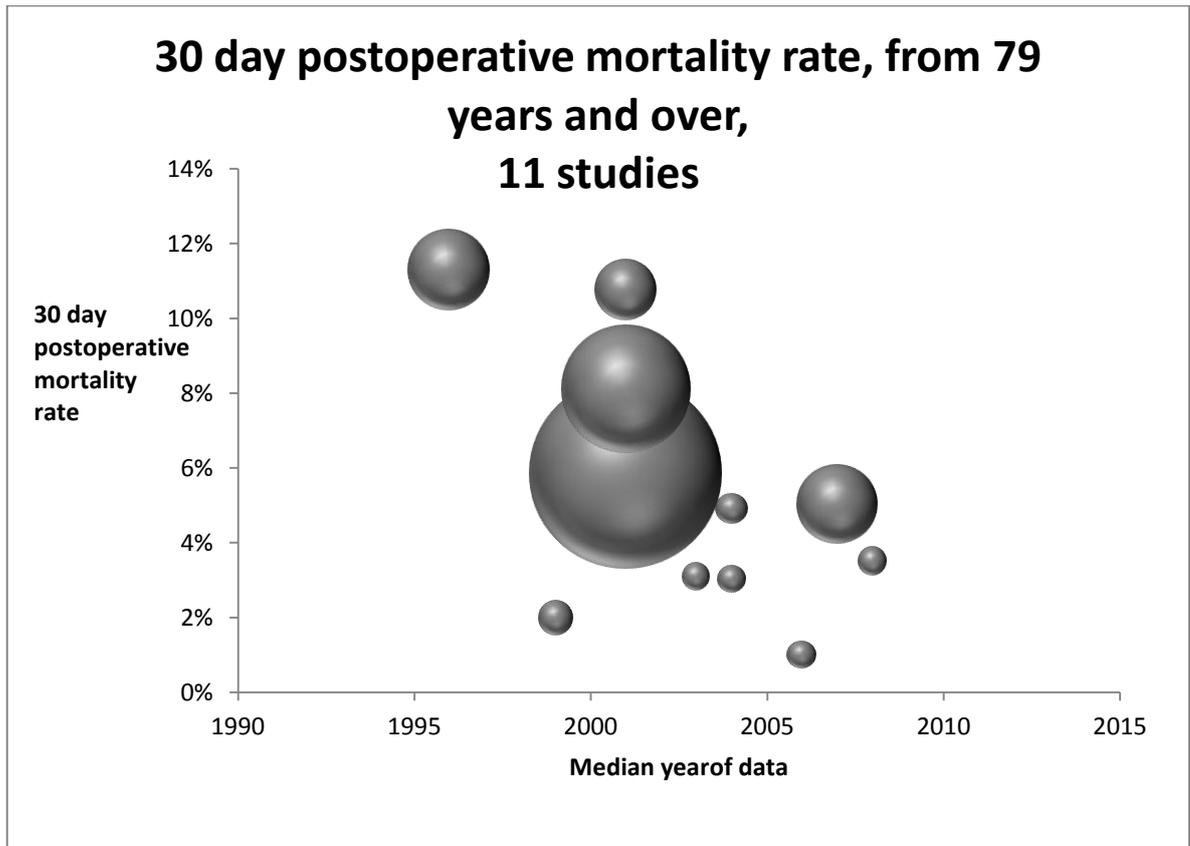
Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Figure 8



Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Figure 9

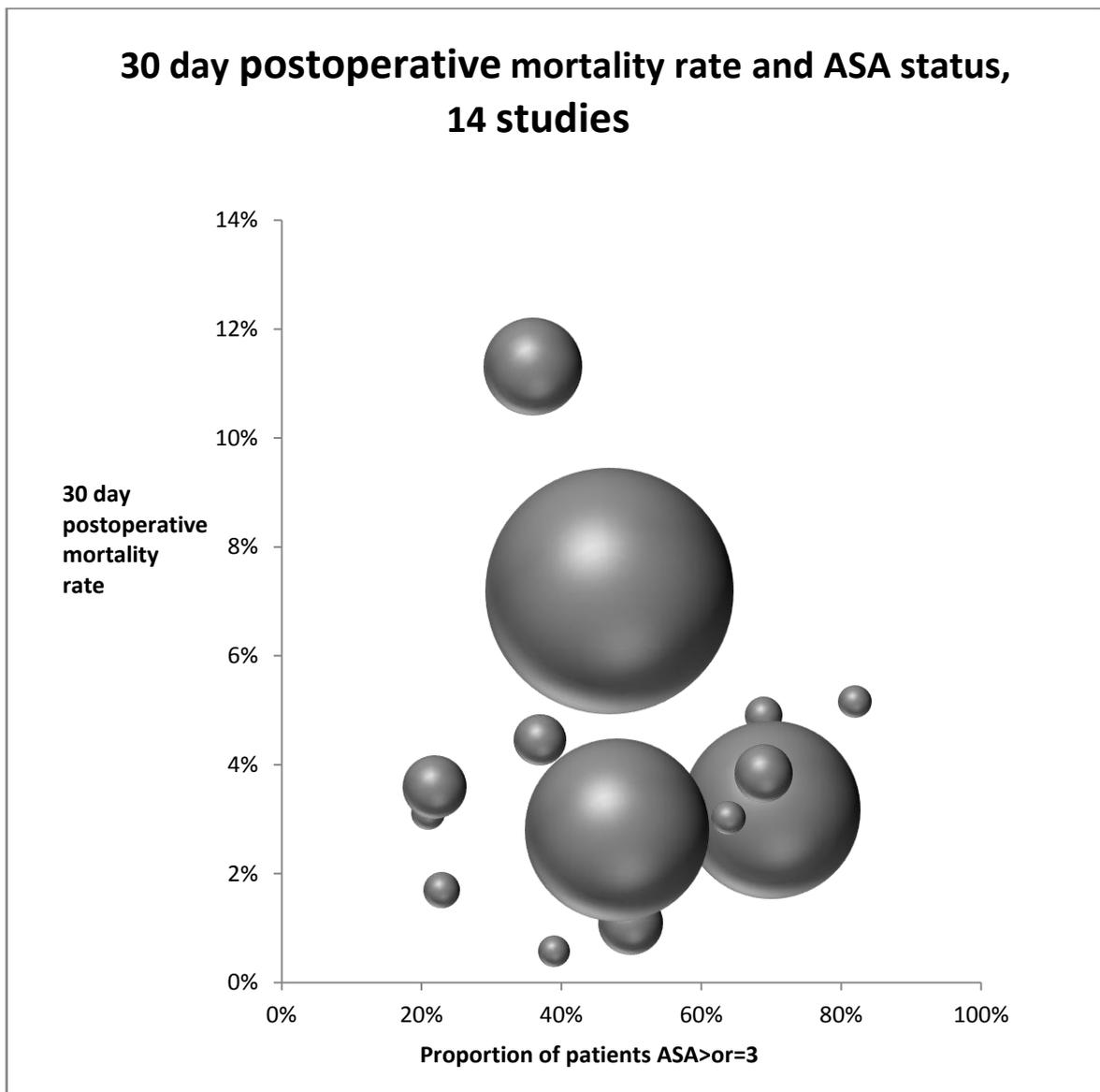


Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Comorbidities

There was no apparent relationship between the proportion of patients with an ASA score of 3 or greater, and mortality. Where the proportion of patients with an ASA score greater than or equal to 3 was recorded, this proportion ranged from 22.3% of patients¹³³ to 82.5% of patients.¹²⁵ Mortality rates and the proportion of patients with ASA score of 3 or greater are shown Figure 10.

Figure 10



Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Pathology

Mortality rates for patients having cancer surgery tended to be higher than mortality rates for patients presenting with mixed indications (including cancer) for surgery. For all patients aged 65 years and over, mortality rates for cancer surgery ranged from 1.69% from an Australian academic centre,¹¹⁹ to 8.00% for England, whole system data.¹⁶ In the age group 65 years and over, for mixed cancer and non-cancer surgery, mortality rates ranged from 0.57% from a New Zealand academic centre¹³² to 6.88% for USA, whole system data.¹²⁰ For other age sub-groups, mortality for cancer surgery ranged from 1.3% for USA, academic centre, patients aged from 75 years with rectal cancer,¹¹⁷ to 11.3% for UK, whole system data for patients with colorectal cancer, aged 80 years and over.¹¹⁸ Where the indication for surgery was mixed cancer and non-cancer, mortality rates ranged from

1.5% for Europe, academic centre, patients aged 70 years and over¹¹⁶ to 5.15% for USA, academic centre, patients aged 80 years and over.¹²⁵

Anatomical site of surgery

There was no obvious correlation between anatomical site of surgery, and mortality rate. Mortality rates for rectal surgery ranged from 1.3% for patients aged 75 years and over, USA, academic centre¹¹⁷ to 5.13% for patients aged 65 years and over, Norway, regional centre.¹²⁹ Mortality rates for patients having colon surgery ranged from 1.08% for patients aged 70 years and over from Europe, academic centre¹²³ to 6.88% for patients aged 65 years and over, whole system data, USA.¹²⁰ Mortality rates for combined colorectal surgery reported for patients aged from 65 years and over ranged from 0.57% for New Zealand, academic centre,¹³² patients with mixed indications for surgery to 8.00% for patients in England having cancer surgery.¹⁶ For other age sub-groups, mortality rates for colorectal surgery ranged from 1.5% for Italy, patients aged 70 years and over¹¹⁶ to 11.3% for UK patients 80 years and over.¹¹⁸

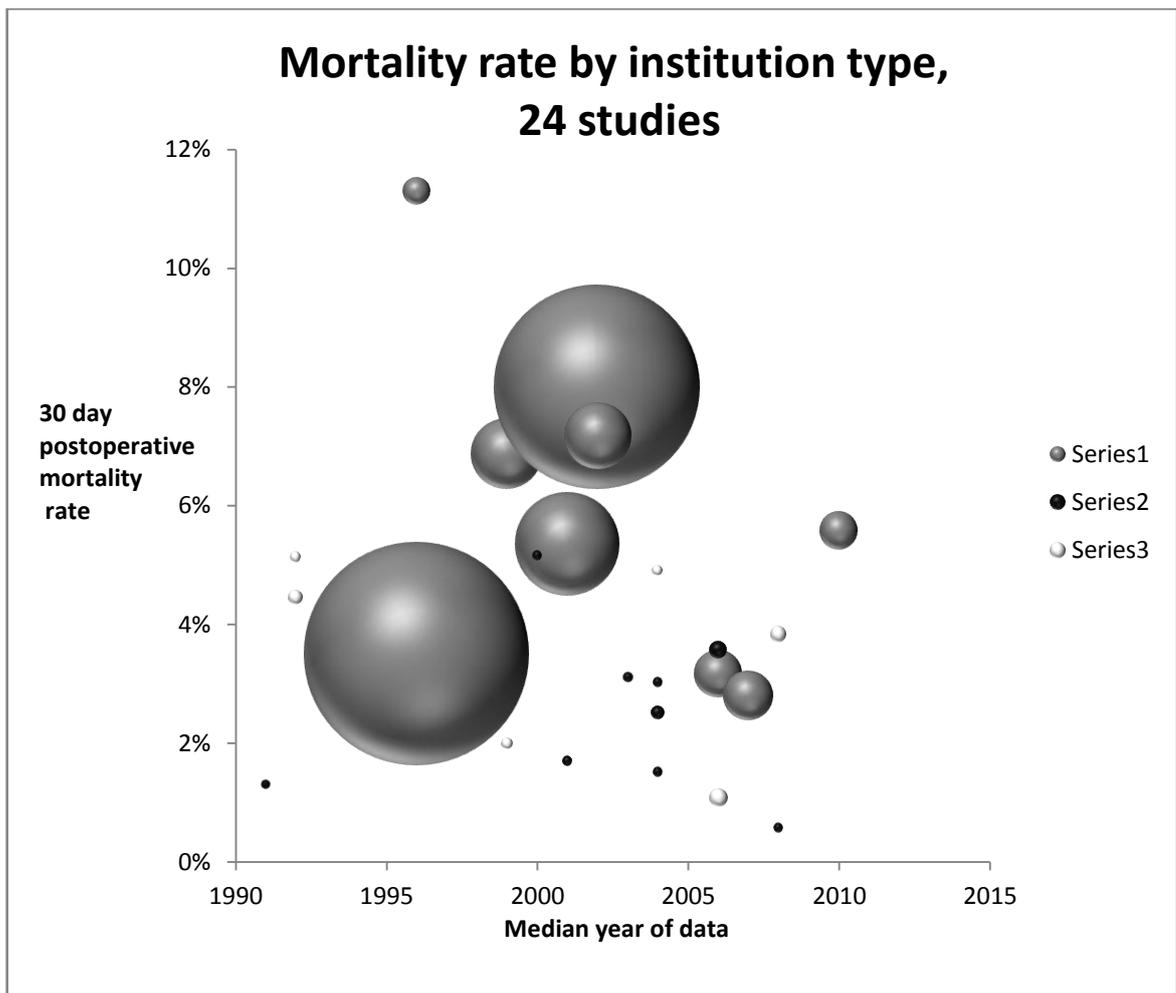
Differences between countries and regions

Mortality rates reported from the UK appeared to be somewhat higher than those reported from the USA, or other parts of Europe, and Australasia. Data from national studies from the UK reported mortality rates ranging from 5.35% for colorectal cancer patients aged 75 years and over,⁶² to 11.3% for colorectal cancer patients aged 80 years and over.¹¹⁸ Data from national studies from the USA reported mortality rates ranging from 3.16% for patients aged 65 years and over with colon cancer,¹³⁰ to 6.88% for patients aged 65 years and over having partial colectomy.¹²⁰ One national study from Europe (other than UK) was identified (from the Netherlands), which reported mortality rates of 5.57% for patients aged 70 years and over presenting for surgery for colorectal cancer.¹³⁵ One national-level study from Australasia was identified, which reported mortality rates of 2.80% for patients in New Zealand aged 65 years and over presenting for colorectal surgery.¹²

Difference between national-level data and results from academic and other institutions

There was a noticeable difference between national-level reported mortality rates, and those reported from academic centres, and from regional and non-academic centres. In general, national-level mortality rates were higher than mortality rates reported from individual centres. For patients aged 65 years and over, national-level data reported mortality rates ranging from 2.8% in New Zealand¹² to 8.0% in the UK.¹⁶ For this same age group of patients, data from academic centres reported mortality rates ranging from 0.57% in New Zealand,¹³² to 1.69% in Australia.¹¹⁹ For patients aged 65 years and over, regional centre and non-academic centre data reported mortality rates ranging from 3.83% (Italy)¹³⁴ to 5.13% (Norway).¹²⁹ Similar variation between national data, academic centres and regional and non-academic centres was seen for mortality rates for other age groups. See Figure 11 for data by national, academic centre and other origin for pooled age groups. For nations where national-level data was reported (UK, USA, Netherlands and New Zealand), only two reports from single centres in the USA reported mortality rates exceeding national mortality rates.^{124,125} However, these two single centre studies included patients only aged from 80 years, whereas the national-level data considered patients from 65 years and over.

Figure 11



Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Series 1 (grey): national-level data

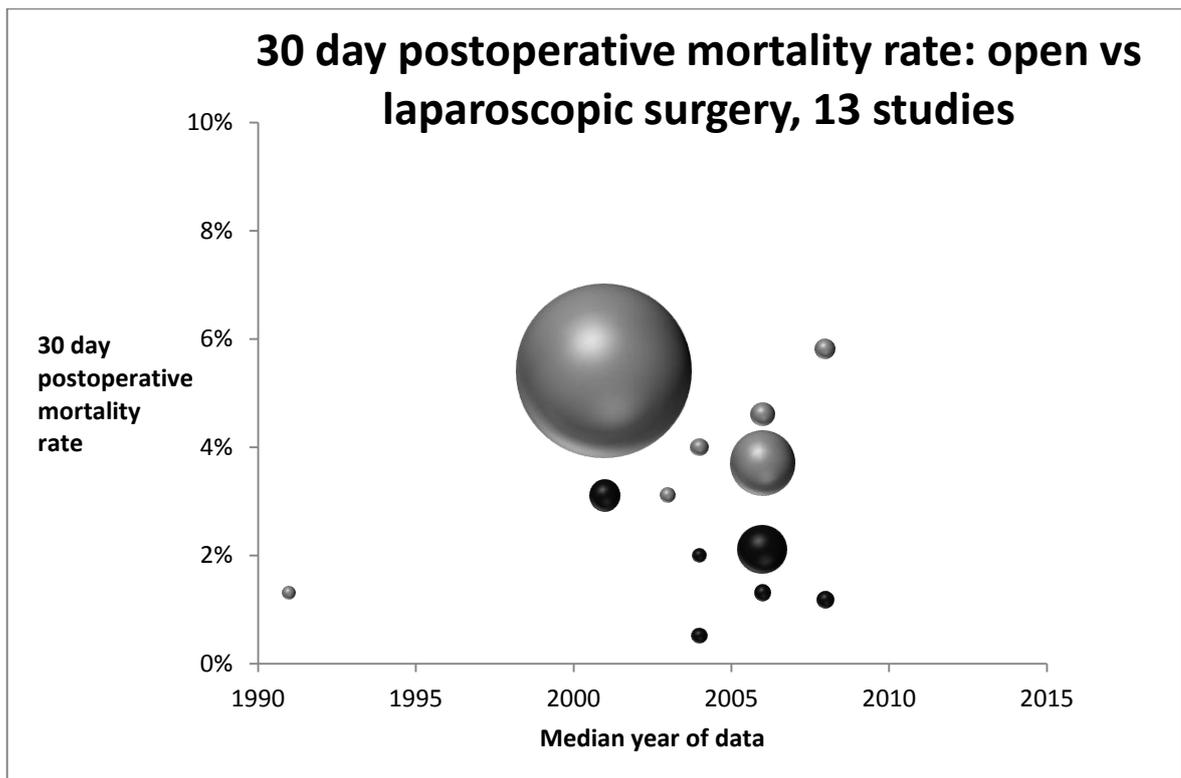
Series 2 (black): data from academic institutions

Series 3 (white): data from regional, non-academic and other centres.

Laparoscopic surgery versus open surgery

Mortality rates were generally higher for open surgery than for laparoscopic surgery. Where data was reported separately for laparoscopic surgery, and where the number of patients in these sub-groups was greater than or equal to 150, the reported mortality rates for laparoscopic surgery ranged from 0.5% for patients aged 75 years and over with colon cancer in Hong Kong,¹²⁶ to 3.1% for patients aged 75 years and over with colorectal cancer in the UK.⁶² For open surgery reported separately, and for sub-groups where the number of patients was greater than or equal to 150, mortality rates ranged from 1.3% for patients with rectal cancer aged 75 years and over in the USA,¹¹⁷ to 5.8% for patients aged 65 years and over with colorectal cancer in Italy.¹³⁴ See Figure 12 for mortality rates for open and laparoscopic surgery.

Figure 12



Please note: each bubble represents a single study; the size of the bubble is proportional to the size of the study.

Open surgery is in grey, laparoscopic surgery in black.

Specialist surgeons versus non-specialist

There was no apparent difference in reported mortality rates for those patients whose surgery was performed by specialist colorectal surgeons, compared with surgery performed by non-specialist colorectal surgeons. Where the grade of surgeon was reported, mortality rates for specialist colorectal surgeons (including trainees) ranged from 1.5% in Italy,¹¹⁶ to 5.13% in Norway.¹²⁹ Where care was reported as provided by a mixture of specialist and non-specialist surgeons, mortality rates ranged from 0.57% in New Zealand¹³² to 4.9% in the USA.¹²⁴

Models of care

The mortality rates in the four studies where a “fast track” or enhanced recovery model of care was described were lower than in other studies where the model of care was not described. Mortality rates for patients receiving “fast track” or enhanced recovery models of care ranged from 0.57% in New Zealand¹³² to 3.83% in Italy.¹³⁴

Qualitative assessment of outcome

In studies where a qualitative outcome assessment was reported, all eleven assessments were positively framed (as “safe”, “favourable”, or described procedures with a “small” mortality). The mortality rates in these eleven studies ranged from 1.08%¹²³ to 5.57%.¹³⁵ In seven studies, results led to assessments that procedures were “safe” or could be “safely performed”. In one study a

postoperative mortality rate of 1.99% was assessed as “small”.¹²⁷ No study referred to “unsafe” or “unfavourable” outcomes.

Summary

Reporting bias and statistical heterogeneity across studies were detected in this review. A pooled mortality rate for all included patients in all studies aged 65 years and over was 5.34% (95% C.I. 5.26-5.41%). The pooled mortality rate was assessed using a fixed effects model. Mortality rates increased with increasing age, and were greater for cancer than for non-cancer surgery, and greater for open than for laparoscopic surgery. Mortality rates were higher for national-level reports, than for reports or studies from individual centres. Mortality rates reported from the UK tended to be higher than mortality rates reported from other countries. The qualitative assessment of surgery as “safe” appeared to be unrelated to the quantitative mortality rate reported. The implications of these findings are discussed in the following chapter, along with some limitations of this study and potential areas for future research.

Chapter 8: Discussion

The results, implications and clinical relevance, challenges and limitations of this review are outlined in this chapter. Areas for future research are suggested.

Although the term “safe” is used frequently in medical and surgical literature, the precise definitions of “safe” and “safety” are not always clear. Other authors have criticized the use of the word “safe” when applied to surgical procedures, and have recommended that the term “safe” be replaced with “precise estimates and confidence intervals of the risk for adverse events” (p1371).¹⁴⁰ The results of this review confirm a wide range of mortality rates which appear to fall within authors’ assessment of what is “safe”. None of the articles included in this systematic review which used qualitative assessments such as “safe” or described mortality rates as “low” or “acceptable” appeared to have based these descriptions on patients’ assessments of safety or acceptability. There is little available research to assist in understanding patients’ assessments of “safety”, particularly as applied to elective surgery. The implications of these observations, derived from outcome studies performed in highly developed countries, are equally applicable to patients in less highly developed countries, as surgical activity becomes more widespread and accessible.⁷⁴

While there have been other systematic reviews which attempt to define mortality after elective colorectal surgery in elderly patients,^{42,141} this review appears to be the first to present pooled data for 30 day all-cause postoperative mortality rates for elderly patients presenting for elective colorectal surgery in highly developed countries. Other systematic review authors have aggregated data in a similar way from individual studies investigating perioperative and anaesthetic-related mortality,¹¹¹ and for postoperative mortality after joint replacement surgery.¹⁴² Therefore, despite the considerable statistical and clinical heterogeneity of study data, we believe the meta-analysis of crude mortality data to provide an overall mortality estimate is justified. Indeed, given the discrepancy between reported mortality rates from individual centres (especially academic centres) and whole systems of care, our pooled result may have more relevance for many institutions than any result from a smaller centre.

Pearse²² has suggested a predicted postoperative mortality risk of greater than 5% meets the criterion for high risk surgery. Other authors¹⁴⁴ have validated this estimate. In the UK, it has been recommended that shared decision-making for surgery should be based on explicit mortality risk prediction, and also that predicted postoperative mortality risk should inform the need for high dependency postoperative care.⁶⁴ The pooled mortality risk for elderly patients undergoing elective colorectal surgery informed by our systematic review was 5.34%(95% C.I. 5.26-5.41%) . This result reflects that, at a population level, these patients meet accepted definitions of “high risk” surgery. It is unclear whether the mortality rates demonstrated in this review are widely appreciated by clinicians, are part of informed consent conversations, or are driving optimal resource allocation for hospital-based postoperative care of these patients. The discrepancy between postoperative resources available for patients presenting for perceived high risk surgery (such as cardiac surgery), and those presenting for colorectal surgery has been discussed elsewhere.²²

For patients aged 65 years and over from highly developed countries undergoing elective colorectal surgery, this review demonstrated that mortality rates increased with age, were higher for cancer surgery than for patients with mixed (cancer and non-cancer) indications for surgery, were higher for open than for laparoscopic surgery, and were higher for traditional models of care than for fast-track

models of care. Mortality rates reported from the UK were higher than mortality rates reported from the USA, Europe and Australasia. Mortality rates reported were generally higher for whole system datasets, than for reports or studies from single institutions. There did not appear to be any relationship between mortality rate and physical status of patients, anatomical site of surgery and grade of surgeon. The lack of apparent relationship between mortality rate and specialist surgeon involvement in care demonstrated in this review is inconsistent with other reports.^{49,65} The inclusion of trainees within the specialist cohort may have influenced our results.

The results of this review demonstrated no clear trend in mortality rates published between 1998 and 2013. Given the increase in laparoscopic surgery, enhanced recovery and multidisciplinary models of care in recent years, this is perhaps surprising. It is of note that in our review, the time lag between interventions and published outcomes appears to be narrowing, likely as the result of increasing ease of data availability, collection and analysis.

The most notable result of the analysis of results in this review was the wide variation in mortality rates between those derived from national, system-wide reports, and those from single institutions (especially academic institutions). This discrepancy between mortality rates drawn from national-level data and those reported by academic institutions has been previously noted in the USA by other authors.⁶¹ In the UK, Faiz reported that between individual hospital groups (trusts), adjusted mortality rates after elective colorectal surgery in elderly patients was from between 0 and 14.5%.⁶² The obvious gap in the worldwide literature is reports from institutions whose mortality rates lie above national averages. Our bias assessment plot (chapter 7, figure 4) demonstrates this in graphical form.

The results of this review have confirmed the challenges to obtaining valid and relevant outcome data for a group of patients presenting for commonly performed elective surgery in highly developed countries. Challenges to identifying the outcome data for this review included the variability of the definition of "elderly" - studies included in this systematic review considered data from patients aged from 65, 70, 75, 79 or 80 years. On initial searching, there was also variability in the time to postoperative follow-up (e.g. 30 day, 60 day, 90 day and in-hospital mortality) which limited the number of otherwise useful studies which may have further informed the results of this review. There was significant clinical heterogeneity with regard to pathologic indication for surgery, anatomical site of surgery, specialization of clinicians involved in care, size and nature of hospital and model of care. While this heterogeneity limited the generalisability of our results, it also strengthened the conclusion that local (or hospital-based) mortality rates cannot be inferred from other individual centre reports.

Another challenge in performing this review was locating the relevant data. Mortality rates were often not reported directly, but reported as odds ratios or relative risk (compared with a reference group, for which absolute mortality rates may also not be reported). Precise outcome numbers needed to be supplied directly by authors for nine of the twenty four included studies. There were other studies identified on searching which were based on collected outcome data, but on attempts to contact authors, no response with data was forthcoming for this review. The reasons for non-response by authors are unclear. It may be that these studies had higher than average mortality rates (or perceived higher mortality rates), and that authors were therefore unwilling to share results which potentially reflected unfavourably on their performance.

Even when outcome data is reported, there was considerable variability in the type of journal used to

disseminate results, and therefore the particular clinical audience likely to read and develop awareness of these results. Of the five largest studies reported,^{16,61,62,120,121} three were published in general medical journals, one in an anaesthesia journal, and only one (Faiz) in a traditional surgical journal. Thus, even specialised colorectal surgeons may not be fully informed of the range of outcome data for elderly patients having elective colorectal surgery. In the absence of locally collected outcome data, clinicians, patients and their carers are unlikely to have easy and timely access to the important information they need when providing informed consent for elective colorectal surgery. Similarly, referring and perioperative clinicians may also not have the outcome data which is required for optimal planning for the surgical journey. Clinicians and patients in institutions outside academic centres may be misled by mortality rates reported in case series and operative trials from academic centres, and also potentially from national-level data, if their own institutional mortality lies above the average.

Individual patient decision-making for elective surgery, particularly for elderly patients with the likelihood of multiple comorbidities, is fraught with uncertainty. In the future, it is likely that a Bayesian approach to postoperative risk estimation will be undertaken, with institutional outcome data (pre-test probability) modified by patient-specific risk factors (likelihood ratio), in order to estimate the patient's postoperative mortality risk (post-test probability).¹⁰⁶ Some researchers have already moved in this direction for cancer care, acknowledging the "accelerating trend towards personalised medicine".¹⁴³ For surgical care, Cohen⁶⁶ refers to the effect of hospital outcomes on patient risk. However, rather than promoting the integration of data, Cohen argues that hospital and patient-level data should be presented separately, partly on the basis that hospital-level effect "might not be large". On the contrary, our review suggests that hospital-level effects on outcome for elective colorectal surgery in elderly patients may be very large indeed. This finding is consistent with reports of other authors from the USA.⁴⁵ Postoperative mortality rates for elective colorectal surgery in elderly patients based on those usually quoted in the surgical literature are rarely applicable outside academic centres. Separate presentation of hospital-specific risk, and patient-level risk (as recommended by Cohen) is likely to be confusing for patients. It is difficult to understand how such an approach can increase the patient-centeredness, and hence quality of healthcare. Local institutional mortality rates will be essential to assure the validity of Bayesian risk scores. Individualized risk scores will be useful to underpin truly informed consent, as well as inform decisions such as the need for postoperative high dependency or intensive care.

Some potential limitations in the review process included restriction of studies to those published in English. Since the review considered patients having surgery in only highly developed nations, we did not consider that this restriction was likely to significantly impact results. The inclusion of some studies which considered both in-hospital and 30 day postoperative mortality could have impacted the pooled mortality estimate. However Damhuis et al³⁶ have demonstrated that fatal events after surgery tend to occur within the first month, and, for colonic cancer surgery, showed a small disparity between in-hospital and 30 day postoperative mortality. There is always the possibility of dataset unreliability, however the results from larger series presented here were derived from previously validated datasets, and we believe ascertainment error for 30 day mortality is unlikely in any case given the short time frame required for patient follow-up. Despite our best efforts, the theoretical possibility of some double counting exists, including for Finlayson⁶¹ and Wu¹²⁰ (two year overlap in data collection), for Tan,¹²¹ Faiz⁶² and Morris¹⁶ (the five year collection time for Tan data is included

in Faiz and Morris datasets), and Keane¹³² and POMRC¹² (Keane numbers are likely included in the POMRC dataset). However, apart from the UK data,^{16, 62, 121} most of these numbers are small, and are unlikely to have influenced overall results significantly. Finally, failure of authors to respond to our requests for data may have altered our pooled mortality estimates. We have proposed that it is likely that data from non-responders was at the higher range, and therefore lack of such results may have led us to under-estimate mortality rates.

With an increasing focus on shared decision-making, and the desirability of incorporating outcomes which are important to patients into the decision-making process, there is a clear need for better information. We have demonstrated the difficulties in discovering valid 30 day postoperative mortality data for elderly patients undergoing elective colorectal surgery. Other outcome data is also needed. Mamidamma¹⁴³ has suggested that 30 day postoperative mortality may be an inappropriate measure for elderly patients, as significant numbers of elderly patients continue to die in the postoperative period up to twelve months after surgery. Kobayashi¹⁴⁴ has suggested that 90 day postoperative mortality should be a “need to know” component of the informed consent process for patients facing right hemicolectomy. Others have suggested other outcomes are important after colorectal surgery, such as the risk of anastomotic leakage,¹⁴⁵ and, for elderly patients, quality of life considerations such as continence and avoidance of a permanent stoma.¹⁴⁶ However some of these outcomes have a technical focus which may or may not be important to patients. There is increasing recognition that patient-reported outcomes (PROs) should be used to complement outcomes such as survival (or mortality).⁷⁵ There is little data to inform which outcomes of colorectal surgery are of greatest importance to elderly patients. Nor is there a good understanding of how patients incorporate competing risks and benefits as complex “trade-offs”, when making decisions for surgery. There is also a lack of evidence as to how patients’ uncertainties regarding treatment and research priorities can or should be elicited.¹⁴⁷ Other authors have reflected on the desirability of incorporation of patient experience (including quality of life and assessment of treatment and service received) as part of a suite of outcome measures of colorectal surgery.³⁵ Merkow¹⁴⁸ has reported that consideration should be given to the development of composite outcomes, but again, that further research is needed in this area.

Contrasting with the significant lack of evidence regarding patient-reported priorities for outcome reporting for colorectal surgery, there is a plethora of studies examining the technical approaches to colorectal cancer. The particular focus has tended to be the precise surgical intervention, potentially reflecting the interests and priorities of surgeons. Of the studies and surveys incorporated in this systematic review, eight were performed to assess outcomes of laparoscopic versus open colorectal surgery. In a systematic review in 2012, Martel et al⁸² have identified considerable overlapping reviews in this area, with a recommendation against any further systematic reviews or meta-analyses examining differences in outcomes between laparoscopic and open colorectal surgery.

The implications for future research regarding outcomes after elective colorectal surgery in elderly patients are that more study is needed, in order to answer these questions:

- How can health systems best report adverse outcomes after surgery?
- What postoperative outcomes are of greatest importance to patients?
- How can qualitative outcomes be incorporated with quantitative outcomes (such as mortality/survival) to produce meaningful metrics for patients?
- How can appropriate outcome data be best incorporated into patient-level risk

- prediction scores for surgery?
- How can outcome data be incorporated into shared decision-making processes for surgery, and how can patient risk-tolerance be assessed?

Chapter 9: Conclusions

There is a lack of valid and transparent mortality outcome data relevant to elderly patients having elective colorectal surgery in highly developed countries. Patients, their carers and healthcare professionals need valid, relevant, transparent and comprehensible outcome data to inform clinical decision-making. The aim of this systematic review was to meet the gap in the published literature, and provide a pooled estimate for the 30 day all-cause postoperative mortality for elderly patients in highly developed countries undergoing elective colorectal surgery. Providing this estimate of postoperative mortality after elective colorectal surgery in elderly patients is likely to enhance decision-making from many perspectives, including public policy makers, healthcare funders, hospitals and clinicians, and patients and their carers.

The systematic review presented included the publication of a protocol in advance of the study, and a rigorous search process for both clinical trial and observational data. The review was restricted to trials or reports with more than 150 patients, in order to minimise the likelihood of small trials skewing the final result. The systematic review was restricted to highly developed countries, and also to articles published in English, in an attempt to minimise clinical heterogeneity as much as practicable. Contact with authors was initiated, in order to access potentially relevant patient-level data wherever possible. After a rigorous search process, the authors critically appraised the articles identified by the search. Where there was obvious duplication of results, or where the quality of trials or reports was inadequate, articles were excluded from further analysis or inclusion. Twenty four articles were included in the final review. Mortality rates were analysed against age, pathology, patient comorbidities, anatomy, country of origin, institution type, surgical expertise and model of care.

The authors of this systematic review believe it is the first of its kind which produces a meta-analysis of mortality rates after elective colorectal surgery in patients 65 years and over, in highly developed countries. This systematic review makes a significant contribution to the knowledge base in the field of elective colorectal surgery, and includes a series of recommendations arising from the findings. This review found a pooled mortality rate for elderly patients in highly developed countries undergoing elective colorectal surgery of 5.34% (95% C.I. 5.26-5.41%). Significant reporting and/or publication bias reflects a lack of reporting from centres with average and higher than average postoperative mortality rates for elderly patients after elective colorectal surgery. Hospitals and departments should therefore collect their own outcome data, for the use of patients, their carers and clinicians. Locally relevant outcome data should be used for informed consent information, and to assist in clinical decision-making and quality improvement activities. These observations are also important for less highly developed nations, as their healthcare systems enable increased access to elective surgery. As their economies grow, less highly developed nations have an opportunity to plan, collect and use valid and accurate outcome data to inform resource allocation and prioritization for healthcare spending.

Implications for practice

Institutions where elective colorectal surgery is performed for elderly patients should not rely on postoperative mortality rates reported in surgical literature from single centres. Local data should be collected and utilized when advising elderly patients of postoperative mortality risk after elective colorectal surgery, and also used to inform clinical decisions, and drive local quality improvement. (Grade A)‡

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

Professional groups and societies should establish minimum datasets for surgical outcomes which can be collected at clinical unit, hospital and national levels. (Grade B)‡

Health policy makers should consider the routine collection of agreed postoperative surgical mortality rates at national or system-wide levels. (Grade B)‡

Implications for research

More research is needed to develop personalized risk scores for surgical outcomes, which incorporate patient-level and hospital-level risk.

Further research is needed to assess which postoperative outcomes are of the greatest importance to elderly patients facing elective colorectal surgery, how patients assess and tolerate surgical risk, and how complex trade-offs between outcomes of importance might be constructed.

‡ The Joanna Briggs Institute Levels of Evidence and Grades of Recommendation 2014.[Internet] Available from: <http://joannabriggs.org/jbi-approach.html#tabbed-nav=Grades-of-Recommendation> [cited 2014 Apr 27]

Appendix I:

PubMed search strategy

colorectal surgery[mh] OR (large intestine[mh] AND surgery[sh]) OR rectal surgery[tw] OR colon surgery[tw] OR large intestine surgery[tw]

AND

mortalit*[tw] OR mortality[sh] OR mortality[mh] OR fatal outcome[mh] OR death[mh:noexp] OR fatal[tw] OR fatalit*[tw] OR death[tiab]

limits: humans, from 1998, English language.

Appendix II:

MAStARI Critical Appraisal Instruments

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer Date

Author Year Record Number

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Were the criteria for inclusion in the sample clearly defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Were confounding factors identified and strategies to deal with them stated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Were outcomes assessed using objective criteria?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. If comparisons are being made, was there sufficient descriptions of the groups?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Was follow up carried out over a sufficient time period?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Were the outcomes of people who withdrew described and included in the analysis?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Were outcomes measured in a reliable way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Was appropriate statistical analysis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include Exclude Seek further info

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer Date

Author Year Record Number

	Yes	No	Unclear	Not Applicable
1. Is sample representative of patients in the population as a whole?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Are the patients at a similar point in the course of their condition/illness?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Has bias been minimised in relation to selection of cases and of controls?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Are confounding factors identified and strategies to deal with them stated?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Are outcomes assessed using objective criteria?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Was follow up carried out over a sufficient time period?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7. Were the outcomes of people who withdrew described and included in the analysis?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Were outcomes measured in a reliable way?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Was appropriate statistical analysis used?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Overall appraisal: Include Exclude Seek further info.

Comments (Including reason for exclusion)

Appendix III: Data extraction instrument

JBI Data Extraction Form for Experimental / Observational Studies

Reviewer Date

Author Year

Journal Record Number

Study Method

RCT Quasi-RCT Longitudinal
Retrospective Observational Other

Participants

Setting _____

Population _____

Sample size

Group A _____ Group B _____

Interventions

Intervention A _____

Intervention B _____

Authors Conclusions:

Reviewers Conclusions:

Study results

Dichotomous data

Outcome	Intervention () number / total number	Intervention () number / total number

Continuous data

Outcome	Intervention () number / total number	Intervention () number / total number

Appendix IV: Studies selected for critical appraisal

Cerdaen C, Vigara M, Ortega M, Jimenez F, Fernandez C, Cerdaen J. Colorectal cancer in patients over 80 years old: early results after surgical treatment. *Eur Geriatr Med.* 2011;2:S186.

Faiz O, Haji A, Bottle A, Clark SK, Darzi AW, Aylin P. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. *Colorectal Dis.* 2011;13(7):779-85.

Feroci F, Baraghini M, Lenzi E, Garzi A, Vannucchi A, Cantafio S, et al. Laparoscopic surgery improves postoperative outcomes in high-risk patients with colorectal cancer. *Surg Endosc.* 2013;27(4):1130-7.

Finlayson EV, Birkmeyer JD. Operative mortality with elective surgery in older adults. *Eff Clin Pract.* 2001;4(4):172-7.

Frasson M, Braga M, Vignali A, Zuliani W, Carlo V. Benefits of laparoscopic colorectal resection are more pronounced in elderly patients. *Dis Colon Rectum.* 2008;51(3):296-300.

Hendry PO, Hansel J, Nygren J, Lassen K, Dejong CHC, Ljungqvist O, et al. Determinants of outcome after colorectal resection within an enhanced recovery programme. *Br J Surg.* 2009;96(2):197-205.

Heriot A, Tekkis P, Smith J, Cohen CR, Montgomery A, Audisio R et al. Prediction of postoperative mortality in elderly patients with colorectal cancer. *Dis Colon Rectum.* 2006;49(6):816-24.

Jullumstrø E, Wibe A, Lydersen S, Edna TH. Colon cancer incidence, presentation, treatment and outcomes over 25 years. *Colorectal Dis.* 2011;13(5):512-8.

Jullumstrø E, Wibe A, Lydersen S, Edna T-H. Violation of treatment guidelines — hazard for rectal cancer patients. *Int J Colorectal Dis.* 2012;27(1):103-9.

Keane C, Savage S, McFarlane K, Seigne R, Robertson G, Eglinton T. Enhanced recovery after surgery versus conventional care in colonic and rectal surgery. *ANZ J Surg.* 2012;82(10):697-703.

Kennedy GD, Rajamanickam V, Oconnor ES, Loconte NK, Foley EF, Levenson G, et al. Optimizing surgical care of colon cancer in the older adult population. *Ann Surg.* 2011;253(3):508-14.

Kolfschoten NE, van Leersum NJ, Gooiker GA, Marang van de Mheen PJ, Eddes EH, Kievit J, et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. *Ann Surg.* 2013;257(5):916-21.

Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen H-O et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Crit Rev Onc Hematol.* 2010;76(3):208-17.

Kurian AA, Suryadevara S, Vaughn D, Zebley M, Hofmann M, Kim S et al. Laparoscopic colectomy in octogenarians and nonagenarians: a preferable option to open surgery? *J Surg Ed.* 2010;67(3):161-6.

Law WL, Chu KW, Tung PHM. Laparoscopic colorectal resection: A safe option for elderly patients. *J Am Coll Surg.* 2002;195(6):768-73.

Law WL. Outcomes of laparoscopic colectomy for cancer in elderly patients. *Surg Endosc.* 2011;25:S235.

Lian L, Kalady M, Geisler D, Kiran RP. Laparoscopic colectomy is safe and leads to a significantly shorter hospital stay for octogenarians. *Surg Endosc.* 2010;24(8):2039-43.

Morris EJ, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirty day postoperative mortality after colorectal cancer surgery in England. *Gut.* 2011;60:806-13.

POMRC. Perioperative mortality in New Zealand: Inaugural report of the Perioperative Mortality Review Committee. Health Quality and Safety Commission. Wellington, New Zealand:2011.

Pinto RA, Ruiz D, Edden Y, Weiss EG, Noguera JJ, Wexner SD. How reliable is laparoscopic colorectal surgery compared with laparotomy for octogenarians? *Surg Endosc.* 2011;25(8):2692-8.

Puig-La Calle Jr J, Quayle J, Thaler HT, Shi W, Paty PB, Quan SHQ, et al. Favorable short-term and long-term outcome after elective radical rectal cancer resection in patients 75 years of age or older. *Dis Colon Rectum.* 2000;43(12):1704-9.

Rothwell LA, Bokey EL, Keshava A, Chapuis PH, Dent OF. Outcomes after admission on the day of elective resection for colorectal cancer. *ANZ J Surg.* 2006;76(1-2):14-9.

Rumstadt B, Guenther N, Wendling P, Engemann R, Germer CT, Schmid M, et al. Multimodal perioperative rehabilitation for colonic surgery in the elderly. *World J Surg.* 2009;33(8):1757-63.

Tan E, Tilney H, Thompson M, Smith J, Tekkis PP. The United Kingdom National Bowel Cancer Project – epidemiology and surgical risk in the elderly. *Eur J Cancer.* 2007;43(15):2285-94.

Tan WS, Chew MH, Lim IA, Ng KH, Tang CL, Eu KW. Evaluation of laparoscopic versus open colorectal surgery in elderly patients more than 70 years old: an evaluation of 727 patients. *Int J Colorectal Dis.* 2012;27(6):773-80.

Wu CL, Rowlingson AJ, Herbert R, Richman JM, Andrews RAF, Fleisher LA. Correlation of postoperative epidural analgesia on morbidity and mortality after colectomy in Medicare patients. *J Clin Anesth.* 2006;18(8):594-99.

Appendix V: Details of included studies

Study	Methods	Participants	Intervention A	Notes
Cerdaen C et al, 2011	retrospective cohort from prospective registry	80 years and over, with colorectal cancer, from 1990-2009.	elective colorectal surgery	This data is from a non peer reviewed abstract.
Faiz O et al, 2011	retrospective analysis from administrative dataset	75 years and over with colorectal cancer, data from 1996-2007.	laparoscopic and open colorectal resection Outcome measure 30 day "in hospital" mortality	Large dataset of pooled cases from a mix of institutions (included all institutions where >15 procedures were performed). Included 30 day "in hospital" mortality.
Feroci F et al, 2013	prospective cohort study	65 years and over, with colorectal cancer. Surgery performed by colorectal fellowship-trained surgeons. Standardized "fast track" protocol. Data from 2005-2011	laparoscopic surgery and open surgery	This study looked at older patients and also other patients deemed "high risk" e.g. with raised BMI, or cardiovascular morbidity. Data supplied by author.

Study	Methods	Participants	Intervention A	Notes
Finlayson E et al, 2001	epidemiological study from national claims database	over 65 years, for cancer surgery. Data from 1994-1999.	colorectal surgery	Included a range of hospitals (academic, non-academic, tertiary, rural and regional). Outcome 30 day and in-hospital mortality
Frasson M et al, 2008	randomized controlled trial	70 years and over, benign and malignant disease. Specialist surgeons, protocol driven care. Data collection time period not stated.	laparoscopic colorectal resection, deaths 2/89 open colorectal resection deaths 1/112	Lower mortality rate for open surgery than laparoscopic surgery is not typical. Small numbers may have skewed results. 30 day postoperative mortality
Hendry P et al, 2009	prospective observational study	80 years and over, benign and malignant disease. Data from 2002-2005. Centres all used an enhanced recovery protocol.	colorectal surgery	This study examined outcomes with relation to BMI. 30 day postoperative mortality.
Heriot A et al, 2006	retrospective analysis of clinical dataset	older than 80 years with colorectal cancer, data collected between 1992-2001	colorectal resection	The purpose of the study was to develop a model for predicting postoperative mortality for elderly patients undergoing surgery for colorectal cancer

Study	Methods	Participants	Intervention A	Notes
Jullumstro E et al, 2012	retrospective analysis from National administrative dataset	65 years and over, with rectal cancer, from 1980-2004	Surgery type not specified. Specialist surgeons and trainees provided care. Protocol-driven operative strategy, radiotherapy and surveillance.	The published article demonstrated demonstrated no significant change to 5 year survival from rectal cancer over the time period 1980-2004 in this series. 30 day and in-hospital mortality reported. Data from the author.
Keane C et al, 2012	retrospective cohort study	65 years and over, with benign and malignant disease, having colonic and rectal surgery Data from 2007-2009.	. Enhanced recovery vs conventional care, included both open and laparoscopic surgery, and both general and colorectal surgeons.	Single death occurred in the conventional care group.30 day postoperative mortality reported. Data supplied by author.
Kennedy G et al, 2011	retrospective analysis of clinical dataset	65 years and over with colon cancer, open and laparoscopic surgery. Data from 2005-2008	Laparoscopic and open surgery	30 day "in-hospital" mortality reported.Data from author
Kolfschoten N et al, 2013	retrospective audit of prospective national database	70 years and over with colorectal cancer, data from 2010.	Laparoscopic vs open colorectal surgery	Excluded hospitals with fewer than 10 patients.Data from author.

Study	Methods	Participants	Intervention A	Notes
Kurian A et al, 2010	retrospective cohort study	80 years and over, benign and malignant disease Cases from years 2002-2007	laparoscopic surgery, open surgery	4.9% mortality overall, 2% for laparoscopic subset (n=150)
Law W L et al, 2011	prospective cohort study	75 years and over with colon cancer, procedures performed by colorectal specialists. Data from 2000-2009	laparoscopic vs open surgery	Reported 30 day mortality. This data from non-peer reviewed abstract.
Lian L et al, 2010	retrospective cohort study	patients older than 80 years, benign and malignant disease, data collected from 1994-2008	open colectomy and laparoscopic colectomy	14 year outcome data from academic centre
Morris E et al, 2011	retrospective analysis from National administrative dataset	65 years and over with colorectal cancer. Data from 1998-2006	colorectal surgery	Very large dataset, showing a slight decline in mortality over the years 1998-2006 for all age groups, and a significant association between age and the likelihood of postoperative death.
POMRC, 2012	retrospective analysis of administrative dataset	65 years and over. Data from 2005-2009	colorectal surgery	30 day and in-hospital mortality reported.

Study	Methods	Participants	Intervention A	Notes
Pinto R et al, 2011	prospective institutional database	80 years and over, benign and malignant disease, open vs laparoscopic colorectal surgery	open vs laparoscopic surgery	3.45% mortality for open surgery, 2.4% for laparoscopic surgery.
Puig-La Calle J et al, 2000	prospective institutional database	75 years and over, with rectal cancer compared with a comparable cohort younger than 75 years	elective radical rectal cancer resection	At this specialized centre, 30day postoperative mortality rate of 1.30% was seen for patients aged 75 years and over undergoing elective radical rectal resection for cancer.
Rothwell L et al, 2006	prospective institutional database	aged over 65 years having elective colorectal cancer surgery	elective colorectal resection	Study performed for the purposes of comparing outcomes for day of surgery admissions.
Rumstadt B et al, 2009	prospective observational study	70 years and over with benign and malignant disease	laparoscopic and open colonic surgery	30 day postoperative mortality rate 1.08%
Tan E et al, 2007	prospective observational study	75 years and over with colorectal cancer	elective colorectal surgery	30 day postoperative mortality rate 7.18%, which decreased over time (most recent data 2004-5: mortality rate 5.4%)

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

Study	Methods	Participants	Intervention A	Notes
Tan W S et al, 2012	retrospective cohort study	70 years and over, benign and malignant disease, laparoscopic and open surgery	laparoscopic vs open colorectal surgery	Overall 30 day mortality rate of 3.58%
Wu C et al, 2006	retrospective analysis from National administrative dataset	over 65 years, having elective colectomy	elective colectomy	30 day postoperative mortality rate 6.88%

Appendix VI: Excluded studies

[1] Kristjansson S et al, Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer

Reason for exclusion: large number of excluded patients, reasons unclear.

[2] Law W L et al, Laparoscopic colorectal resection: a safe option in elderly patients

Reason for exclusion: these data are likely a subset of a later paper.

Appendix VII: Detailed data from included studies

author	date	country	start	end	setting	follow up	age range	pathology	model of care	exclusions	co-ordibities	Deaths n	Total N	Qualitative assessment
Cerdaen	2011	Spain	1990	2009	Not described	30 day postoperative	80 years and over	Colorectal cancer	not specified	not specified	not specified	6	301	"small peri-operative mortality"
Faiz	2011	UK	1996	2007	National data	30-day "in-hospital mortality"	75 years and over	Colorectal cancer	not specified	hospitals performing fewer than 15 procedures	37.2% Charlson 3 or greater	1539	28,746	no
Feroci*	2012	Italy	2005	2011	Non-university tertiary care hospital	30-day postoperative	65 years and over	Colorectal cancer	"fast-track" protocol colorectal fellowship-trained surgeons	emergencies, "unfit for surgery" or with "distant metastases", nonresective surgery	for patients less than 80 years, 68.6% ASA 3 or greater	23*	600*	"laparoscopic colorectal resection can be safely performed on 'high risk' surgical patients..."
Finlayson	2001	USA	1994	1999	National data	30-day postoperative AND in-hospital mortality	Over 65 years	Cancer	not specified	patients with no diagnostic code for cancer, or over 99 years	not specified	not stated (4660)	133,148	no
Frasson	2008	Italy	not stated**	not stated**	Academic centre	30-day postoperative	70 years and over	Benign and malignant disease	specialist surgeons, protocol driven peri-operative care	patients with infiltrating cancer, cardio-respiratory or hepatic dysfunction	mean ASA score 2.15-2.3	3	201 (laparoscopic n=89, open n=112)	no
Hendry	2009	Northern Europe, multi-centre	2002	2005	4 academic centres Norway, Netherlands, Sweden, UK	30-day postoperative	80 years and over	Benign and malignant disease	enhanced recovery protocol	patients requiring total meso-rectal excision excluded	unable to extract	6	194	refers to the "safety" and potential benefits of the ERAS approach
Heriot	2006	UK	1992	2001	National data	30-day postoperative	Older than 80 years	Colorectal cancer	not specified	no surgery, or if risk factors or outcomes were "deficient"	at least 36.6% ASA 3 or greater	198	1,749	no
Jullumstrø2011*	2011	Norway	1980	2004	Regional centre	30-day AND in-hospital mortality	65 years and over	Colon cancer	included surgery by specialists, non-specialists and trainees	patients with neuroendocrine cancer	37.4% ASA 3 or greater	22*	494*	No
Jullumstrø2012*	2012	Norway	1980	2004	Regional centre	30-day AND in-hospital mortality	65 years and over	Rectal cancer	specialist surgeons and trainees	not specified	not specified	12*	234*	" excellent outcomes in the 1980s ... poor results ...during the 1990s..."
Keane*	2012	New Zealand	2007	2009	Academic centre	30-day postoperative	65 years and over	Benign and malignant disease	Enhanced recovery pathway vs conventional care by general and colorectal surgeons	not specified	unable to extract	1*	175*	no
Kennedy*	2011	USA	2005	2008	National data	30-day postoperative	65 years and over	Colon cancer	not specified	emergency patients and ASA 5 patients	66.4% ASA 3 or greater	187*	5914*	No
Kolfschoten*	2013	Netherlands	2010	2010	National data	30-day AND in-hospital mortality	70 years and over	Colorectal cancer	not specified	emergency procedures, hospitals with fewer than 10 patients in the years	not able to extract data	209*	3,746*	"Successful and safe introduction of laparoscopic surgery..."

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

author	date	country	start	end	setting	follow up	age range	pathology	model of care	exclusions	co-orbidities	Deaths n	Total N	Qualitative assessment
Kurian	2010	USA	2002	2007	Single centre, not described	30-day postoperative	80 years and over	Benign and malignant disease	laparoscopic surgeons had advanced training, open surgeons did not	emergent procedures	68.6%ASA 3 or greater	12	245	"laparoscopic colectomy in octogenarians is...safe"
Law	2011	Hong Kong	2000	2009	Academic centre	30-day postoperative	75 years and over	Colon cancer	procedures performed by colorectal specialists	not specified	not specified	11	439	no
Lian	2010	USA	1994	2008	Academic "referral centre"	30-day postoperative	Older than 80 years	Benign and malignant disease	not specified	emergency cases	82.5% ASA 3 or greater	10	194	laparoscopic colectomy "may be performed safely for these patients"
Morris*	2011	England	1998	2006	National data	30-day postoperative	65 years and over	Colorectal cancer	not specified	not specified	unable to extract	8857*	110,698*	No
Pinto	2011	USA	2001	2008	Academic centre	30 day postoperative	80 years and over	Benign and malignant disease	not specified	emergency and perineal procedures, or without resection	64% ASA 3 or greater	6	199	"Laprosopic...resection was effective and safe for octogenarians"
POMRC	2011	New Zealand	2005	2009	National data	30-day AND in-hospital mortality	65 years and over	Benign and malignant disease	not specified	not specified	unable to extract	176	6,291	no
Puig-La Calle	2000	USA	1986	1996	Academic, tertiary Cancer Hospital	30-day postoperative	75 years and over	Rectal cancer	not specified	nil	not specified	2	157	"favorable" outcomes
Rothwell*	2006	Australia	2000	2003	Academic centre	30-day postoperative AND death before hospital discharge	Over 65 years	Cancer surgery	specialist colorectal surgeons	non-elective and non-resection procedures excluded	unable to extract	4*	236*	no
Rumstadt	2009	Germany	2005	2007	24 hospitals, mixed	30-day postoperative	70 years and over	Benign and malignant disease	enhanced recovery protocol	94.7% participation rate	50.3%ASA 3 or greater	8	742	the protocol "can easily and safely be adopted for elderly patients".
Tan	2007	UK	2000	2005	National data	30-day postoperative	75 years and over	Colorectal cancer	not specified	nil	47% ASA 3 or greater	825	11,494	no
Tan	2012	Singapore	2005	2008	Academic centre	30-day postoperative	70 years and over	Benign and malignant disease	Standardised protocol with structured rehabilitation, care by colorectal surgeons	not specified	22.3% ASA 3 or greater	26	727	"laparoscopic surgery in elderly patients was safe "
Wu*	2006	USA	1997	2001	National data	30-day postoperative	Over 65 years	not specified	not specified	emergency cases	not specified	882*	12,817*	no

* data from author, 9 results from 8 authors

** not stated estimated at 2004

BIBLIOGRAPHY

1. World Health Organisation. Quality of care: a process for making strategic choices in health systems, 2006. WHO Press, Geneva, Switzerland.
2. Institute of Medicine. Crossing the quality chasm: a new health system for the 21st century. Washington DC: National Academy Press, 1990, p244.
3. Birkmeyer J D, Dimick J B, Birkmeyer N. Measuring the quality of surgical care: structure, process or outcomes. *J Am Coll Surg.* 2004;198(4):626-32.
4. Khuri SF, Daley J, Henderson W et al. The Department of Veterans' Affairs NSQIP. *Ann Surg.* 1998;228(4):491-507.
5. Noordzij PG, Poldermans D, Schouten O et al. Postoperative mortality in the Netherlands. *Anesthesiology.* 2010;112:1105-15.
6. Khuri SF, Daley J, Henderson WG. The comparative assessment and improvement of quality of surgical care in the Department of Veterans Affairs. *Arch Surg.* 2002; 137: 20-27.
7. Knops A, Legemate D, Goossens A, Bossuyt P, Ubbink D. Decision aids for patients facing a surgical treatment decision: A systematic review and meta-analysis. *Ann Surg.* 2013;257(5):860-66.
8. Woolf SH, Chan ECY, Harris R et al. Promoting informed choice: transforming health care to dispense knowledge for decision-making. *Ann Intern Med.* 2005;143(4):293-301.
9. Mayberry RM, Nicewander DA, Qin H et al. Improving quality and reducing inequities: a challenge in achieving best care. *Proc (Bayl Univ Med Cent).* 2006;19:103-118.
10. McGlynn EA. Introduction and overview of the conceptual framework for a national quality measurement and reporting system. *Med Care.* 2003; 41(1):S11-17.
11. Chen JC. Public reporting of health system performance: review of evidence of impacts on patients, providers and healthcare organisations: An evidence check rapid review brokered by the Sax Institute for the Bureau of Health information 2010.
12. POMRC. Perioperative mortality in New Zealand: Inaugural report of the Perioperative Mortality Review Committee. Health Quality and Safety Commission. Wellington, New Zealand:2011.
13. Dr Foster Intelligence: your mortality rate is your pulse [Internet][cited 2014 April 17]. Available from: <http://myhospitalguide.drfoosterintelligence.co.uk/#/mortality>
14. Royal Australasian College of Surgeons: Audit of Surgical Mortality [Internet][cited 2014 April 17]. Available from: <http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/anzasm/>
15. Ingraham AM, Cohen ME, Bilimoria KY et al. Comparison in hospital performance in non-emergency and emergency colorectal operations at 142 hospitals. *J Am Coll Surg.* 2010;210(2):155-65.
16. Morris EJ, Taylor EF, Thomas JD, Quirke P, Finan PJ, Coleman MP, et al. Thirty day postoperative mortality after colorectal cancer surgery in England. *Gut.* 2011;60:806-13.
17. Iversen LH. Aspects of survival from colorectal cancer in Denmark [Doctor of Medical Science thesis]. *Dan Med J.* 2012;59(4).

18. Ferlay J, Shin H, Bray F et al. GLOBOCAN 2008, Cancer incidence and mortality worldwide. IARC Cancer Base no. 10 International Agency for Research on Cancer, Lyon, France.
19. Australian Government Department of Health National Bowel Cancer Screening Program. [Internet] [updated 2013 Dec 5, cited 2014 Mar 30]. Available from <http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/bowel-about>
20. Whitlock EP, Lin J, Liles E et al. Screening for colorectal cancer: An updated systematic review. Evidence Synthesis No. 65, part 1. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008 Oct. AHRQ Publication no.08-05124-EF-1.
21. Bansal N, Sonnenberg EM, Meise CK et al. The effect of colorectal cancer screening mandates on access to care and clinical outcomes: a retrospective study of patients undergoing operations of the colon and rectum. *Surgery*. 2013;154(2):335-44.
22. Pearse RM, Harrison DA, James P et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Critical Care*. 2006;10:R81
23. Smith JJ, Tekkis P. Risk prediction in surgery [Internet]2014 [revised 2014 Mar 30, cited 2014 Mar 30]. Available from <http://www.riskprediction.org.uk/>
24. Story DA, Leslie K, Myles PS et al. Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study. *Anaesthesia*. 2010;65:1022-30.
25. Pearse R, Moreno R, Bauer P, Pelosi P, Metnitz P, Spies C et al. . Mortality after surgery in Europe: a 7 day cohort study. *Lancet*. 2012;380(9847):1059-65.
26. Gibbs N. Safety of anaesthesia in Australia 2006-2008. Australian and New Zealand College of Anaesthetists 2012.
27. Porter ME. What is Value in Health Care? *N Engl J Med* 2010;363:2477-2481.
28. Khuri SF, Henderson WG, De Palma RG et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242(3):326-41.
29. Manceau G, Karoui M, Werner A, Mortensen N, Hannoun L. Comparative outcomes of rectal cancer surgery between elderly and non-elderly patients: a systematic review. *Lancet Oncol*. 2012;13:e525-36.
30. Kiran RP, Attaluri V, Hammel J, Church J. A novel nomogram accurately quantifies the risk of mortality in elderly patients undergoing colorectal surgery. *Ann Surg*. 2013;257(5):905-908.
31. Masoomi H, Kang CY, Chaudhry O et al. Predictive factors of early bowel obstruction in colon and rectal surgery: data from the Nationwide Inpatient Sample, 2006-2008. *J Am Coll Surg*. 2012;May214(5):831-7.
32. Bentrem DJ, Cohen ME, Hynes DM et al. Identification of specific quality improvement opportunities for the elderly undergoing gastrointestinal surgery. *Arch Surg*.2009;144(11):1013-20.
33. Jin CJ, Matimianakis MA, Kitto S et al. Pressures to “measure up” in surgery: managing your image and managing your patient. *Ann Surg* 2012;256(6):989-93.

34. Obias VJ, Reynolds HL. Multidisciplinary teams in the management of rectal cancer. *Clin Colon Rectal Surg.* 2007;20(3):143-7.
35. Almoudaris AM, Clark S, Vincent C, Faiz O. Establishing quality in colorectal surgery. *Colorectal Dis.* 2011;13:961-73.
36. Damhuis RA, Wijnhoven BP, Plaisier PW et al. Comparison of 30-day, 90-day and in-hospital postoperative mortality for eight different cancer types. *Br J Surg.* 2012;99:1149-54.
37. Tran L, Chand V, Newcomb A et al. Cardiac surgery in Victorian public hospitals, 2010-11. Hospital and health service performance division, Department of Health, Melbourne Victoria 2012.[cited 2014 Apr 18] Available from:
[http://docs.health.vic.gov.au/docs/doc/5CA330E17182A9E1CA257A1300026FCD/\\$FILE/120501_DoH%20Cardiac%20Surgery%20report%20web.pdf](http://docs.health.vic.gov.au/docs/doc/5CA330E17182A9E1CA257A1300026FCD/$FILE/120501_DoH%20Cardiac%20Surgery%20report%20web.pdf)
38. Bureau of Health Information. The Insight series: 30-day mortality following hospitalisation, five clinical conditions, NSW, July 2009-July 2012. Sydney (NSW);BHI;2013.
39. Anderson JH, Hole D, McArdle CS. Elective versus emergency surgery for patients with colorectal cancer. *British Journal of Surgery.* 1992;79(7):706-9.
40. Patel SS, Patel MS, Goldfarb M et al. Elective versus emergency surgery for ulcerative colitis: a National Surgical Quality Improvement Program analysis. *Am J Surg.* 2013 Mar;205(3):333-7.
41. Paulson EC, Mahmoud NN, Wirtalla C et al. Acuity and survival in colon cancer surgery. *Diseases of the colon and rectum.* 2010;53(4):385-92.
42. Simmonds PD, Best L, George S et al. Surgery for colorectal cancer in elderly patients: a systematic review. *Lancet.* 2000;356(9234):968-74.
43. Mehrkhani F, Nasiri S, Donboli K et al. Prognostic factors in survival of colorectal cancer patients after surgery. *Colorectal Dis.* 2009;11:157-61.
44. Benedix F, Kube R, Meyer F et al. Comparison of 17,641 patients with right- and left-sided colon cancer: Differences in epidemiology, perioperative course, histology and survival. *Dis Colon Rectum.* 2010;53:57-64.
45. Ghaferi AM, Birkmeyer JD, Dimick JB. Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. *Ann Surg.* 2009;250:1029-34.
46. Bernard AC, Davenport DL, Chang PK et al. Intraoperative transfusion of 1U to 2U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia and sepsis in general surgery patients. *J Am Coll Surg.* 2009;208(5):931-7.
47. Musallam KM, Tamim HM, Richards T et al. Preoperative anemia and postoperative outcomes in general surgery: a retrospective cohort study. *Lancet.* 2001;378(9800):1396-1407.
48. Halabi WJ, Mehraneh DJ, Nguyen VQ et al. Blood transfusions in colorectal cancer surgery: incidence, outcomes and predictive factors: an American College of Surgeons National Surgical Quality Improvement Project analysis. *Am J Surg.* 2013;206:1024-33.
49. Oliphant R, Nicholson GA, Horgan PG et al. Contribution of surgical specialization to improved colorectal cancer survival. *Br J Surg.* 2013;100:1388-95.
50. Nedrebo BS, Soreide K, Eriksen MT et al. Excess mortality after curative surgery for colorectal cancer changes over time and differs for patients with colon versus rectal cancer. *Acta Oncologica.* 2013;52:933-40.

51. Elferink MA, Wouters MW, Krijnen P et al. Disparities in quality of care for colon cancer between hospitals in the Netherlands. *Eur J Surg Oncol*. 2010;36 Suppl1:S64-73.
52. Zhuang C-L, Ye X-Z, Zhang X-D et al. Enhanced recovery after surgery programs versus traditional care for colorectal surgery: A meta-analysis of randomised controlled trials. *Dis Colon Rectum*. 2013;56:667-678.
53. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet*. 1986;June 28:1479-1482.
54. Rutten HJ, den Dulk M, Lemmens VE et al. Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol*. 2008;9:494-501.
55. Grailey K, Markar SR, Karthikesalingam A, Aboud R, Ziprin P, Faiz O. Laparoscopic versus open colorectal resection in the elderly population. *Surg Endosc*. 2013;27(1):19-30.
56. Schwenk W, Haase O, Neudecker JJ et al. Short term benefits for laparoscopic colorectal resection. *Cochrane Database of systematic reviews*. 2008;4.
57. Vlug MS, Wind J, Hollmann MW et al. Laparoscopy in combination with fast-track multimodal management is the best perioperative strategy in patients undergoing colonic surgery. *Ann Surg*. 2011;254(6):868-75.
58. Tou S, Malik AI, Wexner SD et al. Energy source instruments for laparoscopic colectomy. *Cochrane Database of Systematic Reviews*. 2011;5.
59. Kanji A, Gill R, Shi X et al. Robotic-assisted colon and rectal surgery: a systematic review. *Int J Med Robotics Comput Assist Surg*. 2011;7:401-7.
60. Van Hooff JE, Bemelman WA, Oldenburg B et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. *Lancet Oncol*. 2011;12:344-52.
61. Finlayson EV, Birkmeyer JD. Operative mortality with elective surgery in older adults. *Eff Clin Pract*. 2001;4(4):172-7.
62. Faiz O, Haji A, Bottle A et al. Elective colonic surgery for cancer in the elderly: an investigation into postoperative mortality in English NHS hospitals between 1996 and 2007. *Colorectal Dis*. 2011;13(7):779-85.
63. Mathews J. Surgery and old age: an age old question. *Arch Surg*. 2009;144(11):1020.
64. National Confidential Enquiry into Patient Outcome and Death 2011. Knowing the risk. A review of the peri-operative care of surgical patients.
65. Archampong D, Borowski D, Wille-Jorgensen P, Iversen LH. Workload and surgeon's specialty for outcome after colorectal cancer surgery (Review). *The Cochrane Library* 2012 (3).
66. Cohen ME, Bilimoria KY, Ko CY, Hall BL. Development of an American College of Surgeons National Surgery Quality Improvement Program: Morbidity and Mortality Risk Calculator for Colorectal Surgery. *J Am Coll Surg*. 2009;208(6):1009-16.
67. Billingsley KG, Morris AM, Dornitz JA, et al. Surgeon and hospital characteristics as predictors of major adverse outcomes following colon cancer surgery: Understanding the volume-outcome relationship. *Arch Surg*. 2007;142(1):23-31.
68. Jestin P, Heurgren M, Pahlman L, Glimelius B, Gunnarsson U. Elective surgery for colorectal cancer in a defined Swedish population. *Europ J Surg Oncol*. 2004 ;30(1):26-33.
69. McArdle CS, McKee RF, Finlay IG, Wotherspoon H, Hole DJ. Improvement in survival following surgery for colorectal cancer. *British Journal of Surgery*. 2005;92(8):1008-13.

70. Jafari MD, Jafari F, Halabi WJ et al. Colorectal cancer resections in the aging US population: a trend towards decreasing rates and improved outcomes. *JAMA Surg*. Published online April 09, 2014. doi:10.1001/jamasurg.2013.4930
71. Australian social trends [Internet] Canberra: Australian Bureau of Statistics;2009. Catalogue No. 4102.0 [cited 2014 Apr 19] Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/4102.0Main+Features10March%202009>
72. Yancik R, Ries LA. Cancer in older persons: an international issue in an aging world. *Semin Oncol*. 2004;31(2):128-36.
73. Lewis JH, Kilgor ML, Goldman DP et al. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol*. 2003;21(7):1383-89.
74. Weiser TG, Regenbogen SE, Thompson KD et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*.2008;372:139-44.
75. Higgins JPT, Green S (editors).Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [Updated March 2011, cited 2014 Apr 22]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org
76. Joanna Briggs Institute website [cited 2014 June 9]. Available from <http://www.joannabriggs.org/jbi-approach.html#tabbed-nav=JBI-approach>
77. Glass GV. Primary, secondary, and meta-analysis of research. *Educational researcher*. 1996;5(10):3-8.
78. Mosteller F, Colditz GC. Understanding research synthesis (meta-analysis). *Annu Rev Public Health*. 1996;17:1-23.
79. Athanasiou T, Darzi A (editors). Evidence synthesis in health care. Springer-Verlag London Limited 2011.
80. Pearson A, Stannard D, Yan H. Synthesis science in healthcare series: book 13. Clinical wisdom and evidence-based healthcare. Lippincott, Williams and Wilkins 2012.
81. Jadad AR, Moher D, Klassen TP. Guides for reading and interpreting systematic reviews. *Arch Pediatr Adolesc Med*.1998;152:812-17.
82. Martel G, Duhaime S, Barkin J et al. The quality of research synthesis in surgery: the case of laparoscopic surgery for colorectal cancer. *Systematic Reviews*. 2012;1:14.
83. Simes RJ, Stern JM. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ*. 1997;315:640-45.
84. Goldacre B, Heneghan C. Improving, and auditing, access to clinical trial results. *BMJ*.2014;348:g213.
85. Egger M, Zellweger Z, Schneider M et al. Language bias in randomised controlled trials published in English and German. *Lancet*. 1997;350:326-329.
86. Fletcher J. What is heterogeneity and is it important? *BMJ*. 2007;334:94-6.
87. Cochran W. The combination of estimates from different experiments. *Biometrics*. 1954;10:101-29.
88. Higgins JP, Thompson SG, Deeks JJ. Measuring inconsistency in meta-analysis. *BMJ*. 2003;27:557-60.
89. Moher D, Cook DJ, Eastwood S et al. Improving the quality of reporting of meta-analysis of randomized controlled trials: the QUOROM statement. *Lancet*.1994;367:881-3.

90. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.
91. Stroup DF, Berlin JA, Morton SC et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA.* 2000;283(15):2008-12.
92. Egger M, Davey Smith G, Schneider M et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629.
93. Bailar JC. The promise and problems of meta-analysis. *NEJM.* 1997;337(8):559-61.
94. Naylor CD. Meta-analysis and the meta-epidemiology of clinical research. *BMJ.* 1997;315:617-19.
95. Petticrew M. Why certain systematic reviews reach uncertain conclusions. *BMJ.* 2003;326:756-8.
96. Peltzman S. Regulation and the natural progress of opulence. Washington D.C.: AEI Brookings Centre for Regulatory Studies; 2005 [Internet] Available from: <http://www.aei.org/files/2005/05/16/files/2005/05/16/Peltzman-Lecture.pdf> [cited 2014 30 Apr].
97. Wilde GJS. The theory of risk homeostasis; implications for safety and health. *Risk Analysis.* 1982;2(2):209-25.
98. Chen JC. Public reporting of health system performance: review of evidence of impacts on patients, providers and healthcare organisations: An evidence check rapid review brokered by the Sax Institute for the Bureau of Health information 2010.
99. Kohli E, Ptak J, Smith R, Taylor E, Talbot E, Kirkland K. Variability in the Hawthorne effect with regard to hand hygiene performance in high- and low-performing inpatient care units. *Infect Control Hosp Epidemiol.* 2009;30:222-225.
100. Mangione-Smith R, Eliot M, McDonald L, McGlynn E. An observational study of antibiotic behaviour and the Hawthorne effect. *Health Serv Res.* 2002;37(6):1603-23.
101. Mashta O. Survival after heart surgery improves after data publication. *BMJ.* 2009;339:b3102.
102. Hanley J, Lippman-Hand A. If nothing goes wrong is everything all right? *JAMA.* 1983;249:1743-5.
103. Hall BL, Bilimoria KY, Ko CY. Investigations using clinical data registries: observational studies and risk adjustment. *Surgery.* 2009;145(6):602-10.
104. Finlayson E, Birkmeyer JD. Research based on administrative data. *Surgery.* 2009;145(6):610-16.
105. Berry DA. Bayesian statistics (editorial). *Med Decis Making.* 2006;426:429-30.
106. Devereaux PJ, Goldman L, Cook DJ, Gilbert K, Leslie K, Guyatt GH. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to assess and communicate risk. *CMAJ.* 2005;173(6):627-34.
107. Detsky AL, Abrams HB, McLaughlin JR, Drucker DJ, Sasson Z, Johnston N et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med.* 1986;1:211-19.
108. Sutherland J, Robertson-Malt S, Stern C. All cause 30-day postoperative mortality for older patients in developed countries presenting for elective colorectal surgery: A systematic

- review protocol. JBI database of systematic reviews and implementation reports. 2013;11(8).
109. Human Development Report 2013-The Rise of the South: Human progress in a diverse world. New York: United Nations Development Program, 2013.
 110. Bertelsman Stiftung, BTI 2012-Taiwan Country Report. Gütersloh: Bertelsman Stiftung 2012.
 111. Bainbridge D, Martin J, Arango M et al. Perioperative and anaesthetic- related mortality in developed and developing countries: a systematic review and meta-analysis. *Lancet*. 2012;380:1075-81.
 112. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statist Med*. 2002;21:1539-1558.
 113. The Joanna Briggs Institute. Joanna Briggs Institute Reviewers' Manual:2014 edition/Supplement. The Joanna Briggs Institute, The University of Adelaide, South Australia.
 114. Law WL, Chu KW, Tung PHM. Laparoscopic colorectal resection: A safe option for elderly patients. *J Am Coll Surg*. 2002;195(6):768-73.
 115. Kristjansson SR, Nesbakken A, Jordhøy MS, Skovlund E, Audisio RA, Johannessen H-O et al. Comprehensive geriatric assessment can predict complications in elderly patients after elective surgery for colorectal cancer: A prospective observational cohort study. *Crit Rev Onc Hematol*. 2010;76(3):208-17.
 116. Frasson M, Braga M, Vignali A, Zuliani W, Carlo V. Benefits of laparoscopic colorectal resection are more pronounced in elderly patients. *Dis Colon Rectum*. 2008;51(3):296-300.
 117. Puig-La Calle Jr J, Quayle J, Thaler HT, Shi W, Paty PB, Quan SHQ, et al. Favorable short-term and long-term outcome after elective radical rectal cancer resection in patients 75 years of age or older. *Dis Colon Rectum*. 2000;43(12):1704-9.
 118. Heriot A, Tekkis P, Smith J, Cohen CR, Montgomery A, Audisio R et al. Prediction of postoperative mortality in elderly patients with colorectal cancer. *Dis Colon Rectum*. 2006;49(6):816-24.
 119. Rothwell LA, Bokey EL, Keshava A, Chapuis PH, Dent OF. Outcomes after admission on the day of elective resection for colorectal cancer. *ANZ J Surg*. 2006;76(1-2):14-9.
 120. Wu CL, Rowlingson AJ, Herbert R, Richman JM, Andrews RAF, Fleisher LA. Correlation of postoperative epidural analgesia on morbidity and mortality after colectomy in Medicare patients. *J Clin Anesth*. 2006;18(8):594-99.
 121. Tan E, Tilney H, Thompson M, Smith J, Tekkis PP. The United Kingdom National Bowel Cancer Project – epidemiology and surgical risk in the elderly. *Eur J Cancer*. 2007;43(15):2285-94.
 122. Hendry PO, Hansel J, Nygren J, Lassen K, Dejong CHC, Ljungqvist O, et al. Determinants of outcome after colorectal resection within an enhanced recovery programme. *Br J Surg*. 2009;96(2):197-205.
 123. Rumstadt B, Guenther N, Wendling P, Engemann R, Germer CT, Schmid M, et al. Multimodal perioperative rehabilitation for colonic surgery in the elderly. *World J Surg*. 2009;33(8):1757-63.
 124. Kurian AA, Suryadevara S, Vaughn D, Zebley M, Hofmann M, Kim S et al. Laparoscopic colectomy in octogenarians and nonagenarians: a preferable option to open surgery? *J Surg Ed*. 2010;67(3):161-6.

125. Lian L, Kalady M, Geisler D, Kiran RP. Laparoscopic colectomy is safe and leads to a significantly shorter hospital stay for octogenarians. *Surg Endosc.* 2010;24(8):2039-43.
126. Law WL. Outcomes of laparoscopic colectomy for cancer in elderly patients. *Surg Endosc.* 2011;25:S235.
127. Cerdaen C, Vigara M, Ortega M, Jimenez F, Fernandez C, Cerdaen J. Colorectal cancer in patients over 80 years old: early results after surgical treatment. *Eur Geriatr Med.* 2011;2:S186.
128. Jullumstrø E, Wibe A, Lydersen S, Edna TH. Colon cancer incidence, presentation, treatment and outcomes over 25 years. *Colorectal Dis.* 2011;13(5):512-8.
129. Jullumstrø E, Wibe A, Lydersen S, Edna T-H. Violation of treatment guidelines — hazard for rectal cancer patients. *Int J Colorectal Dis.* 2012;27(1):103-9.
130. Kennedy GD, Rajamanickam V, Oconnor ES, Loconte NK, Foley EF, Levenson G, et al. Optimizing surgical care of colon cancer in the older adult population. *Ann Surg.* 2011;253(3):508-14.
131. Pinto RA, Ruiz D, Edden Y, Weiss EG, Noguera JJ, Wexner SD. How reliable is laparoscopic colorectal surgery compared with laparotomy for octogenarians? *Surg Endosc.* 2011;25(8):2692-8.
132. Keane C, Savage S, McFarlane K, Seigne R, Robertson G, Eglinton T. Enhanced recovery after surgery versus conventional care in colonic and rectal surgery. *ANZ J Surg.* 2012;82(10):697-703.
133. Tan WS, Chew MH, Lim IA, Ng KH, Tang CL, Eu KW. Evaluation of laparoscopic versus open colorectal surgery in elderly patients more than 70 years old: an evaluation of 727 patients. *Int J Colorectal Dis.* 2012;27(6):773-80.
134. Feroci F, Baraghini M, Lenzi E, Garzi A, Vannucchi A, Cantafio S, et al. Laparoscopic surgery improves postoperative outcomes in high-risk patients with colorectal cancer. *Surg Endosc.* 2013;27(4):1130-7.
135. Kofschoten NE, van Leersum NJ, Gooiker GA, Marang van de Mheen PJ, Eddes EH, Kievit J, et al. Successful and safe introduction of laparoscopic colorectal cancer surgery in Dutch hospitals. *Ann Surg.* 2013;257(5):916-21.
136. Saklad M. Grading of patients for surgical procedures. *Anesthesiology.* 1941;2:281-4.
137. Charlson M, Szatrowski T, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245-51.
138. Prytherch D, Whiteley M, Higgins B, Weaver PC, Prout WG, Powell SJ. POSSUM and Portsmouth POSSUM for predicting mortality. *Br J Surg.* 1998;85:1217-20.
139. Walker E, Hernandez A, Kattan M. Meta-analysis: its strength and limitations. *Cleveland Clin J Med.* 2008;75(6):431-39.
140. Weizman D, Cyriac J, Urbach DR. What is meant when a laparoscopic surgical procedure is described as "safe"? *Surg Endosc.* 2007;21:1369-72.
141. Mamidanna R, Almoudaris AM, Faiz O. Is 30-day mortality an appropriate measure of risk in elderly patients undergoing elective colorectal resection? *Colorectal Dis.* 2012;14(10):1175-82.
142. Simpson JC, Moonasinghe SR. Introduction to the postanaesthetic care unit. *Periop Med.* 2013;2:5.

Sutherland, J. Thesis: Masters, Clinical Science (Evidence-Based Healthcare) 2014

143. Sesen MB, Nicholson AE, Banares-Alcantara R, Kadir T, Brady M. Bayesian networks for clinical decision support in lung cancer care. *PLoS ONE* 2013;8(12):e82349.
144. Kobayashi H, Miyata H, Gotoh M, Baba H, Kimura W, Kitagawa Y, et al. Risk model for right hemicolectomy based on 19,070 Japanese patients in the National Clinical Database. *J Gastroenterol.* 2013:1-9.
145. Snijders HS, Henneman D, van Leersum NL, ten Berge M, Fiocco M, Karsten TM et al. Anastomotic leakage as an outcome measure for colorectal surgery. *BMJ Qual Saf.* 2013;00:1-9.
146. Johnston CF, Tomlinson G, Temple LK, Baxter NN. The management of patients with T1 adenocarcinoma of the low rectum: a decision analysis. *Dis Colon Rectum.* 2013;56:400-407.
147. Fenton M, Brice A, Chalmers I. Harvesting and publishing patients' unanswered questions about the effects of treatments. In: Littlejohns P, Rawlins M, eds. *Patients, the public and priorities in healthcare.* Abingdon, Oxon: Radcliffe, 2009, pp 165-80.
148. Merkow RP, Bilimoria KY, Ko CY. Surgical quality measurement: an evolving science. *JAMA.* 2013;148(7):586-7.