Long-term mortality following complications after elective surgery: a secondary analysis of pooled data from two prospective cohort studies.

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ABSTRACT

Background

Complications after surgery affect length and quality of life. We aimed to confirm the ~~contemporary~~ relationship between postoperative complications and death within one year after surgery.

Methods

Secondary analysis of pooled data from two prospective cohort studies of surgical patients in five high-income countries between 2012 and 2014. The exposure was any complication within 30 days after surgery. The primary outcome was death within one year after surgery, ascertained by direct follow-up or linkage to national registers. We adjusted for clinically important covariates using a mixed-effects multivariable Cox proportional hazards regression model. We conducted a planned sub-group analysis by type of complication. Data are presented as mean with standard deviation (SD), n (%) and adjusted hazard ratios (aHR) with 95% confidence intervals.

Results

The pooled cohort included 10132 patients. After excluding 399 (3.9%) patients with missing data or incomplete follow up, 9733 patients were analysed. The mean age was 59 (SD: 16.8) years and 5362 (55.1%) were female. Of 9733 patients, 1841 (18.9%) had a complication within 30 days after surgery and 319 (3.3%) died within one year after surgery. Of 1841 patients with a complication, 138 (7.5%) died within one year after surgery compared to 181 (2.3%) of 7892 patients without a complication (aHR 1.94 [95%CI:1.53-2.46]). Respiratory failure was associated with the greatest risk of death, resulting in 6 deaths among 28 patients (21.4%).

Conclusion

Postoperative complications are associated with increased mortality at one-year. Further research is needed to identify patients at risk of complications and reduce mortality.

Introduction

Over 330 million surgical procedures are carried out worldwide every year.[1] There is substantial variation in estimates of postoperative morbidity and mortality, in part due to heterogeneity in reporting of postoperative outcomes.[2–4] In the United Kingdom, around five million surgical procedures are performed each year, after which one percent of patients die within 30 days.[5 6] Most perioperative research studies use 30-day mortality as a marker of harm associated with surgery.[7] However, there is growing evidence that mortality rates remain elevated between 30 and 90 days after surgery.[5 8] Despite this, studies describing the patterns and determinants of long-term mortality after surgery are few in number.

Complications like infections, cardiovascular conditions, postoperative pulmonary complications, renal impairment etc, occur after one in every five surgical procedures.[9–13] Evidence from a large multi-centre cohort study in the USA identified strong association between postoperative medical complications and reduced long-term survival. However, while the study was ground-breaking at the time of publication, it only investigated eight surgical procedure categories and represents clinical practice from a single country conducted more than twenty years ago.[14] Thus, this study retains only limited relevance for contemporary surgical and perioperative practice, with restricted generalisability to the wider international surgical population.[1,13] Previously, we examined the association between infection, the most common post-operative complication, and 30-day mortality. [10,15] To plan delivery of care for surgical patients, we must better understand the long-term outcomes following complications, in addition to widely reported data describing short-term harms.

The primary aim of the study was to describe the crude and adjusted association between postoperative complications and death within one year after surgery using data from two international, multi-centre observational cohort studies. The secondary aim was to measure the association between the severity of complications and one year survival. Finally, we hypothesised that the rate of mortality would vary with type of complication.

Methods

Study design

This was a secondary analysis of data from two prospective observational cohort studies which have been previously described. The International Surgical Outcome Study (ISOS) was an international multi-centre cohort study of perioperative morbidity and mortality in patients undergoing elective inpatient surgery.[13] Data collection occurred during a seven-day period in 2014. All adult patients admitted to participating centres for elective surgery were eligible. Patients undergoing day-case surgery or radiological procedures were excluded. This analysis was a subgroup of the core ISOS study and included patients from Sweden, New Zealand and England, where we collected mortality data up to one year after surgery. In England, these data were collected with individual patient consent using civil registry data held by NHS Digital (REC: 18/YH/0310; Confidentiality Advisory Group: 18/CAG/0205; DSA:NIC-68740). In Sweden, death was identified from patient notes and confirmed with national registry data. In New Zealand, these data were collected from the Mortality Collection (Ministry of Health, New Zealand). The second cohort is derived from the Measurement of Exercise Tolerance before Surgery (METS) study, a prospective international observational cohort study of surgical outcomes in 25 hospitals across England, Canada, Australia and New Zealand.[12] Data collection occurred between 2012 and 2014. Eligible patients were aged ≥40 years with at least one risk factor for vascular disease or cardiovascular complications, and underwent elective inpatient non-cardiac surgery. Follow-up data were collected for one year after surgery from direct patient follow up. The study was reviewed and approved by the South East Coast (Surrey) Research Ethics Committee (REC: 13/LO/0135). Both studies were conducted in accordance with the Research Governance Framework and the declaration of Helsinki, a summary of each is in supplementary table 1. We developed a statistical analysis plan before starting this analysis and report findings in line with STROBE and RECORD guidance.[16] No sample size calculation was performed for this secondary analysis of the two prospective studies.[17]

Outcomes

The primary outcome measure was death at one year following surgery. The secondary outcome was death within 30 days after surgery.

Exposure

The exposure of interest was presence of any complication within 30 days after surgery. Complications were identified prospectively in both constituent studies. We grouped complications into: infective (including surgical site infection, deep wound infection and pneumonia), cardiovascular (including arrhythmia, myocardial infarction and stroke), bleeding/thromboembolic (including pulmonary embolus and gastrointestinal bleeding), respiratory failure, acute kidney injury, reoperation and other.[13] The grouping of complications, stratified by study, is reported in supplementary table 2.

Variables

Age was recorded in completed years at time of surgery. Sex was recorded as male or female. Smoking status was dichotomised as current smoker or not current smoker. Patients were classified according to the American Society of Anaesthesiologists Physical Status Classification (ASA-PS grade - I, II, III, IV, V).[18] We grouped surgical procedures into eight categories (Vascular, Thoracic, Peritoneal, Orthopaedics, Obstetrics, Urology/Gynaecology, Head & Neck and Neurosurgery) based on the primary procedure performed. The use of a laparoscopic surgical technique, the severity of surgery, and cancer being the indication for surgery were each determined by investigators at time of data collection. We classified anaesthetic techniques as: general anaesthesia alone; combined general anaesthesia and regional anaesthesia; regional anaesthesia alone; and sedation alone. We captured the following chronic diseases: cancer, coronary artery disease, diabetes mellitus, cardiac failure, stroke, chronic obstructive pulmonary disease. We defined chronic kidney disease as an estimated glomerular filtration rate (eGFR) <60ml min^{-1} $1.73m^{-2}$ using creatinine measured within 30 days before surgery. We calculated eGFR using the 2021 CKD-EPI creatinine equation, which does not require patient ethnicity to determine eGFR.[19] Liver cirrhosis was captured only in the ISOS study, so we excluded this disease from statistical testing.

Missing data

We excluded patients from the primary analysis for whom follow up at one year after surgery was incomplete (or linkage incomplete in England); we report their characteristics in supplementary table 3. We report the rate of missingness for all variables and determined the patterns. Data missing completely at random was handled in two ways: first, by complete case analysis for the primary analysis; and second, by imputation of missing variables. Here, we used multiple imputation with chained equations for five imputed datasets and repeated our primary analysis. [20 21]

Statistical methods

We dichotomised the patients according to presence or absence of complications within 30 days after surgery. We present the baseline characteristics, reported as number with percentage for categorical variables and we report continuous data as mean (with standard deviation; SD). We present the crude rate of death at both 30 and 365 days after surgery, stratified by the presence or absence of complications.

We present Kaplan-Meier survival plots for postoperative complications versus no complications, with the associated log-rank test statistic. Mixed effects Cox proportional hazards modelling with country, nested within study, as a random intercept was used to account for the clustered nature of the data. We report univariable and multivariable (adjusted) analysis of complications and one-year survival, presented as hazard ratios (HR) with 95% confidence intervals. Covariates were included based on prior knowledge of association with mortality, and clinical significance. We included the following variables in the multivariable model: age, sex, ASA grade, smoking status, surgical procedure category, surgical severity, cancer surgery, all chronic diseases and count of diseases.[8 11 12 22–28] We explored the proportional hazards assumption using Schoenfeld residuals. We explored linearity of age by comparing a model including age as untransformed variable to a series of models with different transformations.

We identified a violation of the proportional hazards assumption for our primary exposure. This was handled post-hoc using a time-step function and dividing the influence of complications into two time periods (0-20 days, >20 days); we present the hazard ratios for each time period. To determine the variability between nations and studies, we report the intraclass correlation coefficient (ICC). The ICC is the proportion of variability in outcome explained by the clustering structure. All analyses were performed using R (Version 4.0.1), we used *data.table* for data manipulation, *survival* and *coxme* libraries for survival analysis, the *mice* library for multiple imputation and we generated figures using *ggplot2.*

Sensitivity analyses

In the ISOS study, complication severity was graded for each complication using a four-item scale, and in the METS study complications were recorded as either present or absent, with a grading for the most severe complication. We allocated each patient to a group based on the severity of their worst complication and measured the association between worst complication severity and subsequent one-year mortality. To describe the relationship between individual complications and one-year survival, we present the crude rate of one year death and the hazard ratio for death associated with each complication type. For patients who suffered multiple complications, we included each patient in each analysis. To determine the duration of postoperative follow-up identifying most deaths, we report the cumulative rate of death over one year after surgery, stratified by the presence of complications. We did a post-hoc analysis exploring the relationship between anaesthetic approach, development of complications and subsequent one year death.

Results

Patient selection

We included 10132 patients, of whom 8808 were from the ISOS study and 1324 were from the METS study. After pre-defined exclusions, 9952 patients remained, of whom 9733 had complete follow-up data and were included in the analysis. The cohort selection process is outlined in figure 1.

Patient characteristics

The mean age was 59 (SD: 16.8) and 5362 (55.1%) patients were female. Most patients were ASA-PS grade 2 (4991, 51.3%). The ~~commonest~~ most common type of surgery was orthopaedics (2504; 25.5%), and 6609 (67.9%) procedures were performed under general anaesthesia (table 1). The characteristics of patients with incomplete one year follow up is in supplementary table 3.

Incidence of complications

1841 (18.9%) patients suffered a complication within 30 days after surgery. Infections were the ~~commonest~~ most common complication and affected 588 (6.0%) patients. The median age of patients who suffered a complication was 67 years (IQR: 56 to 75) compared to 61 years (IQR: 46 to 71) among patients who did not suffer a complication. Some 995 (54.0%) of patients who suffered a complication were male, compared to 3376 (42.8%) of patients who did not. The prevalence of chronic diseases was greater among patients who suffered complications than those who did not (table 1).

Outcomes

Within 30 days after surgery, 35 of 10132 patients (0.3%) died, within one year after surgery, 319 patients died (3.3%). The characteristics of patients, stratified by survival at one year after surgery is in supplementary table 4.

Association between complications and outcomes

Among 1841 patients who suffered complications, 28 (1.5%) died within 30 days and 187 (7.5%) died within one year after surgery. Among 7892 patients who did not suffer a complication, 7 (0.3%) died within 30 days and 181 (2.3%) died within one year after surgery (table 2 & figure 2). Before adjustment, the HR for death was 3.38 (95%CI: 2.71 – 4.22). After adjustment, the HR for death was 1.94 (95%CI: 1.53 - 2.46) (figure 3). We explored including a non-linear term for age but found minimal improvement in log likelihood. We treated the presence of any complication as a time varying variable with two steps (0-20 days, >20 days) due to non-proportional hazards (supplementary figure 1). These steps were selected based on review of Schoenfeld residual plots. After adjustment, the influence of complications was greatest in the first 20 days after surgery with HR 75.98 [17.93 to 322]) that reduced to 1.61 (1.26 to 2.07) after 20 days. We observed variation between studies and nations, the intraclass correlation coefficient between nations was 0.08 and between studies was 0.265 (supplementary table 5). The greatest risk of death was among patients recruited to the ISOS study in England, and lowest among those recruited to METS in Canada. The adjusted hazard ratios associated with complications at different time points, and for variables included in the multivariable models are reported in tables 3 & supplementary table 6. Our findings were unchanged when we used multiple imputation to derive a complete dataset (supplementary table 7). We constructed a directed acyclic graph to examine causal paths between complications and subsequent one-year survival (supplementary figure 2; supplementary code A). The lack of data in the period between the end of the prospective studies and subsequent one year mortality follow up prevented any assessment of direct or indirect causal relationships.

Sensitivity analyses

To explore the relationship between the severity of complications and one-year survival we did a sensitivity analysis among the subgroup of patients who had suffered any complication, stratifying patients by the severity of their worst complication. Among 1,841 patients who suffered a complication, the worst complication was graded minor among 736 (40.0%), moderate among 774 (46.9%) and severe among 194 (10.5%). Twenty-five patients died during their hospital admission following a complication. There was a clear graduation of effect in long-term outcomes according to severity of complication, with some 25 (12.9%) patients who suffered severe complications dying within one year (HR 6.0 [95% CI: 4.0-9.1]) (table 2).

The complication associated with the greatest crude rate of death within one year after surgery was respiratory failure, resulting in 6 deaths among 28 patients (21.4%; 95% CI: 8.3 – 41.0%) (supplementary figure 2). The complication associated with the lowest crude rate of death within one year after surgery was 'other' complications (26 of 540, 4.8%). Given the low number of events when stratified by type of complication, we did not perform multivariable adjustment in this sensitivity analysis (table 2, supplementary figure 3).

To identify optimal duration of follow up among patients following surgery, we did a post-hoc analysis to demonstrate when deaths occur, stratified by the presence or absence of complications (supplementary figure 4). Among patients with complications, one quarter of deaths occurring in the year after surgery occurred within the first 38 days after surgery, compared to the first 145 days after surgery for patients who did not suffer complications (supplementary table 8).

We did a post-hoc exploratory analysis of the association between different anaesthesia techniques and subsequent risk of complications and death (supplementary table 9). Mixed modality anaesthesia was associated with the greatest risk of complications (odds ratio: 2.52 [95%CI: 2.19 –

2.91]). There was no significant association between anaesthesia technique and survival after including it in the final multivariable, multi-level Cox proportional hazards model. In addition, there was no improvement in model as measured using ANOVA (p=0.31).

Discussion

The principal finding of this analysis of two observational cohort studies across five nations is that complications in the thirty days following elective surgery are associated with a twofold increase in one-year mortality. Infections were the ~~commonest~~ most common complications affecting 1 in 20 patients, of whom 11% died within the year after surgery. The complication associated with the greatest risk of one-year death was respiratory failure, where one in five patients died. Our findings persisted after adjustment for important patient-level characteristics, and for the different study/country combinations included in the dataset.

Our finding that complications are associated with reduced long-term survival is consistent with data from a multi-centre cohort study in the USA, first published in 2005.[14] The authors reported a substantial reduction in survival up to eight years after surgery among patients who sustained complications. However, the study cohort inclusion window ended in 1999 and the authors reported an overall one-year mortality rate of 6.9% among patients without complications, which is much greater than would be expected of contemporary surgical practice, reflected by a three-fold lower mortality rate in our cohort. In contrast to Khuri et al, we observed a 60% increase in the relative hazard of death overtime, which suggest that while the overall risk of death has successfully been reduced overall, the relative influence of complications remains profound.[14] We also identified a strong time-dependent association between complications and survival, with a very high rate of death in the first 20 days after surgery, followed by a lower, but still elevated, risk of death among patients who suffered complications, which persisted after adjusting for confounding factors.

Death after suffering a complication has been described as failure to rescue. The incidence of failure to rescue is subject to substantial inter-hospital variation. [29] We identified a similar variation in one-year survival among patients who suffered complications. Our modelling suggests that 8% of the variability in the rate of one-year death after surgery is explained by country. While these findings may be sensitive to differing inclusion criteria or outcome definition between studies, they are likely to represent true variability that has several possible explanations. There may be between-country variation in selection criteria for surgery, prevalence of risk factors and end-of-life practices.[30] Upcoming studies, such as the Latin America Surgical Outcomes Study will help understand these potential variations.[31] Differences in the management of complications may also alter the likelihood of long-term survival. For example, there is growing evidence of association between repeated acute cellular injury and chronic harm in several organ systems including kidney injury, myocardial injury and cognitive dysfunction.[9 26 27 32] However, the optimal way to improve long-term survival for patients who have suffered complications remains unclear. Future research could focus on individual types of complications or organ systems, for example, the influence of interventions reducing the progression of chronic kidney disease and cardiac risk factors among survivors of acute kidney injury.[33]

We hypothesised that risk of mortality may vary by type of complication. Respiratory failure, while rare, was associated with the greatest risk of postoperative mortality. However, clinical strategies to prevent postoperative pulmonary complications remain elusive. Recent studies have failed to find benefit with routine postoperative continuous positive airway pressure or non-invasive ventilation to prevent pneumonia and respiratory failure.[34 35] Infective complications were the ~~commonest~~ most common, affecting 1 in 20 patients, and were associated with a 1 in 10 rate of death after one year. However, growing evidence suggests only marginal benefit from liberal antimicrobial prophylaxis to prevent postoperative infection.[36] Further research is needed to inform decision making around routine preventative antimicrobial therapy and to develop alternative strategies to reduce total antimicrobial use. During the COVID-19 pandemic, reports have highlighted the very poor short-term outcomes experienced by patients with perioperative SARS-CoV-2 infection.[8,32] Our findings suggest that there is likely to be a persistently increased risk of death in this patient group. We observed that patients with severe complications in the immediate postoperative period had higher rates of death in the year after surgery. Both the type and severity of complications are therefore important in determining the impact on long-term survival. Among survivors of complications, there are broader negative effects such as reduced mobility and loss of function not captured by our data. While we found that the rate of complications was significantly influenced by anaesthesia technique, there was no association after adjustment for other factors. This is likely because major abdominal or thoracic procedures may require mixed anaesthetic which therefore acts as a confounder. One quarter of deaths in the year after surgery occur within 38 days among patients who suffer complications, compared to 145 days among those who don't suffer complications. This suggests that studies reporting short-term measures of mortality are likely to underestimate the influence of complications. This problem may be exacerbated by the legal definition of a surgical complication in different countries which may lead to a failure to recognise that a life limiting complication has occurred.

Our analysis has several strengths. First, we included a large cohort of patients undergoing a wide range of surgical procedures across five nations, which makes our results widely generalisable to perioperative practice in high-income countries. Second, we used linkage to national death registry data to robustly determine postoperative death, with a low rate of missing data (<2%). Third, we incorporated data from two large, prospective cohort studies. Both had detailed and standardised data collection approaches with comparable definitions. Fourth, we did a detailed survival analysis, which was pre-specified and included handling of non-proportional hazards.

The analysis also has limitations. First, despite similarities between the studies, there were some variables, such as liver cirrhosis, which were present in only one study. In addition, there were small differences in the inclusion criteria of each study. We accounted for this, and potential differences in patients within studies, by using a mixed-effects model. By including a broader range of patients across multiple nations, the external generalisability of our study is improved, and between study differences are unlikely to be differential by complication status and therefore would not bias our results. Second, a small number of patients did not have one-year outcome data. These patients were typically younger, with a lower burden of chronic disease (high proportion of ASA-PS grade 1), and a low incidence of postoperative complications. It is possible that some of these patients emigrated, in which case any subsequent death would not be captured in national registry data. However, this is unlikely to vary between patients with or without complications and therefore unlikely to impact our findings. Third, any observational cohort study is prone to unmeasured confounding. We sought to control for sources of confounding through multivariable modelling. However, there may be variables not captured during the study that may influence our findings, like events occurring between the end of the cohort study data collection window and one year following, and variable end-of-life practices.[30] We did not use routinely collected data to capture diagnostic codes, this may have resulted in greater variability in clinical judgement and decreased the prevalence of certain conditions, like cardiovascular diseases. Fourth, there are likely to be a wide variety of negative effects associated with complications such as increased frailty and loss of function that we did not capture, but that are important to patients.

Patients with postoperative complications have a 60% increased risk of death during the first year after surgery compared to patients without complications. Respiratory failure, even before the COVID-19 pandemic, was most strongly associated with one-year mortality. Future studies should collect data over longer time periods to understand the relationship between short-term harm (complications), late effects and subsequent patient outcomes. While one year survival is a useful measure of poor outcome, wider implications such as quality of life and functional capacity should also be explored. Further research is required to determine if it is possible to reduce the incidence of postoperative complications, and strategies to effectively treat complications to prevent poor long-term outcomes.

Contributors

TA, AF, RP were responsible for study design. AF, TA, JP, RP, MC, DC, DW, BHC were responsible for data collection. AF and TA were responsible for data analysis. AF and TA were responsible for data interpretation. AF and TA wrote the first draft of the manuscript. All authors revised the manuscript for important intellectual content and approved the final version. AF and TA had full access to the data and act as guarantors.

Competing interest statement

AJF holds a National Institute for Health Research Doctoral Research fellowship (DRF-2018-11-ST2-062). MSC has received honoraria and travel reimbursements from Edwards Lifesciences and Braun within the last five years and is Deputy Editor-in-Chief for the European Journal of Anaesthesiology. BHC is supported by a Merit Award from the Department of Anesthesiology and Pain Medicine at the University of Toronto. DC hols a Neurological Foundation of New Zealand Senior Clinical Fellowship (2020A/2005 SCF). DNW has received honoraria from Edwards Lifesciences within the last five years and is a member of the Scientific Advisory Board for Surgical Safety Technologies Inc. RP has received honoraria and/or research grants from Edwards Lifesciences, Intersurgical and GlaxoSmithkline within the last five years and holds editorial roles with the British Journal of Anaesthesia and the British Journal of Surgery. TA is an NIHR Clinical Lecturer, an editor of the British Journal of Anaesthesia and has received consultancy fees from MSD unrelated to this work. All other authors report *no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.*

Transparency declaration

TA affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Variable	All	Complications within 30 days	
		Present	Absent
N	9733	1841	7892
Age & Sex			
Mean age (SD)	59 (16.8)	64.7 (14.7)	57.7 (17)
Female sex	5362 (55.1%)	846 (46%)	4516 (57.2%)
Male sex	4371 (44.9%)	995 (54%)	3376 (42.8%)
ASA-PS grade			
I	2113 (21.7%)	197 (10.7%)	1916 (24.3%)
II	4991 (51.3%)	848 (46.1%)	4143 (52.5%)
III	2480 (25.5%)	720 (39.1%)	1760 (22.3%)
IV	149 (1.5%)	76 (4.1%)	73 (0.9%)
Chronic diseases			
COPD	1464 (15%)	318 (17.3%)	1146 (14.5%)
Diabetes mellitus	1254 (12.9%)	306 (16.6%)	948 (12%)
Coronary artery disease	1200 (12.3%)	370 (20.1%)	830 (10.5%)
Chronic kidney disease	1023 (10.5%)	326 (17.7%)	697 (8.8%)
Cancer	953 (9.8%)	329 (17.9%)	624 (7.9%)
Heart Failure	271 (2.8%)	99 (5.4%)	172 (2.2%)
Current smoker	1277 (13.1%)	214 (11.6%)	1063 (13.5%)
Surgical procedure type			
Orthopaedics	2504 (25.7%)	380 (20.6%)	2124 (26.9%)
Peritoneal	1698 (17.4%)	494 (26.8%)	1204 (15.3%)
Obstetrics	1463 (15%)	160 (8.7%)	1303 (16.5%)
Urology & Gynaecological	1410 (14.5%)	271 (14.7%)	1139 (14.4%)
Head & Neck	904 (9.3%)	111 (6%)	793 (10%)
Other	624 (6.4%)	90 (4.9%)	534 (6.8%)
Breast	334 (3.4%)	27 (1.5%)	307 (3.9%)
Thoracic	483 (5%)	219 (11.9%)	264 (3.3%)
Vascular	308 (3.2%)	87 (4.7%)	221 (2.8%)
Neurological	5 (0.1%)	2 (0.1%)	3 (0%)
Surgical features			
Low severity	1113 (11.4%)	80 (4.3%)	1033 (13.1%)
Moderate severity	4187 (43%)	517 (28.1%)	3670 (46.5%)
High severity	4433 (45.5%)	1244 (67.6%)	3189 (40.4%)
Surgery for cancer	2224 (22.9%)	620 (33.7%)	1604 (20.3%)
Laparoscopic surgery	1761 (18.1%)	326 (17.7%)	1435 (18.2%)
Anaesthetic technique			
General only	6609 (67.9%)	1191 (64.7%)	5418 (68.7%)
Regional only	1869 (19.2%)	254 (13.8%)	1615 (20.5%)
General with regional	1040 (10.7%)	371 (20.2%)	669 (8.5%)
Sedation only	215 (2.2%)	25 (1.4%)	190 (2.4%)
Study			
ISOS	8460 (86.9%)	1503 (81.6%)	6957 (88.2%)
METS	1273 (13.1%)	338 (18.4%)	935 (11.8%)
Nation			
United Kingdom	6929 (71.2%)	1256 (68.2%)	5673 (71.9%)
New Zealand	1481 (15.2%)	296 (16.1%)	1185 (15%)
Sweden	681 (7%)	163 (8.9%)	518 (6.6%)
Canada	402 (4.1%)	59 (3.2%)	343 (4.3%)
Australia	240 (2.5%)	67 (3.6%)	173 (2.2%)

Table 1. Characteristics of patients, stratified by the presence of complications within 30 days of surgery. Data are presented as n (%) unless otherwise stated. SD; standard deviation, IQR; inter-quartile range, ASA-PS;

American Society of Anesthesiologists Physical Status classification grading, COPD; Chronic obstructive pulmonary disease.

	Number	Proportion dead		Unadjusted hazard ratio for death by 365 days (95%CI)
		30 days	365 days	
All patients	9733	35 (0.4%)	319 (3.3%)	-
Any complication				
Present	1841	28 (1.5%)	138 (7.5%)	3.38 (2.71 to 4.22)
Absent	7892	7 (0.1%)	181 (2.3%)	ref
Specific complication groups				
Infection	588	8 (1.4%)	65 (11.1%)	4.19 (3.19 to 5.5)
Cardiac	286	18 (6.3%)	38 (13.3%)	4.86 (3.46 to 6.81)
Acute kidney injury	247	6 (2.4%)	20 (8.1%)	2.66 (1.69 to 4.19)
Bleed or thromboembolism	308	5 (1.6%)	28 (9.1%)	3.05 (2.07 to 4.49)
Respiratory failure	28	2 (7.1%)	6 (21.4%)	7.96 (3.55 to 17.86)
Surgical requiring reoperation	348	8 (2.3%)	36 (10.3%)	3.60 (2.55 to 5.1)
Other complications	540	4 (0.7%)	26 (4.8%)	1.53 (1.02 to 2.28)
Severity of worst complication				
Mild	736	1 (0.1%)	27 (3.7%)	1.6 (1.1 – 2.4)
Moderate	864	1 (0.1%)	60 (6.9%)	3.1 (2.3 – 4.1)
Severe	194	1 (0.5%)	25 (12.9)	6.0 (4.0 – 9.1)
Death	25	25 (100%)	25 (100%)	-

Table 2. Rate of death and hazard ratio for death, presented by the presence/absence of complications within 30 days and specific complication groups. Patients may have suffered multiple complications, so the sum of specific complications will not equal the overall number of patients suffering a complication. Hazard ratios are presented with 95% confidence intervals and were unadjusted.

Feature	Adjusted hazard ratio (95% CI)	z
Complication within 30 days	1.94 (1.53 - 2.46)	5.55*
Age (one year increment)	1.04 (1.03 - 1.05)	7.38*
Sex: female vs. Male	0.73 (0.58 - 0.93)	-2.98*
ASA-PS grade: II vs. I	1.63 (0.9 - 2.95)	1.64
ASA-PS grade: III vs. I	3.15 (1.71 - 5.8)	3.72*
ASA-PS grade: IV vs. I	6.11 (2.85 - 13.13)	4.72*
Smoking status: current vs. not current	1.45 (1.04 - 2.02)	6.2*
Operative severity: low vs. high.	1.07 (0.73 - 1.56)	0.41
Operative severity: moderate vs. high.	1.15 (0.89 - 1.48)	1.07
Surgery for cancer	2.89 (2.24 - 3.72)	8.17*
Coronary artery disease	0.36 (0.17 - 0.74)	-2.58*
Cardiac failure	0.65 (0.3 - 1.38)	-0.84
Cancer	1.59 (0.78 - 3.23)	1.72
Diabetes mellitus	0.42 (0.2 - 0.86)	-2.14*
Stroke	1.25 (0.84 - 1.86)	1.08
COPD	0.48 (0.23 - 1)	-1.67
Chronic kidney disease	0.59 (0.29 - 1.23)	-1.23
Number of diseases: 1 vs. 0	2.53 (1.21 - 5.28)	2.10*
Number of diseases: 2 vs. 0	5.64 (1.4 - 22.68)	2.24*
Number of diseases: ≥3 vs. 0	15.33 (1.72 - 136.85)	2.15*
Random effects components:	**Standard deviation**	**Variance**
Study / Country	0.65	0.42
Country	1.20	1.45

Table 3. Variables included in the multivariable adjusted, multi-level Cox proportional hazards model before time-varying stratification of complication. Random effects components were country nested within study and the value represents the standard deviation of the intercept for the log hazard ratio. * p value < 0.05. P value for global Schoenfeld test = 0.03.

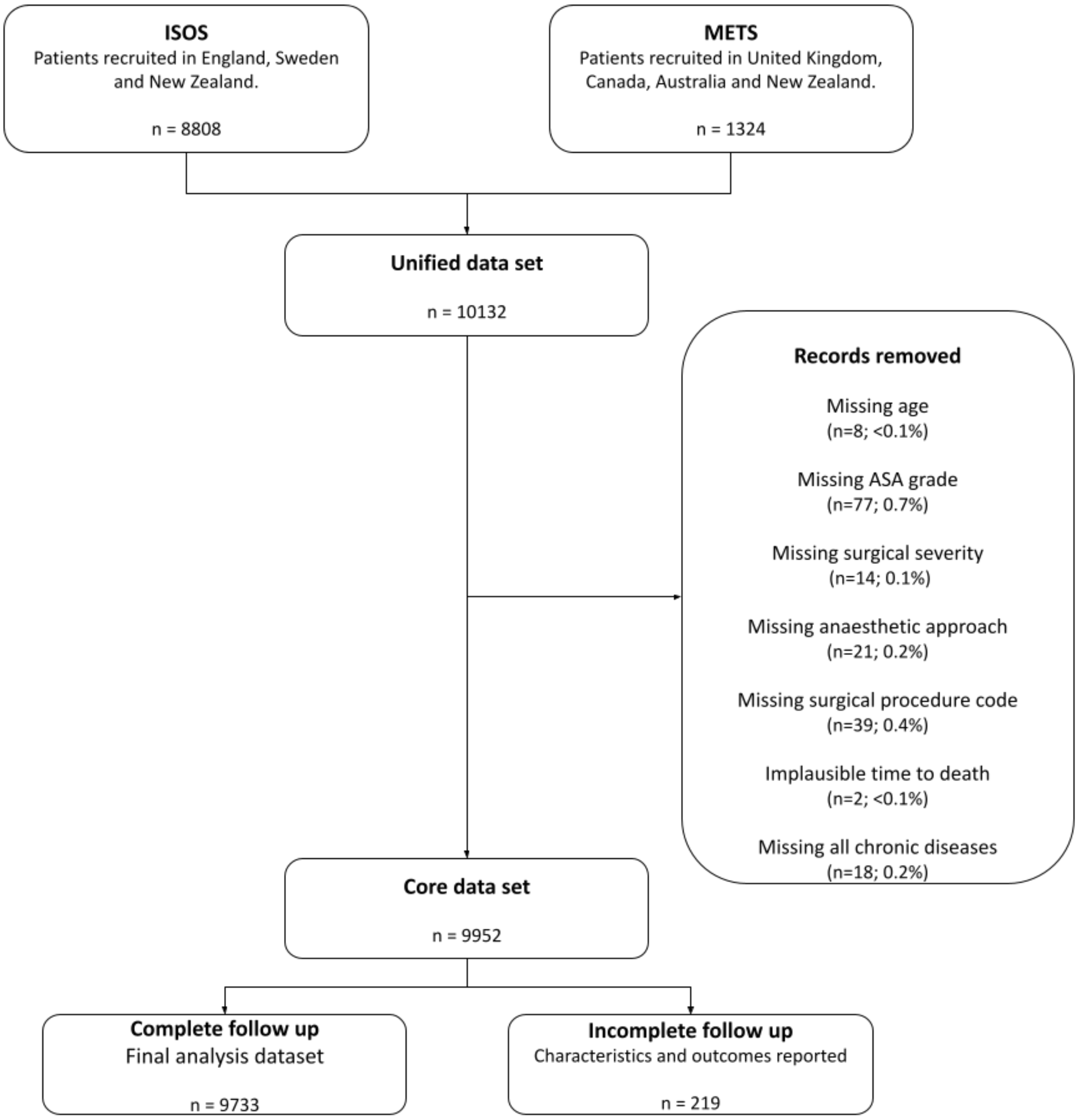

Figure 1. Flow diagram summarising patient inclusion.

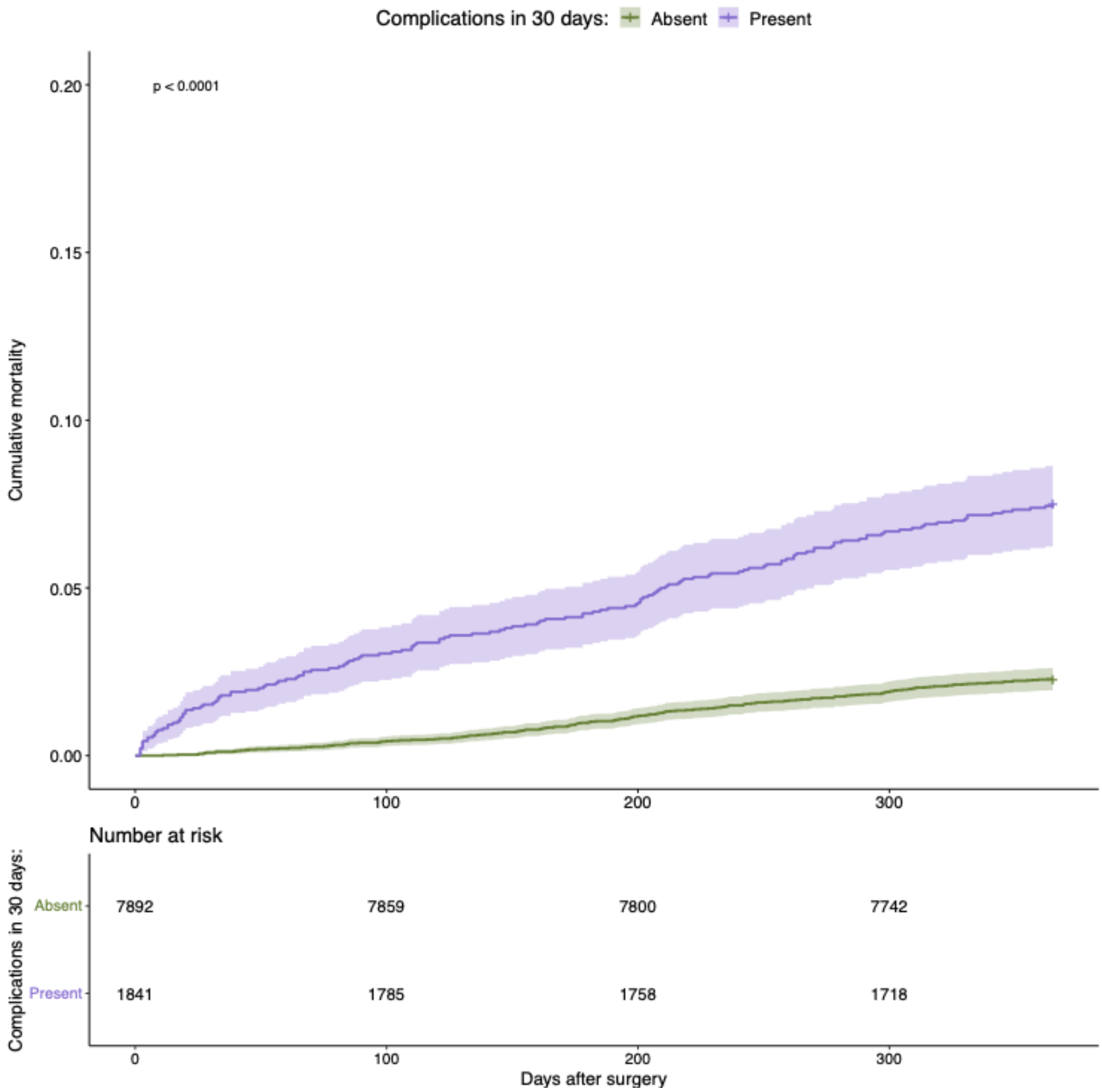

Figure 2. Cumulative mortality after surgery, stratified by the presence of complications within 30 days of surgery. P value derived from a log-rank test.

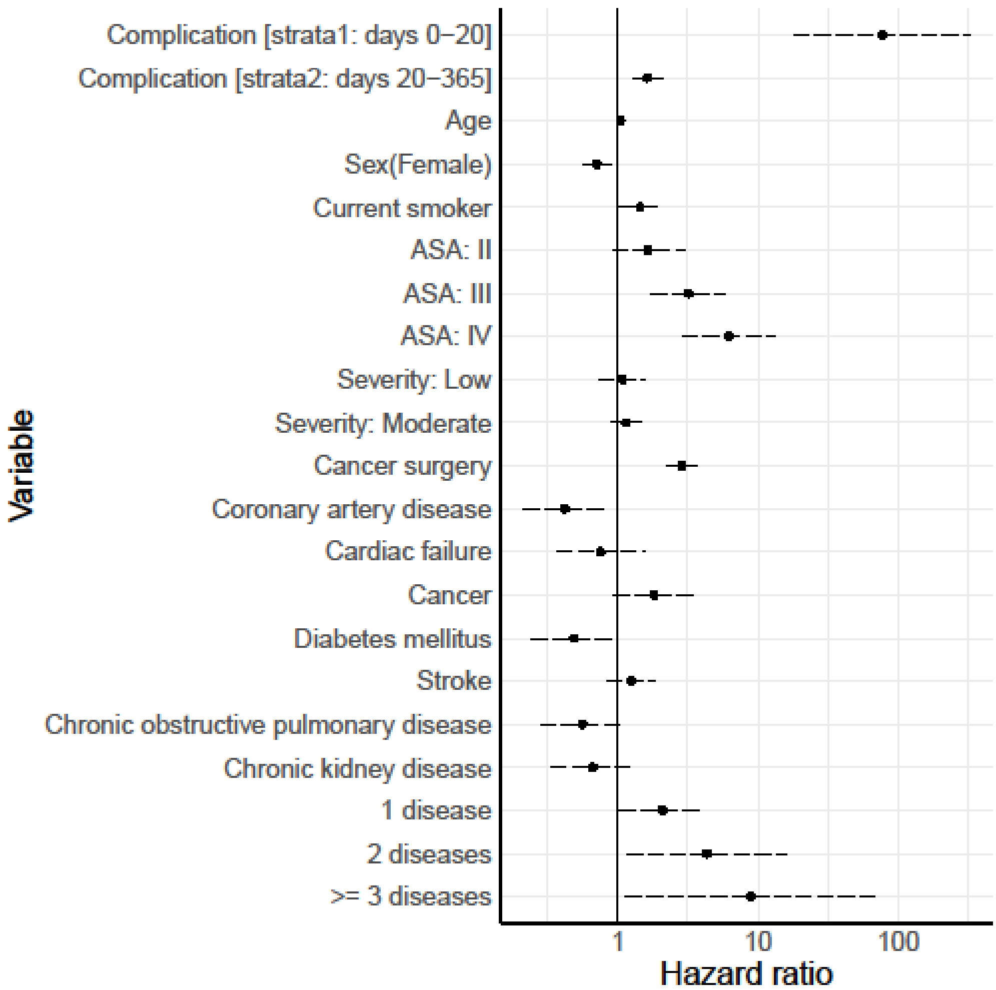

Figure 3. Hazard ratios from the multivariable, multi-level Cox proportional hazards regression model after stratifying complications to resolve non-proportionality. Dashed lines indicate associated 95% confidence intervals.