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Short- and long-term mortality in major non-cardiac surgical patients admitted to the intensive care unit

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Background: The aim of this register-based cohort study was to characterize patients admitted to the intensive care unit (ICU) following non-cardiac surgery and identify risk factors associated with 30-days, 90-days and 1-year mortality after ICU admission.

Methods: Patients aged 18+ years admitted to the intensive care unit within 30-days of non-cardiac surgery at four Capital Region hospitals in Denmark between January 2005 and December 2014 were included. Patients were identified through the Danish National Patient Register. The outcomes were 30-days, 90-days and 1-year mortality after ICU admission. Unadjusted and multivariate logistic regression analyses were performed to identify independent risk factors of mortality.

Results: The study included 3311 ICU patients. Gastrointestinal surgery accounted for 71.3%, orthopaedic surgery for 18.4% and urologic surgery for 10.2% of the population. For the total population, the median length of stay in hospital was 18 days (9-36, 25th-75th percentile) and 2 days (1-4, 25th-75th percentile) in the ICU. Thirty-days, 90-days and 1-year mortality were 37.8%, 44.5% and 51.2% respectively. Mortality within the ICU was 22.3% while the post-ICU in-hospital mortality was 19.4%. Higher age, comorbidity, delayed ICU admission, acute surgery, and gastrointestinal and orthopaedic surgery increased 30-days, 90-days and 1-year mortality.

Conclusions: Short- and long-term mortality in non-cardiac surgical patients admitted to the ICU is very high, especially among the elderly comorbid patients undergoing acute surgery. Future research should focus on targeting clinically modifiable risk factors and performing tailored treatment for these high-risk patients.

1 | INTRODUCTION

Worldwide, more than 310 million surgical procedures are undertaken each year with an in-hospital mortality rate between 1.5% and 1.9% in developed countries.[1-3] High-risk patients represent a smaller proportion of the surgical population but accounts for more than 80% of the post-operative deaths.[2] A large database study reported a post-operative mortality of 0.42% in the standard surgical population and 12.3% in the high-risk population.[2] Post-operative complications seems to be the most important cause for poor surgical outcomes, admission to the intensive care unit (ICU) and short- and long-term post-operative mortality.[4-6] Patients undergoing major non-cardiac surgery make out a considerable proportion of the admissions to the ICU and utilise large amounts of resources.[7] While large population-based studies have characterised the high-risk surgical population in general,[2,3] few studies have specifically identified and characterised the high-risk surgical population admitted to the ICU following surgery. By exploring factors associated with morbidity and mortality on the short and long term for this patient group, it might be possible to identify clinically modifiable factors leading to better outcomes. The aim of this study was to characterize patients admitted to the ICU following non-cardiac surgery and identify risk factors associated with 30-days, 90-days and 1-year mortality after ICU admission.

2 | METHODS

2.1 | Data sources

The study was a register-based cohort study. Patients were identified through the Danish National Patient Register that contain data on all Danish hospital admissions since 1977.[8] In the register, diagnosis codes are recorded according to the International Classification of Diseases (ICD) (10th revision used since 1994). We included the additional variables added to the Danish National Patient Register and monitored by the Danish Intensive care Database that covers ICU admissions in Denmark since 2005.[9] Vital status and cause of death were obtained from the Danish Civil Registration System and the Danish Register of Causes of Death.[10] All Danish residents are registered with a unique personal identification number, which makes it possible to make individual linkage between all Danish nationwide registers. The study was approved by the Danish Data Protection Agency (REG-107-2015). According to Danish legislation, no approval from the Research Ethics Committee System is necessary for studies solely based on registers. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Appendix S1).[11]

2.2 | Study population and setting

The population was limited to patients aged 18+ years admitted to the ICU in one of four Capital Region hospitals (Hvidovre Hospital, Herlev Hospital, Bispebjerg Hospital and Nordsjællands Hospital Hillerød) in Denmark between January 2005 and December 2014. The hospitals were all secondary referral centres. Patients were included if admitted to the ICU within 30-days of major non-cardiac surgery with a minimum stay of 24 hours in the ICU unless deceased. An ICU admission lasting less than 24 hours was likely due to a short need for perioperative optimization. Patients were excluded if admitted to the ICU or having undergone major surgery within 90 days of the hospital admission of the index surgical procedure. Non-cardiac surgery included gastrointestinal surgery, orthopaedic surgery and urologic surgery defined by NOMESCO surgical chapters of KJ, KN and KK. Admissions involving endoscopies and minor surgical procedures including biopsies, minor abscess incision and/or drainage and surgery of the hand, wrist, ankle and foot were excluded.

2.3 | Extracted data and definitions

Data on sex, age, comorbidity, hospital and ICU admission and discharge (date, time), priority of the primary operation (acute or elective), surgical procedure (procedure code, date, time), haemodialysis, invasive ventilation, reoperation, date and cause of death were extracted from the Danish National Patient Register. Surgical procedures were further subdivided according to the site of surgery. Emergency surgery was defined as a surgical procedure performed during an acute admission to a surgical department. Comorbidity was indexed using Charlson comorbidity index[12] (CCI) based on diagnosis codes recorded within 10 years prior to hospital admission. Patients were divided into three age groups commonly used in the ICU literature (18-65 years, 65-75, and >75 years). Length of hospital and ICU stay and days between surgery and ICU admission were calculated based on admission, discharge and operation dates.

Editorial Comment

There is some mortality risk for major (non-cardiac) surgery patients who need post-operative intensive care. In this analysis using Danish national databases, risk of death in this cohort by 30 days, 90 days and 1 year after ICU admission were high- 37.8%, 44.5%, and 51.2% respectively.

2.4 | Outcome parameters

Outcomes were 30-days, 90-days and 1-year mortality after admission to ICU.

2.5 | Statistical analyses

Continuous data were expressed as mean (standard deviation) or median (percentiles) and categorical data as numbers and percentages. Survival stratified by pre-defined categorical variables (age groups, type of surgery, priority (acute/elective surgery), and CCI) was illustrated with Kaplan Meier survival curves. Cox regression was not performed since data did not comply with the proportional hazard assumption. Unadjusted and multivariate logistic regression models were performed to study the association between the pre-defined covariates and the outcomes. Results were expressed as odds ratios (OR) with 95% confidence intervals. Pre-defined covariates included age groups, gender, CCI, priority (acute/elective surgery), delayed ICU admission (days from surgery to ICU admission), reoperation prior to ICU admission, malignant surgery and type of surgery (gastrointestinal, orthopaedic and urological surgery). Based on a pre-defined clinical hypothesis, we tested for the potential interaction between age groups and CCI. If significant, the interaction was included in the multivariate analyses. Model fit was assessed with the Hosmer and Lemeshow Goodness-of-Fit Test. We did a sensitivity analysis including patients with more than 30 days between the major non-cardiac surgery and admission to ICU. Statistics were performed with SAS (version 9.4 for Windows, SAS Institute, Cary, NC).

3 | RESULTS

3.1 | Population

From 1 January 2005 to 31 December 2014, 32 000 admissions to the ICU were registered at the four Capital Region hospitals in Denmark. Due to missing data on ICU discharge, 139 admissions were excluded and we ended up with 31 861 ICU admissions. In the same period, 338 479 major non-cardiac surgeries were performed at the same hospitals. A total of 5849 of the surgical admissions included an ICU admission during the hospital stay. Patients were excluded based on the pre-defined exclusion criteria, Figure 1. Of the 1554 patients that stayed less than 24 hours in the ICU, 326 were included since they deceased within these 24 hours in the ICU. We ended up with a population of 3311 patients undergoing major non-cardiac surgery including 339 patients undergoing urological surgery, 2362 undergoing gastrointestinal surgery and 610 undergoing orthopaedic surgery (Figure 1).

3.2 | Descriptive characteristics

A total of 2465 patients (74.5%) underwent an acute primary operation and 621 patients (18.8%) underwent surgery due to a malignant disease (Table 1). The median length of stay was 18 days

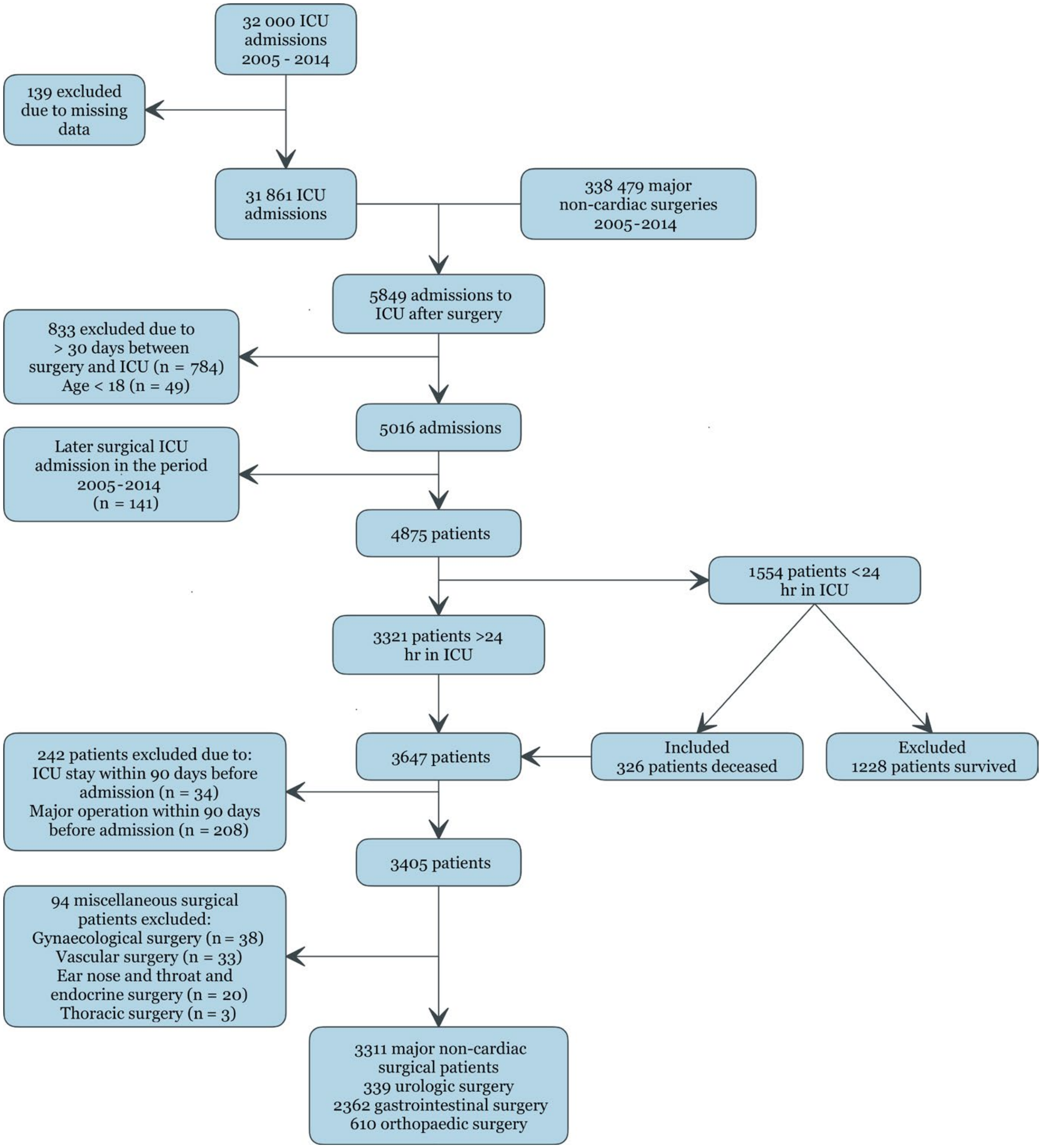

FIGURE 1 Formation of the population based on the Danish National Patient Register. ICU, intensive care unit; OP, operation

TABLE 1 Baseline characteristics of the non-cardiac surgical population in the intensive care unit from 2005-2014 in four Capital Region hospitals in Denmark

Characteristics	All non-cardiac surgical patients in the ICU (n = 3311)	Deceased within 30-d of the operation (n = 1253; 37.8%)
Age		
18-64	1039 (31.4)	199 (19.2)
65-75	1064 (32.1)	381 (35.8)
76-101	1208 (36.5)	673 (55.7)
Male	1702 (51.4)	610 (35.8)
Female	1609 (48.6)	643 (40.0)
Charlson Comorbidity Index		
0	655 (19.8)	153 (23.4)
1-2	1348 (40.7)	487 (36.1)
3-4	865 (26.1)	392 (45.3)
5+	443 (13.4)	221 (49.9)
Surgery		
Acute primary operation	2465 (74.5)	1086 (44.1)
Cancer surgery	621 (18.8)	179 (28.8)
Urologic surgery	339 (10.2)	25 (7.4)
Prostate	32 (0.1)	2 (6.3)
Kidney	243 (7.3)	8 (3.3)
Testis, penis, scrotum	9 (0.3)	1 (11.1)
Ureter, urinary bladder	49 (1.5)	14 (28.6)
Retroperitoneum	6 (0.2)	0 (0)
Gastrointestinal surgery	2362 (71.3)	955 (40.4)
Greater omentum, mesentery, peritoneum	149 (4.5)	57 (38.3)
Abdominal wall	64 (1.9)	20 (31.3)
Explorative laparotomy	412 (12.4)	193 (46.8)
Diaphragm, oesophagus	5 (0.2)	0 (0)
Biliary tract, liver, spleen, pancreas	105 (3.2)	40 (38.1)
Rectum	155 (4.7)	50 (32.3)
Small bowel	412 (12.4)	158 (38.3)
Large bowel	724 (21.9)	285 (39.4)
Stomach, duodenal bulb	336 (10.1)	152 (45.2)
Orthopaedic surgery	610 (18.4)	273 (44.8)
Spinal	10 (0.3)	3 (30.0)
Shoulder, upper extremity	43 (1.3)	10 (23.3)
Pelvis, hip, thighbone	408 (12.3)	205 (50.2)
Knee, lower leg	149 (4.5)	55 (36.9)
Acute reoperation		
Reoperation prior to ICU	417 (12.6)	158 (37.9)
Reoperation during ICU	197 (5.9)	50 (25.4)
Reoperation after ICU	222 (6.7)	66 (29.7)
Intensive Care Unit		
Invasive ventilation	1876 (56.7)	915 (48.8)
Haemodialysis	535 (16.2)	263 (49.2)

Data are expressed as No. (%) unless otherwise indicated.
ICU, intensive care unit; SD, standard deviation.

(9-36, 25th-75th percentile) and the median length of stay in the ICU was 2 days (1-4, 25th-75th percentile). The median time from surgery to ICU admission was 1 day (0-5, 25th-75th percentile), while 417 patients (12.6%) underwent an acute reoperation prior to the ICU admission, 197 patients (5.9%) underwent an acute reoperation during the ICU stay and 222 patients (6.7%) after the ICU stay. In the ICU, 1876 patients (56.7%) underwent invasive ventilation and 535 patients (16.2%) received haemodialysis.

3.3 | Unadjusted mortality risk

In this ICU population, 1253 patients (37.8%) died within 30 days of the ICU admission. The 90-days mortality was 44.5% and 1-year mortality was 51.2%. In the ICU, 22.3% of the patients deceased while 19.4% deceased after ICU discharge. Kaplan-Meier survival curves showed that higher age and higher CCI were associated with a decreased 1-year survival (Figure 2A,B). Moreover, 1-year survival was decreased in patients undergoing gastrointestinal and orthopaedic surgery compared with urologic surgery (Figure 2C) and 1-year survival was decreased after an acute compared with an elective procedure (Figure 2D).

3.4 | Regression analyses

The unadjusted logistic regression showed significantly increased mortality with higher age, higher CCI, delayed ICU admission, acute primary operation, and for gastrointestinal and orthopaedic surgery compared with urologic surgery. Results from the unadjusted logistic regressions are available as Table S1. Adjusted OR showed similar results, Table 2. Furthermore, a significant interaction between age group and CCI was present (30-days $P = 0.01$, 90-days $P = 0.003$ and 1-year $P = 0.002$), see Figure 3.

3.5 | Sensitivity analysis

In the population including the patients with more than 30 days between operation date and admission to ICU, the 30-days, 90-day and 1-year mortality was 37.0%, 44.8% and 51.5% respectively, which was comparable with the main analysis.

4 | DISCUSSION

The study was a register-based cohort study including 3311 patients undergoing major non-cardiac surgery with an admission to the ICU in the post-operative period. The 30-days, 90-days and 1-year mortality after ICU admission were 37.8%, 44.5% and 51.2% respectively. While 22.3% of the patients deceased in the ICU, 19.4% deceased during hospitalization after ICU discharge. Higher age, higher CCI, delayed ICU admission, acute surgery, and gastrointestinal and orthopaedic surgery independently increased 30-days, 90-days and 1-year mortality.

The study shows that the subgroup of patients in the ICU that are admitted within 30 days after non-cardiac surgery represents a population of patients with very high risk of mortality. The majority of the patients underwent emergency major gastrointestinal surgery such as laparotomy with resection of the small or large intestine, suture of a perforated gastroduodenal ulcer or urgent orthopaedic surgery mainly consisting of hip fracture surgery. These procedures are associated with high risk of post-operative complications and mortality.[13-16] Recent studies have reported an overall 30-days mortality rate of 15.6 to 18.5% after emergency gastrointestinal surgery.[13-15] A Danish prospective cohort study on emergency gastrointestinal procedures reported 30-days post-operative mortality of 14.3% in patients cared for in the surgical ward, while 30-days post-operative mortality was 42% in patients transferred to the ICU.[14]

The surgical trauma and associated tissue damage induce acute inflammation, immunosuppression and catabolism, which makes the surgical patient vulnerable to post-operative complications including respiratory failure, cardiovascular complications and severe sepsis.[17,18] Post-operative complications have been shown to be more important for survival after major surgery than pre-operative patient risk factors.[6] In our study, the cause of the ICU admission was not identified. The majority of the ICU admissions might though be due to post-operative complications such as sepsis since the median time from surgery to ICU admission was 1 day. A large study based on the National Surgical Quality Improvement Programme reported on hospital mortality after inpatient general and vascular surgery.[4] They reported similar rates of post-operative complications across hospitals but the rate of death from post-operative complications was almost twice as high in very-high-mortality hospitals compared with very-low-mortality hospitals.[4] This underlines that there may be modifiable factors making identification and timely treatment of post-operative complications crucial for reducing post-operative mortality.[4]

Despite being high-risk patients, the median length of stay in the ICU was short and, in line with previous studies,[2,19] we reported a high post-ICU mortality. A study on 59 424 ICU admissions reported that 40% of deaths occurred after discharge from ICU even though less than 1% of the ICU patients were discharged to palliative care.[2] This suggests that we are not successful in identifying the patients that might still be in need of intensive care. Thus, a large proportion of ICU patients might be discharged too early to the surgical ward where the standard of care and monitoring can be inadequate leading to post-operative life-threatening complications.[19] Some patients might benefit from a semi-intensive department linking the ICU with the surgical ward; however, this should be confirmed in future research.[20]

This study and others have shown that patients admitted directly to the ICU after surgery have an improved survival compared with surgical patients admitted with delay.[3,14,21] This represents a potentially modifiable factor and needs increased attention in future research. Risk scores such as the Surgical Apgar score describe the surgical complexity and the patient's intraoperative response to

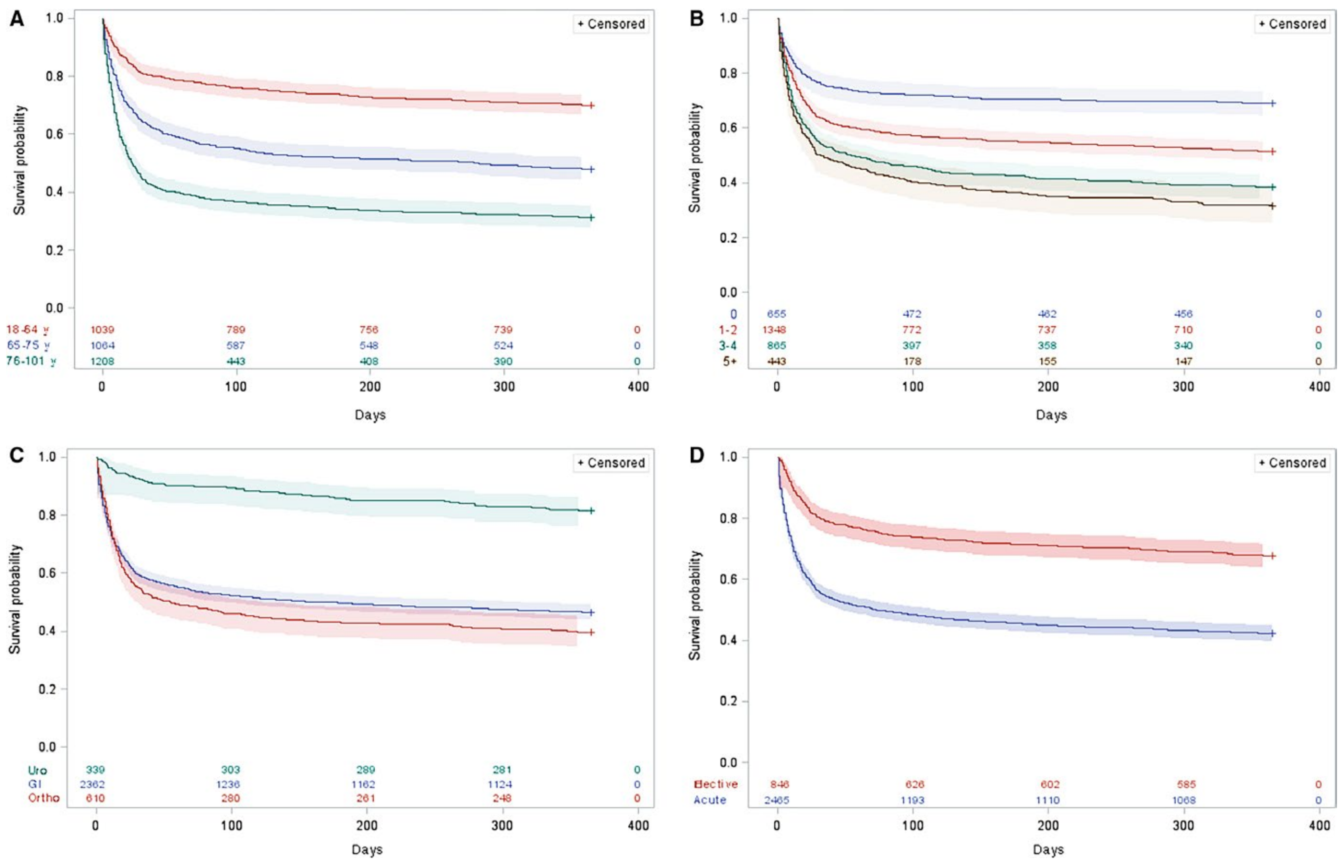

FIGURE 2 1-y survival curves stratified on age (A), Charlson comorbidity index (B), type of surgery (C) and surgical priority (D). GI, gastrointestinal surgery; Ortho, orthopaedic surgery; Uro, urologic surgery; Yrs, years

TABLE 2 Adjusted logistic regression models for 30-d, 90-d and 1-y mortality after ICU admission

Covariates	30-d mortality (95%CI) OR	*P*-value	90-d mortality (95% CI) OR	*P*-value	1-y mortality (95% CI) OR	*P*-value
Sex						
Male	1.0 (REF)	0.64	1.0 (REF)	0.62	1.0 (REF)	0.10
Female	1.0 (0.8-1.1)		1.0 (0.8-1.1)		0.9 (0.8-1.0)	
Age (y)[a]						
18-64	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001
65-75	3.6 (2.1-6.3)		4.2 (2.5-7.0)		3.5 (2.2-5.7)	
75-101	10.0 (6.2-16.2)		10.2 (6.4-16.4)		9.7 (6.2-15.2)	
Charlson comorbidity index[b]						
0	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001
1-2	2.3 (1.5-3.7)		2.6 (1.7-4.0)		2.8 (1.9-4.1)	
3-4	4.7 (2.9-7.7)		5.3 (3.3-8.4)		5.2 (3.3-8.1)	
+5	5.7 (3.3-9.9)		7.5 (4.4-12.8)		9.0 (5.4-15.0)	
Surgical priority						
Elective surgery	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001
Acute surgery	2.2 (1.8-2.8)		2.3 (1.8-2.8)		2.6 (2.1-3.2)	
Cancer						
No	1.0 (REF)	0.16	1.0 (REF)	0.34	1.0 (REF)	0.15
Yes	0.8 (0.7-1.1)		0.9 (0.7-1.1)		1.2 (0.9-1.5)	
Type of surgery						
Urological	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001	1.0 (REF)	<0.0001
Gastrointestinal	3.9 (2.6-6.2)		3.7 (2.5-5.5)		2.4 (1.7-3.4)	
Orthopaedic	4.0 (2.5-6.5)		3.9 (2.5-6.0)		2.8 (1.9-4.0)	
Delayed ICU admission (d)	1.03 (1.02-1.05)	0.0001	1.03 (1.02-1.05)	<0.0001	1.03 (1.02-1.05)	<0.0001
Reoperation prior to ICU admission	0.9 (0.7-1.2)	0.54	1.1 (0.9-1.4)	0.50	1.1 (0.8-1.4)	0.58

All variables in the table were included simultaneously in the multivariate analyses.
The analyses includes interaction between age group and Charlson comorbidity index.
CCI, Charlson comorbidity index; ICU, intensive care unit; OR, Odds ratio; 95%CI, Walds 95% confidence interval.
[a]Risk estimates of age for patients with Charlson comorbidity index 0.
[b]Risk estimates of Charlson comorbidity index for patients with age <65.

surgical stress.[22] Whether the score is useful in guiding post-operative care and triage to the ICU needs to be clarified.[23,24] Recently, two large cohort studies reported no survival benefit from ICU treatment after surgery.[25,26] One explanation could be that critical care are not allocated to the surgical patients that need it the most. These findings strongly support a strategy to define the ideal perioperative care pathway for high-risk patients undergoing major surgery that may or may not include ICU treatment.

Both age and comorbidity were independently associated with post-operative mortality within 1-year of surgery. Both factors are well-known predictors of poor outcomes in critically ill patients.[7,27-30] The exact mechanism that relates age to survival of surgical stress and critical illness is not fully elucidated. The low-grade inflammatory state in the elderly and the age-related decline in the innate and adaptive immune pathways might contribute to the increasing mortality.[17,31,32] The prevalence of frailty increases with age, thus the effect of age may partly be related to frailty.[33,34] Pre-operative frailty has been shown to be a predictor of morbidity and mortality after elective and emergency surgery.[35-37]

The study was based on data from the Danish National Patient Register with high validity of the coding for intensive care admission, mechanical ventilation and haemodialysis.[38] According to the Danish Intensive Care Database Annual Report 2012, two hospitals insufficiently reported ICU discharge in the period 2010-2012.[39] We found that 52.3% of the admissions between 2005 and 2014 were missing data on ICU discharge, however, ICU lengths of stay was registered in number of days for all except 129 admissions. The 129 admissions were excluded. The lengths of stay registration is less precise compared with an exact date and time of discharge from the ICU. Due to the nature of the Danish National Patient Register, information lacked on eg pre-operative frailty, perioperative variables, clinical ICU scores such as the Acute Physiology and Chronic Health Evaluation

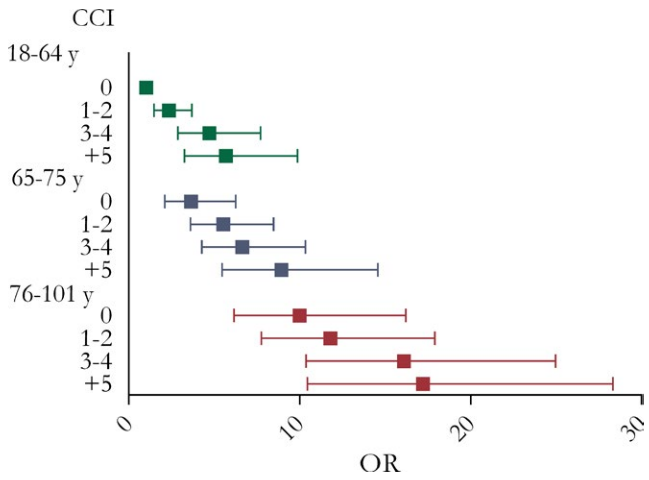

FIGURE 3 Risk of 30-days mortality after ICU admission depending on age and Charlson comorbidity index. The model was adjusted for age, Charlson comorbidity index, sex, surgical priority, reoperation prior to ICU admission, cancer, type of surgery and delayed intensive care unit admission. Odds ratios with 95% confidence intervals. CCI, Charlson comorbidity index; OR, odds ratio

score, post-operative complications and ICU admission diagnosis. Thus, the study may be vulnerable to residual confounding of the association between covariates and mortality. Only patients with a minimum stay of 24 hours in the ICU unless deceased were included; thus 1228 patients were excluded on this basis. We presumed that this group of patients was admitted shortly to the ICU for perioperative optimization only. Moreover, we presumed that the cause of ICU admission if >30 days after the operation was not related to the initial surgery. The sensitivity analysis showed that excluding these patients did not influence on the results.

In conclusion, short- and long-term mortality in non-cardiac surgical patients admitted to the ICU remains high especially among elderly comorbid patients undergoing major acute surgery. A large proportion of the patients deceased after discharge from the ICU. Future research should focus on improving modifiable risk factors and improvement of the perioperative risk stratification especially for high-risk patients in order to timely identify and treat post-operative complications. Moreover, discharge criteria from the ICU and potential benefit of a semi-intensive department should be evaluated further in the future.

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CONFLICTS OF INTEREST

None to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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