INTRODUCTION

Admission to the intensive care unit (ICU) is considered beneficial for patients with or at a high risk of developing serious pathophysiological derangements or adverse events.1-3 Surgical patients constitute a substantial proportion of ICU patients, yet their outcomes are not well-studied.4 It is not known which variables, including exposure to surgery prior to ICU admission, are independent risk factors for long-term mortality. This would be a clinically relevant investigation considering the equipoise regarding the value of ICU admission after non-cardiac surgery,5 and has important implications for the allocation, distribution and cost of this limited resource.6 Sweden has the second lowest number of ICU beds per capita in Europe and has a low ICU-to-acute care bed ratio.7 The available

Background: Long-term outcomes of patients admitted to intensive care units (ICUs) after surgery are unknown. We investigated the long-term effects of surgical exposure prior to ICU admission.

Methods: Registry-based cohort study. The adjusted effect of surgical exposure for mortality was examined using Cox regression. Secondary analysis with conditional logistic regression in a case-control subpopulation matched for age, gender, and Simplified Acute Physiology Score III (SAPS3) was also conducted.

Results: 72 242 adult patients (56.9% males, median age 66 years [IQR 50-76]), admitted to Swedish ICUs in 3-year (2012-2014) were followed for a median of 2026 days (IQR 1745-2293). Cardiovascular diseases (17.5%), respiratory diseases (15.8%), trauma (11.2%), and infections (11.4%) were the leading causes for ICU admission. Mortality at longest follow-up was 49.4%. Age; SAPS3; admissions due to malignancies, respiratory, cardiovascular and renal diseases; and transfer to another ICU were associated with increased mortality. Surgical exposure prior to ICU admission (adjusted hazard ratio [aHR] 0.90; 95% CI 0.87-0.94; P < .001), admissions from the operation theatre (aHR 0.94; CI 0.90-0.99; P = .022) or post-anaesthesia care unit (aHR 0.92; CI 0.87-0.97; P = .003) were associated with decreased mortality. Conditional logistic regression confirmed the association between surgical exposure and decreased mortality (adjusted odds ratio 0.82; CI 0.75-0.91; P < .001).

Conclusions: Long-term ICU mortality was associated with known risk factors such as age and SAPS3. Transfer to other ICUs also appeared to be a risk factor and requires further investigation. Prior surgical exposure was associated with better outcomes, a noteworthy observation given limited ICU admissions after surgery in Sweden.

1 | INTRODUCTION

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epidemiological data reveal that Sweden has lower rates of post-operative ICU admission than other countries.\textsuperscript{8,9} The International Surgical Outcome Study showed that only 1.6% of surgical patients in Sweden were admitted to ICU postoperatively, compared to 9.7% in the rest of the international cohort.\textsuperscript{9} Swedish postoperative outcomes are generally good, arguably because of the provision of some critical care services in post-anaesthesia care units (PACUs).\textsuperscript{10}

The Swedish Intensive Care Registry (SIR) collects data on patients admitted to ICUs, with 100% coverage of patients admitted to general ICUs since 2015. Published data show that patients exposed to surgery prior to ICU admission have better crude ICU mortality rates than other patients.\textsuperscript{11} This suggests that patients admitted to ICU after surgery may benefit more from intensive care than those not undergoing surgeries. However, a more detailed analysis of surgery as an exposure prior to ICU admission has not been made.

This study aimed to determine the long-term outcomes of ICU patients and to investigate its predictive factors. We explored if exposure to surgery prior ICU admission was an independent risk factor for long-term mortality among other predictive variables. Additionally, in a secondary analysis after matching for age, gender and Simplified Acute Physiology Score III (SAPS3) and controlling for confounders, we tested the null hypothesis that there are no differences between long-term survivors and nonsurvivors due to exposure to surgery.

2 | MATERIALS AND METHODS

This study was approved by the Regional Ethics Board in Lund, No. 2016/244 in 2016-04-19 and No. 2019-02898 in 2019-05-15. Our request for data retrieval was accepted by the Swedish Intensive Care Registry (SIR) in 2016-05-30. Data on ICU patients are routinely and prospectively uploaded to SIR. Patients and their relatives were informed of the database and its intention and given the option to opt-out of the registry at any time.

We performed a registry-based retrospective observational cohort study using data from SIR between January 1, 2012 and December 31, 2014. Data on all patients aged ≥18 years and admitted to general ICUs with available follow-up status on December 31, 2018 were extracted. The first ICU admission during this period for each patient was defined as the index admission. Direct transfer to another general ICU was regarded as a continuation of the index admission. Only index admissions were included in the analysis. Patients receiving profiled intensive care (e.g. thoracic and neurosurgical) were excluded because of their different management pathways and outcomes.

The primary endpoint was mortality at longest follow-up, censored on December 31, 2018. Only SIR variables with minimal missing data (<10%), clinical plausibility and previous evidence of effect were chosen a priori for analysis. These variables were age, gender, SAPS3, unplanned ICU admission, surgical exposure (defined as surgery up to 30 days prior to ICU admission), source of ICU admission (ward, accident and emergency department, operation theatre, PACU/other ICU, or other sources), main diagnosis group for ICU admission as defined by SIR, transfers to another ICU, and discharge destination of ICU survivors (ward, another hospital, another ICU not included in the database, or home). Data on patient comorbidities or surgical interventions were not available in SIR, and we could not use data on therapeutic interventions or complications during ICU admission due to poor validity and/or completeness. The clinical characteristics and outcomes are presented in numbers and percentages or median and interquartile range (IQR).

A univariate analysis was conducted for each of the predictor variables. The independent predictive power of each covariate was examined using survival analysis with Cox proportional hazards modelling. We build an exploratory model including all variables as covariates with survival from ICU admission to longest follow-up as the outcome. Their individual adjusted effects within the model were calculated and presented as adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs).

To further explore the effect of surgical exposure, we conducted a conditional logistic regression analysis in a case-control subpopulation individually matched for age, gender and SAPS3 in a 1:1 ratio. Zero tolerance limits were applied for the matched variables in order to get strict similarity between the groups. Other variables were not included for matching because they were already included in SAPS3 calculation. Cases were defined as patients with a positive primary outcome (dead at longest follow-up date) and controls were censored patients (alive as of December 31, 2018). We also conducted a second, less strict matching procedure, to test the robustness of the first one. Conditional logistic regression was applied in the matched population with ICU transfers, source of ICU admission, surgical exposure, unplanned ICU admission, admission diagnosis group, and discharge destination after ICU as predictor variables and mortality at longest follow-up as the outcome. The results are presented as adjusted odds ratio (aOR) and 95% CI.

All tests were double-sided, and the significance level was set at 0.05. IBM® SPSS Statistics® for Windows, Version 24.0. (IBM Corp.) was used for data analysis. All data are reported according to the STROBE guidelines.\textsuperscript{12}
3 | RESULTS

3.1 | Primary analysis

Data from 107,013 admissions were retrieved. After excluding patients with unavailable status on December 31, 2018 (e.g., patients with no Swedish personal identification number) and those who did not actually receive intensive care (i.e., those admitted for observation only with no need for organ support), the final cohort consisted of 72,242 patients, Figure 1. The characteristics and outcomes of the whole cohort and matched subpopulation (n = 32,682) are presented in Table 1. Thirty-day, 1-year and 5-year mortalities in the whole population were 20.2% (14,563/72,242), 31.1% (22,466/72,242) and 44.4% (21,815/49,090), respectively. The follow-up time ranged from 1460 to 2556 days (median 2026 and IQR 1745-2293 days). Nearly one-fifth of the whole cohort was exposed to surgery 30 days prior to ICU admission.

Univariate analyses revealed that all predictor variables except “unplanned ICU admission” were significantly associated with mortality at longest follow-up [Supplemental Digital Content (SDC) 1]. In Cox regression analysis presented in Table 2, exposure to surgery was independently associated with a decreased hazard.
of mortality at the longest follow-up (aHR 0.9; 95% CI 0.87-0.94; \( P < .001 \); Table 2). Further categorization of surgical exposure according to the urgency of surgery showed that this effect was seen for both emergency (aHR 0.90; 95% CI 0.86-0.94; \( P < .001 \)) and scheduled (aHR 0.91; 95% CI 0.87-0.96; \( P < .001 \)) surgeries (SDC 2). Admissions from the operation theatre (aHR 0.94; 95% CI 0.90-0.99; \( P = .022 \)) or PACU (aHR 0.92; 95% CI 0.87-0.97; \( P = .003 \)) were also associated with decreased risk for mortality. Inversely, age, SAPS3,
transfer to another ICU, admission diagnosis group (according to SIR definitions) and ICU discharge destination were associated with increased mortality.

Unplanned ICU admission was not associated with mortality, but since this was the case in 94.5% of the whole cohort, there was a likelihood of convergence failure in the logistic regression. Therefore, we repeated the Cox regression analysis without “unplanned ICU admission” as a predictor variable. This analysis yielded similar estimates as the original model (SDC 3).

Malignancy and respiratory, cardiovascular, and renal diseases were associated with the highest hazards, while obstetric/gynaecological diseases were associated with survival. Admissions due to complications were associated with 10% increased hazard of mortality (aHR 1.1; 95% CI 1.02-1.2; P = .02).

3.2 | Secondary analysis

Case-control 1:1 matching for age, gender and SAPS3 yielded a sample of 32 682 patients (16 341 alive and 16 341 deceased patients). Conditional logistic regression analysis in this subpopulation showed that surgical exposure was associated with lower mortality (aOR 0.82; 95% CI 0.75-0.91; P < .001; Table 2). In general, the covariates that were associated with increased/decreased mortality in the unmatched population were also associated with similar estimates in the matched subpopulation. Since selection bias is an inherent risk when creating matched subpopulations, we also tested our hypothesis using another matched subpopulation with less restrictive tolerance limits (±2 years of age and ±2 points for SAPS3 but same gender). This yielded a subpopulation of 36 600 patients. The conditional logistic regression analysis of both subpopulations showed almost similar results (SDC 4).

4 | DISCUSSION

Our principle finding was that long-term mortality was influenced by known risk factors such as age and SAPS3, but also modifiable risk factors such as ICU transfers and source of admission. Exposure to surgery up to 30 days prior to ICU admission was associated with decreased mortality after a median follow-up time of 2026 days. These data provide valuable insights into factors that affect outcomes long after ICU admission in Sweden. Our primary findings were corroborated by a conditional regression analysis in a subpopulation matched for three factors that have previously been identified to be important determinants of ICU outcome (age, gender and SAPS3). The finding that surgical exposure prior to ICU admission is associated with better outcomes does not mean that surgery in itself has a protective effect, but is likely to be a reflection of different case-mix between surgical and nonsurgical populations that we were unable to adjust for in our study. However, we show that patients admitted to ICU after surgery have substantial long-term benefits than those not undergoing surgeries, even after controlling for baseline characteristics and illness severity.

Our results are consistent with previous studies that found increased long-term survival among surgical ICU patients compared with other ICU subgroups.13 Our analysis confirm the importance of age and SAPS3 as predictive factors for mortality, as shown in previous studies.14-16 We demonstrate that transfer to another general ICU for continuation of intensive care was associated with increased mortality risk, but it did not appear to be related to the number of transfers (SDC 2). Although inter-ICU transfers may represent an epiphenomenon masking patient factors (eg complications needing treatment), this covariate was independently associated with lower survival even when “complications” as an ICU admission cause was included in the multivariable analysis. Inter-ICU transfers have been previously identified as an independent risk factor in a Swedish population.17 It would be relevant to further explore the underlying reasons for transfer (eg lack of ICU beds or staffing, specialized surgical treatment etc), timing of transfer and number of transfers, in order to further elucidate the risk associated with inter-ICU transfer specifically for surgical patients.

Malignancies and respiratory, cardiovascular, and renal diseases were the most important admission diagnoses associated with mortality. ICU admissions due to “medical or surgical complications” were also independently associated with mortality highlighting the risk of failure to rescue in this group of patients.18-20 However, this is inconsistent with the finding that unplanned admissions to ICU were not associated with increased mortality.3 Complications are assumed to result in unplanned ICU admissions, and previous studies have identified this to be an important determinant for outcome.21 We speculate that patients with critical care needs (eg increased monitoring and nursing care) prior to manifest organ failures were possibly identified earlier due to protocolized care pathways, good nursing care and critical care outreach teams that are often available in Swedish hospitals.22-24

Of the various sources of ICU admission, patients from monitored environments, such as the PACU/ICU or operation theatre, were associated with a decreased mortality risk compared to those admitted directly from the wards. These findings strengthen previous assumptions that being in a monitored environment allows early identification of deranged physiology or organ dysfunction and, thus, timely referral to ICU.25 The clinical relevance of our findings that surgical patients may have better long-term outcomes supports the concept of extending their “intensive care” beyond the borders of those monitored environments for better outcome optimization.26

Since the number of ICU beds is extremely limited in Sweden, only patients with a reasonable likelihood of survival are accepted for intensive care. Although we do not expect patients undergoing surgeries to have different admission criteria than those not undergoing surgeries, only about one-fifth of this Swedish ICU population was subjected to surgery prior to ICU admission. This is in contrast with other studies, where almost a half of the ICU population was subjected to surgery prior to admission.27-29 This
difference may be due to the more extensive role of PACU in perioperative patient management in Sweden. Swedish PACUs are generally able to provide some invasive monitoring and therapeutic interventions, which may only be available in ICUs in other countries. These differences between countries should be considered when evaluating our findings.

We chose to conduct a case-control analysis with matching for age, gender, and illness severity, baseline nonmodifiable variables known to be associated with long-term outcomes, to confirm the results of Cox analysis. Ideally, comorbidity should be included in the list of matched variables, but we were unable to do this since these data are not collected in SIR. We did not match for admission diagnoses since surgical causes of admissions are inherently different from medical causes and matching for this variable would incur a large selection bias. Our criteria for identifying the most appropriate sample were strict, employing zero tolerance levels for each of the matched factors. Although there is always a risk of selection bias in case-control studies, we attempted to mitigate this by nonrepetitive random sampling from the control pool. Estimates of risk from both matched populations confirmed

### TABLE 2  Cox regression analysis of the whole cohort and the conditional logistic regression analysis of the subpopulation of matched patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole cohort (n = 72 242)</th>
<th>Matched subpopulation (n = 32 682)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHR  95% CI    P</td>
<td>aOR  95% CI    P</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.031 (1.031-1.032) &lt;.001</td>
<td>1.440 (1.29-1.61) &lt;.001</td>
</tr>
<tr>
<td>Male</td>
<td>1.016 (0.995-1.038) .144</td>
<td></td>
</tr>
<tr>
<td>SAPS3 (per point)</td>
<td>1.028 (1.027-1.029) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Transfers to another ICU</td>
<td>1.331 (1.262-1.404) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Source of ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident and Emergency Department</td>
<td>1.016 (0.991-1.041) .205</td>
<td></td>
</tr>
<tr>
<td>Operating theatre</td>
<td>0.943 (0.897-0.992) .022</td>
<td></td>
</tr>
<tr>
<td>PACU or another ICU not included in the database</td>
<td>0.922 (0.874-0.973) .003</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>0.854 (0.790-0.922) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Ward (reference)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Unplanned ICU admission</td>
<td>0.963 (0.917-1.013) .142</td>
<td></td>
</tr>
<tr>
<td>Surgery within 30 d to ICU admission</td>
<td>0.904 (0.868-0.941) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Group of the main diagnosis for ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular system diseases</td>
<td>1.363 (1.287-1.443) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Respiratory system diseases</td>
<td>1.462 (1.380-1.548) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>0.942 (0.882-1.006) .073</td>
<td></td>
</tr>
<tr>
<td>Sepsis and infections</td>
<td>1.108 (1.044-1.176) .001</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal system diseases</td>
<td>1.270 (1.195-1.350) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Nervous system diseases</td>
<td>1.228 (1.153-1.307) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Fluid balance, blood or endocrine diseases</td>
<td>1.275 (1.192-1.364) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Medical or surgical complications</td>
<td>1.104 (1.016-1.199) .020</td>
<td></td>
</tr>
<tr>
<td>Renal system diseases</td>
<td>1.307 (1.205-1.418) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Malignancies</td>
<td>2.247 (2.050-2.461) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Obstetrics and gynaecological diseases</td>
<td>0.087 (0.041-0.182) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Others (reference)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Discharge destination of ICU survivors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>0.793 (0.725-0.867) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Another ICU not included in the database</td>
<td>0.874 (0.829-0.921) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Another Hospital</td>
<td>0.793 (0.744-0.845) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>Ward (reference)</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: aHR, adjusted hazard risk; CI, confidence interval; aOR, adjusted odds ratio; SAPS3, Simplified Acute Physiology Score III; ICU, intensive care unit; PACU, Post-Anaesthesia Care Unit.

*as defined by the Swedish Intensive Care Registry
the results of the primary Cox regression, strengthening the conclusion that patients exposed to surgery have better survival than others.

The most important limitation of this study is that all analyses only extend to the chosen covariates. Since our choice of covariates was limited by SIR data, data regarding comorbidities, Sequential Organ Failure Assessment (SOFA) score, surgical case mix, use of rescue therapies, ICU complications and therapeutic interventions, socioeconomic status, and university hospital status, which are important possible confounders, were not included in the analysis.

Another limitation was defining surgical patients in our cohort. Since it was impossible to audit individual patient records, we used the only available variable defined by SIR as “Surgery undertaken in current hospital admission but less than 30 days before ICU admission.” This is clearly inadequate since some patients may have been admitted to ICU prior to surgery for various reasons such as resuscitation, hemodynamic optimization, vital organ stabilization, but based on our experience, these reasons constitute only a minority of surgical ICU admissions. Surgical procedures undertaken during or after intensive care are not usually registered in SIR; therefore, little or no data were available on this important clinical variable.

A strength of this study is the almost full coverage of SIR during our inclusion period (95% in 2012, reaching 98% in 2014), completeness and accuracy of the chosen covariates, and validation of these data by SIR. All eligible patients were included to minimize selection bias. Detection bias was avoided by only including variables with a high degree of accuracy and completeness. Long-term outcomes were available for almost all patients and verified in the Swedish Registry of Deaths. Recall bias was not a limitation since data were recorded for other purposes before the occurrence of the outcome and prior to the start of the study.

We stress that our goal was neither to compare surgical vs nonsurgical patients, nor to compare ICU vs no ICU admission of surgical patients. Rather, we aimed only to investigate surgery as an exposure among many other factors that affect outcome. The findings of our study do not imply causality; however, it prompts further investigation into modifiable risk factors, and specific subpopulations that may benefit from intensive care. Therefore, it is immediately relevant as clinicians, health care economists, and strategists struggle to identify patients that will benefit most from intensive care.

Recent studies have not identified any survival benefit from ICU admission after elective surgery. The current findings neither support nor refute these results, since we did not compare surgical patients admitted vs those not admitted to ICU, a randomization that would likely be ethically unjustifiable. However, we demonstrate that patients who underwent surgery appear to benefit from ICU admission more than those who did not undergo surgery, even after controlling for age, gender, severity of illness and other risk factors that may affect mortality. This difference raises several considerations. Firstly, surgical patients seem to take up only a small proportion of ICU beds in Sweden despite comparable severity of illness, making them less competitive for such resources. Yet, survival rates of surgical patients were higher, speaking for the successful disposal of ICU beds in this group of patients. Further studies are needed in an expanding surgical population with increasing proportions of elderly and sicker patients.

5 | CONCLUSION

Long-term mortality in Swedish ICU patients is driven by traditional risk factors such as age and SAPS3 score but is also independently associated with modifiable risk factors such as ICU transfers and source of admission. Exposure to surgery 30 days prior to ICU admission was independently associated with decreased mortality risk.

ACKNOWLEDGEMENTS
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CONFLICT OF INTEREST
Monir Jawad and Michelle Chew have received grants to support the conduct of this study from Region Östergötland, Region Halland County Councils and Linköping University. Amir Baigi has no conflicts of interest.

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REFERENCES


**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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