Effects of night surgery on postoperative mortality and morbidity: a multicentre cohort study

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ABSTRACT

Background Surgery at night (incision time 17:00 to 07:00 hours) may lead to increased postoperative mortality and morbidity. Mechanisms explaining this association remain unclear.

Methods We conducted a multicentre retrospective cohort study of adult patients undergoing non-cardiac surgery with general anaesthesia at two major, competing tertiary care hospital networks. In primary analysis, we imputed missing data and determined whether exposure to night surgery affects 30-day mortality using a mixed-effects model with individual anaesthesia and surgical providers as random effects. Secondary outcomes were 30-day morbidity and the mediating effect of blood transfusion rates and provider handovers on the effect of night surgery on outcomes. We further tested for effect modification by surgical setting.

Results Among 350 235 participants in the primary imputed cohort, the mortality rate was 0.9% (n=2804/322 327) after day and 3.4% (n=940/27 908) after night surgery. Night surgery was associated with an increased risk of mortality (OR_{adj} 1.26, 95% CI 1.15 to 1.38, p<0.001). In secondary analyses, night surgery was associated with increased morbidity (OR_{adj} 1.41, 95% CI 1.33 to 1.48, p<0.001). The proportion of patients receiving intraoperative blood transfusion and anaesthesia handovers were higher during night-time, mediating 9.4% (95% CI 4.7% to 14.2%, p<0.001) of the effect of night surgery on 30-day mortality and 8.4% (95% CI 6.7% to 10.1%, p<0.001) of its effect on morbidity. The primary association was modified by the surgical setting (p-for-interaction<0.001), towards a greater effect in patients undergoing ambulatory/same-day surgery (OR_{adj} 1.81, 95% CI 1.39 to 2.35) compared with inpatients (OR_{adj} 1.17, 95% CI 1.02 to 1.34).

Conclusions Night surgery was associated with an increased risk of postoperative mortality and morbidity. The effect was independent of case acuity and was mediated by potentially preventable factors: higher blood transfusion rates and more frequent provider handovers.

INTRODUCTION

More than 5% of surgeries are performed outside of standard operating room hours and up to 74% of procedures performed at night are planned as elective cases.[1] Although unavoidable in urgent circumstances, night surgery itself may be an independent risk factor of perioperative mortality and morbidity.

Previous studies analysing the effect of night surgery on mortality and morbidity provided equivocal findings: while higher mortality rates were suggested in patients undergoing night surgery across surgical specialties,[2] other studies only found surgery during the early (13:00 to 17:00 hours)[3] or late afternoon and evening (16:00 to 23:00 hours)[4] to be associated with higher mortality or morbidity in non-emergency cases. It remains unclear whether surgery at night affects patient survival, and whether the effect varies by acuity and condition of the patient.

It is important to identify potentially preventable elements of night surgery that contribute to its potential risk. Discussions aiming at understanding mechanisms that may drive a higher risk of night surgery have only focused on providers' sleep deprivation. Studies on healthcare providers suggested that night shift work and variation in daylight exposure disrupt circadian rhythms, leading to increased medical errors.[5–8] Contributing factors may be sleep-deprived fatigue, prolonged reaction time, impaired situational awareness and a natural circadian variability in technical performance.[5 6 9] However, it has not yet been defined whether there are intraoperative factors that notably differ between day and night surgeries and may be modified to improve outcomes.

In this multicentre cohort study, we hypothesised that exposure to surgery at night affects patient survival and postoperative complications. We then tested whether intraoperative blood transfusions and anaesthesia handovers during night-time were potential mediators of the effect of night surgery on adverse outcomes. We further assessed whether the effect of night surgery was driven by a higher case acuity of patients undergoing surgery at night.

METHODS

Study design

Data were obtained for surgical patients at institution A between October 2005 and September 2017 and at institution B and one affiliated community hospital between January 2007 and December 2015. The study was approved by the institutional review boards at each institution (protocol numbers 2018P000786 and 2019P000825). The requirement for written informed consent was waived. Data were collected from hospital-registry databases (online supplemental file 1, section 1). This manuscript adheres to the STROBE guidelines online supplemental file 2.[10]

Study population

We included patients aged 18 years or older who had an American Society of Anaesthesiologists' (ASA) status below 6 and underwent non-cardiac surgery with general anaesthesia. Missing data required for the primary analysis were imputed using multiple imputation with chained equations (online supplemental file 1, section 3). For secondary, sensitivity, and exploratory analyses, the complete-case method was used.

Study exposure and outcomes

Night surgery was defined as a surgical incision time between 17:00 and 07:00 hours. Surgical times were based on timestamps in electronic anaesthesia records. The primary outcome was mortality within 30 days of surgery. Secondary outcomes were 30-day morbidity, defined as a composite outcome including renal, cardiovascular, bleeding, infection, intestinal/digestive, and pulmonary complications within 30 days of surgery, as defined by the International Classification of Diseases, Ninth and Tenth Revision (online supplemental eTable 1)[11] and the mediating effect of blood transfusion rates and provider handovers on the effect of night surgery on outcomes.

Primary analysis and covariates

We used multivariable-adjusted mixed-effects logistic regression to investigate the effect of night surgery on 30-day mortality. We included individual anaesthesia and surgical providers as random effects in the primary model. Analyses were adjusted for confounding variables based on literature review and clinical plausibility (online supplemental eTable 2). Patient factors included age, sex, body mass index, ASA physical status classification, surgical care setting (ambulatory care setting and same-day discharge versus inpatient surgery), Charlson Comorbidity Index, a 1-year history of cancer, home oxygen or respirator dependency, chronic pulmonary disease, coronary artery disease, congestive heart failure and ischaemic stroke. Procedure-related confounding variables included emergency surgery, surgical specialty, duration of surgery, date of surgery and work relative value units. Anaesthesia-related factors were vasopressor dose, intraoperative hypotension (defined as mean arterial pressure <55 mm Hg), SpO_2/FiO_2-ratio, transfusion of packed red blood cell units (PRBC) and handover between anaesthesiologists. Finally, we included the institution (A versus B) in the model. To address potential bias due to missing data, we performed multiple imputation with chained equations for the primary analysis.

Secondary analyses

In secondary analyses, we investigated whether night surgery was associated with 30-day morbidity by using multivariable-adjusted logistic regression. Further, we used path mediation analysis to evaluate the role of intraoperative factors as potential mediators of the effect of night surgery on 30-day mortality and morbidity. The two mediator candidates analysed were the intraoperative transfusion rate (proportion of patients transfused with PRBC) and the proportion of cases with an intraoperative handover between anaesthesiologists. To define complete handovers between anaesthesiologists, we used unique provider identification numbers as well as sign-in and sign-out times.

First, we tested the hypothesis that intraoperative transfusion rates were higher during night cases than day cases. We used a multivariable-adjusted logistic regression model on the association between night surgery and transfusion rate that included all confounding variables of the primary analysis. To verify this observation, we additionally adjusted for intraoperative estimated blood loss (mL) as well as mild and moderate to severe anaemia within 30 days prior to surgery. Preoperative haemoglobin values of ≥11 to ≤12.9 g/dL in men and ≥11 to ≤11.9 g/dL in women were used to define mild anaemia, and values of ≤10.9 g/dL were used to define moderate to severe anaemia in both men and women.[12] In addition, we tested whether variability across individual surgeons and anaesthesiologists had an impact on the association between night surgery and transfusion rate by including provider-related confounding variables and random effects for individual providers into the model (online supplemental file 1, section 5.1). Similarly, we tested the hypothesis that handovers between anaesthesiologists occur more frequently during night-time.

Second, we used adjusted analyses to examine whether transfusion rates and handovers were associated with the outcomes of 30-day mortality and morbidity, indicating potential effect mediation. We additionally tested for a potential interaction between the effects of the two mediators on the outcomes including the interaction term 'transfusion rate*handover' in the model.

Conditional on an association between the mediators and the study outcomes, we performed adjusted formal mediation analysis based on the method by Buis.[13] We estimated ORs of the indirect (mediated) effect of transfusion rate and handovers, respectively, and the total (unmediated) effect of night surgery on mortality and morbidity, using bootstrapping with 1000 replications.[13–15] Percentage mediation by the mediators was calculated using the following form: (ln (indirect effect)/ln (total effect)) × 100.[15] Finally, we combined the two mediators into one model to test the mediating effect of both higher proportions of blood transfusion and handovers during night-time on the association between night surgery and outcomes.

Exploratory analyses

With an exploratory intent, we performed interaction analysis to assess whether the association between night surgery and mortality was modified by the surgical care setting (ambulatory and same-day surgery versus inpatient surgery). Subgroup analyses were performed across groups of the interaction term. Patient characteristics in subgroups are provided in online supplemental eTables 6 and 7. To further address potential concerns that the effect may be driven by a higher case acuity of patients operated at night, we tested the primary association in a subgroup of patients undergoing non-emergency surgery, after excluding emergency and acute care services. In this subgroup, we repeated the interaction analysis by surgical care setting. Conversely, we examined the effect of night surgery on mortality in a subgroup of patients undergoing emergency surgery (online supplemental eTable 8).

Sensitivity analyses

We performed several sensitivity analyses to confirm the robustness of the effect of night surgery on mortality. We repeated the primary multivariable-adjusted mixed-effects logistic regression analysis with random effects for anaesthesia and surgical providers in the complete-case cohort after excluding cases with missing confounder data. We performed propensity score matching and provide patient characteristics in the propensity-matched cohort in online supplemental eTable 9. We further provide data on postoperative major adverse events within 30 days, indicating potential causes of death (online supplemental file 1, section 4). In addition, we tested whether the association between night surgery and mortality was modified by a recent diagnosis of cancer by including an interaction term between night surgery and 1 year diagnosis of cancer (online supplemental file 1, section 6.2). We tested for potential effect modification of the association between night surgery and mortality by case delays (ie, difference between scheduled and actual start time in minutes) by including an interaction term between night surgery and case delay. We also investigated the mediating effect of case delays on the association between night surgery and mortality (online supplemental file 1, section 5.2). Finally, we conducted several subgroup analyses to ensure that the impact of night surgery on mortality was not driven by a narrow patient population. Details on all sensitivity analyses are described in section 6 of online supplemental file 1.

Sample size justification

Assuming a two-sided alpha level of 0.05, an observed proportion of night surgeries of 8.0% in the primary cohort, a baseline mortality risk of 0.6%[16] and a clinically significant risk increase of 30% in the group of patients who underwent night surgery, the sample size of this study provided a power of 94.0% to detect a difference between patients undergoing surgery during the night versus day.

Statistical analyses

Confounding variables demonstrating linear associations with the primary outcome were included as continuous, whereas variables with non-linear associations were categorised into quintiles (online supplemental file 1, section 2). A two-sided $p<0.05$ was considered statistically significant. Analyses were performed using Stata (Stata, V.13) and RStudio (RStudio, V.3.2.5).

Patient and public involvement

No patients or the public were involved in the design or conduct of this study. Patients or the public were not invited to contribute to the writing or editing of this document for readability or accuracy.

RESULTS

Study cohort

In this study, 377 163 cases were considered for inclusion. After application of exclusion criteria and imputation of missing data, the final cohort for the primary analysis consisted of 350 235 cases (figure 1). A total of 322 327 (92.0%) patients underwent day surgery (07:00 to 17:00 hours) and 27 908 (8.0%) underwent night surgery (17:01 to 06:59 hours). In the complete-case cohort, 303 892 cases remained after excluding cases with missing data. Patient characteristics and distribution of variables by study groups are detailed in table 1 and online supplemental eTables 3–5.

Primary analysis

30-day mortality

In total, 3744 (1.5%) patients died within 30 days after surgery, 2804 (0.9%) after day surgery and 940 (3.4%) after night surgery. Night surgery was associated with increased mortality within 30 days of surgery in unadjusted (OR 2.45, 95% CI 2.26 to 2.65, $p<0.001$) as well as adjusted analyses (adjusted OR (OR_{adj}) 1.26, 95% CI 1.15 to 1.38, $p<0.001$; table 2).

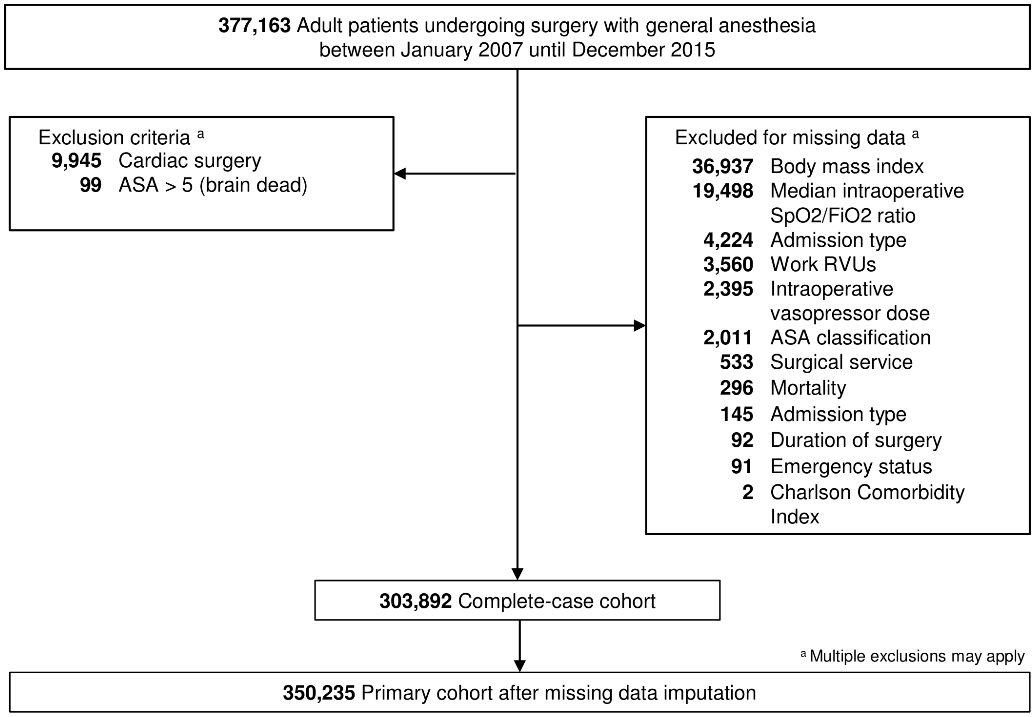

Figure 1 Study flowchart. ASA, American Society of Anesthesiologist's Physical Status Classification System; RVU, relative value unit.

Secondary analyses

30-day morbidity

In total, 2234 (0.7%) patients had complications within 30 days after surgery, 1769 (0.6%) after day surgery and 465 (2.3%) after night surgery. We found a significant association between night surgery and morbidity (OR_{adj} 1.41, 95% CI 1.33 to 1.48, p<0.001; table 2).

Transfusion rate

The proportion of patients receiving intraoperative blood transfusions was 5.5% (n=1149) during night surgeries and 2.8% (n=7882) during day surgeries. Night surgery was significantly associated with a higher transfusion rate in adjusted analysis (OR_{adj} 1.25, 95% CI 1.15 to 1.35, p<0.001). The effect remained robust in a subgroup of cases where data on intraoperative estimated blood loss and preoperative haemoglobin levels were available, after additional adjustment for blood loss, mild anaemia, and moderate to severe anaemia within 30 days prior to surgery (OR_{adj} 1.17, 95% CI 1.04 to 1.31, p=0.009; n=1 31 371), as well as when additionally accounting for a potential variability in transfusion practice across individual anaesthesia providers (OR_{adj} 1.19, 95% CI 1.10 to 1.30, p=0.005; n=1 28 691) and across individual surgeons (OR_{adj} 1.35, 95% CI 1.21 to 1.51, p<0.001, n=1 62 907; online supplemental file 1, section 5).

Higher transfusion rate was significantly associated with an increased risk of 30-day mortality (OR_{adj} 1.72, 95% CI 1.50 to 1.98, p<0.001) and morbidity (OR_{adj} 1.68, 95% CI 1.59 to 1.78, p<0.001). Higher transfusion rates during night surgery mediated 5.9% (95% CI 2.4% to 9.3%; p=0.001) of the effect of night surgery on mortality, and 4.9% (95% CI 3.8% to 6.1%; p<0.001) of its effect on morbidity (table 3 and figure 2).

Handover of anaesthesia care

Anaesthesia handovers occurred in 22.6% (n=4686) of night surgeries and 8.8% (n=24 949) of day surgeries. Night surgery was significantly associated with a higher proportion of handovers in adjusted analysis (OR_{adj} 4.12, 95% CI 3.94 to 4.30, p<0.001). Anaesthesia handovers were significantly associated with an increased risk of morbidity (OR_{adj} 1.10, 95% CI 1.05 to 1.14, p<0.001) and mediated 4.1% (95% CI 2.3% to 5.9%, p<0.001) of the effect of night surgery on morbidity in formal mediation analysis (table 3).

There were no interaction effects between the two mediators on 30-day mortality (p-for-interaction: 0.395) and morbidity (p-for-interaction: 0.125). When combining both mediators into one mediation model, higher transfusion rates together with more handovers during night-time mediated 9.4% (95% CI 2.4% to 16.4%, p<0.001) of the effect of night surgery on 30-day mortality and 8.4% (95% CI 6.3% to 10.4%, p<0.001) of its effect on morbidity (table 3 and figure 2).

Exploratory analyses

Ambulatory and same-day surgery versus inpatient surgery

The effect of night surgery was modified by the surgical care setting (p-for-interaction<0.001) towards a greater effect among patients who underwent ambulatory or same-day surgery (OR_{adj} 1.81, 95% CI 1.39

Table 1 Characteristics and distribution of variables by day versus night surgery in primary cohort

Patient characteristics	Day surgery (n=3 22 327)	Night surgery (n=27 908)	Standardised difference
Sex, male, n (%)	141 869 (44.0%)	14 213 (49.0%)	0.139
Age (years), mean±SD	54.08±16.47	52.77±18.77	0.074
BMI (kg/m^2), mean±SD*	28.35±6.85	27.79±6.91	0.081
ASA status, median (IQR)*	2 (2 to 3)	2 (2 to 3)	−0.241
ASA ≥3, n (%)*	108 366 (33.8%)	113 029 (46.9%)	−0.269
Admission type, n (%)*			−0.703
Ambulatory	119 881 (37.6%)	3536 (12.9%)	
Same day admission	143 328 (45.0%)	12 407 (45.3%)	
Inpatient	55 680 (17.4%)	11 469 (41.8%)	
Institution			0.146
A	186 593 (57.9%)	18 127 (64.9%)	
B	135 734 (42.1%)	9781 (35.1%)	
Intraoperative data			
Duration of surgery (min), median (IQR)*	132.00 (85.00 to 205.00)	113.00 (80.00 to 165.00)	0.234
Handover of anaesthesia care, n (%)	28 827 (8.9%)	6093 (21.8%)	−0.363
Emergency surgery, n (%)*	9464 (2.9%)	10 868 (39.0%)	−0.987
Work RVUs, median (IQR)*	12.75 (7.03 to 19.61)	10.93 (7.07 to 17.80)	0.159
Packed red blood cell units transfused intraoperatively, n (%)			−0.191
0 units	311 914 (96.8%)	25 785 (92.4%)	
1 unit	4475 (1.4%)	819 (2.9%)	
2 units	3745 (1.2%)	666 (2.4%)	
≥3 units	2193 (0.7%)	638 (2.3%)	
Intraoperative hypotensive minutes of MAP <55 mm Hg, median (IQR)	0.00 (0.00 to 2.00)	0.00 (0.00 to 3.00)	−0.036
Total intraoperative vasopressor dose, norepinephrine equivalent (mg), median (IQR)	0.01 (0.00 to 0.10)	0.01 (0.00 to 0.12)	−0.016
Median SpO_2/FiO_2 ratio, median (IQR) *	184.21 (161.29 to 222.27)	178.57 (147.06 to 206.25)	0.190

Frequency distributions of patient comorbidities and surgical services by day versus night surgery are provided in the online supplemental eTables 3 and 4. Characteristics and distribution of variables by day versus night surgery for the complete-case cohort are provided in the online supplemental eTable 5. Normally distributed continuous variables were expressed as mean (±SD), non-normally distributed variables as median (IQR), and categorical variables as frequency (percentages).

*Variables with missing data; Characteristics and distribution of variables by day versus night surgery are presented for cases with observed data.

ASA, American Society of Anesthesiologist's Physical Status Classification System; BMI, body mass index; CCI, Charlson Comorbidity Index; MAP, mean arterial pressure; RVUs, relative value units.

to 2.35, p<0.001) compared with inpatient surgery (OR_{adj} 1.17, 95% CI 1.02 to 1.34, p=0.026; table 4).

Non-emergency surgery

Among 282 526 patients undergoing non-emergency surgery, night surgery was associated with 1.35-fold higher adjusted odds for 30-day mortality compared with day surgery, respectively (95% CI 1.16 to 1.56, p<0.001; table 4). Analysis of this subgroup demonstrated robust results when including an interaction term by the surgical care setting (p-for-interaction=0.001; ambulatory/same-day surgery: OR_{adj} 2.22, 95% CI 1.60 to 3.07, p<0.001; inpatient surgery: OR_{adj} 1.20, 95% CI 1.01 to 1.43, p=0.036) (table 4).

Emergency surgery

Characteristics of emergency cases by night versus day surgery are provided in online supplemental eTable 8. Of 13 566 emergency surgeries, 52.8% (n=7162) were performed at night and 47.2% (n=6404) were performed during the day. Distributions of emergency and non-emergency cases throughout the day are shown in online supplemental eFigure 1. Risks of adverse outcomes were similar between emergency surgeries performed during the night versus day (mortality: OR_{adj} 1.13, 95% CI 0.91 to 1.40, p=0.27; morbidity: OR_{adj} 1.04, 95% CI 0.94 to 1.16, p=0.427).

Sensitivity analyses

Propensity score matching and mixed-effects logistic regression analysis in the complete-case cohort confirmed our primary finding (OR_{adj} 1.21, 95% CI 1.06 to 1.39, p=0.005, n=41 414; OR_{adj} 1.34, 95% CI 1.18 to 1.52, n=2 89 480 cases with provider data available). The case delay time was longer in patients who underwent night surgery compared with day surgery (78 (SD 150) vs 17 (SD 50) min,

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Table 2 Results of 30-day mortality (primary outcome) and 30-day morbidity (secondary outcome) associated with night surgery

			Unadjusted analysis			Adjusted analysis		
Primary outcome	**Day surgery (n=322 327)**	**Night surgery (n=27 908)**	**Absolute difference (95% CI)***	**OR (95% CI)**	**P value**	**Adjusted absolute difference (95% CI)†**	**OR_{adj} (95% CI)**	**P value**
30 day mortality	2804 (0.9%)	940 (3.4%)	–	2.45 (2.26 to 2.65)	<0.001	–	1.26 (1.15 to 1.38)	<0.001
			Unadjusted analysis			**Adjusted analysis**		
Secondary outcome	**Day surgery (n=283 185)**	**Night surgery (n=20 707)**	**Absolute difference (95% CI)***	**OR (95% CI)**	**P value**	**Adjusted absolute difference (95% CI)†**	**OR_{adj} (95% CI)**	**P value**
30-day morbidity	22 919 (8.1%)	2723 (13.2%)	5.1% (4.6% to 5.5%)	1.72 (1.65 to 1.79)	<0.001	2.1% (1.7% to 2.4%)	1.41 (1.33 to 1.48)	<0.001
Cardiovascular	6875 (2.4%)	599 (2.9%)	0.5% (0.2 to 0.7)	1.2 (1.10 to 1.30)	<0.001	0.2% (0.0% to 0.3%)	1.14 (1.03 to 1.27)	0.011
Pulmonary	1533 (0.5%)	203 (1.0%)	0.4% (0.3% to 0.6%)	1.82 (1.57 to 2.11)	<0.001	0.1% (0.1% to 0.2%)	1.46 (1.22 to 1.74)	<0.001
Renal	2565 (0.9%)	409 (2.0%)	1.1% (0.9% to 1.3%)	2.20 (1.98 to 2.45)	<0.001	0.2% (0.1% to 0.3%)	1.42 (1.25 to 1.61)	<0.001
Intestinal/ Digestive	1712 (0.6%)	113 (0.5%)	0.1% (0.2% to 0.1%)	0.90 (0.75 to 1.09)	0.29	0.0% (0.0% to 0.0%)	0.79 (0.62 to 1.0)	0.051
Haemorrhage	9342 (3.3%)	1232 (5.9%)	2.7% (2.3% to 3.5%)	1.85 (1.74 to 1.97)	<0.001	1.2% (0.9 to 1.45)	1.50 (1.39 to 1.62)	<0.001
Infections	6454 (2.3%)	1032 (5.0%)	2.7% (2.4% to 3.0%)	2.25 (2.10 to 2.41)	<0.001	0.9% (0.7% to 1.1%)	1.59 (1.46 to 1.72)	<0.001

Data are expressed as frequency (prevalence in %). Statistical analyses were performed using multivariable logistic regression. OR, absolute differences and adjusted absolute differences are reported.
*Absolute difference indicates the difference in risk between compared groups, as estimated following unadjusted regression analysis.
†Adjusted absolute difference indicates the difference in risk attributable to use of night surgery, as estimated following adjusted regression analysis.

p<0.001). The interaction term between night surgery and case delay in minutes was marginally significant (p=0.055), and the association between night surgery and mortality remained significant in this analysis (OR_{adj} 1.26, 95% CI 1.06 to 1.50, p=0.009, n=1 59 591). Case delay did not mediate the effect of night surgery on mortality. Details of sensitivity analyses are provided in the online supplemental file 1.

DISCUSSION

In this large multicentre study of non-cardiac surgical patients, we made the following observations: first, risks of postoperative mortality and morbidity at 30 days were higher among patients who underwent night surgery compared with day surgery. Second, a higher blood transfusion rate and more frequent anaesthesia handovers during night-time partly mediated

Table 3 Adjusted ORs with 95% CIs and p values obtained from path mediation analysis of intraoperative blood transfusion rates and handovers of anaesthesia care as potential mediators in the association between night surgery and 30-day mortality and morbidity

Mediator	Direct effect* (95% CI)	Indirect effect† (95% CI)	Total effect‡ (95% CI)	Mediated in %§ (95% CI)
Primary outcome: 30-day mortality				
Transfusion rate	1.36 (1.21 to 1.54) P<0.001	1.02 (1.01 to 1.03) P<0.001	1.39 (1.23 to 1.57) P<0.001	5.9% (2.4% to 9.3%) P=0.001
Handover	1.36 (1.21 to 1.54) P<0.001	1.01 (0.99 to 1.03) P=0.175	1.39 (1.23 to 1.56) P<0.001	4.2% (-2.5% to 11.0%) P=0.217
Both mediators combined	1.36 (1.20 to 1.55) P<0.001	1.03 (1.01 to 1.05) P=0.006	1.41 (1.24 to 1.60) P=0.002	9.4% (2.4% to 16.4%) P=0.008
Secondary outcome: 30-day morbidity				
Transfusion rate	1.41 (1.33 to 1.48) P<0.001	1.02 (1.01 to 1.02) P<0.001	1.43 (1.36 to 1.51) P<0.001	4.9% (3.8% to 6.1%) P<0.001
Handover	1.41 (1.34 to 1.49) P<0.001	1.01 (1.01 to 1.02) P<0.001	1.43 (1.36 to 1.51) P<0.001	4.1% (2.3% to 5.9%) P<0.001
Both mediators combined	1.41 (1.34 to 1.48) P<0.001	1.03 (1.02 to 1.04) P<0.001	1.45 (1.38 to 1.53) P<0.001	8.4% (6.3 to 10.4%) P<0.001

Results were justified using bootstrapping analysis with 1000 samples.[13 14]
*Direct effect comparing odds for mortality/morbidity if everyone had undergone night surgery versus odds for mortality/morbidity if everyone had undergone day surgery, thereby fixing rates of blood transfusion/handovers to the value they would have had during day surgery.
†Indirect effect assuming that every patient underwent night surgery. We compare odds for mortality/morbidity when rates of blood transfusion/handovers change from the value during night surgery to the one during day surgery.
‡Total effect comparing odds for mortality/morbidity if everyone had undergone night surgery versus odds for mortality/morbidity if everyone had undergone day surgery.
§Percentage mediation by blood transfusion/handovers was calculated using the following form: (ln (indirect effect)/ln (total effect)) × 100.

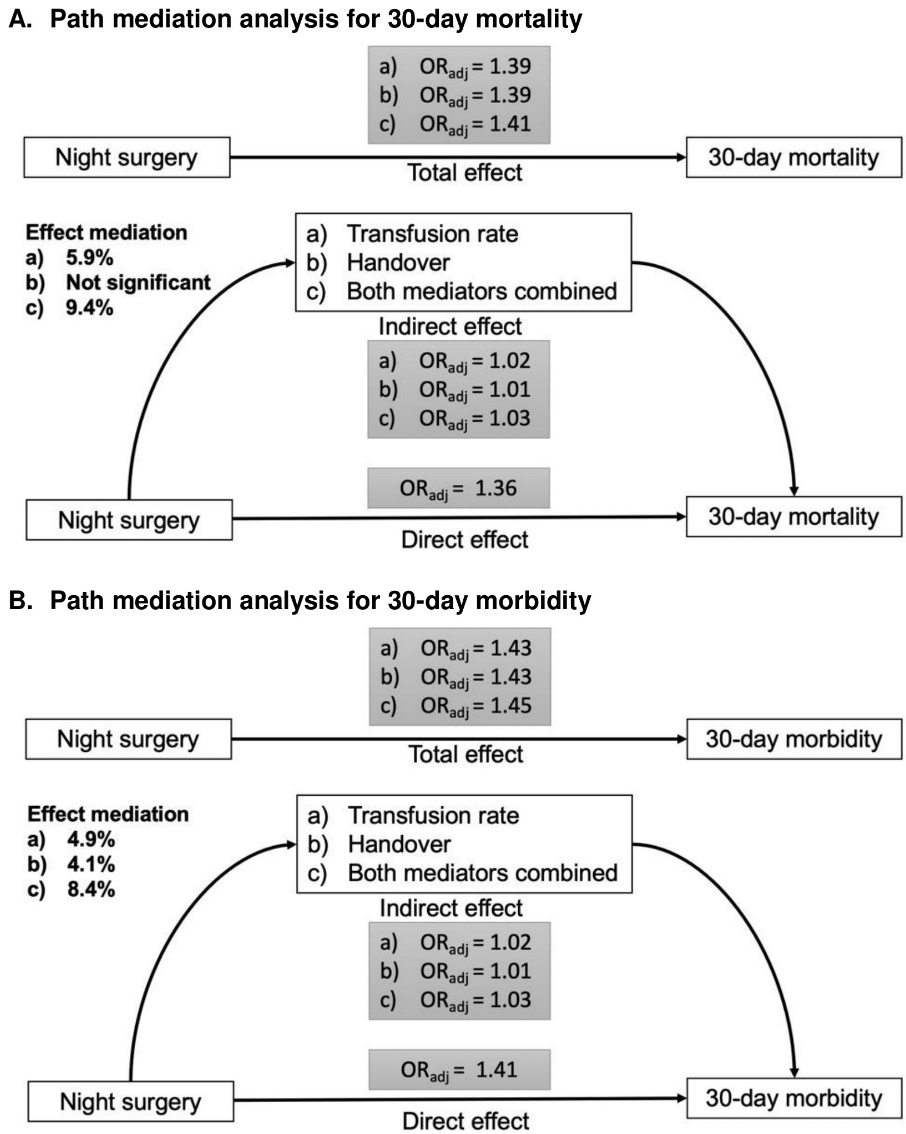

Figure 2 Path mediation analyses for 30-day mortality and morbidity. Mediation effects of (a) intraoperative blood transfusion rates, (b) handovers of anaesthesia care as well as (c) a combination of both mediators on the association between night surgery and 30-day mortality (A) and morbidity (B) are shown. Transfusion rates mediated 5.9% and 4.9% of the effect of night surgery on 30-day mortality and morbidity, respectively. Handovers mediated 4.1% of the effect of night surgery on 30-day morbidity. Combination of handovers and transfusion rates mediated 9.4% and 8.4% of the effect of night surgery on 30-day mortality and morbidity, respectively. Adjusted ORs are shown for total, indirect and direct effect.

Table 4 Results of 30-day mortality across exploratory analyses

Analysis	N	OR_{adj} (95% CI)	P value
Interaction analysis			
Surgical setting			P-for-interaction<0.001
Ambulatory/same-day surgery	253 523	1.81 (1.39 to 2.35)	<0.001
Inpatient surgery	50 369	1.17 (1.02 to 1.34)	=0.026
Subgroup analyses			
Non-emergency surgery	282 526	1.35 (1.16 to 1.56)	<0.001
Interaction analysis by surgical setting:			P-for-interaction=0.001
Ambulatory/same-day surgery	242 247	2.22 (1.60 to 3.07)	<0.001
Inpatient surgery	40 279	1.20 (1.01 to 1.43)	=0.036
Emergency surgery	13 566	1.13 (0.91 to 1.40)	0.27

Statistical analyses were performed using multivariable logistic regression. Interaction terms were included in the primary model to test for effect modification. Subgroup analyses were performed across levels of the interaction term. Adjusted ORs (OR_{adj}) are reported.

the effect of night surgery. The adverse effects of night surgery were modified by admission status and acuity level: magnified adverse effects were observed in patients who underwent ambulatory or same-day surgery while the effect was not significant in patients undergoing emergency surgery. These findings suggest that the increased risk of mortality and morbidity after night surgery was not driven by a higher case acuity, but could be attributed to differences in the surgical management of patients operated during night-time.

Relation to other studies

Previous studies reported inconclusive results on the effect of operation time on postoperative outcome. More complications after surgery at night were previously described in smaller studies among patients undergoing orthopaedic,[17] neurosurgery,[18] and plastic surgery,[19] laparoscopic cholecystectomy,[20] coronary interventions[21] and general and vascular surgery.[4 22] In the latter study,[22] higher mortality was only detected for patients undergoing elective surgery, a finding which we confirm with our study, and was also reported in other studies with negative results in patients who underwent emergency surgery.[23 24]

Other studies did not identify harmful effects of night surgery. A single-centre investigation in Germany including non-emergency cases across surgical fields suggested an increased in-hospital mortality only when the surgery was conducted during the early afternoon (13:00 to 17:00 hours).[3] In a study that used National Surgical Quality Improvement Program data, night-time surgery in patients undergoing elective surgery was not associated with postoperative morbidity and mortality.[4]

Finally, a recent meta-analysis summarised 40 observational studies on the association between night surgery and mortality. The largest study included in this meta-analysis used the National Anesthesia Clinical Outcomes Registry to analyse three patient (age, sex, ASA status) and procedure-related (emergency, surgery type, operation time between 16:00 to 06:59 hours) factors associated with 48-hour mortality after surgery.[2] Our study adds the important information that the association between night surgery and increased mortality is robust even when adjusting for important confounders such as case delays and intraoperative risk factors. In addition, we present potentially preventable mediators of the increased risk of mortality and morbidity observed in patients undergoing night surgery: frequent anaesthesia provider handovers and higher rates of intraoperative blood transfusion.

Meaning of this study

We present a hypothesis driven study from two major tertiary care hospital networks. In our cohort, patients who underwent night surgery were more often hospitalised and underwent more emergency procedures than those undergoing day surgery. The effect of night surgery on mortality was more pronounced in ambulatory and same-day admitted cases compared with inpatients. This novel observation supports the hypothesis that night surgery itself was associated with adverse outcomes and that its effect was not driven by a higher case acuity or a more severe condition of patients undergoing night surgery. This further suggests that patients who were just admitted to the hospital and who may not have received the appropriate preoperative workup may represent a risk group where it would be clinically meaningful to avoid night surgery. Among emergency patients, we did not find a difference in mortality between day and night cases. The effect of night surgery on adverse outcome may be weaker in emergency patients because other factors such as severity of the condition may be more important, while the emergency surgery has to be performed immediately regardless of the time of day or night.

The novelty of this study relates to the identification of preventable mediators of the adverse effects of night surgery. Mediation analysis is a tool for providing explanation of an observed association within observational studies.[25–27] We identified that the risk of receiving intraoperative blood transfusion was higher among patients undergoing night surgery. The effect was robust when accounting for preoperative anaemia, intraoperative blood loss and an individual provider-related variability in transfusion practice. Mediation analysis revealed that the higher transfusion rate observed during night-time explained 5.9% of the increased mortality and 4.9% of the increased complication risk after night surgery. We speculate that higher transfusion rates independent of patient and procedural risk factors may indicate an early and more liberal treatment of conditions that may occur within the postoperative period, such as a decrease in haemoglobin levels, thereby aiming to prevent the need for further therapy during night-time. Multiple studies have shown that a restrictive rather than liberal transfusion strategy with respect to WHO recommended transfusion thresholds and clinical symptoms of anaemia (transfusion triggers) is associated with improved outcomes after surgery.[28–33] Various interventions have been recommended to reduce transfusion rates, such as enhancing a patient's physiological tolerance of anaemia by optimising oxygenation, decreasing oxygen consumption and ensuring normovolaemia.[34 35]

We observed that handovers from one anaesthesia provider to another occurred 2.5 times more often during night surgeries compared with surgeries during day-time. In a recent study published in JAMA, anaesthesia handovers have been identified as a risk factor of increased postoperative mortality and major complications.[11] We were able to confirm in our mediation analysis that the higher proportion of handovers contributed to an increased complication risk after night surgery. This may be explained by the fact that during night-time, circulating teams of surgeons, anaesthesia providers and nurses are stretched and less specialised than day teams. It has been shown that liver and thoracic organ transplants do not have adverse outcomes following night surgery which may be due to the typically permanent and highly specialised composition of transplant teams.[36–38] Based on our findings, we speculate that low acuity cases such as ambulatory surgeries are particularly prone to errors due to reduced attention and improper communication within changing teams. For the high acuity patients, there may be a higher level of communication and rechecking that prevents failures.

We also observed significantly longer case delays among patients who underwent night surgery, which could be related to a longer fasting period in patients undergoing surgery at night-time. Fasting prior to surgery leads to a catabolic metabolism that affects a patient's stress response to surgery and postoperative insulin resistance and increases patient discomfort,[39 40] which might add to the negative effects of night surgery on postoperative outcome. Implementation of case-specific fasting guidelines may help decrease the harmful effects of long fasting periods on postoperative outcomes.

Implications for clinicians and policymakers

The observed higher proportion of blood transfusions and handovers may reflect differences in the surgical management of patients operated during night-time. Different behaviour patterns of providers during night-time may in some cases rather promote self-interest than patient-centred and individualised care. The observed key factors contributing to a higher risk of night surgery should be modified and adapted to practice patterns during the day to improve outcomes after night surgery.

In our study, almost 60% of cases performed at night were non-emergency procedures. Of those, 60% were ambulatory or same-day surgeries, which carried the highest risk of mortality attributable to night surgery. In these cases, postponing a surgical procedure should be considered to allow time for both the patient and provider to prepare for surgery. In a recent study, efforts to implement standardised protocols for patient urgency classification and operating room booking aimed at a more selective out-of-hours use of operation rooms for emergency services.[41] First results demonstrated higher operating room efficiency during standard hours (increased case time during the day), while operation time at night decreased by 26%.[41] Adapted to the local conditions, further hospitals should evaluate the implementation of standardised scheduling tools for non-emergency patients. In addition, if night surgery has to be conducted, we suggest that blood transfusion protocols should be rigorously implemented, and handovers be minimised.

There are several limitations to our study. Patients who underwent night surgery were more often inpatients and emergency cases and may be generally sicker than patients undergoing surgery during standard hours. To address confounding related to these differences, we used an interaction analysis which demonstrated a greater effect of night surgery on mortality among patients undergoing ambulatory/same-day surgery compared with inpatients, while no association between night surgery and mortality was found in a subgroup of emergency patients. We used several sensitivity analyses such as propensity score matching and repeating the primary analysis in the complete-case cohort, and the similar results were confirmatory. In addition, path mediation models have been described as a more complex form of multiple regression models, which still cannot establish causality of an effect (as compared with experimental studies) but can be used to determine whether hypotheses from observational data are plausible.[25 42] However, potential unmeasured confounders may have affected results of this observational study.

Conclusion

We demonstrate that surgery at night was associated with an increased risk of mortality and morbidity in a large multicentre cohort. Patients who underwent ambulatory or same-day surgery were particularly vulnerable to the adverse effect of night surgery. Higher exposures to blood transfusions and anaesthesia handovers during night-time partly explained the increased complication risk. Based on our findings, the risk of night surgery did not appear to be driven by a higher case acuity but could partly be attributed to a different surgical management of patients operated during night-time.

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