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ORIGINAL ARTICLE

Circadian effect of time of anaesthesia on postoperative outcomes in major elective and urgent intervention: a secondary analysis of the Peri-interventional Outcome Study in the Elderly (POSE)

Danny Feike Hoogma, Layth Al Tmimi, Steffen Fieuws, Jos Tournoy, Ana Kowark, Rolf Rossaint, Mark Coburn and Steffen Rex, the POSE study group[#]

BACKGROUND A recent prospective study reported a decrease in postoperative mortality when cardiac surgery was started in the afternoon instead of in the morning. In contrast, several large retrospective analyses have not confirmed this finding. Larger prospective studies are required to elucidate the effects of circadian rhythm on postoperative outcomes.

OBJECTIVE To identify any relation between starting time of anaesthesia/surgery and postoperative outcomes in patients aged 80 years or older to aid in clinical decision making with regard to scheduling surgery.

DESIGN A multivariable model with a priori defined confounders was constructed to evaluate the impact of anaesthesia starting time on hospital length of stay and postoperative complications.

SETTING A European multicentre, observational study of outcomes after geriatric anaesthesia from October 2017 to December 2018.

PATIENTS Patients aged 80 years or older having major elective or urgent intervention with anaesthesia starting time between 7 a.m. and 7 p.m.

MAIN OUTCOME MEASURE Primary outcome measure was the difference in hospital length of stay after any major elective or urgent morning or afternoon intervention.

RESULTS We included 3551 patients of whom 2592 had an intervention starting in the morning (7 a.m. to 1 p.m.). These patients, compared with those with interventions in the afternoon (1 p.m. to 7 p.m.), were slightly younger, were less frail but had a longer duration of the intervention. Hospital length of stay or postoperative complications were not different between morning or afternoon interventions. Multivariable analysis showed no impact of time of anaesthesia (morning vs. afternoon) on hospital length of stay or postoperative complications, hazard ratio of 1.03 (95% CI 0.94 to 1.12) and odds ratio of 1.13 (95% CI 0.92 to 1.39), respectively.

CONCLUSION Our results do not support the hypothesis of circadian effects on postoperative outcomes for elective and urgent major interventions in patients at least 80 years of age.

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[#] The POSE-study group.

From the University Hospitals Leuven, Department of Anesthesiology (DFH, LAT, SR), University Leuven, Biomedical Sciences Group, Department of Cardiovascular Sciences (DFH, LAT, SR), University Leuven, Biomedical Sciences Group, Leuven Biostatistics and Statistical Bioinformatics Centre (L-BioStat) (SF), University Hospitals Leuven, Geriatric Medicine and Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium (JT), Department of Anaesthesiology, Medical Faculty University Hospital RWTH Aachen, Aachen (AK, RR, MC), Department of Anaesthesiology and Intensive Care, University Hospital Bonn, Bonn, Germany (AK, MC)

Correspondence to Danny Feike Hoogma, MD, Department of Anesthesiology, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium Tel: +32 16 34 42 70; e-mail: danny.hoogma@uzleuven.be

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KEY POINTS

- This secondary analysis of the POSE study, with patients aged at least 80 years undergoing major elective or urgent interventions, showed no evidence for circadian effects on postoperative outcomes.
- Increased age, duration of anaesthesia, urgency, ASA physical status, frailty, multimorbidity and in-patient status variables were independently associated with hospital LOS and postoperative complications.
- Median (95% CI) hospital length of stay for interventions in the morning and the afternoon was 7 (6 to 7) and 6 (6 to 6) days, $P = 0.39$, respectively.

Introduction

Within the hypothalamus, a subset of pacemaker neurons in the suprachiasmatic nucleus represents the central circadian clock that regulates the 24-h rhythm of the human body[1] by co-ordinating the activity of peripheral clocks, resulting in synchronised molecular and cellular processes.[2] Environmental influences such as irregular sleep, dining times, artificial light or jet lag after long-distance flights can disturb the circadian system with profound consequences for organ physiology, behaviour, cognition and gene expression.[3,4] Likewise, alterations of the circadian system may increase the risk of cardiovascular and metabolic disorders.[4–6] Current evidence correlating patients' circadian variations with postoperative outcomes is still dubious. A recent translational study in on-pump cardiac surgery reported an increase in the incidence of major adverse peri-operative cardiac events in patients who underwent surgery in the morning compared to those in which surgery was started in the afternoon.[4] Likewise, the incidence of acute ST-segment elevation myocardial infarction (STEMI) onset is known to be highest in the morning (between 6 a.m. and 12 p.m.) compared to the rest of the day.[7,8] In contrast, a large retrospective study of 247 475 patients found the odds for all-cause in-hospital mortality after any surgery to be lowest for operations starting in the morning and highest for those beginning in the afternoon.[9] Another group confirmed these findings.[10] Several other studies, however, could not detect any differences in morbidity or mortality for early vs. late start of cardiac surgery.[11-13]

Compared with younger patients, older patients are perceived to be more vulnerable to noxious insults, resulting in a higher incidence of postoperative problems, in particular, cardiac, pulmonary and renal complications with increased hospital length of stay (LOS).[14,15]

To our knowledge, the impact of circadian variations on postoperative complications and hospital LOS has not yet been investigated in the geriatric population. We hypothesised that hospital LOS and postoperative complications would be increased in older patients having interventions during the morning compared with afternoon interventions.

Materials and methods

Study design, setting and participants

This is a secondary analysis of data recorded by the Peri-interventional Outcome Study in the Elderly (POSE) trial,[16] a European multicentre, observational prospective cohort study of outcomes after geriatric anaesthesia (clinicaltrials.gov: NCT03152734). More than 9000 patients, from 177 hospitals in 20 European countries, were analysed. Ethical approval or waiver was granted for each centre with initial approval from the ethical committee (EK 162/17) of the University Hospital RWTH Aachen, Germany on 18 August 2017. The design of this study has been comprehensively described elsewhere[16] and is available at www.pose-trial.org/study-documents/. In brief, patients were eligible if aged more than 80 years undergoing any kind of surgical or nonsurgical procedure (such as radiological kyphoplasty or gastrointestinal stenting) under anaesthesia (performed by an anaesthetist) from October 2017 to December 2018. The follow-up period was 30 days after the intervention.

Following approval of the Steering Committee of the POSE study, (see https://pose-trial.org/secondary-analysis/), the anonymised data set was transferred with an encrypted, password-protected E-mail for the present prespecified secondary analysis in which all patients were included, and had to undergo a major elective intervention (scheduled admission) or urgent intervention (required within 48 h after unplanned admission) with anaesthesia starting between 7 a.m. and 7 p.m. The predicted end time of anaesthesia was not part of the inclusion criteria. The severity of the interventions was classified as described previously.[16] Patients were excluded if the duration of anaesthesia was not documented or less than 15 min or if patients had to undergo emergency interventions (if patient's life or wellbeing was in direct jeopardy). The present manuscript adheres to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[17]

Outcome measures

The primary outcome measure was hospital LOS after any major elective or urgent intervention. As a secondary outcome measure, we considered (up to 30 days after the index intervention) the occurrence of any postoperative complication, defined as a composite of in-hospital complications, as classified by the American College of

Surgeons National Surgical Quality Improvement Program (ACS-NSQIP), and any complications after hospital discharge that led to hospital re-admission or death (Table 1).

Statistical analysis and variables

Patients were categorised into two different groups: one group with anaesthesia starting time between 7 a.m. and 1 p.m. (morning) and one group with anaesthesia starting time between 1 and 7 p.m. (afternoon). Patient characteristics and intervention data were compared between both periods using χ^2 and Mann–Whitney *U* tests. In addition, the start of anaesthesia was treated as a continuous variable.

For the analysis of the relationship between time of intervention and hospital LOS, death during hospital stay was treated as a competing risk.[18] The time until discharge was visualised using cumulative incidence curves.

Hazard ratios from univariable as well as from multivariable Fine–Gray survival models were reported applying a multivariable model in which the following list of a priori defined and well established confounders were considered (and no model reduction strategy was applied): age, sex, American Society of Anesthesiologist (ASA) physical status, multimorbidity, frailty, elective or urgent intervention, in-patient or out-patient and duration of anaesthesia.[9,16,19] Restricted cubic splines (with five knots) were used for the continuous predictors to allow nonlinearity (on the log-hazard scale). In addition, a subgroup analysis for only elective interventions was performed.

To handle the clustering of the patients in the various centres, the robust sandwich estimate of Lin and Wei (1989) for the covariance matrix was used.[20] A similar approach, however, based on univariable and multivariable logistic regression models with generalised estimating equations (GEEs), was used to evaluate the relation with the presence of any in-hospital complication. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows.

Data sources/measurement

Peri-operative assessments and outcomes are described in the original publication.[16] Briefly, hospital LOS was defined as the sum of days hospitalised, including the day of intervention and excluding the day of discharge.

Results

Participants

The study flow chart is shown in Fig. 1. The POSE trial included 9497 patients of whom 3938 underwent a major intervention. Of those, 274 patients were excluded due to an emergency intervention and 3664 underwent elective or urgent intervention. From the latter, 3556 interventions had anaesthesia started between 7 a.m. and 7 p.m. Due to missing data on the duration of anaesthesia in five interventions, 3551 patients could be included in the final analyses.

Baseline data

The intervention started in the morning for 2592 (73%) patients. These patients were slightly younger and more often scheduled for an elective intervention compared to afternoon patients (Table 2). In addition, patients in the morning were less frail and underwent longer interventions than the patients in the afternoon. There were no significant differences in multimorbidity or ASA physical status (Table 2).

Outcome data

Median (95% CI) hospital LOS for interventions in the morning and the afternoon was 7 (6 to 7) and 6 (6 to 6) days, $P = 0.39$, respectively. There was neither a significant difference for in-hospital mortality between morning or afternoon interventions (3.4 vs. 4.6%, $P = 0.08$) nor for the 30 days discharge rate (Table 3). Furthermore, 733 patients (21%) experienced at least one postoperative complication within 30 days postoperatively, which was not affected by the start of anaesthesia (Table 4). However, increased duration of anaesthesia, age, ASA-grade, frailty, urgency and male sex were independent predictors for the occurrence of postoperative complications (Table 4).

Table 1 Postoperative outcomes evaluated in-hospital or after discharge up to 30 days, in case of readmission or death.

Postoperative outcomes
In-hospital outcome according to the ACS NSQIP
Cardiac arrest
Myocardial infarction
Pneumonia
Pulmonary embolism
Unplanned intubation
Ventilator > 48 h
Return to the operating room
Stroke
Acute kidney injury (creatinine increase >2 mg dl^{-1} or new dialysis)
Deep vein thrombosis
Venous thromboembolism (requiring therapy)
Superficial incisional surgical site infection
Deep incisional surgical site infection
Organ space surgical site infection
Wound disruption
Systemic sepsis
Urinary tract infection
Discharge to postacute care
Complication after hospital discharge leading to readmission or death
Cardiac (cardiac arrest, myocardial infarction)
Pulmonary (pneumonia, pulmonary embolism)
Stroke
Acute kidney injury (only if it led to renal replacement therapy)

ACS NSQIP, American College of Surgeons National Surgical Quality Improvement Program.

Fig. 1 Flow of participants according to the STROBE guideline[17]

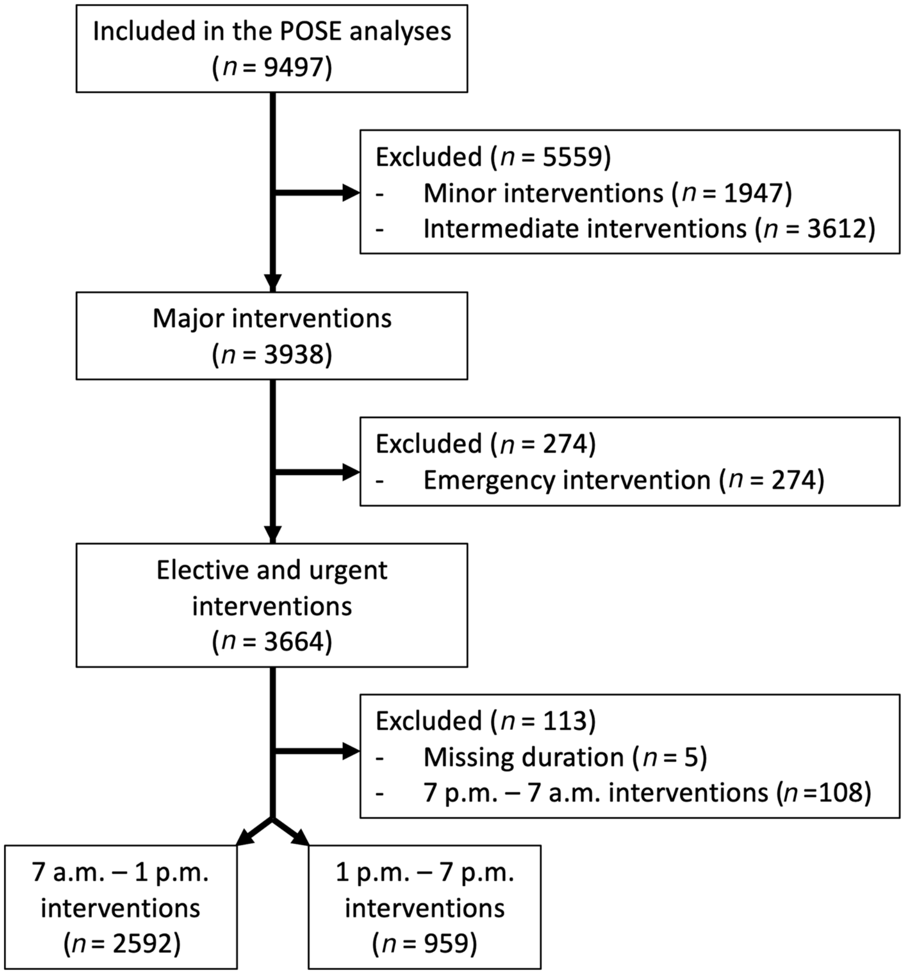


Table 2 Patient characteristics and intervention data.

Variable	All *n* (3551)	Start 7 a.m. to 1 p.m. *n* (2592)	Start 1 p.m. to 7 p.m. *n* (959)	*P*
Patient characteristics				
Age (years)	84 ± 3.9	84 ± 3.8	85 ± 4.2	**<0.001**
Male	1661 (47)	1234 (48)	427 (45)	0.10
Pre-operative status				
ASA grade				0.34
ASA I-II	1202 (34)	881 (34)	321 (33)	
ASA III	2013 (57)	1455 (56)	558 (58)	
ASA IV-V	334 (9)	254 (9.8)	80 (8.3)	
Frailty	553 (16)	378 (15)	175 (18)	**0.007**
Multimorbidity	2864 (81)	2107 (81)	757 (79)	0.12
Anaesthesia and surgery related-data				
Duration of anaesthesia (h)	2,7 ± 1.7	2.9 ± 1.8	2.2 ± 1.3	**<0.001**
Elective	2602 (73)	2052 (79)	550 (57)	**<0.001**
Outpatient intervention	48 (1.4)	28 (1.1)	20 (2.1)	**0.02**

Data are presented as mean with standard deviation ± SD or absolute number (*n*) with the percentages (%) of the whole. All reported *P* values are two sided. Bold indicates statistical significance at $P < 0.05$. ASA, American Society of Anesthesiology.

Table 3 Postoperative outcomes.

Variable	All *n* (3551)	Start 7 a.m. to 1 p.m. *n* (2592)	Start 1 p.m. to 7 p.m. *n* (959)	*P*
In-hospital complication	733 (21)	528 (20)	205 (21)	0.51
Discharged within 30 days	3268 (92)	2391 (92)	877 (91)	0.39
In-hospital death within 30 days	131 (3.7)	87 (3.4)	44 (4.6)	0.08

Data are presented as absolute number with the percentages (%). All reported *P* values are two-sided.

Table 4 Univariable and multivariable regression model investigating the association between interventional starting time and postoperative complications.

	Univariable		Multivariable			
			Two time periods		Time as a continuous variable	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Anaesthesia and surgery-related factors						
Start anaesthesia						
7 a.m. to 1 p.m.	[a]		[a]		–	–
1 p.m. to 7 p.m.	1.09 (0.88 to 1.34)	0.45	1.13 (0.92 to 1.39)	0.24	–	–
Hour start anaesthesia	1.01 (0.97 to 1.04)	0.75	–	–	1.02 (0.99 to 1.06)	0.21
Duration of anaesthesia (h)	1.27 (1.21 to 1.32)	**<0.0001**	1.32 (1.26 to 1.38)	**<0.0001**	1.33 (1.27 to 1.39)	**<0.0001**
Elective	0.60 (0.48 to 0.77)	**<0.0001**	0.56 (0.44 to 0.72)	**<0.0001**	0.57 (0.45 to 0.72)	**<0.0001**
Outpatient intervention	0.57 (0.28 to 1.20)	0.13	0.93 (0.51 to 1.70)	0.81	0.93 (0.51 to 1.69)	0.80
Patient factors						
Age	1.03 (1.01 to 1.05)	**0.001**	1.03 (1.00 to 1.05)	**0.03**	1.03 (1.00 to 1.05)	**0.03**
Male	1.33 (1.13 to 1.56)	**0.0006**	1.40 (1.17 to 1.68)	**0.0003**	1.40 (1.17 to 1.68)	**0.0003**
ASA grade		**<0.0001**		**<0.0001**		**<0.0001**
ASA I-II	[a]		[a]		[a]	
ASA III	1.77 (1.45 to 2.17)	**<0.0001**	1.39 (1.10 to 1.77)	**0.01**	1.39 (1.10 to 1.77)	**0.01**
ASA IV-V	3.26 (2.51 to 4.25)	**<0.0001**	2.38 (1.70 to 3.35)	**<0.0001**	2.39 (1.71 to 3.35)	**<0.0001**
Frailty	1.88 (1.56 to 2.28)	**<0.0001**	1.49 (1.20 to 1.85)	**0.0003**	1.48 (1.20 to 1.84)	**0.0003**
Multimorbidity	1.72 (1.39 to 2.12)	**<0.0001**	1.30 (1.00 to 1.68)	0.05	1.29 (1.00 to 1.67)	0.05

Results from univariable and multivariable logistic regression analyses of variables and their association with any in-hospital complication. Bold indicates statistical significance at $P < 0.05$. ASA, American Society of Anesthesiology grade; CI, confidence interval; OR, odds ratio. [a] Reference category.

After adjusting for the a priori defined confounders, there was neither a statistically significant and, more importantly, nor a clinically relevant association between the time of anaesthesia start and hospital LOS (Fig. 2). Multivariable analysis indicated that increased age, duration of anaesthesia, urgency, ASA physical status, frailty, multimorbidity and in-patient status were independently associated with prolonged hospital LOS (Table 5).

The planned multivariable analysis for only major elective intervention also failed to reveal a significant impact from anaesthesia starting time on 30 days postoperative complications or hospital LOS (Table 6), hence confirming the robustness of the observations in the total population.

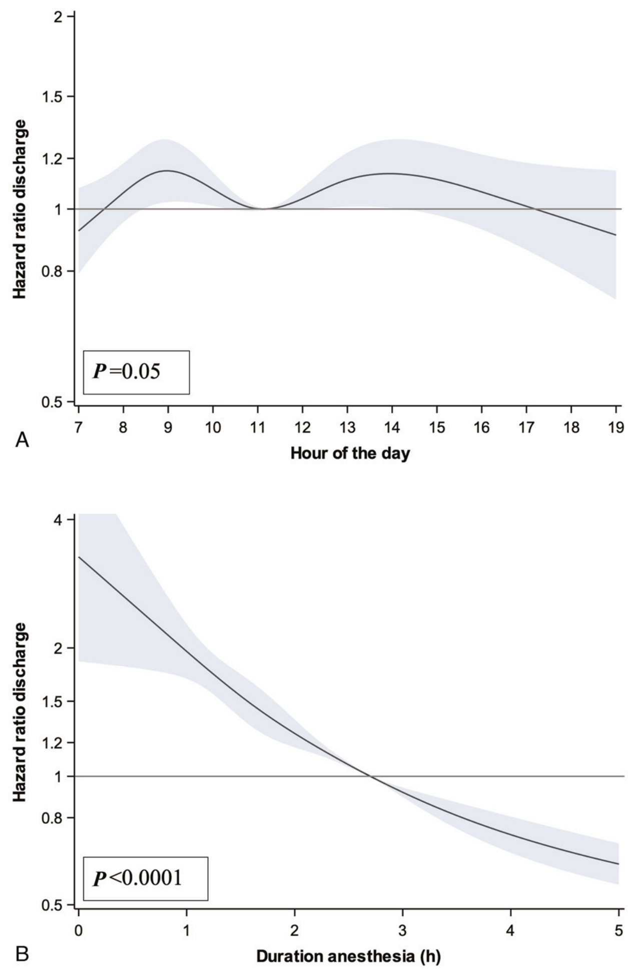
Discussion

In this large pan-European population at least 80 years of age undergoing elective or urgent major interventions between 7 a.m. and 7 p.m., we could not find any association between the time of anaesthesia start and hospital LOS or postoperative complications. The hypothesis of a circadian effect of anaesthesia starting time on hospital LOS or postoperative outcomes has to be refuted.

The debate of circadian effects of anaesthesia starting time on patients' outcome has been revived by the publication of Montaigne *et al.*[4] who reported worse outcomes for cardiac surgery in the morning. In contrast to these results and several retrospective studies dating from before their publication,[4,9,19,21] we could not detect any differences in postoperative outcomes in function of anaesthesia starting time. Notably, we focused on a particularly vulnerable population, as we limited our analysis to major interventions with a considerably higher mortality rate (3,7%) as compared to most other studies in this field (mortalities ranging from 0.03 to 3.7%).[9,10,19,22–26] Moreover, our population was considerably older, and therefore considered to have an increased risk for any adverse event.[14]

The majority of published studies selected the cut-off to distinguish between different intervention times in a dichotomous manner, mainly based on resource availability. Yount *et al.*[10] selected 3 p.m. as the cut-off time

Fig. 2 Hazard ratio from the multivariable regression model (Fine & Gray) for discharge as a function of (a) anaesthesia starting time and (b) duration of anaesthesia. Hazard ratio more than 1 refers to shorter hospital length of stay compared to the mean value (i.e. the hazard ratio equals 1 at the mean values of hour of the day and duration of anaesthesia).



because of operating room personnel turnover and departure of the intensivist before admission of the patient to the ICU. Whitlock *et al.*[19] followed the definition proposed by Kelz *et al.*[21] and used a cut off of 4 p.m. coinciding with off-hour care in the Veteran's Affairs medical system with less staff availability. Only in the study of Kork *et al.*,[9] time was treated as a continuous variable, revealing an increased mortality between 1 p.m. and 5 p.m. In contrast, several smaller retrospective studies in cardiac surgery could not detect any difference in hospital LOS when using a variety of cut-off times (ranging from noon to 4 p.m.) to define afternoon cases.[11,12,24–26] It is plausible that the selection of cut-off hours simply based on 'after hours' will primarily reflect the effect of organisational issues (i.e. reduced resource availability) rather than that of circadian alterations on patients' outcome. Therefore, the design of our prospective study analysing starting time as a continuous variable weakened this confounder and is probably more appropriate to reveal the impact, if any, of circadian effects on postoperative outcomes.

In our older population undergoing major interventions, increased age, duration of anaesthesia, urgency, ASA physical status, frailty, multimorbidity and in-patient status variables were independently associated with hospital LOS and postoperative complications. In the majority of trials suggesting an impact of starting time on mortality, information about these parameters is often limited, complicating a comparison with these studies.[10,19] Any differences in outcomes reported in these trials could, therefore, also be due to baseline confounders the authors were unable to account for.

Finally, with increasing age, amplitude of many circadian rhythms dampens, and in some cases, there is a shift of this dampened peak.[27] Considering the decremental impact of ageing on the circadian system, shift of anaesthesia starting time in patients at least 80 years of age might not cause any additional detectable disturbances of the circadian clock.[28]

Strengths and limitations

The current study provides valuable real-world data by prospectively focusing on a particularly vulnerable population requiring major interventions. In addition, to evaluate circadian alterations instead of organisational issues, timing of the intervention was analysed both as a continuous variable and as a dichotomous variable.

We acknowledge that the present prospective observational study also suffers from several limitations. Despite adjusting our observations for a variety of well known confounders, our analysis could still be affected by unknown factors that can only be addressed in a randomised controlled trial. Second, by including a mixed patient population, any impact of starting time on a specific surgical population was not analysed. Third, it cannot be excluded that the international multicentre study design encompassing differences in national standards and centre and country-specific resource availability may have masked subtle circadian clock effects. Finally, we also included urgent cases, when these were amenable for planning within the following 48 h. However, as urgency is well known to put the patient at a higher risk for postoperative complications and a longer hospital LOS,[9] we included this confounder in our model.

Interpretation and generalisability

In general, the results of this analysis show that in patients at least 80 years of age requiring elective or urgent major interventions, anaesthesia starting time has no impact on outcome when performed between 7 a.m. and 7 p.m.

Table 5 Univariable and multivariable regression model investigating the association between interventional starting time and discharge.

	Univariable		Multivariable			
			Two time periods		Time as a continuous variable	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Anaesthesia and surgery-related factors						
Start anaesthesia						
7 a.m. to 1 p.m.	[a]		[a]		–	–
1 p.m. to 7 p.m.	1.03 (0.95 to 1.13)	0.48	1.03 (0.94 to 1.12)	0.51	–	–
Hour start anaesthesia*		**0.05**	–	–		0.05[b]
Duration of anaesthesia (h)*		**<0.0001**		**<0.0001**		**<0.0001**[b]
Elective	1.49 (1.34 to 1.66)	**<0.0001**	1.76 (1.56 to 2.00)	**<0.0001**	1.80 (1.60 to 2.03)	**<0.0001**
Outpatient intervention	3.77 (2.03 to 6.98)	**<0.0001**	2.75 (1.76 to 4.30)	**<0.0001**	2.83 (1.78 to 4.51)	**<0.0001**
Patient factors						
Age	0.98 (0.97 to 0.99)	**<0.0001**	0.99 (0.98 to 1.00)	**0.004**	0.99 (0.97 to 1.00)	**0.003**
Male	1.05 (0.98 to 1.13)	**0.14**	1.01 (0.94 to 1.09)	0.74	1.02 (0.95 to 1.10)	0.61
ASA grade		**<0.0001**		**<0.0001**		**<0.0001**
ASA I-II	[a]		[a]		[a]	
ASA III	0.77 (0.71 to 0.84)	**<0.0001**	0.90 (0.82 to 0.98)	**0.02**	0.90 (0.82 to 0.98)	**0.02**
ASA IV-V	0.56 (0.50 to 0.64)	**<0.0001**	0.70 (0.59 to 0.82)	**<0.0001**	0.69 (0.58 to 0.81)	**<0.0001**
Frailty	0.65 (0.59 to 0.72)	**<0.0001**	0.76 (0.69 to 0.84)	**<0.0001**	0.74 (0.67 to 0.82)	**<0.0001**
Multimorbidity	0.76 (0.70 to 0.82)	**<0.0001**	0.89 (0.81 to 0.97)	**0.007**	0.88 (0.81 to 0.96)	**0.005**

Results from a univariable and multivariable Fine & Gray model for time to discharge. An HR >1 refers to a shorter length of hospital stay (=higher risk for discharge). Bold indicates statistical significance at $P < 0.05$. ASA, American Society of Anesthesiology grade; CI, confidence interval; HR, hazard ratio. [a] Reference category. [b] Linearity (on the logit scale) was not plausible; hence, cubic spline terms to allow nonlinearity were used as depicted in Fig. 2.

Table 6 Multivariable regression model investigating the association for major elective interventions between anaesthesia starting time and 30-day postoperative complications and hospital length of stay.

	30 days postoperative complications				Hospital length of stay			
	Two time periods		Time as a continuous variable		Two time periods		Time as a continuous variable	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Anaesthesia and surgery-related factors								
Start anaesthesia								
7 a.m. to 1 p.m.	[a]		–	–				
1 p.m. to 7 p.m.	1.07 (0.80 to 1.43)	0.65	–	–	1.07 (0.96 to 1.19)	0.22	–	–
Hour start anaesthesia	–	–	1.00 (0.96 to 1.05)	0.94	–	–		0.20[b]
Duration of anaesthesia (h)	1.34 (1.28 to 1.42)	**<0.0001**	1.34 (1.27t o 1.41)	**<0.0001**		**<0.0001**[b]		**<0.0001**[b]
Outpatient intervention	0.94 (0.51 to 1.76)	0.86	0.95 (0.51 to 1.78)	0.87	3.62 (1.99 to 6.58)	**<0.0001**	3.59 (1.93 to 6.69)	**<0.0001**
Patient factors								
Age	1.02 (0.99 to 1.06)	0.15	1.02 (0.99 to 1.06)	0.15	0.98 (0.97 to 0.99)	**0.001**	0.98 (0.97 to 0.99)	**0.001**
Male	1.32 (1.03 to 1.68)	**0.03**	1.32 (1.03 to 1.68)	**0.03**	1.03 (0.95 to 1.12)	0.44	1.04 (0.96 to 1.13)	0.36
ASA grade		**0.0002**		**0.0002**		**0.002**		**0.001**
ASA I-II	[a]		[a]		[a]		[a]	
ASA III	1.60 (1.20 to 2.12)	**0.001**	1.60 (1.20 to 2.12)	**0.001**	0.89 (0.80 to 0.98)	**0.02**	0.88 (0.80 to 0.97)	**0.01**
ASA IV-V	2.46 (1.61 to 3.75)	**<0.0001**	2.46 (1.61 to 3.75)	**<0.0001**	0.70 (0.58 to 0.86)	**0.0007**	0.70 (0.57 to 0.85)	**0.0004**
Frailty	1.48 (1.11 to 2.00)	**0.009**	1.48 (1.11 to 1.98)	**0.009**	0.72 (0.64 to 0.82)	**<0.0001**	0.70 (0.62 to 0.80)	**<0.0001**
Multimorbidity	1.29 (0.93 to 1.78)	0.13	1.28 (0.93 to 1.78)	0.14	0.91 (0.83 to 1.01)	0.07	0.91 (0.82 to 1.00)	0.05

Results from multivariable logistic regression analyses of variables and their association with any in-hospital complication and Fine & Gray model for time to discharge for patient with elective major interventions. An HR >1 refers to a shorter length of hospital stay (=higher risk for discharge). Bold indicates statistical significance at $P < 0.05$. ASA, American Society of Anesthesiology grade; CI, confidence interval; HR, hazard ratio; OR, odds ratio. [a] Reference category. [b] Linearity (on the logit scale) was not plausible, hence cubic spline terms to allow nonlinearity were used. Bold indicates statistical significance at $P < 0.05$.

Conclusion

To our knowledge, this is the first large prospective study evaluating the impact of circadian clock disturbances on peri-operative outcomes. Our results do not support the hypothesis of a circadian effect of time of anaesthesia on postoperative outcomes in patients at least 80 years of age.

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contact lists and the financial support for holding of three steering committee meetings at the ESAIC Secretariat in Brussels.

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Presentation: none.

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