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비심장 수술에서 수술 중 심박수가 수술 후 30일 사망률에 미치는 영향: 후향적 단일 센터 코호트 연구

Impact of intraoperative heart rate on postoperative 30-day mortality in non-cardiac surgery: A retrospective single-center cohort study

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지 도 교 수 김 성 훈

이 논문을 의학박사 학위논문으로 제출함

2024 년 8 월

울 산 대 학 교 대 학 원

의 학 과

심 지 훈

심지훈의 의학박사 학위논문을 인준함

심사위원 정 성 문 인

심사위원 전 인 구 인

심사위원 김 성 훈 인

심사위원 신 항 식 인

심사위원 최 정 현 인

울 산 대 학 교 대 학 원

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Abstract

Introduction: The management of intraoperative heart rate (HR) during non-cardiac surgery could be crucial, as it has the potential to influence postoperative cardiac complications and outcomes. However, defining HR thresholds and exposure times that affect surgical outcomes is unclear. This study aims to assess the association between intraoperative HR and 30-day mortality, evaluating various HR parameters and specific thresholds for tachycardia and bradycardia.

Methods: This cohort study included patients undergoing non-cardiac surgery between March 2019 and February 2021. HR data were categorized by bradycardia thresholds (≤35, 40, 45, 50, and 60 beats per minute [bpm]) and tachycardia thresholds (≥90, 100, 110, and 120 bpm). Various intraoperative HR parameters such as Minutes/Hour (M/H) and time weighted average (TWA) were assessed. Cox proportional hazard regression was conducted to identify risk factors for 30-day mortality. The primary outcome was on the association between HR parameters and 30-day mortality, while secondary outcome was assessing the impact of specific durations of bradycardia and tachycardia on 30-day mortality.

Results: In Cox regression analysis, HR >100-TWA (hazard ratio [HR]: 1.01, 95% confidence interval [CI]: 1.00–1.02, p = 0.003) was significantly associated with a higher risk of 30-day mortality. While no significant associations were found for bradycardia parameters, prolonged exposure to tachycardia—specifically, HR>90 bpm for over 20 minutes (HR: 1.65, 95% CI: 1.08–2.52, p = 0.020), HR>100 bpm for over 10 minutes (HR: 1.98, 95% CI: 1.30–3.03, p = 0.002), and HR>110 bpm (HR: 2.00, 95% CI: 1.27–3.16, p = 0.003) or HR>120 bpm for more than 5 minutes (HR: 2.08, 95% CI: 1.19–3.65, p = 0.011)—were significantly associated with postoperative 30-day mortality.

Conclusion: Various HR parameters were significantly associated with 30-day mortality. Although bradycardia was not associated with postoperative mortality, prolonged exposure to tachycardia was strongly associated with 30-day mortality, particularly with increased severity and duration of exposure. These thresholds could aid in identifying high-risk patients and improve postoperative outcomes.

Key words: heart rate; intraoperative; tachycardia; non cardiac; mortality

차례

표 목차

그림 목차

Introduction

Heart rate (HR) control, along with blood pressure, is an important part of intraoperative hemodynamic management.[1, 2] Previous studies have described an association between perioperative HR and postoperative cardiac complications and surgical outcomes.[3-5] Tachycardia can reduce myocardial perfusion by reducing coronary blood flow during diastole, and tachycardia itself can increase myocardial oxygen demand; Through these two mechanisms, tachycardia can substantially worsen oxygenation of myocardial tissue.[6, 7] Additionally, bradycardia can reduce cardiac output, which reduces oxygen delivery to end organs.[1, 8] However, the relationship between HR, myocardial damage, and surgical outcomes has not been closely investigated.

Recent studies have investigated HR thresholds in relation to surgical outcomes.[9-11] Despite these efforts, the precise hazard threshold for intraoperative tachycardia or bradycardia, which significantly impacts surgical outcomes, remains elusive, and various definitions and cutoff values for tachycardia and bradycardia during surgery are in use.[1, 8, 9, 12] A standardized definition of intraoperative tachycardia and bradycardia, which can affect the patient's surgical outcome, can play an important role in identifying and managing patients at risk intraoperatively and improving postoperative outcomes.

Therefore, in this retrospective observational study, we aimed to assess the association between intraoperative HR and postoperative 30-day mortality. Initially, we evaluated the association between postoperative mortality rates and various HR parameters, including time-weighted average, area under the threshold, mean HR, median HR, maximum HR, and minimum HR, while considering exposure time and specific HR thresholds. Additionally, we examined the hypothesis that specific bradycardia (<60 beats per minute [bpm], <55 bpm, <50 bpm, <45 bpm, <40 bpm) or tachycardia (>90 bpm, >100 bpm, >110 bpm, >120 bpm) thresholds experienced for a defined duration may be linked to postoperative mortality rates.

Methods

Study design and patients

We included in the study all patients aged 18 years or older who underwent non-cardiac surgery at Asan Medical Center in Seoul from March 2019 to February 2021. Exclusion criteria comprised patients undergoing cardiac-related procedures, pregnancy, organ transplant surgery, and those with incomplete laboratory values or perioperative vital sign data (Figure 1). For patients who underwent multiple surgeries during the study period, only the first surgery performed after admission was included in the analysis. This cohort study received approval from the Institutional Review Board of Asan Medical Center (protocol number 2023-0611), and written informed consent was waived due to the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki (2013 revision). This article adheres to the applicable STROBE (STrengthening the Reporting of OBservational Studies in Epidemiology) guidelines.

Data collection

Baseline characteristics and demographic, perioperative information of enrolled patients was extracted from the database of our center's electronic medical record (EMR) system.

Baseline characteristics and demographic variables included age, sex, height, weight, body mass index (BMI), cerebrovascular accident (CVA), cardiovascular disease (CVD), diabetes mellitus (DM), hypertension (HTN), renal disease, hyperlipidemia, and American Society of Anesthesiologists (ASA) physical status classification. Variables related to resting systolic, diastolic, mean blood pressure (BP), and HR in the preoperative ward were also collected. Preoperative ward HR was the mean value of three or more measurements taken by clinical nursing staff prior to surgery as part of routine medical care.

Preoperative laboratory values included white blood cells (WBC), hemoglobin, platelets, international normalized ratio (INR), aspartate transaminase (AST), alanine transaminase (ALT), uric acid, total bilirubin, protein, albumin, sodium, pottasium, total calcium, glucose, estimated glomerular filtration rate (eGFR), and serum creatinine.

Intraoperative variables included the type of surgery (general, otolaryngology, urology, orthopedic, gynecologic, neurosurgery, thoracic, vascular, and others), high-risk surgery (orthopedic, neurosurgry, thoracic, and vascular), intraoperative systolic BP, diastolic BP, mean BP, and HR. Intraoperative HR data were obtained from the pulse oximeter or ECG. The HR interval ranged from a minimum of 1 minute to a maximum of 5 minutes on the EMR, and HR was measured as the value recorded at the end of the interval time. HRs below 30 bpm or above 150 bpm were considered artefacts and excluded from analysis.[10, 13] Data on the 30-day mortality (all-cause death within 30 days of surgery or before discharge) was also collected.

Study outcomes

The primary endpoint was the association of various parameters describing intraoperative HR with 30-day mortality. Various parameters for intraoperative HR include HR-mean, HR-median, HR-exposure time (minutes) according to specific specific thresholds, HR-Minutes/Hour (M/H) according to specific thresholds, HR-areas under the time curve (AUT) according to specific thresholds, HR-areas above the time curve (AAT) according to specific thresholds, and HR-time weighted average (TWA) according to specific thresholds. Thresholds for HR were defined as ≤35, 40, 45, 50, and 60 bpm for bradycardia and ≥90, 100, 110, and 120 bpm for tachycardia, respectively.

Figure 2 illustrates the linearly interpolated change curve in HR at 1-minute intervals per unit of surgical time. It also defines HR-M/H, HR-AAT, and HR-TWA. HR-M/H was calculated by dividing the HR-exposure time (in minutes) at a specific threshold by the total surgery length (in hours). HR-AAT was calculated as the area above the time curve value for a specific threshold. In other words, the area above HR above a specific threshold is the area between the specific threshold and the HR measurement curve. HR-TWA (bpm) was calculated as the HR-AAT divided by the total surgery length. Since these definitions reflect both the severity and duration of bradycardia and tachycardia, they can be used as values representing the characteristics of HR instead of the commonly used mean and median values.

The secondary endpoints were evaluating the associations between exposure to specific durations of bradycardia (<60 bpm, <55 bpm, <50 bpm, <45 bpm, <40 bpm) or tachycardia (>90 bpm, >100 bpm, >110 bpm, >120 bpm) and postoperative mortality rates. Additionally, we evaluated the association of HR>100_TWA stratified by age (< 65 vs. ≥ 65 years), sex (male vs. female), ASA class (1, 2 vs. 3), CVD (non-CVD vs. ≥ CVD), and high risk surgery (non-high risk surgery vs. high risk surgery) with 30-day mortality.

Statistical analysis

We analysed associations of various parameters representing for intraoperative HR with 30-day all-cause mortality. We categorized the HR sample by thresholds for bradycardia as ≤35, 40, 45, 50, and 60 bpm, and for tachycardia as ≥90, 100, 110, and 120 bpm. We established exposure time intervals based on specific heart rate (HR) thresholds, taking into account both previously reported studies and the distribution of exposure times within our research data. The intervals were set as follows: ≥5 min, ≥10 min, ≥20 min, ≥30 min, and ≥60 min. Due to the minimal number of patients exposed to heart rates below 35, this case was categorized as either exposure or non-exposure. We set parameters by combining various definitions of intraoperative HR thresholds and exposure times and analyzed their associations with 30-day mortality.

Cox proportional hazard regression model was used to identify the risk factors for 30-day mortality. All variables with P<0.1 in the univariate analysis were included in the multivariate analysis. Continuous variables of demographic and perioperative data were presented as mean with standard deviation or median with interquartile range. Categorical variables were presented as frequency with percentage. Baseline characteristics and perioperative variables of the study population were evaluated with Student's t-test or Mann–Whitney U-test for continuous variables and chi-square test or Fisher's exact test for categorical variables, as appropriate. All reported p values were 2-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed using and R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Study population and baseline characteristics

A total of 55,367 eligible patients were evaluated during the study period, and 52,309 were included in the final analytic cohort after excluding 3,058 patients (Figure 1). These patients collectively had a total of 6,540,245 HR time points. The Baseline characteristics and perioperative variables of the study population are summarized in Table 1. The mean age was 57.2 years, and 46.0% were male. Of the study population, all-cause mortality at 30-day was 0.2% (130/52309).

As for demographic related variables, the proportion of male sex (p < 0.001), CVA (p < 0.001), DM (p = 0.023), renal disease (p = 0.031), ASA (p < 0.001), and values of age (p < 0.001), BMI (p < 0.001, ward HR (p < 0.001) were statistically significantly higher in 30-day death group than 30-day survival group. There were no significant differences between the two groups in ward SBP, ward DBP, and ward MBP.

As for operation variables, intraoperative mean MBP (p = 0.033) were statistically significantly lower in in the 30-day death group than the 30-day survival group, and the proportion of high risk surgery (p = 0.010) and values of intraoperative SBP<80-TWA (p = 0.015), MBP<65-TWA (p < 0.001), median HR (p < 0.001), mean HR (p < 0.001), maximum HR (p < 0.001), and minimum HR (p < 0.001) were statistically significantly higher in the 30-day death group than the 30-day survival group. Regarding laboratory variables, the 30-day death group had significantly higher values of WBC (p < 0.001), AST (p < 0.001), total bilirubin (p = 0.001), INR (p < 0.001), glucose (p = 0.007), and creatinine (p = 0.007), whereas had lower values of hemoglobin (p < 0.001), protein (p < 0.001), albumin (p < 0.001), sodium (p < 0.001), potassium (p = 0.006), total calcium (p < 0.001), and eGFR (p = 0.001) than the 30-day survival group.

Table 2 shows the distribution for various parameters for intraoperative HR according to specific thresholds in the study population. In terms of bradycardia, significant differences were observed between the two groups in various parameters, including HR<35-surgery length ($p < 0.001$), HR<35-M/H ($p < 0.001$), HR<35-AUT ($p = 0.021$), HR<35-TWA ($p = 0.001$), HR<40-surgery length ($p < 0.001$), HR<40-M/H ($p < 0.001$), HR<40-AUT ($p < 0.001$), HR<40-TWA ($p < 0.001$), HR<45-surgery length ($p < 0.001$), HR<45-M/H ($p < 0.001$), HR<45-AUT ($p < 0.001$), HR<45-TWA ($p < 0.001$), HR<50-M/H ($p < 0.001$), HR<50-TWA ($p < 0.001$), HR<55-M/H ($p < 0.001$), HR<55-TWA ($p < 0.001$), HR<60-surgery length ($p = 0.031$), HR<60-M/H ($p < 0.001$), HR<60-AUT ($p = 0.020$), and HR<60-TWA ($p < 0.001$), except for HR<50-surgery length ($p = 0.621$), HR<50-AUT ($p = 0.601$), HR<55-surgery length ($p = 0.126$), and HR<55-AUT ($p = 0.096$). In terms of tachycardia, significant differences were observed between the two groups in all of parameters, including HR>90-surgery length ($p < 0.001$), HR>90-M/H ($p < 0.001$), HR>90-AAT ($p < 0.001$), HR>90-TWA ($p < 0.001$), HR>100-surgery length ($p < 0.001$), HR>100-M/H ($p < 0.001$), HR>100-AAT ($p < 0.001$), HR>100-TWA ($p < 0.001$), HR>110-surgery length ($p < 0.001$), HR>110-M/H ($p < 0.001$), HR>110-AAT ($p < 0.001$), HR>110-TWA ($p < 0.001$), HR>120-surgery length ($p = 0.003$), HR>120-M/H ($p = 0.002$), HR>120-AAT ($p = 0.004$), and HR>120-TWA ($p = 0.002$).

Table 3 shows the distribution of intraoperative heart rates by various thresholds and exposure time intervals. In terms of bradycardia, there were significant differences between the two groups at ≥ 5 minutes ($p = 0.001$), ≥ 10 minutes ($p = 0.003$), and ≥ 20 minutes ($p = 0.015$) for HR<50 bpm, and for HR<55 bpm and HR<60 bpm, there were significant differences between the two groups at all exposure times. In terms of tachycardia, there were significant differences between the two groups at all thresholds and exposure times.

Study outcomes: 30-day morality

In Cox regression analysis by backward elimination, HR>100-TWA was significantly associated with a higher risk of 30-day mortality (hazard ratio [HR]: 1.02, 95% confidence interval [CI]:

1.01–1.02, p < 0.001) (Table 4). Additionally, 30-day mortality rate was significantly associated with age (p < 0.001), male sex (p = 0.002), BMI (p < 0.001), CVA (p = 0.049), ASA ≥3 (p = 0.018), ward HR (p < 0.001), MBP<65-TWA (p = 0.013), and albumin (p < 0.001) (Table 4).

Table 5 shows associations between various intraoperative HR parameters and the 30-day mortality. In Cox regression analysis adjusted by age, sex, BMI, CVA, ASA, WARD_HR, MBP<65_TWA, and albumin, median HR (HR: 1.01, 95% CI: 1.01–1.03, p = 0.049), mean HR (HR: 1.02, 95% CI: 1.00–1.04, p = 0.016), maximum HR (HR: 1.01, 95% CI: 1.00–1.02, p = 0.036), and minimum HR (HR: 1.02, 95% CI: 1.00–1.02, p = 0.039) were significantly associated with a higher risk of 30-day mortality. In terms of bradycardia, there were no significant associations between various intraoperative HR parameters and the 30-day mortality (Table 5). In terms of tachycardia, HR>90-M/H (HR: 1.02, 95% CI: 1.01–1.03, p = 0.001), HR>90-TWA (HR: 1.01, 95% CI: 1.00–1.02, p = 0.002), HR>100-M/H (HR: 1.02, 95% CI: 1.01–1.03, p = 0.003), and HR>100-TWA (HR: 1.01, 95% CI: 1.00–1.02, p = 0.003) were significantly associated with a higher risk of 30-day mortality (Table 5).

Table 6 shows associations between various intraoperative HR thresholds according to exposure time and the 30-day mortality. In Cox regression analysis adjusted by age, sex, BMI, CVA, ASA, WARD_HR, MBP<65_TWA, and albumin, there were no significant associations between various intraoperative HR thresholds according to exposure time and the 30-day mortality in terms of bradycardia. (Table 6). In terms of tachycardia, HR>90 for ≥20 minute (HR: 1.65, 95% CI: 1.08–2.52, p = 0.020), HR>90 for ≥30 minute (HR: 1.81, 95% CI: 1.19–2.76, p = 0.006), HR>90 for ≥60 minute (HR: 1.97, 95% CI: 1.29–3.01, p = 0.001), HR>100 for ≥10 minute (HR: 1.98, 95% CI: 1.30–3.03, p = 0.002), HR>100 for ≥20 minute (HR: 2.14, 95% CI: 1.37–3.34, p < 0.001), HR>100 for ≥30 minute (HR: 2.17, 95% CI: 1.37–3.43, p < 0.001), HR>110 for ≥5 minute (HR: 2.00, 95% CI: 1.27–3.16, p = 0.003), HR>110 for ≥10 minute (HR: 2.25, 95% CI: 1.38–3.67, p = 0.001), HR>110 for ≥20 minute (HR: 1.79, 95% CI: 1.02–3.14, p = 0.043), HR>120 for ≥5 minute (HR: 2.08, 95% CI: 1.19–3.65, p = 0.011), and HR>120 for ≥10 minute (HR: 1.91, 95% CI: 1.04–

3.52, p = 0.039), were significantly associated with a higher risk of 30-day mortality (Table 6). In subgroup analysis stratified by age (< 65 vs. ≥ 65 years), sex (male vs. ≥ female), ASA class (1, 2 vs. 3), CVD (non-CVD vs. ≥ CVD), and high risk surgery (non-high risk surgery vs. high risk surgery), the prognostic effects of HR>100_TWA on 30-day mortality was not significantly different according to age, sex, ASA class, CVD, and high risk surgery. (Table 7)."

Discussion

In this study, we found significant associations between various parameters describing intraoperative heart rate (mean HR, median HR, maximum HR, minimum HR, M/H for specific HR thresholds, TWA for specific HR thresholds) and 30-day mortality. Additionally, while the parameters for bradycardia thresholds were not associated with postoperative 30-day mortality, those for tachycardia thresholds were significantly associated with postoperative 30-day mortality. Specifically, considering the specific thresholds and durations of exposure to tachycardia, instances such as HR>90 bpm for over 20 minutes, HR>100 bpm for over 10 minutes, and HR>110 bpm or HR>120 bpm for more than 5 minutes were associated with postoperative 30-day mortality. These findings indicate that various parameters and exposure durations related to bradycardia are not significantly linked to postoperative mortality, whereas several parameters and exposure durations associated with tachycardia may indeed have a significant correlation with mortality.

Recently, multiple studies have highlighted the impact of perioperative HR on surgical outcomes.[3, 5, 9-11, 14, 15] Abbott et al. found that elevated perioperative HR correlates with cardiopulmonary dysfunction, indicating that tachycardia exceeding 96 bpm is associated with myocardial injury after non-cardiac surgery (MINS), myocardial infarction (MI), and mortality following non-cardiac surgery.[3, 14] In a secondary analysis of the Vascular Events in Noncardiac Surgery Cohort Evaluation (VISION) study, it was found that a maximum intraoperative HR exceeding 100 bpm was associated with MINS, MI, and mortality.[11] Conversely, a minimum HR below 55 bpm was associated with a decrease in MINS, MI, and mortality.[11] Two subsequent studies analyzing intraoperative heart rate and postoperative outcomes in non-cardiac surgery yielded contrasting results: Ruetzler found no significant correlation between multiple markers of tachycardia and the composite outcomes of postoperative myocardial injury (MINS) and death in non-cardiac surgery.[10] Conversely, Shcherbakov reported that intraoperative tachycardia, defined as a heart rate (HR) of 100 bpm or higher lasting at least 30 minutes, had the highest predictive power for adverse postoperative outcomes.[9] As of now, the impact of intraoperative HR on postoperative outcomes in non-cardiac surgery remains controversial and inconclusive. Additionally, the definition of intraoperative bradycardia and tachycardia, and the extent of exposure required to influence outcomes, lack clear characterization. Our study rigorously investigated whether intraoperative HR affects postoperative outcomes, utilizing intuitive, user-friendly parameters, including mean, median, maximum, and minimum HR, as well as sophisticated parameters considering total operative time and exposure time at specific HR thresholds. Moreover, we conducted a comprehensive investigation, defining precise thresholds and exposure durations for bradycardia and tachycardia, areas that have not been adequately addressed in the existing literature, thereby providing significant clinical relevance.

In our study, we utilized parameters like TWA and M/H to establish specific thresholds indicative of the duration and severity of bradycardia or tachycardia. For example, a HR>100-TWA of 3.9 bpm implies that, on average, patients maintained a heart rate 3.9 bpm above 100 bpm throughout the surgical procedure. Considering that the average duration of cases in our study approached 170 minutes, a HR>100-TWA of 3.9 corresponds to 3.9 bpm multiplied by 170 minutes, resulting in 663 bpm × minutes. To illustrate, this calculation of 663 bpm × minutes could represent a scenario where a patient spent roughly 44 minutes with a heart rate of 115 bpm or 33 minutes with a heart rate of 120 bpm. These parameters are not currently routinely monitored and may be difficult to calculate intuitively, yet they could serve as more sophisticated indicators due to their consideration of exposure time and total operative duration.

In our study, when backward elimination was applied in Cox regression analysis, HR>100-TWA was the only parameter significantly associated with the 30-day postoperative mortality. This finding aligns with previous reports indicating an association between HR>100 BPM and adverse surgical outcomes in other studies.[9, 11]

Our study further refined the definition and duration of tachycardia. We found that HR>90 bpm for 20 minutes or more, HR>100 bpm for 10 minutes or more, and HR>110 bpm or 120 bpm for 5 minutes or more were associated with 30-day postoperative mortality. These results show that the threshold and duration of HR has a significant impact on outcomes and that even short exposures, especially at high heart rates, can affect postoperative outcomes.[4]

The association between tachycardia and death is not only because tachycardia during surgery can cause myocardial damage, but also because tachycardia itself can mean significant hemodynamic instability during surgery. Intraoperative tachycardia can indicate various conditions such as severe hemorrhage, hypovolemia, low cardia output, septic condition, and sympathetic tone activation.[16, 17] These situations, along with intraoperative hypotension, enhance organ-specific risk.[11, 18, 19]

Additionally, there is limited research on the impact of bradycardia on surgical outcomes. Some studies have suggested a protective effect of bradycardia on surgical outcomes.[11] However, in our study, after refining the definition of bradycardia and exposure time and adjusting for other variables, bradycardia was not significantly associated with 30-day mortality. The protective effect of bradycardia observed in previous reports may be a result of the opposite effect of tachycardia on surgical outcomes, as tachycardia is included on the opposite side of bradycardia in the dichotomous classification, rather than the effect of bradycardia per se.

In our study, subgroup analysis showed that the effects of HR>100_TWA on 30-day mortality was not significantly different according to age, sex, ASA class, CVD, and high risk surgery. These results indicate that HR>100_TWA is associated with adverse surgical prognosis, regardless of age, sex, ASA class, CVD, and high-risk surgery.

Our current study has several limitations. Firstly, being retrospective in nature, there is a possibility of unaccounted confounding or misclassification factors introducing bias. Nevertheless, we attempted to mitigate these effects by adjusting for variables such as relatively accurate quantified blood pressure and related laboratory values and multiple comorbidities.

Secondly, the HR data in this study were recorded at 5-minute intervals in the EMR system, thus limiting the assessment of changes in HR over shorter intervals, such as 1 minute, and potentially leading to missing HR values. Consequently, future investigations utilizing shorter intervals for measurements of HR may be warranted. Thirdly, due to the absence of routine perioperative troponin measurements during the study period, we were unable to evaluate the occurrence of postoperative cardiac complications (MINS, MI) and the association between intraoperative HR and postoperative cardiac complications. Fourthly, in this study, when the HR thresholds were set at 110 and 120 bpm, statistical significance was lost in areas with high exposure times (over 30 minutes or over 60 minutes). This may be because the HRs of patients who experienced an event (30-day mortality) were concentrated within a certain range. Additionally, individual variations in HR might have influenced the results. Therefore, future research will require exploratory studies that intensively analyze HR changes in individual patients, using more extensive datasets. Fifth, patients with severe arrhythmias, autonomic nervous system disorders, and anxiety disorders were not excluded in this study. Lastly, our data are derived from information documented in medical records, predominantly from a single racial group, gathered at a solitary medical institution. Hence, there exists a potential for biased results attributable to the homogeneity or similarity within the study population.

Conclusion

In conclusion, there was a significant association between various intraoperative heart rate parameters and 30-day mortality. While parameters related to bradycardia thresholds did not show a significant association with postoperative mortality especially prolonged exposure to tachycardia such as HR>90 bpm for over 20 minutes, HR>100 bpm for over 10 minutes, and HR>110 bpm or HR>120 bpm for more than 5 minutes, were found to be linked with postoperative 30-day mortality. These findings suggest that while various parameters and exposure durations related to bradycardia may not significantly affect postoperative mortality, multiple parameters and durations associated with tachycardia may indeed have a substantial impact on mortality.

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국문요약

서론: 비심장 수술 중의 심박수 관리는 수술 후 심장 합병증 및 결과에 영향을 미칠 수 있기 때문에 매우 중요합니다. 그러나 수술 결과에 영향을 미치는 심박수 임계값과 노출 시간을 정의하는 것은 명확하지 않습니다. 본 연구는 다양한 심박수 매개변수 및 빈맥과 서맥에 대한 특정 임계값을 평가하여 수술 중 심박수와 30 일 사망률 간의 연관성을 평가하는 것을 목표로 합니다.

방법: 이 코호트 연구에는 2019 년 3 월부터 2021 년 2 월까지 비심장 수술을 받은 환자들이 포함되었습니다. 심박수 데이터는 서맥 임계값(분당 ≤35, 40, 45, 50, 60 박동) 및 빈맥 임계값(분당 ≥90, 100, 110, 120 박동)으로 분류되었습니다. 분당/시간(M/H) 및 시간 가중 평균(TWA)과 같은 다양한 수술 중 심박수 매개변수가 평가되었습니다. 30 일 사망률의 위험 요인을 확인하기 위해 콕스 비례 위험 회귀 분석이 수행되었습니다. 주요 결과는 심박수 매개변수와 30 일 사망률 간의 연관성에 대한 것이며, 부차적인 결과는 서맥 및 빈맥의 특정 지속 시간이 30 일 사망률에 미치는 영향을 평가하는 것이었습니다.

결과: 콕스 회귀 분석에서 심박수 100 박동 초과-시간 가중 평균 (위험비[HR]: 1.01, 95% 신뢰 구간[CI]: 1.00–1.02, p = 0.003)은 30 일 사망률의 높은 위험과 유의하게 연관되었습니다. 서맥 매개변수에 대해서는 유의한 연관성이 발견되지 않았으나, 빈맥에 대한 장기 노출 특히, 분당 90 박동을 초과하는 심박수가 20 분 이상 지속될 경우(위험비: 1.65, 95% 신뢰 구간: 1.08–2.52, p = 0.020), 분당 100 박동을 초과하는 심박수가 10 분 이상 지속될 경우(위험비: 1.98, 95% 신뢰 구간: 1.30–3.03, p = 0.002), 분당 110 박동을 초과할 경우(위험비: 2.00, 95% 신뢰 구간: 1.27–3.16, p = 0.003) 또는 분당 120 박동을 초과하는 심박수가 5 분 이상 지속될

경우(위험비: 2.08, 95% 신뢰구간: 1.19–3.65, p = 0.011)는 수술 후 30 일 사망률과 유의하게 연관되었습니다.

결론: 다양한 심박수 매개변수는 30 일 사망률과 유의하게 연관되었습니다. 비록 서맥은 수술 후 사망률과 연관되지 않았으나, 빈맥에 대한 장기 노출은 특히 노출의 심각성과 지속 시간이 증가함에 따라 30 일 사망률과 강하게 연관되었습니다. 이러한 임계값은 고위험 환자를 식별하고 수술 후 결과를 개선하는 데 도움이 될 수 있습니다.

중심단어: 심박수; 수술 중; 빈맥; 비심장; 사망률

Table 1. Baseline characteristics & perioperative variables of the study population.

	Study population			
	Total, n=52309	**30-day survival, n=52179 (99.8%)**	**30-day death, n=130 (0.2%)**	***P***
Demographic variables				
Age; year	57.2 ± 14.5	57.1 ± 14.5	65.5 ± 13.6	< 0.001
Sex, male	24041 (46.0%)	23957 (45.9%)	84 (64.6%)	< 0.001
Height; cm	162.4 ± 8.7	162.4 ± 8.7	162.5 ± 8.7	0.909
Weight: kg	64.2 ± 12.3	64.3 ± 12.3	57.2 ± 11.1	< 0.001
BMI; kg.m-2	24.3 ± 3.7	24.3 ± 3.7	21.7 ± 3.7	< 0.001
CVA	1081 (2.1%)	1072 (2.1%)	9 (6.9%)	< 0.001
CVD	4009 (7.7%)	3995 (7.7%)	14 (10.8%)	0.243
DM	8776 (16.8%)	8744 (16.8%)	32 (24.6%)	0.023
HTN	17469 (33.4%)	17420 (33.4%)	49 (37.7%)	0.344
Renal	918 (1.8%)	912 (1.7%)	6 (4.6%)	0.031
Hyperlipidemia	6831 (13.1%)	6825 (13.1%)	6 (4.6%)	0.006
ASA				< 0.001
1	4697 (9.0%)	4695 (9.0%)	2 (1.5%)	
2	43003 (82.2%)	42930 (82.3%)	73 (56.2%)	
3	4460 (8.5%)	4410 (8.5%)	50 (38.5%)	
4	146 (0.3%)	141 (0.3%)	5 (3.8%)	
5	3 (0.0%)	3 (0.0%)	0 (0.0%)	

	Study population			
Ward SBP	121.8 ± 14.8	121.8 ± 14.8	121.6 ± 18.9	0.900
Ward DBP	75.5 ± 8.4	75.5 ± 8.4	74.0 ± 11.4	0.129
Ward MBP	90.7 ± 9.8	90.7 ± 9.8	89.6 ± 12.6	0.342
Ward HR	71.7 ± 10.8	71.7 ± 10.8	86.6 ± 17.1	< 0.001
Operation variables				
Type of surgery				0.054
General	24622 (47.1%)	24559 (47.1%)	63 (48.5%)	
Otolaryngology	2010 (3.8%)	2003 (3.8%)	7 (5.4%)	
Urology	5173 (9.9%)	5167 (9.9%)	6 (4.6%)	
Orthopedic	5511 (10.5%)	5491 (10.5%)	20 (15.4%)	
gynecologic	3127 (6.0%)	3122 (6.0%)	5 (3.8%)	
Neurosurgery	4131 (7.9%)	4118 (7.9%)	13 (10.0%)	
Thoracic	3396 (6.5%)	3383 (6.5%)	13 (10.0%)	
Vascular	483 (0.9%)	482 (0.9%)	1 (0.8%)	
others	3856 (7.3%)	3854 (7.4%)	2 (1.5%)	
High risk surgery (orthopedic, neurosurgery, thoracic, vascular)	13521 (25.8%)	13474 (25.8%)	47 (36.2%)	0.010
SBP_mean	117.7 ± 15.3	117.7 ± 15.3	114.8 ± 18.9	0.087
MBP_mean	85.1 ± 10.9	85.1 ± 10.9	82.5 ± 13.7	0.033
MBP<65_TWA	6.3 ± 10.7	6.3 ± 10.7	12.5 ± 13.8	< 0.001
HR_median	66.6 ± 12.4	66.5 ± 12.4	82.2 ± 18.1	< 0.001

	Study population			
HR_mean	67.8 ± 12.0	67.8 ± 11.9	83.3 ± 18.1	< 0.001
HR_maximum	92.0 ± 17.2	92.0 ± 17.2	104.6 ± 20.4	< 0.001
HR_minimum	55.8 ± 10.0	55.8 ± 9.9	68.7 ± 17.1	< 0.001
HR_surgery length	169.7 ± 110.4	169.7 ± 110.3	183.7 ± 133.3	0.233
Laboratory variables				
WBC	6.4 ± 2.3	6.4 ± 2.2	10.1 ± 7.6	< 0.001
Hemoglobin	13.0 ± 1.7	13.0 ± 1.7	10.8 ± 2.2	< 0.001
Platelet	242.2 ± 72.7	242.2 ± 72.5	227.4 ± 110.5	0.128
INR	1.0 ± 0.1	1.0 ± 0.1	1.2 ± 0.2	< 0.001
AST	23.5 ± 14.2	23.4 ± 14.2	32.0 ± 20.1	< 0.001
ALT	22.0 ± 22.1	22.0 ± 22.2	21.4 ± 16.3	0.646
Uric.acid	4.8 ± 1.4	4.8 ± 1.4	4.6 ± 2.3	0.521
Total.bilirubin	0.5 ± 0.4	0.5 ± 0.4	0.7 ± 0.6	0.001
Protein	7.0 ± 0.6	7.0 ± 0.5	6.2 ± 1.0	< 0.001
Albumin	3.8 ± 0.4	3.8 ± 0.4	2.9 ± 0.7	< 0.001
Sodium	140.4 ± 2.5	140.4 ± 2.4	137.0 ± 5.1	< 0.001
Pottasium	4.3 ± 0.4	4.3 ± 0.4	4.1 ± 0.5	0.006
Total.calcium	9.3 ± 0.5	9.3 ± 0.5	8.9 ± 0.9	< 0.001
Glucose	116.4 ± 41.5	116.4 ± 41.4	129.0 ± 52.5	0.007
eGFR	90.6 ± 20.0	90.6 ± 20.0	81.3 ± 31.0	0.001
Creatinine	0.9 ± 0.7	0.9 ± 0.7	1.2 ±1.2	0.007

BMI, body mass index; CVA, cerebral vascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; HR, heart rate; TWA, time weighted average; WBC, white blood cell; AST, aspartate transaminase; ALT, alanine transaminase; INR, international normalized ratio; eGFR, estimated glomerular filtration rate. Values are expressed as the mean ± SD, median (interquartile range), or n (proportion).

Table 2. Distribution for various parameters describing intraoperative heart rate according to specific thresholds in the study population.

	Study population			
	Total, n=52309	30-day survival, n=52179 (99.8%)	30-day death, n=130 (0.2%)	*P*
Bradycardia				
HR <35_surgery length	0.0 ± 0.5	0.0 ± 0.5	0.0 ± 0.0	< 0.001
HR <35_M/H	0.0 ± 0.2	0.0 ± 0.2	0.0 ± 0.0	< 0.001
HR <35_AUT	1.0 ± 95.5	1.0 ± 95.9	0.0 ± 0.0	0.021
HR <35_TWA	0.0 ± 0.3	0.0 ± 0.3	0.0 ± 0.0	0.001
HR <40_surgery length	0.2 ± 3.5	0.2 ± 3.5	0.0 ± 0.0	< 0.001
HR <40_M/H	0.1 ± 1.1	0.1 ± 1.1	0.0 ± 0.0	< 0.001
HR <40_AUT	10.0 ± 163.4	10.0 ± 163.6	0.0 ± 0.0	< 0.001
HR <40_TWA	0.1 ± 0.8	0.1 ± 0.8	0.0 ± 0.0	< 0.001
HR <45_surgery length	2.8 ± 17.2	2.8 ± 17.3	0.8 ± 5.4	< 0.001
HR <45_M/H	1.0 ± 4.8	1.0 ± 4.8	0.1 ± 0.6	< 0.001
HR <45_AUT	127.7 ± 803.2	127.9 ± 804.1	37.0 ± 240.3	< 0.001
HR <45_TWA	0.7 ± 3.5	0.7 ± 3.5	0.1 ± 0.5	< 0.001
HR <50_surgery length	11.6 ± 36.9	11.6 ± 36.8	9.5 ± 48.9	0.621
HR <50_M/H	4.2 ± 10.9	4.3 ± 10.9	1.5 ± 6.2	< 0.001
HR <50_AUT	546.8 ± 1709.8	547.0 ± 1708.2	442.3 ± 2277.2	0.601
HR <50_TWA	3.3 ± 8.4	3.3 ± 8.4	1.2 ± 4.9	< 0.001
HR <55_surgery length	28.5 ± 57.7	28.5 ± 57.7	19.2 ± 68.6	0.126
HR <55_M/H	10.7 ± 17.0	10.7 ± 17.1	4.3 ± 11.4	< 0.001

		Study population		
HR <55_AUT	1440.5 ± 2846.3	1441.7 ± 2844.9	952.5 ± 3325.6	0.096
HR <55_TWA	9.0 ± 14.0	9.0 ± 14.0	3.6 ± 9.4	< 0.001
HR <60_surgery length	50.3 ± 72.9	50.3 ± 72.9	32.2 ± 94.6	0.031
HR <60_M/H	18.9 ± 20.8	18.9 ± 20.8	7.9 ± 16.4	< 0.001
HR <60_AUT	2710.2 ± 3824.1	2712.7 ± 3820.9	1707.0 ± 4871.1	0.020
HR <60_TWA	16.9 ± 18.1	16.9 ± 18.1	7.2 ± 14.4	< 0.001
Tachycardia				
HR >90_surgery length	13.6 ± 42.3	13.5 ± 42.1	58.0 ± 80.9	< 0.001
HR >90_M/H	4.2 ± 10.0	4.2 ± 9.9	21.4 ± 23.7	< 0.001
HR >90_AAT	1492.6 ± 4445.6	1481.0 ± 4423.9	6186.5 ± 8699.2	< 0.001
HR >90_TWA	7.9 ± 18.3	7.8 ± 18.1	37.9 ± 42.7	< 0.001
HR >100_surgery length	4.5 ± 21.6	4.4 ± 21.4	30.3 ± 53.7	< 0.001
HR >100_M/H	1.4 ± 5.4	1.4 ± 5.3	12.1 ± 18.7	< 0.001
HR >100_AAT	596.9 ± 2721.4	589.4 ± 2701.9	3615.1 ± 6396.1	< 0.001
HR >100_TWA	3.2 ± 11.8	3.1 ± 11.6	23.7 ± 36.2	< 0.001
HR >110_surgery length	1.2 ± 9.6	1.2 ± 9.5	13.6 ± 34.8	< 0.001
HR >110_M/H	0.4 ± 2.7	0.4 ± 2.6	5.2 ± 11.6	< 0.001
HR >110_AAT	192.5 ± 1440.2	188.8 ± 1423.6	1671.0 ± 4364.6	< 0.001
HR >110_TWA	1.1 ± 6.9	1.0 ± 6.8	10.5 ± 23.6	< 0.001
HR >120_surgery length	0.3 ± 4.4	0.3 ± 4.3	5.9 ± 21.2	0.003
HR >120_M/H	0.1 ± 1.4	0.1 ± 1.3	1.9 ± 6.6	0.002

		Study population		
HR >120_AAT	55.0 ± 759.1	53.2 ± 745.8	781.7 ± 2858.2	0.004
HR >120_TWA	0.3 ± 3.7	0.3 ± 3.6	4.3 ± 14.3	0.002

HR, heart rate; M/H, Minutes/Hour; AUT, areas under the time curve; AAT, areas above the time curve; TWA, time weighted average. Values are expressed as the mean ± SD, median (interquartile range), or n (proportion).

Table 3. Distribution of intraoperative heart rates by various thresholds and exposure time intervals.

	Study population			
	Total, n=52309	**30-day survival, n=52179 (99.8%)**	**30-day death, n=130 (0.2%)**	***P***
Bradycardia				
Minutes with HR<35 bpm				1.000
0 minute	52267 (99.9%)	52137 (99.9%)	130 (100.0%)	
>0 minute	42 (0.1%)	42 (0.1%)	0 (0%)	
Minutes with HR<40 bpm				
≥ 5 minute	481 (0.9%)	481 (0.9%)	0 (0.0%)	0.522
≥ 10 minute	273 (0.5%)	273 (0.5%)	0 (0.0%)	0.828
≥ 20 minute	155 (0.3%)	155 (0.3%)	0 (0.0%)	1.000
≥ 30 minute	88 (0.2%)	88 (0.2%)	0 (0.0%)	1.000
≥ 60 minute	40 (0.1%)	40 (0.1%)	0 (0.0%)	1.000
Minutes with HR<45 bpm				
≥ 5 minute	3784 (7.2%)	3779 (7.2%)	5 (3.8%)	0.186
≥ 10 minute	2856 (5.5%)	2852 (5.5%)	4 (3.1%)	0.315
≥ 20 minute	1922 (3.7%)	1920 (3.7%)	2 (1.5%)	0.288
≥ 30 minute	1407 (2.7%)	1406 (2.7%)	1 (0.8%)	0.278
≥ 60 minute	700 (1.3%)	700 (1.3%)	0 (0.0%)	0.343
Minutes with HR<50 bpm				
≥ 5 minute	11253 (21.5%)	11241 (21.5%)	12 (9.2%)	0.001
≥ 10 minute	9407 (18.0%)	9397 (18.0%)	10 (7.7%)	0.003

	Study population			
≥ 20 minute	7287 (14.0%)	8 (6.2%)	21 (5.3%)	0.015
≥ 30 minute	5833 (11.2%)	5826 (11.2%)	7 (5.4%)	<0.051
≥ 60 minute	3312 (6.3%)	3307 (6.3%)	5 (3.8%)	0.325
Minutes with HR<55 bpm				
≥ 5 minute	22206 (42.5%)	22181 (42.5%)	25 (19.2%)	< 0.001
≥ 10 minute	19655 (37.6%)	19632 (37.6%)	23 (17.7%)	< 0.001
≥ 20 minute	16418 (31.4%)	16400 (31.4%)	18 (13.8%)	< 0.001
≥ 30 minute	14042 (26.8%)	14026 (26.9%)	16 (12.3%)	< 0.001
≥ 60 minute	8720 (16.7%)	8711 (16.7%)	9 (6.9%)	0.004
Minutes with HR<60 bpm				
≥ 5 minute	32714 (62.5%)	32677 (62.6%)	37 (28.5%)	< 0.001
≥ 10 minute	30210 (57.8%)	30176 (57.8%)	34 (26.2%)	< 0.001
≥ 20 minute	26691 (51.0%)	26661 (51.1%)	30 (23.1%)	< 0.001
≥ 30 minute	23702 (45.3%)	23675 (45.4%)	27 (20.8%)	< 0.001
≥ 60 minute	16134 (30.8%)	16116 (30.9%)	18 (13.8%)	< 0.001
Tachycardia				
Minutes with HR>90 bpm				
≥ 5 minute	16466 (31.5%)	16384 (31.4%)	82 (63.1%)	< 0.001
≥ 10 minute	11366 (21.7%)	11291 (21.6%)	75 (57.7%)	< 0.001
≥ 20 minute	7313 (14.0%)	7246 (13.9%)	67 (51.5%)	< 0.001
≥ 30 minute	5601 (10.7%)	5539 (10.6%)	62 (47.7%)	< 0.001

	Study population			
≥ 60 minute	3216 (6.1%)	3168 (6.1%)	48 (36.9%)	< 0.001
Minutes with HR>100 bpm				
≥ 5 minute	7496 (14.3%)	7439 (14.3%)	57 (43.8%)	< 0.001
≥ 10 minute	4454 (8.5%)	4400 (8.4%)	54 (41.5%)	< 0.001
≥ 20 minute	2552 (4.9%)	2506 (4.8%)	46 (35.4%)	< 0.001
≥ 30 minute	1825 (3.5%)	1785 (3.4%)	40 (30.8%)	< 0.001
≥ 60 minute	983 (1.9%)	959 (1.8%)	24 (18.5%)	< 0.001
Minutes with HR>110 bpm				
≥ 5 minute	2675 (5.1%)	2635 (5.0%)	40 (30.8%)	< 0.001
≥ 10 minute	1379 (2.6%)	1347 (2.6%)	32 (24.6%)	< 0.001
≥ 20 minute	689 (1.3%)	668 (1.3%)	21 (16.2%)	< 0.001
≥ 30 minute	468 (0.9%)	452 (0.9%)	16 (12.3%)	< 0.001
≥ 60 minute	232 (0.4%)	222 (0.4%)	10 (7.7%)	< 0.001
Minutes with HR>120 bpm				
≥ 5 minute	750 (1.4%)	731 (1.4%)	19 (14.6%)	< 0.001
≥ 10 minute	368 (0.7%)	353 (0.7%)	15 (11.5%)	< 0.001
≥ 20 minute	186 (0.4%)	177 (0.3%)	9 (6.9%)	< 0.001
≥ 30 minute	118 (0.2%)	110 (0.2%)	8 (6.2%)	< 0.001
≥ 60 minute	56 (0.1%)	51 (0.1%)	5 (3.8%)	< 0.001

HR, heart rate; BPM, beats per minute. Values are expressed as the mean ± SD, median (interquartile range), or n (proportion)

Table 4. Associations between various parameters describing intra-operative heart rate and the 30-day mortality.

	Univariate			Multivariable*		
	Hazard ratio	**95% CI**	***P***	**Hazard ratio**	**95% CI**	***P***
Age	1.05	1.03–1.06	<0.001	1.03	1.01–1.04	<0.001
Sex (male)	2.15	1.50–3.08	<0.001	1.78	1.23–2.58	0.002
BMI	0.79	0.75–0.84	<0.001	0.90	0.85–0.94	<0.001
CVA	3.54	1.80–6.96	<0.001	2.02	1.00–4.05	0.049
CVD	1.46	0.84–2.53	0.185			
DM	1.62	1.09–2.42	0.018			
HTN	1.21	0.85–1.73	0.299			
ASA						
1, 2	1.00			1.00		
≥3	7.63	5.39–10.80	<0.001	1.60	1.08–2.37	0.018
Ward SBP	1.00	0.99–1.01	0.872			
Ward HR	1.09	1.08–1.10	<0.001	1.04	1.03–1.06	<0.001
High risk surgery (orthopedic, neurosurgery, thoracic, vascular)	1.63	1.14–2.32	0.008			
MBP<65_TWA	1.03	1.02–1.04	<0.001	1.02	1.00–1.03	0.013
Hemoglobin, g/dL	0.57	0.52–0.61	<0.001			
Albumin, g/dL	0.10	0.08–0.12	<0.001	0.27	0.20–0.38	<0.001
HR_median	1.07	1.06–1.09	<0.001			

	Univariate			Multivariable*		
Bradycardia						
HR<45_TWA	0.77	0.58–1.03	0.079			
HR<50_TWA	0.95	0.91–0.99	0.007			
HR<55_TWA	0.96	0.94–0.98	<0.001			
HR<60_TWA	0.96	0.95–0.97	<0.001			
Tachycardia						
HR>90_TWA	1.03	1.03–1.04	<0.001			
HR>100_TWA	1.04	1.03–1.04	<0.001	1.02	1.01–1.02	<0.001
HR>110_TWA	1.04	1.03–1.04	<0.001			
HR>120_TWA	1.04	1.03–1.05	<0.001			

*Backward elimination

BMI, body mass index; CVA, cerebral vascular accident; CVD, cardiovascular disease; DM, diabetes mellitus; HTN, hypertension; ASA, American Society of Anesthesiologists; SBP, systolic blood pressure; HR, heart rate; TWA, time weighted average; CI, confidence interval.

Table 5. Associations between various intraoperative HR parameters and the 30-day mortality.

	Univariate			Multivariable*		
	Hazard ratio	**95% CI**	***P***	**Hazard ratio**	**95% CI**	***P***
HR_median	1.07	1.06–1.09	<0.001	1.01	1.00–1.03	0.049
HR_mean	1.08	1.07–1.09	<0.001	1.02	1.00–1.04	0.016
HR_maximum	1.04	1.03–1.05	<0.001	1.01	1.00–1.02	0.036
HR_minimum	1.08	1.07–1.09	<0.001	1.02	1.00–1.03	0.039
Bradycardia						
HR<45_M/H	0.83	0.67–1.02	0.080	0.93	0.79–1.10	0.397
HR<45_TWA	0.77	0.58–1.03	0.079	0.91	0.73–1.13	0.377
HR<50_M/H	0.96	0.93–0.99	0.008	1.01	0.98–1.03	0.647
HR<50_TWA	0.95	0.91–0.99	0.007	1.01	0.97–1.04	0.679
HR<55_M/H	0.97	0.95–0.98	<0.001	1.01	0.99–1.02	0.422
HR<55_TWA	0.96	0.94–0.98	<0.001	1.01	0.99–1.03	0.456
HR<60_M/H	0.97	0.95–0.98	<0.001	1.00	0.99–1.02	0.589
HR<60_TWA	0.96	0.95–0.97	<0.001	1.00	0.99–1.02	0.595
Tachycardia						
HR>90_M/H	1.06	1.05–1.07	<0.001	1.02	1.01–1.03	0.001
HR>90_TWA	1.03	1.03–1.04	<0.001	1.01	1.00–1.02	0.002
HR>100_M/H	1.07	1.07–1.08	<0.001	1.02	1.01–1.03	0.003
HR>100_TWA	1.04	1.03–1.04	<0.001	1.01	1.00–1.02	0.003
HR>110_M/H	1.08	1.07–1.10	<0.001	1.01	0.99–1.02	0.258

	Univariate			**Multivariable***		
HR>110_TWA	1.04	1.03–1.04	<0.001	1.00	1.00–1.01	0.413
HR>120_M/H	1.09	1.07–1.11	<0.001	1.00	0.98–1.03	0.868
HR>120_TWA	1.04	1.03–1.05	<0.001	1.00	0.99–1.01	0.886

*Adjusted by age, sex, BMI, CVA, ASA, ward HR, MBP<65_TWA, albumin.

HR, heart rate; BMI, body mass index; CVA, cerebral vascular accident; ASA, American Society of Anesthesiologists; MBP, mean blood pressure; M/H, Minutes/Hour; TWA, time weighted average; CI, confidence interval.

Table 6. Associations between various intraoperative HR thresholds according to exposure time and the 30-day mortality.

	Univariate			Multivariable*		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Bradycardia						
Minutes with HR<45 bpm						
≥ 5 minute	0.51	0.21–1.25	0.143	1.42	0.57–3.54	0.449
≥ 10 minute	0.55	0.20–1.49	0.238	1.48	0.54–4.07	0.444
≥ 20 minute	0.41	0.10–1.66	0.210	1.32	0.32–5.45	0.698
≥ 30 minute	0.28	0.04–2.01	0.205	0.87	0.12–6.31	0.891
Minutes with HR<50 bpm						
≥ 5 minute	0.37	0.20–0.67	0.001	1.19	0.63–2.23	0.595
≥ 10 minute	0.38	0.20–0.72	0.003	1.21	0.62–2.39	0.576
≥ 20 minute	0.40	0.20–0.83	0.013	1.38	0.65–2.91	0.402
≥ 30 minute	0.45	0.21–0.97	0.042	1.54	0.69–3.40	0.290
≥ 60 minute	0.59	0.24–1.45	0.250	1.96	0.78–4.92	0.152
Minutes with HR<55 bpm						
≥ 5 minute	0.32	0.21–0.50	<0.001	1.14	0.70–1.87	0.599
≥ 10 minute	0.36	0.23–0.56	<0.001	1.29	0.78–2.14	0.321
≥ 20 minute	0.35	0.21–0.58	<0.001	1.22	0.71–2.10	0.480
≥ 30 minute	0.38	0.23–0.64	<0.001	1.37	0.77–2.44	0.280
≥ 60 minute	0.37	0.19–0.73	0.004	1.22	0.60–2.49	0.587
Minutes with HR<60 bpm						

		Univariate			Multivariable*	
≥ 5 minute	0.24	0.16–0.35	<0.001	0.89	0.57–1.40	0.610
≥ 10 minute	0.26	0.17–0.38	<0.001	0.96	0.61–1.52	0.857
≥ 20 minute	0.29	0.19–0.43	<0.001	1.05	0.66–1.69	0.832
≥ 30 minute	0.32	0.21–0.48	<0.001	1.15	0.71–1.86	0.576
≥ 60 minute	0.36	0.22–0.59	<0.001	1.20	0.70–2.08	0.512
Tachycardia						
Minutes with HR>90 bpm						
≥ 5 minute	3.73	2.61–5.32	<0.001	1.22	0.80–1.85	0.362
≥ 10 minute	4.92	3.48–6.97	<0.001	1.36	0.89–2.08	0.151
≥ 20 minute	6.57	4.66–9.27	<0.001	1.65	1.08–2.52	0.020
≥ 30 minute	7.64	5.42–10.78	<0.001	1.81	1.19–2.76	0.006
≥ 60 minute	8.99	6.30–12.84	<0.001	1.97	1.29–3.01	0.002
Minutes with HR>100 bpm						
≥ 5 minute	4.68	3.31–6.62	<0.001	1.43	0.94–2.16	0.091
≥ 10 minute	7.67	5.41–10.88	<0.001	1.98	1.30–3.03	0.002
≥ 20 minute	10.76	7.51–15.42	<0.001	2.14	1.37–3.34	<0.001
≥ 30 minute	12.41	8.55–18.02	<0.001	2.17	1.37–3.43	<0.001
≥ 60 minute	11.94	7.67–18.60	<0.001	1.58	0.93–2.69	0.092
Minutes with HR>110 bpm						
≥ 5 minute	8.30	5.72–12.04	<0.001	2.00	1.27–3.16	0.003
≥ 10 minute	12.18	8.17–18.15	<0.001	2.25	1.38–3.67	0.001

	Univariate			**Multivariable***		
≥ 20 minute	14.64	9.17–23.35	<0.001	1.79	1.02–3.14	0.043
≥ 30 minute	15.77	9.34–26.61	<0.001	1.68	0.92–3.06	0.092
≥ 60 minute	19.16	10.05–36.53	<0.001	1.39	0.66–2.91	0.389
Minutes with HR>120 bpm						
≥ 5 minute	11.91	7.32–19.37	<0.001	2.08	1.19–3.65	0.011
≥ 10 minute	18.77	10.96–32.15	<0.001	1.91	1.04–3.52	0.038
≥ 20 minute	21.39	10.87–42.10	<0.001	1.36	0.65–2.87	0.417
≥ 30 minute	30.06	14.70–61.47	<0.001	1.94	0.87–4.32	0.105
≥ 60 minute	39.88	16.32–97.45	<0.001	2.08	0.78–5.60	0.146

*Adjusted by age, sex, BMI, CVA, ASA, ward HR, MBP<65_TWA, albumin.

HR, heart rate; BMI, body mass index; CVA, cerebral vascular accident; ASA, American Society of Anesthesiologists; MBP, mean blood pressure; BPM, beats per minute; CI, confidence interval.

Table 7. Subgroup analysis of heart rate>100_time weighted average stratified by age, sex, ASA class, CVD, and high-risk surgery.

			Heart rate>100_time weighted average			
			Event/number	HR (95% CI)	*P* value	P_{int}
30-day Mortality	Age	< 65	59/34815	1.04 (1.03–1.04)	<0.001	0.850
		≥ 65	71/17494	1.04 (1.03–1.04)	<0.001	
	Sex	Male	84/24041	1.03 (1.03–1.04)	<0.001	0.535
		Female	46/28268	1.04 (1.03–1.15)	<0.001	
	ASA	1, 2	75/47700	1.04 (1.03–1.04)	<0.001	0.120
		≥3	55/4609	1.03 (1.02–1.03)	<0.001	
	CVD	Non-CVD	116/48300	1.04 (1.03–1.04)	<0.001	0.691
		CVD	14/4009	1.03 (1.02–1.05)	<0.001	
	High risk surgery	Non-high risk surgery	83/38788	1.04 (1.03–1.04)	<0.001	0.056
		High risk surgery	47/13521	1.03 (1.02–1.04)	<0.001	

HR, hazards ratio; CI, confidence interval; CVD, cardiovascular disease; ASA, American Society of Anesthesiologists.

Figure 1. Flow diagram of the study.

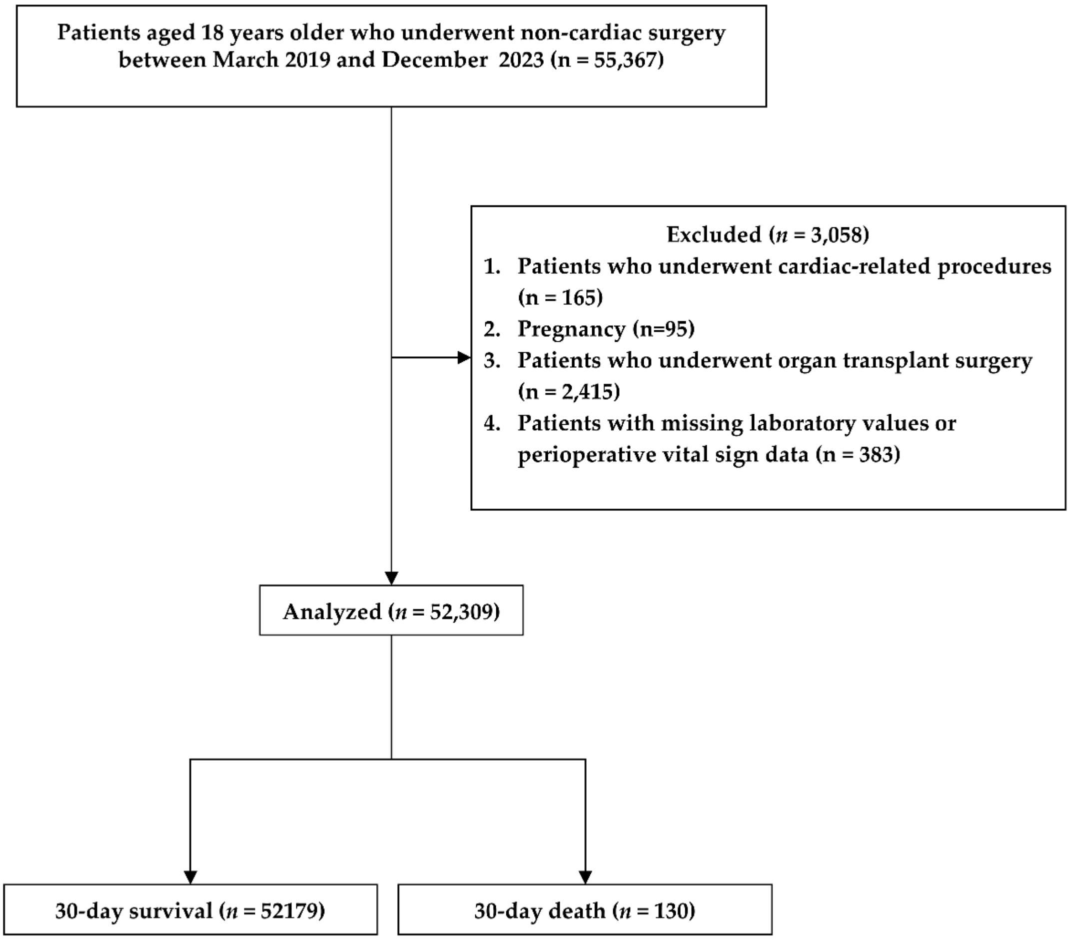

Figure 2. Linearly interpolated heart rate (HR) change curve and definitions of HR-M/H, HR-AAT, and HR-TWA during surgery. HR-M/H was calculated by dividing the HR-exposure time (in minutes) at a specific threshold by the total surgery length (in hours). HR-AAT was calculated as the area above the time curve value for a specific threshold. HR-TWA (bpm) was calculated as the HR-AAT divided by the total surgery length.