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Association between resting heart rate and prognosis in patients with gastric cancer

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This study aimed to evaluate prognostic value of resting heart rate (RHR) in patients with gastric cancer. We analyzed 1,561 patients who underwent radical gastrectomy at Severance Hospital, Korea. RHRs were measured after surgery, and detailed medical, treatment, and lifestyle information was collected. Cox regression models were used to estimate the hazard ratios (HRs) and 95% confidence interval (95% CI) for the association between postoperative RHR and prognostic outcomes. During a median of 4 years of follow-up, we identified 174 total deaths, 92 major complications (within 30 days), 186 recurrences, and 106 gastric-cancer-specific deaths. In multivariable-adjusted models, HRs (95% CI) per 10 beats per minute increase in RHR were 1.18 (1.07–1.31) for all-cause mortality, 1.45 (1.33–1.59) for major complication within 30 days, 1.13 (1.02–1.26) for recurrence, and 1.07 (0.93–1.24) for gastric cancer-specific mortality. We consistently observed that higher postoperative RHR is associated with poor prognostic outcomes regardless of demographics, lifestyle, and cancer stage in patients with gastric cancer. In conclusion, an elevated postoperative RHR was associated with an increased risk of all-cause mortality, major complications, and recurrence in patients with gastric cancer. RHR can potentially be used to predict the prognosis of patients with gastric cancer.

Keywords Heart rate, Prognosis, Mortality, Stomach neoplasms

Gastric cancer (GC) is the fifth most commonly diagnosed cancer and the fourth leading cause of cancer-related deaths worldwide[1]. The incidence of gastric cancer varies by region, with the highest incidence rate noted in East Asia, including South Korea[1,2]. Although gastric cancer prognosis has improved during the past decade, more than one-third of patients with advanced gastric cancer died within five years since diagnosis[3,4]. Therefore, identifying prognostic factors influencing gastric cancer treatment outcomes is essential.

Resting heart rate (RHR) is a simple and non-invasive measure closely related to and influenced by multiple modifiable factors, such as cardiopulmonary fitness, physical activity, obesity, smoking, and sleep[5]. Therefore, RHR has been proposed to be a predictor of several major health outcomes. Several prospective cohort studies have consistently found that a higher RHR is associated with an increased risk of all-cause mortality, cardiovascular disease, and diabetes in general and patient populations[5–9].

Recently, we showed promising results that RHR helps predict the prognosis of breast and colorectal cancer patients[10–12]. Moreover, a few small studies have found similar results suggesting the predictive value of RHR in cancer patients, such as those with non-small cell lung, pancreatic, and gastrointestinal cancers[13,14]. However, the predictive value of RHR for prognosis of GC patients remains unknown. As RHRs are routinely measured before and after surgery for cancer patients during their hospitalization, RHR has the potential to serve as a clinically meaningful tool for cancer patients including risk of recurrence and mortality, contingent upon the confirmation of its prognostic value. Furthermore, RHR could also be predictive tool for post-operative complications, however, association between RHR and post-operative complication has not been fully elucidated[15,16].

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Therefore, we examined whether RHR is associated with prognostic outcomes, including major complications, recurrence, gastric cancer-specific mortality and all-cause mortality in patients with GC. We also examined the association between RHR and prognostic outcomes stratified by demographics, lifestyle, and cancer stage.

Methods

Study population

A total of 1806 patients with stage I–III GC who underwent R0 resection (total or subtotal gastrectomy) were retrospectively selected from Severance Hospital, Department of Surgery, Yonsei University College of Medicine, Seoul, Republic of Korea. All patients underwent surgery for GC between March 2009 and June 2018. We excluded patients with missing RHR information after GC surgery ($N=245$). In the final analysis, 1,561 patients with GC were included. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System, Seoul, Republic of Korea (IRB No. 4-2023-0229), which waived the requirement for informed consent because of its retrospective nature. This study was conducted in accord with the ethical standards of the Helsinki Declaration of 1975.

Clinicopathological characteristics

RHR was defined as the highest heart rate among at least four measurements of vital signs on that day. RHRs were measured 1 day before surgery, on the day of surgery, and at 1, 2, 3, and 5 days after surgery. The RHR measured five days after surgery was used as the primary exposure because it is more stable and representative of the typical RHR after recovery. For secondary analyses, we used other RHRs measured 1 day before the surgery, on the date of surgery, and 1, 2, and 3 days after surgery. As patients underwent medical tests and preparation processes which could significantly affect their RHR, the preoperative RHR measure was used for the secondary analysis.

We also collected details of the patients' clinicopathological characteristics, lifestyle (e.g. smoking and alcohol consumption), medical morbidities (e.g. hypertension, diabetes, and cardiovascular disease), perioperative chemotherapy history (neoadjuvant, adjuvant, and radiation therapy), operative parameters, and postoperative recovery data (e.g. surgery type and extent, stage, and morbidities). The primary outcome was all-cause mortality, and the secondary outcomes were major complications within 30 days after surgery, recurrence, and gastric cancer-specific mortality. Postoperative complications were graded using the Clavien–Dindo classification as defined previously[17]. Major complications of grade 3 or higher were analysed for surgical outcomes.

Statistical analyses

Person-years were calculated from the time of RHR measurement 5 days after gastric surgery until the time of death, recurrence, or end of the study. The participants were categorised into quartiles based on their RHR (bpm). RHR was also used as a continuous variable (per 10 bpm increment) to increase statistical power. Cox regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the RHR and all-cause mortality, major complications within 30 days, recurrence, and gastric cancer-specific mortality. Multivariable models were adjusted for age (continuous), sex, pathological cancer stage (1, 2, or 3), BMI (continuous), smoking (never, current, or past), alcohol consumption (never, current, or past), family history of GC (yes or no), hypertension (yes or no), diabetes (yes or no), CVD (yes or no), adjuvant therapy (yes or no), and radiation therapy (yes or no), neoadjuvant therapy (yes or no), surgery type (open, laparoscopic or robotic surgery) and extent of surgery (distal subtotal gastrectomy or total gastrectomy). Kaplan–Meier curves were generated for overall survival, gastric cancer-specific survival, and recurrence according to RHR quartiles. Because cancer stage and major complication are strong predictors of survival, we conducted additional survival curves stratified by cancer stage and presence of major complications within 30 days. The log-rank test was used to test statistical differences in the survival curves of the RHR groups.

To evaluate whether the association between RHR and prognosis differed according to potential effect modifiers, we performed stratified analyses according to age, sex, BMI, alcohol consumption, smoking, hypertension, and cancer stage. Test for interaction was done by including the product term of the RHR and the stratification variables in the models. Finally, we conducted sensitivity analyses by examining the association of RHR measured on different days (1 day before surgery, surgery date, and 1, 2, and 3 days after surgery) with prognostic outcomes. All the statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

The characteristics of the patients with GC are summarised in Table 1. Participants with a higher postoperative RHR showed a higher percentage of receiving adjuvant therapy ($P<.001$) and being in the advanced cancer stage ($P<.001$). They also underwent more open surgeries than minimally invasive surgery (laparoscopic or robotic surgery) ($P<.001$) and more total gastrectomies than subtotal gastrectomies ($P<.001$). We did not find a clear association between postoperative RHR, lifestyle factors, and medical history.

During a median follow-up of 4 years in 1,561 GC, we documented 174 total deaths, 92 major complications within 30 days, 186 recurrences, and 106 gastric cancer-specific deaths. Kaplan–Meier curves indicated statistically significant differences in overall survival, gastric cancer-specific survival, and recurrence in patients with GC according to the quartiles of postoperative RHR ($P<.001$) (Fig. 1). Similar results were observed when stratified by cancer stage or presence of major complications within 30 days (Supplementary Figs. 1 and 2).

In the age- and sex-adjusted models (Model 1), the postoperative RHR was associated with all prognostic outcomes (Table 2). Compared to patients in the lowest quartile of postoperative RHR, those in the highest quartile had 2.42 (1.51–3.88), 9.90 (3.96–24.7), 3.07 (1.93–4.87), and 3.23 (1.69–6.18) times higher risk of

	Postoperative resting heart rate, bpm				
	Quartile 1 (≤69 bpm)	Quartile 2 (70–77 bpm)	Quartile 3 (78–86 bpm)	Quartile 4 (≥87 bpm)	*P*-value
Resting heart rate, bpm	63.9 (4.6)	73.4 (2.3)	81.5 (2.6)	97.2 (12.9)	
Age, yr	60.2 (11.1)	60.2 (11.9)	60.1 (11.9)	61.2 (12.4)	0.50
BMI, kg/m^2	24.1 (3.4)	23.6 (3.2)	23.7 (3.3)	23.5 (3.5)	0.15
Hospital stay, day	6.4 (3.2)	6.9 (3.7)	7.8 (5.2)	11.5 (12.1)	<0.001
Male, %	66.7	61.9	62.2	72.0	0.009
Smoking, %					
Never	44.0	50.2	49.5	40.3	0.02
Current	27.7	20.5	24.5	25.4	
Past	28.3	29.3	26.0	34.3	
Alcohol, %					0.48
Never	36.7	40.0	43.4	38.7	
Current	38.1	38.1	34.2	35.3	
Past	25.2	21.9	22.5	25.9	
Family history of gastric cancer, %	19.9	21.9	17.1	18.3	0.34
Hypertension, %	32.8	38.1	33.9	37.4	0.32
Diabetes, %	14.6	15.6	15.3	18.9	0.39
Cardiovascular disease, %	5.6	6.3	5.1	7.6	0.51
Adjuvant therapy, %	21.9	20.0	30.9	35.1	<0.001
Radiation therapy, %	0	0.7	0.3	1.1	0.19
Neoadjuvant therapy, %	0.3	1.4	0.8	2.1	0.11
Pathological cancer stage, %					<0.001
1	75.4	76.7	64.5	55.8	
2	12.3	11.2	15.8	18.1	
3	12.3	12.1	19.6	26.2	
Surgery type					<0.001
Open	15.7	18.6	23.7	33.0	
Lapa	58.3	55.1	53.1	42.9	
Robot	26.1	26.3	23.2	24.1	
Extent of surgery					<0.001
Subtotal gastrectomy	86.0	79.3	77.5	69.9	
Total gastrectomy	14.0	20.7	22.5	30.1	

Table 1. Characteristics of gastric cancer patients according to quartiles of postoperative resting heart rate ($N=1561$).

all-cause mortality, major complications within 30 days, recurrence, and gastric cancer-specific mortality, respectively. After adjusting for potential confounders, including lifestyle and clinical variables (Model 2), the magnitude of the associations between postoperative RHR and prognostic outcomes weakened but remained statistically significant for all-cause mortality, major complications within 30 days, and recurrence; in contrast, gastric cancer-specific mortality became non-significant. HRs (95% CI) per 10 bpm RHR increment were 1.18 (1.07–1.31) for all-cause mortality, 1.45 (1.33–1.59) for major complication within 30 days, 1.13 (1.02–1.26) for recurrence, and 1.07 (0.93–1.24) for gastric cancer-specific mortality.

In the stratified analyses, we consistently found a positive association between postoperative RHR and all-cause mortality, major complications within 30 days, and recurrence, regardless of stratification according to age, sex, BMI, alcohol consumption, smoking, hypertension, and cancer stage (Table 3). There was no significant interaction between the postoperative RHR and stratification variables in relation to prognosis in patients with GC. In secondary analyses using RHR measured on different days, we observed that the mean RHR was highest on the surgery date and decreased over time (Supplementary Table S1). The mean (standard deviation [SD]) of RHR was 87.2 (12.8) on the day of surgery, 89.1 (14.0) 1 day after surgery, 88.9 (14.8) 2 days after surgery, 84.0 (14.6) 3 days after surgery, and 79.1 (13.9) 5 days after surgery. Examination of the association between RHRs measured on different days and prognostic outcomes revealed consistent patterns, suggesting a positive association between postoperative RHR and all-cause mortality, major complications within 30 days, and recurrence. In contrast, no association was observed between preoperative RHR and prognostic outcomes (Supplementary Table S2).

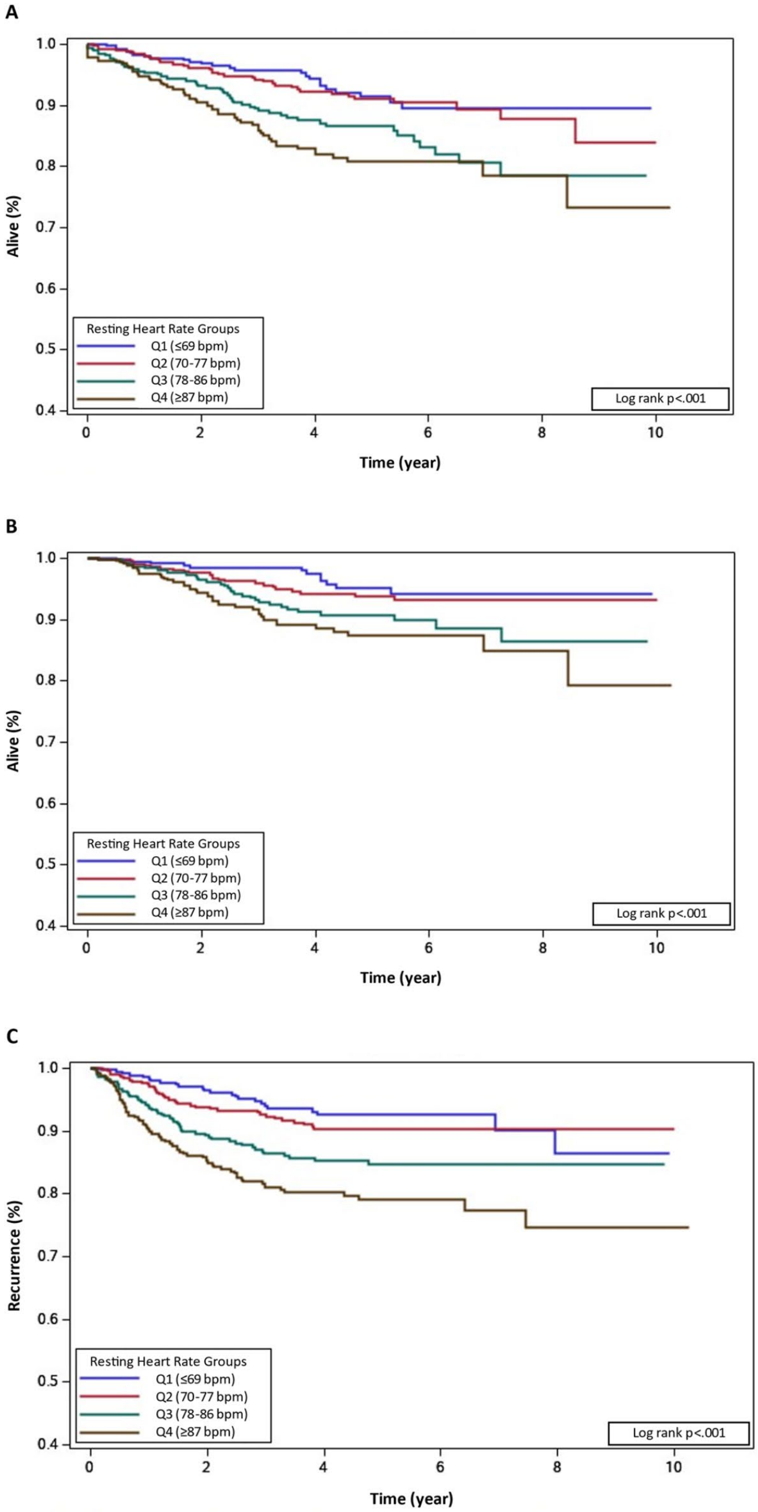

Fig. 1. Kaplan–Meier curve for (**A**) overall, (**B**) gastric cancer-specific survival and (**C**) recurrence according to quartiles of postoperative resting heart rate.

Discussion

Among 1,561 patients with cancer who underwent gastrectomy, elevated postoperative RHR was associated with an increased risk of all-cause mortality, major complications within 30 days, and recurrence. We consistently found positive associations between the postoperative RHR and prognostic outcomes, regardless of demographics, lifestyle, and cancer stage, in patients with GC. Our study provides evidence that the postoperative RHR may predict prognosis, including mortality and recurrence, in patients with GC.

	Postoperative resting heart rate, bpm					
	Quartile 1 (≤ 69 bpm)	Quartile 2 (70–77 bpm)	Quartile 3 (78–86 bpm)	Quartile 4 (≥ 87 bpm)	Per 10 bpm	*P*-trend
All-cause mortality						
Event	24	36	52	62		
Model 1	1 (ref)	1.15 (0.69–1.93)	2.02 (1.24–3.27)	2.42 (1.51–3.88)	1.34 (1.23–1.45)	< 0.001
Model 2	1 (ref)	1.09 (0.65–1.85)	1.43 (0.87–2.33)	1.43 (0.88–2.33)	1.18 (1.07–1.32)	0.001
Major complication within 30 days						
Event	5	17	14	56		
Model 1	1 (ref)	2.91 (1.07–7.88)	2.63 (0.95–7.30)	9.90 (3.96–24.7)	1.41 (1.31–1.50)	< 0.001
Model 2	1 (ref)	2.63 (0.96–7.17)	2.35 (0.84–6.55)	8.21 (3.25–20.7)	1.45 (1.33–1.59)	< 0.001
Recurrence						
Event	24	37	53	72		
Model 1	1 (ref)	1.26 (0.75–2.10)	2.14 (1.32–3.47)	3.07 (1.93–4.87)	1.31 (1.21–1.42)	< 0.001
Model 2	1 (ref)	1.22 (0.72–2.05)	1.51 (0.92–2.47)	1.66 (1.03–2.68)	1.13 (1.02–1.25)	0.02
Gastric cancer-specific mortality						
Event	12	23	32	39		
Model 1	1 (ref)	1.50 (0.74–3.01)	2.49 (1.28–4.83)	3.23 (1.69–6.18)	1.33 (1.18–1.49)	< 0.001
Model 2	1 (ref)	1.46 (0.71–3.00)	1.38 (0.70–2.73)	1.56 (0.80–3.04)	1.07 (0.93–1.24)	0.35

Table 2. Association of resting heart rate with all-cause mortality, major complications, recurrence, and gastric cancer-specific mortality in patients with gastric cancer. Model 1: adjusted for age (continuous) and sex. Model 2: Model 1 + pathological cancer stage (1, 2, 3), BMI (continuous), smoking (never, current, or past), alcohol (never, current, or past), family history of gastric cancer (yes or no), hypertension (yes or no), diabetes (yes or no), CVD (yes or no), adjuvant therapy (yes or no), radiation therapy (yes or no), neoadjuvant therapy (yes or no), surgery type (open, laparoscopic, or robotic surgery) and extent of surgery (subtotal or total gastrectomy).

Numerous prospective cohort studies have shown that RHR is positively associated with major health outcomes, including cardiovascular disease, diabetes and mortality[6–9]. However, only a few studies have examined the association between RHR and prognostic outcomes in patients with cancer. In a large Korean study of 4,786 breast cancer patients, a 10 bpm increase in RHR was significantly associated with 15% and 22% increased risk of all-cause mortality and breast cancer-specific mortality, respectively, after adjusting for important confounders, including detailed tumour characteristics and medical and treatment factors[10]. In a subsequent study with the same breast cancer patients, elevated RHR was found to be strongly associated with metabolic risk factors, including higher levels of fasting glucose, triglycerides, and diastolic blood pressure, which may explain the observed relationship between RHR and prognostic outcomes in breast cancer patients[11]. Similar association was observed for colorectal cancer. In a study of 300 colorectal cancer survivors, patients in the highest quartile (≥ 81 bpm) had 6.18 (95% CI:1.18–32.4) times higher recurrence of colorectal polyps compared to those in the lowest quartile (≤ 66 bpm)[12]. Besides breast and colorectal cancers, there was one Austrian study that analysed 548 unselected treatment-naïve cancer patients and found that higher RHR was associated with higher levels of cardiovascular biomarkers (N-terminal pro-B-type natriuretic peptide and high-sensitivity troponin T) and all-cause mortality, especially in lung (HR per 5 bpm increase:1.13, 95% CI:1.02–1.24) and gastrointestinal (HR per 5 bpm increase:1.31, 95% CI:1.13–1.51) cancer patients[14].

To the best of our knowledge, this is the first study to examine the association between RHR and prognosis in patients with GC. Consistent with previous studies in patients with non-GC, we found a strong positive association between postoperative RHR and prognostic outcomes in patients with GC. As shown in Table 1, we observed a clear pattern that GC patients with advanced cancer stage or cancer treatments (e.g. open surgery and total gastrectomy) had a higher RHR. This implies that RHR may be affected by disease severity in patients with GC. Therefore, there was a considerable reduction in the magnitude of the association between RHR and prognostic outcomes when we thoroughly adjusted for detailed treatment variables (e.g. cancer stage, type, extent of surgery, and cancer treatments). The positive association between RHR and prognosis remained statistically significant for all-cause mortality, major complications within 30 days, and recurrence. However, no association was observed for gastric cancer-specific mortality after adjustment. A similar pattern of attenuation in multivariable models and statistically significant associations was observed in a previous study among breast cancer patients[10]. These findings provide evidence that RHR is a significant prognostic marker independent of known cancer related treatment factors.

The underlying biological mechanisms linking RHR to cancer prognosis remain unknown. One potential explanation is that an increased RHR is a marker of an imbalanced autonomic nervous system, reflecting sympathetic overactivity. Studies have shown that sympathetic overactivity is associated with tumour progression and metastasis[18,19]. and intermediate markers such as inflammation and insulin resistance that could facilitate GC progression[20–22]. Second, RHR is a marker of individuals' physical fitness[23]. Lower RHR indicates higher cardiorespiratory fitness and is affected by one's physical activity level[24]. Previous studies have shown that high levels of pre- and post-diagnosis physical activity are associated with lower all-cause and cause-specific mortality

	Postoperative resting heart rate (per 10 bpm increase)			
	All-cause mortality	Major complication within 30 days	Recurrence	Gastric cancer-specific mortality
Age				
Event[a]	53/121	33/59	67/119	38/68
<60 years	1.19 (1.00–1.42)	1.43 (1.20–1.71)	1.11 (0.93–1.33)	1.05 (0.82–1.34)
≥60 years	1.18 (1.04–1.34)	1.58 (1.39–1.80)	1.13 (0.99–1.29)	1.05 (0.87–1.27)
P-interaction	0.45	0.87	0.67	0.98
Sex				
Event	129/45	78/14	127/59	72/34
Men	1.20 (1.07–1.35)	1.44 (1.31–1.58)	1.13 (1.00–1.28)	1.08 (0.90–1.29)
Women	1.08 (0.82–1.42)	2.05 (1.26–3.32)	1.26 (1.00–1.59)	1.20 (0.87–1.66)
P-interaction	0.92	0.21	0.17	0.33
BMI				
Event	91/83	52/40	94/92	51/55
<23 kg/m^2	1.07 (0.92–1.25)	1.49 (1.29–1.72)	1.13 (0.98–1.30)	1.02 (0.82–1.27)
≥23 kg/m^2	1.35 (1.18–1.54)	1.51 (1.31–1.73)	1.21 (1.03–1.42)	1.27 (1.02–1.58)
P-interaction	0.06	0.20	0.89	0.44
Alcohol				
Event	79/95	26/66	85/101	51/55
No	1.09 (0.93–1.28)	1.32 (1.10–1.58)	1.18 (1.02–1.37)	1.03 (0.83–1.29)
Yes	1.24 (1.08–1.42)	1.50 (1.35–1.68)	1.12 (0.97–1.30)	1.11 (0.90–1.38)
P-interaction	0.13	0.35	0.23	0.90
Smoking				
Event	77/97	32/60	90/96	54/52
No	1.26 (1.05–1.52)	1.57 (1.26–1.96)	1.22 (1.02–1.45)	1.23 (0.96–1.56)
Yes	1.17 (1.03–1.34)	1.44 (1.30–1.60)	1.11 (0.97–1.28)	1.00 (0.82–1.23)
P-interaction	0.29	0.35	0.25	0.91
Hypertension				
Event	95/79	51/41	113/73	63/43
No	1.17 (1.02–1.34)	1.46 (1.25–1.71)	1.21 (1.06–1.37)	1.13 (0.95–1.35)
Yes	1.30 (1.12–1.50)	1.58 (1.37–1.83)	1.16 (0.97–1.39)	1.15 (0.89–1.51)
P-interaction	0.77	0.88	0.06	0.14
Stage				
Event	51/123	48/44	30/156	10/96
1	1.27 (1.01–1.59)	1.63 (1.40–1.90)	1.27 (0.95–1.70)	1.54 (0.85–2.77)
2/3	1.19 (1.06–1.34)	1.48 (1.30–1.69)	1.12 (1.00–1.24)	1.05 (0.90–1.22)
P-interaction	0.77	0.07	0.65	0.25

Table 3. Association between resting heart rate and prognostic outcomes in patients with gastric cancer, stratified by demographic, lifestyle and stages. All models were adjusted for age, sex, pathological cancer stage (1, 2, 3), BMI (continuous), smoking (never, current, or past), alcohol (never, current, or past), family history of gastric cancer (yes or no), hypertension (yes or no), diabetes (yes or no), CVD (yes or no), adjuvant therapy (yes or no), radiation therapy (yes or no), neoadjuvant therapy (yes or no), surgery type (open, laparoscopic, or robotic surgery) and extent of surgery (subtotal or total gastrectomy). [a]Event for each stratum.

in cancer patients[25,26]. Therefore, GC patients who have a lower RHR may be individuals with higher levels of physical fitness and/or physical activity, potentially leading to better prognostic outcomes.

We observed an increased RHR on the surgery date, which stabilised after 3–5 days, near the discharge date. We consistently found a similar pattern of association when examining the RHR measured on different days. However, the associations tended to show a clearer pattern toward the discharge date. In Korea, patients are typically discharged approximately 5 days after gastrectomy. Our findings suggest that RHR recorded 3–5 days after surgery could reasonably capture the true relationship between postoperative RHR and prognosis in patients with GC. RHR is a simple, easy, and non-invasive measure that is routinely measured during inpatient surgery and treatment; thus, it has significant potential to be widely used as a prognostic factor in cancer patients. As our study was conducted retrospectively in a tertiary centre in Korea, prospective cohort studies are needed to replicate our findings, preferably performed in multiple centres or clinics. If our findings are confirmed, RHR may play an important role in refining clinical guideline for cancer patients.

The current study had several limitations. First, RHR was measured after surgery because preoperative anxiety and fasting during endoscopic clip application might potentially influence the heart rate. Five days after surgery, the postoperative hearing rate was likely higher than the typical RHR. However, we primarily used the RHR measured five days after surgery when the RHR was stable. Moreover, our sensitivity analyses using the RHR measured on different days after surgery showed consistent results. Second, the value of the RHR in predicting major complications might be low because a high RHR on postoperative day 5 may not be a predictor of major complications but partially a consequence of major complications. Third, although we comprehensively adjusted for potential confounders, including detailed medical and treatment-related factors, we cannot rule out residual confounding by unmeasured factors.

In conclusion, this is the first study to report an independent association between elevated postoperative RHR with poor prognosis, including all-cause mortality, major complications within 30 days, and recurrence, in patients with GC after adjustment for detailed medical and treatment-related factors. Our findings underscore the significance of monitoring RHR in individuals with GC as RHR may serve as an independent risk factor for major complications, cancer progression and mortality, offering valuable insights that could contribute to informed treatment decisions.

Data availability

Data are available upon reasonable request from the corresponding authors.

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Author contributions

DHL, JYJ, and HK conceived and designed the study. DHL conducted data analyses. DHL prepared the first draft. All authors aided in interpreting the results. All authors contributed to critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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