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Short-Term Heart Rate Variability and Blood Biomarkers of Gastric Cancer Prognosis

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ABSTRACT Inflammation, nutrition, and coagulation play significant roles in cancer prognosis. Autonomic function is also actively involved in tumorigenesis. Previous studies have shown that an elevated C-reactive protein (CRP) level, a serum marker for inflammation, is associated with low heart rate variability (HRV), a common clinical tool for the assessment of autonomic function. It is yet to be investigated whether HRV links to these prognostic factors in cancer patients. Sixty-one patients who were first diagnosed with gastric cancer (GC) were enrolled in this study. Fasting blood samples were collected in the morning seven days before surgery. Blood CRP, prealbumin (PA), and fibrinogen (FIB) were used to assess the inflammation level, nutritional status, and coagulation function respectively. Five-minute resting electrocardiogram (ECG) signals were collected one day before surgical treatment. Short-term HRV time-series were extracted from ECG recordings and were analyzed using commonly-used time- and frequency-domain parameters including standard deviation of normal-to-normal intervals (SDNN), root mean square of successive heartbeat interval differences (RMSSD), very-low-frequency power (VLF), low-frequency power (LF), high-frequency power (HF), total power (TP), LF power in normalized units (LF n.u.), HF power in normalized units (HF n.u.), and ratio of LF to HF (LF/HF). After adjusted for sex, age, body mass index, alcohol consumption, history of diabetes, left ventricular ejection fraction, and hemoglobin levels, our results demonstrated negative associations of HRV with levels of CRP and FIB, while positive associations between HRV and PA level, with effect sizes of as high as 35%–52% standard deviations (SD) changes in CRP, FIB, or PA per 1-SD change in HRV parameters. Therefore, decreased HRV in patients with GC predicts increased burdens of inflammation and coagulation and perturbed nutrition, suggesting that short-term HRV measurement can potentially be a noninvasive biomarker for GC prognosis.

INDEX TERMS Gastric cancer, cancer prognosis, heart rate variability, blood biomarker.

I. INTRODUCTION

Gastric cancer (GC) is the second leading cause of cancer death. In 2018, there were approximately 1.03 million new cases of GC globally and about 0.78 million deaths occurred because of GC [1]. Surgery-based comprehensive treatment is currently the main treatment approach for GC [2]. However, the postoperative 5-year survival rate of GC patients is relatively low. For example, in China, the 5-year survival rate is only 20%–30% [3]. To improve this situation, it is believed that better and comprehensive assessments of prognosis both before the treatment and after it at a regular basis are vitally necessary.

Inflammation [4], nutrition [5], and coagulation [6], [7] are believed to be related to cancer prognosis either directly or indirectly. Blood biomarkers including C-reactive protein (CRP), prealbumin (PA), and fibrinogen (FIB) are usually used in clinical practice to assess these physiological functions. However, blood samples are usually ordered by medical professionals in clinic and the measurement of these

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serum biomarkers usually rely on well-trained technicians and professional equipment. It is thus not feasible for them to be used as a tool for the regular monitoring of patients. Noninvasive tools that require less involvement of professionals and are less obtrusive are better preferred.

Autonomic function is found to be involved in tumorigenesis [8]–[10]. Studies in both humans and animals have evidenced the role of the vagal nerve in tumor-inhibiting process through its effects in anti-inflammation, antioxidative stress, and sympathetic inhibition [11]–[13]. Cancer patients were found to have perturbed autonomic regulation as indicated by reduced heart rate variability (HRV), a commonly-used approach in clinical practice for assessing the autonomic control [14], [15]. In addition, lower HRV was found to be associated with increased carcinoembryonic antigen [16]. Adverse effects of decreased HRV including shorter survival time, higher tumor burden, and more advanced metastasis stage have been concluded in a recent systematic reviewer on HRV and cancer prognosis [17]. Regarding the link between HRV and inflammation, many studies in other patient populations have been done. For example, Hamaad *et al.* [18] found that HRV in patients with acute coronary syndrome was negatively correlated with CRP, interleukin 6 (IL-6), and other inflammatory markers during the onset of the disease. In a study of 347 male patients with unstable angina pectoris, Lanza *et al.* [19] showed that elevated CRP was significantly associated with decreased HRV, suggesting a potential pathophysiological pathway between cardiac autonomic control and inflammation process. Madsen *et al.* [20] found that CRP was independently associated with HRV, suggesting a possible link between low-level inflammation and autonomic disorders. In GC patients, there is only one published study that has shown a negative correlation between HRV and serum CRP [15]. Replication using a different population is warranted. Besides, the associations of HRV and other cancer prognostic factors including nutrition and coagulation also worth further investigation.

Therefore, we sought to elucidate the associations of short-term HRV with blood markers of cancer prognosis including inflammation, nutrition, and coagulation in the current study. Once verified, short-term HRV can potentially be a clinical feasible tool for the evaluation of GC prognosis and the long-term monitoring of GC patients given the noninvasive and unobtrusive nature of HRV measurements.

II. METHODS

A. PATIENTS AND DATA COLLECTION

This study was approved by the Clinical Medical Research Ethics Committee of The First Affiliated Hospital of Bengbu Medical College, China. The Department of Gastrointestinal Surgery of The First Affiliated Hospital of Bengbu Medical College treated 126 patients who were diagnosed with GC between March 2018 and December 2018. The diagnoses were confirmed by gastroscopy and pathological examination. Data of 90 GC patients were collected after obtaining informed consent from these subjects.

Fasting venous blood was collected from each patient early in the morning one week prior to the surgery. CRP and PA were determined respectively by immunoturbidimetry and the velocity method (Cobas 8000, Roche, Meylan, France). FIB was detected by the coagulation method (Sysmex CS51000, Sysmex Corporation, Kobe, Japan). All reagents used were original imported from the manufacturers of the corresponding instrument.

ECG data were collected one day prior to surgery using a HeaLink-R211B Micro-ECG recorder (Healink Ltd., Bengbu, China). The bandwidth of the device was 0.5 - 40 Hz, and the sampling rate was 400 Hz. During ECG collection, patients were in the supine position; the test environment was kept quiet; and the temperature was maintained at $23 \pm 1°C$. The duration of data collection was 5 min. The V5-lead was employed, and the measuring electrodes were Ag/AgCl disposable ECG electrode sheets (Junkang Ltd., Shanghai, China).

Patients of recurrent GC ($n = 1$), with poor-quality ECG ($n = 2$), with too many ectopic beats (i.e., >10% of all beats; $n = 8$), accepted blood transfusion before ECG ($n = 15$), or administered chemotherapy prior to ECG collection ($n = 3$) were excluded. Therefore, data of 61 GC patients were analyzed in this study.

B. HRV ANALYSIS

ECG data were imported into a computer and R-R interval (RRI) time series were extracted using a customized MATLAB program (The Mathworks Inc., Natick, MA, USA).

Commonly-used time- and frequency-domain HRV indices were calculated. Specifically, time-domain indices include the standard deviation of normal-to-normal (NN) intervals (SDNN) and the root mean square of the normal difference between successive NNs (RMSSD) [21].

Frequency domain parameters included very-low-frequency power (VLF), low-frequency power (LF), high-frequency power (HF), total power (TP), LF power in normalized units (LF n.u.), HF power in normalized units (HF n.u.), and ratio of LF to HF (LF/HF). To perform the power spectral analysis, RRI time series were first evenly resampled to 4 Hz by spline interpolation. Power spectral density (PSD) was obtained by fast Fourier transform [22], [23]. The corresponding frequency bands of VLF, LF, HF, were 0 - 0.04 Hz, 0.04 - 0.15 Hz, and 0.15 - 0.4 Hz, respectively. TP was calculated as the power of RRI over 0–0.4 Hz.

C. STATISTICAL ANALYSIS

CRP, VLF, LF, HF, TP, and LF/HF were natural-logarithmically transformed prior to further analysis as they were right-skewed. Bivariate Pearson correlation was used to analyze the relationship of CRP, PA, and FIB with HRV parameters. Multiple linear regression models were performed to account for potential confounding effects of sex, age, body mass index (BMI), alcohol consumption, history of diabetes, left ventricular ejection fraction (LVEF),

and hemoglobin (Hb). Considering increased false positive rate due to multiple comparisons, we performed multiple comparison correction within the set of tests for each outcome (i.e., CRP, PA, or FIB) based on Bonferroni criterion. Statistical significance was accepted if corrected $P < 0.05$. All statistical analyses were performed using the SPSS statistical software (ver. 22.0, IBM Corp., USA).

III. RESULTS

A. CHARACTERISTICS OF PATIENTS

The basic and clinical characteristics of the studied GC patients in this study are shown in Table 1.

TABLE 1. Basic and clinical characteristics of the study patients.

Variables	Values
N (Female/Male)	61 (16/45)
Age (years)	63.6 (10.4)
BMI (kg/m^2)	22.6 (3.3)
History of alcohol consumption (yes/no)	9/52
History of diabetes (yes/no)	11/50
LVEF	57 (4)
Hb(g/L)	126 (21)
CRP (mg/L)	1.5 [4.0]
PA (mg/L)	227 (70)
FIB (g/L)	3.49 (0.84)
SDNN (ms)	31.4 (14.4)
RMSSD (ms)	20.5 (12.4)
VLF (ms^2)	343 [543]
LF (ms^2)	131 [230]
HF (ms^2)	93 [154]
TP (ms^2)	615 [903]
LF n.u.	60.0 (17.0)
HF n.u.	39.9 (17.0)
LF/HF	1.658 [1.768]

Values are expressed as the number of patients, mean (standard deviation), or median [inter quantile range].

B. PEARSON CORRELATION AND MULTIVARIATE ANALYSES

Bivariate Pearson correlation analyses (Table 2) show that elevated CRP and FIB and decreased PA were significantly associated with RMSSD and HF reduction ($P < 0.05$). Moreover, increased CRP and decreased PA were also significantly correlated with decreased SDNN, VLF, LF, and TP ($P < 0.05$). Elevated FIB was also significantly correlated with increased LF n.u., increased LF/HF, and decreased HF n.u.

TABLE 2. Bivariate correlation between blood biomarker and HRV parameters.

	CRP	PA	FIB
SDNN	**(-0.318, 0.013)**	**(0.376, 0.003)**	(-0.106, 0.418)
RMSSD	**(-0.356, 0.005)**	**(0.385, 0.002)**	**(-0.295, 0.021)**
VLF	**(-0.392, 0.002)**	**(0.329, 0.010)**	(-0.036, 0.784)
LF	**(-0.375, 0.003)**	**(0.367, 0.004)**	(-0.085, 0.516)
HF	**(-0.409, 0.001)**	**(0.376, 0.003)**	**(-0.343, 0.007)**
TP	**(-0.404, 0.001)**	**(0.364, 0.004)**	(-0.112, 0.390)
LF n.u.	(0.157, 0.227)	(-0.101, 0.437)	**(0.433, 0.000)**
HF n.u.	(-0.157, 0.227)	(0.101, 0.437)	**(-0.432, 0.000)**
LF/HF	(0.165, 0.205)	(-0.121, 0.353)	**(0.444, 0.000)**

Values are expressed as (r, P).
Bold indicates $P < 0.05$.

To eliminate the influence of potential confounding factors, we performed multiple linear regression models accounting for sex, age, BMI, alcohol consumption, history of diabetes, LVEF, and Hb. Results are shown in Table 3. Reduced VLF, HF, and TP were significantly associated with elevated CRP. Specifically, for each 1-standard deviation (SD) decrease in lnVLF, lnHF, lnTP, the level of lnCRP increased by 0.419 ± 0.131, 0.416 ± 0.133, and 0.422 ± 0.133 SD, respectively (all Bonferroni-corrected P's < 0.05). Besides, reduced RMSSD and HF were significantly associated with decreased PA with each 1-SD decrease in RMSSD and lnHF corresponding to 0.358 ± 0.116 and 0.392 ± 0.119 SD decrease in PA (both Bonferroni-corrected P's < 0.05). In addition, increased LF n.u., increased LF/HF, and decreased HF n.u. were significantly associated with elevated FIB. For each 1-SD increase in LF n.u., ln(LF/HF), or each 1-SD decrease in HF n.u., the level of FIB increased by 0.514 ± 0.124, -0.513 ± 0.124, and 0.520 ± 0.123 SD, respectively (all Bonferroni-corrected P's < 0.05). Figure 1 is showing the partial correlation plot between each pair of the outcome (CRP, PA, and FIB) and HRV parameters after accounting for sex, age, BMI, alcohol consumption, history of diabetes, LVEF, and Hb. The regression analysis results were consistent with the results of the bivariate Pearson correlation analysis, indicating that these associations are independent of those known risk factors.

IV. DISCUSSION

With 61 GC patients, we verified the association between blood CRP and HRV parameters. Besides, we observed strong associations of serum FIB and PA with HRV parameters as well. Among all HRV parameters, RMSSD and

TABLE 3. Results from multiple linear regression models adjusted for age, sex, BMI, alcohol consumption, history of diabetes, LVEF, and Hb.

	CRP				PA				FIB			
	B	**SE**	***P***	**Corrected *P***	**B**	**SE**	***P***	**Corrected *P***	**B**	**SE**	***P***	**Corrected *P***
SDNN	-0.340	0.132	0.013	>0.05	0.340	0.118	0.006	>0.05	-0.130	0.141	0.362	>0.05
RMSSD	-0.360	0.130	0.008	>0.05	**0.358**	**0.116**	**0.003**	**0.03**	-0.320	0.134	0.021	>0.05
VLF	**-0.419**	**0.131**	**0.002**	**0.02**	0.252	0.124	0.048	>0.05	-0.041	0.145	0.777	>0.05
LF	-0.342	0.137	0.016	>0.05	0.306	0.124	0.017	>0.05	-0.046	0.147	0.756	>0.05
HF	**-0.416**	**0.133**	**0.003**	**0.03**	**0.392**	**0.119**	**0.002**	**0.02**	-0.376	0.137	0.008	>0.05
TP	**-0.422**	**0.133**	**0.003**	**0.03**	0.303	0.124	0.019	>0.05	-0.116	0.147	0.433	>0.05
LF n.u.	0.209	0.138	0.136	>0.05	-0.187	0.125	0.140	>0.05	**0.514**	**0.124**	**0.000**	**0.000**
HF n.u.	-0.209	0.138	0.136	>0.05	0.187	0.125	0.140	>0.05	**-0.513**	**0.124**	**0.000**	**0.000**
LF/HF	0.211	0.138	0.132	>0.05	-0.218	0.124	0.084	>0.05	**0.520**	**0.123**	**0.000**	**0.000**

Bold indicates statistically significant at Bonferroni-corrected $P < 0.05$.

HF are considered to reflect the parasympathetic activity, whereas SDNN and LF are earlier considered to be a balanced outcome of the parasympathetic and sympathetic regulation and are more recently believed to come from parasympathetically- mediated respiratory sinus arrythmia and baroreflex activity [24]–[26]. Therefore, our results directly support the link between cardiac autonomic function and GC prognostic factors. More importantly, this link is highly independent from many known factors such as sex, age, BMI, alcohol consumption, history of diabetes, cardiac systolic function, and anemia, suggesting that autonomic dysregulation may serve as an independent predictor of GC-related inflammation, malnutrition, and coagulation perturbation.

Directly related to inflammation process, CRP is an acute-phase reactive protein that is produced by the liver under the action of interleukin 6 (IL-6). CRP production is regulated and stimulated by IL-1 and tumor necrosis factor α [27]. Preoperative serum CRP level has been used as an independent predictor of survival time in a variety of cancers [28]–[32]. In keeping with two previous studies [15], [33], we also observed negative associations between CRP and HRV parameters. With these baseline associations, this study also encourages further explorations to test whether preoperative autonomic function and inflammation are synergistic to affect survival of these patients.

Besides, we also expanded the link of autonomic function with GC by showing its relationships with nutrition and coagulation. GC patients often experience varying degrees of malnutrition that can subsequently damage the body's immune system and inhibit cell-mediated immune function, a critical process in cancer defense [34]–[36]. Furthermore, malnutrition may increase the risk of postoperative infection and thereby activate the systemic inflammatory response, reducing the therapeutic effects of surgery [37], [38]. Increasing evidence supports the idea that nutritional status is significantly associated with long-term outcomes in cancer patients [39], [40]. As a common nutrition marker, blood PA was found to be related to the 5-year survival rate in patients with malignant tumors such as resected esophageal squamous cell carcinoma and hepatocellular carcinoma [41]–[43].

Changes in coagulation is another common symptom in patients with malignant tumors. Worse coagulation function often predicts early metastasis and poor prognosis [7], [44]. Studies have found that preoperative plasma FIB, an essential coagulation protein in the plasma, is intimately related to postoperative survival in GC patients; higher preoperative plasma FIB levels are associated with lower survival rate. Besides, a combined detection of FIB and serum tumor-associated materials can improve the early diagnosis of GC patients and at the same time has value in the clinical staging and metastasis assessment of GC patients [45]–[48].

Direct link between autonomic function and tumorigenesis exists, too, in previous animal and human studies that together suggested an important role of the autonomic regulation in the microenvironment of tumor formation and tumorigenesis processes (such as occurrence, progression, local and systemic immune responses, immune tolerance, vascular invasion, and lymphatic metastasis) [49]. Specifically, both overactivity of sympathetic nerves or decreased vagal tune by surgical removal of vagus nerve were shown to promote tumorigenesis and tumor development [10], [50]. Erin et al. [51] showed that anti-inflammatory drugs that affect the vagus nerve reduced tumor metastasis in tumor-bearing mice. Borovikova *et al.* [52] showed that acetylcholine released by the vagus nerve affects the immune system through a cholinergic anti-inflammatory pathway. Zhou *et al.* [53] found that higher HRV was associated with

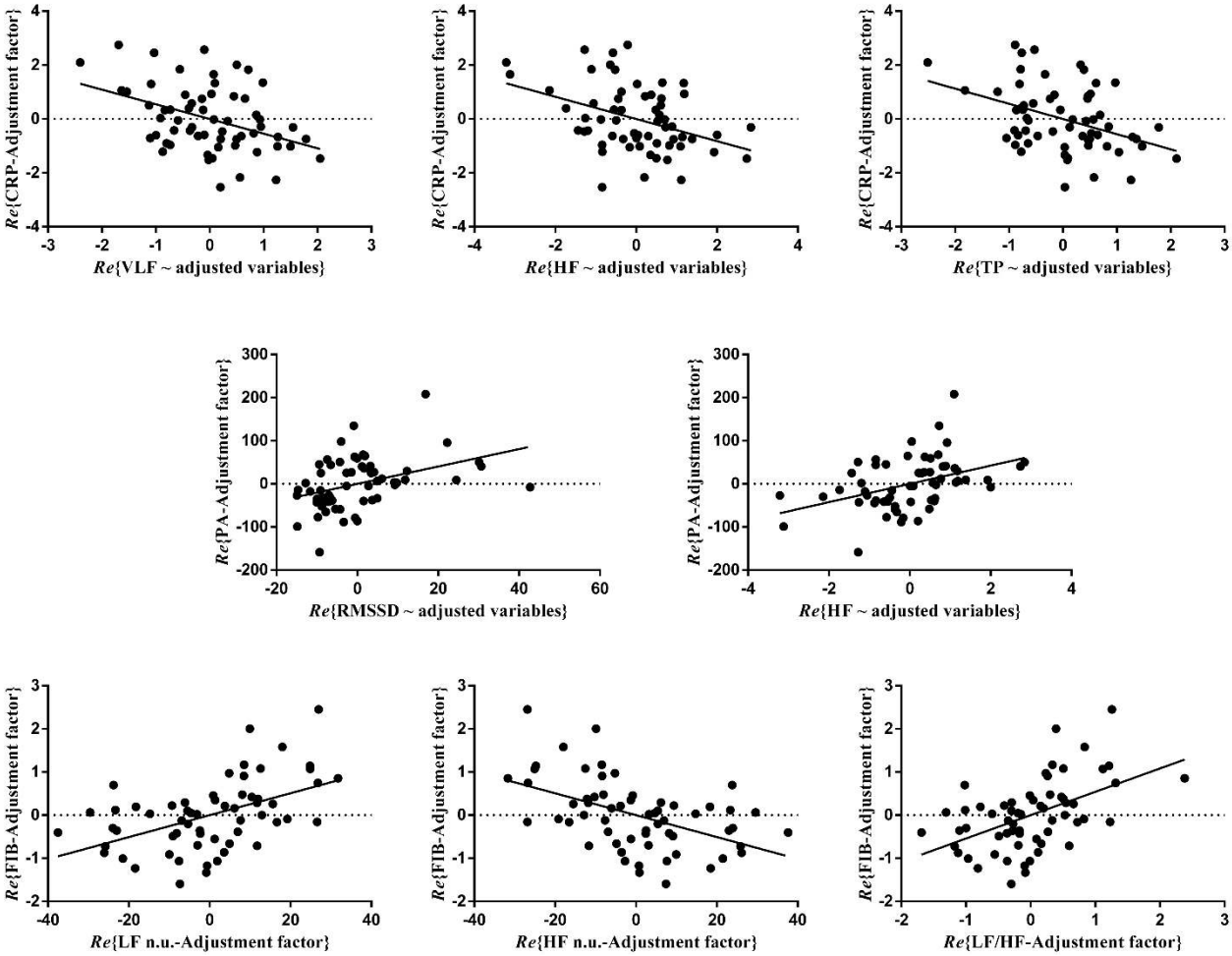

FIGURE 1. Partial correlation plots of the relationship between blood biomarkers (CRP, PA, and FIB) and HRV parameters (RMSSD, VLF, LF, HF, TP, LF n.u., HF n.u., and LF/HF). *Re*{y ~ x} indicates the residuals of regressing y against x.

greater vagus nerve activity and better prognosis in tumor patients.

GC is characterized by high morbidity and mortality. Currently, no prognostic assessment or monitoring in any form is conducted after discharge of GC patients. Although serum markers can be used in the prognostic assessment of cancer patients, they are not convenient for home use. HRV, a noninvasive method of assessing ANS activity, is usually achieved by analyzing the RR interval time series in the ECG signal. This study found that ANS activity was significantly associated with inflammation level, nutritional status, and coagulation function. The measurement of ECG with portable devices appears to be more feasible than blood tests as an ambulatory practice. Therefore, our study shows a potential of short-term ECG as an alternative tool for comprehensively evaluating GC prognosis or monitoring GC patients in long term noninvasively and unobtrusively. Moving forward, a larger sample size is required to verify these observations, and most importantly, to construct threshold values of HRV parameters for concerns of GC prognosis to promote their clinical usability.

Although this current study suggests promising of HRV assessment for GC prognosis, we are aware of several limitations as well. A major notable limitation is that the current study design is cross sectional. Baseline associations limit our inference about the potential of HRV parameters in predicting long-term outcomes. Besides, a comprehensive understanding of the relationships of HRV VLF and TP parameters with blood CRP and PA levels is currently lacking. It depends on the understanding of the underlying mechanisms that are related especially to VLF component in HRV. Future cohort studies are also warranted to address the relationships of HRV parameters with hematological indices and long-term prognosis including survival time of GC patients.

V. CONCLUSION

In conclusion, decreased HRV in patients with GC predicts increased CRP, increased FIB, and decreased PA. The results of this study suggest that short-term HRV can potentially be used as a noninvasive biomarker for the comprehensive assessment of inflammation, nutrition, and coagulation in patients with GC. Short-term HRV assessment could

potentially be used to monitor the prognosis of cancer patients outside the hospital, an application that is of great significance for further improving the effects of therapy for GC.

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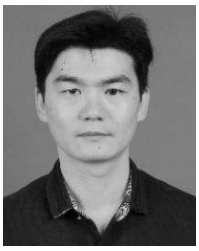

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