Using heart rate variability to evaluate the association between the autonomic nervous system and coagulation function in patients with endometrial cancer

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Received March 6, 2024; Accepted July 29, 2024

DOI: 10.3892/ol.2024.14632

Abstract. The incidence of endometrial cancer (EC) is increasing worldwide, but the specific mechanism of coagulation dysfunction in EC is not fully understood. The objective of the present study was to explore the relationship between autonomic nervous system function and coagulation function in patients with EC using heart rate variability (HRV) analysis. The study included 100 patients with EC who were treated at the Department of Gynecological Oncology of The First Affiliated Hospital of Bengbu Medical University (Bengbu, China) from December 2021 to March 2023. A 5-min resting electrocardiogram was collected from each patient to analyze HRV parameters, including the time domain parameters standard deviation of the normal-normal intervals (SDNN) and root mean square of successive interval differences (RMSSD), and the frequency domain parameters low-frequency power and high-frequency power (HF). Blood samples were submitted to biochemistry tests to measure coagulation markers, namely prothrombin time (PT), international normalized ratio of PT (PT-INR), prothrombin activity (PTA), activated partial thromboplastin time (APTT) and fibrinogen. Bivariate Spearman correlation analyses revealed that PT, PT-INR and APTT were significantly positively correlated with SDNN, RMSSD and HF, while PTA was significantly negatively correlated with RMSSD. Following adjustments for confounding factors, namely age, body mass index, menopause, ligation of the fallopian tubes, diabetes, hypertension, adjuvant chemotherapy and mean heart rate, linear regression analysis demonstrated that SDNN, RMSSD and HF were independent factors influencing PT and PT-INR in patients with EC. The findings of the present study indicate that certain HRV parameters correlate with coagulation markers in EC and provide new insight into the occurrence of cancer-associated coagulation dysfunction.

Introduction

Endometrial cancer (EC) is one of the most common malignant tumors of the female reproductive system (1), and its incidence is increasing worldwide (2). In total, >410,000 new cases and >90,000 associated deaths were estimated to occur globally in 2020 (1). Previous studies have confirmed that patients with malignant tumors are 7-10 fold more likely to exhibit abnormalities in coagulation and/or fibrinolysis than are patients in the general population (3-5). For patients with EC, changes in the levels of coagulation biomarkers, including fibrinogen (FIB) and D-dimer, may indicate the occurrence of coagulation dysfunction (6,7). Some treatments administered to patients with EC, such as chemotherapy and radiotherapy can cause changes in the physiological status of the patient; for example, changes in coagulation status or autonomic nervous system (ANS) function may occur as side effects of chemotherapy (8,9). However, the specific physiological mechanism of coagulation in patients with EC is not fully understood, and further in-depth research is needed.

The ANS plays a vital role in the maintenance of homeostasis in the human body. Activation of the sympathetic nervous system via the intravenous injection of adrenaline has been reported to accelerate blood clotting (10). Specifically, the activities of blood FIB, coagulation factor VIII, von Willebrand factor, platelets and other substances associated with clotting are increased, indicating that the ANS contributes to the regulation of blood coagulation (11). Dysfunction of the ANS due to the presence of malignant tumors can lead to cytokine release and the occurrence of inflammatory

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Key words: heart rate variability, autonomic nervous system, endometrial cancer, tumor coagulation

responses (12,13). This may induce tumor coagulation, such as extravascular coagulation in the tumor (12-14). However, the induction of coagulation disorders by tumor-induced inflammatory reactions and the cytokines released from tumors may also require participation by the ANS (14,15). Heart rate variability (HRV) analysis is commonly used to evaluate the status of the ANS and has been widely used to assess ANS activity in patients with various types of cancers (16). Previous studies have confirmed that the ANS participates in regulation of the tumor microenvironment and mediates the occurrence of inflammation in patients with cancer, and that these physiological processes are associated with specific HRV parameters (17,18). The interaction between tumor coagulation and inflammation in patients with malignant tumors may be the basis for the regulatory role of the ANS. In a study of gastric cancer and HRV, Hu *et al* (19) reported that downregulated HRV indices in patients with gastric cancer may be associated with an unbalanced inflammatory response. This inflammation, caused by an immune response, may lead to a coagulation disorder (20). In addition, Wang *et al* (21) reported an association between HRV and coagulation parameters in patients with breast cancer, indicating that it is feasible to use HRV to assess the association between ANS function and tumor coagulation. However, there is a paucity of research on the relationship between HRV and coagulation function in patients with EC. Therefore, in the present study, the aim was to investigate the association between the ANS and coagulation function in patients with EC via HRV analysis.

Materials and methods

Patients. A total of 122 patients (age range, 34-80 years) with EC who were treated at the Department of Gynecological Oncology of The First Affiliated Hospital of Bengbu Medical University (Bengbu, China) from December 2021 to March 2023 were enrolled in the study. The inclusion criterion was EC confirmed by postoperative pathology as pathological type adenocarcinoma. The exclusion criteria were as follows: i) Complicated with at least one other malignant tumor; ii) cerebral embolism; iii) abnormal or poor electrocardiogram quality; iv) atrial fibrillation; and v) ectopic heartbeats comprising >5% of total heartbeats. It was identified that 22 patients did not meet the exclusion and inclusion criteria, and 100 patients were eventually included. The present study was approved by the Institutional Review Committee of the First Affiliated Hospital of Bengbu Medical University (approval no. 2021KY010), and conducted in strict accordance with the principles of the Declaration of Helsinki. All patients signed informed consent forms.

Data collection. An electrocardiogram recorder (HeaLink-R211B; HeaLink Ltd.) was used to collect 5-min single-lead electrocardiogram data from the patients before surgery for HRV analysis. The electrocardiograph sampling rate was 400 Hz, and a V6 lead was used. During electrocardiogram collection, the subjects were required to remain quiet and were tested in a supine position at 25±2˚C. Ligation was performed by ligation of the bilateral fallopian tubes in patients with EC. The staging of this study adopted the International Federation of Gynecology and Obstetrics guidelines 2023 (22).

Venous blood was collected from all patients in the fasting state prior to surgery. To prevent coagulation, the anticoagulant sodium citrate was combined with the blood samples at a ratio of 1:9 by volume, respectively. The collected blood samples were analyzed using an automatic coagulation analyzer (Sysmex CS51000; Sysmex Corporation). Five coagulation biomarkers were measured, namely prothrombin time (PT), international normalized ratio of PT (PT-INR), prothrombin activity (PTA), activated partial thromboplastin time (APTT) and FIB using test reagents supplied by the instrument manufacturer.

HRV analysis. Kubios HRV software (version 3.1.0; https://www.kubios.com; Kubios Oy) was used for HRV analysis of the time and frequency domains.

The time domain parameters included the standard deviation of the normal-normal intervals (SDNN) and the root mean square of successive interval differences (RMSSD). The specific time-domain calculation formulae are as follows (23):

$$\mathrm{SDNN} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(RRI_i - \overline{RRI})^2}$$

$$\mathrm{RMSSD} = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N-1}(RRI_{i+1} - RRI_i)^2}$$

In these formulae, $\overline{RRI}$ is the mean of the R-to-R intervals (RRIs).

The frequency domain parameters included low-frequency power (0.04-0.15 Hz) and high-frequency power (HF; 0.15-0.4 Hz). Prior to frequency domain analysis, the RRI time series was resampled using cubic spline interpolation (24). Fast Fourier transform based on the Welch periodogram method (with a 150-sec window width and 50% overlapping window) was used to estimate the power spectral density of the RRI time series (25). These operations equalized the spectrum of the overlapping segments to reduce the variance of the -spectrum.

Statistical analysis. Before data analysis, the Shapiro-Wilk test was used to evaluate the normality of continuous data. Since the hematological and HRV parameters were found to be non-normally distributed, bivariate Spearman correlation analysis was used to explore the correlations between the hematological and HRV parameters. The HRV parameters with significant correlations were subsequently incorporated into a separate model for multiple linear regression analysis to test the relationships between the hematological indicators and HRV parameters. In each model, hematological indicators were used as the dependent variable, and HRV indicators as the independent variable. In addition, the model was adjusted for confounding factors, namely age, body mass index (BMI), menopause, ligation, diabetes, hypertension, adjuvant chemotherapy and mean heart rate (HR). $P<0.05$ was considered to indicate a statistically significant result. Statistical analysis was performed using SPSS 26.0 software (IBM Corp.).

Table I. Basic clinical data of the patients with endometrial cancer.

Variables	Values
Age, years	55.2±7.3
BMI, kg/m^2	26.4±4.3
Mean HR, bpm	72.2±10.9
Menopausal, n	
Yes	59
No	41
Ligation, n	
Yes	58
No	42
Diabetes, n	
Yes	15
No	85
Hypertension, n	
Yes	25
No	75
Adjuvant chemotherapy, n	
Yes	2
No	98
FIGO, n	
I	83
II	11
III	5
IV	1
LF	85 (44, 144)
HF	79 (34, 228)
SDNN, msec	14.7 (11.1, 21.4)
RMSSD, msec	15.6 (9.6, 26.7)
PT, sec	10.7 (10.4, 11.2)
PT-INR	0.9 (0.9, 1.0)
PTA, %	113.8 (104.5, 121.0)
APTT, sec	24.9±2.0
FIB, g/l	2.5 (2.2, 3.0)

Values are expressed as counts, the mean ± standard deviation or median (first quartile, third quartile). BMI, body mass index; HR, heart rate; FIGO, International Federation of Gynecology and Obstetrics; LF, low-frequency power; HF, high-frequency power; SDNN, standard deviation of all normal-to-normal intervals; RMSSD, root mean square of successive interval differences; PT, prothrombin time; PT-INR, international normalized ratio of PT; PTA, prothrombin activity; APTT, activated partial thromboplastin time; FIB, fibrinogen.

Results

The general demographic characteristics, coagulation biomarkers and HRV parameters of the patients with EC are summarized in Table I.

Bivariate Spearman correlation analyses (Table II) revealed that PT, PT-INR and APTT were significantly positively correlated with SDNN and RMSSD (P<0.05). In addition, PTA was significantly negatively correlated with RMSSD, while PT and PT-INR were significantly positively correlated with HF (all P<0.05).

To evaluate the independent associations of SDNN, RMSSD and HF with coagulation biomarkers in patients with EC, a linear regression analysis was conducted, excluding confounding factors such as age, BMI, menopause and ligation. The results revealed that SDNN, RMSSD and HF still significantly correlated with PT and PT-INR (P<0.05; Table IIIA). Specifically, when the SDNN, RMSSD and HF decreased by 1 standard deviation, PT decreased by 0.320, 0.307 and 0.298 sec, respectively, and PT-INR decreased by 0.322, 0.309 and 0.303, respectively. The changes of 1 standard deviation were calculated by the β value.

After further incorporating mean HR into the confounding factors, the SDNN, RMSSD and HF remained significantly correlated with PT and PT-INR (P<0.05; Table IIIB). When the SDNN, RMSSD and HF decreased by 1 standard deviation, PT decreased by 0.256, 0.240 and 0.237 sec, respectively, and PT-INR decreased by 0.265, 0.247 and 0.246, respectively.

Correlation scatter plots for each pair of outcomes, namely PT and PT-INR, and the HRV parameters SDNN, RMSSD and HF, with adjustment for age, BMI, menopause, ligation, diabetes, hypertension, adjuvant chemotherapy and mean HR are presented in Fig. 1.

Discussion

In the present study, the relationships of coagulation biomarkers with HRV time and frequency domain parameters in patients with EC were explored. The results revealed that SDNN, RMSSD and HF were significantly positively correlated with PT and PT-INR, independent of the confounding factors age, BMI, menopausal status, ligation, diabetes, hypertension, adjuvant chemotherapy and mean HR.

Previous explanations of the mechanisms underlying tumor coagulation disorders have focused mainly on the coagulation cascade and the pathophysiological role of platelets. The upregulation of coagulation factors in the tumor stroma and vascular endothelial cells promotes the formation of cancer-associated thrombosis (26,27). During tumor progression, the upregulation of certain fibroin degradation inhibitors, such as plasminogen activator inhibitor-1, leads to the inhibition of fibrinolysis and the occurrence of abnormal coagulation (28,29). Furthermore, specific changes in the microenvironment of malignant tumors increase the release of platelets, thereby directly or indirectly affecting thrombosis and affecting coagulation processes in the body (20,30). Coagulation biomarkers are considered reliable indicators of the coagulation status of the body (7,31,32). The present study confirmed correlations between coagulation biomarkers and HRV parameters, implying an association between the ANS and tumor coagulation abnormalities.

The ANS is a vital system comprising sympathetic and parasympathetic nervous systems which regulate various human physiological functions (33). Interactions between the sympathetic and parasympathetic nervous systems can affect the occurrence, development, metastasis and prognosis of cancer (34-36). Previous studies have shown that the stress reflex system, which is regulated by the central nervous system, affects tumor angiogenesis

Table II. Correlation analysis of HRV parameters and coagulation markers.

Coagulation markers	HRV parameters							
	SDNN		RMSSD		LF		HF	
	ρ	P-value	ρ	P-value	ρ	P-value	ρ	P-value
PT	0.265	0.008	0.282	0.004	0.195	0.052	0.269	0.007
PT-INR	0.259	0.009	0.276	0.005	0.189	0.059	0.262	0.008
PTA	-0.187	0.063	-0.208	0.038	-0.154	0.126	-0.192	0.055
APTT	0.223	0.025	0.239	0.017	0.255	0.255	0.177	0.078
FIB	-0.136	0.177	-0.121	0.229	-0.085	0.401	-0.153	0.128

HRV, heart rate variability; SDNN, standard deviation of all normal-to-normal intervals; RMSSD, root mean square of successive interval differences; LF, low-frequency power; HF, high-frequency power; PT, prothrombin time; PT-INR, international normalized ratio of PT; PTA, prothrombin activity; APTT, activated partial thromboplastin time; FIB, fibrinogen.

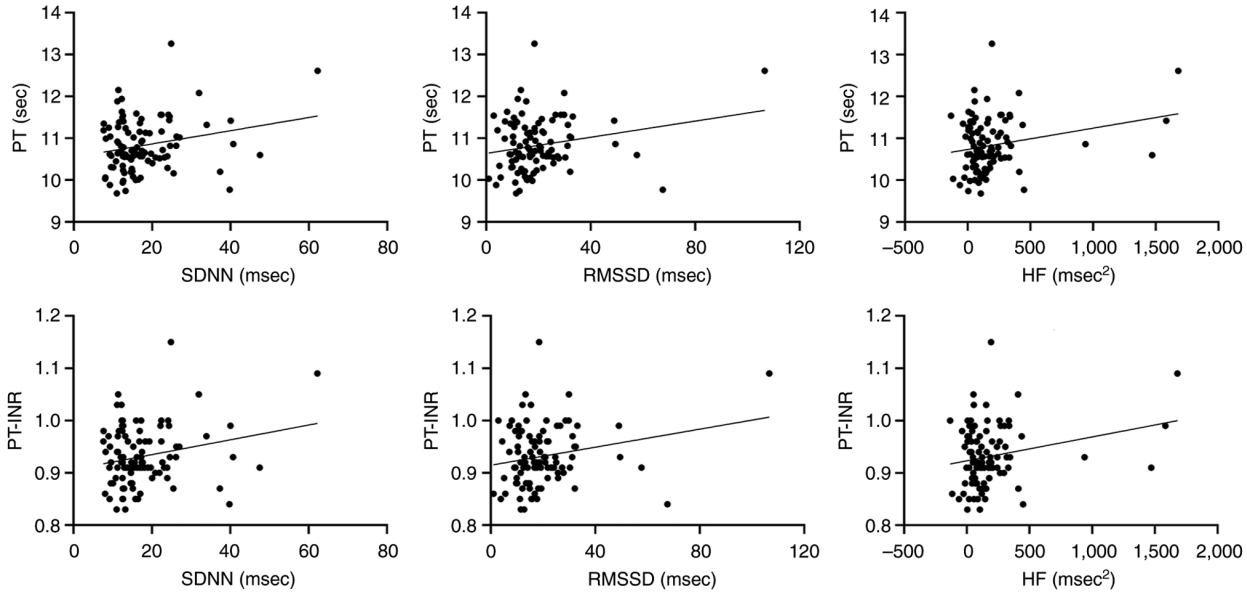

Figure 1. Partial correlation plots for heart rate variability parameters and blood biomarkers, following the exclusion of the confounding factors age, body mass index, menopause, ligation, diabetes, hypertension, adjuvant chemotherapy and mean heart rate. PT, prothrombin time; PT-INR, international normalized ratio of PT; SDNN, standard deviation of the normal-normal intervals; RMSSD, root mean square of successive interval differences; HF, high-frequency power.

via β_2 adrenergic receptors (12,14). Abnormal cell proliferation in tumors has been indicated to lead to the upregulation of vascular endothelial growth factor expression and downregulation of thrombospondin-1 expression, which in turn cause extracellular coagulation (13,37). In addition to the aforementioned pathways, tumor cells can also increase thrombin levels by directly activating the coagulation system (38) or promoting the synthesis and expression of multiple coagulation factors through various physicochemical pathways (15,39). These pathways leading to coagulation may involve the participation of the ANS (Fig. 2).

As aforementioned, the ANS comprises sympathetic and parasympathetic components, and the vagus nerve is an important parasympathetic nerve. The regulatory effects of the nerves from both types of ANS on body physiology are nonlinear and complex (40). In HRV analysis, SDNN represents overall autonomous regulation, whereas RMSSD and HF reflect changes in vagal nerve tension (41,42). The present study revealed that coagulation parameters PT and PT-INR were positively correlated with SDNN, RMSSD and HF, which suggests that changes in the coagulation function of patients with EC may be influenced by both the sympathetic and parasympathetic nervous systems. PT and its derivative PT-INR are currently the most commonly used coagulation biomarkers for assessing the status of human coagulation function (43,44). Malignant tumors can adversely affect the coagulation function of patients with cancer, leading to thromboembolism, increased blood clotting and changes in hemodynamics, such as increased vascular resistance, the activation of coagulation factors and imbalance of the fibrinolytic system (45). The associated changes in blood flow may increase baroreceptor activity and reflexivity, leading to the activation of sympathetic nerve activity and vagal nerve excitation, which can manifest as increases in the SDNN and RMSSD (45). In a study on vagus nerve activity and breast cancer, Ricon-Becker *et al* (46) reported a positive correlation of SDNN

Table III. Linear regression analysis of HRV and coagulation markers.

A, Excluding main confounding factors

HRV parameters	PT	PT-INR	PTA	APTT
SDNN				
B	0.016	0.001	-	-0.008
SE	0.007	0.001	-	0.021
β	0.253	0.263	-	-0.043
P-value	0.034	0.027	-	0.709
RMSSD				
B	0.010	0.001	-0.038	-0.005
SE	0.005	0.000	0.121	0.014
β	0.238	0.247	-0.082	-0.043
P-value	0.043	0.036	0.495	0.707
HF				
B	0.000	0.000	-	-
SE	0.000	0.000	-	-
β	0.232	0.243	-	-
P-value	0.031	0.024	-	-

B, Excluding main confounding factors and HR

HRV parameters	PT	PT-INR	PTA	APTT
SDNN				
B	0.019	0.002	-	0.028
SE	0.006	0.001	-	0.020
β	0.303	0.309	-	0.154
P-value	0.004	0.003	-	0.150
RMSSD				
B	0.012	0.001	-0.100	0.019
SE	0.004	0.000	0.104	0.013
β	0.290	0.294	-0.099	0.156
P-value	0.005	0.004	0.340	0.136
HF				
B	0.001	0.000	-	-
SE	0.000	0.000	-	-
β	0.280	0.288	-	-
P-value	0.007	0.005	-	-

Main confounding factors are age, body mass index, menopause, ligation, diabetes, hypertension and adjuvant chemotherapy. HRV, heart rate variability; PT, prothrombin time; PT-INR, international normalized ratio of PT; PTA, prothrombin activity; APTT, activated partial thromboplastin time; SDNN, standard deviation of all normal-to-normal intervals; RMSSD, root mean square of successive interval differences; HF, high-frequency power; B, regression coefficient; SE, standard error; β, standardized regression coefficient.

with proinflammatory transcription factor activity and serum cytokine levels, which are involved in physiological processes that require baroreceptor mediation. Vagus nerve excitation caused by coagulation dysfunction increases the levels of certain cytokines, such as tissue factor, leading to an inflammatory response (13). Notably, ANS function and tumor coagulation interact with and influence each other. Van den Berg *et al* (47) reported that the tumor-induced inflammatory response and tumor-driven cytokine expression can be influenced by the involvement or mediating effects of the ANS. When the ANS is disturbed or dysfunctional, the vagus-mediated immune and inflammatory responses are affected, which leads to changes in coagulation function (8,48). In addition, Wang *et al* (21) observed that PT increased as RMSSD increased in patients with breast cancer, which provides evidence for involvement of the ANS in the regulation of coagulation function. However, these studies did not elucidate precise physiological mechanisms to support their conclusions, which may be a potential research direction in the future.

There are several limitations to the present study. First, although the type of cancer was restricted to endometrial adenocarcinoma, a stratified analysis based on clinical stage was not performed due to the limited sample size, which may affect the experimental results to some extent. Second, the collected data were measured at a single time point, and changes in the HRV and coagulation parameters of patients after treatment were not considered. However, the collection of more treatment data is planned in the future. Factors such as diet and drug therapy may have affected the HRV parameters and coagulation function of the experimental subjects, and subsequent studies should control for these factors. Finally, this was a single-center study, and no data were included from healthy individuals for comparison with the study cohort. In the future, multicenter and multigroup data will be included to support the findings of the present study.

In summary, the present study revealed a correlation between coagulation biomarkers and HRV indicators in EC patients, with lower SDNN, RMSSD and HF values being indicative of lower PT and PT-INR values. Given that HRV is a quantitative indicator of the ANS, the results suggest an association between the ANS and coagulation function in patients with EC. Further exploration of the physiological mechanism of abnormal coagulation in patients with malignant tumors may aid in the identification of novel strategies for clinical treatment. The use of wearable HRV devices may enable the functional ANS status of patients with cancer to be monitored more effectively and noninvasively.

Acknowledgements

Not applicable.

Funding

This research was funded by the Natural Science Research Project of the Anhui Educational Committee (grant nos. KJ2021A0803 and 2022AH051471).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YQW, WZG, YFZ, YLW, BS, JL and SZ contributed to study conception and design. Material preparation, data collection

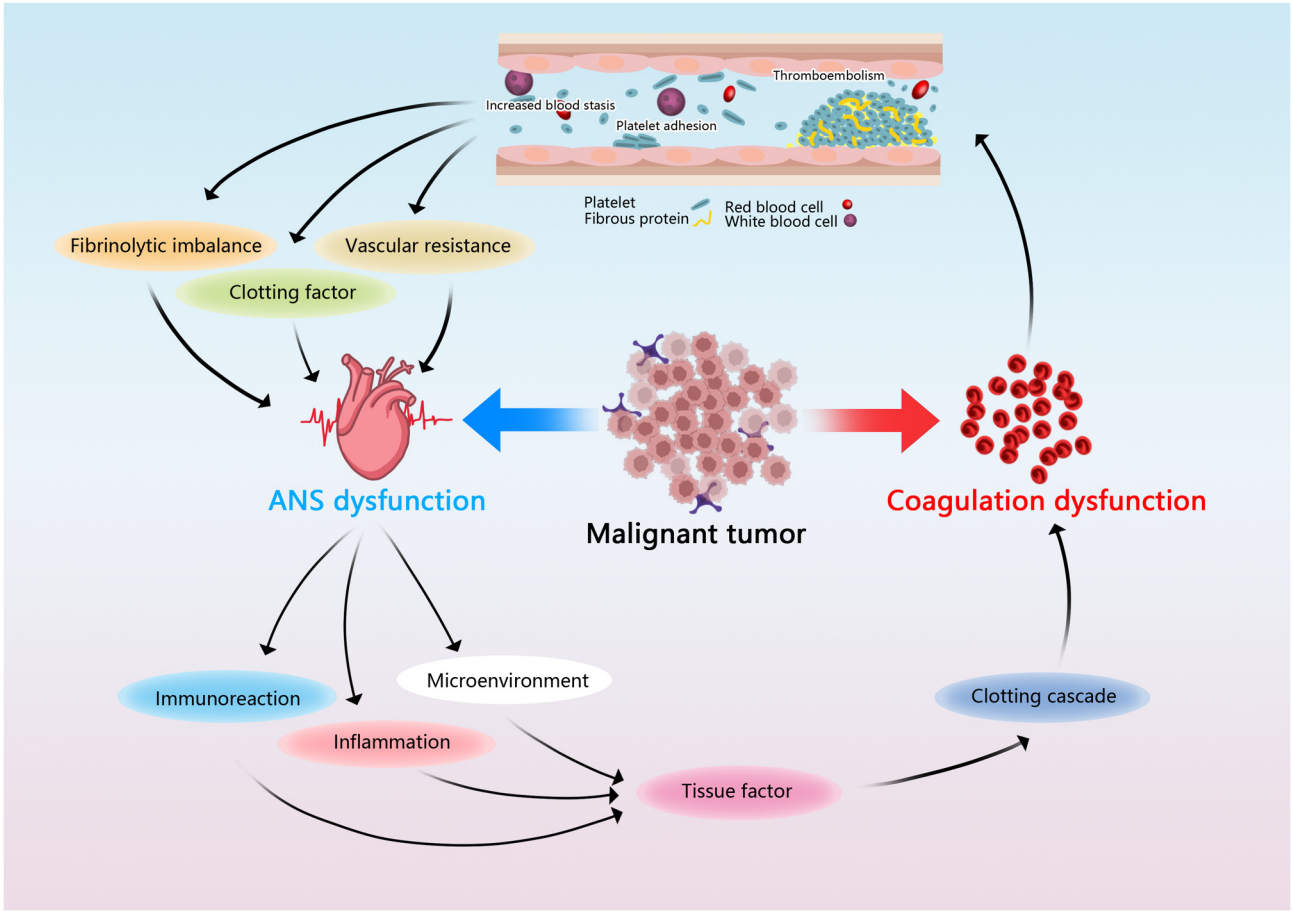

Figure 2. Pathophysiological changes in malignant tumors can disturb ANS function as well as coagulation function. ANS dysfunction caused by malignant tumors can lead to changes in immune reactions, inflammation and the tumor microenvironment, which may increase the release of some procoagulant factors, such as tissue factor. Tissue factor can influence the clotting cascade by regulating a variety of thrombin and clotting factors, which alters the clotting state of the body. In addition, coagulation dysfunction can trigger increased blood stasis, platelet adhesion and thromboembolism. These changes in physiological functions can cause increased vascular resistance, activation of coagulation factors and imbalance of the fibrinolytic system, resulting in ANS dysfunction. ANS, autonomic nervous system.

and analysis were performed by WZG, YFZ and YLW. The first draft of the manuscript was written by YQW and all authors commented on previous versions of the manuscript. YFZ and YLW confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethical approval and consent to participate

This study was approved by the Institutional Review Committee of the First Affiliated Hospital of Bengbu Medical College (No. 2021KY010) and was conducted in strict accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all individual participants included in the study.

Patient consent for publication

Not applicable.

Competing interests

A direct family member of BS owns stock in HeaLink Ltd. The other authors declare that they have no competing interests.

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