World Journal of Gastrointestinal Oncology

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World J Gastrointest Oncol 2024 May 15; 16(5): 1787-1795

DOI: 10.4251/wjgo.v16.i5.1787

ISSN 1948-5204 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Prognostic relevance of ventricular arrhythmias in surgical patients with gastrointestinal tumors

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Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Sahin TT, Türkiye

Received: January 14, 2024
Peer-review started: January 14, 2024
First decision: January 30, 2024
Revised: February 19, 2024
Accepted: March 26, 2024
Article in press: March 26, 2024
Published online: May 15, 2024

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Abstract

BACKGROUND

Individuals diagnosed with gastrointestinal tumors are at an increased risk of developing cardiovascular diseases. Among which, ventricular arrhythmia is a prevalent clinical concern. This suggests that ventricular arrhythmias may have predictive value in the prognosis of patients with gastrointestinal tumors.

AIM

To explore the prognostic value of ventricular arrhythmias in patients with gastrointestinal tumors receiving surgery.

METHODS

We retrospectively analyzed data from 130 patients undergoing gastrointestinal tumor resection. These patients were evaluated by a 24-h ambulatory electrocardiogram (ECG) at the Sixth Affiliated Hospital of Sun Yat-sen University from January 2018 to June 2020. Additionally, 41 general healthy age-matched and sex-matched controls were included. Patients were categorized into survival and non-survival groups. The primary endpoint was all-cause mortality, and secondary endpoints included major adverse cardiovascular events (MACEs).

RESULTS

Colorectal tumors comprised 90% of cases. Preoperative ambulatory ECG monitoring revealed that among the 130 patients with gastrointestinal tumors, 100 (76.92%) exhibited varying degrees of premature ventricular contractions (PVCs). Ten patients (7.69%) manifested non-sustained ventricular tachycardia (NSVT). The patients with gastrointestinal tumors exhibited higher PVCs compared to the healthy controls on both conventional ECG [27 (21.3) *vs* 1 (2.5), $P = 0.012$] and 24-h ambulatory ECG [14 (1.0, 405) *vs* 1 (0, 6.5), $P < 0.001$]. Non-survivors had a higher PVC count than survivors [150.50 (7.25, 1690.50) *vs* 9 (0, 229.25), $P = 0.020$]. During the follow-up period, 24 patients died and 11 patients experienced MACEs. Univariate analysis linked PVC > 35/24 h to all-cause mortality, and NSVT was associated with MACE. However, neither PVC burden nor NSVT independently predicted outcomes according to multivariate analysis.

CONCLUSION

Patients with gastrointestinal tumors exhibited elevated PVCs. PVCs > 35/24 h and NSVT detected by 24-h ambulatory ECG were prognostically significant but were not found to be independent predictors.

Key Words: Ventricular arrhythmia; Gastrointestinal tumor; Major adverse cardiovascular events; Prognostic; Surgery

Core Tip: We retrospectively analyzed data from 130 patients undergoing gastrointestinal tumor resection who were evaluated by a 24-h ambulatory electrocardiogram to determine the prognostic value of ventricular arrhythmias in these types of patients. Additionally, 41 age-matched and sex-matched general healthy controls were evaluated. In a long-term follow-up, we found that patients with gastrointestinal tumors exhibited elevated premature ventricular contractions. Premature ventricular contractions > 35/24 h and non-sustained ventricular tachycardia were prognostically significant but were not found to be independent predictors.

Citation: Xue JJ, Hu ST, Wang CC, Chen ZC, Cheng SY, Yu SQ, Peng HJ, Zhang YT, Zeng WJ. Prognostic relevance of ventricular arrhythmias in surgical patients with gastrointestinal tumors. *World J Gastrointest Oncol* 2024; 16(5): 1787-1795
URL: https://www.wjgnet.com/1948-5204/full/v16/i5/1787.htm
DOI: https://dx.doi.org/10.4251/wjgo.v16.i5.1787

INTRODUCTION

Gastrointestinal tumors are a major global health concern[1], posing a significant threat to human life. Currently, surgery is the preferred treatment option for complete tumor removal[2]. However, patients undergoing surgical removal of gastrointestinal tumors often face critical and at times fatal challenges due to the occurrence of cardiovascular events[3,4]. An underlying link between cardiovascular disease and gastrointestinal tumors has been proposed. Cardiovascular risk factors are associated with an increased risk of colorectal cancer[5,6], and patients with colorectal cancer face a higher risk of cardiovascular death, especially within the 1st year after diagnosis[7]. Moreover, various anticancer treatments, including anthracyclines, trastuzumab, and cyclophosphamide, can induce cardiotoxicity in up to half of cancer patients. Even in cancer patients not subjected to chemotherapy, there is a risk of cardiovascular function deterioration[8]. Therefore, it is essential to identify patients with gastrointestinal tumor at risk of cardiovascular issues before, during, and after treatment to implement preventive measures effectively.

Ventricular arrhythmia, a common disorder with an estimated prevalence ranging from 1%-4% by routine electrocardiogram (ECG), is a significant clinical concern[9]. Ambulatory ECG reveals an even higher prevalence, with as many as 40%-75% of patients exhibiting premature ventricular contractions (PVCs)[10,11]. However, the prognostic significance of PVCs remains unclear. While PVCs are known to increase the risk of mortality and cardiovascular events in patients with structural heart disease or apparent heart disease[12-17], one study suggested that there was no direct correlation between higher PVC counts and increased mortality, particularly in patients with structural heart disease[18]. The question of whether ventricular arrhythmias have prognostic value for patients with gastrointestinal tumors has drawn clinical attention. Studies have shown that non-sustained ventricular tachycardia (NSVT) ≥ 4 heartbeats and PVCs ≥ 20/24 h measured by 24-h ambulatory ECG have prognostic value for cancer patients. NSVT and PVC burdens are crucial predictors of mortality, independent of other prognostic factors[19].

Unfortunately, these studies are limited by small sample sizes of patients with colorectal cancer and the exclusion of important indicators like cardiac troponin I (cTnI), which is an independent risk factor for patients with gastrointestinal tumors[20]. Additionally, UCG parameters were not included in the multivariate analyses of these studies, and there was a lack of major adverse cardiovascular events (MACEs) analysis. Moreover, the heterogeneous etiology might lead to inconsistent results. For example, cTnI demonstrated significant predictive value in patients with colorectal cancer patients, but its effectiveness was limited to patients undergoing orthopedic surgery or patients with head and neck squamous cell carcinoma[21,22]. Therefore, further research must evaluate the prognostic impact of ventricular

arrhythmia in patients with specific etiologies, such as gastrointestinal tumors. The present study explored the prognostic value of ventricular arrhythmias in patients with gastrointestinal tumors through 24-h ambulatory ECG monitoring.

MATERIALS AND METHODS

Study population and endpoints

The study was a single-center retrospective cohort study. We included patients with gastrointestinal tumors scheduled for surgery between January 2018 and June 2020. The inclusion criteria were major abdominal surgery under general anesthesia, an age of 18 years or older, high-sensitivity cTnI (hs-cTnI) testing at least 7 d prior to surgery, and preoperative ambulatory ECG examination. Exclusion criteria included emergent surgery, failure to perform surgery, or clinical evidence of unstable coronary artery disease (cardiac chest pain with or without ischemic ECG changes) according to the medical records at the preoperative evaluation. Patients with left ventricular ejection fractions < 45% were also excluded.

In total, 130 patients were included in our study to further analyze the prognostic value of ventricular arrhythmias in patients undergoing gastrointestinal tumor resection. Additionally, we included 41 age-matched and sex-matched general healthy controls from the same period. The control group was free of significant cardiovascular events and cancer, except for well-controlled hypertension. The study was approved by the local ethics committee of the Sixth Affiliated Hospital of Sun Yat-sen University. The study methods were compliant with the STROBE checklist.

The primary endpoint of the study was all-cause mortality during the follow-up period. Secondary combined endpoints included MACEs, such as myocardial infarction, congestive heart failure, sudden cardiac death, ischemic stroke, and other related outcomes.

Study definitions

The diagnosis of myocardial infarction was made according to the universal definition of myocardial infarction[23]. A history of coronary artery disease was defined as prior bypass surgery, coronary intervention, myocardial infarction, or compliance with the guideline definition[24]. The Lee index (revised cardiac index) was calculated as described previously[25]. Briefly, one point was assigned to each of the following factors: Coronary artery disease history; a history of cerebrovascular disease, heart failure, insulin-dependent diabetes mellitus, impaired renal function; and a high-risk surgery[25]. Staging was performed according to the tumor, node, and metastasis (TNM) staging system developed by the 8th edition of the American Joint Committee on Cancer Staging Manual. In our study, TNM stage III or higher was defined as advanced disease. PVC referred to a ventricular beat produced in advance by ectopic pacemakers below the atrioventricular node. NSVT was defined as runs of beats arising from the ventricles with a duration between 3 beats and 30 s and with a cycle length of < 600 ms (> 100 beats per minute).

Data collection

Clinical, laboratory, ECG parameters, medication, and surgery were collected from medical records during the initial assessment. Follow-up data were obtained through telephone interviews with patients and a review of their records. Hs-cTnI was measured by a high-sensitivity electrochemiluminescence immunoassay on an automatic analyzer (Architect i1000SR; Abbott Core Laboratory Systems, Lake Forest, IL, United States). UCG images were obtained following the guidelines outlined by the American Society of Echocardiography[26] and were stored using a digital ultrasound system (Vivid E9; GE HealthCare, Chicago, IL, United States). The ambulatory ECG recording was obtained using a portable Holter machine and conducted for 24 h by professional technicians.

Statistical analysis

Continuous variables were compared using the independent *t*-test or nonparametric test (Mann-Whitney *U*) and expressed as mean ± SD or median (25%, 75%) as appropriate. Categorical variables were compared using the χ^2 test or Fisher's exact test where appropriate and reported as frequencies (percentage). The optimal cutoff value for the PVCs was determined using the receiver operating characteristic curve. Survival curves were constructed using the Kaplan-Meier method and compared using the log-rank test. Postoperative long-term survival was calculated from the date of discharge after the initial tumor resection until the time of death or MACE. Patients who did not reach the endpoints during the follow-up period were censored on November 1, 2021 or the date of loss to follow-up.

To identify independent predictors of all-cause death and MACE in the population, Cox multivariate regression analysis was conducted. The multivariate model was constructed using forward stepwise selection, with candidate variables included if they met the entry criterion of $P < 0.05$ in the univariate analysis. Hazard ratios and 95% confidence intervals were estimated using Cox regression models. Statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., Armonk, NY, United States), and significance was set at $P < 0.05$. The study was reviewed by our expert biostatistician, Li-Shuo Shi, MD.

RESULTS

Study population

Our study included 130 patients with gastrointestinal tumors and 41 controls. The study flow diagram is shown in Figure 1. The baseline characteristics of all patients are shown in Supplementary Table 1. Among these patients, 117 primary tumors (90.0%) were in the colorectal region, 12 tumors (9.2%) in the stomach, and 1 tumor (0.8%) in the small intestine. Advanced TNM stages were present in 57 patients (43.8%). Preoperative ambulatory ECG monitoring revealed that 100 patients (76.9%) exhibited varying degrees of PVCs, while 10 patients (7.7%) exhibited NSVT. Patients with gastrointestinal tumors exhibited higher PVCs compared to the control group in both conventional and 24-h ambulatory ECG recordings. The incidence of NSVT did not significantly differ between patients with gastrointestinal tumors and the controls.

A comparison between survivors and non-survivors indicated that non-survivors were characterized by advanced age and elevated levels of hs-cTnI. Additionally, non-survivors demonstrated a thicker interventricular septum and left ventricular posterior wall. Non-survivors exhibited a Lee index > 2, a higher tumor burden, and higher PVC counts compared to survivors [150.50 (7.25, 1690.50) *vs* 9.0 (0, 229.25), respectively, $P = 0.020$]. Furthermore, non-survivors had lower diastolic blood pressure, reduced hemoglobin levels, and lower levels of low-density lipoprotein cholesterol. There were no significant differences in comorbidities and medication history between the survivor and non-survivor groups.

Over a median follow-up period of 36 mo, 24 patients died, with 7 deaths attributed to cardiovascular events, 13 to tumor-related causes, and 4 to other causes such as infections. Additionally, 11 patients with gastrointestinal tumors experienced MACE, including 2 cases of myocardial infarction, 2 cases of heart failure, 4 cases of sudden cardiac death, 1 case of ischemic stroke, and 2 cases due to other reasons.

Receiver operating characteristic analysis identified a PVC count of 35 as the optimal cutoff value for predicting all-cause mortality. The sensitivity and specificity of a PVC count of 35/24 h were 66.7% and 61.3%, respectively. The area under the curve (c-statistics) for the PVC count was 0.651 (95% confidence interval: 0.530-0.771, $P = 0.022$) (Figure 2A). However, when predicting MACE, there was no significant difference in PVC counts ($P = 0.454$) (Figure 2B).

Patients with PVC counts > 35/24 h had a significantly higher mortality rate ($P = 0.012$) (Figure 3A). However, no significant differences were detected in the occurrence of MACE between patients with PVC counts ≤ 35/24 h and those with higher PVC burdens ($P = 0.527$) (Figure 3B).

Notably, the presence of NSVT was associated with an increased risk of MACE compared to patients without NSVT during follow-up ($P = 0.005$) (Figure 3C). However, no significant differences were detected in the occurrence of all-cause death between these two groups ($P = 0.239$) (Figure 3D).

Survival analyses

Univariate analysis identified significant associations between mortality and various factors, including age, diastolic blood pressure, TnI levels, hemoglobin count, carcinoembryonic antigen levels, carbohydrate antigen 125 levels, low-density lipoprotein cholesterol levels, more advanced tumor stage, history of radical operation, Lee score ≥ 2, increased left ventricular posterior wall thickness, and PVC > 35/24 h (Table 1). Similarly, age, creatinine levels, TnI levels, and the incidence of NSVT were significantly associated with the occurrence of MACE (Table 2). However, in the multivariate Cox regression analyses, neither high PVC burdens nor the presence of NSVT emerged as independent predictors for all-cause death or the occurrence of MACE.

DISCUSSION

Our study found that patients with gastrointestinal tumors have a higher burden of PVCs than healthy controls. Patients exhibiting PVCs exceeding 35 per 24 h by 24-h ambulatory ECG were at a higher risk of all-cause mortality. Additionally, patients with the presence of NSVT had an increased risk of MACE. Nevertheless, neither high PVC burdens nor the presence of NSVT emerged as independent predictors for all-cause death or the occurrence of MACE.

Our findings underscored that the incidence of PVCs in patients with gastrointestinal tumors surpassed that in the healthy population. These results were consistent with the findings reported by Anker *et al*[19]. The underlying mechanisms contributing to arrhythmias in patients with tumors are intricate and diverse, involving factors such as electrolyte imbalances, inflammatory reactions, autonomic nervous system dysregulation, cachexia, and the cardiotoxic effects of anticancer treatments[27-33]. Our findings highlight the significance and rationale for dynamic monitoring in patients with gastrointestinal tumors.

Notably, our study observed that patients with gastrointestinal tumors with PVC > 35/24 h demonstrated a higher risk for all-cause mortality. A prospective study conducted by Anker *et al*[19], involving patients with non-small lung, colon, and pancreatic cancers, demonstrated a significant rise in overall mortality among individuals experiencing PVCs at a frequency of ≥ 50 per day. Likewise, Albrecht *et al*[34] observed that PVCs ≥ 20 per day were indicative of a poor prognosis in cancer patients. Our findings align with these prior studies. However, it is crucial to note the variation in PVC cutoff values across these studies. When interpreting PVC burden, daily fluctuations are a vital consideration. Mullis *et al*[35] discovered that in a 14-d study involving 59 patients the median of absolute changes in PVC/24 h was 9.9% (interquartile range: 5.4%-14.5%). Remarkably, 72.9% of patients experienced shifts across at least two categories of PVC burdens based on the 24-h period under consideration.

Table 1 Risk factors for all-cause mortality among patients with gastrointestinal tumors

Risk factors	Univariable Cox regression		Multivariable Cox regression	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age as per 1 yr increase	1.088 (1.039-1.140)	< 0.001	1.067 (1.015-1.121)	0.011
Diastolic blood pressure as per 1 mmHg increase	0.954 (0.917-0.993)	0.020	0.935 (0.887-0.985)	0.011
Hemoglobin as per 1 g/L increase	0.980 (0.965-0.995)	0.011		
Troponin I > 0.028 as per 1 μg/L increase	6.377 (2.841-14.311)	0.001	6.576 (2.586-16.727)	< 0.001
Carcinoembryonic antigen as per 1 ng/mL increase	1.009 (1.005-1.013)	< 0.001	1.009 (1.004-1.015)	< 0.001
Carbohydrate antigen 125 as per 1 ng/mL increase	1.015 (1.004-1.026)	0.008		
LVPW as per 1 mm increase	1.375 (1.112-1.701)	0.003		
LDL-C as per 1 mmol/L increase	0.570 (0.328-0.989)	0.046		
Tumor stage, TNM 3-4 *vs* 1-2	3.211 (1.329-7.762)	0.010		
Radical operation history as yes *vs* no	0.295 (0.100-0.868)	0.027		
Lee score ≥ 2 as yes *vs* no	6.201 (1.424-27.003)	0.015		
Premature ventricular contractions > 35 as yes *vs* no	2.764 (1.181-6.468)	0.019		
NSVT as yes *vs* no	1.836 (0.547-6.163)	0.326		

CI: Confidence interval; HR: Hazard ratio; LDL-C: Low density lipoprotein cholesterol; LVPW: Left ventricular posterior wall; NSVT: Non-sustained ventricular tachycardia; TNM: Tumor, node, metastasis.

Table 2 Risk factors for major adverse cardiovascular events among patients with gastrointestinal tumors

Risk factors	Univariable Cox regression		Multivariable Cox regression	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age as per 1 yr increase	1.161 (1.066-1.264)	0.001	1.150 (1.058-1.251)	0.001
Creatinine as per 1 μmol/L increase	1.021 (1.006-1.036)	0.006		
Troponin I > 0.028 as yes *vs* no	4.981 (1.445-17.167)	0.011	4.208 (1.098-16.127)	0.036
Premature ventricular contractions > 35 as yes *vs* no	1.222 (0.372-4.010)	0.741		
NSVT as yes *vs* no	4.775 (1.266-18.013)	0.021		

CI: Confidence interval; HR: Hazard ratio; NSVT: Non-sustained ventricular tachycardia.

Our study demonstrated that PVC burden was not an independent risk factor for all-cause mortality. However, a meta-analysis conducted by Ataklte *et al*[36] demonstrated a significant association between frequent PVCs in apparently healthy individuals and an elevated risk of all-cause death and cardiac-related mortality. Our study results deviate from those observed in previous studies focused on populations with cancer[19,34]. The inconsistency may be attributed to etiological heterogeneity. Anker *et al*[19] highlighted the differential prognostic impact of PVC burdens, emphasizing its greater significance in colorectal and pancreatic cancer patients compared to those with non-small cell lung cancer. Consequently, these results cannot be directly extrapolated to patients with gastrointestinal tumors.

Our study exclusively focused on patients with gastrointestinal tumors, avoiding the potential confounding effects introduced by disease heterogeneity present in previous studies. Additionally, our study had the advantage of including more measures that could affect prognosis compared with previous studies. We confirmed that hs-cTnI is an independent prognostic factor in colorectal cancer[37]. Previous research indicates that patients with colorectal tumors may experience impaired cardiac function[8], and elevated cTnI levels are closely associated with impaired cardiac function[38]. Our results suggest that in the prognostic assessment of patients with gastrointestinal tumors cTnI has more advantages compared to PVC measurements.

Interestingly, we found that NSVT rather than a PVC burden was associated with an increased risk of MACE in patients with gastrointestinal tumors. This aligns with prior research indicating that the presence of NSVT is associated with an increased likelihood of cardiovascular events, encompassing outcomes like cardiovascular mortality, acute myocardial infarction, coronary revascularization, or stroke, particularly in individuals lacking apparent or manifest structural heart disease[39]. Our research expands on this foundation, underscoring the significance of vigilant NSVT

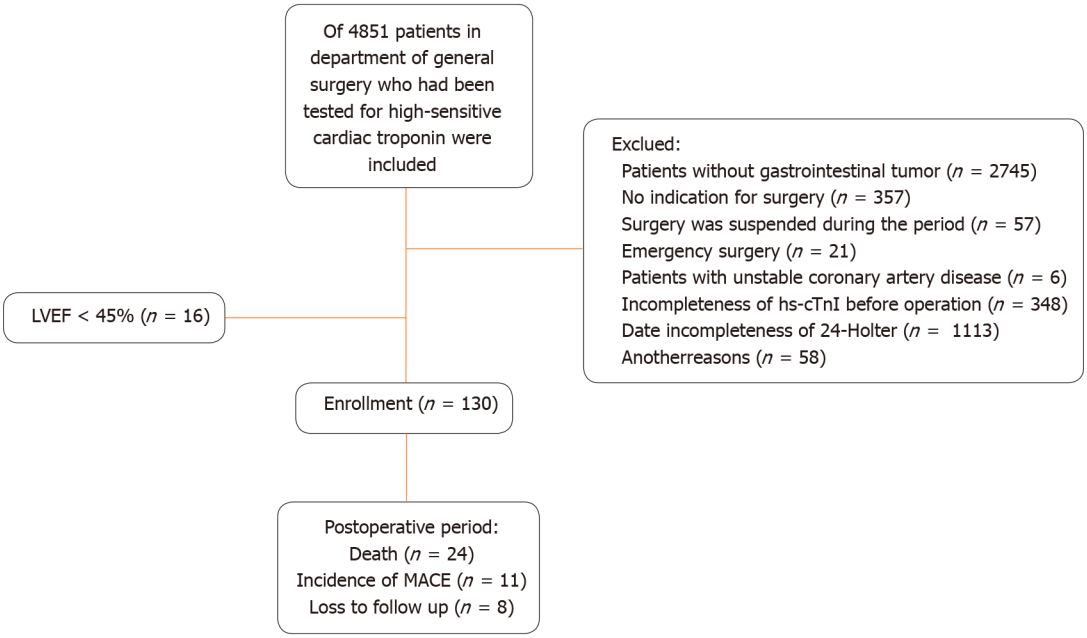

Figure 1 Study flow, including patient enrollment and outcomes. hs-cTnI: High-sensitivity cardiac troponin I; LVEF: Left ventricular ejection fraction; MACE: Major adverse cardiovascular event.

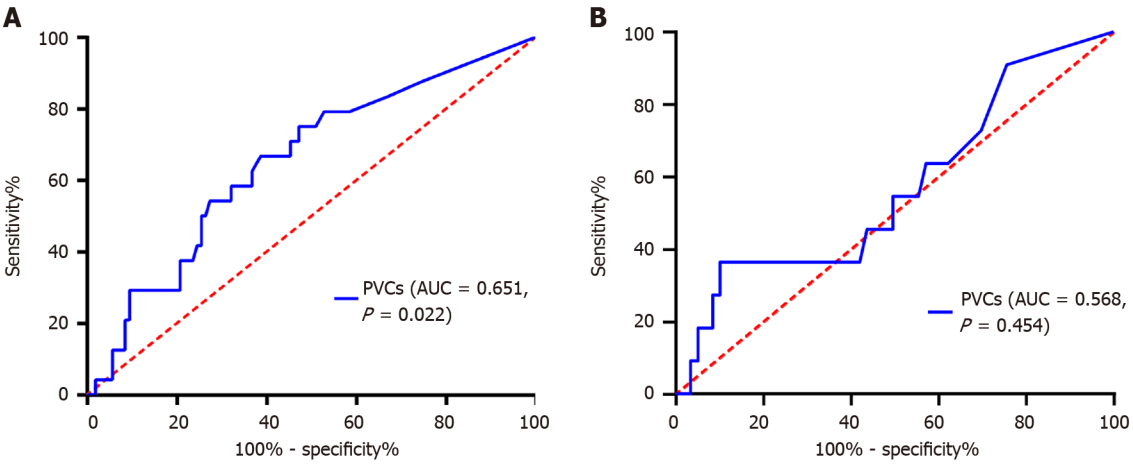

Figure 2 Receiver operating characteristic curves of premature ventricular contractions for combined endpoints. A: Receiver operating characteristic curve of premature ventricular contractions (PVCs) for all-cause mortality among patients with gastrointestinal tumors; B: Receiver operating characteristic curve of PVCs for major adverse cardiovascular events among patients with gastrointestinal tumors. PVC: Premature ventricular contraction; AUC: Area under the curve.

monitoring specifically in patients with tumors.

Nevertheless, it is crucial to acknowledge the limitations of our study. This research is a single-center retrospective study. Despite having the largest sample size for evaluating the prognostic significance of ventricular arrhythmias in patients with gastrointestinal tumors, a prospective, multicenter study is essential to gain more comprehensive insights. This approach will provide a broader perspective and enhance the robustness of our findings.

CONCLUSION

Our study found that patients with gastrointestinal tumors had a higher burden of PVC than healthy controls. The presence of PVC > 35/24 h and NSVT observed hold prognostic significance. However, they are not independent predictors, indicating the complexity of factors influencing postoperative outcomes in this patient population.

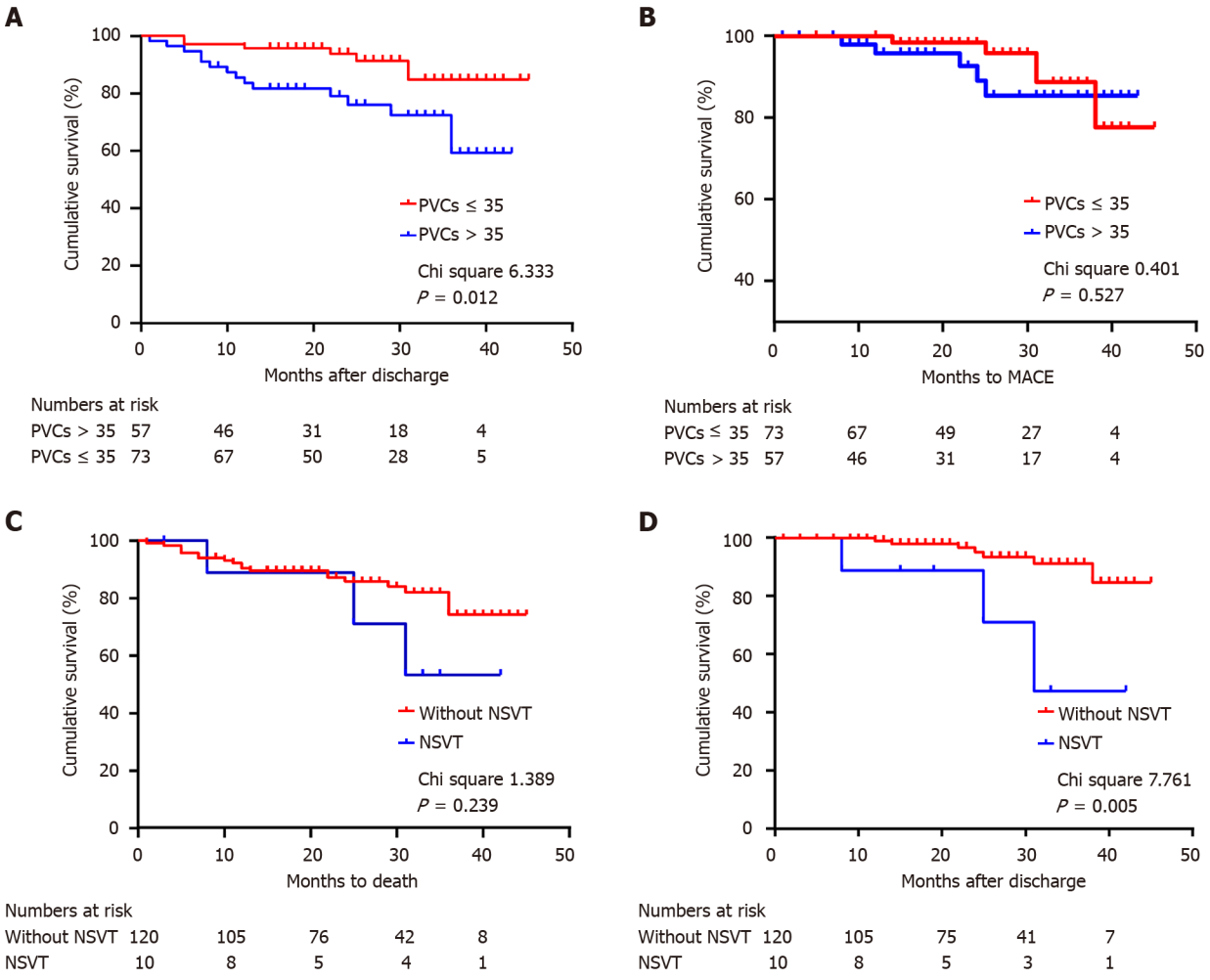

Figure 3 Cumulative survival of all patients. A: Cumulative survival of all-cause mortality among patients with gastrointestinal tumors divided by premature ventricular contractions (PVCs) (*n* = 130); B: Cumulative survival of major adverse cardiovascular events (MACEs) among patients with gastrointestinal tumors divided by PVCs (*n* = 130); C: Cumulative survival of all-cause mortality among patients with gastrointestinal tumors divided by non-sustained ventricular tachycardia (*n* = 130); D: Cumulative survival of MACEs among patients with gastrointestinal tumors divided by non-sustained ventricular tachycardia (*n* = 130). PVC: Premature ventricular contraction; MACE: Major adverse cardiovascular event; NSVT: Non-sustained ventricular tachycardia.

FOOTNOTES

Co-first authors: Jiao-Jie Xue and Su-Tian Hu.

Co-corresponding authors: Yi-Tao Zhang and Wei-Jie Zeng.

Author contributions: Xue JJ made contributions to study design, data collection and data analyses. Hu ST contributed to the draft of the manuscript. They are the co-first authors of this article. Zeng WJ made contributions to study design, data collection and data analyses. Zhang YT helped critically revise the manuscript for intellectual content. They are the co-corresponding authors of this article. Xue JJ and Zeng WJ made contributions to study design, data collection, and data analyses; Hu ST and Wang CC contributed to the draft of the manuscript; Chen ZC, Cheng SY, Yu SQ, and Peng HJ were responsible for data collection and creation of the tables and figures presented in the manuscript; Zhang YT and Zeng WJ helped critically revise the manuscript for intellectual content; and all authors read and approved the final manuscript.

Supported by the Sixth Affiliated Hospital of Sun Yat-sen University Clinical Research-1010 Program, No. 1010PY (2023)-06; the National Nature Science Foundation of China, No. 81400301; the Fundamental Research Funds for the Central Universities, No. 19ykpy10; and Guangzhou Health Science and Technology Project, No. 20231A010068.

Institutional review board statement: The study has been approved by the local ethics committee of the Sixth Affiliated Hospital of Sun Yat-sen University (Approval No. E2021140).

Informed consent statement: This is a retrospective cohort study. Patients were not required to give informed consent for the study, as the analysis used anonymized clinical data obtained after each patient had consented to treatment by means of written consent. Waiver informed consent had been obtained prior to conducting the study.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: The original anonymous dataset is available upon reasonable request from the corresponding author at zengweijie@mail.sysu.edu.cn.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Li X

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