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Clinical characteristics and prognostic factors of primary malignant cardiac tumors

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Primary malignant cardiac tumors (PMCTs) are rare but highly lethal, and up to 75% of them are sarcomas, followed by lymphoma and mesothelioma.[1] Due to the rarity of this disease, most studies to date were small series or single case report. Although a few of them investigated the clinical characteristics and survival of PMCT patients, the factors influencing overall survival have not been well elucidated.[2-4] The Surveillance, Epidemiology, and End Results (SEER) program covers about 28% of the US population, collecting data on patient demographics, primary tumor site, tumor morphology, stage at diagnosis, survival, and mortality, including rich data of cardiac tumors.[5] In the present study, we described the clinical characteristics, identified the variables affecting the prognosis, and constructed a nomogram for patients with PMCTs using the data from the SEER database.

We selected all patients from the SEER database who were diagnosed with PMCTs according to the international classification of diseases-0-3/World Health Organization 2008 (international classification of diseases-0-3 = 38.0) between 1975 and 2016. The following exclusion criteria were applied: diagnosis not proven by histology, diagnosis by autopsy or death certificate only, not the primary malignant tumor, incomplete or missing staging and primary site surgery data. Demographic features and clinicopathological characteristics of patients were collected using the following variables: patient identification, age at diagnosis, race/ethnicity, histology, marital status at diagnosis (unmarried status is defined as a single, divorced, and widowed), stage (local, regional, and distant), surgery, radiation therapy, chemotherapy, vital status, and survival (months).

Clinicopathological factors were compared between different histological types using Pearson χ^2 test. Overall survival was estimated using Kaplan-Meier curves. Cox regression was used to identify the factors of PMCTs. A forward stepwise approach (Likelihood Ratio test) was used with variables entered into the multivariable model. Statistical analysis was performed using SPSS 25.0 (IBM Corporation, Armonk, NY, USA) and a nomogram was created using R 4.0.0 (R Foundation for Statistical Computing, Austria) software packages. All reported P values were two-tailed and P value < 0.05 was considered significant.

From 1975 to 2016, a total of 10,450,709 cancer cases were recorded in the SEER database, and 826 patients were diagnosed with PMCTs among them. Finally, 411 patients with PMCTs were selected for analysis [Supplementary Figure 1, http://links.lww.com/CM9/A657]. Among the 411 patients, 219 (53.3%) were female and 192 (46.7%) were male, with a median age of 50 years old. The majority of the patients were white (75.2%). A total of 241 (58.6%) and 229 (55.7%) patients received surgery and chemotherapy, respectively. Only 82 (20%) patients received radiotherapy. There were 322 cases (78.3%) of primary cardiac sarcomas (PCSs), 74 cases (18.0%) of primary cardiac lymphomas (PCLs), and 15 cases (3.6%) with other histological types. Patients with PCSs were more likely to be young ($P < 0.01$) and have a later stage at presentation (regional or distant) (70.8% [228/322] *vs.* 59.4% [44/74], $P < 0.01$) than those with PCLs. In addition, more patients with PCSs received surgery (67.1% [216/322] *vs.* 25.7% [19/74], $P < 0.01$), while chemotherapy was administered more often in PCLs (77.0% [57/74] *vs.* 52.2% [168/322]). Radiation was not the preferred therapeutic regimen in either of the two groups (18.9% [14/74] and 21.1% [68/322], respectively, see Supplementary Table 1, http://links.lww.com/CM9/A660). The median overall survival time of PMCTs was 11 months (95% confidence interval [CI], 8.5–

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Table 1: Univariable and multivariable analyses of factors affecting the overall survival of patients with PCSs and PCLs.

	PCSs				PCLs			
	Univariable analysis		Multivariable analysis		Univariable analysis		Multivariable analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Race		0.31						
White	1.15 (0.88–1.52)	0.31			1.65 (0.80–3.44)	0.16		
Others	Ref				Ref			
Marital status		0.59				0.57		
Yes	1.07 (0.84–1.35)	0.59			0.84 (0.47–1.52)	0.57		
No	Ref				Ref			
Age (years)		<0.01		<0.01		0.02		
≤44	0.38 (0.23–0.61)	<0.01	0.39 (0.23–0.64)	<0.01	0.24 (0.07–0.81)	0.02		
45–59	0.57 (0.35–0.92)	0.02	0.53 (0.32–0.87)	0.01	0.33 (0.15–0.73)	<0.01		
60–74	0.60 (0.35–1.00)	<0.05	0.62 (0.37–1.04)	0.07	0.52 (0.26–1.06)	0.07		
≥75	Ref		Ref		Ref			
Sex		0.72				0.98		
Female	0.96 (0.76–1.21)	0.72			1.01 (0.55–1.84)	0.98		
Male	Ref				Ref			
Stage		<0.01		<0.01		0.50		
Local	0.43 (0.32–0.59)	<0.01	0.39 (0.27–0.56)	<0.01	1.25 (0.63–2.47)	0.52		
Regional	0.67 (0.50–0.89)		0.63 (0.47–0.86)	<0.01	0.81 (0.36–1.82)	0.60		
Distant	Ref		Ref		Ref			
Surgery		<0.01				0.82		
Yes	0.49 (0.38–0.63)	<0.01	0.52 (0.39–0.70)	<0.01	0.93 (0.47–1.82)	0.82		
No	Ref		Ref		Ref			
Radiation		0.68				0.56		
Yes	0.94 (0.71–1.25)	0.68			0.80 (0.37–1.72)	0.56		
No	Ref				Ref			
Chemotherapy		<0.01				<0.01		<0.01
Yes	0.71 (0.56–0.90)	<0.01	0.52 (0.39–0.69)	<0.01	0.29 (0.15–0.56)	<0.01	0.29 (0.15–0.56)	<0.01
No	Ref		Ref		Ref		Ref	

CI: Confidence interval; HR: Hazard ratio; PCLs: Primary cardiac lymphomas; PCSs: Primary cardiac sarcomas.

13.5 months). In the PCLs group, the median survival was 38 months (95% CI, 15.1–60.9 months), compared to only 11 months (95% CI, 8.8–13.2 months) in the PCSs group ($P < 0.01$, see Supplementary Figure 2, http://links.lww.com/CM9/A658).

Prognostic variables which potentially influenced the overall survival were analyzed using the Cox proportional hazards model. Race, marital status, age, sex, stage, surgery, radiation, and chemotherapy were included [Table 1]. For patients with PCSs, the univariable Cox analysis indicated that younger age ($P < 0.01$), early-stage ($P < 0.01$), surgical resection ($P < 0.01$), and chemotherapy ($P < 0.01$) were the prognostic factors associated with prolonged overall survival. Although the *P* value of radiation is >0.05, considering that is an important way of anti-cancer therapy, we also included it in the multivariable analysis. In the multivariable Cox regression analysis, age, stage, surgery, and chemotherapy were the independent prognostic factors for overall survival. Among different treatment methods, surgery and chemotherapy were independent protective factors that decreased the risk of death all by 48%. For patients with PCLs, in univariable Cox analysis, race, marital status, sex, stage, surgery, and radiation were not identified as prognostic factors. Also considering the clinical potential benefits of radiotherapy and surgery, we took age, chemotherapy, and these two variables into multivariable Cox regression analysis, which indicated that only chemotherapy was an independent protective factor, decreasing the risk of death by 71% (hazard ratio = 0.29, 95% CI, 0.15–0.56).

A nomogram was constructed based on the identified independent risk factors [Supplementary Figure 3, http://links.lww.com/CM9/A659], including age, stage, surgery, and chemotherapy, to predict the 6-month and 1-year overall survival probability of PCS patients. The results indicated that age had the highest effect on prognosis, followed by stage, surgery, and chemotherapy. The concordance index (C-index) of the nomogram was 0.71. Validation of the nomogram was performed using 1000 bootstrap iterations, which gave a C-index of 0.70. The calibration curve and concordance for the nomogram were also illustrated.

PMCTs had an overall poor prognosis across all histopathology types, with median overall survival of only 11 months. Moreover, the prognosis of PCSs was worse than that of PCLs, which may be due to the pathological type and high malignancy of PCSs. According to the Cox model, age, stage, surgical resection, and chemotherapy were four independent factors that affect

the overall survival of PCSs. However, only chemotherapy was found to prolong the survival of PCLs. In our study, radiotherapy did not provide good results in terms of survival rate for PMCTs and neither surgery nor radiation did affect the prognosis of the patients with PCLs, which may be because the neoplasm often involves a large area of the myocardium, leading to radiation field not fully covered, or it may have systemic diffusion.

Another unique aspect of our study is that we constructed a nomogram with four variables of age, stage, surgical resection, and chemotherapy, to predict the probability of 6-month and 1-year survival of PCS patients. It had a C-index of 0.71 in the development cohort and 0.70 in the bootstrap validations, and the calibration curves also performed well. Therefore, we conclude that this nomogram model might facilitate clinical situations by providing a friendly tool that may be useful for PMCT patients' counseling, follow-up scheduling, and visualizing the associations between each predictor variable and survival.

We acknowledge that this study has several limitations. First, this is a retrospective study that is open to selection bias. For example, those diagnosed pre-mortem and not receiving chemotherapy or surgery likely had shorter survival times. Second, the database utilized in this study does not provide all characteristics like tumor size, location, etc that may impact survival and treatment decisions. Finally, more data are needed for external validation to improve the credibility and demonstrate the universality of this nomogram.

In conclusion, PMCTs are rare malignancies with poor prognosis, especially PCSs. Patient age, tumor stage, surgery, and chemotherapy are independently associated with the prognosis of PCSs, and our nomogram can efficiently predict the outcomes.

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Conflicts of interest

None.

Author contributions

Qiu Jiaojiao and Sun Yun analyzed and interpreted the data of the patient.

Wang Shuxia and Dong Jing collected the data of the patient. Zhu Ping was major contributor in writing the manuscript. All authors read and approved the final manuscript.

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