Original Article



# Development and validation of a nomogram prediction model for early mortality in patients with primary malignant cardiac tumors

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**Background:** Primary malignant cardiac tumors (PMCTs) are correlated with an unfavourable prognosis. The aim of the current study was to establish and validate a nomogram model for 3-month mortality prediction for patients with PMCT.

**Methods:** A total of 638 PMCT patients diagnosed between 1975 to 2016 in the Surveillance, Epidemiology, and End Results (SEER) database were randomly enrolled and assigned into a training cohort (N=448) and validation cohort (N=190). Early mortality cases were analyzed, and related risk factors were identified by logistic regression models, and significant risk factors were used to establish a predictive nomogram model. The predictive capability of the model was validated by calibration analysis and receiver operating curve (ROC) in both training and validation cohorts.

**Results:** Multivariate logistic analysis revealed the independent risk factors for early mortality were old age, chemotherapy, surgery, and tumor stage, and these were used to construct the nomogram. In terms of calibration and discrimination, both the internal and external validation calibration curves revealed consistency between the nomogram prediction and the actual observation. The area under the curve (AUC) of the nomogram for 3-month mortality in the internal and external validation was 0.816 and 0.805, respectively.

**Conclusions:** Old age and advanced tumor stage are involved in higher odds of early mortality, while surgery and chemotherapy could reduce this. The nomogram model provides an accurate, user-friendly, and reproducible tool for predicting early mortality in PMCT patients.

**Keywords:** Nomogram; primary malignant cardiac tumor (PMCT); early mortality

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## Introduction

Although primary cardiac tumors (PCTs) are mainly benign, primary malignant cardiac tumors (PMCTs) account for 5.1–28.7% of PCTs (1). As PMCTs are rare, with an incidence of 34 to 46.6 cases per 100 million, the core knowledge about these tumors has been mostly based on single center studies, case reports, and small case series. Despite the continuous improvement in different treatment modalities, such as surgery, radiotherapy and chemotherapy, the prognosis of PMCT patients is still poor, with a 1-year survival rate of 46%, which is worse than extracardiac cancer of similar histopathology (2,3). In recent years, clinical researchers have paid more attention to PMCTs,

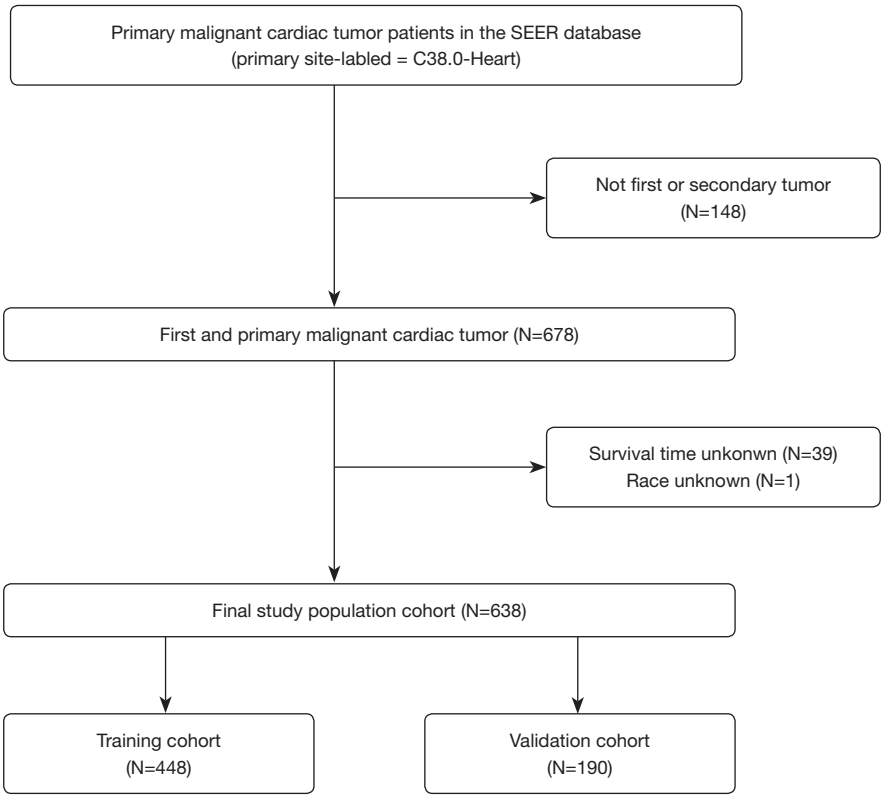


**Figure 1** Flow-chart for patient selection with PMCT. PMCT, primary malignant cardiac tumor.

and a predictive model was established to estimate 1- and 3-year survival rate using data from the SEER database (4). However, PMCT patients who died early after diagnosis have received little attention. The identification of PMCT patients with high risk of early mortality is conducive to early implementation of preventive interventions, supportive care, and individualized treatment to improve their life quality and survival rate.

Nomograms provide personalized disease-related risk predictions and estimate a specific endpoint via incorporating several variables (5,6). As graphical calculating devices, they provide better user friendliness, discriminatory degree, and predictive accuracy. Nomogram prediction models are helpful for clinical physicians to manage patients in different survival prediction and risk stratification (7,8), and have been successfully developed to estimate early mortality for many malignant tumors, such as gastric cancer, colorectal cancer, and glioma (9-11). However, to our knowledge, a nomogram model for predicting early mortality in PMCT patients has not been established and is worthy of further investigation.

Based on data from the SEER databases, the risk factors for early mortality for PMCT patients were old age, advanced tumor stages, and no surgical resection and non-chemotherapy. Based on the risk factors, we developed and validated an early mortality prediction nomogram model to assist physicians during the therapeutic decision-making process. We present the following article in accordance with the TRIPOD reporting checklist (available at https://dx.doi.org/10.21037/atm-21-5574).

## Methods

### *Patient selection*

We obtained data from the SEER database version Incidence-SEER 18 Regs Custom Data (with additional treatment fields), Nov 2018 Sub (1975–2016 varying). The SEER*Stat, 8.3.8, software program was applied to extract eligible patient information and the selection and exclusion criteria are shown in *Figure 1*. Finally, a total of 638 patients with a PMCT diagnosis between 1975 to 2016 were included. As public data from the SEER database which

did not include human subject use or personal identifying information was used, and ethics committee approval was not required. This study was complied with the Helsinki Declaration (as revised in 2013).

### *Parameters and definition of early mortality*

Patient demographic and clinical characteristics included age at diagnosis, gender, marital status, insurance state, tumor grade, tumor stage, tumor histopathology, surgery, radiotherapy, chemotherapy, and year of diagnosis. Age at diagnosis was classified (cut-off points 44 and 76) and year of diagnosis was categorized (cut-off points 2001 and 2008) via the X-tile 3.6.1 program. Race was classified into three groups: black, white, and others, and marital status was classified into married, single, others, and unknown. Insurance state was divided into insured, uninsured, and unknown. Histopathology was grouped into three subgroups: sarcoma, lymphoma, and others, while tumor stage was classified as local, regional, distant, and unknown. Tumor grade was classified into I level, II level, III level, IV level, and unknown, and cancer-directed surgery, radiotherapy, and chemotherapy were divided into yes and no evidence comprising no treatment and unknown. The variables mentioned above without specific information were listed as "unknown" and were also involved in the construction of final nomogram. In the present study, the outcome of each patient was recorded as alive or death. Based on previous studies, early mortality was defined as overall survival (OS) time ≤3 months after diagnosis (12-14).

### *Statistical analysis*

SPSS version 21.0 (SPSS, Chicago, IL, USA), R software version 3.6.2, and X-tile program (Yale University) were used in the analysis. Categorical variables (age at diagnosis, gender, race, marital status, insurance, histopathology, tumor stage, tumor grade, tumor-directed surgery, chemotherapy, radiotherapy, and year of diagnosis) were compared using the Chi-square test or Fisher's exact test. Variables (with P<0.05) in univariate analysis were further analyzed using a multivariate forward-conditional stepwise logistic regression model. We used multiple logistic regression analysis to identify the independent prognostic factors, which were further used in the construction of the predictive nomogram model for early mortality, and the performance of the model was evaluated by the calibration curve and ROC curve in the training and validation cohort. The calibration plots were established by bootstrapping with 1,000 re-samples in the training and validation cohorts to evaluate the calibration of the nomogram model, and the relationship between predicted probabilities and observed probabilities of early mortality was described graphically. In terms of the ROC curve, the larger the AUC, which was close to 1.0, the more perfect discrimination ability. All statistical tests were two-sided, and P value <0.05 was considered significant.

## Results

### *Patient characteristics*

A total of 448 eligible patients were assigned to the training cohort and 190 to the validation cohort. The baseline characteristics of both are shown in *Table 1*, which also shows there was no significant difference between the two (P>0.05).

### *Risk factors for early mortality in the training cohort*

Univariate analysis revealed that age (year, P<0.001), histopathology (P<0.001), tumor stage (P<0.001), surgery (P<0.001), radiotherapy (P=0.006), chemotherapy (P<0.001), and insurance state (P=0.021) were factors related with 3-month mortality for PMCT patients in the training cohort, as shown in *Table 2*.

Based on multivariate logistic analysis, old age (P=0.05), advanced tumor stage (P<0.001), no surgery (P=0.001), and no chemotherapy (P<0.001) were identified as independent risk factors for early mortality in PMCT patients, as shown in *Table 3*.

### *Performance of the nomogram for predicting early mortality*

Based on the results of the multivariate logistic regression analysis, the four variables, including age, tumor stage, surgery, and chemotherapy, were selected to construct the predictive nomogram model for early mortality, as shown in *Figure 2*. By summing up the scores in the top scale assigned to the variable, the total points could be calculated, which could be easily converted to the probability of early mortality. The nomogram scoring system is shown in *Table 4* for a more precise calculation.

 

**Table 1** Characteristics of training cohort and validation cohort

| Variable | Full cohort (n=638) (%) | Training cohort (n=448) (%) | Validation cohort (n=190) (%) | P value |
|---|---|---|---|---|
| Total early mortality | | | | 0.171 |
| Yes | 418 (65.5) | 286 (63.8) | 132 (69.5) | |
| No | 220 (34.5) | 162 (36.2) | 58 (30.5) | |
| Age at diagnosis | | | | 0.495 |
| <44 | 216 (33.9) | 158 (35.3) | 58 (30.5) | |
| 44–76 | 339 (53.1) | 232 (51.8) | 107 (56.3) | |
| >76 | 83 (13.0) | 58 (12.9) | 25 (13.2) | |
| Gender | | | | 0.632 |
| Male | 335 (52.5) | 238 (53.1) | 97 (51.1) | |
| Female | 303 (47.5) | 210 (46.9) | 93 (48.9) | |
| Race | | | | 0.826 |
| White | 494 (77.4) | 344 (76.8) | 150 (78.9) | |
| Black | 70 (11.0) | 51 (11.4) | 19 (10.0) | |
| Others | 74 (11.6) | 53 (11.8) | 21 (11.1) | |
| Marital status | | | | 0.203 |
| Married | 337 (52.8) | 231 (51.6) | 106 (55.8) | |
| Single | 168 (26.3) | 119 (26.6) | 49 (25.8) | |
| Others | 112 (17.6) | 79 (17.6) | 33 (17.3) | |
| Unknown | 21 (3.3) | 19 (4.2) | 2 (1.1) | |
| Insurance state | | | | 0.686 |
| Insured | 233 (36.5) | 165 (36.8) | 68 (35.8) | |
| Uninsured | 18 (2.8) | 11 (2.5) | 7 (3.7) | |
| Unknown | 387 (60.7) | 272 (60.7) | 115 (60.5) | |
| Grade | | | | 0.598 |
| I | 3 (0.5) | 3 (0.7) | 0 (0.0) | |
| II | 20 (3.1) | 15 (3.3) | 5 (2.6) | |
| III | 79 (12.4) | 54 (12.1) | 25 (13.2) | |
| IV | 141 (22.1) | 105 (23.4) | 36 (18.9) | |
| Unknown | 395 (61.9) | 271 (60.5) | 124 (65.3) | |
| Histopathology | | | | 0.483 |
| Sarcoma | 393 (61.6) | 272 (60.7) | 121 (63.7) | |
| Lymphoma | 144 (22.6) | 100 (22.3) | 44 (23.1) | |
| Others | 101 (15.8) | 76 (17.0) | 25 (13.2) | |

**Table 1** (*continued*)

**Table 1** (*continued*)

| Variable | Full cohort (n=638) (%) | Training cohort (n=448) (%) | Validation cohort (n=190) (%) | P value |
|---|---|---|---|---|
| Stage | | | | 0.25 |
| Local | 126 (19.7) | 95 (21.2) | 31 (16.3) | |
| Regional | 125 (19.6) | 90 (20.1) | 35 (18.4) | |
| Distant | 171 (26.8) | 111 (24.8) | 60 (31.6) | |
| Unknown | 216 (33.9) | 152 (33.9) | 64 (33.7) | |
| Surgery | | | | 0.82 |
| Yes | 239 (37.4) | 170 (37.9) | 69 (36.3) | |
| No | 250 (39.2) | 172 (38.4) | 78 (41.1) | |
| Unknown | 149 (23.4) | 106 (23.7) | 43 (22.6) | |
| Radiotherapy | | | | 0.726 |
| Yes | 68 (10.7) | 49 (10.9) | 19 (10.0) | |
| No | 570 (89.3) | 399 (89.1) | 171 (90.0) | |
| Chemotherapy | | | | 0.188 |
| Yes | 317 (49.7) | 215 (48.0) | 102 (53.7) | |
| No/unknown | 321 (50.3) | 233 (52.0) | 88 (46.3) | |
| Year of diagnosis | | | | 0.319 |
| 1975–2000 | 183 (28.7) | 122 (27.2) | 61 (32.1) | |
| 2001–2008 | 190 (29.8) | 132 (29.5) | 58 (30.5) | |
| 2009–2016 | 265 (41.5) | 194 (43.3) | 71 (37.4) | |

In the calibration curve, the mortality estimated by the nomogram was labeled on the x-axis and the actual mortality was labeled on the y-axis. An ideal model indicated as dash lines predicted the same mortality as the outcome of that observed clinically. In the training cohort, the calibration curve showed proper agreement between the predicted and observed probability, with the former close to the 45-degree line (*Figure 3A*). The AUC of the nomogram model for early mortality prediction was 0.816 in the training cohort, which revealed a satisfactory strength of discrimination (*Figure 3B*). The calibration curve of the validation cohort revealed that the early mortality predicted by the nomogram was in compliance with actual observation at a high level (*Figure 3C*), and the AUC of the nomogram model for early mortality prediction was 0.805 in the validation cohort (*Figure 3D*).

## Discussion

PMCTs are extremely rare and fatal malignancies, with 65.5% of patients dying within 3 months of diagnosis in our study. The high percentage of early mortality demonstrates it is crucial to offer attention to patients at high risk of early death. Apart from the aggressive biological behaviour, the lack of a prediction model contributes to the poor survival of PMCT patients. We conducted a retrospective analysis to develop a credible nomogram model to predict early mortality in PMCTs patients using a large population in the SEER database.

As reported in previous studies, old age has been proven to be related with poor survival in patients with breast cancer (15), prostate cancer (16), and osteosarcoma (17). However, the precise cut-off value of age in PMCT remains

**Table 2** Univariate analysis for early mortality in training cohort

| Variable | All patients (n=448) (%) | Not early mortality (n=286) (%) | Early mortality (n=162) (%) | P value |
|---|---|---|---|---|
| Age at diagnosis | | | | <0.001 |
| <44 | 158 (35.3) | 118 (41.3) | 40 (24.7) | |
| 44–76 | 232 (51.8) | 141 (49.3) | 91 (56.2) | |
| >76 | 58 (12.9) | 27 (9.4) | 31 (19.1) | |
| Gender | | | | 0.118 |
| Male | 238 (53.1) | 144 (50.3) | 94 (58.0) | |
| Female | 210 (46.9) | 142 (49.7) | 68 (42.0) | |
| Race | | | | 0.888 |
| White | 344 (76.8) | 219 (76.6) | 125 (77.2) | |
| Black | 51 (11.4) | 34 (11.9) | 17 (10.5) | |
| Others | 53 (11.8) | 33 (11.5) | 20 (12.3) | |
| Marital status | | | | 0.516 |
| Married | 231 (51.6) | 147 (51.4) | 84 (51.8) | |
| Single | 119 (26.6) | 81 (28.3) | 38 (23.5) | |
| Others | 79 (17.6) | 48 (16.8) | 31 (19.1) | |
| Unknown | 19 (4.2) | 10 (3.5) | 9 (5.6) | |
| Insurance state | | | | 0.021 |
| Insured | 165 (36.8) | 118 (41.3) | 47 (29.0) | |
| Uninsured | 11 (2.5) | 5 (1.7) | 6 (3.7) | |
| Unknown | 272 (60.7) | 163 (57.0) | 109 (67.3) | |
| Grade | | | | 0.395 |
| I | 3 (0.7) | 3 (1.0) | 0 (0.0) | |
| II | 15 (3.3) | 9 (3.2) | 6 (3.7) | |
| III | 54 (12.1) | 38 (13.3) | 16 (9.9) | |
| IV | 105 (23.4) | 71 (24.8) | 34 (21.0) | |
| Unknown | 271 (60.5) | 165 (57.7) | 106 (65.4) | |
| Histopathology | | | | <0.001 |
| Sarcoma | 272 (60.7) | 178 (62.2) | 94 (58.0) | |
| Lymphoma | 100 (22.3) | 74 (25.9) | 26 (16.1) | |
| Others | 76 (17.0) | 34 (11.9) | 42 (25.9) | |
| Tumor stage | | | | <0.001 |
| Local | 95 (21.2) | 74 (25.9) | 21 (13.0) | |
| Regional | 90 (20.1) | 60 (21.0) | 30 (18.5) | |
| Distant | 111 (24.8) | 55 (19.2) | 56 (34.5) | |
| Unknown | 152 (33.9) | 97 (33.9) | 55 (34.0) | |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Variable | All patients (n=448) (%) | Not early mortality (n=286) (%) | Early mortality (n=162) (%) | P value |
|---|---|---|---|---|
| Surgery | | | | <0.001 |
| Yes | 170 (37.9) | 130 (45.5) | 40 (24.7) | |
| No | 172 (38.4) | 93 (32.5) | 79 (48.8) | |
| Unknown | 106 (23.7) | 63 (22.0) | 43 (26.5) | |
| Radiotherapy | | | | 0.006 |
| Yes | 49 (10.9) | 40 (14.0) | 9 (5.6) | |
| No | 399 (89.1) | 246 (86.0) | 153 (94.4) | |
| Chemotherapy | | | | <0.001 |
| Yes | 215 (48.0) | 181 (63.3) | 34 (21.0) | |
| No | 233 (52.0) | 105 (36.7) | 128 (79.0) | |
| Year of diagnosis | | | | 0.053 |
| 1975–2000 | 122 (27.2) | 73 (25.5) | 49 (30.2) | |
| 2001–2008 | 132 (29.5) | 77 (26.9) | 55 (34.0) | |
| 2009–2016 | 194 (43.3) | 136 (47.6) | 58 (35.8) | |

**Table 3** Multivariate analysis for early mortality in training cohort

| Variable | HR | 95% CI | | P value |
|---|---|---|---|---|
| | | Low | High | |
| Age at diagnosis | | | | 0.05 |
| <44 | Reference | Reference | | |
| 44–76 | 1.827 | 1.072 | 3.144 | |
| >76 | 2.307 | 1.018 | 5.231 | |
| Tumor stage | | | | <0.001 |
| Local | Reference | Reference | | |
| Regional | 1.956 | 0.934 | 4.095 | |
| Distant | 7.728 | 3.592 | 16.625 | |
| Unknown | 1.976 | 0.949 | 4.113 | |
| Surgery | | | | 0.001 |
| Yes | Reference | Reference | | |
| No | 2.696 | 1.515 | 4.797 | |
| Unknown | 2.425 | 1.313 | 4.477 | |
| Chemotherapy | | | | <0.001 |
| Yes | Reference | Reference | | |
| No | 10.453 | 6.048 | 18.066 | |

HR, hazard ratio; CI, confidence interval.

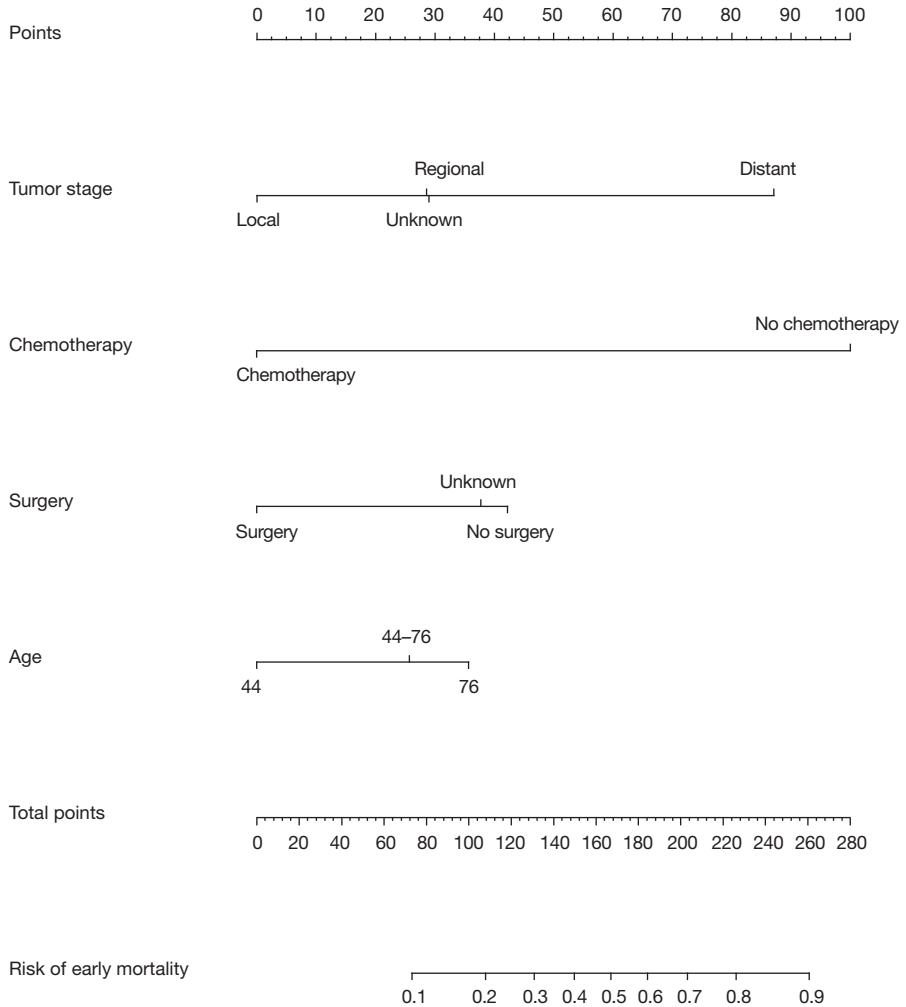


**Figure 2** Nomogram for predicting early mortality in patients with PMCT. PMCT, primary malignant cardiac tumor.

controversial. Based on the maximum $\chi^2$ and minimum P value in the X-tile software (18), the optimal cut-off value for age in PMCTs patients was objectively identified as 44 and 76 in the current study, which is considered to be more credible and accurate. In previous studies on PMCTs patients, age at diagnosis showed a strong prognostic association with OS (4,19). In our study, older age was found to be associated with higher odds of early mortality, with patients over 76-year old having the highest odds of early mortality, followed by the 44–76 age group and 44, which was similar to the optical age cut-off value for OS for PMCT patients (4). Accordingly, patients older than 76 years are considered as a high risk group and should be provided with specific detailed treatment plans and strengthened care.

Advanced tumor stages (regional and distant stage) were also associated with higher odds of early mortality. In previous cancer related study, advanced tumor stages were identified as independent risk factors for early mortality (20) in colorectal cancer (21) and hepatocellular carcinoma (22). Blood vessel tumors constitute most PMCTs, and manifest nonspecific clinical symptoms, such as fever, weakness, and weight (23-25), and many patients are already in an advanced clinical stage at presentation. Hence, a complete resection of the tumor and timely treatment cannot be performed, which contributes to the high odds of early mortality.

Although PMCT patients have a dismal prognosis,

 

**Table 4** Nomogram scoring system

| Variable | Point |
|---|---|
| Age at diagnosis | |
| <44 | 0 |
| 44–76 | 26 |
| >76 | 36 |
| Chemotherapy | |
| Yes | 0 |
| No | 100 |
| Surgery | |
| Yes | 0 |
| No | 42 |
| Unknown | 38 |
| Tumor stage | |
| Local | 0 |
| Regional | 29 |
| Distant | 87 |
| Unknown | 29 |

our study confirms surgical resection and chemotherapy are associated with a favourable early prognosis. In one study, clinical experience suggested cancer-directed surgical excision was associated with better survival in PMCTs patients (26-28). Surgery intervention is mostly performed in those at an advanced tumor stage, as without it PMCTs can cause hemodynamics disorder, heart failure, hemorrhagic pericardial effusion, and supra-ventricular arrhythmia in a short time. Surgery should be encouraged for eligible patients to decrease the odds of early mortality. Lymphoma is the main pathological type of malignant cardiac tumor and is sensitivity to chemotherapy making this the primary treatment modality (29,30). Sarcoma is also believed to benefit from chemotherapy treatment (4,31,32). In our study, chemotherapy was found to be significantly associated with a decreased incidence of early mortality. Analyze data from China cases showed that the PMCTs accounted 16.03% of the all primary cardiac tumor, and the 1-, 3-, and 5-year survival rate of primary cardiac patient was 83.20%, 78.62% and 66.41% respectively. The prognostic data of Chinese PMCT patients was dismal, and further researches on cardiac tumor were urgently needed in the future (33). According to our research conclusion, it is suggested that active surgical treatment and chemotherapy should be given if the PMCTs patient's condition permits. For the elderly and patients with advanced tumor stage, early mortality risk should be paid attention to.

The present study has some limitations. Due to the nature of a retrospective study spanning over four decades, there are unavoidable confounding factors despite adjustment. Secondly, data in the SEER database does not include molecular factors, which may influence prognosis and limit our conclusion. The histopathology type of PMCTs has been reclassified many times since the 1970's, making inference about the early mortality of its sub-types less reliable, so the risk factors for early mortality analysis were not thoroughly performed in each histopathology type.. In addition, we did not analyze cancer specific death separately. Despite these limitations, no other study has provided such a high number of PMCT patients, covering all age range and all kinds of histopathology. The wide range of data, retrieved from SEER, consisting of 18 cancer registries and covering approximately 34.6% of the US population, allows the nomogram to be applied widely. More importantly, we constructed a reliable prognostic nomogram for early mortality in PMCT patients for the first time, the predictive accuracy of which has been validated in several ways. While as an auxiliary screening tool, the nomogram model can be potentially used by physicians, further studies are required validate and refine the nomogram model.

## Conclusions

In conclusion, the results of this study showed old age (44–76 and >76 years) and advantaged tumor stage (regional and distant stage) were related with a higher probability of early mortality in PMCT patients, whereas surgery and chemotherapy could reduce this. A nomogram model based on the independent risk factors can be utilized to predict the probability of early mortality in PMCT patients, following which, individual treatment or supportive care can be scheduled in patients with high risk.

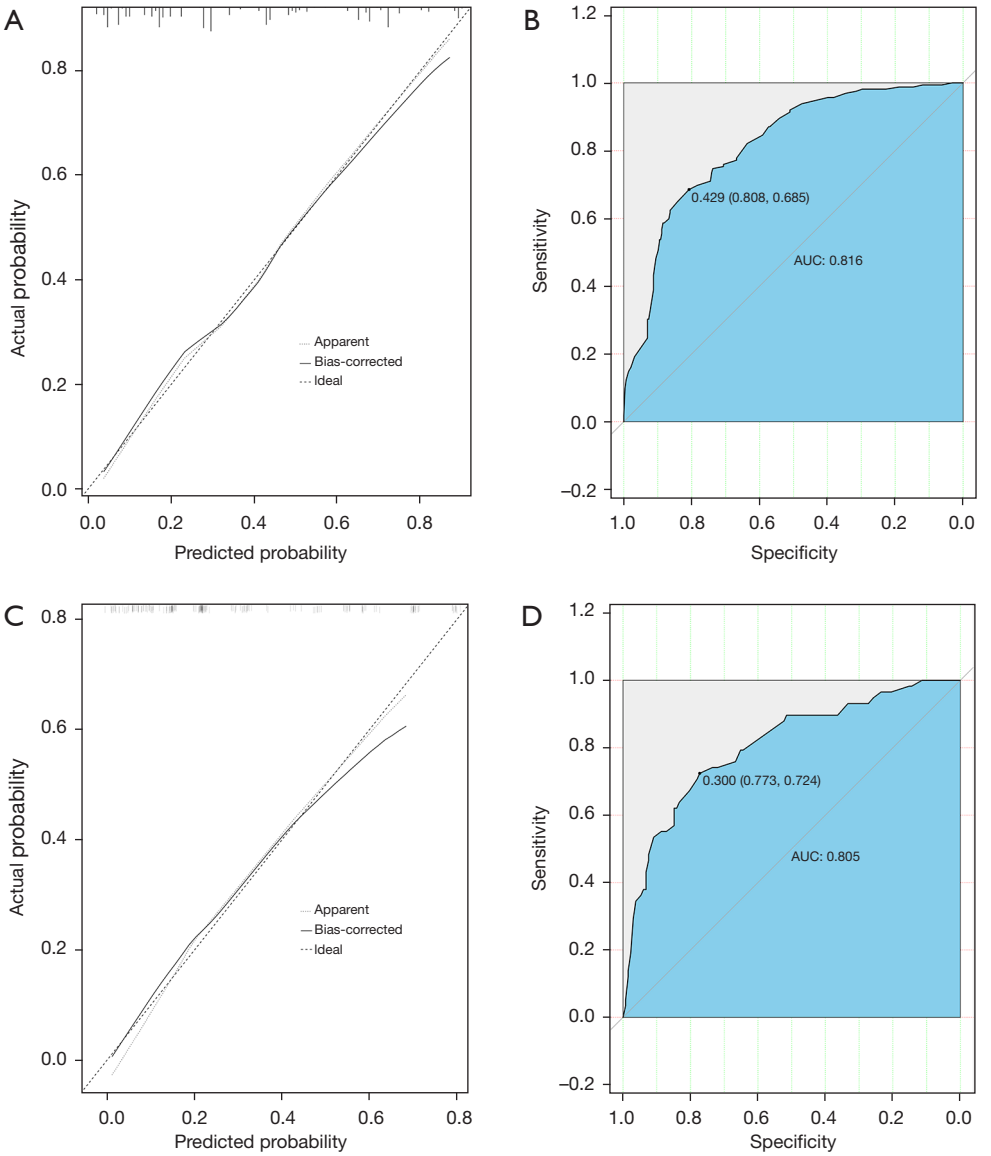


**Figure 3** The calibration curve and ROC curve for assessing the calibration and discrimination of the nomogram in predicting early mortality. Calibration curve in training cohort (A); ROC curve in training cohort (B); calibration curve in validation cohort (C); ROC curve in validation cohort (D). ROC, receiver operating curve.

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## Footnote

*Reporting Checklist:* The authors have completed the TRIPOD reporting checklist. Available at https://dx.doi.org/10.21037/atm-21-5574

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/atm-21-5574). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related

 

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Participant consent was not required as the study involved the use of a previously published de-identified database according to the SEER database.



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