Clinical Features and Prognostic Factors of Elderly Patients with Gallbladder Cancer: A Population-Based Study

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Abstract

Background: Elderly patients with gallbladder cancer (GBC) may be a special group of individuals. The present study aimed to explore the clinical features and prognostic factors of elderly patients with GBC and establish nomogram to predict their overall survival (OS).

Methods: Patients diagnosed with GBC from 2010 to 2015 were identified from the Surveillance Epidemiology and End Results database. Clinical characteristics and prognostic factors in elderly GBC patients were examined.

Results: Elderly patients and young patients with GBC differed in many aspects, including race, marital status, AJCC stage, T stage, N stage, M stage, surgery, lymph node dissection, radiation, chemotherapy, and OS ($P<0.05$). Analysis of prognostic factors showed that chemotherapy and surgery with lymph node dissection (radical surgery), as the main treatment for elderly patients, can significantly improve prognosis. Other factors, including being unmarried, higher grade of histological type and AJCC stage, had a negative effect on OS. Nomogram was developed based on the above prognostic factors. The C-indexes of 1-year survival and 3-year survival nomogram were 0.73 and 0.736 and AUCs at 1 and 3 years were 0.789 and 0.780, respectively.

Conclusions: Elderly patients with GBC comprise a distinct group of individuals whose clinical characteristics differ from those of young patients, and the nomogram constructed accurately predicted OS in elderly patients with GBC.

Background

With the trend of the aging global population, the incidence of cancer has also increased [1]. Approximately 70% of malignancies and 85% of cancer-related deaths are expected to occur in the elderly population by 2030 [2]. As the fifth most common gastrointestinal tract malignancy, gallbladder cancer (GBC) is a highly malignant tumor with a poor prognosis [3–5]. It is estimated that in 2020, there will be 2115,949 new cases of GBC and 84,695 new deaths from GBC worldwide [6]. Several studies have shown that GBC is more likely to occur in the elderly and tends to be a geriatric disease [7–9]. Therefore, treating elderly patients with GBC will be a serious clinical challenge.

Due to immune system dysfunction and chronic inflammation, cancer is more likely to develop in the elderly under the stimulation of carcinogens [10, 11]. It has been reported that the lymphocyte-to-monocyte ratio, which acts as a tumor suppressor indicator, is significantly lower in elderly GBC patients than in young GBC patients [12]. Moreover, it has been proven that age is a significant negative prognostic factor for GBC [8, 9]. Hence, elderly patients may represent a special subgroup that needs more clinical attention. Currently, radical surgery with lymph node dissection and chemotherapy are highly recommended for GBC, but the role of radiotherapy remains controversial [3, 5, 12, 13]. However, the utility of these methods for the treatment of GBC in elderly patients is still unknown. Our study

evaluated the clinical characteristics and prognostic factors of elderly patients with GBC and developed a valid but simple prediction tool for OS using only characteristics that are readily available.

Methods

Patient cohort

Data from the Surveillance Epidemiology and End Results (SEER) database-18 registry of the National Cancer Institute were retrieved through SEER*Stat Software Version 8.3.5. The SEER database is a publicly available database, and the application of its data did not need approval from the institutional review board. Detailed information on patients with a primary site of 'gallbladder' between January 1, 2010, and December 31, 2015, was obtained. Patients without information about American Joint Committee on Cancer (AJCC) stage (7th edition), T stage or N stage were excluded.

Data collection

Information including age, sex, race, marital status, AJCC stage, T stage, N stage, M stage, distant organ metastasis (liver, lung, bone, and brain), histological type, surgery, lymph node dissection, surgery for distant metastasis, chemotherapy, radiation, survival time, and vital status was collected for each patient. As lymph node dissection is performed as a surgical procedure, in this study, patients who had undergone lymph node dissection were also considered as undergoing radical surgery.

Statistical analyses

X-tile software v3.6.1 (Yale University, New Haven, CT, USA) was utilized to determine the optimal cutoff values for age[14]. Empower Stats 2.2 (http://www.empowerstats.com/cn/) and R-project (version 4.0.1) were applied for statistical analyses. Continuous variables are reported as the mean ± standard deviation, and independent samples t-tests were performed for comparisons between groups. The odds ratio (OR) and chi-square ($\chi 2$) test were used for analysis of categorical variables. Possible prognostic factors were explored through univariate and multivariate Cox regression analyses. Curve fitting was conducted to evaluate the relationship between age and vital status. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) were determined. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 5053 GBC cases (1586 males and 3467 females) were enrolled in our study. We first detected prognostic factors among all the participants through univariate Cox regression analysis (Supplemental Table 1). Our data indicated that age, marital status, histological type, AJCC stage, T stage, N stage, M stage, surgery, lymph node dissection, surgery for distant metastasis, radiation, chemotherapy, and distant organ metastasis (liver, lung, bone, and brain) were prognostic factors for OS ($P < 0.05$). Multivariate analysis was then performed (Supplemental Table 2), and the results showed that age,

marital status, AJCC stage, T stage, N stage, M stage, surgery, lymph node dissection, surgery for distant metastasis, chemotherapy, radiation, and distant organ metastasis (liver, lung, bone, and brain) were prognostic factors ($P < 0.05$). Therefore, age is an independent prognostic factor significantly associated with OS in GBC.

We applied X-tile software to divide the patients by age into two groups (Supplemental Fig. 1). The age of 65 years was estimated as the optimal cutoff value, which divided the GBC patients into two age groups. A total of 3263 GBC patients diagnosed at an age older than 65 years old were identified as the elderly group; 1790 patients were classified in the young group (≤ 65 years old). The characteristics of the elderly and young groups were then compared, and the data showed significant differences in many aspects, such as race, marital status, AJCC stage, T stage, N stage, M stage, surgery, lymph node dissection, radiation, and chemotherapy ($P < 0.05$, Table 1). Of the 5053 patients, mortality occurred in 3296 (65.2% of 105053) by the end of follow-up, 2423 (47.9% of 5053) of whom died due to GBC. Elderly GBC patients had a higher overall mortality rate (69.4%) than young GBC patients (57.7%) at the end of follow-up (P **< 0.001**) but a similar cancer-specific mortality rate (47.7% vs. 48.1%, P **= 0.799**).

Table 1
Characteristics of participants.

Variables	≤ 65 years	⊠65 years	P-value
Number	1790(100%)	3263(100%)	
Sex			0.453
Male	550 (30.73%)	1036 (31.75%)	
Female	1240 (69.27%)	2227 (68.25%)	
Race			< 0.001
White	1250 (69.83%)	2562 (78.52%)	
Other	540 (30.17%)	701 (21.48%)	
Marital status			< 0.001
Married	1010 (59.45%)	1471 (47.15%)	
Other	689 (40.55%)	1649 (52.85%)	
Year of diagnosis			0.462
2010	256 (14.30%)	516 (15.81%)	
2011	280 (15.64%)	507 (15.54%)	
2012	302 (16.87%)	554 (16.98%)	
2013	301 (16.82%)	554 (16.98%)	
2014	346 (19.33%)	563 (17.25%)	
2015	305 (17.04%)	569 (17.44%)	
Histological type			0.796
Well differentiated; Grade I	209 (15.12%)	354 (14.42%)	
Moderately differentiated; Grade II	609 (44.07%)	1061 (43.22%)	
Poorly differentiated; Grade III	528 (38.21%)	977 (39.80%)	
Undifferentiated; Grade IV	36 (2.60%)	63 (2.57%)	
Derived AJCC Stage Group, 7th			< 0.001
I	207 (11.56%)	373 (11.43%)	
II	327 (18.27%)	756 (23.17%)	
IIIA	261 (14.58%)	558 (17.10%)	
IIIB	305 (17.04%)	490 (15.02%)	

Variables	≤ 65 years	⊠65 years	P-value
IV	690 (38.55%)	1086 (33.28%)	
T stage			0.003
T0-T1	301 (16.82%)	543 (16.64%)	
T2	544 (30.39%)	1116 (34.20%)	
T3	818 (45.70%)	1439 (44.10%)	
T4	127 (7.09%)	165 (5.06%)	
N stage			< 0.001
N0	1116 (62.35%)	2293 (70.27%)	
N1	525 (29.33%)	806 (24.70%)	
N2	149 (8.32%)	164 (5.03%)	
M stage			0.006
M0	1203 (67.21%)	2314 (70.92%)	
M1	587 (32.79%)	949 (29.08%)	
Surgery			0.036
No	446 (24.92%)	902 (27.64%)	
Yes	1344 (75.08%)	2361 (72.36%)	
Lymph node dissection			< 0.001
None	1046 (58.44%)	2259 (69.23%)	
1 to 3 regional lymph nodes removed	436 (24.36%)	679 (20.81%)	
4 or more regional lymph nodes removed	308 (17.21%)	325 (9.96%)	
Surgical Resection of the Distant metastasis			0.182
No	1771 (98.94%)	3240 (99.30%)	
Yes	19 (1.06%)	23 (0.70%)	
Radiation			< 0.001
No	1493 (83.41%)	2913 (89.27%)	
Yes	297 (16.59%)	350 (10.73%)	
Chemotherapy			< 0.001
No	822 (45.92%)	2277 (69.78%)	

Variables	≤ 65 years	▯65 years	P-value
Yes	968 (54.08%)	986 (30.22%)	
Overall survival			< 0.001
Live	758 (42.35%)	999 (30.62%)	
Dead	1032 (57.65%)	2264 (69.38%)	
Bone metastasis			0.580
No	1734 (98.08%)	3168 (98.29%)	
Yes	34 (1.92%)	55 (1.71%)	
Brain metastasis			0.164
No	1760 (99.60%)	3217 (99.81%)	
Yes	7 (0.40%)	6 (0.19%)	
Liver metastasis			0.119
No	1400 (78.96%)	2609 (80.80%)	
Yes	373 (21.04%)	620 (19.20%)	
Lung metastasis			0.800
No	1699 (96.32%)	3102 (96.46%)	
Yes	65 (3.68%)	114 (3.54%)	

Prognostic factors of elderly GBC patients

Univariate Cox regression analysis revealed that marital status, histological type, AJCC stage, T stage, N stage, M stage, surgery, lymph node dissection, radiation, chemotherapy, and distant metastasis (liver, lung, bone, and brain metastasis) had a significant impact on OS ($P < 0.05$ Table 2).

Table 2
Univariate analysis of overall survival rates of the elderly patients with gallbladder cancer.

Variables	HR (95%CI), P value
Sex	
Male	1.0
Female	1.01 (0.92, 1.10) 0.8316
Race	
White	1.0
Other	0.95 (0.86, 1.06) 0.3671
Marital status	
Married	1.0
Other	1.21 (1.11, 1.31) < 0.0001
Year of diagnosis	
2010	1.0
2011	0.93 (0.82, 1.07) 0.3135
2012	0.92 (0.80, 1.05) 0.2054
2013	0.95 (0.83, 1.08) 0.4212
2014	0.95 (0.82, 1.09) 0.4746
2015	0.87 (0.73, 1.03) 0.1155
Histological type	
Well differentiated; Grade I	1.0
Moderately differentiated; Grade II	1.40 (1.19, 1.66) < 0.0001
Poorly differentiated; Grade III	2.32 (1.97, 2.74) < 0.0001
Undifferentiated; Grade IV	2.57 (1.88, 3.52) < 0.0001
Derived AJCC Stage Group, 7th	
I	1.0
II	1.08 (0.90, 1.29) 0.4152
IIIA	3.08 (2.58, 3.68) < 0.0001
IIIB	1.95 (1.62, 2.34) < 0.0001

Variables	HR (95%CI), P value
IV	4.58 (3.88, 5.41) < 0.0001
T stage	
T0-T1	1.0
T2	0.82 (0.72, 0.94) 0.0053
T3	2.28 (2.01, 2.58) < 0.0001
T4	2.99 (2.45, 3.65) < 0.0001
N stage	
N0	1.0
N1	1.32 (1.20, 1.45) < 0.0001
N2	1.84 (1.54, 2.20) < 0.0001
M stage	
M0	1.0
M1	2.71 (2.48, 2.96) < 0.0001
Surgery	
No	1.0
Yes	0.31 (0.28, 0.34) < 0.0001
Lymph node dissection	
None	1.0
1 to 3 regional lymph nodes removed	0.50 (0.45, 0.56) < 0.0001
4 or more regional lymph nodes removed	0.38 (0.32, 0.45) < 0.0001
Surgical Resection of the Distant metastasis	
No	1.0
Yes	0.61 (0.36, 1.06) 0.0782
Radiation	
No	1.0
Yes	0.53 (0.46, 0.61) < 0.0001
Chemotherapy	
No	1.0

Variables	HR (95%CI), P value
Yes	0.80 (0.73, 0.88) < 0.0001
Bone Metastasis	
No	1.0
Yes	3.04 (2.31, 4.00) < 0.0001
Liver Metastasis	
No	1.0
Yes	2.56 (2.31, 2.82) < 0.0001
Brain Metastasis	
No	1.0
Yes	3.48 (1.56, 7.77) 0.0023
Lung Metastasis	
No	1.0
Yes	2.34 (1.91, 2.87) < 0.0001

Further multivariate Cox regression analysis was performed based on univariate Cox regression, and five independent predictors (marital status, histological type, AJCC stage, lymph node dissection, and chemotherapy) for OS were identified. The data demonstrated that being unmarried was associated with worse OS (HR = 1.17, 95% CI = 1.05–1.31). A higher histological type grade was also associated with a worse OS. Grade II (HR = 1.30, 95% CI = 11.09–1.55), Grade III (HR = 1.74, 95% CI = 11.46–2.08), and Grade IV (HR = 1.97, 95% CI = 11.43–2.73) were associated with a worse OS compared to Grade I. Moreover, higher grades of AJCC stage were associated with a worse OS. Compared to stage I, stage II (HR = 1.79, 95% CI = 1.22–2.62), stage IIIA (HR = 2.91, 95% CI = 2.02–4.19), stage IIIB (HR = 3.20, 95% CI = 2.14–4.78) and stage IV (HR = 4.58, 95% CI = 3.88–5.41) were associated with worse OS.

Regarding treatment, surgery with lymph node dissection (radical surgery) had a significantly positive impact on OS. The data indicated that elderly GBC patients who had 1 to 3 regional lymph nodes removed (HR = 0.66, 95% CI = 0.57–0.76) and 4 or more regional lymph nodes removed (HR = 0.48, 95% CI = 0.40–0.59) had a significantly better OS than those who did not undergo lymph node dissection. Chemotherapy, as one of the most important treatments for GBC, also showed a positive effect on both OS (HR = 0.49, 95% CI = 0.43–0.57). The detailed results are provided in Table 3. Correlations of the five independent predictors (marital status, histological type, AJCC stage, lymph node dissection, and chemotherapy) with OS obtained by the log-rank test were detected through survival curve analysis (supplemental Fig. 2 respectively). Then, nomogram was constructed based on these factors.

Table 3
Multivariate analysis of overall survival rates of the elderly patients with gallbladder cancer.

Variables	HR (95%CI), P value
Sex	
Male	1.0
Female	0.88 (0.78, 0.99) 0.0312
Race	
White	1.0
Other	0.89 (0.79, 1.02) 0.0928
Marital status	
Married	1.0
Other	1.17 (1.05, 1.31) 0.0056
Year of diagnosis	
2010	1.0
2011	1.03 (0.87, 1.20) 0.7620
2012	0.99 (0.84, 1.17) 0.9194
2013	1.05 (0.89, 1.24) 0.5564
2014	0.99 (0.83, 1.18) 0.8891
2015	0.82 (0.65, 1.04) 0.0964
Histological type	
Well differentiated; Grade I	1.0
Moderately differentiated; Grade II	1.30 (1.09, 1.55) 0.0030
Poorly differentiated; Grade III	1.74 (1.46, 2.08) < 0.0001
Undifferentiated; Grade IV	1.97 (1.43, 2.73) < 0.0001
Derived AJCC Stage Group, 7th	
I	1.0
II	1.79 (1.22, 2.62) 0.0028
IIIA	2.91 (2.02, 4.19) < 0.0001
IIIB	3.19 (2.14, 4.76) < 0.0001

Variables	HR (95%CI), P value
IV	4.94 (3.03, 8.05) < 0.0001
T stage	
T0-T1	1.0
T2	0.73 (0.53, 1.01) 0.0542
T3	1.22 (0.91, 1.63) 0.1897
T4	1.24 (0.77, 2.02) 0.3784
N stage	
N0	1.0
N1	1.16 (0.94, 1.43) 0.1702
N2	1.04 (0.72, 1.48) 0.8465
M stage	
M0	1.0
M1	1.22 (0.72, 2.05) 0.4605
Surgery	
No	1.0
Yes	0.88 (0.73, 1.07) 0.2091
Lymph node dissection	
None	1.0
1 to 3 regional lymph nodes removed	0.66 (0.57, 0.76) < 0.0001
4 or more regional lymph nodes removed	0.48 (0.40, 0.59) < 0.0001
Surgical Resection of the Distant metastasis	
No	1.0
Yes	0.76 (0.42, 1.39) 0.3773
Radiation	
No	1.0
Yes	0.91 (0.76, 1.08) 0.2825
Chemotherapy	
No	1.0

Variables	HR (95%CI), P value
Yes	0.49 (0.43, 0.57) < 0.0001
Bone Metastasis	
No	1.0
Yes	1.31 (0.86, 2.01) 0.2118
Liver Metastasis	
No	1.0
Yes	1.10 (0.90, 1.35) 0.3580
Brain Metastasis	
No	1.0
Yes	1.76 (0.55, 5.66) 0.3399
Lung Metastasis	
No	1.0
Yes	0.90 (0.63, 1.29) 0.5663

Nomogram Construction

According to multivariate model, nomogram that combined all five independent prognostic factors were developed to predict OS at 1 and 3 years (Fig. 1).

Calibration and Validation of the Nomogram

The C-index of the 1-year survival and 3-year survival nomogram were 0.736 (95%CI 0.721–0.7450) and 0.736 (95%CI 0.721–0.750) for OS. The discrimination ability of the nomogram in different years was next examined. AUCs at 1 and 3 years for the nomogram were 0.789 and 0.780 (Figs. 2). Acceptable agreement between the predicted death rate and observed values of OS were illustrated in calibration curves (Figs. 3). Thus, we believe that the nomogram has high accuracy for OS prediction at 1 and 3 years for elderly GBC patients.

Discussion

In this study, GBC patients were first divided into a young group (≤ 65 years old) and an elderly group (> 65 years) according to fitting curves between age and OS. Most of the GBC patients were in the elderly group (64.6%). Comparison between the two age groups revealed that more GBC patients older than 65 years old were white, possibly because white patients tend to have better access to health care and are more likely to have a longer life span than are individuals of other races [15, 16]. Additionally, the

proportion of patients over 65 years old who were married (1471/3263, 47.15%) was significantly lower than that in the young group (1010/1790, 59.45%), which may be due to the high mortality rate for spouses in that age range. Prognostic analysis demonstrated that being unmarried is unfavorable for survival among elderly GBC patients, which agrees with many previous studies [17–20]. The results indicate that elderly people who lack care from a marriage partner have a poor prognosis.

Further analysis revealed that the proportion of AJCC stage II or IIIA, T2, N0 and M0 stage was decreased in elderly GBC patients. These results can be attributed to the frequent routine check-ups of elderly patients, which can allow for the early diagnosis of disease. The AJCC stage has also been proven to be an independent prognostic factor for OS in elderly GBC patients. It is worth noting that the AJCC subdivides the T2 stage into T2a and T2b, stages with diagnosis and treatment that have been the subject of intense discussion and debate [21]. The controversy lies in the fact that in the clinical setting, the GBC T2 stage can be divided into various substages, such as IIA, IIB, IIIB, and IVB, and might be treatable [21]. Therefore, the results indicate that as a particular group, more clinical attention should be paid to the elderly group of GBC patients.

Moreover, our study indicated a higher overall mortality rate for the elderly group, though the cancer-specific mortality rate was similar to that of the young group. The reason may be that the older the cancer patient is, the more basic diseases he or she has and the more likely he or she will die from these diseases [2]. Therefore, clinical workers should pay more attention to systemic conditions and basic diseases when treating elderly GBC patients.

Treatment data indicated that patients over 65 years old were less likely to receive all kinds of treatment, such as surgery, lymph node dissection, radiation, and chemotherapy. Nonetheless, surgery and chemotherapy were the main forms of treatment, and radiation was obviously applied less often. Further analysis suggested that radical surgery (surgery with lymph node dissection) and chemotherapy have the greatest therapeutic benefit for patients, and they are the main treatment option for GBC [4, 13, 22–27]. Gemcitabine combined with cisplatin was the standard of care for GBC in 2010; however, recent phase III studies support alternatives such as gemcitabine in combination with oxaliplatin or S1 [24]. Systemic therapy is the only option for those diagnosed with an advanced, unresectable stage [23]. Although radiotherapy had a positive impact on OS in univariate analysis, no correlation with OS in multivariate analysis was observed. Such a result may be attributed to the lower sensitivity of GBC to radiotherapy [22, 28, 29].

There are many differences between elderly and young individuals, indicating that elderly GBC patients are a special group of individuals. To better evaluate the prognosis of this distinct population, a nomogram for the prediction of OS were constructed. In addition, due to the high degree of malignancy of GBC, patients often have a short survival time once diagnosed. We developed prediction evaluation models for 1 year and 3 years by combining all independent predictors (marital status, histological type, AJCC stage, lymph node dissection and chemotherapy) to predict OS. To the best of our knowledge, to date, no nomogram has been constructed specifically for elderly GBC patients. Our constructed

prognostic nomogram showed good discrimination and predictive accuracy for this special group of GBC patients based on a population-based cohort.

Our study had several main limitations. The relatively incomplete clinical information hindered further evaluations of treatment in the elderly patients. For example, data were lacking for many of the patients, including T stage, N stage, and AJCC stage. Information on the specific chemotherapy regimen used, detailed surgical scope and procedure, and radiation dose also were not available. Therefore, alternative explanations for some of the findings of the present study cannot be ruled out. Nevertheless, our findings will be useful for assessing prognosis in elderly GBC patients and in establishing treatment policies.

Conclusions

Elderly patients with GBC are a special group of individuals whose clinical characteristics differ from those of younger patients. Our developed nomogram accurately predicted OS in elderly patients with GBC, facilitating the selection of beneficial treatment strategies.

List Of Abbreviations

AJCC American Joint Committee on Cancer

AUC Area under the curve

GBC Gallbladder cancer

CI Confidence interval

HR Hazard ratio

OR Odds ratio

OS Overall survival

SEER Surveillance Epidemiology and End Results

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication

Not applicable

Authors' contributions

Concept and design: TLY, JS. Data analysis and interpretation: TLY, JS, LDY. Interpretation of Data: TLY, JS, LDY, YHB and TGJ. Manuscript writing: TLY, JS, LDY. The authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no conflicts of interest.

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Figures

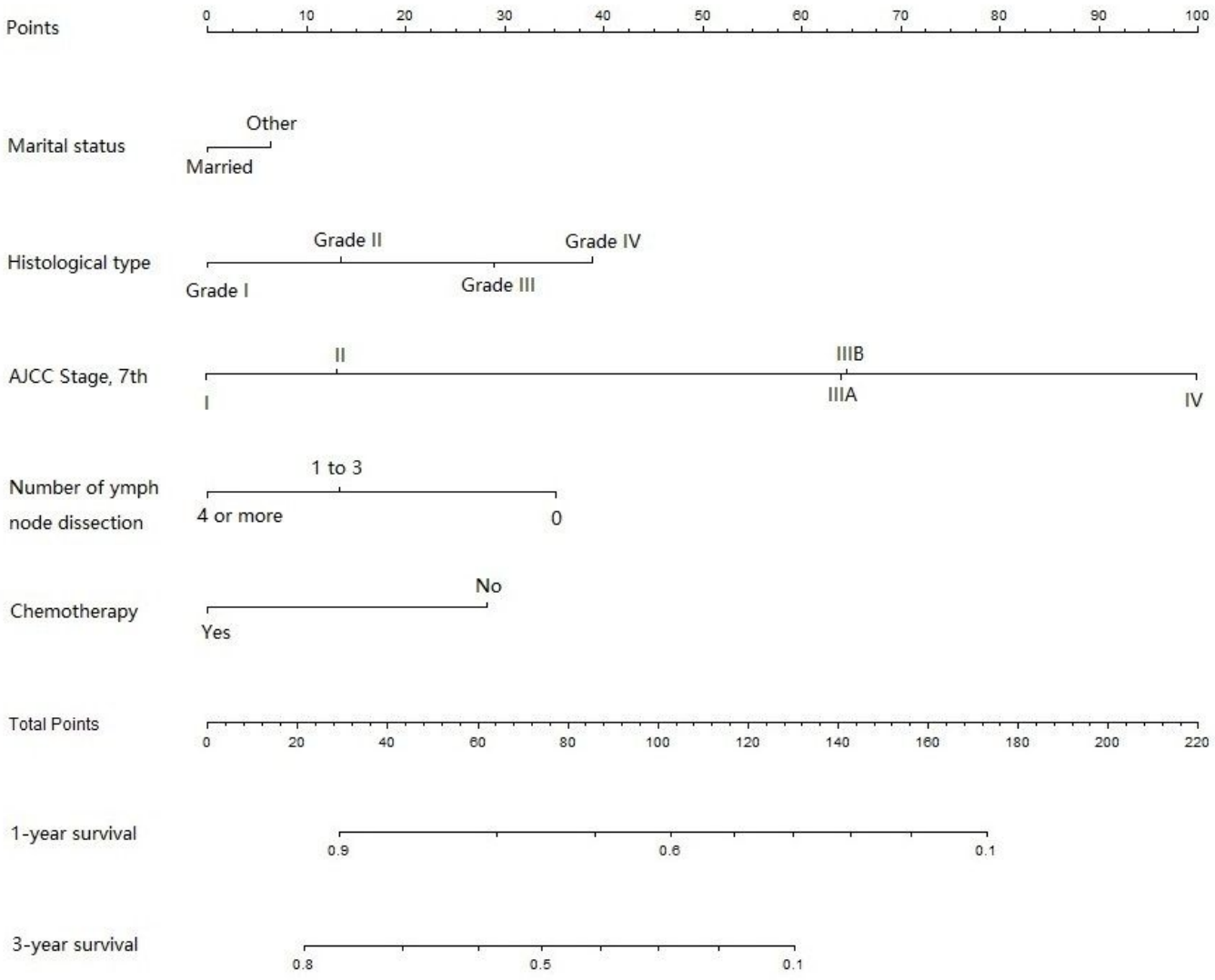

Figure 1

Nomogram for predicting 1- and 3-year overall survival. An individual patient's value is located on each variable axis, and the number of points received for each variable value can be determined by drawing a line upward. The sum of these numbers is located on the total points axis, and the likelihood of 1- or 3-year survival can be determined by drawing a line downward to the survival axes.

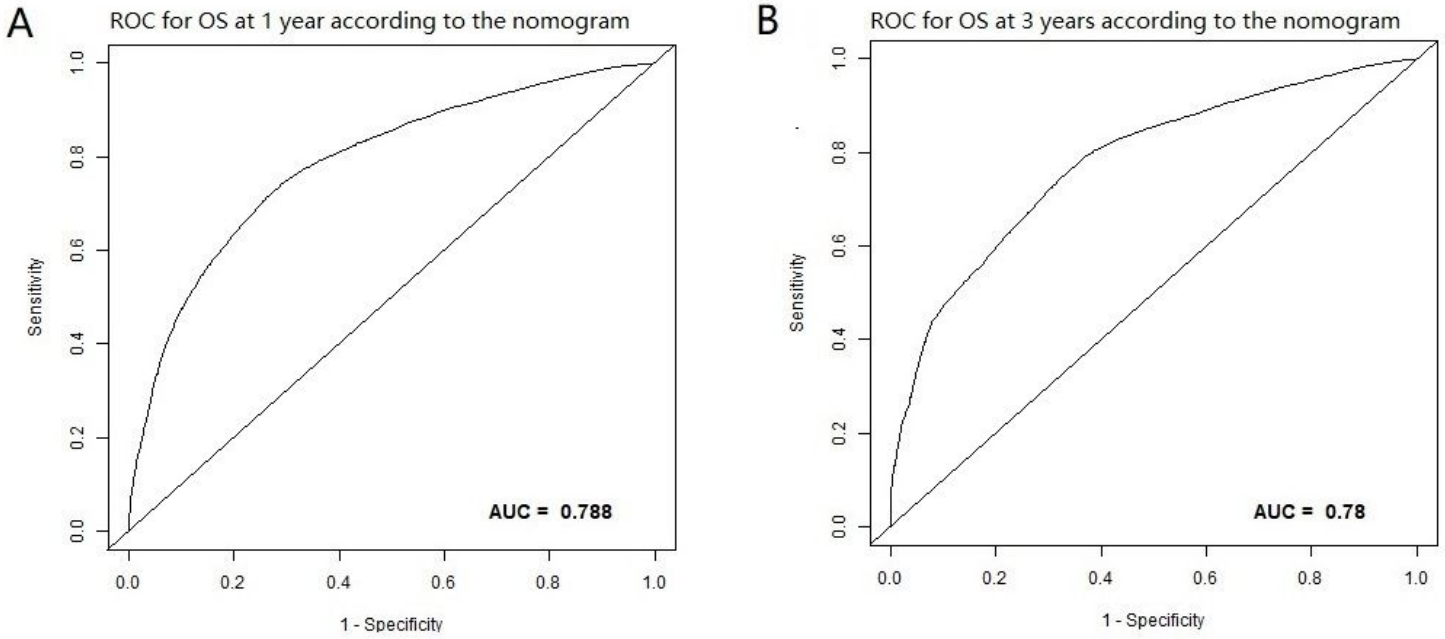

Figure 2

Receiver operating characteristic (ROC) curves for overall survival at 1- and 3- years according to the nomogram. The AUCs at 1 and 3 years for the nomogram were 0.789 and 0.7880, respectively.

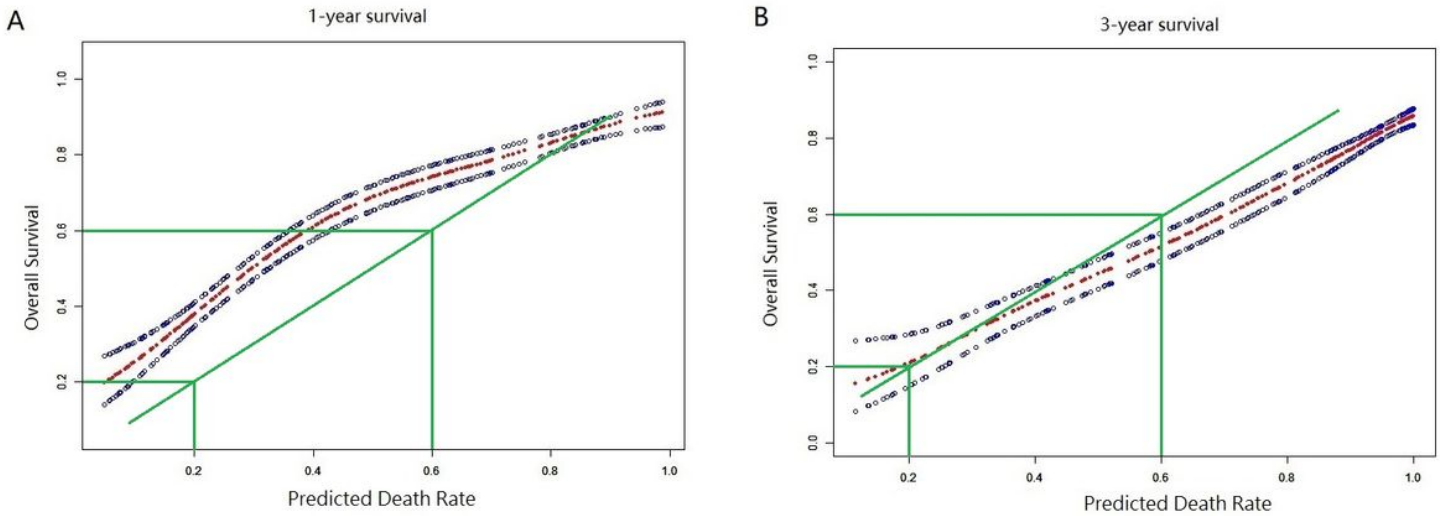

Figure 3

Calibration plot for overall survival prediction at 1- and 3- years according to the nomogram. Calibration curves showed acceptable agreement between the predicted death rate and observed OS values.

Supplementary Files

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- Supplementalmaterial.doc