Tumor marker based survival analysis for patients with pseudomyxoma peritonei of appendiceal origin: A retrospective cohort study

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Abstract

Background Pseudomyxoma peritonei (PMP) is a rare disease, the prognosis of overall survival (OS) is affected by many factors, present study aim to screen independent prediction indicators and establish a nomogram for PMP. Methods 119 PMP patients received cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in our center for the first time were included between 01/06/2013 and 22/11/2019 . The log-rank test was used to compare the OS rate among groups, subsequently, variables with P<0.10 were subjected to multivariate Cox model for screening independent prediction indicators. Finally, the nomogram prediction models will be established. Results Univariate analysis showed that Barthel Index Score, Albumin, D-Dimer, CEA, CA125, CA19-9, CA724, CA242, PCI, degree of radical surgery, histopathological grade were significant predictors for OS in PMP. At multivariate analysis, Sex, D-Dimer, CA125, CA19-9, PCI, and degree of radical surgery were independently associated with OS rate in PMP. A nomogram was plotted based on the independent predictive factors for PMP and undergone internal validation, ROC analysis was performed to calculate discrimination ability of prediction model, the area under curves (AUC) was 0.880 (95% CI : 0.806- 0.933). Conclusions Several factors (Sex, D-Dimer, CA125, CA19-9, PCI, and degree of radical surgery) have independent prognostic value for survival in PMP, the tumor based prediction model has a better prediction value, more researches are need to verify and improve the prediction model.

Background

Pseudomyxoma peritonei (PMP) is a rare disease characterized by disseminated mucinous ascites within peritoneal cavity which most often originating from perforated appendiceal epithelial neoplasma.[1] Smeenk et al.[2] estimated the incidence of PMP is about two per million annually from the Netherlands, other major reseach centers suggests that the actual incidence may be higher at 3–4 operable cases per million per year.[3] Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is recommended as the optimal treatment for PMP,[4] the recurrence rate has been obviously decreased than before, oppositely, the overall survival (OS) rate improved greatly.

The long-term outcomes after treatment are impressive for patients with PMP, nevertheless, there's still a significant recurrence of the disease.[5, 6] It has been confirmed that there are many factors related to the prognosis of PMP, for instense, sex[7], extent of previous surgery[8], histopathological grade of tumor, tumor marker levels[9], degree of radical surgery[1], and so on, among of tumor markers, CA19-9, CEA, and CA125 had been widely verified.[10]

Although several demonstrated factors could affect the prognosis of patients with PMP, to our best knowledge, there were very few studies had established prediction model for PMP patients. In present study, we want to reevaluate whether all the above traditional factors have predictive value for PMP patients, simultaneously, we intend to evaluate the predictive value of new tumor markers (CA724 and CA242) for PMP. On this foundation, a tumor markers based model to predict the prognosis of PMP will

be established, which may be helpful in the prognosis judgment and treatment intervention for PMP patients.

Methods

Patients

The ethics committee of Peking University Aerospace School of Clinical Medicine approved of present study, all patients signed informed consent before CRS and consented to be followed up after surgery.

We retrieved the diagnostic name of'pseudomyxoma peritonei'in the special follow-up database from Peking University Aerospace School of Clinical Medicine between 01/06/2013 and 22/11/2019, a total of 886 patients with PMP diagnosis were acquired. In order to ensure the reliability of the research, 734 patients with PMP whose operation were performed not in our center were excluded from present study, the detailed reasons were as follows, for first, different hospitals may use different instruments or methods to detect tumor markers, which cannot guarantee the consistency of test results; secondly, although CRS combined with HIPEC are the optimal treatment for PMP patients, we found that there were still many patients who had only undergone CRS or chemotherapy (intravenous or intraperitoneal) in non-specilist hospitals, PMP treatment is best in an inter professional team approach including specialists, oncology trained specialty nursing, and when necessary, pharmacists, collaborating for optimal patient care and outcomes[5], therefore, the above 734 subjects were ruled out.

Thus, the 152 remaining cases received CRS and HIPEC treatment in our center for the first time were included. Among the 152 subjects, one patients of sigmoid colon origin and four died after CRS due to serious infection during hospitalization were all excluded from this study. During the follow up period, 15 patients lost of follow up, afterwards, 132 patients were followed up, among of whom, whose follow up time less than 6 months were also excluded (n=13), ultimately, 119 PMP patients were included in present study, study schematic was shown in Fig.1.

Histopathological results of resected specimens were interpreted by two experienced pathologists according to the WHO 2010 classification, which were categorized into low-grade appendiceal mucinous neoplasms (LAMNs) and mucinous adenocarcinomas (MACAs). [11]

Follow up protocol

All patients were routinely followed up every 3 to 6 months, tumor markers (such as CEA, CA19-9, CA125, CA72-4 and CA242) and enhanced computed tomography (CT) of abdominopelvic were routinely examined, If any discomfort occurs during discharge, the patient should return to the hospital at any time. If the patient does not return to our hospital for further consultation, we will follow up the patient by telephone to record the the patient's examination results.

Endpoint event determination

Due to the limitation of medical conditions in china, most patients with PMP missed the opportunity for early operation for complete CRS (CCRS), so a large proportion of whom were performed maximal tumor debulking surgery (MTD), the endpoint event was the death of PMP patients.

Tumor markers determination

All tumor markers were determined within 7 days. All marker measurements were performed according to manufacturer instructions, CEA (ng/ml), CA125 (U/ml), and CA19-9 (U/ml) were measured by chemiluminescence immunoassay (CMIA) (Abbott, America), the same to CA724 (U/ml) (Autobio, China), while CA242 (kU/L) was tested by flow fluorescent technology (Luminex, America). Internal Quality Control (IQC) was performed for all five tumor markers before testing, at the same time, we also participated in the External Quality Assessment (EQC) twice a year.

peritoneal carcinomatosis index (PCI)

The PCI scoring system divides the abdomen into nine anatomical areas with four further areas of the small bowel. Tumor is assessed in each area and a score of 0–3 is given for each of the 13 areas (0 for no tumor, 1 for nodules <0.5cm, 2 for nodules between 0.5 and 5cm, and 3 for nodules >5cm). The total score is then calculated by adding all the scores, and ranges from 0 to 39[12].

CRS and HIPEC

The CRS of PMP was performed consistent with standard operation method, complete removal of all visible disease is scored as CC0 cytoreduction and residual disease less than 0.25cm is scored as CC1, CC0 and CC1 are considered CCRS. If the patient cannot achieve complete cytoreduction, debulking treatment would be performed, any residual tumor deposit between 0.25 and 2.5cm is scored as a CC2 cytoreduction while residual tumor deposits >2.5cm are scored as CC3 cytoreduction, CC2 and CC3 are considered as having MTD.[13] Once cytoreduction is complete, intra-operative hyperthermic chemotherapy is delivered. 5-fluorouracil (5-Fu) (1000mg) together with Cisplatin (80mg) heated to 43℃ and continuously infused using a HIPEC machine for 1h.

Statistical Analysis

Statistical analysis were performed by *SPSS* (Version 16.0), *MedCalc* (Version 15.2.2), *X-Tile* (3.6.1), and *R* Software (3.6.2). All continuous data will be compared by using *t* test or *ManneWhitney U* test, as appropriate. *Pearson's* χ^2 test or *Fisher's exact* test, where appropriate, was used for analysis of categorical data. The *Kaplan-Meier* method and *log-rank* test were used to compare the OS rate among groups, afterwards, variables with P<0.10 were subjected to multivariate *Cox* models, *Cox proportional hazards models* were used to calculate the hazard ratio and 95% confidence interval (CI). A nomogram was plotted by *R* software to facilitate risk assessment for PMP, the nomogram will be subjected to 1,000 bootstrap resamples for internal validation, and the model performance for predicting OS was evaluated

by calculating the concordance index (C-index). Two sided *p* values < 0.05 were considered statistically significant.

Results

Patient demographics

Among the 152 subjects, comparative analysis of the baseline data was performed between the included (*n*=119) and excluded (*n*=33) subjects, there was no significant difference in sex ratio, age, PCI, Barthel Index Score, and the degree of radical operation between the two groups (all *P*>0.05), however, different proportion of histopathological grading was found between the two groups (*P*<0.05) (Table 1).

There were 22 (18.49%) deaths occurred during the follow-up period of 119 included subjects, the present study were unable to calculate the overall cohort median survival time due to the low number of endpoints during follow-up period, the 1-year, 3-year, and 5-year survival rates were 95.4% (95%*CI*: 91.5-99.3), 75.4% (95%*CI*: 65.5-85.3), and 72.0% (95%*CI*: 60.5-83.5), respectively (Fig. 2).

Independent prognostic variables on survival

X-Tile software was used to calculate the best cut-point of continuous variables (Age, Barthel Index Score, Albumin, D-Dimer, CEA, CA125, CA19-9, CA724, CA242, and PCI), however, we did not calculate the cut-off value for Hemoglobin, because the Hemoglobin level for anemia diagnosis in female and male is different (110g/L for female and 120g/L for male).

At univariate analysis, Barthel Index Score, albumin, D-Dimer, CEA, CA125, CA19-9, CA724, CA242, PCI, degree of radical surgery, pathology were all significantly associated with OS rate in PMP. Although sex factor did not meet the criteria for inclusion in multivariate analysis, literature reported women tend to present at an earlier stage than men[1], we speculate that sex has a great influence on the prognosis of PMP, ultimately, sex was also included into multivariate analysis. After *Cox* proportional hazard regression (Backward stepwise: likelihood ratio) analysis, sex, D-Dimer, CA125, CA19-9, PCI, and degree of radical surgery were independently associated with OS in PMP.(Table 2).

Prognostic Nomogram for OS

A nomogram that incorporated the above significant prognostic factors was established (Fig.3). The calibration curve for nomogram was shown in Fig 4. The C-index was calculated by the following method, when *Cox regression* analysis generated independent variables, which also including SUR and XBE, afterwards, we calculated new variables risk based on the formula: risk=1-SUR**EXP (XBE), according to the risk variable, ROC analysis was performed to calculate discrimination ability of prediction model, the area under curves (AUC) was 0.880 (95%*CI*: 0.806- 0.933) (Fig. 5).

Discussion

PMP is a rare disease, which tends to be an incidental finding either on imaging or during exploratory surgery performed for other indications. Present study demonstrated several independent factors for predicting survival of PMP patients, including sex, D-Dimer, CA125, CA19-9, PCI, and degree of radical surgery. Subsequently, we established a nomogram prediction model based on the identified significant prognostic factors, afterwards, the model was subjected to bootstrap internal validation by calibration curve and C-index.

Among the three routinely used tumor markers in PMP[14], CA19-9 seems to be optimal independent prognosticators for PMP, which not only could predict survival but also recurrence, a lot of researches confirmed this conclusion[15-18], present study result was entirely consistent with the previous studies, CA19-9 possess highest prediction coefficient and was the best prediction index in our predition model. CA125 can predict ovarian cancer in general practice[19], which is also expressed in peritoneal malignancy, and can be elevated in patients with any source of peritoneal irritation.[1] In present study, CA125 seems also to be a usefull marker for prediction survival of PMP, a high CA125 level denotes a poor prognosis for PMP. Although univariate analysis revealed elevated CEA level was associated with worse survival in PMP, nevertheless, multivariate analysis did not reach a significant statistics, former study also confirmed CEA owns low value in prediction survival of PMP[15].

Present study also evaluated the predicting value of new tumor markers (CA724 and CA242) in PMP patients, univariate analysis all showed elevated levels of the two markers were all associated poor survival for PMP, while in multivariate analysis, all the two did not show significant prognostic value, due to extremely low incidence rate of PMP, fewer cases were included in present study, therefore, researches with larger sample size and longer follow-up time are needed to assess the predictive value of CA724 and CA242 for PMP.

Gender is considered an important factor for patient's oncologic outcome[20]. A meta-analysis showed that there was an influence of gender on OS in colorectal cancer patients, females had significantly better OS than males. [21] Also, there was a better OS in women compared to men in bladder and kidney cancer patients. [20] This study found that males with PMP had a poor survival than females, which is consistent with previous research reports[2, 7], women tend to present at an earlier stage than men for secondary to the rapidly enlarging ovarian masses, which become symptomatic or are obvious clinically[1], so women can get more timely treatment. These results suggest that gender seems to be a significant factor influencing survival results among PMP patients.

Elevated pretreatment D-Dimer level has been confirmed markedly correlated with TNM staging[22] and associated with poor OS in patients with solid tumors [23], for instance, colorectal cancer[22], pancreatic carcinoma[24], lung cancer[25, 26], and so on. Interestingly, we discovered a high D-Dimer level was also associated with a poor survival prognosis in PMP, to our knowledge, this was the first study to evaluate the prediction value of D-Dimer in PMP, in the future clinical practice, clinicians should pay more attention to the D-Dimer level of in PMP patients, the analysis of preoperative D-Dimer can be useful in predicting postoperative survival rate for PMP.

Tumor burden is a prognostic factor in predicting OS for cancer patients. The extent of disease in PMP is assessed by the PCI, a PCI≥20 always representing unresectable disease.[27] Former studies confirmed that PCI was the risk factors for postoperative morbidity in univariate analysis, however, no statistical significant correlation was found during the multivariate analysis[28], however, in present study, we found a higher PCI denotes a poor prognosis in PMP, it is easy to understand, a high tumor load often means a poor prognosis, this difference may be due to the small number of cases (*n*=53) and different variables included in the previous study. Completeness of cytoreduction is one of the most important prognostic factors for PMP[1], present study revealed that the MTD subgroup had a obvious poor survival than the CCRS group, this result was similar to the previous studies[29, 30], differently, a large proportion of participants in the former study can reach CCRS, while in our study, the majority of patient can only undergone major debulking surgery, we speculate that most PMP patients in China could not get correct PMP diagnosis timely and receive standard treatment. To summarise, a higher PCI and MTD indicates a poor survival for PMP, and vice versa.

A part of researchers reckon that the prognosis of PMP correlates closely to histopathological classification[31], oppositely, different opinions suggest that PMP is unlike other tumors, histopathology does not reliably predict tumor behaviour[32]. Present study revealed a high grade histopathology denotes a poor survival for PMP in univariate analysis, while in multivariate analysis, there was no correlation between histopathological grade and OS rate, so we speculate that predictive value of histopathological grade for PMP is relatively small. Similarly, although Barthel Index Score and albumin seemed to associated with prognosis of PMP in univariate analysis, which was similar to the former study[33, 34], the multivariate analysis did not reach significant difference, Barthel Index Score reflect the ability to perform the activities of daily life[35] and albumin reflect nutrition condition, which suggest that those effects on the prognosis of PMP patients is limited, but this conclusion needs to be confirmed by a large number of studies.

The present study established prognostic model for OS in PMP, the discrimination ability of OS in PMP was 0.880, so we think this is a valuable prediction model for PMP, which could provide more help for the prognosis judgment and treatment intervention of PMP patients, however, more studies are needed to confirm the conclusion, in particular with prospective large sample studies.

There were several limitations of present study. Firstly, due to the limitation of retrospective study, some data have not been followed up. Secondly, because the survival time of PMP patients is significantly longer than before, the proportion of end-point events is relatively small, it may lead to the instability of statistical conclusions, therefore, a longer follow-up is needed to confirm the conclusions in the future. Thirdly, the predictive accuracy and discriminative ability of established prognositic model in present study only undergone internal validation, a external validation with a separate cohort will be realized in the future. Finally, although the prediction model is relatively good for PMP, we think that there is still some other factors not included into the prediction model, such as KRAS mutations, which had been proved independently prognostic for progress free survival (PFS) in PMP patients, we speculate that

KRAS mutations may also be independent prognostic factors for OS in PMP, future work will further verify this hypothesis.

Conclusions

To conclude, several factors (sex, D-Dimer, CA125, CA19-9, PCI, and degree of radical surgery) have independent prognostic value for OS in PMP, the prediction model based on the above factors possessed a better prediction value, more researches are need to verify and improve the prediction model.

Abbreviations

PMP-pseudomyxoma peritonei, CRS-cytoreductive surgery, HIPEC-hyperthermic intraperitoneal chemotherapy, OS-overall survival, LAMNs-low-grade appendiceal mucinous neoplasms, MACAs-mucinous adenocarcinomas, CT-computed tomography, CCRS- complete cytoreductive surgery, MTD-maximal tumor debulking surgery, CMIA-chemiluminescence immunoassay, IQC-internal quality control, EQC- external quality assessment, PCI-peritoneal carcinomatosis index, AUC- area under curves.

Declarations

-Ethics approval and consent to participate

The study protocol was established, according to the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Peking University Aerospace School of Clinical Medicine. Ethics approval No. (20200113-LCYJ-01)

-Consent to publish

Not applicable.

-Availability of data and materials

All data analysed during present study were included in this published article.

-Competing interests

Not applicable.

-Funding

Not applicable.

-Authors' contributions

Sl W was responsible for database establishment and PMP patients follow-up, Mj B, Gw L, Rq M, Y C, Nz H, M Z were responsible for design, implementation, data statistical and articles writing, Yy L was responsible for interpretation of pathological results, while Hb X was responsible for surgical operation. All authors read and approved the final manuscript.

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Tables

Table 1. Baseline data between included and excluded patients of PMP

	Included group(*n*=119)	Excluded group (*n*=33)	*P*-values
Sex(Male/Female)	80/39	20/13	0.478
Age (years)	58±12	57±10	0.552
Barthel Index Score	95±11	93±14	0.608
Chemotherapy prior to CRS			0.229
No	112	28	
Yes	7	4	
Data missing	0	1	
Operating time (hours)	8(6-9)	8(7-10)	0.279
PCI	27±9	28±10	0.420
Degree of radical operation			0.251
CCRS	31	10	
MTD	88	17	
Data missing	0	6	
Pathology			0.004
Low grade	92	16	
High grade	24	14	
Data missing	3	3	
Signet ring cell histology	9	5	—
Hospital stay (days)	26±6	27±9	0.351
Number of deaths during follow-up	22	—	—

Pearson's X^2 test or Fisher's exact test, where appropriate, was used for analysis of categorical data while inter group continuous data was compared using independent sample *t* test.

* the hemoglobin normal range of male was no less than 120g/L, as for female, it was no less than 110g/L.

—PMP-pseudomyxoma peritonei; CRS-cytoreduction surgery; PCI-peritoneal carcinomatosis index; CCRS-complete cytoreduction surgery; MTD- maximal tumor debulking

Table 2. Univariate and multivariate analysis of factors predicting overall survival in patients with PMP

Variable	No.	Univariate analysis		Multivariate analysis		Selected Factors for Building the Model	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Sex							
Female	80	Ref	—	Ref	—	Ref	—
Male	39	1.95(0.82-4.64)	0.177	3.33(0.99-11.23)	0.052	3.38(1.00-11.46)	0.050
Age (years)							
0-50	25	Ref	—	—	—	—	—
>50	94	1.66(0.56-4.86)	0.281	—	—	—	—
Chemotherapy prior to CRS							
No	112	Ref	—	—	—	—	—
Yes	7	0.70(0.13-3.91)	0.727	—	—	—	—
Barthel Index Score							
0-70	7	Ref	—	—	—	—	—
>70	98	0.18(0.01-2.24)	0.002	—	—	—	—
Data missing	14	—	—	—	—	—	—
Albumin (g/L)							
0-33.7	33	Ref	—	—	—	—	—
>33.7	86	0.45(0.17-1.20)	0.055	—	—	—	—
Hemoglobin (g/L)							
Normal	75	Ref	—	—	—	—	—
Anemia	44	1.40(0.58-3.41)	0.427	—	—	—	—
D-Dimer (mg/L)							
0-1948	104	Ref	—	Ref	—	Ref	—
>1948	11	3.66(0.74-18.00)	0.005	3.93(1.20-12.82)	0.024	3.86(1.18-12.66)	0.026
Data missing	4	—	—	—	—	—	—
Preoperative CEA levels (ng/ml)							
0-17.3	46	Ref	—	—	—	—	—
>17.3	73	2.87(1.24-6.64)	0.027	—	—	—	—
Preoperative CA125 levels (U/ml)							
0-120.7	81	Ref	—	Ref	—	Ref	—
>120.7	38	5.62(2.21-14.33)	0.001	4.87(1.83-12.94)	0.002	4.98(1.89-13.16)	0.001
Preoperative CA19-9 levels (U/ml)							
0-27.8	59	Ref	—	Ref	—	Ref	—
>27.8	60	5.41(2.29-12.77)	0.001	7.64(2.54-22.99)	0.001	7.64(2.54-23.03)	0.001
Preoperative CA724 levels (U/ml)							
0-47.5	50	Ref	—	—	—	—	—
>47.5	67	3.01(1.30-6.96)	0.021	—	—	—	—
Data missing	2	—	—	—	—	—	—
Preoperative CA242 levels (kU/L)							
0-395.9	91	Ref	—	—	—	—	—
>395.9	23	4.04(1.42-11.53)	0.001	—	—	—	—
Data missing	5	—	—	—	—	—	—
PCI							
0-27	57	Ref	—	Ref	—	Ref	—
>27	62	2.36(1.02-5.46)	0.060	3.89(1.47-10.30)	0.006	3.86(1.46-10.21)	0.007
Degree of radical surgery							
CCRS	31	Ref	—	Ref	—	Ref	—
MTD	88	4.37(1.76-10.84)	0.027	5.27(1.20-23.12)	0.028	5.25(1.20-23.06)	0.028
Pathology							
Low grade	92	Ref	—	—	—	—	—
High grade	24	2.60(0.88-7.72)	0.025	—	—	—	—
Data missing	3	—	—	—	—	—	—

—PMP-pseudomyxoma peritonei; PCI-peritoneal carcinomatosis index; CCRS-complete cytoreductive surgery; MTD-maximal tumor debulking

Figures

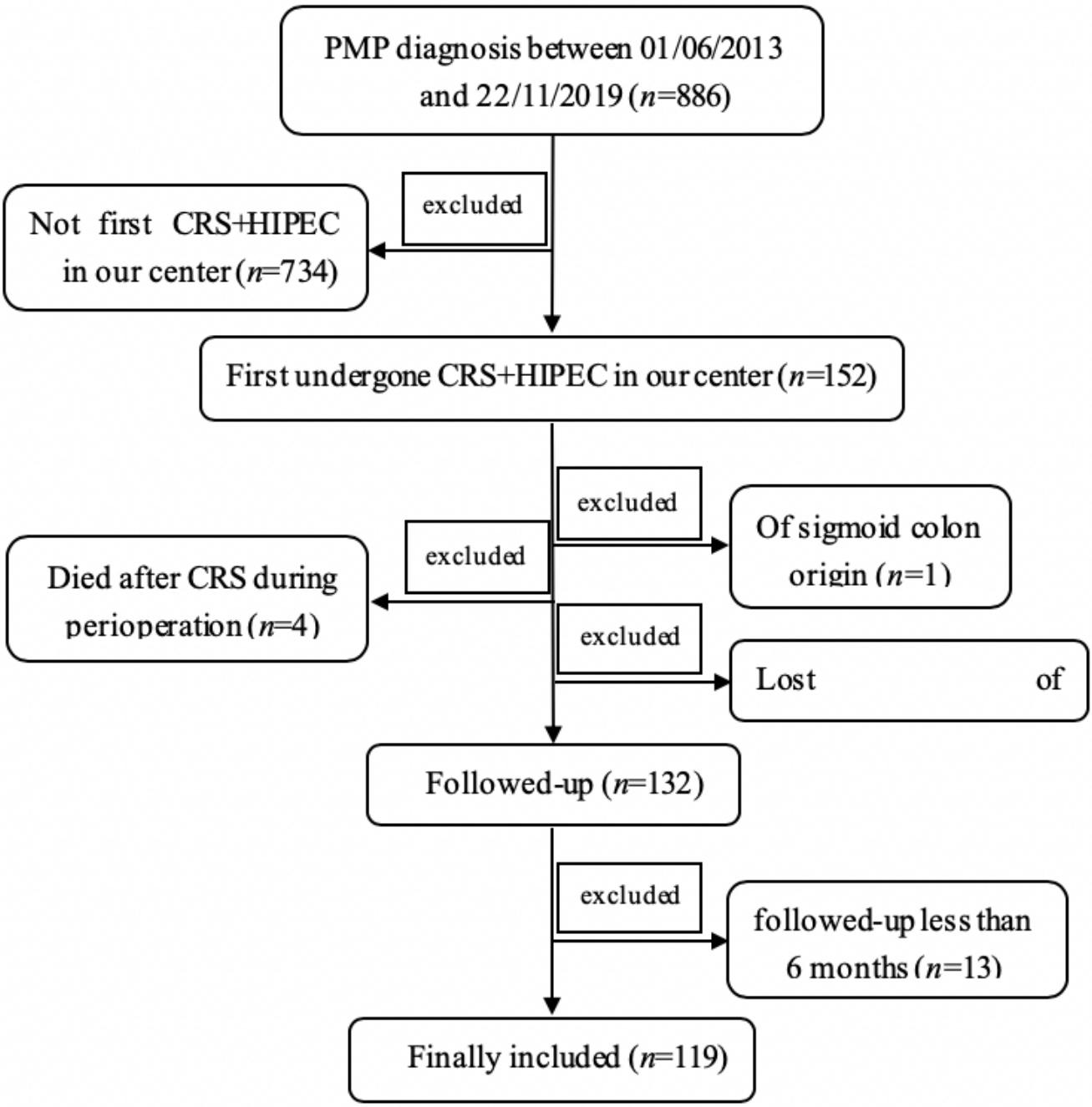

Figure 1

Study schematic. A total of 886 patients with PMP was retrieved , 734 patients not undergone CRS+HIPEC in our center for the first time were excluded the remaining 152 patients undergone CRS+HIPEC were included, patients of sigmoid colon origin (n=1) and died during hospitalization (n=4) were excluded. Patients lost of follow up (n=15) and whose follow up time less than 6 months (n=13) were also excluded, ultimately, 119 PMP patients were included in present study. PMP-pseudomyxoma peritonei; CRS- cytoreductive surgery; HIPEC-hyperthermic intraperitoneal chemotherapy.

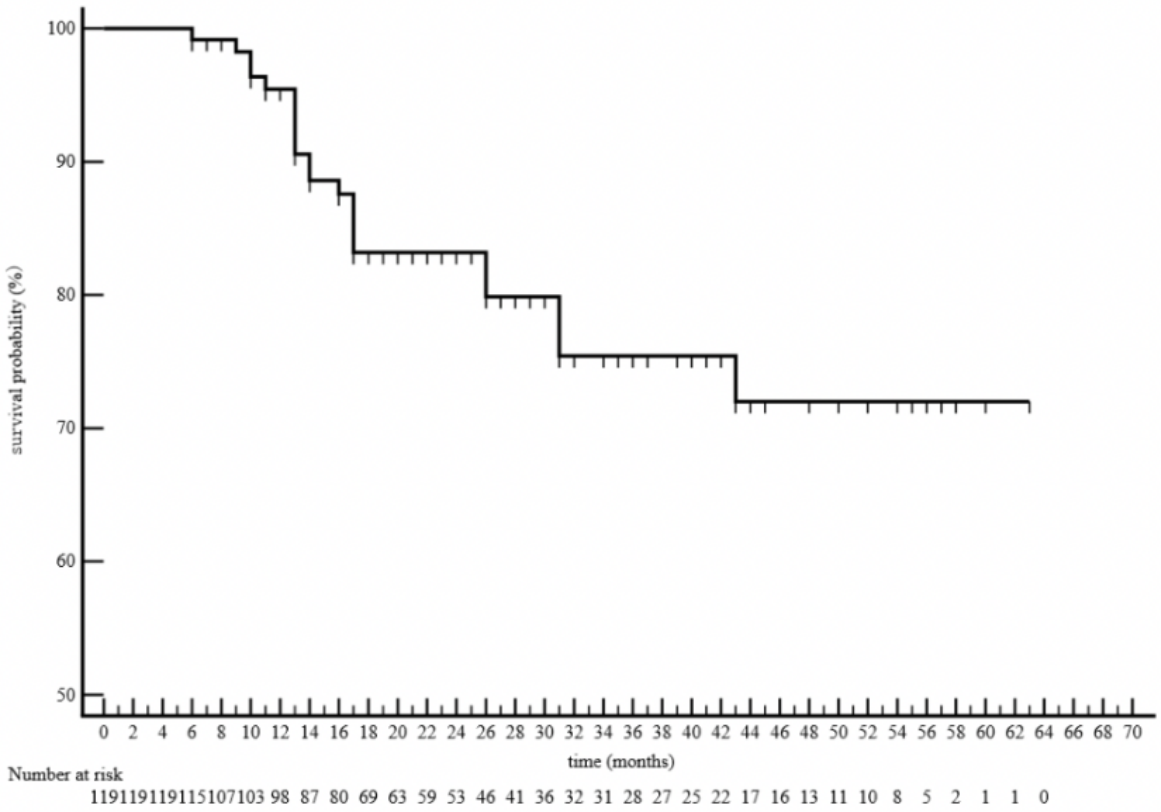

Figure 2

Overall survival curve of 119 PMP patients.

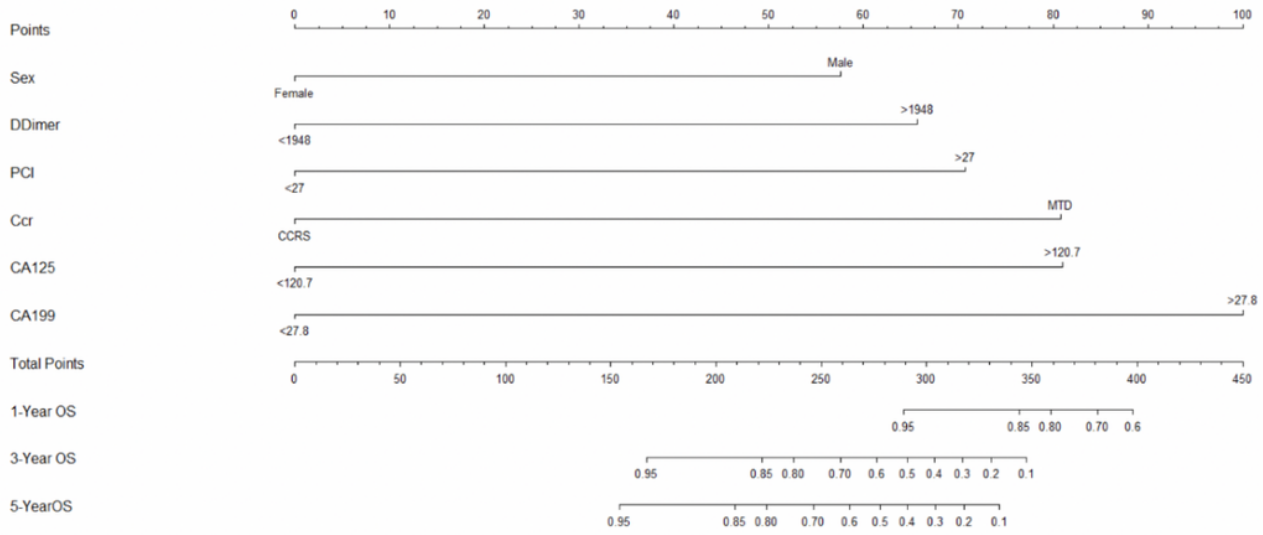

Figure 3

Nomogram for prediction of overall survival rate in PMP patients.

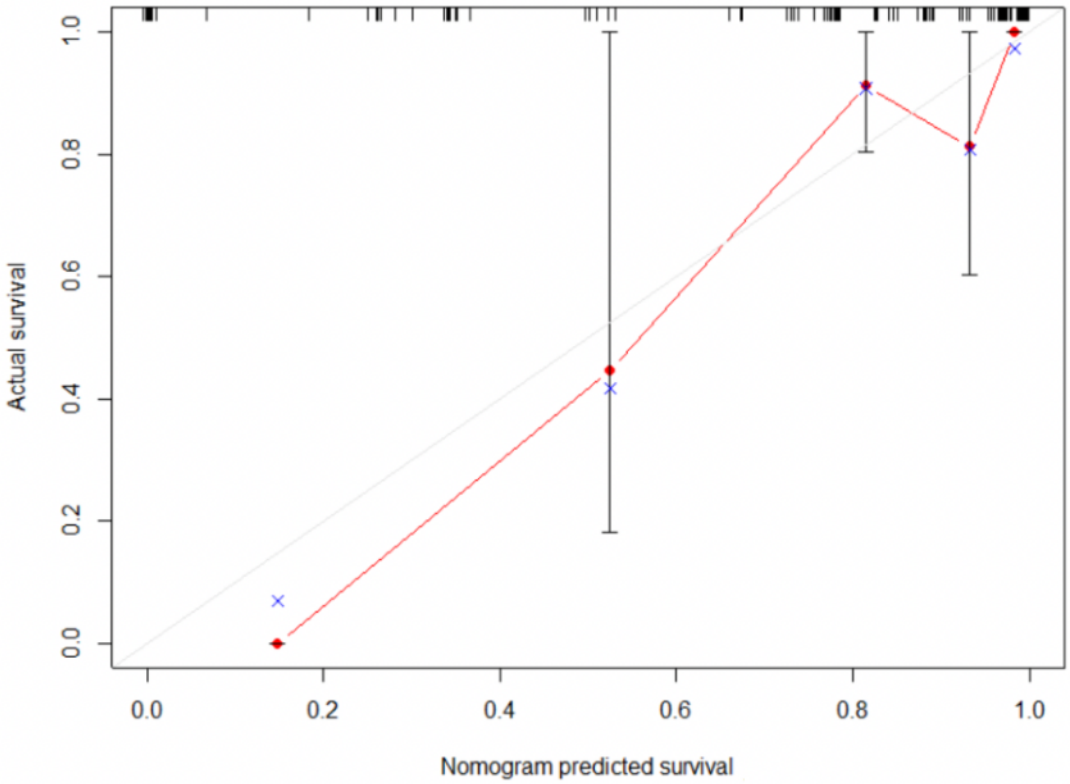

Figure 4

Calibration curve for nomogram-predicted overall survival of PMP patients.

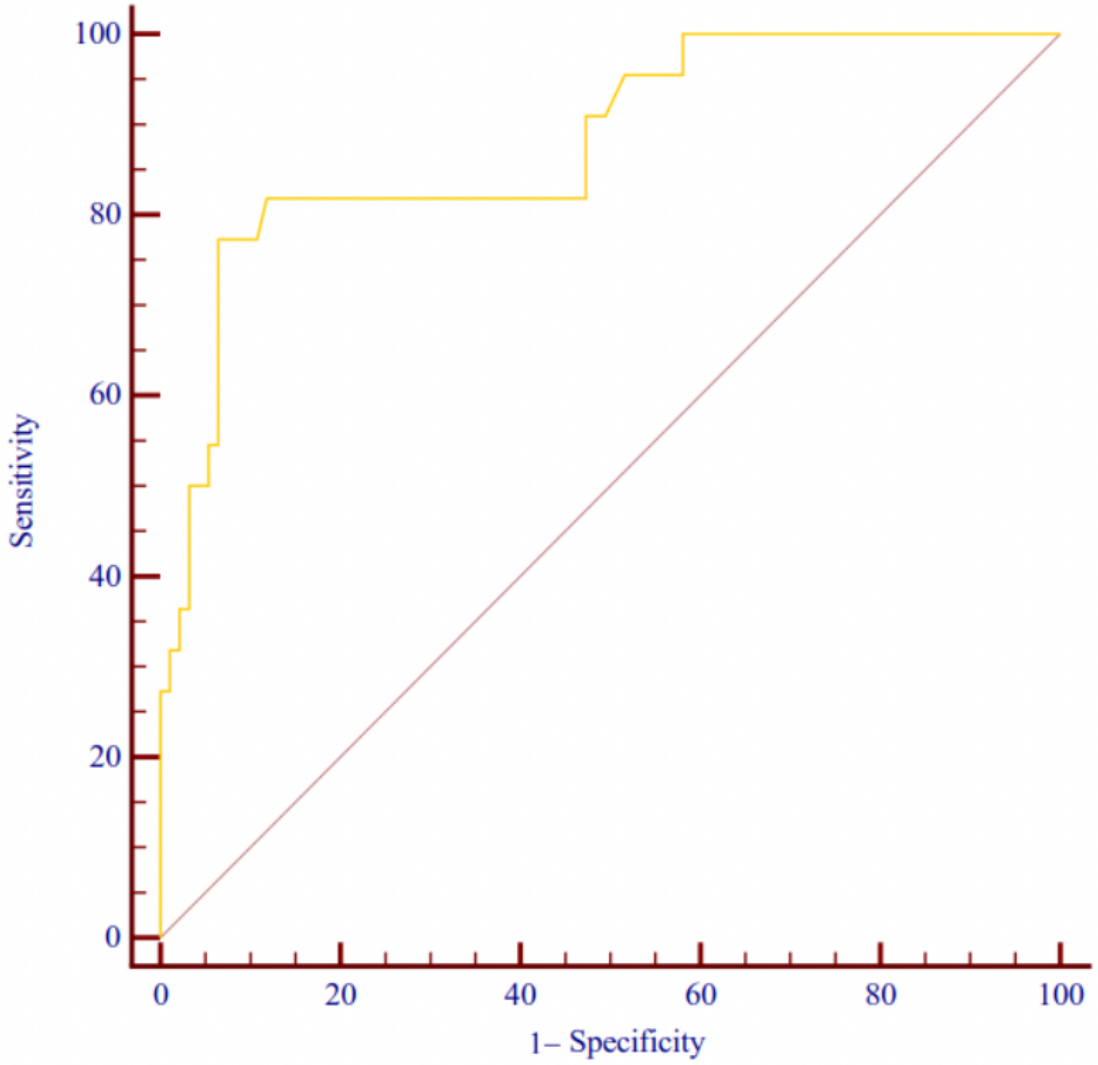

Figure 5

ROC analysis of nomogram prediction model in PMP patients.