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 for PMP and establish prediction model for OS rates in 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 prediction models for OS in PMP 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, and degree of radical surgery were independently associated with OS rate in PMP. ROC analysis was performed to calculate discrimination ability of prediction model and the area under curves (AUC) was 0.902 (95% CI: 0.823-0.954). Finally, nomogram was plotted by the independent predictive factors for PMP.

Conclusions Several factors (sex, degree of radical surgery, D-dimer, preoperative CA125 and CA19-9) have independent prognostic value for survival in PMP, the tumor based prediction model has 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 research 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 patients with PMP[4] the recurrence rate has been obviously decreased than before, oppositely, the overall survival (OS) rate improved greatly.

Although the long-term outcomes after treatment are impressive for patients with PMP, 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 instance, 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 are 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, subsequently, 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 for the prognosis judgment and treatment intervention in 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-specialist hospitals, PMP treatment is best in an interprofessional 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. 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 patient's examination results.

Endpoint event determination
Due to the limitation of medical conditions in China, most patients with PMP missed the opportunity of 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 5 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°C 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 \( \text{ManneWhitney} \ U \) test, as appropriate. \( \text{Pearson's} \ c^2 \) test or \( \text{Fisher's exact} \) 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. Two sided \( p \) values < 0.05 were considered statistically significant.
Results

Patient demographics

152 PMP subjects underwent CRS and HIPEC for the first time in our center, one patients of sigmoid colon origin and four died after CRS due to serious infection during hospitalization were 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 Figure 1.

In order to avoid bias in the study population as much as possible, 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).

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 (Figure 2).

Correlation of serum tumor markers and PCI

The Spearman correlation between PCI and serum preoperative CEA, CA125, CA19-9, CA724, CA242 were 0.269 \((P=0.003)\), 0.259 \((P=0.005)\), 0.352 \((P=0.001)\), 0.243 \((P=0.008)\), 0.237 \((P=0.012)\), respectively.

Impact of independent variables on patient survival

The ability to parse tumors into subsets based on biomarker expression has many clinical applications, many former studies employed the upper limit of reference range of tumor markers as the best cut-point. In 2004, Camp, R. L.[14] reported \textit{X-Tile} plot could serve as a new bio-informatics tool to visualize the best cut-points for creating such divisions. In this study, \textit{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 ) in independent variables, 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 factor was also included into Cox regression analysis. At multivariate analysis, sex, D-dimer, CA125, CA19-9, and degree of radical surgery were independently associated with OS rate in PMP (Table 2). Cox regression analysis generated variables including SUR and XBE, afterwards, we calculated new variables risk based on generated variables, the formula was as follows: 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 0.902 (95% CI: 0.823- 0.954) (Figure 3). Finally, the independent predicting factors were used for drawing nomogram for PMP (Figure 4).

Discussion

PMP is a rare disease, which tends to be an incidental finding either on imaging or during exploratory surgery performed for other indications. In present study, we demonstrated several factors for predicting OS rate of PMP, such as degree of radical surgery and so on, subsequently, we established prediction model for OS in PMP. Cox proportional hazard regression model showed that male, MTD, an increase of preoperative CA125 and CA19-9 level, and elevated D-dimer level were independently associated with poor survival for PMP. Among the three commonly used tumor markers for PMP[15], CA19-9 seems to be optimal independent prognosticators for PMP, which not only could predict survival but also predict recurrence, a lot of researches confirmed this conclusion[16-19]. CA125 can predict ovarian cancer in general practice[20], 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, researches with larger sample size and longer follow-up time are needed to verify this conclusion. 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[16]. Present study also evaluated CA724 and CA242 in PMP patients, univariate analysis all showed elevated levels of the two markers were all associated poor survival of PMP, while in multivariate analysis, CA724 did not show significant prognostic value for survival of PMP, while CA242 was closed to statistical significant, more researches are needed to affirm it.

Completeness of cytoreduction is one of the most important prognostic factors for PMP[1], the present study revealed that MTD subgroup had a obvious poor survival than the CCRS group, this result was similar to the previous studies[21,22], 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 cannot get correct PMP diagnosis timely and receive standard treatment. This study found that male of PMP had a low level OS rate than female, 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. The extent of disease is assessed by the PCI, a $\text{PCI} \geq 20$ always representing unresectable disease,[23] 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.[24] Present study found that a high D-dimer level was associated with a poor survival for 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.

A part of researchers reckon that the prognosis of PMP correlates closely to histopathological classification,[25] oppositely, different opinions suggest that PMP is unlike other tumors, histopathology does not reliably predict tumor behaviour, including the likelihood of recurrence.[26] Present study revealed a high grade histopathology denotes a poor survival for PMP in univariate analysis, while in multivariate analysis, no correlation between histopathological grade and OS rate was found, 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,[27,28] the multivariate analysis did not reach significant difference, Barthel Index Score reflect the ability to perform the activities of daily life[29] and albumin reflect nutrition condition in PMP, 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 0.902, 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. First, 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. 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.

**Conclusion**

To conclude, several factors (sex, degree of radical surgery, D-dimer, preoperative CA125 and CA19-9) have independent prognostic value for OS rate in PMP, the prediction model based on the above factors has 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 datas 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 $c^2$ 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 debulk

Table 2. Univariate and multivariate analysis of factors predicting overall survival in patients with PMP
| Variable                               | Number | univariate analysis | multivariate analysis |
|----------------------------------------|--------|---------------------|-----------------------|
|                                        |        | HR (95%CI)          | P values              |
|                                        |        |                     | HR (95%CI)            | P values                |
| Sex                                    |        |                     |                       |                        |
| Female                                 | 80     | Ref                 | —                     | Ref                    |
| Male                                   | 39     | 1.95(0.82-4.64)     | 0.177                 | 44.07(2.64-736.21)     | 0.008                  |
| 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                 | —                     | Ref                    |
| >70                                    | 98     | 0.18(0.01-2.24)     | 0.002                 | 0.308(0.04-2.52)       | 0.272                  |
| Data missing                           | 14     | —                   | —                     | —                      |
| Albumin (g/L)                          |        |                     |                       |                        |
| 0-33.7                                 | 33     | Ref                 | —                     | Ref                    |
| >33.7                                  | 86     | 0.45(0.17-1.20)     | 0.055                 | 0.40(0.10-1.64)        | 0.203                  |
| 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                    |
| >1948                                  | 11     | 3.66(0.74-18.00)    | 0.005                 | 5.62(1.17-27.03)       | 0.031                  |
| Data missing                           | 4      | —                   | —                     | —                      |
| Preoperative CEA levels (ng/ml)        |        |                     |                       |                        |
| 0-17.3                                 | 46     | Ref                 | —                     | Ref                    |
| >17.3                                  | 73     | 2.87(1.24-6.64)     | 0.027                 | 1.12(0.17-7.39)        | 0.905                  |
| Preoperative CA125 levels (U/ml)       |        |                     |                       |                        |
| 0-120.7                                | 81     | Ref                 | —                     | Ref                    |
| >120.7                                 | 38     | 5.62(2.21-14.33)    | 0.001                 | 8.78(1.17-65.94)       | 0.035                  |
| Preoperative CA19-9 levels (U/ml)      |        |                     |                       |                        |
| 0-27.8                                 | 59     | Ref                 | —                     | C                      |
| >27.8                                  | 60     | 5.41(2.29-12.77)    | 0.001                 | 7.64(1.01-57.74)       | 0.049                  |
| Preoperative CA724 levels (U/ml)       |        |                     |                       |                        |
| 0-47.5                                 | 50     | Ref                 | —                     | Ref                    |
| >47.5                                  | 67     | 3.01(1.30-6.96)     | 0.021                 | 2.69(0.51-14.31)       | 0.245                  |
| Data missing                           | 2      | —                   | —                     | —                      |
| Preoperative CA242 levels (kU/L)       |        |                     |                       |                        |
| 0-395.9                                | 91     | Ref                 | —                     | Ref                    |
| >395.9                                 | 23     | 4.04(1.42-11.53)    | 0.001                 | 7.60(0.79-72.15)       | 0.079                  |
| Data missing                           | 5      | —                   | —                     | —                      |
| PCI                                    |        |                     |                       |                        |
| 0-27                                   | 57     | Ref                 | —                     | Ref                    |
| >27                                    | 62     | 2.36(1.02-5.46)     | 0.060                 | 3.46(0.75-16.07)       | 0.113                  |
| Degree of radical surgery              |        |                     |                       |                        |
| CCRS                                   | 31     | Ref                 | —                     | Ref                    |
| MTD                                    | 88     | 4.37(1.76-10.84)    | 0.027                 | 15.03(1.39-162.16)     | 0.026                  |
| Pathology                              |        |                     |                       |                        |
| Low grade                              | 92     | Ref                 | —                     | Ref                    |
| High grade                             | 24     | 2.60(0.88-7.72)     | 0.025                 | 1.83(0.37-9.04)        | 0.460                  |
| 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

ROC analysis of overall survival prediction model in PMP based on the multivariate Cox regression
Figure 4

Nomogram for prediction of overall survival rate in PMP patients