Tumor Markers Reflect Tumor Burden of Pseudomyxoma Peritonei

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Abstract

Background: Accurate assessment of preoperative tumor burden contribute to formulate a scientific surgical plan and improve the prognosis of patients with pseudomyxoma peritonei (PMP). Present study aimed to assess whether preoperative serum tumor markers could reflect tumor burden.

Methods: A total of 198 PMP patients were included, the peritoneal cancer index (PCI) was employed to reflect tumor burden for PMP patients. All participants were divided into low ($PCI \leq 19$) and high ($PCI \geq 20$) tumor burden subgroups according to PCI. All serum tumor markers (carcinoembryonic antigen (CEA), carbohydrate antigen 125 (CA125), CA 19-9, CA 724, and CA 242) were compared between the two subgroups. The correlation between tumor markers and PCI will be calculated and compared with each other. Two-sided P value less than 0.05 is considered statistically significant.

Results: The level of CEA (ng/ml), CA125 (U/ml), CA 19-9 (U/ml), CA 724 (U/ml), and CA 242 (kU/L) between low and high tumor burden subgroup were [3.35 (1.64, 16.31) vs. 23.12 (8.80, 67.62), $Z = -5.381$, $p < 0.001$], [19.10 (7.61, 56.95) vs. 72.75 (40.41, 130.55), $Z = -5.978$, $p < 0.001$], [6.17 (3.26, 16.22) vs. 45.50 (13.95, 123.61), $Z = -5.413$, $p < 0.001$], [7.89 (1.57, 45.10) vs. 84.61 (33.87, 236.93), $Z = -5.898$, $p < 0.001$], and [13.32 (3.39, 96.50) vs. 150.00 (102.13, 308.88), $Z = -5.166$, $p < 0.001$], respectively. The Spearman correlation between tumor markers and PCI were 0.415 for CEA ($p < 0.001$), 0.372 for CA 125 ($p < 0.001$), 0.466 for CA 19-9 ($p < 0.001$), 0.379 for CA 724 ($p < 0.001$), and 0.317 for CA 242 ($p < 0.001$), respectively.

Conclusions: Preoperative serum tumor markers could moderately reflect tumor burden for PMP, which may contribute to develop a better surgical plan before operation.

Background

Pseudomyxoma peritonei (PMP) is a rare abdominal cancer characterized by extensive growth of mucinous tumor in the peritoneal cavity^[1]. The reliable epidemiological data is still difficult to determine until now, a survey suggested that the prevalence rate of PMP was 22 per million in European countries^[2]. The main characteristic feature of PMP is the abundant secretion of mucinous ascites, which slowly fills the peritoneal cavity and leads to abdominal distension^[3]. Complete cytoreduction surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) were the recommended standard treatment for PMP^[4].

The extent of peritoneal involvement was quantified by the peritoneal cancer index (PCI)^[5], which is the surgical variable commonly used to determine the feasibility of tumor reduction^[6]. PCI is a rather well established scoring system with scores from 0 to 39 and also been employed to reflect tumor burden in PMP patients.

Although the goal of CRS is to remove all visible tumors, however, when PMP patients with a $PCI \geq 20$ often representing unresectable disease^[7], hence, usually PCI 0–19 is considered low burden disease

while PCI 20–39 is considered high burden disease^[8]. Furthermore, former study reported a higher PCI was correlated with poor prognosis in PMP patients^[9]. For these reasons, accurate preoperative determination of the PCI is critical to optimize the selection of patients who will benefit from CRS.

To date, several investigational modalities could reflect tumor burden of peritoneal surface malignancy and identify appropriate surgical candidates, for instance, contrast-enhanced multi-sliced computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), laparoscopy, and serum tumor markers^[10]. CT was the fundamental imaging modality, a research showed there was a moderately good correlation between the CT-PCI and surgical PCI with a correlation coefficient of 0.65, however, CT in prediction of PCI was related to the experience of the radiologist^[11]. A former study had demonstrated the number of elevated tumor markers was positively correlated with pre-operative PCI^[12]. Further research calculated the correlation of absolute tumor marker levels with PCI in PMP patients, specifically, the correlation coefficients is 0.29 for carcinoembryonic antigen (CEA)

, 0.36 for carbohydrate antigen 19 – 9 (CA 19 – 9), and 0.42 for CA 125, the correlation between the three tumor markers and PCI is general and the comparison of the correlation coefficient size has not been carried out^[13].

Present study aimed to evaluate the association between tumor markers and tumor burden in PMP patients, including CEA, CA 125, CA 19 – 9, CA 724, and CA 242, in addition, as far as we know, the correlation of CA 724 and CA 242 with tumor burden has not been evaluated in PMP patients. First, according to PCI, all PMP patients will be divided into low and high tumor burden subgroups, the level of five tumor markers will be compared between the two subgroups. Second, the correlation coefficients will be calculated between five tumor markers and PCI, furtherly, the strength of correlation coefficient will be compared in order to select tumor marker with the best correlation.

Methods

Patients

The present study was approved by Institution Review Board (IRB) of Aerospace Center Hospital (Ethical approval number: 20200113-LCYJ-01). All data were retrieved from a prospective follow-up database of Myxoma Department in Aerospace Center Hospital between June 1, 2013 and February 28, 2021. PMP diagnosis was confirmed by two experienced pathologists according to the Peritoneal Surface Oncology Group International (PSOGI) criteria^[14], as the criteria was published in 2016, pathologist in our center reviewed all the pathology specimens of patients diagnosed before 2016.

A total of 1029 patients with PMP diagnosis were retrieved from our database. The exclusion and inclusion criteria were as follows. The exclusion criteria including: a. The first time CRS of patients were not performed in our center ($n = 807$); b. Patients received systemic chemotherapy before CRS ($n = 17$); c. Due to excessive tumor burden, accurate PCI assessment cannot be performed at the time of laparotomy

($n = 4$); d. Patients also suffered from other types of tumors ($n = 2$, one patient with breast cancer, another one with both breast and thyroid cancer); e. Patients with incomplete operation record ($n = 1$). While CRS of patients performed in our center for first time was the inclusion criteria. Ultimately, 198 participants were included, they were further divided into low (PCI from 0 to 19, $n = 47$) and high (PCI ≥ 20 , $n = 151$) tumor burden subgroups, respectively. (Fig. 1).

Tumor markers determination

All serum tumor markers were tested before CRS. Tests were performed according to manufacturer's instructions (Abbott, America) with chemiluminescence immunoassay (CMIA) method. All tumor markers underwent Internal Quality Control (IQC) and External Quality Assessment (EQC) to ensure the stability and accuracy of results.

PCI assessment

PCI score calculation was performed by comprehensive abdominal exploration according to Sugarbaker's criteria^[15]. The PCI scoring system divides the abdomen into thirteen areas, a score of 0–3 is given for each of the 13 areas (0 for no tumor, 1 for nodules < 0.5 cm, 2 for nodules between 0.5 and 5 cm, and 3 for nodules > 5 cm). The total score is then calculated by adding all the scores, and ranges from 0 to 39.

Statistical analysis

Statistics analyses were performed by SPSS (version 16.0) and GraphPad Prism 5. Chi-square test was used to compare categorical data between groups. While continuous data between groups was compared by independent T test or Mann-Whitney U test, as appropriate.

Due to the large distribution results of tumor markers, outliers will seriously affect the comparison of tumor marker levels between groups, so we discarded outliers using the inter-quartile range (*IQR*) rule^[16], an outlier would be a point below $[Q1 - (1.5) IQR]$ or above $[Q3 + (1.5) IQR]$. *Pearson* or *Spearman* correlation coefficients will be calculated between tumor marker levels and PCI depending on whether they are normally distributed. Interim values of the correlation coefficient are interpreted by convention, values > 0.7 may be regarded as “strong” correlation, values between 0.50 and 0.70 may be interpreted as “good” correlation, between 0.3 and 0.5 may be treated as “moderate” correlation, and any value < 0.30 would be poor correlation^[17]. Subsequently, statistical comparison of correlations will be performed according to Meng, Rosenthal, and Rubin's method^[18], by which, the better tumor markers will be suggested for predicting tumor burden in PMP patients. Two-sided *P* value less than 0.05 is considered statistically significant difference.

Results

A total of 198 patients were included in present study. There were 120 males and 78 females, the mean age was 58 ± 11 years. The median duration from tumor markers detection to CRS was 7 (5,10) days. There were 68 participants underwent radical surgery, while 130 underwent debulking surgery. All the

participants had four histological subtypes, including 1 acellular mucin, 150 diffuse peritoneal mucinous adenoma (DPAM), 29 peritoneal mucinous carcinoma (PMCA), and 18 peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S), respectively (Table 1).

Table 1
Baseline characteristics of 198 included PMP patients.

Clinicopathological variables	
Sex (Male/Female)	120/78
Age (years)	58 ± 11
Operation time (hours)	7.8 ± 2.3
Operation method	
Radical surgery (<i>n</i>)	68
Debulking surgery (<i>n</i>)	130
Hospital time (days)	25.4 ± 7.7
Histological subtype	
Acellular mucin (<i>n</i>)	1
DPAM (<i>n</i>)	150
PMCA (<i>n</i>)	29
PMCA-S (<i>n</i>)	18
CEA (collected/missed)	198/1
CA 125 (collected/missed)	198/1
CA 19 – 9 (collected/missed)	198/1
CA 724 (collected/missed)	166/32
CA 242 (collected/missed)	145/53
DPAM: diffuse peritoneal mucinous adenoma; PMCA: peritoneal mucinous carcinoma; PMCA-S: peritoneal mucinous carcinomatosis with signet ring cells.	

All tumor markers were tested for normality after eliminating the outliers, unfortunately, none of them obeyed normal distribution. Five tumor markers were all statistically elevated in high tumor burden group compared with low burden group, the level of CEA (ng/ml), CA 125 (U/ml), CA 19 – 9 (U/ml), CA 724 (U/ml), and CA 242 (kU/L) between low and high tumor burden subgroup were [3.35 (1.64, 16.31) vs. 23.12 (8.80, 67.62), $Z=-5.381$, $p<0.001$], [19.10 (7.61, 56.95) vs. 72.75 (40.41, 130.55), $Z=-5.978$, $p<0.001$], [6.17 (3.26, 16.22) vs. 45.50 (13.95, 123.61), $Z=-5.413$, $p<0.001$], [7.89 (1.57, 45.10) vs. 84.61

(33.87, 236.93), $Z=-5.898$, $p<0.001$], and [13.32 (3.39, 96.50) vs. 150.00 (102.13, 308.88), $Z=-5.166$, $p<0.001$], respectively (Table 2 and Fig. 2).

Table 2
Tumor marker levels between low and high tumor burden group.

Tumor markers	Low tumor burden	High tumor burden	Z	P-value
CEA (ng/ml)	3.35 (1.64, 16.31)	23.12 (8.80, 67.62)	-5.381	0.001
CA 125 (U/ml)	19.10 (7.61, 56.95)	72.75 (40.41, 130.55)	-5.978	0.001
CA 19 – 9 (U/ml)	6.17 (3.26, 16.22)	45.50 (13.95, 123.61)	-5.413	0.001
CA 724 (U/ml)	7.89 (1.57, 45.10)	84.61 (33.87, 236.93)	-5.898	0.001
CA 242 (kU/L)	13.32 (3.39, 96.50)	150.00 (102.13, 308.88)	-5.166	0.001
All tumor markers were expressed as <i>IQR</i> .				

The Spearman rank correlation between tumor markers and PCI were 0.415 for CEA ($p<0.001$), 0.372 for CA 125 ($p<0.001$), 0.466 for CA 19 – 9 ($p<0.001$), 0.379 for CA 724 ($p<0.001$), and 0.317 for CA 242 ($p<0.001$), respectively. Subsequently, the correlation coefficients were compared with each other, among which, the correlation between CA 19 – 9 and PCI was significantly higher than that of CA 242, details were shown in Table 3.

Table 3
Statistical comparison of correlations between tumor markers and PCI.

	CEA	CA 125	CA 19 – 9	CA 724	CA 242
CEA	—				
CA 125	$z=0.625$ ($p=0.532$)	—			
CA 19 – 9	$z=0.784$ ($p=0.433$)	$z=-1.411$ ($p=0.158$)	—		
CA 724	$z=0.541$ ($p=0.589$)	$z=-0.095$ ($p=0.925$)	$z=1.142$ ($p=0.253$)	—	
CA 242	$z=1.233$ ($p=0.218$)	$z=0.570$ ($p=0.569$)	$z=2.628$ ($p=0.009$)	$z=0.737$ ($p=0.461$)	—

Discussion

Present study found that all five tumor markers were significantly higher in high tumor burden group than that of low tumor burden group. There was a significant correlation between PCI and tumor markers.

Complete resectability depending mainly on the extent and spread of the peritoneal disease^[19]. The PCI is widely used for assessing PMP in surgery^[20]. Therefore, accurate preoperative assessment of disease burden is essential to avoid nontherapeutic laparotomies in many patients or withholding of potentially beneficial therapy in others. The median tumor markers detection time before CRS was 7 days, which guaranteed the reliability of the research results to a large extent.

Although five tumor markers were all statistically associated with PCI, only moderate correlation was discovered between them. CA 19 – 9 seems to have the strongest correlation with tumor burden in present study, while in the former study, CA 125 seemed to be the better marker^[21]. After statistical comparison of coefficients, CA 19 – 9 was only significantly higher than that of CA 242 and did not reach a statistic significance with the other three markers. Unfortunately, the new tumor markers (CA 724 and CA 242) had no advantage over commonly used markers (CEA, CA 125, and CA 19 – 9) in the ability to reflect tumor burden, in the future, we can further evaluate the ability of CA 724 and CA 242 in predicting prognosis for PMP.

Tumor markers are helpful in predicting aggressiveness of disease in PMP, patients with normal tumor markers preoperatively had significantly higher disease free (DFS) and overall survival (OS) when compared with patients with elevated tumor markers^[22]. Former research also concluded that elevated tumor markers were the predictors of incomplete cytoreduction^[23]. Present study found tumor markers could reflect tumor burden for PMP, it seemed that CA 19 – 9 performs best, but the correlation was not very satisfactory. We believe that further work should be done to predict the preoperative tumor burden of PMP patients, such as combining tumor markers and preoperative abdominal CT to establish a predictive model, which can more accurately predict the preoperative tumor burden of patients, in order to make a better surgical plan.

There were two limitations in present study. First, many missing data on tumor markers, especially for CA 724 and CA 242, may make it difficult to find statistically differences of correlation coefficients. Second, the majority PMP patients did not undergo CRS for the first time in our hospital and not included in present study, which might lead to selection bias.

Conclusions

To conclude, serum tumor markers could reflect tumor burden to some extent, CA 19 – 9 seemed had best correlation coefficients, which may help surgeons to develop a more precise surgical plan for the PMP patients before the operation.

List Of Abbreviations

PMP-pseudomyxoma peritonei; CRS-complete cytoreduction surgery; HIPEC- hyperthermic intraperitoneal chemotherapy; PCI-peritoneal cancer index; CT- computed tomography; MRI-magnetic resonance imaging; PET-positron emission tomography; CEA-carcinoembryonic antigen; CA 19 – 9 - carbohydrate antigen 19 –

9; IRB-Institution Review Board; PSOGI-Peritoneal Surface Oncology Group International; CMIA-chemiluminescence immunoassay; IQC-Internal Quality Control; EQC-External Quality Assessment; IQR-inter-quartile range; DPAM-diffuse peritoneal mucinous adenoma; PMCA-peritoneal mucinous carcinoma; PMCA-S- peritoneal mucinous carcinomatosis with signet ring cells; DFS- disease free survival; OS-overall survival.

Declarations

Ethics approval and consent to participate

Institution Review Board (IRB) of Aerospace Center Hospital approved the present study (Ethical number: 20200113-LCYJ-01).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

None declared.

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Authors' contributions

MJB collected and analyzed the data of the patients. JF, SJP, HJW, YYL and NZH interpreted the patient data. MJB wrote the paper and was a major contributor in writing the manuscript. HBX and GWL revised the article. All authors read and approved the final manuscript.

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Figures

Figure 1

Study schematic. A total of 1029 PMP patients were retrieved in the follow-up database, 807 patients not underwent CRS at our institution for first time were excluded. Seventeen patients received systemic chemotherapy before CRS, four patients without PCI assessment, two patients combined with other tumors and one with incomplete operation record were also excluded. Ultimately, 198 patients were included, who were further divided into low ($PCI \leq 19$, $n = 47$) and high ($PCI \geq 20$, $n = 151$) tumor burden subgroups, respectively. PMP: pseudomyxoma peritonei; CRS: cytoreductive surgery; PCI: peritoneal cancer index.

Figure 2

Tumor marker levels between low and high tumor burden subgroups.