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ABOUT COVER

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Oncology* (*WJGO*, *World J Gastrointest Oncol*) is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc*.

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ORIGINAL ARTICLE

Retrospective Study

Combining prognostic value of serum carbohydrate antigen 19-9 and tumor size reduction ratio in pancreatic ductal adenocarcinoma

Dong-Qin Xia, Yong Zhou, Shuang Yang, Fang-Fei Li, Li-Ya Tian, Yan-Hua Li, Hai-Yan Xu, Cai-Zhi Xiao, Wei Wang

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Abstract

BACKGROUND

Pancreatic ductal adenocarcinoma (PDAC) is a common cancer with increasing morbidity and mortality due to changes of social environment.

AIM

To evaluate the significance of serum carbohydrate antigen 19-9 (CA19-9) and tumor size changes pre- and post-neoadjuvant therapy (NAT).

METHODS

This retrospective study was conducted at the Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital. This study specifically assessed CA19-9 levels and tumor size before and after NAT.

RESULTS

A total of 156 patients who completed NAT and subsequently underwent tumor resection were included in this study. The average age was 65.4 ± 10.6 years and 72 (46.2%) patients were female. Before survival analysis, we defined the post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level as the CA19-9 ratio (CR). The patients were divided into three groups: CR < 0.5, CR > 0.5 and < 1 and CR > 1. With regard to tumor size measured by both computed tomography and magnetic resonance imaging, we defined the post-NAT tumor size/pre-NAT

tumor size as the tumor size ratio (TR). The patients were then divided into three groups: TR < 0.5, TR > 0.5 and < 1 and TR > 1. Based on these groups divided according to CR and TR, we performed both overall survival (OS) and disease-free survival (DFS) analyses. Log-rank tests showed that both OS and DFS were significantly different among the groups according to CR and TR ($P < 0.05$). CR and TR after NAT were associated with increased odds of achieving a complete or near-complete pathologic response. Moreover, CR (hazard ratio: 1.721, 95%CI: 1.373-3.762; $P = 0.006$), and TR (hazard ratio: 1.435, 95%CI: 1.275-4.363; $P = 0.014$) were identified as independent factors associated with OS.

CONCLUSION

This study demonstrated that post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level and post-NAT tumor size/pre-NAT tumor size were independent factors associated with OS in patients with PDAC who received NAT and subsequent surgical resection.

Key Words: Pancreatic ductal adenocarcinoma; Carbohydrate antigen 19-9; Tumor size; Pathologic response; Biomarkers

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Core Tip: Our study demonstrated that post-neoadjuvant therapy (NAT) serum carbohydrate antigen 19-9 (CA19-9) level/pre-NAT serum CA19-9 level and post-NAT tumor size/pre-NAT tumor size were independent factors associated with overall survival for patients receiving NAT and subsequently surgical resection for pancreatic ductal adenocarcinoma.

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INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a relatively common cancer with increasing morbidity and mortality due to changes of social environment. Cancer-related death was the second leading cause of death in 2019, with PDAC the third most common cause of cancer death[1,2]. At the time of diagnosis, less than 20% of patients are eligible for curative surgery. For patients with advanced pancreatic cancer (either locally advanced or metastatic disease), the mainstay of treatment is systemic chemotherapy[3]. Gemcitabine-based regimens and 5-FU-based regimens display survival benefit and have been recommended as first-line therapies. Recently researchers have demonstrated that neoadjuvant therapy (NAT), including chemotherapy and radiotherapy, is related with increased R0 surgical resection and the overall survival (OS), especially those with distant and locally advanced PDAC[4-6].

Carbohydrate antigen 19-9 (CA19-9) is a dialkylated Lewis blood group antigen and is the most widely investigated tumor marker in patients with PDAC. CA19-9 has proven useful for the diagnosis of PDAC in symptomatic patients with a sensitivity and specificity of 79%-81% and 82%-90%, respectively[7,8]. Previous studies concluded that CA19-9 was an ineffective screening tool in asymptomatic patients. Nearly 7% of patients lack this tumor antigen and may be non-secretors[9,10]. Kane *et al*[11], in a retrospective analysis, showed that serum CA19-9 is significantly upregulated compared with the normal range to 2 years prior to the first diagnosis of PDAC. Pre-and post-operative CA19-9 levels and the changing of CA19-9 levels after operation might even predict prognosis of patients after resection. Furthermore, studies have showed that CA19-9 levels were related with tumor size and the stage[12,13]. However, there were several limitations when CA19-9 was identified as a biomarker: The routine use of CA19-9 as a PDAC screening tool in the general population is invalid, and because the incidence rate of PDAC in the general population is relatively low, the positive predictive value is low. This is also reflected in two large-scale population studies. In addition, false positive results were observed in benign pancreatic and biliary diseases such as cholangitis, pancreatitis, and obstructive jaundice. In addition, liver cysts and pancreatic cysts may interfere with CA19-9 levels. Despite these challenges, the use of CA19-9 has shifted from screening biomarkers to prognostic biomarkers[14-17].

To address this issue, and due to the increasing utilization and importance of NAT in PDAC treatment, it is necessary to identify biomarkers of the response to guide the management of these patients. In particular, the role of serum CA19-9 and tumor size in predicting resectability, pathological response, disease recurrence, and OS has been examined. Research has shown that changes in tumor size and serum CA19-9 during NAT can capture individual differences that cannot be recognized by individual measurements at a single time point.

This study aimed to evaluate the significance of serum CA19-9 and tumor size changes pre-and post-NAT. The ratio of post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level and the ratio of post-NAT tumor size/pre-NAT tumor size were used to identify the prognostic value of these factors in patients with PDAC. Moreover, we evaluated the combined prognostic value of these factors in predicting OS in patients with PDAC.

MATERIALS AND METHODS

Participants

This retrospective study was conducted at the Chongqing Key Laboratory of Translational Research for Cancer Metastasis and Individualized Treatment, Chongqing University Cancer Hospital.

Inclusion criteria: Patients aged 18- 70 years; have a histopathological confirmed diagnosis of PDAC at stage IA to IIB (the 8th edition of the American Joint Committee on Cancer staging system); be deemed suitable for potentially R0 surgical resection; have an Eastern Cooperative Oncology Group performance status score of 0 or 1; and have measurable disease and adequate pulmonary and organ function.

Exclusion criteria: Multiple primary malignancies, active or history of autoimmune disease, active or suspected interstitial lung disease or moderate-to-severe pneumonia, human immunodeficiency virus or active hepatitis B or C virus infection, previous systemic antitumor therapy and chest radiation, and previous use of immunostimulants, immunosuppressants, and live vaccine within 4 wk before the first dose of study treatment.

Variables and definitions

Collected variables included age, sex, comorbidities, body mass index, National Comprehensive Cancer Network (NCCN) resectability definitions and criteria, tumor size, serum levels of CA19-9, resection status, margin status, and pathologic response to NAT following resection. Comorbidities were evaluated using the Charlson Comorbidity Index. Patients were classified as upfront resectable, borderline resectable, and locally advanced according to the NCCN resectability criteria and were evaluated by a multidisciplinary panel of experts, including hepatopancreatobiliary surgeons, medical oncologists, radiation oncologists, and radiologists using pancreatic protocol computed tomography (CT).

The study included CA19-9 levels after resolution of biliary obstruction, with total bilirubin less than 2 mg/dL. Levels of CA19-9 were compared against laboratory references. The CA19-9 response throughout surveillance was stratified on the basis of normalization. Levels of CA19-9 were assessed at diagnosis, preoperatively, after resection, and at 6-mo follow-up intervals. Patients were included in the study if they had all baseline data and a minimum of one postoperative data point. This study specifically assessed CA19-9 levels and tumor size before and after NAT. Pre-operative levels closest to the operative date but within 4 wk were recorded. Pancreatic protocol multidetector CT scans (MDCT) were obtained at these 6-mo intervals to assess recurrence. All charts with discordance between CA19-9 and MDCT scan results were re-reviewed. Recurrence was defined as radiographic evidence of disease based on radiologist, multidisciplinary tumor board review of scans, or both. Levels of CA19-9 at baseline and at follow-up assessment were correlated with disease-free survival (DFS) and OS.

The primary endpoints of this study were OS and DFS. Pathologic complete response was evaluated and defined as the absence of viable tumor cells in the resected specimen. Pathologic response to treatment was defined according to the College of American Pathologists as complete, near-complete, partial, or poor response. Overall response rate (ORR) was determined by the investigator, with ORR defined as the proportion of patients with complete response or partial response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST version 1.1). DFS was defined as the time from the first dose of the study drug to disease progression, local recurrence, distant metastasis, or death, whichever occurred first. Treatment-related adverse events were monitored and recorded.

Statistical analysis

The *t*-test was employed to evaluate the differences in microbiome species abundance between the groups. Two-sided *P* values were used, and the significance level was set at 0.05 for all analyses unless otherwise stated. SPSS software (version 26; IBM Corp., Armonk, NY, United States) and R software (version 4.1.2) were used for statistical analyses.

RESULTS

Patients and treatment

Between July 2, 2021 and May 17, 2022, a total of 156 patients with histopathologically confirmed PDAC were screened for eligibility. These patients met the inclusion criteria and were enrolled in the study. All 156 patients completed NAT and subsequently underwent tumor resection. According to the scheduled NAT protocol, 87.2% (136/156) completed NAT. The average age of the patients was 65.4 ± 10.6 years and 72 (46.2%) were female. The median follow-up period was 34.3 months (95%CI: 26.5-56.3). Most of the patients underwent pancreaticoduodenectomy (n = 117, 75%), followed by distal pancreatectomy (n = 30, 19.2%) and distal pancreatectomy with celiac axis resection (n = 9, 4.8%). The majority (n = 88, 56.4%) had open procedures, but 50 patients (32.1%) underwent laparoscopic resection and 18 (11.5%) had robotic resection. Patients were classified as resectable PDAC (n = 30, 19.2%), 76 (48.7%) as borderline resectable PDAC, and 50 (32.1%) as locally advanced PDAC, according to the NCCN resectability criteria. Detailed results of the patient cohort are presented in Table 1.

OS and DFS

Prior to survival analysis, we defined the post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level as the CA19-9 ratio (CR). The patients were then divided into the following three groups: CR < 0.5, CR > 0.5 and < 1 and CR > 1. With respect to tumor size measured by both CT and magnetic resonance imaging, we defined the post-NAT tumor size/pre-NAT tumor size as the tumor size ratio (TR). We then divided the patients into the following three groups: TR < 0.5, TR >

Table 1 Characteristics of all pancreatic ductal adenocarcinoma patients

Variables	Total patients, *n* = 156	%
Age in yr	65.4 ± 10.6	
Sex		
Female	72	46.2
Male	84	53.8
ASA-score classification		
2	58	37.2
3	60	62.8
BMI	23.3 ± 6.5	
CR		
< 0.5	45	28.8
≥ 0.5 or < 1	90	57.7
≥ 1	21	13.5
Charlson comorbidity Index		
0	117	75
1	29	18.6
2	10	6.4
Tumor and pathologic characteristics		
AJCC TNM stage		
Ia	12	7.7
Ib	41	26.3
Iia	58	37.2
Iib	45	28.8
Grade		
0	10	6.4
G1	35	22.4
G2	75	48.1
G3	36	23.1
Neoadjuvant Chx		
Yes	128	82.1
No	28	17.9
Neoadjuvant Rtx		
Yes	37	33.7
No	119	76.3
TR		
< 0.5	4	2.6
≥ 0.5 or < 1	123	78.8
≥ 1	29	18.6
Neural invasion		
Yes	65	41.7
No	91	58.3
Vascular invasion		

Yes	76	48.7
No	80	51.3
Positive lymph nodes		
0	50	32.1
1-2	37	33.7
> 2	69	44.2
Tumor resection		
R0	65	41.7
R1	91	58.3
Operation type		
Whipple	117	75.0
Distal pancreatectomy	30	19.2
Distal pancreatectomy with celiac axis resection	9	4.8

AJCC: American Joint Committee on Cancer; ASA: American Society of Anesthesiologists; BMI: Body mass index; Chx: Chemotherapy; CR: Carbohydrate antigen 19-9 ratio; Rtx: Radiotherapy; TR: Tumor size ratio.

0.5 and < 1 and TR > 1. Based on these groups divided according to CR and TR, we determined both OS and DFS. Log-rank tests showed that both OS and DFS were significantly different among the groups divided according to CR and TR ($P < 0.05$). Kaplan-Meier curves for OS and DFS are presented for CR in Figure 1 and TR in Figure 2, respectively.

Efficacy and pathologic response

After 4-6 cycles of preoperative treatment with FOLFIRINOX or gemcitabine combined with nab-paclitaxel, 138 of 156 patients (88.6%, 95%CI: 77.5%-99.7%) had an objective response, with 10 patients (28.6%) achieving complete response, 21 patients (60%) achieving PR, and 60 patients (11.4%) achieving stable disease. Eighteen patients had progressive disease during NAT. After dividing the patients into different groups according to CR and TR, the efficacy of NAT is shown in Figure 3A and B. Furthermore, univariable analyses revealed that female sex, TNM stage, neoadjuvant chemotherapy, CR and TR were associated with complete or near-complete pathologic responses. Multivariable analyses identified that neoadjuvant chemotherapy, CR and TR were associated with increased odds of achieving a complete or near-complete pathologic response. Detailed results of the model are presented in Figure 3C.

Multivariable analysis to identify prognostic factors associated with OS

Cox proportional hazards models were used to quantify the prognostic factors associated with OS in patients with PDAC. The results of both univariable and multivariable analysis are shown in Table 2. Following univariable analysis, a multivariable analysis was performed to evaluate the factors that showed statistical significance in univariable analysis. After adjusting for competing risk factors, TNM stage [hazard ratio (HR): 1.526, 95%CI: 1.226-4.165; $P = 0.007$], vascular invasion (HR: 1.653, 95%CI: 1.253-3.651; $P = 0.021$), CR (HR: 1.721, 95%CI: 1.373-3.762; $P = 0.006$), and TR (HR: 1.435, 95%CI: 1.275-4.363; $P = 0.014$) were identified as independent factors associated with OS. Interestingly, we found that both CR and TR were independent risk factors for OS in PDAC patients. Furthermore, as shown in Figure 4A, we found that in patients with a TR < 0.5, 24 patients had CR < 0.5, 10 patients had CR ≥ 0.5 and < 1, and 1 patient had CR ≥ 1. In patients with a TR ≥ 0.5 and < 1, 21 patients had CR < 0.5, 65 patients had CR ≥ 0.5 and < 1 and 14 patients had CR ≥ 1. In patients with a TR ≥ 1, 0 patients had CR < 0.5, 15 patients had CR ≥ 0.5 and <1 and 6 patients had CR ≥ 1. Furthermore, the area under the receiver operating characteristic curves (AUROCs) were determined to compare the predictive values of CR, TR and the combined predictive value of CR and TR. The CR showed a significantly improved predictive value (AUROC: 0.674, 95%CI: 0.558-0.734) than the TR (AUROC: 0.681, 95%CI: 0.547-0.728, shown in Figure 4B and C). After combining both CR and TR, the model showed significantly improved predictive value compared with the single variables (AUROC: 0.758, 95%CI: 0.684-0.815) as shown in Figure 4D.

DISCUSSION

There have been several studies on the prognostic value of serum CA19-9 and tumor size changes in patients with PDAC undergoing NAT[14,18,19]. However, to our knowledge, this is the first study to evaluate the combined value of CA19-9 reduction and tumor size reduction following NAT with chemotherapy plus radiotherapy in patients with potentially resectable PDAC. NAT did not increase surgical complexity, with 43.6% of patients undergoing minimally invasive surgery[20-22].

Table 2 Cox proportional hazard regression analysis of patients' demographic and clinical characteristics related with overall survival

Variable	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age in yr, median range	1.043	0.795-1.149	0.857			
Sex, male/female	0.948	0.743-1.219	0.395			
ASA score classification, 0/1 or 2	1.103	0.854-1.754	0.194			
BMI	0.931	0.803-1.140	0.454			
TNM stage, I or II/III	1.436	1.217-2.695	0.015	1.526	1.226-4.165	0.007
Neoadjuvant Chx, yes/no	1.201	1.114-2.742	0.024			
Neoadjuvant Rtx, yes/no	1.121	0.901-1.537	0.142			
Neural invasion, yes/no	1.103	0.965-2.542	0.104			
Vascular invasion, yes/no	1.439	1.294-3.594	0.003	1.653	1.253-3.651	0.021
Positive lymph nodes, yes/no	1.729	1.487-4.325	0.001			
Tumor resection, R0/R1	0.568	0.321-0.843	0.005			
Operation type, Whipple	1.104	0.549-2.130	0.392			
CR, ≥ 1/< 1	1.796	1.429-4.104	0.001	1.721	1.373-3.762	0.006
TR, ≥ 1/< 1	1.573	1.282-2.752	0.012	1.435	1.275-4.363	0.014

BMI: Body mass index; Chx: Chemotherapy; CR: Carbohydrate antigen 19-9 ratio; Rtx: Radiotherapy; TR: Tumor size ratio.

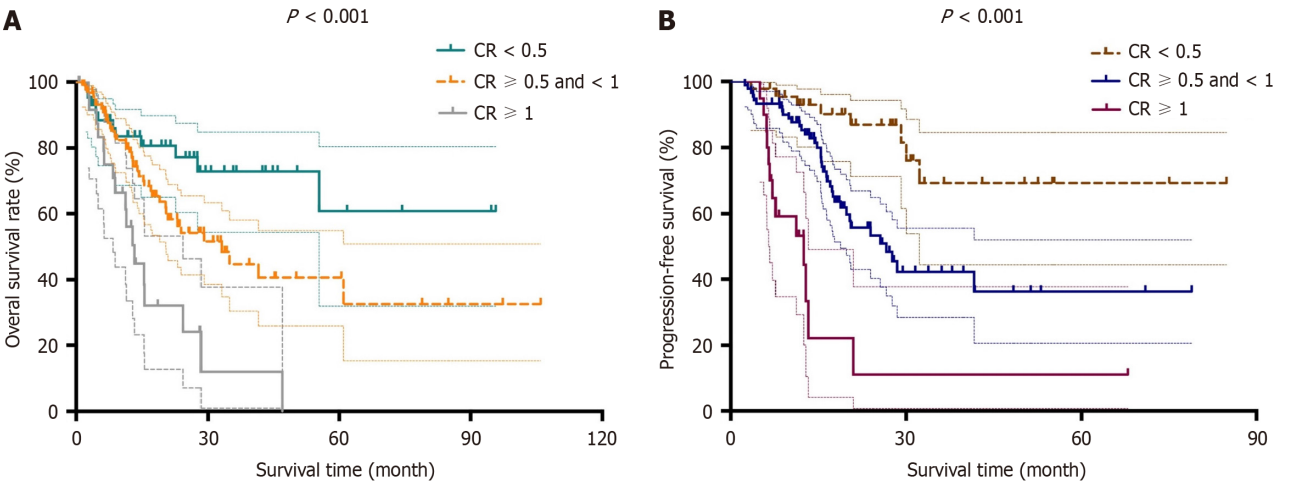

Figure 1 Kaplan-Meier curves for patients according to carbohydrate antigen 19-9. A and B: Kaplan-Meier curves for overall survival (A) and disease-free survival (B) are presented for post-neoadjuvant therapy (NAT) serum carbohydrate antigen 19-9 (CA19-9) level/pre-NAT serum CA19-9 level, which was defined as the carbohydrate antigen 19-9 ratio (CR).

PDAC is frequently considered as one of the worst cancers in terms of survival, with most patients dying < 2 years after diagnosis. In locally advanced pancreatic cancer, the 5-year survival rate is < 10%, making initial surgical treatment challenging[23-27]. CA19-9 has become a standard parameter in the diagnosis and monitoring of PDAC. High rates of recurrence represent significant hurdles to improving the outcome of patients with resectable disease. Elevations in CA19-9 have prognostic significance in early- and late-stage PDAC[28-30]. Studies in patients presenting with metastatic/unresectable disease showed that CA19-9 elevation is associated with worse survival, whereas CA19-9 response correlates with improved survival[31,32]. A CA19-9 decline in response to NAT can predict survival, margins, and pathologic outcome even in the absence of radiographic response[33-35]. Radiologic assessment remains a cornerstone in the decision-making process during the different stages of PDAC treatment. Currently, deep learning-based CT imaging-derived biomarkers enabled the objective and unbiased OS prediction for patients with resectable PDAC[36]. Although traditional NCCN resectability criteria have been shown to be unreliable in patients receiving NAT treatment, patients are followed up through imaging examinations during NAT to monitor disease progression[37-39]. On the other hand, since the tumor size at a single time point cannot reflect the changes observed during treatment, predicting resectability

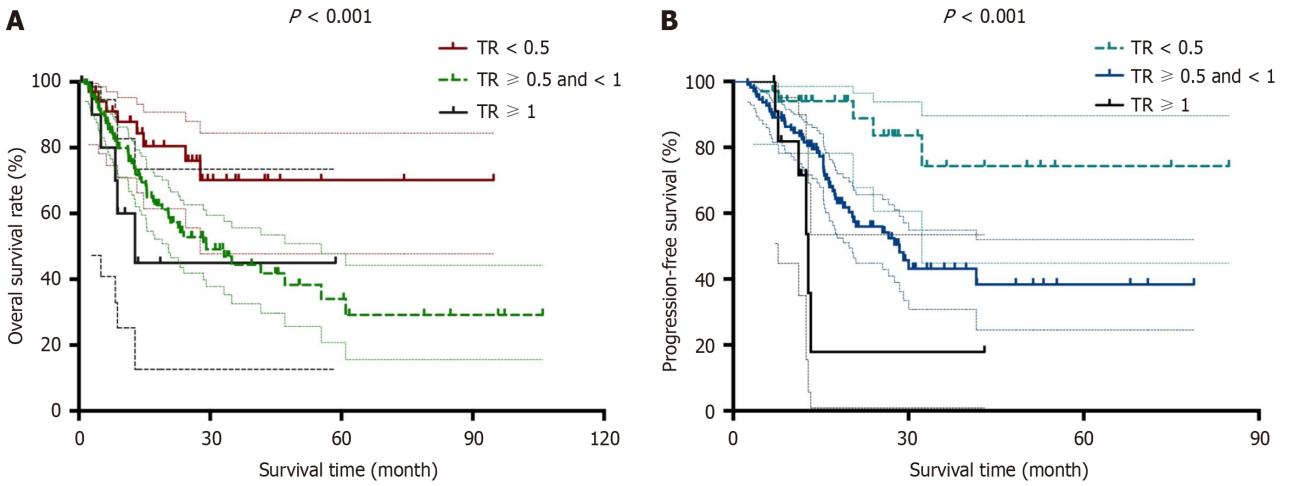

Figure 2 Kaplan-Meier curves for patients according to tumor size. A and B: Kaplan-Meier curves for overall survival (A) and disease-free survival (B) are presented for post-neoadjuvant therapy (NAT) tumor size/pre-NAT tumor size, which was defined as tumor size ratio (TR).

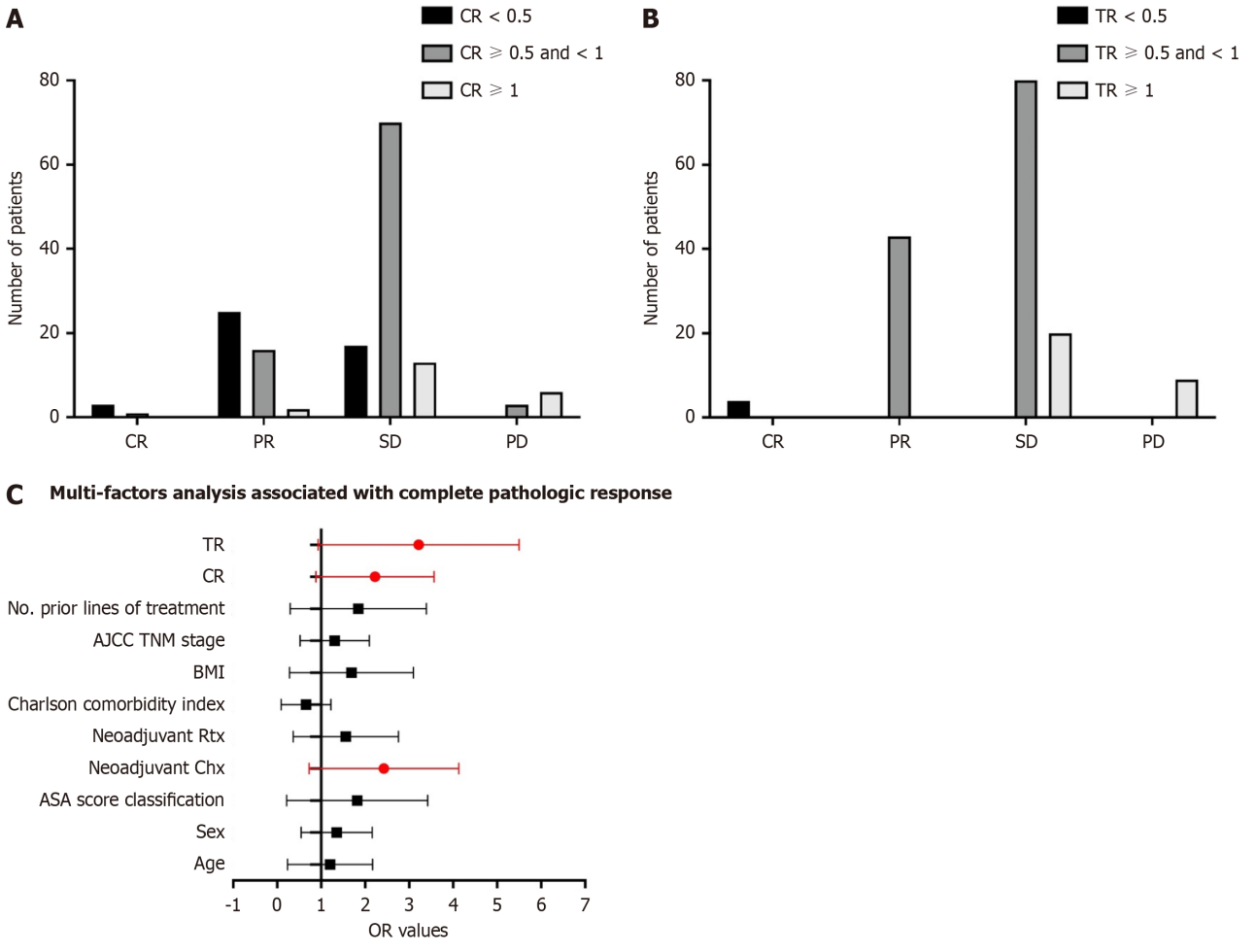

Figure 3 Treatment efficacy of all patients based on the groups divided by carbohydrate antigen 19-9 ratio and tumor size ratio. A: Treatment efficacy based on the groups divided by carbohydrate antigen 19-9 ratio (CR); B: Treatment efficacy based on the groups divided by tumor size ratio (TR); C: Multivariable analysis showed that CR and TR of neoadjuvant therapy were associated with increased odds of achieving a complete or near-complete pathologic response. AJCC: American Joint Committee on Cancer; BMI: Body mass index; PD: Progressive disease; SD: Stable disease.

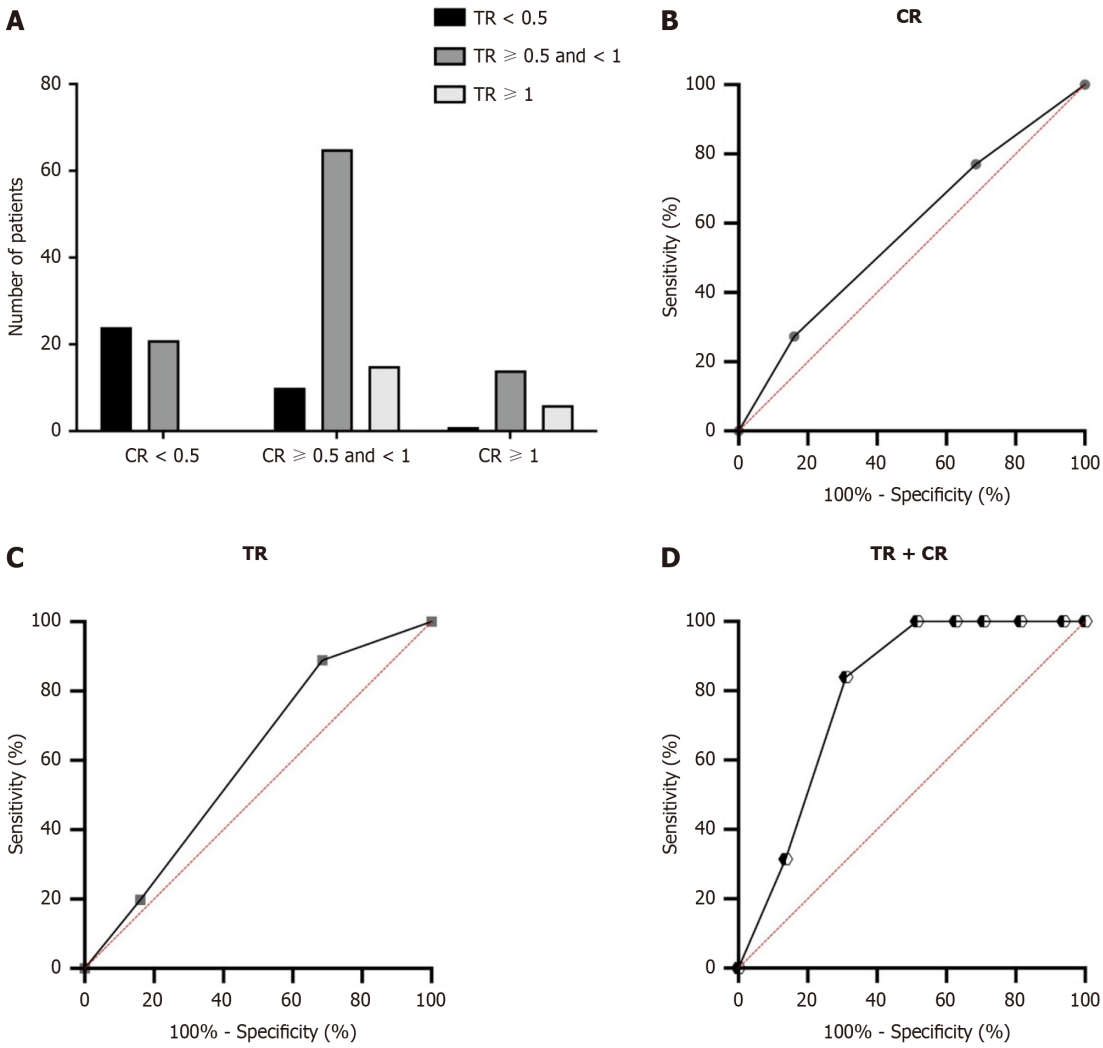

Figure 4 Prognostic values for both carbohydrate antigen 19-9 ratio and tumor size ratio. A-D: Interaction between carbohydrate antigen 19-9 ratio (CR) and tumor size ratio (TR; A) and area under the receiver operating characteristic curves performed to compare the predictive overall survival values of the variable of CR (B), TR (C) and the combined predictive value of CR and TR (D).

solely based on tumor size is inconsistent. Therefore, for patients undergoing NAT, the demand for new predictive strategies has not been met to improve prognostic assessment of these patients through radiological assessment using the combined effects of CA19-9 and tumor size.

In this study, based on the groups divided according to the CR and TR, we analyzed OS and DFS. Log-rank tests showed that both OS and DFS were significantly different among the groups divided according to the CR and TR (P < 0.05). In our study, the CR and TR were associated with increased odds of achieving a complete or near-complete pathologic response. More recently, serum CA19-9 has also been proposed as a marker of chemo-responsiveness. Moreover, multivariable analysis was performed to evaluate factors that demonstrated statistical significance during univariable analysis. The CR (HR: 1.721, 95%CI: 1.373-3.762; P = 0.006), and TR (HR: 1.435, 95%CI: 1.275-4.363; P = 0.014) were identified as independent factors associated with OS.

Several limitations exist in our study. Firstly, this study was retrospective, the sample size was relatively small, and it lacked a randomized control group, which could have introduced bias into the baseline histologic distribution. Secondly, the follow-up period in terms of survival data was limited at the time of data cutoff and longer-term follow-up is necessary to fully evaluate the impact of NAT on survival outcomes. Finally, while our biomarker analysis was exploratory, our study had a limited number of pre- and post-treatment samples, and a larger number of samples is needed to confirm our findings. These limitations underscore the need for future studies with larger patient cohorts and randomized control groups to validate our results and further evaluate the role of biomarkers in predicting response to NAT.

CONCLUSION

Our study demonstrated that post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level and post-NAT tumor size/pre-NAT tumor size were independent factors associated with OS in patients with PDAC who received NAT and subsequent surgical resection.

ARTICLE HIGHLIGHTS

Research background

Pancreatic ductal adenocarcinoma (PDAC) is a relatively common cancer with increasing morbidity and mortality due to changes of social environment. Studies have demonstrated that neoadjuvant therapy (NAT) is associated with increased resectability, negative surgical margins, and increased survival among patients with more locally advanced disease. Carbohydrate antigen 19-9 (CA19-9) is a dialkylated Lewis blood group antigen and is the most widely investigated tumor marker in patients with PDAC. However, CA19-9 as a biomarker has known limitations: Routine usage of CA19-9 as a screening tool for PDAC in the general public is ineffective and results in a low positive predictive value due to the relatively low incidence of PDAC in the general population. It has been shown that changes in tumor size and serum CA19-9 during NAT can capture differences that are not identified by individual measurements at a single point in time.

Research motivation

Our study demonstrated that post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level and post-NAT tumor size/pre-NAT tumor size were independent factors associated with overall survival (OS) in patients with PDAC who received NAT and subsequent surgical resection.

Research objectives

This study aimed to evaluate the significance of serum CA19-9 and tumor size changes pre-and post-NAT. The ratio of post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level and the ratio of post-NAT tumor size/pre-NAT tumor size were used to identify the prognostic value of these factors in patients with PDAC. Moreover, we evaluated the combined prognostic value of these factors in predicting OS in patients with PDAC.

Research methods

The *t*-test was employed to evaluate the differences in microbiome species abundance between the groups. Two-sided *P* values were used, and the significance level was set at 0.05 for all analyses unless otherwise stated. SPSS software (version 26) and R software (version 4.1.2) were used for statistical analyses.

Research results

A total of 156 patients who completed NAT and subsequently underwent tumor resection were included in this study. The average age was 65.4 ± 10.6 years and 72 (46.2%) patients were female. Before survival analysis, we defined the post-NAT serum CA19-9 level/ pre-NAT serum CA19-9 level as the CA19-9 ratio (CR). The patients were divided into three groups: CR < 0.5, CR > 0.5 and < 1 and CR > 1. With regard to tumor size measured by both computed tomography and magnetic resonance imaging, we defined the post-NAT tumor size/pre-NAT tumor size as the tumor size ratio (TR). The patients were then divided into three groups: TR < 0.5, TR > 0.5 and < 1 and TR > 1. Based on these groups divided according to CR and TR, we performed both OS and disease-free survival (DFS) analyses. Log-rank tests showed that both OS and DFS were significantly different among the groups according to CR and TR ($P < 0.05$). CR and TR after NAT were associated with increased odds of achieving a complete or near-complete pathologic response. Moreover, CR (HR: 1.721, 95%CI: 1.373-3.762; $P = 0.006$), and TR (HR: 1.435, 95%CI: 1.275-4.363; $P = 0.014$) were identified as independent factors associated with OS.

Research conclusions

Our study demonstrated that post-NAT serum CA19-9 level/pre-NAT serum CA19-9 level and post-NAT tumor size/pre-NAT tumor size were independent factors associated with OS in patients with PDAC who received NAT and subsequent surgical resection.

Research perspectives

Serum CA19-9 level and post-NAT tumor size/pre-NAT tumor size were independent factors associated with OS in patients with PDAC who received NAT and subsequent surgical resection.

FOOTNOTES

Co-first authors: Dong-Qin Xia and Shuang Yang.

Co-corresponding authors: Cai-Zhi Xiao and Wei Wang.

Author contributions: All authors contributed to the study's conception and design; Yang S, Li FF, Tian LY, Li YH, Xu HY, Xiao CZ performed data collection and analysis; Xia DQ, Zhou Y, and Wang W wrote the manuscript; Xia DQ, Zhou Y polished and revised the manuscript; Xiao CZ, Wang W performed supervision; Xiao CZ, Wang W performed project administration; All authors commented on previous versions of the manuscript and read and approved the final manuscript. Xia DQ and Yang S contributed equally to this work as co-first authors. Xiao CZ and Wang W contributed equally to this work as co-corresponding authors. The reasons for designating Xia DQ and Yang S as co-first authors, Xiao CZ and Wang W as co-corresponding authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-first authors and co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper. This also ensures

effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-first authors and co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Xia DQ and Yang S, Xiao CZ and Wang W contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors and co-corresponding authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study. In summary, we believe that designating Xia DQ and Yang S as co-first authors, Xiao CZ and Wang W as co-corresponding authors are fitting for our manuscript as it accurately reflects our team's collaborative spirit, equal contributions, and diversity.

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Informed consent statement: The written informed consent was waived owing to the retrospective and deidentified nature of this study.

Conflict-of-interest statement: The authors who have taken part in this study have nothing to disclose.

Data sharing statement: No additional data are available.

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