Original Article
Prognostic value of serological markers in carcinoma of the ampulla of Vater after radical surgery

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Abstract: Objectives: Increased CA199 serum level is a key prognostic factor of carcinoma of the ampulla of vater (CAV) after surgery; the prognostic value of other serum markers like CA242, CEA, LDH, NLR and TBIL has yet not been defined. Methods: We pooled one week pre-treatment data on serum factors from 147 CAV patients in Tumor Hospital of Chinese Academy of Medical Sciences from January 1998 to December 2012. The serum factors related to the recurrence and prognosis of patients after surgical resection were retrospectively analyzed using univariate and multivariate methods. Results: Univariate analysis revealed that CA199 (P=0.000), CA242 (P=0.003), NLR (P=0.005) and TBIL (P=0.018) were factors that significantly affected the prognosis of CAV. Multivariate analysis showed that the CA199 (P=0.006), CA242 (P=0.022) and NLR (P=0.025) were independent risk factors of recurrence. Conclusion: The preoperative CA199, CA242 and NLR serum level are key prognostic factors of CAV after radical surgery, which is valuable in diagnosis and prognosis in CAV.

Keywords: Carcinoma of the ampulla of Vater, radical surgery, prognosis, serum factors

Introduction

Adenocarcinomas of the ampulla of Vater (CAV) are rare malignant neoplasmas, accounting for 0.2% of gastrointestinal cancers [1]. This tumor can occur inside the ampulla of Vater or on the duodenal nipple [2]. With technological advances in endoscopic imaging, ampullary adenocarcinomas tend to be detected relatively in the early stage, have a greater resectable rate at the time of diagnosis than other periampullary cancers, and have a more favorable prognosis than adenocarcinomas from the pancreas or common bile duct [3-5]. The prognosis of CAV is relatively good, with reported 5-year survival rates ranging at 36.8-75.2% [6-8]. Therefore, assessment of prognostic indicators is important for the postoperative management of patients with CAV. Several prognostic factors, including pancreatic invasion, lymph nodal metastasis, resection marginal status, and histological differentiation have been found to predict adverse outcome in CAV [9-12].

The detection of serum tumor markers is an effective and non-invasive diagnostic or prognostic tool for cancers. In other tumors, serum biomarkers were widely used in diagnosis, in which carbohydrate antigen 199 (CA199), carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), ratio of neutrophil count and lymphocyte count (NLR) and total bilirubin (TBIL) served as potential markers in prostate cancers, pancreas cancers and biliary neoplasm [13-17]. To date, however, there is only one assured marker CA199 which might predict the prognosis of CAV. The primary aim of this retrospective analysis was to investigate the influence of several serum factors (like CA199, CEA, CA242, LDH, NLR and TBIL) on the prognosis, with an attempt to define the prognostic biomarkers of CAV.

Patients and methods

Patient population and treatment

Patients included in this study were recruited from Tumor Hospital of Chinese Academy of Medical Sciences from January 1998 to December 2012. The patients were excluded from the study as following: the patients who died within 30 days after surgery, the patients with autoimmune diseases, the patients with preop-

Table 1. Univariate analysis of serum factors in prognosis of CAV

Items	Cases (%)	5-year survival (%)	p
CA199			0.000
≤37 U/ml	56 (42.11)	78.0	
>37 U/ml	77 (57.89)	32.4	
CEA			0.039
≤5 ng/ml	114 (83.82)	57.2	
>5 ng/ml	22 (16.18)	38.5	
CA242			0.001
<20 U/ml	81 (79.41)	61.0	
≥20 U/ml	21 (20.59)	14.1	
LDH			0.274
135-225	108 (73.97)	54.9	
<135 >225	38 (26.02)	43.8	
NLR			0.005
<5	121 (82.31)	57.9	
≥5	26 (17.69)	27.6	
TBIL			0.018
<3 mg/dL	58 (39.46)	73.3	
≥3 mg/dL	89 (60.54)	38.7	

erative systemic infection, and patients with active hepatitis history.

All of the 147 patients had histologically or cytologically proven CAV according to the 7th edition of the AJCC cancer staging and were treated with resection surgery. The details of clinical data for patients were complete. All the 147 CAV patients were diagnosed by experienced pathologists from the Department of Pathology of the Cancer Hospital & Institute of Chinese Academy of Medical Sciences. Postoperative pathology confirmed that there were 161 cases of adenocarcinoma and one case of adenosquamous carcinoma. CAV is defined as malignancies originated from the ampulla of Vater (the confluence of the common bile duct and pancreatic duct) or from the duodenal papilla. For larger tumors that are difficult to judge, a diagnosis of CAV can be made only if the tumors are closely related with the ampulla of Vater or duodenal papilla. The sera were collected before operation from these patients with informed consent for analysis of serum parameters.

Serum assays for parameters

The baseline concentrations of CA 199, CEA, LDH, hemoglobin and bilirubin were measured routinely in each included patient before treat-

ment initiation. As described previously, a subgroup of patients whose CA 199 and CEA values had been measured using electrochemiluminescence immunoassay on the Roche Elecsys 1010/2010 and MODULAR ANALYTICS E170 (Elecsys module) immunoassay analyser (Roche Diagnostics, Mennheim, Germany). Serum CA242 was measured by CanAg CA242 enzyme immunometric assay kit (CanAg Diagnostics AB, Gothenbury, Sweden). Serum LDH was measured by enzymatic assays (Roche Diagnostics). The neutrophil count (N) and lymphocyte count (L) in routine blood was recorded by flow counting method (Bush's Business), and then the NLR was calculated to the ratio (R) of N with L. Serum total bilirubin was measured using diazonium method by HITACHI 7600-020 Automatic Analyser (Hitachi, Tokyo, Japan). The recommended cut-off levels of serum CEA, CA199, and CA242 were 5 ng/ml, 37 U/ml and 20 U/ml, respectively. The normal range for LDH was 135~225 U/L. The cut-off point for NLR was 5 according to previous, low NLR group (NLR<5) and high NLR group (NLR≥5). Jaundice is defined as the concentration of total serum bilirubin exceeding 3 mg/dL (51.3 µmol/L). All serum markers were measured prospectively in each participating patient.

Statistical analysis

Follow-up was conducted via telephone calls, outpatient visits and letters. The deadline of the follow-up was December 31, 2012, and the median follow-up duration was 30 months (range 1-240 months). Data were analyzed using SPSS 19.0 software (IBM SPSS Inc., Chicago, IL, USA). The survival curves were drawn by the Kaplan-Meier method. The overall disease-free survival (DFS) rate and overall survival (OS) rate were calculated, and the difference in survival was compared with log rank test. The relapse/metastasis and death were used as the endpoints, and univariate and multivariate analyses were performed for the clinicopathological factors. Chi-square test was used for the enumeration data. A *P* value of <0.05 was regarded as statistically significant.

Results

Patient characteristics

Of these 147 CAV patients, there were 90 men (61.2%) and 57 women (38.8%) aged 29-78 years (median 56 years). The tumors sized 0.5-7 cm (median 2.0 cm). Postoperative com-
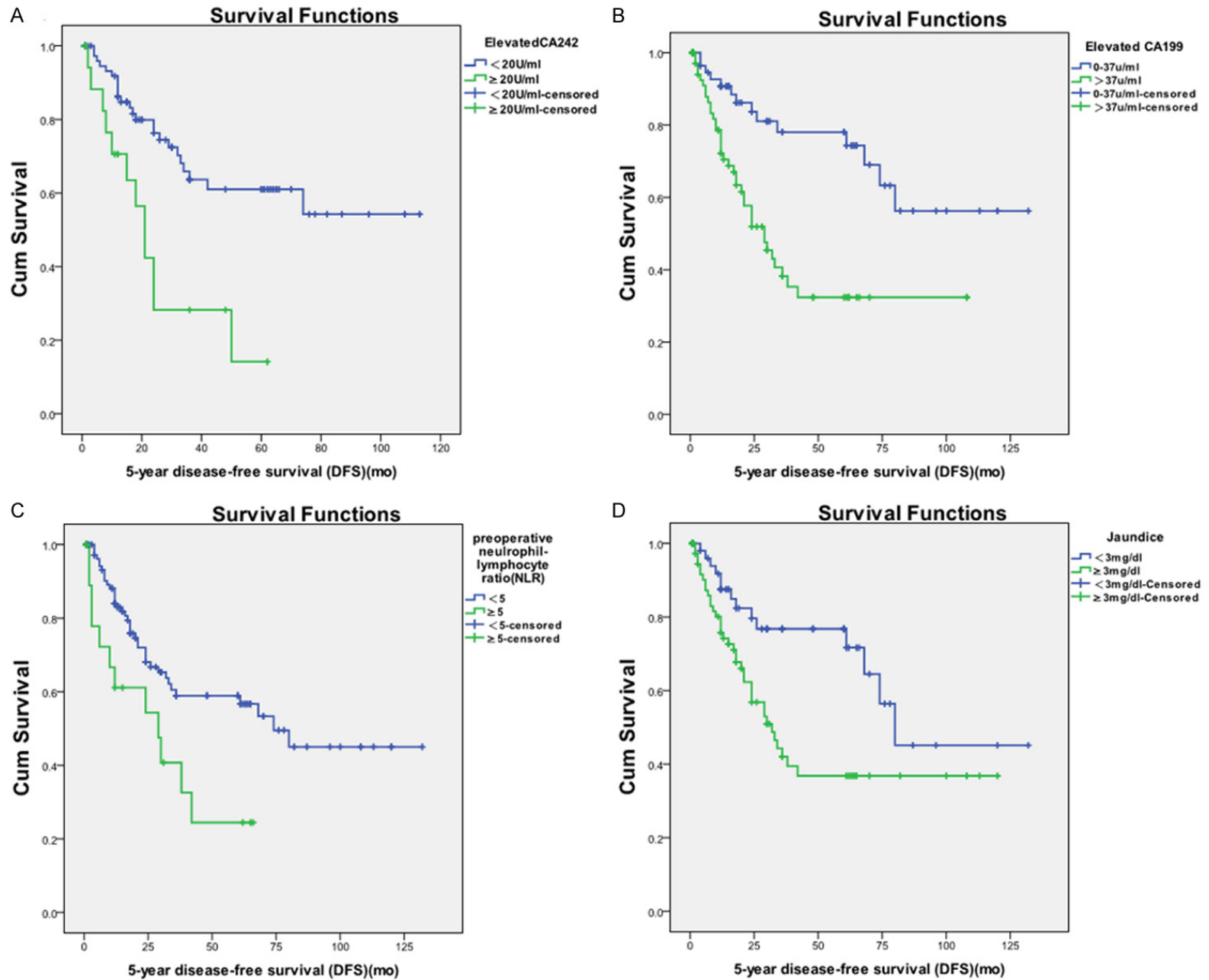
Figure 1. Kaplan-Meier curves for 5-year disease-free survival (DFS) of patients with carcinomas of the ampulla according to the status of elevated CA242 (A), CA199 (B), preoperative NLR (C), and Jaundice (D).

Table 2. Multivariate analysis of serum factors in prognosis of CAV

Items	P	RR	95.0% CI for RR	
			Lower	Upper
TBIL	.166	1.582	.826	3.027
CA199	.006	2.540	1.299	4.966
CA242	.022	2.536	1.143	5.626
NLR	.025	2.041	1.094	3.807

plications occurred in 58 patients (39.45%), which included anastomotic leakage, bile leakage, and pancreatic leakage (n=21, 36.21%); gastroparesis (n=16, 27.59%); gastrointestinal hemorrhage (n=12, 20.70%); lung infections (n=5, 8.62%); and abdominal cavity infections (n=5, 8.62%).

Radical resection was performed in 147 CAV patients, among whom 141 received pancreaticoduodenectomy (PD), and 6 received local resection. After the surgery, 25 patients received adjuvant therapy, among whom 22 underwent one to four cycles of chemotherapy with drugs including gemcitabine, oxaliplatin, cisplatin, and capecitabine (5-fluorouracil-leucovorin-oxaliplatin (FOLFOX)/CapeOX/cisplatin and gemcitabine), and 3 received radiation therapy (intensitymodulated radiation therapy (IMRT) 45 Gy).

The level of CA199 was determined in 133 cases, among whom 56 cases was with a value less than 37 U/ml and 77 cases with higher than 37 U/ml, within a positive rate of 57.89%. The CA242 level was determined in 102 patients, among whom 81 cases was less than 20 U/ml and 21 cases higher than 20 U/ml, within a positive rate of 21.57%. The CEA level was determined in 136 cases, among whom the values were ≤5 ng/ml in 114 cases and >5 ng/ml in 22 cases, within a positive rate of 16.18%. The LDH was determined in 146 cases, among whom the values were 135~225 U/ml in 108 cases and total of <135 U/ml and >225 U/ml in 38 cases, within a positive rate of 36.02%. The TBIL was determined in 147 cases, among whom the values were <3 mg/dl in 58 cases and ≥3 mg/dl in 89 cases, within a positive rate of 60.54%. The NLR was determined in 147 cases, among whom the values were <5 in 121

cases and ≥5 in 26 cases, within a positive rate of 17.69% (**Table 1**).

Univariate analysis of pre-treatment prognostic factors

The 5-year disease-free survival rate was 52.3% and the OS was 59.5% in the 147 CAV patients. Univariate analyses of 6 different clinical characteristics and laboratory parameters were conducted regarding overall survival (OS), respectively. Regarding OS, the following serum parameters revealed a statistical significance in relationship with OS: pre-treatment CA199 (P=0.000), CA242 (P=0.003), NLR (P=0.005), and TBIL (P=0.018) (**Figure 1**). Pre-treatment CEA and LDH had no significant correlations with OS (P>0.05). Among these factors, normal CA199 values (defined as ≤37 U/ml) had a prognostic significance for OS (78.0% vs. 32.4%, P=0.000). Similarly, measurements of serum CEA, CA242, NLR and TBIL at baseline also had a significant prognostic impact for OS at cut-off values (P<0.05) (**Table 1**).

Multivariate analysis of factors in disease-free survival

Multivariate analysis showed that increased CA199 (P=0.006), CA242 (P=0.022), and NLR serum level (P=0.025) were the independent risk factors of CAV. The correlation of pre-treatment CA199 values with disease-free survival was significant and the RR was 2.540 (95% CI 1.299-4.966, n=133). A similar significant correlation between serum factors and disease-free survival was observed in CA242 and NLR (P<0.05). The significant correlation was not found between TBIL with disease-free survival (P=0.166) and the RR value was 1.582 (95% CI 0.826-3.027), which was the least among all of the RR values in other factors (**Table 2**). These results suggested that CA199, CA242 and NLR were significantly related with the OS in CAV.

Relationship between serum factors and prognostic factors in CAV

There have been reported that many clinicopathological factors were used for CAV prognosis, including tumor size, tumor differentiation, tumor pancreatic invasion, lymph node metas-

Table 3. The correlation of serum factors with clinicopathological factors in CAV prognosis

Items	CA199[a] (U/ml)		p	CA242[b] (U/ml)		p	NLR[c]		P
	(-)	(+)		(-)	(+)		<5	≥5	
Tumor size			.189			.004			.291
<2.0 cm	31	34		48	5		65	11	
≥2.0 cm	24	42		33	16		56	15	
Differentiation			.021			.039			.245
Well	20	14		26	2		37	5	
Moderately-poorly	35	62		55	19		84	21	
Lymph node metastasis			.234			.141			.003
No	46	57		69	15		101	15	
Yes	9	19		12	6		20	11	
Pancreatic invasion			.038			.021			.392
No	34	33		46	6		67	12	
Yes	21	43		35	15		54	14	
Depth of tumor invasion			.074			.070			.549
T1	14	10		17	2		24	3	
T2	20	23		29	4		43	9	
T3	21	43		35	15		54	14	
Stage			.062			.181			.026
IA	14	10		17	2		24	3	
IB	17	15		23	3		34	7	
IIA	15	32		29	10		43	5	
IIB	9	19		12	6		20	11	

[a]N=133; [b]N=102; [c]N=147.

tasis and stage. It was found that the increase of CA199 was significantly related with tumor differentiation tumor pancreatic invasion. The patients with moderately-poorly differentiated tumor always had a higher frequency of high CA199 (>37 ng/ml) than those with highly differentiated tumor (P=0.021). As for tumor pancreatic invasion, the number of patients in high CA199 group was 2 folds more than that in low CA199 group (**Table 3**). The increase of CA242 was obviously correlated to tumor size, tumor differentiation, and tumor pancreatic invasion (P<0.05). The frequency of moderately-poorly differentiated tumor was higher in increased CA242 patients than that in normal CA242 patients, and higher frequency of tumor size ≥2 cm and pancreatic invasion was found in patients with increased CA242 than those with normal CA242 (P<0.05). As for NLR, it was observed that NLR was significantly correlated with age, lymph node metastasis and stage. Especially, the high CEA was significantly with tumor size, as the frequency of tumor ≥2 cm was 3 folds higher than that of <2 cm in the high CEA group. In addition, the jaundice was significantly correlated with tumor differentiation, lymph node metastasis and pancreatic invasion (P<0.05) (**Table 4**). These results suggested that these serum factors were closely related with previous clinicopathological factors in CAV prognosis.

Relationship between postoperative adjuvant therapy with serum factors in CAV

The effect of adjuvant therapy on the prognosis of CAV has been well investigated, while few reports have explored the relationship between postoperative adjuvant therapy with serum factors, which could be used as prognosis factors in CAV. After surgery, 25 patients received adjuvant therapy, among whom 22 underwent chemotherapy with drugs including gemcitabine, oxaliplatin, cisplatin, and capecitabine for one to four cycles (FOLFOX/CapeOX/cisplatin and gemcitabine), and five received radiation therapy (IMRT 45 Gy). After adjuvant therapy, the 5-year disease-free survival in normal CA199 (≤37 U/ml) was significantly higher than that in high CA199 (>37 U/ml) (P=0.033), similar higher survival rates were observed in normal CA242, low NLR and low TBIL groups than their corresponding abnormal groups, respectively (P<0.05). However, the survival rates in normal CEA or LDH groups were not significantly higher (**Table 5**). The adjuvant therapy was correlated with CA199, NLR, CA242 and jaundice (P<0.05). The adjuvant therapy can improve the 4 serum factors and the 5-year OS significantly.

Discussion

Detection of cancer biomarkers has been widely used for the diagnosis of malignant diseases and the evaluation of prognosis outcomes. Previously, CEA, CA199 and CA242, as three mucins, are well used in the diagnosis and

Table 4. The correlation of serum factors with clinicopathological factors in CAV prognosis

Items	LDH[d] (U/ml)		p	CEA[e] (U/ml)		p	Jaundice		p
	(-)	(+)		(-)	(+)		(-)	(+)	
Tumor size			.0.934			.013			.732
<2.0 cm	56	20		64	6		31	45	
≥2.0 cm	52	18		50	16		27	44	
Differentiation			.421			.810			.006
Well	33	9		34	6		24	18	
Moderately-poorly	75	29		80	16		34	71	
Lymph node metastasis			.015			.288			.080
No	91	25		94	16		50	66	
Yes	17	13		20	6		8	23	
Pancreatic invasion			.554			.929			.008
No	60	19		61	12		39	40	
Yes	48	19		53	10		19	49	
Depth of tumor invasion			.809			.955			.000
T1	20	7		23	4		21	6	
T2	40	12		38	8		18	34	
T3	48	19		53	10		19	49	
Stage			.096			.733			.000
IA	20	7		23	4		21	6	
IB	32	9		31	6		14	27	
IIA	39	9		40	6		15	33	
IIB	17	13		20	6		8	23	

[d]N=146; [e]N=136.

Table 5. The correlation between postoperative adjuvant therapy with serum factors in CAV

Items	Cases	5-year survival (%)	p
CA199			0.033
≤37 U/ml	11	43.8	
>37 U/ml	13	20.0	
CEA			0.067
≤5 ng/ml	20	38.8	
>5 ng/ml	4	0.00	
CA242			0.024
<20 U/ml	12	39.8	
≥20 U/ml	5	0.00	
LDH			0.316
135-225	14	33.0	
<135 >225	10	22.2	
NLR			0.001
<5	16	42.1	
≥5	9	0.00	
TBIL			0.022
<3 mg/dL	10	70.0	
≥3 mg/dL	15	15.2	

prognosis of digest tract tumors [16, 17]. The 7th edition of the AJCC cancer staging system did not change its definition of ampullary carcinoma TNM stage grouping from the 6th edition, despite many updates in substaging of the N classification for carcinomas from other organs, such as breast and gastrointestinal tract [18]. To date, the reported prognostic factors of CAV were mainly clinicopathological parameters, including depth of tumor invasion, lymph node metastasis, tumor differentiation, and pancreatic invasion [19]. Zhou found that the prognosis of CAV was related with tumor size, tumor differentiation, lymph node metastasis, pancreatic invasion, depth of invasion and tumor TNM staging in 162 CAV patients, which was similar to those findings in Winter's study [20]. However, it still has not been reported tumor biomarkers for the diagnosis and prognosis of CAV. The detection of serum tumour markers is an effective and non-invasive diagnostic or prognostic tool for cancer. In the present study, we investigated the relationship between serum factors and CAV prognosis in 147 patients. We found that the pre-treatment serum factors CA199, CA-242, NLR and TBIL were key factors for CAV prognosis. A multivariate analysis revealed that CA199, CA242 and NLR were independent risk of prognosis in CAV.

CA199 (carbohydrate antigen 199, also called cancer antigen 199 or sialylated Lewis (a) antigen) is a tumor marker that is used primarily in the management of pancreatic cancer. As a mucin, serum CA199 is elevated most obviously in tumors of the digestive system, pancreas, and biliary tract. CA199 is not only a diagnostic indicator, but also a predictor of the therapeutic effect and prognosis of pancreatic cancers. However, CA199 is not specific for pancreatic cancer [13, 21]. Therefore, CA199 should be combined with other imaging tests to diagnose

pancreatic cancer. Recently, Zhou reported that increased CA199 serum level was a key prognostic factor of CAV after surgery. In this study, the positive rate of elevated CA199 was 57.89% in the 133 cases of CAV, which suggested that CA199 may be important for CAV diagnosis [15]. However, the sensitivity of CA199 in CAV diagnosis is difficult to assay, as for the retrospective study. In other literatures, it was found that the elevated CA199 and CEA serum levels were associated with digestive tumor metastasis [22-24]. In this study, we found that the patients with elevated CA199 experienced worse outcomes than those with normal CA199. Moreover, the elevated CA199 predicted a worse tumor differentiation and a higher risk of pancreatic invasion than normal CA199.

CA242 (carbohydrate antigen 242, also called cancer antigen 242 or sialylated Lewis (a) antigen) was expressed in cancer cells, and its monoclonal antibody was obtained by immunization of colon cancer cell line Colo202 in mice. It was widely known that CA242 in patients with pancreatic cancer were higher than that of other malignant diseases and benign pancreatic diseases. CA242 was expressed in pancreatic cancer and colon cancer, with a high specificity in pancreatic cancer, but not in benign biliary tract disease and acut pancreatitis [23, 25]. In this study, the positive rate of elevated CA242 was 21.5%, close to previous 21% in gastric cancer. In addition, we found that elevated CA242 related to prognosis of CAV, as patients with elevated CA242 suffered a bad prognosis. CA242 was also significantly associated with tumor size, tumor differentiation, and pancreatic invasion. According to the histological definition, CAV included the four parts, epithelium of 1/3 distal bile duct, epithelium of the main pancreatic duct, common epithelium of periampullary and surface mucous of duodenal papilla. It is still unclear whether the elevated CA242 is originated from the epithelium of main pancreatic duct and whether the elevated CA242 is a key factor in CAV prognosis, and these are needed to be verified in future.

CEA, CA19-9 and CA242, as three mucins, are well used in the diagnosis and prognosis of pancreatic cancer. Single and combined serum CEA, CA19-9, and CA242 detection showed that the sensitivity of the CA19-9 assay individually was clearly the highest in pancreatic cancer (80%) and cholangioampulla carcinoma (73%) as described in previous reports by others [26], although with the lowest specificity, which suggested that CA19-9 was not a marker to discriminate pancreatic cancer and cholangioampulla carcinoma [13]. CEA and CA242 had a similar sensitivity and specificity in pancreatic cancer. The major advantage of CEA and CA242 over CA19-9 was their higher specificity resulting from the less frequent and only slight elevation in the serum levels in patients with cholangioampulla carcinoma.

Response of immune system to tumor is very complex and the mechanism is still unknown. Recent studies have demonstrated that the evaluation of immune factors played an important role in the development of carcinogenesis [27]. For example, the leukocyte has been used as a factor in cancer diagnosis and prognosis. It is convenient and economic to evaluate inflammatory reaction of tumor in clinics. A distinguished feature of inflammatory reaction is the change of relative content of leukocyte in blood circulation, which has been broadly accepted that the increase of neutrophils accompanied with the decrease of lymphocyte [28]. NLR has been to an independent risk factor in tumor prognosis, such as gastric cancer, colorectal cancer, liver cancer, pancreatic cancer, and breast cancer. In this study, we also found that NLR was an independent risk in CAV prognosis in 147 CAV patients. The 5-year OS in patients with NLR<5 was significantly higher than that in NLR>5, which was also confirmed in gastric cancer and colorectal cancer.

Detection of pre-treatment cancer biomarkers is crucial to the diagnosis and classification of digestive tract tumors. In the latest European Group on Tumor Markers (EGTM) guidelines, it was not sure whether the choice of adjuvant chemotherapy according to the preoperative CEA level was beneficial to patients with Stage II colorectal cancer. At present, it is not consistent in the adjuvant therapy after CAV surgery. Zhou reported that the long-term survival was not significantly different when performing adjuvant chemotherapy in 111 cases of CAV patients underwent surgery. However, a multi-central analysis in Jonh Hopkins revealed that adjuvant chemoradiotherapy with 5-Fu after surgery significantly improved the long-term survival in 290 CAV patients with positive lymph nodes [29]. In this study, the outcomes of adju-

vant chemotherapy in patients with elevated serum factors including CA199, CA242, NLR and jaundice were worse than outcomes in normal group. Therefore, it is necessary to perform adjuvant therapy in patients with elevated pre-treatment CA199, CA242, NLR and jaundice. Moreover, the pre-treatment CA199, CA242, NLR was significantly associated with tumor size, tumor differentiation, pancreatic invasion and lymph node metastasis. The elevation of these serum factors indicated poor tumor differentiation and high risk of pancreatic invasion and lymph node metastasis. It would be better to combine preoperation image for the choice of surgery strategy and lymph node cleaning scope.

This retrospective study analyzed the serological parameters in 147 CAV patients and it was found that pre-treatment serum factors were helpful in assessment of disease development. Combination of preoperative image and histological results, preoperative assessment of tumor differentiation, potential lymph node metastasis, invasion depth and clinical staging in CAV patients, is beneficial for strategy-making and surgery decision. However, lack of large sample size limits the researches focusing on the CAV and how to choose adequate strategies for therapy. Our study has compensated the serum factor significance in CAV.

In conclusion, elevated CA199, elevated CA242 and NLR≥5 predict late stage cancer, bad prognosis, and pancreatic invasion, respectively. Poor-moderate cancer differentiation always appeared in patients with elevated CA199 and CA242. Detection of pre-treatment of CA199, CA242 and NLR is beneficial for the diagnosis and prognosis of CAV, and these three serum factors are independent risk factors in CAV prognosis.

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Disclosure of conflict of interest

None.

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