Clin. Lab. 2020;66:XXX-XXX

ORIGINAL ARTICLE

Single and Combined Use of Preoperative Inflammatory Biomarkers and CA199 in Diagnosing Pancreatic Cancer

Yu Lu [1, 2, *], Hongli Yu [2, *], Shanzi Qin [1], Mingxing Chen [1], Huaping Chen [1], Zuojian Hu [1], Shan Li [1], Xue Qin [1]

[*] *These authors contributed equally to this work and should be considered as co-first authors*
[1] *Department of Clinical Laboratory, First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, China*
[2] *Department of Clinical Laboratory, Liuzhou People's Hospital, Liuzhou, Guangxi, China*

SUMMARY

Background: **To determine the diagnostic value of preoperative inflammatory biomarkers and CA199, alone or in combination, in diagnosing pancreatic cancer (PCC).**
Methods: **This retrospective study was comprised of 75 PCC patients and 83 healthy controls (HC). The participant's medical data was mined from the electronic records of the First Affiliated Hospital of Guangxi Medical University. The data included the preoperative circulating albumin/fibrinogen ratio (AFR), the platelet/lymphocyte ratio (PLR), the lymphocyte/monocyte ratio (LMR), the neutrophil/lymphocyte ratio (NLR), and the derived NLR (dNLR). The receiver operating characteristic (ROC) curve and the area under the ROC curve (AUROC) were used to evaluate the diagnostic efficacy of these candidate biomarkers for PCC.**
Results: **A single AFR significantly distinguished PCC from the healthy controls (AUROC: 0.903, 95% CI: 0.846 - 0.945) and had a significantly higher sensitivity and larger AUROC than CA199 (AUROC: 0.814, 95% CI: 0.774 - 0.871). The combinations of AFR with CA199 (AUROC: 0.932, 95% CI: 0.881 - 0.966), RDW with CA199 (AUROC: 0.905, 95% CI: 0.849 - 0.946), Alb with CA199 (AUROC: 0.869, 95% CI: 0.806 - 0.917), and Fib with CA199 (AUROC: 0.921, 95% CI: 0.868 - 0.958) also yielded higher sensitivities and larger AUROCs than CA199 alone.**
Conclusions: **Circulating AFR was an effective biomarker in diagnosing PCC. Combining AFR, RDW, Alb, and Fib with CA199 could improve the diagnostic efficacy for PCC.**
(Clin. Lab. 2020;66:xx-xx. DOI: 10.7754/Clin.Lab.2020.200111)

Correspondence:
Shan Li and Xue Qin
Department of Clinical Laboratory
First Affiliated Hospital of
Guangxi Medical University
Nanning 530021, Guangxi
China
Phone: +86 771-5356052
Fax: +86 771-5353342
Email: lis8858@126.com
qinxue919@126.com

Manuscript accepted March 3, 2020

KEY WORDS

pancreatic cancer, CA199, inflammatory biomarkers

LIST OF ABBREVIATIONS

PCC - pancreatic cancer
CA199 - cancer antigen 199
NEU - neutrophils
LYM - lymphocytes
MON - monocytes
CRP - C-reactive protein (CRP)
Fib - fibrinogen
Alb - albumin
NLR - neutrophil-to-lymphocyte ratio

PLR - platelet-to-lymphocyte ratio
dNLR - derived NLR
WBC - white blood cells
PLT - platelets
RDW - red cell distribution width
LMR - lymphocyte/monocyte ratio
HC - healthy controls
SD - standard deviation
ROC - receiver operating characteristic
AUROC - area under the ROC curve

INTRODUCTION

Pancreatic cancer (PCC) is the fourth leading cause of cancer mortality in the United States with about 46,420 new cases annually. It is projected to surpass breast, colorectal, and prostate cancers as the second leading cause of cancer-related deaths by 2030 [1]. The 5-year survival rate for PCC has remained at less than 10% for the past 30 years [2], mainly due to the difficulties in making an early diagnosis, its ease of metastasis, and its unresponsiveness to most treatments [3]. Hence, the discovery of promising diagnostic biomarkers for early and effective detection of PCC is an essential step in improving the patient's survival.

PCC poses a significant diagnostic challenge due to the non-specific symptoms of the disease and the close proximity of major blood vessels, which can be easily invaded by the tumor [4]. So far, imaging examinations, such as secretin-enhanced magnetic resonance imaging, magnetic resonance cholangiopancreatography, and endoscopic ultrasound, have shown promising results when used as a one-time screening modality. However, these methods are not economical, are time-consuming, and only suitable for the high risk population [5]. For general population-based screening, cancer antigen 199 (CA199) is the most effective non-invasive PCC biomarker. It has been reported to be the single most important predictive biomarker of malignancy in mass-forming chronic pancreatitis [6]. However, its sensitivity and specificity for detection of early PCC are 40 - 50% and 68 - 91%, respectively. Furthermore, a false-positive rate of approximately 23% indicates that the role of CA199 in mass screenings of asymptomatic patients is limited [7,8].

To improve its accuracy, combinations of CA199 with other indicators have been widely studied. As is known, PCC is a classical inflammation-related cancer. The incidence of PCC in patients with chronic pancreatitis is as high as 5% and inflammation has been shown to play pivotal roles in PCC from initiation and progression to metastasis [9]. It has been shown that the severity of systematic inflammation can be reflected by circulating immune cells, including neutrophils (NEU), lymphocytes (LYM), monocytes (MON), C-reactive protein (CRP), fibrinogen (Fib), albumin (Alb), and others. Moreover, numerous studies have shown that circulating inflammation-reflected immune cells and acute-phase reactive proteins can be assessed and have predictive value in various cancers [10-13], including PCC [14,15]. Our previous studies explored the role of the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) in combination with CA199 in the diagnosis of PCC in patients with type 2 diabetes. Our results suggested that combining PLR with CA199 could significantly improve the diagnostic efficacy for PCC in type 2 diabetic patients [16]. Furthermore, circulating derived NLR (dNLR) has recently been shown to be an effective biomarker for the diagnosis and identification of early-stage PCC. Combining dNLR with Alb could significantly improve the diagnostic ability of the disease [17]. However, the potential diagnostic value of these inflammation-related biomarkers combined with CA199 in the diagnosis of PCC remains unclear. Therefore, we carried out the present retrospective study to determine the value of various preoperative indicators. These indicators included circulating white blood cells (WBC), NEU, LYM, MON, platelets (PLT), red cell distribution width (RDW), Alb, Fib, the Alb/Fib ratio (AFR), the lymphocyte/monocyte ratio (LMR), PLR, NLR, and dNLR, alone or combined with CA199 in the diagnosis of PCC.

MATERIALS AND METHODS

Participants

This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, China, in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). A total of 75 patients with PCC, who were first diagnosed at the First Affiliated Hospital of Guangxi Medical University from January 2012 to August 2018, were included in this study. The criteria for enrollment were as follows: 1) all patients were confirmed PCC patients according to their clinical symptoms and pathological examination; 2) patient's pretreatment routine blood indices, biochemical parameters, coagulation indicators, and CA199 levels were available. Patients were excluded if they had an infection, hematological, autoimmune, or liver diseases, or other malignancies. For the control group, the health-, age-, and gender-matched individuals were without any diseases, and there were no clinically confirmed cancer patients. In total, 75 patients with PCC and 83 healthy controls (HC) were enrolled in our study.

Data collection

The demographic data of all participants were extracted from their medical records, including age, gender, and the following blood tests: CA199, Alb, Fib, total WBC and PLT, absolute value of NEU, LYM, and MON. AFR, PLR, LMR, and NLR were derived from these values, and dNLR was calculated using the formula: (WBC - LYM)/LYM.

Laboratory methods

The CA199 levels were measured using a Roche E6000 analyzer (Roche Diagnostics, Basel, Switzerland). The biochemical parameter Alb was determined using an automatic analyzer (Hitachi 7600, Tokyo, Japan). The coagulation indicator Fib was analyzed using an ACL-TOP700 automatic coagulation analyzer (Werfen, Barcelona, Spain). Routine blood indices were measured using a COULTER LH 780 Hematology Blood Analyzer (Beckman Coulter, Brea, CA, USA).

Statistical analysis

All data were analyzed using SPSS 23.0 software (IBM Corp., Armonk, NY, USA) and MedCalc version 15.0 (MedCalc Software, Mariakerke, Belgium) statistical software. To assess whether variables had a normal distribution, the Shapiro-Wilk normality test was first used. Continuous variables with a normal distribution were expressed as mean ± standard deviation (SD). Skewed variables were reported as the median with the interquartile range, and categorical variables were expressed as numbers or percentages. Differences in quantitative variables were compared using the Student's *t*-test if they were normally distributed, while the Mann-Whitney *U* test was used if they were not normally distributed. The χ^2 test was used to analyze categorical data. MedCalc version 15.0 was used to calculate the diagnostic efficacy of WBC, NEU, LYM, MON, PLT, RDW, Alb, Fib, AFR, LMR, PLR, NLR, and dNLR combined or alone, and further compared with CA199. The diagnostic efficacies of candidate biomarkers were evaluated with receiver operating characteristic (ROC) curves and the area under the ROC curve (AUROC). Sensitivity and specificity were defined by ROC curves. A p-value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristic of the study population

Our study included two groups: the PCC group (n = 75, including 42 men and 33 women, with a mean age of 53.23 ± 12.01 years) and the HC group (n = 83, including 45 men and 38 women, with a mean age of 54.75 ± 9.34 years). No significant differences in age or gender were found between the two groups (Table 1).

The CA199 level in the PCC group was significantly higher than in the HC group (p < 0.001). Similar results were also found for WBC, NEU, MON, RDW, Fib, PLR, NLR, and dNLR (p < 0.05 for all; Figure 1). However, Alb, AFR, and LMR were significantly lower in the PCC group than in the HC group (p < 0.001 for all; Figure 2). No significant differences in LYM and PLT were observed between the two groups (p = 0.08 and 0.057, respectively; Table 1).

Diagnostic values of single and combined indicators in PCC

ROC analysis was used to distinguish the PCC patients from the HCs. As shown in Table 2, with the HC group as a reference, the highest AUC of the candidate biomarkers was AFR (AUROC: 0.903, 95% CI: 0.846 - 0.945). The AUROC of AFR used alone to diagnose PCC was significantly higher than CA199 (AUROC: 0.814, 95% CI: 0.774 - 0.871, p = 0.037; Figure 3). Moreover, the sensitivity and specificity for AFR and CA199 were 86.67%, 84.34% and 66.67%, 98.80, respectively. The AUROC of RDW, Alb, Fib, and LMR in the PCC group did not show any significant differences compared with the HC group, while the AUROC of the remaining indicators, including WBC, NEU, LYM, MON, PLT, PLR, NLR, dNLR were significantly lower than for CA199.

The combination of AFR with CA199 yielded a higher sensitivity (80.00%) than CA199 alone (66.67%), and its specificity remained at 98.80%. However, their combination produced a larger AUROC than either AFR or CA199 alone (AUROC: 0.932, 95% CI: 0.881 - 0.966, p = 0.001 compared with CA199; p = 0.028 compared with AFR). The combination of RDW with CA199, Alb with CA199 and Fib with CA199 also yielded higher sensitivities (81.33%, 78.67%, and 78.67%, respectively) than CA199 alone. Furthermore, all three combinations of RDW with CA199 (AUROC: 0.905, 95% CI: 0.849 - 0.946, p = 0.003), Alb with CA199 (AUROC: 0.869, 95% CI: 0.806 - 0.917, p = 0.01), and Fib with CA199 (AUROC: 0.921, 95% CI: 0.868 - 0.958, p = 0.003) resulted in larger AUROCs than CA199 alone. Details are presented in Table 2 and Figure 4.

DISCUSSION

PCC is considered the "king" of all cancers because it is one of the most aggressive solid organ malignancies. Patient survival rates vary based on the stages of the cancer. The earlier the disease is detected, the higher the survival rate [18]. Even though there are several methods to screen and diagnose PCC, all have their own characteristics, applications, and limitations. CA199 is the only marker approved by the United States Food and Drug Administration for use in the routine management of PCC [19]; however, its low positive predictive value means it has a low efficiency in mass screening of asymptomatic patients [20]. Therefore, significant effort has been made to improve the diagnostic capacity of CA199, and recent studies into hematology-related indicators have shown promising results in the early diagnosis of PCC.

In the present study, we evaluated the diagnostic value of preoperative hematology-related indicators, including circulating WBC, NEU, LYM, MON, PLT, RDW, Alb, Fib, AFR, LMR, PLR, NLR, and dNLR, alone or in combination with CA199, in the diagnosis of PCC. We observed significantly higher circulating Fib and RDW

Table 1. Comparison of demographic, clinical characteristics, and laboratory indicators between healthy controls and pancreatic cancer patients.

Indicators	Healthy controls (83)	Pancreatic cancer patients (75)	p-value
Age (years)	54.75 ± 9.34	53.23 ± 12.01	0.378
Gender (male/female)	45/38	42/33	0.822
CA199 (U/mL)	9.76 (6.04 - 12.90)	278.60 (14.84 - 1,262.55)	< 0.001
WBC (10^9/L)	6.02 (5.24 - 7.07)	6.87 (5.60 - 8.47)	0.002
Neutrophil (10^9/L)	3.51 (2.81 - 4.53)	4.19 (3.26 - 5.40)	0.001
Lymphocyte (10^9/L)	1.78 (1.52 - 2.22)	1.53 (1.21 - 2.06)	0.08
Monocyte (10^9/L)	0.43 (0.35 - 0.50)	0.54 (0.39 - 0.75)	< 0.001
Platelet (10^9/L)	232.44 ± 45.67	255.44 ± 94.18	0.057
RDW (%)	0.13 (0.13 - 0.13)	0.14 (0.13 - 0.16)	< 0.001
Alb (g/L)	44.06 ± 3.00	39.88 ± 4.80	< 0.001
Fib (g/L)	2.94 (2.67 - 3.18)	4.27 (3.55 - 5.15)	< 0.001
AFR	14.91 (13.65 - 16.15)	9.17 (7.51 - 12.12)	< 0.001
PLR	128.01 (98.03 - 156.10)	158.28 (107.54 - 218.99)	< 0.001
LMR	4.44 (3.54 - 5.52)	3.00 (2.10 - 4.19)	< 0.001
NLR	1.96 (1.50 - 2.48)	2.70 (1.73 - 3.98)	< 0.001
dNLR	2.32 (1.79 - 2.94)	3.24 (2.18 - 4.66)	< 0.001

Data are expressed as mean ± standard deviation or median (interquartile range). CA19-9 - cancer antigen 19-9, WBC - white blood cells, RDW - red cell distribution width, AFR - Alb/Fib ratio, PLR - platelet/lymphocyte ratio, LMR - Lymphocyte/monocyte ratio, NLR - neutrophil-to-lymphocyte ratio.

Table 2. Diagnostic efficiency of single and combined used biomarkers for pancreatic cancer.

Indicators	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC (95% CI)	p-value [a]
CA199	66.67	98.80	98.0	76.6	0.655	0.814 (0.774 - 0.871)	Reference
WBC	40.00	83.13	68.2	60.5	0.231	0.618 (0.538 - 0.694)	0.002
Neutrophil	40.00	84.34	69.8	60.9	0.243	0.627 (0.547 - 0.703)	0.001
Lymphocyte	54.67	72.29	64.1	63.8	0.270	0.621 (0.540 - 0.697)	< 0.001
Monocyte	45.33	100.00	100.0	66.9	0.453	0.689 (0.611 - 0.760)	0.045
Platelet	22.67	100.00	100.0	58.9	0.227	0.538 (0.457 - 0.617)	< 0.001
RDW	48.00	100.00	100.0	68.0	0.480	0.773 (0.700 - 0.836)	0.428
Alb	46.67	100.00	100.0	67.5	0.467	0.772 (0.699 - 0.835)	0.342
Fib	84.00	80.72	79.7	89.8	0.647	0.859 (0.794 - 0.909)	0.354
AFR [b]	86.67	84.34	83.3	87.5	0.710	0.903 (0.846 - 0.945)	0.037
PLR	52.00	75.90	66.1	63.6	0.279	0.636 (0.555 - 0.711)	0.002
LMR	65.33	75.90	71.0	70.8	0.412	0.758 (0.648 - 0.823)	0.300
NLR	44.00	90.36	80.5	64.1	0.344	0.671 (0.592 - 0.744)	0.008
dNLR	57.33	83.13	75.4	68.3	0.405	0.698 (0.620 - 0.769)	0.03
RDW + CA199 [b]	81.33	98.80	98.4	85.4	0.801	0.905 (0.849 - 0.946)	0.003
Alb + CA199 [b]	78.67	95.18	93.7	83.2	0.739	0.869 (0.806 - 0.917)	0.01
Fib + CA199 [b]	78.67	100.00	100.0	83.8	0.787	0.921 (0.868 - 0.958)	0.003
AFR + CA199 [b]	80.00	98.80	98.4	84.5	0.788	0.932 (0.881 - 0.966)	0.001
LMR + CA199	68.0	100.0	100.0	77.6	0.680	0.873 (0.811 - 0.920)	0.053

CA19-9, cancer antigen 19-9; WBC - white blood cells, RDW - red cell distribution width, AFR - Alb/Fib ratio, PLR - platelet/lymphocyte ratio, LMR - lymphocyte/monocyte ratio, NLR - neutrophil-to-lymphocyte ratio.
[a] - All compared with CA199; [b] - The ROC curve of AFR, RDW + CA199, Alb + CA199, Fib + CA199 and AFR + CA199 were significantly higher than CA199, all p-value < 0.05.

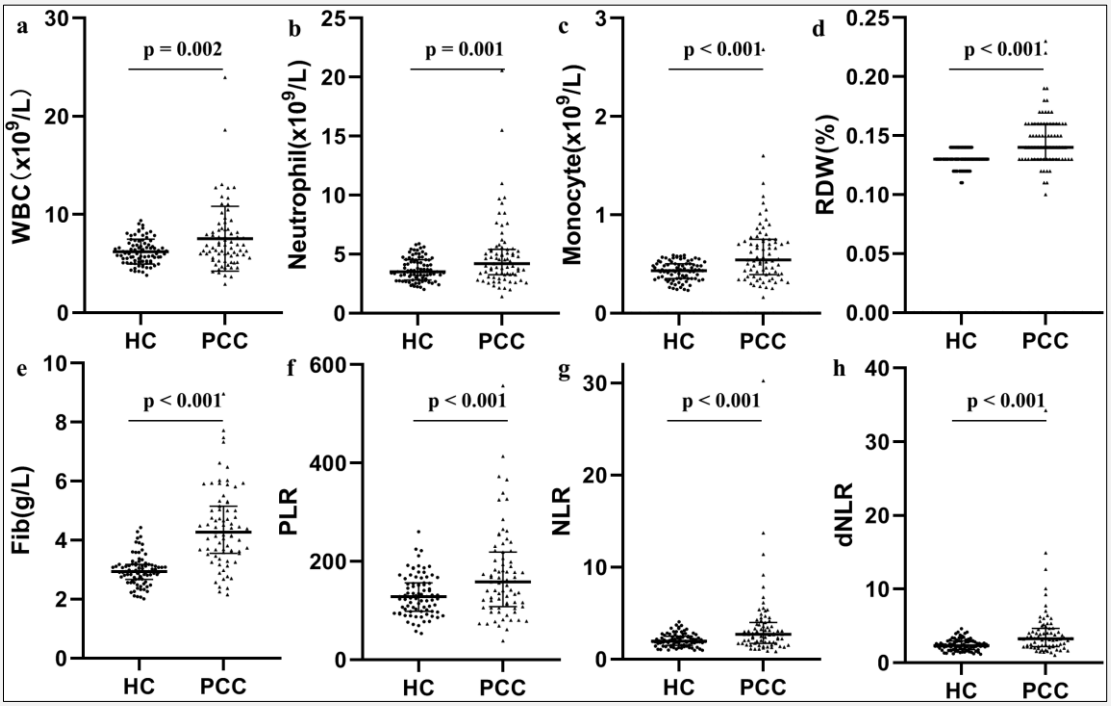

Figure 1. Circulating preoperative white blood cells, neutrophils, monocytes, red cell distribution width, fibrinogen, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, derived NLR in the PCC group was significantly higher than the HC group.

a - WBC, b - Neutrophils, c - Monocytes, d - RDW, e - Fib, f - PLR, g - NLR, h - dNLR. WBC - white blood cells, RDW - red cell distribution width, Fib - fibrinogen, PLR - platelet-to-lymphocyte ratio, NLR - neutrophil-to-lymphocyte ratio, dNLR - derived NLR, PCC - pancreatic cancer, HC - healthy control.

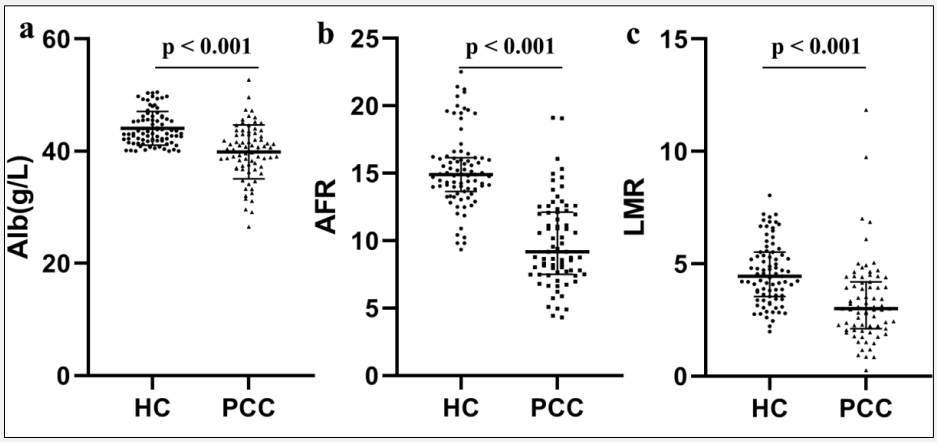

Figure 2. Alb, AFR, and LMR were significantly lower in the PCC group than in the HC group.

a - Alb, b - AFR, c - LMR. Alb - albumin, AFR - albumin/fibrinogen ratio, LMR - lymphocyte/monocyte ratio. PCC - pancreatic cancer, HC - healthy control.

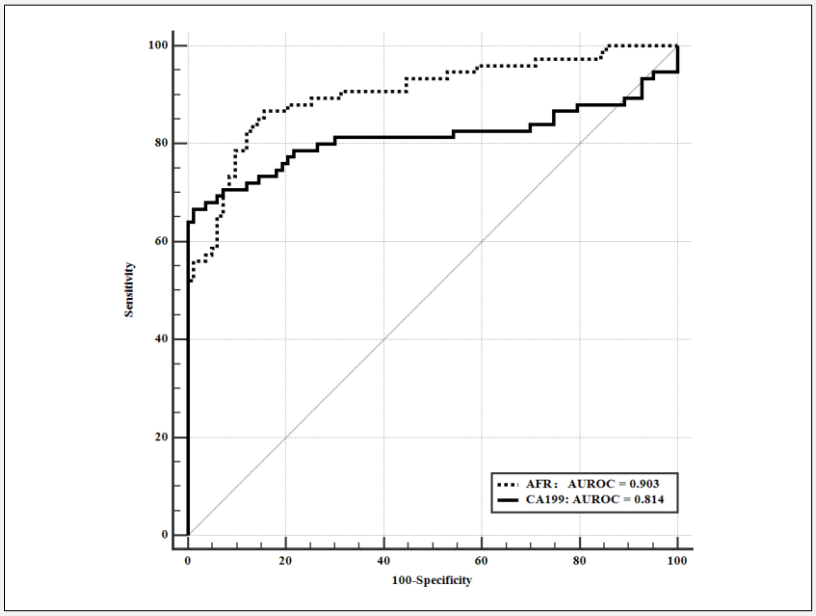

Figure 3. The AUROC of AFR used alone to diagnose PCC was significantly higher than CA199.

AUROC - area under the receiver operating characteristic curve, AFR - albumin/fibrinogen ratio, PCC - pancreatic cancer.

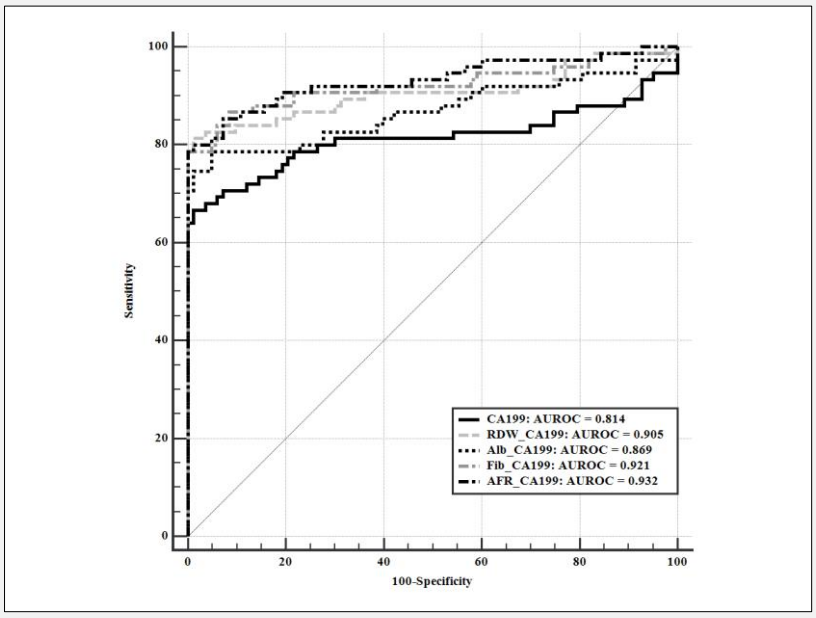

Figure 4. Combination of RDW, Alb, Fib, AFR with CA199 yielded higher AUROC in diagnosing PCC than CA199 alone.

RDW - red cell distribution width, Alb - albumin, Fib - fibrinogen, AFR - albumin/fibrinogen ratio, AUROC - area under the receiver operating characteristic curve, PCC - pancreatic cancer.

and lower Alb and AFR in the PCC group. Furthermore, the diagnostic AUROC of AFR alone was superior to all other investigated indicators, including CA199, at distinguishing PCC from HCs. The combination of Fib, RDW, Alb, and AFR with CA199 all resulted in higher sensitivity and larger AUROCs than CA199 alone. This suggests that circulating AFR alone is a promising diagnostic biomarker for PCC, and the combination of Fib, RDW, Alb, and AFR with CA199 could improve the diagnostic efficacy for PCC. However, our findings were only partially consistent with the results of Liu et al. [17], who also aimed to investigate the diagnostic value of the same inflammatory biomarkers in PCC. Both studies observed significantly higher WBC, NEU, MON, NLR, and dNLR and lower Alb, AFR, and LMR values in the PCC group. However, they found the AUROC of dNLR was the highest among all the indicators, while we observed the highest AUROC in AFR. They also did not combine these indicators with CA199 to evaluate their diagnostic values.

As mentioned above, AFR is the ratio of Alb and Fib, which are indictors for hypoalbuminemia and hyperfibrinogenemia, respectively. These also serve as indicators of chronic inflammation and nutrition [21]. Thus, AFR is a novel biomarker, which has mainly been investigated in inflammation-related cancers. Li et al. [22] found that pretreatment for high circulating levels of Fib, low AFR and Alb were significantly associated with an increased risk of death for lung cancer patients, and AFR might be a prognostic biomarker for non-small-cell lung cancer individuals. Liu et al. [23] demonstrated that Alb and AFR are significantly different between gastric cancer patients and HCs, and are important independent markers of gastric cancer progression and patient survival. Here, we also observed significantly higher Fib and lower Alb and AFR in PCC patients and found that AFR could be a promising diagnostic biomarker for PCC. This would indicate that serum Fib, Alb, and AFR are promising markers reflecting inflammation, tumor metastasis, and patient nutrition. Thus, as a ratio of serum Alb to plasma Fib, AFR could amplify the sensitivity of inflammation and nutrition status in PCC patients, and it was therefore superior to the single Alb and Fib in diagnosing PCC.

In addition to the AFR results, we also found a significantly higher AUROC in the combination of RDW with CA199 in diagnosing PCC. As is known, RDW is a main descriptive parameter for erythrocyte variations and can be used on a daily basis. It has also been shown to be related to chronic inflammation and nutritional complications [24]. Increasing evidence has shown that RDW plays a pivotal role in the diagnosis of malignant tumors. Seretis et al. [25] found that RDW was significantly higher in patients with breast cancer. Yilmaz et al. [14] demonstrated RDW levels can be used as a marker to show PCC stages, and decreased survival rates accompanied those higher RDW values. In the present study, we also found a significantly higher RDW value in the PCC group than in the HCs. Furthermore, RDW combined with CA199 resulted in a significantly higher AUROC than CA199 alone, possibly due to the role of RDW in chronic inflammation.

CONCLUSION

In summary, to improve the diagnostic efficacy for PCC, our study is the first to comprehensively evaluate the diagnostic value of circulating inflammatory biomarkers alone and combined with CA199. Our results suggest that circulating AFR was an effective biomarker in distinguishing PCC patients from HCs, and combining AFR, RDW, Alb, and Fib with CA199 could significantly improve the diagnostic efficacy for PCC. However, as a retrospective single-center cohort with relatively small sample sizes, larger-scale and multi-center studies are warranted to confirm our findings.

Acknowledgment:
This research was funded by the Guangxi Health Department Self Financing Research Project (Z20190218).

Declaration of Interest:
The authors declare that they have no conflicts of interest.

References:

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21 (PMID: 24840647).

2. Evans DB, Lee JE, Pisters PW, et al. Advances in the diagnosis and treatment of adenocarcinoma of the pancreas. Cancer Treat Res, 1997;90:109-25 (PMID: 9367080).

3. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol, 2018;24:4846-61 (PMID: 30487695).

4. Canto MI, Harinck F, Hruban RH et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62:339-47 (PMID: 23135763).

5. Unger K, Mehta KY, Kaur P et al. Metabolomics based predictive classifier for early detection of pancreatic ductal adenocarcinoma. Oncotarget 2018;9:23078-90 (PMID: 29796173).

6. Kaur S, Smith LM, Patel A, et al. A Combination of MUC5AC and CA19-9 Improves the Diagnosis of Pancreatic Cancer: A Multicenter Study. Am J Gastroenterol 2017;112:172-83 (PMID: 27845339).

7. Kaur S, Baine MJ, Jain M et al. Early diagnosis of pancreatic cancer: challenges and new developments. Biomark Med 2012;6: 597-612 (PMID: 23075238).

8. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer. J Clin Oncol 2006;24:5313-27 (PMID: 17060676).

9. Shi J, Xue J. Inflammation and development of pancreatic ductal adenocarcinoma. Chin Clin Oncol 2019;8:19 (PMID: 31070039).

10. Guo F, Zhu X, Qin X. Platelet Distribution Width in Hepatocellular Carcinoma. Med Sci Monit 2018;24:2518-23 (PMID: 29689031).

11. Wu Y, Jiang M, Qin Y, Lin F, Lai M. Single and combined use of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and carcinoembryonic antigen in diagnosing gastric cancer. Clin Chim Acta 2018;481:20-4 (PMID: 29476736).

12. Qin YY, Wu YY, Xian XY, et al. Single and combined use of red cell distribution width, mean platelet volume, and cancer antigen 125 for differential diagnosis of ovarian cancer and benign ovarian tumors. J Ovarian Res, 2018. 11:10 (PMID**:** 29357908**).**

13. Wang L, Jia J, Lin L, et al. Predictive value of hematological markers of systemic inflammation for managing cervical cancer. Oncotarget 2017;8:44824-32 (PMID: 28148894).

14. Yilmaz A, Malya F, Ozturk G, et al. Effect of pre-operative red blood cell distribution on cancer stage and morbidity rate in patients with pancreatic cancer. Int J Clin Exp Med 2014;7:3072-5 (PMID: 25356183).

15. Tingle SJ, Severs GR, Goodfellow M, Moir JA, White SA. NARCA: A novel prognostic scoring system using neutrophil-albumin ratio and Ca19-9 to predict overall survival in palliative pancreatic cancer. J Surg Oncol 2018;118:680-6 (PMID: 30196571).

16. Qin S, Lu Y, Chen S et al. The Relationship of Neutrophil-to-Lymphocyte Ratio or Platelet-to-Lymphocyte Ratio and Pancreatic Cancer in Patients with Type 2 Diabetes. Clin Lab 2019;65 (PMID: 31307172).

17. Liu JX, Li A, Zhou LY et al. Significance of combined preoperative serum Alb and dNLR for diagnosis of pancreatic cancer. Future Oncol 2018;14:229-39 (PMID: 29338337).

18. Hidalgo M. Pancreatic cancer. N Engl J Med 2010;362:1605-17 (PMID: 20427809).

19. Kim JE, Lee KT, Lee JK, et al. Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population. J Gastroenterol Hepatol 2004;19:182-6 (PMID: 14731128).

20. Fahrmann JF, Bantis LE, Capello M, et al. A Plasma-Derived Protein-Metabolite Multiplexed Panel for Early-Stage Pancreatic Cancer. J Natl Cancer Inst 2019;111:372-9 (PMID: 30137376).

21. Bremnes RM, Al-Shibli K, Donnem T, et al. The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer. J Thorac Oncol 2011;6:824-33 (PMID: 21173711).

22. Li SQ, Jiang YH, Lin J, et al. Albumin-to-fibrinogen ratio as a promising biomarker to predict clinical outcome of non-small cell lung cancer individuals. Cancer Med 2018;7:1221-31 (PMID: 29533009).

23. Liu C, Li X. Stage-Dependent Changes in Albumin, NLR, PLR, and AFR are Correlated with Shorter Survival in Patients with Gastric Cancer. Clin Lab 2019;65 (PMID: 31532095).

24. Förhécz Z, Gombos T, Borgulya G, et al. Red cell distribution width in heart failure: prediction of clinical events and relationship with markers of ineffective erythropoiesis, inflammation, renal function, and nutritional state. Am Heart J, 2009;158:659-66 (PMID: 19781428).

25. Seretis C, Seretis F, Lagoudianakis E, Gemenetzis G, Salemis NS. Is red cell distribution width a novel biomarker of breast cancer activity? Data from a pilot study. J Clin Med Res 2013;5:121-6 (PMID: 23518817).