International Immunopharmacology 67 (2019) 372–377

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Association of CCL11, CCL24 and CCL26 with primary biliary cholangitis

Feng Lin[a,1], Hong Shi[b,1], Donghong Liu[c,1], Zhencheng Zhang[c], Wanwan Luo[c], Panying Mao[c], Renqian Zhong[b], Yan Liang[b,*], Zaixing Yang[c,*]

[a] Department of General Surgery, Huangyan Hospital of Wenzhou Medical University, Taizhou First People's Hospital, Taizhou, Zhejiang, China
[b] Department of Laboratory Diagnostics, Changzheng Hospital, Second Military Medical University, Shanghai, China
[c] Department of Laboratory Medicine, Huangyan Hospital of Wenzhou Medical University, Taizhou First People's Hospital, Taizhou, Zhejiang, China

ARTICLE INFO

Keywords:
CCL11
CCL24
CCL26
Primary biliary cholangitis

ABSTRACT

Background: CCL11, CCL24 and CCL26 are potent chemokines for eosinophils. Since there has been no study reporting the association serum CCL11, CCL24 and CCL26 with fibrotic progression of PBC, the aim of this study is to explore the association.

Methods: One hundred and eight PBC patients, 52 patients with chronic hepatitis B (CHB) and 50 healthy controls (HC) were recruited. The sera were detected for CCL11, CCL24 and CCL26 using multiplex immunoassay. Other laboratory indicators were routinely measured. PBC was divided into four stages according to Scheuer's classification.

Results: Serum CCL11, CCL24 and CCL26 levels were significantly higher in PBC patients than those with CHB and HC ($P < 0.05$). The ROC analyses showed that all of the three CCLs performed well for identification of PBC (all $P <$ or $= 0.001$). The multiple linear regression analysis showed an independent relationship of CCL26 with APRI and FIB-4 in PBC patients, but no relationship of CCL11 and CCL24 with fibrotic indicators. Additionally, serum CCL11 and CCL26 were negatively correlated with histological stage of PBC, while serum CCL24 showed no statistical correlation.

Conclusion: Serum CCL11, CCL24 and CCL26 are upregulated in PBC. CCL11 and CCL26 are associated with fibrotic progression of PBC, but CCL24 is not.

1. Introduction

Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease of unknown cause, characterized by the inflammatory destruction of intrahepatic bile ducts, affecting predominantly middle-aged women. If untreated, the disease may progress toward cirrhosis, liver failure and even liver cancer. Although anti-mitochondrial antibodies (AMAs) are key diagnostic markers of PBC, with a prevalence of 90% or so for PBC, they have no ability to identify the severity and progression of PBC [1]. Therefore, up to date, the search for new serum markers associated with disease severity and progression has been a hot spot in PBC study field.

Although the pathogenesis of PBC has remained elusive, several studies showed a large number of eosinophils infiltrating in portal tract of liver in PBC patients, suggesting that eosinophils may play an important role in PBC [2–4]. Furthermore, some studies indicated that treatment of ursodeoxycholic Acid (UDCA), one of the most important drugs for PBC treatment, can ameliorate eosinophilia and inhibit eosinophil activation/degranulation in PBC patients, further supporting the speculation about the association of eosinophil with PBC [4–6]. However, the mechanism by which eosinophil was recruited into portal tract in PBC has remained challenging.

Eotaxins, including C-C motif chemokine ligand 11 (CCL11) (eotaxin), CCL24 (eotaxin-2) and CCL26 (eotaxin-3), belong to the family of CC chemokines. These three eotaxins, as potent chemoattractants for eosinophils, have been reported to be increased in some allergic diseases, such as allergic asthma, allergic rhinitis, and atopic dermatitis [7–9]. Additionally, the increased CCL26 is also correlated with bullous pemphigoid [10], eosinophilic granulomatosis with polyangiitis [11] and eosinophilic esophagitis [12]. A recent study found the decreased serum CCL11 levels and increased CCL26 in PBC patients [13], but the association of these two eotaxins with staging and fibrosis progression of PBC has remained unclear.

In the present study, we determined serum CCL11, CCL24 and CCL26 levels and explored whether or not they were associated with the fibrotic progression of PBC which is divided into four histological

* Corresponding authors.
E-mail addresses: liangyan0829@163.com (Y. Liang), yangzaixingdiyi@163.com (Z. Yang).
[1] Feng Lin, Hong Shi and Donghong Liu contributed equally to this work.

https://doi.org/10.1016/j.intimp.2018.12.026
Received 30 May 2018; Received in revised form 15 November 2018; Accepted 11 December 2018
Available online 22 December 2018
1567-5769/ © 2018 Published by Elsevier B.V.

Table 1
Clinical, laboratory, and histological characteristics of PBC patients.

Characteristics	PBC patients		CHB patients		HC	
	n	Results	n	Results	n	Results
Age (years)	108	59 ± 11	52	52 ± 9	50	55 ± 7
Female, n (%)	108	96 (89)	52	41 (79)	50	44 (88)
WBC count (10^9/L)	106	3.95 (2.50–5.30)	/	/	/	/
Neutrophil (10^9/L)	106	2.01 (1.38–3.02)	/	/	/	/
Lymphocyte (10^9/L)	106	1.21 (0.80–1.74)	/	/	/	/
Eosinophil (10^9/L)	106	0.08 (0.05–0.14)				
Platelet (10^9/L)	106	121 (65–171)	/	/	/	/
NLR	106	1.71 (1.23–2.36)	/	/	/	/
PLR	106	105.06 (71.55–133.33)	/	/	/	/
Bilirubin (mg/dl)	108	19 (13–45)	/	/	/	/
ALT (IU/L)	108	45 (24–88)	/	/	/	/
AST (IU/L)	108	59 (36–103)	/	/	/	/
ALP (IU/L)	108	179 (122–298)	/	/	/	/
GGT (IU/L)	108	127 (64–283)	/	/	/	/
AST/ALT ratio	108	1.32 (0.91–1.83)	/	/	/	/
APRI	106	1.45 (0.70–2.55)	/	/	/	/
FIB-4 index	106	4.16 (2.68–9.99)	/	/	/	/
AMA positive, n (%)	108	97 (90)	/	/	/	/
ANA positive, n (%)	108	78 (72)	/	/	/	/
Anti-centromere positive, n (%)	108	30 (28)	/	/	/	/
Anti-gp210 positive, n (%)	108	35 (32)	/	/	/	/
Anti-sp100 positive, n (%)	108	15 (14)	/	/	/	/
Scheuer's stage (I:II:III:IV)	78	18:15:25:20	/	/	/	/

Age is expressed as mean ± SD, while other continuous variables as median and interquartile range. Categorical variables were expressed as total number (%).
WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; APRI, AST to platelet ratio index; FIB-4, fibrosis index based on the 4 factors; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; PBC, primary biliary cholangitis.

stages in accordance with internationally recognized Scheuer's classification.

2. Patients and methods

2.1. Subjects

We recruited 108 treat-naïve patients from Changzheng Hospital between January 2009 and October 2018. All of them fulfilled the criteria from the American Association for the Study of Liver Diseases for PBC [14]. Of those, 78 patients received liver biopsy. The exclusion criteria included primary sclerosing cholangitis, autoimmune hepatitis, other focal intrahepatic or extrahepatic lesions or obstruction, any clinically significant concomitant liver disease, or receiving corticosteroids or immunosuppressive medications. During the same period, 52 age- and sex-matched patients with chronic hepatitis B (CHB) and 50 age- and sex-matched healthy individuals were enrolled as disease and healthy controls, respectively, in the same hospital (Table 1). The clinical and laboratory characteristics of our subjects were listed in Table 1. The institutional ethics committee approved this study and all of the subjects gave their signed informed consent.

2.2. Serological determinations

Sera were isolated within 60 min of venous blood sample collection and stored at −80 °C temperature until used. CCL11, CCL24 and CCL26 in sera were determined by Meso Scale Discovery (MSD) multiplex immunoassay according to manufacturer's instructions (MSD SCALE DISCOVERY, Rockville, MD). Other laboratory indicators were routinely measured. Briefly, Antinuclear antibodies (ANA) and AMA were detected by indirect immunofluorescence (IIF) (EUROPIN, Germany), and anti-centromere, gp210 and sp100 antibodies by immunoblot assay (EUROPIN, Germany). Blood routine testing was performed in Sysmex XE-2100 analyzer (Sysmex Corporation, Kobe, Japan). Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT) and total bilirubin were measured using the Cobas P800 analyzer (Roche diagnostic system).

2.3. Calculation of indirect laboratory indicators

The indirect laboratory indicators included Neutrophil- (NLR) and platelet-lymphocyte (PLR), AST to ALT ratio, AST to platelet ratio index (APRI) calculated by Wai's formula: (AST/upper limit of normal) / platelet count (10^9/L) × 100 [15], and FIB-4 index calculated by Sterling's formula as: age (years) × AST (IU/L) / platelet count (×10^9/L) × √ALT (IU/L) [16].

2.4. Histological staging

PBC is divided into four histological stages in accordance with Scheuer's classification [17]. In Stage 1, inflammatory damage is localized to the portal triads. In stage 2 shows the damage extending beyond the portal triads into the surrounding parenchyma and the loss of some bile ducts. Stage 3 shows the damage characterized by fibrous septa linking adjacent portal triads. In stage 4, cirrhosis is clear.

2.5. Statistical analysis

Statistical analysis was performed by SPSS 17.0 software. Mean ± standard deviation (SD) and median (interquartile range (IQR)) were used to describe normal-distributed and skewed variables, respectively. All the continuous variables were compared by Student's *t*-test or Mann–Whitney *U* test when appropriate. Receiver operating characteristic (ROC) curves were plotted and the areas under the curves (AUC) were calculated for assessing the diagnostic value of CCL11, CCL24 or CCL26 for PBC. Spearman's correlation coefficient was used to evaluate the correlation between CCL11, CCL24 or CCL26 and other continuous variables. The multiple linear regression analysis was used to assess the independent relationships of CCL11 and CCL26 with other variables. Results were considered significant if the two-tailed P-value was < 0.05.

3. Results

3.1. The comparisons of serum CCL11, CCL24 and CCL26 levels between different populations

The median levels of serum CCL11, CCL24 and CCL26 were 264.48 pg/mL (IQR, 204.51–358.84 pg/ml), 4799.22 pg/ml, (IQR, 2274.54–7853.72 pg/ml) and 32.68 pg/ml, (IQR, 23.23–44.86 pg/ml), respectively, in PBC patients, significantly higher than those with CHB (median, IQR, CCL11: 193.81, 133.65–242.84 pg/ml; CCL24: 1975.95, 1155.44–2554.96 pg/ml; CCL26: 28.96, 18.16–38.37 pg/ml) (all $P < 0.05$) and HC (median, IQR, CCL11: 213.79, 172.89–284.06 pg/ml; CCL24: 1878.65, 1419.79–2236.92 pg/ml; CCL26: 27.77, 18.51–36.88 pg/ml) (all $P < 0.05$). No significant difference for the three CCLs was found between CHB patients and HC. See Fig. 1.

3.2. Diagnostic performance of serum CCL11, CCL24 and CCL26 for PBC

The ROC analyses showed that all of the three CCLs performed well for identification of PBC. Further, the diagnostic value of serum CCL24

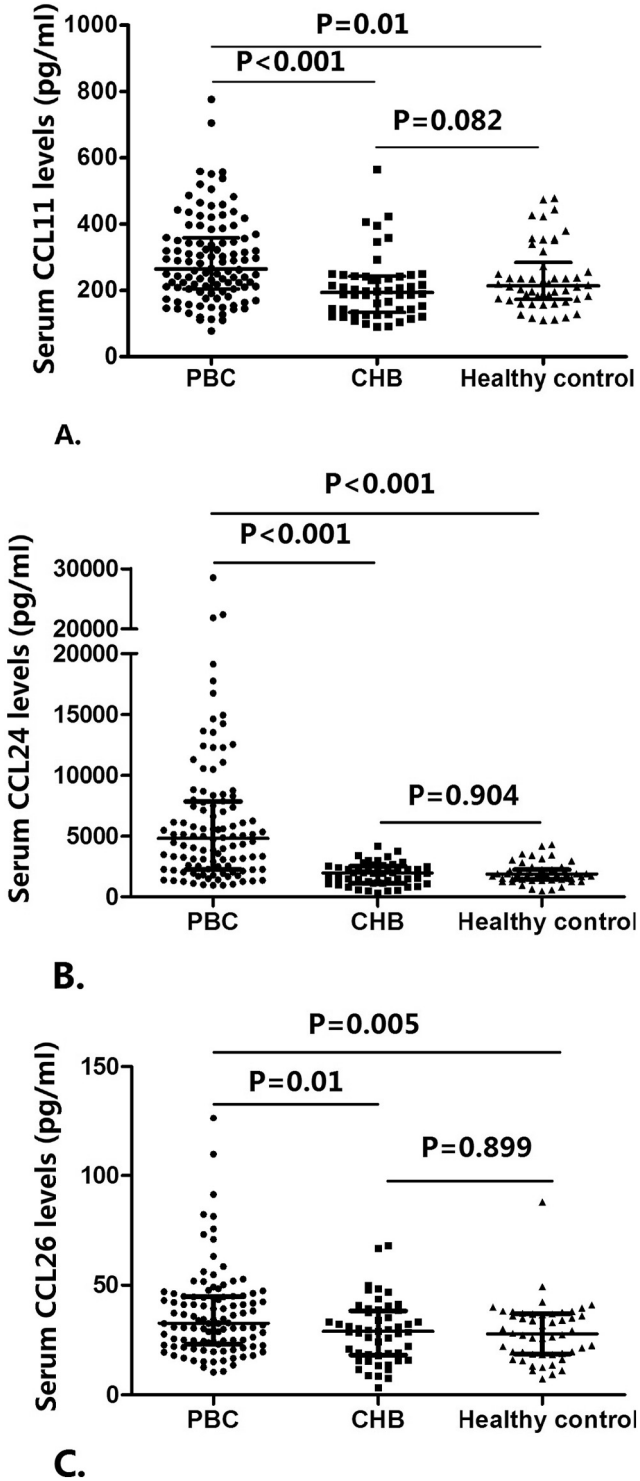

Fig. 1. Serum CCL11, CCL24 and CCL26 levels in various populations. A: CCL11, B: CCL24, C: CCL26. Results are reported as median and interquartile range (IQR). Statistical significance between groups was determined using a Mann Whitney *U* test. PBC, primary biliary cholangitis (n = 108); CHB, chronic hepatitis B (n = 52); HC, healthy control (n = 50).

was the best for PBC, with AUC of 0.820 (95%CI, 0.762–0.879) (P < 0.001), followed by CCL11 (AUC, 0.675; 95% CI, 0.602–0.748; P < 0.001) and CCL26 (AUC, 0.632; 95% CI, 0.558–0.707; P = 0.001). See Fig. 2.

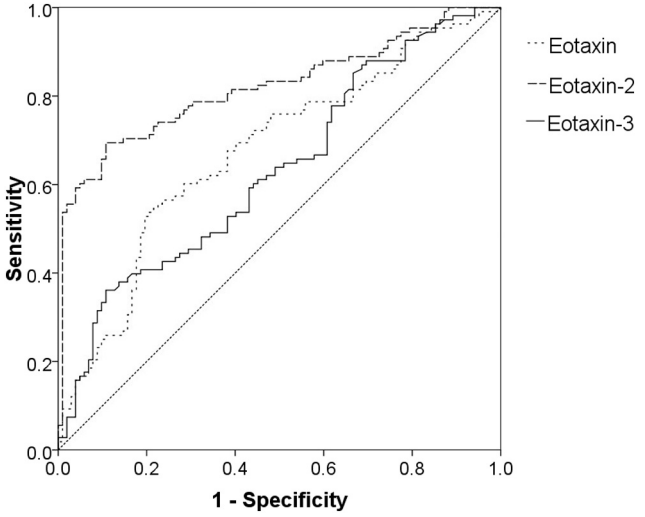

Fig. 2. The ROC curve analyses for diagnostic performance of serum CCL11, CCL24 and CCL26 for PBC. The AUC value was 0.675 (95%CI: 0.602–0.748), 0.820. (95%CI: 0.762–0.879) and 0.632 (95%CI: 0.558–0.707) for CCL11, CCL24 and CCL26, respectively. ROC, receiver operating characteristic; AUC, areas under the curve; CI, confidence interval.

3.3. Correlations between CCL11, CCL24, CCL26 and clinical and laboratory characteristics in PBC

Various univariate analyses showed that serum CCL11 level was positively correlated with platelet, but negatively with APRI in PBC patients. There was no significant relationship between CCL11 and other clinical and laboratory characteristics, including age, sex, AMA, ANA, anti-gp210, sp100 and centromere antibodies, ALP, GGT, platelet, WBC, NLR, PLR, AST/ALT and FIB-4 (P > 0.05) (Tables 2 and 3). Serum CCL24 was significantly associated with ANA and GGT, but not with other variables. PBC patients with the presence of ANA had significantly lower CCL24 levels than those without ANA. Serum CCL24 was weakly correlated with GGT. Serum CCL26 was positively correlated with WBC, neutrophil, lymphocyte and platelet, but negatively with FIB-4 and APRI. No significant relationship was found between CCL26 and other clinical and laboratory characteristics (Tables 2 and 3).

The multiple linear regression analysis showed an independent relationship of CCL26 with APRI and FIB-4 and of CCL11 with platelet in PBC patients (Table 4).

3.4. Correlations between CCL11, CCL24, CCL26 and histological stage of PBC

Serum CCL11 and CCL26 were statistically negatively correlated with histological stage of PBC (CCL11, $r = -0.257$, P = 0.023; CCL26, $r = -0.333$, P = 0.003), while serum CCL24 showed no statistical correlation with histological stage of PBC ($r = -0.221$, P = 0.052) (Fig. 3).

4. Discussion

This is, to the best of our knowledge, the first study to investigate the association of CCL11 CCL24 and CCL26 with the fibrotic progression of PBC. In this study, we found that serum CCL11 and CCL26 are upregulated in PBC and negatively associated with the fibrotic progression of PBC. Serum CCL24 is also upregulated in PBC but not associated with the fibrotic progression.

One result of our current study indicated that serum CCL11 was not only increased in PBC patients, but also performed well for differentiating this disease from CHB and healthy individuals. This is

Table 2
Relationships between serum CCL11, CCL24 and CCL26 and categorical variables in PBC patients.

	CCL11 (pg/ml)		CCL24 (pg/ml)		CCL26 (pg/ml)	
	Median (IQR)	P value	Median (IQR)	P value	Median (IQR)	P value
Sex						
Male	332.13 (230.47–433.86)		3658.64 (1494.76–7783.45)		28.10 (15.88–43.52)	
Female	259.06 (198.82–349.39)	0.276	4936.43 (2352.78–7853.72)	0.458	33.39 (24.33–44.95)	0.224
AMA						
Positive	262.33 (204.56–385.99)		4989.27 (2282.12–8147.99)		32.53 (23.65–44.93)	
Negative	285.95 (175.59–309.24)	0.506	3836.35 (1923.82–5592.54)	0.279	37.29 (22.02–43.06)	0.903
ANA						
Positive	284.49 (204.60–368.53)		4089.90 (2007.49–7395.56)		34.12 (22.46–46.52)	
Negative	261.08 (179.69–334.28)	0.499	5507.79 (3750.73–11,023.40)	0.017	32.53 (25.04–41.34)	0.709
Anti-centromere						
Positive	299.52 (224.53–372.06)		4339.88 (1781.83–6547.46)		32.33 (22.02–46.88)	
Negative	256.53 (194.09–361.97)	0.235	4936.43 (2537.64–8068.08)	0.255	32.68 (24.59–44.74)	0.997
Anti-gp210						
Positive	244.28 (207.67–338.29)		5370.68 (3042.61–10,626.25)		36.24 (22.69–47.43)	
Negative	288.54 (180.17–396.26)	0.410	4217.88 (2226.89–6344.85)	0.076	31.38 (23.65–44.68)	0.465
Anti-sp100						
Positive	263.97 (190.23–396.13)		4638.45 (1798.68–7219.22)		30.63 (19.88–48.98)	
Negative	264.48 (204.60–352.67)	0.949	4936.43 (2463.76–8068.08)	0.470	33.39 (24.17–44.68)	0.798

PBC, primary biliary cholangitis; ANA, antinuclear antibody; AMA, anti-mitochondrial antibody; IQR, interquartile range.

Table 3
Correlations between serum CCL11, CCL24 and CCL26 and continuous variables in PBC patients.

	CCL11		CCL24		CCL26	
	r	P value	r	P value	r	P value
Age	0.147	0.129	−0.131	0.178	0.117	0.230
Bilirubin	−0.141	0.147	0.137	0.157	−0.151	0.119
ALT	−0.021	0.830	0.139	0.152	−0.012	0.903
AST	−0.034	0.728	0.057	0.560	−0.144	0.136
ALP	0.049	0.620	0.168	0.089	0.041	0.678
GGT	0.043	0.656	0.245	0.010	0.025	0.795
FIB-4	−0.164	0.094	−0.129	0.188	−0.350	< 0.001
APRI	−0.208	0.032	−0.034	0.728	−0.386	< 0.001
AST/ALT	−0.001	0.998	−0.168	0.082	−0.171	0.077
WBC	0.099	0.313	0.071	0.467	0.283	0.003
Neutrophil	0.059	0.549	0.149	0.128	0.268	0.006
Lymphocyte	0.181	0.064	0.054	0.582	0.283	0.003
Eosinophil	0.064	0.514	0.007	0.946	0.092	0.350
Platelet	0.260	0.007	0.124	0.206	0.367	< 0.001
NLR	−0.168	0.087	0.074	0.454	−0.083	0.399
PLR	0.107	0.280	0.105	0.288	0.104	0.293

PBC, primary biliary cholangitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltransferase; FIB-4, fibrosis index based on the 4 factors; APRI, AST to platelet ratio index; WBC, white blood cell; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

completely opposite to the previous study that reported decreased eotaxin levels in PBC patients [13]. We do not know the detailed reason for this great difference between the present study and the previous one. It may be due to different ethnicity or selection bias of subjects, since the sizes of both studies are small (108 PBC patients in our study and 50 in the previous one). In addition, we found that increased serum CCL11 is weakly associated with fibrotic pression of PBC. Therefore, whether CCL11 is associated with the onset and progression of PBC remains to be confirmed by a larger number of studies, although a few studies found that CCL11 may be involved in fibrotic process of some liver diseases [18,19].

We found the upregulation of serum CCL24 in PBC patients for the first time. It has remained controversy whether serum CCL24 is a predictive marker for liver fibrosis among different liver diseases. Rodrigues Oliveira et al. reported that CCL24 can be used as predictive maker of Schistosoma-induced liver fibrosis [20], contrary with another study in which no association between CCL24 and liver fibrosis was found in patients with chronic hepatitis C virus infection [21]. In the present study, although CCL24 performs very well for identification of PBC, it may not be useful marker for fibrotic process of PBC.

Serum CCL26 is not only increased, but also negatively correlated with fibrosis indicators in PBC patients. Although Landi et al. also found the upregulation of serum CCL26 in PBC [13], they did not investigate the association with PBC staging and fibrosis progression. The present study provides more novel information about clinical significance of serum CCL26 in PBC. It has been reviewed that, in contrast to CCL11 which was secreted by eosinophils, macrophages, lymphocytes, fibroblasts, smooth muscle endothelial cells, epithelial cells and chondrocytes, CCL26 is mainly released by epithelial and endothelial cells [22]. Therefore, we speculated that biliary epithelial cells (BECs) may produce amount of CCL26 under some conditions in early PBC. A number of eosinophils may be recruited into portal area by the

Table 4
Multiple linear regression analysis of the correlation between serum CCL11 and CCL26 and continuous variables in PBC patients.

	CCL11			CCL26		
	Coefficient	Std. error	P value	Coefficient	Std. error	P value
FIB-4	/	/	/	−1.766	0.702	0.015
APRI	−2.105	2.400	0.382	−2.537	1.149	0.032
WBC	/	/	/	−2.549	4.413	0.860
Neutrophil	/	/	/	0.691	15.345	0.964
Lymphocyte	/	/	/	15.998	17.351	0.361
Platelet	0.366	0.141	0.011	−0.027	0.061	0.658

PBC, primary biliary cholangitis; FIB-4, fibrosis index based on the 4 factors; APRI, AST to platelet ratio index; WBC, white blood cell.

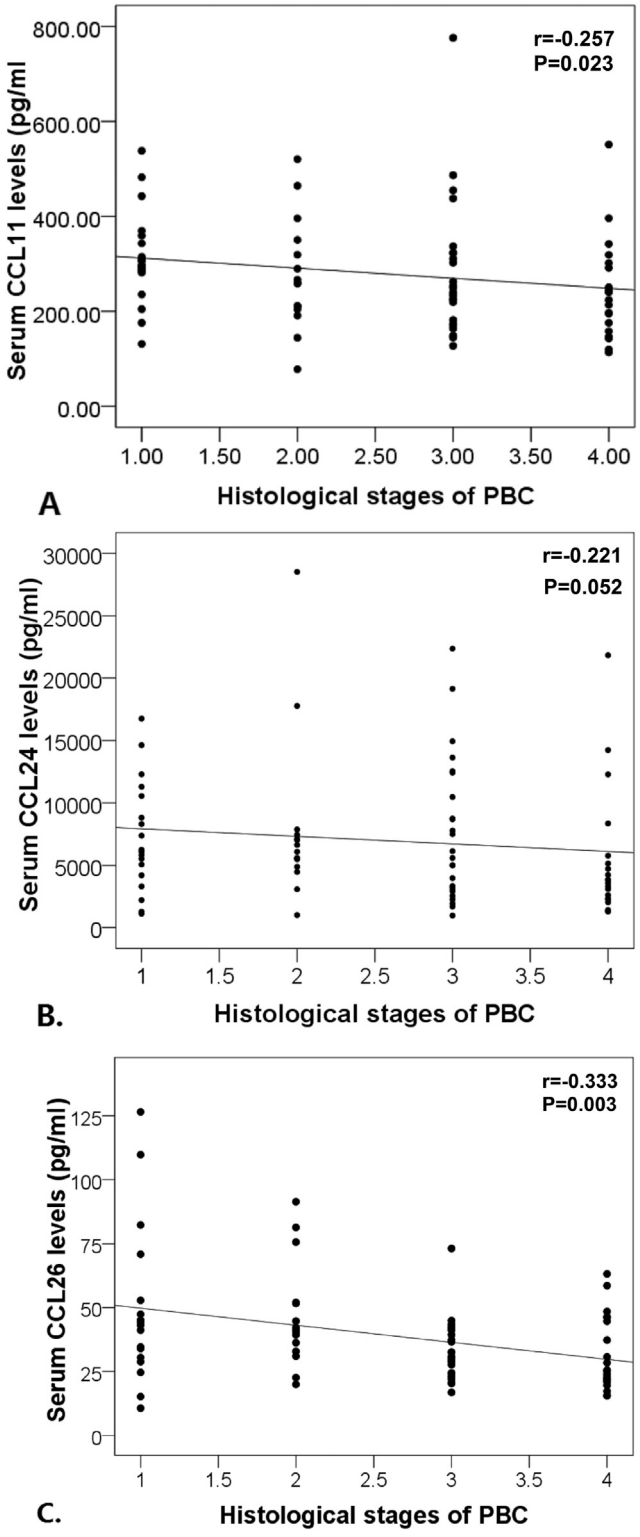

Fig. 3. Correlation between serum CCL11, CCL24, CCL26 and histological stage of PBC. A: CCL11, B: CCL24, C: CCL26. Spearman's correlation coefficient was used to evaluate the correlation.

increased CCL26 and participate in the inflammatory damage of PBC. However, with the great reduction of BECs in moderate to advance stage of PBC, CCL26 is gradually decreased. Admittedly, this speculation needs to be confirmed by a number of studies. Anyway, the present study showed that serum CCL26 may be a useful marker for identify the early stage of PBC.

In addition, we found no correlation between the three CCLs and the number of eosinophils in PBC patients in the present study. Therefore, we speculated that they have a role in eosinophil recruiting, but they may have no direct role in the eosinophil number of peripheral blood.

There are some limitations in this study. Firstly, this cross-sectional study can not confirm the causality between the three CCLs and PBC development. Accordingly, the longitudinal studies are needed to confirm it. Secondly, since the sample size of this study is small, there may be selection bias. It could be partly due to the selection bias that the result of this study, with respect to serum CCL11, is inconsistent with that of the previous one. The interpretation of our findings should be made cautiously and the conclusions need to be confirmed in further studies with a larger size. Finally, the detailed mechanism by which CCL26 takes part in the pathogenesis of PBC is speculated, but not investigated in the present study. It remains to be clarified whether and how the three CCLs exert a role in immune-mediated cholangitis of PBC.

In conclusion, this study suggested that serum CCL11, CCL24 and CCL26 are upregulated in PBC. Furthermore, CCL11 and CCL26 are associated with fibrosis progression of PBC. Our current study provides a useful clue for further exploring the role of eotaxins and eosinophils in pathogenesis of PBC.

Conflicts of interests

None.

Acknowledgments

This study was supported by three grants from the National Natural Science Foundation of China and Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (81671594, 81571591 and 2019309067).

References

[1] E.J. Carey, A.H. Ali, K.D. Lindor, Primary biliary cirrhosis, Lancet 386 (10003) (2015) 1565–1575, https://doi.org/10.1016/S0140-6736(15)00154-3.
[2] N.S. Goldstein, A. Soman, S.C. Gordon, Portal tract eosinophils and hepatocyte cytokeratin 7 immunoreactivity helps distinguish early-stage, mildly active primary biliary cirrhosis and autoimmune hepatitis, Am. J. Clin. Pathol. 116 (6) (2001) 846–853, https://doi.org/10.1309/VHHD-HTRU-N8J2-5X7R.
[3] A. Nakamura, et al., Increased portal tract infiltration of mast cells and eosinophils in primary biliary cirrhosis, Am. J. Gastroenterol. 92 (12) (1997) 2245–2249.
[4] K. Yamazaki, et al., Eosinophilia in primary biliary cirrhosis, Am. J. Gastroenterol. 91 (3) (1996) 516–522.
[5] K. Yamazaki, et al., Ursodeoxycholic acid inhibits eosinophil degranulation in patients with primary biliary cirrhosis, Hepatology 30 (1) (1999) 71–78, https://doi.org/10.1002/hep.510300121.
[6] H.P. Wirth, et al., Eosinophilia in primary biliary cirrhosis: regression under therapy with ursodeoxycholic acid, Schweiz. Med. Wochenschr. 124 (19) (1994) 810–815.
[7] G. Garcia, V. Godot, M. Humbert, New chemokine targets for asthma therapy, Curr Allergy Asthma Rep 5 (2) (2005) 155–160.
[8] Z. Ahmadi, et al., An overlook to the characteristics and roles played by eotaxin network in the pathophysiology of food allergies: allergic asthma and atopic dermatitis, Inflammation 39 (3) (2016) 1253–1267, https://doi.org/10.1007/s10753-016-0303-9.
[9] M. Paplińska, et al., Expression of eotaxins in the material from nasal brushing in asthma, allergic rhinitis and COPD patients, Cytokine 60 (2) (2012) 393–399, https://doi.org/10.1016/j.cyto.2012.07.001.
[10] C. Günther, et al., Up-regulation of CCL11 and CCL26 is associated with activated eosinophils in bullous pemphigoid, Clin. Exp. Immunol. 166 (2) (2011) 145–153, https://doi.org/10.1111/j.1365-2249.2011.04464.x.
[11] K. Polzer, et al., Eotaxin-3 is involved in Churg-Strauss syndrome—a serum marker closely correlating with disease activity, Rheumatology (Oxford) 47 (6) (2008) 804–808, https://doi.org/10.1093/rheumatology/ken033.
[12] E.S. Dellon, et al., Markers of eosinophilic inflammation for diagnosis of eosinophilic esophagitis and proton pump inhibitor-responsive esophageal eosinophilia: a prospective study, Clin. Gastroenterol. Hepatol. 12 (12) (2014) 2015–2022, https://doi.org/10.1016/j.cgh.2014.06.019.
[13] A. Landi, et al., Differential serum levels of eosinophilic eotaxins in primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis, J. Interf. Cytokine Res. 34 (3) (2014) 204–214, https://doi.org/10.1089/jir.2013.0075.
[14] K.D. Lindor, et al., Primary biliary cirrhosis, Hepatology 50 (1) (2009) 291–308,

https://doi.org/10.1002/hep.22906.
[15] C.T. Wai, et al., A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C, Hepatology 38 (2) (2003) 518–526, https://doi.org/10.1053/jhep.2003.50346.
[16] R.K. Sterling, et al., Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection, Hepatology 43 (6) (2006) 1317–1325, https://doi.org/10.1002/hep.21178.
[17] P. Scheuer, Primary biliary cirrhosis, Proc. R. Soc. Med. 60 (12) (1967) 1257–1260.
[18] F. Tacke, et al., Up-regulated eotaxin plasma levels in chronic liver disease patients indicate hepatic inflammation, advanced fibrosis and adverse clinical course, J. Gastroenterol. Hepatol. 22 (8) (2007) 1256–1264, https://doi.org/10.1111/j.1440-1746.2006.04621.x.
[19] M.L. Burke, et al., Temporal expression of chemokines dictates the hepatic inflammatory infiltrate in a murine model of schistosomiasis, PLoS Negl. Trop. Dis. 4 (2) (2010) e598, , https://doi.org/10.1371/journal.pntd.0000598.
[20] J.L. Rodrigues Oliveira, et al., Plasma levels of innate immune mediators are associated with liver fibrosis in low parasite burden Schistosoma mansoni-infected individuals, Scand. J. Immunol. 87 (3) (2018), https://doi.org/10.1111/sji.12642.
[21] A.S. Moura, et al., Soluble inflammatory markers as predictors of liver histological changes in patients with chronic hepatitis C virus infection, Eur. J. Clin. Microbiol. Infect. Dis. 29 (9) (2010) 1153–1161, https://doi.org/10.1007/s10096-010-0981-4.
[22] T. Adar, et al., From airway inflammation to inflammatory bowel disease: eotaxin-1, a key regulator of intestinal inflammation, Clin. Immunol. 153 (1) (2014) 199–208, https://doi.org/10.1016/j.clim.2014.04.012.