Cytokine 117 (2019) 72–78

Contents lists available at ScienceDirect

Cytokine

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

Circulating levels of CXCL11 and CXCL12 are biomarkers of cirrhosis in patients with chronic hepatitis C infection

Arnaud Chalin[a,d], Benjamin Lefevre[a,b], Christelle Devisme[a], Nathalie Barget[c], Laurence Amiot[a,b], Michel Samson[a,*]

[a] Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail), UMR_S 1085, F-35000 Rennes, France
[b] Univ Rennes, CHU Rennes, F-35033 Rennes, France
[c] Centre de Ressources Biologiques, Hôpitaux Universitaires Paris Seine-Saint-Denis, APHP, Bondy, France
[d] NG Biotech, 35480 Guipry-Messac, France

ARTICLE INFO

Keywords:
Chronical HCV infection
CXCL10
CXCL11
CXCL12
Fibrosis

ABSTRACT

Background & aims: The chemokines CXCL10 (interferon ϒ-inducible protein 10 [IP-10]), CXCL11 (Human interferon inducible T cell alpha chemokine [I-TAC]), and CXCL12 (stromal cell derived factor 1 [SDF-1]) contribute to cell recruitment, migration, activation, and homing in liver diseases and their serum levels have been shown to be associated with the degree of liver inflammation or fibrosis in various etiologies. However, the data may be contradictory or insufficient, particularly for CXCL12, in the field of chronic HCV infection. Here, we aimed to provide evidence for these chemokines as biomarkers for chronic HCV infection.

Methods: We analyzed the serum concentration of the three chemokines in healthy donors (n = 39) and patients (n = 87) with chronic HCV infection. Chemokine serum levels were compared to the stage of liver inflammation and fibrosis obtained from liver biopsies.

Results: Serum CXCL10 and CXCL11 levels were higher at advanced stages of liver inflammation than at earlier stages, but the results were only of medium significance. Both serum CXCL11 and CXCL12 levels were significantly higher in cirrhotic patients than those with low or medium stages of fibrosis. The AUROCs were 0.8167 and 0.8574, respectively, for the diagnosis of cirrhotic patients.

Conclusion: These data provide evidence for the value of CXCL10, CXCL11, and CXCL12 as biomarkers of liver inflammation and fibrosis during chronic HCV infection. Serum CXCL10 and CXCL11 levels were associated with liver inflammation, but the level of significance was insufficient. However, serum CXCL11 and CXCL12 levels were elevated in cirrhotic patients, showing equivalent diagnostic accuracy as the existing established single serum fibrosis markers or algorithms.

1. Introduction

Hepatitis C virus (HCV) is one of the major cause of chronical hepatitis and is responsible for up to 500,000 deaths each year with more than 185 million estimated cases worldwide [1,2]. Chronical hepatitis C infection is a leading cause of cirrhosis, hepatic failure, and/or hepatocellular carcinoma [3]. Although liver fibrosis is a key factor in disease progression, the exact mechanisms leading to liver parenchymal injury and fibrosis deposit in chronic HCV infection are not completely described [4,5]. Nevertheless, the immune response to is known to be an important contributor of hepatic fibrogenesis progression [6].

Cytokines and chemokines orchestrate inflammation in chronic HCV infection [7]. Among them, CXCL10 (IP-10) and CXCL11 (I-TAC) have been shown to be involved in chemotactic events through their common receptor CXCR3, leading to T-lymphocyte trafficking into the liver [8]. CXCL12 (SDF-1) is a major liver homeostatic chemokine and highly potent lymphocyte chemoattractant [9,10]. Apart from its chemotactic effects, CXCL12 is also involved in liver regeneration by

Abbreviations: ALT, alanine aminotransferase; APRI, AST to Platelet Ratio Index; AST, aspartate aminotransferase; ELISA, enzyme-linked immunosorbent assay; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IP-10 (CXCL10), interferon ϒ-inducible protein 10; I-TAC (CXCL11), human interferon inducible T cell alpha chemokine; LSEC, liver sinusoidal endothelial cell; SDF-1 (CXCL12), stromal cell derived factor 1; ROC, receiver-operating characteristic

* Corresponding author at: Inserm-U.1085, Irset (Institut de recherche en santé, environnement et travail), Université de Rennes, 2, Avenue du Professeur Léon Bernard, 35043 RENNES Cedex, France.
E-mail address: michel.samson@inserm.fr (M. Samson).

https://doi.org/10.1016/j.cyto.2019.02.006
Received 6 November 2018; Received in revised form 21 January 2019; Accepted 1 February 2019
Available online 28 February 2019
1043-4666/

Table 1
HCV patients/healthy donors main characteristics and ALT/AST activity.

	Healthy donors	HCV patients
Case (n)	39	87
Sex (male/female) (n)	23/16	56/31
Age (year)	47 (32–65)	51 (29–83)
ALT (IU/L)	22.4 (12–42)	88.9 (15,0–471,0)
AST (IU/L)	25.3 (16.0–40.0)	70.6 (19.0–503.0)

recruiting bone marrow cells through its receptor, CXCR4, to the site of injury [11]. The CXCL12 – CXCR4 interaction also promotes hepatic stellate cell activation, leading to cell proliferation and fibrogenesis, thus participating in the deposit of extracellular matrix during chronic HCV infection [12]. CXCL11 and CXCL12 share a common more recently discovered receptor, CXCR7 [13]. In the liver, CXCR7 is found on liver sinusoidal endothelial cells (LSECs), as well as circulating LSEC progenitors, underlining the importance of this receptor for vascular homeostasis and angiogenesis [14]. CXCR7 signaling pathway activation leads to increased cell proliferation and adhesion properties [13]. However, a mouse model of chronic liver injury showed the loss of CXCR7 and concomitant CXCR4 upregulation on LSECs, leading to the progression of fibrosis in the liver [14].

Circulating levels of those 3 chemokines were found in chronic but also acute liver injuries [15]. In patients with chronic HCV infection, serum CXCL10 and CXCL11 levels may be elevated [16–22]. However, the available data concerning serum chemokine levels and their correlation with the extent of fibrosis and/or liver inflammation are contradictory. In addition, there is little data regarding CXCL12 serum levels in chronic HCV infection, but CXCL12 levels were shown to be elevated in chronic HCV infection and associated with the severity of fibrosis in a limited cohort of only 20 patients [23].

Here, we aimed to provide new data on circulating CXCL10, CXCL11, and CXCL12 chemokines in patients with chronic HCV infection and to assess their potential as biomarkers for liver fibrosis and inflammation staging.

2. Materials and methods

2.1. Patients and healthy donors

Samples were collected and stored by the liver disease biobank, Groupe Hospitalier Paris Seine-Saint-Denis BB-0033-00027. The inclusion criteria was any patients with chronic HCV infection. Patients were excluded if they were infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV). Patients with acute-on-chronic liver injury were also excluded. A total of 87 patients were recruited. Thirty-nine healthy subject samples from the French Blood Institute were collected. Those were negative for HBV, HCV, and HIV, and had normal alanine aminotransferase (ALT) activity (< 43 UI/L). Healthy subjects' and patients' main characteristics (age, sex, and transaminase activity) are given in Table 1.

2.2. Liver histology

All patients in the study population of 87 patients with chronic HCV infection had a liver biopsy at the time of study entry. The fibrosis and inflammation staging of liver samples were performed according to the histological Metavir scoring system by a pathologist who was blinded to the experimental data [24].

2.3. Chemokine detection

Serum was collected within 24 h before or after liver biopsy in separator tubes, centrifuged at 2000*g* at 4 °C for 10 min, and stored at −80 °C until further analysis. Serum concentrations of CXCL10 were measured using enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Wiesbaden, Germany), according to the manufacturer's protocol and those of CXCL11 and CXCL12 ELISA kits from Peprotech (Rocky Hill, USA). All chemokine measurements were carried out in duplicate. The lower detection limits were 31.2 pg/ml for CXCL10, 32 pg/ml for CXCL11, and 63 pg/ml for CXCL12.

2.4. Statistical analysis

Data are shown graphically as box-and-whisker plots. The box-and-whisker plots display a statistical summary of the median, quartiles, inter-quartile range, and extreme values. The degree of association between two variables was assessed by Spearman's parametric test rank correlation. Comparisons of parameters between two groups were analyzed by the Mann-Whitney u-test with $\alpha = 0.05$. Receiver-operating characteristic (ROC) curve analysis was used as a global and standardized measure of the accuracy of predicting advanced hepatic fibrosis or cirrhosis. The ROC curve represents the plotting of sensitivity against specificity. All statistical analyses were performed using GRAPHPAD PRISM (GraphPad software Inc., La Jolla, CA, USA).

Table 2
Serum levels of CXCL10, CXCL11 and CXCL12 chemokines among healthy donors and HCV patients. Chemokines levels are shown according to fibrosis and inflammation stages obtained from liver biopsy. Mean and range (in parenthesis) for CXCL10, CXCL11 and CXCL12 are given. Concentrations are given in pg/ml.

			Fibrosis stage (Metavir scale)				Necroinflammatory activity stage (Metavir scale)			
	Healthy donors	HCV patients	F1	F2	F3	F4	A0	A1	A2	A3
n	39	87	27	23	22	15	1	45	38	3
CXCL10 (pg/ml)	62.5 (0.0–630.9)	244.1 (26.9–617.3)	201.8 (56.9–404.3)	233.1 (26.9–575.9)	250.0 (33.0–510.6)	328.3 (120.4–617.3)	301.6 (301.6–301.6)	199.3 (26.9–617.3)	279.4 (33.0–612.6)	447.7 (328.1–594.2)
CXCL11 (pg/ml)	107.5 (0.0–411.6)	142.4 (0.0–634.8)	104.4 (0.0–448.4)	151.5 (0.0–634.8)	102.1 (0.0–406.6)	256.0 (96.7–510.9)	135.5 (135.5–135.5)	109.6 (0.0–448.4)	178.7 (0.0–634.8)	177.6 (110.3–216.6)
CXCL12 (pg/ml)	438.2 (0.0–1356.0)	542.5 (0.0–2882.5)	421.3 (0.0–1281.0)	437.8 (0.0–2122.0)	301.5 (0.0–2882.5)	1275.0 (235.0–2597.8)	595.0 (595.0–595.0)	408.4 (0.0–1964.0)	694.8 (0.0–2882.5)	607.2 (101.3–1485.3)

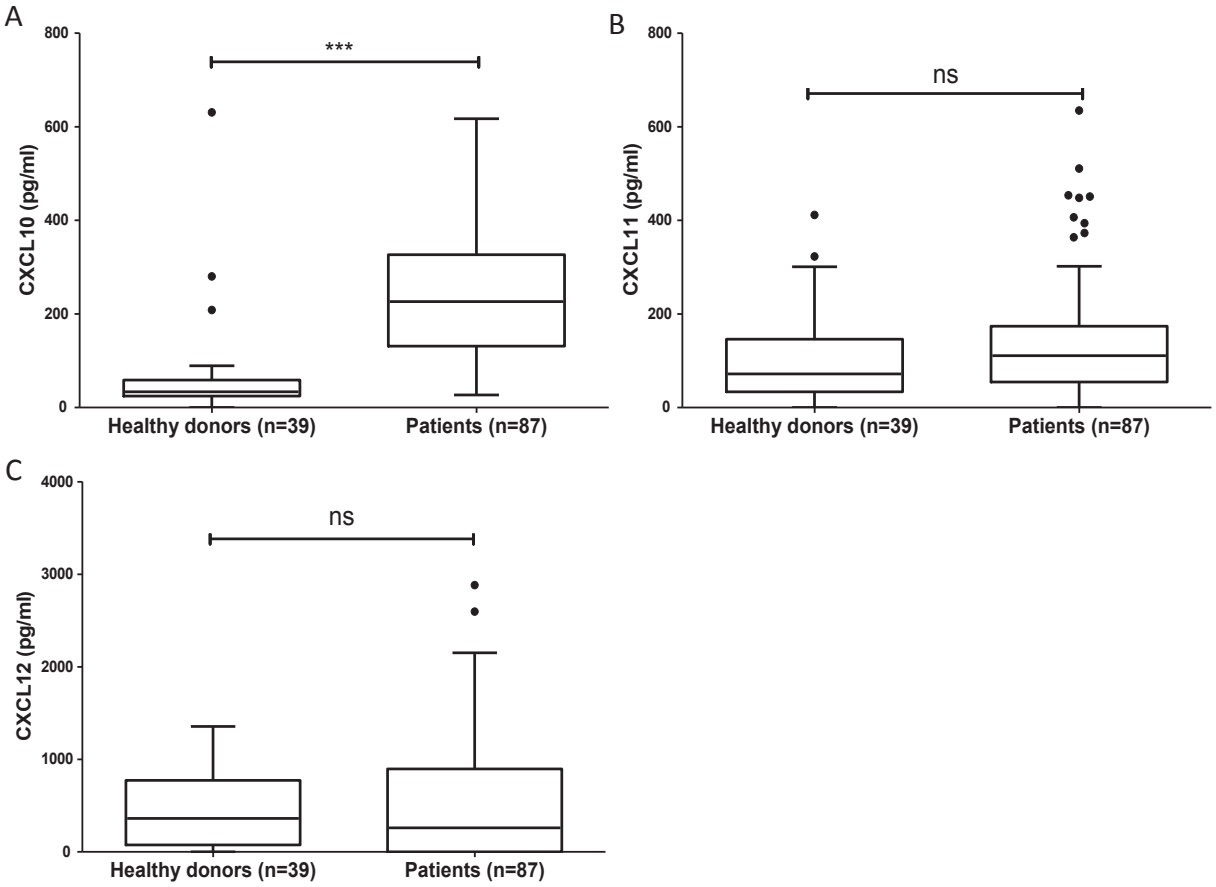

Fig. 1. Box-and-whisker plots illustrating serum chemokine levels in patients (n = 87) and healthy donors (n = 39). The box extends from the 25th to 75th percentile. The line in the middle denote the median value, and the lines extending from either end of each box denote the extent of the data beyond the 25th and 75th percentiles and outliers, if any. (A–C) ELISA for CXCL10, CXCL11 and CXCL12. (*** $p < 0.0001$; statistical significance was determined by Mann-Whitney u-test).

3. Results

3.1. Demographic characteristics

We determined the levels of the chemokines CXCL10, CXCL11, and CXCL12 in sera samples obtained from 87 patients with chronic HCV infection to test whether the peripheral levels of these three chemokines are associated with intrahepatic inflammation and fibrosis. The mean age of the 87 patients was 51 years (range, 29–83); 64% were male; and then ALT and aspartate aminotransferase (AST) values were 88.9 (range, 15.0–471.0) and 70.6 (range, 19.0–503.0), respectively (Table 1). The mean age and gender ratio between the healthy donors and HCV-infected patients were not statistically different. Low (grade 1), mild (grade 2), or severe (grade 3) fibrosis or cirrhosis (grade 4) were detected in 31%, 27%, 25%, and 17% of patients respectively. Most of the patients had low (grade 1) or mild (grade 2) intrahepatic inflammation, accounting for 52% and 44% of patients, respectively (Table 2).

3.2. CXCL10 is the only circulating chemokine with higher levels in all HCV patients than healthy donors

We first compared the serum levels of each chemokine of all patients to those of healthy donors. CXCL10 was the only chemokine which showed significantly higher serum levels ($p < 0.0001$) in patient than donor samples (Fig. 1). Serum CXCL11 and CXCL12 levels were not significantly elevated in patients.

3.3. CXCL10 and CXCL11 levels, but not those of CXCL12 are associated with the histological severity of liver inflammation

The results of correlating the serum and biopsy samples from the 87 patients are shown in Table 2. Overall, only serum CXCL10 and CXCL11 levels were significantly associated with the histological severity of liver inflammation in our cohort (A0-A1 vs A2-A3: $P = 0.0030$ for CXCL10 and $P = 0.0034$ for CXCL11) (Fig. 2). Notably, serum CXCL12 concentrations were not positively associated with the histological severity of liver inflammation in our cohort. Serum CXCL10 and CXCL11 levels, both interferon-inducible, also positively correlated with each other ($P < 0.0001$) (Fig. 3). Surprisingly, the serum levels of none of these intra-hepatic inflammation-associated chemokines correlated with serum ALT levels (data not shown).

3.4. CXCL11 and CXCL12 are biomarkers of cirrhosis

We next tested whether serum concentrations of CXCL10, CXCL11, and CXCL12 were higher in patients with established cirrhosis than those with liver fibrosis, but not yet established cirrhosis. The median concentrations of CXCL11 and CXCL12 were higher in patients with cirrhosis (grade 4) than those with lower stages of intrahepatic fibrosis

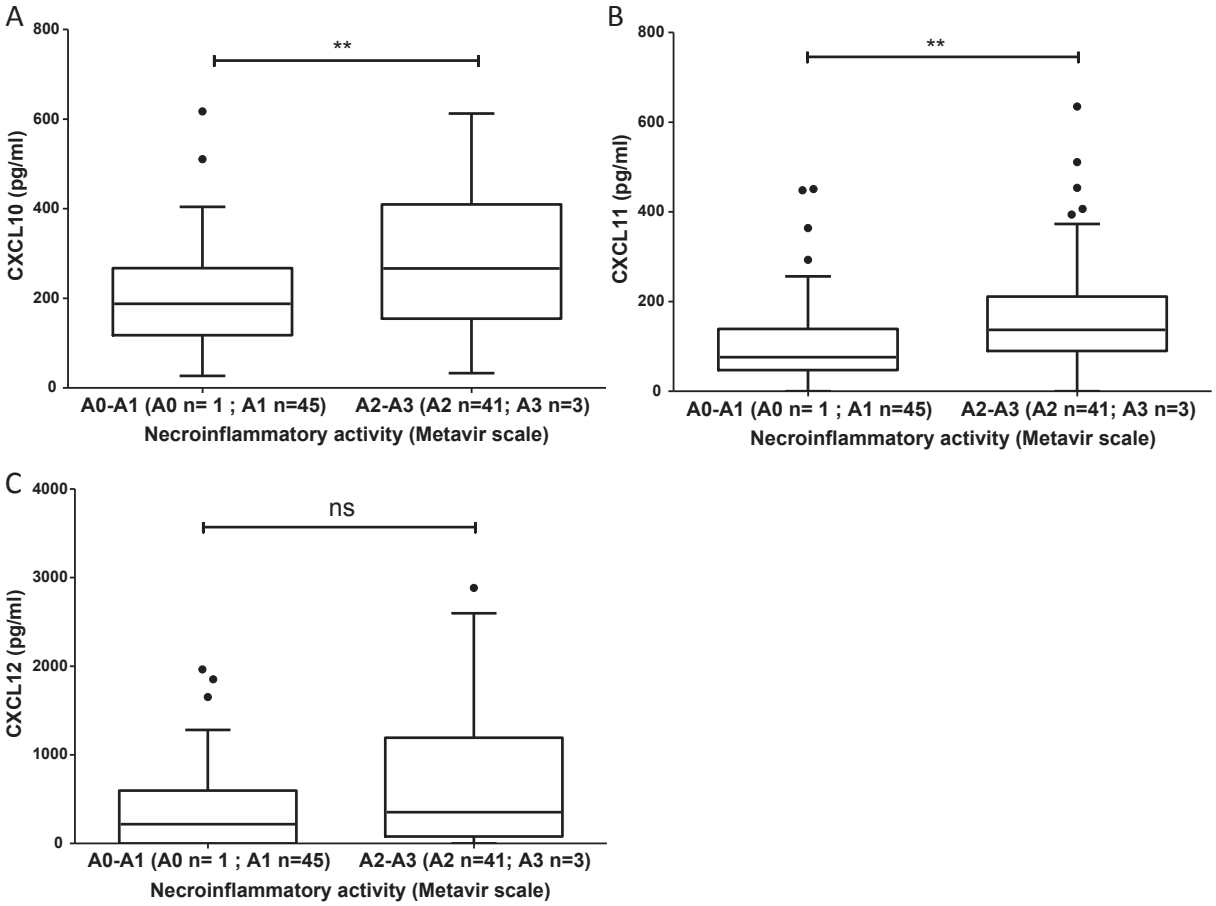

Fig. 2. Box-and-whisker plots illustrating serum chemokine levels in HCV patients according to necroinflammatory stages obtained from liver biopsy. (A-C) ELISA for CXCL10, CXCL11 and CXCL12. (ns non-significant; ** $p < 0.001$; *** $p < 0.0001$; statistical significance was determined by Mann-Whitney u-test).

(Fig. 4): F1 vs F4, P = 0.0002; F2 vs F4, P = 0.0094, and F3 vs F4, P = 0.0005 for CXCL11 and F1 vs F4, P = 0.0003; F2 vs F4, P = 0.0005, and F3 vs F4, P < 0.0001 for CXCL12. In contrast, CXCL10 serum levels were either slightly (F1 vs F4, P = 0.0224) or non-significantly higher in cirrhotic than non-cirrhotic patients. We next evaluated whether the serum concentrations of CXCL11 and CXCL12 also correlated with each other, given that the levels of both were associated with advanced fibrosis. The serum concentrations of CXCL11 and CXCL12 indeed strongly correlated with each other (Spearman r rank = 0.7351) with a high degree of significance (P < 0.0001) (Fig. 4), suggesting that they may follow a shared and unknown induction pathway. Finally, we assessed the value of CXCL11 and CXCL12 as biomarkers in diagnosing cirrhotic patients. We calculated the area under the ROC curve for both chemokines. The AUC for CXCL11 was 0.8167 and that for CXCL12, 0.8574 (Fig. 5), establishing high diagnostic accuracy for both chemokines to identify cirrhosis in patients with chronic HCV infection.

4. Discussion

Overall, our results confirm previous findings of an association of serum CXCL10, CXCL11, and CXCL12 levels with the histological progression of liver fibrosis and inflammation in patients with chronic HCV infection [8,17,23,25]. However, we are the first to measure the three chemokines together in a large cohort of chronically HCV infected patients, extending the degree of association between the serum levels of these chemokines and the histological evaluation of liver biopsies, as well as demonstrating their diagnostic value in distinguishing cirrhotic from non-cirrhotic patients.

In our cohort, serum CXCL10 levels were much higher in all patients than in healthy donors. We found, at best, a weak association between serum CXCL10 levels and the stages of liver fibrosis obtained from liver biopsies, contrary to published data [17]. In contrast, CXCL10 serum levels were found to be higher in patients with mild to advanced liver inflammation, obtained from liver biopsies, than those with low inflammation, in accordance with previous findings [8,17]. These results suggest that the action of CXCL10 is mostly anti-viral, consistent with its described role in the literature [8]. However, the degree of association between serum CXCL10 levels and liver inflammation obtained from liver biopsies was too weak to consider CXCL10 as a good non-invasive biomarker of liver inflammation in our cohort. This may be explained by the uneven distribution of patients among liver inflammation staging groups. Indeed, 95% of patients were either stage A1 or A2.

Given the strong association between CXCL11 and CXCL12 serum levels with intrahepatic fibrosis, we evaluated the diagnostic accuracy of these chemokines to identify cirrhosis by ROC curve analysis. The AUROC for CXCL11 was 0.8167 and 0.8574 for CXCL12, which are close to the best-established single serum fibrosis marker, hyaluronic acid, or the various current algorithms, including Fibrometer®, FibroTest®, or the AST to Platelet Ratio Index (APRI) score [26–28]. This diagnostic performance is also comparable to that obtained from

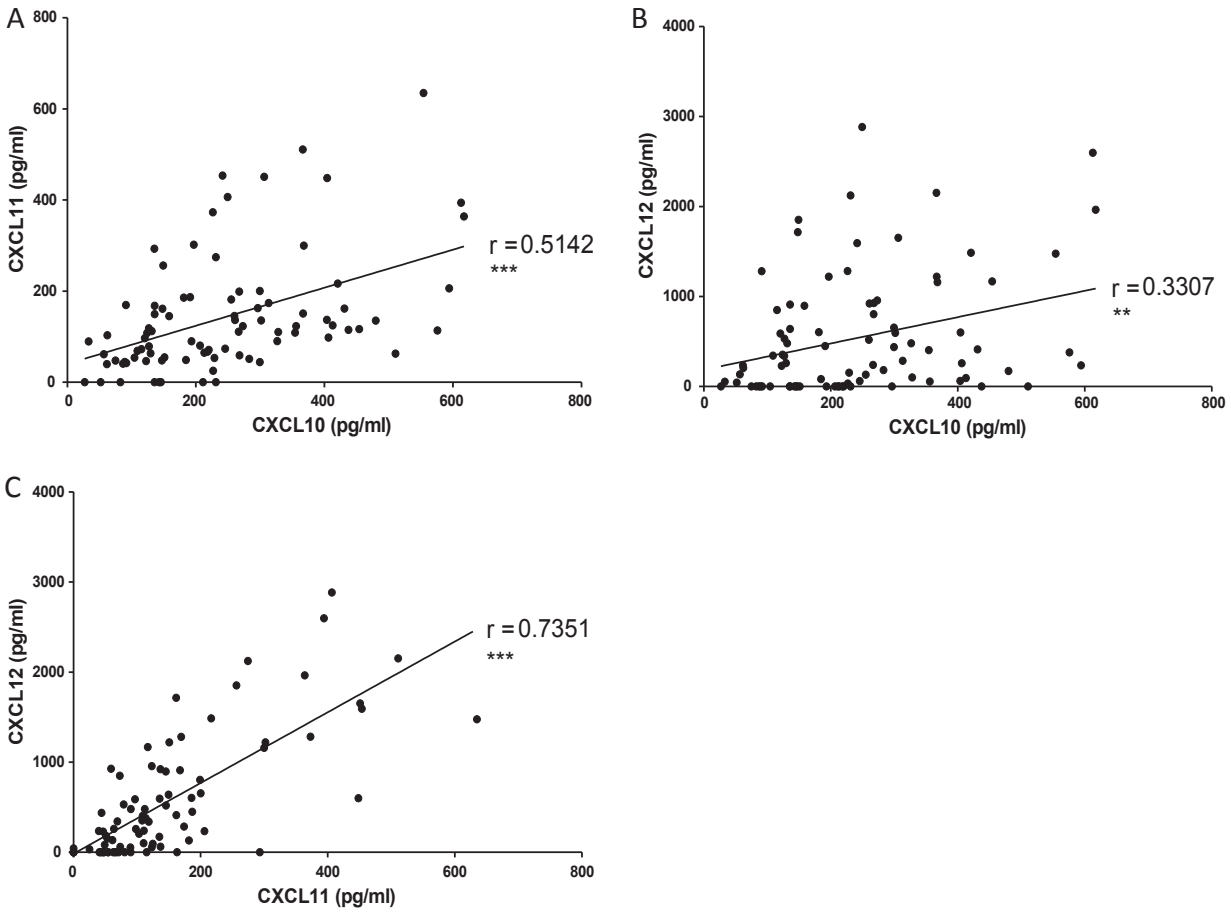

Fig. 3. (A) Correlation between CXCL10 and CXCL11, (B) CXCL12 and CXCL10 and (C) CXCL12 and CXCL11 in the study cohort as determined by Spearman rank analysis (** $p < 0.001$; *** $p < 0.0001$).

transient elastography [27,28]. Moreover, the serum levels of CXCL11 and CXCL12 in our cohort rose markedly between F3 and F4, whereas other serum biomarkers or liver stiffness obtained from transient elastography rise proportionally with the degree of liver fibrosis. This allows better discrimination between low and mild intrahepatic fibrosis from cirrhosis, improving the diagnostic accuracy for cirrhotic patients. Thus, in future studies, CXCL11 and CXCL12 might be considered for combinatory panels of fibrosis markers, or associated with transient elastography, to reach a higher diagnostic accuracy than that of single markers.

Serum CXCL11 level have been shown to correlate with liver fibrosis in a cohort of patients with various etiologies of chronic liver diseases [16]. Furthermore, both serum CXCL10 and CXCL11 levels were shown to be variously expressed according to cirrhosis stages in the same study. Given the results presented here, the accuracy of CXCL12 in detecting cirrhosis should be studied in other chronic liver diseases, such as alcoholism, non-alcoholic steatohepatitis, or hepatitis B virus. Additionally, the relationship between serum CXCL12 levels and the stage of cirrhosis could be assessed to evaluate the value of this chemokine as a biomarker for cirrhosis staging.

Both CXCL10 and CXCL11 were shown to be associated to mixed HCV and cryoglobulinemia [29–31]. Unfortunately, the studied population was not screened for cryoglobulinemia. Consequently, the statistical significance might be affected by this unknown factor. CXCL12 has however never been associated to mixed HCV and cryoglobulinemia so far. Interestingly, recent data suggest that interferon-gamma inducible chemokines polymorphism including CXCL10 and CXCL11 are related to the likelihood of having liver fibrosis in HCV infection [32]. Thus, chemokines polymorphism and cryoglobulinemia should be considered when exploring the diagnosis accuracy of CXCL11 for cirrhosis in chronic HCV infection in future studies.

Serum CXCL12 levels correlated with liver fibrosis but not inflammation in our cohort. These results support that CXCL12 mostly contributes to pro-fibrotic events through CXCR4 on LSECs [12,14] or regeneration processes through the recruitment of hematopoietic progenitors [33], more than lymphocyte trafficking into the liver. Surprisingly, serum CXCL11 and CXCL12 levels strongly correlated with each other in our cohort, suggesting a shared and unknown induction pathway.

In conclusion, we showed that serum concentrations of CXCL10 were higher in all patients than in healthy donors and correlated with liver inflammation. However, the significance was too low to consider the circulating level of CXCL10 as a good biomarker for liver inflammation staging in our cohort. In contrast, serum CXCL11 and CXCL12 levels were strongly associated with cirrhosis and were highly accurate biomarkers for the diagnosis of cirrhosis in patients with chronic HCV infection.

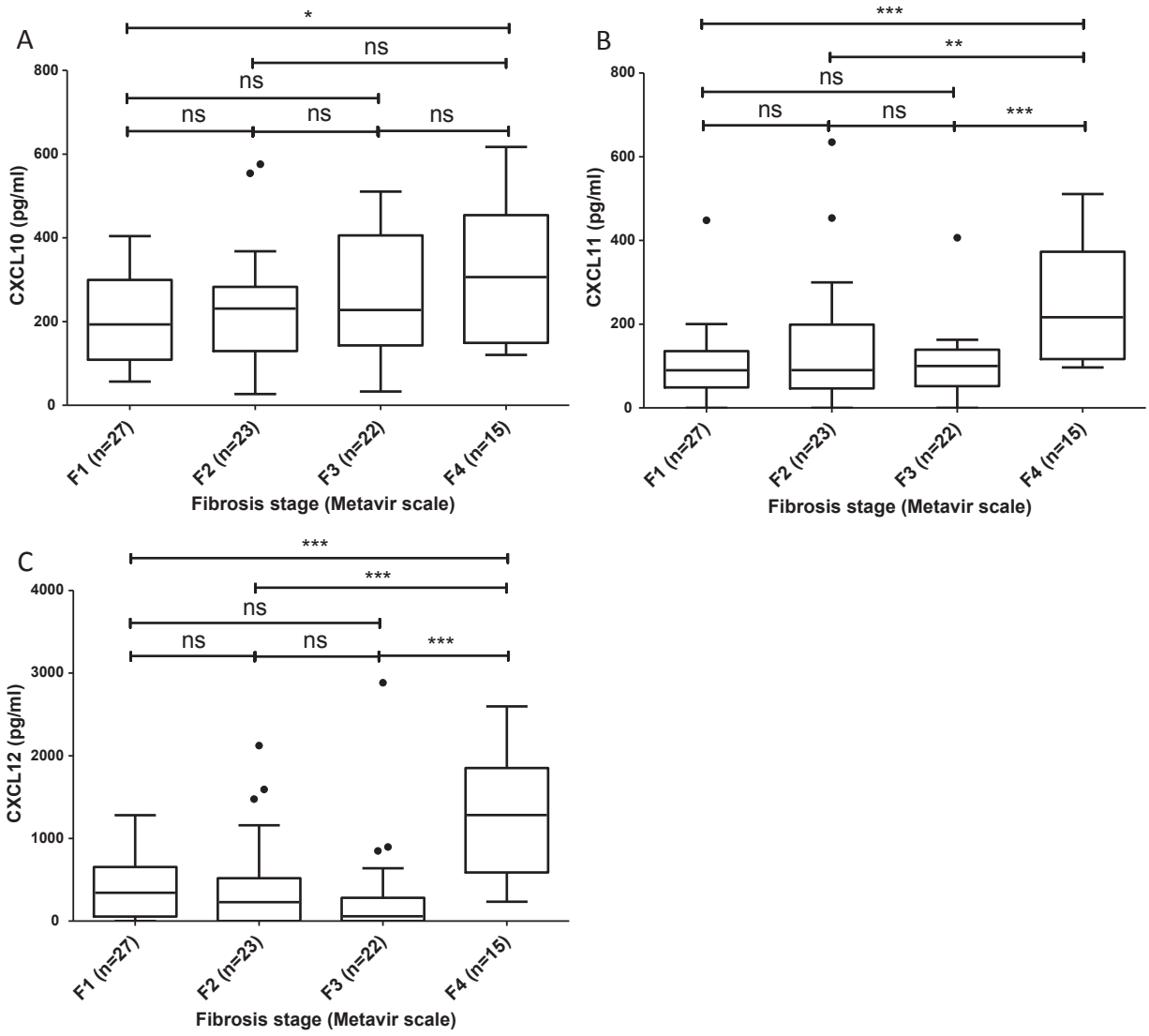

Fig. 4. Box-and-whisker plots illustrating serum chemokine levels in HCV patients according to fibrosis stages obtained from liver biopsy. (A–C) ELISA for CXCL10, CXCL11 and CXCL12. (ns non-significant, *** $p < 0.0001$; statistical significance was determined by Mann-Whitney u-test).

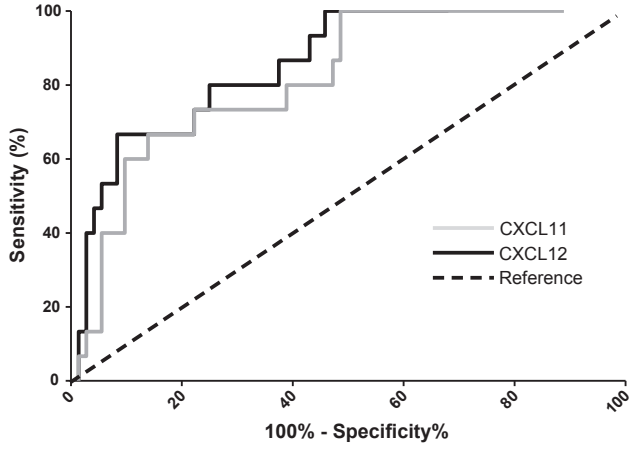

Fig. 5. Receiver-operating characteristics curve of CXCL11 and CXCL12 in diagnosing cirrhosis in all subjects as compared to the other fibrosis stages. (AUROC CXCL11: 0.8167 (95% confidence interval: 0.7112–0.9222; $p < 0.0001$); AUROC CXCL12: 0.8574 (95% confidence interval: 0.7641–0.9507; $p < 0.0001$).

Acknowledgement

We thank Inserm, The “Ministère de l’Education Nationale de la Recherche et de la Technologie“, the University of Rennes 1, the “Région Bretagne“ and ANRT for their financial support. We also thank Biosit for the access to the “Secteur de culture L3”.

Conflict of interest

The authors have no financial or commercial conflict of interest to declare.

Funding statement

This work was supported by INSERM, The “Ministère de l’Education Nationale de la Recherche et de la Technologie“, the University of Rennes 1 and the “Région Bretagne”. AC was supported by a PhD fellowship from ANRT-CIFRE fellowship with NG Biotech. CD was supported by a PhD fellowship from the “Région Bretagne” and Inserm.

References

[1] K. Mohd Hanafiah, J. Groeger, A.D. Flaxman, S.T. Wiersma, Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence, Hepatology 57 (4) (2013) 1333–1342.

[2] A.P. Thrift, H.B. El-Serag, F. Kanwal, Global epidemiology and burden of HCV infection and HCV-related disease, Nat. Rev. Gastroenterol. Hepatol. 14 (2) (2017) 122–132.

[3] L.B. Seeff, Natural history of chronic hepatitis C, Hepatology 36 (5 Suppl 1) (2002) S35–S46.

[4] T. Poynard, V. Ratziu, F. Charlotte, Z. Goodman, J. McHutchison, J. Albrecht, Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c, J. Hepatol. 34 (5) (2001) 730–739.

[5] M.G. Ghany, D.E. Kleiner, H. Alter, E. Doo, F. Khokar, K. Promrat, et al., Progression of fibrosis in chronic hepatitis C, Gastroenterology 124 (1) (2003) 97–104.

[6] A. Cerny, F.V. Chisari, Pathogenesis of chronic hepatitis C: immunological features of hepatic injury and viral persistence, Hepatology 30 (3) (1999) 595–601.

[7] M. Heydtmann, P. Shields, G. McCaughan, D. Adams, Cytokines and chemokines in the immune response to hepatitis C infection, Curr. Opin. Infect. Dis. 14 (3) (2001) 279–287.

[8] C.E. Harvey, J.J. Post, P. Palladinetti, A.J. Freeman, R.A. Ffrench, R.K. Kumar, et al., Expression of the chemokine IP-10 (CXCL10) by hepatocytes in chronic hepatitis C virus infection correlates with histological severity and lobular inflammation, J. Leukoc. Biol. 74 (3) (2003) 360–369.

[9] C.C. Bleul, R.C. Fuhlbrigge, J.M. Casasnovas, A. Aiuti, T.A. Springer, A highly efficacious lymphocyte chemoattractant, stromal cell-derived factor 1 (SDF-1), J. Exp. Med. 184 (3) (1996) 1101–1109.

[10] A. Liepelt, F. Tacke, Stromal cell-derived factor-1 (SDF-1) as a target in liver diseases, Am. J. Physiol. Gastrointest. Liver Physiol. 311 (2) (2016) G203–G209.

[11] K. Xiao Ling, L. Peng, Z. Jian Feng, C. Wei, Y. Wei Yan, S. Nan, et al., Stromal derived factor-1/CXCR4 axis involved in bone marrow mesenchymal stem cells recruitment to injured liver, Stem Cells Int. 2016 (2016) 8906945.

[12] F. Hong, A. Tuyama, T.F. Lee, J. Loke, R. Agarwal, X. Cheng, et al., Hepatic stellate cells express functional CXCR4: role in stromal cell-derived factor-1alpha-mediated stellate cell activation, Hepatology 49 (6) (2009) 2055–2067.

[13] J.M. Burns, B.C. Summers, Y. Wang, A. Melikian, R. Berahovich, Z. Miao, et al., A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development, J. Exp. Med. 203 (9) (2006) 2201–2213.

[14] B.S. Ding, Z. Cao, R. Lis, D.J. Nolan, P. Guo, M. Simons, et al., Divergent angiocrine signals from vascular niche balance liver regeneration and fibrosis, Nature 505 (7481) (2014) 97–102.

[15] A. Chalin, B. Lefevre, C. Devisme, C. Pronier, V. Carriere, V. Thibault, et al., Serum CXCL10, CXCL11, CXCL12, and CXCL14 chemokine patterns in patients with acute liver injury, Cytokine (2018).

[16] F. Tacke, H.W. Zimmermann, M.L. Berres, C. Trautwein, H.E. Wasmuth, Serum chemokine receptor CXCR3 ligands are associated with progression, organ dysfunction and complications of chronic liver diseases, Liver Int. 31 (6) (2011) 840–849.

[17] M. Zeremski, R. Dimova, Q. Brown, I.M. Jacobson, M. Markatou, A.H. Talal, Peripheral CXCR3-associated chemokines as biomarkers of fibrosis in chronic hepatitis C virus infection, J. Infect Dis. 200 (11) (2009) 1774–1780.

[18] K.J. Helbig, A. Ruszkiewicz, R.E. Lanford, M.D. Berzsenyi, H.A. Harley, S.R. McColl, et al., Differential expression of the CXCR3 ligands in chronic hepatitis C virus (HCV) infection and their modulation by HCV in vitro, J. Virol. 83 (2) (2009) 836–846.

[19] K. Patel, K.S. Remlinger, T.G. Walker, P. Leitner, J.E. Lucas, S.D. Gardner, et al., Multiplex protein analysis to determine fibrosis stage and progression in patients with chronic hepatitis C, Clin. Gastroenterol. Hepatol. 12 (12) (2014) 2113–2120 e1–3.

[20] D. Crisan, M.D. Grigorescu, C. Radu, A. Suciu, M. Grigorescu, Interferon-gamma-inducible protein-10 in chronic hepatitis C: correlations with insulin resistance, histological features & sustained virological response, Indian J. Med. Res. 145 (4) (2017) 543–550.

[21] C. Mascia, M. Lichtner, P. Zuccala, S. Vita, T. Tieghi, R. Marocco, et al., Active HCV infection is associated with increased circulating levels of interferon-gamma (IFN-gamma)-inducible protein-10 (IP-10), soluble CD163 and inflammatory monocytes regardless of liver fibrosis and HIV coinfection, Clin. Res. Hepatol. Gastroenterol. 41 (6) (2017) 644–655.

[22] N.A. Arsent'eva, A.V. Semenov, N.E. Lyubimova, Y.V. Ostankov, D.S. Elezo, I.V. Kudryavtsev, et al., Chemokine receptors CXCR3 and CCR6 and their ligands in the liver and blood of patients with chronic hepatitis C, Bull. Exp. Biol. Med. 160 (2) (2015) 252–255.

[23] O. Wald, O. Pappo, R. Safadi, M. Dagan-Berger, K. Beider, H. Wald, et al., Involvement of the CXCL12/CXCR4 pathway in the advanced liver disease that is associated with hepatitis C virus or hepatitis B virus, Eur. J. Immunol. 34 (4) (2004) 1164–1174.

[24] P. Bedossa, Presentation of a grid for computer analysis for compilation of histopathologic lesions in chronic viral hepatitis C. Cooperative study of the METAVIR group, Ann. Pathol. 13 (4) (1993) 260–265.

[25] K.J. Helbig, A. Ruszkiewicz, L. Semendric, H.A. Harley, S.R. McColl, M.R. Beard, Expression of the CXCR3 ligand I-TAC by hepatocytes in chronic hepatitis C and its correlation with hepatic inflammation, Hepatology 39 (5) (2004) 1220–1229.

[26] R. Chou, N. Wasson, Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review, Ann. Int. Med. 158 (11) (2013) 807–820.

[27] L. Castera, J. Vergniol, J. Foucher, B. Le Bail, E. Chanteloup, M. Haaser, et al., Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C, Gastroenterology 128 (2) (2005) 343–350.

[28] A.A. Shaheen, A.F. Wan, R.P. Myers, FibroTest and FibroScan for the prediction of hepatitis C-related fibrosis: a systematic review of diagnostic test accuracy, Am. J. Gastroenterol. 102 (11) (2007) 2589–2600.

[29] A. Antonelli, P. Fallahi, S.M. Ferrari, M. Sebastiani, A. Manfredi, V. Mazzi, et al., Circulating CXCL11 and CXCL10 are increased in hepatitis C-associated cryoglobulinemia in the presence of autoimmune thyroiditis, Mod. Rheumatol. 22 (5) (2012) 659–667.

[30] A. Antonelli, P. Fallahi, S.M. Ferrari, S. Frascerra, C. Mancusi, M. Colaci, et al., High circulating chemokines (C-X-C motif) ligand 9, and (C-X-C motif) ligand 11, in hepatitis C-associated cryoglobulinemia, Int. J. Immunopathol. Pharmacol. 26 (1) (2013) 49–57.

[31] A. Antonelli, P. Fallahi, S.M. Ferrari, A. Corrado, M. Sebastiani, D. Giuggioli, et al., Parallel increase of circulating CXCL11 and CXCL10 in mixed cryoglobulinemia, while the proinflammatory cytokine IL-6 is associated with high serum Th2 chemokine CCL2, Clin. Rheumatol. 32 (8) (2013) 1147–1154.

[32] M.A. Jimenez-Sousa, A.Z. Gomez-Moreno, D. Pineda-Tenor, L.M. Medrano, J.J. Sanchez-Ruano, A. Fernandez-Rodriguez, et al., CXCL9-11 polymorphisms are associated with liver fibrosis in patients with chronic hepatitis C: a cross-sectional study, Clin. Transl. Med. 6 (1) (2017) 26.

[33] U.M. Gehling, M. Willems, K. Schlagner, R.A. Benndorf, M. Dandri, J. Petersen, et al., Mobilization of hematopoietic progenitor cells in patients with liver cirrhosis, World J. Gastroenterol. 16 (2) (2010) 217–224.