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ORIGINAL ARTICLE

Serum keratin 19 (CYFRA21-1) is a prognostic biomarker in severe alcoholic hepatitis

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Abstract

Background and Aims: Up to 30% of patients with severe alcoholic hepatitis (sAH) die within 3 months of presentation. The degree of ductular reaction, characterized by accumulation of biliary and liver progenitor cells, confers a poor prognosis. Keratin fragments are established serological surrogates of liver injury and keratin 19 (K19) is a histological marker of the ductular reaction. We assessed the relationship between serum K19 levels (viz. CYFRA21-1), histology and outcome in patients with sAH.

Methods: Serum CYFRA21-1 was quantified in pre-treatment serum samples from 824 patients enrolled in the STOPAH trial. The cohort was randomly divided into two groups to test mortality associations; histological analyses were performed using the 87 cases with suitable samples.

Results: CYFRA21-1 levels were elevated in sAH and strongly predicted alcoholic steatohepatitis (ASH) on biopsy (area under the receiver operated characteristic [AUROC] 0.785 [95% Confidence Interval 0.602–0.967]) and 90-day survival (AUROC 0.684/0.693). The predictive ability of CYFRA21-1 was comparable with the model of end-stage liver disease (MELD) score and was independently associated with survival in multivariable analysis. CYFRA21-1 moderately correlated with hepatocellular injury markers M30/M65 but displayed a more robust predictive ability. A combination of MELD and CYFRA21-1 conferred a modest improvement in the AUROC value (0.731/0.743).

Conclusions: In sAH serum, CYFRA21-1 levels associate with the presence of ASH on biopsy and independently predict 90-day survival. As a single marker performance is comparable to established scoring systems. Therefore, CYFRA21-1, which is available in many clinical laboratories, may become a useful component of prognostic models.

KEYWORDS
AH, cytokeratin, K19, liver disease, mortality

Abbreviations: ABIC, Age-Bilirubin-INR-Creatinine; AH, Alcoholic hepatitis; AHHS, alcoholic hepatitis histological scoring; ASH, alcoholic steatohepatitis; DF, discriminant function; GAHS, the Glasgow alcoholic hepatitis score; K19, keratin 19; MELD, model of end-stage liver disease; sAH, severe alcoholic hepatitis.

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1 | INTRODUCTION

Alcoholic hepatitis (AH) is a clinical syndrome characterized by the rapid onset of jaundice and liver failure in patients with ongoing chronic and heavy alcohol misuse.[1,2] Up to 30% of patients with severe alcoholic hepatitis, defined as a Maddrey's discriminant function (DF) >32[3] die within 3 months of presentation making prompt diagnosis and appropriate treatment essential.[4] Several clinical scoring systems have been devised to predict outcomes in severe AH including DF,[3] the Glasgow alcoholic hepatitis score (GAHS)[5] and the Age-Bilirubin-INR-Creatinine (ABIC) score.[6] The model for end-stage liver disease (MELD) score, which is a predictor of outcome in several liver diseases, is currently the best predictor of short-term outcome in severe AH; despite its accuracy is modest.[7,8]

Whilst a diagnosis of alcoholic hepatitis may be made based upon clinical features, additional demonstration of alcoholic steatohepatitis (ASH) on liver biopsy is considered definitive.[9] The key histopathological features of ASH include steatosis, fibrosis, hepatocyte ballooning, an inflammatory infiltrate, and the formation of Mallory-Denk bodies. Additionally, a phenomenon termed the 'ductular reaction' may be observed, particularly in those with the clinical syndrome of severe AH. This comprises a variety of cell types with the characteristic ones being biliary cells and immature liver progenitor cells or 'oval cells'.[10] The magnitude of the ductular reaction has been associated with short-term outcomes from severe AH in a number of studies[11–13] with a more profound reaction associated with a worse prognosis. Keratins 7 and 19 (*KRT7*/*KRT19* genes; K7/K19 proteins) are expressed as a pair in cholangiocytes and oval cells, but not mature hepatocytes and consequently have been used as histological markers of the ductular reaction.[14,15] The C-terminal end of K19 is known as CYFRA21-1 and can be detected by a commercially available ELISA.[16] It is employed clinically as a tumour marker and is routinely available in many clinical laboratories.[16] Evaluation of serum CYFRA21-1 as a biomarker in cirrhosis demonstrated that serum levels correlate with hepatic expression of *KRT19* and predict adverse outcomes including death and the development of hepatocellular carcinoma.[17] In contrast to that, serum levels of total (M65) or apoptosis-specific keratin 18 (*KRT18*/K18) fragments (M30) serve as hepatocellular injury markers[16,18] and in AH, correlate with histological disease activity and response to prednisolone.[19]

In view of the association between the ductular reaction and outcome in severe AH as well as the established importance of keratin fragments as liver injury markers, we analysed whether serum CYFRA21-1, as a putative circulating biomarker of the ductular reaction, could act as a predictor of outcome in this setting.

Lay Summary

Severe alcoholic hepatitis display a strong regenerative response known as a ductular reaction. Since keratin 19 represents a ductular reaction marker, we measured keratin 19 serum levels with the CYFRA21-1 assay. Elevated CYFRA21-1 levels were concordant with the characteristic microscopic appearance of severe alcoholic hepatitis and independently predicted poor 90-day survival.

2 | METHODS

2.1 | Study populations

Patients with clinically diagnosed severe alcoholic hepatitis were recruited via the STOPAH trial as per the trial protocol.[20,21] Patients were randomized to treatment with prednisolone or pentoxifylline for 28 days using a double-blind, double-dummy factorial 2 × 2 design. Outcome data were collected for mortality at 28 and 90 days. Patients were consented for follow-up via the NHS Information Centre Data Linkage service ensuring ongoing follow-up and complete capture of mortality data. Ethical approval was granted for this study by the Wales Research Ethics Committee (REC 09/MRE09/59). The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment) and Good Clinical Practice (European guidelines). All participants, or their legally appointed representatives, provided written informed consent.

2.2 | Measurement of laboratory parameters

Clinical data were recorded at the baseline visit. Pre-treatment serum samples were collected from 866 patients, sufficient serum was available for quantification of serum biomarkers in 824 (95%). The cohort was randomly subdivided into two groups designated discovery and validation cohorts. This division was achieved based upon allocation to prednisolone treatment as part of the original STOPAH trial as a) this leveraged the original randomization strategy of the trial and b) prednisolone had no effect on mortality at 90 days (Table S1). Serum CYFRA21-1 (EIA-5070; working range: 0.15–50 ng/ml; DRG Instruments) and osteopontin (EIA-5920; DRG Instruments) concentrations were determined by ELISA. Measurements were performed according to the manufacturer's instruction, samples with high values outside the standard curve were reassessed after dilution. AST was determined in serum from patients where clinical data was unavailable.[19] Circulating bacterial DNA (bDNA), KRT18-M30 and KRT18-M65 levels were quantified as described previously.[3,19,22]

2.3 | Histological analyses

Two experienced histopathologists (RG and AQ), blinded to patient treatment and outcomes, independently assessed the histological features of each biopsy using the alcoholic hepatitis histological scoring system (AHHS),[10] fibrosis was graded using the Laennec system[23] (Table S2). The presence or absence of Mallory-Denk bodies and megamitochondria was also recorded. The degree of the ductular reaction was semi-quantitatively graded on a four-point scale (Table S2, Figure S1).[24]

2.4 | Statistical methods

The association between serum biomarkers and histological features was tested using the Jonckheere-Terpstra test (ordered categorical groups) or Mann–Whitney *U* test (binary categorical features), as appropriate. Correlations between clinical variables and serum biomarkers were tested in a pairwise manner using Spearman's rank correlation test. The Benjamini-Hochberg method was used to adjust for multiple testing. The associations between serum biomarkers or combinations thereof and 90-day mortality were tested by logistic regression. To avoid over-fitting models were derived applying to leave 1 out 10-fold cross-validation. In all cases, the area under the receiver operated characteristic (AUROC) analysis was used to assess the predictive performance. Samples non-diagnostic of ASH were excluded from analyses of the prediction of severe inflammation. Interaction testing was performed by including a multiplicative term for the product of prednisolone and serum CYFRA21-1 with the additional inclusion of a term between prednisolone and the quadratic of serum CYFRA21-1 to model a curvilinear interaction, as previously described.[19]

Unsupervised hierarchical clustering was conducted by applying pair-wise distance measures between all included variables and was based upon their similarity provided by a Gower distance matrix.[25] Linkage of clusters was determined via the average-linkage method.[26] Statistical analyses were conducted in R (R Foundation, Vienna, Austria) using 'DescTools', 'dplyr', 'qwraps2', 'pROC', 'OptimalCutpoints', 'ggplot2', 'survival', 'psych', 'factoextra', 'cluster', 'NbClust', 'ggpubr', 'gplots', 'viridis' and ' missCompare'.

3 | RESULTS

3.1 | Histological analyses

In total, 87 samples with suitable histopathology were available. Serum CYFRA21-1 was successfully determined in 84/87 (97%) of these cases. Serum CYFRA21-1 values in this cohort ranged from 1.63 ng/mL to 32.2 ng/mL with median (IQR) of 5.50 ng/mL (4.15, 7.93) (Table 1). These values were slightly elevated compared to previously published values in patients with advanced chronic liver disease.[17]

There was no association between serum CYFRA21-1 and the Laennec fibrosis grade ($p = .1764$, Figure 1A), severity of hepatocyte ballooning ($p = .4389$, Figure 1B) or presence of megamitochondria ($p = .2451$, Figure 1C) (Table 1). The presence of severe inflammation (moderate: median (IQR) 5.10 ng/mL (4.13, 7.08) vs. severe: 8.00 (4.89, 20.68); $p = .01722$) and Mallory-Denk bodies (absent: 4.94 (3.59, 6.49) vs. present: 5.82 (4.60, 8.60); $p = .01941$) were both associated with higher serum CYFRA21-1 levels (Figure 1D, E) (Table 1). A trend to lower levels of serum CYFRA21-1 with increasing grade of ductular reaction did not reach statistical significance ($p = .08848$; Figure 1F). Serum osteopontin was assayed in a random subset of patients as a second putative marker of the ductular reaction/portal inflammation, of these 44 patients had available histology. Serum osteopontin was higher in cases with severe inflammation (moderate: 174.12 (147.00, 244.03) vs. severe: 272.23 (205.15, 324.52), $p = .0331$) but did not correlate with the grade of ductular reaction ($p = .9756$, data not shown).

TABLE 1 Serum CYFRA21-1 levels in subgroups defined by histological features of alcoholic hepatitis histological scoring system (AHHS)

Inflammation grade	
Moderate ($n = 68$)	Severe ($n = 19$)
5.10 (4.13, 7.08)	8.00 (4.89, 20.68)
Mallory-Denk bodies	
Absent ($n = 34$)	Present ($n = 53$)
4.94 (3.59, 6.49)	5.82 (4.60, 8.60)
Hepatocyte Ballooning	
Occasional ($n = 42$)	Marked ($n = 45$)
5.08 (4.09, 7.11)	5.68 (4.32, 8.23)
Megamitochondria	
Absent ($n = 50$)	Present ($n = 37$)
5.91 (4.08, 9.16)	5.07 (4.42, 6.78)

Note: CYFRA21-1 values in ng/ml indicate medians, interquartile range are shown in parentheses.

The AUROC for CYFRA21-1 for the prediction of steatohepatitis on biopsy was 0.785 (95% confidence interval [CI]: 0.602–0.967, Figure 2A). This was similar to K18-M30 (0.787 [95% CI 0.670–0.903]) as previously reported in the same cohort and superior to transaminases or white cell count. In the 79 cases with definitive ASH analysed, 60 (76%) had moderate inflammation with the remainder classified as severe. The AUROC for CYFRA21-1 in the prediction of severe inflammation was only 0.665 (95% CI 0.492–0.838). This compared unfavourably to K18-M30 (AUC 0.847 [95% CI: 0.749–0.945]) but was similar or slightly better than white cell count, serum AST and ALT (Figure 2B).

3.2 | Clinical associations

The association between serum CYFRA21-1 and 90-day mortality was examined initially in prednisolone-untreated patients ($n = 417$); the prednisolone-treated cohort ($n = 407$) was used to validate these findings. The two cohorts were well matched for size, baseline demographics, including exposure to pentoxifylline, and outcomes (Table S1). Serum CYFRA21-1 levels were detectable in >96% of samples; the median (IQR) concentration was 5.46 ng/ml (4.07–7.61) in the prednisolone-untreated and 5.83 ng/ml (4.35–7.76) in the prednisolone-treated cohort (Table S1). These are well in excess of the normal CYFRA21-1 range of <3.3 ng/ml. CYFRA21-1 serum levels correlated moderately with K18 serum fragments M30 ($\rho = 0.40$, $p_{adj} < 0.0001$), M65 ($\rho = 0.42$, $p_{adj} < .0001$), markers of renal function [viz. urea levels ($\rho = 0.36$, $p_{adj} < .0001$) and creatinine ($r^2 = 0.27$, $p_{adj} < .0001$)] and inflammation [viz. white cell count

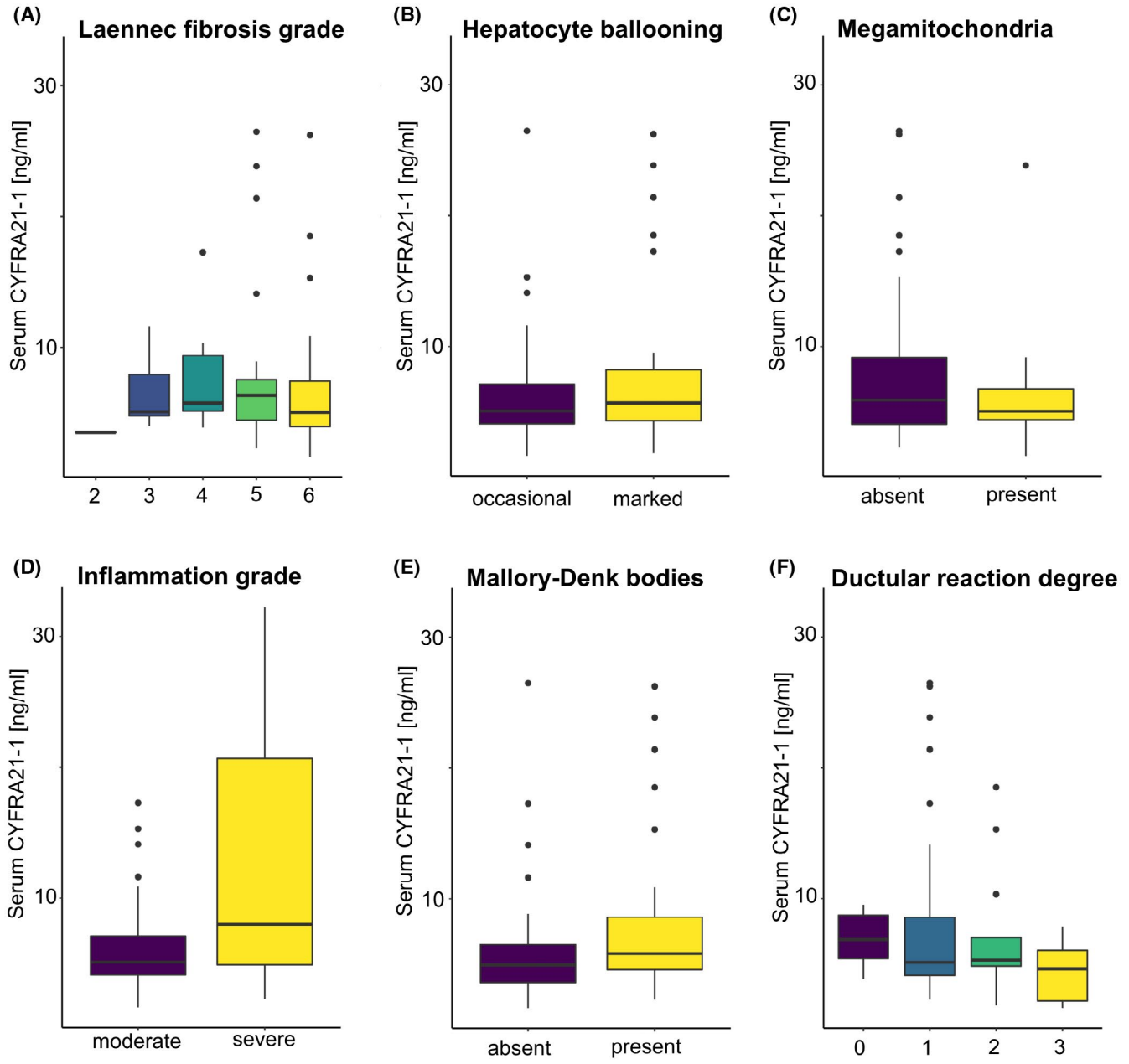


FIGURE 1 Levels of serum CYFRA21-1 in groups defined by histological features of alcoholic hepatitis histological scoring system (AHHS). The plots display CYFRA levels based on Laennec fibrosis grades (A), inflammation grades (B), extent of hepatocyte ballooning (C), presence of Mallory-Denk bodies (D), megamitochondria (E) and the extent of ductular reaction (F). Boxplots display median with first and third quartile, whilst whiskers indicate smallest and largest non-outlier values. Outliers are depicted as dots

and CRP ($\rho = 0.23$, $p_{adj} < .0001$ and $\rho = .23$, $p_{adj} < .0001$, respectively, Figure 3A]. Accordingly, in hierarchical clustering analysis, CYFRA21-1 was most closely related to serum K18 fragments M30 and M65 (Figure 3B) but was located in a large cluster including two sub-clusters consisting primarily of inflammatory markers (viz. neutrophils, C-reactive protein) and parameters of hepatic and renal function (viz. bilirubin, urea and creatinine). Serum osteopontin as an alternate marker of the ductular reaction/portal inflammation was assayed in a random subset ($n = 412$) of the entire cohort; only a weak correlation was noted between serum CYFRA21-1 and osteopontin in this group ($\rho = 0.239$, $p < .0001$).

There was no correlation between circulating bacterial DNA, as a putative marker of gut permeability, and serum CYFRA21-1 ($\rho = 0.0396$, $p = .3199$). In total, 32 patients had an active lung infection at baseline, 74 patients had an active extra-pulmonary infection at baseline and 718 patients had no infection at baseline. Serum CYFRA levels were significantly higher in patients with a baseline infection (median 6.22 (IQR 4.59–8.85) vs. 5.55 (4.18–7.58), $p = .0292$). However, no difference was observed between groups defined by a pulmonary or extra-pulmonary infection (5.61 (4.74–9.00) vs. 6.28 (4.59–8.55), $p = .881$). In total, 30 patients had significant lung disease recorded at baseline. There was no significant

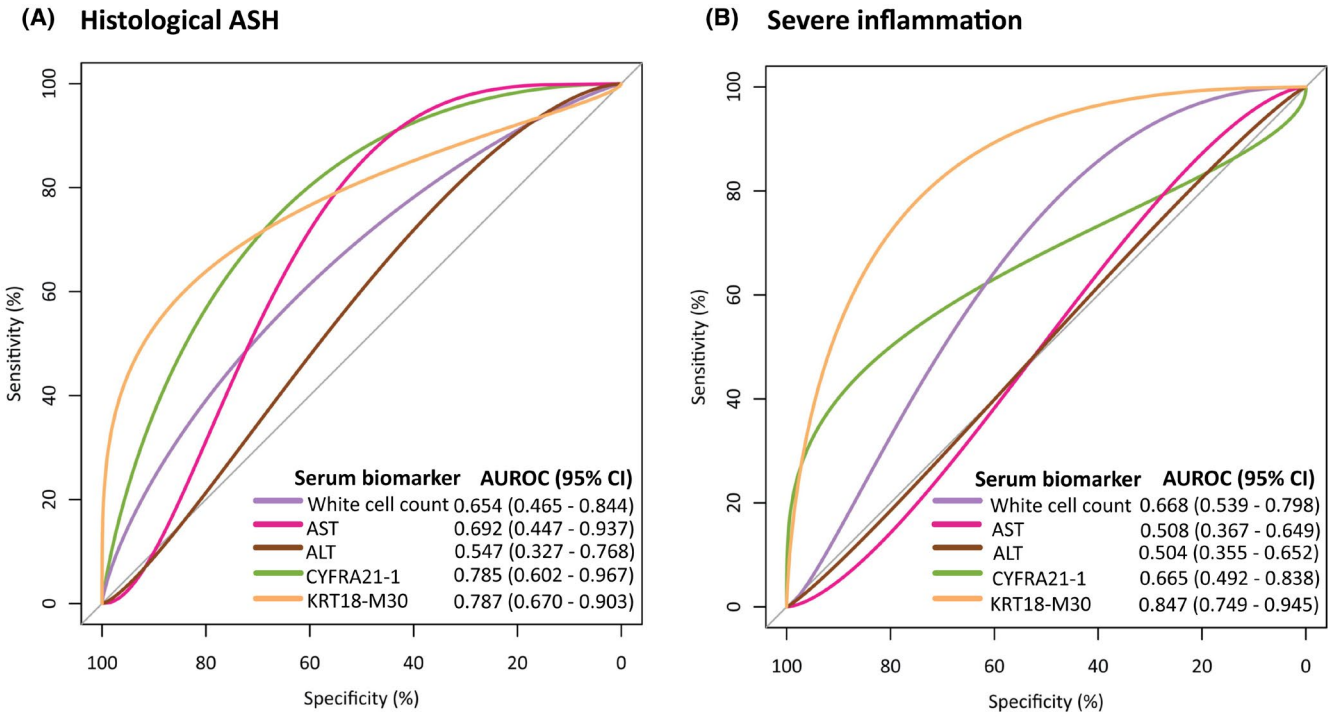


FIGURE 2 Receiver operating characteristic (ROC) curves for the identification of histological alcoholic steatohepatitis (ASH) in patients with clinically diagnosed alcoholic hepatitis (AH) (A) and the presence of severe inflammation in patients with clinically diagnosed AH and ASH on biopsy (B). The area under the receiver operated characteristic (AUROC) values with the corresponding 95% confidence intervals are shown. AST, aspartate transaminase; ALT, alanine transaminase; CI, confidence interval; KRT18, keratin-18

difference in serum CYFRA levels between groups defined the presence or absence of lung disease at baseline (5.92 (4.30, 7.01) vs. 5.56 (4.16, 7.64), $p = .886$).

3.3 | Mortality associations

Serum CYFRA21-1 was significantly associated with 90-day mortality in prednisolone untreated patients (odds ratio [OR]: 1.162, 95% CI 1.101–1.233, $p < .0001$); independent significance was retained on multivariate analysis incorporating age and MELD score (Table 2). These associations were replicated in the prednisolone-treated cohort (Table 2). The discriminative ability of CYFRA21-1 in relation to mortality was moderate and similar in both the prednisolone untreated (AUC: 0.684, 95% CI 0.620–0.748) and prednisolone-treated populations (AUC: 0.693, 95% CI 0.632–0.754) but numerically greater than the biomarkers K18-M30 and transferrin previously evaluated in this cohort (Figure 4). This performance was similar to that of the clinical scoring systems including MELD score (AUC: 0.710, 95% CI 0.652–0.769 and 0.710, 95% CI 0.640–0.761 in prednisolone untreated and treated cohorts, respectively), DF (AUC: 0.679 95% CI 0.620–0.738 and AUC: 0.694 95% CI 0.637–0.751 in prednisolone-treated and -untreated cohorts, respectively) and GAHS (AUC: 0.726 95% CI 0.620–0.783 and AUC: 0.709 95% CI 0.651–0.767 in prednisolone-treated and -untreated cohorts, respectively) (Table S3).

A predictor combining the MELD score with serum CYFRA21-1 offered a modest improvement in the AUC in both the prednisolone untreated (0.743 (95% CI 0.686–0.801) and treated (0.731 (95% CI 0.672–0.789) cohorts (Figure 4; Table 3).

Interaction testing did not reveal either a multiplicative or curvilinear interaction between serum CYFRA21-1 and prednisolone treatment in relation to 90-day mortality (data not shown).

4 | DISCUSSION

In the present manuscript, the significance of CYFRA21-1 serum levels in individuals with a clinical diagnosis of severe AH was evaluated by assessing their relationship with histological features, clinicodemographic variables, other serum biomarkers and clinical outcomes. These data indicate that serum CYFRA21-1 levels in patients with the clinical syndrome of severe AH i) are somewhat higher than concentrations detected in advanced liver fibrosis[17]; ii) predict the presence of ASH and severe inflammation on biopsy; and iii) are significantly independently associated with 90-day mortality and predict outcomes with performance similar to clinical scoring systems.

Serum CYFRA 21-1 was assayed as a putative serum marker of the extent of the ductular reaction. However, serum CYFRA did not positively correlate with the degree of ductular reaction observed on liver biopsy; indeed, a trend towards an inverse relationship was seen. In view of this finding, serum osteopontin was

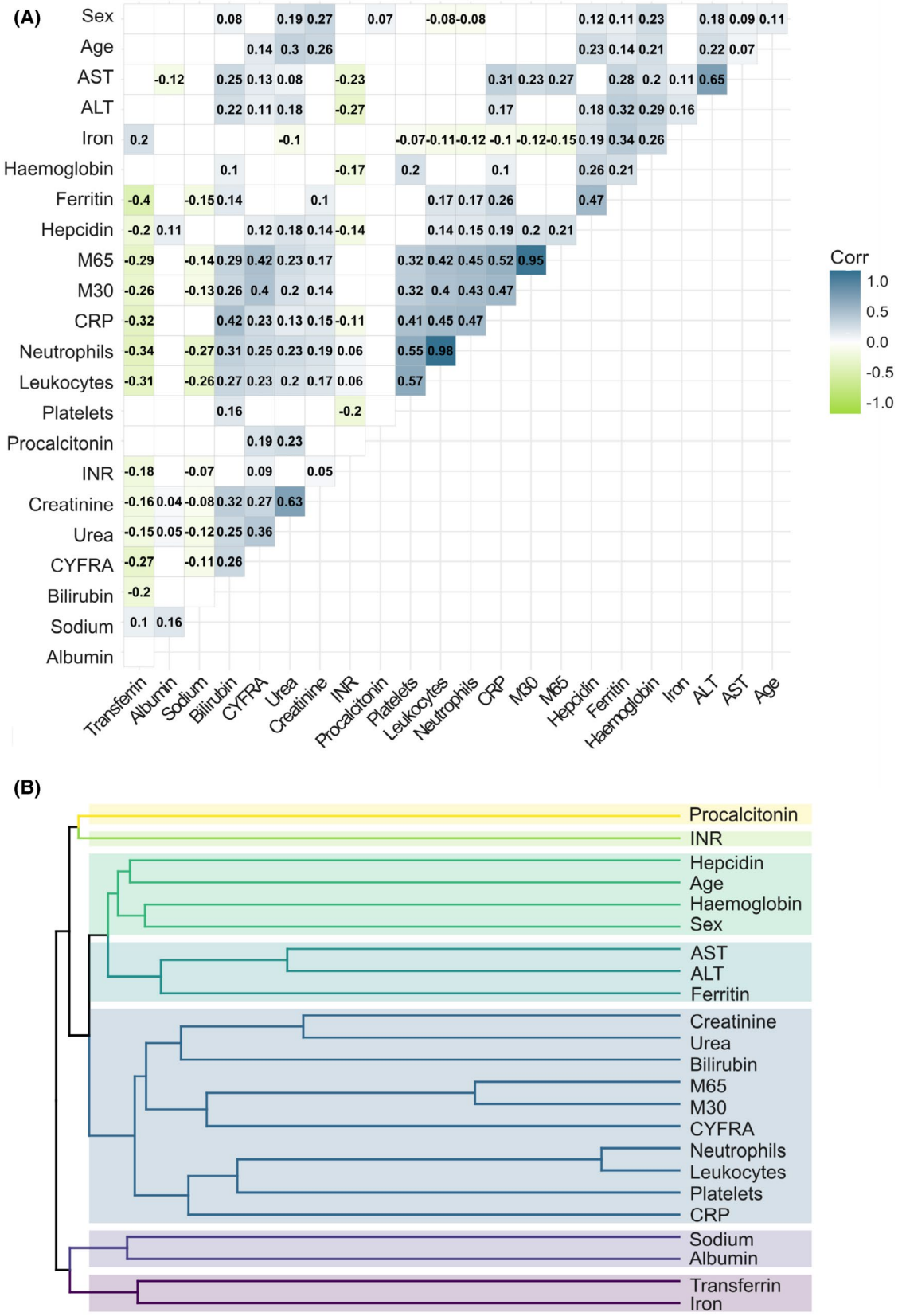


FIGURE 3 Correlation between serum CYFRA21-1 levels and demographic/laboratory parameters. (A) Spearman rank correlation factors that remained statistically significant after correction for multiple testing via Benjamini-Hochberg ($p_{adj} < .01$) method are displayed. (B) Unsupervised hierarchical clustering subdivides the assessed parameters into groups based on similarities. Note that keratin-based fragments cluster together whilst transaminases are less closely related. ALT, alanine transaminase; AST, aspartate transaminase; CRP, C-reactive protein; CYFRA, CYFRA21-1; INR, International Normalized Ratio

TABLE 2 Logistic regression analyses for serum CYFRA21-1 in relation to 90-day mortality

	Exploratory (– prednisolone)			Validation (+ prednisolone)		
	OR[a]	95% CI	*p*	OR[a]	95% CI	*p*
Univariate analysis						
CYFRA (ng/ml)	1.162	1.101–1.233	<.0001	1.133	1.077–1.199	<.0001
Multivariate analysis						
Age (years)	1.037	1.010–1.065	.0069	1.085	1.054–1.119	<.0001
MELD (points)	1.180	1.061–1.193	<.0001	1.137	1.074–1.207	<.0001
CYFRA (ng/ml)	1.120	1.061–1.193	.0001	1.084	1.018–1.161	.016

Abbreviations: CI, confidence interval; CYFRA, CYFRA21-1; MELD, Model for End-stage Liver Disease; OR, odds ratio.

[a]ORs are based on a 1 unit increase in the predictor variable as indicated in the parentheses.

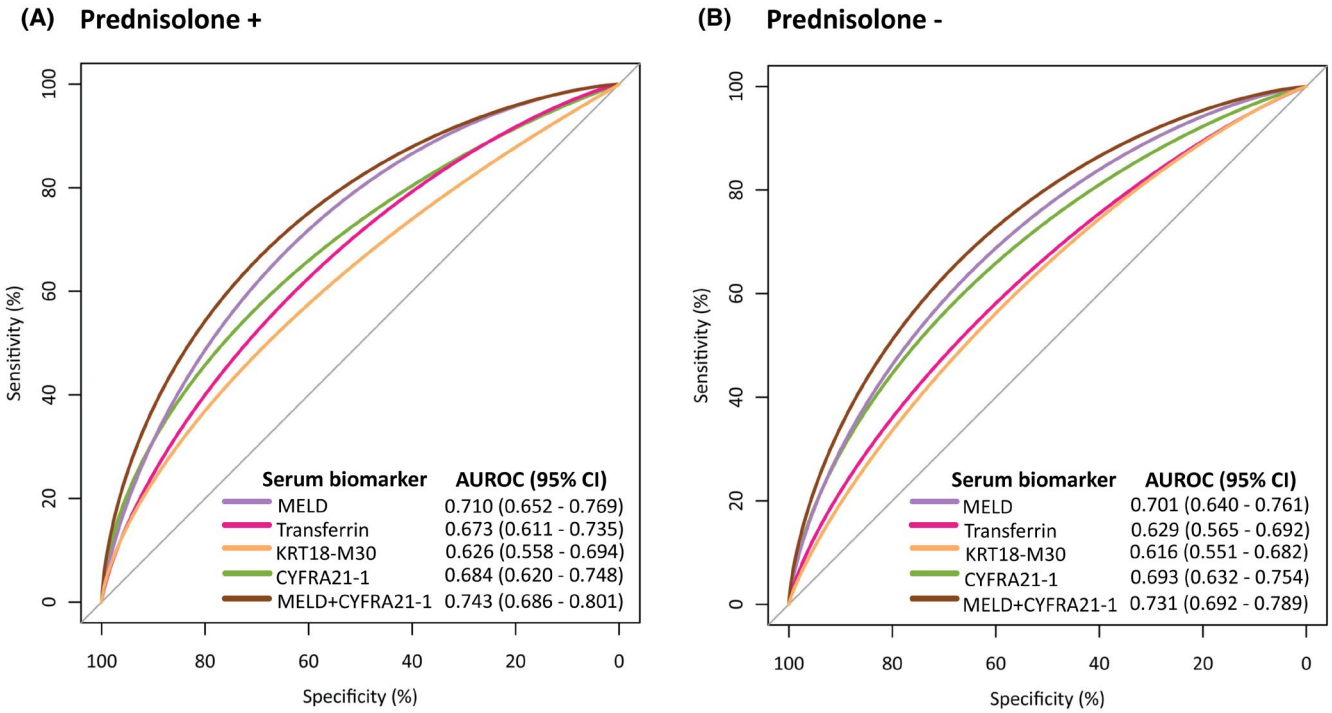


FIGURE 4 Receiver operating characteristic (ROC) curves for the prediction of 90-day mortality by serum CYFRA21-1 alone or combination with the Model for End-stage Liver Disease score (MELD) in patients with clinically diagnosed AH and treated without (A) or with (B) prednisolone. The area under the receiver operated characteristic (AUROC) values with the corresponding 95% confidence intervals (CI) are shown. KRT18, keratin 18

assayed as a second putative marker of the ductular reaction/portal inflammation. However, this did not appear to correlate with the ductular reaction histologically and correlated only weakly with serum CYFRA21-1. The lack of association between serum CYFRA21-1 and the histological ductular reaction is potentially attributable to several factors acting individually or in concert.

First, keratins are abundant epithelial proteins that are released into the circulation as a result of cellular injury and death.[14,16] In line with this, serum M30/M65 is able to discriminate between severe AH and decompensated liver cirrhosis.[19,27,28] The association between serum CYFRA 21-1 and the severity of inflammation on liver biopsy seen here in patients with severe AH suggests that in this context, much like serum K18 fragments, they at least partially reflect the extent of the liver injury and cell loss. Consequently, serum CYFRA 21-1 levels in severe AH may be more indicative of hepatic progenitor cell loss than overall abundance. Notably, mice treated with 0.1% DDC as an established ductular injury model, displayed increased serum K19 levels (not shown). The weaker relationship between serum CYFRA21-1 levels and histological inflammation in severe AH may explain why it does not predict responsiveness to prednisolone, unlike K18-M30 concentrations.[19] This may be attributable to the fact that *KRT19* is not expressed in hepatocytes and its overall abundance in the liver is much lower than that of *KRT18* which may make it more susceptible to additional confounding effects described below.

TABLE 3 Predictive ability of highlighted serum biomarkers for 90-day mortality

	Non-prednisolone treated		Prednisolone treated	
	AUC	95% CI	AUC	95% CI
MELD	0.710	0.652–0.769	0.701	0.640–0.761
Transferrin	0.673	0.611–0.735	0.629	0.565–0.692
K18-M30	0.626	0.558–0.694	0.616	0.551–0.682
CYFRA	0.684	0.620–0.748	0.693	0.632–0.754
MELD+CYFRA	0.743	0.686–0.801	0.731	0.672–0.789

Abbreviations: AUC, area under the curve; CI, confidence interval; CYFRA, CYFRA21-1; K18, Keratin 18; MELD, Model for End-stage Liver Disease; OR, odds ratio.

Second, since *KRT19* expression in the liver is relatively low; other tissues express comparatively greater levels of *KRT19* which may act as extrahepatic sources of elevated serum CYFRA21-1 in severe AH. The gut epithelium highly expresses *KRT19*.[29] Intestinal injury attributable to direct alcohol toxicity[30] and dysbiosis in the intestinal microbiome is increasingly recognized as an aetiological factor in the pathogenesis of several liver diseases including severe AH[31,32] and mice exposed to *Citrobacter rodentium* infection displayed increased serum K19 levels (not shown). This intestinal injury is implicated in increased gut permeability and the translocation of bacterial products to the liver, via portal circulation. However, we were unable to demonstrate an association between serum CYFRA21-1 and circulating bacterial DNA as markers of gut epithelial injury. In clinical practice, CYFRA21-1 is most widely used as a tumour marker for lung cancer[16,33] but may also reflect the extent of non-carcinogenic lung damage.[16] Thus the development of lung injury or infection, an adverse prognostic development in severe AH,[34,35] could translate into elevated serum levels. However, within our cohort patients with pulmonary infections did not have greater serum CYFRA21-1 levels than those with extra-pulmonary infection nor was there any association with a prior diagnosis of lung disease.

Third, CYFRA21-1 has a smaller molecular weight and a shorter serum half-life than K18 fragments.[16] As a result, levels will be more dynamic in response to alterations in liver inflammation or renal function. Indeed, serum CYFRA21-1 levels are reported to increase with falling glomerular filtration rate.[36] This is supported by the correlation of CYFRA21-1 with creatinine and urea levels and that these correlations are stronger than seen between KRT18 fragments and the same markers of renal function.

Consequently, the lack of association between serum CYFRA 21-1 and histological grading of the ductular reaction may be variously attributable to i) limitations in terms of sample size; ii) the semi-quantitative nature of the grading system used; iii) a reflection of injury and ductular cell death rather than simply the absolute quantity of ductular reaction cells; iv) an extrahepatic source. Certainly, our histological findings suggest that serum CYFRA21-1 concentrations do not solely reflect the sheer abundance of the ductular reaction in the liver. The lack of correlation between osteopontin and the ductular reaction supports the idea that, in severe AH, pathophysiological mechanisms serve to disrupt the relationships between histological phenomena and their putative serum correlates. Larger and more extensive studies are required to determine the best serum markers of the ductular reaction in severe AH.

Interestingly, CYFRA21-1 levels display a significant association with 90-day mortality and a superior discriminative ability than other epithelial products such as K18 M30 and M65 or serum transferrin which were previously assessed and reported in this cohort.[19,37] This observation extends an earlier report on the predictive capability of CYFRA21-1 in advanced liver fibrosis.[17] In line with the above CYFRA21-1 may more specifically reflect the severity of injury within the hepatic progenitor compartment. Hepatocyte mitosis and progenitor cell division and differentiation are the two major regenerative responses of the liver, the latter particularly important in severe and/or chronic liver injury. Consequently, it is potentially of great prognostic importance in AH.[11–13,38,39]

Our study has several strengths. It assessed the prognostic value of a routinely available biomarker and analysed a very large cohort of patients recruited via a prospective multicentre trial with well-defined inclusion and exclusion criteria. Consequently, the study design could also be exploited to subdivide the population into an exploration and validation cohort using the allocation to prednisolone treatment and thereby minimizing the risk of systemic bias. Whilst the diagnostic accuracy of CYFRA21-1 did not surpass the precision of routinely used, composite scores, it was associated with mortality independently of the MELD score and did yield an incremental improvement in AUROC value when the two were combined. In patients with AH, the prognostic relevance of CYFRA21-1 does not appear related to the extent of fibrosis or simply the extent of the ductular reaction; it may, however, reflect inflammation and injury within the hepatic progenitor cell compartment. Extrahepatic features of disease such as renal impairment may also influence serum CYFRA21-1 levels. Further studies are needed to corroborate these observations as well as to identify the exact underlying mechanisms including the potential contribution of extrahepatic sources.

CONFLICT OF INTEREST

None of the authors has conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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