Age and Ageing 2023; **52:** 1–11
https://doi.org/10.1093/ageing/afac313

RESEARCH PAPER

A novel prognostic nomogram for older patients with acute-on-chronic liver diseases (AoCLD): a nationwide, multicentre, prospective cohort study

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Abstract

Background: the incidence of acute-on-chronic liver disease (AoCLD) is increasing.
Objective: to investigate the clinical features and risk factors of AoCLD and construct an effective prognostic nomogram model for older patients with AoCLD.
Methods: data from 3,970 patients included in the CATCH-LIFE study were used, including 2,600 and 1,370 patients in the training and validation sets, respectively. Multivariate Cox regression analyses were performed to identify predictive risk

factors in older individuals, and an easy-to-use nomogram was established. Performance was assessed using area under the curve, calibration plots and decision curve analysis (DCA).
Results: of the 3,949 patients with AoCLD, 809 were older with a higher proportion of autoimmune-related abnormalities, hepatitis C viral infection and schistosomiasis. In the older patient group, the incidence of cirrhosis, hepatic encephalopathy (HE), infection, ascites and gastrointestinal bleeding; neutrophil-to-lymphocyte ratio (NLR), aspartate-to-alanine transaminase ratio (AST/ALT), creatinine and blood urea nitrogen levels were higher, whereas incidence of acute-on-chronic liver failure, white blood cell, platelet and haemoglobin levels; albumin, total bilirubin (TB), AST and ALT levels; international normalised ratio (INR), estimated glomerular filtration rate and blood potassium levels were lower than in the younger group. The final nomogram was developed based on the multivariate Cox analysis in training cohort using six risk factors: ascites, HE grades, NLR, TB, INR and AST/ALT. Liver transplantation-free mortality predictions were comparable between the training and validation sets. DCA showed higher net benefit for the nomograph than the treat-all or treat-none strategies, with wider threshold probabilities ranges.
Conclusions: our analysis will assist clinical predictions and prognoses in older patients with AoCLD.

Keywords: nomogram, risk factors, prognosis, older people

Key Points

- The clinical characteristics and outcomes of acute-on-chronic liver disease (AoCLD) differed between older and younger patients.
- We constructed an accurate, widely beneficial and user-friendly prognostic model specific to older patients with acute-on-chronic liver disease (AoCLD).
- The area under the receiver operating characteristic (auROC) of the nomogram model was better than that for several common scores in predicting liver transplantation-free (LT-free) mortality in older acute-on-chronic liver disease (AoCLD) patients.

Introduction

Chronic liver disease (CLD) is a growing cause of morbidity and mortality worldwide [1], particularly in low-to-middle income countries with a high economic burden and limited treatment availability [2]. Patients with CLD and acute events are considered to have acute-on-chronic liver disease (AoCLD) [3]. Acute events, including acute decompensation (AD) and acute liver injury (ALI), can aggravate liver dysfunction in patients with CLD and lead to liver failure if continued [4, 5].

Life expectancy for populations in developing and developed countries is increasing due to improvements in living standards [6]. According to incomplete statistics, 14% of the European population is aged ≥65; this is expected to reach 23% by 2030 [7]. Preliminary results from China's decadal 2020 census confirmed that those aged ≥60 years now constitute 18.7% of the total population [8], some 5.4% higher than the proportion in 2010 [9]. Indeed, the pace of population ageing already represents crucial healthcare and social issues. Specific age-related hepatic changes reportedly including the liver sinusoidal cells, hepatocyte size, mitochondrial number and blood flow, resulting in an increase in the incidence of CLD and worsening of its prognosis in older patients [10, 11]. However, large-scale, multicentre, prospective cohort studies and knowledge regarding the clinical features and risk factors for AoCLD in older patients are lacking. Therefore, an accurate evaluation of disease severity, early screening and diagnosis remains critical.

To investigate its clinical features and generate an effective prognostic model for older patients with AoCLD, we performed a prospective cohort study of patients with AoCLD who participated in the CATCH-LIFE study, established by the Chinese Chronic Liver Failure Consortium, from January 2015 to December 2016 (n = 2,600) and July 2018 to January 2019 (n = 1,370). Multivariate Cox regression was used to identify risk factors for older patients with AoCLD, and a nomogram model was constructed. Our findings' purpose is to help clinicians promptly identify high-risk patients and conduct targeted screening and individualised treatment.

Materials and methods

Setting and patients

This study was established by the Chinese Chronic Liver Failure Consortium and named CATCH-LIFE (NCT02457637 and NCT03641872), including two prospective multicentre cohorts involving patients with acute CLD events. Data were collected from 15 tertiary hospitals in hepatitis B virus (HBV) endemic areas from January 2015 to December 2017 and from July 2018 to January 2019 [12], including 2,600 and 1,370 patients, respectively. More details of the study's design have been reported in Figure S1.

Table 1. The comparison of baseline characteristics of AoCLD patients between under-60 (younger) and over-60 (older) group

	Under-60(n = 3,140)	Over-60 (n = 809)	P value
Demographic data			
Age [median (IQR)]	45.6 [37.7;51.8]	65.0 [62.0;69.0]	<0.001
Male	2,438 (77.6%)	472 (58.3%)	<0.001
Aetiology			
HBV	2,390 (76.1%)	408 (50.4%)	<0.001
Alcohol	573 (18.2%)	151 (18.7%)	0.824
Autoimmune	260 (8.28%)	131 (16.2%)	<0.001
HCV	91 (2.90%)	52 (6.43%)	<0.001
HEV	72 (2.29%)	16 (1.98%)	0.683
NAFLD	129 (4.11%)	22 (2.72%)	0.083
Schistosomiasis	23 (0.73%)	32 (3.96%)	<0.001
Cryptogenic	103 (3.28%)	93 (11.5%)	<0.001
Cirrhosis status			
Yes	2,111 (67.2%)	695 (85.9%)	<0.001
AD			
HE			0.004
Grade 1–2	183 (5.83%)	73 (9.02%)	
Grade 3–4	65 (2.07%)	18 (2.22%)	
Infection	638 (20.3%)	203 (25.1%)	0.004
Jaundice	1,558 (49.6%)	298 (36.8%)	<0.001
Ascites	1,387 (44.2%)	463 (57.2%)	<0.001
GI bleeding	404 (12.9%)	174 (21.5%)	<0.001
ACLF			
Yes	541 (17.2%)	113 (14.0%)	0.03
Blood routine			
WBC (× 109/L) (3.5–9.5)	5.18 [3.78;7.12]	4.50 [3.29;6.48]	<0.001
PLT (× 109/L) (125–350)	97.0 [60.0;152]	83.0 [52.0;120]	<0.001
HGB (g/L) (115–150)	121 [100;138]	107 [86.0;123]	<0.001
NLR	2.49 [1.56;4.28]	2.79 [1.67;5.06]	0.001
Liver function			
ALB(g/L) (40–55)	32.7 [28.5;37.4]	30.4 [26.9;34.0]	<0.001
TB (mg/dl) (0.3–1.3)	4.94 [1.74;15.3]	2.49 [1.23;9.99]	<0.001
ALT (U/L) (9–50)	120 [38.5;485]	44.0 [22.0;137]	<0.001
AST (U/L) (15–40)	124 [54.0;314]	65.3 [33.5;161]	<0.001
AST/ALT	1.04 [0.61;1.62]	1.41 [1.01;1.87]	<0.001
Inflammatory indicators			
CRP (mg/L) (0–8)	8.07 [3.23;17.4]	7.60 [3.48;16.4]	0.956
PCT (ng/ml) (≤0.1)	0.26 [0.12;0.61]	0.28 [0.11;0.69]	0.706
Coagulation function			
PT(s) (9–14)	16.5 [13.7;20.9]	16.6 [14.0;21.3]	0.197
INR (0.8–1.2)	1.44 [1.18;1.85]	1.37 [1.19;1.70]	0.011
Kidney function			
CR (mg/dl) (0.46–1.26)	0.76 [0.63;0.92]	0.80 [0.64;1.00]	<0.001
BUN (mmol/L) (2.6–7.5)	4.36 [3.32;6.00]	5.62 [4.10;8.28]	<0.001
eGFR (ml/min) (90–120)	110 [87.5;134]	102 [80.3;127]	<0.001
Electrolyte			
K^+(mmol/L) (3.5–5.3)	3.89 [3.56;4.20]	3.80 [3.41;4.18]	0.001
Na^+(mmol/L) (135–155)	138 [135;141]	138 [135;141]	0.853

ALT, alanine aminotransferase; AST, aspartate transaminase; AST/ALT, aspartate-to-alanine transaminase ratio; ALB, albumin; BUN, blood urea nitrogen; CRP, C reactive protein; CR, creatinine; GI bleeding, gastrointestinal bleeding; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HE, hepatic encephalopathy; HGB, haemoglobin; IQR, inter-quartile range; INR, international standardised ratio; K^+, blood potassium; NAFLD, non-alcoholic fatty liver disease; NLR, neutrophil-to-lymphocyte ratio; Na^+, blood sodium; PLT, platelet; PCT, procalcitonin; PT, prothrombin time; TB, total bilirubin; WBC, white blood cell.

Definition

The CLD, ALI, AD and AoCLD, as well as the exclusion criteria, have already been defined in published CATCH-LIFE manuscripts [3, 13–15]. Acute-on-chronic liver failure (ACLF) [16] was defined according to the updated consensus recommendations of the European Association for the Study of Chronic Liver Failure consortium [17]. There is no global consensus regarding the definition of 'older patient';

therefore, we adopted the generally accepted definition that older people are being older than the average life expectancy minus 15 years [18]. The average life expectancy of the Chinese population in 2015 and 2016 (the main period of recruitment in the CATCH-LIFE cohort) was 76.1 and 76.4 years, respectively, according to the World Health Statistics released by the World Health Organization [19–21]. Hence, the definition of an older patient in our study referred to those ≥60 years of age.

Statistical analysis

All statistical tests were two-sided with a statistical significance level set at $P < 0.05$. All analyses were performed using R software version 4.0.4 (http://www.r-project.org). Statistical analyses are detailed in the Supplementary Materials, available in *Age and Aging* online.

Results

Comparison of clinical characteristics and outcomes between older and younger patients

Among the 3,949 patients, 3,140 (79.5%) were aged <60 years, whereas 809 (20.5%) were aged ≥60 years (Table 1). The median age was 45.6 years (interquartile range [IQR]: 37.7–51.8) for the younger group and 65 years (IQR: 62–69) for the older group. The proportion of men in the older group was lower than that in the younger group (older group: 58.3% vs. younger group: 77.6%, $P < 0.001$; the same order of comparison below). Regarding aetiology, the top three in both groups were HBV infection, alcohol abuse and autoimmune-related causes. Notably, HBV infection was common in the younger group (50.4 vs. 76.1%), whereas autoimmune-related causes (16.2 vs. 8.28%), hepatitis C virus (HCV) infection (6.43 vs. 2.90%) and schistosomiasis (3.96 vs. 0.73%) were significantly higher in the older group ($P < 0.001$); the older group tended to develop liver cirrhosis (85.9 vs. 67.2%, $P < 0.001$). In addition, younger patients were more likely to develop ACLF (14.0 vs. 17.2%, $P = 0.03$). Regarding AD events, there was a significantly high incidence of HE (11.24 vs. 7.90%), infection (25.1 vs. 20.3%), ascites (57.2 vs. 44.2%) and gastrointestinal bleeding (21.5 vs. 12.9%), and a significantly low incidence of jaundice (36.8 vs. 49.6%) in the older group ($P < 0.001$).

Older individuals showed a significant reduction ($P < 0.001$) in complete blood count (white blood cells, platelets and haemoglobin), worse hepatic synthetic function (albumin) and greater deterioration of renal function (creatinine, blood urea nitrogen [BUN] and estimated glomerular filtration rate). Parameters of liver (total bilirubin [TB], alanine aminotransferase [ALT] and aspartate transaminase [AST]) and coagulation (INR) functions, and blood potassium were significantly higher in the younger ($P < 0.05$, Table 1). The neutrophil-to-lymphocyte ratio (NLR) and AST/ALT were significantly higher in older patients ($P < 0.05$, Table 1). In conclusion, these alterations in clinical parameters indicate a significant frequency of renal failure in the older group. Contrarily, the incidences of haemorrhage were higher in younger patients than in older patients. C-reactive protein, procalcitonin and blood sodium levels and prothrombin time did not differ significantly between the two groups.

Both of the adverse outcome rates (including death and LT) and LT-free mortalities at 28, 90, 180 and 365 days were significantly higher ($P < 0.05$) in the older, as shown in Figure S2.

Construction of the prognostic nomogram in the training cohort

The clinical characteristics of older patients with AoCLD between training and validation cohorts are summarised in Table S1 (no significant difference in variables, $P > 0.05$). Furthermore, the results of univariable and multivariable Cox regression analyses associated with the 90-day LT-free mortality for the patients in the training dataset are shown in Table 2. Subsequently, a nomogram was developed based on the results of multivariate Cox analysis with six risk factors (ascites, hepatic encephalopathy [HE] grades, NLR, TB, INR and AST/ALT, Figure 1). Based on this nomogram, we developed a dynamic nomogram web-based application (https://catch-life.shinyapps.io/DynNomapp/) to precisely calculate the survival probability of older patients with AoCLD at any time point within 1 year. We also analysed the risk factors in patients aged 60–69 ($n = 590$) and 70–79 ($n = 178$) years using the multivariate Cox analysis, as shown in Table S2.

Discriminative ability of the nomogram

The auROC of the model for predicting 28-, 90- and 365-day LT-free mortality in the training set was 0.892 (95% confidence internal [CI]: 0.841–0.944), 0.839 (95% CI: 0.789–0.899) and 0.853 (95% CI: 0.805–0.902), respectively (Figure S4A). Similarly, for the validation set, the auROC was 0.843 (95% CI: 0.769–0.917), 0.841 (95% CI: 0.775–0.907) and 0.853 (95% CI: 0.790–0.917), respectively (Figure S4B).

Compared with several generic prognostic scoring systems for end-stage liver disease, including the Model for End-Stage Liver Disease (MELD), MELD-sodium (MELD-Na), integrated MELD (iMELD), Sepsis-related Organ Failure Assessment (SOFA), Age, serum Bilirubin, INR and serum Creatinine (ABIC), albumin-bilirubin (ALBI), Chronic Liver Failure Consortium ACLF (CLIF-C ACLF) and the Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH ACLF) scores (Table S3), the nomogram model yielded a significantly more accurate prognosis ($P < 0.05$), with the highest auROC for predicting the 28-, 90- and 365-day LT-free mortality of older patients with AoCLD both in the training and validation datasets (Figures 2 and S3).

Table 2. Risk factors associated with 90-day LT-free mortality of older (over-60) patients with AoCLD in the training cohort using univariate and multivariate cox analysis

Variables	Univariate Cox regression			Multivariate Cox regression		
	HR	95%CI	*P*	HR	95%CI	*P*
Demographic data						
Age	1.032	0.989–1.077	0.148	-	-	-
Male	1.19	0.777–1.822	0.424	-	-	-
Aetiology						
HBV	1.749	1.139–2.686	0.011	1.758	0.82–3.76	0.145
Alcohol	1.355	0.831–2.208	0.223	-	-	-
Autoimmune	0.589	0.305–1.137	0.115	-	-	-
HCV	0	0-Inf	0.994	-	-	-
HEV	1.323	0.326–5.375	0.695	-	-	-
NAFLD	0.708	0.174–2.874	0.629	-	-	-
Schistosomiasis	1.027	0.325–3.246	0.964	-	-	-
Cryptogenic	0.993	0.515–1.917	0.984	-	-	-
AD						
HE grades 1–2	2.606	1.531–4.435	<0.001	2.67	1.15–6.19	0.022
HE grades 3–4	5.009	2.017–12.434	0.001	17.264	2.06–144.95	0.009
Infection	1.905	1.247–2.911	0.003	0.853	0.45–1.62	0.628
Jaundice	5.485	3.455–8.708	<0.001	-	-	-
Ascites	2.383	1.493–3.802	<0.001	3.068	1.34–7.02	0.008
GI bleeding	0.572	0.305–1.076	0.083	-	-	-
Cirrhosis	1.738	0.841–3.593	0.135	1.066	0.23–4.88	0.934
Laboratory results						
WBC ($\times 10^9$/L) (3.5–9.5)	1.166	1.108–1.228	<0.001	0.97	0.87–1.08	0.586
PLT ($\times 10^9$/L) (125–350)	1	0.998–1.002	0.761	0.998	0.98–1.02	0.798
HGB(g/L) (115–150)	1.003	0.995–1.011	0.506	-	-	-
NLR	1.075	1.046–1.105	<0.001	1.119	1.02–1.23	0.015
ALB(g/L) (40–55)	0.971	0.935–1.008	0.118	1.037	0.99–1.08	0.116
TB (mg/dl) (0.3–1.3)	1.09	1.071–1.109	<0.001	1.044	1.01–1.08	0.021
AST/ALT	1.358	1.131–1.63	0.001	1.591	1.07–2.36	0.021
CRP (mg/L) (0–8)	1.001	0.991–1.011	0.882	-	-	-
PCT (ng/ml) (≤0.1)	0.999	0.989–1.009	0.83	-	-	-
PT(s) (9–14)	1.008	0.99–1.027	0.374	-	-	-
INR (0.8–1.2)	2.878	2.432–3.406	<0.001	2.25	1.66–3.05	<0.001
CR (mg/dl) (0.46–1.26)	1.295	1.156–1.451	<0.001	1.107	0.87–1.41	0.412
BUN (mmol/L) (2.6–7.5)	1.013	1.005–1.02	0.001	1.013	1.00–1.03	0.065
K^+(mmol/L) (3.5–5.3)	1.129	0.84–1.518	0.422	-	-	-
Na^+(mmol/L) (135–155)	0.92	0.893–0.948	<0.001	0.984	0.94–1.03	0.492

ALT, alanine aminotransferase; AST, aspartate transaminase; AST/ALT, aspartate-to-alanine transaminase ratio; ALB, albumin; BUN, blood urea nitrogen; CRP, C reactive protein; CR, creatinine; GI bleeding, gastrointestinal bleeding; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HE, hepatic encephalopathy; HGB, haemoglobin; INR, international standardized ratio; K^+, blood potassium; NAFLD, non-alcoholic fatty liver disease; NLR, neutrophil-to-lymphocyte ratio; Na^+, blood sodium; PLT, platelet; PCT, procalcitonin; PT, prothrombin time; TB, total bilirubin; WBC, white blood cell.

In all 769 older patients, a comparison of the auROC values for predicting the 28-, 90- and 365-day LT-free mortality between the cirrhosis (Figure S5A) and non-cirrhosis (Figure S5B) groups is shown in the supplementary materials. In addition, the auROC values of the nomogram for predicting the aged 60–69 group and 70–79 group are also shown in Figure S6A and B, respectively.

Calibration plot

The calibration plot of the new model in the training (Figure 3A) and validation (Figure 3B) cohorts showed good agreement between predicted and observed probabilities, with a calibration slope close to 1 and intercept close to 0. The Hosmer–Lemeshow test revealed high concordance between the predicted and observed probabilities for both the training and validation sets at 28, 90 and 365 days (all $P > 0.05$).

Decision curve analysis

Figures S8–S10 show the decision curves of the nomogram model for the training and validation datasets at 28, 90 and 365 days. For all day periods and both datasets, the DCA indicated that the nomogram model presented a greater net benefit than the treat-all or treat-none strategy, with a wider range of threshold probabilities for predicting LT-free mortality in older patients with AoCLD.

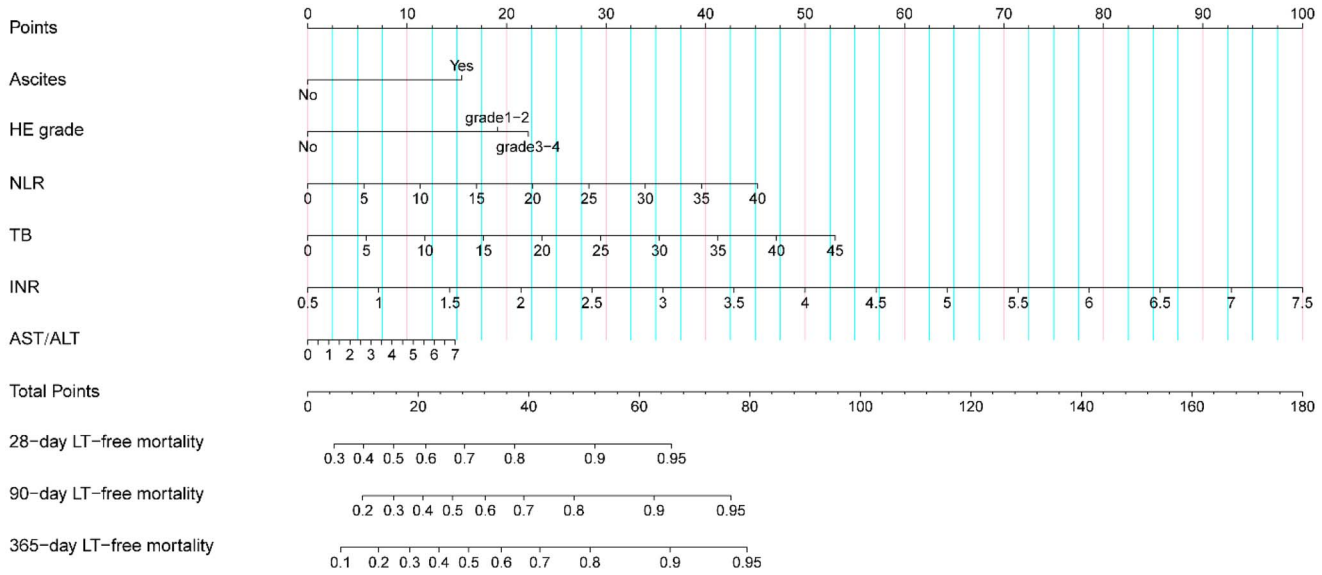

Figure 1. A nomogram for predicting 28-, 90- and 365-day LT-free mortality of older (over-60) AoCLD patients. In addition, an easy-to-use web nomogram model calculation was developed at https://catch-life.shinyapps.io/DynNomapp/ and the most updated version will also be available online.

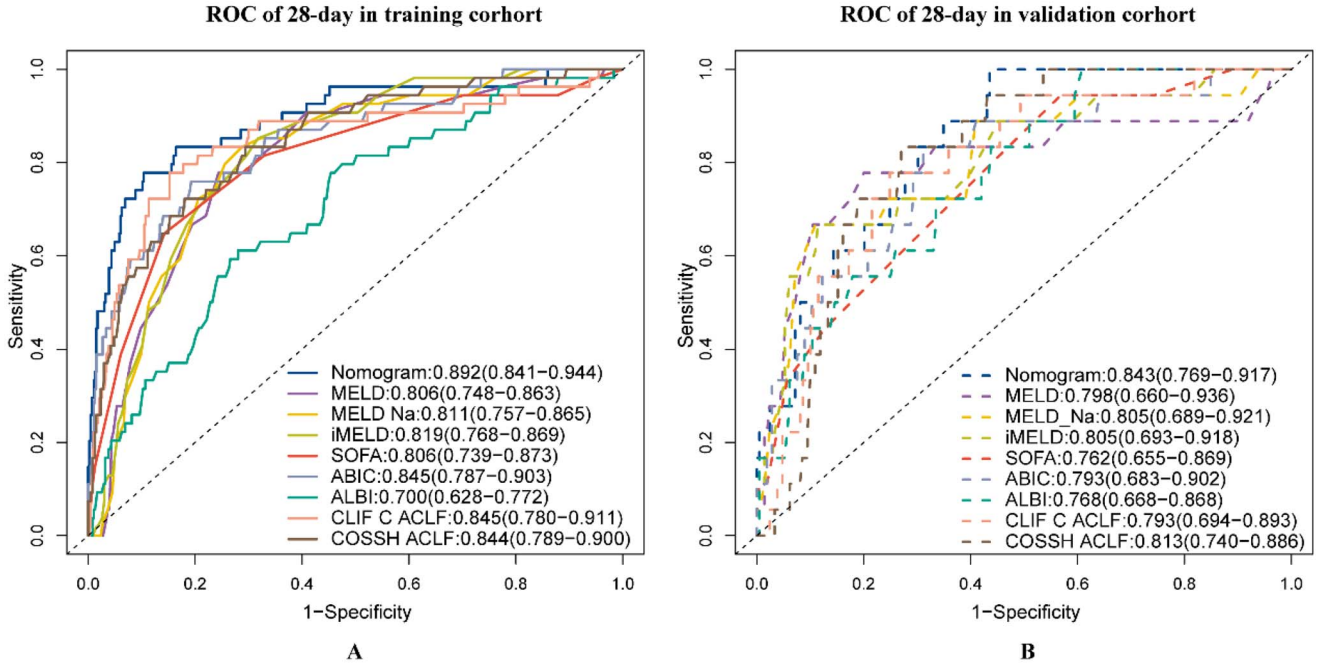

Figure 2. Receiver operating curves (ROCs) for the abilities of prognostic models to predict the 28-day LT-free mortality of older (over-60) patients with AoCLD in training dataset (A) and validation dataset (B).

Discussion

With an increasingly ageing society, clinicians now encounter more older patients in clinical practice, for which AoCLD in older patients attracts more attention. However, little is known about the clinical features and risk factors of this condition in older patients. Thus, we identified the clinical characteristics of older patients with AoCLD in a multicentre, prospective CATCH-LIFE study and developed a new simplified nomogram model to accurately predict the 28-, 90- and 365-day LT-free mortality in these patients.

Our study described, for the first time, the clinical characteristics of older patients with AoCLD. Demographically, our data showed a higher proportion of women in the older group; this is likely because the proportion of women in the general population gradually increases with age [22]. HBV infection still constituted a major part of the aetiology of liver disease in both groups. Furthermore, the

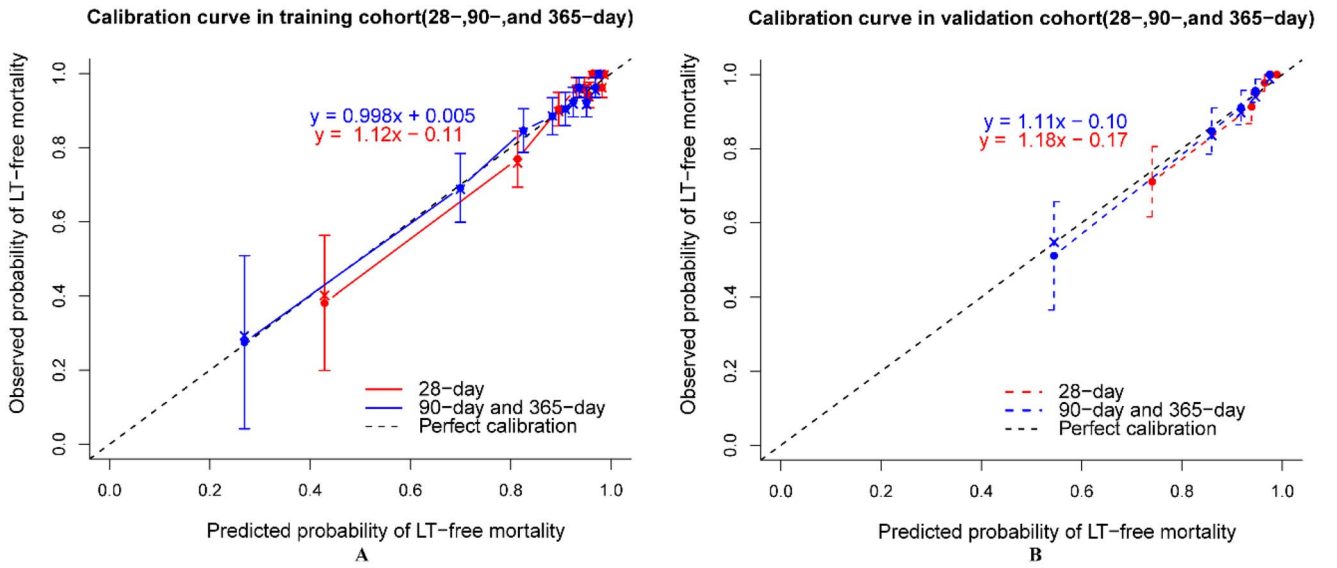

Figure 3. The calibration curve for predicting LT-free mortality of older patients with AoCLD at 28-, 90- and 365-day in the training cohort (A) and validation cohort (B). Nomograms-predicted probability of LT-free mortality is plotted on the *x*-axis, and actual probability is plotted on the *y*-axis. The dotted line indicates an ideal model, and the solid line indicates the predictive performance of the nomogram. The closer the distance between two lines, the better the performance of the nomogram.

proportion of autoimmune-related infections, HCV infection and schistosomiasis was significantly more common in older individuals. Thus, routine screening for the above diseases is recommended when liver damage is confirmed. HCV infection frequently occurs in older individuals, with a prevalence of 16–42% in individuals aged >60 years [23, 24]. Epidemiological progress in screening and therapeutic techniques for HCV will reduce the number of infections in the older population. Despite these findings, there are no liver diseases unique to older patients. Furthermore, it was reported that there might be an age window in which the liver becomes resistant to the development of injury. The incidence of liver diseases in humans increases with age up to 75 years. Interestingly, subjects aged <75 years have a significantly reduced incidence of hepatocellular cancer [11], which might be explained by a decline in autophagy ability [25, 26] and dysregulation of hepatocyte Hedgehog signalling [27] in extremely older patients aged ≥75 years. It had also been suggested that this paradox might reflect the cumulative effects of age-related declines in insulin growth factor-1 signalling [28]. However, more research is needed to explore this association in older patients with CLD.

We observed that with older age, fewer patients were diagnosed with ACLF; that is, younger AoCLD patients were more prone to developing ACLF, which is similar to the study by Atul *et al*. [29, 30]. Young age is associated with more vigorous immune response [30].The distinct clinical features of the older group also included higher rates of AD events (except for jaundice). Our study indicated a significantly higher frequency of brain and renal insufficiency or even failure in older patients than in younger individuals. In our study, the TB and liver transaminase levels in the younger group were notably higher than those in the older group. The relation between age and serum ALT activity is not a simple linear correlation, but rather an inverted-U-like relation, with a peak value between 40 and 55 years of age [31]. Thus, AST and ALT levels decrease after 55 years of age. The base levels in older patients were lower than that in the younger group. In addition, in animal studies [32–34], older livers were shown to have a slower and weaker regenerative capacity, reduced organ weight, lower inflammatory response rate and increased fibrosis when compared with younger livers. Thus, decreasing liver transaminase in aged livers may lead to these conditions during ageing in response to diseases. Moreover, older individuals who meet the currently accepted normal range of ALT may harbour clinically significant liver disease [35]. Low ALT activity in older people is associated with greater mortality [36]. Clinicians must be aware that a slight deviation in, or even 'normal', serum ALT may indicate severe liver injury in older patients. Overall, more relentless efforts are required to enhance screening of causal factors of AoCLD among older patients. Furthermore, it is important for gastroenterologists and infectious disease specialists to prevent the development of AoCLD and pay more attention to the worsening of renal and brain function among older patients; the prevention of progression to ACLF is an important therapeutic goal.

Unlike previous studies [37, 38], age was not a predictor for patients with AoCLD in our study, which could be attributed to study population heterogeneity. In previous studies [37, 39, 40] including all age groups, age is a parameter of the prognostic indicator, usually as a

dichotomous or multi-categorical variable. However, our model was based primarily on data from people >60 years of age. Moreover, about half of the older patients included were 60–65 years old ($n = 394$, 48.70%), which somewhat impaired the efficacy of age as a prognostic indicator. We also compared age between the survival group and the death group in older AoCLD patients, finding no significant difference between the two groups (survival group: 65 [62–69] vs. death group: 66.4 [62.2–71.4] years; $P = 0.081$), which was consistent with the results of univariate Cox analysis ($P = 0.148$, Table 2). Furthermore, the significant association between age and liver function is not a simple linear correlation [31].

Furthermore, the aetiology of liver disease was not associated with prognosis in older patients with AoCLD. Our results were consistent with other prognostic models applicable to patients with AoCLD of all ages, such as CLIF-C ACLF [38] and APASL ACLF Research Consortium ACLF [AARC-ACLF] scores [41](Table S3), which also do not include aetiology as a parameter. It furthermore illustrated our model has good generality and expansibility to patients with AoCLD of all aetiologies, in different countries and areas. Compared with aetiologies, the severity of acute injury and AD events in aged livers has more impact on prognosis in older patients. For example, the effect of severe complications of liver disease (such as HE grades 3–4, HR = 17.264 in multiple Cox analysis) may mask the influence of aetiologies themselves. In addition, the most common aetiologies of AoCLD are HBV infection and alcohol abuse [16], which makes it difficult to assess the prognostic impact of rarer aetiologies, such as autoimmune-related disease.

Several scoring systems have been proposed to facilitate prognostication for liver disease, including MELD [42], MELD-Na [43], iMELD [37], SOFA [44], ABIC [45], ALBI [46], CLIF ACLF [38] and COSSH ACLF [47] scores (Table S3). In addition to these, several related studies have evaluated the prognosis of ACLF patients with nomograms [48–54]. However, none of them are used for patients of a specific age, nor are any of them simple to apply. Furthermore, all were used to predict patients with ACLF, even HVB-related ACLF [48, 50–52, 54], and none of them were applied to AoCLD. With an ageing society, a simplified and practical prognostic model is important for early prediction of poor outcomes. Thus, we constructed an effective prognostic model specific to older patients with AoCLD. Currently, the development of nomograms allows clinicians to standardise clinical decisions through an evidence-based and fully individualised tool. In addition to building a statistical nomogram that roughly calculates an approximation, our study created a web-based dynamic nomogram (https://catch-life.shinyapps.io/DynNomapp/) that precisely calculates the risk probability for older patients with AoCLD.

In our study, six independent risk factors—ascites, HE grades, NLR, TB, INR and AST/ALT—were selected to construct an easy-to-use nomogram model. Among these factors, two parameters that require subjective assessment—ascites and HE—and objective laboratory variables were included to maximise its clinical applicability and generalisability. Ascites is a combination index that indicates patient nutrition, infection and portal hypertension status. HE, indicating brain failure [3], was used for both scores, similar to other scores. TB and INR are associated with liver and coagulation failure and have been commonly used in previous scoring systems [37, 43, 45, 47, 55]. INR has also been reported to be a known parameter often used for liver fibrosis assessment [56–58]. Compared with existing scores, we showed for the first time that AST/ALT and NLR were potential predictors for identifying high-risk older individuals with AoCLD. NLR, an inflammatory factor, has been verified to be prognostic in a variety of different liver disease contexts: patients on the liver transplant waiting list [59], those with low MELD scores [60], hospitalised patients with cirrhosis [61], patients with ACLF [62] and patients with decompensated liver disease without ACLF [49]. In addition, studies observed an increased frequency of liver-related complications [63] and higher mortality [53] in the higher NLR group with HBV-related decompensated cirrhosis. Recently, AST/ALT was shown to be a useful prognostic index for survival in patients with severe acute viral hepatitis [64] and in those with alcoholic hepatitis and cirrhosis [65]. In addition, the ratio reportedly correlates with the histological degree of fibrosis in patients with chronic hepatitis [66] and with the clinical severity of disease in patients with liver cirrhosis [67]. Thus, these six independent risk factors reflect the unique pathophysiology of older patients with AoCLD.

The discriminative and predictive ability of a new prognostic score is critical for decision making regarding intensive treatment strategies and for predicting outcomes in older patients with AoCLD. The nomogram we constructed showed superior predictive ability (all auROCs were > 0.75) in both the training and validation cohorts. The calibration curves for the probability of 28-, 90- and 365-day LT-free mortality also showed excellent accuracy (all $P > 0.05$) in the predictive modelling of the nomogram. Furthermore, DCA displayed the clinical usefulness of this nomogram for predicting LT-free mortality, demonstrating a superior benefit across a wider range of threshold probabilities. Thus, the nomograms we have established are accurate, widely beneficial and user-friendly in clinical practice. This model has shown superior predictive ability compared with several common scores in predicting LT-free mortality in older patients with AoCLD according to the auROC (Figures 2 and S3). In addition, the nomogram model exhibited higher predictive value in the older group than in the younger group in predicting short- and long-term LT-free mortality, according to the auROC value (Figure S7). The superior predictive ability in both the cirrhotic and non-cirrhotic groups (Figure S5) and different age groups (Figure S6) of older patients with AoCLD illustrates that the nomogram we constructed is applicable to all older patients with CLD.

These results also indicate that our newly developed prognostic score is more accurate, convenient, feasible and available for predicting disease severity in older patients with AoCLD.

A major strength of our study is that we developed a nomogram from a large-scale, multicentre study in China that has excellent applicability to the general population. To our knowledge, this study is the first to develop a 28-, 90- and 365-day LT-free mortality predictive nomogram for an older Chinese population with AoCLD using easily obtained clinical parameters without extra costs or discomfort. Our nomogram model demonstrated high discriminative and celebratory abilities. Thus, it may be used for the accurate prognosis of mortality in older patients with AoCLD. However, the potential limitations of this study should also be considered. First, although the established nomogram showed good discrimination and validation, further validation based on large-scale external cohorts is required. Second, the data in our study were obtained from multiple centres and may have led to measurement errors, since they were processed in different laboratories.

Conclusions

Our study described baseline characteristics and risk factors in older patients with AoCLD and constructed a nomogram with high accuracy and validity for the first time, which is promising for their prognosis prediction and clinical course management.

Supplementary Data: Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

Data Availability Statement: The original datasets generated in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author.

Acknowledgements: We thank the study participants for volunteering in this study. We sincerely thank Yixiang, Zheng and Li Wu of Xiangya hospital for their instruction in the statistics of this manuscript. We would like to thank Editage for English language editing.

Declaration of Conflicts of Interest: None.

Declaration of Sources of Funding: National Natural Sciences Foundation of China [grant numbers 82,070,613, 81,970,550], the National Natural Sciences Foundation of Hunan Province [grant number 2019JJ30041)], the National Major Science and Technology Projects (grant numbers 2018ZX10302206, 2018ZX10723203], the Innovation-Driven Project of Central South University [grant number 2020CX044] and the Science and Technology Innovation Program of Hunan Province (2022RC1212 to R.C).

Ethics Statement: Studies involving human participants were reviewed and approved by the Renji Hospital Ethics Committee of Shanghai Jiaotong University School of Medicine [ethics codes: (2014)148 k and (2016)142 k]. All patients provided written informed consent to participate in the study. Written informed consent was obtained from each individual for publication of potentially identifiable images or data included in this article.

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Received 4 July 2022; editorial decision 11 November 2022