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ORIGINAL RESEARCH

Clinical Utility of the Trajectory of Serum Bilirubin and International Normalized Ratio Values in Hepatitis B Virus-Related Acute-on-Chronic Liver Failure

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Background and Aim: Acute-on-chronic liver failure (ACLF) is a rapidly progressive and highly fatal condition. Early identification of critically ill patients is crucial. Hepatitis B virus-related ACLF (HBV-ACLF), the main cause of ACLF in China, is characterized by liver failure and coagulation dysfunction. Dynamic changes in total bilirubin (TB) and international normalized ratio (INR) can reflect disease progression. This study aims to investigate the clinical application of dynamic trajectories of TB and INR in HBV-ACLF patients.

Methods: Retrospective data from 194 patients at Taizhou Hospital, China (Jan 2012 - June 2023), meeting COSSH-ACLF criteria, were analyzed. A latent class mixed model (LCMM) identified three trajectory groups (declining, stable, fluctuating) based on bilirubin and INR changes. Clinical applicability of these groups was investigated.

Results: The 194 patients were divided into the trajectory groups mentioned above. The declining group had lower predicted scores and a better prognosis. The stable and fluctuating groups had worse prognosis compared to the declining group (P<0.001). Artificial liver support did not improve short-term prognosis for the stable group; instead, it was a risk factor (OR 2.16, 95% CI [0.23–3.79], P=0.007). Subgroup analysis showed no interaction between predictive models and trajectory groups. Additionally, trajectory grouping improved the predictive effectiveness of existing models.

Conclusion: Based on our trajectory analysis, patients with a continuous declining in bilirubin and INR values showed the best prognosis, highlighting the clinical significance of trajectory grouping in treatment decisions. Trajectory grouping can complement existing scoring models, improving predictive effectiveness.

Keywords: dynamic trajectories, short-term prognosis, artificial liver support, acute-on-chronic liver failure

Introduction

Acute-on-chronic liver failure (ACLF) is a complex syndrome with a short-term mortality rate ranging from 50% to 90%.[1,2] Controversies exist concerning the diagnostic criteria and clinical classification of ACLF due to regional and etiological differences. In Western countries, alcoholic liver disease is a major cause, whereas in China, hepatitis B virus (HBV) infection is the primary trigger, (termed HBV-ACLF).[3] Regardless of its etiology, ACLF is characterized by rapid disease progression and high short-term mortality, emphasizing the importance of early identification of critically ill

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patients and proactive treatment.[1,4] At present, various models are used to predict the prognosis of patients with ACLF, including the Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD), and Chronic Liver Failure Consortium-ACLFs (CLIF-C ACLFs).[5–7] Despite these limitations, these scores play a role in assessing disease severity and guiding clinical decisions.

The Chinese Study Group for Severe Hepatitis B (COSSH) has proposed new diagnostic criteria for Hepatitis B Virus-Associated Acute-on-Chronic Liver Failure (HBV-ACLF) based on their prospective study conducted on the Chinese population. Additionally, they have developed a prognostic scoring model (COSSH-ACLFs) for HBV-ACLF patients, which exhibits high accuracy in predicting 28-day and 90-day mortality rates. The study has also revealed a high incidence of liver and coagulation system dysfunction in HBV-ACLF patients, with coagulation dysfunction occurring earlier and more frequently. As a result, the study proposes a new calculation formula to assess the condition (0.741*INR +0.523*HBV-SOFA+0.026*age+0.003*TB).[1] Both the total bilirubin level and the international normalized ratio (INR) are considered independent risk factors for ACLF, reflecting the extent of liver and coagulation failure, respectively.[1,8,9] However, cross-sectional data may not accurately reflect disease dynamics.

In recent years, trajectory-based classification methods for dynamic data have found broad applications in various fields.[10–12] These methods consider the heterogeneity among individuals and can more accurately reflect the progression of the disease than truncated data, thereby offering clinical utility for assessing prognosis and making treatment decisions.

Given the rapid changes in the condition of ACLF patients, precise identification of disease dynamics is crucial. Dynamic monitoring through scoring systems is one such approach, although complex calculations and clinical assessments pose challenges. Against this backdrop, this study adapted dynamic monitoring of serum total bilirubin and INR data during hospitalization for patients with ACLF. These data were transformed into trajectory curves, and latent-class mixture models were used for trajectory classification. By identifying trajectory groups with similar patterns of change and analyzing their relationship with short-term survival rates in ACLF patients, this research presents the impact on the patient prognosis and offers treatment guidance.

Methods

Research Population

We retrospectively collected information on 350 patients diagnosed with HBV-ACLF who were hospitalized between January 2012 and June 2023 at Taizhou Hospital, Zhejiang Province, China. Based on the inclusion and exclusion criteria, 156 cases were excluded, and ultimately 194 cases were included in the analysis. The study was ethically approved by the Ethics Committee of Taizhou Hospital affiliated to Wenzhou Medical University, and informed consent was waived due to its retrospective nature.

Inclusion Criteria: 1) Patients meeting the COSSH-ACLF diagnostic criteria: 1) Hepatitis B virus infection; 2) On the basis of chronic liver disease, liver failure characterized by acute worsening of jaundice and coagulation dysfunction caused by various triggers (serum total bilirubin (TBil) ≥10 times the upper limit of normal or daily increase ≥17.1 μmol/L; presence of bleeding symptoms, prothrombin activity (PTA) ≤40% or INR ≥1.5).

Exclusion Criteria: 1) Age <18 or >80 years old; 2) patients with malignant tumors such as liver cancer or lymphoma; 3) patients with elevated bilirubin levels due to bile stasis-related conditions such as bile duct stones; 4) pregnant and postpartum women; 5) patients with other causes of chronic liver disease, including alcoholic liver disease, hepatitis C, autoimmune liver disease, genetic metabolic liver diseases, and schistosomiasis-associated liver disease; 6) patients with severe coexisting chronic extrahepatic diseases, such as severe congestive heart failure, cor pulmonale, and advanced chronic kidney disease; 7) recipients of liver transplantation; and 8) patients with short hospital stays, <2 measurements of bilirubin and INR, or unclear clinical outcomes.

For patient follow-up, statistics were made by case data and telephone follow-up. An outcome event was defined as a death due to an exacerbation of ACLF.

All enrolled patients were classified according to the severity of the disease into ACLF grades 1 to 3. ACLF Grade 1 included those with isolated kidney failure; isolated liver failure with an INR >1.5, renal impairment (creatinine

1.5–1.9 mg/dL), or grade I–II hepatic encephalopathy; single-organ failure (coagulation, respiration, circulation) with associated renal impairment or grade I–II hepatic encephalopathy; and isolated cerebral failure with associated renal impairment. ACLF Grade 2 includes those with failure in two organ systems, and ACLF Grade 3 included those with involvement of failure in three or more organs.[1]

Regarding the definitions of organ failure, liver failure involved serum total bilirubin ≥12 mg/dL, coagulation system failure involved an INR ≥2.5 or platelet count ≤20 × 10^9/L, cerebral failure involved hepatic encephalopathy of grade III or IV, kidney failure involved serum creatinine >2 mg/dL, circulatory failure involved the use of vasopressors (eg dopamine or dobutamine), and respiratory failure involved an arterial partial pressure of oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ≤200 or oxygen saturation (SpO_2)/FiO_2 ≥200[1].

Indications for artificial liver support therapy include: 1) Patients in the early, middle, or late stages of liver failure due to various causes, with a prothrombin activity ranging from 20% to 40%; 2) Patients with end-stage liver disease awaiting liver transplantation, experiencing post-transplant rejection reactions, or in the non-functional phase of the transplanted liver; 3) Patients with severe cholestatic liver disease who have inadequate response to internal medicine treatment; and 4) Patients with severe hyperbilirubinemia caused by various reasons.[13] Contraindications include: 1) Severe active bleeding or disseminated intravascular coagulation; 2) Hypersensitivity to blood products or medications used during the treatment, such as plasma, heparin, and fish gelatin; 3) Cardiovascular failure; 4) Patients in the unstable period of myocardial or cerebral infarction; and 5) Patients in the late stage of pregnancy.[13]

Research Methods

General information collected included age, sex, complication with cirrhosis, number of organ failures, presence of artificial liver support treatment, and laboratory test results at admission. In addition, calculations were performed for the CTP, MELD, MELD-Na, CLIF-OFs, CLIF-CACLFs, and COSSH-ACLFs. The calculation formula and scoring table can be found in the supplementary materials, Tables S4-S6, as well as in the "Other scoring models" section 1–4.

Data on the bilirubin level and INR were collected within 28 days after admission. The bilirubin level and INR measured within 24 h after admission were recorded as the first data point. For cases with multiple measurements within a day, only one data point was selected. The measurements of TB and INR should be conducted on the same day, with a minimum of two or more measurements performed. The frequency of testing is adjusted by the attending physician based on the patient's condition. During hospitalization, the median number of tests recorded for each patient is 6 (5–8).

Data Analyses

Establishment of Trajectory Models

A latent class mixed model (LCMM) was employed to segregate heterogeneous longitudinal data into groups exhibiting similar patterns, enabling the fitting of individual curves. The longitudinal measurements were set as linear or nonlinear functions of time (days between each measurement date and the initial measurement). These are represented as time, time-squared, or time-cubed terms. The data were divided into two to seven possible groups, with the specific outcomes outlined in the supplementary materials. The optimal number of groups and best-fitting shapes were determined using the Bayesian Information Criterion (BIC), ensuring that each group maintained an acceptable overall proportion (>5%) and posterior probability (>70%). Thus, in this study, a cubic function with three groups was chosen for subsequent analyses.[14]

Baseline information comparisons were performed using chi-square tests, analyses of variance, and Kruskal–Wallis rank sum tests. Multivariate and prognostic analyses were conducted using Cox regression models. The data processing software employed was R (version 4.2.3), and a significance level of $P < 0.05$ indicates statistical significance.

Results

Patient Analysis

Initially, this study included 350 patients who were diagnosed with ACLF. Among them, 156 patients were excluded, including 66 with concomitant liver cancer or other malignancies, 2 pregnant women, 21 with alcoholic liver disease, 28

with other severe liver diseases (eg autoimmune liver diseases and hepatitis C), 2 liver transplant recipients (Still alive as of the end of the study), and 37 with <2 measurements of TB and INR. A total of 194 patients were included in the subsequent analyses. Among the 194 patients, the average age was 51.39±12.44 years old, with the majority being male (154 cases, 79.38%) and 40 being female (20.62%). Among these 194 patients, 160 (82.47%) had cirrhosis, and the most common complication was ascites (135 patients, 69.58%), followed by bacterial infection (70 patients, 36.08%). According to the ACLF grading system, there were 142 cases of ACLF grade 1, 41 cases of grade 2, and 11 cases of grade 3. During hospitalization, 94 patients received artificial liver support treatment. Among those who received artificial liver support treatment, the median number of treatments was 2, with an average of 2.5 times. The maximum number of artificial liver treatments received by the patients was five. During follow-up, 71 patients died within 28 days after admission (36.60%), and 86 died within 90 days after admission (44.33%), see Table 1.

Trajectory Model Construction and Distribution of Each Trajectory Group

An analysis of 1380 measurements of bilirubin and INR values was conducted, and a new scoring index was computed using the formula 0.741 INR+0.003TB. Given the formula being utilized, the inclusion of age in the scoring formula (0.741*INR+0.523*HBV-SOFA+0.026*age+0.003*TB) remains constant throughout the progression of the disease. Additionally, due to the retrospective nature of the analysis, we are unable to account for the dynamic changes in Hepatitis B virus-related Sequential Organ Failure Assessment (HBV-SOFA) scores. Therefore, in this study, we will employ the simplified formula of 0.741 INR+0.003TB. Trajectory models for bilirubin, INR, and the new index were separately constructed using a LCMM (Figure 1–3). Figures 1–3 illustrate the fitting process of bilirubin, INR, and combined indices from linear, quadratic to cubic models. All three indices achieved the best fitting performance with the cubic model; thus, the cubic fitting results were used as the basis for trajectory grouping. The parameters from the fitting process are presented in Supplementary Tables S1-S3. Based on the literature, it is believed that the trajectory model of the new index better reflects the progression of HBV-ACLF. Among the trajectory models, the cubic fitting model yielded

Table 1 Basic Information of Patients

	Total Patients (194)
Age	51.39 (±12.44)
Gender	
Male	154 (79.38%)
Female	40 (20.62%)
Cirrhosis	
Yes	160 (82.47%)
No	34 (17.53%)
Complications	
Ascites	135(69.58%)
Bacterial infection	70(69.58%)
ACLF grade	
Grade 1	142(73.20%)
Grade 2	41(21.135)
Grade 3	11(5.67%)
Artificial Liver Support therapy	
Yes	94(48.45%)
No	100(51.55%)
28-day prognosis	
Alive	123(63.40%)
Dead	71(36.60%)
90-day prognosis	
Alive	108(55.67%)
Dead	86(44.33%)

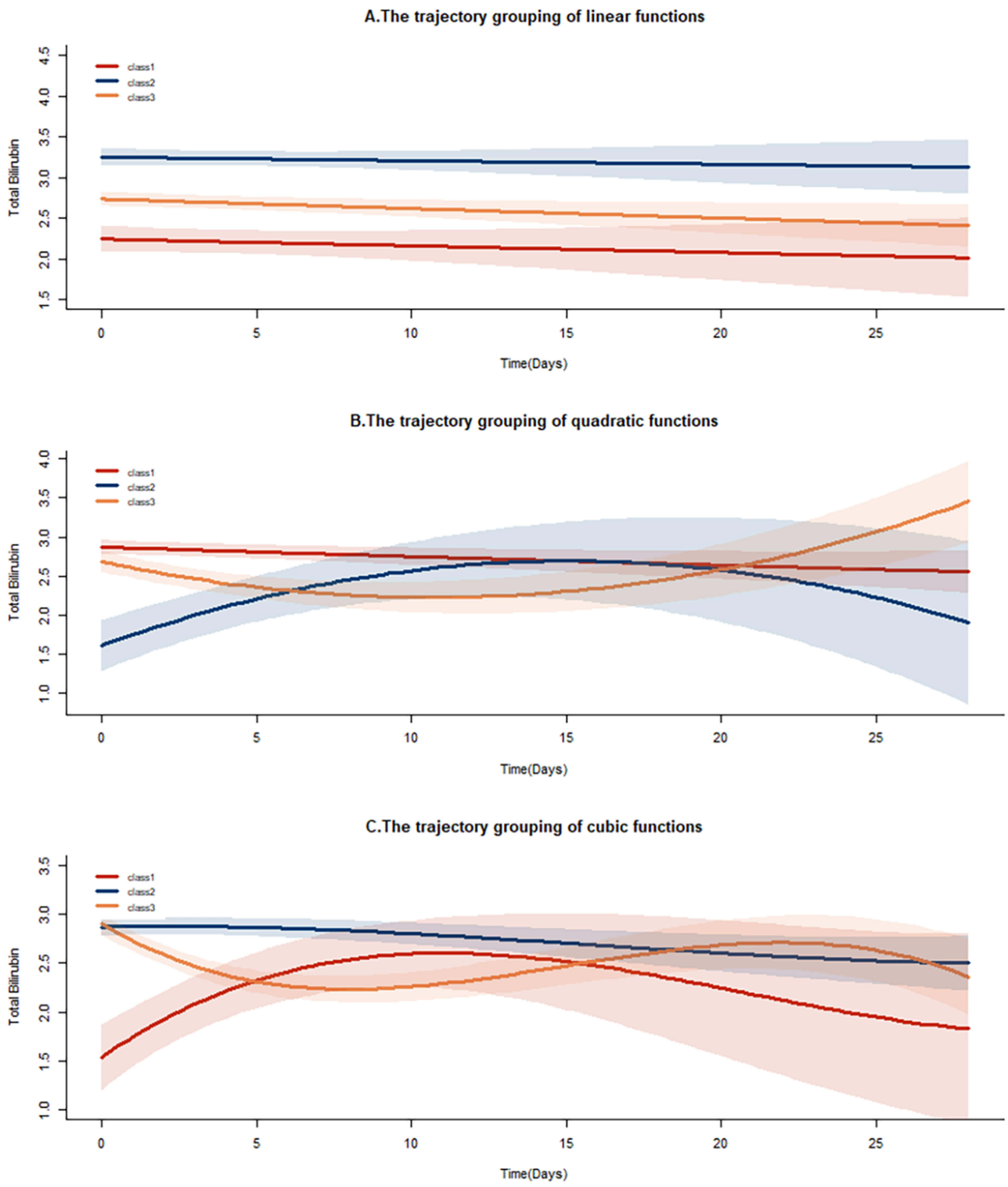

Figure 1 The trajectory curves of serum bilirubin after fitting. (**A**) represents a linear trajectory curve, (**B**) represents a quadratic trajectory curve, and (**C**) represents a cubic trajectory curve.

the best result.[1] Therefore, we selected the cubic fitting curve of the new index for subsequent analyses. The curves were named the declining group (class 1), stable group (class 2), and fluctuating group (class 3). The declining group included 32 cases (16.49%), the stable group 109 cases (56.19%), and the fluctuating group 53 cases (27.32%). Significant intergroup differences were observed in the CTP score, MELD score, MELD-Na score, CLIF-OFs, COSSH ACLFs, and

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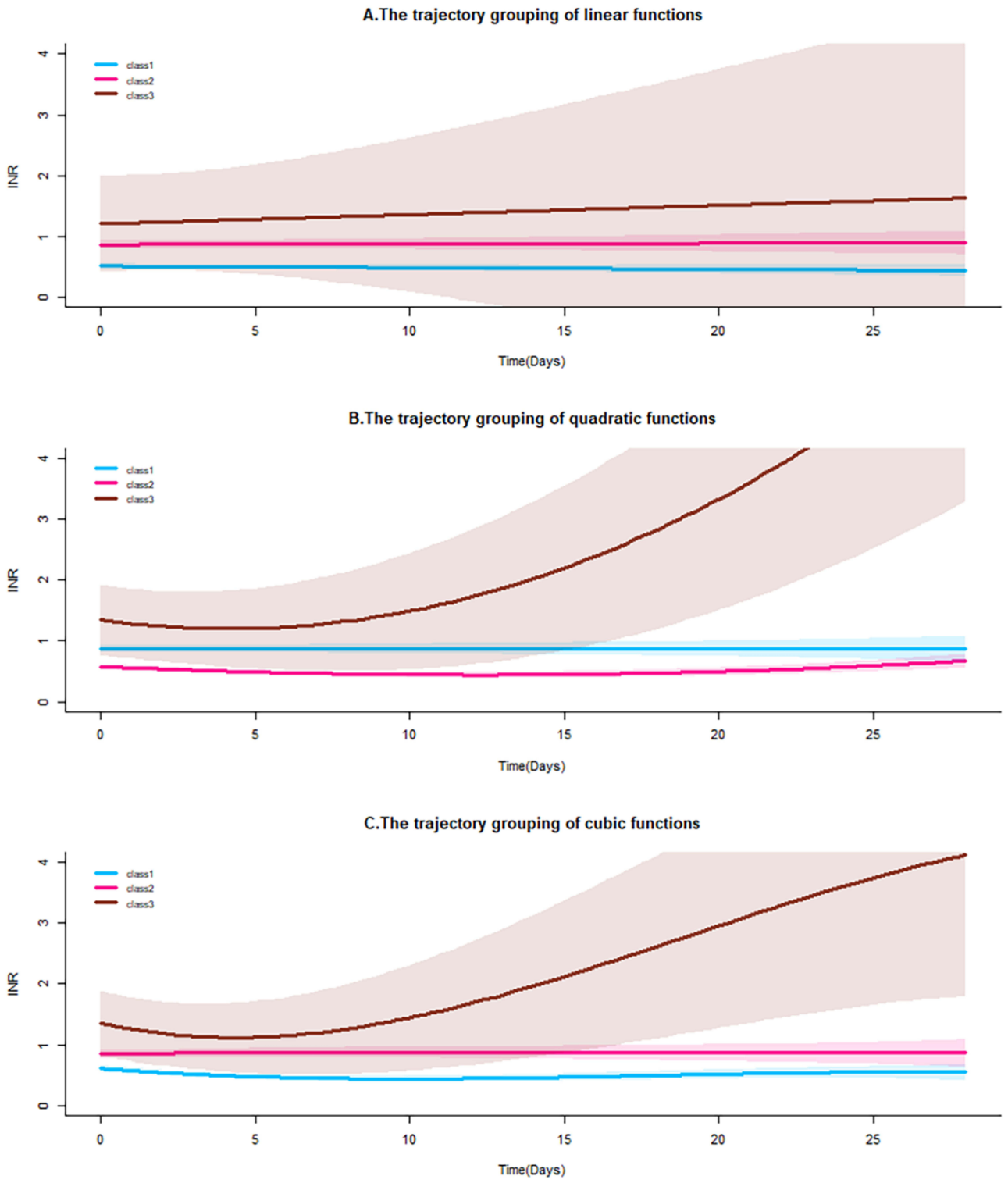

Figure 2 International normalized ratio (INR) fitted trajectory curves. (**A**) is a linear trajectory curve, (**B**) is a quadratic trajectory curve, and (**C**) is a cubic trajectory curve.

ACLF grade (P <0.05), with no intergroup differences in CLIF-CACLF scores (P=0.056). Regarding the ACLF grade, 142 cases (73%) were classified as grade 1, 41 cases (21%) as grade 2, and 11 cases (6%) as grade 3. Significant intergroup differences were observed in ACLF grades within the trajectory groups (P=0.009). All 3 groups showed statistically significant differences in terms of artificial liver support treatment as well as 28- and 90-day mortality rates,

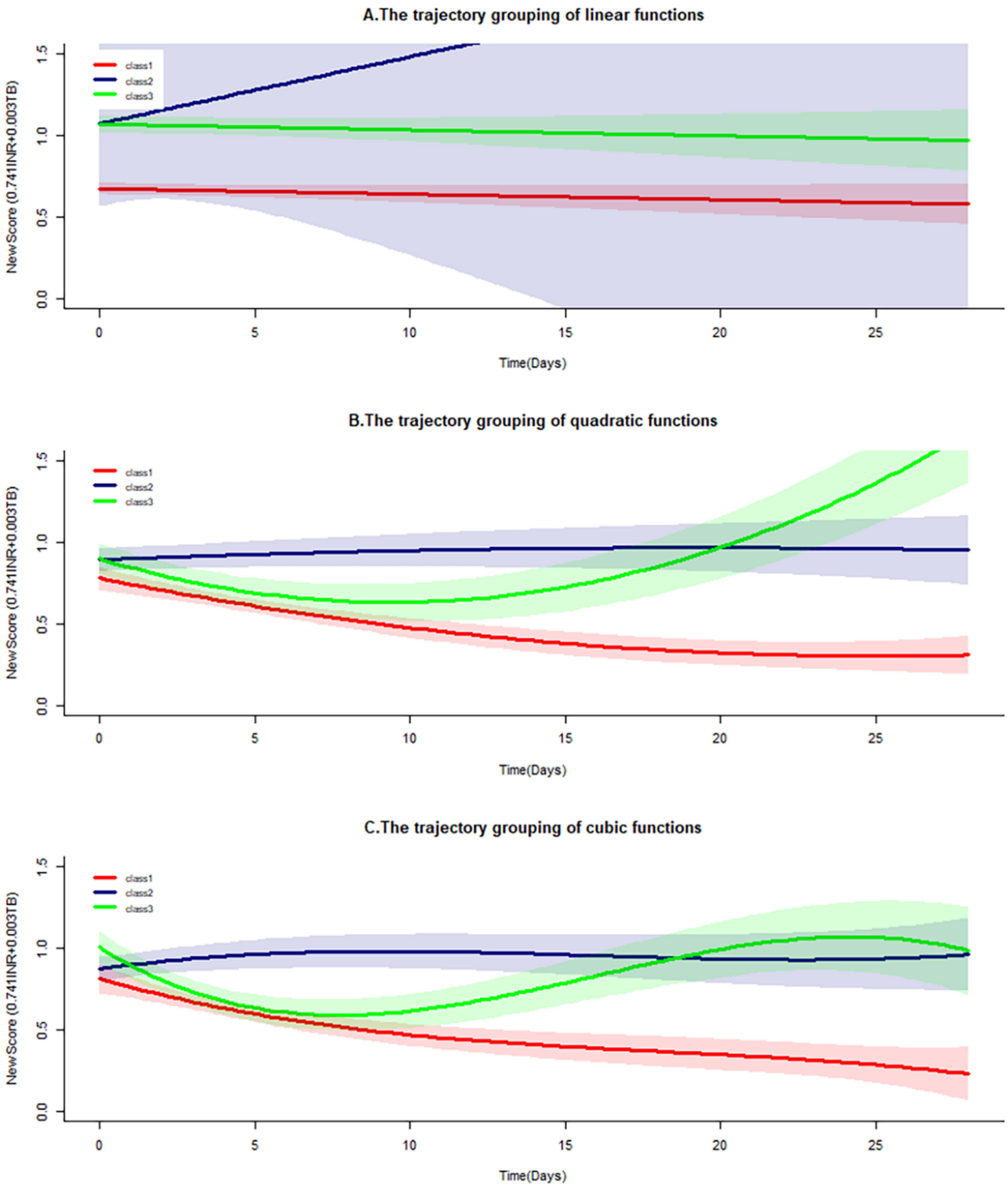

Figure 3 The trajectory curves based on the new index constructed with the international normalized ratio (INR) and bilirubin (0.741 × INR + 0.003 × TB). (**A**) represents a linear trajectory curve, (**B**) represents a quadratic trajectory curve, and (**C**) represents a cubic trajectory curve.

as detailed in Table 2. The prognosis differed among the three trajectory groups, with the declining group showing better outcomes compared to the other two groups. Additionally, the effectiveness of artificial liver support treatment also varied among the trajectory groups. In both the stable and fluctuating groups, artificial liver support treatment did not improve prognosis and could worsen the condition, leading to poor outcomes.

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Table 2 Distribution of Trajectory Groups

Variable	Overall, N = 194[a]	Decline Group N = 32	Stable Group N = 109	Fluctuation Group N = 53	p-value[b]
Gender					0.14
Male	154 (79%)	28 (88%)	81 (74%)	45 (85%)	
Female	40 (21%)	4 (12%)	28 (26%)	8 (15%)	
Age	50 (42, 60)	48 (42, 57)	51 (44, 61)	50 (40, 60)	0.2
Artificial liver support therapy					<0.001
No	100(52%)	13(41%)	77(71%)	10(19%)	
Yes	94(48%)	19(59%)	32(29%)	43(81%)	
Number of artificial liver support therapy	0(0,2)	0(0,3)	0(0,1)	2(1,3)	<0.001
CTP	11(10,12)	11(10,11.25)	11(10,13)	11(10,12)	0.004
MELD	21.5 (19.1, 25.3)	20.5 (19.2, 21.4)	23.0 (18.7, 27.4)	21.7 (19.4, 24.1)	0.009
MELD-Na	22 (19, 27)	21 (19, 22)	24 (19, 30)	22 (20, 25)	0.019
CLIF-OFs	9(8,10)	8(8,9)	9(8,10)	9(8,10)	0.005
CLIF-CACLFs	41 (36, 48)	39 (36, 42)	42 (37, 48)	41 (37, 50)	0.056
COSSH-ACLFs	4.10 (3.46, 5.17)	3.56 (3.28, 3.80)	4.47 (3.61, 5.73)	4.12 (3.41, 5.04)	<0.001
ACLF grade					0.009
1	142 (73%)	31 (97%)	73 (67%)	38 (72%)	
2	41 (21%)	1 (3%)	29 (27%)	11 (21%)	
3	11 (6%)	0 (0%)	7 (6%)	4 (7%)	
28-day prognosis					<0.001
Alive	123(63%)	31(97%)	59(54%)	33(62%)	
Death	71(37%)	1(3%)	50(46%)	20(38%)	
90-day prognosis					<0.001
Alive	108(56%)	30(94%)	48(44%)	30(57%)	
Death	86(44%)	2(6%)	61(56%)	23(43%)	

Notes: [a]n (%); Median (IQR); [b]Pearson's Chi-squared test; Kruskal–Wallis rank sum test; Fisher's exact test.

Abbreviations: CTP, CTP score; MELD, Model for End-Stage Liver Disease; MELD-Na, Model for End-Stage Liver Disease with serum sodium; CLIF-OFs, Chronic Liver Failure-Organ Failure score; CLIF-C ACLFs, Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure score; COSSH-ACLFs, Chinese Group on the Study of Severe Hepatitis B-Acute-on-Chronic Liver Failure score.

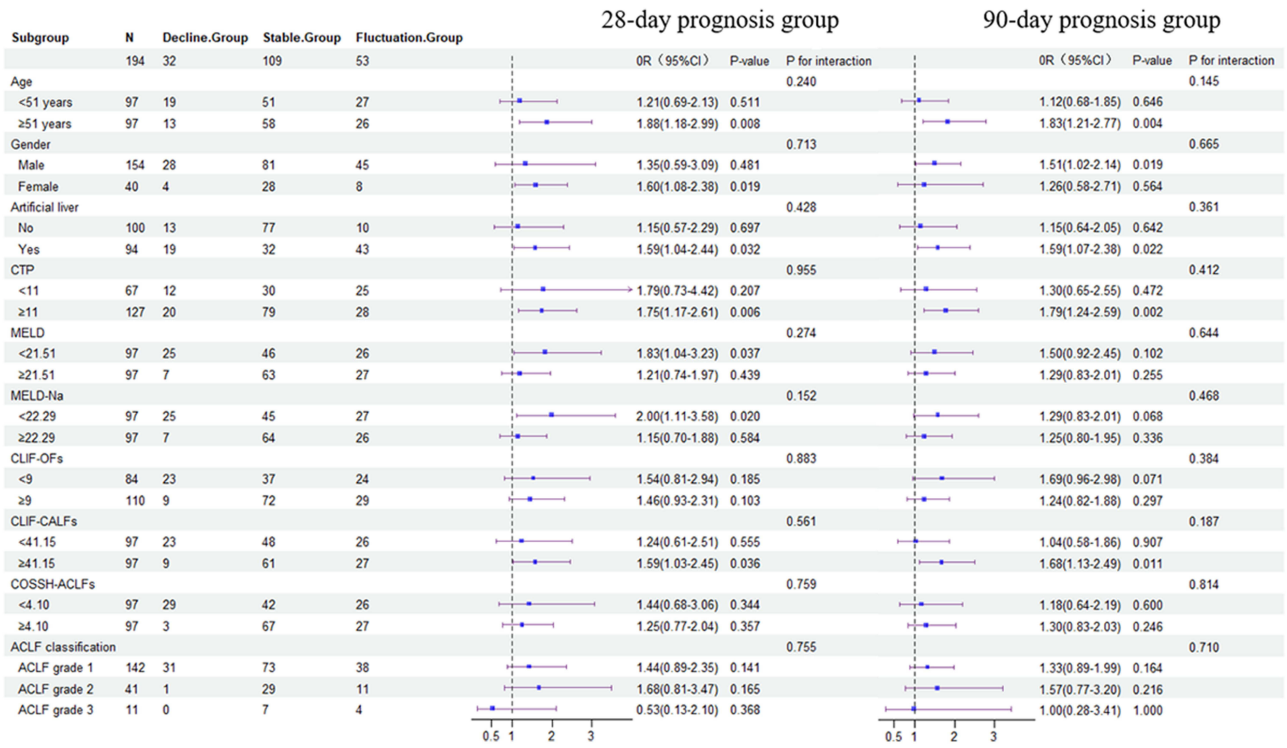
Subgroup Analyses Based on Trajectory Grouping

Age, CTP score, MELD score, MELD-Na score, CLIF-OFs, CLIF-CALFs, and COSSH-ACLFs were divided into two groups based on the median values. A Cox regression analysis was performed to calculate the prognosis of each group within the trajectory grouping, and the results were visualized using a forest plot (Figure 4).

In the group ≥51 years old, both the 28-day and 90-day prognoses were consistently worse, indicating a poorer overall prognosis regardless of the follow-up duration. Within the age subgroups, females exhibited worse prognoses at 28 days than males, whereas males had a worse prognosis at 90 days than females. In patients with CLIF CALFs ≥ 41.15, the prognosis is significantly better than in the group with scores < 41.15. Furthermore, patients who received artificial liver support treatment had unfavorable prognoses at both 28 and 90 days. Patients with MELD scores < 21.51 and MELD-Na scores < 22.59 have a better 28-day prognosis compared to those with scores ≥ 21.51 and ≥ 22.59. Within the CTP score ≥11 group, both the 28-day and 90-day prognoses were unfavorable. No significant differences in prognosis were observed between the remaining factors. The forest plot (Figure 4) visually represents the differential prognoses among the trajectory groups and provides valuable insights into the impact of various factors on the prognosis of patients with ACLF.

The Prognosis of the Descending Group is the Best

In the 28-day follow-up, 71 patients died, including 1 case (1.41%) in the declining group, 50 cases (70.42%) in the stable group, and 20 cases (28.17%) in the fluctuating group. Patients in the declining group had a better prognosis than the stable group and the fluctuating group. Compared to the declining group, the stable group had a worse prognosis



Subgroup	N	Decline.Group	Stable.Group	Fluctuation.Group	0R（95%CI）	P-value	P for interaction	0R（95%CI）	P-value	P for interaction
	194	32	109	53						
Age							0.240			0.145
<51 years	97	19	51	27	1.21(0.69-2.13)	0.511		1.12(0.68-1.85)	0.646	
≥51 years	97	13	58	26	1.88(1.18-2.99)	0.008		1.83(1.21-2.77)	0.004	
Gender							0.713			0.665
Male	154	28	81	45	1.35(0.59-3.09)	0.481		1.51(1.02-2.14)	0.019	
Female	40	4	28	8	1.60(1.08-2.38)	0.019		1.26(0.58-2.71)	0.564	
Artificial liver							0.428			0.361
No	100	13	77	10	1.15(0.57-2.29)	0.697		1.15(0.64-2.05)	0.642	
Yes	94	19	32	43	1.59(1.04-2.44)	0.032		1.59(1.07-2.38)	0.022	
CTP							0.955			0.412
<11	67	12	30	25	1.79(0.73-4.42)	0.207		1.30(0.65-2.55)	0.472	
≥11	127	20	79	28	1.75(1.17-2.61)	0.006		1.79(1.24-2.59)	0.002	
MELD							0.274			0.644
<21.51	97	25	46	26	1.83(1.04-3.23)	0.037		1.50(0.92-2.45)	0.102	
≥21.51	97	7	63	27	1.21(0.74-1.97)	0.439		1.29(0.83-2.01)	0.255	
MELD-Na							0.152			0.468
<22.29	97	25	45	27	2.00(1.11-3.58)	0.020		1.29(0.83-2.01)	0.068	
≥22.29	97	7	64	26	1.15(0.70-1.88)	0.584		1.25(0.80-1.95)	0.336	
CLIF-OFs							0.883			0.384
<9	84	23	37	24	1.54(0.81-2.94)	0.185		1.69(0.96-2.98)	0.071	
≥9	110	9	72	29	1.46(0.93-2.31)	0.103		1.24(0.82-1.88)	0.297	
CLIF-CALFs							0.561			0.187
<41.15	97	23	48	26	1.24(0.61-2.51)	0.555		1.04(0.58-1.86)	0.907	
≥41.15	97	9	61	27	1.59(1.03-2.45)	0.036		1.68(1.13-2.49)	0.011	
COSSH-ACLFs							0.759			0.814
<4.10	97	29	42	26	1.44(0.68-3.06)	0.344		1.18(0.64-2.19)	0.600	
≥4.10	97	3	67	27	1.25(0.77-2.04)	0.357		1.30(0.83-2.03)	0.246	
ACLF classification							0.755			0.710
ACLF grade 1	142	31	73	38	1.44(0.89-2.35)	0.141		1.33(0.89-1.99)	0.164	
ACLF grade 2	41	1	29	11	1.68(0.81-3.47)	0.165		1.57(0.77-3.20)	0.216	
ACLF grade 3	11	0	7	4	0.53(0.13-2.10)	0.368		1.00(0.28-3.41)	1.000	

Figure 4 Subgroup forest plots for the 28- and 90-day prognoses based on trajectory grouping.

(OR19.18, CI 2.64–138.90, P=0.003), and the fluctuating group had a higher risk (OR 14.91, CI 2.00–111.10, P=0.008). Patients with scores greater than or equal to the median were classified into the high-score group, while those below the median were classified as the low-score group. The declining group had more patients with low scores, whereas the stable group had a higher proportion of patients with high scores. The distribution of the patients in the fluctuating group was similar to that in the stable group.

In the 90-day follow-up, 86 patients died, including 2 cases (2.33%) in the declining group, 56 cases (65.12%) in the stable group, and 23 cases (23.26%) in the fluctuating Group. Compared to the declining group, the stable group had a worse prognosis (OR 12.53, CI 3.06–51.29, P <0.001), and the fluctuating group also had a higher risk (OR 8.83, CI 2.08–37.45, P=0.003). Both the stable and fluctuating groups have decreased OR for the 90-day prognosis, but the fluctuating group has a better prognosis compared to the stable group.

Differences in the Treatment Effectiveness of Artificial Liver Support in Various Trajectory Groups

Among the patients included in the analysis, 94 received artificial liver support treatment, with a median number of treatments of 2. Within the trajectory groups, 19 individuals in the declining group underwent artificial liver support treatment, with a median of 2 treatments; 32 individuals in the stable group received a median of 2 treatments; and 43 individuals in the fluctuating group received a median of 3 treatments. A regression analysis revealed that the receipt of artificial liver support treatment was unrelated to the 28-day (P=0.100) and 90-day (P=0.344) prognoses. In the 28-day prognosis analysis of the stable group, the receipt of artificial liver support treatment emerged as a risk factor for the prognosis (OR 2.16, 95% CI 1.23–3.79, P=0.007). The presence or absence of artificial liver support treatment had no marked influence on the prognosis in the other groups (Table 3).

To further explore the impact of artificial liver support treatment on trajectory grouping indicators, changes in bilirubin and INR values were visualized using line graphs (Figure 5–7). In the declining group, both bilirubin and INR values continued to decrease, regardless of whether or not artificial liver support treatment was administered. In the

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Table 3 Impact of Artificial Liver Therapy on the Prognosis of Trajectory Subgroups

	28-Day			90-Day		
	OR	**95% CI**	**P-value**	**OR**	**95% CI**	**P-value**
With or without artificial liver support therapy						
Total	1.48	0.93–2.37	0.100	1.24	0.80–1.87	0.344
Declining Group	<0.001	0.00-Inf	1.000	0.68	0.04–10.87	0.785
Stable Group	2.16	1.23–3.79	0.007	1.58	0.94–2.67	0.086
Fluctuating Group	5.44	0.73–40.67	0.099	6.67	0.90–49.50	0.064
No. of artificial liver support therapy (≥3)						
Total	1.46	0.68–0.88	0.143	1.57	0.99–2.49	0.055
Declining Group	-	-	-	-	-	-
Stable Group	0.75	0.30–1.86	0.538	0.92	0.39–2.20	0.857
Fluctuating Group	2.44	0.88–6.80	0.087	3.32	1.22–9.03	0.019

Abbreviations: OR, Odds Ratio; 95% CI, 95% Confidence interval.

stable group, regardless of treatment, both bilirubin and INR values remained relatively stable In addition, the treatment group exhibited a fluctuating trend compared with the non-treatment group, but without a declining trend. In the fluctuating group, bilirubin and INR values displayed significant fluctuations, with bilirubin showing a more pronounced amplitude of variation than INR.

Using a cutoff of three-fold the number of artificial liver support treatments, two groups were created. A regression analysis revealed that, in the fluctuating group, receiving ≥3 treatments of artificial liver support therapy was a risk factor for the 90-day prognosis (OR 3.32, CI 1.22–9.03, P=0.019). There were no significant differences between the other groups (Table 2).

Trajectory Grouping Enhances the Predictive Accuracy of Liver Scoring Systems

Based on the receiver operating characteristic (ROC) curve visualization, the prognostic efficacy of various scoring systems for 28- and 90-day outcomes was able to be determined. The predictive performance of the scoring systems combined with trajectory grouping is illustrated in Figure 8. The combination of CTP, MELD, MELD-Na, CLIF-OFs, CLIF-CACLFs, and COSSH-ACLFs with trajectory grouping enhanced the predictive accuracy of these prognostic scores.

Discussion

This study analyzed the trajectory of bilirubin and INR changes within 28 days of admission for patients with ACLF. Based on the HBV-ACLF prognosis scoring model, a new index was constructed by considering dynamic changes in bilirubin and INR. Using this new index, three groups with different clinical phenotypes were identified, and patients in the different trajectory groups exhibited varying prognoses. The analysis revealed that patients in the declining group had the best prognosis, followed by those in the fluctuating group, while the stable group had the poorest prognosis. Both serum bilirubin and INR have been identified as independent prognostic risk factors for HBV-ACLF, leading to the development of various prognostic models. However, these models are primarily based on baseline data at admission and do not consider individual variations or the dynamic nature of disease progression.

Building upon the HBV-ACLF prognosis scoring model developed by the Lan-juan Li team, the novel index 0.741*INR + 0.003 *TB was formulated to indirectly reflect the evolution of the disease through dynamic changes in this index.[1] By fitting trajectories, this study identified three distinct trajectory distributions for INR and TB changes in ACLF patients. Further analyses revealed significant differences in the prognosis based on the trajectory grouping. The declining group exhibited the best prognosis, consistently reflecting lower scores in several metrics, such as MELD and MELD-Na. Conversely, the stable group demonstrated the poorest prognosis and the highest scores in relevant metrics. Our findings suggest that a stable and unchanging state of the INR and TB does not necessarily indicate disease stability;

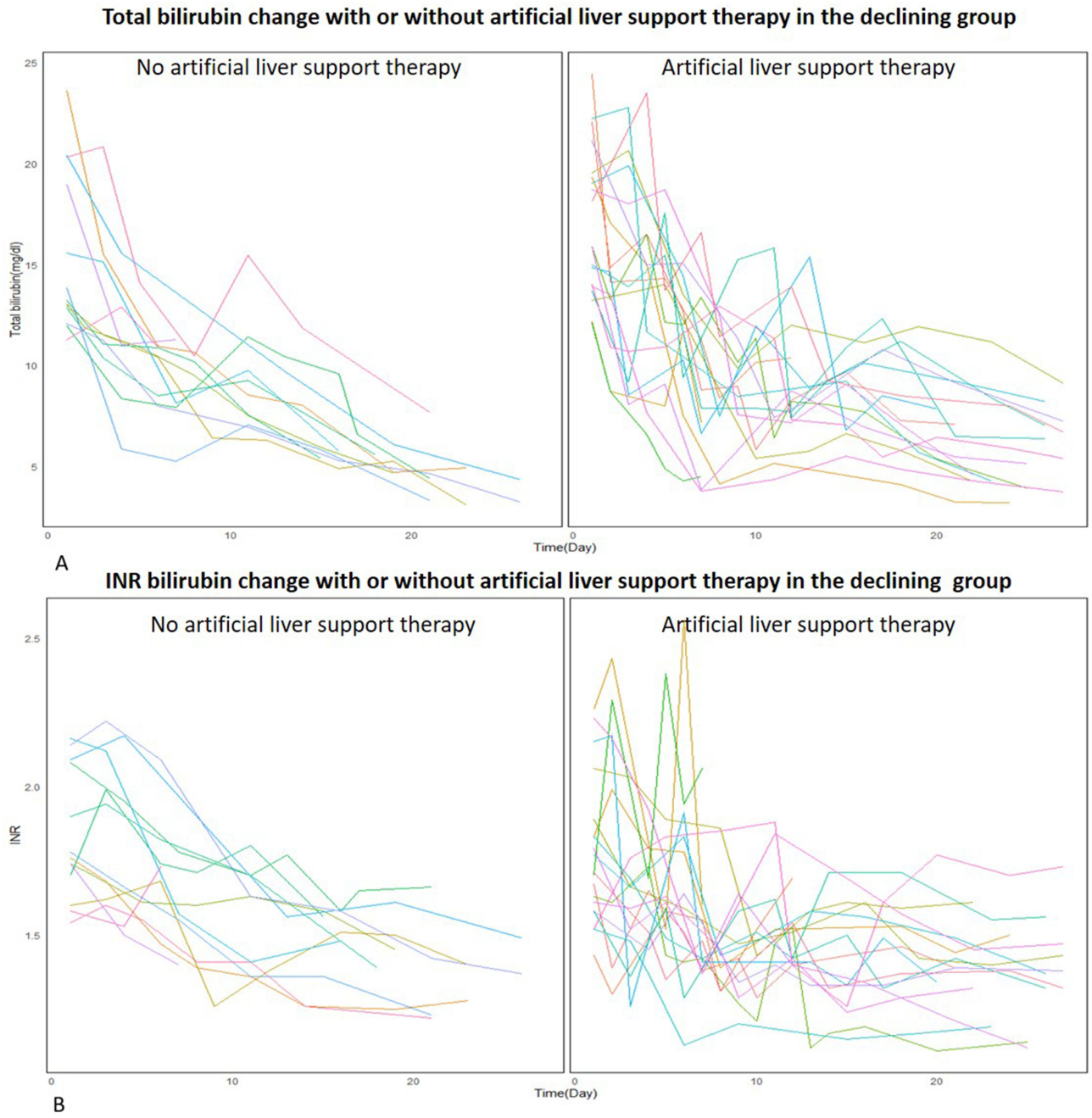

Figure 5 Timeline plots of bilirubin and the international normalized ratio (INR) in the declining group in patients with and without artificial liver therapy. (**A**) Timeline plots of bilirubin in the group with or without artificial liver treatment; (**B**) timeline plots of INR in the group with or without artificial liver treatment.

instead, it may actually indicate a poor prognosis. Furthermore, this approach better captures a patient's prognosis than cross-sectional data, providing more effective guidance for clinical treatment decisions.

Through our subgroup analyses, we discovered that within trajectory groups, higher-score groups exhibited worse prognoses according to the CTP score, CLIF-OFs, and CLIF-CALFs. However, while high MELD and MELD-Na scores showed no significant correlation with the prognosis ($P > 0.05$), marked differences in prognoses were present for low scores ($P < 0.05$). Based on this observation, we speculated that this phenomenon might be attributed to the lower weight assigned to the INR in the MELD and MELD-Na scores than with other scores. The index used in our trajectory fitting places a higher weight on the INR and a lower weight on the TB. This is because the COSSH-ACLFs considers coagulation failure more common.[1]

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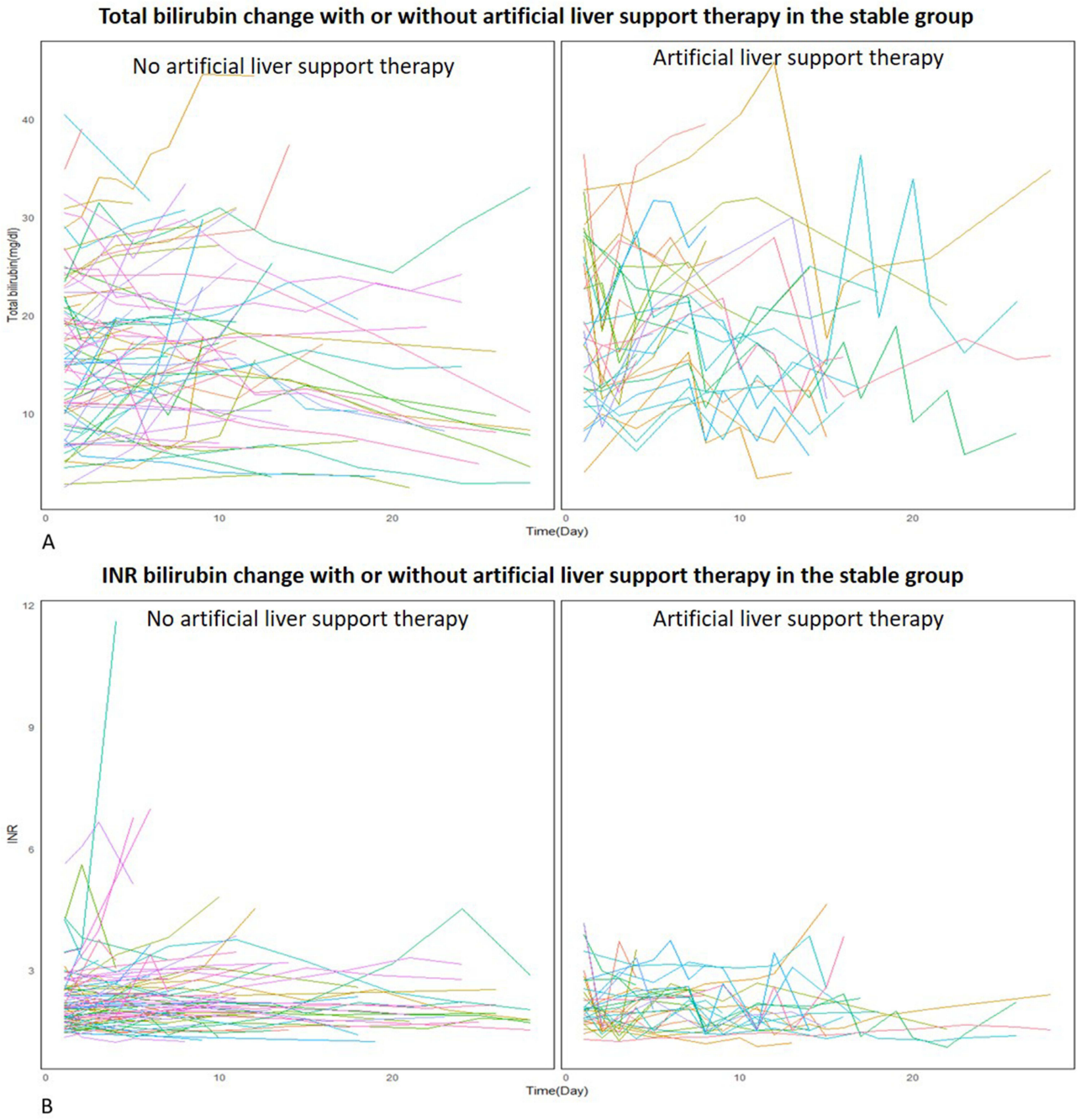

Figure 6 Timeline plots of bilirubin and the international normalized ratio (INR) in the stable group in patients with and without artificial liver therapy. (**A**) Timeline plots of bilirubin in the group with or without artificial liver treatment; (**B**) timeline plots of INR in the group with or without artificial liver treatment.

Thus, in this scoring system, the weight coefficient for INR is 0.741, whereas that for TB is 0.003, which forms the basis for our index calculation.[1] In addition, ACLF grading was not correlated with the prognosis, possibly due to the sample size included in our study. Further validation is necessary for confirmation, as this requires further investigation.

The incidence of ACLF is high, and so are the short-term mortality rates.[15] Early and effective recognition of ACLF is crucial for improving prognosis.[16] The challenge lies in the disease's rapid progression from a chronic state to acute failure, which hampers timely intervention in clinical practice, often resulting in suboptimal treatment outcomes.[16,17] However, with timely and effective management, some patients can achieve a relatively stable phase. Current treatments for ACLF primarily include medical therapy, artificial liver support therapy, liver transplantation, stem cell therapy, and granulocyte colony-

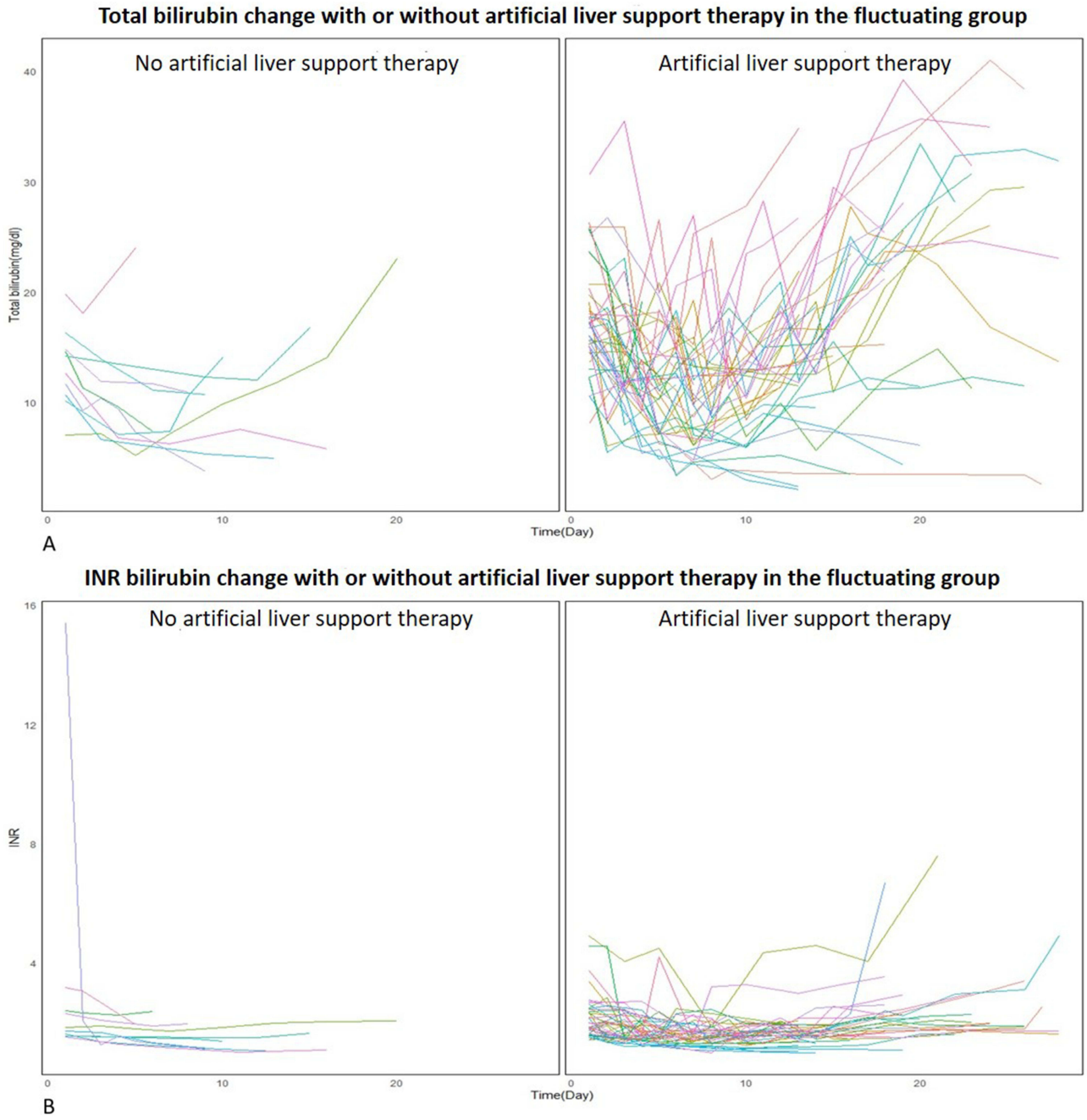

Figure 7 Timeline plots of bilirubin and the international normalized ratio (INR) in the fluctuating group in patients with and without artificial liver therapy. (**A**) Timeline plots of bilirubin in the group with or without artificial liver treatment; (**B**) timeline plots of INR in the group with or without artificial liver treatment.

stimulating factor.[18] Among these, artificial liver support therapy, particularly plasma exchange, is the most widely utilized.[19] Nonetheless, there is ongoing debate about its efficacy in improving ACLF prognosis.[20] Several studies have demonstrated that artificial liver support therapy can reduce mortality;[21,22] for instance, a trial by Qin et al on HBV-ACLF patients showed that plasma exchange improved both short- and long-term outcomes compared to standard medical treatment.[21,23]

Conversely, some studies have reported that artificial liver support therapy does not enhance ACLF prognosis.[20,24] A large multicenter randomized controlled trial in Europe found no significant improvement in outcomes with artificial liver support.[25] Our study also concluded that while theoretically promising, artificial liver support therapy did not improve patient prognosis. The latest US guidelines echo this, emphasizing the lack of a unified definition for ACLF and standardized management

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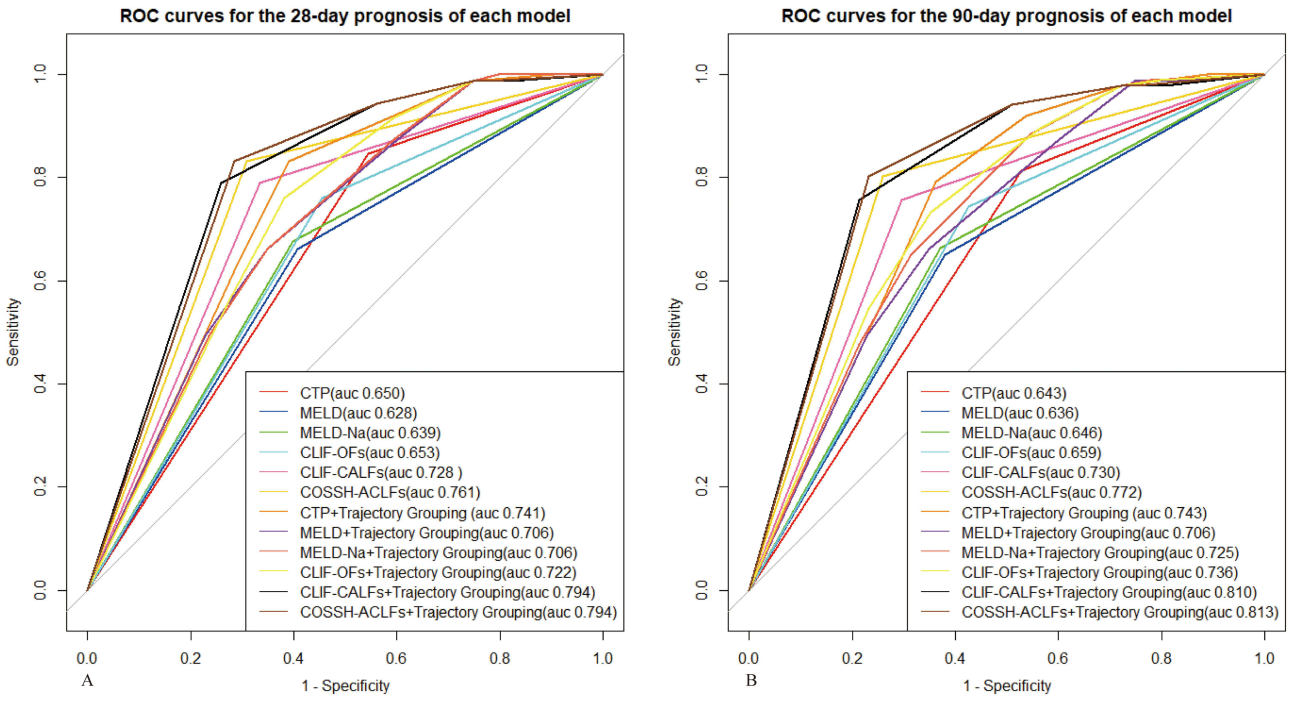

Figure 8 Receiver operating characteristic plots of the predictive effect of each predictive model for 28- and 90-day prognoses.

protocols, which limits data quality and general applicability.[26] A recent meta-analysis further indicated that standard medical treatment combined with artificial liver support does not improve survival rates.[26] Subgroup analyses revealed variations in the effectiveness of artificial liver support therapy among different patient groups. In the stable group, the therapy unexpectedly became a risk factor, doubling the mortality risk. Analysis of bilirubin levels and INR showed that, in the stable group receiving therapy, these indicators fluctuated without an overall decrease. Meanwhile, in the declining group, both indicators trended downward regardless of therapy. For the fluctuating group, most patients received therapy, which led to significant fluctuations in bilirubin levels without consistent improvement. Given these insights, we suggest that artificial liver support therapy might be unnecessary for the declining group, as it does not expedite improvement in indicators. In the stable group, therapy did not change the trend of bilirubin and INR levels. Our regression analysis showed higher mortality rates for patients in the stable group undergoing therapy compared to other groups, indicating limited benefit. Although artificial liver support can remove accumulated substances in ACLF patients, it does not address coagulation dysfunction. Therefore, for the stable group, it should not be the first-choice treatment, and its advantages and disadvantages must be carefully weighed. In the fluctuating group, bilirubin levels in patients receiving therapy fluctuated more noticeably than INR. Further analysis revealed that patients who received three or more treatments had a higher risk of poor 90-day outcomes, suggesting heightened sensitivity to therapy and its potential to exacerbate coagulation dysfunction. This finding underscores the need for tailored approaches in managing ACLF with artificial liver support therapy.

In China, the primary etiology of ACLF is chronic HBV infection.[1] HBV-ACLF is characterized by the early and frequent occurrence of coagulation dysfunction.[1] Although artificial liver support systems can adsorb various substances and mitigate their detrimental effects on the body, they do not address coagulation dysfunctions. Furthermore, research has indicated that artificial liver support may exacerbate coagulation dysfunction.[27] Therefore, the therapeutic efficacy of artificial liver support for HBV-ACLF requires further validation.

The present study employed the dynamic fitting of indicators, such as the INR and total bilirubin, to construct three trajectory-based subgroups, offering instructive guidance for the clinical management of HBV-ACLF. For patients in the declining group, we consider artificial liver support to be safe but nonessential, as it does not contribute to an improved prognosis. For patients in the stable and fluctuating groups, the decision to employ artificial liver support requires thorough consideration of pros and cons, with the aim of avoiding indiscriminate use. In a clinical context, the trajectory-

based groups proposed in this study could further enhance the optimization of scoring models for chronic liver diseases, thus augmenting the predictive effectiveness of these models. The improvement in predictive efficacy for COSSH-ACLF through trajectory grouping is limited, possibly due to the retrospective nature of this study, which hampers precise and consistent measurement of indicators. They could also assist in identifying high-risk patients and guide the implementation of appropriate treatment strategies, ultimately leading to an improved prognosis.

Several limitations of this study need to be highlighted. Firstly, it was conducted as a single-center, small-sample, retrospective investigation. The conclusions derived from this study require further validation through larger sample sizes, collaboration across multiple centers, and prospective studies for enhanced reliability and clinical applicability. Secondly, the indicators used to track patient trajectories were measured from the time of hospital admission. This timing may introduce bias because some patients were admitted after their disease had progressed. Thirdly, the complex nature of ACLF, involving both liver failure and coagulation dysfunction, adds another layer of complexity. While this study used total bilirubin and INR values as trajectory indicators to capture disease progression, the limitations inherent in retrospective studies, such as inconsistent measurement intervals, were unavoidable. Despite our stringent criteria to minimize asynchronous data, the need for prospective validation remains.

In conclusion, our research identified three distinct groups based on bilirubin and INR trajectories that showed significant differences in patient outcomes. The group with declining values had the best prognosis, while the stable group had the worst. Our findings emphasize the careful weighing of benefits and risks when considering artificial liver support for the stable and fluctuating groups, noting that indiscriminate use may not improve and might even worsen outcomes. Furthermore, employing dynamic trajectory analysis can improve the predictive accuracy of liver disease scoring models, aiding in identifying high-risk patients to enhance outcomes.

Ultimately, the practical implications of these findings can inform clinical treatment decisions. Dynamic monitoring of INR and total bilirubin should be considered an essential complement to existing scoring systems, aiming to better predict the prognosis for patients with HBV-ACLF.

Data Sharing Statement

Data supporting the findings of this study are available upon request from the corresponding author.

Ethics Statement

The study was ethically approved by the Ethics Committee of Taizhou Hospital affiliated to Wenzhou Medical University (K20220234), and informed consent was waived due to its retrospective nature and conducted in accordance with the 1964 helsinki Declaration.

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Disclosure

The authors declare no conflicts of interest in this work.

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