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ORIGINAL ARTICLE

A Predictive Framework for Acute Liver Failure Outcomes: Insights from Nonbiological Artificial Liver Treatment

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ABSTRACT

Background: **The aim of this study was to evaluate the efficacy of nonbiological artificial liver (NBAL) in the treatment of acute liver failure (ALF) and to screen prognostic predictors.**
Methods: **This study was a single-center retrospective observational study that included 186 ALF patients treated with NBAL (plasma exchange alone, DPMAS alone, or combination therapy). Laboratory parameters (TBil, INR, Cr, etc.) before and after 24 hours of treatment and 28-day and 90-day survival data were collected. Prognostic features were screened by XGBoost and Random Forest, independent risk factors were analyzed by Cox regression, and column-line plots were constructed.**
Results: **The 90-day poor prognosis group (mortality/liver transplantation) presented a significant high-risk phenotype as evidenced by a higher MELD score (34.46 vs. 29.84, $p < 0.001$), greater severity of hepatic encephalopathy (64.6% vs. 38.8% share of grades III - IV, $p < 0.001$), and concomitant overall deterioration in the indicators of hepatic and renal impairment (TBil, INR, and Cr) (all $p < 0.001$). The machine learning model further validated the predictive value of the dynamic metrics, with TBil% on day 1 of treatment with a decision-tree significance of 26.3%, significantly outperforming traditional baseline metrics (e.g., MELD score and TBil). Risk stratification based on median TBil% (14.26%) showed a 28-day all-cause mortality rate of 46.24% (vs. 10.75% in the low-risk group, $p < 0.001$) in the high-risk group and a 90-day survival of only 36.6% (vs. 75.3% in the low-risk group, $p < 0.0001$). Each 1% decrease in 24-hour TBil% increased the risk of mortality by 7% (HR = 0.93, $p < 0.001$), while baseline MELD score (HR = 1.07, $p < 0.001$) and 24-hour INR (HR = 1.70, $p < 0.001$) were independent risk factors.**
Conclusions: **Early TBil clearance in ALF treated with NBAL is a strong predictor of 90-day survival, and baseline MELD score and post-treatment INR are also independent risk factors.**
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KEYWORDS

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INTRODUCTION

Acute liver failure (ALF) is a clinical syndrome based on extensive necrosis or severe functional impairment of hepatocytes caused by a variety of etiologic factors. Clinical manifestations include hepatic encephalopathy, coagulation dysfunction (international normalized ratio [INR] ≥ 1.5), and multiorgan failure within 26 weeks of

onset of the disease [1]. Even though liver transplantation technology has progressed, providing some patients with a survival chance [2], challenges such as donor scarcity, high treatment costs, and postoperative complications still greatly hinder its clinical application [3], so there is an urgent clinical need to explore effective alternative treatment options.

The use of nonbiological artificial liver (NBAL) has gained importance in treating ALF with methods such as plasma exchange (PE) and dual plasma molecular adsorbent system (DPMAS), offering temporary liver detoxification, metabolism, and synthesis functions and buying time for hepatocyte regeneration or liver transplantation [4-6]. Even with treatment, there are individual differences in the clinical success of NBAL, with some patients still experiencing unfavorable outcomes like death or the necessity for a liver transplant. The use of ALF therapy currently hinges on the monitoring of laboratory metrics, including total bilirubin (TBil) and INR. In the short term, artificial liver support systems can significantly improve physiological indices like heart rate, mean arterial pressure, and respiratory index, while also reducing TBil and alanine aminotransferase (ALT) levels to some extent [4]. However, this approach has limitations in assessing treatment efficacy and fails to offer a comprehensive analysis of the dynamic response to treatment, such as early post-treatment changes in TBil clearance. In addition, the lack of multidimensional metrics, such as the comprehensive assessment of inflammatory response, metabolic status, and organ function, limits the accurate judgment of the overall patient condition. Tools such as the MELD score are extensively used for liver failure prognosis [7], yet they are based on baseline data and fail to include dynamic changes during treatment. Moreover, the MELD score is not as valuable as the chronic liver failure organ failure score for assessing patients with acute-on-chronic liver failure [8]. This suggests that the assessed value of the MELD score in different types of liver failure is not absolute.

Comprehensive analysis of dynamic treatment responses, like early post-treatment TBil clearance, and multidimensional metrics, including inflammation, metabolism, and organ function, is lacking to completely reflect the long-term clinical value of NBAL. In this study, machine learning algorithms (XGBoost, Random Forest) were used to screen baseline characteristics (age, MELD score) with early post-treatment metrics (change in 24-hour TBil%, INR), and a Cox regression-based column plot model was developed to achieve accurate prediction of 90-day survival.

MATERIALS AND METHODS

Subjects

This was a single-center retrospective observational study that included patients with ALF who were treated with NBAL between January 2020 and January 2025 at Organ Transplantation Center of the Affiliated Hospital of Qingdao University.

Inclusion criteria were the following: 1) patients who met the Asian Pacific Association for the Study of the Liver diagnostic criteria [9] (INR $\geq$ 1.5 with hepatic encephalopathy, duration of disease < 26 weeks); 2) patients aged 18 - 70 years; 3) patients who had completed $\geq$ 2 treatments (PE and DPMAS alone or in combination); 4) patients with complete laboratory data such as TBil/INR/creatinine (Cr) within 24 hours before and 24 hours after treatment and 28-day survival records. The screening process in the electronic medical record yielded 245 potential cases.

Exclusion criteria were as follows: 1) Patients who were pregnant or breastfeeding (n = 2); 2) patients with human immunodeficiency virus infection and other viral infections (n = 5); 3) patients with hepatocellular carcinoma and other malignant neoplasms (n = 5); 4) patients with any other serious extra-hepatic chronic disease, including severe renal, cardiac, respiratory, neurologic, or other systemic diseases (n = 10); 5) patients lacking timely follow-up and complete data (n = 37). Finally, 186 patients who met the requirements for analysis were included. In accordance with the Declaration of Helsinki, the study ensured data anonymity and received the Ethics Committee's approval from Organ Transplantation Center of the Affiliated Hospital of Qingdao University.

Treatment and follow-up

In addition to conventional medical and symptomatic supportive care, patients received NBAL regimen, which consists of three treatment modalities. The PE group experienced plasma exchange 1.0 - 1.5 times using fresh frozen plasma mixed with surrogate plasma, utilizing specific equipment and anticoagulated with low molecular weight heparin (anti-Factor Xa 0.3 - 0.5 IU/mL). The DPMAS group implemented 2.0 - 2.5 hours of treatment through a dedicated perfusion device, with blood flow controlled at 120 - 150 mL/minute, and an anticoagulation regimen consistent with that of the PE group. The combined treatment group (PE + DPMAS) implemented both modes sequentially, with intervals of no more than 4 hours, and with the same parameter settings as the single mode. All procedures were executed by certified hepatologists working alongside nurses with expertise in blood purification.

Data collection

This retrospective cohort study relied on the electronic medical record system for information collection. During the baseline period (24-hour window prior to NBAL treatment), baseline information was recorded, including demographic characteristics (age, gender), disease status (ascites, MELD score, ALF subtypes), as well as etiology (hepatitis virus, drug, alcohol, or other factors). Treatment modality was recorded.

Indicators of liver function were measured, including TBil, prothrombin activity (PTA), INR, ALT, and as-

partate aminotransferase (AST). Renal function was assessed by measuring Cr. Metabolic and inflammatory indicators, including lactate (arterial blood), C-reactive protein (CRP), procalcitonin (PCT), and neutrophil-lymphocyte ratio (NLR) were recorded. Data on TBil, INR, and Cr were collected 24 hours preoperatively and 1 day after treatment (i.e. 18 to 36 hours after the first treatment). MELD score was calculated as 3.78 × ln (TBil (mg/dL)) + 11.2 × ln (INR) + 9.57 × ln (Cr (mg/dL)) + 6.43 × (etiologic assignment: 0 for biliary or alcoholic cirrhosis, 1 for other causes of cirrhosis). The rate of change in TBil was calculated as (preoperative TBil - 24-hour postoperative TBil)/preoperative TBil. Improvement in MELD score was assessed by calculating ΔMELD, defined as preoperative MELD - 24-hour postoperative MELD, and rate of change in MELD score was expressed as MELD% = ΔMELD/preoperative MELD.

The primary endpoint was the survival endpoint, 90-day transplantation-free survival (time from enrollment to "undergoing graft transplantation" or "death"). The inherent missing data issue was addressed by prioritizing a multiple imputation reconstruction strategy. Endpoint assessment was conducted with ensured objectivity and reproducibility. Secondary endpoints were 28-day all-cause mortality and the incidence of serious complications related to NBAL treatment itself or progression of ALF (including severe bleeding, severe allergic reactions, line coagulation, hemodynamic instability requiring intervention, etc.).

Statistical analysis

SPSS 26.0 was used for statistical analysis. Measurements were tested for normality, and those with a normal distribution were expressed as mean ± standard deviation (SD) and compared using Student's *t*-test. Non-normal distribution data were expressed as median and interquartile range M (IQR) and compared using the Mann-Whitney U test. Enumeration data were expressed as number of cases (percentage) and compared using the chi-squared test. XGBoost, Random Forest, and Decision Tree classification were used to find characteristic independent variables. Patients were grouped into high-risk and low-risk groups and analyzed for 28-day all-cause mortality and serious adverse complications. Patients' 90-day mortality/transplantation were plotted and analyzed using Kaplan Meier curves. Based on the first 10 significant characteristics, independent variables with high covariance (variance inflation factor > 5) were excluded, followed by Cox regression risk analysis using R software version 4.2.1. Column line plots were constructed using the R package "RMS".

RESULTS

Clinical baseline of patients

Out of the 186 patients with ALF in this study, 103 (55.4%) achieved 90-day survival (good prognosis group) and 83 (44.6%) experienced death or liver transplantation (poor prognosis group). In the poor prognosis group, the average age was significantly higher (52.50 vs. 48.50 years old, $p = 0.047$). This group also exhibited more severe disease, as evidenced by a higher MELD score (34.46 vs. 29.84, $p < 0.001$) and a higher percentage of severe hepatic encephalopathy cases (64.6% at grade III - IV vs. 38.8%, $p < 0.001$). More significant hepatic and renal impairments were observed in the poor prognosis group, with increased TBil (423.05 vs. 353.98 μmol/L, $p < 0.001$), INR (2.87 vs. 2.42, $p = 0.001$), and Cr (167.72 vs. 138.93 μmol/L, $p < 0.001$). AST was lower in the good prognosis group (148.00 U/L vs. 196.00, $p = 0.004$). In contrast, gender ($p = 0.576$), ascites ($p = 0.120$), ALF subtype ($p = 0.835$), etiologic distribution ($p = 0.791$), treatment regimen ($p = 0.739$), PCT, and NLR were not statistically different between the two groups (Table 1).

Machine learning model´s screen feature components

XGBoost, Random Forest, and Decision Tree classification results showed that early treatment response metrics were the core drivers of prognostic prediction, with the percentage of TBil reduction on day 1 of treatment (1 day TBil%) showing the highest significance in all three models (Decision Tree: 26.3%, XGBoost: 17.1%, and Random Forest: 16.6%). MELD score (Decision Tree: 16.7%, XGBoost: 7.5%) and TBil (Decision Tree: 7.2%, XGBoost: 6.6%) were of moderate predictive value, whereas hepatic encephalopathy classification was only significant in Random Forest (5.0%). Notably, clinical characteristics such as treatment pattern, etiology, and gender had an importance of less than 1.1% (near-zero contribution) in all models, and the importance of dynamic metrics (1 day Tbil%, 1 day MELD) generally exceeded their baseline counterparts, highlighting the clinical predictive advantages of early treatment response monitoring.

On the visualized data (Figure 1), the poor prognosis group had a lower Tbil% (12.06 [IQR 5.36 - 15.43] vs. 17.23 [11.27 - 24.02], $p < 0.001$) and a higher MELD score (median 4.45 [2.90 - 6.29] vs. 3.16 [1.43 - 5.09], $p = 0.008$), compared to the good prognosis group. There was no statistically significant difference in ΔMELD scores between the two groups (median 28.14 [24.82 - 31.42] vs. 28.98 [23.04 - 35.23], $p = 0.480$).

28-day all-cause mortality and adverse complications based on risk stratification by key characteristics

Risk stratification based on the median Tbil% of 14.26% on day 1 of treatment showed (Table 2): the high-risk group presented significantly worse 28-day clinical outcomes compared to the low-risk group - a surge in all-cause mortality of 4.3-fold (46.24% vs. 10.75%, $p < 0.001$) and hemodynamic instability (18.28% vs. 7.53%, $p = 0.029$). Meanwhile, there was a trend toward higher severe coagulation events in the

Table 1. Baseline characteristics of the study population.

Variables	Total (n = 186)	Good prognosis (n = 103)	Poor prognosis (n = 83)	p
Age, years	50.75 (42.40, 57.53)	48.50 (42.05, 54.75)	52.50 (44.50, 59.75)	0.047
Gender				
Female	60 (32.26)	35 (33.98)	25 (30.12)	0.576
Male	126 (67.74)	68 (66.02)	58 (69.88)	
Ascites, n (%)	114 (61.29)	58 (56.31)	56 (67.47)	0.12
MELD	31.90 ± 6.82	29.84 ± 6.56	34.46 ± 6.29	< 0.001
ALF subtypes				
ALF	74 (39.78)	39 (37.86)	35 (42.17)	0.835
SALF	19 (10.22)	11 (10.68)	8 (9.64)	
ACLF	93 (50.00)	53 (51.46)	40 (48.19)	
Etiology, n (%)				
Hepatitis virus	77 (41.62)	42 (40.78)	35 (42.68)	0.791
Drugs	56 (30.27)	31 (30.10)	25 (30.49)	
Alcohol	30 (16.22)	19 (18.45)	11 (13.41)	
Others	22 (11.89)	11 (10.68)	11 (13.41)	
Treatment regimen				
PE	141 (75.81)	79 (76.70)	62 (73.49)	0.739
DPMAS	23 (12.37)	13 (12.62)	10 (12.05)	
Combination	23 (11.29)	11 (10.68)	12 (14.46)	
Hepatic encephalopathy grading				
1	26 (13.98)	18 (17.48)	8 (9.64)	< 0.001
2	86 (46.24)	60 (58.25)	26 (31.33)	
3	54 (29.03)	21 (20.39)	33 (39.76)	
4	20 (10.75)	4 (3.88)	16 (19.28)	
Tbil (μmol/L)	384.80 ± 115.15	353.98 ± 115.58	423.05 ± 103.08	< 0.001
PTA%	25.71 ± 10.75	26.65 ± 11.25	24.55 ± 10.05	0.186
INR	2.56 (2.10, 3.13)	2.42 (2.00, 2.90)	2.87 (2.17, 3.45)	0.001
ALT(U/L)	160.50 (87.50, 356.50)	134.00 (83.00, 367.50)	170.00 (96.50, 314.00)	0.967
AST(U/L)	166.50 (107.25, 240.75)	148.00 (109.00, 209.00)	196.00 (107.00, 277.00)	0.004
Cr (μmol/L)	151.77 ± 50.23	138.93 ± 46.66	167.72 ± 50.20	< 0.001
Lactate (mmol/L)	4.75 (3.20, 6.70)	4.60 (3.20, 6.80)	5.30 (3.40, 6.60)	0.946
CRP (mg/L)	51.85 (27.15, 72.25)	45.30 (25.30, 73.15)	58.30 (34.50, 70.45)	0.245
PCT	3.20 (1.80, 4.70)	3.10 (1.65, 5.10)	3.20 (1.90, 4.25)	0.657
NLR	6.77 ± 3.17	6.53 ± 3.47	7.06 ± 2.75	0.263

TBil: total bilirubin, PTA%: prothrombin activity, INR: international normalized ratio, ALT (U/L): alanine aminotransferase, AST: aspartate aminotransferase, Cr: creatinine, CRP: C-reactive protein, PCT: procalcitonin, NLR: neutrophil-to-lymphocyte ratio.
Qualitative data were expressed as the number of cases (%) and compared between groups using the chi-squared test. Quantitative data were expressed as x ± SD or M (IQR) and compared using Student's *t*-test or Mann-Whitney U test. p < 0.05 was statistically significant.

high-risk group (12.90% vs. 5.38%, p = 0.075), while there was no statistically significant difference in the rate of liver transplantation (7.53% vs. 4.30%, p = 0.351), hemorrhage (13.98% vs. 10.75%, p = 0.504), and severe allergy (4.30% vs. 4.30%, p = 1.000).

90-day transplantation-free survival of patients

A 90-day survival analysis stratified on the basis of Tbil% on day 1 of treatment showed that survival in the high-risk group was significantly worse than that in the low-risk group (log-rank p < 0.0001, Figure 2).

Table 2. Key feature variables used for machine modeling analysis.

Features	XGBoost	Random Forest	Decision Tree
	importance	importance	importance
Age	1.40%	2.30%	0.00%
Gender	0.10%	0.30%	0.00%
Ascites	2.70%	0.50%	0.00%
Hepatic encephalopathy grading	2.60%	5.00%	0.00%
Baseline MELD	7.50%	5.10%	16.70%
ALF subtype	1.10%	0.70%	0.00%
Etiology	2.90%	1.00%	0.00%
Treatment regimen	0.00%	0.40%	0.00%
TBil (μmol/L)	6.60%	4.10%	7.20%
PTA %	4.20%	3.70%	11.00%
INR	3.20%	3.40%	1.60%
ALT (U/L)	4.30%	4.70%	4.30%
AST (U/L)	7.60%	10.10%	11.90%
Cr (μmol/L)	3.00%	3.90%	0.00%
Lactate (mmol/L)	2.80%	3.70%	0.00%
CRP (mg/L)	5.00%	2.90%	0.00%
PCT%	5.60%	3.30%	0.00%
NLR	0.50%	3.90%	0.00%
24-hour Tbil (μmol/L)	2.30%	6.60%	7.60%
24-hour INR	6.50%	4.50%	0.00%
24-hour Cr (μmol/L)	4.00%	2.30%	4.30%
24-hour TBil%	17.10%	16.60%	26.30%
△MELD	4.00%	3.30%	1.60%
24-hour MELD	4.60%	5.20%	7.60%
MELD%	0.40%	2.60%	0.00%

TBil: total bilirubin, PTA%: prothrombin activity, INR: international normalized ratio, ALT (U/L): alanine aminotransferase, AST: aspartate aminotransferase, Cr: creatinine, CRP: C-reactive protein, PCT: procalcitonin, NLR: neutrophil-to-lymphocyte ratio, 24-hour TBil: 24-hour total bilirubin on treatment, 24-hour INR: 24-hour international normalized ratio of treatment, 24-hour Cr: 24-hour postoperative creatinine. TBil% = (pre-treatment TBil-24-hour treatment TBil)/treatment TBil, improvement in MELD score, △MELD = pre-treatment MELD-24-hour treatment MELD, rate of change in MELD score, MELD% = △MELD/preoperative MELD.

Table 3. 28-day all-cause mortality and adverse complications.

	High-risk (n = 93)	Low-risk (n = 93)	p-value
All-cause mortality	43 (46.24%)	10 (10.75%)	< 0.001
Liver transplantation	7 (7.53%)	4 (4.30%)	0.351
Adverse complications			
Hemorrhage	13 (13.98%)	10 (10.75%)	0.504
Severe allergy	4 (4.30%)	4 (4.30%)	1
Severe coagulation	12 (12.90%)	5 (5.38%)	0.075
Hemodynamic instability	17 (18.28%)	7 (7.53%)	0.029

Grouping was based on median Tbil% (1 day), with < 14.26% for high-risk group and ≥ 14.26% for low-risk group.
p < 0.05 was statistically significant.

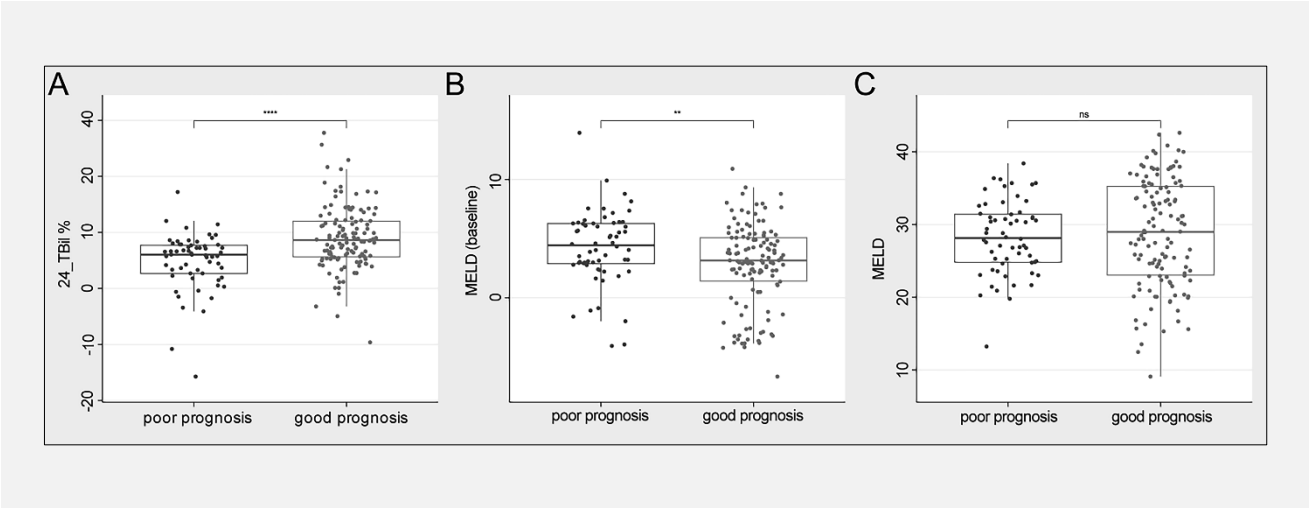

Figure 1. TBil%, MELD, and △MELD characteristics of patients at 24 hours postoperatively.

Grouping was based on 90-day survival. Comparisons were made using the Mann-Whitney U-test. $p < 0.05$ was statistically significant. ns $p > 0.05$, ** $p < 0.01$, **** $p < 0.0001$.

The probability of survival in the high-risk group within 20 days dropped from 100% to 58.1% (54/93), while the low-risk group only slightly decreased to 92.5% (86/93). Survival by 60 days was only 39.8% (37/93) in the high-risk group and maintained 77.4% (72/93) in the low-risk group. Survival by 90 days fell to 36.6% (34/93) in the high-risk group and reached 75.3% (70/93) in the low-risk group (2.8-fold increase in relative risk of mortality).

Multifactorial cox analysis of risk factors for 90-day survival

Through the abovementioned machine classification analysis (XGBoost, accuracy of 0.822, precision of 0.831, F1 value of 0.821, AUC value of 0.866 for the 5-fold cross-validation set), the key feature variables were obtained, including 10 key features, 24-hour TBil%, AST, baseline MELD, baseline TBil, 24-hour INR, PCT, CRP, 24-hour MELD, ALT, and PTA%. Subsequently, the variance inflation factor (VIF) method was utilized to exclude independent variables with substantial covariance (VIF > 5), leaving the final independent variables for analysis as 24-hour TBil%, AST, baseline MELD, 24-hour INR, PCT, CRP, ALT, and PTA%. Cox regression analysis showed a significant 7% increase in the risk of death for every 1% decrease in 24-hour TBil% (HR = 0.93, 95% CI: 0.91 - 0.95, $p < 0.001$). Every 1 U/L decrease in AST (HR = 1.00, 95% CI: 0.99 - 1.00, $p < 0.001$), each 1-point increase in baseline MELD score (HR = 1.07, 95% CI: 1.04 - 1.11, $p < 0.001$), and each 0.1 increase in 24-hour INR (HR = 1.70, 95% CI: 1.29 - 2.24, $p < 0.001$) independently predicted an increased risk of mortality (Figure 3).

DISCUSSION

A single-center retrospective cohort analysis was conducted on 186 patients with ALF treated with NBAL between 2020 and 2025. The core findings showed that 24-hour TBil% was the strongest independent predictor of short-term all-cause mortality and 90-day transplantation-free survival. Those with poor TBil clearance (TBil% < 14.26%) had a 4.3-fold increase in 28-day mortality and a significant decrease in 90-day survival (36.6% vs. 75.3%, HR = 2.8). Cox regression confirmed a 7% increase in risk of mortality for every 1% decrease in 24-hour TBil% (HR = 0.93, $p < 0.001$). Baseline MELD score, 24-hour INR and AST were also key prognostic factors.

This study demonstrated for the first time that 24-hour TBil% is the strongest predictor of short-term (28-day) all-cause mortality and long-term (90-day) poor prognosis using a machine-learning approach. This finding complements previous studies focusing on static baseline metrics, such as MELD scores, and highlights the clinical value of dynamic efficacy metrics. For example, a 1% decrease in Tbil% was associated with a 7% increase in the risk of 90-day mortality, with the 28-day mortality rate in the high-risk group (Tbil% < 14.26%) being 46.24%, which was significantly greater than the 10.75% in the low-risk group. In liver failure, Tbil acts as a core toxicant and directly reflects the detoxification efficacy of artificial liver therapy [10]. Efficient clearance of TBil signifies the efficacy of NBAL and is more likely to mitigate intrahepatic cholestasis and systemic inflammation, granting time for liver cell regeneration. Pairing PE with hemoperfusion and continuous veno-venous hemodialysis filtration enhances the clearance of

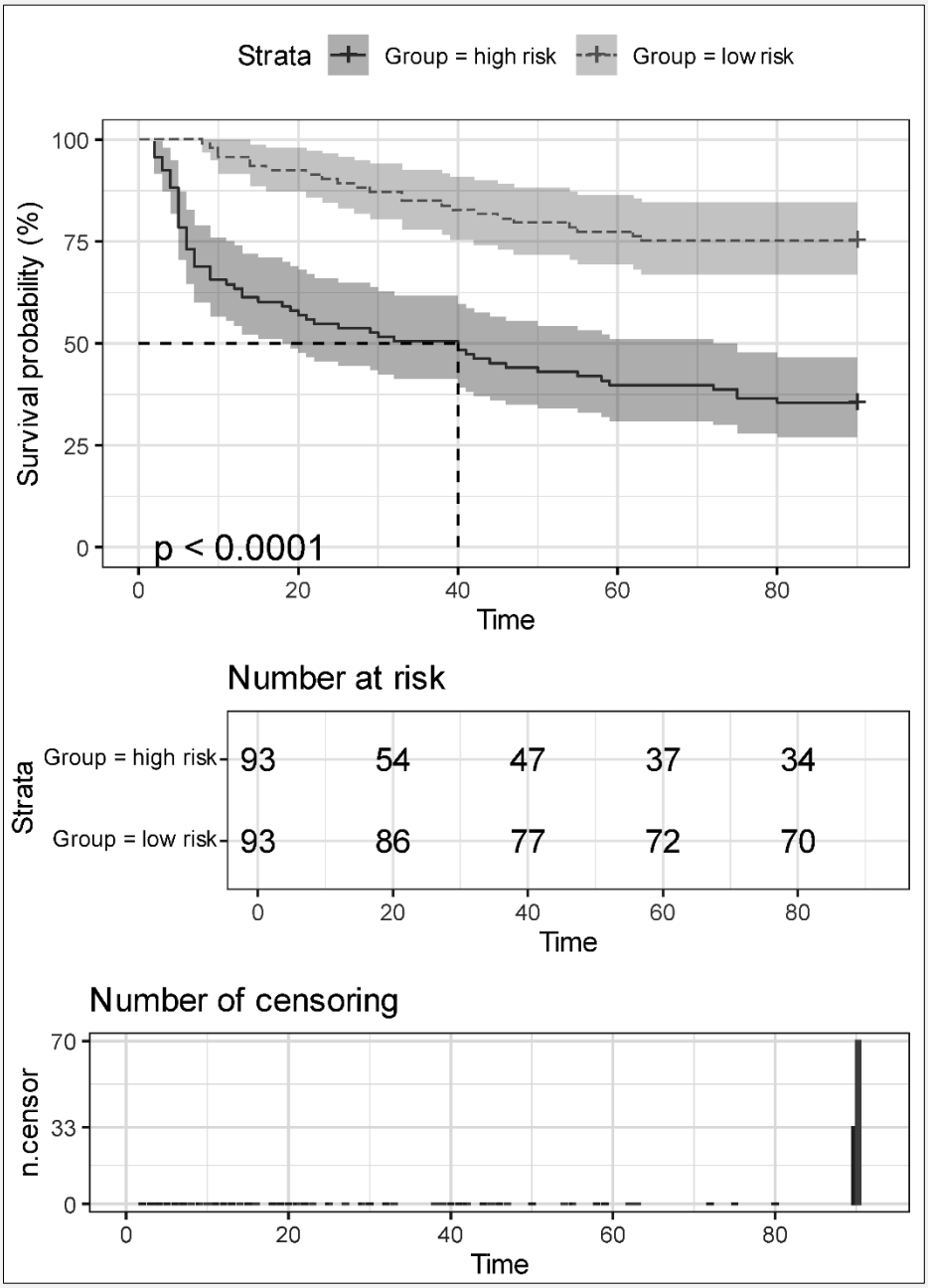

Figure 2. Kaplan Meier curves of patients' 90-day transplantation-free survival.

Grouping was based on median Tbil% (1 day), < 14.26% for high-risk group and ≥ 14.26% for low-risk group. The log-rank test was used. $p < 0.05$ was statistically significant.

TBil and other toxic substances, particularly in patients suffering from non-viral liver failure, leading to improvements in survival [11]. Notably, our study showed significantly higher CRP (median 24.3 vs. 18.7 mg/L) and PCT (1.2 vs. 0.8 ng/mL) in the high-risk group. TBil offers protection to the vascular endothelium against oxidative stress injuries, possibly decreasing the inflammatory response [12]. In ALF, high TBil levels mainly indicate extensive hepatocellular necrosis and reduced bile excretion, rather than being directly caused

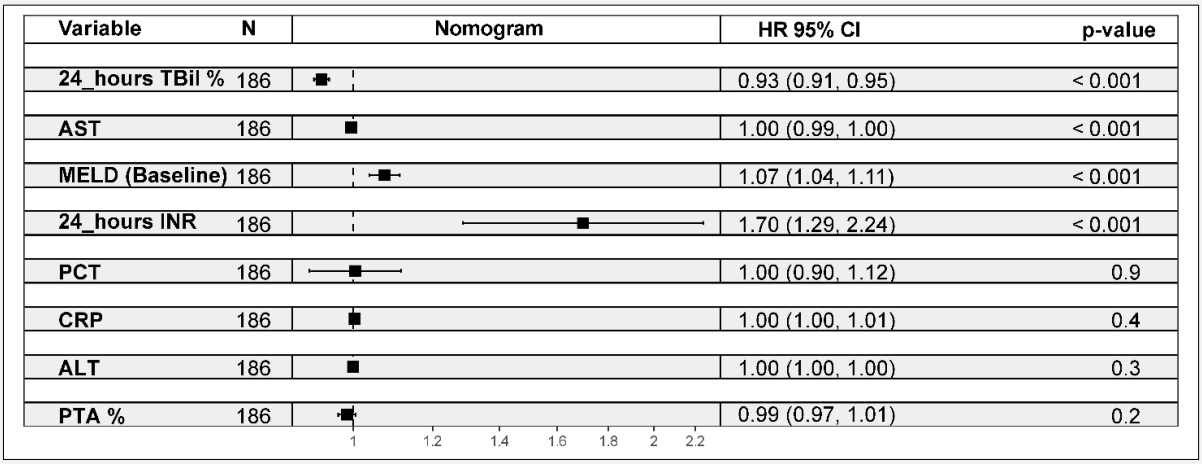

Figure 3. Multifactorial cox risk analysis of patients' 90-day survival.

by inflammation. At this point, hyperbilirubinemia is the result of liver injury rather than the primary cause of inflammation. Low Tbil clearance may lead to persistent intrahepatic cholestasis, a condition that exacerbates hepatocyte apoptosis. Intrahepatic cholestasis is closely associated with excessive accumulation of bile acids in hepatocytes, and this accumulation leads to apoptosis and increased oxidative stress [13]. In addition, cholestasis induces or exacerbates hepatic encephalopathy, and hemodynamic instability (the prevalence of hemodynamic instability in the high-risk group was significantly higher in this study) [14].

The present study confirmed the stability of the baseline MELD score as a core prognostic indicator for ALF, with each 1-point increase significantly associated with a 7% higher risk of 90-day mortality (HR = 1.07). The MELD score, which includes the systemic functional parameters of Cr, TBil, and INR, continues to effectively indicate organ failure in liver failure patients and offers a foundational guide for treatment decisions [15, 16]. The independent predictive role of 24-hour INR (HR = 1.70/0.1 unit increase) reveals the clinical significance of dynamic monitoring of coagulation. In this study, despite the use of a standardized anticoagulation regimen (anti-Factor Xa 0.3 - 0.5 IU/mL) for all treatments, the level of INR reduction in the high-risk group (median ΔINR 0.2, IQR = 0.07 - 0.37) was less than that in the low-risk group (median ΔINR 0.3, IQR = 0.2 - 0.5), suggesting the need for a system of dynamic coagulation monitoring. For instance, fibrinolytic status can be evaluated alongside thromboelastography, or short-acting factors like coagulation factors V and VII can be measured [17,18], in order to differentiate between the effects of liver failure and treatment-related factors on INR, so as to optimize anticoagulation strategy.

Machine learning screening in this study consistently ranked 24-hour TBil% as the highest importance metric (top in XGBoost/Random Forest/Decision Tree). Recent evidence suggests that in acute settings, dynamic markers are more effective than static scores. Dynamic markers such as 24-hour TBil% and MELD were generally higher in importance than baseline values, which may be attributed to 1) the disease heterogeneity of ALF: baseline metrics show the initial condition, while dynamic metrics in the early post-treatment period capture real-time individual responses to interventions [19]; 2) the “window period effect” of NBAL: early (24 - 48 hours) toxin clearance efficiency may be closely related to the chance of subsequent hepatocyte regeneration.

This study constructed for the first time an integrated prediction model containing a timely post-treatment dynamic efficacy metric (24-hour TBil clearance) and baseline functional metrics (MELD, INR, and AST), which provides a quantifiable risk assessment tool for clinical use. In particular, the bedside accessibility of TBil% makes it a core metric for immediate prognostication, helping to identify high-risk patients early and guiding therapeutic strategy adjustments [20].

In addition, 24-hour TBil clearance can be used as an early triage tool to identify high-risk patients (TBil% < 14.26%).

This study has several limitations: being a single-center retrospective study, its findings might be influenced by selection bias and unmeasured confounding factors, such as immunosuppressant or antibiotic usage. With only 186 samples, the study lacked sufficient power to effectively test for rare complications or specific causes,

possibly underestimating differences in some subgroups. Further, uniform use of specific NBAL devices and anticoagulation protocols limits extrapolation of findings to different clinical practice scenarios. Evaluating dynamic indicators relies on a single time point (24 hours) and does not include ongoing biomarker monitoring post-treatment, hindering a full understanding of the long-term pathophysiological changes. Defining "early response" within a 24-hour timeframe is clinically viable, yet it could fail to capture the initial recovery signals in certain rapid treatment responders. Future expansion of the sample size and inclusion of patients with different etiologies and ALF subtypes is needed to validate model generalizability. Also, the molecular pathways linking inadequate TBil clearance to impaired hepatocyte regeneration can be analyzed by metabolomics and transcriptomics, and the complementary predictive value of 72-hour post-treatment metrics (e.g., PTA, lactate clearance) for long-term prognosis can be explored.

CONCLUSION

For ALF patients treated with NBAL, 24-hour TBil% is a prime predictor of survival and complications, with value beyond traditional baseline markers. A TBil% threshold of 14.26% categorizes patients into prognostic tiers, with those at high risk requiring aggressive intervention. The constructed column chart (integrating 24-hour TBil%, baseline MELD, 24-hour INR and AST) provides a clinically actionable tool for real-time risk assessment.

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Availability of Data and Materials:
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate:
The present study was approved by the Ethics Committee of Organ Transplantation Center of the Affiliated Hospital of Qingdao University, and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki and its later amendments or comparable ethical standards.

Declaration of Interest:
The authors have no conflicts of interest to declare.

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