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ORIGINAL RESEARCH

The Predictive Role of FGF21 in Acute Liver Injury Caused by Bacterial Infectious Diseases in Critical Care: A Retrospective Cohort Study

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Background: Acute liver injury (ALI) is a common complication in critically ill patients and has been strongly associated with adverse clinical outcomes. Early detection and timely management of ALI in these patients are crucial for implementing effective therapeutic strategies to prevent disease progression and improve patient outcomes.

Methods: In this study, 112 critically ill patients with bacterial infectious diseases were categorized into two groups based on the presence or absence of ALI within 24 hours of the intensive care unit (ICU) admission. Serum concentrations of fibroblast growth factor 21 (FGF21), interleukin(IL)-6, IL-22, IL-10, liver enzymes, hypersensitive C-reactive protein (hs-CRP), and D-Dimer (D2) were measured within 24 hours of ICU admission. Demographic and clinical data were recorded. Logistic regression analysis was performed to identify potentially predictive biomarkers for ALI. Receiver operating characteristic (ROC) curve analysis was employed to determine the optimal model for predicting ALI in critically ill patients.

Results: Patients in the ALI group exhibited significantly higher serum levels of IL-6, IL-10, IL-22, FGF21, liver enzymes, lactic acid, procalcitonin, D2, APACHE II scores, shorter survival time and higher 28-day mortality compared to those in the non-ALI group. Logistic regression analysis indicated that age, gender, plasma D2, and serum levels of direct bilirubin (DBIL), IL-22 and FGF21 were valuable predictors of ALI among critically ill patients. ROC curve revealed that this predictive model achieved a high area under the curve of 0.885, demonstrating excellent discriminatory ability.

Conclusion: Elevated levels of serum FGF21 in the early stages of critical illness may represent a promising novel biomarker for predicting ALI.

Keywords: critically ill patients, acute liver injury, FGF21, prediction, biomarkers

Introduction

Liver is a highly complex and vital multifunctional organ in the human body, playing crucial physiological roles in protein synthesis, detoxification, drug metabolism, and immune regulation.[1] Due to its extensive blood supply and central role in metabolic processes, the liver is particularly susceptible to various endogenous and exogenous pathogenic factors, which may lead to a spectrum of hepatic disorders, including acute liver injury (ALI). Although there is currently no universally accepted standardized definition of liver injury, it is commonly assessed using routine biochemical markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT) levels. Based on the patterns of these hepatic enzyme levels, liver injury can be categorized into hepatocellular injury, cholestatic injury, or mixed types.[2] Hepatocellular injury is characterized by elevated serum

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aminotransferases, whereas cholestatic injury is associated with significantly increased ALP and GGT levels, accompanied by normal or moderately elevated aminotransferases.[3]

The liver plays a pivotal role in the development and progression of critical illness, contributing to the body's response mechanisms and aiding in the clearance of harmful substances and metabolic byproducts. Critical illness and its therapeutic interventions, including sepsis, shock, drugs, and parenteral nutrition, are prone to induce liver injury.[4] It has been reported that up to 61% of patients exhibit abnormal biochemical test results upon admission to the intensive care unit (ICU), which correlates with short-term mortality rates.[5] In critically ill individuals, hypoxia alongside toxic or inflammatory insults may impair hepatic excretory, synthetic, and purifying functions synthetic and purifying functions, leading to systemic complications such as coagulopathy, increased infection risk, hypoglycemia, and ALI.[6] Severe cases may progress to hepatic encephalopathy or acute liver failure. Liver failure represents a prevalent and severe hepatic syndrome among ICU patients, characterized by high mortality rates, challenging clinical diagnosis and management, and often requiring liver transplantation.[7] Emerging evidence from preclinical studies indicates that bacterial infection is a predominant etiological factor of ALI.[8] Experimental data from animal models have demonstrated that bacterially-induced cytokine storms,[9–11] particularly involving pro-inflammatory mediators such as interleukin-6 (IL-6)[9–11] and interleukin-27 (IL-27),[11] are mechanistically linked to inflammatory hepatic damage. Mechanistic investigations further reveal that infection-derived inflammatory cytokines may trigger hepatocyte injury through dual programmed cell death pathways: apoptosis mediated by mitochondrial signaling cascades and pyroptosis driven by inflammasome activation.[12,13] Notably, these cytokines also orchestrate hepatic leukocyte infiltration by promoting the proliferation and tissue-specific migration of neutrophils, lymphocytes, and plasma cells via chemokine-mediated pathways, resulting liver injury.[9,14] Paradoxically, the liver's immunocompetent status significantly influences systemic infection susceptibility. In a murine model of acetaminophen-induced ALI, disruption of the Kupffer cell niche was shown to establish a transient pathogen susceptibility window facilitating systemic bacterial dissemination.[15] Furthermore, hepatocyte dysfunction following hepatic injury compromises the synthesis of complement proteins and acute-phase reactants, thereby impairing innate immune defenses and predisposing to secondary bacterial infections.[16] However, the assessment and diagnosis of liver injury in critically ill patients with bacterial infection remain challenging due to the lack of specific diagnostic evaluation tools and insufficient clinical understanding of liver injury. The lack of specificity inherent in standard laboratory tests renders the detection of hepatic damage in critically ill individuals with bacterial infection to be a significant challenge. Moreover, the heterogeneity in criteria used to define the ramifications of liver injury complicates clinicians' ability to accurately interpret biochemical abnormalities associated with hepatic function. Early detection and timely intervention for liver injury in critically ill patients with bacterial infections enable effective therapeutic strategies aimed at preventing disease progression and improving patient outcomes. Therefore, liver injury caused by critical illness represents an important link in the worsening of the condition.

Fibroblast growth factor 21 (FGF21) is a secreted protein consisting of 209 amino acids Unlike classical members of the FGF family, FGF21 lacks heparin-binding properties and is therefore capable of being released into circulation.[17] FGF21 is mainly expressed by liver cells and functions as a stress-induced endocrine hormone, significantly influencing systemic metabolism and contributing to liver protection.[17] Currently, several FGF21 analogues are under development, among which efruxifermin and pegozafermin represent the most advanced candidates in this class.[18,19] Both agents have met primary and secondary endpoints in Phase 2b trials involving patients with metabolic dysfunction-associated steatohepatitis (MASH).[18,19] In a randomized phase 2b study, the addition of efruxifermin to glucagon-like peptide-1 receptor agonists (GLP-1RAs) therapy further improved hepatic health outcomes in patients previously receiving GLP-1RA treatment.[20] Both animal and clinical studies support the role of FGF21 as a liver protector.[17,21] Clinical studies have shown that FGF21 can protect the liver from acute damage caused by external stimuli.[21] Animal experiments have shown that levels of FGF21 in the liver and serum are dramatically increased in the mouse model of acetaminophen-induced liver injury.[22] Furthermore, FGF21-knockout mice fed a lipotoxic diet exhibited exacerbated liver damage, which could be prevented by an exogenous FGF21 infusion.[23] In addition, FGF21 has been shown to alleviate septic-associated liver injury by restraining proinflammatory macrophages activation via the autophagy/hypoxia inducible factor-1α (HIF-1α) axis,[24] and to ameliorate cholestatic liver injury through the hepatic fibroblast growth factor receptor 4-c-Jun N-terminal kinases (FGFR4-JNK) pathway.[25]

In this retrospective study, we measured serum FGF21 concentrations within 24 hours of ICU admission in critically ill patients with and without ALI, aiming to evaluate its potential as an early diagnostic biomarker for ALI in critically ill patients.

Patients and Methods

Ethics Statement

The clinical study was approved by the National Ethics Committee of Chengdu Fifth People's Hospital(2023–001-01) and Chengdu Wenjiang District People's hospital(2023–013) and complied with the Declaration of Helsinki. Although this retrospective study adhered all required ethical regulations, it was not prospectively registered in a clinical trial registry as it did not involve experimental interventions. Written informed consent was obtained from the guardians of participants prior to their inclusion in the study.

Patients

This prospective cohort study enrolled 112 consecutive patients admitted to the department of ICU of Chengdu Fifth People's Hospital (Sichuan, China) and Chengdu Wenjiang District People's hospital (Sichuan, China) from March 2023 to October 2024. All included patients were critically ill adults aged over 18 years with bacterial infectious diseases. Exclusion criteria comprised pregnant or lactating women, individuals with a history of liver disease, those with incomplete clinical data, patients who had been re-admitted to the ICU, as well as cases of ALI resulting from trauma, specific medications, tumor metastasis, or acute poisoning (Figure 1).

All eligible patients were divided into two groups: the non-ALI group (patients without evidence of ALI after ICU admission) and the ALI group (patients who developed ALI within 24 hours of ICU admission). ALI was diagnosed

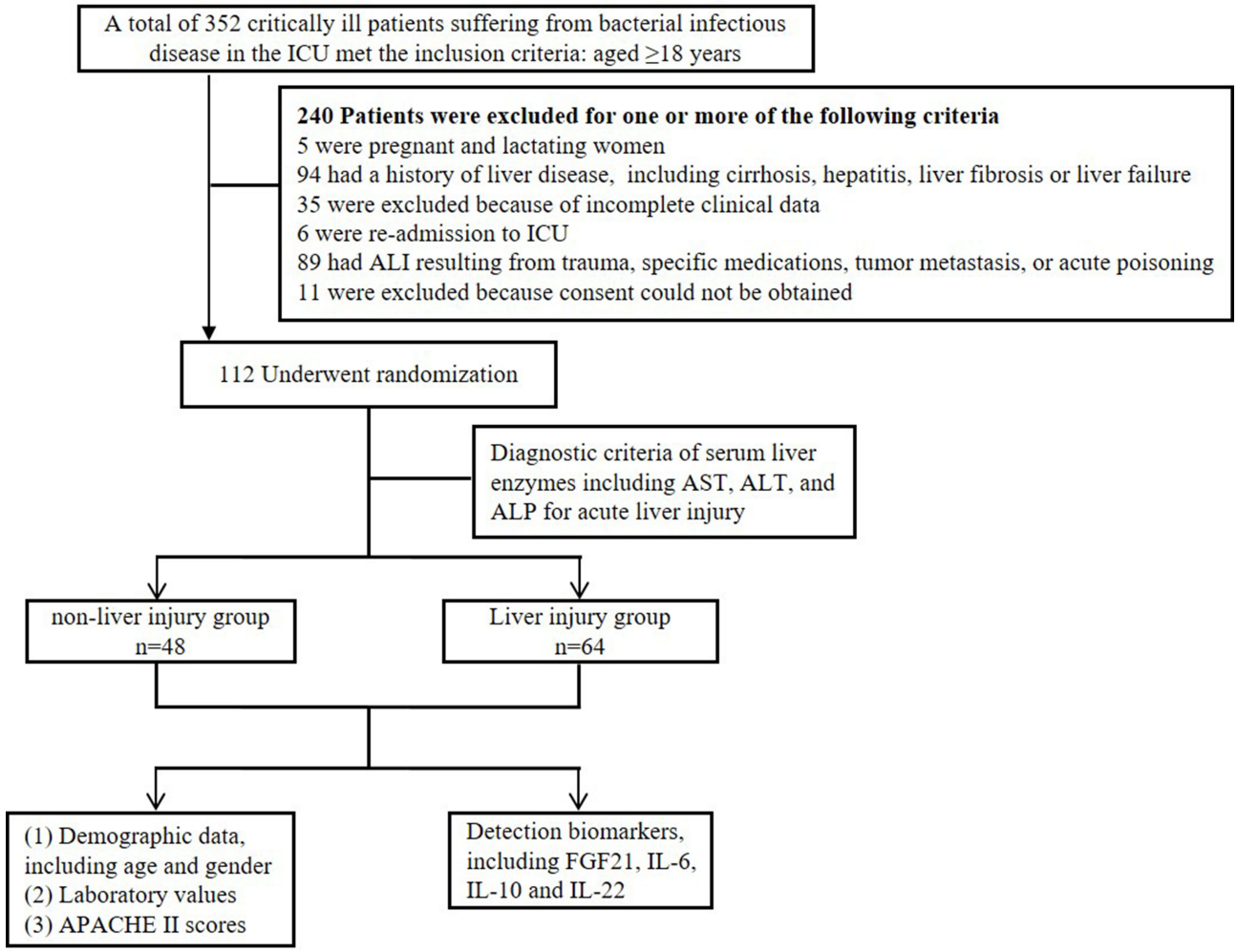

Figure 1 Flow diagram patients' enrolment.
Abbreviations: ICU, intensive care unit; IL, interleukin; APACHE II, acute physiology and chronic health evaluation II; FGF21, fibroblast growth factor 21.

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according to the consensus of emergency medicine experts on the diagnosis and management of adult ALI published in the Chinese Journal of Emergency Medicine.[26] This diagnostic approach primarily relied on biochemical indicators, particularly abnormalities in liver enzymes such as ALT, AST, and ALP.[26–28] Demographic data, including age and gender, were recorded. Laboratory values were documented at the onset of the disease. Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were calculated. The primary clinical outcome measures included 28-day mortality and incidence of ALI following ICU admission. Standard treatment protocols were administered to all patients during their stay in the ICU.

FGF21 and Inflammatory Cytokines Measurements

Blood samples were collected within 24 hours of ICU admission. Serum levels of FGF21, IL-6, IL-10, and IL-22 were measured using enzyme-linked immunosorbent assays (ELISAs) kit (MultiSciences Biotech, China) according to the manufacturer's instructions. Routine blood tests were performed in the hospital's clinical laboratory.

Statistical Analysis

The normality of the distribution of a quantitative variable was tested using the Kolmogorov–Smirnov test ($P>0.10$). Normally distributed data were expressed as means and standard deviations (SDs), and non-normally distributed data as medians and interquartile ranges (IQRs). Qualitative data were presented as number (%). For continuous variables, two-group comparisons were performed using Student's *t*-test or the Mann–Whitney *U*-test, depending on the normality of the distribution. A two tailed *P* value less than 0.05 was considered statistically significant. For categorical variables, the Chi-square test or Fisher's exact test was applied as appropriate. Multivariate logistic regression analyses were performed to identify risk factors for the prediction of incidence of critical illness associated ALI, with results reported as the odds ratio (OR) and 95% confidence interval (CI). For each model, a receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) as well as the 95% CI (binomial exact method) were calculated. Differences between AUCs were tested by pairwise comparison of ROC curves. The predictive performance was evaluated by calculating model sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy, and optimal cutoff value using the R programming language. All statistical analysis were performed using SPSS 26.0 software (IBM SPSS, USA). $P<0.05$ was considered statistically significant.

Results

Patients Characteristics

A total of 112 cases were included, with 64 cases (57.14%) in the ALI group and 48 cases (42.86%) in the non-ALI group. No significant differences were observed between the two groups regarding gender, white blood cell (WBC) count, red blood cell (RBC) count, platelet count, lymphocyte count, monocyte count, hemoglobin, hematocrit, albumin, hyper-sensitive C-reactive proteins (hs-CRP), immunoglobulin, bloodstream infection (BSI) and original infection sites (Table 1). However, the proportion of bacterial infection was slightly higher in the ALI group compared to the non-ALI group, but not statistically significant ($P= 0.058$). Furthermore, higher levels of procalcitonin, plasma D2, lactic acid, GGT, AST, ALT, ALP, direct bilirubin (DBIL), total bilirubin (TBIL) as well as APACHE II scores were detected along with increased mortality within 28 days among patients with ALI when compared to those without ALI ($P<0.05$). Additionally, patients with ALI exhibited elevated serum levels of IL-6, IL-10, IL-22 and FGF21 when compared to patients without ALI ($P<0.05$) (Table 1).

Correlations of Serum FGF21 Level with Clinical Parameters and Blood Markers in Critically Ill Patients with ALI

The serum FGF21 level exhibited a significant positive correlation with BSI and blood markers, including IL-10 and IL-6 ($P<0.05$), in critically ill patients with ALI (Table 2). Additionally, negative correlations were observed between FGF21 and albumin levels ($P<0.05$) in critically ill patients with ALI (Table 2). No statistically significant correlations were identified between FGF21 and other markers.

Table 1 Clinical Characteristics of Critically Ill Patients with or without Liver Injury Groups

Clinical Characteristics	Liver Injury Group (N = 64)	Non-Liver Injury Group (N = 48)	*P* value
Age (years)	68.67±13.49	61.33±15.27	0.008
Gender (male/female)	44/20	25/23	0.073
WBC count (10^9/L)	13.00±7.53	12.34±7.17	0.64
RBC count (10^{12}/L)	3.52±0.89	3.51±0.91	0.946
Platelet count (10^9/L)	149.95±112.70	156.13±98.12	0.763
Lymphocyte count (10^9/L)	0.51(0.30–0.97)	0.71(0.37–1.23)	0.224
Monocyte count (10^9/L)	0.39(0.16–0.68)	0.37(0.20–0.85)	0.86
Hemoglobin (g/L)	105.42±26.09	105.29±27.27	0.980
Hematocrit (%)	32.16±7.65	31.60±7.95	0.704
Albumin (g/L)	27.97±5.17	30.44±7.48	0.053
hs-CRP (mg/L)	137.10(32.00–239.20)	107.65(32.85–184.30)	0.685
Procalcitonin (ng/mL)	6.20(0.78–47.42)	2.75(0.39–10.43)	0.036
D2	9.06(2.65–28.78)	3.85(1.92–9.26)	0.001
Lactic acid	2.85(1.80–4.90)	2.30(1.60–3.05)	0.019
GGT	57.00(22.50–130.00)	29.00(18.50–87.50)	0.105
AST	50.50(27.00–117.50)	29.00(17.50–41.00)	<0.001
ALP	100.50(69.00–141.50)	71.50(55.00–97.00)	0.002
ALT	30.00(16.50–86.00)	19.00(13.00–33.00)	0.006
DBIL	6.15(2.70–19.15)	3.30(2.70–6.75)	0.025
TBIL	11.05(5.25–33.60)	8.30(6.00–13.30)	0.088
APACHE II scores	26.63±8.66	20.25±7.76	<0.001
BSI (positive/negative)	19/45	11/37	0.423
Positive rate of bacterial or fungal culture (positive/negative)	30/34	14/34	0.058
Infection type			0.230
G^- bacilli	18(28.13)	10(20.83)	
G^+ coccus	3(4.69)	1(2.08)	
Fungus	5(7.81)	3(6.25)	
Mixed infection	4(6.25)	0(0.0)	
Unknown bacterial infection	34(53.13)	34(70.83)	
Original infection site, n (%)			0.443
Lung	39 (60.94)	24 (50.00)	
Biliary tract infection	5 (7.81)	1 (2.08)	
Peritonitis	5 (7.81)	4 (8.33)	
Intestinal	3 (4.69)	3 (6.25)	
Urinary system	4 (6.25)	6 (12.50)	
Others*	8 (12.50)	10 (20.83)	
IL-6 (pg/mL)	221.46(47.61–457.06)	38.37(12.85–243.17)	0.001
IL-10 (pg/mL)	86.03(41.06–313.77)	24.04(11.58–131.27)	0.001
IL-22 (pg/mL)	38.85(5.03–158.63)	9.98(5.03–31.78)	0.013
FGF21 (pg/mL)	1429.55(500.91–4449.38)	645.80(187.54–1230.49)	<0.001
Survival time, days	20(6.25–28)	28(13.25–28)	0.041
28-day mortality (non-survival/survival)	39/25	19/29	0.025

Notes: Others* include blood infection, cellulitis and nerve system infection. Quantitative data are shown as mean ± SD or median (interquartile ranges); Categorical data are expressed as absolute values (percentages).

Abbreviations: WBC, white blood cell; RBC, red blood cell; hs-CRP, high sensitivity C-reactive protein; D2, D-dimer; GGT, gamma-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; DBIL, direct bilirubin; TBIL, total bilirubin; APACHE II, acute physiology and chronic health evaluation II; BSI, bloodstream infection; IL, interleukin; FGF21, fibroblast growth factor 21.

Logistic Regression Analysis to Identify Predictors of ALI in Critically Ill Patients

Logistic regression analysis was performed to predict ALI in critically ill patients using independent variables such as age, gender, bacterial infection, APACHE II score, and serum concentrations of albumin, procalcitonin, plasma D2, lactic

Table 2 Correlations of Serum FGF21 Levels with Clinical Parameters and Blood Markers

Parameters	Spearman Correlation Coefficients	*P* value
Age	−0.061	0.622
Gender	−0.120	0.334
WBC count	−0.206	0.095
RBC count	−0.082	0.511
Platelet count	−0.036	0.772
Lymphocyte count	−0.194	0.115
Monocyte count	−0.187	0.129
Hemoglobin	−0.086	0.491
Hematocrit	−0.060	0.631
Albumin	−0.245	0.046
Hs-CRP	0.132	0.286
Procalcitonin	0.224	0.069
D2	0.004	0.971
Lactic acid	0.203	0.107
GGT	0.120	0.346
AST	0.132	0.300
ALP	0.128	0.313
ALT	0.101	0.427
DBIL	0.185	0.143
TBIL	0.121	0.341
APACHE II score	0.062	0.616
BSI	0.246	0.045
Positive rate of bacterial or fungal culture	0.175	0.157
IL-6	0.422	<0.001
IL-10	0.328	0.007
IL-22	0.167	0.176

Abbreviations: WBC, white blood cell; RBC, red blood cell; hs-CRP, high sensitivity C-reactive protein; D2, D-dimer; GGT, gamma-glutamyltransferase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; DBIL, direct bilirubin; TBIL, total bilirubin; APACHE II, acute physiology and chronic health evaluation II; BSI, bloodstream infection; IL, interleukin; FGF21, fibroblast growth factor 21.

acid, GGT, AST, ALP, ALT, DBIL, TBIL, as well as IL-22, IL-6, IL-10, and FGF21 values. Univariate analysis revealed that age, APACHE II scores, plasma D2, serum levels of albumin, lactic acid, AST, ALP, ALT, DBIL, TBIL, IL-6, IL-22, and FGF21 emerged as significant risk factors for the incidence of ALI in critically ill patients. Subsequently, multivariate analysis was conducted utilizing a stepwise regression approach with these independent variables, identifying age, gender, plasma D2, and serum levels of DBIL, IL-22 and FGF21 as risk factors for incidence of ALI in critically ill patients (Table 3). The predictive model was further refined to include only age, gender, D2 concentration, and serum levels of DBIL, IL-22 and FGF21.

ROC Curve for the Incidence of ALI for Patients Admitted to ICU

The ROC curves were constructed to compare the predictive abilities of the model for ALI incidence in early-stage for patients admitted to ICU. The AUC values of FGF21, clinical data (age and gender), and laboratory indicators (D2, DBIL, and IL-22) in predicting ALI in critically ill patients were 0.694 (95% CI 0.596–0.791), 0.668 (95% CI 0.567–0.770), 0.798 (95% CI 0.716–0.879), respectively (Figure 2). In contrast, the AUC values of the FGF21 prediction model for ALI in critically ill patients increased to 0.751 (95% CI 0.663–0.839) and 0.826 (95% CI 0.750–0.903) when integrated with clinical data (age and gender) or laboratory indicators (D2, DBIL, and IL-22) (Figure 2 and Table 4). The model incorporating age, gender, plasma D2, and serum levels of DBIL, IL-22 and FGF21 demonstrated highest AUC of

Table 3 Univariate and Multivariate Analysis for Prediction of Liver Injury in Critically Ill Patients

Variables	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	1.036	1.008–1.065	0.011	1.064	1.019–1.111	0.005
Gender	2.024	0.933–4.392	0.074	3.518	1.139–10.867	0.029
Bacterial infection	0.467	0.211–1.031	0.06			
APACHE II score	1.102	1.045–1.163	<0.001			
Procalcitonin	1.009	0.997–1.021	0.137			
D2	1.071	1.024–1.121	0.003	1.083	1.028–1.141	0.003
Albumin	0.937	0.879–0.999	0.046			
Lactic acid	1.199	1.022–1.408	0.026			
AST	1.016	1.005–1.027	0.004			
ALP	1.007	1.000–1.014	0.035			
ALT	1.009	1.000–1.017	0.052			
DBIL	1.055	1.008–1.104	0.02	1.037	0.995–1.082	0.087
TBIL	1.025	1.003–1.048	0.026			
IL-6	1.000	1.000–1.001	0.047			
IL-10	1.001	1.000–1.002	0.104			
IL-22	1.008	1.002–1.013	0.005	1.008	1.001–1.014	0.016
FGF21	1.000	1.000–1.001	0.004	1	1–1.001	0.007

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; D2, D-dimer; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; DBIL, direct bilirubin; TBIL, total bilirubin; IL, interleukin; FGF21, fibroblast growth factor 21; HR, hazard ratio; CI, confidence interval.

0.885 (95% CI 0.825–0.945), as shown in Figure 2 and Table 4. The performance of the combined model for predicting ALI is summarized in Table 5. The results demonstrated that this integrated model exhibits favorable efficacy in the early prediction of ALI occurrence among critically ill patients.

Discussion

Up to 20% of ICU-admitted patients develop liver injury or failure,[29] and daily biochemical assessments of liver function are routinely performed, but interpreting abnormal results remains challenging. Liver injury has been associated with poor prognosis in critically ill patients, underscoring the importance timely identification and early management interventions to minimize adverse outcomes. Causes of liver injury in the ICU include hypoxic hepatitis due to ischemia and shock, bacterial infections, medications, and parenteral nutrition therapy, which can cause mild liver injury.[6] Our study revealed an ALI of 57.14% among critically ill patients with bacterial infectious diseases, consistent with findings by *Thomson SJ*[5] and another study reporting liver function tests abnormality in 58% of ICU-admitted COVID-19 patients.[30] Furthermore, our research indicated that significantly elevated serum FGF21 levels in critically ill patients with bacterial infectious diseases accompanied by ALI compared to those without ALI. Elevated serum FGF21 concentrations have been consistently observed in both clinical septic patients and experimental murine sepsis models.[24,31] Exogenous administration of recombinant FGF21 demonstrated hepatoprotective efficacy in sepsis-induced liver injury through suppression of inflammatory cascade activation.[24] This therapeutic effect was also corroborated by subsequent preclinical investigations showing recombinant FGF21 administration significantly mitigated hepatic ischemia/reperfusion injury in animal models.[32] The observed upregulation of endogenous FGF21 in current study may represent a compensatory protective response to liver injury, suggesting its potential role as both a diagnostic biomarker and therapeutic target in sepsis-associated liver injury. Despite this, various confounding factors in critically ill patients may influence the utility of serum FGF21 as a diagnostic biomarker for liver injury. Prolonged elevation of serum FGF21 levels was found to be non-detrimental, showing no adverse effects on serum AST, ALT, or other biomarker levels.[33] This finding aligns with our results, where correlation analysis revealed no significant association between serum FGF21 and liver markers such as AST, ALT, GGT, and ALP in critically ill patients with ALI. However,

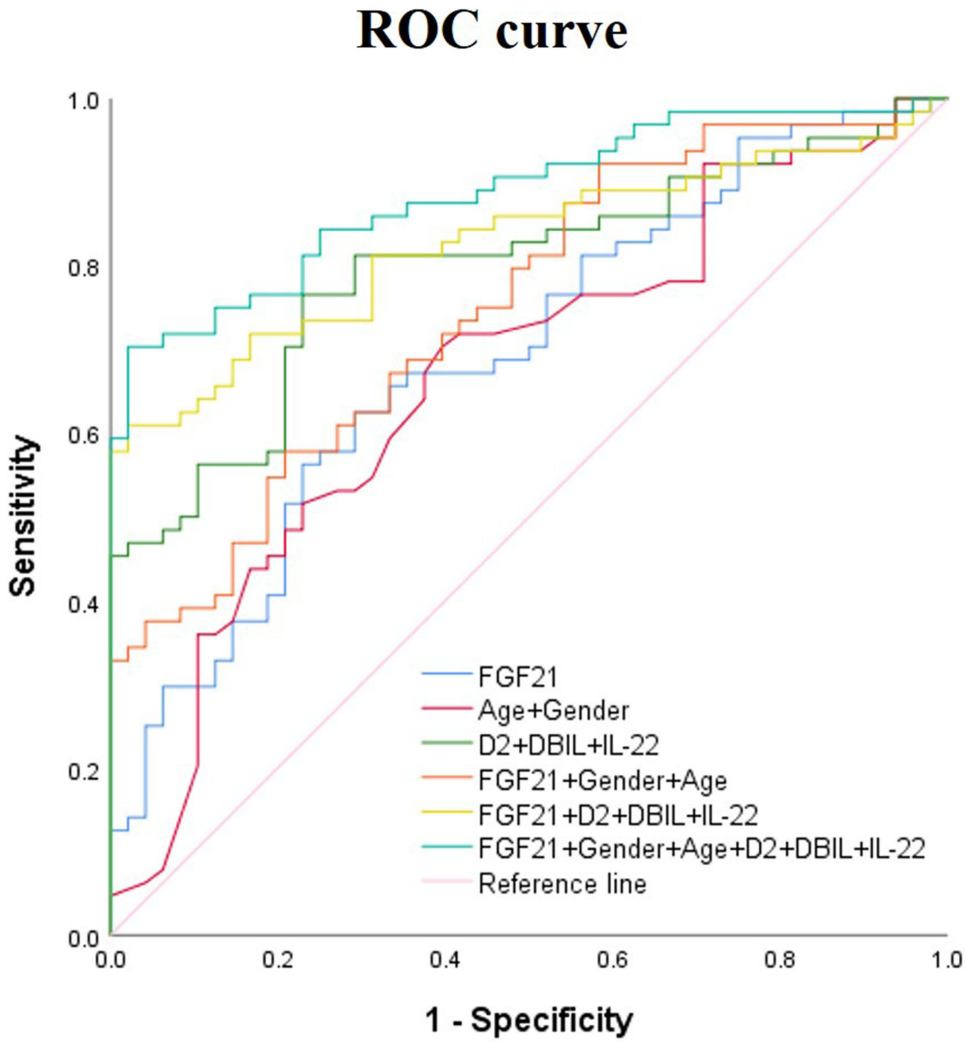

Figure 2 ROC curve of the predictive model predicting the incidence of acute liver injury in the early-stage of critically ill patients.
Abbreviations: FGF21, fibroblast growth factor 21; D2, D-dimer; DBIL, direct bilirubin; IL, interleukin; APACHE II, acute physiology and chronic health evaluation II.

in *Wu Liang*'s study, serum FGF21 was positively correlated with elevated levels of serum aminotransferases and CRP in patients with acute hepatitis B (AHB),[34] which contrasts with our findings. This discrepancy may arise from the predominance of bacterial infections rather than viral infections in our studied population. Furthermore, studies have demonstrated that FGF21 levels markedly increase prior to the elevation of ALT and AST,[22] highlighting one of the key advantages of FGF21 as a biomarker for the early prediction of ALI. Nevertheless, our study revealed no significant correlation between elevated FGF21 in patients with severe liver injury and variables such as age, sex, bilirubin, or blood cell counts in critically ill patients with liver injury, suggesting that FGF21 may not be affected by these factors. The serum FGF21 level was significantly positively correlated with BSI, IL-10 and IL-6 (P<0.05) in critically ill patients with

Table 4 AUCs Analysis for Different Prediction Models

	AUC	SE	95% CI
FGF21	0.694	0.050	0.596–0.791
FGF21+Gender+Age	0.751	0.045	0.663–0.839
FGF21+D2+DBIL+IL-22	0.826	0.039	0.750–0.903
FGF21+Gender+Age+D2+DBIL+IL-22	0.885	0.031	0.825–0.945

Abbreviations: AUC, area under curve; SE, standard error; CI, confidence interval.

Table 5 Performance of the Best Combined Model for Predicting ALI

Model	Cut-off (95% CI)	Accuracy (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
FGF21+Gender+Age+D2 +DBIL+IL-22	0.634 (0.593–0.675)	0.775 (0.648–0.902)	0.725 (0.567–0.883)	0.858 (0.704–1.012)	0.880 (0.750–1.010)	0.718 (0.572–0.864)

Abbreviations: PPV, positive predictive value; NPV, negative predictive value.

liver injury, indicating that BSI and inflammatory response may contribute to the increase in FGF21 levels, though further research is needed to confirm this. IL-10, as a crucial anti-inflammatory cytokine, demonstrated a positive correlation with FGF21 levels in this study. Previous investigations have revealed that FGF21 enhances IL-10 production through the ERK1/2 pathway in lipopolysaccharide (LPS)-stimulated cells.[35] We hypothesize that elevated FGF21 levels in critically ill patients with bacterial infection complicated by ALI may stimulate IL-10 generation, thereby collectively exerting hepatoprotective effects via anti-inflammatory mechanisms. However, our findings revealed a positive association between FGF21 and IL-6, which appears inconsistent with existing literature. Experimental evidence indicates that FGF21 reduces NF-κB pathway-mediated IL-6 expression in LPS-challenged cells.[35,36] Furthermore, a separate study demonstrated that FGF21 suppresses macrophage proinflammatory activation through HIF-1α downregulation, subsequently reducing inflammatory cytokines including IL-6, thereby mitigating cecal ligation and puncture (CLP)-induced septic liver injury.[24] Notably, a clinical investigation has observed positive correlation between serum FGF21 and IL-6 levels in septic patients.[31] This discrepancy suggests that the FGF21-IL-6 correlation observed in our cohort may be population-specific, potentially attributable to the critical condition of enrolled patients. The regulation of serum IL-6 production in these individuals likely involves multiple complex mechanisms that warrant further exploration. Serum FGF21 is primarily synthesized in the liver in response to nutritional stress but can also be produced in reaction to increased mitochondrial and endoplasmic reticulum stress.[37] In patients suffering from chronic hepatitis B (CHB), cirrhosis, or liver failure, FGF21 synthesis may decline alongside reduced serum levels due to severe fibrosis or hepatic damage.[34] However, this study exclusively included patients experiencing ALI, thus, FGF21 might exert a protective role against stress-induced hepatic injury. Previous research has indicated an increase in circulating liver-derived FGF21 during bacterial inflammation[38] and demonstrated higher mortality rates among FGF21-deficient mice following lipopolysaccharide (LPS) administration, highlighting a potential protective effect conferred by FGF21 against bacterial infections.[39] Moreover, all patients in the ALI group included in this study exhibited symptoms of infection, with 46.88% tested positive for laboratory bacterial or fungal cultures. Infection emerged as a potentially significant contributor to these findings of this study. Integrating these observations with previous research, we hypothesize that the elevation of FGF21 may be associated with microbial infections. However, further investigation is warranted to substantiate this hypothesis within our cohort. Notably, patients experiencing ALI did not progress to more severe forms of liver failure in this study, which may be attributed to the limited number of individuals included in the analysis and the fact that the patients selected were critically ill with infections. Studies have shown that FGF21 plays an important role in various critical diseases, including acute lung injury/acute respiratory distress syndrome (ALI/ARDS), acute myocardial injury (AMI), acute kidney injury (AKI), sepsis, and liver failure.[40] Circulating FGF21 levels are primarily derived from the liver and are low under normal physiological conditions, while FGF21 levels increase with the onset and progression of disease. Currently, more clinical studies have found that FGF21 can serve as a new biomarker with great potential for clinical applications. Early elevation of FGF21 is observed in septic patients[24,31] and can be used as a prognostic biomarker of survival.[31] FGF21 also plays a crucial role in liver diseases, with significantly elevated in AHB patients and rapidly normalizing following treatment, correlating with the degree of liver injury induced by AHB.[34] Conversely, FGF21 levels are diminished in individuals with CHB and cirrhosis, potentially reflecting impaired hepatic protein synthesis capacity.[34] Additionally, FGF21 has been found to be elevated in the early stages of cirrhosis and hepatocellular carcinoma (HCC) and can serve as an early diagnostic factor for HCC.[41,42] These findings suggest that FGF21 may serve as a valuable biomarker for the early monitoring of ALI. In mitochondrial diseases, FGF21 demonstrated greater accuracy in identifying primary muscle-manifesting respiratory chain deficiencies compared to conventional

biomarkers.[43] Serum and liver FGF21 levels in patients with nonalcoholic fatty liver disease (NAFLD) are significantly higher than those in healthy controls, potentially serving as a new biomarker for the diagnosis of NAFLD.[44] In summary, as a serum marker, FGF21 holds broad application prospects in the prevention, diagnosis, treatment and efficacy evaluation of diseases and has been partially applied in clinical settings. However, no research has explored the role of FGF21 in the occurrence of ALI in critically ill patients. Our findings indicate that serum FGF21 level in critically ill patients with ALI are significantly higher than that in critically ill patients without ALI, and prove that it may serve as an early biomarker for ALI in critically ill patients, which is consistent with the results in the above studies. In the diagnostic model for early liver injury among critically ill cases, the AUC value of FGF21 combined with age, gender, D2, DBIL, and IL-22 reached an impressive 0.885.

Unexpectedly, our study revealed a negative correlation between FGF21 and albumin in critically ill patients with liver injury. However, a study on patients with chronic hepatitis C virus (CHC) infection demonstrated that serum FGF21 levels in CHC patients exhibited a significant positive correlation with serum albumin levels.[45] The researchers suggested that this might be attributed to the fact that the liver serves as the primary source for both FGF21 and albumin, making them reliable indicators of adequate hepatic synthetic function.[45] Nevertheless, the observed discrepancy may be attributed to the specific characteristics of our study cohort comprising patients with ALI, in whom impaired hepatic synthetic function could potentially compromise the production of these biomarkers, ultimately resulting in the negative correlation detected in our analysis. Albumin, a protein synthesized by hepatocytes in the liver, serves as a carrier for various compounds in the blood and also acts as a transporter.[46,47] Moreover, serum albumin is a highly sensitive marker of nutritional status and disease severity, particularly in chronically and critically ill individuals.[48] Notably, *Chikamatsu M* reported that human serum albumin fused with long-acting FGF21 analogs holds potential for the treating nonalcoholic fatty liver disease.[49] In a study investigating a novel therapeutic approach for non-alcoholic fatty liver disease (NAFLD), administration of chimeric FGF21/hepatocyte growth factor receptor (HGFR) was found to promote increased expression of albumin at the transcriptional level.[50] To date, no studies have been conducted to elucidate the definitive relationship or interaction between FGF21 and albumin. Consequently, the observed negative correlation between FGF21 and albumin in critically ill patients with liver injury requires further investigation. It remains unclear whether albumin influences FGF21 synthesis or functions as a carrier facilitating its transport, which will also be a focus of our subsequent research.

In summary, this study demonstrates for the first time that serum FGF21 levels are significantly elevated in critical patients with severe bacterial infections who develop ALI. Furthermore, serum FGF21 levels in these patients correlate with IL-6, IL-10, BSI, and albumin levels. These observations suggest that elevated FGF21 may act as a compensatory mechanism, playing a protective role in the immune response induced by bacterial infections. A predictive model incorporating FGF21, gender, age, D2, DBIL, and IL-22 was established to effectively enable early prediction of ALI in critical patients with bacterial infections. Finally, further investigations are required to elucidate the precise role of FGF21 in the progression of ALI among patients with severe bacterial infections.

Limitations

First, although the sample size in this study was analyzed using G Power software and met the statistical requirements, the single-center nature of this research still resulted in a relatively limited sample size. Given that the patients were critically ill individuals with bacterial infections, a larger multi-center study should be conducted to validate our findings. Second, we did not measure the dynamic changes in FGF21 levels in critically ill patients, which could provide valuable insights into disease progression and treatment efficacy.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors took part in drafting, revising or critically reviewing the article. All author gave final approval of the version to be published. All author have agreed on the journal to which the article has been submitted and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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