Acute kidney injury is an unfavorable prognostic factor in acute liver failure and is associated with tumor necrosis factor-alpha

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出版情報：Medicine. 102 (45), pp.e35931-, 2023-11-10. Ovid Technologies (Wolters Kluwer Health)
バージョン：
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Observational Study

Medicine

OPEN

Acute kidney injury is an unfavorable prognostic factor in acute liver failure and is associated with tumor necrosis factor-alpha

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Abstract

Acute kidney injury (AKI) is a common complication of acute liver failure (ALF); but its pathogenesis is unknown. ALF was divided into 2 subgroups; ALF with hepatic coma, which corresponds to ALF in the US and Europe, and ALF without hepatic coma. AKI has been shown to worsen the prognosis of ALF patients with hepatic coma; however, its prognostic significance in ALF without hepatic coma remains unknown. A single-center retrospective study of 174 patients with ALF was performed. AKI was defined according to KDIGO criteria. AKI developed in 29 (66.0%) of 44 ALF patients with hepatic coma and 27 (38.5%) of 130 ALF patients without hepatic coma. Systemic inflammatory response syndrome (SIRS) was found to be significantly associated with AKI incidence in ALF patients ($P < .001$). Tumor necrosis factor-alpha (TNF-α) was found to be significantly associated with the presence and severity of AKI ($P = .0039$ and $P = .0140$, respectively). On multivariate analysis, TNF-α was an independent risk factor linked with AKI ($P = .0103$). Even in the absence of hepatic coma, the transplant-free survival rate of ALF was significantly associated with the presence and severity of AKI. Even when hepatic coma is absent, AKI complicated in ALF is strongly associated with TNF-α and worsens the transplant-free survival rate. Before the onset of hepatic coma, plasma exchange, or extracorporeal blood purification to remove inflammatory cytokines should be considered in ALF patients.

Abbreviations: AKI = acute kidney injury, ALF = acute liver failure, HRS = hepatorenal syndrome, INRs = international normalized ratios, LPS = lipopolysaccharide, SCr = serum creatinine, SIRS = systemic inflammatory response syndrome, SS = spontaneous survival, TNFR1 = TNF receptor 1.

Keywords: acute liver failure, acute liver failure without hepatic coma, acute kidney injury, tumor necrosis factor-alpha, prognosis

1. Introduction

Acute liver failure (ALF) is defined as the occurrence of severe acute liver injury with jaundice, coagulopathy, and hepatic encephalopathy in patients who do not have the underlying chronic liver disease.[1] Although patients with ALF receive multidisciplinary therapies such as plasma exchange and extracorporeal blood purification, only liver transplantation has been shown to improve the prognosis of ALF patients.[2] In Japan, ALF is defined as patients who had previously normal liver functions and progressed to severe liver damage with prothrombin time values of 40% or less of the standardized value, or international normalized ratios (INRs) of 1.5 or more within 8 weeks of the onset of disease symptoms.[3] And ALF is divided into 2 subgroups; ALF with hepatic coma, which corresponds to ALF in the United States and Europe, and ALF without hepatic coma.[3]

ALF has a high mortality rate and is frequently complicated by multiple organ failure, including acute kidney failure (AKI). AKI is known to be associated with increased mortality in ALF with hepatic coma,[4,5] but its prognostic significance in ALF without hepatic coma is unknown. The primary aim of this study is to elucidate the prognostic impact of AKI on ALF without hepatic coma.

The EASL clinical practice guidelines state that biomarkers are required to predict ALF progression to improve ALF

This work was supported in part by the Takeda Science Foundation, Smoking Research Foundation, and JSPS KAKENHI (Grant Numbers: JP17K09430, JP18H05039, JP19H01054, JP19K17496, JP20K22877, JP20H04949, JP22K16021, JP22K07963, JP22K07987).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Supplemental Digital Content is available for this article.

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How to cite this article: Imoto K, Tanaka M, Goya T, Azuma Y, Hioki T, Aoyagi T, Takahashi M, Kurokawa M, Kato M, Kohjima M, Ogawa Y. Acute kidney injury is an unfavorable prognostic factor in acute liver failure and is associated with tumor necrosis factor-alpha. Medicine 2023;102:45(e35931).

Received: 10 July 2023 / Received in final form: 15 September 2023 / Accepted: 12 October 2023

http://dx.doi.org/10.1097/MD.0000000000035931

survival rates.[1] Although systemic inflammatory response syndrome (SIRS) has been linked to AKI in ALF patients,[6,7] it has not been determined which cytokines cause AKI in the context of ALF. The secondary goal of this research is to identify the cytokines associated with AKI development in ALF, which could be used as prognostic biomarkers for ALF.

2. Patients and methods

2.1. Patients

A single-center retrospective study of 177 ALF patients admitted to Kyushu University Hospital between January 2007 and February 2019 was carried out. One patient with HIV and 1 with lymphoma were excluded as these diseases could influence cytokine expressions. Due to the higher frequency of AKI with paracetamol-induced ALF than with ALF caused by other etiologies, 1 patient with paracetamol toxicity was excluded.[7] Therefore, this cohort comprised 174 patients. The study was carried out in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kyushu University Hospital (approval number: No. 27-377 and 2021-77).

ALF was diagnosed by the criteria established by the Intractable Hepato-Biliary Diseases Study Group in Japan.[4] ALF was diagnosed in patients who had previously normal liver functions and progressed to severe liver damage with prothrombin time values of 40% or less of the standardized value or international normalized ratios (INRs) of 1.5 or more within 8 weeks of the onset of disease symptoms. Furthermore, ALF was divided into 2 types: ALF without hepatic coma and ALF with hepatic coma; No or grade I hepatic encephalopathy was defined in the former, while grade II, or more severe hepatic encephalopathy was defined in the latter.

The KDIGO criteria were used to diagnose AKI: an increase in baseline serum creatinine (SCr) ≥ 50%, an increase in SCr ≥ 0.3 mg/dL within 48 hours, or a urine output < 0.5 mL/kg/h for 6 hours.[8] The following AKI stages were established: The first stage was defined as an increase in SCr to 1.5–1.9 times baseline, an increase in SCr of ≥ 0.3 mg/dL, or a decrease in urine output of < 0.5 mL/kg/hour for 6–12 hours; stage 2 was defined as an increase in SCr to 2.0–2.9 times baseline, or a decrease in urine output to < 0.5 mL/kg/hour for ≥ 12 hours; stage 3 was defined as an increase in SCr to 3.0 times baseline, or an increase in SCr to ≥ 4.0 mg/dL, or a decrease in urine output to < 0.3 mL/kg/hour for ≥ 24 hours, or anuria for ≥ 12 hours, or the start of renal replacement therapy, regardless of stage. The baseline SCr was defined as the pre-admission SCr (obtained no more than 365 days prior) available from the hospital records.

SIRS was defined as 2 or more of temperature > 38°C or < 36°C, heart rate > 90 beats per min or PaCO2 < 4.3 kPa, white cell count < $4 \times 10^3/mm^3$ or > $12 \times 10^3/mm^3$.[9]

2.2. Cytokine assays

Serum samples were obtained from ALF patients at the time of hospital admission. The Human TNF alpha ELISA Kit (Abcam), Human IFN gamma ELISA Kit (Abcam), and Human IL-6 Human ELISA Kit (Abcam), were used to measure serum levels of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), and interleukin-6 (IL-6), respectively.

2.3. Statistical analysis

Continuous variables are denoted as mean values and standard deviations or median and interquartile range if they were not normally distributed. The Wilcoxon rank sum test and the Kruskal–Wallis test were used to compare continuous variables. The Chi-squared test was used to compare categorical variables. Log-rank tests (Kaplan–Meier) examined 90 days of transplant-free survival. Multivariate analysis was carried out by logistic regression analysis. $P < .05$ was regarded as statistically significant. The JMP software package was used to analyze the data (version 16.1.0; SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Patients' characteristics

Table 1 shows the clinical and biochemical characteristics of ALF patients without AKI (non-AKI group) and with AKI (AKI group), and Table S1, http://links.lww.com/MD/K616 shows the clinical and biochemical characteristics of ALF patients classified according to the AKI stage. The median age was 49 years (IQR 34–59), and the male ratio was 54.6%. In comparison to the non-AKI group, the AKI group displayed a significantly higher age and lower male ratio. Hepatitis B virus (26.4%), hepatitis A virus (14.4%), autoimmune hepatitis (9.8%), drug-induced liver injury (2.9%), others (10.3%), and unknown etiologies (36.2%) were the etiologies of ALF. There is no significant difference in the etiology between the non-AKI group and the AKI group. Hepatic coma, SIRS, and infection complications related to ALF were noted in 44 patients (25.3%), 68 patients (39.1%), and 4 patients (2.3%), respectively. Comparing the AKI group to the non-AKI group, the AKI group had significantly higher rates of hepatic coma ($P < .001$) and SIRS ($P < .001$), whereas the rate of infection did not show any significance ($P = .153$).

In terms of prognosis, 20 patients (11.5%) died, 20 patients (11.5%) underwent liver transplantation, and 137 patients (78.7%) survived without liver transplant. Compared to the non-AKI group, the AKI group had a significantly higher mortality rate and lower overall survival and transplant-free survival rate.

3.2. Relationship between AKI and proinflammatory cytokines

We measured the serum levels of 3 representative proinflammatory cytokines because the AKI group had a significantly higher incidence of SIRS (Fig. 1). TNF-α was significantly increased in the AKI group compared to the non-AKI group (non-AKI 52.9 ± 56.6 pg/mL vs AKI 175.1 ± 227.9 pg/mL, $P = .0039$), whereas IFN-γ and IL-6 showed no significant difference (IFN-γ: non-AKI 41.7 ± 50.2 pg/mL vs AKI 52.1 ± 78.1 pg/mL, $P = .8110$, IL-6: non-AKI 46.3 ± 54.5 pg/mL vs AKI 84.6 ± 80.8 pg/mL, $P = .0973$). TNF-α was also associated with AKI severity in ALF patients (non-AKI 52.9 ± 56.6 pg/mL vs AKI stage 1-2 160.6 ± 40.1 pg/mL vs AKI stage 3 225.5 ± 284.5 pg/mL, $P = .0140$; Figure S1, http://links.lww.com/MD/K613), whereas IFN-γ and IL-6 were not (IFN-γ: non-AKI 41.7 ± 50.2 pg/mL vs AKI stage 1-2 49.3 ± 90.0 pg/mL vs AKI stage 3 55.2 ± 65.2 pg/mL, $P = .7196$, IL-6: non-AKI 46.3 ± 54.5 pg/mL vs AKI stage 1-2 82.9 ± 80.7 pg/mL, AKI stage 3 87.4 ± 87.3 pg/mL, $P = .249$; Figure S1, http://links.lww.com/MD/K613).

3.3. Independent risk factors for the development of AKI

To identify the independent risk factors associated with AKI development in the setting of ALF, a multivariate analysis was performed (Table 2). TNF-α ($P = .0103$) and gender ($P = .0351$) were independently associated with AKI in ALF patients.

3.4. The survival rate of ALF stratified by the presence and the stage of AKI

The overall survival rate was 88.5% and the transplant-free survival rate was 78.7% (Table 1). The overall survival rate and transplant-free survival rate in the AKI group were significantly lower than in the non-AKI group (non-AKI 97.2% vs

Table 1

Clinical and biochemical characteristics on the admission of ALF patients by AKI status (non-AKI vs AKI).

Variable	Total	Non-AKI	AKI	*P* value
Number of patients	174	108	66	
Age (yr)	49.0 (34.0–59.0)	42.5 (32.3–58.8)	50.0 (42.0–59.5)	.0341
Gender (M/F)	95/79 (54.6%)	67/41 (62.0%)	28/38 (42.4%)	.0117
ALF etiology (n, %)				.0775
HAV	25 (14.4%)	21 (19.4%)	4 (6.1%)	
HBV	46 (26.4%)	32 (29.6%)	14 (21.2%)	
AIH	17 (9.8%)	9 (8.1%)	8 (12.1%)	
DILI	5 (2.9%)	2 (1.9%)	3 (4.6%)	
Undetermined	63 (36.2%)	34 (31.5%)	29 (43.9%)	
Others	18 (10.3%)	10 (9.3%)	8 (12.1%)	
Labo data				
T-Bil (mg/dL)	4.7 (3.2–10.9)	4.4 (2.7–10.4)	6.0 (3.6–11.9)	.0537
Alb (g/dL)	3.5 (3.1–3.8)	3.6 (3.2–3.9)	3.3 (3.0–3.7)	.0066
AST (IU/l)	3510 (1005–7159)	3310 (1235–5734)	4578 (618–10910)	.5239
ALT (IU/l)	3292 (1202–5477)	3459 (1646–5393)	2970 (707–5845)	.3442
Plt (/mL)	13.1 (9.1–17.2)	14.5 (11.2–18.5)	10.3 (7.4–14.8)	<.0001
PT-INR	2.01 (1.65–2.82)	1.81 (1.58–2.32)	2.60 (1.93–3.90)	<.0001
Cr (mg/dL)	0.79 (0.58–1.33)	0.66 (0.51–0.82)	1.61 (1.09–3.47)	<.0001
Basal Cr (mg/dL)	0.61 (0.5–0.72)	0.58 (0.47–0.70)	0.66 (0.51–0.84)	.0034
Peak Cr (mg/dL)	0.84 (0.61–1.42)	0.66 (0.52–0.84)	1.72 (1.10–3.53)	<.0001
MELD	19 (15–29)	16 (13–19)	30.5 (23.8–37.3)	<.0001
Coma (n, %)	44 (25.3%)	15 (13.9%)	29 (43.9%)	<.0001
SIRS (n, %)	68 (39.1%)	25 (23.2%)	43 (65.2%)	<.0001
Infection (n, %)	4 (2.3%)	1 (0.9%)	3 (4.6%)	.153
Outcome				<.0001
Overall survival (n, %)	154 (88.5%)	105 (97.2%)	49 (74.2%)	<.0001
Transplant-free survival (n, %)	137 (78.7%)	98 (90.7%)	39 (59.1%)	<.0001
Transplanted (n, %)	20 (11.5%)	8 (7.41%)	12 (18.2%)	.0479

AIH = autoimmune hepatitis, AKI = acute kidney injury, Alb = albumin, ALF = acute liver failure, ALT = alanine aminotransferase, AST = aspartate aminotransferase, Cr = creatinine, DILI = drug-induced liver injury, HAV = hepatitis A virus, HBV = hepatitis B virus, T-Bil = total bilirubin, Plt = platelet, PT-INR = prothrombin time-international normalized ratio, SIRS = systemic inflammatory response syndrome.

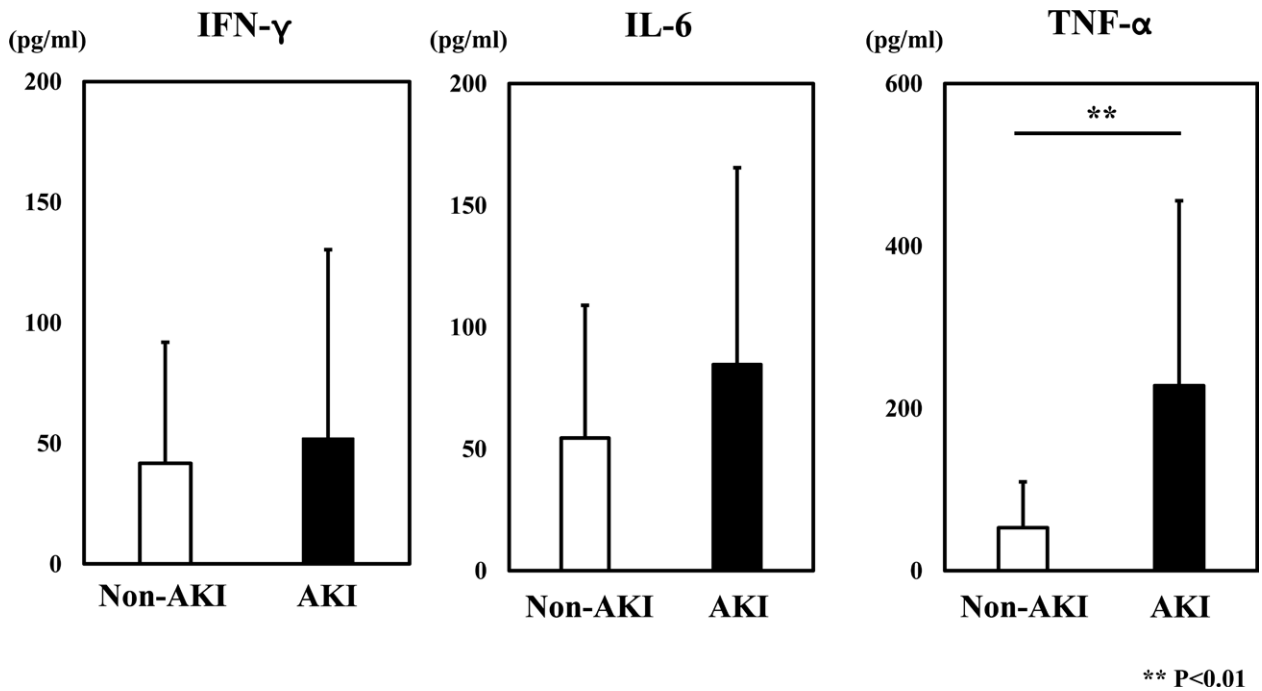

Figure 1. Proinflammatory cytokine levels in serum of ALF patients according to AKI status (non-AKI vs AKI). AKI = acute kidney injury, ALF = acute liver failure, IFN-γ = interferon-gamma, IL-6 = interleukin-6, TNF-α = tumor necrosis factor-alpha.

AKI 74.2%, $P < .0001$, non-AKI 90.7% vs AKI 59.1%, $P < .0001$, respectively). In ALF patients, the overall survival rate and transplant-free survival rate were also significantly correlated with AKI severity (non-AKI 97.2% vs AKI stage 1-2 87.5% vs AKI stage 3 61.7%, $P < .0001$, non-AKI 90.7% vs AKI stage 1-2 75.0% vs AKI stage 3 44.1%, $P < .0001$; Table S1, http://links.lww.com/MD/K616). The cumulative survival rate at 90 days after admission was lesser in the AKI group equated to the non-AKI group (Fig. 2). The non-AKI group had a mean survival time of 79.8 days (95% CI, 73.6–85.9) while the AKI group had a mean survival time of 48.9 days (95% CI, 37.1–60.7) (log-rank, $P < .001$; Fig. 2A). Similar results

were observed even though ALF patients were stratified by the presence of hepatic coma (Fig. 2B and 2C). The mean survival time in ALF patients without hepatic coma was 83.8 days (95% CI, 77.6–88.6) in the non-AKI group and 69.4 days (95% CI, 55.7–83.1) in the AKI group (log-rank, $P < .0454$; Fig. 2B). The mean survival time in ALF patients with hepatic coma was 58.5 days (95% CI, 32.4–84.6) in the non-AKI group and 38.1 days (95% CI, 33.1–43.2) in the AKI group (log-rank, $P < .0233$; Fig. 2C).

The cumulative survival rate at 90 days after admission was also significantly correlated with AKI severity (Fig. 3). The non-AKI group had a mean survival time of 79.8 days (95% CI, 73.6–85.9), the non-AKI stage 1-2 group had a mean survival time of 63.5 days (95% CI, 37.1–60.7), and the AKI stage 3 group had a mean survival time of 36.9 days (95% CI, 21.4–52.4) (log-rank, $P < .001$; Fig. 3A). In ALF patients without hepatic coma, the mean survival time was 83.8 days (95% CI, 79.0–88.6) in the non-AKI group, 77.0 days (95% CI, 59.9–94.1) in the AKI stage 1-2 group, and 60.8 days (95% CI, 39.5–82.0) in the AKI stage 3 group (log-rank, $P = .0204$; Fig. 3B). The average survival time in ALF patients with hepatic coma was 58.5 days (95% CI, 32.4–84.6) in the non-AKI group, and 40.5 days (95% CI, 14.0–67.0) in the AKI stage 3 group and 17.5 days (95% CI, 0.21–34.8) int the AKI stage 3 group (log-rank, $P = .0446$; Fig. 3C).

Table 2

Factors related to AKI in ALF patients on multivariate analysis.

Variable	Odds ratio (95% CI)	*P* value
Age (yr)	1.021 (0.979–1.065)	.3149
Gender (M)	0.241 (0.060–0. 967)	.0351
Alb (g/dL)	0.263 (0.055–1.250)	.0723
Plt (/mL)	0.917 (0.825–1.029)	.1019
Coma	3.789 (0.903–15.91)	.0607
TNF-α (pg/mL)[a]	1.647 (1.012–2.682)	.0103

AKI = acute kidney injury, ALF = acute liver failure, TNF-α = tumor necrosis factor-alpha.
[a]Per 50 pg/ml increase in TNF-α.

3.5. Relationship between disease severity and proinflammatory cytokines

The correlation between disease severity and proinflammatory cytokines was examined. TNF-α was significantly higher in non-spontaneous survival (non-spontaneous survival 192.6 ± 293.7 pg/mL vs spontaneous survival 82.7 ± 93.5 pg/mL, $P = .0251$; Figure S2a, http://links.lww.com/MD/K614), but IFN-γ and IL-6 were not significantly different (IFN-γ: non-spontaneous survival 27.5 ± 43.6 pg/mL vs spontaneous survival 52.9 ± 69.3 pg/mL, $P = .1749$, IL-6: non-spontaneous survival 63.0 ± 68.3 pg/mL vs spontaneous survival 63.2 ± 74.2 pg/mL, $P = .8407$; Figure S2a). IFN-γ was significantly lower in the ALF with coma group compared to the ALF without coma group (with coma 17.8 ± 16.3 pg/mL vs without coma 58.7 ± 73.0 pg/mL, $P = .0191$; Figure S2b, http://links.lww.com/MD/K614), whereas TNF-α and IL-6 showed no significant difference (TNF-α: with coma 148.0 ± 206.3 pg/mL vs without coma 94.2 ± 154.0 pg/mL, $P = .2540$, IL-6: with coma 66.5 ± 86.3 pg/

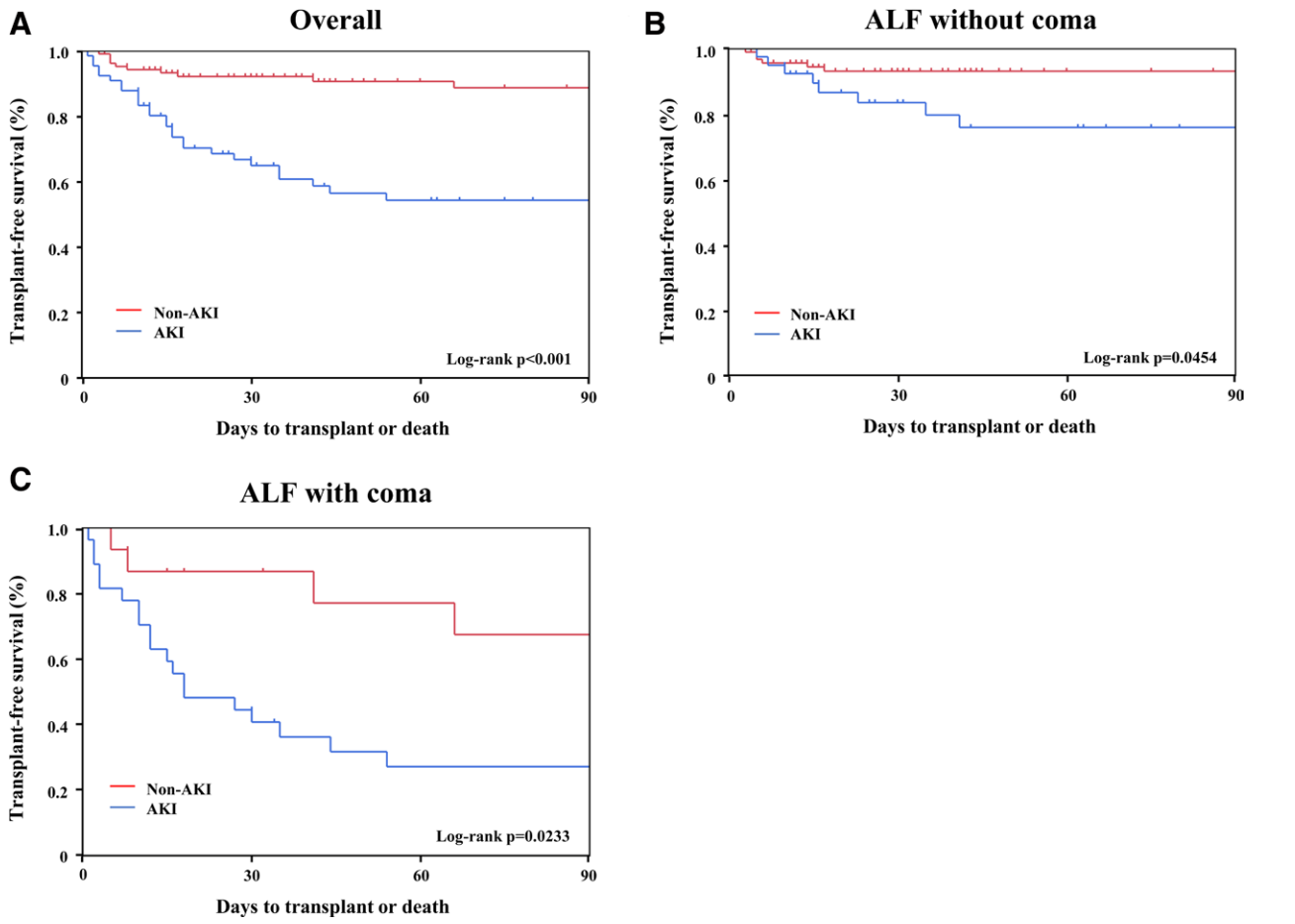

Figure 2. Kaplan–Meier survival curves for the transplant-free survival of ALF patients stratified by AKI (non-AKI vs AKI). AKI = acute kidney injury, ALF = acute liver failure.

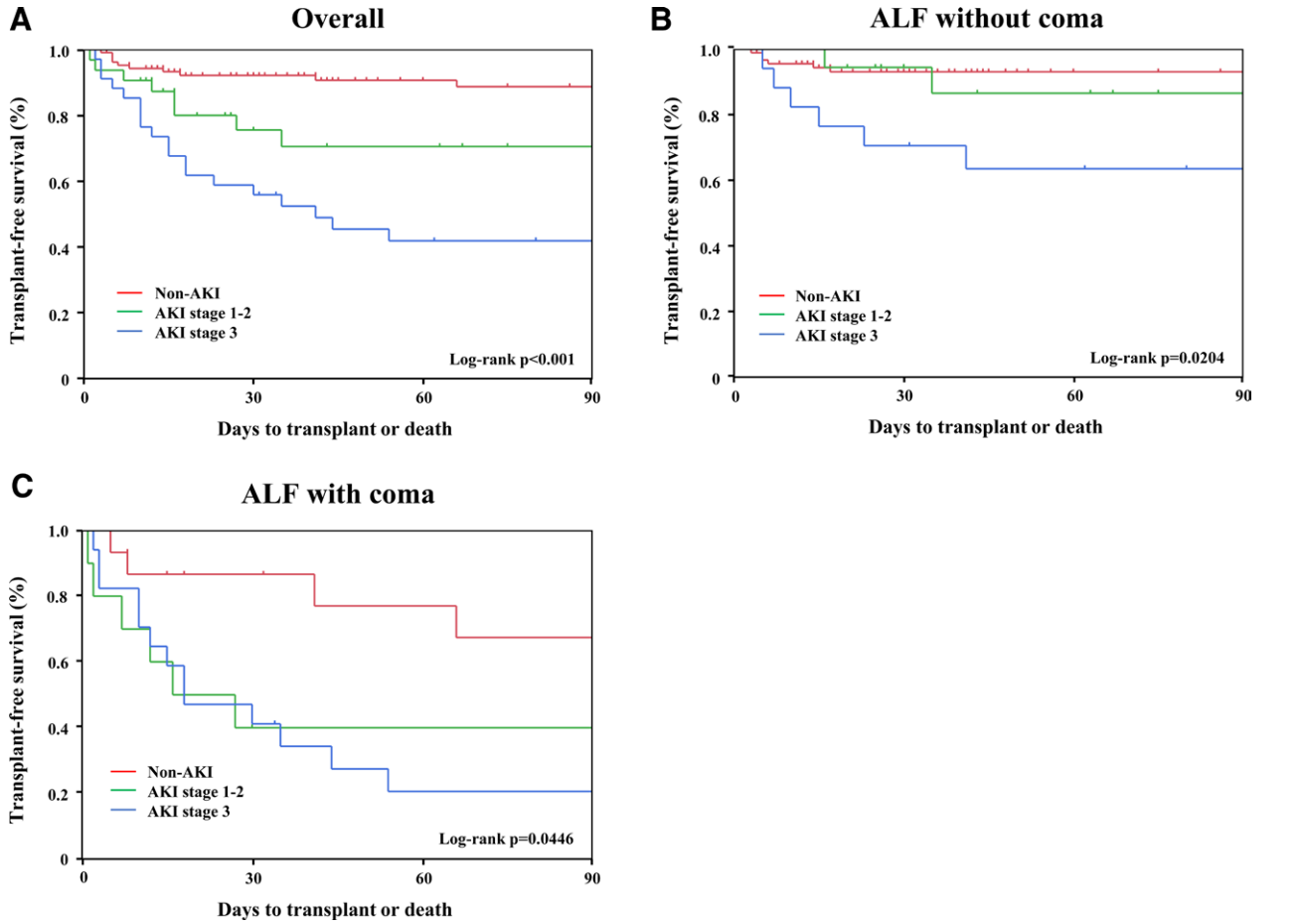

Figure 3. Kaplan–Meier survival curves for the transplant-free survival of ALF patients stratified by AKI stage (non-AKI vs AKI stage 1-2 vs AKI stage 3). AKI = acute kidney injury, ALF = acute liver failure.

mL vs without coma 61.9 ± 62.2 pg/mL, P = .8542; Figure S2b, http://links.lww.com/MD/K614). MELD score was significantly related with TNF-α (R = 0.46, P = .0002; Figure S3, http://links.lww.com/MD/K615), whereas IFN-γ and IL-6 showed no significant relation (IFN-γ: r = –0.02, P = .847, IL-6: R = 0.08, P = .6285; Figure S3, http://links.lww.com/MD/K615).

4. Discussion

In this study, multivariate analysis revealed that AKI complicated in ALF is strongly associated with TNFα independent of the presence of infection. A further novel finding of our study was that ALF patients with AKI have reduced transplant-free survival, regardless of the presence of hepatic coma.

AKI is one of the common complications of ALF. As circulatory changes such as decreased systemic vascular resistance and increased cardiac output is observed in ALF, it has been proposed that this is the pathogenesis of AKI in ALF.[10] However, in the early stages of ALF animal models, vasodilatation is observed in systemic organs such as muscle and the kidneys[11,12] whereas hepatorenal syndrome is limited to the splanchnic circulation. Furthermore, the mean hepatic venous pressure gradient in ALF with AKI is significantly lower than that in hepatorenal syndrome.[13–15] These findings showed another mechanism in AKI development in ALF.

Several studies have found elevated levels of proinflammatory cytokines including TNF-α in ALF patient.[16–18] SIRS is reported to be linked with AKI developed in ALF[7]; however, the relationship between proinflammatory cytokines and AKI developed in ALF has not been revealed yet. Our research demonstrated that the serum TNF-α level was important associated with AKI in ALF. Furthermore, multivariate analysis affirmed that TNF-α was an independent risk factor for the development of AKI. A lipopolysaccharide (LPS)-induced mouse sepsis model was used to investigate the pathological role of TNF-α on AKI in the setting of sepsis. Because TNF receptor 1 (TNFR1) is expressed in glomerular and peritubular endothelial cells in the kidney,[19] TNFR1 knockout[20] and soluble TNF receptor administration[21] alleviated LPS-induced renal failure. TNF-α/high mobility group box 1 (HMGB1) inflammation signaling pathway was found to play an important role in the LPS/D-galactosamine mouse model, which develops AKI and ALF at the same time, and TNF-α inhibitors alleviated liver and kidney pathological damages.[22] It is feasible that TNF-α could cause AKI via TNFR1 in glomerular and peritubular endothelial cells in the kidney in the setting of ALF as with sepsis. Multivariate analysis also affirmed that female gender was an independent risk factor for the development of AKI. This finding was consistent with AKI practice guidelines, which state that female gender is one of the "shared susceptibility factors" that increase the risk of AKI.[23]

Cytokine removal using continuous renal replacement therapy with polyacrylonitrile membrane has been shown to improve septic patient outcomes.[24,25] Plasma exchange has also been shown to reduce TNF-α, histone-related DNA (a DAMP family member), IL-6, and ammonia, resulting in improved coagulopathy in ALF patients.[26,27] Furthermore, high-volume plasma exchange was reported to improve transplant-free survival rates in ALF patients.[27] This study demonstrated TNF-α was an independent risk factor linked with AKI. Even in the

absence of hepatic coma, the transplant-free survival rate of ALF was significantly associated with the presence and severity of AKI. These extracorporeal blood purification techniques to remove serum inflammatory cytokines, including TNF-α, may improve the prognosis of ALF patients by suppressing hepatitis and preventing AKI development.

In Japan, the Intractable Hepato-Biliary Diseases Study Group defines ALF as "prothrombin time values of 40% or less of the standardized values or international normalized ratios of 1.5 or more caused by severe liver damage" and divides ALF into 2 subgroups; ALF with hepatic coma, which corresponds to ALF in the US and Europe, and ALF without hepatic coma.[4] AKI has been shown to worsen the prognosis of ALF patients with hepatic coma[5,28]; but its prognostic significance in ALF without hepatic coma has yet to be determined. Despite the absence of hepatic coma, our study found that ALF patients with AKI have lower transplant-free survival rates at 90 days. Given that hepatic coma typically develops as ALF progresses, early therapeutic intervention to suppress AKI development may improve ALF patients' prognosis.

Our study has some potential limitations. First, this is a single-center study with a small sample size. Further study with a larger cohort assigned from multiple institutions is needed. Furthermore, because ALF patients receive multidisciplinary care, drug-induced kidney dysfunction cannot be completely avoided.

In conclusion, we demonstrated that AKI complicated in ALF is strongly associated with TNF-α and worsens the transplant-free survival rate even in the absence of hepatic coma. Given that TNF-α may play a role in the development of AKI, the therapeutic interventions to remove inflammatory cytokines, such as plasma exchange, and extracorporeal blood purification, should be considered in ALF patients before the onset of hepatic coma to prevent AKI and improve ALF patients' prognosis.

Acknowledgments

We would like to thank Enago (https://www.enago.jp/) for the English language review.

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