CLIF-C Organ Failure Score and Liver Volume Predict Prognosis in Steroid-Treated Severe Acute Autoimmune Hepatitis

Akihiko Ikura,[1] Po-sung Chu [ID],[1] Nobuhiro Nakamoto,[1] Keisuke Ojiro,[1,2] Nobuhito Taniki,[1] Aya Yoshida,[1] Masahiro Shinoda,[3] Rei Morikawa,[1] Karin Yamataka,[1] Fumie Noguchi,[1] Hitomi Hoshi,[1] Shingo Usui,[1,4] Hirotoshi Ebinuma,[1,5] Yuko Kitagawa,[3] Hidetsugu Saito,[1,6] and Takanori Kanai[1]

Controversies and debates remain regarding the best management of severe acute-onset autoimmune hepatitis (SA-AIH) due to the lack of useful outcome or complication prediction systems. We conducted this clinical practice-based observational study to clarify whether Chronic Liver Failure Consortium Organ Failure scores (CLIF-C OFs) and the computed tomography–derived liver volume to standard liver volume (CTLV/SLV) ratio at admission to a tertiary transplant center can predict outcomes and complications due to infection. Thirty-four consecutive corticosteroid-treated patients with SA-AIH from 2007 to 2018 were included. Severe hepatitis was defined as an international normalized ratio (of prothrombin time) over 1.3 any time before admission. Of the 34 corticosteroid-treated patients with SA-AIH inclusive of 25 (73.5%) acute liver failure cases, transplant-free survival was observed in 24 patients (70.6%). Any infection was noticed in 10 patients (29.4%). CLIF-C OFs, at the cutoff of 9, significantly predicted survival ($P = 0.0002$, log-rank test), outperformed the Model for End-stage Liver Disease system in predicting outcome ($P = 0.0325$), and significantly discriminated between liver transplant and death in a competing risk analysis. SA-AIH was characterized as having decreased CTLV/SLV, which was also predictive of survival ($P < 0.0001$). Interestingly, CLIF-C OFs, especially the subscores for respiratory dysfunction, also predicted infection ($P = 0.007$). *Conclusion:* In corticosteroid-treated patients with SA-AIH, CLIF-C OFs and CTLV/SLV ratios predicted both survival outcome and complications due to infection. Further investigation is warranted to determine whether making decisions based on CLIF-C OFs or CTLV/SLV ratios is useful. (*Hepatology Communications* 2020;4:1019-1033).

Autoimmune hepatitis (AIH) is an immune-mediated necro-inflammatory disease that typically causes chronic progressive liver injury if left untreated. However, it is estimated that about 20%-25% of patients with AIH have an acute presentation[1,2], which has been reported to be a major cause of acute liver failure (ALF).[3,4] AIH with an acute presentation may display unapparent clinical findings and is usually difficult to diagnose.[5] An increasing number of studies are also focusing on

ALF with indeterminate causes. Some experts have demonstrated that these cases might be reclassified as probable AIH by a review of serological or clinical demographics[6,7] or by examining histopathological features characteristic of autoimmunity.[8] It has been approximated that up to 50% of indeterminate ALF cases might have an autoimmune background.

Although AIH was the first liver disease for which medical therapeutic intervention with corticosteroids demonstrated efficacy in controlled clinical studies,[9,10] the proper management of patients with severe acute-onset AIH (SA-AIH) is still highly debated.[11,12] Current international guidelines suggest treating patients with SA-AIH with high doses of intravenous corticosteroids ($\geq$ 1 mg/kg) in a timely manner, and listing the patient for urgent liver transplantation (LT) if improvements are not observed within 1-2 weeks.[2,13] However, the definitions of "responsiveness" or "improvement" are still not established.[11] One of the most challenging issues is the lack of useful prognostic systems to guide in the choice of adequate immunosuppression and the best timing for LT in patients with SA-AIH. Yeoman et al. demonstrated that in 23 corticosteroid-treated patients with ALF due to AIH, no significant difference was observed between responders or failures

in the Model of End-Stage Liver Disease (MELD) score, which is the most extensively used prognostic system for ALF.[14] Another challenging issue is whether subsequent complications of infection in corticosteroid-treated patients with SA-AIH can be predicted. Severe infection or sepsis (major complications of corticosteroid treatment) may hinder proper timing for LT, which is the only established therapeutic choice for ALF with advanced encephalopathy.[15,16]

The Chronic Liver Failure Consortium Organ Failure scores[17] (CLIF-C OFs) developed by the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) Consortium is a prognostic system that is derived from the simplification of CLIF-sequential organ failure assessment scores (CLIF-SOFAs), a scoring system adapted from SOFA scores. SOFA scores are used widely in intensive care units.[18] CLIF-C OFs consist of six subscores (ranging from 1 to 3) that evaluate organ dysfunction, including dysfunction of the liver, kidney, coagulation, brain, circulation and respiration, and are useful for predicting prognosis in acute decompensation of liver cirrhosis or acute-on-chronic liver failure (ACLF).[19] Patients with SA-AIH usually present with acute illness, complicated by infection or sepsis, and are in need of critical care. Therefore,

ARTICLE INFORMATION:

From the [1]Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan; [2]Department of Gastroenterology and Hepatology, Tokyo Dental College Ichikawa General Hospital, Ichikawa City, Japan; [3]Department of Surgery, Keio University School of Medicine, Tokyo, Japan; [4]Department of Gastroenterology and Hepatology, National Hospital Organization Saitama Hospital, Wako City, Japan; [5]Department of Gastroenterology, International University of Health and Welfare School of Medicine, Narita City, Japan; [6]Division of Pharmacotherapeutics, Keio University School of Pharmacy, Tokyo, Japan.

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO:

Po-sung Chu, M.D., Ph.D.
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Keio University School of Medicine
35 Shinanomachi, Shinjuku-ku
Tokyo 160-8582, Japan
E-mail: pschu0928@iCloud.com
Tel.: +81-3-3353-1211
or

Takanori Kanai, M.D., Ph.D.
Division of Gastroenterology and Hepatology
Department of Internal Medicine
Keio University School of Medicine
35 Shinanomachi, Shinjuku-ku
Tokyo 160-8582, Japan
E-mail: takagast@z2.keio.jp
Tel.: +81-3-3353-1211

the usefulness of the SOFA-based CLIF-C OFs in predicting the outcomes of these patients is of clinical interest.

Our previous report demonstrated that reduced liver volume is a negative prognostic factor for ALF.[20] The presence of liver atrophy is also one of the indicators for considering urgent LT in the scoring system applied by the Japanese national guidelines.[21] According to a recent study by Zabron et al., ALF due to AIH usually presents a more indolent clinical course and is characterized by reduced liver volumes when compared with acetaminophen-associated ALF or ALF due to viral infection.[22] Whether the severity of liver volume reduction is associated with prognosis in corticosteroid-treated SA-AIH is still not elucidated.

In this study, we used a detailed comparison of clinical parameters collected from corticosteroid-treated patients with SA-AIH primarily at admission to clarify whether CLIF-C OFs or liver volume analyses would be prognostic and if they are associated with subsequent infection complications.

Materials and Methods

STUDY PARTICIPANTS

The institutional review board of Keio University School of Medicine approved this observational study (No. 20120395 and No. 20160453) according to the guidelines of the 1975 Declaration of Helsinki (2008 revision). Study participants were prospectively recruited, and each participant provided previous written informed consent to blood sampling, study participation, and analysis of clinical data. All study participants received standard care and treatment according to their clinical presentations. All analyses were conducted retrospectively.

Between June 2007 and September 2018, consecutive 113 adult patients who were admitted to our tertiary center, a transplant center in metropolitan Tokyo, due to acute liver dysfunction (no known background chronic liver diseases) with prolonged international normalized ratio (INR) of prothrombin time over 1.30 were observed. Severe hepatitis was defined as acute liver injury with an INR over 1.30, a cutoff with significant prognostic value as reported by Mawatari et al.[23] We finally included 57 cases who had SA-AIH

(34 cases), severe acute hepatitis of indeterminate causes (SAH-IND, 15 cases), or severe acute hepatitis due to drug-induced liver injury (SAH-DILI, 8 cases), as shown in Supporting Fig. S1. Because SAH-IND and SAH-DILI were thought to have possible autoimmune background,[8,24] and may not be excluded from one another at the early period of management, they were chosen to be controls for SA-AIH in the subanalyses. In most cases, laboratory data and image studies performed at the time of admission to our hospital were used for analysis in order to maintain a meaningful and thorough analysis unless otherwise specified. Most patients were transferred within a median of 3 days (range 0-6 days), after patients seeking medical help. Background characteristics of SA-AIH, SAH-IND, and SAH-DILI are compared in Table 1.

The primary predetermined endpoint was survival outcome, which included transplant-free survival, LT, and death based on the patients' status within 180 days of admission. Transplant-free survival was defined as survival with improved liver function by standard medical management without LT. No donor organs were obtained from executed prisoners or other institutionalized persons. The secondary predetermined endpoint was complication by any infectious episodes within 180 days of observation (defined subsequently).

DIAGNOSIS

Because there is not a validated diagnostic criteria for acute-onset AIH, we first applied the 1999 International Autoimmune Hepatitis Group (IAIHG) criteria[25] for typical chronic AIH for diagnosis. However, because the 1999 IAIHG criteria has about 60% positive predictive value in AIH cases presented as ALF,[26] total clinical perception and evaluation including treatment responsiveness were also applied. The severity of acute-onset AIH was defined according to the Japanese clinical practice guideline for AIH.[27] In short, SA-AIH is defined as the acute onset of symptoms of AIH with decreased prothrombin activity less than 60% (e.g., INR over 1.30 in our hospital) at any time before admission in a patient who does not have any previous signs or symptoms of liver diseases. It is note-worthy that although the standard definition of severe acute AIH is lacking and still debatable, the latest American Association for the Study of Liver Diseases (AASLD) guideline for AIH suggests an INR of prothrombin time

TABLE 1. BACKGROUND CHARACTERISTICS COMPARISON OF THE STUDY SUBJECTS IN SA-AIH, SAH-IND, AND SAH-DILI GROUPS

Parameters	SA-AIH	SAH-IND	SAH-DILI	P
N	34	15	8	—
Age, years	52 [40.5-59.3]	39 [30-58]	51 [30.5-69.8]	0.32
Sex, male/female	11 (32%)/23 (68%)	8 (53%)/7 (47%)	6 (75%)/2 (25%)	0.06
Type of disease pattern				0.26
Severe acute hepatitis	9 (26.5%)	3 (20.0%)	2 (25.0%)	—
ALF without HE	14 (41.2%)	4 (26.7%)	3 (37.5%)	—
ALF with HE over grade 2	11 (32.3%)	8 (53.3%)	3 (37.5%)	—
Clinical presentation				
AST, maximum before admission, IU/L	692 [447-1,102]	531 [243-1,478]	419 [86-1,927]	0.21
ALT, maximum before admission, IU/L	641 [347-1,124]	688 [288-2,969]	417 [240-1,776]	0.43
Platelet count, $\times 10^4/\mu L$	13.6 [8.3-18.3]	8.3 [3.2-13.1]	15.7 [10.9-34.8]	0.03*
INR	1.85 [1.45-2.41]	2.30 [1.48-3.36]	1.82 [1.30-2.37]	0.20
T-Bil, mg/dL	16.7 [7.7-25.1]	16.5 [6.8-28.7]	18.6 [9.7-36.7]	0.72
Cre, mg/dL	0.7 [0.54-0.89]	0.7 [0.52-0.88]	1.02 [0.69-2.43]	0.22
CTLV/SLV ratio	0.75 [0.57-0.93]	0.96 [0.62-1.28]	0.96 [0.70-1.13]	0.04*
AIH diagnosis				
IAIHG score (pretreatment)	13 [11-17]	7 [6-9]	2 [1-6]	< 0.0001***
ANA ≥ 80 times	13 (38%)	0 (0%)	0 (0%)	0.004**
ANA ≥ 40 times	18 (53%)	0 (0%)	2 (25%)	0.005**
Other autoantibodies/ANA < 40 times[†]	2/16 (12.5%)	2/15 (13.3%)	1/6 (16.7%)	0.07
IgG, mg/dL	1,592 [1,218-2,069]	1,197 [1,009-1,381]	1,295 [989-1,833]	0.03*
Histology available, n (%)	24 (70.6%)	10 (66.7%)	6 (75%)	0.07
Medical management				
Corticosteroids, n (%)	34 (100%)	10 (67%)	8 (100%)	0.90
Accumulated corticosteroid dose[†], mg	5,260 ± 2,360	3,100 ± 3,020	1,740 ± 1,470	0.0005**
Immunosuppressant combined, n (%)	11 (32%)	1 (6.7%)	0 (0%)	0.10
Use of CHDF/PE, n (%)	12 (35%)	9 (60%)	4 (50%)	0.26
Prognostic systems				
MELD	25 [21-29]	27 [20-29]	27 [26-32]	0.46
KCC, positive/negative	17 (50.0%)/17 (50.0%)	7 (46.7%)/8 (53.3%)	4 (50.0%)/4 (50.0%)	0.98
CLIF-C OFs	9 [7-11]	10 [9-12]	10 [9-11]	0.17
Infectious episodes complicated, n (%)	10 (29.4%)	5 (33.3%)	1 (12.5%)	0.55
Outcomes				0.53
Transplant-free survivors	24 (70.6%)	9 (60.0%)	5 (62.5%)	—-
Transplanted	4 (11.8%)	1 (6.7%)	2 (25.0%)	—
Died without LT	6 (17.6%)	5 (33.3%)	1 (12.5%)	—

Note: The data from clinical parameters and prognostic systems used for analyses were retrieved at admission. Data are expressed as median with the interquartile range within brackets, or numbers with percentage within parentheses.
*P < 0.05.
**P < 0.01.
***P < 0.0001.
[†]Inclusive of two SA-AIH cases with positive anti-LKM-1 antibody, one SAH-IND case with both positive antismooth muscle antibody and positive anti-LKM-1 antibody, one SAH-IND case with positive anti-LKM-1 antibody, and one SAH-DILI case with positive anti-LKM-1 antibody.
Abbreviations: ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CHDF/PE, continuous hemodiafiltration/plasma exchange; Cre, creatine; IgG, immunoglobulin G; T-Bil, total bilirubin.

over 1.5,[13] which differs from our current study and the Japanese guideline. The reference range of serum immunoglobulin G is 870 to 1700 mg/dL. Autoantibodies including antinuclear antibody, antismooth muscle antibody, and anti-LKM-1 antibody were measured. Acute exacerbation of chronic

progressive AIH was excluded primarily by history-taking (none of the included study subjects presented persistent liver dysfunction over 6 months) with a global assessment of clinical findings of cirrhosis. Drug-induced liver injury (DILI) was diagnosed using the diagnostic scale of Digestive Disease Week–Japan 2004,[28] which is similar to the Roussel Uclaf Causality Assessment Method of the Council for International Organizations of Medical Sciences.[29] Notably, none of the eight cases of SAH-DILI were due to acetaminophen-associated DILI. Other causes of acute liver injury, including viral infection, Wilson disease or other hemodynamic disorders, and the definition of an "indeterminate" cause, were described previously.[30] Because corticosteroid response is also a clinical feature supporting the diagnosis of AIH, two cases that had first been categorized as "indeterminate" were re-assessed for possible histological autoimmune features[8] (distinctive patterns of massive hepatic necrosis, presence of lymphoid follicles, plasma cell-enriched inflammatory infiltrate, and central perivenulitis) and corticosteroid response, and were re-assigned as AIH group. This retrospective re-assignment was to avoid any underdiagnosis of acute-onset AIH, and was coherent with the methods reported by Karkhanis et al.[24] ALF was diagnosed according to the criteria for ALF in Japan.[31]

STANDARD MANAGEMENT AND CORTICOSTEROID REGIMEN

Immediately after admission and blood sampling, computed tomography (CT) from the head to the pelvis was performed and medical management was initiated. Because the final diagnosis of AIH, DILI, or hepatitis due to indeterminate causes is time-consuming, and the exclusion of one another is needed at times, corticosteroids have to be initiated in this rapidly deteriorating disease state. Corticosteroids for cases considered as AIH (prednisolone, at least 0.6 mg/kg/day, or intravenous methylprednisolone, 1 g/day given as a 3-day pulse therapy with subsequent maintenance corticosteroids), for cases of SAH-DILI satisfying the Hy's Law,[13,32] or SAH-IND cases with clinical perceptions favoring higher IAIHG scores with elevated serum aminotransferases, were administered in a timely manner. Due to the extreme insufficiency of liver donors in Japan, even patients with hepatic encephalopathy (HE) over grade 2 are allowed to have this "corticosteroid trial" for several days, as long as they are intensively cared. Corticosteroids were decreased gradually, and azathioprine was started in the recovery phase as generally illustrated in international guidelines.[2] Based on a global (laboratory and clinical) assessment of the patient, second-line immunosuppression such as calcineurin inhibitors were initiated, as reported by Yeoman et al.[33], especially in those with hyperbilirubinemia, as initiation of azathioprine is not suggested by international guidelines by EASL,[2] whereas the AASLD practice guidance suggests against using azathioprine in cases of acute AIH with INR over 1.5.[13]

Patients diagnosed with ALF were managed as outlined by Sugawara et al. and in our previous report.[30,34] Liver biopsies were performed as soon as possible before coagulation dysregulation deteriorated. However, in patients with ALF and a generally unstable condition, liver biopsies were not performed, as routine liver biopsies are discouraged by the American Gastroenterological Association Institute guidelines.[35] In patients who were highly suspected to have AIH, liver biopsies were performed as soon as the coagulation dysregulation improved.

MONITORING AND DIAGNOSIS OF INFECTION

The occurrence of bacterial infection was carefully monitored with blood/urine/tissue fluid surveillance, image studies, and appropriate culture sampling before antibiotics. Prophylactic antibiotics or antifungal therapies were not routinely administered. For patients under prolonged immunosuppression over 4 weeks, prophylactic sulfamethoxazole trimethoprim for *Pneumocystis jiroveci* pneumonia was considered. (1, 3)-β-D-glucan and cytomegalovirus antigenemia (pp65-positive cells in peripheral blood) were monitored weekly or monthly as appropriate.

INDICATIONS FOR LT

We used the guidelines suggested by the Intractable Hepato-Biliary Diseases Study Group in Japan or its minor revision in 2012[21,36] during the study period to evaluate indications for LT. According to this guideline, patients with HE over grade 2 at primary assessment were evaluated using the scoring system suggested by

Naiki et al.,[21] which consisted of the duration from onset to HE, prothrombin activity, total bilirubin, ratio of direct-to-total bilirubin, platelet count, and liver atrophy. A patient with a collective score more than 5 at the initial assessment was evaluated for LT. After 5 days of appropriate intensive care, LT was considered in cases in which the INR did not recover to less than 1.5 or HE did not recover to grade 1 or less (secondary assessment). After approval by the institutional review board, patients for whom LT was considered appropriate underwent this procedure if a living donor existed, as illustrated by Yasutomi et al.,[37] or else patients were enrolled on the waiting list of the national allocation system for a cadaveric liver.

PROGNOSTIC SYSTEMS

Clinical presentations and laboratory data collected on the day of admission to our liver unit were used for the evaluation of MELD,[38] King's College Hospital criteria (KCC) for non-acetaminophen-associated ALF,[39] and CLIF-C OFs (also known as simplified CLIF-SOFA scores).[17,19] To obtain a detailed analysis of the diagnostic ability of CLIF-C OFs, the six subscores (liver : total bilirubin; coagulation : INR; kidney : creatinine; central nervous system [CNS] : West-Haven HE grade; circulation : mean blood pressure and/or the use of vasopressors; and respiration : SpO_2/FiO_2 ratio and/or the use of mechanical ventilation unrelated to loss of CNS drive due to HE) were analyzed individually.

CT-DERIVED LIVER VOLUME ANALYSIS

CT-derived liver volume (CTLV) was calculated using whole-body CT films examined at admission to our center, as illustrated in previous studies.[20,40] In short, using ImageJ (version 1.52a) developed by the National Institutes of Health, serial transverse CT images of 5-mm intervals from the most superior to the most inferior poles of the liver were all used for calculation after excluding the major vessels and the gallbladder. Body surface area was calculated using the Mosteller method. Standard liver volume (SLV) was calculated using the formula reported by Urata et al. (i.e., SLV [mL] = 706.2 × bovine serum albumin [m²] + 2.4).[41] The CTLV/SLV ratio was used for comparison and analysis.

STATISTICAL ANALYSIS

The data were analyzed using JMP12 (SAS Institute, Inc., Cary, NC) and are expressed as medians with interquartile ranges or as mean ± SD, as appropriate. Graphs and linear correlations were constructed using Prism 8.1 (GraphPad Software, Inc., San Diego, CA). Nonparametric Kruskal–Wallis tests were used to assess differences among groups. Categorical variables were analyzed using chi-square analysis. Spearman correlation was used for correlation analysis. Area under receiver operating characteristic (AUROC) analysis was performed to confirm the usefulness of various parameters for predicting outcome and generating optimal cutoffs based on the Youden Index. The DeLong method was used to compare differences among AUROC curves. Kaplan–Meier analysis was used to determine the cumulative percentage of survival, and differences among groups were compared using log-rank tests. Competing risk estimates of cumulative incidence function for death (with transplantation as a competing risk) were calculated using Gray's test. Because the extreme liver donor insufficiency causes longer wait-list time even in patients with ALF in Japan, and because infectious episodes such as sepsis might hinder LT, we considered that the competing risk analysis was necessary. R software (version 3.3.3) was used for internal validation performed by bootstrapping analysis and for competing risk analysis. The results were considered significant when P was less than 0.05.

Results

OVERALL CLINICAL CHARACTERISTICS AND OUTCOMES

Clinical characteristics and outcomes are summarized in Table 1. Of the 57 patients recruited in this study, 73.7% (42 of 57) presented with ALF, and 50% (21 of 42) presented with HE over grade 2 at admission. Seven patients (12.3%) underwent urgent LT, and all of them survived for at least 6 months. Thirty-eight patients (66.7%) survived without LT for at least 180 days. Among the remaining 12 patients (21.1%) who died without LT within 180 days, 6 patients died on the wait list for cadaveric LT (median wait time of 58 days; range 11-110 days) due to sepsis (three

cases) and multi-organ failure (three cases); the other 6 patients died without consideration of LT because of old age (four cases), comorbid extrahepatic malignancy (one case), and uncontrolled sepsis before the emergence of HE (one case).

Patients with SA-AIH, SAH-IND, or SAH-DILI differed significantly in their CTLV/SLV ratio (P = 0.04), platelet count (P = 0.03) at admission, and in clinical features related to the diagnosis and management of AIH, including IAIHG scoring, autoantibody positivity, and the use of corticosteroids. However, the three groups did not differ in other clinical parameters and prognostic systems assessed at admission, nor in infection episode complications or overall clinical outcomes (Table 1). A Kaplan-Meier analysis of transplant-free survival also demonstrated no significant difference among the three groups (Fig. 1). Among patients who did not survive spontaneously, 4 of 5 (80%) with SAH-IND died or underwent LT within 14 days compared with only 2 of 8 (25%) with SA-AIH who did so during the same time period (P = 0.09), suggesting a more indolent course in corticosteroid-treated patients with SA-AIH.

In the SA-AIH group, 30 cases (88.2%) presented with at least 10 points of the pretreatment IAIHG 1999 scoring[25] and could therefore be diagnosed as probable-to-definite AIH. The remaining four cases (11.8%) that presented with less than 10 points all survived and responded well to corticosteroids, and their liver histology all showed typical features of AIH during subsequent relapses. It is also noticeable that the positivity (≥80 times) of antinuclear antibody in this group was 38%. Lower positivity for autoantibodies in acute-onset AIH has been previously reviewed.[42]

CLINICAL PARAMETERS THAT PREDICTED TRANSPLANT-FREE SURVIVAL IN CORTICOSTEROID-TREATED PATIENTS WITH SA-AIH

Of the 34 corticosteroid-treated patients with SA-AIH, 24 (70.6%) survived without LT (transplant-free survivor; transplant-free survivor group), and 10 (29.4%) either underwent urgent LT (4; 11.8%) or died (6; 17.6%; transplanted/died group). In a univariate analysis, patients in the transplant-free survivor group had a significantly smaller percentage of HE over grade 2, less prolonged INR, and higher CTLV/SLV ratio compared with the transplanted/died group (all P < 0.05). KCC and CLIF-C OFs
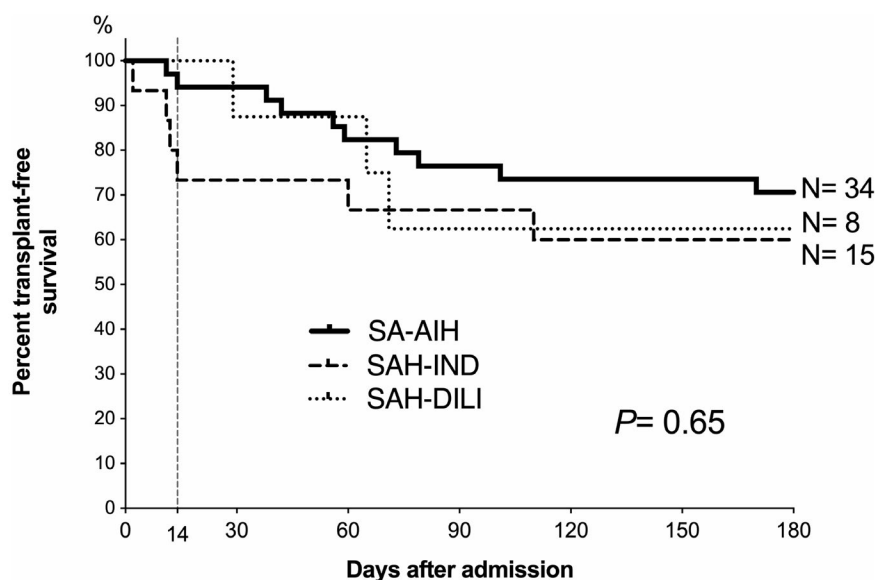
FIG. 1. Survival analysis of CLIF-C OFs in 34 patients with severe acute-onset AIH. In a total of 57 patients recruited in this study, transplant-free survival from the day of admission up to 180 days is compared with background diseases by Kaplan-Meier analysis, with 10 SA-AIH events, six SAH-IND events, and three SAH-DILI events. There is a tendency for a patient with SAH-IND to encounter an event within 14 days, compared with SA-AIH (P = 0.09 from a log-rank test).

evaluated at admission were significantly different; however, the prognostic ability of the MELD system did not reach statistical significance ($P = 0.05$). Patients complicated with infectious episodes were significantly less likely to survive without LT. These results are summarized in Table 2. The details of each CLIF-C OF subscore were also analyzed. Only the subscores of coagulopathies, brain, and respiratory dysfunction reached statistical significance (Table 2).

CLIF-C OFs WERE SUPERIOR TO THE MELD SYSTEM IN PREDICTING TRANSPLANT-FREE SURVIVAL

When the MELD system (cutoff at 24 points), KCC, and CLIF-C OFs (cutoff at 9 points) were compared for their diagnostic ability to predict transplant-free survival in corticosteroid-treated patients with SA-AIH, only KCC and CLIF-C

TABLE 2. BACKGROUND CHARACTERISTICS AND CLINICAL PARAMETERS COMPARISON OF TRANSPLANT-FREE SURVIVOR OR TRANSPLANTED/DIED IN SA-AIH GROUP

Parameters	Transplant-Free Survivor	Transplanted/Died	P
N (%)	24 (71%)	10 (29%)	—
Age, years	49.5 [36-60]	56 [46-60]	0.30
Sex, male/female	8 (33.3%)/16 (66.7%)	3 (30%)/7 (70%)	1.00
Clinical presentation			
HE over grade 2	2 (5.8%)	7 (70%)	0.0007**
AST, maximum before admission, IU/L	620 [436-1,127]	772 [562-1,069]	0.55
ALT, maximum before admission, IU/L	664 [320-987]	589 [394-1,162]	0.47
Platelets, $\times 10^4/\mu L$	14.7 [8.6-20.0]	12.5 [7.7-17.5]	0.47
INR	1.69 [1.38-1.86]	2.41 [1.90-2.79]	0.02*
T-Bil, mg/dL	16.7 [7.6-25.3]	16.3 [8.4-22.0]	0.88
Cre, mg/dL	0.65 [0.51-0.87]	0.83 [0.60-1.12]	0.31
NH_3, μg/dL	43 [28-56]	52 [46-81]	0.08
CTLV/SLV ratio	0.820 [0.686-0.971]	0.511 [0.386-0.577]	0.0004**
AIH diagnosis			
IAIHG score (pretreatment)	13 [11-18]	13 [11-15]	0.57
ANA ≥ 80 times	10 (76.9%)	3 (30%)	0.70
IgG, mg/dL	1,474 [1,140-1,935]	1,875 [1,236-2,456]	0.52
Medical management			
Accumulated corticosteroid dose, mg	5,130 ± 2,070	5,580 ± 3,040	0.64
Immunosuppressant combined, n (%)	10 (41.7%)	1 (10%)	0.14
Prognostic systems			
MELD	24 [19-29]	28 [25-30]	0.05
KCC, positive/negative	8 (33.3%)/16 (66.7%)	9 (90%)/1 (10%)	0.007**
CLIF-C OF score	8 [7-9]	10 [9-13]	0.0008**
Subscore: liver	3 [1-3]	3 [2-3]	0.36
Subscore: kidney	1 [1-1]	1 [1-1]	0.51
Subscore: coagulopathy	1 [1-2]	2 [1.75-3]	0.009**
Subscore: CNS	2 [1-2]	2.5 [2-3]	0.007**
Subscore: circulatory	1 [1-1]	1 [1-1]	0.51
Subscore: respiratory	1 [1-1]	1.5 [1-2.25]	0.0003**
Infectious episodes complicated, n (%)	4 (16.7%)	6 (60.0%)	0.03*

Note: The data of clinical parameters and prognostic systems retrieved at admission were used for analyses. Data are expressed as median with the interquartile range within brackets, or numbers with percentage within parentheses.
*$P < 0.05$.
**$P < 0.01$.
Abbreviations: ALS, artificial liver support; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; CNS, central nervous system; Cre, creatine; IgG, immunoglobulin G; T-Bil, total bilirubin.

OFs reached statistical significance (Table 3). Furthermore, CLIF-C OFs demonstrated statistical significance compared with MELD by the DeLong method (P = 0.0325). The diagnostic abilities of each prognostic system for SAH-IND and SAH-DILI are summarized in the Supporting Table S1. It is noteworthy that unlike with corticosteroid-treated patients with SA-AIH, MELD performed as well as KCC or CLIF-C OFs in patients with SAH-IND (Supporting Table S1).

In a Kaplan-Meier analysis, the 180-day survival curves beginning at admission demonstrated significant differences in transplant-free survival according to the CLIF-C OFs (Fig. 2A). In cases of CLIF-C OFs of 9 or higher, the median transplant-free survival is 101 days. In Figure 2B, when the competing-risk estimates of cumulative incidence function for death (with transplantation as a competing risk) were analyzed by Gray's test, only CLIF-C OFs, but not the MELD system (Supporting Fig. S2A), were

TABLE 3. COMPARISON BETWEEN AUROCS FOR DIFFERENTIATION BETWEEN TRANSPLANT-FREE SURVIVOR VERSUS TRANSPLANTED/DIED IN SA-AIH GROUP

| Parameters	Cutoff	AUROC	95% CI Lower	95% CI Upper	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	P	$P^\dagger$ vs, MELD
MELD	24	0.70	0.54	0.82	90	50	43	92	62	0.11	—
KCC	-	0.78	0.62	0.89	90	67	53	94	74	0.0066**	0.1482
CLIF-C OFs	9	0.85	0.74	0.93	100	71	59	100	79	0.0006**	0.0325*

Note: The Data of prognostic systems retrieved at admission were used for analyses.
*P < 0.05.
**P < 0.01.
†Using the DeLong method, in comparison with the MELD system.
Abbreviations: CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value.
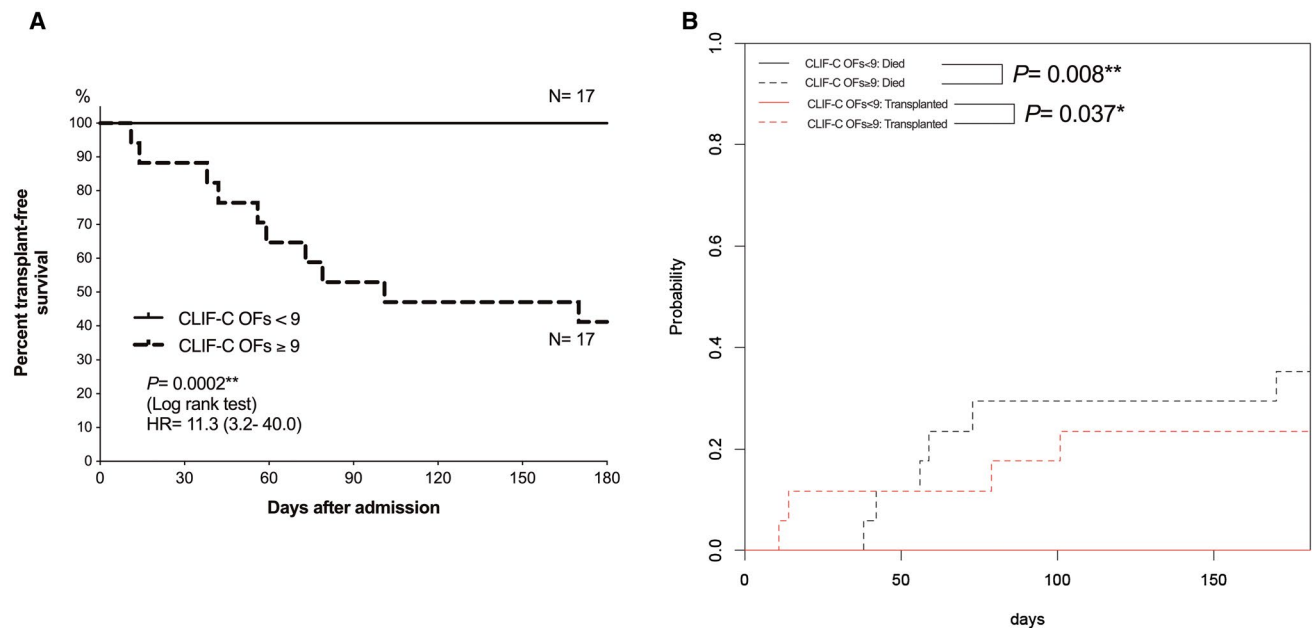
FIG. 2. Survival analysis and competing risk analysis of CLIF-C OFs in corticosteroid-treated patients with SA-AIH. In 34 corticosteroid-treated patients with SA-AIH, survival was evaluated from admission up to 180 days. Patients were stratified by CLIF-C OFs at the optimal cutoff value, as identified by the Youden Index. Kaplan-Meier analysis was performed for 180-day transplant-free survival (A), comparing 0 versus 10 events (B). Competing risk estimates of cumulative incidence function for death (with transplantation as a competing risk) using Gray's test of CLIF-C OFs. P values from log-rank tests and hazard ratios are shown. *P < 0.05; **P < 0.01.

able to significantly discriminate both transplanted cases versus transplant-free survivors (P = 0.037) and death cases versus transplant-free survivors (P = 0.008). KCC failed to significantly discriminate transplant-free survival versus death (P = 0.067; Supporting Fig. S2B).

By using 1,000 bootstrapped samples, a correlation analysis between CLIF-C OFs and outcomes in the SA-AIH group was internally validated. Bootstrap Spearman's coefficient (0.598, 95% confidence interval = 0.385-0.827) was consistent with the original Spearman's coefficient (0.615).

REDUCED CTLV/SLV RATIO PREDICTED WORSE PROGNOSIS

As given in Table 1, SA-AIH, SAH-IND, and SAH-DILI differed significantly in the CTLV/SLV ratio. When comparing transplant-free survival and transplanted/died, the CTLV/SLV ratio was significantly different only in the SA-AIH group (Fig. 3A). Associations between the CTLV/SLV ratio and various clinical parameters in each group are found in Supporting Table S2. Briefly, in the SA-AIH group, older age of onset, presence of HE over grade 2, and higher CLIF-C OFs were significantly associated with reduced CTLV/SLV ratios. When the CTLV/SLV ratio was stratified at the optimal cutoff (0.584, as indicated by the dashed grid line in Fig. 3A) as determined by the Youden index in the SA-AIH group, patients with a CTLV/SLV ratio over 0.584 had a significantly higher transplant-free survival compared to those with a CTLV/SLV ratio less than 0.584, as shown in the Kaplan-Meier analysis in Figure 3B. When competing risk estimates of cumulative incidence function for death (with transplantation as a competing risk) were analyzed by Gray's test, the CTLV/SLV ratio also demonstrated a significant ability to discriminate for both transplanted cases versus transplant-free survivors (P = 0.0079) and death cases versus transplant-free survivors (P = 0.015) (Fig. 3C). The CTLV/SLV ratio itself had a good prognostic ability (cutoff at 0.584; AUROC = 0.89; Supporting Fig. S3A), and it tended to help improve the prognostic ability of the MELD system (P = 0.06; Supporting Fig. S3B), although not the CLIF-C OFs (P = 0.49; Supporting Fig. S3C).

RESPIRATORY FAILURE SUBSCORE ASSESSED BY THE CLIF-C OFs PREDICTED INFECTIOUS COMPLICATIONS

Detailed complications of infection in the SA-AIH group and clinical outcomes are summarized in Supporting Table S3. Briefly, 10 corticosteroid-treated patients with SA-AIH (29.4%) experienced at least one episode of infection, and 4 (11.8%) of those 10 patients with bacteremia all experienced at least one other episode of infection, and all died without LT.

In this study, corticosteroid-treated patients with SA-AIH who were complicated by any episode of infection had significantly worse transplant-free survival than those without (Fig. 4A). When the clinical parameters at admission were compared using a univariate analysis between patients with any infectious complication and those without, the INR, CTLV/SLV ratio, and CLIF-C OFs were significant factors. It is noteworthy that the CTLV/SLV ratio cutoff for complications due to infection is 0.665, which is higher than that for predicting survival outcomes (0.584).

Furthermore, within the six subscores of the CLIF-C OFs, only the respiratory dysfunction subscore (i.e., SpO_2/FiO_2 ratio less than 357) was statistically significant (P = 0.007). These results are summarized in Table 4. Any patient with CLIF-C OFs over 9 or a respiratory subscore over 2 (SpO_2/FiO_2 ratio less than 357) also had a significantly lower infectious episode-free frequency than those without (Fig. 4B,C).

Discussion

To the best of our knowledge, this current study is the first to show that CLIF-C OFs and CTLV/SLV ratio are useful for predicting prognosis and complications by using only the initial clinical parameters at admission (i.e., without a subsequent response trial period).

Yeoman et al. reported that a lack of improvement in MELD scores 7 days after initiation of corticosteroid predicts treatment failure based on an analysis of 72 patients with icteric AIH, of whom 53% were not cirrhotic.[33] In another important study from Yeoman
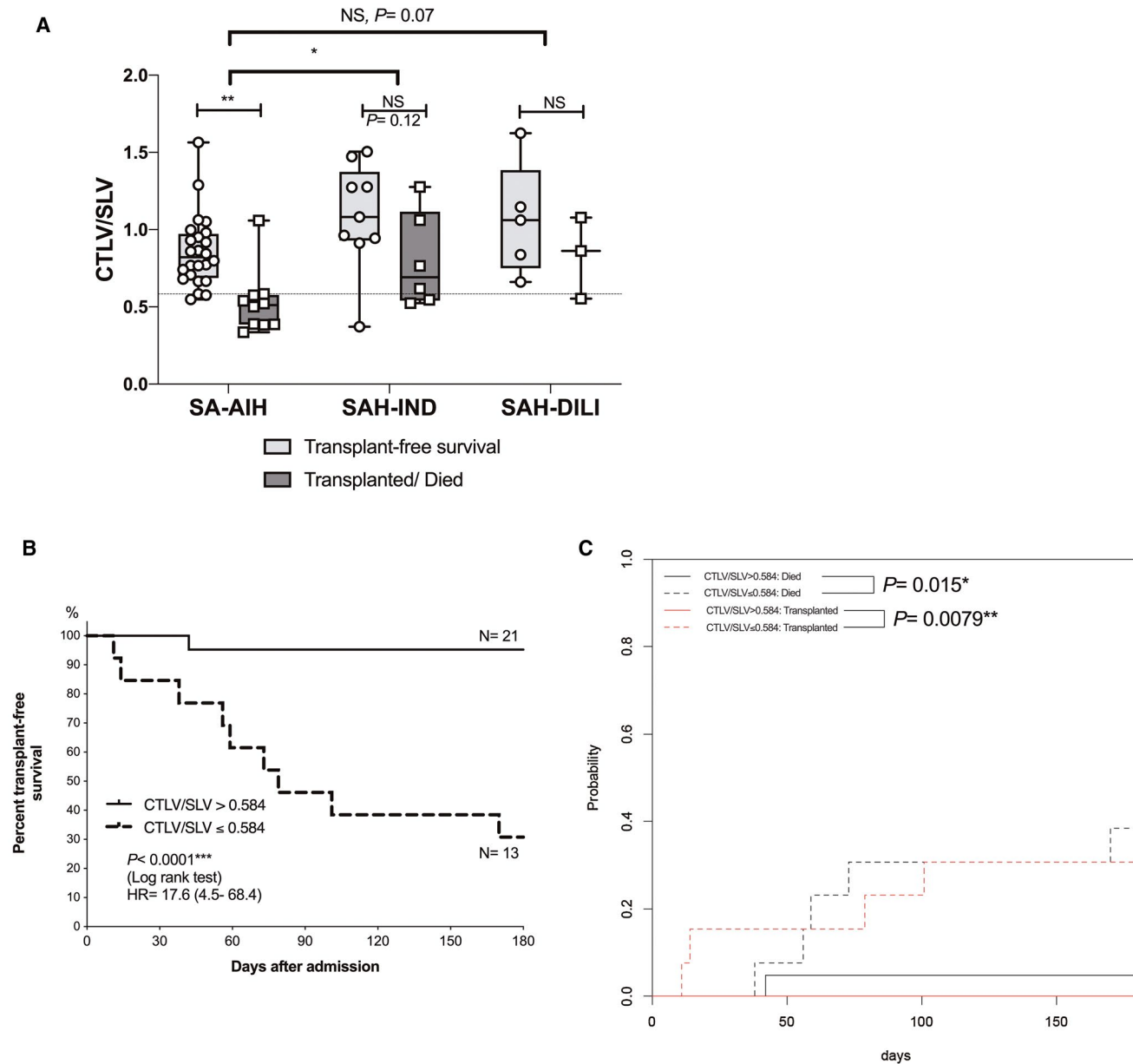
FIG. 3. CTLV/SLV ratios and their utility for survival analysis and competing risk analysis. (A) CTLV/SLV ratios evaluated at admission were stratified by survival outcomes (circle for transplant-free survival; square for transplanted/died) and were compared among patients with SA-AIH, SAH-IND, and SAH-DILI. The dotted line represents the optimal cutoff (0.584) for survival outcomes. *P* values from nonparametric Kruskal-Wallis tests are shown (*$P < 0.05$; **$P < 0.01$). (B,C) Of the 34 corticosteroid-treated patients with SA-AIH, survival from admission up to 180 days is compared. Patients are stratified by CTLV/SLV ratios at the optimal cutoff value as identified by the Youden Index. (B) Kaplan-Meier analysis was performed for 180-day transplant-free survival, comparing one versus nine events. (C) Competing risk estimates of cumulative incidence function for death (with transplantation as a competing risk) using Gray's test for CLIF-C OFs. *P* values from log-rank tests and hazard ratios are shown (*$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$). Abbreviation: NS, not significant.

et al. of 23 patients with ALF-AIH who underwent immunosuppressive therapy, MELD or the United Kingdom End-Stage Liver Disease scores did not significantly predict responsiveness or transplant-free survival.[14] De Martin et al. reported in an analysis of 128 patients with ALF-AIH that INR at admission
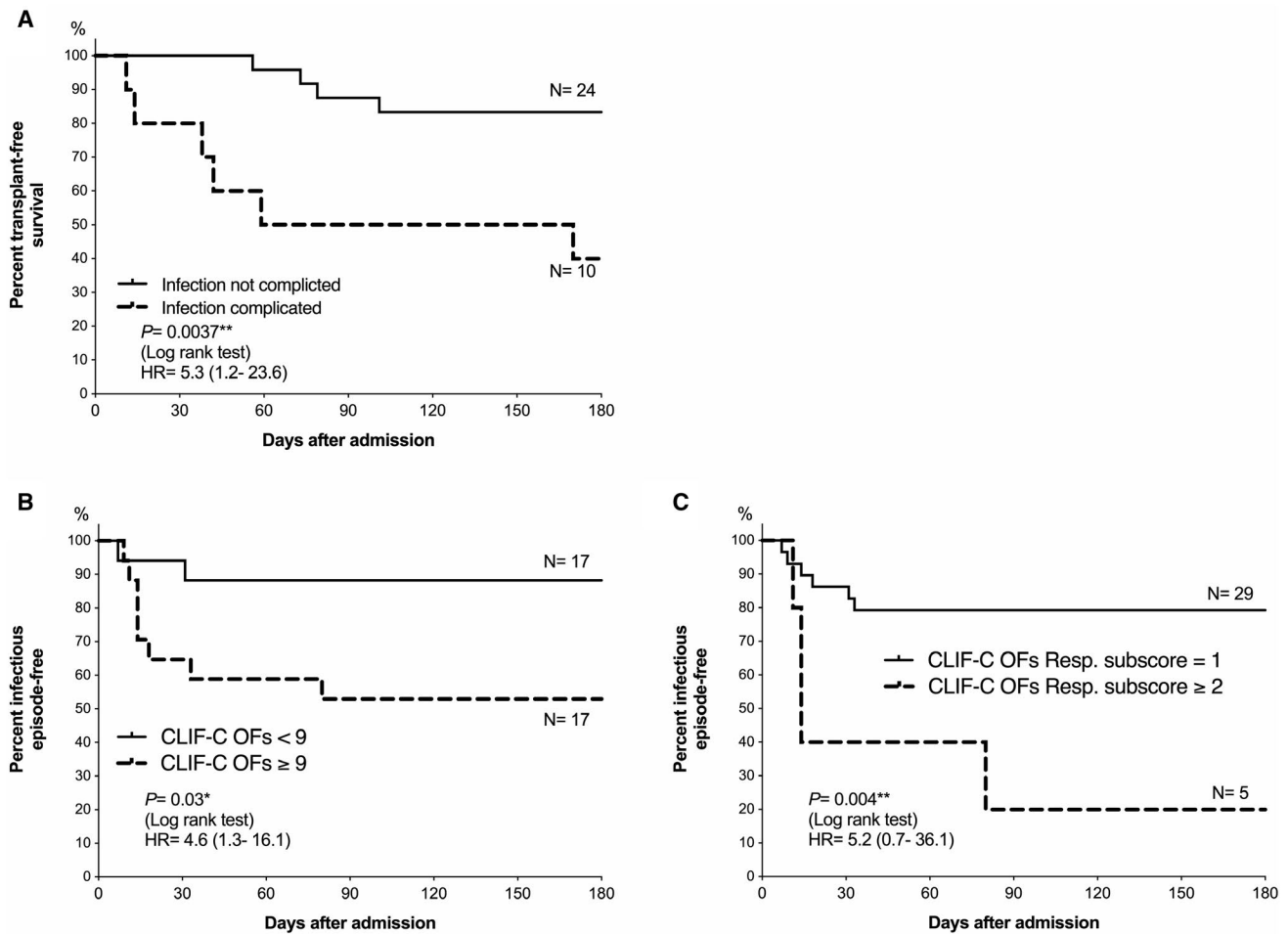
FIG. 4. Survival and frequency of infectious episode-free analyses in corticosteroid-treated patients with SA-AIH. In 34 corticosteroid-treated patients with SA-AIH, survival and frequency of infectious episode-free analyses were evaluated from admission up to 180 days. Patients were stratified by presence or absence of complications due to infection. (A) Kaplan-Meier analysis was performed for 180-day transplant-free survival, comparing four versus six events. (B,C) Kaplan-Meier analysis was performed for 180-day infectious episode-free frequency, when stratified by CLIF-C OFs (at a cutoff of 9, comparing two vs. eight events) (B) and by subscores of CLIF-C OFs in respiratory dysfunction (at a cutoff of 2, comparing six vs. four events) (C). P values from log-rank tests and hazard ratios are shown (*$P < 0.05$; **$P < 0.01$; ***$P < 0.0001$).

and improvement of bilirubin on days 3 and 7 were independently correlated with treatment response (presentation abstract at the annual AASLD meeting, 2017). Zachou et al. identified that prompt high-dose intravenous corticosteroid treatment resulted in 97% transplant-free survival in a group of 34 patients with SA-AIH and INR over 1.5 and without overt HE.[43] However, these studies may differ in some aspects, such as the definition of severity, inclusion of cirrhosis cases, unclear endpoints such as "responsiveness," lack of common rules for corticosteroid administration, intensive care and LT, descriptive analyses for complicated infections, and varying choices for controls,

which suggests that careful interpretation is needed to generalize meaningful conclusions.

Because the original SOFA score is useful for any acute-onset critical disease that needs intensive care, little doubt exists that the CLIF-C OFs may be useful for predicting prognosis in corticosteroid-treated patients with SA-AIH. What is surprising is that subscores of coagulopathies, along with those of brain and respiratory dysfunction (both are not included in the MELD system), but not liver or kidney dysfunction, are significantly correlated with survival outcomes (Table 2). In addition, we also demonstrated that the diagnostic superiority of CLIF-C

TABLE 4. BACKGROUND CHARACTERISTICS AND CLINICAL PARAMETERS COMPARISON BETWEEN PATIENTS WHO WERE COMPLICATED WITH ANY INFECTIOUS EPISODES OR NOT IN SA-AIH GROUP

Parameters	Infection Complicated	Infection Not Complicated	P
N (%)	10 (29%)	24 (71%)	—
Age, years	51 [42-63.5]	52 [36-59]	0.54
Sex, male/female	2 (20%)/8 (80%)	9 (38%)/15 (63%)	0.44
Clinical presentation			
HE over grade 2	5 (50%)	4 (17%)	0.08
Platelets, ×10^4/μL	13.5 [9.3-22.7]	14.7 [7.8-18.0]	0.53
INR	2.05 [1.84-2.82]	1.69 [1.38-2.26]	0.02*
T-Bil, mg/dL	16.6 [9.3-24.4]	16.7 [7.5-25.1]	0.75
Cre, mg/dL	0.83 [0.53-1.12]	0.65 [0.53-0.87]	0.53
NH$_3$, μg/dL	50 [40-108]	44 [32-56]	0.23
CTLV/SLV ratio	0.548 [0.386-0.728]	0.784 [0.608-0.972]	0.01*
Medical management			
Accumulated corticosteroid dose, mg	5,410 ± 2,990	5,,200 ± 2,110	0.86
Immunosuppressant combined, n (%)	4 (40%)	7 (29%)	0.69
Prognostic systems			
MELD	28 [24-30]	24 [19-29]	0.14
KCC, positive/negative	7 (70%)/3 (30%)	10 (42%)/14 (58%)	0.26
CLIF-C OF score	9.5 [8.75-12.25]	8 [7-10]	0.04*
Subscore: liver	3 [2-3]	2 [1-3]	0.10
Subscore: kidney	1 [1-1]	1 [1-1]	0.52
Subscore: coagulopathy	2 [1-3]	1 [1-2]	0.13
Subscore: CNS	2 [1-3]	2 [1-2]	0.39
Subscore: circulatory	1 [1-1]	1 [1-1]	0.52
Subscore: respiratory	1 [1-2.25]	1 [1-1]	0.007**
Outcome: Transplant-free survivor/transplanted/died	4 (40%)/2 (20%)/4 (40%)	20 (83%)/2 (8%)/2 (8%)	0.03**

Note: Data of clinical parameters and prognostic systems retrieved at admission were used for analyses. Data are shown as median with the interquartile range within brackets, or numbers with percentage within parenthesis.
*$P < 0.05$.
**$P < 0.01$.
Abbreviations: CNS, central nervous system; Cre, creatine; T-Bil, total bilirubin.

OFs over MELD observed in patients with SA-AIH was not seen in patients with SAH-IND or SAH-DILI (Table 3 and Supporting Table S1). Possible massive hepatocyte loss with subsequent liver regeneration failure might occur, as corticosteroids relieve inflammation but do not promote liver regeneration, a phenomenon that has been shown in murine models.[44] Significantly reduced CTLV/SLV ratios and inferior survival outcomes demonstrated in this study (Fig. 3A) might therefore be explained. Extrahepatic organ dysfunctions may restrain an environment that is good enough for the liver to regenerate and to maintain immune competence.

Increasing amounts of clinical and translational evidence has demonstrated that the existence of so-called "immune paralysis" contributes to the pathogenesis of ALF[45] and ACLF.[46] Recently, we reported that, in human peripheral blood, liver samples, and murine models, the decreased frequency and dysfunction of plasmacytoid dendritic cells, a key component in innate immunity, play an important role in the pathogenesis of AIH-associated acute liver failure.[47] The resemblance between the immuno-pathogenesis of ACLF and corticosteroid-treated SA-AIH may help explain why the CLIF-C OFs are useful in both ALF and ACLF.

Why the respiratory dysfunction subscore of the CLIF-C OFs is the most significant predictor of infection complications is also of interest. In a large multicenter retrospective analysis, Karkhanis et al. studied 361 patients with ALF due to AIH, indeterminate causes, and DILI, of which 17% were treated

with corticosteroids, and reported that the need for ventilation support, along with a higher MELD score and lower ALT, has a high odds ratio as a significant negative factor for spontaneous survival.[24] They also demonstrated that the overall rate of infection is not associated with corticosteroid treatment. These results complement the findings presented in our current study.

Although internally validated, one of the major limitations of this study is that analyses were conducted retrospectively, and further external validation is needed. Additionally, because SA-AIH is rare, the number of cases accumulating in a single center is not enough for matched analysis to erase the possible confounder effects that may lead to selection bias. Furthermore, we cannot conclude whether immunosuppression or LT is more beneficial to untreated patients with SA-AIH, and we cannot judge a more important question about whether or how long the corticosteroid trial is adequate with the results in this study. One patient died between 30 and 60 days after admission, despite having a relatively well-maintained CTLV/SLV ratio at admission (Fig. 3B). Hence, caution should be taken, given that the CTLV/SLV ratio at admission might falsely categorize an unfavorable prognosis as being more favorable. Further study is still needed to determine whether a dynamic assessment of CTLV/SLV ratios might help refine prognostic predictions.

In the interim, based on the results presented, when managing a patient with SA-AIH, a high CLIF-OF score, and a reduced CTLV/SLV ratio at admission, transplantation should be considered, and immunosuppressive therapy should be used cautiously. We hope that refinements in predicting outcomes and complications, along with improvements in understanding the natural history, will help make preclinical research on new immune-modulating therapeutics for SA-AIH possible in the future.

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Author names in bold designate shared co-first authorship.

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