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A Novel Model to Predict 1-Month Risk of Transplant or Death in Hepatitis A-Related Acute Liver Failure

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List of Abbreviations: HAV, hepatitis A virus; ALF, acute liver failure; INR, international normalized ratio; KCC, King's College criteria; ALFSG, Acute Liver Failure Study Group; MELD, model for end-stage liver disease; MELD-Na, MELD including serum sodium; IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; WBC, white blood cell; BUN, blood urea nitrogen; ALFA, hepatitis A-related ALF; CI, confidence interval.

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Abstract

Acute liver failure (ALF) caused by hepatitis A is a rare but fatal disease. Here, we developed a model to predict outcome in patients with ALF caused by hepatitis A. The derivation set consisted of 294 patients diagnosed with hepatitis A-related ALF from Korea, and a validation set of 56 patients from Japan, India, and United Kingdom. Using multivariate proportional hazard model, a risk-prediction model (ALFA score) comprised of age, international normalized ratio, bilirubin, ammonia, creatinine, and hemoglobin levels acquired on the day of ALF diagnosis was developed. The ALFA score showed the highest discrimination in the prediction of liver transplant or death at 1 month (c-statistic, 0.87; 95% confidence interval [CI], 0.84-0.92) versus King's College criteria (KCC; c-statistic, 0.56; 95% CI, 0.53-0.59), US Acute Liver Failure Study Group index specific for hepatitis A virus (HAV-ALFSG; c-statistic, 0.70; 95% CI, 0.65-0.76), the new ALFSG index (c-statistic, 0.79; 95% CI, 0.74-0.84), Model for End-stage Liver Disease (MELD; c-statistic, 0.79; 95% CI, 0.74-0.84) and MELD including sodium (MELD-Na; c-statistic, 0.78; 95% CI, 0.73-

0.84) in the derivation set (all *P*<0.01). In the validation set, the performance of the ALFA score (c-statistic, 0.84; 95% CI, 0.74-0.94) was significantly better than that of KCC (c-statistic, 0.65; 95% CI, 0.52-0.79), MELD (c-statistic, 0.74; 95% CI, 0.61-0.87), and MELD-Na (c-statistic, 0.72; 95% CI, 0.58-0.85) (all *P* < 0.05) and better, but not statistically significant, than that of the HAV-ALFSG (c-statistic, 0.76; 95% CI, 0.61-0.90; *P*=0.28) and new ALFSG indices (c-statistic, 0.79; 95% CI, 0.65-0.93; *P*=0.41). The model was well calibrated in both sets. ***Conclusion:*** Our new disease-specific score provides refined prediction of outcome in patients with ALF caused by hepatitis A.

Improvements in both public health and socio-economic status have reduced the incidence of hepatitis A virus (HAV) infection; however, 1.5 million cases of HAV infection still occur globally every year and represent a significant cause of morbidity and occasional mortality (1, 2). Moreover, the decrease in childhood HAV infection has led to a reduction in the adult population with protective immunity to HAV, leading to several outbreaks of HAV infection in developed countries (2-4). Because the risk of developing clinically apparent disease increases with age, the possibility of severe morbidity and mortality in susceptible adults is substantial during an outbreak of HAV infection. Acute liver failure (ALF) develops in less than 1% of HAV patients; however, approximately half of patients with ALF follow a course of liver transplant or death (5, 6). Therefore, the precise identification of patients with a poor prognosis from HAV infection is important for effective utilization of limited medical resources.

Several prognostic models have been proposed for use in patients with ALF, regardless of the causes, to identify those who are likely to benefit from transplant; however, most of these models have failed to show consistent and reliable accuracy (7). Because the prognosis of patients with ALF varies substantially according to etiology, an etiology-specific prognostic model may be more useful than previous ones if a sufficient number of cases can be studied. In the late 2000s, there was an unprecedented epidemic of acute HAV infection in Korea, and a substantial number of cases of ALF caused by HAV occurred consequently (8, 9). Based on this, we developed a model to predict the need for liver transplant or the occurrence of death in patients with ALF caused by HAV and validated the model both internally and externally.

Materials and Methods

PATIENTS

A total of 294 consecutive patients diagnosed with HAV-induced ALF from 18 university-affiliated hospitals in Korea, between January 2007 and December 2013, were included in the derivation set. The validation set consisted of 56 patients from 21 liver centers in Japan, India and United Kingdom between February 2005 and March 2014 (10-16). Data of clinical and biochemical variables were retrospectively derived from the medical records or registry databases.

ALF was defined as the presence of coagulopathy (prothrombin time international normalized ratio [INR] >1.5) and hepatic encephalopathy within 26 weeks of the first symptoms in the absence of cirrhosis or pre-existing liver disease (17). ALF was

attributed to HAV infection when immunoglobulin M anti-HAV antibodies were present in the serum and competing causes of ALF, including acute viral hepatitis (caused by hepatitis B virus, hepatitis C virus, hepatitis D virus, hepatitis E virus, varicella-zoster virus, herpes simplex virus, Epstein-Barr virus, cytomegalovirus, adenovirus or human immunodeficiency virus infections), alcohol, acetaminophen or drug use, ischemic injury, autoimmune hepatitis, Wilson's disease, alpha-1 antitrypsin deficiency, hemochromatosis, pregnancy-associated liver disease, malignant infiltration or vascular disorders (including Budd-Chiari syndrome) were excluded.

Demographic, clinical and laboratory variables on the day of diagnosis of ALF were collected. The decision to proceed with the transplant was determined at the individual centers according to guidelines of each country. All transplant recipients fulfilled the United Network for Organ Sharing status 1 criteria (fulminant liver failure with life expectancy <7 days).

For predicting outcomes, the King's College criteria (KCC) for nonparacetamol-related ALF, the US Acute Liver Failure Study Group (ALFSG) index for fulminant HAV infection (HAV-ALFSG), the new ALFSG prognostic index published in 2016, the United Network for Organ Sharing-modified Model for End-stage Liver Disease (MELD) and MELD-Na scores according to Organ Procurement and Transplantation Network guidelines were assessed at the time of diagnosis of ALF (18-21).

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the institutional review boards of each participating center.

STATISTICAL ANALYSIS

Demographic characteristics were summarized either as median and interquartile ranges (IQRs), or in percentages. For development of a prediction model, easily and readily available variables were assessed as potential predictors. This included age, sex, grade of encephalopathy, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, albumin, INR, white blood cell (WBC), hemoglobin, platelets, blood urea nitrogen (BUN), creatinine, ammonia, arterial pH, and sodium. Missing values of variables with missing rate < 25% were imputed using the multiple imputation by chained equations, which made ten imputed datasets from ten iterations (22). Variables with missing rate 25% or more were excluded from the model. Cox proportional hazards regression analysis was performed. Variables with $P < 0.2$ in the univariate analysis were subjected to multivariate analysis. Variables with $P < 0.2$ in the multiple Cox regression models were included in the model. Interactions between identified predictors were evaluated by including interaction terms along with main-effect variables. A risk score (ALFA score) was developed based on the regression coefficients from the final model. The probability of transplant or death at 1 month was calculated using the following equation: $P=1-S_0(t)^{\exp(\text{ALFA score})}$. $S_0(t)$ is the baseline survival function at time t.

The performance of the model in predicting a 1-month probability of transplant or death was evaluated with the c-statistic and max-rescaled R-square. Calibration was evaluated by the Hosmer–Lemeshow goodness-of-fit test. The model was validated by 5-fold cross validation with 100 times bootstrapping, and externally validated using the aforementioned independent set.

Statistical analyses and graph generations were performed using R 3.2 (R core team, Vienna, Austria).

Results

PATIENT CHARACTERISTICS AND OUTCOMES

The baseline characteristics of patients in the derivation and validation sets are presented in Table 1. Patients in the derivation set differed from those in the validation set in terms of the distribution of age, presence of hyperacute ALF, and the levels of hemoglobin, platelets, AST, ALT, ALP, creatinine, sodium, ammonia, and MELD score. However, spontaneous survival rates were similar in both groups (59.2% for the derivation set and 58.9% for the validation set, respectively; $P = 1.00$). In the derivation set, 74 patients (25.2%) underwent liver transplantation, and living-donor liver transplantation comprised 66.2% (49) of the cases. The median time to transplantation was 2 days (IQR, 1-5 days). The remaining 46 patients (15.6%) died without transplantation, and the median time to death was 8 days (IQR, 4-16 days). In the validation set, 3 patients (5.4%) underwent transplantation (two from a living-donor and one from a deceased-donor) and 20 (35.7%) died without transplantation. The median time-to-transplantation was 20 days (range, 10-45 days), and the median time-to-death was 14 days (IQR, 3-36 days), respectively.

When we compared the characteristics of patients who died or underwent transplant in the derivation and validation sets, patients in the derivation set were younger and had a higher prevalence of hyperacute liver failure (Supplementary Table 1). There were no significant differences in sex, hepatic encephalopathy

grade, vasopressor use, mechanical ventilation or renal replacement therapy on hospital day 1, and the levels of INR, MELD and MELD-Na scores between the derivation and validation sets.

DERIVATION OF RISK SCORE

In the derivation set, variables reflecting liver disease severity and major organ dysfunction were significantly associated with the risk of transplant or death in Cox proportional hazard model; however, serum sodium level and sex showed no significant impact. When 14 variables with significance were included in a multivariate model, age, serum bilirubin, INR, ammonia, creatinine, and hemoglobin levels were selected as independent predictors of transplant or death (Table 2). Based on the model, ALFA score could be calculated as follows: ALFA score = 0.024 × age + 0.054 × bilirubin + 1.551 × (PT-INR: 1 if >3; 0 if ≤ 3) + 0.003 × ammonia + 0.495 × (creatinine: 1 if > 1.1 for female or > 1.2 for male; 0 if ≤ 1.1 for female or ≤ 1.2 for male) - 0.075 × hemoglobin - 2.332. The probability of transplant or death at 1 month could be calculated by the following equation: $P = 1 – 0.623^{\exp(\text{ALFA score})}$. An online ALFA score calculator is available at http://www.thealfascore.com.

The performances of the various prognostic models for predicting transplant or death at 1 month were compared by 5-fold cross validation (Fig. 1A). The ALFA score showed the highest discrimination as indicated by a c-statistic of 0.87 (95% CI (confidence interval), 0.84-0.92) compared with the KCC (c-statistic, 0.56; 95% CI, 0.53-0.59; $P < 0.001$), the HAV-ALFSG index (c-statistic, 0.70; 95% CI, 0.65-0.76; $P < 0.001$), the new ALFSG index (c-statistic, 0.79; 95% CI, 0.74-0.84; $P = 0.01$), MELD (c-statistic, 0.79; 95% CI, 0.74-0.84; $P = 0.02$) and MELD-Na scores (c-

statistic, 0.78; 95% CI, 0.73-0.84; *P* = 0.008). As shown in Fig. 1B, the calibration of the ALFA score was acceptable (Hosmer-Lemeshow, *P* = 0.08), indicating that the observed and predicted numbers of patients with and without transplant or death at 1 month were not significantly different.

EXTERNAL VALIDATION OF RISK SCORE

The ALFA score was further tested in the external validation set. Similar to the findings from the derivation set, the ALFA score (c-statistic, 0.84; 95% CI, 0.74-0.94) significantly outperformed the KCC (c-statistic, 0.65; 95% CI, 0.52-0.79; *P* = 0.002), MELD (c-statistic, 0.74, 95% CI, 0.61-0.87, *P* = 0.03) and MELD-Na scores (c-statistic, 0.72, 95% CI, 0.58-0.85, *P* = 0.008) in predicting transplant or death at 1 month (Fig. 2A). A similar trend was observed when compared with the performance of the HAV-ALFSG index (c-statistic, 0.76; 95% CI, 0.61-0.90; *P* = 0.28) and the new ALFSG index (c-statistic, 0.79; 95% CI, 0.65-0.93; *P* = 0.41), although it did not reach statistical significance. The ALFA score also calibrated well (Hosmer-Lemeshow test, *P* = 0.25; Fig. 2B).

Discussion

In the present study, we analyzed the largest number of patients with ALF caused by HAV infection to date and identified predictive factors for outcomes, including age, bilirubin, INR, ammonia, creatinine, and hemoglobin levels. With these 6 variables, which are both objective and reproducible, we established an ALFA score, which was found to outperform other models developed to predict outcomes in patients with ALF. In addition, the ALFA score assigned a 1-month probability of transplant or

death which calibrated well in the external validation set as well as in the internal cross validation. Although there were dissimilarities in the disease severity and outcomes of patients between the derivation and validation sets, the value of the ALFA score was convincingly validated. This suggests that the ALFA score may be applicable to patients beyond the derivation cohort.

Although several criteria have been developed for prognostication of ALF outcomes, they leave much to be desired in terms of objectivity and accuracy. KCC, one of the most widely used models, has shown relatively good specificity but poor sensitivity (6). Furthermore, it has been shown that KCC has limited value in identifying patients with a good prognosis (survival without transplant) compared to those patients with a poor prognosis (transplant or death) (23). Thus, the predictive value of KCC may be lower in an ALF subgroup with better outcomes, such as HAV-related ALF. The MELD score, which is commonly used to predict mortality in patients with chronic liver disease, has shown lower specificity with a high false-positive rate compared with KCC (24, 25). A recent study revealed that the ALFSG index, a disease-specific prognostic model consisting of 4 variables (serum ALT <2600 IU/L, creatinine >2.0 mg/dL, need for mechanical ventilation and need for vasopressors) derived from 29 patients with ALF caused by HAV, predicted the likelihood of transplant or death significantly better than KCC or MELD (sensitivity, 92%; specificity, 88%) (19). However, this study was limited to a small number of patients. More recently, the new ALFSG prognostic index derived from patients with ALF of varying etiologies was developed (20). This model predicted 21-day transplant-free survival with a c-statistic of 0.84 using five clinical variables (hepatic encephalopathy grade, etiology of ALF, vasopressor use, bilirubin, and INR). When we compared the performance of the new ALFSG index with that of the ALFA score,

the ALFA score showed better performance than the new ALFSG index in the prediction of transplant or death in the derivation set, whereas these trends did not reach significance in the validation set. This may be due to the low statistical power because of the small number of events (transplant or death). External validation of a prognostic model requires more than 100 events (26); however, the decreasing incidence of HAV infection makes it hard to collect such a large number of patients developing HAV-related ALF. Therefore, validation of the usefulness and generalizability of the ALFA score should be performed in a future large, global cohort study.

The variables of the ALFA score reflect the severity of liver disease or accompanied complications (27). INR, by definition a key component of the diagnosis of ALF, was also an important prognostic parameter in the ALFA score. Hyperbilirubinemia could be the result of severe hepatocyte necrosis and dysfunction. Consistent with the pathogenic role of ammonia in cerebral edema or herniation, high ammonia levels were correlated with poor outcomes. Low levels of hemoglobin might reflect bleeding due to coagulopathy and accompanying portal hypertension with ALF. Acute kidney injury, a well-known complication of ALF, also indicated a poor prognosis in the present study (18, 28). In addition, an older age was predictive of outcome, as was seen in other studies of ALF (29, 30). In contrast, the interval between the onset of jaundice and the development of encephalopathy was not significantly associated with outcome in our study. It seems that the duration of disease per se, at least in patients with HAV-related ALF, does not have significant prognostic value distinct from the etiology, as suggested by previous reports (6, 31).

There are several limitations to the present study. First, the ALFA score is based on a single assessment on the day of ALF diagnosis, and we were unable to get serial measurements during the dynamic course of ALF; therefore, the predictive power of our score might be lower than those based on serial measurements. However, there is no clear evidence that repetitive information improves decision-making for physicians and patients with HAV-related ALF. Furthermore, considering the risk of rapid disease progression and mortality, early prognostication based on an initial assessment that facilitates a timely decision for transplant could be strength of this study. Second, we could not verify virologic factors, such as viral load, genotype, or substitution rate in the 5' untranslated region of the viral genome, which have been associated with fulminant disease (32, 33); therefore, virus-specific variables were not included in the model. However, it is still unclear whether unique viral genome patterns or a specific HAV genotype is more fatal or more likely associated with ALF (34, 35). Third, patients in the validation set were significantly older than those in the derivation set, and enrolled from multiple counties with differences in access to liver transplantation; therefore, patients in the validation set differed considerably from those in the derivation set. Fourth, our model was derived from retrospectively collected data which might lead to lower prediction power. In addition, we included HAV-related ALF patients from referral hospitals, and referral bias may have affected the composition of the study population. A population-based prospective registry of HAV-related ALF could resolve this limitation.

Despite these limitations, our study is relevant and may provide important findings. ALF is a rare, heterogeneous and complex disease entity. Thus, it is a challenging task to develop a reliable prognostic model for each of the etiologies of ALF. In the present study, we developed a single etiology-specific scoring system based on a

large number of patients with HAV-related ALF and compared its value to other well-known models. The ALFA score is composed of simple, easily available and objective basic laboratory findings, which can be obtained at the time of ALF diagnosis. Therefore, it may have important clinical implications, especially in regions of intermediate endemicity such as Asia, South America, Eastern Europe and the Middle East as well as low endemic areas including North America and Western Europe, which have a high proportion of susceptible adults at an increased risk of severe symptomatic disease including ALF (2).

In conclusion, we present an HAV-specific prognostic model based on a recent epidemiologic shift toward a low endemicity and subsequent disease outbreak in Korea, and externally validated it. This model may be helpful in more precise decision-making and management of patients with ALF caused by HAV.

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Figure Legends

Fig. 1. (A) ROC curves for 1-month risk of transplant or death, and (B) calibration plot for predicted versus observed risk in patients with acute liver failure caused by hepatitis A in the internal cross validation.

ROC, receiver operating characteristic; ALFA, risk score for acute liver failure caused by hepatitis A; HAV-ALFSG index, Acute Liver Failure Study Group index specific for hepatitis A virus; new ALFSG index, ALFSG index published in 2016; MELD, model for end-stage liver disease; MELD-Na, MELD including serum sodium.

Fig. 2. (A) ROC curves for 1-month risk of transplant or death, and (B) calibration plot for predicted versus observed risk in patients with acute liver failure caused by hepatitis A in the external validation.

ROC, receiver operating characteristic; ALFA, risk score for acute liver failure caused by hepatitis A; HAV-ALFSG index, Acute Liver Failure Study Group index specific for hepatitis A virus; new ALFSG index, ALFSG index published in 2016; MELD, model for end-stage liver disease; MELD-Na, MELD including serum sodium.

TABLE 1. Baseline Characteristics of the Derivation and Validation Sets

Characteristic	Derivation set (n=294)	Validation set (n=56)	*P*
Age (years)	35 (29-40)	47 (26-62)	0.002
Male	192 (65.3)	30 (53.6)	0.10
Hyperacute*	260 (88.4)	41 (73.2)	0.005
Grade of encephalopathy			0.38
I or II	167 (56.8)	28 (50.0)	
III or IV	127 (43.2)	28 (50.0)	
Vasopressor use	28 (9.5)	8 (14.3)	0.33
Mechanical ventilation	48 (16.3)	18 (32.1)	0.009
Renal replacement therapy	92 (31.3)	25 (44.6)	0.06
WBC (/mm^3)	8585 (5577-13747)	9190 (5675-13300)	0.84
Hemoglobin (g/dL)	13.9 (12.3-15.5)	11.9 (10.5-13.4)	< 0.001
Platelets (×10^3/mm^3)	119 (90-165)	150 (99-265)	< 0.001
INR	2.50 (1.79-3.53)	211 (1.70-4.28)	0.58
Albumin (g/dL)	3.3 (2.9-3.5)	3.2 (2.8-3.7)	0.50
Bilirubin (mg/dL)	7.3 (5.2-11.0)	8.5 (5.6-15.3)	0.06
AST (IU/L)	3062 (936-7704)	1026 (290-3040)	< 0.001
ALT (IU/L)	4126 (2386-5920)	1267 (554-3481)	< 0.001
ALP (IU/mL)	158 (124-199)	369 (175-454)	< 0.001
BUN (mg/dL)	17.0 (9.0-37.4)	19.0 (13.0-28.0)	0.40
Creatinine (mg/dL)	1.75 (0.80-5.29)	0.90 (0.60-1.49)	< 0.001

Sodium (mEq/L)	136 (132-138)	141 (137-145)	< 0.001
Ammonia (μg/dL)	152 (94-224)	114 (74-161)	0.008
pH, arterial blood	7.42 (7.35-7.47)	7.40 (7.38-7.50)	0.82
MELD score	32 (24-38)	28 (21-33)	0.03
MELD-Na score	33 (24-38)	30 (22-34)	0.10
Outcome			< 0.001
Spontaneous survival	174 (59.2)	33 (58.9)	
Transplanted	74 (25.2)	3 (5.4)	
Death without transplantation	46 (15.6)	20 (35.7)	

Data are medians (interquartile range) or numbers (%), unless otherwise indicated.

* Encephalopathy < 7 days of jaundice.

WBC, white blood cell; INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; MELD, model for end-stage liver disease; MELD-Na, MELD including serum sodium.

TABLE 2. Multivariate Cox Proportional Hazards Model from the Derivation Cohort and Corresponding Risk Score for Prediction of 1-month Probability of Transplant or Death

Variables	β coefficient	HR (95% CI)	*P*
Age	0.024	1.024 (1.001-1.047)	0.039
Total bilirubin (mg/dL)	0.054	1.055 (1.034-1.076)	<0.001
INR			
> 3	1.551	4.718 (3.184-6.992)	<0.001
≤ 3	0	1	
Ammonia (μg/dL)	0.003	1.003 (1.002-1.005)	<0.001
Creatinine (mg/dL)			
> 1.1 for female or >1.2 for male	0.495	1.640 (1.096-2.455)	0.016
≤ 1.1 for female or ≤ 1.2 for male	0	1	
Hemoglobin (g/dL)	-0.075	0.928 (0.859-1.002)	0.057

HR, hazard ratio; CI, confidence interval; INR, international normalized ratio.