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Admission Factor V Predicts Transplant-Free Survival in Acute Liver Failure

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Abstract

Background and Aims—Traditional laboratory markers are insensitive in distinguishing between patients with acute liver failure (ALF) who will require urgent liver transplantation (LT) from those who will recover spontaneously, particularly within 24 h of presentation. Coagulation factor-V (FV) may improve the accuracy of outcome prediction in ALF due to its predominant synthesis in the liver and short half-life in plasma.

Methods—Patients enrolled in the ALF Study Group Registry from a single site had FV determined within 24 h of presentation (Derivation-Cohort). Area under the receiver operating characteristic curves (AUROC) dichotomized by ALF etiology [acetaminophen (APAP) or non-APAP] were constructed to evaluate the diagnostic performance of FV for transplant-free-survival (TFS). Multivariate logistic regression modeling was performed using FV and other clinical variables to predict TFS. Accuracy of FV and multivariable model were performed in a Validation-Cohort from a different site.

Results—90-patients (56% with APAP) were included in the Derivation-Cohort. Median FV was significantly higher in TFS versus those who died/LT (31% vs. 15%, respectively; $p = 0.001$). When dichotomized by etiology, AUROC for FV was 0.77 for APAP (cutoff, sensitivity, specificity 10.5%, 79%, 69%, respectively) and 0.77 for non-APAP (22%, 85%, 67%, respectively). When the optimal cutoffs for FV in the Derivation-Cohort were applied to the

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Validation-Cohort (*N* = 51; 59% with APAP), AUROC for FV was 0.75 for APAP (sensitivity/specificity 81/44) and 0.95 for non-APAP (sensitivity/specificity 90/73). In multivariate analyses, AUROC for FV model was 0.86 in the Derivation-Cohort and 0.90 in the Validation-Cohort.

Conclusion—Admission FV may improve selection of patients who are likely to improve without LT.

Keywords

Acetaminophen overdose; Liver transplantation; Fulminant liver failure; Intensive care unit; MELD; Kings College Criteria

Introduction

Acute liver failure (ALF) is a rare and devastating clinical syndrome characterized by abrupt and severe hepatic parenchymal injury associated with hepatic encephalopathy (HE) and coagulopathy in patients without preexisting liver disease [1]. The clinical course of ALF varies from complete recovery of native liver function to rapid deterioration with development of cerebral edema and multi-organ failure. Overall, transplant-free survival (TFS) rates are low (less than 50%), but vary by etiology [2]; liver transplantation (LT) can be lifesaving, improving survival rates to above 92% [2, 3]. Due to poor sensitivity in traditional clinical and laboratory markers [4-6], the extreme variability between patients—particularly with regard to etiology—poorly distinguishes patients who will require urgent LT from those who will recover with their native liver. Thus, there is a major unmet need for an accurate, sensitive, and simple tool to identify patients who require urgent LT listing.

Coagulation factor five (FV) is synthesized primarily by the liver, and persists in circulation for only a few hours, features which suggest it may be potentially useful as a marker of severe liver injury and regeneration in patients with ALF. More than 30 years ago in the pre-LT era, FV level was first proposed as a prognostic tool in a cohort of patients with fulminant hepatitis, in whom a FV level < 20% predicted death (17 and 32% of normal in those who died vs. those who survived, respectively; $p < 0.001$) [7, 8]. In one of the first studies describing the use of LT as a treatment of ALF, all 17 patients had FV level of < 20% [9]. Subsequently, the absence of improvement in FV after admission for ALF of diverse etiology was also shown to predict death, presumably as evidence of poor hepatic regeneration [10-12]. Factor V has also been explored in a ratio with factor VIII (FVIII/FV), a pro-hemostatic, endothelial cell-derived protein increased in ALF due to systemic inflammation and found to accurately predict prognosis [12]. However, the use of a single FV level on admission for ALF has not been validated as a prognostic marker in a contemporary cohort of ALF of mixed etiologies, in whom greatly improved prognosis has been documented due to the widespread use of *N*-acetylcysteine (NAC) and improved intensive care management [13, 14].

Thus, the aim of this study was to evaluate the accuracy of admission FV, alone and in multivariate analyses, for predicting 21-day TFS in a diverse cohort of ALF patients presenting to two US tertiary care hospitals. We developed a “FV predictive model” in a cohort at one academic center, and validated the model in a population of similar

clinical characteristics at second center, and compared the accuracy of the model with other proposed prognostic systems of 21-day outcome [4, 6, 15].

Patients and Methods

Patients

Consecutive patients with ALF who were enrolled at Virginia Commonwealth University (VCU) as part of the United States ALF Study Group Registry between July 2001 and December 2017 were retrospectively assessed for eligibility. Inclusion criteria included patients over the age of 18 with ALF (defined by acute liver injury (jaundice to HE interval within 26 weeks), evidence of coagulopathy with an international normalized ratio (INR) ≥ 1.5, and the presence of HE in a patient without any preexisting liver disease [16]) who had FV obtained within 24 h of admission. Patients who did not have FV levels within 24 h of presentation and missing clinical variables were excluded. External validation was performed on a retrospective cohort of consecutive ALF patients admitted to Indiana University Hospital (IU) from May 2004 to December 2017. Similar inclusion and exclusion criteria were applied to the validation cohort. The institutional review boards at Virginia Commonwealth University and at Indiana University Hospital approved the study protocol.

Data Collection

Data collected for both the derivation and validation cohorts included vital signs, HE grade (as defined by the West Haven Criteria [17]), laboratory data (complete blood count, metabolic panel, hepatic panel, international normalized ratio of the prothrombin time (INR), venous ammonia, arterial blood gas), FV level, FVIII level (only in the Derivation Cohort), presence of infection, vasopressor use, and etiology of ALF [dichotomized as either *n*-acetyl-p-aminophenol (APAP) or non-APAP induced]. If more than one value for FV and FVIII was collected within 24 h of admission, the lowest value was recorded. For non-APAP-induced ALF, adjudications for ALF etiology were determined by investigators at each center (KRP-IU, MSG-IU, RTS-VCU). Clinical status and laboratory data up to 7 days after admission were recorded, or until death, transplant if prior to 7 days, or discharge. Outcome at 21 days from admission (TFS, death or LT) was also recorded. In addition, day 3 FV level was collected, if available.

Hemostasis Testing—Prothrombin time/INR, FV, and FVIII level in the Derivation Cohort were assayed by the Clinical Coagulation Laboratory at VCU using the STA-R Evolution® clot detection system. The prothrombin time/INR was determined using re-calcified plasma and recombinant human tissue factor and synthetic thromboplastin (Dade® Innovin® Reagent; Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany). Factor V and VIII activity level were performed using calibration curves generated from ≥ 6 dilutions of specific factor-deficient substrates and expressed as a percentage of normal. In the Validation Cohort, prothrombin/INR and FV level were assayed by the Coagulation Laboratory at IU using Instrumentation Laboratory ACL TOP system® (MA, USA). Rediplastin® by Instrumentation Laboratory was used to determine the prothrombin time/INR and FV level using calibration curves generated at 0 to 130 dilutions.

Primary Outcome

The primary outcome was TFS, defined as being alive without having undergone LT 21 days following admission for ALF.

Statistical Analysis

Patients were stratified based on TFS versus death/LT and their characteristics on admission were compared. Continuous variables were presented as mean ± standard deviation (SD) and median with interquartile range (IQR) where appropriate. Categorical variables were presented as percentages. Differences across groups with respect to categorical variables were analyzed using Chi-square and Fishers exact tests, whereas continuous variables were analyzed using the nonparametric Kruskal–Wallis test and student *t* tests. A two-sided nominal p value ≤ 0.05 was considered significant.

Prediction Analysis for FV and FV Model

FV: To evaluate the diagnostic performance of FV, area under the receiver operating characteristic curve (AUROC) and 95% confidence interval (CI) dichotomized by APAP and non-APAP ALF etiology was performed for 21-day TFS in the derivation cohort. The optimal cutoff for each group was determined by the Youden index. Sensitivity (Sens), specificity (Spec), negative predictive value (NPV), and positive predictive value (PPV) were investigated. Performances of cutoff values at a fixed sensitivity and specificity at ≥ 90% were also investigated.

FV Multivariate Model: For development of the FV predictive model, admission FV and other known admission variables of clinical significance were considered. These variables were selected based on their known influence on ALF outcomes [4, 6, 15] and included: age, high-grade HE (grades 3 or 4), total bilirubin, INR, vasopressor use, and etiology of ALF (APAP vs. non-APAP). Highly correlated variables ($p < 0.10$) were included in the multivariate model. The final FV model selection was based on minimizing Akaike information criterion (AIC) and maximizing the AUROC. Sensitivity, specificity, NPV, PPV, and performances at various TFS thresholds (maximum Youden Index, 70%, 80%, and 90%) were investigated. The final FV predictive model was compared to other validated predictive models for ALF (the model for end-stage liver disease (MELD) [15], acute liver failure study group prognostic index (ALFSG) [6], and Kings College Criteria (KCC) [4]) using DeLong's method. Akaike information criterion analysis was also performed for each of the predictive models.

The optimal cutoffs for FV alone and the final FV model were applied to the Validation Cohort. AUROC analysis was performed for prediction of TFS. Sensitivity, specificity, PPV, and NPV were also investigated.

To assess if FV is a dynamic predictor, day 3 FV and its delta (difference between day 3 FV and admission FV) were compared between TFS versus death/LT. In addition, day 3 clinical and laboratory data were applied to the multivariate logistic regression FV predictive model for TFS and were compared to MELD, ALFSG, and KCC.

Statistical analysis was performed using SPSS software for Windows, version 24 (SPSS, Inc, Chicago, IL) and SAS 9.4 (SAS, Cary, NC).

Results

Derivation Cohort

A total of 197 patients were enrolled into ALF Study Group Registry during the study time period of which 107 patients were excluded [95 had no admission FV levels and 12 had missing admission clinical information). Ninety patients met inclusion criteria.

Demographic and clinical characteristics of TFS versus death/LT are compared in Table 1. The mean age of study patients was 42 ± 13 years, and the majority were Caucasian (64%) and female (69%). Major etiologies of ALF were APAP (56%), autoimmune hepatitis (10%), idiosyncratic drug induced liver injury (DILI) (9%), and indeterminate (9%). Patients with TFS were more likely to have had APAP as the etiology of ALF compared to death/LT (72% vs. 37%, $p = 0.001$). Furthermore, patients with TFS had significantly higher admission mean arterial pressure and lower total bilirubin compared to death/LT patients. There were no differences between the two groups for INR, FVIII, high-grade HE (3 or 4), and vasopressor use on admission. MELD and ALFSG scores were significantly different between both groups but were not for KCC (Table 1). Admission FV level in TFS was significantly higher when compared to death/LT [median (IQR) 24% (12, 5) vs. 15% (7, 24), respectively; $p = 0.007$)]. FVIII/V ratio was found to be significantly higher in death/LT patients [median (IQR) 27 (16, 50) vs. 18 (8, 30), respectively; $p = 0.002$], but was largely due to differences in FV levels. When dichotomized by ALF etiology (APAP vs. non-APAP), FV was significantly higher in TFS compared to death/LT for APAP (16% vs. 6%, respectively; $p = 0.002$) and non-APAP (45% vs. 17%, respectively; $p = 0.006$).

Fourteen percent of patients underwent LT. The most common causes of death were multi-organ failure (43%), followed by liver failure causing cerebral herniation (17%), cardiopulmonary arrest (13%), and septic shock (10%).

Validation Cohort

A total of 152 patients were screened for inclusion criteria outlined above. One hundred and one were excluded due to missing admission FV levels, leaving 51 patients for analysis (20 death/LT and 31 TFS). Similar to the Derivation Cohort, the mean age of study patients was 39 ± 13 years, and the majority were female (63%) and Caucasians (84%). Also similar to the Derivation Cohort, the most common etiology of ALF was APAP (59%), followed by indeterminate (27%) and idiosyncratic DILI (23%). Patients with TFS had lower total bilirubin compared to death/LT patients (Table 2). However, in contrast to the Derivation Cohort, TFS patients had significantly lower INR and a greater proportion were admitted with lower grade HE compared to death/LT patients ($p = 0.007$ and $p = 0.002$, respectively). Similar to the derivation cohort, MELD and ALFSG scores were significantly different between both groups and not for KCC (Table 2). FV level in TFS was significantly higher compared to death/LT [median (IQR) 31% (18, 50) vs. 14.5% (9, 19.5), respectively; $p = 0.001$)]. In addition, FV was found to be significantly higher in the TFS compared to

death/LT for APAP (27% vs. 11%, $p = 0.031$) and non-APAP ALF (28.5% vs. 16%, $p = 0.001$). Fourteen percent of patients underwent LT, and the most common causes of death were multi-organ failure (44%) and cerebral herniation (38%). Comparisons between the Derivation and Validation Cohorts are shown in Supplementary Table 1.

Diagnostic Accuracy of FV for the Prediction of TFS

Derivation Cohort—The AUROC for FV as a predictor of TFS in patients with APAP ALF was 0.77 (95% CI 0.58, 0.79; $p = 0.002$), and the optimal cutoff was determined to be 10.5%. A value > 10.5% predicted TFS with a 79% sensitivity and 69% specificity, with a PPV and NPV of 84% and 61%, respectively (Table 3). When the sensitivity was fixed at 90%, the specificity decreased to 50% (cutoff > 5.5%) and at 90% specificity the sensitivity dropped to 32% (cutoff > 26.5%). Similarly, the AUROC for FV in patients with non-APAP ALF was 0.77 (95% CI 0.60, 0.95; $p = 0.006$), but the optimal cutoff was found to be higher at 22% (> 22%; 85% sensitivity, 67% specificity, 55% PPV, and 90% NPV). At a fixed sensitivity of 90% (cutoff > 13%), the specificity was 47%, and when the specificity was fixed at 90% (cutoff > 46%), the sensitivity was 46% (Table 3).

Validation Cohort—The optimal cutoffs for FV identified in the Derivation Cohort were applied to the Validation Cohort. The AUROC for FV in APAP ALF was 0.75 (95% CI 0.57, 0.93; $p = 0.071$), with a sensitivity, specificity, PPV, and NPV of 81%, 44%, 77%, and 50%, respectively. The AUROC for FV in non-APAP ALF in the Validation Cohort was 0.95 (95% CI 0.86, 1.00; $p = 0.014$), with sensitivity (90%) and specificity (73%) (Table 3).

Factor V Multivariate Model

Admission FV was then used in multivariate models including admission vasopressor use, total bilirubin, etiology of ALF (APAP or non-APAP), and high-grade HE. Admission INR was not included in the final model as it was not found to be significantly associated with TFS on univariate analysis ($p = 0.558$); when forced into the final multivariate model, the AUROC decreased, with a concomitant increase in AIC. Using the aforementioned admission variables, the following multivariate logistic regression model was created for prediction of TFS:

$$\begin{aligned}\text{Logit TFS} : 0.6969 + 0.0516(\text{Factor V}) - 0.5801(\text{vasopressor use} *) - 0.0953 \\ (\text{total bilirubin} - 0.7146(\text{ALF etiology} *) - 0.2914\,(\text{grade 3 or 4 HE} *)\end{aligned}$$

*Insert 0 for no vasopressor use and 1 for vasopressor use; if etiology of ALF is non-APAP insert 1 and if etiology of ALF is APAP insert 0; for grade 3 or 4 HE insert 1 and for grade 1 or 2 HE insert 0

$$\text{Predicted TFS} = \exp(\text{Logit TFS}) \,/\, \left[1 + \exp^{(\text{Logit TFS})}\right]$$

The AUROC for TFS for the FV prediction model was 0.86 in the Derivation Cohort (95 CI% 0.78, 0.94; $p = 0.006$). When compared to MELD [AUROC 0.64 (0.54, 0.74)] and KCC [APAP etiology AUROC 0.53 (0.49, 0.58); non-APAP etiology AUROC 0.68 (0.58, 0.78)], the FV model was significantly more accurate ($p < 0.001$ for both) (Fig. 1). Although the

AUROC for the FV model was numerically higher than the ALFSG (0.86 vs. 0.77), there were no significant differences between the two models ($p = 0.069$) (Table 4). The AIC for the FV Model was numerically lower than MELD, KCC, and ALFSG. When the FV Model was applied to the Validation Cohort, the AUROC improved to 0.90 (95% CI 0.92, 0.99; $p = 0.009$). Diagnostic performances of the FV Model in both Derivation Cohort and Validation Cohort are shown in Supplementary Table 2.

Since the threshold to initiate LT evaluation varies for each clinician and their respective center, diagnostic performances at the optimal cutoff for TFS probability and at various thresholds (70%, 80%, and 90%) in the derivation cohort were performed and are shown in Supplementary Table 3. With increasing TFS probability thresholds, the model's diagnostic accuracy (% accurate classification) slightly decreases and plateaus at 60% when the threshold is ≥ 80%. However, with increasing thresholds, the percent of incorrectly predicting survival decreases to nearly 1–2%.

Predictive Dynamics of FV

Thirty-two patients in the Derivation Cohort and 18 patients in the Validation Cohort had day 3 FV levels available. These patients were combined ($N = 52$) to assess the dynamics of FV. Compared to death/LT, day 3 median (IQR) FV was significantly higher in TFS [overall 46.5% (13, 28) vs. 22% (29, 69), $p < 0.001$; in APAP ALF 44% (28, 73) vs. 15.5% (3, 26), $p = 0.001$; and in non-APAP ALF 52% (43, 54) vs. 23.5% (18, 29), $p = 0.009$ in TFS vs. death/LT, respectively]. A median decrease of 6% for FV was observed in death/LT while a median increase of 23.5% occurred in TFS. Comparisons of other pertinent day 3 laboratory and clinical data can be found in Supplementary Table 4.

When day 3 data were applied to multivariate logistic regression analysis (as described above), the AUROC for TFS was found to be 0.93 (95% CI 0.85, 1.00; $p < 0.0001$). Additionally, when compared to the AUROC's for MELD [0.75 (0.63, 0.87)], KCC [0.53 (0.50, 0.56)], and ALFSG [0.89 (0.78, 1.00)], the FV Model was significantly more accurate ($p = 0.002$, $p < 0.001$, and $p = 0.004$, respectively).

Discussion

In this contemporaneous US cohort of ALF patients, we have demonstrated that admission FV has high predictive ability for TFS. We have shown that our FV predictive model, which is composed of other clinically relevant predictors for poor outcomes (vasopressor use, total bilirubin, ALF etiology, and grade 3 or 4 HE), has an excellent predictive ability for TFS in the Derivation Cohort (AUROC of 0.86) and in an independent Validation Cohort (AUROC 0.90). Importantly, our FV model was found to be a better predictor for TFS when compared to other validated predictive models (Table 4). Furthermore, we were able to demonstrate the dynamic predictive ability for our FV model with improvement in AUROC to 0.93 when applying day 3 clinical and laboratory information.

Factor V levels fall rapidly in patients with ALF due to extensive hepatic necrosis and short half-life in plasma. Although INR has traditionally been used to determine the need for LT in patients with ALF [11], we found that a single determination of INR on admission was

not accurate in determining prognosis across all etiologies of ALF. Indeed, INR was not an independent predictor of TFS even when forced into multivariable analyses. In contrast, a single FV level on presentation may better predict outcome than INR because it relies on only one protein with short half-life rather than a functional test involving multiple proteins of various half-lives. Also, in contrast to older studies, we found that FVIII and FVIII/V ratio did not improve prediction of outcome over FV. FVIII, a pro-coagulant protein released from endothelial cells from all vascular beds, has been linked to the systemic inflammatory response syndrome [18] and found to be increased in ALF patients, particularly in those who died [10]. A plausible explanation for this finding in our study could be because of improvements in intensive care management of the systemic inflammatory complications of ALF, and therefore survival [13, 14].

The application of a single admission FV level to predict spontaneous survival performed with superior accuracy compared to several widely applied and more cumbersome prognostic indices which have been used for many years. For example, a patient presenting with an APAP overdose and an admission FV of 40% and grade 2 HE, a total bilirubin of 5, and off vasopressors would have a predicted TFS of 71%—a survival threshold high enough that may steer a clinician not to initiate LT evaluation. In the same patient, if the admission FV were 10%, the predicted TFS would be 34%, which may lead the clinician toward LT evaluation on day 1 of presentation. Similarly, if the same patient had non-APAP ALF with a FV of 30%, the predicted TFS would be 42%, a threshold low enough to consider urgent LT evaluation on day 1.

Compared to previous prognostic models for ALF, our FV model was developed to predict TFS (vs. an endpoint of death/LT) and thus interpretation of the NPV warrants further discussion. It should be first mentioned that the applicability of LT to patients with ALF is limited by the shortage of donor organs, and even with priority listing, many patients develop contraindications to LT or die before a donor becomes available. For this reason, reliable and early predictors for survival are required to accurately risk stratify patients. This would ensure that patients who are likely not to survive to be evaluated for LT candidacy and listed as early as possible. Our model was designed for this clinical scenario. Accordingly, the NPV in our model can be interpreted as the proportion of those patients who survived who had favorable TFS predictors (i.e. TFS probability). Thus, a good NPV for TFS (85% in our model) could potentially avoid LT listing.

There are several limitations to our study. Frist, we did not exclude patients who received plasma at an outside hospital prior to obtaining FV levels at the study center. Although prior receipt of plasma could affect FV levels on presentation, the impact on FV would likely be minimal given the short half-life of FV in plasma [19]. Second, we were unable to track and analyze changes in FV level on subsequent days on all patients. Finally, in the era of LT, true TFS in ALF is never actually known as LT may be performed in patients who otherwise would have survived. Last, our long study period may increase the possibility of unmeasured confounders that impact survival.

In conclusion, in this contemporary US cohort of ALF patients, we found FV to be a useful predictor for TFS. FV is a readily available biomarker at most LT centers, and

accordingly should be included in the armamentarium for the prognostication of ALF. Further prospective multi-center studies are needed to validate its utility early in the course of ALF and ultimately if early LT evaluation and listing guided by FV can translate to improved outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

ALF	Acute liver failure
HE	Hepatic encephalopathy
TFS	Transplant-free survival
LT	Liver transplantation
FV	Factor V
NAC	*N*-acetylcysteine
APAP	*N*-acetyl-p-aminophenol (acetaminophen)
INR	International normalized ratio of the prothrombin time
VCU	Virginia Commonwealth University
IU	Indiana University Hospital
SD	Standard deviation
IQR	Interquartile range
AUROC	Area underneath the receiver characteristic
CI	Confidence interval
Sens	Sensitivity
Spec	Specificity
NPV	Negative predictive value
PPV	Positive predictive value
AIC	Akaike information criterion
MELD	Model for end-stage liver disease
ALFSG	Acute liver failure study group prognostic index
KCC	Kings College Criteria

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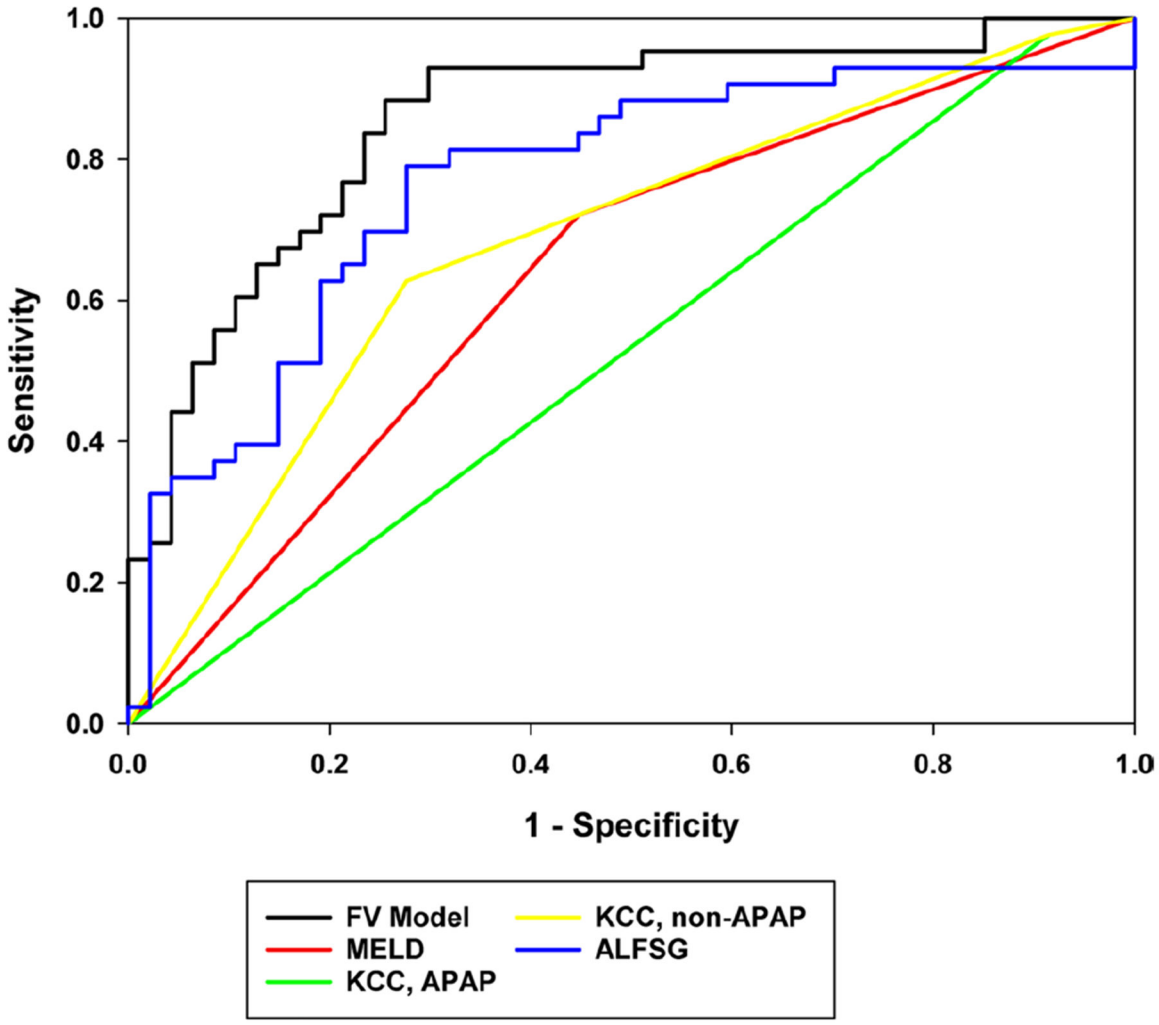

Fig. 1.

Comparison of FV model to MELD, KCC, and ALFSG for transplant-free survival. *FV* factor five, *MELD* model for end-stage liver disease, *KCC* Kings College Criteria, *ALFSG* acute liver failure study group, *APAP* acetyl-para-aminophenol

Table 1

Patient demographics and clinical information stratified by 21-day transplant-free survival—validation cohor

	Death/LT (*n* = 43)	**TFS (*n* = 47)**	***p* value**
Age (y ± SD)	42.7 ± 14.2	42.0 ± 12.8	0.800
Race (*n* ([%] Caucasian)	25 (58)	33 (70)	0.417
Gender (% female)	24 (56)	38 (81)	0.010
Etiology of ALF (*n* [%] APAP)	16 (37)	34 (72)	0.001
Admission vital signs (± SD)			
Pulse	98 ± 24	100 ± 24	0.716
Respiratory rate	22 ± 13	19 ± 5	0.194
MAP (mmHg)	84 ± 14	92 ± 17	0.015
Temperature (°F)	98 ± 2	98 ± 1	0.140
Admission stage HE (*n* [%] 3 or 4)	20 (47)	15 (32)	0.156
Infection on admission (*n* [%])	15 (35)	14 (30)	0.605
Admission vasopressor use (*n* [%])	12 (28)	5 (11)	0.058
Admission Labs (median [IQR])			
Sodium (mmol/L)	137 (132, 142)	138 (134, 141)	0.659
Phosphorus (mmol/L)	3.0 (2.0, 4.4)	2.4 (1.8, 3.6)	0.128
Creatinine (mg/dL)	1.45 (0.86, 2.80)	1.14 (0.68, 2.96)	0.734
AST (units/L)	2856 (582, 8208)	5678 (1930, 11562)	0.041
ALT (units/L)	2654 (595, 4954)	3846 (1178, 6816)	0.065
ALP (units/L)	158 (113, 223)	130 (86, 179)	0.038
Total bilirubin (mg/dL)	12.2 (3.9, 21.5)	3.8 (1.4, 5.9)	< 0.001
INR	3.7 (2.8, 5.6)	3.5 (2.1, 5.1)	0.407
WBC (10^9/L)	10.9 (7.3, 15.7)	10.5 (7.0, 12.3)	0.497
Platelets (10^9/L)	154 (64, 211)	160 (86, 244)	0.274
Arterial pH	7.4 (7.3, 7.5)	7.4 (7.3, 7.5)	0.218
Ammonia (μmol/L)	101 (69.5, 134.5)	88 (55, 105)	0.226
Factor VIII (median% normal [IQR])	377 (293, 564)	458 (281, 586)	0.825
Factor VIII/V (median [IQR])	27 (16, 50)	18 (8, 30)	0.002
Factor V (median% normal [IQR])	15 (7, 24)	24 (12, 53)	0.007

	Death/LT (*n* = 43)	TFS (*n* = 47)	*p* value
Factor V (median% normal [IQR]), APAP	6 (3, 16)	16 (11, 36)	0.002
Factor V (median% normal [IQR]), non-APAP	17 (12, 28)	45 (33, 60)	0.006
MELD score (± SD)	35.4 ± 7.0	31.3 ± 10.0	0.026
ALFSG score (± SD)	− 0.6 ± 1.8	0.8 ± 1.4	< 0.001
KCC, *n* (%) (overall)	1 (2)	4 (9)	0.363
APAP	0 (0)	0 (0)	
Non-APAP	1 (2)	4 (9)	

LT liver transplant, *TFS* transplant-free survival, *APAP* acetyl-para-aminophenol, *HR* heart rate, *RR* respiratory rate, *MAP* mean arterial pressure, *F* Fahrenheit, *HE* hepatic encephalopathy, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *INR* internal normalized ratio, *WBC* white blood cell count, *pH* potential of hydrogen, *MELD* model for end-stage liver disease, *ALFSG* acute liver failure study group prognostic index, *KCC* Kings College Criteria

Table 2

Patient demographics and clinical information stratified by 21-day transplant-free survival—validation cohort

	Death/LT (*n* = 20)	TFS (*n* = 31)	*p* value
Age (y ± SD)	40.0 ± 15.5	38.7 ± 11.5	0.728
Race (*n* [%] Caucasian)	15 (75)	28 (90)	0.189
Gender (% female)	11 (55)	21 (68)	0.358
Etiology of ALF (*n* [%] APAP)	9 (45)	21 (68)	0.107
Admission vital signs (± SD)			
Pulse	103 ± 16	102 ± 23	0.856
Respiratory rate	22 ± 7	20 ± 6	0.387
MAP (mmHg)	79 ± 19	87 ± 18	0.141
Temperature (°F)	98.0 ± 2	98.0 ± 1	0.939
Admission stage HE (*n* [%] 3 or 4)	17 (85)	13 (42)	0.002
Infection on admission (*n* [%])	5 (25)	4 (13)	0.496
Admission vasopressor use (*n* [%])	8 (40)	7 (23)	0.183
Admission labs (median [IQR])			
Sodium (mmol/L)	138 (135, 142)	137 (134, 141)	0.568
Phosphorus (mmol/L)	3.2 (1.1, 6.5)	3.1 (1.9, 4.9)	0.975
Creatinine (mg/dL)	1.66 (0.90, 4.05)	1.40 (0.97, 3.46)	0.582
AST (units/L)	3363 (948, 5870)	4250 (1132, 9341)	0.375
ALT (units/L)	1844 (1112, 3082)	3720 (1134, 6460)	0.056
ALP (units/L)	142 (109, 179)	128 (83, 161)	0.073
Total bilirubin (mg/dL)	6.8 (4.8, 19.2)	4.8 (2.9, 6.1)	0.004
INR	4.5 (3.4, 6.0)	2.9 (2.0, 4.7)	0.007
WBC (10^9/L)	9.5 (7.0, 19.4)	8.5 (7.6, 14.3)	0.692
Platelets (10^9/L)	163 (82, 237)	138 (80, 184)	0.463
Arterial pH	7.4 (7.2, 7.4)	7.4 (7.3, 7.4)	0.419
Ammonia (μmol/L)	113 (88, 182)	95 (59, 133)	0.056
Factor V (median% normal [IQR])	14.5 (9, 19.5)	31 (18, 50)	0.001
Factor V (median% normal [IQR]), APAP	11 (8, 14)	27 (12, 41)	0.031
Factor V (median% normal [IQR]), non-APAP	16 (14, 24)	28.5 (35, 50)	0.001

	Death/LT (*n* = 20)	TFS (*n* = 31)	*p* value
MELD score (± SD)	40.13 (10.93)	31.17 (10.38)	0.005
ALFSG score (± SD)	− 1.60 ± 1.54	0.69 ± 1.55	< 0.001
KCC, *n* (%)	1 (5.0)	4 (12.9)	0.636
APAP	0 (0)	0 (0)	
Non-APAP	1 95.0)	4 (12.9)	

LT liver transplant, *TFS* transplant-free survival, *APAP* acetyl-para-aminophenol, *HR* heart rate, *RR* respiratory rate, *MAP* mean arterial pressure, *F* Fahrenheit, *HE* hepatic encephalopathy, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *INR* internal normalized ratio, *WBC* white blood cell count, *pH* potential of hydrogen, *MELD* model for end-stage liver disease *ALFSG* acute liver failure study group prognostic index, *KCC* Kings College Criteria

Table 3

Factor V alone for the prediction of 21-day transplant-free survival

ALF etiology	AUC (95% CI)	Maximum Youden index					Specificity fixed at 90% or max					Sensitivity fixed at 90% or max				
		CO	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	CO	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	CO	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Derivation cohort																
APAP	0.77 (0.62, 0.92) $p = 0.002$)	>10.5	79	69	84	61	>26.5	32	94	92	40	>5.5	94	50	80	80
Non-APAP	0.77 (0.60, 0.95) $p = 0.006$	>22	85	67	55	90	>46	46	89	68	77	> 13	91	47	56	88
Validation cohort																
APAP	0.75 (0.57, 0.93) $p = 0.071$	–	81	44	77	50	–	52	89	92	44	–	81	11	68	20
Non-APAP	0.95 (0.86, 1.00) $p = 0.014$	–	90	73	75	89	–	30	0	100	61	–	100	50	82	100

APAP acetyl-para-aminophenol, *CO* cutoff, *Sens* sensitivity, *Spec* specificity, *PPV* positive predictive value, *NPV* negative predictive value

Table 4

Comparison of FV model to MELD, KCC, and ALFSG scores for 21-day transplant-free survival

Model	AUROC (95% CI)	*p* value*	AIC
FV model	0.86 (0.78, 0.94)	Reference group	99.34
MELD	0.64 (0.54, 0.74)	< 0.001	121.55
KCC, APAP	0.53 (0.49, 0.58)	< 0.001	126.83
KCC, non-APAP	0.68 (0.58, 0.78)	0.001	118.74
ALGSG	0.77 (0.66, 0.87)	0.069	111.93

AUROC area underneath the receiver operative curve, *AIC* Akaike information criterion, *FV* factor five, *MELD* model for end-stage liver disease, *KCC* Kings College Criteria, *ALFSG* acute liver failure study group index, *APAP* acetyl-para-aminophenol

*Comparison to FV model