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ORIGINAL ARTICLE

Value of Factor V in the diagnosis of early graft dysfunction after liver transplantation: Internal validation

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Abstract

Primary graft dysfunction is a major early complication following liver transplantation, potentially leading to retransplantation or patient death. Coagulation Factor V (FV) and ALT have emerged as important biomarkers in assessing liver function, yet their role as early predictors of graft loss has not been fully validated. The aim of this study is to conduct an internal validation of published results on the applicability of FV and ALT for diagnosing graft dysfunction and its predictive ability for graft loss within the first 90 days. We conducted a retrospective cohort study including 513 adult recipients from 2012 to 2023 at the Regional University Hospital of Málaga. FV and ALT levels were measured on postoperative day 2, and patients were categorized based on FV <37.5 and ALT >1539. The association with 90-day graft loss was analyzed. Graft loss occurred in 43 patients (8.4%) within the first 90 days. The combination of FV <37.5 and ALT >1539 on postoperative day 2 demonstrated a specificity of 99% and a test efficiency of 94% in predicting graft loss. Patients meeting both criteria had a 74-fold increased risk of graft loss, with most losses occurring within the first week, and a median survival of 4 days. These findings suggest that FV and ALT on postoperative day 2 are reliable early markers for predicting graft loss, enabling risk stratification and guiding critical decisions regarding early retransplantation in the immediate postoperative period.

Keywords: Factor V, graft dysfunction, graft loss, liver transplant, retransplantation

Abbreviations: CHAID, Chi-squared Automatic Interaction Detector; DBD, donation after brain death; EAD, early allograft dysfunction; FHF, fulminant hepatic failure; FV, Factor V; HAT, hepatic artery thrombosis; LT, liver transplantation; PNF, primary nonfunction; POD, postoperative day.

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INTRODUCTION

Primary graft dysfunction is one of the main early complications after liver transplantation (LT).[1–3] It is one of the most feared complications due to its severe consequences, potentially leading to retransplantation or patient death. It can be divided into early allograft dysfunction (EAD) and primary nonfunction (PNF),[4,5] being the first initial graft dysfunction with recovery potential, while PNF is irreversible and severe without an identifiable cause.[6–8] The incidence of primary graft dysfunction varies, partly due to definition inconsistencies. EAD occurs in 15%–30% of cases.[9,10] Graft failure leads to an increased rate of postoperative complications, mortality, and higher graft loss risk.[11] Hence, primary graft dysfunction is a significant complication in the immediate postoperative period of LT.

There is no consensus on the definition of primary graft dysfunction. From Makowka's definition in 1987[12] to Halle-Smith et al's proposal of C-reactive protein and urea in 2023,[13] various criteria have been proposed for EAD[10,14–22] (Supplemental Table S1, http://links.lww.com/LVT/A667). This lack of consensus causes problems in studies, leading to heterogeneity that complicates comparisons and conclusions. It also complicates daily practice, hindering decision-making in life-threatening situations that require early diagnosis and treatment.

The most used criteria are Olthoff's, based on international normalized ratio, transaminase, and total bilirubin levels during the first 7 postoperative days (PODs).[23] This late diagnosis at 1 week has led to new promising criteria, validated by different groups, to address this lack of consensus[13,23–26] (Supplemental Table S2, http://links.lww.com/LVT/A668). Recent authors consider graft loss as the need for retransplantation or patient death, with most considering the first 3 months posttransplant a reliable period to assess graft survival.[25–27] Some define this complication in a shorter timeframe,[13,26] while others continue longer periods incompatible with EAD evolution.[24,25]

The importance of this situation lies in the prognosis of these patients and the implications of their only treatment, retransplantation. Patients with EAD have an

TABLE 1 Characteristics of patients included in the study

Variable	Total	Graft		*p*
		Lost	Not lost	
Recipient characteristics		43	470	
Sex, male (%)	76.4	81.4	76	0.42
Age, median (y)	59	62 (55–66)	59 (53–64)	0.22
BMI, median	26.6	26.2 (23.6–29.7)	26.6 (23.6–30.4)	0.85
LT indication (%)				0.56
HCC	35.5	27.9	36.2	
Chronic alcoholic hepatitis	28.1	34.9	27.4	
Viral hepatitis (HCV)	9.4	11.6	9.1	
PSC/PBC	6.2	4.7	6.4	
Metabolic	3.7	4.7	3.6	
Autoimmune	3.5	0	3.8	
Viral hepatitis (HBV)	1.4	2.3	1.3	
Primary hyperoxaluria	0.4	2.3	0.2	
Other	11.9	11.6	11.9	
MELD, median	13	15 (11–20)	13 (9–18)	0.07
Intervention characteristics				
TIT, median (min)	355	384 (305–465)	354.5 (295–426)	0.34
Transfusión CH, median (mL)	307	600 (260–1652)	300 (0–963)	<0.001
Donor characteristics				
Sex, male (%)	55.9	53.5	56.2	0.74
Age, median (y)	61	65 (52–75)	60 (50–69)	0.08
Donor type (%)				0.26
DBD	84.6	88.4	84.3	
DCD-ECMO	11.9	4.7	12.6	
DCD Super-rapid	3.5	7.0	3.2	

Abbreviations: BMI, body mass index; DBD, donation after brain death; DCD, donation after circulatory death; ECMO, extracorporeal membrane oxygenation; LT, liver transplantation; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; TIT, total ischemia time.

TABLE 2 Contingency table results of both criteria versus 90-day graft loss

	90-day graft loss No	Yes	Total	
Meet both criteria (FV < 37.5 + ALT > 1539)				
No	465	24 2[a]	489	NPV: 95%
Yes	5	19	24	PPV: 79%
Total	470	43	513	
	E: 99%	S: 44% 91%[a]		Efficiency 94%

[a]Defining graft loss as death or retransplantation includes cases of patient death without graft impairment (22 out of 43 in this study), limiting the sensitivity to a maximum of 51% (achieving 44% in our scenario). However, when considering only patients with graft impairment, the sensitivity significantly improves to 90.5% (19 true positives and only 2 false negatives).
Abbreviations: E, specificity; FV, Factor V; NPV, negative predictive value; PPV, positive predictive value; S, sensibility.

increased risk of graft loss or death in the early postoperative period,[16] and PNF leads inevitably to retransplantation.[5,10,28]

Reliable and early parameters are needed to detect primary graft dysfunction and guide urgent retransplantation. Coagulation Factor V (FV) is a good liver function marker as it is not dependent on vitamin K, implying its synthesis solely depends on liver function. It has a short half-life (12–36 h), so its plasma levels reflect liver function at the time of measurement. FV levels are considered in diagnosing fulminant hepatic failure (FHF), being one of the Clichy criteria.[29,30] In 2015, FV levels were studied in relation to LT, showing it as a prognostic biomarker of short-term mortality after LT.[31] In 2019, FV was analyzed as a potential marker of EAD after LT, showing it as a marker of EAD and a good predictor of graft loss after LT.[32]

We recently reported the value of FV on POD2 as a specific marker with a high negative predictive value of graft loss in the first 90 PODs.[33] In the current study, we sought to internally validate FV and ALT as an early prediction tool of a marker of graft loss in a larger cohort study.

METHODS

Study design and patient selection

The inclusion criteria, while derived from the pilot study,[33] were adapted to include all adult patients who received a liver transplant at the Regional University Hospital of Málaga and did not meet exclusion criteria between January 2012 and August 2023, reflecting an extended timeframe compared to the pilot study. The same exclusion criteria as our pilot study[33] were applied to ensure sample homogeneity and avoid biasing the applicability of the results: patients without FV or ALT available (in this case only on POD2), emergency LT due to FHF, and those with graft loss due to hepatic artery thrombosis (HAT) without liver dysfunction. Patients with FHF were excluded due to their severely critical condition, which leads to low levels of FV, which could bias the study's findings. Moreover, as this study focuses on identifying patients with graft dysfunction, cases of retransplantation due to HAT without liver dysfunction were deemed outside the scope.

FV and ALT values were collected on POD2. Patients were classified based on whether they met the pilot study criteria on POD2 (FV < 37.5 + ALT > 1539) and analyzed for graft loss within the first 90 days after transplant. In addition, a subanalysis was conducted to assess graft loss within the first 7 days.

To understand the influence of each variable on graft loss, both individually and in combination, and to stratify patients into different risk levels, 4 patient groups were identified based on whether they met 1 cutoff point, both, or neither. The 90-day graft loss risk was studied for each group.

Variables

The collected variables included donor demographics (sex, age, and donor type), recipient demographics (sex, age, MELD[34] score on the day of transplantation, and liver disease indicating LT), as well as surgical intervention details (total ischemia time and red blood cell transfusion).

Biochemical test results on POD2 included FV and ALT.

Data on graft loss at 90 and 7 days, including its cause (death or retransplantation), the need for retransplantation, and patient survival within the same time periods, were collected.

FV was analyzed using the "Factor V Deficient" reagent from Siemens Healthineers AG, an in vitro diagnostic reagent used for the quantitative and standardized determination of FV activity by WHO standards.

TABLE 3 Multivariate logistic regression results: 90-day loss

	OR (95% CI)	*p*	Nagelkerke R^2	Hosmer and Lemeshow test
FV < 37.5	17.4 (7.9–38.2)	< 0.001	0.3	0.1
ALT > 1539	3.8 (1.7–8.4)	< 0.001		

Abbreviation: FV, Factor V.

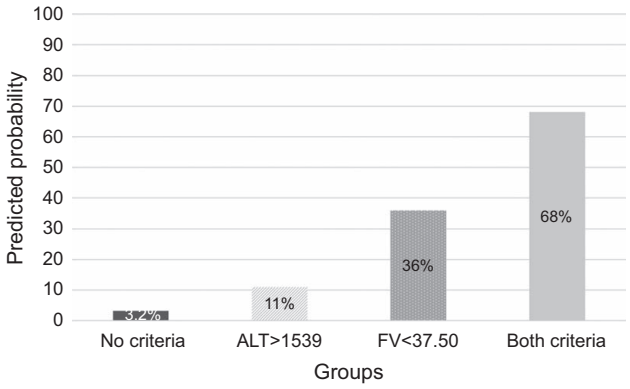


FIGURE 1 Probability of graft loss at 90 days by FV and ALT groups. Graphical representation of the predicted probability of graft loss derived from the logistic regression model. It shows the increase in probability in the 4 different groups: the black column represents patients who do not comply with any criteria (3.2% risk), the lined column represents patients who only have an ALT > 1539 (11% risk), the dotted column represents patients who only have an FV < 37.50 (36% risk), and the gray column represents patients who meet both criteria: FV < 37.50 and ALT > 1539 (68% risk). Abbreviation: FV, Factor V.

Statistical analysis

Descriptive data were expressed as mean ± standard deviation or median ± IQR and compared using the Student *t* test or Mann-Whitney *U* test based on distribution. Normality was assessed with the Kolmogorov-Smirnov test and variance homogeneity with the Levene F test. Qualitative variables were compared using the χ^2 test or Fisher exact test.

A 2 × 2 contingency table was used to calculate internal and external validity parameters, and the relationship between variables and graft survival was compared using the χ^2 test.

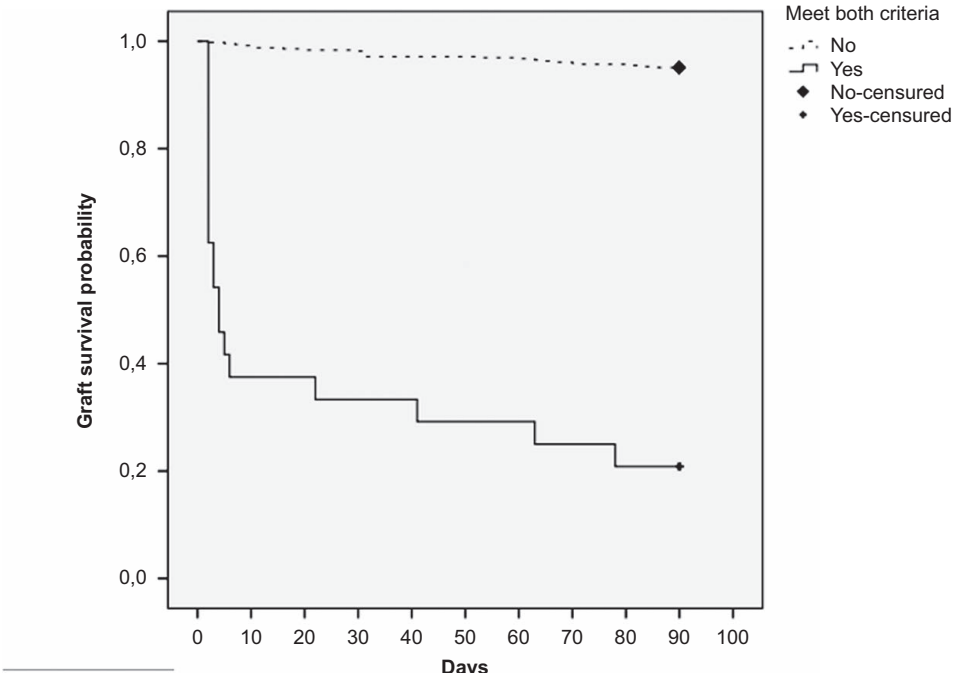
Binary logistic regression analyzed the association between variables and graft loss, predicting the probability of the event based on criteria compliance.

Graft survival curves for patients meeting both criteria and those who did not were calculated using the Kaplan-Meier method and compared with the log-rank test.

Data were analyzed using IBM SPSS Statistics (version 22.0) and R software (version 4.3.3).

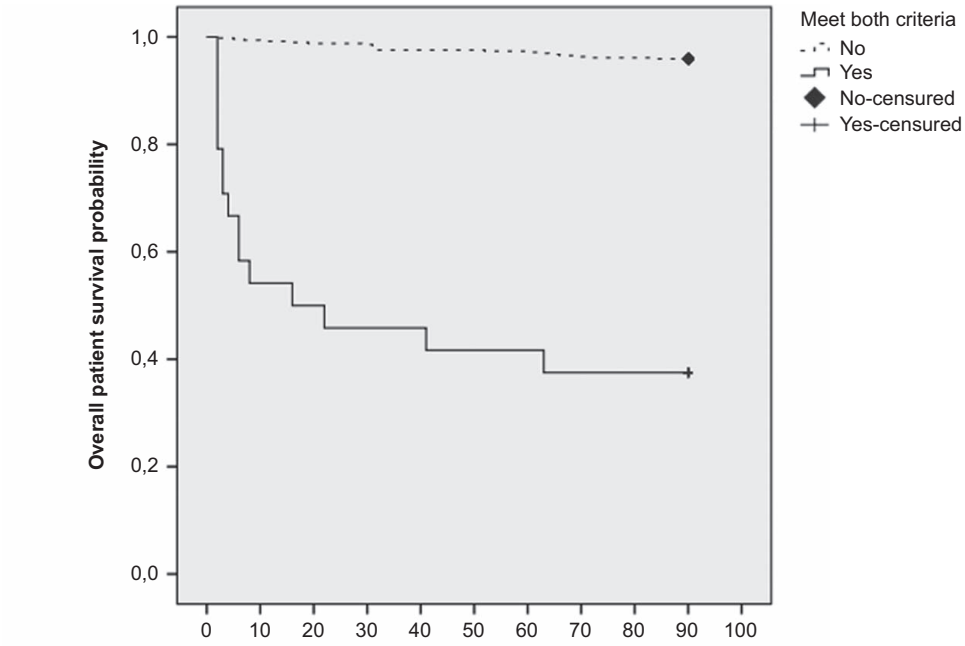
IRB statement

The Provincial Research Ethical Committee of Malaga, Spain, provided ethical approval for this study on January 25, 2024. All research was conducted in accordance with the Declarations of Helsinki and Istanbul. All subjects gave written consent.



No. at risk										
No criteria	489	485	481	480	475	475	474	470	468	465
Both criteria	24	9	9	8	8	7	7	6	5	5

FIGURE 2 Kaplan-Meier survival curve for graft survival at 90 days. This Kaplan-Meier survival curve illustrates the graft survival probability over a 90-day period. The curve represents the proportion of grafts surviving at different time points from the start of the study. Groups: does not meet criteria (dotted line): This group includes patients with FV ≥ 37.5 and/or ALT ≤ 1539. Meets criteria (continuous line): This group includes patients with FV < 37.5 and ALT > 1539. Abbreviation: FV, Factor V.



No. at risk										
No criteria	489	486	483	482	477	477	476	472	470	469
Meet criteria	24	13	12	11	11	10	10	9	9	9

FIGURE 3 Kaplan-Meier survival curve for overall patient survival at 90 days. This Kaplan-Meier survival curve illustrates the overall survival probability of patients over a 90-day period. The curve represents the proportion of patients surviving at different time points from the start of the study. Groups: does not meet criteria (dotted line): This group includes patients with FV $\geq$37.5 and/or ALT $\leq$1539. Meets criteria (continuous line): This group includes patients with FV $<$37.5 and ALT $>$1539. Abbreviation: FV, Factor V.

RESULTS

Study population

A total of 598 patients were recruited, with 29 excluded due to an emergency LT secondary to FHF, 33 excluded due to unavailable FV values on POD2, and 23 excluded due to graft loss secondary to HAT without dysfunction. Therefore, 513 patients were included in the study. The demographic characteristics of the patients included are detailed in Table 1.

Forty-three patients (8.4%) experienced graft loss within the first 90 days after transplant, with 15 patients (2.9%) losing the graft within the first 7 days due to severe dysfunction.

FV + ALT

In the contingency table comparing the fulfillment of both criteria (FV $<$37.5 + ALT $>$1539) with graft loss at 90 days, a specificity of 99% and test efficiency of 94% were obtained. When only graft impairment was considered, a sensitivity of 91% was achieved. The χ^2 test was significant with an OR of 73.6 (95% CI: [25.3–214]); $p < 0.001$ (Table 2).

In the analysis of both cutoff points independently, the multivariate regression model obtained an OR for FV $>$ or $<$37.5 of 17.4 (95% CI [7.9–38.2]) and an OR for ALT $>$ or $<$1539 of 3.8 (95% CI [1.7–8.4]) (Table 3).

Based on the established cutoff points, patients were classified into 4 groups: FV $<$37.5 and ALT $>$1539; FV $<$37.5 and ALT $<$1539; FV $>$37.5 and ALT $>$1539; and FV $>$37.5 and ALT $<$1539. The predicted probabilities of graft loss obtained from the logistic regression model for each group were 68%, 36%, 11%, and 3.2%, respectively (Figure 1).

In the 7-day subanalysis, a sensitivity of 100%, specificity of 98%, and efficiency test of 98% were obtained, with an OR of 807.2 (95% CI [105–6205.1]), $p < 0.001$. The predicted probabilities of graft loss for each risk group were 95.2%, 26.3%, 17.1%, and 0.4%, respectively.

Survival analysis

Figure 2 shows the graft survival curve, and Figure 3 shows the overall survival of patients who met both criteria and those who did not. The log-rank test was significant in both cases ($p < 0.05$).

DISCUSSION

Despite the critical need, no consensus has been reached on early markers that can predict graft loss due

TABLE 4 Patients with graft loss who do not meet FV + ALT criteria

	FV	ALT	Graft loss (d)	Cause
1	38.5	1399	31	Sepsis with ATN (pulmonary aspergillosis, superinfection with enterococcus, and pancreatitis)
2	**18.8**	1168	8	**HAT with graft dysfunction**
3	67.7	300	31	MOF: RF with reintubation + ARF
4	**18**	561	63	APE with RF
5	**30.4**	935	81	Chronic rejection with reLT
6	**31.6**	375	10	**HAT with graft dysfunction**
7	**26**	694	31	Hemorrhagic shock due to hemoperitoneum (lesser curvature bleed)
8	64.4	504	31	Myelotoxicity due to IS + RF with reintubation. Exitus due to cardiorespiratory arrest
9	40	706	71	Septic shock due to sigmoid colon perforation
10	70.1	1137	31	ARDS with hypoxia and bradycardia
11	103	**2677**	29	Cardiorespiratory arrest
12	57.7	195	10	Cardiorespiratory arrest due to shock (FA, respiratory acidosis, and anuria)
13	61.8	286	19	MOF: right pneumothorax with bronchopleural leak with reintubation, aspergillus and candida sepsis and ARF
14	62.7	201	60	Exitus due to severe cerebral damage
15	61	332	70	ARF due to ATN
16	80.6	492	64	Sepsis in patients with bone marrow aplasia
17	96	573	83	Cardiorespiratory arrest
18	46.3	228	52	Pancytopenia due to everolimus. Exitus due to liver encephalopathy
19	84	195	86	Chronic rejection with reLT
20	70	194	66	Intraparenchymal cerebral hemorrhage
21	**29**	200	16	Hypovolemic shock due to hemoperitoneum
22	54.8	58	2	Cardiorespiratory arrest due to STEMI
23	68	**1758**	5	Cardiorespiratory arrest
24	82.8	112	7	Septic shock

Bold values meet the criteria set in this study.
Abbreviations: AF, auricular fibrillation; ARDS, acute respiratory distress syndrome; APE, acute pulmonary edema; ARF, acute renal failure; ATN, acute tubular necrosis; FV, Factor V; HAT, hepatic artery thrombosis; IS, immunosuppression; MOF, multiorgan failure; reLT, retransplantation; RF, respiratory failure; STEMI, acute ST-elevation myocardial infarction.

to graft impairment. In this study, we validated the high predictive value of both FV and ALT and proposed an easy-to-use tool to guide decision-making in the early postoperative period.

In this study, the graft loss rate at 90 days was 8%, significantly lower than the 15%–30% reported in the literature.[9] This disparity may be due to our exclusion of patients with HAT without graft dysfunction and FHF, differences in graft loss definitions, our evaluation periods, or methodologies. No significant differences were observed in the characteristics of recipients or donors (Table 1), aligning with recent evidence suggesting comparable results from donation after circulatory death and donation after brain death when normothermic regional perfusion is used.[35–37] However, significant differences in red blood cell transfusions were noted, with higher volumes associated with graft loss. This relationship, previously documented in 2016[38] and explored by Hudcova et al,[39] indicates that higher transfusion volumes may reflect more complex surgeries, greater recipient comorbidities, or more severe liver disease, contributing to poorer outcomes.

Our pilot study achieved a specificity of 96% and a test efficiency of 83%.[33] Internal validation improved specificity to 99%, reducing the false positive rate to 1%. Sensitivity remained low, likely due to the definition of graft loss as death or retransplantation, which includes cases without graft dysfunction (and therefore cannot meet our criteria). This hypothesis was corroborated by reviewing the specific cases of patients who lost the graft but did not meet our criteria. Of these 24 patients, only 2 had graft dysfunction, in these cases due to HAT. Interestingly, both cases presented with an FV below 37.50 but an ALT below 1539 (Table 4). However, when only patients with graft dysfunction were considered, a sensitivity of 91% was observed. Table 5 presents the causes of graft loss of those patients who did meet both criteria. A high OR indicated that patients meeting both criteria had a 74 times greater risk of graft loss compared to those who did not. Moreover, as stated in our pilot study,[33] it is

TABLE 5 Patients with graft loss who meet FV+ALT criteria

	FV	ALT	Graft loss (d)	Death/ReLT	Cause
1	12.7	1735	63	Death	Graft dysfunction, MOF
2	36.6	2459	41	Death	Graft dysfunction, MOF
3	23.6	4965	22	Death	Graft dysfunction
4	9.9	4192	78	ReLT	Graft dysfunction due to HAT
5	31.8	3917	2	ReLT	PRS. Graft dysfunction due to HAT
6	17.3	3115	2	ReLT	Graft dysfunction due to HAT
7	37.4	5245	2	ReLT	Graft dysfunction due to HAT
8	12.5	2872	4	ReLT	Graft dysfunction due to HAT
9	32.7	1792	5	ReLT	Graft dysfunction due to HAT
10	24.5	1759	4	ReLT	Graft dysfunction due to HAT
11	5	2591	2	Death	Graft dysfunction
12	8	3459	2	Death	Graft dysfunction
13	18	3050	2	Death	Graft dysfunction
14	24	3519	6	Death	Graft dysfunction, MOF
15	0	3260	3	Death	Graft dysfunction, MOF
16	33	4074	2	ReLT	Graft dysfunction
17	6.8	5490	2	ReLT	Graft dysfunction
18	4.5	10,422	2	ReLT	Graft dysfunction
19	15	6620	3	ReLT	Graft dysfunction

Abbreviations: FV, Factor V; HAT, hepatic artery thrombosis; MOF, multiorgan failure; PRS, postreperfusion syndrome; reLT, retransplantation.

important to prioritize a high specificity due to the severe consequences of a wrongful indication for retransplantation.

Independent analysis of variables showed that FV had a higher predictive capacity for graft loss than ALT, with OR of 17 and 4, respectively. This reinforces the findings of our pilot study,[33] where FV demonstrated superior AUC values for graft loss prediction.

For clinical practice, it is useful to stratify patients into different risk groups, providing not only a measure of how much the risk of graft loss increases but also the specific probability for each patient. Figure 1 illustrates how graft loss risk increases according to the classification of groups based on FV and ALT values. A patient who does not meet any of the established criteria has a relatively low risk (3.2%) of graft loss. Conversely, patients with FV >37.5 but elevated ALT face an 11% risk. This risk rises to 36% for those with FV below 37.5 despite low ALT. As expected, patients with the highest risk profile—FV below 37.5 and ALT above 1539—show a high probability of 68% for graft loss within the first 90 days after LT. This risk stratification would allow us to identify and prioritize efforts and resources toward patients most susceptible to graft loss while also minimizing unnecessary treatments for those unlikely to experience short-term graft loss. This approach was highlighted by Pareja et al,[26] who argued that the originality of their score lay in the ability to classify patients according to the severity of graft dysfunction. Later, in 2020, Avolio et al[24] also used their score to stratify patients into 5 risk groups.

Traditionally, risk scores have determined the probability of graft loss based on the strict compliance with predefined values for a high number of variables,[13,23,31,32] or have used scoring systems that increase the risk according to complex formulas, which require specific calculators.[24–26] In comparison, our predictive tool with FV and ALT could guide clinical decision-making by providing a straightforward method that does not require complex calculations or additional tools, enabling immediate bedside decisions.

Our tool demonstrated a higher predictive value for 7-day graft loss, which is particularly valuable in practical settings where patients who present graft loss within the first week face an emergent situation requiring immediate decisions. Patients meeting both criteria are at an exceptionally high risk of graft loss and may benefit from early consideration of retransplantation.

We propose using FV + ALT to guide posttransplantation management decisions. Patients who meet neither criterion are at low risk of graft loss and may not require immediate intervention regarding graft function. In contrast, those meeting both criteria are at a high risk of graft loss, and early retransplantation should be considered. For patients at intermediate risk who meet only 1 criterion, retransplantation may be deferred, but close monitoring is essential. This advantage of patient stratification for assessing the risk-benefit of retransplantation was already

identified by Avolio et al,[24] who emphasized the importance of early retransplant indication to reduce the need for technically more challenging late retransplants due to ischemic cholangiopathies.

Graft survival analysis showed significant differences between groups. Patients meeting both criteria had a cumulative graft survival of 21% compared to 95% in those not meeting the criteria. Most graft losses among those meeting both criteria occurred within the first week, with a median survival of 4 days. In fact, 7-day graft survival for those not meeting the criteria and those who did was 99% and 38%, respectively. Patient survival was also significantly lower in the group meeting both criteria, consistent with literature associating EAD or PNF criteria with lower patient survival.[24,26,40] It is noteworthy that overall patient survival was higher than graft survival (21% vs. 28% at 90 days and 38% vs. 54% at 7 d). This may reflect how early retransplantation addressing graft loss can influence patient survival.

Our study has several strengths. Although the relationship between FV and graft loss has been studied in previous years, there has been no in-depth analysis or internal validation. Our study not only provides a thorough analysis but also validates these findings internally, enhancing their reliability. Furthermore, our good results serve as a strong hypothesis for more robust future studies. Despite these improvements, our study faced some limitations. The internal validation and single-center design may limit the generalizability of our results, suggesting the need for future external validation and multicenter studies that encompass a broader range of clinical settings and populations. In addition, while the retrospective nature of the study ensures that all clinical decisions, including retransplantation, were made before assessing these results, it is acknowledged that the inclusion of retransplantation as part of the definition of graft loss could be perceived as a potential bias, though this was not influenced by our findings.

CONCLUSIONS

We have validated the results in a large internal cohort. The combination of FV and ALT is a reliable and early marker for predicting graft loss within the first 90 and 7 days. In addition, it allows for the stratification of patients into different risk groups to guide difficult decisions arising from this complication, such as the indication for early retransplantation. Moreover, an FV < 37.50 + ALT > 1539 is not only associated with graft loss but also with overall patient survival, both in the first week and within the first 3 months.

DATA AVAILABILITY STATEMENT

The data used in this study are available in our liver transplant database and can be accessed by requesting access from the corresponding author of the article.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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