Primary Graft Dysfunction: Factor V's Value for Its Early Diagnosis

Claudia Sanchez-Gonzalez[a*], José Luis Fernández Aguilar[a], Belinda Sánchez Pérez[a], Miguel Ángel Suárez Muñoz[b], José Antonio Pérez Daga[a], María Pérez Reyes[a], and Julio Santoyo Santoyo[a]

[a]General Surgery and Digestive System Department, Regional University Hospital of Málaga, Málaga, Spain; and [b]General Surgery and Digestive System Department, Clinic University Hospital of Málaga, Málaga, Spain

ABSTRACT

Background. Primary graft dysfunction is a common postoperative complication, lacking consensus regarding diagnostic criteria. Olthoff criteria are the most used, based on blood parameters in the first 7 postoperative days. This lack of consensus and late diagnosis evidence the need of early parameters.

This study proposes factor V (FV) as a marker in the first 3 postoperative days for primary graft dysfunction.

Methods. Within a 500-patient database, 27 patients with graft loss in the first 90 days were chosen and compared with a group of 54 patients composed of the immediately preceding and following transplant to each case. Through receiver operating characteristic curves, FV and maximum glutamic pyruvic transaminase (GPT) predictive value on the first 3 postoperative days were assessed. The best threshold value was selected according to the Youden index.

Results. FV was significantly higher in the control group, with second postoperative day as the highest discriminative one (area under the curve = 0.893). In addition, a cutoff point of FV 37.50 exhibited a specificity of 92% and sensibility of 69% in predicting allograft failure in the first 3 months. GPT showed a lower validity with area under the curve = 0.77, and a GPT of 1539 presented a specificity of 82% and sensibility of 67%. Combining FV < 37.5 and GPT > 1539, a specificity of 98% and sensibility of 55% was reached.

Conclusions. FV could postulate as an early marker of primary graft dysfunction because of its high specificity despite having a lower sensibility. With de association of FV and GPT the maximum specificity for predicting graft loss in the first 3 months was reached, becoming a promising parameter for further analysis.

PRIMARY graft dysfunction is a common postoperative complication. Olthoff criteria are the most used, which are based on blood parameters in the first 7 postoperative days [1]. The lack of consensus and late diagnosis evidence the need of early parameters. Factor V (FV) is considered one of the prognostic factors of acute liver failure of the Clichy criteria. The aim of this study is to assess whether FV is a useful marker of primary graft dysfunction.

MATERIALS AND METHODS

Study Design and Patient Selection

This is a case-control study that assessed a 500-patient database of transplants between 2008 and 2018. The case group was composed of those with graft loss in the first 90 postoperative days (PODs) and was compared with a randomized control group composed of the immediately preceding and following transplant to each case. Discriminative value of FV and glutamic pyruvic transaminase (GPT) variables for 3-month graft loss was assessed with receiver operating characteristic curves, choosing the most discriminative day and the optimum threshold value. With this cutoff point, sensibility and specificity for predicting graft loss was studied. Moreover, we combined both FV and GPT cutoff points and divided patients into 2 groups: those who had both FV lower and GPT higher than the selected value and those who did not, obtaining sensibility and specificity to predict graft loss.

*Address correspondence to Claudia Sanchez-Gonzalez, Universidad of Málaga, Av. de Cervantes, 2, 29016 Málaga, Spain. Tel: +34 678 118 839. E-mail: csangon95@gmail.com

230 Park Avenue, New York, NY 10169

0041-1345/20
https://doi.org/10.1016/j.transproceed.2022.09.017

Statistical analysis

Categorical variables were compared by the χ^2 test. A receiver operating characteristic curve was plotted for FV and GPT as predictors for graft loss, calculating the area under the curve (AUC). The best cutoff value was defined by the Youden index. A contingency table was used to evaluate internal and external validity, and both threshold values were compared with graft loss by the χ^2 test. Data were analyzed using SPSS 1.0.0.1327 for Windows (IBM, Armonk, NY).

RESULTS

Study Population

The study was composed of a total of 81 patients, including 27 patients with graft loss in the first 90 days and 54 in the control group, whose characteristics are displayed in Table 1.

Factor V

The mean values of FV on POD 1 were 24.59 and 53.89 in the case and control group, respectively, 32.30 and 81.70 on POD 2, and 52.69 and 98.11 on POD 3. POD 2 was selected as the one with highest discriminatory power: AUC 0.893 (95% CI, 0.814-0.972) (Fig 1). The best cutoff point on POD 2 was FV 37.50, with 70% sensibility and 91% specificity. When compared with graft loss, it exhibited a 69% sensibility and 92% specificity. The positive predictive value (PPV) was 83%, and the negative predictive value (NPV) 84%. The diagnostic accuracy of the test was 84%.

Glutamic pyruvic transaminase

The mean maximum values were 5752.89 and 1135.13 in the case and control group, respectively. GPT exhibited an AUC of 0.77 ($P < .05$) (Fig 1). The best threshold value was 1539, with a sensibility of 67% and specificity of 82%. When comparing with graft loss, we observed a sensibility of 66% and specificity of 82%, with a PPV of 68% and NPV of 81%. The diagnostic accuracy of the test was 77%.

Factor V + glutamic pyruvic transaminase

When comparing patients who complied with both FV < 37.50 and GPT > 1539 and those who did not with graft loss, a sensibility of 56% and specificity of 96% was exhibited, with PPV of 88% and NPV of 81%. The diagnostic accuracy of the test was 83%. The χ^2 test was statistically significant, with $P < .05$.

In Fig 2 we describe how 88% of those 17 patients who complied with both cutoff points lost their graft. In comparison, only an 18% of those 64 patients who did not satisfy both threshold values lost their graft. Furthermore, in this last group only 1 of them was secondary to primary graft dysfunction.

Table 1. Baseline Characteristics of Patients in This Study

Variable	Overall (%)	Respective Group		*P* Value
		Case	Control	
Recipient characteristics				
Sex, % male	65.43	62.96	66.67	.741
Age, mean (range), y	54	54.85 (35-69)	53.69 (25-69)	.946
BMI, mean (range)	27.49	28 (18-42)	27.23 (20.43)	.504
Underlying liver disease, %				.914
Viral hepatitis	28.40	29.63	27.78	
Alcoholic hepatitis	20.99	22.22	20.37	
Hepatocellular carcinoma	23.46	25.93	22.22	
Other	27.16	22.22	29.63	
MELD, mean (range)	17.28	15.67 (6-40)	18.09 (6-39)	.205
Surgical characteristics				
Indication				.453
Elective	88.89	92.59	87.04	
Emergent	11.11	7.41	12.96	
Total ischemic time, mean (range), min	427	394.16 (165-567)	442.19 (217-777)	.103
Red blood cells transfusions, mean (range), mL	887.48	1105 (0-5600)	778.72 (0-2824)	.135
Donor characteristics				
Sex, % male	53.09	59.26	50	.431
Age, mean (range), y	56	60 (19-84)	54 (15-82)	.125
Type of donor, mean				.155
Encephalic	98.77	96.3	100	
Asystolic	1.23	3.7	0	

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MELD, Model for End-Stage Liver Disease; GPT, **glutamic pyruvic transaminase**

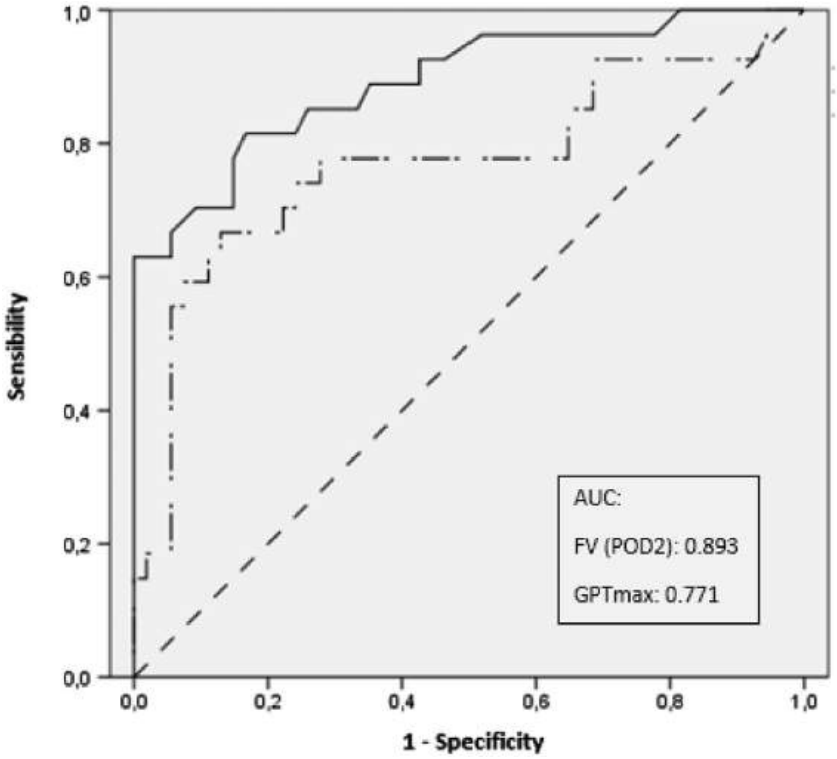

Fig 1. ROC curve factor V and GPT vs graft loss graft loss. ROC curve of factor V on POD 2 (continuous line). ROC curve of GPT max (dots-dash line)
GPT; POD, postoperative day; ROC, receiver operating characteristic.

DISCUSSION

The differences in the mean values of both groups support our hypothesis because we see how those with graft loss were the ones with lower FV levels, which could display the fact that FV could embody graft functioning. Regarding the threshold value, we should prime a higher specificity even at the expense of a lower sensibility because we are not evaluating a screening test; thus, we need to minimize false positives. The above exposed is supported by Gorgen et al [2] because in 2019 they established the best threshold value to be an FV of 36.1, although with a

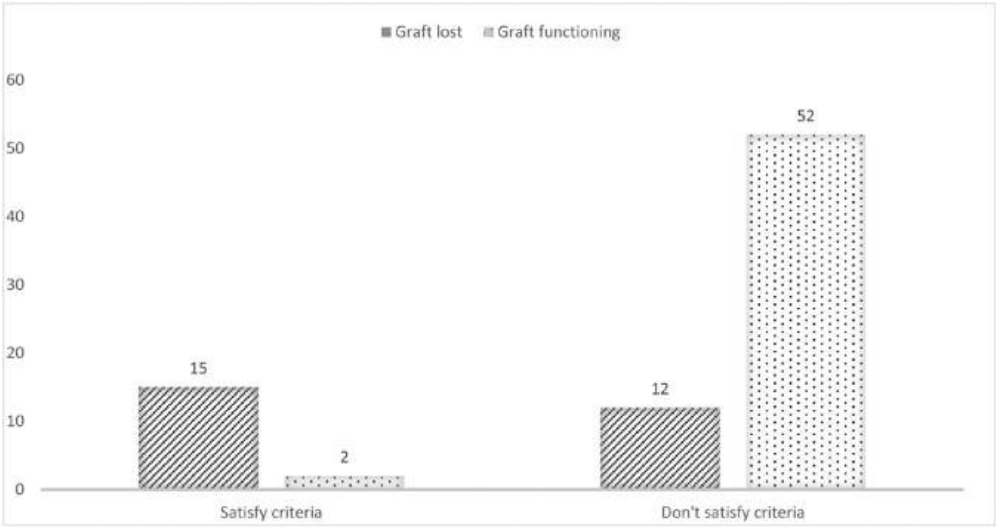

Fig 2. Factor V < 37.50 + GPT > 1539 vs graft loss.
The χ^2 test was statistically significant, with $P < .05$.

.

lower sensibility (73%) and specificity (70%). In this same study, an AUC of 0.79 was exhibited, which was lower than the one obtained in our study. It could be justified by the fact that their work was a cohort study, and we could be biasing the discriminative power with our case-control study. Another feasible reason could be they considered a 6-month graft loss compared with our 3-month follow-up. When analyzing FV in relation to graft loss, it could depend on levels lower than the threshold value. Furthermore, a significantly high specificity was exhibited along with a reasonable sensibility, with its accuracy also important. We also assessed GPT and compared it with FV, exhibiting a lower AUC and therefore a lower discriminative power. This difference was assessed by Zulian et al [3], who compared FV, GPT, and glutamic oxaloacetic transaminase and obtained the highest AUC with FV. GPT cutoff value was also related to graft loss with a lower grade of association. All the above leads us to assert FV could be a better marker for primary graft dysfunction, being novel because it was first proposed for this use in 2015 [3]. By relating both threshold values we obtained a specificity of close to 100% despite a lower sensibility, which can be secondary to other causes of graft loss (such as septic shock, acute pulmonary edema, acute pancreatitis, tacrolimus toxicity). We must recognize the small sample and the retrospective design, so despite being statistically significant, a larger study should be conducted to obtain more solid conclusions.

CONCLUSIONS

FV could postulate as an early marker of primary graft dysfunction because of its high specificity despite having a lower sensibility. With de association of FV and GPT, the maximum specificity for predicting graft loss in the first 3 months was reached, becoming a promising parameter for further analysis.

DISCLOSURES

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

REFERENCES

[1] Valdivieso López A. Abdominal organs transplants guide. Madrid, Spain:. Arán Ediciones 2016 SL.

[2] Gorgen A, Prediger C, Prediger JE, Chedid MF, Backes AN, de Araujo A, et al. Serum factor V is a continuous biomarker of graft dysfunction and a predictor of graft loss after liver transplantation. Transplantation 2019;103:944–51.

[3] Zulian MC, Chedid MF, Chedid AD, Grezzana Filho TJM, Leipnitz I, de Araujo A, et al. Low serum factor V level: early predictor of allograft failure and death following liver transplantation. Langenbecks Arch Surg 2015;400:589–97.