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## Contents

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## REVIEW

- 1669 Understanding the multifaceted etiopathogenesis of foot complications in individuals with diabetes  
*Matijević T, Talapko J, Meštrović T, Matijević M, Erić S, Erić I, Škrlec I*

## MINIREVIEWS

- 1684 Diabetic foot ulcer: A comprehensive review of pathophysiology and management modalities  
*Raja JM, Maturana MA, Kayali S, Khouzam A, Efevbokhan N*
- 1694 Isoperistaltic vs antiperistaltic anastomosis after right hemicolectomy: A comprehensive review  
*Symeonidis D, Karakantas KS, Kissa L, Samara AA, Bompou E, Tepetes K, Tzovaras G*
- 1702 Evolving paradigm of thrombolysis in pulmonary embolism: Comprehensive review of clinical manifestations, indications, recent advances and guideline  
*Ochani RK, Aibani R, Jatoi HN, Anwar M, Khan SA, Ratnani I, Surani S*
- 1712 Corneal endothelial cells and acoustic cavitation in phacoemulsification  
*Chen K, Xu WY, Sun SS, Zhou HW*
- 1719 Modern blepharoplasty: From bench to bedside  
*Miotti G, Zeppieri M, Pederzani G, Salati C, Parodi PC*
- 1730 Pregnancy and medications for inflammatory bowel disease: An updated narrative review  
*Akiyama S, Steinberg JM, Kobayashi M, Suzuki H, Tsuchiya K*
- 1741 Pathogenesis, clinical manifestations, diagnosis, and treatment progress of achalasia of cardia  
*Li MY, Wang QH, Chen RP, Su XF, Wang DY*

## ORIGINAL ARTICLE

## Retrospective Study

- 1753 Patients with hepatocellular carcinoma that die during the first year of liver transplantation have high blood sFasL concentrations  
*Lorente L, Rodriguez ST, Sanz P, González-Rivero AF, Pérez-Cejas A, Padilla J, Díaz D, González A, Martín MM, Jiménez A, Cerro P, Portero J, Barrera MA*

## Prospective Study

- 1761 Epidemiological and clinical characteristics of COVID-19 in a Brazilian public hospital  
*Pinheiro FD, Lopes LW, Dórea RSDM, Araújo GRL, Silva FAFD, de Brito BB, Cordeiro Santos ML, Júnior GMS, de Lorenzo Barcia MTA, Marques RA, Botelho AB, Dantas ACS, Costa DT, Teixeira AF, Souza CL, Marques LM, Campos GB, Oliveira MV, de Magalhães Queiroz DM, Freire de Melo F*

## CASE REPORT

- 1771 Pediatric acute heart failure caused by endocardial fibroelastosis mimicking dilated cardiomyopathy: A case report  
*Xie YY, Li QL, Li XL, Yang F*
- 1782 Extensively infarcted giant solitary hamartomatous polyp treated with endoscopic full-thickness resection: A case report  
*Ye L, Zhong JH, Liu YP, Chen DD, Ni SY, Peng FQ, Zhang S*
- 1788 Combined hamartoma of the retina and retinal pigment epithelium: A case report  
*Ren Q, Han N, Zhang R, Chen RF, Yu P*
- 1794 Testicular pain originating from lumbar disc degeneration: A case report  
*Yan XJ, Wu B, He X, Tian ZK, Peng BG*
- 1799 Glucocorticoid-induced thrombotic microangiopathy in paroxysmal nocturnal hemoglobinuria: A case report and review of literature  
*Yang XD, Ju B, Xu J, Xiu NN, Sun XY, Zhao XC*
- 1808 Giant juvenile fibroadenoma in a 14-year old Chinese female: A case report  
*Wang J, Zhang DD, Cheng JM, Chen HY, Yang RJ*
- 1814 A complementary comment on primary hepatic angiosarcoma: A case report  
*Gulmez AO, Aydin S, Kantarci M*
- 1823 Primary membranous nephrotic syndrome with chylothorax as first presentation: A case report and literature review  
*Feng LL, Du J, Wang C, Wang SL*
- 1830 Continuous positive airway pressure for treating hypoxemia due to pulmonary vein injury: A case report  
*Zhou C, Song S, Fu JF, Zhao XL, Liu HQ, Pei HS, Guo HB*
- 1837 False positive detection of serum cryptococcal antigens due to insufficient sample dilution: A case series  
*Chen WY, Zhong C, Zhou JY, Zhou H*
- 1847 Lactation breast abscess treated with Gualou Xiaoyong decoction and painless lactation manipulation: A case report and review of literature  
*Jin LH, Zheng HL, Lin YX, Yang Y, Liu JL, Li RL, Ye HJ*
- 1857 Treatment of a large area perioral viral herpes infection following noninvasive ventilation: A case report  
*Tang AM, Xu JY, Wang R, Li YM*
- 1862 Gastroparesis after video-assisted thoracic surgery: A case report  
*An H, Liu YC*
- 1869 Hyperlactemia associated with secondary hepatocellular carcinoma resection in relation to circulation stability and quality of recovery: A case report  
*Meng Y, Pei HS, Yu JJ*

- 1878** Sclerosing odontogenic carcinoma of maxilla: A case report

*Soh HY, Zhang WB, Yu Y, Zhang R, Chen Y, Gao Y, Peng X*

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Retrospective Study

# Patients with hepatocellular carcinoma that die during the first year of liver transplantation have high blood sFasL concentrations

Leonardo Lorente, Sergio T Rodriguez, Pablo Sanz, Agustín F González-Rivero, Antonia Pérez-Cejas, Javier Padilla, Dácil Díaz, Antonio González, María M Martín, Alejandro Jiménez, Purificación Cerro, Julián Portero, Manuel A Barrera

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## Abstract

### BACKGROUND

Fas ligand (FasL) is one ligand that activates extrinsic apoptosis pathway. High expression in lymphocytes of FasL have been found in patients with acute rejection of liver transplantation (LT). No high blood concentrations of soluble FasL (sFasL) have been found in patients with acute LT rejection; however, the samples size of those studies was small.

### AIM



To determine whether patients with hepatocellular carcinoma (HCC) that died during the first year of LT have higher blood sFasL concentrations previously to LT than those who remain alive in a study of higher sample size.

## METHODS

Patients underwent LT due to HCC were included in this retrospective study. Serum sFasL levels prior to LT were measured and one-year LT mortality was registered.

## RESULTS

Non-surviving patients ( $n = 14$ ) showed higher serum sFasL levels [477 (269-496) *vs* 85 (44-382) pg/mL;  $P < 0.001$ ] than surviving patients ( $n = 113$ ). Serum sFasL levels (pg/mL) were associated with mortality (OR = 1.006; 95%CI = 1.003-1.010;  $P = 0.001$ ) independently of age of LT donor in the logistic regression analysis.

## CONCLUSION

We report for the first time that HCC patients who die within the first year of LT have higher blood sFasL concentrations prior to LT than those who remain alive.

**Key Words:** sFasL; Hepatocellular carcinoma; Liver transplantation; Mortality; Outcome

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**Core Tip:** Fas ligand (FasL) is one of the main ligands that activate apoptosis *via* the extrinsic pathway. Elevated blood concentrations of soluble FasL (sFasL) have not been found in patients with acute liver transplant (LT) rejection; however, the sample sizes of those studies were small. We found in this retrospective study of 127 patients with hepatocellular carcinoma underwent to LT that patients that die during the first year of LT have higher blood sFasL concentrations previously to LT than those who remain alive. The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies with the highest attributable mortality[1-4]. Liver transplantation (LT) in some HCC patients is the treatment of choice, as it removes the liver tumour and treats liver failure[5-8].

Apoptotic cell death occurs in healthy subjects (for morphogenesis and tissue remodelling) and in different diseases such as liver diseases[9-13]. Apoptosis can be activated by so-called extrinsic and intrinsic pathways. Extrinsic apoptosis pathway is activated when binding a protein of ligands superfamily of the tumour necrosis factor (TNFSF) to its receptor of membrane receptors superfamily of the tumour necrosis factor (TNFRSF). Fas ligand (FasL) is a major ligand for TNFSF, and Fas is a major receptor for TNFRSF. Upon binding of FasL to Fas, a death signal appears that will activate caspase 8. Subsequently, caspase 8 will produce caspase-3 activation, leading to cell death[9-13].

Little data has been reported on the FasL/Fas system in LT patients. Higher lymphocyte expression of Fas[14,15] and FasL[15] has been found in patients with acute LT rejection than in patients without rejection. In addition, higher blood sFas levels have been found in patients with acute LT rejection than in patients without rejection[16-18]; however, two of these studies found no difference in blood sFasL levels between patients with and without LT rejection[16,17] and one study did not report blood sFasL levels[18]. Finally, another study found no differences in sFas and sFasL blood levels between patients with and without LT rejection[19]. However, the sample size in all these studies was small (less than 70 patients undergoing LT). Therefore, we aimed to determine whether HCC patients who die during the first year of LT have higher pre-LT blood sFasL concentrations than those who remain alive in a larger sample size study.

## MATERIALS AND METHODS

### Design and patients

Inclusion criteria were the following: Patients undergoing donor LT in brain death by HCC. Patients were recruited at the Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain). Recruitment period was from January 1996 to May 2017 by HCC. No exclusion criteria were considered. This retrospective study was performed with Institutional Ethic Review Board approval and with informed (and written) consent of patients (or a legal guardian). Formerly, we determined DNA and RNA oxidative damage[20] in some of those LT patients. Now, in this research, we have measured serum levels of sFasL concentrations.

### Variables recorded

Variables recorded for each patient were serum alpha-fetoprotein (AFP) levels, Child-Pugh score[21], nodule size, within Milan criteria[22] pre- and post-LT, degree of tumour differentiation, age of liver donor, model for end-stage liver disease (MELD) score[23] by liver function, liver recipient age, sex, infiltration, macrovascular and microvascular invasion, LT technique, portal hypertension, multinodular tumour, pre-LT treatment and 1-year survival from LT (our endpoint study).

### Determination of serum levels of sFasL

Analyses to measure serum FasL concentrations were performed at the Laboratory Department of the Hospital Universitario de Canarias (Tenerife, Spain) by enzyme-linked immunosorbent assay. The human FasL ELISA kit (Elabscience, Houston, TX, United States) with intra-assay and inter-assay coefficients of variation of less than 6% and a limit of detection of 15.6 pg/mL was used.

### Statistical methods

We employed  $\chi^2$  test to compare categorical variables (reported as frequencies and percentages) and Mann-Whitney test to compare continuous variables (reported as medians and interquartile ranges). Receiver operating characteristic (ROC) curve was employed to test the predictive capability of LT 1-year mortality with pre-LT serum sFasL levels. Kaplan-Meier survival curves were constructed using 1-year LT survival and pre-LT serum sFasL levels below/above 190 pg/mL (this cut-off point was selected based on Youden-Jindex). We employed logistic regression analysis to determine a possible association between pre-LT serum sFasL levels and mortality at 1-year post-LT, controlling for LT donor age. Statistical analyses were performed with SPSS 17.0 (SPSS Inc., Chicago, IL, United States) and MedCal 15.2.1 (Ostend, Belgium).

## RESULTS

A total of 127 patients were included in the study, 113 (89.0%) of them remain alive at one year post-LT and 14 (11.0%) dead during the first year of LT. Their mean age was  $51 \pm 17$  years, 109 (85.8%) were males and 18 (14.2%) were females. Of them, 121 (95.3%) were inside Milan criteria previously to LT and 107 (84.3%) after LT, 41 had (32.3%) infiltration, 29 (22.8%) microvascular invasion, 87 (68.5%) portal hypertension, 44 (34.6%) multinodular tumor, and 7 (5.5%) macrovascular invasion.

We found that 1-year LT survivors revealed younger LT donors ( $P = 0.049$ ) and lower serum sFasL levels ( $P < 0.001$ ) than non-surviving ones (Table 1). However, serum AFP levels, Child-Pugh score, nodule size, fulfilment of Milan criteria before and after LT, degree of tumour differentiation, MELD score by liver function, age of the liver recipient, sex, infiltration, macrovascular invasion, microvascular invasion, LT technique, portal hypertension, multinodular tumour and pre-LT treatment showed no statistical difference in the comparison between surviving and non-surviving patients (Table 1).

Serum sFasL levels (pg/mL) were associated mortality (Odds Ratio = 1.006; 95% CI = 1.003-1.010;  $P = 0.001$ ) independently of LT donor age in logistic regression analysis (Table 2). We found an area under the curve of 84% (95% CI = 75%-93%;  $P < 0.001$ ) for prediction of mortality by serum sFasL levels (Figure 1). Kaplan-Meier analysis showed that patients with serum sFasL concentrations higher than 190 pg/mL had an increased risk of death (Hazard ratio = 13.5; 95% CI = 4.5-40.7;  $P < 0.001$ ) (Figure 2).

We found a positive correlation between serum levels of sFasL and AFP ( $\rho = 0.73$ ;  $P < 0.001$ ). However, we no found significant differences in serum sFasL levels related to LT recipient age ( $P = 0.36$ ), sex ( $P = 0.27$ ), MELD score ( $P = 0.12$ ), Child-Pugh score ( $P = 0.48$ ), portal hypertension ( $P = 0.82$ ), multinodular tumor ( $P = 0.16$ ), macrovascular invasion ( $P = 0.48$ ), degree of tumor differentiation ( $P = 0.22$ ), microvascular invasion ( $P = 0.19$ ), serum protein concentration ( $P = 0.67$ ), serum albumin concentration ( $P = 0.07$ ) and serum creatinine concentration ( $P = 0.96$ ).



**Table 1 Clinical and biochemical characteristics of one-year liver transplantation survivor and non-survivor patients**

	1 yr survivor patients, (n = 113)	1 yr non-survivor patients, (n = 14)	P value
Serum sFasL (pg/mL) - median (p 25-75)	85 (44-382)	477 (269-496)	< 0.001
Age of liver donor (yr) - median (p 25-75)	52 (35-64)	62 (49-73)	0.049
Age of liver recipient (yr) - median (p 25-75)	59 (52-62)	56 (53-62)	0.88
Serum alpha-fetoprotein (ng/dL) - median (p 25-75)	8 (4-37)	13 (5-180)	0.36
MELD score - median (p 25-75)	15 (12-18)	16 (14-18)	0.78
Nodules size (cm) - median (p 25-75)	3.0 (2.0-3.5)	2.8 (1.6-4.3)	0.94
Protein (g/dL) - median (p 25-75)	6.7 (6.0-7.1)	6.7 (5.7-7.7)	0.83
Leukocytes (count/mm <sup>3</sup> ) - median (p 25-75)	4800 (3590-6200)	4940 (3490-7920)	0.60
Albumin (g/dL) - median (p 25-75)	3.3 (2.9-4.1)	3.3 (2.9-4.2)	0.91
Creatinine (mg/dL) - median (p 25-75)	0.9 (0.8-1.1)	1.0 (0.8-1.1)	0.43
BMI (kg/m <sup>2</sup> ) - median (p 25-75)	27.6 (24.5-30.0)	28.1 (23.1-31.1)	0.80
Gender female - n (%)	18 (15.9)	0	0.11
Portal hypertension - n (%)	77 (68.1)	10 (71.4)	0.80
Child-Pugh score - n (%)			0.47
A	53 (46.9)	9 (64.3)	
B	34 (30.1)	3 (21.4)	
C	26 (23.0)	2 (14.3)	
Multinodular tumor- n (%)	33 (29.2)	5 (35.7)	0.62
Macrovascular invasion - n (%)	7 (6.2)	0	0.34
Microvascular invasion - n (%)	26 (23.0)	3 (21.4)	0.89
Infiltration - n (%)	38 (33.6)	3 (21.4)	0.36
Inside Milan criteria previously to LT - n (%)	108 (95.6)	13 (92.9)	0.65
Inside Milan criteria after LT - n (%)	97 (85.8)	10 (71.4)	0.16
Treatment previously to LT - n (%)	62 (54.9)	10 (71.4)	0.24
Transplantation technique - n (%)			0.63
By-pass	41 (36.3)	6 (42.9)	
Piggy back	72 (63.7)	8 (57.1)	
Degree of tumor differentiation - n (%)			0.51
Well	83 (73.5)	11 (78.6)	
Moderate	27 (23.9)	2 (14.3)	
Poor	3 (2.7)	1 (7.1)	

MELD: Model for end-stage liver disease; BMI: Body mass index; sFasL: Soluble FasL.

## DISCUSSION

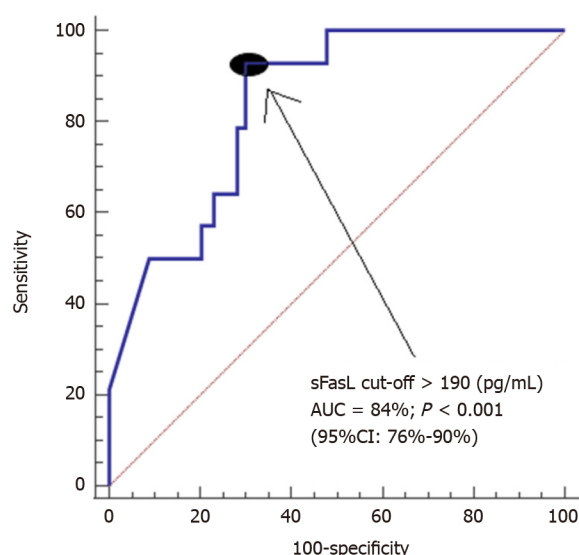
The main novel finding that showed our study was that association between elevated serum sFasL levels prior to LT and increased risk of death during the first year after LT. The 1-year survival rate from LT in our series (89%) is similar to those reported in other series (75%-95%)[24-28]. Several factors associated with worse prognosis in HCC patients undergoing LT have been reported (tumour size, outside Milan criteria, hepatic microinvasion, tumour number, degree of differentiation, vascular infiltration, serum AFP levels, and invasion)[29]; however, only higher serum sFasL levels and age of the LT donor were factors associated with worse prognosis in our series.

Previously, higher lymphocyte expression of FasL[15] has been found in patients with acute LT rejection than in patients without rejection. Furthermore, three studies found no difference in blood sFasL levels between patients with and without LT rejection[16,17,19]. Therefore, the association

**Table 2** Logistic regression analysis for the variables associated with one-year liver transplantation mortality

	Odds ratio	95% confidence interval	P value
Age of liver donor (age)	1.044	1.001-1.088	0.045
Serum sFasL levels (pg/mL)	1.006	1.003-1.010	0.001

sFasL: Soluble FasL.



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**Figure 1** Receiver operation characteristic of serum soluble FasL levels previously to liver transplantation due to hepatocellular carcinoma for the prediction of one-year liver transplantation mortality. Area under curve of serum soluble FasL (sFasL) levels and sensitivity/specificity of serum sFasL levels > 190 pg/mL are reported. AUC: Area under curve; sFasL: Soluble FasL.

between elevated serum sFasL levels before LT and death is a new finding of our study. Possibly the larger sample size (127 patients) of our study compared to that of previous studies (less than 70 patients) contributes to this new finding.

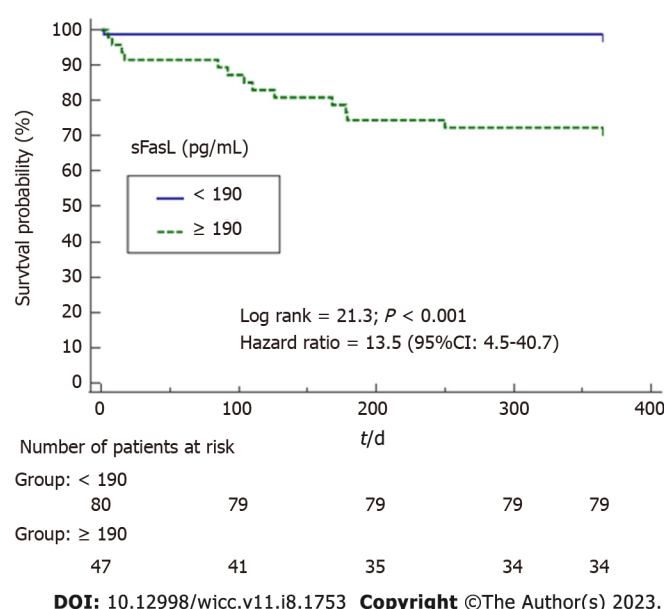
In addition, we also found a positive association between serum levels of sFasL and AFP, and that association is according to the findings of one previous study[30]; however, we did not find an association between serum sFasL levels and other variables.

FasL is one of TNFSF that activates apoptosis extrinsic pathway when binding to its receptor Fas. Due to this binding, a death signal is generated (which will activate caspase 8). Subsequently, caspase 8 will lead to the activation of caspase 3 (responsible for cell death)[9-13]. Therefore, we think that the findings of our study that non-surviving patients showed higher serum sFasL levels compared to surviving ones could be related to a higher activation of apoptosis. Although limitations of our study were the absence of data on apoptosis in liver tissue and data on blood sFasL levels during patient follow-up. Another limitation was the relatively low sample size of our study to include more variables in the regression model.

In rodent animal models of hepatic ischaemia-reperfusion injury, administration of Fas and/or FasL-blocking agents reduced hepatic caspase-3 activity and hepatocyte apoptosis, and increased animal survival[31-33]. We think that the findings from our study with patients undergoing HT due to HCC could encourage research to clarify the potential role of serum sFasL levels in estimating the prognosis of HT patients in a larger series. In addition, the findings from rodent animal models could encourage research to clarify the potential role of administration of Fas/FasL-blocking agents in improving the prognosis of these patients.

## CONCLUSION

We report for the first time that HCC patients who die during the first year of LT have higher blood sFasL concentrations prior to LT than those who remain alive.



**Figure 2** Kaplan-Meier survival analysis using mortality (as dependent variable) during first year of liver transplantation due to hepatocellular carcinoma and serum soluble FasL levels previously to liver transplantation lower/higher than 190 pg/mL (as independent variable). Both survival curves were compared by log rank and hazard ratio. sFasL: Soluble FasL.

## ARTICLE HIGHLIGHTS

### Research background

Fas ligand (FasL) is one ligands that activates extrinsic apoptosis pathway. High expression in lymphocytes of FasL have been found in patients with acute rejection of liver transplantation (LT).

### Research motivation

No high blood concentrations of soluble FasL (sFasL) have been found in patients with acute LT rejection; however, the samples size of those studies was small.

### Research objectives

To determine whether patients with hepatocellular carcinoma (HCC) that dead during the first year of LT have higher blood sFasL concentrations previously to LT that those who that remain alive in a study of higher sample size.

### Research methods

Patients underwent LT due to HCC were included in this retrospective study. Serum sFasL levels prior to LT were measured and one-year LT mortality was registered.

### Research results

Non-surviving patients ( $n = 14$ ) showed higher serum sFasL levels [477 (269-496) *vs* 85 (44-382) pg/mL;  $P < 0.001$ ] than surviving patients ( $n = 113$ ). Serum sFasL levels (pg/mL) were associated with mortality (OR = 1.006; 95%CI = 1.003-1.010;  $P = 0.001$ ) independently of LT donor in the logistic regression analysis.

### Research conclusions

We report for the first time that HCC patients who die within the first year of HT have higher blood sFasL concentrations prior to HT than those who remain alive.

### Research perspectives

The beneficial results of blockade of the Fas system in animal models could motivate its investigation in these patients.

## FOOTNOTES

**Author contributions:** Lorente L was responsible of conceive, design and coordinate the study, made substantial contributions to acquisition of data, analysis and interpretation of data, and drafted the manuscript; Rodriguez ST, Sanz P, Padilla J, Díaz D, González A, Martín MM, Cerro P, Portero J and Barrera MA have made substantial contributions to acquisition of data and provided useful suggestions; González-Rivero AF and Pérez-Cejas A participated in blood determination levels; Jiménez A have made substantial contributions to analysis and interpretation of data; All authors read critically and approved the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Institutional review board statement:** The Institutional Board of the Hospital Universitario Nuestra Señora de Candelaria (Santa Cruz de Tenerife, Spain) approved the study protocol.

**Informed consent statement:** The informed consent to participate in the study was signed by the patient or a family member.

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**Data sharing statement:** The datasets generated during the current study are available from the corresponding author on reasonable request.

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