



Serum Sphingosine-1-Phosphate Is Decreased in Patients With Acute-on-Chronic Liver Failure and Predicts Early Mortality

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Sphingosine-1-phosphate (S1P) regulates pathophysiological processes, including liver regeneration, vascular tone control, and immune response. In patients with liver cirrhosis, acute deterioration of liver function is associated with high mortality rates. The present study investigated whether serum S1P concentrations are associated with disease severity in patients with chronic liver disease from compensated cirrhosis (CC), acute decompensation (AD), or acute-on-chronic liver failure (ACLF). From August 2013 to October 2017, patients who were admitted to the University Hospital Frankfurt with CC, AD, or ACLF were enrolled in our cirrhosis cohort study. Tandem mass spectrometry was performed on serum samples of 127 patients to assess S1P concentration. Our study comprised 19 patients with CC, 55 with AD, and 51 with ACLF, aged 29 to 76 years. We observed a significant decrease of S1P according to advanced liver injury from CC and AD up to ACLF ($P < 0.001$). S1P levels further decreased with progression to ACLF grade 3 ($P < 0.05$), and S1P highly inversely correlated with the Model for End-Stage Liver Disease score ($r = -0.508$; $P < 0.001$). In multivariate analysis, S1P remained an independent predictor of 7-day mortality with high diagnostic accuracy (area under the curve, 0.874; $P < 0.001$). *Conclusion:* In patients with chronic liver disease, serum S1P levels dramatically decreased with advanced stages of liver disease and were predictive of early mortality. Because S1P is a potent regulator of endothelial integrity and immune response, low S1P levels may significantly influence progressive multiorgan failure. Our data justify further elucidation of the diagnostic and therapeutic role of S1P in ACLF. (*Hepatology Communications* 2020;4:1477-1486).

In patients with chronic liver disease, acute deterioration of liver function is associated with high short-term mortality.⁽¹⁾ Acute deterioration of liver function and complication of patients with compensated liver cirrhosis (CC) can be classified as acute decompensation (AD) or if organ failure is present as acute-on-chronic liver failure (ACLF).^(1,2) The prevalence of ACLF in hospitalized patients is

Abbreviations: ACLF, acute-on-chronic liver failure; AD, acute decompensation; AUC, area under the curve; CC, compensated cirrhosis; CI, confidence interval; CRP, C-reactive protein; FTY720, fingolimod; INR, international normalized ratio; LSEC, liver sinusoidal endothelial cell; MELD, Model for End-Stage Liver Disease; OR, odds ratio; ROC, receiver operating characteristics; S1P, sphingosine-1-phosphate; SL, sphingolipid.

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24%–40%.⁽²⁾ Precipitating events, such as excessive alcohol intake, viral hepatitis, or drug intake, can be triggers of acute deterioration, whereas ACLF triggered by bacterial infection is linked to exceptional high patient mortality rates.^(3,4)

To date, little is known about the role of sphingolipids (SLs) in ACLF, although there is a growing body of evidence that SLs are not only components of cellular membranes but also bioactive molecules with multiple mediating effects, especially in inflammatory diseases.⁽⁵⁾ Recent data report that SLs play a pivotal role in liver injury, repair, and regeneration.⁽⁶⁾ Likewise, our group has also repetitively shown that SLs could be veritable biomarkers and mediators in different hepatopathies, e.g., acute liver graft dysfunctions,⁽⁷⁾ virologic events in patients with chronic hepatitis B and C infection,^(8,9) or development of hepatocellular carcinoma.^(10,11) In 2017, Rohrbach et al.⁽¹²⁾ reviewed recent research on the importance of sphingosine-1-phosphate (S1P) metabolism in liver pathobiology, reporting pleiotropic effects of S1P depending on the receptor and cell type targeted. They underlined the key role of S1P, its metabolites, and controlling enzymes in multiple essential hepatic functions. In addition, Becker et al.⁽¹³⁾ recently described low S1P plasma levels as predictive for increased mortality in patients with liver cirrhosis.

S1P is one of the key SLs that regulate many pivotal physiological and pathophysiological processes, such as cellular barrier protection,⁽¹⁴⁾ vascular tone control,⁽¹⁵⁾ and immune responses.⁽¹⁶⁾ It can be synthesized either *de novo* from serine and palmitoyl-coenzyme A or produced by the degradation of more complex SLs by ceramide and sphingosine intermediates⁽¹⁷⁾ (Supporting Fig. S1). Extracellular S1P can bind to five different G protein-coupled receptors,

named S1P1-5, activating different signaling pathways.⁽¹⁸⁾ Modulation of extracellular S1P levels or activation/inactivation of S1P receptors has recently been of great interest in preclinical/clinical trials and is already established in medical treatment recommendations of chronic inflammatory diseases.⁽¹⁹⁾

Bacterial infections frequently precipitate ACLF.⁽⁴⁾ Both infectious and sterile triggers of ACLF result in a systemic inflammatory response,^(20,21) with a storm of different proinflammatory and anti-inflammatory molecules, such as cytokines^(22,23) and acute-phase proteins.^(24–26) Interestingly, Winkler et al.⁽²⁷⁾ reported that decreased serum S1P levels significantly associate with disease severity of patients with sepsis and may be useful as predictors of clinical course. Hence, we aimed to investigate whether serum S1P concentrations are also associated with disease severity in patients with different stages of end-stage liver disease and short-term mortality.

Patients and Methods

This study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee of the Johann Wolfgang Goethe-Universität Frankfurt (file no. 314/13). Standards of good clinical practice were followed during patient care and study conduct at all times. From August 2013 to October 2017, patients who were admitted to the University Hospital Frankfurt with CC, AD, or ACLF, according to European diagnostic criteria, were prospectively enrolled in our cirrhosis cohort study. All included patients signed informed consent forms, including an agreement on storage of serum samples for further future analyses. General

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exclusion criteria comprised age <18 years, pregnancy, or disagreement to participation. Subsequently, we excluded 9 patients with active hepatocellular carcinoma from further analyses. Serum samples were taken on fasting patients at baseline (day of admission +3 days), and further clinical parameters were obtained from clinical charts. Serum samples were routinely stored at -80°C . For the present analysis, all patients with available serum to assess SL concentrations were selected for this study. We used 10 μL serum and performed high-performance liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) to calculate SL concentrations, as described.⁽⁷⁾ In this study, we analyzed only S1P concentrations to test our hypothesis based on current scientific knowledge and to avoid multiple testing errors.

All statistical calculations, including scatterplots and receiver operating characteristics (ROC) curves, were performed by using BiAS software for Windows (version 11.05; Epsilon-Verlag, Darmstadt, Germany). Analysis for the presented box plots was performed with GraphPad Prism for Windows (v5.02; GraphPad Software Inc., San Diego, CA). First, the Shapiro-Wilk test was used to evaluate the normality assumption of the variables. Further calculations were then performed with nonparametric tests due to opposed assumption of normal distribution. Multiple-group nonparametric analyses were performed using the Kruskal-Wallis test; two-group nonparametric calculations were done with the Wilcoxon-Mann-Whitney U test. Spearman rank correlations were performed for nonparametric correlation analyses. Univariate analyses were calculated by logistic regression models, and all single parameters with $P < 0.05$ in univariate analysis were further included in multivariate logistic regression models. Diagnostic ROC curves were analyzed by the De Long test, and log-rank tests were analyzed by the Cox-Mantel test. $P < 0.05$ was considered statistically significant.

Results

PATIENT CHARACTERISTICS

This final study cohort included 127 patients. The median age was 55 years, and the majority of

patients were men (71%, $n = 90$) and Caucasian (73%, $n = 93$). The cohort included 19 patients with CC, 57 patients with AD, and 51 patients with ACLF. Of these ACLF patients, 18 were categorized in ACLF grade 1, 16 in ACLF grade 2, and 17 in ACLF grade 3. The patient selection process and cohort divisions are shown in Supporting Fig. S2. Alcohol consumption ($n = 77$, 61%) was the leading etiology of liver cirrhosis, followed by chronic hepatitis C ($n = 13$, 10%). The median Model for End-Stage Liver Disease (MELD) score was 20; patients with ACLF had a significant higher MELD score than patients with AD or CC ($P < 0.001$). Concordantly, bilirubin ($P = 0.015$), creatinine ($P < 0.001$), and international normalized ratio (INR) ($P < 0.001$) levels were significantly higher in patients with ACLF. C-reactive protein (CRP) ($P < 0.001$) and leucocytes ($P < 0.001$) differed significantly among the three patient subgroups. Additionally, only patients with ACLF needed vasopressor therapy ($P < 0.001$) or ventilation therapy ($P < 0.001$). Seven patients (6%) died within 7 days of inclusion; all 7 fulfilled ACLF criteria at admission. Further detailed characteristics of our study cohort are listed in Table 1. All blood samples were processed the same way, and no age- or sex-dependent variations of S1P concentrations were noted ($P > 0.05$). In all available serum samples, S1P concentrations could be determined using LC-MS/MS. The median S1P level was 204 ng/mL, with an interquartile range of 120 ng/mL.

S1P LEVELS ARE DECREASED IN ADVANCED STAGES OF LIVER DISEASE

At baseline, we compared serum S1P levels of patients with CC, AD, and ACLF. Using the Kruskal-Wallis test for multiple groups, we could observe significantly decreased S1P concentrations in patients with ACLF compared to patients with CC ($P = 0.021$) and AD ($P \leq 0.001$) (Fig. 1A). Furthermore, S1P was significantly lower in patients with ACLF grade 3 compared to patients with ACLF grade 1 ($P = 0.003$) or patients with ACLF grade 2 ($P = 0.002$) (Fig. 1B).

In subgroup analyses, we compared patient S1P levels to common complications of end-stage liver disease (infection, active alcohol consumption, and gastrointestinal bleeding) and a possible trigger of AD

TABLE 1. PATIENT CHARACTERISTICS

Parameter	All Patients (N = 127)	CC (n = 19)	AD (n = 57)	ACLF (n = 51)	PValue*
Age (years)	55 (14)	54 (18)	55 (13)	55 (13)	0.712
BMI (kg/m ²)	25 (9)	24 (9)	25 (7)	26 (8)	0.551
Male, n (%)	90 (71)	12 (63)	38 (67)	40 (78)	0.297
Ethnicity					0.780
Caucasian, n (%)	93 (73)	12 (63)	47 (82)	34 (67)	
Asian, n (%)	2 (2)	1 (5)	0 (0)	1 (2)	
African (sub-Sahara), n (%)	1 (1)	0 (0)	1 (2)	0 (0)	
Oriental, n (%)	7 (6)	1 (5)	3 (5)	3 (6)	
Etiology of liver cirrhosis					0.812
Alcohol, n (%)	77 (61)	12 (63)	33 (58)	32 (63)	
Nonalcoholic-steatosis-hepatitis, n (%)	6 (5)	0 (0)	2 (4)	4 (8)	
Hepatitis B, n (%)	4 (3)	1 (5)	2 (4)	1 (2)	
Hepatitis C, n (%)	13 (10)	1 (5)	8 (14)	4 (8)	
Others, n (%)	27 (21)	5 (26)	12 (21)	10 (20)	
Precipitating events					
Active alcohol consumption, n (%)	30 (24)	3 (16)	17 (30)	10 (20)	0.464
Gastrointestinal bleeding, n (%)	23 (18)	0 (0)	11 (19)	12 (24)	0.073
Infection, n (%)	76 (58)	0 (0)	36 (63)	40 (78)	<0.001
Biochemical parameters					
Sodium (mmol/L)	135 (8)	136 (3)	136 (6)	133 (10)	0.019
ALT (IU/L)	34 (40)	31 (28)	39 (41)	37 (41)	0.615
GGT (IU/L)	142 (190)	91 (119)	142 (195)	159 (205)	0.278
Bilirubin (mg/dL)	3.7 (11.5)	4.8 (5.6)	2.8 (5.1)	8.9 (19.1)	0.015
Creatinine (mg/dL)	1.20 (1.20)	0.84 (0.24)	1.00 (0.63)	2.20 (1.80)	<0.001
INR	1.54 (0.65)	1.50 (0.48)	1.39 (0.41)	1.93 (1.17)	<0.001
Albumin (g/dL)	2.9 (0.8)	2.8 (0.6)	3.0 (0.7)	2.8 (0.9)	0.671
CRP	2.42 (4.01)	0.77 (0.81)	1.96 (3.22)	4.11 (4.20)	<0.001
Leucocytes	7.37 (7.16)	5.23 (3.26)	6.17 (3.95)	10.30 (7.24)	<0.001
Hemoglobin (mg/dL)	9.8 (3.3)	10.2 (4.9)	10.7 (3.3)	9.0 (2.6)	0.012
Thrombocytes (/nL)	92 (71)	96 (68)	99 (77)	81 (63)	0.317
MELD score	20 (11)	18 (8)	16 (7)	28 (16)	<0.001
Clinical parameters					
Hepatic encephalopathy, n (%)	35 (28)	0 (0)	10 (18)	26 (51)	<0.001
Vasopressor therapy, n (%)	17 (13)	0 (0)	1 (2)	16 (31)	<0.001
Ventilation therapy, n (%)	10 (59)	0 (0)	0 (0)	10 (20)	<0.001
Ascites, n (%)	91 (72)	7 (37)	43 (75)	41 (80)	<0.001
7-day mortality	7 (6)	0 (0)	0 (0)	7 (14)	0.004
Liver transplantation within 7 days	0 (0)	0 (0)	0 (0)	0 (0)	1.0
28-day mortality	12 (9)	0 (0)	0 (0)	12 (24)	<0.001
Liver transplantation within 28 days	2 (2)	1 (5)	0 (0)	1 (2)	0.265

Values are shown as median (interquartile range) if not otherwise stated.

* $P < 0.05$ is significant. P values are calculated by nonparametric Kruskal-Wallis test for multiple groups.

Missing values: BMI (n = 13), ethnicity (n = 24), sodium (n = 6), CRP (n = 12), bilirubin (n = 3), ALT (n = 2), INR (n = 6), MELD score (n = 8), albumin (n = 51), ascites (n = 1), hepatic encephalopathy (n = 1), 28-day mortality (n = 22).

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyltransferase.

and ACLF (Supporting Fig. S3). At the study inclusion, patients with infections tended to show lower S1P concentrations than patients without infections

($P = 0.081$). Other triggers, such as alcohol consumption or gastrointestinal bleeding, did not associate significantly with S1P levels.

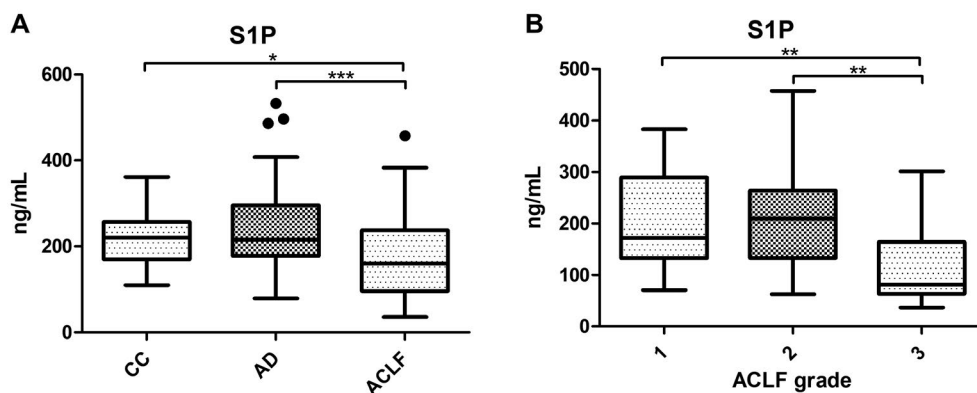


FIG. 1. S1P in relation to ACLF, CC, and AD. (A) S1P is decreased in patients with ACLF compared to patients with CC or AD. (B) S1P is further decreased in severe stages of ACLF. The floating data point refer to S1P concentrations beyond the range illustrated in the box plot with its SD. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

S1P INVERSELY CORRELATES WITH MELD SCORE AND ACLF GRADE

Using Spearman rank correlation, we observed a highly significant inverse correlation between S1P levels and MELD score ($P < 0.001$), with a moderate effect size of $r = -0.508$, as shown in the scatter-plot of Fig. 2. Further detailed correlations of serum S1P levels with biochemical parameters representing inflammatory response, kidney, and liver function are shown in Table 2.

SERUM S1P PREDICTS SHORT-TERM MORTALITY

In the Wilcoxon-Mann-Whitney U test, we observed significant differences of serum S1P concentrations between patients who died versus those who survived 7 days ($P < 0.001$) and 28 days after study inclusion (Fig. 3). Two patients received orthopic liver transplantation within 28 days of study inclusion, but none received this within 7 days of study inclusion. These 2 patients were excluded from all 28-day mortality analyses.

To further evaluate the predictive potential of serum S1P levels on short-term mortality in our patients, we conducted univariate logistic regression analysis. Lower levels of S1P were predictive of 7-day mortality (odds ratio [OR], 0.974; 95% confidence interval [CI], 0.953-0.995; $P = 0.014$) and 28-day mortality (OR, 0.988; 95% CI, 0.979-0.996; $P = 0.004$) in our study cohort. Univariate logistic regression analyses of various clinical and

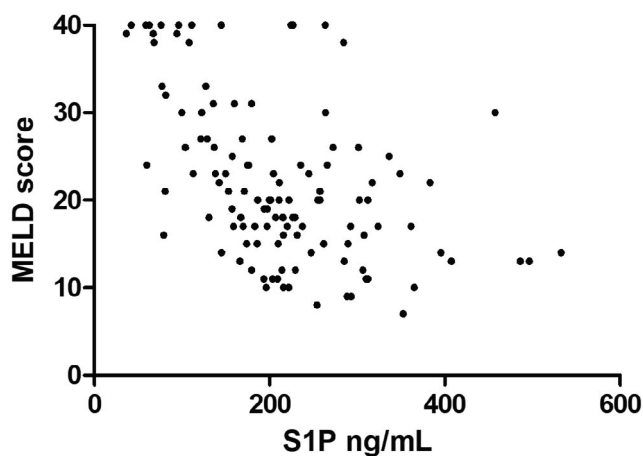


FIG. 2. S1P levels inversely correlate to the MELD score. Data show a moderate effect size of $r = -0.508$.

TABLE 2. CORRELATIONS OF SERUM S1P LEVELS AND VARIOUS BIOCHEMICAL PARAMETERS

Parameter	Spearman Rho	Significance (P Value)
CRP	-0.157	0.096
Leucocytes	-0.121	0.175
Creatinine	-0.410	<0.001
Bilirubin	-0.329	<0.001
INR	-0.480	<0.001
Albumin	0.314	0.006
ACLF grade	-0.381	<0.001

biochemical parameters, MELD score, and ACLF grade regarding 7- and 28-day mortality are shown in Table 3 and Supporting Table S1.

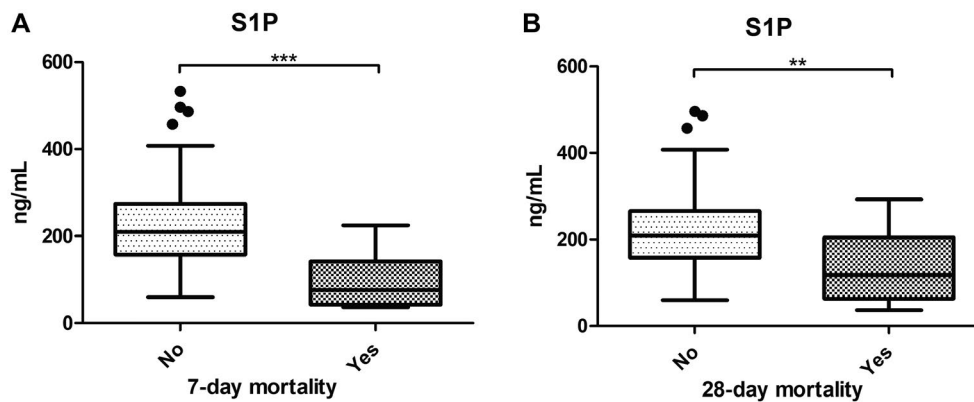


FIG. 3. S1P concentrations and mortality. S1P concentrations were lower in patients who died versus those who survived (A) 7 days and (B) 28 days after study inclusion. The floating data point refer to S1P concentrations beyond the range illustrated in the box plot with its SD. ** $P < 0.01$; *** $P < 0.001$.

TABLE 3. UNIVARIATE LOGISTIC REGRESSION ANALYSIS OF VARIOUS CLINICAL AND BIOCHEMICAL PARAMETERS REGARDING 7-DAY MORTALITY

Parameter	OR	CI	PValue*
Age	0.953	0.8885-1.025	0.195
Sex	8.049E-06	0.000-8.364E+97	0.923
BMI	1.044	0.926-1.178	0.478
Sodium	0.831	0.662-1.044	0.112
ALT	1.003	0.996-1.009	0.444
GGT	0.994	0.985-1.003	0.206
Bilirubin	1.079	1.022-1.139	0.006
Creatinine	2.244	1.379-3.651	0.001
INR	4.048	1.684-9.733	0.002
Albumin	0.139	0.009-2.075	0.153
CRP	1.075	0.896-1.290	0.438
Leucocytes	1.123	1.010-1.246	0.032
Hemoglobin	0.720	0.479-1.083	0.114
Thrombocytes	0.986	0.966-1.007	0.195
S1P	0.974	0.953-0.995	0.014
MELD score	1.225	1.080-1.389	0.002
ACLF grade	6.293	1.831-21.624	0.003

* $P < 0.05$ is significant.

Abbreviations: ALT, alanine transferase; BMI, body mass index; GGT, gamma glutamyl transferase.

In the following multivariate logistic regression analysis, we included all single clinical and biochemical parameters with $P < 0.05$. S1P was the only significant independent predictor of 7-day mortality (Table 4) but not 28-day mortality (Supporting Table S2).

In additional multivariate analysis that also included MELD score and ACLF grade, only ACLF

grade stayed as an independent predictor of 7-day mortality (Supporting Table S3). We then conducted ROC analysis with the estimation of correspondent area under the curve (AUC) to calculate the predictive potential of S1P on 7-day mortality (AUC, 0.874; 95% CI, 0.710-1.000; SD, 0.083; $P \leq 0.001$). ROC curves of S1P and ACLF grade on 7-day mortality are compared in Supporting Fig. S4 (ACLF: AUC, 0.919; 95% CI, 0.843-0.994; SD, 0.039; $P < 0.001$ and S1P: AUC, 0.874; 95% CI, 0.710-1.000; SD, 0.083; $P < 0.001$; cutoff, 78.23 ng/mL). Using the S1P cutoff level of 78.23 ng/mL, we finally conducted a Kaplan-Meier log-rank test for ≤ 78.23 ng/mL versus >78.23 ng/mL regarding 7-day mortality (Fig. 4). The Cox-Mantel test revealed a significant increased risk (hazard ratio, 1.78) of 7-day mortality for patients with S1P levels ≤ 78.23 ng/mL ($P < 0.001$).

Discussion

Our main findings of this study are that patients with severe stages of chronic liver disease and particularly those with ACLF grade 3 have significantly decreased serum S1P levels compared to patients with CC or AD. S1P concentrations inversely correlate with the MELD score and are able to predict short-term mortality independently.

The study cohort included 127 well-characterized patients who were prospectively recruited for our cirrhosis cohort study in a tertiary center for liver diseases and liver transplantation. Serum S1P levels were lower in patients with ACLF compared to patients

TABLE 4. MULTIVARIATE LOGISTIC REGRESSION ANALYSIS REGARDING 7-DAY MORTALITY, INCLUDING ALL SINGLE PARAMETERS WITH $P < 0.05$ IN PREVIOUS UNIVARIATE ANALYSIS

Parameter	Univariate Analysis			Multivariate Analysis		
	OR	CI	PValue*	OR	CI	PValue*
Bilirubin	1.077	1.020-1.137	0.008			
Creatinine	2.233	1.373-3.631	0.001	1.785	0.953-3.340	0.070
INR	4.008	1.668-9.628	0.002			
Leucocytes	1.116	1.003-1.241	0.044			
S1P	0.973	0.953-0.994	0.013	0.979	0.962-0.997	0.019

* $P < 0.05$ is significant.

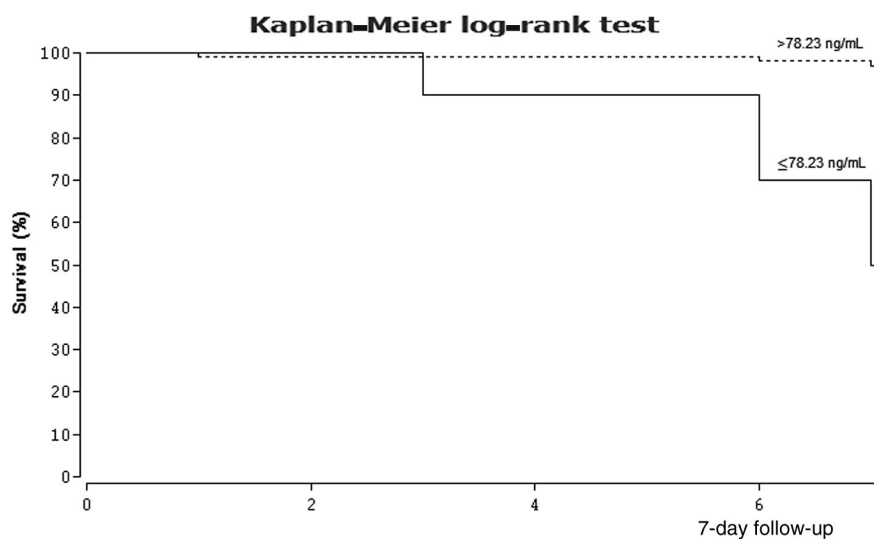


FIG. 4. Kaplan-Meier log-rank test for S1P levels ≤ 78.23 ng/mL versus >78.23 ng/mL for 7-day mortality.

with CC or AD and lowest in patients with ACLF grade 3 in comparison to ACLF grade 1 or 2. ACLF is characterized by multiple pathophysiological series of events, including acute deterioration of liver function, release of toxic metabolites, systemic inflammation, immunologic response, coagulopathy, and endothelial barrier changes.⁽²⁾ Precipitating bacterial infections in particular can be triggers of an acute deterioration and are linked to exceptional high patient mortality rates. Interestingly, we also found significant lower S1P concentrations in patients with bacterial infections at hospital admission.

In the circulating system, red blood cells constituting 95% of total blood cells represent a main source of S1P, followed by endothelial cells.⁽²⁸⁾ However, the liver also plays a crucial role in maintaining the S1P gradient in the blood as hepatocytes express and

secrete the majority of apolipoprotein M (apoM) and albumin, representing the main carriers of S1P in the blood, with 65% and 30%, respectively.⁽²⁹⁾ ApoM binds S1P with high affinity in a hydrophobic binding pocket and is the preferred carrier of this SL.⁽³⁰⁾ In severe systemic inflammation as is found in progressing ACLF, the maintenance of vascular barrier integrity is a crucial process to prevent consecutive complications, such as hemorrhage, tissue ischemia, and edema, encouraging aggravating inflammation, fluid imbalances, and patients' circulatory instability.⁽³¹⁾ S1P has been repetitively identified as a pivotal protector of endothelial integrity,⁽³²⁾ so our observations of significantly decreased S1P levels in ACLF and especially in advanced ACLF (grade 3) may reflect the severity of a failing pathway trying to preserve vascular stability. Furthermore, S1P has also been identified as a mutual

link between blood coagulation and inflammation.⁽³³⁾ For example, the release of S1P from activated platelets inhibits platelet aggregation,⁽³⁴⁾ and interactions of S1P receptors with thrombin receptors contribute substantially to the complex reaction of endothelial cells in pathologic storms of acutely released cytokines.⁽³⁵⁾ In ACLF, exogenous and endogenous inducers of inflammation start and maintain a vicious circle of excessive immune response.⁽³⁶⁾ However, lymphocyte egress from lymphoid tissues to the blood is significantly modulated by S1P/S1P1 interactions.⁽³⁷⁾ *In vitro* and *in vivo* studies recently revealed that hepatocyte exosomes require intracellular S1P for exosome-derived regeneration after ischemia/reperfusion injury or partial hepatectomy.⁽³⁸⁾ *In vitro* models of Osawa et al.^(39,40) also showed that extracellular S1P seems to have anti-apoptotic effects on hepatocytes. Interestingly, a recent study of Nowatari et al.⁽⁴¹⁾ investigated the role of S1P on human liver sinusoidal endothelial cells (LSECs) and the interaction between S1P and LSECs in hepatocyte proliferation *in vitro*. They showed that S1P has proliferative and anti-apoptotic effects and promotes the production of interleukin 6 and vascular endothelial growth factor in human LSECs, thereby promoting hepatocyte proliferation. Considering all these tightly interlinked protective roles of S1P in pivotal pathophysiological parts of progressing ACLF, we see our findings in line with potential underlying mechanisms. It may also seem a logical approach to therapeutically elevate S1P levels to stop the above-described vicious circle; however, the use of S1P itself is probably not feasible as rodent models showed a very short half-life of intravenously administered endogenous S1P.⁽⁴²⁾ It should also be taken into account that S1P has pleiotropic effects that mainly depend on the S1P receptor expression pattern on targeted cell types.⁽¹²⁾ Therefore, activating or deactivating specific S1P receptors may be a more suitable approach to new therapy strategies. Of note, the structural analogue of S1P phosphorylated fingolimod (FTY720) is a potent functional antagonist of the S1P1 receptor and has been in use and approved to treat patients with relapsing multiple sclerosis since 2010.⁽⁴³⁾ Treatment with this novel immunomodulator FTY720 seems to reduce endothelial permeability in systemic inflammation⁽⁴⁴⁾; it has also been shown to modulate S1P-related lymphocyte egress into the blood.⁽⁴⁵⁾ These preclinical observations promise more studies to come to investigate the use of this novel

drug in the role of endothelial barrier enhancement and specific immunomodulation. Specific hepatoprotective effects of FTY720 have been described in rodent ischemia reperfusion models with both normal and cirrhotic liver conditions.⁽⁴⁶⁾ However, in patients with multiple sclerosis who have been treated with FTY720, critical incidents of drug-induced liver injury have been reported.⁽⁴³⁾

To date, complex scoring systems addressing clinical and biochemical parameters of different organ systems are established to predict short- and long-term mortality in patients with end-stage liver disease.^(1,47) We observed a significant inverse correlation of S1P levels with the MELD score, and S1P stayed the sole single independent predictor of 7-day mortality with a significant AUC. It is remarkable that S1P as a single parameter reaches the power of a significant predictive potential of short-term mortality from such a multifactorial process. It would be of great interest in further studies if S1P combined with the above-named established scoring systems could ameliorate prediction of patient survival.

Our current study has some limitations: The study was carried out at only one center and in a retrospective design. Therefore, we were limited in evaluating associations of S1P with other biochemical parameters that were not primarily measured the day of blood withdrawal, e.g., differential white blood cell counts. We examined a small, mainly male, Caucasian patient collective. However, our cohort resembles a representative liver cirrhosis cohort in Western society. Our findings cannot prove underlying mechanistic relationships of S1P in ACLF. Nevertheless, we believe that our observations stand in line with current knowledge of the role of S1P in severe inflammatory and hepatic diseases, and we possibly identified a potential key mediator in the complex ACLF pathogenesis and a new predictive biomarker of short-term mortality in ACLF.

Hence, we are the first to describe low serum S1P concentrations in patients with ACLF. Lowest S1P levels were especially seen in patients with advanced multiorgan failure. S1P was an independent predictor of 7-day mortality and may resemble a new prognostic biomarker of early mortality. We believe that S1P might play a pivotal role in regulating immune response, vascular barrier protection, and hepatocyte regeneration in the pathophysiology of ACLF. Our data justify further elucidation of the diagnostic and therapeutic role of S1P in ACLF.

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