Hepatopulmonary Syndrome is Related to The Development of Acute-On-Chronic Liver Failure and Poor Prognosis in Cirrhotic Patients

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Abstract

Background & Aims:

Long-term prospective data on hepatopulmonary syndrome (HPS) from a large number of patients, especially in Asian patients, are lacking. We evaluated the long-term prognosis of HPS and the development of acute-on-chronic liver failure (ACLF), and related factors.

Methods:

A total of 142 patients with cirrhosis who underwent saline-agitated contrast echocardiography for the diagnosis of HPS were enrolled and observed prospectively from 2014 to 2019.

Results:

A total of 59 patients (41%) were diagnosed with HPS (24 grade 1, 23 grade 2, 12 grade 3). Thirty-eight and 37 patients died in the HPS and non-HPS groups, respectively ($p < 0.01$). The 5-year survival rate was 47% in the HPS group and 62% in the non-HPS group. In the Cox proportional hazards model, HPS and Model for End-stage Liver Disease (MELD) score≥18, and Child–Turcotte–Pugh (CTP) class B/C were significant risk factors for mortality after adjusting for other risk factors (HPS hazard ratio [HR] = 1.9, $p = 0.01$; MELD score≥18 HR = 2.3, $p < 0.01$; CTP class B/C HR = 2.9, $p < 0.01$). Compared to that in non-HPS group, the HPS group had a significantly higher incidence of ACLF during follow-up ($p < 0.01$) and more frequently presented with lung involvement of ACLF ($p = 0.03$).

Conclusions:

In the long-term follow-up cohort, patients with HPS showed poorer prognosis than that of patients without HPS. HPS was a risk factor for ACLF development independent of hepatic dysfunction, and lung involvement was significantly common than without patients

Lay Summary

In this study, patients with cirrhosis diagnosed with hepatopulmonary syndrome had a poor prognosis and higher probability of Acute-on-Chronic failure than those who did not.

Introduction

Hepatopulmonary syndrome (HPS) is characterized as a defect in arterial oxygenation caused by pulmonary vascular dilatation in the setting of chronic liver disease.[1–6] It is defined by positive echocardiography findings and a more than 15 mmHg increase in differentiation of oxygen pressure, inducing hypoxia and dyspnea, in patients with cirrhosis.[1,4,7] While the prevalence of HPS varies, it is estimated to occur in approximately 4–32% of cirrhosis patients who are waiting for liver

transplantation.[2,4,8–15] In our previous study of Korean patients with cirrhosis, the prevalence of HPS was relatively high, at 41.5%.[16]

There are no specific symptoms of HPS, and the exact pathogenic mechanism of HPS is not fully understood. The poor prognosis is generally known.[2,3,13,17] However, long-term prospective data from a large number of patients are lacking, especially in Asian countries. Longitudinal data of HPS and risk factors related to HPS remain insufficient. This study evaluated the long-term prognosis and the development of acute-on-chronic liver failure (ACLF) in HPS and its related factors based on a previously reported HPS study cohort at our institution.[16]

Patients And Methods

This prospective longitudinal observational study analyzed data from the cohort described in our previous study.[16] We followed this cohort from 2014 to December 2019. The eligibility criteria included liver cirrhosis and age between 20 and 70 years. We performed saline-agitated contrast-enhanced echocardiography on all consecutive patients who were diagnosed with cirrhosis. The contrast-enhanced echocardiography protocol was described previously.[16] According to the echocardiography results, the cohort was divided into the HPS and non-HPS groups. The HPS group was also classified according to the HPS grade based on echocardiographic findings. Severity grade 1 was defined as 1–11 microbubbles identified during echocardiography. Grade 2 corresponded to ≥ 12 microbubbles, while grade 3 was defined as the presence of > 12 microbubbles homogeneously or heterogeneously distributed throughout the left ventricle.[16,18,19] During follow-up, endoscopy was performed every 2 years for patients without esophageal varices and every year for patients with significant esophageal varices. All patients underwent ultrasonography every 6–12 months and laboratory assessment every 6 months. as well as ultrasonography every 6–12 months and laboratory assessment every 6 months. The follow-up visits to the hospital were scheduled every 3–6 months, according to the clinical condition. All events related to cirrhosis were monitored. Follow-up loss was prevented by phone call to patients who did not visit the planned follow-up schedule. Patients who did not report for a visit for more than 3 months beyond the indicated schedule were considered as lost to follow-up, and we later checked whether they were still alive. Liver transplantation (LT) was considered censored data and included as a mortality case.

This study was approved by the Institutional Review Board for Human Research at Yonsei University Wonju Severance Christian Hospital (CR 314038), and written informed consent for participation in the study was obtained from all patients.

Statistical analysis

Descriptive statistics were produced for the demographic, clinical, and laboratory characteristics of the patients enrolled in this study. The quantitative and qualitative variables were expressed as means ± standard deviation or median (interquartile range) values and number (%), respectively. Comparisons were made using independent sample t-tests for continuous variables. Chi-square tests were used to

compare groups. Survival and ACLF incidence were assessed by the Kaplan–Meier method and differences between patients were assessed by log-rank tests. An exploratory analysis using the proportional hazards Cox model was performed to investigate whether the risk factors of cirrhosis and HPS played an independent prognostic role for mortality. Data were analyzed using IBM SPSS Statistics for Windows, version 21.0, (IBM Corp., Armonk, NY, USA), with statistical significance defined as $p < 0.05$.

Results

Patient population

The median follow-up period was 28 months (maximum: 70 months). Among the 142 patients enrolled in this study, 59 (41.5%) were diagnosed with HPS (24 grade 1, 23 grade 2, 12 grade 3) and 83 patients were not. During the study period, nine patients in the non-HPS group and eight patients in the HPS group were lost to follow-up. Five patients with HPS and four patients without HPS underwent LT. The baseline characteristics of the patients are shown in Table 1.

Table 1
Baseline characteristics of the included patients.

	None (n = 83)	HPS (n = 59)	*p* value
Sex, (male: women, n)	62 : 21	45 : 14	0.49
Age (years)	57.9 ± 8.9	54.3 ± 10.1	0.02
Etiology, (n)			
Alcohol	60	47	
HBV	14	6	
HCV	2	1	
HBV/HCV + alcohol	1	3	
Others	6	2	
Albumin	3.1 ± 0.6	3.1 ± 0.6	0.53
Total bilirubin	3.0 ± 5.2	3.7 ± 6.9	0.52
Prothrombin time (INR)	1.4 ± 0.4	1.5 ± 0.4	0.92
CTP class, (n)			
Grade A	30	11	
Grade B	37	34	
Grade C	16	14	
MELD score	13.3 ± 5.2	14.6 ± 5.9	0.18
ACLF development, (n)	13	24	< 0.01
Mortality, (n)	37	38	< 0.01
1-year survival rate	80%	77%	
2-year survival rate	69%	62%	
3-year survival rate	62%	47%	

ACLF, acute-on-chronic liver failure; CTP, Child–Turcotte–Pugh; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; INR, international normalized ratio; MELD, Model for End-stage Liver Disease

Prognosis of the overall cohort

During the follow-up, mortalities, including LT, occurred in 37 patients in the non-HPS group and 38 patients in the HPS group ($p < 0.01$; Table 1 and Fig. 1). Survival was significantly better in patients without HPS than in patients with HPS (Table 1 and Fig. 2). In the Kaplan–Meier analysis, the median

survival differed significantly between the HPS (33.7 months ± 3.42) and non-HPS (47.5 months ± 3.33; $p = 0.01$; Fig. 2) groups. The 5-year survival rate was lower in the HPS group (32.7%) than in the non-HPS group (60.6%; $p = 0.03$). The causes of mortality are described in Fig. 1, and hepatorenal syndrome and gastrointestinal bleeding events were common.

Hepatopulmonary syndrome is a risk factor for mortality

In the univariate analysis, HPS, Child–Turcotte–Pugh (CTP) class, Model for End-stage Liver Disease (MELD) score, albumin concentration, and prothrombin time were significantly associated with mortality in the overall study group. However, in the multivariate Cox hazard regression model, HPS, CTP class B/C, and MELD score ≥ 18 were significant risk factors for mortality (Table 2). In Model 1, HPS, albumin, and prothrombin time (international normalized ratio [INR]) were identified as risk factors for mortality (HPS hazard ratio [HR] = 1.9, 95% confidence interval [CI] = 1.13–3.12, $p = 0.01$; albumin HR = 0.59, 95% CI = 0.35–1.00, $p = 0.05$; INR HR = 1.8, 95% CI = 1.03–3.26, $p = 0.04$). In Model 2, HPS was identified as a borderline risk factor, and CTP class B/C was a risk factor after adjusting for other factors (HPS HR = 1.6, 95% CI = 0.93–2.59, $p = 0.09$; CTP class B/C (vs. A) HR = 2.9, 95% CI = 1.36–6.17, $p < 0.01$). In Model 3, HPS and MELD scores ≥ 18 were identified as significant variable factors (HPS HR = 1.8, 95% CI = 1.09–2.98, $p = 0.02$; MELD score ≥ 18 HR = 2.3, 95% CI = 1.40–3.85, $p < 0.01$; Table 2).

Table 2
Univariate and multivariate Cox regression analyses of mortality

Model 1						
	Univariate			**Multivariate**		
	HR	**95% CI**	p **value**	**HR**	**95% CI**	p **value**
HPS	1.90	1.20–3.06	< 0.01	1.98	1.24–3.17	< 0.01
Cr	1.12	0.89–1.41	0.32			
Hb	0.87	0.76–0.98	0.03			
Plt	1.00	1.00–1.00	0.01			
Alb	0.42	0.27–0.65	< 0.01	0.56	0.34–0.93	0.03
INR	2.62	1.75–3.92	< 0.01	1.95	1.16–3.26	0.01
Bilirubin	1.02	0.98–1.06	0.28			
Model 2						
	Univariate			**Multivariate**		
HPS	1.90	1.20–3.06	< 0.01	1.59	0.93–2.58	0.05
CTP class B/C	2.95	1.51–5.76	< 0.01	2.59	1.31–5.14	< 0.01
Model 3						
	Univariate			**Multivariate**		
HPS	1.90	1.20–3.06	< 0.01	1.83	1.14–2.93	0.01
MELD score ≥ 18	2.29	1.43–3.68	< 0.01	2.20	1.37–3.54	< 0.01

ACLF, acute-on-chronic liver failure; Alb, albumin; Cr, creatinine; CI, confidence interval; CTP, Child–Turcotte–Pugh; Hb, hemoglobin; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HPS, hepatopulmonary syndrome; HR, hazard ratio; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; Plt, platelet

Hepatopulmonary syndrome is a risk factor for the development of ACLF

During the follow-up period, 37 patients in each group developed ACLF (13 [15.6%] in the non-HPS group and 24 cases [40.6%] in the HPS group). The proportion of patients developing ACLF was higher in the HPS group during long-term follow-up ($p < 0.01$; Fig. 3). HPS is a risk factor for ACLF development, and it was significant even after adjusting for other variables.

In Model 1, HPS, creatinine, albumin, and bilirubin were identified as risk factors for ACLF in the multivariate model (HPS HR = 3.88, 95% CI = 1.91–7.86, $p < 0.01$; creatinine HR = 1.37, 95% CI = 1.07–1.76,

$p = 0.01$; albumin HR = 0.19, 95% CI = 0.09–0.41, $p < 0.01$; bilirubin HR = 1.1, 95% CI = 1.02–1.11, $p < 0.01$). In Model 2, HPS and CTP class B/C were identified as risk factors for ACLF (HPS HR = 2.6, 96% CI = 1.30–5.21, $p < 0.01$; CTP class B/C HR = 3.24 95% CI = 1.13–9.31, $p = 0.03$). In Model 3, HPS and MELD score ≥ 18 were risk factors of ACLF after adjusting for other variables (HPS HR = 3.0, 95% CI = 1.53–6.07, $p < 0.01$; MELD score ≥ 18 HR = 3.5, 95% CI = 1.80–6.79, $p < 0.01$; Table 3). In ACLF cases, lung involvement (ratio of arterial oxygen partial pressure to fractional inspired oxygen < 200) was more common in HPS than in non-HPS (10 cases vs. 1 case, $p = 0.03$; Supplement 2).

Table 3
Univariate and multivariate Cox regression analysis of ACLF development

Model 1						
	Univariate			**Multivariate**		
	HR	**95% CI**	p **value**	**HR**	**95% CI**	p **value**
HPS	3.15	1.59–6.26	< 0.01	3.88	1.91–7.86	< 0.01
Cr	1.27	1.00–1.61	0.04	1.37	1.07–1.76	0.01
Hb	0.91	0.77–1.08	0.30			
Plt	1.00	1.00–1.00	0.13			
Alb	0.27	0.14–0.52	< 0.01	0.19	0.09–0.41	< 0.01
INR	2.97	1.78–4.93	< 0.01			
Bilirubin	1.00	0.96–1.05	0.77	1.06	1.02–1.10	< 0.01
Model 2						
	Univariate			**Multivariate**		
HPS	3.15	1.59–6.26	< 0.01	2.60	1.30–5.21	< 0.01
CTP class B/C	4.11	1.45–11.63	< 0.01	3.24	1.13–9.31	0.03
Model 3						
	Univariate			**Multivariate**		
HPS	3.15	1.59–6.26	< 0.01	3.04	1.53–6.07	< 0.01
MELD score ≥ 18	3.62	1.87–7.00	< 0.01	3.50	1.80–6.79	< 0.01

ACLF, acute-on-chronic liver failure; Alb, albumin; Cr, creatinine; CI, confidence interval; CTP, Child–Turcotte–Pugh; Hb, hemoglobin; HBV, hepatitis B virus infection; HCV, hepatitis C virus infection; HR, hazard ratio; HPS, hepatopulmonary syndrome; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; Plt, platelet

In HPS, MELD score and CTP class are risk factors for mortality and ACLF

An additional subgroup analysis about the risk factors for mortality and ACLF development in the HPS group showed that the prognosis differed according to the severity of baseline liver function, as represented by the CTP class and MELD scores (Supplement 1). HPS severity according to echocardiographic findings had no effect on mortality in the HPS group ($p = 0.46$). However, CTP class B/C and MELD score ≥ 18 were identified as risk factors for mortality in the HPS group in univariate analysis (CTP class B/C HR = 1.75, 95% CI = 0.6–5.0, $p = 0.29$; MELD score ≥ 18 HR = 2.51, 95% CI = 1.32–4.8, $p < 0.01$).

Regarding ACLF development, the echocardiographic severity of HPS did not affect ACLF development ($p = 0.90$). However, CTP B/C and MELD ≥ 18 were analyzed as risk factors for ACLF development (CTP class B/C HR = 1.6, 95% CI = 0.5–5.5, $p = 0.44$; MELD score ≥ 18 HR = 3.8, 95% CI = 1.6–8.9, $p < 0.01$).

Discussion

HPS reportedly occurs in 4–32% of patients with cirrhosis[2,9,10,13,17]; however, our previous study reported a relatively higher prevalence of 41.5%.[16] This discordance may be due to the non-standardized diagnosis method and heterogeneous cohort compositions. HPS has received less attention compared to other cirrhosis-related complications. In general, HPS does not have any symptoms when in a stable state; therefore, clinicians usually do not perform special screening tests or confirmative echocardiography tests for cirrhotic patients who do not show respiratory symptoms. Therefore, in terms of clinical impact, longitudinal data on HPS are insufficient. The present study analyzed long-term follow-up data to determine the prognostic impact of HPS on cirrhosis and ACLF. In the overall cohort, HPS was a significant prognostic factor for short-term survival independent of underlying liver dysfunction. In particular, HPS was more commonly observed in decompensated cirrhotic patients[16,20], suggesting that active efforts to identify HPS in decompensated patients can help predict the prognosis in this population.

The exact mechanism by which HPS influences prognosis is not well established. The cause of mortality is multifactorial, while the main causes of death are related to liver-related complications.[1,13,21] A previous animal study identified intestinal endotoxemia as an important mechanism in the development of HPS.[22,23] Moreover, our previous study reported significantly increased levels of factors in HPS group, such as lipopolysaccharides, nitric oxide, and endothelin, that are related to bacterial translocation.[16] In the present study, events related to bacterial translocation (bacteremia, spontaneous bacterial peritonitis [SBP]) were more likely to occur in the HPS group than in the non-HPS group. Seven cases of SBP and four cases of bacteremia were observed in the HPS group, while eight cases of SBP and three cases of bacteremia occurred in the non-HPS group. This difference may explain why ACLF more commonly developed in patients with HPS in our study, as the development of ACLF is closely related to the precipitation of infection.[16,24,25] This study showed that HPS was related to a higher risk of ACLF independent of underlying cirrhosis severity. In addition, lung involvement of ACLF was more common in

patients with HPS than in those without HPS. Thus, HPS can result in a poor prognosis in patients with cirrhosis via a high incidence of ACLF development with respiratory failure.

In patients with HPS, underlying liver dysfunction estimated using the CTP and MELD scores is related to mortality.[1,2,8,10,26,27] This finding was also observed in the development of ACLF; moreover, the underlying severity of cirrhosis was a risk factor for the development of ACLF.[25,28] However, the severity of HPS was not a risk factor for poor prognosis in patients with HPS. Contrast-enhanced transthoracic echocardiography with saline is accepted as the most practical method of HPS diagnosis.[1,7,19,29] We assessed the HPS grade according to these echocardiographic findings. Our previous study reported a difference in the levels of lipopolysaccharides, nitric oxide, and endothelin according to the echocardiographic severity grade of HPS[16]. Therefore, we expected to observe a difference in prognosis according to the HPS severity. However, there was no relationship between the HPS severity and mortality and ACLF development in the HPS group. The exact reason for this finding is not clear but suggests the existence of a pulmonary shunt itself, rather than the severity of shunts, as a risk factor for the development of respiratory complications in acute decompensation. Further study on this topic, including pathogenesis, is needed in a well-designed study with a larger population.

The strengths of this study were its prospective observational design and relatively long follow-up period of over 5 years.
The severity of HPS was classified according to echocardiographic findings, and it was evaluated as a prognostic factor. This is the first study to report the relationship between ACLF and HPS.

However, this study has a few limitations. For instance, we were not able to perform repeated serologic evaluations for bacterial translocation; therefore, we could not present data on the direct relationship between HPS, bacterial translocation, and the development of ACLF. In addition, a relatively large number of participants were lost to follow-up.

In conclusion, HPS was a poor prognostic factor for cirrhosis and a risk factor for ACLF. CTP class B/C and MELD score ≥ 18 were also risk factors for mortality and occurrence of ACLF in the long-term follow-up. The HPS group showed more frequent development of infection-related complications and lung involvement of ACLF than that seen in the non-HPS group. Further evaluation of the underlying pathogenesis and related factors is needed through a well-designed prospective study with a larger population.

Abbreviations

HPS, hepatopulmonary syndrome; ACLF, acute-on-chronic liver failure; LT, liver transplantation; CPT, Child–Turcotte–Pugh; MELD, Model for End-stage Liver Disease; INR, international normalized ratio; HR, hazard ratio; CI, confidence interval; SBP, spontaneous bacterial peritonitis; HBV, hepatitis B virus

infection; HCV, hepatitis C virus infection; Cr, creatinine; Hb, hemoglobin; Plt, platelet; Alb, albumin; HRS, hepatorenal syndrome; HCC, hepatocellular carcinoma

Declarations

Declaration of conflict of interests: None.

Patient consent statement: Written informed consent for participation in the study was obtained from all patients.

Ethics approval statement: This study was approved by the Institutional Review Board for Human Research at Yonsei University Wonju Severance Christian Hospital (CR 314038).

Author contribution: All authors contributed to the study conception and design, material preparation, data collection and analysis were performed by Seul Ki Han, Moon Young Kim. The first draft of the manuscript was written by Seul Ki Han and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability: Data will be available according to request.

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Figures

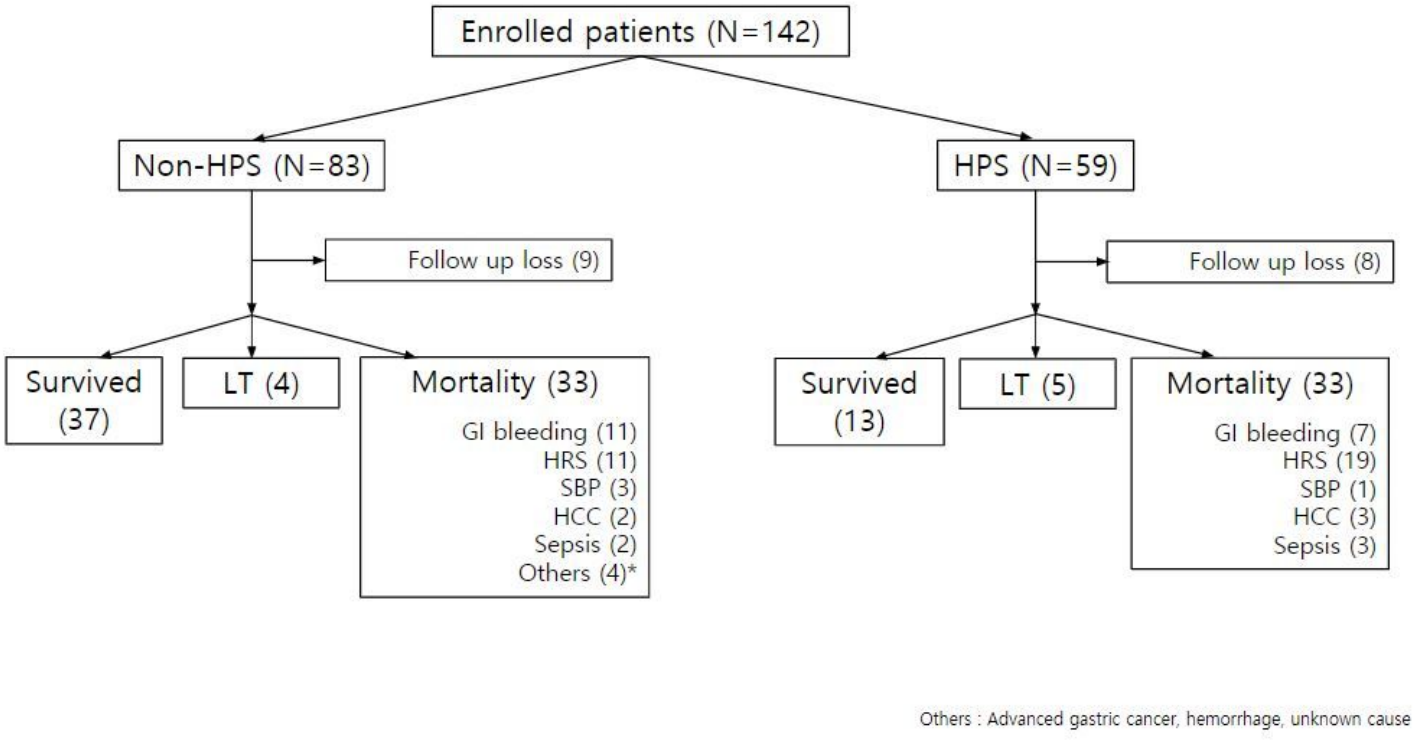

Figure 1

Overview of the study patients diagnosed with and without HPS and their outcomes. ACLF, acute-on-chronic liver failure; LT, liver transplantation; GI, gastrointestinal; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; HCC, hepatocellular carcinoma; HPS, hepatopulmonary syndrome

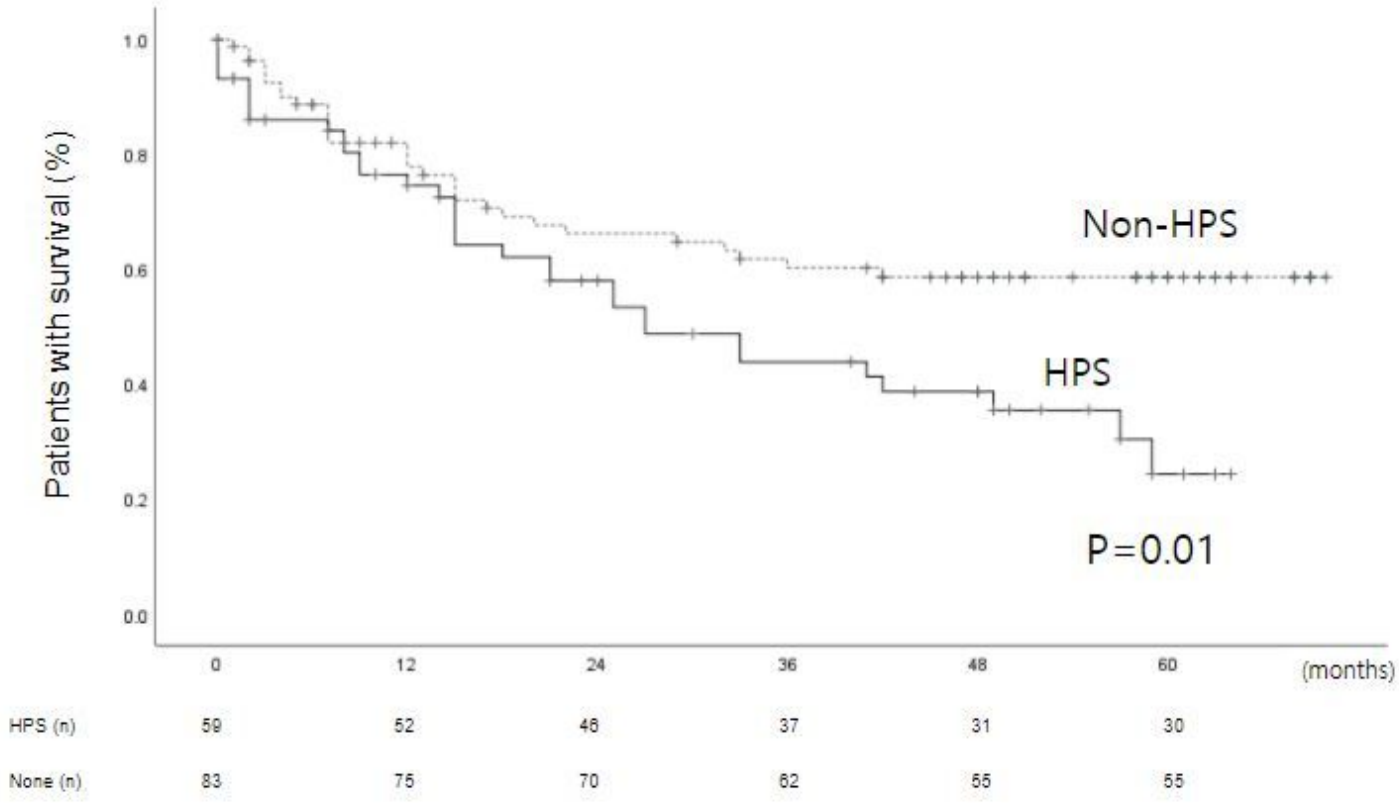

Figure 2

Comparison of survival according to the presence of hepatopulmonary syndrome (HPS) in patients with cirrhosis. The median survival differed significantly between the HPS (30.7 months) and non-HPS (45.3 months; $p < 0.01$) groups.

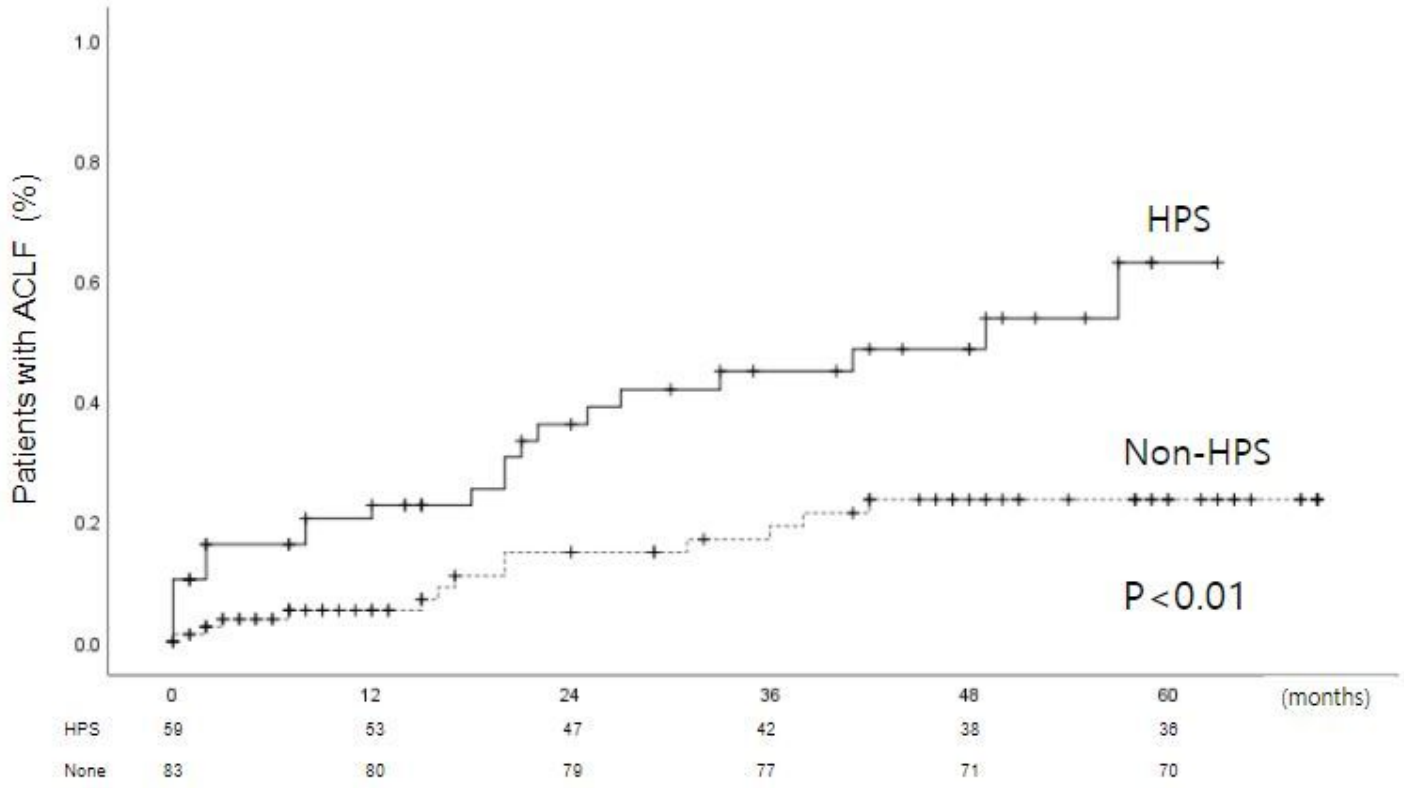

Figure 3

Comparison of acute-on-chronic liver failure (ACLF) development according to the presence of hepatopulmonary syndrome (HPS) in patients with cirrhosis. The cumulative ACLF incidence rate was higher in the HPS group than in the non-HPS group during the long-term follow-up ($p < 0.01$).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuppTables.docx