

PD-L1 and the risk of bacterial infection in patients with chronic liver diseases: An international multicohort study

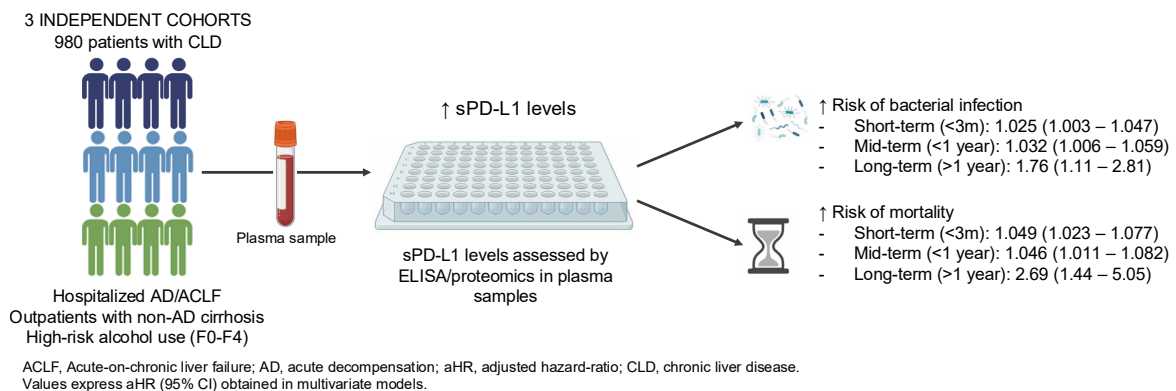
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Graphical abstract



Highlights:

- SPD-L1 plasma levels increase with liver disease progression, reaching the highest levels in patients with ACLF.
- SPD-L1 levels independently predict the development of bacterial infections and mortality among patients with chronic liver disease.
- SPD-L1 plasma levels identify an immune dysfunction phenotype in patients with chronic liver disease.
- SPD-L1 may help guide early preventive strategies in patients with chronic liver disease who are at high risk of developing bacterial infections.

Impact and implications:

This study explores the role of soluble PD-L1 as a biomarker of immune dysfunction and its association with clinical outcomes in patients with chronic liver disease. Our findings demonstrate that soluble PD-L1 levels increase with the progression of liver disease and they are independently associated with an increased risk of bacterial infection development and mortality. These results could help physicians identify high-risk individuals earlier and implement preventive strategies.

PD-L1 and the risk of bacterial infection in patients with chronic liver diseases: An international multicohort study

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Background & Aims: Impaired phagocytic capacity due to activation of the PD-1/PD-L1 pathway has been implicated in the development of bacterial infections in patients with cirrhosis. Soluble PD-L1 (sPD-L1) is easily measurable in plasma and has been proposed as a biomarker of sepsis. In the current study, we aim to evaluate the role of sPD-L1 as a biomarker of bacterial infection development in patients with cirrhosis.

Methods: Plasma samples from 995 patients with chronic liver disease grouped in three cohorts were analyzed: an initial cohort of 268 hospitalized patients with acute decompensated cirrhosis, 327 out-patients with non-acute decompensated cirrhosis and finally 400 patients with high-risk alcohol consumption, including all stages of liver fibrosis, from mild/no fibrosis to cirrhosis (F0–F4). The main outcomes of the study were development of bacterial infection and mortality.

Results: Patients who developed bacterial infections had higher median levels of sPD-L1 than those who did not (160 [IQR 116–221] vs. 136 [IQR 97–193] pg/ml, respectively, p value <0.001; hazard ratio 1.034, 95% CI 1.014–1.055). Levels of sPD-L1 were associated with bacterial infection development after adjustment for confounding factors. During follow-up, patients who died had higher median sPD-L1 levels than survivors, after adjustment for MELD Na (180 [IQR 143–267] vs. 134 [IQR 97–187] pg/ml, respectively; p value <0.001; HR 1.066, 95% CI 1.043–1.089). These findings were observed in all cohorts.

Conclusions: Plasma levels of sPD-L1 are associated with the risk of bacterial infection development irrespective of the stage of chronic liver disease. Furthermore, higher sPD-L1 levels are linked to increased mortality. Measurement of sPD-L1 levels may help identify patients at high risk of developing bacterial infections and guide the implementation of new preventive strategies.

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Introduction

Patients with cirrhosis are at risk of developing complications, including ascites/edema, gastrointestinal bleeding, hepatic encephalopathy (HE), and bacterial infections.¹ Bacterial infections are frequent, have a high tendency to recur, and are associated with high mortality, ranging between 10% to 20% within 30 days.^{1–3} Moreover, infections may act as the triggering factor of other complications of cirrhosis, particularly portal hypertensive-related bleeding, acute kidney injury, and acute-on-chronic liver failure (ACLF).^{1–3}

The mechanisms responsible for the high prevalence of bacterial infections in cirrhosis are only partially understood.^{2,3} Several lines of evidence indicate that infections in cirrhosis are related to alterations in the gut-liver axis. Profound disturbances in the composition of the intestinal and oral microbiome and increased gut permeability lead to increased

translocation of bacteria and bacterial products from the gut to the systemic circulation.^{2,4,5} Moreover, cirrhosis is characterized by important alterations of immune function that affect not only the innate immune system but also the adaptive immune system. The alteration of the adaptive immune system is characterized by features of systemic inflammation, with increased plasma levels of inflammatory cytokines that parallel clinical disease progression, associated with progressive overexpression of immune-suppressive factors that lead to immune paralysis.⁶ However, it is unknown whether immune paralysis phenomena also occur in early stages of the disease, in the same manner as systemic inflammation.⁷ The immune alterations that occur in patients with cirrhosis alongside the progression of the disease are known as cirrhosis-associated immune dysfunction and are thought to be due to the unremitting stimulation of the immune system by antigens of

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intestinal origin (pathogen-associated molecular patterns) and/or from the liver parenchyma (damage-associated molecular patterns).^{8,9}

One of the most important immunosuppressive factors of the adaptive immune response is the programmed cell death protein 1 (PD-1).¹⁰ PD-1 is expressed during T-cell activation and opposes positive signals through the T-cell receptor, and co-stimulatory signals such as CD28, by engaging its ligands, mainly PD-L1, but also PD-L2. This system functions as a break for the adaptive immune response. In advanced cirrhosis, there is an overexpression of the PD-1/PD-L1 pathway. Experimental and *in vitro* studies have shown that this system plays a role in the impaired phagocytic activity of both monocytes and liver macrophages and blockade of the PD-1/PD-L1 pathway improves phagocytic activity of both cell types.^{11,12} We therefore hypothesize that overexpression of the PD-1/PD-L1 pathway could be an important pathogenic factor contributing to bacterial infections in patients with advanced cirrhosis. The aim of the present study was to evaluate the association between soluble PD-L1 (sPD-L1) levels, as a surrogate marker of the activity of PD-1/PD-L1 pathway, and the development of bacterial infections and mortality in patients with chronic liver disease.

Patients and methods

Study population

This study was conducted in 995 patients prospectively recruited in three independent cohorts representing the complete spectrum of chronic liver disease, including patients with cirrhosis (both decompensated and compensated), as well as patients with different degrees of fibrosis but without cirrhosis. The description of the three cohorts is summarized below.

Cohort 1

This cohort includes 268 patients with decompensated cirrhosis who were hospitalized for treatment of complications in the Liver Unit of the Hospital Clinic of Barcelona (Catalonia, Spain) between April 2015 and November 2019. Patients were prospectively enrolled at admission and followed up for 3 months, with collection of clinical data and survival status. Emphasis was placed on the collection of information about bacterial infections that occurred during follow-up.

Cohort 2

The second cohort was composed of 327 outpatients with decompensated cirrhosis, with ascites as the most common complication. This cohort included two subsets of patients recruited prospectively: 113 patients from the University of Padova (Padova, Italy) and 214 patients who participated in the LiverHope Efficacy Trial (NCT03150459), a randomized controlled trial evaluating the efficacy of the combination of simvastatin and rifaximin vs. placebo in the prevention of ACLF performed in seven European countries (France, Italy, Germany, United Kingdom, Holland, Belgium, and Spain). The results of this latter study showed no effect of treatment on the incidence of bacterial infections or other complications of cirrhosis.¹³ All patients in this cohort were followed up for 1 year. Data on bacterial infections and survival were collected.

Cohort 3

The last cohort was composed of 400 individuals with high-risk alcohol consumption included in a prospective study assessing the presence of liver disease performed in the Region of Southern Denmark between April 2013 and September 2018.¹⁴ This cohort included all stages of liver fibrosis, from mild/no fibrosis (F0–F1), moderate fibrosis (F2) to advanced fibrosis (F3) or cirrhosis (F4) (238, 88, 20 and 54 individuals, respectively). No patient had decompensated cirrhosis.

The inclusion and exclusion criteria for each cohort are detailed in [Table S1](#). All patients provided written informed consent and the study protocols were approved by the institutional review board of the Hospital Clinic of Barcelona and the other participating centers (HCB/2014/0577 & HCB2/2015/0653, HCB/2018/1141, NCT03780673, 392n/AO and S-20120071 and S-20160021).

Main outcomes and study design

This is a prospective, observational, multicohort study. The primary objective of the study was to assess the association between plasma sPD-L1 and the development of bacterial infections during follow-up. The secondary objective was to investigate the association between plasma sPD-L1 and mortality rate during follow-up.

Follow-up timeline and duration

Due to the different nature of the cohorts (inpatients with decompensated cirrhosis, outpatients with decompensated cirrhosis and patients with alcohol risk consumption from mild/no fibrosis to cirrhosis) timeframes for outcome evaluation differed between them. Patients in Cohort 1 were followed-up during a 3-month period, while patients in Cohort 2 were followed-up during a 1-year period. In both cohorts, patients who underwent liver transplantation (LT) or were lost to follow-up were censored at the time of LT or last registry. In case of patients from Cohort 3, follow-up started at inclusion and ended on October 1st, 2020 (median follow-up time: 4.3 [IQR 2.8–6.3] years). Demographic and clinical data, together with standard liver and kidney tests were collected from all patients at enrollment. Plasma samples were collected at the time of enrollment to measure sPD-L1.

Bacterial infection criteria

The criteria used to define bacterial infection were very similar among the three cohorts. In Cohorts 1 and 2, bacterial infections were established based on at least one of the following criteria: a) positive cultures of blood or other organic fluids together with need for antibiotic treatment, or b) clinical suspicion of infection based on clinical and/or analytical data requiring empiric antibiotic therapy in the presence of negative cultures.¹⁵ In Cohort 3, infections were collected from electronic healthcare files, and were defined on the basis of the presence of at least 3 of the following criteria: 1) biochemical signs of infection including elevated C-reactive protein, leukocytosis, and neutrophilia; 2) relevant clinical symptoms including fever and organ-specific symptoms; 3) radiological signs of infection; 4) prescription of antibiotic/antiviral/antifungal medication; and 5) positive cultures.¹⁴

Management of infections in the three cohorts was done according to international guidelines.^{15–18}

sPD-L1 measurement

The activity of the PD-1/PD-L1 pathway was assessed by measuring the plasma levels of sPD-L1, a form with biological activity, which is generated through the shedding of the membrane-bound form or as alternate splice variants.¹⁹

Plasma samples for sPD-L1 measurement were centrifuged at 2,000 rpm for 10 min and the supernatant stored at -80 °C until analysis. In Cohort 1 and 2, plasma sPD-L1 levels were measured using the human/cynomolgus monkey PD-L1/B7-H1 quantikine ELISA kit (R&D systems, Minneapolis, MN, USA) following the manufacturer's protocol. The intra-assay and inter-assay coefficients of variation were lower than 2% and 8%, respectively, with mean values of sPD-L1 ranging from 244 to 878 pg/ml.

In Cohort 3, plasma sPD-L1 levels were measured by Olink Proteomics using the Target-96 Inflammation panel (Uppsala, Sweden). The proteomics panel was evaluated in serum using Proximity Extension Assay technology. sPD-L1 is expressed with arbitrary units (normalized protein expression [NPX]) on the log₂ scale.

Methodological differences in sPD-L1 measurement mean that levels are not directly comparable across cohorts; therefore, the cohorts could not be merged.

Statistical analysis

Categorical variables are reported as absolute frequencies and percentages. Quantitative variables are reported as median and IQR. Comparisons between variables were performed using the Cox proportional hazard model either for categorical variables or for continuous variables. Survival function was described using the Kaplan-Meier method and log-rank test. Hazard ratios for sPD-L1 levels when measured by ELISA were calculated based on a 10-unit increase in picograms per milliliter; in case of OLINK determination, HRs were calculated based on a 1-unit increase. Since the aim of the study was to analyze the relationship between plasma levels of sPD-L1 and the development of bacterial infections and mortality in patients with cirrhosis we performed a series of bivariate Cox regression models including the biomarker and one potential confounder at a time. This statistical approach, known as a “change-in-estimate analysis”, allowed us to assess whether the estimated HR for sPD-L1 remains stable after accounting for single covariates. Unlike multivariable modeling, this method is not intended for prediction, but rather to evaluate the consistency of the association in the presence of potential confounding factors.^{20,21} Candidate confounding factors were selected based on clinical rationale and the results of univariate analyses for bacterial infection development or mortality. Transplanted patients or patients lost during follow-up were censored at the time of intervention or last follow-up.

Additionally, a second statistical approach was also conducted and factors present in the univariate analysis were selected for the multivariate analysis. The final model was fitted using a stepwise forward method based on the improvement in model likelihood ratios. Significance levels to enter and drop model variables were adopted as 5% and 10%, respectively.

All statistical analyses were conducted using Stata 16.1 software, StataCorp® and R v4.4.1, R Studio®. This article adheres to the “Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies”²² (Table S12).

Results

Baseline characteristics of the study population

A total of 995 patients were included across three cohorts. Baseline characteristics of each cohort are summarized in Table 1. The majority of patients were male (75%), and alcohol-related liver disease was the most common etiology. Liver function, as assessed by the model for end-stage liver disease (MELD) score, was most severely impaired in Cohort 1, which comprised hospitalized patients with acute decompensation and/or ACLF. As expected, patients from Cohort 2 had less severe cirrhosis compared to patients from Cohort 1 (median MELD Na score 13 [IQR 9–17] vs. 19,^{13–26} respectively; $p < 0.001$), while those in Cohort 3 exhibited normal or only mildly altered liver function (median MELD score 6 [IQR 6–8]).

Regarding sPD-L1 levels, a stepwise increase was observed across clinical stages in patients from Cohort 1 and 2, with median values rising from non-acute decompensation to acute decompensation and peaking in patients with ACLF (non-AD: 101 [IQR 77–132] pg/ml; AD: 130 [IQR 96–182] pg/ml; ACLF: 172 [IQR 131–219] pg/ml; $p < 0.001$) (Fig. S1). Regarding patients from Cohort 3, patients categorized as F3–F4 displayed higher sPD-L1 levels measured by proteomics than F0–F2 individuals (median 6.2 [5.8–6.5] vs. 5.6 [5.3–5.9] NPX, $p < 0.001$).

Bacterial infections and sPD-L1 levels

Over the 3-month follow-up period, 101 patients (38%) from Cohort 1 developed at least one episode of bacterial infection (median time 14 [6–33] days). The most common type of bacterial infection was urinary tract infection (UTI), followed by respiratory tract infection, spontaneous bacteremia, and spontaneous bacterial peritonitis (SBP) (36%, 21%, 11%, and 9%, respectively) (Table S2). Table S3 reports univariate analysis for factors associated with bacterial infection development. Patients who developed bacterial infections during follow-up had higher baseline plasma levels of sPD-L1 compared to patients who did not develop bacterial infections (median 160 [IQR 116–221] vs. 136 [IQR 97–193] pg/ml, respectively, $p < 0.001$; HR 1.034, 95% CI 1.014–1.055). Fig. 1 shows the probability of developing bacterial infections in patients categorized into two groups according to the median value of sPD-L1 (HR 1.696, 95% CI 1.139–2.525, $p = 0.009$).

sPD-L1 remained associated with the development of bacterial infection after adjustment for potential confounders (Fig. 2). In a multivariate analysis, sPD-L1, together with MELD Na score, history of previous bacterial infection, leukocyte count and presence of HE, were independently associated with the development of bacterial infection (Table 2).

In Cohort 2, 82 of the 327 patients (25%) developed at least one episode of bacterial infection during follow-up (median time 149 [29–249] days). The most common infection subtypes were UTI, followed by SBP (27% and 22%, respectively; Table S2). Factors associated with bacterial infection development in Cohort 2 are reported in Table S4. As with Cohort 1,

Table 1. Baseline demographic and clinical characteristics of patients included in the three cohorts.

| Variable | Cohort 1 (n = 268) | Cohort 2 (n = 312) | Cohort 3 (n = 400) |
|--|----------------------------|---------------------------|--------------------------|
| Age (years) | 60 (53 - 67) | 58 (52 - 66) | 58 (51 - 64) |
| Sex (female) | 73 (27) | 85 (26) | 92 (23) |
| Etiology liver disease | | | |
| Alcohol-related | 165 (62) | 232 (71) | 400 (100) |
| HCV | 38 (14) | 23 (7) | - |
| Alcohol + viral | 21 (8) | 8 (3) | - |
| MASLD | 22 (8.5) | 26 (8) | - |
| Other | 22 (8.5) | 37 (11) | - |
| Type 2 DM | 85 (32) | - | 41 (10) |
| Ascites at inclusion | 179 (67) | 226 (69) | - |
| HE at inclusion | 94 (35) | 21 (6) | - |
| Treatment with norfloxacin | 48 (18) | 22 (7) | - |
| Treatment with rifaximin | 48 (18) | 40 (12) | - |
| Previous infection | 90 (34) | 67 (20) | - |
| Previous SBP | 41 (15) | 18 (5.5) | - |
| Previous non SBP infection | 72 (27) | 59 (18) | - |
| Infection at inclusion | 145 (54) | - | - |
| AKI at inclusion | 104 (39) | - | - |
| ACLF at inclusion | 81 (30) | - | - |
| Grade 1 | 40 (15) | | |
| Grade 2 | 22 (8) | | |
| Grade 3 | 19 (7) | | |
| Serum bilirubin (mg/dl) | 2.6 (1.3-6.6) | 2.0 (1.3-2.9) | 0.6 (0.4-0.8) |
| Serum albumin (g/L) | 29 (25-33) | - | 43 (40-45) |
| INR | 1.5 (1.3-1.9) | 1.32 (1.19-1.47) | 1.0 (0.9-1.1) |
| Serum creatinine (mg/dl) | 1.0 (0.7-1.6) | 0.8 (0.7-1.0) | 0.8 (0.7-0.9) |
| Serum sodium (mEq/L) | 136 (133-139) | 137 (135-139) | 140 (138-141) |
| MELD sodium score | 19 (13-26) | 13 (9-17) | 6 (6-8) |
| Leukocyte count (x10 ⁹ /mm ³) | 5.4 (3.8-8.4) | 5.1 (4.0-6.7) | 6.6 (5.3-8.3) |
| CRP (mg/dl) | 2.3 (0.9-5.0) | - | 2.5 (1-5) |
| sPD-L1 (pg/ml or NPX) | 148 (104-205) [†] | 100 (77-133) [†] | 5.7 (5.3-6) [*] |

Values are presented as median (IQR) for continuous variables and number (percentage) for categorical variables.

ACLF, acute-on-chronic liver failure; AKI, acute kidney injury; CRP, C-reactive protein; HE, hepatic encephalopathy; INR, international normalized ratio; MASLD, Metabolic associated steatotic liver disease; MELD, model for end-stage liver disease; SBP, spontaneous bacterial peritonitis; sPD-L1, soluble programmed death-ligand 1.

[†]Values expressed in pg/ml;

^{*}values expressed in NPX.

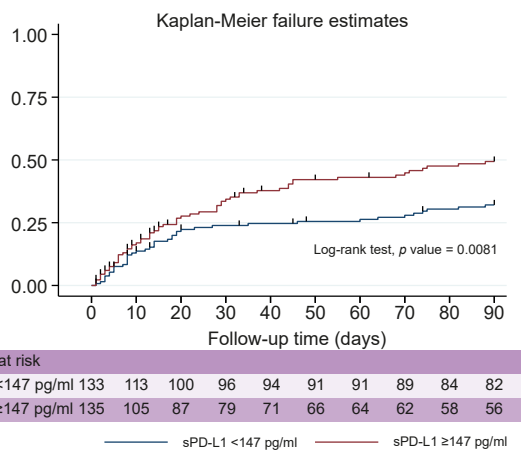


Fig. 1. Cumulative incidence curves of bacterial infections in patients from Cohort 1 categorized according to sPD-L1 median levels. Cumulative incidence estimates for 3-month bacterial infection development in patients from Cohort 1 stratified by sPD-L1 plasma levels using the cohort-specific median cut-off of 147 pg/ml. The blue curve represents patients with sPD-L1 <147 pg/ml, and the red curve represents those with sPD-L1 ≥147 pg/ml. The log-rank test was used to compare survival distributions between groups, with a statistically significant difference observed ($p = 0.0081$). Censoring is indicated by tick marks, and the number at risk is displayed below the time axis. sPD-L1, soluble programmed death-ligand 1.

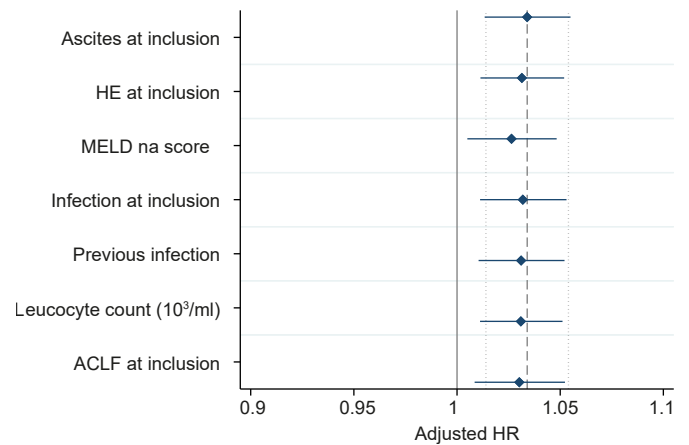


Fig. 2. Adjusted HRs for sPD-L1 and potential confounders associated with 3-month bacterial infection in patients from Cohort 1. Each diamond represents the adjusted HR of sPD-L1 when accounting for the indicated variable, based on a Cox proportional hazards model. The blue horizontal lines indicate the 95% CIs for each adjusted HR. The grey dashed vertical line marks the unadjusted HR of sPD-L1, and the grey dotted lines represent its corresponding 95% CI. Variables included in this analysis were selected based on significance in the univariate analysis. HR, hazard ratio; sPD-L1, soluble programmed death-ligand 1.

Table 2. Multivariate analysis for the prediction of bacterial infection in Cohort 1.

| Variable | p value | HR | 95% CI |
|--|---------|--------------------|--------------------------|
| sPD-L1 (pg/ml) | 0.037 | 1.025 [#] | 1.003-1.047 [#] |
| MELD sodium score | <0.001 | 1.071 | 1.045-1.096 |
| Previous infection | <0.001 | 2.101 | 1.396-3.163 |
| HE at inclusion | 0.046 | 1.515 | 1.008-2.276 |
| Leukocyte count (x10 ³ /mm ³) | 0.049 | 1.038 | 1.0002-1.077 |

Stepwise forward Cox analysis including factors with positive association (p value <0.05) in the univariate analysis.

HE, hepatic encephalopathy; HR, hazard ratio; MELD, model for end-stage liver disease; sPD-L1, soluble programmed death-ligand 1.

[#]HR evaluated per 10 units.

patients from Cohort 2 who developed bacterial infection had higher baseline plasma levels of sPD-L1 compared to patients who did not develop infection during follow-up (median 113 [IQR 87-150] vs. 99 [IQR 76-129] pg/ml, respectively; $p = 0.015$). After adjustment for potential confounders, sPD-L1 remained significantly associated with bacterial infections (Fig. 3). Multivariate analysis confirmed that sPD-L1 levels, together with MELD Na, past history of infection and presence of HE and ascites at inclusion were independently associated with bacterial infection development (Table 3). Fig. S2 shows the cumulative incidence curves of bacterial infections in patients from Cohort 2 categorized according to sPD-L1 level (147 pg/ml).

Finally, 108 of the 400 patients from Cohort 3 (27%) developed at least one episode of bacterial infection during follow-up (median time: 2.3 [1.2-4.2] years). The most common infections were respiratory tract infections followed by UTI and skin and soft tissue infections (38%, 15% and 12% respectively). Only two patients (2%) developed SBP (Table S2). In line with Cohorts 1 and 2, plasma levels of sPD-L1 were associated with bacterial infection development during the follow-up period (HR 2.30, 95% CI 1.67-3.16, $p < 0.001$). The univariate analysis for factors associated with the development

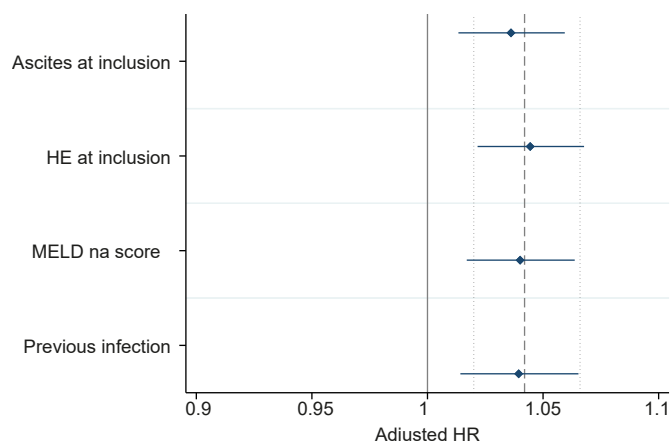


Fig. 3. Adjusted HRs for sPD-L1 and potential confounders associated with 3-month bacterial infection in patients from Cohort 2. Each diamond represents the adjusted HR of sPD-L1 when accounting for the indicated variable, based on a Cox proportional hazards model. The blue horizontal lines indicate the 95% CIs for each adjusted HR. The grey dashed vertical line marks the unadjusted HR of sPD-L1, and the grey dotted lines represent its corresponding 95% CI. Variables included in this analysis were selected based on significance in the univariate analysis. HR, hazard ratio; sPD-L1, soluble programmed death-ligand 1.

Table 3. Multivariate analysis for the prediction of bacterial infection in Cohort 2.

| Variable | p value | HR | 95% CI |
|----------------------|---------|-------|-------------|
| sPD-L1 (pg/ml) | 0.015 | 1.032 | 1.006–1.059 |
| MELD sodium score | 0.009 | 1.050 | 1.012–1.089 |
| HE at inclusion | 0.003 | 2.785 | 1.421–5.458 |
| Previous infection | <0.001 | 2.554 | 1.611–4.050 |
| Ascites at inclusion | 0.009 | 2.399 | 1.245–4.622 |

Stepwise forward Cox analysis including factors with positive association (p value <0.05) in the univariate analysis.

#HR evaluated per 10 units.

HE, hepatic encephalopathy; R, hazard ratio; MELD, model for end-stage liver disease; sPD-L1, soluble programmed death-ligand 1.

of bacterial infection in Cohort 3 is shown in [Table S5](#). Moreover, after adjustment for potential confounders, sPD-L1 remained significantly associated with the development of bacterial infections ([Fig. S3](#)). In multivariate analysis, only sPD-L1 and the severity of liver fibrosis, as estimated by liver stiffness measurement assessed by vibration-controlled transient elastography, were associated with the development of bacterial infection ([Table 4](#)). [Fig. S4](#) shows the cumulative incidence of bacterial infection in individuals from Cohort 3

Table 4. Multivariate analysis for bacterial infection development in patients from Cohort 3.

| Variable | p value | HR | 95% CI |
|--------------|---------|-------|-----------|
| sPD-L1 (NPX) | 0.017 | 1.176 | 1.11–2.81 |
| LSM (kPa) | 0.003 | 1.02 | 1.01–1.03 |
| MELD | 0.049 | 1.11 | 1.00–1.23 |

Stepwise forward Cox analysis, according to its statistical significance (p <0.05) in univariate analysis. The total cohort includes 400 patients with 108 events. In this regression, 386 patients are included in a complete case analysis due to missing values of transient elastography ($n = 13$) and MELD ($n = 1$).

HR, hazard ratio; LSM, liver stiffness measurement; MELD, model for end-stage liver disease; NPX, normalized protein expression; sPD-L1, soluble programmed death-ligand 1.

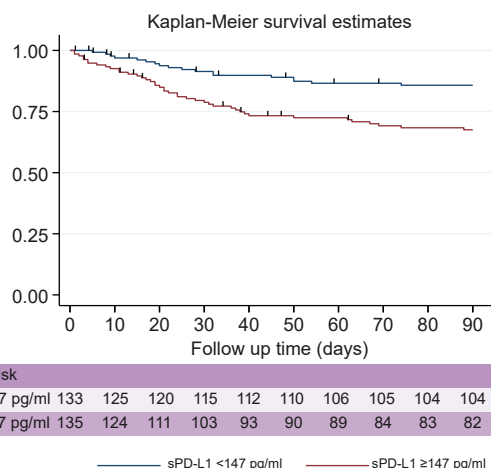


Fig. 4. Kaplan-Meier survival curves in patients from Cohort 1 categorized by median sPD-L1 plasma levels. Kaplan-Meier survival estimates for 3-month mortality in patients from Cohort 1 stratified by sPD-L1 plasma levels using the cohort-specific median cut-off of 147 pg/ml. The blue curve represents patients with sPD-L1 <147 pg/ml, and the red curve represents those with sPD-L1 ≥147 pg/ml. The log-rank test was used to compare survival distributions between groups, with a statistically significant difference observed ($p = 0.0005$). Censoring is indicated by tick marks, and the number at risk is displayed below the time axis. sPD-L1, soluble programmed death-ligand 1.

stratified by median sPD-L1 value in this cohort (5.7 normalized protein expression).

Association between sPD-L1 levels and mortality

During the 90-day follow-up, 60 of the 268 patients from Cohort 1 died (22.4%), 11 (4.1%) underwent LT, 186 (69.4%) remained alive, and 11 (4.1%) were lost to follow-up. Patients who died or were transplanted had higher plasma sPD-L1 levels compared to patients who remained alive (median 180 [IQR 143–267] vs. 134 [97–187] pg/ml, respectively; $p < 0.001$; HR 1.066, 95% CI 1.043–1.089). [Table S6](#) shows the factors associated with 90-day mortality in patients from Cohort 1. The 90-day survival curves of patients categorized into two groups according to the median value of sPD-L1 are shown in [Fig. 4](#) (HR 2.567, 95% CI 1.478–4.461, $p = 0.001$).

To further investigate the relationship between sPD-L1 and 90-day mortality, serum sPD-L1 levels were tested with each variable potentially related to mortality. Results showed consistent statistical significance of sPD-L1 with minimal changes in the HR value ([Fig. S5](#)). Moreover, a multivariate analysis showed that MELD Na, leucocyte count, presence of HE, and sPD-L1 levels were independently associated with 90-day mortality ([Table S7](#)).

With respect to Cohort 2, 37 of the 327 patients (11%) died, 13 (4%) underwent LT, 9 (3%) were lost to follow-up, and 268 (82%) remained alive at the end of the 1-year follow-up period. Patients who died during follow-up had plasma levels of sPD-L1 higher than those of patients who survived (median 124 [IQR 91–152] vs. 99 [76–128] pg/ml, respectively; $p = 0.002$). [Table S8](#) presents the results of univariate analysis for 1-year mortality. After adjustment for potential confounders, sPD-L1 levels remained significantly associated with mortality with stable HR ([Figs. S6 and S7](#)). Moreover, multivariate analysis confirmed findings from Cohort 1, showing that sPD-L1, MELD

Na score, and presence of HE were independently associated with 1-year mortality (Table S9).

Concerning Cohort 3, 56 of the 400 (14%) patients died, 8 (2%) were lost to follow-up, and the remaining 336 (84%) were alive at the end of the follow-up period. No patient was transplanted in this cohort. Plasma levels of sPD-L1 were increased in patients who died compared to patients who survived (see Table S10 for univariate analysis for factors associated with mortality in patients from Cohort 3). Notably, after adjustment for potential confounders, sPD-L1 remained independently associated with mortality, together with liver fibrosis stage assessed by liver stiffness measurement (Figs. S8 and S9; Table S11).

Discussion

The findings of the current study demonstrate that in chronic liver diseases plasma levels of sPD-L1 are associated with the risk of bacterial infections. This association was consistent in all cohorts studied encompassing all stages of the natural history of chronic liver disease, from patients with fibrosis without cirrhosis to patients with compensated and decompensated cirrhosis, strengthening the relevance of the association. Interestingly, the association between sPD-L1 and bacterial infections was independent from factors known to be important in the susceptibility of these patients to infection, such as the severity of liver disease, as evaluated by liver function tests as well as prognostic scores, and inflammatory parameters, such as leukocyte count or C-reactive protein levels. Finally, the plasma levels of sPD-L1 were an independent predictive factor of mortality. Taken together, these findings suggest that the PD-1/PD-L1 pathway plays a role in the pathogenesis of bacterial infections in chronic liver diseases in general and, particularly, in cirrhosis.

PD-1 and PD-L1 are expressed by different immune cell types, including T lymphocytes, dendritic cells, B lymphocytes, monocytes, and macrophages, and their expression is induced in a transient manner by inflammatory cytokines.¹⁰ In normal conditions, signals through the PD-1/PD-L1 pathway contribute to regulation of T-cell activation, fine-tuning of T-cell fate and functions, and T-cell tolerance, thus helping maintain an adequate balance in the immune system. When the activating factor is not cleared, such as during chronic infections or cancer, the PD-1/PD-L1 pathway remains persistently activated leading to constant inhibitory signals.^{23,24} The soluble form of PD-L1 (sPD-L1) exerts similar functions to the membrane-bound PD-L1 and is a prognostic factor in patients with sepsis without cirrhosis.²⁵ Our group previously reported the presence of overexpression of PD-L1 in peripheral mononuclear cells from patients with cirrhosis that paralleled disease progression.¹¹ Moreover, overexpression of the system was also found in liver macrophages of experimental animals with chronic liver disease.¹¹ Notably, blockade of PD-L1 with a PD-L1 antibody restored the markedly impaired liver macrophage activity in an *in vivo* model of chronic liver diseases in mice.¹¹ Furthermore, overexpression of the PD-1/PD-L1 pathway has also been demonstrated in monocytes of patients with alcohol-related hepatitis and *in vitro* blockade of the system is associated with improved monocyte function.¹² The findings of the current study extend these previous experimental observations to clinical grounds by demonstrating the

existence of a strong association between plasma sPD-L1 levels and the risk of infection in a large multicohort study encompassing the broad spectrum of patients with chronic liver disease. Importantly, the current findings not only account for patients with decompensated cirrhosis, but also for patients with advanced fibrosis and compensated cirrhosis, showing that immune paralysis phenomena also occur in early stages of the disease, in the same manner that systemic inflammation is not only restricted to advanced stages but also occurs in early stages of chronic liver disease.⁶

The risk of infection is not homogeneous across the spectrum of chronic liver disease.³ The risk is very high in patients with decompensated cirrhosis, particularly in hospitalized patients, while patients with stable decompensated cirrhosis have comparably lower risk. Patients with compensated cirrhosis are also at risk of infections even though these patients have relatively good liver function and absence of complications; importantly, infections may trigger decompensation in these patients.¹⁴ Moreover, even patients with fibrosis without cirrhosis have significant risk of infection.¹⁴ In addition to a diverse risk of infection, the type of infection is also different across disease stages. Our study was designed as a multicohort study to be able to capture the heterogeneity of chronic liver disease stages and the different prevalence and type of bacterial infections. Interestingly, sPD-L1 was consistently associated with the risk of infection in the three cohorts, with different prevalences and types of infection. These findings unveil an important role of the PD-1/PD-L1 pathway in the pathogenesis of infections and suggest that the overexpression of the PD-1/PD-L1 pathway is already present in early stages of chronic liver diseases and increases in parallel with disease progression, which may explain, at least in part, the progressively increased risk of infections throughout the course of chronic liver disease. The current findings, in conjunction with previously reported data,^{11,12,26} may represent a potential target for specific therapies to help prevent infections in patients with cirrhosis.

Despite the strengths of the current study, there are some limitations that should be acknowledged. First, the levels of sPD-L1 were measured at a single time-point; thus, we have no information as to the evolution of plasma sPD-L1 levels over time and how they may change in individual patients as the disease progresses. Despite this limitation, the consistent association between baseline sPD-L1 levels and clinical outcomes across three independent cohorts supports its potential as a prognostic biomarker. We believe that the predictive capacity of sPD-L1 observed in this study is comparable to that of other well-established predictors of mortality in patients with cirrhosis, such as mild to moderate elevations in serum bilirubin and reduced albumin levels – both of which have been associated with long-term mortality, even several years after the initial assessment.^{27,28} As for the cause-effect relationship between PDL-1 levels and bacterial infections, definitive proof would require performing a randomized controlled trial evaluating the effects of a blockade/antagonism of PD-L1 on the risk of bacterial infections in patients with cirrhosis. Second, most patients in this study had alcohol-related liver disease; therefore, there is limited information on expression of the PD-1/PD-L1 pathway in other etiologies of liver disease and its association with bacterial infections.¹² However, increased PD-L1 expression has been demonstrated in peripheral

monocytes of patients with HBV-decompensated cirrhosis and is associated with sepsis and ACLF risk, which suggests that overexpression of the pathway is independent of the etiology of cirrhosis.²⁶ Finally, in Cohort 3, plasma sPD-L1 levels were measured using proteomic analysis instead of ELISA. Consequently, these levels cannot be directly compared to those of the other two cohorts, which limits the ability to establish a threshold associated with increased risk of infections across disease stages. Nonetheless, the consistency of results with two different methods of measurement of sPD-L1 underscores the robustness of the findings.

In conclusion, the current study indicates the existence of an association between plasma sPD-L1 levels and risk of bacterial infections and mortality in patients encompassing all stages of chronic liver disease from mild to moderate liver fibrosis without cirrhosis, to compensated cirrhosis, and finally decompensated cirrhosis. This study provides evidence on the existence of an immune dysfunction state that progressively increases with the progression of the disease and which is associated with the development of bacterial infections and increased mortality.

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Abbreviations

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy; HR, hazard ratio; MELD, model for end-stage liver disease; PD-1, programmed cell death receptor 1; PD-L1, programmed death ligand 1; SBP, spontaneous bacterial peritonitis; sPD-L1, soluble programmed death ligand 1; UTI, urinary tract infection.

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Conflict of interest

IG reports received consulting fees and speaking fees from Boehringer-Ingelheim and a research grant from Pfizer. AC is a consultant for Mallinckrodt Pharmaceuticals, Boston Scientific Corp, B. Braun and has participated on Advisory Boards for Mallinckrodt Pharmaceuticals and has received grant support from Mallinckrodt and Boston Scientific Corp. TH owns stocks in Novo Nordisk and Genmab, and has received research support from Novo Nordisk. The remaining authors have no conflicts to report. SP served as consultant for Plasma Protein Therapeutics Association, Boehringer Ingelheim and Resolution

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Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

The authors listed above have all contributed to this manuscript and approve the version of this submission. AJ, EP, ES, PG contributed to the conception and design of the study, acquisition of data, the analysis and interpretation of the data and drafting the manuscript; GM, EP, MJM, SI, RG, SJ, NT, MI, NJE, JAC, JR, JGG, AS, AC, MPG, MC, RN, MT, TH, ES, YH, VV, GZ, CA, FEU, UB, CF, RPM, WL, CS, RF, BC, XA, MC, IG, NF, MMR, MT, AK, PA and SP participated in the generation and collection of data, assembly of data, analyses of the results, interpretation of data, and/or critical revision of the manuscript for important intellectual content.

Data availability

The data supporting the findings of this study are not publicly available. Data will only be shared upon reasonable request to the Principal Investigator (PI). Interested researchers must contact the PI directly, outlining the purpose and scope

of the intended use. Access may be granted at the discretion of the PI and may require additional agreements to ensure data confidentiality and ethical use.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2025.101597>.

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