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# Ascetic Soluble CD206 and Serum Interleukin-4 Can Predict Mortality in Acute Decompensated and Acute-on-Chronic Liver Failure

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**Aim.** Acute-on-chronic liver failure (ACLF) is the most severe form of acute decompensation with intense systemic inflammation and immune dysfunction. IL-4 polarizes macrophages toward the M2 phenotype. CD206 can identify inflammatory peritoneal macrophages in cirrhotic patients and could be linked to prognosis in ACLF. We investigated the predictive value of serum IL-4 and ascitic soluble CD206 in patients with acute decompensation and ACLF and their relation to morbidity and early mortality.
**Materials and methods.** We included 60 patients with ACLF and acute decompensation as well as 30 cirrhotic controls. Clinical data were collected, and survival was followed for 1 and 3 months. Blood samples were analyzed at admission for liver and renal function tests as well as serum IL-4 and ascitic soluble CD206 levels. Correlation with liver function indicators and prognosis was assessed.
**Results.** IL-4 and CD206 were significantly higher in acute decompensation and ACLF patients compared to control and were positively correlated with each other's Child — Pugh score, MELD-Na, and ACLF severity scores. Multivariate regression showed that baseline Child — Pugh score, ascitic soluble CD206, and serum IL-4 level are the only independent predictors of 1-month as well as 3-month mortality.
**Conclusion.** Serum IL-4 and ascitic soluble CD206 (macrophage markers) could predict early mortality in acute decompensation and ACLF. Incorporation of these markers into the traditional liver disease scores can improve their prognostic/predictive performance.
**Keywords:** liver cirrhosis, CD206, interleukin-4, acute decompensation, acute on chronic liver failure, ACLF
**Conflict of interest:** the authors declare no conflict of interest.
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## Растворимый CD206 в асцитической жидкости и уровень интерлейкина-4 в сыворотке крови могут прогнозировать смертность при острой декомпенсированной и острой на фоне хронической печеночной недостаточности

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**Цель.** Острая на фоне хронической печеночная недостаточность (ОХПН) представляет собой наиболее тяжелую форму острой декомпенсации цирроза печени, характеризующуюся интенсивным системным воспалением и дисфункцией иммунной системы. Известно, что интерлейкин-4 (IL-4) поляризует макрофаги в сторону M2-фенотипа. Рецептор CD206 позволяет идентифицировать воспалительные перитонеальные макрофаги у пациентов с циррозом и может быть связан с прогнозом при ОХПН. Мы изучили прогностическую ценность сывороточного IL-4 и уровня растворимого CD206 (sCD206) в асцитической жидкости у пациентов с острой декомпенсацией и ОХПН, а также их связь с развитием осложнений и ранней летальностью.
**Материалы и методы.** В исследование были включены 60 пациентов с ОХПН и острой декомпенсацией, а также 30 пациентов с циррозом печени в качестве контрольной группы. Были собраны клинические данные, наблюдение за выживаемостью проводилось в течение 1 и 3 месяцев. При поступлении были проанализированы образцы крови для оценки функции печени и почек, а также определены уровни сывороточного IL-4 и CD206, растворимого в асцитической жидкости. Оценена корреляция с показателями функции печени и прогнозом.
**Результаты.** Уровни IL-4 и CD206 были достоверно выше у пациентов с острой декомпенсацией и ОХПН по сравнению с контрольной группой и положительно коррелировали друг с другом, а также со шкалами Чайлда — Пью, MELD-Na и степени тяжести ОХПН. Многофакторный регрессионный анализ показал, что исходный балл по шкале Чайлда — Пью, уровень асцитического sCD206 и сывороточного IL-4 являются единственными независимыми предикторами летальности в течение как одного, так и трех месяцев.

**Выводы.** Сывороточный IL-4 и асцитический sCD206 (маркеры макрофагов) могут прогнозировать раннюю летальность при острой декомпенсации и ОХПН. Включение этих маркеров в традиционные шкалы оценки заболеваний печени может повысить их прогностическую эффективность.
**Ключевые слова:** цирроз печени, CD206, интерлейкин-4, острая декомпенсация, острая на фоне хронической печеночная недостаточность, ОХПН
**Конфликт интересов:** авторы заявляют об отсутствии конфликта интересов.
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## Introduction and aim

During the course of liver cirrhosis, acute decompensation represents the typical complication, with the acute-on-chronic liver failure (ACLF) representing the most severe phenotype. ACLF is marked by organ failures, significant systemic inflammation, and increased 28-day mortality [1, 2].

Peritoneal macrophages make up most of the immune cells residing in the peritoneum. They produce and regulate hepatic and systemic inflammation by identifying damage-associated and pathogen-associated molecular patterns [3]. Macrophages are typically categorized into M1 (pro-inflammatory) or M2 (anti-inflammatory) types as they adapt to the local environment during liver injury [4]. Recent evidence indicates a link between immune activation in the peritoneum, systemic inflammation, complications, and outcomes in decompensated cirrhosis [5].

Interleukin-4 (IL-4) directs macrophages to adopt the M2 phenotype. Depending on the type of cell, IL-4 may trigger regulatory, suppressive, or pro-inflammatory reactions [6]. CD206, previously utilized for identifying activated (M2) macrophages, is a membrane-bound C-type lectin that acts as a pattern recognition scavenger receptor [7]. CD206 facilitates endocytosis, enhances antigen presentation, and activates T-cells. Soluble variants of CD206 are released peripherally following proteolytic cleavage from the surface of macrophages and can modify both adaptive and innate immune responses [8].

Markers of macrophages have been used as surrogate parameters to predict disease severity and outcomes in a wide range of disorders [9]. In this context, the present study aimed to evaluate serum levels of IL-4 and ascitic levels of soluble CD206 (sCD206) in cirrhotic patients with acute decompensation and ACLF and their relation to the severity of liver disease and patient survival.

## Materials and methods

In a prospective case-control design, we included patients with liver cirrhosis who presented to our hospital with acute decompensation or ACLF, whose symptoms started within two weeks before admission. The sample size was calculated assuming a power of 95 %, an α-error of 0.05, a between-groups variance of 0.2 and a prevalence of 30 % for ACLF in Egyptian tertiary hospitals [10].

Among 130 patients who were screened, 70 patients were excluded due to non-eligibility (patients with hepatocellular carcinoma or other malignancies, chronic heart failure, chronic pulmonary, renal, or rheumatological diseases, severe alcoholic hepatitis, and patients with incomplete records). Finally, 60 participants were included. We also included 30 patients as a control group.

*Cohort definition*

The total 90 patients were assigned into three groups as following:

- *Group A* (patients with acute decompensation) consisted of patients with liver cirrhosis with acute decompensation, defined as jaundice, coagulopathy (international normalized ratio (INR) ≥ 1.5), and presence of large ascites (Grade 2 or 3) within < 2 weeks of presentation, those with acute hepatic encephalopathy, and with gastrointestinal bleeding.
- *Group B* (ACLF patients) included patients with acute hepatic insult plus organ failure: liver failure as defined by a serum bilirubin level > 5 mg/dL; renal failure as defined by a serum creatinine ≥ 2 mg/dL; cerebral failure as defined by hepatic encephalopathy Grade III or IV; coagulation failure (INR ≥ 2.5 and/or platelet count of less than $20 \times 10^9$/L); circulatory failure as defined by the use of vasopressors; and respiratory failure as defined by a peripheral capillary oxygen saturation ($SpO_2$) to $FiO_2$ ratio of ≤ 200, within the last 4 weeks [11].
- *Group C* (control group) included patients with cirrhotic ascites who did not fulfill the criteria of patients in Group A or B.

All patients were followed for a minimum of 90 days through outpatient systems and by telephone to assess survival. The endpoint of the study was the occurrence of death or end of follow up, whichever comes first.

All patients received a clinical evaluation. Blood samples were collected at the time of admission

for complete blood cell count, and blood chemistry including liver profile, renal function tests, and electrolytes. Serum IL-4 levels were measured using a commercially available ELISA kit (Finetest, Wuhan, China; cat. No. EH0199). Ascitic fluid analysis was done with ascitic sCD206 quantification using a commercially available ELISA kit (Finetest, Wuhan, China; cat. No. EH1802).

The severity of liver disease was graded according to Child — Turcotte — Pugh, and the Model for End-Stage Liver Disease (MELD-Na) scores. CLIF-C acute decompensation score was used for patients with acute decompensation while ACLF was assessed by the CLIF-SOFA score [12]. Severity was stratified by considering the number of organs failed (OF): Grade 1 (1 OF), Grade 2 (2 OFs), and Grade 3 (3 to 6 OFs). Survival rates were assessed for 1 and 3 months.

*Ethics*

The study was approved by the institutional ethical committee board (IRB No. 0107126), and conducted following the provisions of the Declaration of Helsinki of 1975, as revised in 2008. The informed consent was obtained from all subjects (or their legal guardians when applicable) included in the study. We have no financial support.

*Statistical analysis*

The IBM SPSS software package version 26.0 (IBM Corp., USA) was used for statistical analysis. The sample size was calculated using STATA 15.1 package (StataCorp, USA). Data were presented as (minimum-maximum), median, Mean ± SD, or number (per cent). Categorical variables were compared using the Chi-square test or Fisher's exact test. Means were compared by Kruskal — Wallis or Mann — Whitney *U* tests. ROC analysis was done on MELD-NA, serum IL-4, and ascitic sCD206. Kaplan — Meier analysis for 1-, and 3-month mortality as well as Cox regression analysis were used to evaluate the effect of baseline parameters on mortality risk.

## Results

*Demographic data*

The baseline data of the study groups are shown in Table 1. Precipitating factors for acute presentation included acute HCV infection, variceal bleeding, and recent infections other than viral hepatitis [pneumonia (38 %), soft tissue infections (21 %), and urinary tract (17 %)]. Spontaneous bacterial peritonitis was met in 7 (22.6 %) patients (2 patients in the group with acute decompensation, 5 patients in the ACLF group).

*Comparison between groups as regards the serum IL-4 and levels of ascitic sCD206*

The serum levels of IL-4 ranged between 0.21–11.28 pg/mL, 1.03–16.82 pg/mL, and 0.06–2.14 pg/mL in acute decompensation, ACLF patients, and the control group, respectively. The median level of serum IL-4 was significantly higher in acute decompensation group and ACLF patients when compared to the control group, and in ACLF patients compared to patients with acute decompensation ($p < 0.001$).

The level of sCD206 in ascitic fluid ranged between 1.40–49.77 ng/mL, 4.23–59.70 ng/mL and 0.20–17.12 ng/mL in acute decompensation, ACLF patients, and the control group, respectively. The median level of ascitic sCD206 was significantly higher in acute decompensation and ACLF groups compared to the control group, and in ACLF patients compared to patients with acute decompensation ($p < 0.001$) (Table 1).

In a subgroup analysis, patients with clinical sepsis were compared to patients with no sepsis as regards the mean levels of serum IL-4 and ascitic sCD206. There was no statistically significant difference between subgroups ($p > 0.05$).

*ROC analysis for serum IL-4 and levels of ascitic sCD206 and its relation to cumulative mortality at one-month mortality*

ROC analysis was performed for the serum IL-4 and ascitic level of sCD206 to investigate their performance in predicting one-month mortality among patients with acute decompensation and ACLF. At a cut-off value 3.60 pg/mL for serum IL-4 and 19.30 ng/mL for sCD206 both could predict mortality at one month with a sensitivity of 92.9 %, 89.3 %, and specificity of 75 % and 90.5 % respectively (AUC = 0.91 ($p = 0.001$) and AUC = 0.94 ($p = 0.002$), respectively), compared to sensitivity and specificity of 82.1 % and 62.5 % respectively for MELD-Na (Fig. 1).

When we applied the rule of having both IL-4 ≥ 3.6 pg/mL and CD206 ≥ 19.3 ng/mL, at the same time, the sensitivity and specificity, positive predictive value, and negative predictive value of this combination in the prediction of 1-month mortality were 85.7 %, 95.2 %, 88.9 %, and 93.7 %, respectively. When we applied the rule of having both MELD-Na ≥ 26.5 together with ascitic sCD206 ≥ 19.3 ng/mL, at the same time, the sensitivity and specificity, positive predictive value, and negative predictive value of this combination in the prediction of 1-month mortality were 78.6 %, 93.4 %, 91.6 %, and 83.3 %, respectively.

*Correlation between serum IL-4 and ascitic sCD206 and different parameters*

Serum IL-4 and ascitic level of sCD206 were positively correlated with history of recent infection, white blood cells count, absolute neutrophil count, C-reactive protein, ascitic fluid polymorph nuclear leucocytes, Child — Turcotte — Pugh score, MELD-Na in all patients, CLIF-AD in acute decompensation patients; and CLIF-C ACLF, and CLIF-OF scores in ACLF patients. Serum IL-4 showed a significant correlation to ascitic sCD206 in all patients (Table 2).

***Table 1.*** Baseline demographic data of study population at admission
***Таблица 1.*** Исходные демографические данные исследуемой популяции на момент поступления

| | **Acute decompensation (*n* = 30)** | **Acute-on-chronic liver failure (*n* = 30)** | **Cirrhotic control (*n* = 30)** | ***p*[b]** |
|---|---|---|---|---|
| Age | 56.62 ± 16.45 | 59.41 ± 14.90 | 56.10 ± 8.78 | 0.60 |
| Gender (male), *n* (%) | 13 (43.30) | 15 (50.00) | 17 (56.70) | 0.58[f] |
| Etiology of chronic liver disease | | | | |
| Viral hepatitis, *n* (%) | 21 (70) | 21 (70) | 14 (46.66) | 0.08 |
| - Post DAAs for HCV | 12 (40.00) | 8 (26.66) | 7 (23.33) | 0.22[e] |
| - Active chronic HCV | 4 (13.33) | 8 (26.66) | 4 (13.33) | |
| - HCV/HBV co-infection | 2 (6.66) | 1 (3.33) | 0 (0.00) | |
| - Chronic hepatitis B | 3 (10) | 4 (13.3) | 3 (10.00) | |
| Alcoholic liver disease | 2 (6.66) | 2 (6.66) | 3 (10.00) | 0.94[e] |
| MASLD | 4 (13.33) | 5 (16.66) | 3 (10.00) | 0.91[e] |
| Autoimmune hepatitis | 1 (3.33) | 2 (6.66) | 2 (6.66) | 0.99[e] |
| Budd — Chiari syndrome | 1 (3.33) | 0 (0.00) | 1 (3.33) | 0.99[e] |
| Unknown | 1 (13.33) | 0 (0.00) | 7 (23.3) | 0.34[e] |
| Precipitating factors of acute presentation | | | | |
| - Acute HCV infection | 0 (0.00) | 2 (6.66) | 0 (0.00) | — |
| - Recent infection[£] | 12 (40.00) | 17 (56.66) | 2 (6.66) | <0.001[f] |
| - Variceal bleeding | 18 (60.00) | 16 (53.33) | 0 (0.00) | 0.001 |
| Clinical examination | | | | |
| MBP (mmHg) | 83.84 ± 12.21 | 82.12 ± 12.73 | 80.54 ± 8.52 | 0.53 |
| Hepatic encephalopathy: | | | | |
| - Absent | 11 (36.67) | 7 (23.33) | 30 (100) | <0.001[e] |
| - Grade 1 | 6 (20.00) | 0 | 0 | |
| - Grade 2 | 11 (36.67) | 0 | 0 | |
| - Grade 3 | 2 (6.66) | 6 (20.0) | 0 | |
| - Grade 4 | 0 (0.00) | 17 (56.70) | 0 | |
| Ascites grades: | | | | |
| - Mild | 1 (3.33) | 5 (16.67) | 4 (13.33) | 0.03[e] |
| - Moderate | 13 (43.33) | 17 (56.66) | 8 (26.67) | |
| - Marked/tense | 16 (53.34) | 8 (26.67) | 18 (60.00) | |
| Baseline laboratory parameters | | | | |
| Hemoglobin, g/dL | 9.01 ± 2.23[cd] | 10.23 ± 2.30[d] | 10.30 ± 1.78 | 0.033 |
| Platelets, ×10³ c/cmm[a] | 32.00–551.00 (104.00) | 14.00–478.00 (87.00) | 26.00–516.00 (101) | 0.125[g] |
| TLC, ×10³ c/cmm[a] | 2.70–18.57 (6.54) | 1.88–23.60 (9.48) | 2.09–10.4 (5.24) | <0.001[g] |
| ALT, IU/L[a] | 12.00–450.00 (31.50) | 14.00–2031.00 (43.50) | 13.00–103.00 (30.50) | 0.047[g] |
| AST, IU/L[a] | 18.00–1760.00 (66.00) | 23.00–4397.00 (104.0) | 20.00–200.00 (47.00) | 0.001[g] |
| Albumen, g/dL | 2.73 ± 0.57 | 2.55 ± 0.50 | 2.67 ± 0.31 | 0.30 |
| Bilirubin, mg/dL[a] | 0.60–12.00 (3.10) | 2.10–35.10 (11.90) | 0.72–4.80 (1.90) | <0.001[g] |
| INR | 1.67 ± 0.30[cd] | 2.28 ± 0.87[d] | 1.33 ± 0.17 | <0.001 |
| Blood urea, mg/dL | 74.14 ± 44.57[cd] | 152.56 ± 73.50[d] | 42.69 ± 14.61 | <0.001 |
| Creatinine, mg/dL | 1.26 ± 0.54[c] | 4.10 ± 2.24[d] | 0.98 ± 0.24 | <0.001 |
| Serum Na, meq/L | 130.46 ± 7.23 | 131.53 ± 6.30 | 132.30 ± 4.76 | 0.51 |
| Serum potassium, meq/L | 4.11 ± 0.63 | 4.28 ± 0.90 | 4.17 ± 0.64 | 0.65 |
| Serum IL-4, pg/mL[a] | 0.21–11.28 (1.03)[cd] | 1.03–16.82 (12.08)[d] | 0.06–2.14 (0.22) | <0.001[g] |
| Ascitic CD206, ng/mL[a] | 1.40–49.77 (13.95)[cd] | 4.23–59.70 (35.59)[d] | 0.20–17.12 (5.00) | <0.001[g] |
| Severity of liver disease | | | | |
| CTP score | 10.53 ± 1.33[cd] | 11.97 ± 1.44[d] | 9.23 ± 1.33 | <0.001 |
| CTP class | | | | |
| - A | 0 (0.00) | 0 | 0 | <0.001[f] |
| - B | 8 (26.67) | 0 | 19 (63.30) | |
| - C | 22 (73.33) | 30 (100) | 11 (36.70) | |
| MELD-Na score | 22.8 ± 6.44[cd] | 35.83 ± 6.60[d] | 16.80 ± 4.70 | <0.001 |

***End of table 1.*** Baseline demographic data of study population at admission

***Окончание таблицы 1.*** Исходные демографические данные исследуемой популяции на момент поступления

| | | | | |
|---|---|---|---|---|
| ACLF grade | | | | |
| - I | – | 1 (3.33) | – | – |
| - II | – | 8 (26.67) | – | – |
| - III | – | 21 (70.00) | – | – |
| CLIF-C AD | 58.97 ± 8.64 | – | – | – |
| CLIF-C ACLF | – | 58.73 ± 11.24 | – | – |
| CLIF-OF | – | 12.16 ± 2.46 | – | – |
| CLIF SOFA-ACLF | – | 12.16 ± 2.46 | – | – |

***Note:*** *ACLF — acute on chronic liver failure; AD — acute decompensation; ALT — alanine aminotransferase; AST — aspartate aminotransferase; CTP — Child — Pugh — Turcotte; DAAs — direct-acting antiviral drugs; HBV — hepatitis B virus; HCV — hepatitis C virus; IL — interleukin; INR — International Normalization Ratio; MASLD — Metabolic Dysfunction-Associated Steatotic Liver Disease; MBP — mean blood pressure; MELD — Model of End-stage Liver Disease; TLC — total leucocyte count; [a] — data is expressed as minimum-maximum (median); [b] — One-way ANOVA test; [c] — significant difference from the ACLF group (Mann — Whitney U test); [d] — significant difference from the control group (Mann — Whitney U test); [e] — Fisher's Exact test; [f] — Chi-square test; [g] — Kruskal — Wallis test; [Σ] — other than hepatotropic viruses.*

***Примечание:*** *ACLF — острая печеночная недостаточность на фоне хронической; AD — острая декомпенсация; ALT — аланин-аминотрансфераза; AST — аспартат-аминотрансфераза; CTP — шкала Чайлда — Тюркотта — Пью; DAAs — противовирусные препараты прямого действия; HBV — вирус гепатита B; HCV — вирус гепатита C; IL — интерлейкин; INR — международное нормализованное отношение; MASLD — стеатотическая болезнь печени, связанная с метаболической дисфункцией; MBP — среднее артериальное давление; MELD — модель терминальной стадии заболевания печени; TLC — общее количество лейкоцитов; [a] — данные представлены как минимум-максимум (медиана); [b] — однофакторный дисперсионный анализ (ANOVA); [c] — значимое различие по сравнению с группой ACLF (критерий Манна — Уитни); [d] — значимое различие по сравнению с контрольной группой (критерий Манна — Уитни); [e] — точный критерий Фишера; [f] — критерий хи-квадрат; [g] — критерий Краскала — Уоллиса; [Σ] — за исключением гепатотропных вирусов.*

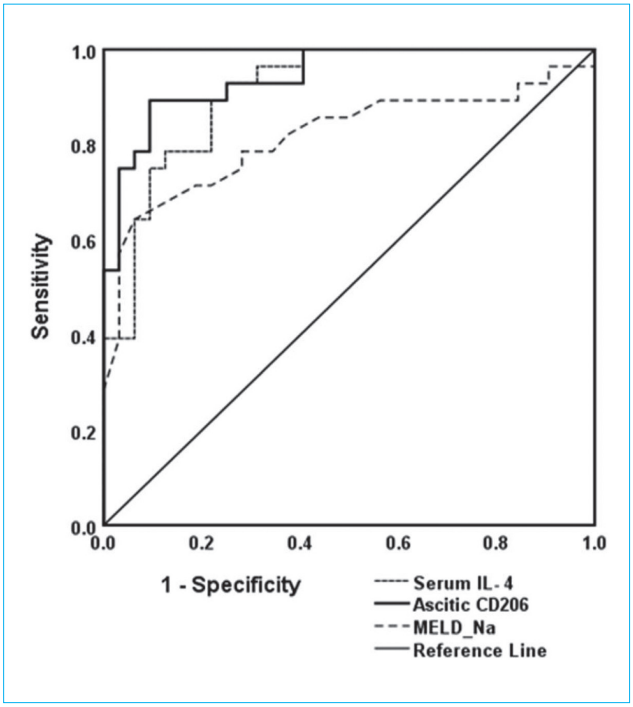


***Figure 1.*** ROC curve analysis for serum IL-4, levels of ascitic sCD206 and MELD-Na to find cut-off value for risk of mortality at one month

***Рисунок 1.*** Анализ ROC-кривой для уровней сывороточного IL-4, асцитического sCD206 и MELD-Na для определения порогового значения риска смертности через один месяц

*Mortality/survival assessment and Kaplan — Meier analysis*

The cumulative 1- and 3-month mortality rates were significantly different between groups. At one month, 8 (26.7 %) patients in the acute decompensation group, 20 (66.7 %) patients in the ACLF group and none of the control group died ($p < 0.001$; $\chi^2 = 31.5$). At 3 months, 12 (40 %) patients with acute decompensation group, 24 (80 %) patients in the ACLF group, and 5 (16.7 %) patients in the control group died ($p < 0.001$; $\chi^2 = 24.81$).

Patients with serum IL-4 levels ≥ 3.6 pg/mL had higher mortality rates than patients with IL-4 levels < 3.6 pg/mL at 1- and 3 months, respectively ($p < 0.001$). Similarly, patients with ascitic sCD206 levels ≥ 19.30 ng/mL had higher mortality rates than patients with sCD206 levels < 19.30 ng/mL at 1- and 3-months, respectively ($p < 0.001$) (Table 3).

The overall survival rate was significantly different among the three study groups. Patients in the ACLF group had a median of 8 days of survival (95% CI: 2.00–9.99), patients in the acute decompensation group had a median of 30 days of survival (95% CI: 24.56–35.44), while the control group had a median of 88 days (log-rank test $\chi^2 = 43.5$, $p < 0.001$; 95% CI: 16.15–159.86).

Kaplan — Meier analysis was done only for the serum IL-4 and ascitic CD206 to stratify cases, and the analysis was done for the acute decompensation and ACLF groups ($n = 60$). At 1 month,

***Table 2.*** Correlations between serum IL-4, ascitic sCD206, and clinical laboratory parameters
***Таблица 2.*** Корреляции между сывороточным IL-4, асцитическим sCD206 и клиническими лабораторными параметрами

| Parameter* | IL-4 | | sCD206 | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| History of infection# | 0.48 | <0.001 | 0.47 | <0.001 |
| White blood cells count | 0.36 | <0.001 | 0.46 | <0.001 |
| Absolute neutrophil count | 0.43 | <0.001 | 0.53 | <0.001 |
| C-reactive protein | 0.38 | <0.001 | 0.33 | 0.002 |
| IL-4 | – | – | 0.87 | <0.001 |
| Ascitic PMN | 0.63 | <0.001 | 0.74 | <0.001 |
| CTP score | 0.67 | <0.001 | 0.68 | <0.001 |
| MELD-Na | 0.79 | <0.001 | 0.75 | <0.001 |
| CLIF-AD** | 0.49 | 0.006 | 0.41 | 0.027 |
| CLIF-C-ACLF*** | 0.48 | 0.007 | 0.65 | <0.001 |
| CLIF-OF*** | 0.57 | 0.001 | 0.59 | 0.001 |

***Note:*** *IL-4 — interleukin-4; PMN — polymorph nuclear leucocytes; CTP — Child — Turcotte — Pugh; MELD-Na — the Model for End-Stage Liver Disease-Sodium; CLIF — chronic liver failure; AD — acute decompensation; ACLF — acute-on-chronic liver failure; OF — organ failure; # — Pearson correlation; * — analysis for the three groups (n = 90); ** — patients with acute decompensation (n = 30); *** — ACLF patients (n = 30).*
***Примечание:*** *IL-4 — интерлейкин-4; PMN — полиморфноядерные лейкоциты; CTP — шкала Чайлда — Тюркотта — Пью; MELD-Na — модель оценки тяжести заболевания печени на конечной стадии с использованием натрия; CLIF — хроническая печеночная недостаточность; AD — острая декомпенсация; ACLF — острая печеночная недостаточность на фоне хронической; OF — органная недостаточность; # — корреляция Пирсона; * — анализ для трех групп (n = 90); ** — пациенты с острой декомпенсацией (n = 30); *** — пациенты с ACLF (n = 30).*

***Table 3.*** Comparison of cumulative 1- and 3-months mortality according to IL-4 and sCD206 cut-off values among patients with acute decompensation and acute-on-chronic liver failure (*n* = 60)
***Таблица 3.*** Сравнение кумулятивной смертности за 1 и 3 месяца в зависимости от пороговых значений IL-4 и sCD206 среди пациентов с острой декомпенсацией и острой печеночной недостаточностью на фоне хронической (*n* = 60)

| **IL-4** | **IL-4 ≥ 3.60 pg/mL (*n* = 34)** | | **IL-4 < 3.60 pg/mL (*n* = 26)** | | | |
|---|---|---|---|---|---|---|
| *Mortality* | *Yes* | *No* | *Yes* | *No* | $\chi^2$ | *p* |
| At 1 month | 26 (76.50 %) | 8 (23.50 %) | 2 (7.70 %) | 24 (92.30 %) | 28.0 | <0.001 |
| At 3 months | 32 (94.10 %) | 2 (5.90 %) | 4 (15.4 %) | 22 (84.6 %) | 38.10 | <0.001 |
| **CD206** | **sCD206 ≥ 19.30 ng/mL (*n* = 28)** | | **sCD206 < 19.30 ng/mL (*n* = 32)** | | | |
| *Mortality* | *Yes* | *No* | *Yes* | *No* | $\chi^2$ | *p* |
| At 1 month | 25 (89.30 %) | 3 (10.70 %) | 3 (9.40 %) | 29 (90.60 %) | 38.30 | <0.001 |
| At 3 months | 28 (100 %) | 0 | 8 (25.0 %) | 24 (75.0 %) | 35.00 | <0.001 |

***Note:*** *IL — interleukin, sCD206 — soluble CD206.*
***Примечание:*** *IL — интерлейкин, sCD206 — растворимый CD206.*

patients with serum IL-4 ≥ 3.6 pg/mL had a significantly shorter median overall survival compared to patients with IL-4 < 3.6 pg/mL — 15 vs. 29 days (Log-rank test $\chi^2 = 44.21$; $p < 0.001$; 95 % CI: 11.2–19.2 and 95% CI: 28.1–30.7, respectively) (Fig. 2A). Similarly, at 1 month, patients with ascitic CD206 ≥ 19.3 ng/mL had a significantly shorter median overall survival compared to patients with ascitic CD206 < 19.3 ng/mL — 8 vs. 28 days (Log-rank test $\chi^2 = 44.80$; $p < 0.001$; 95% CI: 5.6–17.1 and 95% CI: 27.4–30.1, respectively) (Fig. 2B).

At 3 months, patients with serum IL-4 ≥ 3.6 pg/mL had significantly shorter median survival compared to patients with IL-4 < 3.6 pg/mL — 18 vs. 81 days (Log-rank test $\chi^2 = 52.51$; $p < 0.001$; 95% CI: 12.7–24.9 and 95% CI: 72.4–90.2, respectively) (Fig. 2C). Similarly, at 3 months, patients with ascitic sCD206 ≥ 19.3 ng/mL had a significantly shorter median overall survival compared to patients with ascitic sCD206 < 19.3 ng/mL — 14 vs. 76 days (Log-rank test $\chi^2 = 57.20$; $p < 0.001$; 95 % CI: 9.0–18.9 and 95 % CI: 67.5–85.0, respectively) (Fig. 2D).

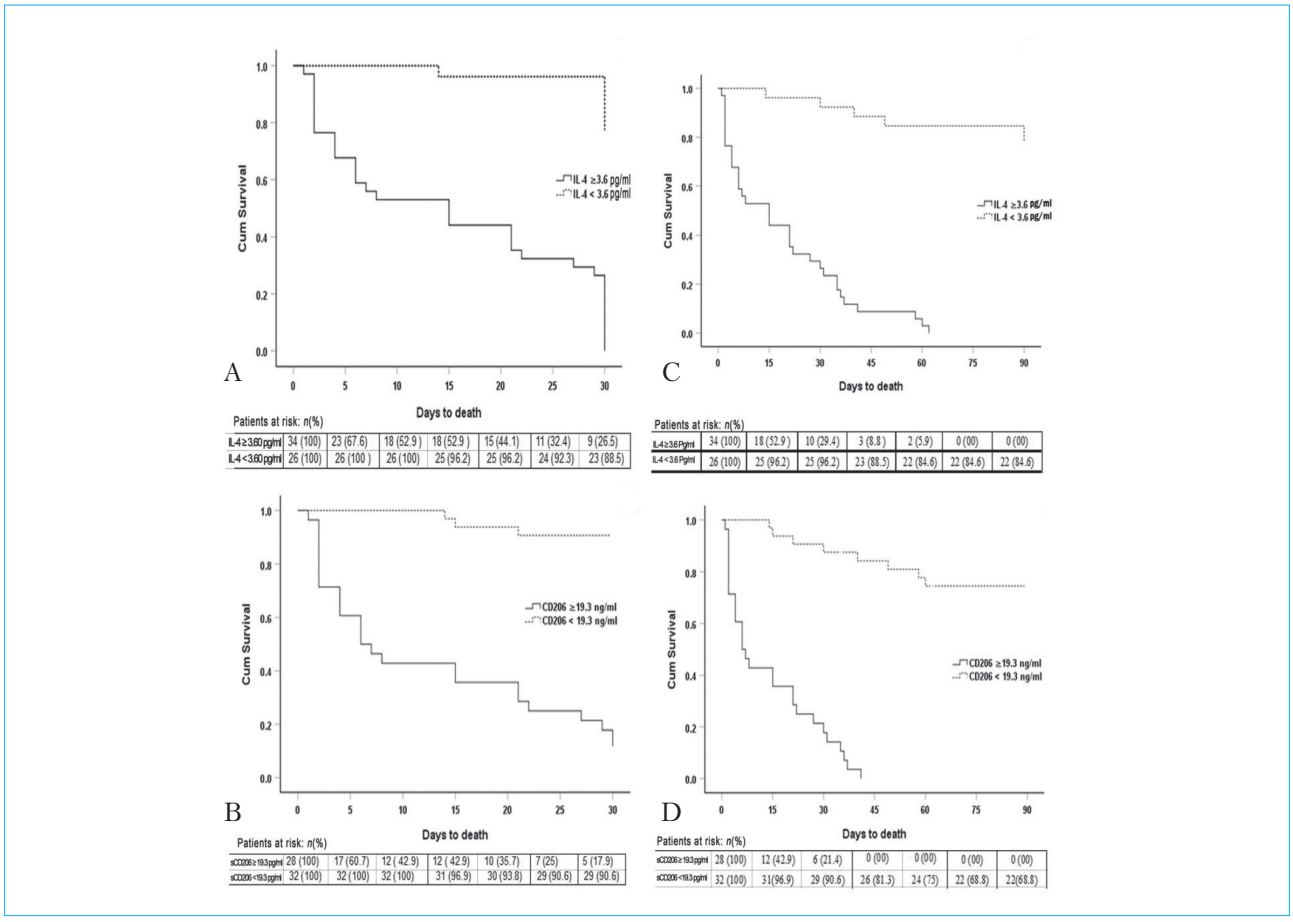


***Figure 2.*** Kaplan — Meier analysis for serum IL-4 and levels of ascitic sCD206 as regards 1- and 3-months mortality (A) mortality at one month for serum IL-4, (B) mortality at one month for ascitic sCD206, (C) mortality at three months for serum IL-4, (D) mortality at three months for ascitic sCD206

***Рисунок 2.*** Анализ Каплана — Мейера для уровней сывороточного IL-4 и асцитического sCD206 в отношении смертности через 1 и 3 месяца: A — смертность через один месяц для сывороточного IL-4; B — смертность через один месяц для асцитического sCD206; C — смертность через три месяца для сывороточного IL-4; D — смертность через три месяца для асцитического sCD206

***Table 4.*** Cox regression for predictors of in-hospital as well as 3 months mortality among acute decompensation and acute-on-chronic liver failure patients ($n$ = 60)

***Таблица 4.*** Регрессионный анализ Кокса для прогнозирования внутрибольничной и 3-месячной смертности среди пациентов с острой декомпенсацией и острой на фоне хронической печеночной недостаточности ($n$ = 60)

| Parameter | One month mortality | | | Three months mortality | | |
|---|---|---|---|---|---|---|
| | *p* | OR | 95% CI | *p* | OR | 95% CI |
| CTP score | 0.01 | 0.59 | 0.39–0.89 | 0.018 | 0.64 | 0.45–0.93 |
| MELD-Na | 0.40 | – | – | 0.66 | – | – |
| Creatinine | 0.22 | – | – | 0.52 | – | – |
| Bilirubin | 0.95 | – | – | 0.65 | – | – |
| INR | 0.08 | – | – | 0.18 | – | – |
| Serum IL-4 | <0.001 | 1.3 | 1.12–1.47 | < 0.001 | 1.27 | 1.14–1.42 |
| Ascitic CD206 | 0.001 | 1.1 | 1.03–1.13 | < 0.001 | 1.08 | 1.04–1.14 |

***Note:*** *OR — odd's ratio; CI — confidence interval; CTP — Child — Turcotte — Pugh; MELD — model of end-stage liver disease; INR — international normalization ratio; IL-4 — interleukin-4.*

***Примечание:*** *OR — отношение шансов; CI — доверительный интервал; CTP — шкала Чайлда — Тюркотта — Пью; MELD — модель оценки тяжести заболевания печени на конечной стадии; INR — международное нормализованное отношение; IL-4 — интерлейкин-4.*

*Cox regression analysis for predictors of mortality*

The univariate analysis identified baseline parameters (Child — Turcotte — Pugh score, MELD-Na, serum creatinine, serum bilirubin, INR, ascitic sCD206, and serum IL-4) as significant for the prediction of 1- and 3-month mortality. However, cox regression analysis showed that baseline Child — Turcotte — Pugh score, ascitic sCD206, and serum IL-4 level are the only independent predictors of 1- and 3-month mortality ($p < 0.001$) (Table 4).

## Discussion

Immune dysregulation is the cornerstone for the progression of ACLF. As portal hypertension progresses, immune dysfunction intensifies and ultimately leads to total immune exhaustion [13]. CD206 is regarded as a marker of M2 macrophage phenotype, and can be released into the bloodstream as a soluble form [14]. While numerous scores have been developed to estimate mortality in ACLF and acute decompensation, these metrics fall short of incorporating indicators that reflect disease progression or pathogenesis. Thus, it is essential to identify novel promising markers that accurately forecast prognosis. In this research, we measured the serum concentration of IL-4 and ascitic sCD206 in cirrhotic individuals with ACLF or acute decompensation, and analyzed their association with liver disease severity and patient survival.

Our study's initial finding reveals that both ascitic sCD206 and serum IL-4 levels were notably elevated in patients with acute decompensation and ACLF, showing a positive correlation with liver disease severity scores; additionally, these markers effectively categorized patients with increased risks of mortality at 1 and 3 months. Simultaneously, patients exhibiting IL-4 levels ≥ 3.6 pg/mL and sCD206 levels ≥ 19.3 ng/mL experienced increased mortality rates and reduced survival times.

Typically, CD206 functions in recognizing and internalizing pathogens. Although sCD206 is consistently found in the plasma of healthy individuals, its concentration rises across various diseases when triggered by activation from fungi and lipopolysaccharide both *in vivo* and *in vitro* [8]. CD206 associated with macrophage-derived extracellular vesicles can influence the immune response by modifying the phenotype of endothelial cells and T cells, leading to enhanced recruitment and activation of leukocytes [15].

Patients with liver diseases, severe illness, sepsis, and organ failure exhibited notably elevated sCD206 levels [16]. sCD206 is not specific to any disease; instead, it reflects the overall status of the immune system. It shows a strong association with indicators of significant immune activation, such as tumor necrosis factor [9]. sCD206 levels show a relationship with inflammation and fibrosis in metabolic dysfunction-associated steatotic liver disease, chronic hepatitis C viral infection, and primary biliary cirrhosis patients. In liver cirrhosis, elevated serum sCD206 levels were observed compared to healthy individuals and were linked to liver decompensation [17]. Additionally, levels of CD206 were reduced following antiviral therapy [18]. Patients with acute alcoholic hepatitis, acute liver failure, and ACLF exhibit the highest concentrations of sCD206 [8, 19].

A connection exists between sCD206 and changes in metabolic pathways associated with mitochondrial energy production, contributing to the advancement of organ failure in ACLF. Activation of macrophages in cirrhosis might indicate a persistent inflammatory upregulation, which may be further intensified by an overall systemic inflammatory condition, resulting in immune activation [20]. Due to its large molecular size, the renal clearance of sCD206 protein is improbable. In addition, decreased hepatic metabolism, and shunting of portal blood may also explain the elevated levels of sCD206 in our study.

All participants in our research experienced portal hypertension, which, along with the impaired gut-blood barrier, facilitates the translocation of intestinal bacteria and pathogen-associated molecular patterns. These can stimulate the toll-like receptors of resident hepatic macrophages inside the liver. sCD206 showed a correlation with gut permeability indicators. sCD206 also has been assessed in predictive scores for clinically significant portal hypertension [21, 22].

In our research, ascitic sCD206 and serum IL-4 emerged as independent predictors for mortality at 1 and 3 months. Incorporating sCD206 into MELD-Na enhanced its effectiveness in predicting patient survival. Serum sCD206 was linked to mortality at 28 and 90 days in ACLF [18, 21]. Integrating sCD206 with the CLIF-C acute decompensation score significantly enhances the accuracy of predicting mortality at 90 and 180 days for patients with acute decompensation [19, 23]. ACLF patients with elevated sCD206 levels exhibited more severe liver, coagulation, cardiovascular, or cerebral failures and encountered bacterial infections and sepsis. Additionally, sCD206 influenced the prognosis in cirrhotic patients without ALCF, suggesting a role that is separate from severe inflammation [19].

In ACLF patients, the level of sCD206 was related to the severity of the disease [24]. sCD206 has the ability to bind with CD45 on macrophages, resulting in cellular reprogramming towards an inflammatory phenotype driven by Src/Akt/NF-κB pathway. Moreover, sCD206 is involved in removing glycoproteins through the breakdown of endogenous glycoproteins like β-glucuronidase and procollagen, which increase during inflammation [25].

Only a single prior study examined ascitic sCD206 in individuals with spontaneous bacterial peritonitis. At concentrations greater than 0.53 mg/L, sCD206 indicated poorer survival at 3 months. The disparity in the outcomes between our findings and those of S. Stengel et al. (2020), might be attributed to the greater number of patients with spontaneous bacterial peritonitis in their research, unlike ours [5].

Live bacteria and toll-like receptor agonists can stimulate peritoneal macrophages, resulting in alterations to their CD206 expression, triggering the release of sCD206 [5]. Comparing sCD206 levels across studies is difficult because there is no standardized assay available for detecting sCD206. The peritoneal concentration of sCD206 correlates with an inflammatory macrophage phenotype and activation of macrophages. Peritoneal macrophages expressing sCD206 showed notably elevated levels of toll-like receptors and chemokines when stimulated. Additionally, sCD206 is involved in the capture of antigens and their transport to cells that participate in the humoral immune response. This contradicts the earlier thought that CD206+ macrophages have anti-inflammatory properties, indicating their plasticity [26].

In our study, we found a correlation between IL-4 and sCD206. Previous research has demonstrated that IL-4 enhances the expression of CD206 [27]. IL-4 prompts monocytes and macrophages to differentiate into M2 phenotypes. The transcription factors STAT6, IRF4, and PPARγ, responsible for regulating genes associated with M2a macrophages such as CD206, are activated and relocated by IL-4. In M2a macrophages, the mRNA expression of the mannose receptor CD206 reached its highest level 72 hours following IL-4 stimulation [28].

Macrophages primed with IL-4 exhibit a strong proinflammatory capacity when compared to naive and M1 macrophages. IL-4Rα on macrophages facilitates hepatic inflammation and fibrosis, and blocking it reverses these effects [29]. IL-4 also triggers hepatocyte apoptosis via a pathway that is independent of Fas. Other research suggested encouraging reparative and fibrotic function of IL-4 in hepatocytes [6]. Furthermore, IL-4 serves as an indicator of the TH2 response in ACLF [30].

We acknowledge that the limited sample size in our study poses a restriction, yet a significant advantage of this study is that it represents the first assessment of ascitic sCD206 as a potential marker for predicting mortality risk in patients with acute decompensation and ACLF, regardless of spontaneous bacterial peritonitis existence. However, future research is suggested to investigate the influence of spontaneous bacterial peritonitis on sCD206 levels using a larger group. In addition, our research is one of few studies that investigate IL-4 in ACLF patients and its relation to sCD206 *in vivo*.

## Conclusion

The link between ascitic sCD206 and serum IL-4 levels with acute decompensation and ACLF severity, as well as mortality, indicates the crucial role of peritoneal macrophages in the progression and outcomes of ACLF. Incorporating macrophage biomarkers (ascitic sCD206 and serum IL-4) into the ACLF and acute decompensation scores is proposed to enhance the prognostic and predictive capabilities beyond those of conventional scores.

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