**ORIGINAL PAPER**

Surg. Gastroenterol. Oncol. 2024;29(2):89-95 DOI: 10.21614/sgo-688

# Predictive Factors for Mortality and Infection Surveillance in Romanian Candidates for Liver Transplantation

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## ABSTRACT

**Introduction:** Infections in cirrhotic patients represent an important cause of decompensation, with an increased risk of sepsis and death and the most frequently incriminated infections are spontaneous bacterial peritonitis, urinary tract infections and pneumonia.
**Materials and Methods:** In a single – center retrospective cohort study, we analyzed data from 155 patients included on the waiting list for liver transplantation, such as biochemical parameters – serum C reactive protein and procalcitonin values, prognostic scores for end – stage liver disease, positive colonization and occurrence of active infections.
**Results:** Positive colonization with different microorganisms was found in 49.67% from patients included on the waiting list for liver transplantation and active infections in 41.93%. Patients presented spontaneous bacterial peritonitis in 15.48% of cases, followed by urinary tract infections (14.83%) and pneumonia (12.25%). Positive pharyngeal swab in patients with a CRP levels > 4.6 mg/dl correlated with occurrence of pneumonia ($p=0.0033$) and also positive rectal swab in patients with CRP levels > 7.1 mg/dl was associated with spontaneous bacterial peritonitis ($p=0.0155$). Occurrence of active infections and MELD Na score were found as independent predictors for death on the waiting list for liver transplantation ($p=0.029$, respective $p<0.0001$). Liver transplantation was performed in 91 patients (58.7%) and 28 patients (18.06%) died awaiting liver transplantation.
**Conclusions:** Rectal colonization may play an important role in the development of bacterial infections, especially with multidrug resistant bacteria. In cirrhotic patients, a bacteriological screening should be performed, in order to diagnose active infections and empirical antibiotic treatment should be established according to local epidemiology. For candidates included on the waiting list for liver transplantation, occurrence of infections and MELD Na score can be independent predictive factors for mortality.
**Key words:** infections, positive colonization, liver transplantation

**Abbreviations:**
ACLF: acute – on – chronic liver failure;
SBP: spontaneous bacterial peritonitis,
LT: liver transplant;
MELD: Model of End-Stage Liver Disease;
WL: waiting list;
INR: International normalized ratio;
CRP: C reactive protein;
NLR: neutrophil-to-lymphocyte ratio;
PLR: platelet-to-lymphocyte ratio;
DM: diabetes mellitus;
VRE: Vancomycin-resistant Enterococcus;
MRSA: Methicillin-resistant Staphylococcus aureus;
MDR – multidrug resistant.

## INTRODUCTION

In patients with chronic liver diseases, evolution to liver cirrhosis represents a cause of morbidity and mortality (1). There has been an increase in the prevalence of hepatic decompensation, with a rate of 5 – 12 % per year in

Received: 07.05.2024
Accepted: 25.06.2024

the transition from a compensated stage to a decompensated stage, with occurrence of complications, such as ascites, hepatic encephalopathy, variceal bleeding (2,3,4). In the Global Burden Disease study from 2017, there has been reported an increase in the global number of decompensated cirrhosis, from 5.2 million in 1990 to 10.6 million in 2017 (5). In the Global Burden Disease study from 2019, the number of worldwide deaths related to cirrhosis was estimated to 1472000 (6). Acute-on-chronic liver failure (ACLF) represents the decompensation of chronic liver disease, with one or more organ failures and with a high mortality rate (7,8).

An important cause of liver disease decompensation is represented by bacterial infections, with an increased risk of sepsis and death, at about 38% at 1 month (9,10). In about 32% of cases, the most frequent triggers of ACLF are bacterial infections (11). The most frequent infections in cirrhotic patients are: spontaneous bacterial peritonitis (SBP), urinary tract infections, pneumonia and cellulitis (12).

Liver transplant (LT) is the curative treatment for end-stage liver diseases and has the objective to improve the outcome of patients, to reintegrate them into the social and familial environment and the allocation is based on the Model of End Stage Liver Disease (MELD) score. In the European transplant centers, the number of liver transplants per year varies largely, in 2018 in Romania being registered a low-rate of LT, of 4.1 per million population (pmp) (13). The low-rates of LT are due to the lack of organ donors and the patients remain more on the waiting list (WL), with increased risk of occurrence of complications and high mortality. Comparing to other European countries, in 2018 were reported higher rates of LT, like in Croatia (32.4 pmp), Belgium (27.3 pmp) and Spain (26.3 pmp) (13), and the aim of our study was to analyze the epidemiology of infections in end- stage liver diseases included on the WL and to identify new models and factors to predict mortality on the WL.

## MATERIALS AND METHODS

We performed a single-center retrospective cohort study that evaluated data from 155 candidates from the WL for LT, added from January 2018 to December 2023 in the Center for Liver Diseases and Liver transplantation, Fundeni Clinical Institute, Romania.

We recorded and analyzed the following characteristics:

1. Patient demographics: gender, age, blood type;
2. Etiology of liver disease, presence of hepatocellular carcinoma, associated diabetes mellitus;
3. Biological parameters: serum albumin, total bilirubin, serum creatinine, international normalized ratio (INR), serum sodium, serum leucocytes, neutrophils, lymphocytes, monocytes, platelets, C reactive protein (CRP), procalcitonin;
4. Prognostic scores: MELD, MELD Na, MELD 3.0 scores, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio;
5. Bacteriological samples: pharyngeal exudate, nasal exudate, rectal exudate, urinalysis, coproculture, hemocultures, cardio-pulmonary x-ray, ascites / pleural analysis;
6. Complications of liver diseases: acute kidney injury, hepatic encephalopathy, ascites, jaundice, history of variceal bleeding.

### *Statistical analyses*

Data was analyzed using MedCalc® version number 22.023. Patient survival was calculated using Kaplan-Meier method and univariate and multivariate regression were performed using Cox proportional hazard method. A $p<0.05$ was considered as statistically significant.

## RESULTS

For the 155 patients included on the WL the mean age was 52 ± 11.12 years, with ages from 18 years old to 70 years old. Regarding the gender, most patients were male (105 – 67.74%). The blood type distribution was: 0I – 58 patients (37.41%), AII – 52 patients (33.54%), BIII – 37 patients (23.87%) and only 8 patients with ABIV blood type (5.16%).

Regarding the etiology of the liver disease, hepatitis B and D is the most frequent (36.77%), followed by alcoholic liver disease (26.45%), hepatitis C (11.61%), and other etiologies, like primary sclerosing cholangitis (3.22%) and others (21.95%). Hepatocellular carcinoma was associated in 51 patients (32.9% of cases). The mean MELD score at inclusion on the WL was 17.19 ± 6.8, and we also calculated the mean MELD Na score at inclusion 18.8 ± 7.75 and mean MELD 3.0 at inclusion 19.14 ± 7.8.

Diabetes mellitus was associated in 28 cases (18.06%).

The calculated median waiting time on the liver transplantation list for all patient was 150 days (from 1 to 1860 days). 91 patients (58.7%) from those included in this study were transplanted in this period and 28

patients (18.06%) died awaiting liver transplantation.

The complications of end-stage liver disease on the WL included: hepatic encephalopathy (n=62, 40%), refractory ascites (n=47, 30.32%), acute kidney injury (n=41, 26.45%), portal vein thrombosis (n=26, 16.77%), variceal bleeding (n=29, 18.7%), ACLF (n=46, 29.67%) (*table 1*).

In 41.93% of cases (65 patients) infectious complications occurred during the waiting time, such as: spontaneous bacterial peritonitis (n=24, 15.48%), urinary tract infections (n=23, 14.83%), pneumonia (n=19, 12.25%), bacteriemia (n=15, 9.67%), bacterial enterocolitis (n=15, 9.67%), cutaneous infections (n=8, 5.16%), acute cholangitis (n=4, 2.58%), empyema (n=2, 1.29%).

The microorganisms isolated in the urinary cultures were: Escherichia coli (n=15) representing the etiology in 65.21% of the urinary tract infections, Candida albicans (n=4, 17.39%), Proteus Mirabilis (n=2, 8.69%), Enterococcus faecalis (n=1, 4.34%) and Myroides odoratum multidrug resistant (MDR) (n=1, 4.34%).

Regarding the etiology of the enterocolitis, the most frequent recorded was Clostridioides Difficile infections in 8 cases (53.3%), 3 cases with Enterococcus faecalis (20%), 2 cases with Proteus Mirabilis, respectively Candida albicans (13.3%).

The blood cultures collected showed different microorganisms, such as: Escherichia coli (most of the cases – 40%), but also Staphylococcus epidermidis, coagulase-negative Staphylococcus, methicillin-resistant Staphylococcus aureus, Staphylococcus Haemolyticus, methicillin-sensitive Staphylococcus aureus, Enterococcus species, Candida albicans and Klebsiella pneumoniae.

For the patients included on the WL, a bacteriological screening was recorded during different hospitalization times, and an important number (77, 49.67%) presented positive swabs awaiting liver transplantation, as followed in the *table 2*.

For patients with positive rectal swab a CRP level higher than 7.1 mg/dl (normal CRP levels = 0 - 5 mg/dl) was established as a cut-of, with a sensitivity of 92% and a specificity of 50.79% (Area under the ROC curve AUC 0.676, p=0.001) (*fig. 1*).

Patients with a positive rectal swab and a CRP level > 7.1 mg/dl were predisposed to develop spontaneous bacterial peritonitis (p=0.0155) (*fig. 2*).

A cut-of value for CRP > 4.6 mg/dl was found with a sensitivity of 87.5% and a specificity of 44.21% in patients with positive pharyngeal swabs (AUC 0.639, p=0.003). Also, positive pharyngeal swab in patients with a CRP level > 4.6 mg/dl correlated with occurrence of pneumonia (p=0.0033) (*fig. 3*).

We also calculated the cut-of level of 4 mg/dl for CRP in patients with positive nasal swab, with a sensitivity of 86.49% and a specificity of 35.78% (AUC 0.604, p=0.0474), but no correlations were found with occurrence of pneumonia (p=0.326).

**Table 1 - Patient characteristics on the waiting list**

| Characteristics | n=155 patients |
|---|---|
| Age (mean ± SD) years | 52 ± 11.12 |
| Gender, n (male) | 105 (67.74%) |
| Blood type | |
| 0I | 58 (37.41%) |
| AII | 52 (33.54%) |
| BIII | 37 (23.87%) |
| ABIV | 8 (5.16%) |
| Etiology | |
| HBV + HDV | 55 (36.77%) |
| ALD | 41 (26.45%) |
| HCV | 14 (11.61%) |
| Others | 45 (27.75%) |
| HCC | 51 (32.9%) |
| DM | 28 (18.06%) |
| MELD score at inclusion (mean ± SD) | 17.19 ± 6.8 |
| MELD Na score at inclusion (mean ± SD) | 18.8 ± 7.75 |
| MELD 3.0 score at inclusion (mean ± SD) | 19.14 ± 7.8 |
| Waiting time on the LT list (median) | 150 days |
| Complications of liver cirrhosis | |
| Hepatic encephalopathy | 62 (40%) |
| Refractory ascites | 47 (30.32%) |
| Acute kidney injury | 41 (26.45%) |
| Portal vein thrombosis | 26 (16.77%) |
| Variceal bleeding | 29 (18.7%) |
| ACLF | 46 (29.67%) |
| Active infections | 65 (41.93%) |
| Positive colonization | 77 (49.67%) |

HBV – hepatitis B virus, HDV – hepatitis Delta virus, ALD – alcoholic liver disease, HCV – hepatitis C virus, HCC – hepatocellular carcinoma, DM – diabetes mellitus, MELD – Model of End Stage Liver Disease, ACLF – acute-on-chronic liver failure.

In order to evaluate the risk factors associated with death on the WL, we performed a univariate and a multivariate analysis using Cox proportional hazard method.

In univariate analysis, we found a series of factors and prognostic models that were associated with high mortality on the WL: occurrence of ACLF (from grade 1 to 3), refractory ascites, bacteriemia, acute kidney injury, hepatic encephalopathy, active infections, NLR, urinary tract infections, MELD score, MELD Na score, MELD 3.0 score, pneumonia, enterocolitis, variceal bleeding, SBP, positive colonization. In multivariate analysis, active infections and MELD Na score were found as independent predictors for death on the waiting list for liver transplantation (p=0.029, respective p<0.0001) (*table 3*).

Active infections, found in univariate analysis with a statistically significance, were included in the multivariate analysis to identify specific infections that can

**Table 2 - Colonization with different microorganisms, isolated in positive swabs in candidates awaiting LT**

| Microorganism | Number of patients with positive swabs | | | |
|---|---|---|---|---|
| | Pharyngeal swab (n=48) | Nasal swab (n=37) | Rectal swab (n=25) | Vaginal swab (n=25) |
| Pseudomonas aeruginosa | 2 | 1 | 2 | |
| Klebsiella species | 2 | 2 | 3 | |
| Candida albicans | 33 | | 11 | 23 |
| Fusobacterium nucleatum | | | 1 | |
| Escherichia coli | 5 | | 1 | 8 |
| Chryseobacterium species | | | 1 | |
| Vancomycin-resistant Enterococcus species (VRE) | | | 3 | |
| Enterococcus species | | | 8 | |
| Proteus mirabilis | 1 | | 3 | 1 |
| Acinetobacter baumanii | 2 | 2 | 1 | |
| Streptococcus agalactiae | | | | 5 |
| Methicillin-sensitive Staphylococcus aureus | 6 | 27 | | |
| Methicillin-resistant Staphylococcus aureus (MRSA) | 2 | 6 | | |
| Candida glabrata | 2 | | | |
| Streptococcus pyogenes | 3 | | | |
| Moraxella catharralis | | 1 | | |

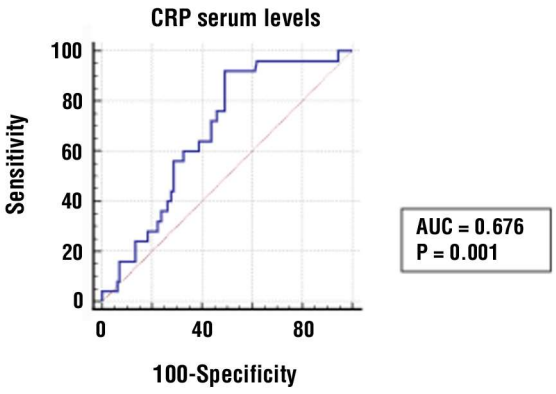


**Figure 1 - Cut-of serum level for CRP in patients with positive rectal swab**

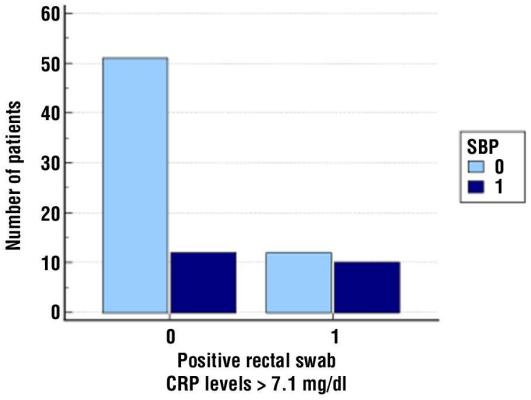


**Figure 2 - Correlation between positive rectal swabs and occurrence of SBP, at CRP levels higher than 7.1 mg/dl**

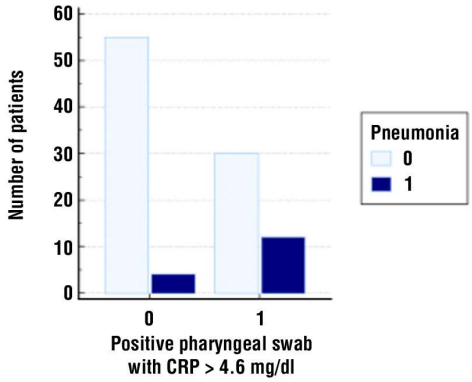


**Figure 3 - Correlation between positive pharyngeal swab and occurrence of pneumonia in patients with CRP levels >4.6 mg/dl**

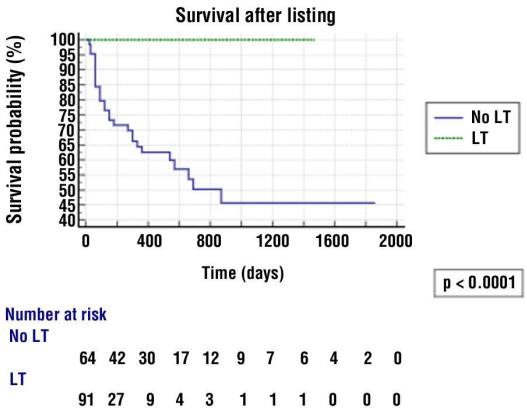


**Figure 4 - Survival probability after listing for liver transplantation – comparison between patients undergoing LT and not undergoing LT**

**Table 3 - Predictive factors for death on the WL – univariate and multivariate analysis**

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | Odds ratio (95% - CI) | p Value | Odds ratio (95% - CI) | p Value |
| ACLF (grade 1 to 3) | 4.91 (2.31 – 10.44) | <0.0001 | | |
| Refractory ascites | 5.24 (2.35 – 11.71) | <0.0001 | | |
| Bacteriemia | 3.42 (1.25 – 9.39) | 0.033 | | |
| Acute kidney injury | 3.78 (1.76 – 8.1) | 0.0007 | | |
| Hepatic encephalopathy | 7.71 (3.1 – 19.13) | <0.0001 | | |
| Active infections | 10.93 (3.77 – 31.69) | <0.0001 | 3.72 (1.14 – 12.14) | 0.029 |
| NLR | 1.13 (1.06 – 1.19) | 0.0003 | | |
| Urinary tract infections | 2.39 (1.04 – 5.45) | 0.038 | | |
| MELD score | 1.08 (1.04 – 1.13) | 0.0002 | | |
| MELD Na score | 1.1 (1.05 – 1.14) | <0.0001 | 1.1 (1.05 – 1.15) | <0.0001 |
| MELD 3.0 score | 1.09 (1.05 – 1.13) | <0.0001 | | |
| Pneumonia | 4.43 (1.92 – 10.2) | 0.0019 | | |
| Bacterial enterocolitis | 3.77 (1.48 – 9.57) | 0.0132 | | |
| Variceal bleeding | 2.32 (1.06 – 5.07) | 0.0436 | | |
| SBP | 4.99 (2.34 – 10.63) | 0.0001 | | |
| Positive colonization | 5.87 (2.22 – 15.55) | <0.0001 | | |

ACLF – acute-on-chronic liver failure, NLR – neutrophil-to-lymphocyte ratio, MELD – Model of End Stage Liver Disease, SBP – spontaneous bacterial peritonitis.

be independent factors for death on the WL. We found that spontaneous bacterial peritonitis is an independent risk factor for death in patients with end-stage liver disease (p=0.0018) (*table 4*).

Regarding survival on the WL, from 155 patients, 28 (18.06%) died awaiting liver transplantation, with a mean waiting time of 1279 days (1078 – 1480 days) and median survival time of 870 days (95% CI 360 – 870 days) (p<0.0001).

## DISCUSSIONS

The prevalence of bacterial or fungal infections in cirrhotic patient that are hospitalized occur in 25 – 50% of cases (11), and can be diagnosed within 48 hours from admission or can be nosocomial infections (14). Patients with an acute decompensation of liver cirrhosis, with / without ACLF, at admission, should be investigated in order to identify infections – chest X-ray, urinalysis, ascites analysis, blood cultures (14).

Regarding the type of microorganism isolated in patients with cirrhosis, the most frequent Gram-negative bacteria are Enterobacteriaceae (as Klebsiella pneumoniae, Escherichia coli) and Staphylococci, Enterococci and Streptococci from the Gram-positive bacteria (14), and only in less cases fungal infections 3-7% (15).

There is an increase in the prevalence of multidrug resistant (MDR) bacteria in cirrhotic patients (16-18), most frequently incriminated being extended-spectrum beta-lactamase producing Enterobacteriaceae, MRSA and VRE and previous antibiotic therapy and nosocomial infections are the risk factors for infections with MDR organisms (14).

Recent studies showed that rectal colonization with MDR bacteria is frequent in cirrhotic patients and can be associated with a higher risk of developing MDR bacterial infections, but more data is needed to evaluate if antibiotic therapy should be given according to positive colonization (19).

Our study showed that patients with rectal colonization have a predisposition to develop SBP, at serum levels of CRP higher than 7.1 mg/dl. The most frequent microorganisms isolated in rectal swabs were Gram-negative bacteria, such as Escherichia coli, Klebsiella species, Enterococcus species, Proteus mirabilis, fungi – Candida albicans most common, but also VRE and Acinetobacter Baumanii usually being incriminated in

**Table 4 - Multivariate analysis of active infections**

| Variable | Odds ratio (95% - CI) | p Value |
|---|---|---|
| Bacteriemia | 1.68 (0.56 – 5.06) | 0.35 |
| Urinary tract infections | 1.98 (0.76 – 5.1) | 0.15 |
| Pneumonia | 2.48 (0.93 – 6.61) | 0.06 |
| Bacterial enterocolitis | 1.17 (0.36 – 3.75) | 0.78 |
| SBP | 3.84 (1.64 – 8.97) | 0.0018 |

nosocomial infections. Although the established cut-of levels of CRP are slightly higher than upper limit of normal, special attention should be given to these patients, especially to patients with ascites, and this should prompt further bacteriological screening, including ascites cultures.

Also, in our study, in patients with positive pharyngeal swabs were isolated Gram-negative bacteria, such as Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, fungi – Candida glabrata and Candida albicans, but also Acinetobacter baumanii and MRSA. Cut-of values for CRP in these patients are lower than in patients with rectal colonization, (at a level of 4.6 mg/dl) and the association with pneumonia in these patients was higher compared to patients with negative pharyngeal swabs.

Regarding risk factors for high mortality in patients with end-stage liver diseases, candidates for liver transplantation, in univariate analysis we found with statistically significance most of the complications of cirrhosis, such as: refractory ascites ($p<0.0001$), acute kidney injury ($p=0.0007$), variceal bleeding ($p=0.0436$), grade 1 to 3 ACLF ($p<0.0001$), hepatic encephalopathy ($p< 0.0001$) and also active infections ($p<0.0001$), including bacteriemia ($p=0.033$), urinary tract infections ($p=0.038$), pneumonia ($p=0.0019$), bacterial enterocolitis ($p=0.0132$) and SBP ($p=0.0001$). Prognostic scores, such as MELD, MELD Na, MELD 3.0 scores and NLR were found with statistically significance also. In multivariable analysis, active infections and MELD Na score in cirrhotic patients awaiting liver transplantation were identified as independent predictive factors for mortality on the WL ($p=0.029$, respective $p<0.0001$).

Reports in literature also show that height, cardiac valvular disease, history of abdominal surgery, MELD score, intensive care unit treatment, mechanical ventilation, inotropic treatment, dialysis and hepatorenal syndrome, encephalopathy, ascites are incriminated as predictive factors for death on the WL in univariable analysis, most of them identified also in multivariable analysis (20).

Since 2002, with the introduction of MELD score in the liver allocation system, there was a decrease in waiting list mortality (21). MELD Na score, a model that includes international normalized ratio (INR), total serum bilirubin, serum creatinine and serum sodium was more predictive for the risk of death in patients with end-stage liver disease, that associated hyponatremia (22). In Europe and Eurotransplant region, prioritization for non-urgent LT is based on the MELD score (13).

In cirrhotic patients, an adequate empirical antibiotic therapy is an essential measure that should be taken in order to improve prognosis (23-25) and there is no standard protocol for the optimal treatment and the choice of an empirical antibiotic must be guided by the severity and type of infection, local epidemiology and antibiotic safety (14).

## CONCLUSIONS

Infections are the most frequent triggers incriminated in occurrence of ACLF and therefore special attention should be given to prevent further decompensation in cirrhotic patient.

Positive rectal swabs, especially with MDR bacteria seem to have an importance in the prevalence of infections in cirrhotic patients and antibiotic therapy may be guided according to the microorganism isolated, but there is still need for further studies to validate these data.

### *Conflicts of interest and sources of funding*

There are no conflicts of interest and no sources of funding.

### *Ethical statement*

This study was approved by local Ethics Committee.

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