Predictors of the short-term mortality in patients with hepatorenal syndrome

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This research is aimed to determine the most important predictors of the short-term mortality of patients with hepatorenal syndrome using the CLIF-C-ACLF score. The study enrolled 109 patients with alcoholic liver cirrhosis, complicated with hepatorenal syndrome, admitted to the Chernivtsi Region Narcology Dispensary between January 2013 to August 2019. The patients were 29 to 60 years old at the time of inclusion to the study. The average duration of the alcoholic liver cirrhosis (ALC) was 3.5 ± 1.54 years; average history of alcohol abuse – 8.42 ± 3.53 years; gender distribution was: 77.9% (n=85) males and 22.1% (n=24) – females. All patients were prescribed the standard therapy and were distributed into 2 groups depending on the response to treatment: group 1 (n=57) – responders, group 2 (n=52) – non-responders. The number of patients who survived after 1 and 3 months differed significantly in both groups: 40/57 (70.2%) and 33/57 (57.9%), respectively, in the group of responders; and 10/52 (19.2%) and 0/52 (0%), respectively, in the group of non-responders (p <0.001). The estimates of the probability of survival for each of the group members were found using Kaplan Meyer's procedure. Type 1 of hepatorenal syndrome, response to the treatment in the first 24 hours, and the high baseline score by CLIF-C-ACLF scale were identified as the predictors of short-term mortality. Improvement in renal function during treatment was observed in most patients in group 1: a decrease of the level of serum creatinine in patients with a response ranged from 323.2 ± 91.1 to 121.6 ± 30.0 mmol/l. The results of the study indicate that type 1 of hepatorenal syndrome, no response to treatment in the first 24 hours, and high CLIF-C-ACLF score are the most important predictors of survival in patients with hepatorenal syndrome. Monitoring of these indicators allows to identify the group of patients with the worst prognosis and to put them in priority to the liver transplantation list.

Предиктори короткострокової смертності у хворих на гепаторенальний синдром

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Це дослідження спрямоване на визначення найважливіших предикторів короткострокової смертності пацієнтів із гепаторенальним синдромом за допомогою шкали CLIF-C-ACLF. У дослідженні взяли участь 109 пацієнтів із алкогольним цирозом печінки, ускладненим гепаторенальним синдромом, госпіталізованих до Чернівецького обласного наркологічного диспансеру із січня 2013 року по серпень 2019 року. На момент включення у дослідження пацієнтам було від 29 до 60 років. Середня тривалість алкогольного цирозу печінки (АЦП) становила 3,5±1,54 року; середній анамнез зловживання алкоголем – 8,42±3,53 року; розподіл за статтю становив: 77,9% (n=85) чоловіків та 22,1% (n=24) – жінок. Усі пацієнти отримували стандартну терапію та були розподілені на 2 групи залежно від реакції на лікування: група 1 (n = 57) – респондери, група 2 (n = 52) – нон-респондери. Кількість пацієнтів, які вижили через 1 та 3 місяці, суттєво різнилася в обох групах: 40/57 (70,2%) та 33/57 (57,9%) відповідно у групі респондерів; та 10/52 (19,2%) та 0/52 (0%) відповідно у групі нон-респондерів (p <0,001). Оцінки ймовірності виживання для кожного з членів групи були знайдені за допомогою тесту Каплана-Мейєра. Тип 1 гепаторенального синдрому, відсутність відповіді на лікування протягом перших 24 годин та високий базовий бал за шкалою CLIF-C-ACLF були визначені як предиктори короткострокової смертності. Поліпшення функції нирок під час лікування спостерігалось у більшості пацієнтів групи 1: зниження рівня креатиніну в сироватці крові у респондерів становило від 323,2±91,1 до 121,6±30,0 ммоль/л. Результати дослідження вказують на те, що тип 1 гепаторенального синдрому, відсутність відповіді на лікування протягом перших 24 годин та високий бал CLIF-C-ACLF є найважливішими предикторами виживання у пацієнтів із гепаторенальним синдромом. Моніторинг цих показників дозволяє визначити групу пацієнтів з найгіршим прогнозом та поставити їх на перше місце у списку для трансплантації печінки.

Introduction

Hepatorenal syndrome (HRS) is a potentially reversible form of renal failure that occurs in patients with liver cirrhosis. The average life expectancy in untreated patients with HRS is about 2 weeks and saving their lives is challenging[1–3]. There are many instruments for assessing the severity of HRS in patients with cirrhosis, like hepatic failure scores (i.e. Child-Pugh and MELD)[4], renal failure scores (i.e. RIFLE and AKI)[5] but their accuracy depends on the clinical situation (acute or chronic course of the disease, presence or absence of complications, etc.) and on the goal set (estimation of risk of the disease aggravation, stratification of the current condition severity or prediction of the outcome)[6].

Recently, the concept of acute-on-chronic liver failure (ACLF)[7], which involves a sharp deterioration of the liver function in patients with cirrhosis, is becoming more and more recognized, i.e. development of the fulminant liver failure caused by secondary or extrahepatic causative factors – precipitating factors, such as infections and HRS in particular. In regards to this approach, the new score was developed to estimate the risk of short-term mortality (within the first 28 days after admission to the hospital) in patients with sudden deterioration of the chronic liver disease – CLIF-C-ACLF score (Chronic Liver Failure Consortium of Acute-on-Chronic Liver Failure)[8–14].

However, these scales are complex to use as they contain many indicators to predict the short-term mortality in patients who were treated for HRS. The aim of this study was to determine the most important predictors of the short-term mortality of patients with HRS using the CLIF-C-ACLF score.

Material and methods

The research enrolled 109 patients of Chernivtsi Region Narcology Dispensary admitted between January 2013 to August 2019.

Inclusion criteria: patients with alcoholic liver cirrhosis complicated with the hepatorenal syndrome within the age range between 20 and 65 years old, fulfilling the definition of CLIF-C-ACLF (the organ/system failure criteria were: liver – bilirubin, kidney – creatinine, brain – liver encephalopathy, coagulation – international normalized ratio (INR), blood circulation – use of vasopressors, lungs – SpO_2/FiO_2)[7].

Exclusion criteria: chronic kidney disease, terminal conditions, age less than 29 and more than 60 years old, viral etiology of cirrhosis (all patients were tested anti-HCV and HBsAg by ELISA method when admitted to the hospital), surgical interventions and gastrointestinal bleeding during the last 8 weeks, acute alcoholic intoxication, acute portal vein thrombosis, obstructive jaundice, decompensation of concomitant pathology.

Bioethical considerations: the study was approved by the ethics committee of the Bukovinian State Medical University, Chernivtsi, Ukraine (Ethics Committee No. 2019/12, August 22, 2019) in compliance with the recommendations of Declaration of Helsinki, 1964, amended by the World Medical Association, 2001[15].

HRS was diagnosed based on criteria of the Clinical Guidelines on Liver Cirrhosis and Its Complications of Ministry of Health of Ukraine, No. 751 dated September 28, 2012 and EASL (European association for the study of the liver) Clinical Practice Guidelines for the management of patients with decompensated cirrhosis, 2018[16].

According to both guidelines, all enrolled patients with ALC and HRS were prescribed 20% albumin intravenously (i/v) at the same dosage (1 g/kg per day on the first day of treatment and 20–40 g/day – in the next six days) and terlipressin (0,1mg/ml) in standard dosage by continuous intravenous administration for 7 days.

All patients with HRS were distributed into 2 groups depending on the response to treatment: group 1 (n=57) – responders (decrease of sCr to ≤133 mmol/l), group 2 (n=52) – non-responders (decrease of sCr less than 50% of baseline). In both groups, the treatment was evaluated every 48 hours and performed until the sCr level decreased to 133 mmol/l (or for a maximum of 14 days) and continued for another 24 hours after the response to treatment. The response to treatment was taken as the primary endpoint of the study and was used to calculate the sample size.

Statistical processing of the study results was carried out using the program package RStudio1.1.463. Patients survival was assessed by the Kaplan-Meier method[17] and was compared in both groups using a logarithmic test. Variables that were detected as predictors of response to treatment and survival with a value of p <0.1 in one-dimensional analysis, were included in the multivariate logistic regression model; where the results were presented as odds with a 95% confidence interval. All tests were two-tailed. The value of p<0.05 was considered statistically significant with an error of α 5% and β error of 20%.

Results

The patients were 29 to 60 years old at the time of inclusion to the study. The average duration of the alcoholic liver cirrhosis (ALC) was 3.5±1.54 years; average history of alcohol abuse – 8.42±3.53 years; gender distribution was: 77.9% (n=85) males and 22.1% (n=24) – females (Table 1).

HRS in both groups was mostly represented with the type 1: group 1 – 89.5%; group 2 – 90.4% (p>0.05) and had the initial scoring by CLIF-C-ACLF scale (Table 2).

The number of patients who survived after 1 and 3 months differed significantly in both groups: 40/57 (70.2%) and 33/57 (57.9%), respectively, in the group of responders; and 10/52 (19.2%) and 0/52 (0%),

Table 1 – Demographic and clinical characteristic of patients with hepatorenal syndrome enrolled in the study

Characteristic	Group 1, responders (n=57)	Group 2, non-responders (n=52)
Gender		
Male, (n, %)	44 (77.2%)	41 (78.8%)
Female, (n, %)	13 (22.8%)	11 (21.2%)
Both gender age groups, years		
29–40, (n, %)	9 (15.8%)	7 (13.5%)
40–50, (n, %)	32 (56.1%)	31 (59.6%)
50–60, (n, %)	16 (28.1%)	14 (26.9%)
Clinical characteristics		
History of alcohol abuse, years	8.31±3.48	8.43±3.59
History of ALC, years	3.6±1.55	3.4±1.53

respectively, in the group of non-responders (p <0.001).

The estimates of the probability of survival for each of the group members were found using Kaplan Meyer's procedure (Fig. 1).

Next, we determined the magnitudes of risks for each of the groups, which were characterized by the risk function. The risk function λ was defined as the speed of the event at time *t* under the condition of survival before time *t* or later:

$$\lambda(t) = \lim_{dt \to 0} \frac{\Pr(t \le T < t + dt)}{dt \cdot S(t)} = \frac{f(t)}{S(t)} = -\frac{S'(t)}{S(t)}.$$

Here $f(t) = F'(t) = (1 - S(t))'$ is a lifetime density function.

That is, for the group 1 the average risk of death was 0.153 ± 0.026, and it was 0.958 ± 0.034 for the group 2. Risk in the group 2 increased in 6.26 times compared to the group 1.

For the multivariate analysis were chosen those clinical and laboratory parameters which have revealed the significant correlation with the short-term mortality: age, gender, response to treatment in the first 24 hours, type of HRS and CLIF-C-ACLF score. The analysis did not reveal age and gender to be the predictors of short-term mortality. Type 1 of HRS, no response to the treatment in the first 24 hours and the high baseline score by CLIF-C-ACLF scale were identified as the predictors of the short-term mortality (Table 3).

Improvement in renal function during treatment was observed in most patients in the group 1: a decrease of the level of serum creatinine in patients with a response ranged from 323.2±91.1 to 121.6±30.0
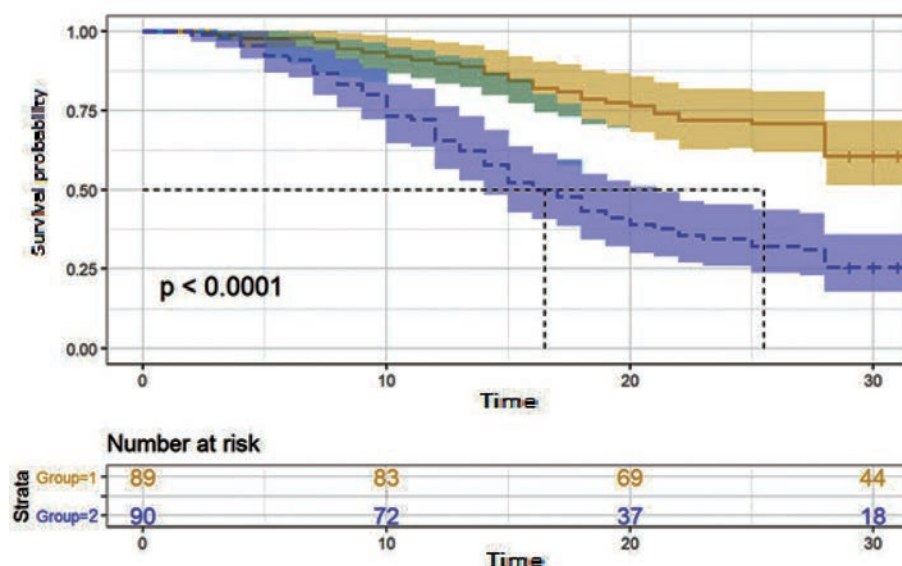
Fig. 1. Graph of the survival function of patients with HRS depending on the type of response to treatment in the first 24 hours

Table 2 – Stratification of the enrolled patients by the type of hepatorenal syndrome and the severity by CLIF-C-ACLF score

CLIF-C-ACLF score	Group 1, responders (n=57)		Group 2, non-responders (n=52)	
	HRS type 1	HRS type 2	HRS type 1	HRS type 2
I – n, (%)	15 (26.3%)		19 (36.5%)	
	12 (21.1%)	3 (5.2%)	16 (30.8%)	3 (5.7%)
II – n, (%)	25 (43.9%)		23 (44.2%)	
	22 (38.6%)	3 (5.3%)	21 (40.4%)	2 (3.8%)
III – n, (%)	12 (21.1%)		8 (15.4%)	
	12 (21.1%)	0	12 (21.1%)	0
IV – n, (%)	6 (10.5%)		2 (3.8%)	
	12 (21.1%)	0	12 (21.1%)	0

Note: there was no statistical significance for all data between groups 1 and 2 (p>0.05)

Table 3 – Predictors of the short-term mortality for patients with the hepatorenal syndrome

Variable	Risk ratio	95% CI	p value
Age, years	0.96	0.24–0.98	p>0.05
Gender, male/female	0.54	0.16–0.87	p>0.05
Response to treatment in the first 24 hours (sCr decreased to ≤133 mmol/l)	23.92	3.21–15.75	p<0.002
Type of HRS, 1 or 2	9.8	1.1–1.2	p<0.01
CLIF-C-ACLF score (I, II, III, IV)	1.18	1.4–1.42	p<0,02

mmol/l. There were no significant differences between the two groups in terms of the treatment duration (8.2±4.4 days in the group 1 versus 9.1±5.0 days in the group 2; p>0.05).

Discussion

Type 2 HRS is considered to be more favourable for survival prognosis, as it develops slowly and gives more time for adequate treatment measures[18]. However, some studies have shown no differences between responders and non-responders to albumin+terlipressin treatment in the mortality rate of type 2 HRS patients[19]. Besides, the authors did not report any significant differences regarding the development of acute kidney injury, need for renal replacement therapy, frequency of chronic kidney disease 1 year after transplant, length of hospitalization, and survival. We could not address these issues in the present study due to the very low incidence of type 2 HRS. The small number of type 2 HRS patients in this study (10.5% of group 1 and 9.5% of group 2) is in keeping with data from the previous reports. Further investigations are needed to obtain the precise data. This may take a long time, as type 2 HRS is much rarer than type 1 HRS[20].

One of the most powerful predictors of mortality in the present study was the lack of patients' response to treatment, which goes in a line with the literature data[21]. By contrast, patients' age was not proved as the mortality predictor for both types of HRS in our research, while in the investigations of type 1 HRS only it was associated with no reversibility and poor prognosis of the disease[21].

Another concern is probably different pathogenetic mechanisms of types 1 and 2 HRS. As type 1 HRS develops rapidly and suddenly, it is mostly associated with ACLF, while type 2 HRS develops slowly and corresponds to chronic liver disease. Due to this fact, different scoring systems could be considered for the risk assessment of short-term mortality according to the type of HRS. Obviously, CLIF-C-ACLF might be more accurate for the type 1 HRS patients, while MELD score – for type 2 HRS patients. D. Perdigoto[22] attempted to compare the accuracy of CLIF-C-ACLF and MELD scores for liver cirrhosis, but the type of HRS was not considered in his study, so further endeavours are needed to answer this question.

Terlipressin, used in our study is a rather expensive medication and is not affordable sometimes. Dopamine is a commonly used substitute for terlipressin, but it has shown fewer efficacies in some studies[23], so another research is required to compare the impact of both drugs on the short-term survival of patients with HRS.

Conclusions

The results of the study indicate that the type 1 of hepatorenal syndrome, no response to treatment in the first 24 hours and high CLIF-C-ACLF score are the most important predictors of survival in patients with hepatorenal syndrome. Patients' age and gender were not revealed as predictors of short-term mortality. Monitoring of these indicators allows to identify the group of patients with the worst prognosis and to put them in priority to the liver transplantation list.

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