Risk factors and outcome in ICU patients with end-stage liver disease

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Background/aim
Acute or chronic liver failure is associated with numerous complications that may occur in combination, and patients may require ICU treatment. Therefore, it seems necessary to identify prognostic clinical parameters and risk factors at the time of ICU admission. The present study aims to estimate the frequency of mortality and evaluate morbidity from cirrhosis in patients with end-stage liver disease (ESLD) admitted to the ICU and evaluate the relationship between the demographic, clinical, and laboratory data (potential risk factors) of those patients and mortality.

Patients and methods
A total of 120 patients with ESLD were enrolled [102 (85%) male and 18 (15%) female patients]. History taking, clinical examination, and other laboratory investigations were carried out, and patients were classified according to the Child–Turcotte–Pugh (CTP) and the model for end-stage liver disease (MELD) scores.

Results
Regarding the clinical presentation, hepatic encephalopathy (HE) was found in 87.5% of patients, jaundice in 60%, hematemesis in 41.7%, hepatorenal syndrome (HRS) in 35.8%, and spontaneous bacterial peritonitis in 20.8% of patients. The mortality rate was 57.5%; the main causes of death were HRS (40.8%), HE (21.7%), aspiration pneumonia (10%), septic shock (2.5%), and irreversible shock (1.7%). There was a significant relationship between mortality and old age, CTP and MELD scores, and a longer stay at the ICU. Increased white blood cell count, increased hemoglobin and decreased prothrombin concentration, and elevated creatinine were independent risk factors of mortality in ESLD patients in the ICU. Mortality rates were higher in patients with 5–6 risk factors (86.2%) than in those with 1–2 risk factors (21.7%).

Conclusion
Mortality rate in ESLD patients admitted to the ICU was 57.5% and the most common cause of death was HRS. CTP, MELD score, HE, HRS, and jaundice were significant predictors of mortality in ESLD patients. Mortality increased with increased number of risk factors. Creatinine level, white blood cell count, hemoglobin, and prothrombin concentration were independent risk factors of mortality in ESLD patients.

Keywords:
end-stage liver disease, ICU, outcomes, prognosis, risk factors

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Introduction

Cirrhotic patients are susceptible to a variety of complications and their life expectancy is markedly reduced [1]. Acute or chronic liver failure is associated with numerous complications and patients may require ICU treatment. The most important reasons for ICU admission are hemorrhage, infections, hepatic encephalopathy (HE), and complications that include hepatorenal syndrome (HRS), hepatopulmonary syndrome, malnutrition, ascites, cachexia, hepatocellular carcinoma (HCC), and hepatic failure [2,3].

Despite the use of sophisticated diagnostic and therapeutic approaches, including expensive microbiological evaluations, many patients do not survive. Therefore, identification of clinical parameters that allow risk stratification at the time of ICU admission is required [4–6]. In a recent large systematic review, the Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD) scores were found to be predictive of death [7]. The most consistent and 'robust' predictor of death in cirrhosis is the CTP score, followed by all its components [albumin, bilirubin, ascites, encephalopathy, and prothrombin time (PT). However, it does not help predict mortality or resource utilization in cirrhotic patients who have multiorgan failure [8–10].

The MELD score showed high discrimination among the patients, almost the same as Sequential Organ Failure Assessment and superior to Acute Physiology and Chronic Health Evaluation II [11,12]. Moreover, it was shown to predict 3-month mortality more accurately than the traditional CTP system for patients within the United Network of Organ Sharing [10,13–15]. More importantly, its components continue to be used as predictors

of survival in patients with end-stage liver disease (ESLD) [16–19]. It has also been shown to be a good prognostic marker in patients with variceal bleeding, spontaneous bacterial peritonitis (SBP), and HRS [20–23]. However, MELD score did not show any correlation with clinical or subclinical HE and underestimates the risk of death in patients with ESLD and intractable HE or in patients with acute disease in addition to chronic liver disease who developed HE [24–26].

Cirrhotic patients admitted to the ICU have high hospital mortality, which increases further if patients require mechanical ventilation or renal replacement therapy [27,28]. Another study showed that cirrhotic patients admitted to the ICU with at least three failing organ systems have 90% mortality, which is higher than that of general ICU patients in the same condition [11]. The problem is likely to worsen if adequate facilities are either nonexistent or are beyond the financial reach of patients [29]. Therefore, predicting the prognosis is a crucial issue while allocating patients to liver transplantation, the only definite treatment for ESLD patients.

The aims of the present study were to estimate the frequency of mortality and evaluate the morbidity from cirrhosis among patients with ESLD admitted to the ICU and to evaluate the relation between demographic, clinical, and laboratory data (potential risk factors) of those patients and mortality.

Patients and methods

Patients

A total of 120 patients (102 male and 18 female patients) with ESLD secondary to various etiologies, mostly due to HCV infection, were enrolled in this study. All were consecutively admitted to the ICU at the Tropical Medicine and Gastroenterology Department, Assiut University Hospital, from 1 May to 31 August 2013. Full history taking, thorough clinical examination, and other laboratory investigations were performed and patients were closely monitored and followed up.

Inclusion criteria

Patients were admitted to the ICU if they had chronic liver cell failure, upper or lower gastrointestinal bleeding, HE, HRS, or infection at any site. Diagnosis of liver cirrhosis was based on full history taking, complete clinical examination, laboratory investigations, abdominal ultrasonography, and upper endoscopy, if present.

Exclusion criteria

Patients with cardiac cirrhosis, primary renal disease, or primary pulmonary disease were excluded from the study.

Methods

All patients were subjected to full clinical evaluation including full clinical history taking with special stress on the precipitating factors of gastrointestinal (GIT) bleeding, HE, or HRS, if present. Examination was performed to detect signs of liver cell failure (e.g. jaundice, HE and its grade, ascites, etc.), signs of infection (e.g. SBP, chest infection, or sepsis at any site), signs of GIT bleeding, or HRS with careful attention paid to detecting HCC. Laboratory and imaging investigations included:

(1) Complete blood picture.
(2) Liver function tests [total and direct bilirubin, total proteins and serum albumin, serum transaminases, γ-glutamyl transferase and alkaline phosphatase, PT, prothrombin concentration (PC), and international normalized ratio (INR)].
(3) Renal function tests (blood urea and serum creatinine).
(4) Serum sodium and potassium.
(5) Blood sugar.
(6) Urine and stool analysis.
(7) Ascitic fluid study for cells and proteins (polymorphonuclear leukocytes>250/mm [3] to diagnose SBP), including serum albumin ascetic fluid albumin gradient.
(8) Other investigations specific for some patients according to the clinical situation – e.g. blood culture, urine culture, sputum culture, ascetic or pleural fluid culture, and culture from any site of infection, as well as specific bacteriological and pathological examinations.
(9) Abdominal ultrasonography and abdominal computer tomography (CT) (when needed).
(10) Upper and lower GIT endoscopy.

Patients were assessed according to CTP class and MELD [12] score to grade the severity of hepatic dysfunction.

MELD score = 3.8[Ln serum bilirubin (mg/dl)] + 112[Ln INR] + 9.6[Ln serum creatinine (mg/dl)] + 6.4 (constant for liver disease etiology).

Patients were followed up daily by means of physical examination, their vital signs were monitored, and laboratory investigations were carried out according to the clinical situation. Treatment of complications as GIT bleeding with sclerotherapy or band ligation, HE, coma, ascites, SBP, and infection (with proper

antibiotics according to culture results and clinical response).

Ethical consideration

A written informed consent was obtained from each patient according to the Faculty of Medicine, Assiut University ethical committee requirements.

Statistical analysis

Data entry and data analysis were carried out using SPSS program (version 16; SPSS Inc., Chicago, Illinois, USA). Data were presented as numbers, percentages, means, and SDs. The χ^2-test was used to compare qualitative data between groups. The Mann–Whitney *U*-test was used to compare means of continuous variables between groups. Multivariate logistic regression analysis was performed to evaluate independent risk factors of mortality. *P* value less than 0.05 was considered statistically significant.

Results

The mean age of patients with ESLD was 56.23 ± 11.21 years; most of them were above 50 years (81.7%). Of the patients 102 (85%) were male and 18 (15%) were female. Basic demographic and clinical data are shown in Table 1. Twenty-five (20.85%) patients had HCC and 35 (29.2%) had diabetes mellitus. The mean CTP score was 11.25 ± 0.34 and MELD score was 24.57 ± 0.7. The baseline laboratory data of ESLD patients in the ICU are given in Table 2.

Outcome of end-stage liver disease patients

In the ICU, 69 (57.5%) ESLD patients died, whereas the condition of 51 (42.5%) patients improved. The cause of death in ESLD patients is shown in Figure 1.

Predictive risk factors for mortality in end-stage liver disease patients in the intensive care unit

The predictive demographic, clinical, and laboratory risk factors for mortality in ESLD in the ICU are shown in Tables 3–5, respectively. A significantly higher mortality was noticed among patients above 50 years (*P* = 0.006). The mean CTP and MELD scores were significantly higher in ESLD patients who died in the ICU (*P* = 0.001 and 0.000, respectively). The mean hospital stay time was significantly higher in ESLD patients who died in the ICU (*P* = 0.000).

HE, HRS, and jaundice were significantly more common among ESLD patients who died in the ICU (*P* = 0.010, 0.001, and 0.035, respectively). Among the 25 patients with HCC, 17 (68%) died.

Table 1 Baseline demographic/clinical data in end-stage liver disease patients in the intensive care unit

Variables	*N* (%) (*n* = 120)
Age (years)	
<50	22 (18.3)
≥50	98 (81.7)
Sex	
Male	102 (85.0)
Female	18 (15.0)
Clinical presentation	
Hepatic encephalopathy	105 (87.5)
Jaundice	72 (60.0)
Hematemesis	50 (41.7)
HRS	43 (35.8)
SBP	25 (20.8)
Chest infection	10 (8.3)
Sepsis	9 (7.5)
Shock	8 (6.7)
Child–Pugh classification	
Child class A	4 (3.3)
Child class B	12 (10.0)
Child class C	104 (86.7)

HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

Table 2 Baseline laboratory data in end-stage liver disease patients in the intensive care unit

Variables	Mean ± SE
CBC	
WBC (×10³/Ul)	12.1 ± 0.60
Hb (g/dl)	9.4 ± 0.19
PLT (×10³/Ul)	110.9 ± 4.85
Liver functions	
Total bilirubin (mg/dl)	7.5 ± 0.68
Direct bilirubin (mg/dl)	4.8 ± 0.46
Albumin (g/dl)	3.7 ± 0.55
AST (IU/l)	143.0 ± 12.97
ALT (IU/l)	92.3 ± 9.28
Alkaline phosphates (IU/l)	160.2 ± 9.74
Prothrombin time (s)	21.3 ± 0.69
Prothrombin concentration (%)	44.8 ± 1.37
INR	1.8 ± 0.06
Electrolytes	
Sodium (mmol/l)	131.5 ± 0.85
Potassium (mmol/l)	4.5 ± 0.08
Urea (mmol/l)	24.8 ± 1.96
Creatinine (mmol/l)	241.9 ± 16.39

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; Hb, hemoglobin; INR, international normalized ratio; PLT, platelet; WBC, white blood cell.

Among the 35 patients with diabetes mellitus, 20 (57.1%) died. The mean values of white blood cell (WBC) count, hemoglobin (Hb), total bilirubin, direct bilirubin, PT, INR, urea, and creatinine were significantly higher in ESLD patients who died in the ICU (*P* = 0.001, 0.042, 0.024, 0.034, 0.001, 0.001, 0.000, and 0.000, respectively). However, the mean PC was significantly lower in those patients (*P* = 0.001).

Table 3 Demographic data and risk of mortality in end-stage liver disease patients in the intensive care unit

Variables	Outcome [*N* (%)]		*P* value
	Died (*n* = 69)	Improved (*n* = 51)	
Age (years)			
Mean ± SD	58.14 ± 10.89	53.65 ± 11.24	0.029*
<50	11 (50)	11 (50)	0.006
≥50	58 (59)	40 (40.8)	
Sex			0.393
Male	57 (55.9)	45 (44.1)	
Female	12 (66.7)	6 (33.3)	
Child classification			0.071
Child class A	1 (25.0)	3 (75.0)	
Child class B	4 (33.3)	8 (66.7)	
Child class C	64 (61.5)	40 (38.5)	
Child score (mean ± SE)	12.68 ± 1.88	11.25 ± 2.41	0.001*
MELD score (mean ± SE)	27.83 ± 2.42	20.16 ± 1.02	0.000*
Hospital stay (mean ± SE)	4.81 ± 0.19	3.73 ± 0.19	0.000*

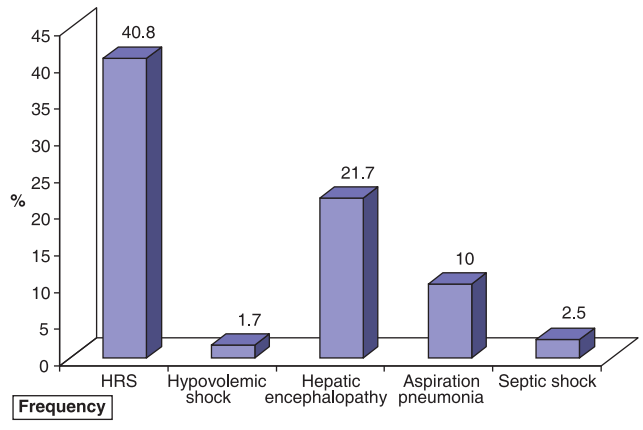
MELD, model for end-stage liver disease; *Statistical significance, χ^2-test is used.

Table 4 Clinical presentations and risk of mortality in end-stage liver disease patients in the intensive care unit

Variables	Outcome [*N* (%)]		*P* value
	Died (*n* = 69)	Improved (*n* = 51)	
Hepatic encephalopathy	65 (61.9)	40 (38.1)	0.010*
Hematemesis	25 (50.0)	25 (50.0)	0.160
HRS	33 (76.7)	10 (23.3)	0.001*
Chest infection	7 (70.0)	3 (30.0)	0.616
SBP	13 (52.0)	12 (48.0)	0.532
Sepsis	3 (33.3)	6 (66.7)	0.240
Hypovolemic shock	5 (62.5)	3 (37.5)	0.767
Jaundice	47 (65.3)	25 (34.7)	0.035*

Note that the same patient may have more than one clinical presentation; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis; *Statistical significance, the χ^2-test is used.

Figure 1



NB: the same patient may have more than one cause of death.

Causes of death in end-stage liver disease patients in the ICU. Note that the same patient may have more than one cause of death. HRS, hepatorenal syndrome.

Multivariate analysis of predictive independent risk factors for mortality in end-stage liver disease in the intensive care unit

There were four significant predictive risk factors for mortality in ESLD in the ICU: WBC count (P = 0.039), Hb (P = 0.026), creatinine (P = 0.014), and PC (P = 0.000) (Table 6).

Relation between risk factors and outcome

Among 69 ESLD patients who died in the ICU, five (21.7%) patients had 1–2 risk factors, 39 (57.4%) had 3–4 risk factors, and 25 (86.2%) had 5–6 risk factors with statistically significant difference (P = 0.000). With regard to improvement, it was the highest in 18 (78.3%) patients with 1–2 risk factors, moderate in 29 (42.6%) with 3–4 risk factors, and the least in four (13.8%) with 5–6 risk factors, with statistical significance (P = 0.000) (Figure 2).

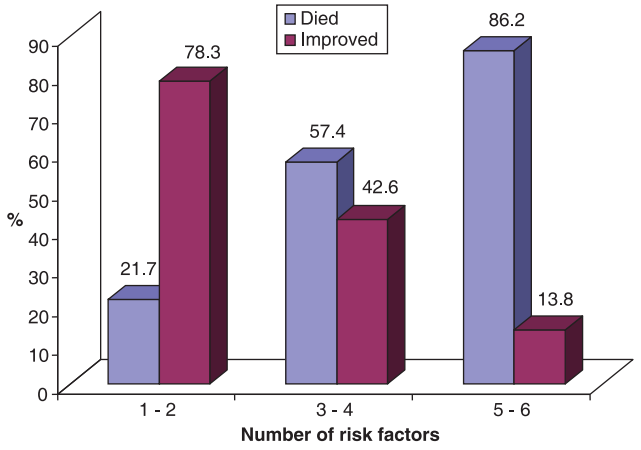
Discussion

The high mortality in ESLD patients is a global public health problem. The course of cirrhosis is extremely variable from patient to patient because of several factors, including hepatic synthetic function, the cause of cirrhosis, and the occurrence of liver malignancy. Therefore, establishing a prognosis in a given patient with cirrhosis remains a challenging issue.

Many prognostic models and scores have been proposed in the last two decades to predict prognosis in patients with ESLD and to determine the most appropriate therapeutic option [30].

A study by Gunnarsdottir *et al.* [30] on patient characteristics with ESLD showed that the mean age was around 60 years, whereas O'Brien *et al.* [31]

Figure 2



Relation between risk factors and outcome.

Table 5 Laboratory test results and risk of mortality in end-stage liver disease patients in the intensive care unit

Variables	Outcome (mean ± SE)		*P* value
	Died (*n* = 69)	Improved (*n* = 51)	
WBC (×10³/Ul)	13.7 ± 0.85	9.94 ± 0.71	0.001*
Hb (g/dl)	9.7 ± 0.27	8.98 ± 0.26	0.042*
PLT (×10³/Ul)	108.2 ± 6.26	114.49 ± 7.69	0.333
Total bilirubin (mg/dl)	8.6 ± 0.96	5.95 ± 0.91	0.024*
Direct bilirubin (mg/dl)	5.5 ± 0.63	3.91 ± 0.65	0.034*
Albumin (g/dl)	3.6 ± 0.71	3.90 ± 0.88	0.236
AST (IU/l)	156.1 ± 16.92	125.23 ± 20.12	0.086
ALT (IU/l)	96.8 ± 12.25	86.15 ± 14.33	0.287
ALP (IU/l)	172.06 ± 14.39	144.25 ± 11.90	0.194
PT (s)	23.00 ± 1.05	18.96 ± 0.69	0.001*
PC (%)	40.87 ± 1.63	50.11 ± 2.15	0.001*
INR	1.97 ± 0.09	1.61 ± 0.06	0.001*
Na^+ (mmol/l)	130.62 ± 1.00	132.75 ± 1.47	0.234
K^+ (mmol/l)	4.53 ± 0.12	4.38 ± 0.12	0.412
Urea (mmol/l)	27.47 ± 1.90	21.12 ± 3.79	0.000*
Creatinine (mmol/l)	300.69 ± 23.94	162.56 ± 15.17	0.000*

Mann–Whitney *U*-test; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Hb, hemoglobin; INR, international normalized ratio; PC, prothrombin concentration; PLT, platelet; PT, prothrombin time; WBC, white blood cell; *Statistically significant.

Table 6 Multivariate logistic regression analysis of risk factors of mortality in end-stage liver disease patients in the intensive care unit

Variables	*P* value	OR	95% CI	
			Lower	Upper
Total bilirubin (mg/dl)	0.902	0.984	0.763	1.269
Direct bilirubin (mg/dl)	0.673	1.076	0.766	1.512
WBC (×10³/Ul)	0.039*	0.922	0.854	0.996
Hb (g/dl)	0.026*	0.757	0.593	0.967
Urea (mmol/l)	0.383	1.011	0.986	1.037
Creatinine (mmol/l)	0.014*	0.993	0.987	0.999
PT (s)	0.065	1.096	0.994	1.208
PC (%)	0.000*	1.092	1.045	1.141
Child score	0.403	0.896	0.693	1.159
MELD	0.875	0.989	0.864	1.133

CI, confidence interval; Hb, hemoglobin; MELD, model for end-stage liver disease; OR, odds ratio; PC, prothrombin concentration; PT, prothrombin time; WBC, white blood cell. *Statistically significant.

reported that the mean age was 52.5 years with male preponderance (60%). In a study by Parkash *et al.* [32], more men with liver disease (60%) were admitted to the ICU compared with women (40%). Similarly, in our ESLD patients the mean age of our patients with ESLD was 56.23+11.21 and the majority were men (85%).

Saliba *et al.* [33] showed that the ICU mortality rate of cirrhotic patients ranged from 34 to 69%. Parkash *et al.* [32] reported that 47% of all patients who were admitted to the ICU with liver disease died. Also in another study, hospital mortality of patients with ESLD admitted to the ICU was high (>55%) [31]. Moreover, Tu *et al.* [34] showed that in cirrhotic patients admitted to ICUs in a tertiary care university hospital in Taiwan the overall hospital mortality was 59.9%. In concordance with the previous studies, the mortality rate in our study was 57.5%.

Studies showed that patients with decompensated cirrhosis had a poor prognosis, particularly when they develop complications related to ESLD, such as HE, SBP, or GIT bleeding with or without diminished renal function [2,35]. The latter is a well-established important predictor of survival in those patients [11,28,36]. Pan *et al.* [37] showed that cirrhotic patients with acute kidney injury admitted to ICUs show extremely high mortality rates. This came in agreement with our study as 35.8% of our ESLD patients admitted to the ICU presented with HRS, which constituted the most common cause of death (40.8%).

Several studies reported that after the development of the first episode of HE alone the survival probability is 42% at 1 year of follow-up and 23% at 3 years [25,26]. In another study, HE comprised the single most common presentation of liver disease, as seen in 47% of patients, of whom 50% died in hospital [32]. Moreover, other studies reported that HE was the most common complication of cirrhosis requiring admission to the ICU (33%) where it also was the most common cause of death (50%) [38,39]. Similarly, in our study, HE was the most common complication of cirrhosis requiring admission to the ICU (87.5%) where it was the second most common cause of death (21.7%).

Gunnarsdottir *et al.* [30] stated that in Sweden causes of death among ESLD patients were liver failure in 26% of cases and variceal bleeding in 19%; the remaining patients died due to other causes. It was also reported that the major cause of ICU admission was upper GIT bleeding (36%) [34]. In concordance, our study showed that 41.7% of ESLD patients admitted to the ICU had upper GIT bleeding. However, only 1.7% died with intractable shock. This may differ from the results of Gunnarsdottir *et al.* [30] and could be attributed to different settings as our patients received treatment in an ICU in a tertiary center with advanced facilities.

There is often more than one decompensating event for a patient with chronic liver disease (CLD) and these events also differ somewhat in their impact on mortality. A study showed that 13% of all patients admitted to the ICU with liver disease had more than one complicating event, with 86% mortality [32]. This came in agreement with our study as we found a highly significant statistical correlation between the number of risk factors and mortality. Mortality was least (21.7%) with 1–2 risk

factors and reached 86.2% with 5–6 risk factors. In contrast, improvement was highest (78.3%) with 1–2 risk factors and the least (13.8%) with 5–6 risk factors.

O'Brien *et al*. [31] reported that mortality in cirrhotic patients with severe sepsis requiring organ support was 65–90%, compared with 33–39% in those without. In contrast, our study showed that 33.3% of ESLD patients admitted to the ICU died from sepsis. This difference may be due to difference in patient selection (cirrhotic vs. ESLD) between the two studies.

A systematic review found that the Child–Pugh score has been the reference for assessing the prognosis of cirrhosis in several studies and is still considered the most significant predictor of death, indicating that even subtle abnormalities in its laboratory components, bilirubin, albumin, and PT are predictive of death [7,8,40]. This was also true in our study wherein bilirubin, PT, PC, and INR were statistically higher in ESLD patients who died in the ICU (P = 0.024, 0.001, 0.001, and 0.000, respectively).

It was reported that the INR, serum creatinine, and bilirubin values were significantly higher in ESLD patients who died (P < 0.001) [41]. Similarly in our study, INR, serum creatinine, and bilirubin (MELD components) were statistically significantly higher in ESLD patients who died in the ICU (P = 0.001, 0.001, 0.001, 0.000, and 0.024, respectively).

In a large systematic review, the CTP and MELD scores were found to be predictive of death. Therefore, whether CTP score should be definitely abandoned for the MELD score remains uncertain [8,9,42]. The CTP and MELD scores, as well as ascites and HE, significantly differed between patients who survived and those who died (P < 0.001) [41]. The findings in the previous studies matched ours as we found CTP and MELD scores as well as HE, HRS, and jaundice to be significantly different between ESLD patients who improved and those who died in the ICU (P = 0.001, 0.000, 0.010, 0.001, and 0.035, respectively).

Independent risk factors for in-hospital mortality were age, hypoalbuminemia, INR, and the modified Sequential Organ Failure Assessment score [43]. Heuman *et al*. [44] stated that in multivariate analysis the MELD score, persistent ascites, and low Na (<130 mmol/l) were the only factors independently associated with 6-month mortality. Other studies showed that HE, MELD, and CTP scores were the only factors associated independently with short-term and long-term mortality in cirrhotic patients [25,26]. In our study we showed that there are four independent risk factors affecting the outcome of ESLD patients in the ICU; they were creatinine, WBC count, Hb, and PC.

In conclusion, the mortality rate of ESLD patients admitted to the ICU was 57.5% and the most common cause of death was HRS. Higher rate among ESLD patients in the ICU was associated with high mean value of CTP and MELD scores as well as the presence of HE, HRS, and jaundice. Mortality increased with increase in the number of risk factors. Creatinine level, WBC count, Hb level, and PC were independent risk factors affecting mortality among ESLD patients in the ICU. We recommend that early referral of ESLD patients and identification of clinical parameters and risk factors at the time of ICU admission will improve the outcome.

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Conflicts of interest

There are no conflicts of interest.

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