An evaluation of the usefulness of extracorporeal liver support techniques in patients with severe liver dysfunction

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Abstract

Introduction: The mortality rate in patients with severe liver dysfunction with no option of transplantation is unacceptably high. The main aim of this study was to evaluate the usefulness of applying extracorporeal liver support (ECLS) techniques in this group of patients.

Material and methods: Data from hospital admissions of 101 patients with severe liver dysfunction who were admitted to the department of Anaesthesiology and intensive therapy between 2006 and 2015 were retrospectively analysed. The study group was divided into two subgroups. Standard Medical therapy (SMT) was a subgroup of patients receiving standard Medical therapy, and SMT + ECLS was a subgroup containing patients receiving standard medical therapy complemented by at least one extracorporeal liver support procedure.

Results: Significantly lower intensive care unit (ICU) mortality and 30-day mortality rates were found in the SMT + ECLS subgroup (p = 0.0138 and p = 0.0238 respectively). No difference in 3-month mortality was identified between the two groups. In a multivariate model, independent risk factors for ICU mortality proved to be the SOFA score and prothrombin time. The highest discriminatory power for ICU mortality was demonstrated for the SOFA score, followed by APACHE II, SAPS II, MELD UNOS and GCS scores. For 30-day mortality, however, the best discriminatory power was shown for the SAPS II score, followed by SOFA, APACHE II, MELD UNOS and GCS scores.

Conclusions: Further studies are needed to assess the contribution of non-biological extracorporeal liver support procedures to a decrease in mortality rates in the population of patients with severe liver dysfunction.

Key words: fractionated plasma separation and adsorption, single pass albumin dialysis, sequential organ failure assessment.

Introduction

Patients with severe liver dysfunction (MELD UNOS Modification score of 18 or higher) represent an important clinical problem. If standard medical therapy (SMT) is ineffective and the option of liver transplant is not

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available (due to ineligibility for various causes), the mortality rate in this group of patients is unacceptably high [1–3]. In this context, some hope can be placed in non-biological extracorporeal liver support techniques in this group of patients. Extracorporeal liver support (ECLS) can be provided using the fractionated plasma separation and adsorption (FPSA) technique with the Prometheus system, the Molecular Adsorbent Recirculating System (MARS) or single pass albumin dialysis (SPAD) [4–12].

The use of non-biological extracorporeal liver support techniques in patients with severe liver dysfunction is not, strictly speaking, a therapeutic method. However, it is an approach which helps to gain time necessary for the regeneration of the damaged organ, whenever potentially achievable.

There are only limited data available on the benefits of using extracorporeal liver support techniques in patients with severe liver dysfunction [12–14]. One of the main reasons for the scarcity of data seems to be the limited number of studied patients. Another notable fact is that there are no standards applicable to the use of these techniques [7, 11–21].

The main aim of this study was to evaluate the usefulness of applying extracorporeal liver support techniques in this group of patients. The secondary aims were to identify the independent risk factors and to assess the predictive values of the following scoring systems: Glasgow Coma Scale (GCS), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation II (APACHE II), Simplified Acute Physiology Score II (SAPS II) and Model of End-stage Liver Disease (MELD) United Network for Organ Sharing (UNOS) Modification in patients with severe liver dysfunction.

Material and methods

Study population and data collection

We retrospectively analysed the data of 101 patients with severe liver dysfunction (70 men and 31 women) aged between 24 and 83 years who were admitted to the Department of Anaesthesiology and Intensive Therapy (A&IT) at the Dr Wł. Biegański Regional Specialist Hospital in Lodz between 2006 and 2015. Severe liver dysfunction was defined as a MELD UNOS Modification score of 18 or higher. Where a MELD UNOS score was not included in the medical files, it was determined using an online calculator based on relevant data found in the medical documentation.

The patients were divided into two groups depending on the therapeutic management they received. The SMT subgroup comprised patients who were given standard medical therapy (patients treated in the period 2006–2012). The SMT + ECLS subgroup included patients who received standard medical therapy complemented by at least one extracorporeal liver support procedure (patients treated in the period 2013–2015). Extracorporeal liver support techniques used included FPSA administered with a PROMETHEUS unit or SPAD using MULTIFILTRATE devices.

The medical records of the patients were examined, focusing in particular on the patients' age; sex; reason for A&IT Department admission; primary and concomitant diseases; GCS and MELD UNOS Modification and DF scores upon admission to the A&IT Department; SOFA, APACHE II and SAPS II scores on the first day of hospitalization in the A&IT Department; the duration of stay in the A&IT Department (in days); and the total duration of hospitalization. The following parameters were also considered: total bilirubin levels, direct bilirubin levels, bile acid levels, ammonia levels, creatinine levels, prothrombin time, prothrombin ratio (INR) and albumin levels prior to the first liver dialysis, as well as the direct bilirubin levels, total bilirubin levels, bile acid levels, ammonia levels and INR after performing the final albumin dialysis.

Extracorporeal liver support techniques administered

FPSA treatment

The FPSA eliminates water-soluble and protein-bound toxins and metabolic breakdown products. In the FPSA circuit, venous blood passes through a separator with a pore size of 250 kDa (AlbuFlow, Fresenius AG, Bad Homburg, Germany). The separated plasma then passes through a neutral resin absorbent column (Prometh01, Fresenius AG, Bad Homburg, Germany) and an anion exchange resin absorber (Prometh02, Fresenius AG, Bad Homburg, Germany) to remove albumin-bound toxins. The plasma phase is then returned to the filter and dialyzed as whole blood in a high flow dialyzer (F60S, Fresenius) to remove water-soluble toxins [22]. After a preliminary phase involving a gradual increase in the blood and plasma flow rates in the secondary circuit, which required approximately 12 min, the treatment was performed with a blood flow of 180 ml/min and a plasma flow of 270–360 ml/min. In 1 case, the plasma flow rate in the secondary circuit was increased to 450 ml/min during the final hours of the procedure to increase the efficacy of FPSA. Sodium citrate was used as an anticoagulant. The typical duration of an individual procedure was between 6 and 10 h. Some individual procedures were completed in less than 6 h be-

cause of technical problems (which were likely caused by coagulation on the albumin filter).

Single pass albumin dialysis

Liver dialysis was performed using the SPAD technique with the aid of standard equipment for continuous venovenous haemodialysis. The patients' blood was dialysed against a standard dialysis solution containing 2% or 4% albumin, through a high-flux hollow-fibre haemodiafilter. The treatment was performed with a blood flow rate of 100–200 ml/min and a dialysate flow rate of 1,000 ml/min. The dialysate, which was enriched with albumin following a single contact with the patient's blood in the haemofilter, was drained into the waste bag and disposed of. The procedure used 10,000 ml of dialysate containing 2% albumin or 5,000 ml of dialysate containing 4% albumin. Sodium citrate was used as an anticoagulant. Depending on the albumin concentration in the dialysate, the duration of a single procedure was between 5 and 10 h.

Statistical analysis

All the calculations were performed using Statistica (StatSoft, Inc. (2009), Statistica (data analysis software system), version 10, Tulsa, USA) and SPSS (IBM SPSS Statistics, version 21, USA) software.

Quantitative variables were expressed as mean ± SD (standard deviation). Minimum, maximum, median and interquartile range (IQR: Q25–Q75) were also presented. For categorical variables the number of observations (*N*) and corresponding percentages (%) were calculated.

Normality was tested using the Shapiro-Wilk test for normality.

Differences between two independent samples for continuous data were analysed with the Mann-Whitney *U* test (if the distributions of variables were different from normal) or Student's *t*-test (for normal distributions). For categorical variables, the statistical analysis was based either on the χ^2 test or the χ^2 test with Yates' adjustment.

Wilcoxon signed rank test or Student's *t*-test for two dependent samples was applied to compare patients' characteristics on admission and discharge from the hospital. Two-way ANOVA with repeated measures was used if more factors were taken into consideration.

For quantitative variables significantly associated with mortality, ROC curves were drawn and decision thresholds were determined (based on Youden's index). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated. The area under the ROC curve (AUC) with SE (standard error), 95% CI and corresponding *p*-value were also presented.

A multivariate forward stepwise logistic regression model was used to identify the set of independent risk factors for mortality.

The results were considered significant for *p* < 0.05.

Ethics statement

The study was approved by the Bioethics Committee of the Medical University of Lodz (RNN/297/15/KE). Because of the retrospective nature of the study and according to the Polish law, no informed consent was required.

Results

Among 101 patients included in the study, 49 patients were diagnosed with hepatic encephalopathy, 24 with hepatorenal syndrome, 60 with cirrhosis with ascites and 59 with alcoholic liver disease. The group included 70 (69.31%) men. A total of 67 patients died during their intensive care unit (ICU) stay (66.34%).

The SMT subgroup included 53 patients (17 women and 36 men), and the SMT + ECLS subgroup included 48 patients (14 women and 34 men). Descriptive statistics for the study group and the SMT and SMT + ECLS subgroups are listed in Table I.

Significantly lower ICU mortality and 30-day mortality rates were found in the SMT + ECLS subgroup. No difference in 3-month mortality was identified between the two groups (Table II).

Since significant differences in ICU mortality and 30-day mortality were found between the study groups, the inclusion in a particular group was regarded as a death risk factor, and multidimensional models were used to determine whether it represented an independent risk factor.

Risk of ICU mortality

Compared to ICU survivors, the patients who died in the ICU were older, had lower GCS scores and lower serum albumin levels, higher SOFA, APACHE II, SAPS II and MELD UNOS scores as well as higher INR, prothrombin time and creatinine levels. Furthermore, the group of patients who died in the ICU included more cases of hepatic encephalopathy, cirrhosis with ascites and hepatorenal syndrome. Also, they more commonly received continuous renal replacement therapy (CRRT) than ECLS treatment. For the remaining variables, no statistically significant differences were found (Table III).

Consequently, the following parameters were considered as potential risk factors for ICU mortality: patient age (years), GCS (score), SOFA (score), APACHE II (score), SAPS II (score), MELD UNOS Modification (score), INR on ICU admission, prothrombin time (s) on ICU admission, creatinine (mg/dl) on ICU admission, and serum albumin

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Table I. Characteristics of the study group and subgroups: a subgroup of patients receiving standard medical therapy, and a subgroup containing patients receiving standard medical therapy complemented by at least one extracorporeal liver support procedure

Variable		Total (N = 101)	SMT group (N = 53)	SMT + ECLS group (N = 48)	p-value (SMT group vs. SMT + ECLS group)
Age [years]	Mean ± SD	47.89 ±13.41	51.26 ±12.40	44.17 ±13.62	0.0073
	Me (IQR)	49 (38–57)	51 (44–59)	43.5 (34.5–55.5)	
	Min.–max.	24–83	27–83	24–73	
Etiology of severe liver dysfunction:					
Alcoholic	N (%)	56 (55.45)	27 (50.94)	29 (60.42)	
Viral	N (%)	11 (10.89)	9 (16.98)	2 (4.17)	
Drugs	N (%)	4 (3.96)	3 (5.66)	1 (2.08)	
Other	N (%)	11 (10.89)	4 (7.55)	7 (14.58)	
Mixed	N (%)	4 (3.96)	2 (3.77)	2 (4.17)	
Unknown	N (%)	15 (14.85)	8 (15.09)	7 (14.58)	
Hepatic encephalopathy	N (%)	49 (49.00)	27 (50.94)	22 (46.81)	0.6797
Cirrhosis with ascites	N (%)	60 (59.41)	34 (64.15)	26 (54.17)	0.3075
Hepatorenal syndrome	N (%)	24 (23.76)	6 (11.32)	18 (37.50)	0.0017
Alcoholic liver disease	N (%)	59 (60.20)	29 (58.00)	30 (62.50)	0.6491
GCS score	Mean ± SD	10.48 ±4.73	7.72 ±4.32	13.52 ±3.00	< 0.0001
	Me (IQR)	13 (5–15)	7 (4–12)	15 (14–15)	
	Min.–max.	3–15	3–15	3–15	
SOFA score	Mean ± SD	13.68 ±4.42	15.49 ±3.20	11.59 ±4.73	< 0.0001
	Me (IQR)	14 (11–17)	15 (13–17)	12.5 (7–14)	
	Min.–max.	5–22	10–22	5–21	
APACHE II score	Mean ± SD	25.39 ±9.99	29.94 ±8.15	20.15 ±9.39	< 0.0001
	Me (IQR)	25 (18–32)	29 (24–35)	18.5 (14–25)	
	Min.–max.	4–55	15–55	4–43	
SAPS II score	Mean ± SD	54.84 ±22.16	66.21 ±17.55	41.74 ±19.64	< 0.0001
	Me (IQR)	54 (37–71)	66 (56–78)	40 (27–52)	
	Min.–max.	15–103	28–103	15–95	
MELD UNOS Modification score	Mean ± SD	31.63 ±8.15	30.58 ±8.13	32.79 ±8.09	0.1681
	Me (IQR)	31 (25–39)	29 (23–37)	32.5 (26–39)	
	Min.–max.	18–48	18–48	18–48	
Length of hospital stay [days]	Mean ± SD	21.25 ±16.41	19.85 ±16.76	22.79 ±16.04	0.2645
	Me (IQR)	18 (7–29)	16 (7–29)	20 (9.5–29.5)	
	Min.–max.	1–63	1–63	3–60	
Length of ICU stay [days]	Mean ± SD	10.80 ±10.63	9.66 ±10.32	12.06 ±10.92	0.0643
	Me (IQR)	7 (4–13)	7 (2–12)	8.5 (5–13.5)	
	Min.–max.	1–51	1–48	3–51	
Total bilirubin [mg/dl]	Mean ± SD	18.91 ±12.60	10.55 ±8.89	28.14 ±9.20	< 0.0001
	Me (IQR)	18.77 (7.07–28.48)	7.27 (4.35–15.83)	28.15 (21.87–35.70)	
	Min.–max.	0.66–45.54	0.66–36.8	2.71–45.54	
Direct bilirubin [mg/dl]	Mean ± SD	21.62 ±9.47	12.32 ±7.60	23.75 ±8.58	0.0001
	Me (IQR)	21.3 (14.8–29.14)	12.83 (6.48–14.8)	22.69 (16.63–29.65)	
	Min.–max.	0.71–43.21	0.71–28.26	2.08–43.21	
Bile acids [µmol/l]	Mean ± SD	113.96 ±93.28	67.60 ±25.07	119.00 ±96.68	0.1408
	Me (IQR)	93.2 (61.1–138.7)	70.6 (65.7–75.1)	94.80 (61.10–140.60)	
	Min.–max.	28.4–549.3	28.6–98	28.40–549.30	
Ammonia [µg/dl])	Mean ± SD	149.78 ±196.80	194.3 ±256.49	105.34 ±92.07	0.5138
	Me (IQR)	96.5 (70–148)	112 (73–191)	83 (62–135)	
	Min.–max.	13–1535	24–1535	13–620	

Table I. Cont.

Variable		Total (N = 101)	SMT group (N = 53)	SMT + ECLS group (N = 48)	p-value (SMT group vs. SMT + ECLS group)
INR	Mean ± SD	2.42 ±0.94	2.48 ±0.94	2.35 ±0.95	0.0314
	Me (IQR)	2.27 (1.64–3.07)	2.31 (1.66–3.17)	2.16 (1.62–2.86)	
	Min.–max.	0.86–5.46	1.23–4.73	0.86–5.46	
Prothrombin time [s]	Mean ± SD	30.16 ±19.74	32.82 ±25.00	27.23 ±11.00	0.2826
	Me (IQR)	26.6 (18.4–36.9)	27.9 (18.4–39.88)	25.60 (18.65–32.45)	
	Min.–max.	9.9–189.7	14.4–189.7	9.90–63.90	
Creatinine [mg/dl]	Mean ± SD	2.58 ±2.27	2.88 ±2.45	2.25 ±2.02	0.0316
	Me (IQR)	1.85 (0.9–3.57)	2.39 (1.1–4.11)	1.59 (0.77–3.07)	
	Min.–max.	0.1–13.52	0.33–13.52	0.10–7.76	
Albumin [g/dl]	Mean ± SD	2.77 ±0.68	2.60 ±0.73	2.93 ±0.61	0.0793
	Me (IQR)	2.88 (2.21–3.21)	2.545 (2.11–3.1)	3.00 (2.47–3.21)	
	Min.–max.	0.9–4.47	0.9–4.16	1.80–4.47	
Liver dialyses	Mean ± SD		–	4.35 ±2.78	
	Me (IQR)			3 (3–6)	
	Min.–max.			1–12	
FPSA	Mean ± SD		–	0.35 ±0.91	
	Me (IQR)			0 (0–0)	
	Min.–max.			0–5	
SPAD	Mean ± SD		–	4.00 ±2.63	
	Me (IQR)			3 (2–5.5)	
	Min.–max.			0–12	
CRRT during ICU stay	N (%)	42 (41.58)	17 (32.08)	25 (52.08)	0.0416

APACHE – Acute Physiology and Chronic Health Evaluation, CRRT – continuous renal replacement therapy, ECLS – extracorporeal liver support, GCS – Glasgow Coma Scale, FPSA – fractionated plasma separation and adsorption, ICU – intensive care unit, INR – prothrombin ratio, IQR – interquartile range, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, SAPS – Simplified Acute Physiology Score, SD – standard deviation, SMT – standard medical therapy, SOFA – Sequential Organ Failure Assessment, SPAD – single pass albumin dialysis.

Table II. Comparison of mortality between a subgroup of patients receiving standard medical therapy, and a subgroup containing patients receiving standard medical therapy complemented by at least one extracorporeal liver support procedure

Group		ICU mortality		30-day mortality		3-month mortality	
		Patients who survived	Patients who died	Patients who survived	Patients who died	Patients who survived	Patients who died
SMT	N	12	41	9	44	7	46
	%	22.64	77.36	16.98	83.02	13.21	86.79
SMT + ECLS	N	22	26	17	29	11	34
	%	45.83	54.17	36.96	63.04	24.44	75.56
Total		34	67	26	73	18	80
P-value		0.0138		0.0238		0.1523	

ECLS – extracorporeal liver support, ICU – intensive care unit, SMT – standard medical therapy.

level on ICU admission (g/dl). For these variables, ROC curves were drawn in order to assess discriminatory power (Table IV).

Based on Youden's index, optimum cut-off points were determined. For them, basic performance metrics which evaluate the resulting diagnostic tests suitable for predicting ICU mortality were calculated (Table V).

The highest values of all four measures (sensitivity, specificity, PPV and NPV) were determined for SOFA ≥ 10.5, SAPS II ≥ 39.5 and APACHE II ≥ 21.

Univariate logistic regression identified the following risk factors for ICU mortality in patients with severe liver dysfunction: age ($p < 0.009$; OR = 1.046, 95% CI: 1.011–1.083), SOFA ($p < 0.001$; OR = 1.547, 95% CI: 1.299–1.841), APACHE II

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Table III. The ICU mortality. Descriptive characteristics of survivors and deceased patients

Variable		Survivors (*N* = 34)	Deceased patients (*N* = 67)	*P*-value
Age [years]	Mean ± SD Me (IQR) Min.–max.	42.91 ±13.63 43 (31–51) 24–78	50.42 ±12.66 52 (43–59) 27–83	0.0095
Hepatic encephalopathy	*N* (%)	12 (35.29)	37 (56.06)	0.0491
Cirrhosis with ascites	*N* (%)	14 (41.18)	46 (68.66)	0.0079
Hepatorenal syndrome	*N* (%)	3 (8.82)	21 (31.34)	0.0235
Alcoholic liver disease	*N* (%)	20 (60.61)	39 (60.00)	0.9538
GCS score	Mean ± SD Me (IQR) Min.–max.	12.18 ±4.11 15 (9–15) 3–15	9.61 ±4.82 11 (5–14) 3–15	0.0016
SOFA score	Mean ± SD Me (IQR) Min.–max.	9.78 ±4.12 8 (6.5–13) 5–17	15.54 ±3.19 15 (13–18) 10–22	< 0.0001
APACHE II score	Mean ± SD Me (IQR) Min.–max.	17.72 ±7.80 17 (13–21) 4–36	29.06 ±8.81 29 (23–36) 12–55	< 0.0001
SAPS II score	Mean ± SD Me (IQR) Min.–max.	37.66 ±18.86 31 (25–52) 15–81	63.04 ±18.73 64 (48–73) 22–103	< 0.0001
MELD UNOS Modification score	Mean ± SD Me (IQR) Min.–max.	27.15 ±5.49 26.5 (23–31) 18–40	33.91 ±8.36 35 (27–41) 18–48	0.0001
Length of hospital stay [days]	Mean ± SD Me (IQR) Min.–max.	26.82 ±16.81 26 (14–38) 3–60	18.42 ±15.57 14 (7–28) 1–63	0.0113
Length of ICU stay [days]	Mean ± SD Me (IQR) Min.–max.	11.32 ±11.23 7 (5–12) 3–48	10.54 ±10.38 8 (3–14) 1–51	0.6761
Total bilirubin [mg/dl]	Mean ± SD Me (IQR) Min.–max.	21.95 ±13.25 22.03 (9.47–30.48) 0.66–45.54	17.37 ±12.07 17.51 (6.15–25.71) 0.69–43.22	0.0913
Direct bilirubin [mg/dl]	Mean ± SD Me (IQR) Min.–max.	23.66 ±9.58 23.98 (15.51–29.44) 2.08–43.21	20.11 ±9.25 20.96 (13.24–28.26) 0.71–42.85	0.1592
Bile acids [µmol/l]	Mean ± SD Me (IQR) Min.–max.	127.80 ±106.95 96.2 (79.9–133) 28.7–549.3	100.66 ±77.75 76.65 (51.8–138.7) 28.4–415.8	0.1549
Ammonia [µg/dl]	Mean ± SD Me (IQR) Min.–max.	107.75 ±87.99 94 (67–123) 16–543.6	172.52 ±233.25 103.6 (72–165) 13–1535	0.2743
INR	Mean ± SD Me (IQR) Min.–max.	1.91 ±0.60 1.88 (1.5–2.31) 0.86–3.51	2.67 ±0.98 2.59 (1.8–3.45) 1.24–5.46	0.0002
Prothrombin time [s]	Mean ± SD Me (IQR) Min.–max.	22.24 ±6.66 21.85 (17.2–27.2) 9.9–40.4	34.19 ±22.80 30.7 (20.9–42.9) 14.4–189.7	0.0001
Creatinine [mg/dl]	Mean ± SD Me (IQR) Min.–max.	1.65 ±1.60 1 (0.74–1.8) 0.39–6.81	3.05 ±2.42 2.58 (1.35–4.13) 0.1–13.52	0.0002
Albumin [g/dl]	Mean ± SD Me (IQR) Min.–max.	3.11 ±0.60 3.10 (2.835–3.515) 1.45–4.47	2.58 ±0.66 2.53 (2.09–3.09) 0.9–4.16	0.0003

Table III. Cont.

Variable		Survivors (*N* = 34)	Deceased patients (*N* = 67)	*P*-value
ECLS during ICU stay	*N* (%)	22 (64.71)	26 (38.81)	0.0138
CRRT during ICU stay	*N* (%)	8 (23.53)	34 (50.75)	0.0074

APACHE – Acute Physiology and Chronic Health Evaluation, CRRT – continuous renal replacement therapy, ECLS – extracorporeal liver support, GCS – Glasgow Coma Scale, ICU – intensive care unit, INR – prothrombin ratio, IQR – interquartile range, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, SAPS – Simplified Acute Physiology Score, SD – standard deviation, SOFA – Sequential Organ Failure Assessment.

Table IV. Risk of ICU mortality. AUC characteristics for test variables

Test variable	AUC	Standard error	*P*-value	95% CI for AUC	
Age	0.666	0.059	0.008	0.549	0.782
SOFA	0.841	0.048	< 0.001	0.746	0.936
APACHE II	0.832	0.044	< 0.001	0.745	0.919
SAPS II	0.826	0.049	< 0.001	0.730	0.921
MELD UNOS	0.749	0.048	< 0.001	0.654	0.843
INR	0.730	0.050	< 0.001	0.632	0.829
Prothrombin time	0.732	0.049	< 0.001	0.635	0.828
Creatinine	0.743	0.053	< 0.001	0.639	0.846
GCS	0.660	0.061	0.013	0.542	0.779
Albumin	0.728	0.055	< 0.001	0.620	0.836

APACHE – Acute Physiology and Chronic Health Evaluation, AUC – area under the curve, CI – confidence interval, GCS – Glasgow Coma Scale, INR – prothrombin ratio, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, SAPS – Simplified Acute Physiology Score, SOFA – Sequential Organ Failure Assessment.

Table V. Risk of ICU mortality. Optimum cut-off points and indicators

Test variable	Sensitivity	Specificity	PPV	NPV	OR	95% CI for OR		*P*-value
Age ≥ 51.5	0.5075	0.7647	0.8095	0.4407	3.3485	1.3265	8.4523	0.0087
SOFA ≥ 10.5	0.9701	0.6563	0.8553	0.9130	62.0455	12.7167	302.7232	< 0.0001
APACHE II ≥ 21	0.8507	0.7500	0.8769	0.7059	17.1000	6.0145	48.6174	< 0.0001
SAPS II ≥ 39.5	0.9254	0.6875	0.8611	0.8148	27.2800	8.3944	88.6537	< 0.0001
MELD UNOS ≥ 33.5	0.5522	0.8824	0.9024	0.5000	9.2500	2.9317	29.1858	< 0.0001
INR ≥ 2.41	0.5821	0.8529	0.8864	0.5088	8.0786	2.7819	23.4596	< 0.0001
Prothrombin time ≥ 31.2	0.4925	0.9706	0.9706	0.4925	32.0294	4.1385	247.8866	< 0.0001
Creatinine ≥ 1.83	0.6716	0.7941	0.8654	0.5510	7.8896	2.9752	20.9214	< 0.0001
GCS ≤ 14.5	0.8060	0.5294	0.7714	0.5806	4.6731	1.8893	11.5588	0.0006
Albumin ≤ 2.545	0.5273	0.8750	0.8788	0.5185	7.8077	2.4140	25.2523	0.0002

APACHE – Acute Physiology and Chronic Health Evaluation, CI – confidence interval, GCS – Glasgow Coma Scale, INR – prothrombin ratio, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, NPV – negative predictive value, OR – odds ratio, PPV – positive predictive value, SAPS – Simplified Acute Physiology Score, SOFA – Sequential Organ Failure Assessment.

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($p < 0.001$; OR = 1.188, 95% CI: 1.103–1.280), SAPS II ($p < 0.001$; OR = 1.076, 95% CI: 1.043–1.109), GCS (p = 0.012; OR = 0.880, 95% CI: 0.797–0.972), MELD UNOS (p = 0.001; OR = 1.128, 95% CI: 1.058–1.203) scores, INR (p = 0.001; OR = 3.149, 95% CI: 1.677–5.915), prothrombin time (p = 0.001; OR = 1.102, 95% CI: 1.046–1.162), creatinine (p = 0.005; OR = 1.555, 95% CI: 1.145–2.110), albumin (p = 0.001; OR = 0.258, 95% CI: 0.115–0.580), ECLS (p = 0.015; OR = 0.346; 95% CI: 0.147–0.816), hepatorenal syndrome (p = 0.019; OR = 4.717, 95% CI: 1.295–17.182), presence of cirrhosis with ascites (p = 0.009; OR = 3.129, 95% CI: 1.329–7.366) and CRRT (p = 0.011; OR = 3.348, 95% CI: 1.327–8.452).

A stepwise (both forward and backward) regression model results in the selection of two variables: SOFA (p = 0.001; OR = 1.451, 95% CI: 1.202–1.757) and prothrombin time (p = 0.024; OR = 1.085, 95% CI: 1.011–1.165) from that set of variables. Each of these variables represents an independent risk factor for ICU mortality.

The model thus obtained is statistically significant: χ^2 = 41.17; df = 2; $p < 0.001$. Based on that model, it is possible to correctly classify 20 out of 30 surviving patients (66.7%), and 50 out of 55 deceased patients (90.9%).

Risk of 30-day mortality

Compared to 30-day survivors, the patients who died during the 30-day period were older on ICU admission, had lower GCS scores and lower serum albumin levels, higher SOFA, APACHE II, SAPS II and MELD UNOS scores, and higher INR, prothrombin time and creatinine levels (Table VI). In the group of patients who died during the 30-day period, ECLS procedures were performed less commonly than CRRT procedures. For the remaining variables, no statistically significant differences were found (Table VI).

Consequently, the following parameters were considered as potential risk factors for 30-day mortality: patient age (years), GCS (score), SOFA (score), APACHE II (score), SAPS II (score), MELD UNOS Modification (score), INR on ICU admission, prothrombin time (s) on ICU admission, creatinine (mg/dl) on ICU admission, and serum albumin level on ICU admission (g/dl). For these variables, ROC curves were drawn in order to assess discriminatory power (Table VII).

The highest discriminatory power was shown for the SAPS II score followed by SOFA and APACHE II scores. Age and GCS score were found to have the lowest discriminatory power.

Based on Youden's index, optimum cut-off points were determined. For them, basic performance metrics which evaluate the resulting diagnostic tests suitable for predicting 30-day death were calculated (Table VIII).

The highest values of all four measures (sensitivity, specificity, PPV and NPV) were determined for SAPS II ≥ 39.5.

With univariate logistic regression, the following risk factors were identified for 30-day mortality in patients with severe liver dysfunction: age ($p < 0.009$; OR = 1.052, 95% CI: 1.013–1.093), SOFA ($p < 0.001$; OR = 1.504, 95% CI: 1.265–1.789), APACHE II ($p < 0.001$; OR = 1.191, 95% CI: 1.098–1.291), SAPS II ($p < 0.001$; OR = 1.081, 95% CI: 1.045–1.119), GCS (p = 0.022; OR = 0.878, 95% CI: 0.785–0.981), MELD UNOS (p = 0.001; OR = 1.126, 95% CI: 1.050–1.207) scores, INR (p = 0.001; OR = 3.447, 95% CI: 1.655–7.182), prothrombin time (p = 0.001; OR = 1.107, 95% CI: 1.042–1.176), creatinine (p = 0.009; OR = 1.587, 95% CI: 1.121–2.248), albumin (p = 0.002; OR = 0.237, 95% CI: 0.096–0.585), ECLS (p = 0.027; OR = 0.349; 95% CI: 0.137–0.888), and CRRT (p = 0.024; OR = 3.243, 95% CI: 1.168–9.005).

A stepwise (both forward and backward) regression model results in the selection of two variables: SOFA (p = 0.001; OR = 1.440, 95% CI: 1.186–1.749) and prothrombin time (p = 0.018; OR = 1.105, 95% CI: 1.017–1.200) from that set of variables. Each of them represents an independent risk factor for 30-day mortality.

The model thus obtained is statistically significant: χ^2 = 36.31 df = 2; $p < 0.001$. Based on that model, it is possible to correctly classify 15 out of 24 surviving patients (62.5%), and 55 out of 59 deceased patients (93.2%).

Discussion

In our study, short-term mortality was very high (73.74%), but in the group of patients receiving standard treatment it was 83.02%, and in the group receiving standard treatment in conjunction with liver dialysis therapy it was 63.04%. The observed high mortality was attributable mainly to the fact that the patients' clinical condition was very severe: the mean values of the SOFA, APACHE II and SAPS II scores determined on admission in the study group were, respectively, 13.68, 25.39 and 54.84 points. Also notable is the high incidence of hepatorenal syndrome (23.76%), cirrhosis with ascites (59.41%), alcoholic liver disease (60.20%) and hepatic encephalopathy (49.00%) in the study group.

In our study, over 90% of extracorporeal liver support procedures were liver dialysis treatments based on the SPAD technique. Taking into account results obtained in both subgroups (Table II), it needs to be concluded that SPAD is an effective method of eliminating bilirubin and ammonia.

In the present study, the SOFA, APACHE II, and SAPS II scores were shown to be better predictors of death than the MELD UNOS Modification

Table VI. 30-day mortality. Descriptive characteristics of survivors and deceased patients

Variable		Patients who survived 30 days (*N* = 26)	Patients who died during 30 days (*N* = 67)	*P*-value
Age [years]	Mean ± SD Me (IQR) Min.–max.	42.04 ±13.56 40.5 (31–51) 24–78	50.14 ±12.59 51 (43–58) 25.83	0.0069
Hepatic encephalopathy	*N* (%)	9 (34.62)	40 (55.56)	0.0655
Cirrhosis with ascites	*N* (%)	12 (46.15)	48 (65.75)	0.0790
Hepatorenal syndrome	*N* (%)	3 (11.54)	21 (28.77)	0.1352
Alcoholic liver disease	*N* (%)	17 (68.00)	42 (59.15)	0.4307
GCS score	Mean ± SD Me (IQR) Min.–max.	12.27 ±4.08 15 (9–15) 3–15	9.71 ±4.79 11 (5–14) 3–15	0.0041
SOFA score	Mean ± SD Me (IQR) Min.–max.	9.76 ±4.01 8 (7–12) 5–17	15.26 ±3.41 15 (13–17.5) 7–22	< 0.0001
APACHE II score	Mean ± SD Me (IQR) Min.–max.	17.56 ±7.61 17 (13–20) 6–36	28.57 ±8.84 28 (22.5–34) 12–55	< 0.0001
SAPS II score	Mean ± SD Me (IQR) Min.–max.	36.00 ±18.83 29 (24–39) 15–81	62.08 ±18.86 63 (48–73) 22–103	< 0.0001
MELD UNOS Modification score	Mean ± SD Me (IQR) Min.–max.	27.00 ±5.49 26.5 (23–30) 18–40	33.56 ±8.20 34 (27–40) 18–48	0.0005
Length of hospital stay [days]	Mean ± SD Me (IQR) Min.–max.	28.12 ±18.25 27 (13–46) 5–60	18.67 ±15.29 15 (7–28) 1–63	0.0193
Length of ICU stay [days]	Mean ± SD Me (IQR) Min.–max.	12.42 ±12.58 7 (5–14) 3–48	10.37 ±10.00 8 (3–13) 1–51	0.6128
Total bilirubin [mg/dl]	Mean ± SD Me (IQR) Min.–max.	21.66 ±13.79 20.76 (9.02–32.63) 0.66–45.54	17.52 ±11.97 17.51 (6.83–26.64) 0.69–43.22	0.1895
Direct bilirubin [mg/dl]	Mean ± SD Me (IQR) Min.–max.	24.23 ±10.37 22.56 (15.51–32.28) 2.08–43.21	20.06 ±8.98 21.16 (13.24–27.4) 0.71–42.85	0.1271
Bile acids [µmol/l]	Mean ± SD Me (IQR) Min.–max.	119.68 ±107.24 95.05 (77.5–127.25) 28.7–549.3	101.06 ±75.88 80.4 (51.8–138.7) 28.4–415.8	0.3238
Ammonia [µg/dl]	Mean ± SD Me (IQR) Min.–max.	93.76 ±39.10 92 (67–119) 23–165	174.17 ±227.60 108 (73–165) 13–1535	0.1334
INR	Mean ± SD Me (IQR) Min.–max.	1.89 ±0.48 1.915 (1.5–2.31) 1.05–2.7	2.64 ±0.97 2.52 (1.8–3.33) 1.24–5.46	0.0005
Prothrombin time [s]	Mean ± SD Me (IQR) Min.–max.	22.10 ±5.39 22.35 (17.2–26.5) 12.1–31.1	33.55 ±22.05 30.04 (20.9–42.1) 14.4–189.7	0.0005
Creatinine [mg/dl]	Mean ± SD Me (IQR) Min.–max.	1.59 ±1.45 1 (0.75–1.71) 0.4–6.5	2.97 ±2.42 2.43 (1.22–4.12) 0.1–13.52	0.0014
Albumin [g/dl]	Mean ± SD Me (IQR) Min.–max.	3.12 ±0.50 3.11 (2.85–3.49) 2.11–4.15	2.60 ±0.67 2.565 (2.105–3.10) 0.9–4.16	0.0007

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Table VI. Cont.

Variable		Patients who survived 30 days (N = 26)	Patients who died during 30 days (N = 67)	P-value
ECLS during ICU stay	N (%)	17 (65.38)	29 (39.73)	0.0238
CRRT during ICU stay	N (%)	6 (23.08)	36 (49.32)	0.0171

APACHE – Acute Physiology and Chronic Health Evaluation, CRRT – continuous renal replacement therapy, ECLS – extracorporeal liver support, GCS – Glasgow Coma Scale, ICU – intensive care unit, INR – prothrombin ratio, IQR – interquartile range, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, SAPS – Simplified Acute Physiology Score, SD – standard deviation, SOFA – Sequential Organ Failure Assessment.

Table VII. Risk of 30-day mortality. AUC characteristics for test variables

Test variable	AUC	Standard error	P-value	95% CI for AUC	
Age	0.670	0.064	0.011	0.545	0.796
GCS	0.687	0.061	0.005	0.567	0.807
SOFA	0.834	0.053	< 0.001	0.731	0.937
APACHE II	0.828	0.049	< 0.001	0.732	0.924
SAPS II	0.838	0.054	< 0.001	0.733	0.944
MELD UNOS	0.731	0.052	0.001	0.630	0.833
INR	0.743	0.050	< 0.001	0.646	0.840
Prothrombin time	0.743	0.049	< 0.001	0.647	0.838
Creatinine	0.702	0.060	0.003	0.585	0.820
Albumin	0.751	0.054	< 0.001	0.645	0.856

APACHE – Acute Physiology and Chronic Health Evaluation, AUC – area under the curve, CI – confidence interval, GCS – Glasgow Coma Scale, INR – prothrombin ratio, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, SAPS – Simplified Acute Physiology Score, SOFA – Sequential Organ Failure Assessment.

Table VIII. Risk of 30-day mortality. Optimum cut-off points and indicators

Variable	Sensitivity	Specificity	PPV	NPV	OR	95% CI for OR		P-value
Age ≥ 46.5	0.6301	0.7308	0.8679	0.4130	4.6243	1.7212	12.4243	0.0015
SOFA ≥ 12.5	0.8194	0.7600	0.9077	0.5938	14.3718	4.7991	43.0394	< 0.0001
APACHE II ≥ 21	0.8194	0.7600	0.9077	0.5938	14.3718	4.7991	43.0394	< 0.0001
SAPS II ≥ 39.5	0.9028	0.7600	0.9155	0.7308	29.4048	8.8185	98.0487	< 0.0001
MELD UNOS ≥ 31.5	0.6164	0.8077	0.9000	0.4286	6.7500	2.2844	19.9449	0.0002
INR ≥ 2.71	0.4658	1.0000	1.0000	0.4000	OR could not be determined			< 0.0001
Prothrombin time ≥ 29.75	0.5205	0.9615	0.9744	0.4167	27.1429	3.4912	211.0292	< 0.0001
Creatinine ≥ 1.81	0.6575	0.8077	0.9057	0.4565	8.0640	2.7152	23.9499	< 0.0001
GCS ≤ 14.5	0.7945	0.5385	0.8286	0.4828	4.5111	1.7315	11.7527	0.0014
Albumin ≤ 2.935	0.6667	0.7200	0.8511	0.4737	5.1429	1.8455	14.3317	0.0011

APACHE – Acute Physiology and Chronic Health Evaluation, CI – confidence interval, GCS – Glasgow Coma Scale, INR – prothrombin ratio, MELD UNOS – Model of End-stage Liver Disease United Network for Organ Sharing, NPV – negative predictive value, OR – odds ratio, PPV – positive predictive value, SAPS – Simplified Acute Physiology Score, SOFA – Sequential Organ Failure Assessment.

score, which is dedicated to the assessment of patients with liver disease. The findings are consistent with our previous studies and reports by other authors [21].

Orthotopic liver transplant is the only method which contributes to prolonging the survival of patients with liver dysfunction. The overall post-transplant survival rate is 84%, and in patients with ALF it reaches even 92% [17]. Liver transplantation, however, is not a widely accessible therapeutic method. Its limited accessibility results on the one hand from a low availability of organs for transplantation, and on the other hand from indications and contraindications involved in the application of the procedure in a particular patient.

If the transplant option is unavailable, there are no clinically effective treatment methods that can be used in patients with severe liver dysfunction (MELD UNOS score ≥ 18), which results in poor predicted prognosis [12].

Some hope, at least theoretically, can be placed on extracorporeal liver support techniques which help to win additional time, so that patients are able to regenerate damaged liver in cases where such regeneration is potentially possible.

There are only scarce data about the application of FPSA in patients with severe liver dysfunction. The first uncontrolled study conducted in 11 patients with acute-on-chronic liver failure (ACLF) and coexisting renal insufficiency showed FPSA to significantly reduce the level of conjugated bilirubin in the serum, and the levels of bile acids, ammonia, cholinesterase, creatinine and urea [23]. There were no significant changes in the level of haemoglobin and blood platelet count, while the leukocyte count was found to have increased [23]. The findings were corroborated in another uncontrolled study [24].

The study by Kribben et al. failed to demonstrate any differences in short-term and long-term mortality [12]. The probability of 28-day survival in the FPSA group was 66%, and 90-day survival was 47%. In contrast, the probability of 28-day survival in the SMT group was 63%, and 90-day survival was 38%. The difference was noticeable, but statistically insignificant. It was significant only in the subgroup of patients whose MELD score was above 30. A multivariate analysis also demonstrated better survival rates in FPSA-treated patients with hepatorenal syndrome type 1. The same finding was obtained for patients with alcoholic liver cirrhosis. The treatment triggered a significant decrease in bilirubin concentration. No statistical differences were noted for the remaining parameters. The authors of the study claimed that the result may have been influenced by the fact that the study group comprised patients with end-stage liver cirrhosis which was irreversible. The authors had no specific tool for differentiating between patients with end-stage liver failure and ACLF which is potentially reversible even with standard treatment methods.

A metaanalysis of four randomized and two selected non-randomized studies involving the administration of MARS to ACLF patients failed to demonstrate any effect on mortality [13, 14, 25–29]. An in-depth analysis of non-randomized studies, however, corroborated a significant decrease in mortality in the MARS group compared to the group of patients who received standard treatment [25]. A recently published observational study highlights a higher incidence of survival in ALF patients without a transplant compared to expected values [30]. In ALF syndrome induced by drugs (paracetamol) or toxins (mushroom poisoning), MARS yielded a beneficial effect observed in a larger population of patients (a non-randomized study) [31, 32].

A metaanalysis comprising 10 randomized clinical studies, of which four assessed the usefulness of MARS in ALF (93 patients) and six in ACLF (453 patients), compared the effects of MARS therapy with standard treatment. MARS was shown to prolong the survival of ALF patients, but no evidence that it improved survival in patients with ACLF was found [33].

The MARS turned out to be an effective method in decreasing portal hypertension, increasing circulatory efficiency and reducing the degree of hepatic encephalopathy. By eliminating endogenous substances which accumulate during insufficiency of the liver, and hence the kidneys, and impair the metabolism and haemodynamics, it was found to improve circulatory efficiency in patients with advanced liver cirrhosis. The development of a systemic inflammatory response was shown to have a potential to induce a progression from stable liver cirrhosis and lead to organ damage. Inflammation and oxidative stress may result in increased production of NO, which leads to circulatory and renal insufficiency and, as a consequence, impairs liver function [15]. Several studies, including small randomized studies, have shown albumin dialysis to be an effective method of prolonging survival, decreasing the concentration of bilirubin and degree of hepatic encephalopathy, and improving circulatory and renal function in patients with ACLF [15].

A study comparing FPSA with MARS demonstrated FPSA to have higher efficacy in eliminating bilirubin and urea, and comparable efficacy in eliminating bile acids. However, only MARS has been shown to significantly attenuate hyperdynamic circulation in patients with ACLF [7, 34, 35].

In case reports and small-scale clinical trials, researchers have noted that SPAD albumin dialysis brings down the concentration of bilirubin and im-

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proves the clinical condition of patients, especially in ALF induced by toxins (e.g. paracetamol) and in Wilson's disease [36–39].

The SPAD-based liver dialysis should be performed with a dialysate flow rate of at least 1,000 ml/h [40]. The higher the dialysate flow rate, the greater the efficacy of the dialysis procedure manifested by a decrease in the plasma concentrations of bilirubin, bile acids and ammonia [40]. Furthermore, provided that the dialysate flow is properly adjusted depending on the patient, the risk of metabolic and electrolyte disorders reported by Sponholz *et al.* during citrate anticoagulation is very low [40, 41].

A vast majority of patients with severe liver dysfunction accompanied by the failure of several other organs have a poor prognosis regardless of whether extracorporeal liver support (Prometheus, MARS or SPAD) is administered or not. The 30-day mortality rate in this patient group often exceeds 70% [1, 42].

In spite of proven biochemical efficacy of non-biological extracorporeal liver support techniques, the data on clinical endpoints are very scanty. In their metaanalysis, Stutchfield *et al.* assessed the effect of extracorporeal liver support on the survival of patients with ALF and ACLF [43]. Extracorporeal liver support prolongs patient survival in ALF (RR 0.70, 95% CI: 0.49–1.00). Number needed to treat (NNT), i.e. the number of patients who must undergo a particular intervention for a defined time to prevent one unfavourable endpoint, was eight. No significant differences in mortality were found between extracorporeal liver support and standard medical therapy in ACLF (RR = 0.87, 95% CI: 0.64–1.18) [43].

The ALF patients seem to be the most appropriate patient group for treatment based on non-biological extracorporeal liver support techniques, because in these patients there is a potential for complete liver regeneration (i.e. restoration of the initial condition). Nevertheless, extracorporeal liver support techniques are most commonly administered to patients with chronic liver damage, often at the cirrhosis stage. In this case, severe liver dysfunction (MELD UNOS ≥ 18) is often associated with the failure of other organs and high mortality rates. In end-stage liver cirrhosis, non-biological extracorporeal liver support should be restricted to patients who are on the transplant waiting list.

Depending on the degree of liver insufficiency, short-term (28-day) mortality among ACLF patients ranges from 22% to 73%, and in patients with chronic insufficiency without exacerbations it is 4.9% [44, 45].

The main limitation of the present study is its retrospective nature.

The results obtained in the study were affected by the fact that even though there was no statistical difference between the two study subgroups (SMT and SMT + ECLS) in terms of the basic criterion, i.e. the MELD UNOS score, the subgroups differed significantly in some important parameters. SMT was a subgroup comprising older patients who had lower GCS scores and higher SOFA, APACHE II and SAPS II scores, and higher INR and creatinine levels than those in the SMT + ECLS subgroup. On the other hand, SMT + ECLS subgroup patients were more commonly diagnosed with hepatorenal syndrome, and had higher total and direct bilirubin levels on ICU admission. In view of the above, the lower mortality level observed in the SMT + ECLS subgroup in comparison to SMT may not be a result of treatment but rather a consequence of differences in the clinical condition of the patients in both subgroups reflected by their SOFA, APACHE II and SAPS II scores. The statistical analysis performed for the study showed that the SOFA score was an independent risk factor for ICU mortality and 30-day mortality. A one-point increase in the SOFA score increases the risk of ICU mortality by 45.1%, and the risk of 30-day mortality by 44%. These findings are consistent with the outcomes reported by Jalan *et al.*, who found that the SOFA and APACHE II scores had the highest prognostic predictive value for mortality [44].

However, taking into account the logistic regression model estimates calculated individually for each variable, it cannot be ruled out that the decrease in mortality was a consequence of performing extracorporeal liver support procedures in the SMT + ECLS subgroup. A univariate logistic regression model showed that ECLS procedures reduced the risk of ICU mortality ($p = 0.015$; OR = 0.346, 95% CI: 0.147–0.816) and 30-day mortality ($p = 0.027$; OR = 0.349, 95% CI: 0.137–0.888). The effect, however, was not confirmed in a multivariate model. Further studies, conducted in a larger population of patients, are needed to assess the benefit of ECLS procedures in patients with severe liver dysfunction.

In conclusion, extracorporeal liver support techniques (SPAD, FPSA) effectively eliminate bilirubin and ammonia in patients with severe liver dysfunction (MELD UNOS ≥ 18). Further studies are needed in order to assess the contribution of non-biological extracorporeal liver support procedures to a decrease in mortality rates in the group of patients with severe liver dysfunction. Independent risk factors for ICU mortality and 30-day mortality were shown to be the SOFA score and prothrombin time. The SOFA, APACHE II, and SAPS II scores were shown to be better predictors of death than the MELD UNOS Modification score, which is dedicated to the assessment of patients with liver disease.

Conflict of interest

The authors declare no conflict of interest.

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