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A Novel Use of Model for End-Stage Liver Disease (MELD) Score in Guiding Therapeutic Antibiotics Choice for Critically Ill Cirrhotic Patients

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Inappropriate use of antibiotics results in antimicrobial resistance and dysbacteriosis. Among critically ill cirrhotic patients, consensus regarding the most optimal prescription strategy for antibiotics use has not been achieved. For these patients, the score for end-stage liver disease (MELD) demonstrated its value in predicting prognosis of cirrhosis. This study investigated use of the MELD score to guide antibiotics choice.

Material/Methods: We enrolled 1250 patients with cirrhosis. We collected patient information, including antibiotics administration. Linear regression analyses were performed to determine independent predictors of antibiotic administration. Survival curves were constructed based on Cox regression models. Cox proportional hazard models were used to calculate the hazard ratio, shown by forest plots.

Results: The population was equally stratified into 4 groups based on the MELD score (Q1: MELD <10; Q2: 10≤ MELD <17; Q3: 17≤ MELD <26; Q4: 26≤ MELD). In Q1, all the HR (hazard ratio) related to the duration of antibiotics use demonstrated no statistical significance. In Q2, the HR related to the duration of antibiotics use revealed a successive decrease. In Q3, the HR showed statistical significance only with a duration of antibiotics use of 7 days or more. In Q4, all the HR were statistically significant. As for categories of antibiotics use, whatever the MELD score was, the HR continued to increase with ascending categories.

Conclusions: For low MELD score patients (MELD <17), changing the duration of antibiotics use was not associated with a better prognosis. For high MELD score patients (MELD ≥17), longer duration of antibiotics use was associated with a reduction in mortality. Whatever the MELD score was, an increase of number of antibiotic categories was positively associat ed with poor prognosis.

MeSH Keywords: **Antibiotic Prophylaxis • Liver Cirrhosis • Mortality**

Abbreviations: **BUN** – blood urea nitrogen; **CI** – confidence interval; **DBP** – diastolic blood pressure; **FIO_2** – fraction of inspiration oxygen; **HR** – hazard ratio; **ICU** – Intensive Care Unit; **INR** – international normalized ratio; **HCT** – hematocrit; **MAP** – mean arterial pressure; **MDRO** – multidrug-resistant microorganisms; **MELD score** – model for end-stage liver disease score; **MIMIC** – Multi-Parameter Intelligent Monitoring in Intensive Care; **MOR** – multiple-organ failure; **NS** – not significant; **$PaCO_2$** – partial pressure of carbon dioxide; **PaO_2** – partial pressure of oxygen; **RBC** – red blood cell; **SBP** – systolic blood pressure; **UGIB** – upper-gastrointestinal bleeding; **WBC** – white blood cell

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2780 5 4 25

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Background

Inappropriate use of antibiotics results in impairment of the microbiome of intestinal flora, which is reported to play a significant role in liver development [1]. Additionally, there is an increasing global concern that inappropriate prescription of antibiotics results in antimicrobial resistance and the formation of multidrug-resistant microorganisms (MDRO) [2–4]. MDRO drastically weaken the effects of antibiotics and increase medical cost and mortality [5]. There is insufficient consensus regarding the optimal prescription strategy for antibiotics use in critically ill cirrhotic patients. The dilemma of maintaining therapeutic efficacy while minimizing the potential risks related to MDRO continues to be an important debate [1,6–9].

Cirrhosis is the result of chronic liver injury and inflammation. The development of regenerative nodules ultimately leads to portal hypertension and end-stage liver disease [10]. Cirrhotic patients generally have inefficient drug metabolism and are sensitive to changes in pharmacodynamic and pharmacykinetic processes [11]. It has been demonstrated that shortening the duration of antibiotics use leads to better outcomes. Similarly, combined use of multiple antibiotics is associated with increased adverse effects [12]. Shortening the duration of antibiotics use or reducing the number of categories of antibiotics used may not be suitable for all patients. Consequently, it is necessary to find an index to control appropriate antibiotics use by evaluating the severity of cirrhosis, for which the MELD score might by a good tool. The MELD score was originally developed to assess the prognosis of patients after transjugular intrahepatic portosystemic shunt (TIPSS) interventions and is now approved in other contexts such as the allocation of organs for liver transplantation, determination of optimal therapy for patients with hepatocellular carcinoma, and predicting the outcomes of cirrhotic patients [13–15]. Previous studies suggest that MELD score outperforms Child-Pugh score in discriminative power to estimate the likelihood of developing certain endpoints in ICU patients [16].

In this study, we evaluated the relationship between the prognosis of critically ill cirrhotic patients and the choice of antibiotics treatment. We also investigated the feasibility of using MELD scores to guide use of antibiotics, which may improve decision-making.

Material and Methods

Study population

The Multi-parameter Intelligent Monitoring in Intensive Care III version 3.0 (MIMIC-III v3.0) is a publicly available, large-scale ICU database, currently consisting of 46 520 ICU patients admitted to Beth Israel Deaconess Medical Center (Boston, MA) from 2001 to 2012. We received permission to access the database after completion of the NIH web-based training course named "Protecting Human Research Participants" (certification number: 1605699). The inclusion criteria included: with cirrhosis, using antibiotics, eligible to calculate MELD score, and staying in ICU at least 1 day. The exclusion criteria were: at least 1 kind of basic characteristic missing, at least 1 kind of clinical parameter missing, at least 1 kind of basic laboratory parameters missing, and more than 10% of data missing.

The basic characteristics such as age, sex, height, weight, and ethnicity were available for all the patients. Clinical parameters comprised of vasopressin used, respiratory rate, heart rate, temperature, systolic blood pressure (SBP), and diastolic blood pressure (DBP) on the first day of admission to the ICU were recorded from the hospital's online information systems. Laboratory parameters, including albumin, hemoglobin, glucose, red blood cell count (RBC), white blood cell count (WBC), platelet count, hematocrit (HCT), sodium, potassium, PO_2, PCO_2, FIO_2, blood lactic acid, bicarbonate, creatinine, international normalized ratio (INR), bilirubin, urine output, and blood urea nitrogen (BUN), were also collected on ICU admission. The MELD score was calculated for all eligible patients. The study population was equally stratified by MELD score.

Critically ill cirrhotic patients were defined as patients with cirrhosis admitted to an ICU. Upper-gastrointestinal bleeding (UGIB) was defined by the presence of hematemesis and melena. Hepatic encephalopathy was defined by the presence of impaired liver function and increased ammonia levels and coma.

Provision of antibiotics

For each patient, the duration of antibiotics use, the type antibiotic, and the route of administration were recorded. When antibiotics had different names and routes, as long as the active molecule was similar, these antibiotics were defined as part of a single category (e.g., piperacillin-tazobactam and piperacillin). Because therapeutic antibiotics choice included too many parameters, which was too complex to assess in in a single study, and the limitation of MIMIC-III v3.0 (e.g., some patients had fragmentary antibiotics use records, so we could not include all parameters of antibiotics choice), we used duration of antibiotics use and category of antibiotics as 2 parameters to reflect the administration of antibiotics in this study.

Data collection

Patient records were extracted from the MIMIC database, including basic characteristics, clinical parameters and laboratory parameters. Basic characteristics included age, sex, height, weight, ethnicity, and survival time. The continuous

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real-time signals, including heart rate, respiration rate, temperature, SBP, DBP, and MAP, were obtained by ICU nurses from the hospital's online information systems. The laboratory parameters, such as albumin, hemoglobin, glucose, RBC, WBC, platelet count, HCT, sodium, potassium, PO_2, PCO_2, FIO_2, blood lactic acid, bicarbonate, creatinine, INR, bilirubin, urine output, and BUN, were obtained from routine tests and were organized into a relational database. MELD scores were calculated by the formula: $R=9.57\times\log_e$ (creatinine (mg/dL))$+3.78\times\log_e$ (bilirubin (mg/dL))$+11.2\times\log_e$ (INR)+6.4 (constant for liver disease etiology) [17]. Mortality data were collected after hospital discharge and were obtained by Social Security Death Records from the United States government.

Data extraction was performed using Oracle SQL Developer version 3.0 (Oracle Corporation, Redwood Shores, CA). Since this was a retrospective study, no ethics approval was required for analyses of these non-identifiable data.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation or median, and categorical values are expressed as relative frequencies and proportions. Univariate methods were used to compare baseline demographic among the different MELD score groups. The chi-square test was used to compare categorical variables, while analysis of variance was used to compare continuous variables. Univariate and multivariate linear regression analyses were performed to determine independent predictors of antibiotic administration. To show the relationship between MELD score and patients' outcomes in the same condition (mean value) of antibiotics duration or category, survival curves were constructed based on Cox regression analysis. To demonstrate the association between each level of antibiotics duration or category and patients' outcomes in each level of MELD score, Cox proportional hazard models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI). Forest plots were used to demonstrate hazard ratios for each group.

For all analyses, a P-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL) and R 3.3.2 (R Development Core Team, *http://www.r-project.org*).

Results

Baseline characteristics

A total of 46 520 individuals were initially enrolled into this study, but according to the exclusion criteria, only 1250 subjects were included (Supplementary Figure 1). Baseline characteristics of subjects are shown in Table 1 according to their quartile values of the MELD score. From Q1 to Q4, the ranges of MELD scores were 0.1–9.9, 10.0–16.9, 17.0–25.9, and 26.0–58.7, respectively. The mean age was 57.74 years at the time of admission, and patients were predominantly male and white in the included study population. The mean ages of subjects in Q1 and Q2 were slightly higher than in Q3 and Q4. Males and whites were represented proportionally more from Q1 to Q4. Additionally, whatever the MELD score was, there were more patients with hepatic encephalopathy than with UGIB.

Antibiotic administration and independent predictors

Most antibiotics were administered intravenously in Q1 (91.2%), Q2 (90.7%), Q3 (95.3%), and Q4 (97.8%) (all P<0.001). For all included patients, vancomycin, fluoroquinolones, broad-spectrum penicillin, third-generation cephalosporin, and metronidazole were the 5 most frequently prescribed antibiotics. In addition, ciprofloxacin and levofloxacin were the 2 most commonly used fluoroquinolones in this population. Broad-spectrum penicillin mainly consisted of piperacillin, ampicillin, and amoxicillin. Third-generation cephalosporin predominantly included ceftazidime and ceftriaxone. According to each patients' duration of antibiotics use, subjects were relatively equally separated into 4 groups: 1–4 days, 5–7 days, 8–15 days, and 16+ days. Similarly, subjects were split into 3 relatively equal populations by categories of antibiotics (Table 2). Furthermore, ethnic distribution slightly changed with increased duration of antibiotics use (all P=0.492). Patients with hepatic encephalopathy were more likely to receive antibiotics in each duration group compared to patients without hepatic encephalopathy (all P=0.225). However, patients with UGIB occupied a smaller proportion in each duration group compared to patients without UGIB (all P=0.018) (Table 3). For the categories of antibiotics use, the ethnic distribution was associated with an increased number of categories of antibiotics used (all P=0.290). Compared to patients without hepatic encephalopathy, patients with hepatic encephalopathy were more likely to use antibiotics independent of the number of categories (all P=0.857). When using 5–12 categories, patients with UGIB were more predominant, but patients without UGIB made up a higher proportion in 1–4 categories (all P=0.040) (Table 4).

Because antibiotics use is closely related to infection, we focused on 4 infection-related variables (infection, white blood cell, albumin, and temperature) and 3 basic variables (age, sex, ethnicity) entered into linear regression analysis to investigate the correlation of antibiotics use (duration and category) with patients' characteristics. For the duration of antibiotics use, in univariate analysis, we found that differences in infection (P<0.001), white blood cell (P=0.003), albumin (P<0.001), temperature (P=0.020), sex (P=0.011), and age (P<0.001) were statistically significant. In multivariate analysis, independent

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Table 1. Baseline characteristics of 1250 critically ill cirrhotic patients, stratified by MELD score.

Characteristic	MELD score quartiles					P value
	All	Q1	Q2	Q3	Q4	
Range of MELD score	0.1–58.7	0.1–9.9	10.0–16.9	17.0–25.9	26.0–58.7	
No.	1250	295	321	321	313	
Age, years	57.74±11.40	58.91±11.21	59.72±11.88	57.88±11.41	54.46±10.37	<0.001
Gender, male no. (%)	856 (68.5%)	199 (67.5%)	222 (69.2%)	213 (66.4%)	222 (70.9%)	NS (0.626)
BMI, kg/m^2	28.13±8.40	29.07±12.57	27.32±6.29	27.99±6.96	28.26±6.91	NS (0.339)
Height, cm	158.84±5.36	170.60±10.13	171.89±10.45	172.05±9.79	172.78±9.93	NS (0.288)
Weight, kg	81.83±22.50	81.13±27.34	80.83±20.75	82.04±20.07	83.3±21.71	NS (0.579)
Ethnicity, n (%)						NS (0.184)
White	905 (72.4%)	214 (72.5%)	245 (76.3%)	236 (73.5%)	210 (67.1%)	
Black	93 (7.4%)	18 (6.1%)	24 (7.5%)	24 (7.5%)	27 (8.6%)	
Other	252 (20.2%)	63 (21.4%)	52 (16.2%)	61 (19.0%)	76 (24.3%)	
Complications, n (%)						
UGIB	508 (40.6%)	113 (30.3%)	142 (44.2%)	129 (40.2%)	124 (30.6%)	NS (0.466)
Hepatic encephalopathy	688 (55.0%)	171 (58.0%)	179 (55.8%)	171 (53.3%)	167 (53.4%)	NS (0.603)
Respiratory rate, n	38.89±32.62	38.64±33.12	38.97±33.10	40.45±32.37	37.46±38.89	NS (0.716)
Heart rate, n	90.66±19.08	90.71±18.30	90.48±19.32	91.30±19.50	90.14±19.50	NS (0.893)
Temperature, °C	36.63±0.98	36.80±1.02	36.79±0.83	36.58±0.89	36.38±1.13	<0.001
SBP, mmHg	118.75±23.26	122.69±25.06	119.55±23.37	118.72±22.82	114.23±21.05	<0.001
DBP, mmHg	62.44±16.33	65.40±16.59	63.76±15.74	62.01±17.46	58.74±14.75	<0.001
MAP, mmHg	81.21±16.78	84.50±17.54	82.38±16.53	80.91±17.16	77.24±15.08	<0.001
Vasopressin used, n. (%)	552 (44.2%)	97 (32.9%)	122 (38%)	145 (45.2%)	188 (60.1%)	<0.001
Albumin, g/dL	2.90±0.64	3.16±0.69	2.93±0.57	2.79±0.58	2.76±0.63	<0.001
Hemoglobin, g/dL	10.77±2.26	11.10±2.46	10.98±2.29	10.74±2.13	10.29±2.08	<0.001
Glucose, mg/dL	135.31±66.87	140.01±64.16	141.42±66.21	138.50±69.05	121.32±66.09	<0.001
Red blood cell, 10^9/L	3.36±0.74	3.60±0.76	3.45±0.76	3.30±0.69	3.09±0.67	<0.001
White blood cell, 10^9/L	10.45±6.90	8.97±5.15	9.27±5.60	10.84±7.59	12.66±8.10	<0.001
Platelet count, 10^9/L	144.77±103.50	178.37±122.41	148.64±103.65	130.27±88.28	124.02±89.57	<0.001
HCT, %	31.94±6.48	32.85±6.74	32.57±6.59	31.86±6.46	30.53±5.90	<0.001
Sodium, mEq/L	135.34±6.74	137.96±5.16	136.57±5.99	134.37±7.19	132.60±7.11	<0.001
Potassium, mEq/L	4.24±0.88	4.08±0.77	4.18±0.70	4.22±0.86	4.47±1.08	<0.001
PaO_2, mmHg	161.38±120.28	199.03±134.16	177.87±127.39	149.82±133.24	120.84±88.08	<0.001
$PaCO_2$, mmHg	38.57±10.66	41.86±10.70	39.60±10.47	37.87±10.93	35.14±9.39	<0.001
FIO_2, %	59.76±33.27	59.08±33.00	56.93±33.42	58.15±33.58	64.97±32.65	0.012

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Table 1 continued. Baseline characteristics of 1250 critically ill cirrhotic patients, stratified by MELD score.

Characteristic	MELD score quartiles					P value
	All	Q1	Q2	Q3	Q4	
Blood lactic acid, mmol/L	3.04±2.62	2.19±1.89	2.61±1.85	3.23±2.59	3.90±3.33	<0.001
Bicarbonate, mEq/L	22.47±5.27	24.83±4.50	23.82±4.30	22.04±5.11	19.29±5.37	<0.001
Creatinine, mg/dL	1.68±1.50	0.81±0.29	1.03±0.39	1.71±1.16	3.13±2.03	<0.001
Creatinine (24 h), mg/dL	1.62±1.46	0.84±0.31	1.02±0.44	1.62±1.25	2.97±1.98	<0.001
Creatinine (48 h), mg/dL	1.61±1.44	0.87±0.44	1.04±0.51	1.60±1.91	2.91±1.96	<0.001
INR	1.84±0.92	1.33±0.22	1.55±0.33	1.84±0.60	2.63±1.37	<0.001
Bilirubin, mg/dL	5.88±8.37	1.25±0.95	2.73±2.44	6.08±6.72	13.27±11.90	<0.001
Urine output (24h), ml	1707.16±2327.99	2279.99±2545.42	1925.07±2638.04	1487.59±2072.07	1161.70±1821.85	<0.001
BUN, mmol/L	32.76±.25.44	16.69±9.60	23.04±13.72	35.27±22.42	55.06±30.93	<0.001

BUN – blood urea nitrogen; DBP – diastolic blood pressure; FIO_2 – fraction of inspiration oxygen; HCT – hematocrit; INR – international normalized ratio; MAP – mean arterial pressure; MELD score – model for end-stage liver disease score; NS – not significant; $PaCO_2$ – partial pressure of carbon dioxide; PaO_2 – partial pressure of oxygen; SBP – systolic blood pressure; UGIB – upper gastrointestinal bleeding.

Table 2. ICU antibiotic use, stratified by MELD score.

	MELD score quartiles					P value
	All	Q1	Q2	Q3	Q4	
Intravenous route, %	93.9	91.2	90.7	95.3	97.8	<0.001
Antibiotics class, %*						NS (0.199)
Vancomycin	64.7	51.2	55.5	70.7	80.8	
Fluoroquinolones	63.3	54.6	63.9	70.1	63.9	
Broad-spectrum penicillin	50.1	43.7	43.9	51.4	61.0	
Third-generation cephalosporin	38.5	28.8	34.3	40.5	49.8	
Metronidazole	37.3	28.1	30.1	43.3	47.3	
Duration of antibiotics use, n						<0.001
1–4 days	333	106	91	63	73	
5–7 days	273	64	81	73	55	
8–15 days	346	78	84	91	93	
≥16 days	298	47	65	94	92	
Categories of antibiotics, n						<0.001
1–2	470	158	143	94	75	
3–4	406	84	95	110	117	
5–12	374	53	83	117	121	

* Percentage among the ICU patients with cirrhosis who were administrated certain antibiotics in specific range of MELD scores. Due to the limited space, five most frequently used antibiotics were showed in the table. For the whole subjects, fluoroquinolones mainly included ciprofloxacin, levofloxacin. Broad-spectrum penicillin mainly included piperacillin, ampicillin, amoxicillin. Third-generation cephalosporin mainly included ceftazidime, ceftriaxone. NS – not significant.

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Table 3. Duration of antibiotics use in specific population.

Variable	Duration of antibiotics use, day				P value
	1–4	5–7	8–15	≥16	
White race	235 (70.6%)	205 (75.1%)	249 (72.0%)	216 (72.5%)	NS (0.492)
Black race	24 (7.2%)	23 (8.4%)	29 (8.4%)	17 (5.7%)	
Other race	74 (22.2%)	45 (16.5%)	68 (19.6%)	65 (21.8%)	
Hepatic encephalopathy	199 (59.8%)	142 (52.0%)	186 (53.8%)	161 (54.0%)	NS (0.225)
No Hepatic encephalopathy	134 (40.2%)	131 (48.0%)	160 (46.2%)	137 (46.0%)	
UGIB	120 (36.0%)	121 (44.3%)	129 (37.3%)	138 (46.3%)	0.018
No UGIB	213 (64.0%)	152 (55.7%)	217 (62.7%)	160 (53.7%)	

NS – not significant; UGIB – upper gastrointestinal bleeding.

Table 4. Categories of antibiotics use in specific population.

Variable	Categories of antibiotics use, n (%)			P value
	1–2	3–4	5–12	
White race	345 (73.4%)	295 (72.7%)	265 (70.9%)	NS (0.290)
Black race	33 (7.02%)	37 (9.1%)	23 (6.1%)	
Other race	92 (19.6%)	74 (18.2%)	86 (23.0%)	
Hepatic encephalopathy	258 (54.9%)	220 (54.2%)	210 (56.1%)	NS (0.857)
No Hepatic encephalopathy	212 (45.1%)	186 (45.8%)	164 (43.9%)	
UGIB	203 (43.2%)	145 (35.7%)	214 (57.2%)	0.040
No UGIB	267 (56.8%)	261 (64.3%)	160 (42.8%)	

NS – not significant; UGIB – upper gastrointestinal bleeding.

Table 5. Association of antibiotics use with patients' characteristics.

Variable	Duration of antibiotics use		Categories of antibiotics use	
	Univariate P-value	Multivariate P-value	Univariate P-value	Multivariate P-value
Infection	<0.001	<0.001	<0.001	<0.001
White blood cell	0.003	0.023	<0.001	0.013
Albumin	<0.001	0.006	<0.001	<0.001
Temperature	0.020	0.031	NS (0.232)	
Ethnicity	NS (0.961)		NS (0.389)	
Gender	0.011	NS (0.150)	0.021	NS (0.881)
Age	<0.001	<0.001	<0.001	<0.001

NS – not significant.

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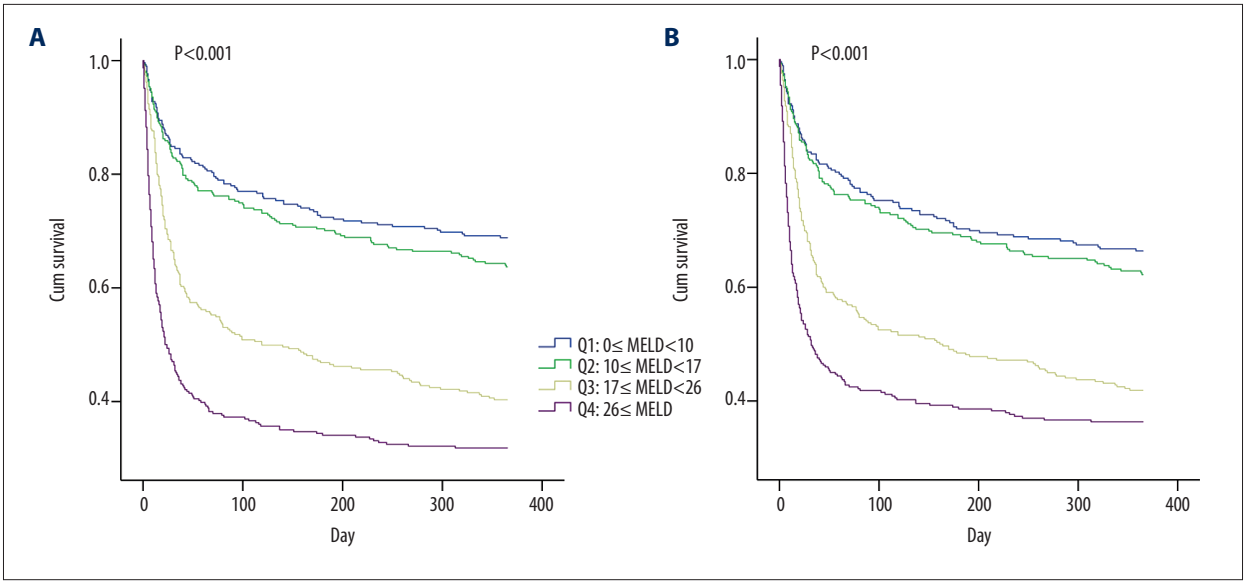

Figure 1. Survival curves reflecting cumulative survival rate of critically ill cirrhosis. (**A**) The covariate was duration of antibiotics use, and subjects were stratified by quartiles of MELD score. The duration of antibiotics use was kept at mean value (11.4 days). (**B**) The covariate was categories of antibiotics use and subjects were stratified by quartiles of MELD score. The categories of antibiotics use were kept at mean value (3.5 categories). MELD – model for end-stage liver disease.

predictors of duration of antibiotics use included infection (P<0.001), white blood cell (P=0.023), albumin (P=0.006), temperature (P=0.031), and age (P<0.001). For categories of antibiotics used, in univariate analysis, only infection (P<0.001), white blood cell (P<0.001), albumin (P<0.001), sex (P=0.021), and age (P<0.001) had statistical significance. In multivariate analysis, independent predictors of categories of antibiotics used included infection (P<0.001), white blood cell (P=0.013), albumin (P<0.001), and age (P<0.001) (Table 5).

Antibiotic administration and mortality

Figure 1 shows the cumulative survival rate of critically ill cirrhotic patients, stratified by MELD score. The covariate in Figure 1A was duration of antibiotics use. The cumulative survival rate of critically ill cirrhotic patients decreased with increased duration and MELD score. There was no significant difference between the 2 survival curves of Q1 and Q2. However, the divergence between Q2 and Q3 was noticeably greater than the divergence between Q1 and Q2 and between Q3 and Q4. The covariate in Figure 1B illustrated the categories of antibiotics use. Likewise, the cumulative survival rate of critically ill cirrhotic patients was decreasing with the increase of duration and MELD score, and the divergence between Q2 and Q3 was highest between Q1 and Q2 and between Q3 and Q4.

Figures 2, 3 show the hazard rate (HR) of mortality. Subjects were stratified into Q1 (MELD <10), Q2 (10≤ MELD <17), Q3 (17≤ MELD <26), and Q4 (26≤ MELD). In Figure 2, each subgroup continued to be stratified by duration of antibiotics and with 1–4 days as the reference. When the MELD score was in the range of 0 to 17, all the HR demonstrated no statistical significance. In contrast, in Q2, risk factors showed a successive decrease in HR. In Q3, the HR was statistically significant only with a duration of antibiotic use of 7 days or more. In Q4, all the HRs showed statistical significance. In Figure 3, each subgroup was stratified by categories of antibiotics use and 1–2 categories were used as a reference. In each subgroup, HR continued to increase with increasing number of categories involved, and all HR demonstrated statistical significance.

Discussion

We performed a retrospective study of 1250 critically ill cirrhotic patients. We presented stratified data according to MELD score quartiles. To quantify antibiotics use, we focused on 2 common parameters: duration of antibiotics use and the number of antibiotic categories prescribed.

The liver has a vital role in drug metabolism and liver dysfunction; critically ill cirrhotic patients are more sensitive to pharmacokinetic and pharmacodynamic alterations. In this research, the 5 most frequently used antibiotics were vancomycin, fluoroquinolones (ciprofloxacin; levofloxacin), broad-spectrum penicillin (piperacillin; ampicillin; amoxicillin), third-generation cephalosporin (ceftazidime; ceftriaxone), and metronidazole. For critically ill cirrhotic patients, antibiotics without hepatotoxicity or liver metabolism are considered the optimal choice. However, few antibiotics are metabolized extrahepatically.

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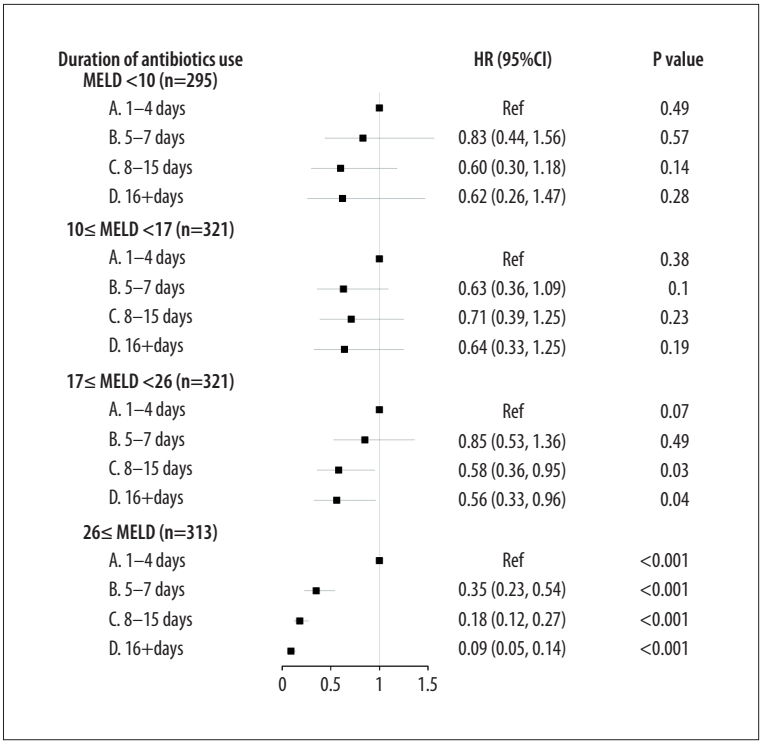

Figure 2. Forest plots of HR (95% CI) for quartiles of MELD score (duration of antibiotics use). Decreasing trends of HR with the increases of duration of antibiotics use when MELD ≥17 and duration of antibiotics use ≥8 or MELD ≥26. CI – confidence interval; HR – hazard ratios; MELD – model for end-stage liver disease.

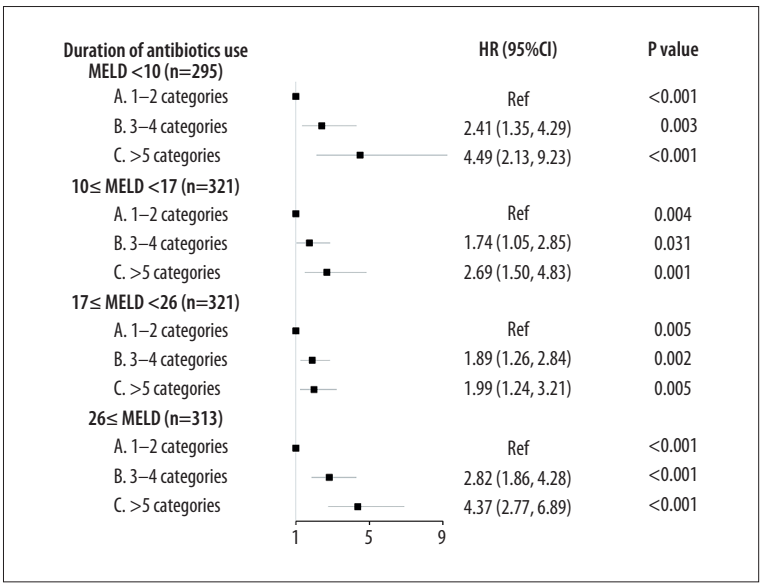

Figure 3. Forest plots of HR (95% CI) for quartiles of MELD score (categories of antibiotics use). Increasing trends of HR with the increases of categories of antibiotics use whatever the MELD score was. CI – confidence interval; HR – hazard ratios; MELD – model for end-stage liver disease.

Severe cirrhosis often leads to multiple-organ failure (MOF), which can significantly exacerbate the adverse effects that are irrelevant to the liver. Alteration of intestinal flora is one of the consequences of antibiotic use (especially broad-spectrum antibiotics) and can result in severe microbial inflammations or even intestinal endotoxemia [18–22]. Antibiotics are not without risk for critically ill cirrhotic patients, even if the antibiotic has a low liver metabolism.

As shown in Figure 1, when the duration or categories of antibiotics use were kept at the mean value (11.4 days and 3.5 categories), the prognosis of critically ill cirrhosis patients was still deteriorating with an increase of MELD score. Compared to other quartiles, the survival curves of Q1 and Q2 nearly overlapped, which indicates that, in the same condition of antibiotics use, patients with MELD scores below 17 had similar prognoses. Moreover, there might be a cut-off point between Q2 and Q3. When MELD scores are below this point, it seems unnecessary to increase the intensity of antibiotics administration.

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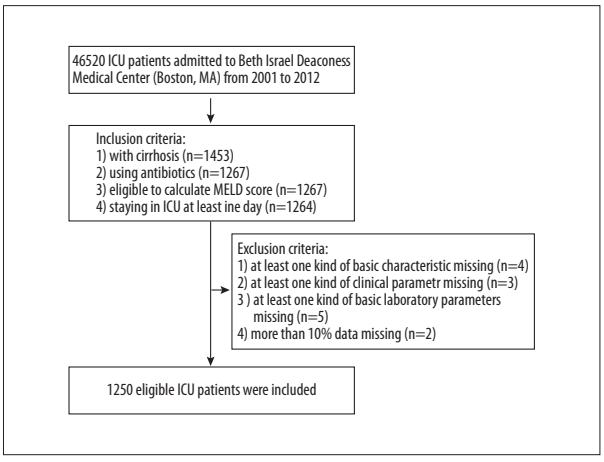
The HR in Figure 2 provides evidence for this hypothesis. When the MELD score was lower than 17 (Q1 and Q2), the change of duration of antibiotics use was not associated with poor clinical outcome. In contrast, when MELD score was in the range of 17 to 26 (Q3), a long course of therapy (≥8 days) was related to mortality, and the prognosis of cirrhosis tended to be better with the increased duration. For patients with a MELD score exceeding 26 (Q4), prolonging the duration of antibiotics use could improve the prognosis. In Figure 3, increasing the categories of antibiotics use was always related with poor prognosis, regardless of MELD score. Based on the above analyses, the MELD score is a valuable guide to antibiotics administration for critically ill cirrhotic patients, with a MELD score of 17 used as the cut-off point for duration of antibiotics use.

We propose 2 possible explanations for these results: (1) Traditionally, there is a belief that the progression of microbial diseases due to ongoing replication of pathogens, and antibiotics are used until clinical and laboratory parameters show the infection has resolved. However, some severe complication (e.g., SIRS) are more related to host immune activity than to the bacteria. As such, a long duration of antibiotics use is unnecessary, as been demonstrated in in respiratory system disease [23,24]. For patients with low MELD scores (MELD <17), immune activities probably affect prognosis of critically ill cirrhotic patients more than do bacteria. However, when patients have high MELD scores (MELD ≥17), long-term use of antibiotics is prophylactic. (2) Although the combined use of different antibiotics can increase the anti-bacterial spectrum and have synergism, there is still evidence that demonstrates adverse effects of this approach [25]. Combined therapy further stresses the kidneys and can cause nephrotoxicity [12]; for critically ill cirrhotic patients, it may increase the risk of MOF.

Our research had several notable strengths. Firstly, to the best of our knowledge, it is the first and largest study specifically aimed at using MELD score to guide the choice of antibiotics used for critically ill cirrhotic patients. Secondly, we analyzed the relation of MELD score, antibiotics use, and prognosis of critically ill cirrhosis, and also defined a cut-off point for the MELD score. Thirdly, our study provides a new method to prevent inappropriate use of antibiotics. Our study also has some limitations. Firstly, to simplify the analysis, we only used duration and category to represent the intensity of antibiotics use, which might not reflect antibiotics use comprehensively. Secondly, different antibiotics have diverse adverse effects, and the total adverse effect is sometimes not linearly related to the cumulative number of categories. Drawing a more precise conclusion requires a more specific classification of antibiotics. Thirdly, the duration of antibiotics use in this study was the sum of all antibiotics each patient used. Fourthly, the cut-off point (MELD=17) is merely the result of the quartile definition, and this requires validation in more clinical trials. Finally, as with all retrospective research, accuracy of results depends on accuracy of data collection.



Conclusions

We evaluated the relationship between the prognosis of critically ill cirrhosis patients and the administration of antibiotics combined with MELD score. For low MELD score patients (MELD <17), changing duration of antibiotics use was not related to prognosis of critically ill cirrhosis patients. For high MELD score patients (MELD ≥17), a long course of antibiotics use could reduce the mortality. Whatever the MELD score was, increasing the number of antibiotic categories predicted a poor prognosis.

Conflict of interest

None.

Acknowledgments

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Supplementary Figure 1. Study flow diagram. A total of 46 520 participants were enrolled initially, while 1250 ICU patients with cirrhosis were included. ICU – Intensive Care Unit.

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