Int.J.Curr.Microbiol.App.Sci (2018) *7*(3): 3410-3421

International Journal of Current Microbiology and Applied Sciences
ISSN: 2319-7706 **Volume 7 Number 03 (2018)**
Journal homepage: http://www.ijcmas.com

Original Research Article https://doi.org/10.20546/ijcmas.2018.703.393

Predictors of In-Hospital Mortality in Cirrhotic Patients with Spontaneous Bacterial Peritonitis

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Keywords

Spontaneous bacterial peritonitis (SBP), Cirrhosis MELD, SOFA

Article Info

Accepted:
26 February 2018
Available Online:
10 March 2018

A B S T R A C T

Spontaneous bacterial peritonitis (SBP) is a major complication of cirrhosis and ascites and is responsible for significant morbidity and mortality, The aim of this work is to determine prognostic factors and scores for SBP-related in-hospital mortality, compare the predictive power of CP, MELD, SOFA and AIMS65scores for the prediction of the mortality also to identify the best score cut-off point. This prospective study included 111 patients (76 males and 35 females) with liver cirrhosis, ascites and spontaneous bacterial peritonitis confirmed by laboratory investigations especially peritoneal fluid study was done. There were statistically significant differences between cirrhotic patients with SBP who survive and who don't survive as regard mental status, hepatorenal syndrome, ALT and AST, serum sodium, MELD score, SOFA score and AMS65 score. MELD score and serum sodium have the most excellent prognostic accuracy for SBP-related in-hospital mortality with p= 0.006 for both of them, by identifying cut-off point for MELD score (>25) and for serum sodium (≤126 mEq/L) we can predict mortality in about 73.3 and 93.3 of cirrhotic patients with SBP respectively, as regard serum Sodium and MELD score; the lower the sodium and the higher the MELD score, the more probability for mortality in cirrhotic patients with SBP.

Introduction

Spontaneous bacterial peritonitis (SBP) is a major complication of cirrhosis and ascites and is responsible for significant morbidity and mortality (Runyon *et al.*, 2006).

Improvements in patient management, including the higher index of suspicion of infection and the clarification of diagnostic criteria, together with the use of better and safer antibiotics, significantly improve the short-term prognosis of these patients (Frances *et al.*, 2008) and the use of prophylactic antibiotics has resulted in a decline in in-hospital mortality (Hou *et al.*, 2004).

It was shown that in-hospital mortality in cirrhotic patients admitted with SBP has decreased more than 50% over the past 40 years (Curry *et al.*, 1974).

Identification of patients who are at high risk for mortality in SBP has been shown to be critical for prognostic improvement (Frances *et al.*, 2008). Available scores, for example

Child–Pugh (CP) and model of end-stage liver disease (MELD) scores have been investigated for their predictive accuracy in patients with end-stage liver disease; however; these scores may have some shortages, making their utilization in prediction of SBP-related in-hospital mortality affected (Hassan and Abdel Rehim 2015). The Sequential Organ Failure Assessment (SOFA) Score has been developed by European Society of Critical Care Medicine (ESCCM) in 1994,as a system for measuring the status of the patient in the ICU (Ferreira *et al.,* 2001). Another available score is AIMS65 score which is consists of the following components: albumin level <3.0 g/dL (A), international normalized ratio (INR) >1.5 (I), altered mental status (M), systolic blood pressure ≤90 mm Hg (S), and age >65 years (65) (Saltzman *et al.,* 2011).

To determine prognostic factors and scores for SBP-related in-hospital mortality.

To evaluate and compare the predictive power of CP, MELD, SOFA and AIMS65scores for prediction of SBP-related in-hospital mortality.

To identify the best score cut-off point to predict this mortality.

Patients and Methods

Patients

The study was conducted on 111 (76 males and 35 females) patients with liver cirrhosis, ascites and spontaneous bacterial peritonitis confirmed by peritoneal fluid study who were admitted to the Department of Tropical Medicine and Gastroenterology, Sohag University Hospital, Egypt over a period of 1 year. All patients signed an informed written consent before starting the data collection with respect to patients' confidentiality, and the study was approved by the local ethical committee of Sohag Faculty of Medicine.

Inclusion Criteria

All patients with liver cirrhosis who were diagnosed to have spontaneous bacterial peritonitis by diagnostic paracentesis within 24 hours of admission with ascitic fluid polymorphs >250 cells/mm^3.

Exclusion criteria

Ascites fluid PMNs < 250 cells/mm3.
Ascites unrelated to cirrhosis.
Secondary bacterial peritonitis.

Methods

All the patients were subjected to:

Complete history taking

This includes age, sex and duration of ascites, history of fever, history of abdominal pain or change of bowel habits, history of previous maneuver as paracentesis or ultra-filtration. History suggestive of previous episode of SBP, history suggestive of portal hypertension and/or liver cell failure and history suggesting other significant co morbid conditions.

Clinical examination

General examination including vital signs, signs of encephalopathy, manifestations of liver cell failure such as jaundice, spider naevi, lower limb edema, etc.

Systemic examination with stress on signs of SBP.

Abdominal examination with stress on abdominal tenderness, organomegaly, ascites and manifestations of portal hypertension.

Abdominal ultrasonography with stress on

Size of the liver, surface, echopattern, periportal thickening, hepatic focal lesion, portal vein diameter and portal vein thrombosis.

Size of the spleen, splenic vein diameter, porto-systemic collaterals.

Ascites as regard amount, adhesion and turbidity.

Kidneys size, echogenicity, any abnormalities.

Laboratory investigations: including

Routine laboratory investigations including

Complete blood count (CBC).

Liver function test (serum albumin and bilirubin).

Prothrombin time and concentration.

Serum Creatinine.
Serum electrolyte.
Arterial blood gases.

Paracentesis of ascitic fluid

Paracentesis was done under complete aseptic conditions at the time of admission to investigate ascites.

Peritoneal fluid study including

Total leucocytes count in ascitic fluid and differentiation into polymorphnuclears and lymphocytes.

Protein level in the ascitic fluid.

Presence of red blood cells or malignant cells.

Diagnostic criteria for SBP were

The ascitic fluid PMN cells count is equal or more than 250 cells/mm^3.

Total protein in ascitic fluid is less than 3 gm/dl.

Absence of abnormal cells, RBCs or high lymphocytic count (Wong *et al.*, 2005, Moore and Aithal 2006).

Management and follow up

Treatment by antibiotics.

Daily clinical, physiological, laboratory variables.

Follow up ascitic fluid study.

Prognostic scores for survival after SBP infection

Liver prognostic indicators will be calculated from data available on day-1 of hospital admission.

Child–Turcotte–Pugh (CTP) score will be calculated according to the Pugh modification. Model for end-stage liver disease (MELD) score will be calculated according to the United Network of Organ Sharing (UNOS) adjustments.

Sequential organ failure assessment (SOFA) score will be calculated according to (Knaus *et al.*, 1985) and (Vincent *et al.*, 1996).

AIMS65 score will be calculated according to Saltzman *et al.*, (2011).

We will compare CP, MELD, SOFA and AIMS65 scores of patients with spontaneous bacterial peritonitis to find possibility of using them as methods to predict mortality.

Statistical analysis

The patients were grouped into two groups: group I of patients who are survivor and group II of patients who are non-survivor. The demographic and clinical data were compared between the two groups using STATA intercooled version 12.1. Quantitative data was represented as mean, standard deviation, median and range. Data was analyzed using student t-test to compare means of two groups. When the data was not normally distributed Mann-Whitney test was used to compare two groups.

Qualitative data was presented as number and percentage and compared using either Chi square test or fisher exact test. Roc curve analysis was used to detect best cutoff of different variables that predict mortality in patients with SBP. Sensitivity, specificity, positive predicted value and negative predictive value were also calculated. Odds ratios were obtained from logistic regression analysis. Graphs were produced by using Excel or STATA program. P value was considered significant if it was less than 0.05.

Results and Discussion

We included 111 patients from September 2016 to September 2017 (mean age 57.54 ± 9.89 years, range 25-85 years; 76 men (68.47%) 35 women (31.53%). We found that the prevalence of mortality among patients with SBP is 15/111 (13.51%).

Baseline characteristics:

Based on the results of ascitic fluid study, patients were diagnosed as SBP if polymorphs ≥ 250 cells/mm^3. Accordingly, patients were categorized into 2 groups; group I is formed of 96 patients (86.49%) who survived SBP infection and group II is formed of 15 patients (13.51%) who are non-survivors.

Comparison between survivors and non-survivors as regard clinical characteristics

There is no statistically significant difference as regard age and sex between survivors and non-survivors (Table 1).

There is statistically significant difference (P value < 0.5) as regard mental status and hepatorenal syndrome between survivors and non-survivors. There is no statically significant difference as regard GIT bleeding, jaundice, abdominal pain, fever, previous SBP and hepatocellular carcinoma between survivors and non-survivors (Table 2).

Comparison between survivors and non-survivors as regard lab investigations

There is statistically significant difference as regard ALT and AST between survivors and non-survivors. Also, there is highly statically significant difference (P value <0.0001) as regard serum sodium between survivors and non-survivors. There is no statically significant difference as regard WBCs and serum potassium between survivors and non-survivors (Table 3).

Comparison between survivors and non-survivors as regard ascitic fluid study of the study patients

There is no statistically significant difference as regard WBCs, polymorphs and protein in the ascitic fluid study in the patient with SBP between survivors and non-survivors (Table 4).

Comparison between different scores (Child-pugh, MELD, SOFA and AIMS65) in predicating the mortality in the patients with SBP

MELD score, SOFA score and AMS65 score are good predicator (statistically significant

between survivors and non-survivors), but Child-pugh score is not a good predicator (Table 5).

Multivariate logistic regression analysis of factors predicting mortality in patients with SBP (include significant variables in univariate analysis)

Using multivariate logistic regression analysis we found MELD score, serum sodium can predict mortality (statically significant between survivors and non-survivors), but mental status, ALT, AST, SOFA score and AIMS65 score are not predictor for mortality (Table 6).

Accuracy of serum sodium and MELD score to predict SBP-related in-hospital mortality with the best predictive cut-offs

We can get the best cut off point for MELD score at more than 25 with accuracy 78.3% with sensitivity about 73.3% and specificity about 83.3% and the best cut off point for serum sodium at less than 126 with accuracy 82.1% with sensitivity about 93.3 % and specificity about 70.8% (Table 7, and figures 1-3).

SBP is the most frequent and life-threatening infection in patients with cirrhosis (Wiest *et al.,* 2012), its prevalence in outpatients has been reported to be 1.5%-3.5% and among in-patients is around 10% (Nousbaum *et al.,* 2007).

Our study assessed different prognostic factors and scores to elaborate reliable methods to predict outcome, which were useful for increasing suspicions of high-risk group in hospitalized cirrhotic patients with SBP.

In this study, SBP-related in-hospital mortality rate was 13.5% and that is correlated with what recorded by (Cardenas *et al.,* 2001). This is not surprising as most of our patients presented with advanced liver disease at the time of SBP diagnosis, as assessed by high mean total bilirubin and INR levels, and low serum albumin. Besides, 87.39% were classified as grade C according to the Child–Turcotte score classification. We found that age is not an independent predictor of survival in these series, this is agreed with studies as (Bal *et al.,* 2016) and disagreed with (Thuluvath *et al.,* 2001) who found that the age is an independent risk factor for survival. We found that hepatic encephalopathy, hepatorenal syndrome, SGOT, SGPT and MELD score significantly associated with mortality and this result coincided with what recorded by (Thuluvath *et al.,* 2001) and (Nobre *et al.,* 2008).

In our study, creatinine was significantly higher in SBP patients who died during hospitalization than in survivors, where 20 % of dead patients had HRS. These findings agreed with (Kamath *et al.,* 2001) and (Tandon and Garcia-Tsao 2011) that showed that renal impairment or HRS was an independent predictor for in-hospital mortality in patients with SBP, also presence of SBP may also be considered an important sign of deterioration of the liver disease, with more frequent fatal outcome due to the development of HRS owing to the reduction of effective circulating volume (Sanchez *et al.,* 2007).

In this study we found that the hyponatremia as a good predictor of death in patients with SBP, as it is also an important prognostic factor in cirrhosis and ascites as it is associated with the HRS, that is agreed with (Gines *et al.,* 1993).

Also in our study we found that ALT, AST, WBCs count and serum potassium are not an independent predictor for mortality in the patients with SBP that reported by (Hassan and Abdel Rehim 2015).

Table.1 Demographic characteristics of the study patients with SBP (survivors and non-survivors)

Variable	Survivor	Non-survivor	Total	P value
Age/year				
Mean ± SD	57.84±9.83	55.60±10.43	57.54±9.89	0.42
Median (range)	58 (25-85)	53 (40-75)	58 (25-85)	
Gender				
Females	32 (33.33%)	3 (20.00%)	35 (31.53%)	0.38
Males	64 (66.67%)	12 (80.00%)	76 (68.47%)	

Table.2 Clinical characteristics of the patients included in the study (survivors and non-survivors)

Variable	Survivor N=96	Non-survivor N=15	Total	P value
Mental status				
Conscious	38 (39.58%)	1 (6.67%)	39 (35.14%)	0.01
Disturbed	58 (60.42%)	14 (93.33%)	72 (64.86%)	
GIT bleeding	21 (21.88%)	1 (6.67%)	1 (6.67%)	0.30
Jaundice	38 (39.58%)	9 (60.00%)	47 (42.34%)	0.14
Abdominal pain	26 (27.08%)	2 (13.33%)	28 (25.23%)	0.35
Fever	25 (26.04%)	2 (13.33%)	27 (24.32%)	0.35
Previous SBP	4 (4.17%)	0	4 (3.60%)	1.00

Table.3 Lab investigation and sonographic finding of the study patients with SBP (survivors and non-survivors)

Variable	Survivor N=96	Non-survivor N=15	Total	P value
WBCs				
Mean ± SD	12.93±9.17	14.41±7.42	13.13±8.93	0.18
Median (range)	10.7 (2.7-62.2)	13.3 (4.3-32)	11 (2.7-62.2)	
ALT				
Mean ± SD	60.43±43.53	74.07±22.91	62.27±41.54	0.03
Median (range)	49 (6-236)	77 (15-112)	54 (6-236)	
AST				
Mean ± SD	67.45±63.19	78.4±32.34	68.93±32.33	0.03
Median (range)	47 (14-514)	67 (38-155)	67 (14-514)	
K				
Mean ± SD	3.72±0.68	4.07±1.10	3.77±0.76	0.10
Median (range)	3.7 (2.3-5.8)	4.5 (2.4-5.5)	3.7 (2.3-5.8)	
Na				
Mean ± SD	128.40±4.75	122.2±4.09	127.56±5.12	<0.0001
Median (range)	128 (118-139)	123 (112-129)	128 (112-139)	
Hepatorenal syndrome	0	3 (20.00%)	3 (2.70%)	0.002
Hepatocellular carcinoma	17 (17.71%)	3 (20.00%)	20 (18.02%)	0.73

WBCs= White blood cells, ALT= Alanine Amino Transferase, AST= Aspartate Amino Transferase, K= Serum Potassium, Na= Serum Sodium.

Table.4 Ascitic fluid study of the studied patients with SBP (survivors and non-survivors)

Variable	Survivor N=96	Non-survivor N=15	Total	P value
WBCs				
Mean ± SD	8714±39152	7596±9499	8563±36544	0.15
Median (range)	1732 (330-377750)	5000 (425-34800)	1780 (330-377750)	
Polymorph				
Mean ± SD	3638±36890	6771±9266	7521±34443	0.13
Median (range)	1336 (255-355085)	1920 (382-33060)	1347 (255-355085)	
Protein				
Mean ± SD	1.93±1.32	2.34±1.34	1.99±1.32	0.15
Median (range)	1.6 (0.2-5.9)	1.9 (0.9-5)	1.75 (0.2-5.9)	

Table.5 Comparison between different scores (Child-pugh, MELD, SOFA and AIMS65) in predicating the mortality in the patients with SBP

Variable	Survivor N=96	Non-survivor N=15	Total	P value
Child				
B	14 (14.58%)	0	14 (12.61%)	0.21
C	82 (85.42%)	15 (100%)	97 (87.39%)	
MELD score				
Mean ± SD	19.83±5.65	27.13±6.12	20.82±6.21	<0.0001
Median (range)	19.5 (7-35)	28 (13-35)	21 (7-35)	
SOFA				
Mean ± SD	9.97±8.27	10.47±2.03	10.05±7.72	0.03
Median (range)	9 (4-88)	11 (7-13)	9 (4-88)	
AIMS65				
Mean ± SD	2.43±0.72	3.13±0.52	2.53±0.74	0.0006
Median (range)	3 (1-4)	3 (2-4)	3 (1-4)	

Table.6 Multivariate logistic regression analysis of factors predicting mortality in patients with SBP (include significant variables in univariate analysis)

Variable	Odds ratio (95% confidence interval)	P value
Disturbed mental status	13.45 (0.16-1113.46)	0.25
ALT	0.997 (0.97-1.03)	0.87
AST	0.995 (0.097-1.02)	0.71
Na	0.72 (0.56-0.91)	0.006
MELD score	1.37 (1.09-1.71)	0.006
SOFA	0.52 (0.24-1.13)	0.10
AIMS65	2.44 (0.24-24.63)	0.45

Table.7 Accuracy of serum sodium and MELD score to predict SBP-related in-hospital mortality with the best predictive cut-offs

Score	cut-off	AUC 95%CI	Sensitivity %	Specificity %	PPV %	NPV %	Accuracy
MELD score	>25	0.81 (0.68-0.95)	73.3	83.3	40.7	95.2	78.3
Na	≤126	0.84 (0.76-0.91)	93.3	70.8	33.3	98.6	82.1

Fig.1 Roc curve analysis of MELD score in predicting mortality

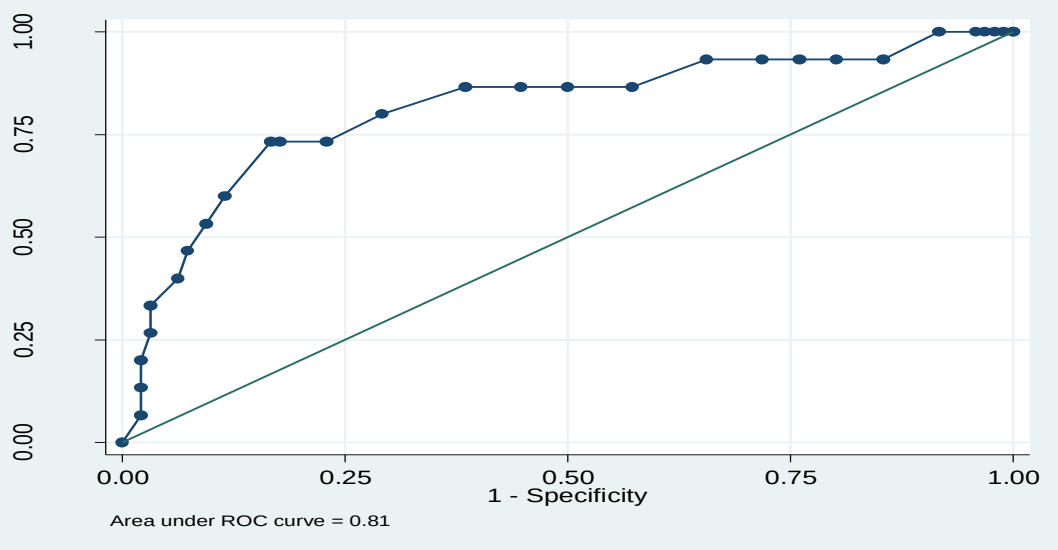


Fig.2 Roc curve analysis of Na in predicting mortality

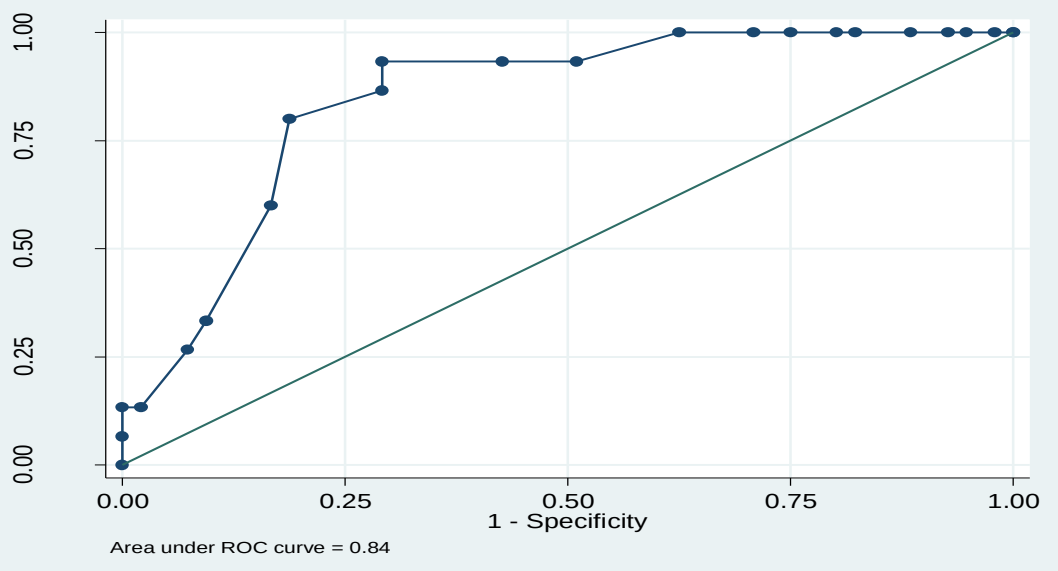
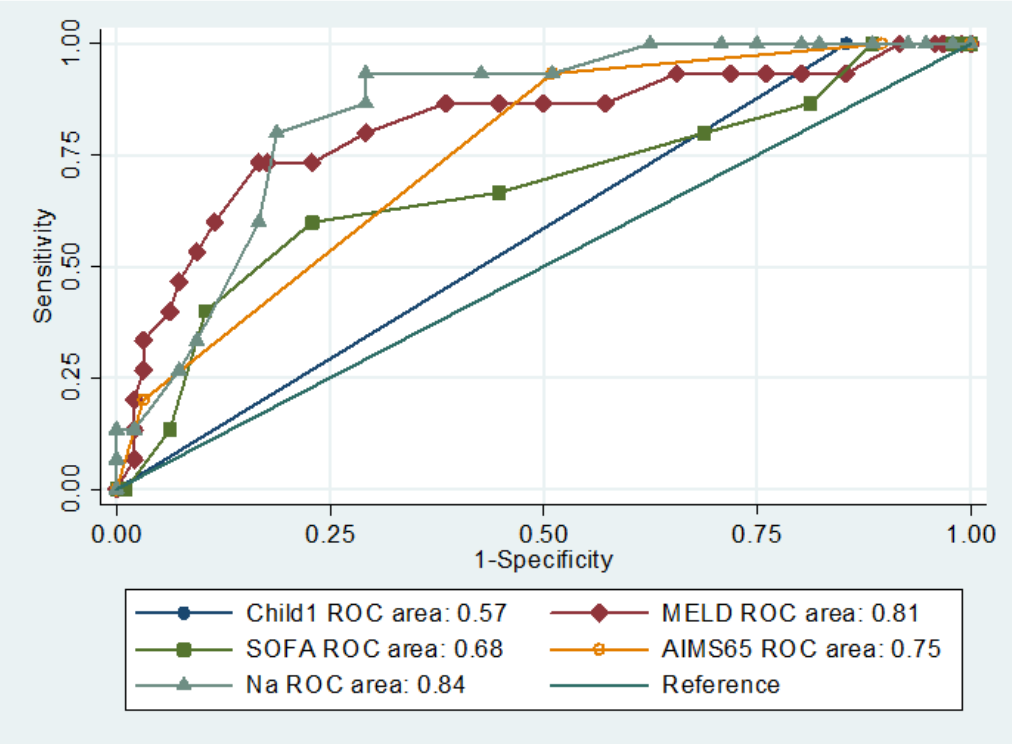


Fig.3 Roc curve of different variables in predicting mortality



MELD score has been evaluated for its predictive value in various liver disease-related research settings outside liver allocation. Indeed, it was originally developed to assess the short-term prognosis of patients with cirrhosis undergoing the transjugular intrahepatic portosystemic shunt procedure (Freeman 2007). In fact, it is a reliable measure of short-term mortality risk in patients with end-stage liver disease of diverse etiologies and is applicable over a wide spectrum of disease severity (Kamath *et al.*, 2001). The prognostic ability of this scoring system for short-term survival was also confirmed in European (Botta *et al.*, 2003) and Indian (Mishra *et al.*, 2007) series. In our study, we found MELD score to be a strong independent predictor of short-term mortality in SBP patients, with an excellent discriminatory ability that is supported by many studies as (Hassan and Abdel Rehim 2015).

We might speculate that the development of complications of cirrhosis, such as SBP, could interfere with the predictive capacity of MELD score, but retrospective analysis showed that the presence of ascites, SBP, variceal bleeding, and hepatic encephalopathy do not affect the ability of MELD score to predict survival (Wiesner *et al.*, 2001).

We found that MELD, SOFA and AIM65 scores were significantly higher in deceased patients than survivors. However, incorporating independent predictors of survival as serum creatinine, sodium, and liver enzymes into these scores improve their prognostic ability, demonstrating a better diagnostic accuracy and superiority of MELD score and serum sodium over them to predict SBP-related in-hospital mortality. These findings agreed with previous studies as (Hassan and Abdel Rehim 2015) that showed that MELD score and serum sodium has

predictive accuracy for in-hospital mortality in patients with SBP.

In our study, child-pugh score was not a significant predictive factor which is confirmed by previous studies as Wiesner *et al.,* 2001, that is because the score has shortcomings mainly related to the inability to discriminate disease severity among the sickest patients, and the subjectivity in the assessment of ascites and encephalopathy, which are also very much dependent on treatment. Moreover, even laboratory parameters, in particular prothrombin time and serum albumin, may vary from one institution to another. Besides, routine tests of renal function are not included in the score.

In addition, we have demonstrated that MELD score can significantly predict SBP-related in-hospital mortality with the greatest diagnostic accuracy (AUC = 0.81) correlated with (Hassan and Abdel Rehim 2015) who found that (AUC = 0.862).

Similarly the serum sodium is considered a good predictor with the greatest diagnostic accuracy (AUC = 84). Identifying its cut-off (≤126 mEq/L) and < 130 mEq/L according to (Musskopf *et al.,* 2012), which had very high NPV (98.6%) and sensitivity (93.3 %), that indicate they are a very good predictor of SBP-related in-hospital mortality and may construct more intensive measures in order to reduce the high mortality rates in patients with SBP and to improve transplant prioritization.

Hepatic encephalopathy, serum creatinine, liver enzymes, MELD score, SOFA score, AIMS 65 score and serum sodium are predictors of SBP-related in-hospital mortality. The incorporation of these variables together, we found that MELD score and serum sodium have the most excellent prognostic accuracy for SBP-related in-hospital mortality that may aid in further improvement of the quality of care of SBP patients and in further reduction of their short-term mortality rate. So these findings may offer a useful strategy to stratify high-risk patients on hospital admission who would benefit by intensive treatment, or to recommend prophylactic antibiotics even without previous episodes of SBP, which may need further studies.

MELD score and serum sodium were confirmed as prognostic factors for mortality in cirrhotic patients with SBP. Using one simple formula, significant mortality can be predicted accurately in these patients. Further prospective studies are needed to validate the MELD score and serum sodium in a larger number of cirrhotic patients with SBP in other institutes, in particular, community-based practices where the prevalence of death may be higher or lower.

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How to cite this article:

Khairy H. Morsy, El-zahraa M. Meghezel and Selvana T. Labib. 2018. Predictors of In-Hospital Mortality in Cirrhotic Patients with Spontaneous Bacterial Peritonitis. *Int.J.Curr.Microbiol.App.Sci.* 7(03): 3410-3421. doi: https://doi.org/10.20546/ijcmas.2018.703.393