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Research Article

EVALUATION OF PROGNOSTIC MARKERS IN PATIENTS OF DECOMPENSATED CIRRHOSIS AWAITING LIVER TRANSPLANT

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A R T I C L E I N F O

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A B S T R A C T

Introduction: In an era of liver transplantation, being readily available at major metro cities in India, the need for optimal prioritization of organ transplant waiting list has become more than a far-fetched reality. This article is a part of study done on patients presenting with end of line spectra of liver diseases, both acute and chronic(acute liver failure, acute on chronic liver failure and decompensated cirrhosis) to evaluate their descriptive markers which govern the morbidity and mortality and hence helpful in prioritizing the waiting list. **Objectives** of this study is to study the the descriptive clinico-laboratory markers of prognosis and their relationship with acute mortality(within 30 days of admission) and morbidity(number of days of hospital stay in a month) in patients of decompensated cirrhosis *and* to determine and compare the diagnostic performance of these clinico-laboratory markers to ascertain acute mortality (within 30 days of admission) and morbidity**. Methodology**: The study was a prospective descriptive and observational study, which included the indoor patients admitted under department of medicine, Gandhi medical college Bhopal, who fulfilled selection criteria(inclusion and exclusion) .A written informed consent was taken and their clinical and laboratory parameters at the time of admission and during the course of hospital stay were recorded. These patients were followed up till a period of 1 month from admission to note outcomes.**Results and conclusion:** In patients of decompensated cirrhosis markers of acute inflammation (neutrophil to lymphocyte ratio, C-reactive protein , Q-SOFA) had better diagnostic performance than MELD score and serum sodium levels for predicting short term mortality. When these markers were assesed to predict morbidity in terms of total number of days spent in hospital in a month, significant correlation was found only with higher MELD score and low seum sodium levels.

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INTRODUCTION

In the era of liver transplant which is now available in major metro cities in India and in near future will be available in other cities as well there is need for prognostic indicators to prioritize the waiting list for liver transplant patients. The model for end stage liver disease has been a validated prognostic marker used in US and other countries which accurately predicts mortality, however there have been discrepancy between the mortality and MELD scores(1) of patients, which creates a lacunae for search of newer prognostic markers which predict mortality and morbidity in patients of cirrhosis and help better prioritizing the liver transplant waiting list.

The prognostic markers included in this study are those which are feasible at a tertiary care level hospital which in near future may be equipped by liver transplantation facilities.

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As the input of patients is very high in the donor deficient scenario the priority listing is must to categorize patients needing transplant on an urgent basis and those who can predictably survive transplant procedure and post-transplant care. Due to the limitations of unavailability of the transplantation at present the study is focused mainly on pre-procedure patients with a descriptive analysis on their characteristics and mortality outcomes as a function of laboratory and clinical scores which may be in future be utilized to prioritize the waiting list.

Objectives

1. To study the descriptive clinico-laboratory markers of prognosis and their relationship with acute mortality(within 30 days of admission) and morbidity(number of days of hospital stay in a month) in patients of decompensated cirrhosis
2. To determine and compare the diagnostic performance of these clinico-laboratory markers to ascertain acute mortality (within 30 days of admission) and morbidity.

Methodology

The study was a prospective descriptive and observational study, which included the indoor patients admitted under department of medicine, Gandhi medical college Bhopal, who fulfilled selection criteria(inclusion and exclusion) .A written informed consent was taken and their clinical and laboratory parameters at the time of admission and during the course of hospital stay were recorded. These patients were followed up till a period of 1 month from admission to note outcomes.

Sample Size: 90 patients

Definition for Inclusion

A Patient of Cirrhosis as proven by histology or by clinic-radiological criteria fulfilling at-least 2 out of 3

1. In-homogenous Hepatic Surface with Splenomegaly
2. Portal Hypertension on Radiological Finding
3. Platelet counts less than 100,000/m3 or Variceal Changes in Endoscopy

Criteria for Exclusion

1. Acute Hepatitis
2. Hematological Disorders
3. Hepatocellular Carcinoma
4. Other Concurrent Malignancies
5. Immunocompromised State
6. Parameters Noted

Main Event of Hospitalization*:* This includes the main concern for which the patient was primarily brought to hospital 1: Uncontrolled Ascites 2: Hepatic Encephalopathy, 3: Variceal Bleed 4: Other. If the patient was brought to hospital with overlapping events, in such scenario Variceal bleeding when coincident with other conditions was considered main cause of admission whereas Hepatic encephalopathy will be given weightage over uncontrolled ascites

Q-SOFA: is a bedside prompt that identifies patients with suspected infections who are at greater risk for a poor outcome outside Intensive care unit. 1) Low blood pressure less than 100 mm hg, high respiratory rate > 22 breaths per minute or altered mentation (Glasgow Coma scale of less than 15).(2)

SIRS(systemic inflammatory response syndrome): According to Recommendations of American College of Chest Physicians/Society of Critical Care Medicine, Patients are considered to have SIRS if they fulfilled at-least two of the following Criteria (a) Core temperature of > 38 C or less than 36 C. (b) Heart rate of > 90 beats per minute (c) Respiratory rate of > 20 breaths/ min , Partial Carbon monoxide pressure (PaCO2) <33mmhg or need of mechanical ventilation (d) WBC counts of > 12000 or < 4000, or differential count showing > 10 percent immature polymorphonuclear cells.(3)

Neutrophil to Lymphocyte Ratio*:* Neutrophil to Lymphocyte ratio is defined as absolute Neutrophil count divided by absolute lymphocyte count if it is more than 5 it is considered to be elevated. The participants will be divided into 3 categorical groups with A) NLR less than 2; B) NLR 2-5 C) NLR more than 5.

C Reactive Protein*:* The baseline C reactive Protein using qualitative method was noted at the time of admission (ELISA test with a positive test indicative of C reactive Protein levels more than 10mg/l)

Serum Sodium Levels: Patients Serum Sodium levels will be noted during the time of admission and the results will be plotted by dividing the participants in three groups in respect to the sodium levels;1) Less than 130 Mmol/L 2) 131 to 135 Mmol/L 3) 136 Mmol/L

These will be plotted against mortality at end of one month and the total number of days spent in hospital and compared with MELD score.

Results

Baseline Characterstics

The participants mean age was 47.12 years (std dev ± 12.71) of which 73 were males and 17 being female. the maximum age 70 years and minimum age 18 years.The main complain requiring admission amongst these patients was hepatic encephalopathy (36.6% n=33), uncontrolled ascites(33.3% n=30), Gastrointestinal bleed (28.8% n=26).

Table 1 Main event of hospitalization

Main Event of Hospitalization	Frequency	Percent
1. Uncontrolled Ascites	30	33.33%
2. Hepati Encephalopathy	33	36.67%
3. Upper GI Bleed	26	28.89%
4. Other	1	1.11%
5. TOTAL	90	100%

The most common etiology of the patients with decompensated cirrhosis observed was alcohol related liver disease (49%),hepatitis B virus(30%), HCV (1%) and other unknown (18%).A total of 22 out of 90 participants had mortality. The mean Age (Years) in the Mortality group was 48.91 (±12.22), and in the survivor group was 46.54 (±12.91).There was no significant difference noted in patients in terms of age, sex, etiology of hospitalization and mortality.

Main event of hospitalization

Patients admitted with hepatic encephalopathy had the maximum mortality39.4%(n=13) followed by variceal bleed 23.1%(n=6), and uncontrolled ascites 10%(n=3).

Table 2 Main Event of Hospitalization and Mortality

Main Event of Hospitalization	Mortality				Total		Chi-Square Test	
	Yes		No					
	N	%	N	%	N	%	χ^2	*P* Value
Uncontrolled Ascites	3	10.0%	27	90.0%	30	100.0%	7.732	0.038
Hepatic Encephalopathy	13	39.4%	20	60.6%	33	100.0%		
Upper GI Bleed	6	23.1%	20	76.9%	26	100.0%		
Others	0	0.0%	1	100.0%	1	100.0%		
Total	22	24.4%	68	75.6%	90	100.0%		

SIRS criteria

a. 60.7% (n=17)patients who fulfilled SIRS criteria had Mortality and 39.3%(n=28) patients survived.

b. 8.1% (n=5)patients who did not fulfil SIRS criteria had Mortality Present, whereas 91.9%(n=62) survived.

There was a significant difference in the two groups in terms of Mortality ($\chi 2 = 28.950$, $p = 0.000$).

The area under the ROC curve (AUROC) for SIRS predicting Mortality was 0.805 (95% CI: 0.706 - 0.905), thus demonstrating good diagnostic performance. It was statistically significant (p = 0). At a cutoff of Present, SIRS predict Mortality with a sensitivity of 77.3%, and a specificity of 83.8%.

QSOFA criteria

a. 59.4%(n=19) patients who fulfilled Q-SOFA criteria had Mortality and 40.6%(n=32) survived.
b. 5.2% (n=3)patients who did not fulfill Q-SOFA criteria had Mortality and 94.8%(n=55) patients survived.

There was a significant difference in the two groups in terms of Mortality ($\chi 2 = 32.804$, $p = 0.000$)

The area under the ROC curve (AUROC) for Q-SOFA predicting Mortality was 0.836 (95% CI: 0.749 - 0.923), thus demonstrating good diagnostic performance. It was statistically significant (p = 0). At a cutoff of Positive, Q-SOFA predicts Mortality with a sensitivity of 86.4%, and a specificity of 80.9%.

Neutrophil to lymphocyte ratio

Table 3 Comparison of Two Groups in Terms of Neutrophil to Lymphocyte Ratio

Neutrophil to Lymphocyte Ratio	Mortality				Total		Chi-Square Test	
	Present		Absent					
	N	%	N	%	N	%	χ^2	*P* Value
Less than 2	0	0.0%	16	100.0%	16	100.0%	25.784	0.000
2 to 5	8	15.4%	44	84.6%	52	100.0%		
More than 5	14	63.6%	8	36.4%	22	100.0%		
Total	22	24.4%	68	75.6%	90	100.0%		

a. **Neutrophil to lymphocyte ratio less than 2**: this group consisted of 16 patients amongst which all of them survived(n=16) and no mortality was observed(n=0).
b. **Neutrophil to lymphocyte ratio from 2 to 5** : amongst this group(n=52), 15.4%(n=8) did not survive, whereas 84.6%(n=44) survived.
c. **Neutrophil to lymphocyte ratio more than 5:** Amongst this group (n=22), 63.6% (n=14) did not survive, whereas 36.4%(n=8) survived.

There was a significant difference in the groups in terms of Mortality ($\chi 2 = 25.784$, $p = 0.000$)

The area under the ROC curve (AUROC) for Neutrophil to Lymphocyte Ratio (Categorical) predicting Mortality was 0.802 (95% CI: 0.711 - 0.893), thus demonstrating good diagnostic performance. It was statistically significant (p = 0). At a cutoff of more than 5, Neutrophil to Lymphocyte Ratio (Categorical) predicts Mortality with a sensitivity of 63.6%, and a specificity of 88.2%.

C Reactive Protein test (qualitative)

Table 4 Comparison of Two Groups in Terms of C-Reactive Protein

C-Reactive Protein	Mortality				Total		Chi-Square Test	
	Present		Absent					
	N	%	N	%	N	%	χ^2	*P* Value
Positive	21	52.5%	19	47.5%	40	100.0%	30.685	0.000
Negative	1	2.0%	49	98.0%	50	100.0%		
Total	22	24.4%	68	75.6%	90	100.0%		

a. C reactive protein Qualitative Positive(n=40): amongst this group 52.5%(n=21) had mortality and 47.5%(n=19) survived.
b. C reactive protein Qualitative Negative(n=50): amongst this group 2%(n=1) had mortality and 98% (n=49) patients survived.

There was a significant difference in the two groups in terms of Mortality ($\chi 2 = 30.685$, $p = 0.000$)

The area under the ROC curve (AUROC) for C Reactive Protein predicting Mortality was 0.838 (95% CI: 0.768 - 0.907), thus demonstrating good diagnostic performance. It was statistically significant (p = 0). At a cutoff of Positive, C Reactive Protein predicts Mortality with a sensitivity of 95.5%, and a specificity of 72.1%.

Serum sodium levels

Table 5 Comparison of Two Groups in Terms of Serum Sodium Level (categorical)

Serum Sodium Level	Mortality				Total		Chi-Square Test	
	Present		Absent					
	N	%	N	%	N	%	χ^2	*P* Value
<130 mmol/L	16	39.0%	25	61.0%	41	100.0%	9.971	0.005
130-135 mmol/L	2	6.7%	28	93.3%	30	100.0%		
>135 mmol/L	4	21.1%	15	78.9%	19	100.0%		
Total	22	24.4%	68	75.6%	90	100.0%		

When Serum sodium Levels where categorized in three sub-groups(less than 130 mmol/L, 130-135mMol/L, More than 135 mMol/L)

a. Less than 130 mMol/L (n=41): 39.0%(n=16) patients of this group had Mortality and 61.0% (n=25) survived.
b. 130-135mMol/L(n=30): 6.7%(n=2) patients in this group had mortality and 93.3%(n=30) survived.
c. More than 135mMol/L(n=19): 21.1%(n=4) patients had mortality and 78.9%(n=15) survived.

There was a significant difference in the groups in terms of Mortality ($\chi 2 = 9.971$, $p = 0.005$).

The area under the ROC curve (AUROC) for Serum Sodium Level predicting Mortality was 0.652 (95% CI: 0.522 - 0.783), thus demonstrating poor diagnostic performance. It was statistically significant (p = 0.021). At a cutoff of less than 130 mmol per L, Serum Sodium Level predicts Mortality with a sensitivity of 72.7%, and a specificity of 63.2%

MELD Score

Table 6 MELD Score

	Mortality				Student's t-test	
	Present		Absent			
	Mean	SD	Mean	SD	t	p value
MELD Score	19.64	6.63	14.24	4.95	3.517	0.001

a. The mean MELD Score amongst the non-survivor group was 19.64 (±6.63), and amongst the survivor group was 14.24 (±4.95). There was a significant difference in the two groups in terms of MELD Score (t = 3.517, p = 0.001), with the MELD Score being significantly higher amongst the non survivors.
b. The area under the ROC curve (AUROC) for MELD Score predicting Mortality was 0.74 (95% CI: 0.614 - 0.867), thus demonstrating fair diagnostic performance. It was statistically significant (p = 0.001).At a cutoff of >17.5, MELD Score predicts Mortality with a sensitivity of 63.6%, and a specificity of 75.0%

Morbity Characteristics

Correlation of Number of days of hospital stay in a month with Categorical Clinical Parameters

Parameters		Number of days of hospital stay in a month		Student's t-test/ One-Way ANOVA	
		Mean	SD	t/F value	p value
Gender	Male	9.62	3.81	0.635	0.531
	Female	8.94	3.98		
Etiology	HBsAg Positive	8.85	3.46	0.403	0.752
	HCV Positive	11.00	-		
	Alcohol	9.82	3.99		
	Other or Unknown	9.56	4.15		
Main Event of Hospitalization	Uncontrolled Ascites	9.50	3.46	2.687	0.051
	Hepatic Encephalopathy	10.58	4.56		
	Visceral Bleed	7.96	2.71		
	Others	13.00	-		
SIRS	Present	9.89	4.70	0.594	0.556
	Absent	9.31	3.40		
Q-SOFA*	Positive	10.75	4.62	2.137	0.038
	Negative	8.79	3.15		
Neutrophil to Lymphocyte Ratio (Categorical)	<2	8.50	3.37	0.995	0.374
	2-5	9.46	3.27		
	>5	10.27	5.17		
C Reactive Protein	Positive	9.95	4.53	0.982	0.329
	Negative	9.12	3.16		
Serum Sodium Level*	<130 mmol/L	10.61	4.35	3.636	0.030
	130-135 mmol/L	8.83	3.12		
	>135 mmol/L	8.11	3.03		

***Significant at p<0.05**

Table sub-group A-1: Categorical Parameters and their relation to mortality

There was a significant association of Number of days of hospital stay in a month with serum sodium levels, but no other parameters.

DISCUSSION AND CONCLUSION

The study constituted of 90 patients of decompensated cirrhosis, neutrophil to lymphocyte ratio, c- reactive Protein levels, and MELD score and QSOFA were compared with short term mortality (at the end of 30 days from admission). Out of total 90 patients 22 patients (24.4%) observed mortality and 68 patients (75.6%) survived.

Predictors of Mortality in Decompensated Cirrhosis

Neutrophil to Lymphocyte ratio: The mean NLR was found significantly (t = 5.544, p = 0.000) higher amongst patients who observed mortality 6.15(±2.33) than those who survived 3.14 (±1.8) at the end of 1 month , When it was grouped in three categories (<2,2-5,>5), the group more than 5 had highest mortality of 63.6%(n=14) , and patient with ratio less than 2 had no mortality. which when compared to previous studies by Kalra *et al*(4), Moreau *et al*(5) and Zhang *et al*(6). Also, the area under the ROC curve (AUROC) for Neutrophil to Lymphocyte Ratio (Categorical) predicting Mortality was 0.859 (95% CI: 0.775 - 0.943), thus demonstrating good diagnostic performance. It was statistically significant (p = 0) and at a cutoff of >4.43, Neutrophil to Lymphocyte Ratio predicts Mortality with a sensitivity of 77.3%, and a specificity of 86.8%,.

C reactive protein positive patients had a mortality of 52.5% (n=21) and that in negative group had a mortality of 2%(n=1) with a statistically significant difference between two groups. ($\chi2$ = 30.685, p = 0.000).which was consistent with the previous studies as by Cervoni *et al*(7) in 2016, Ha and colleagues(8), and Zhao *et al*(9)The area under the ROC curve (AUROC) for C Reactive Protein predicting Mortality was 0.838 (95% CI: 0.768 - 0.907), thus demonstrating good diagnostic performance. It was statistically significant (p = 0). At a cutoff of Positive, C Reactive Protein predicts Mortality with a sensitivity of 95.5%, and a specificity of 72.1%.

The mean **serum sodium levels** in patients who had mortality was 127.32 (±11.97), and those who survived had a mean sodium level of 130.03 (±7.02) and there was no significant difference between two groups. (t = -1.341, p = 0.192), however when serum sodium levels were categorized(<130, 130-135, > 135) the group with serum sodium levels less than 130 mEq/L had a mortality of 39.0%(n=16) which was significantly higher than the remaining two groups ($\chi2$ = 9.971, p = 0.005). A Study by Jong Hoon Kim, at el (10) also observed the similar trends with lower serum sodium levels having higher mortality rates.area under the ROC curve (AUROC) for Serum Sodium Level predicting Mortality was 0.671 (95% CI: 0.524 - 0.819), thus demonstrating poor diagnostic performance. It was statistically significant (p = 0.016). At a cutoff of less than 127.5, Serum Sodium Level predicts Mortality with a sensitivity of 63.6%, and a specificity of 73.5%.

Q-SOFA Patients who qualified QSOFA had a mortality of 59.4%(n=19) and that in Q-SOFA negative group had a mortality of 5.2%($\chi2$ = 32.804, p = 0.000) The area under the ROC curve (AUROC) for Q-SOFA predicting Mortality was 0.836 (95% CI: 0.749 - 0.923), thus demonstrating good diagnostic performance. It was statistically significant (p = 0). At a cutoff of Positive, Q-SOFA predicts Mortality with a sensitivity of 86.4%, and a specificity of 80.9%.

MELD score in patients who had mortality was 19.64 (±6.63),and in survivor group was 14.24 (±4.95). with a significant difference between two groups (t = 3.517, p = 0.001). The area under the ROC curve (AUROC) for MELD Score predicting Mortality was 0.74 (95% CI: 0.614 - 0.867), thus demonstrating fair diagnostic performance. It was statistically significant (p = 0.001). At a cutoff of >17.5, MELD Score predicts Mortality with a sensitivity of 63.6%, and a specificity of 75.0%.

Which was the best predictive marker for short term mortality?

When the Prognostic markers were compared using receiver operator curve analysis it was observed that markers of Inflammation such as Neutrophil to lymphocyte ratio, C-reactive protein and QSOFA had higher diagnostic performance to predict early mortality(within 30 days) among the patients than that of MELD score or serum sodium levels. Amongst the markers of inflammation, C-reactive protein, Neutrophil to lymphocyte ratio and Q-SOFA in following order had sensitivity and specificity.

Prognostic marker	AUROC	Sensitivity	Specificity	p-value
Neutrophil to lymphocyte ratio(more than 4.43)	0.859	77.3%	86.8%	0.00
C reactive Protein positive (More than 10mg/L)	0.838	95.5%	72.1%.	0.00
Q-SOFA	0.836	86.4%	80.9%	0.00
MELD score more than 17.5	0.74	63.6%	75.0%	0.001
Serum Sodium levels Less than 127.5mEq/L	0.671	63.6%	73.5%.	0.016

Table showing diagnostic performance of prognostic markers in sub group A.

Whereas low Serum sodium levels in terms of sensitivity and specificity showed the least accurate performance, and was less predictive of short term mortality, however independently the serum sodium levels less than 130mEQ/l had significantly higher mortality 39.0% when compared to those who had a value higher than 130 mEQ/L.

Morbidity(in terms of number of days spent in hospital):
An increasing MELD score showed a mild positive correlation (r= 0.307,p = 0.003) with number of days spent in hospital, and Serum Sodium levels showed a negative correlation(pearson's r=-0.310) (p=0.003), suggesting that lower the serum sodium levels longer is the stay in hospital.

CONCLUSION

In patients of decompensated cirrhosis markers of acute inflammation (neutrophil to lymphocyte ratio, C-reactive protein , Q-SOFA) had better diagnostic performance than MELD score and serum sodium levels for predicting short term mortality. When these markers were assesed to predict morbidity in terms of total number of days spent in hospital in a month, significant correlation was found only with higher MELD score and low seum sodium levels.

References

1. Peng Y, Qi X, Guo X. Child–Pugh Versus MELD Score for the Assessment of Prognosis in Liver Cirrhosis. Medicine (Baltimore) [Internet]. 2016 Mar 3 [cited 2019 Sep 9];95(8). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4779019/
2. Osatnik J, Tort-Oribea B, Folco J, Sosa A, Ivulich D, Kleinert MM, *et al*. Predictive Performance of Quick Sequential Organ Failure Assessment Scoring in an Argentinian Hospital. JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH [Internet]. 2018 [cited 2019 Jun 12]; Available from: https://jcdr.net/article_fulltext.asp?issn=0973-709x&year=2018&volume=12&issue=10&page=OC22&issn=0973-709x&id=12150
3. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM Consensus Conference on Sepsis and Organ Failure. CHEST. 1992 Jun 1;101(6):1481–3.
4. Kalra A, Wedd JP, Bambha KM, Gralla J, Golden-Mason L, Collins C, *et al*. Neutrophil-to-lymphocyte ratio correlates with proinflammatory neutrophils and predicts death in low model for end-stage liver disease patients with cirrhosis. Liver Transpl. 2017;23(2):155–65.
5. Moreau N, Wittebole X, Fleury Y, Forget P, Laterre P-F, Castanares-Zapatero D. Neutrophil-to-Lymphocyte Ratio Predicts Death in Acute-on-Chronic Liver Failure Patients Admitted to the Intensive Care Unit: A Retrospective Cohort Study. Shock. 2018 Apr;49(4):385–92.
6. Zhang H, Sun Q, Mao W, Fan J, Ye B. Neutrophil-to-Lymphocyte Ratio Predicts Early Mortality in Patients with HBV-Related Decompensated Cirrhosis. GastroenterolResPract. 2016;2016:4394650.
7. Cervoni J-P, Amorós À, Bañares R, Luis Montero J, Soriano G, Weil D, *et al*. Prognostic value of C-reactive protein in cirrhosis: external validation from the CANONIC cohort. Eur J Gastroenterol Hepatol. 2016 Sep;28(9):1028–34.
8. Ha YE, Kang C-I, Joo E-J, Joung M-K, Chung DR, Peck KR, *et al*. Usefulness of C-Reactive Protein for Evaluating Clinical Outcomes in Cirrhotic Patients with Bacteremia. Korean J Intern Med. 2011 Jun;26(2):195–200.
9. Zhu S, Waili Y, Qi X, Chen Y, Lou Y, Chen B. Serum C-reactive protein predicts early mortality in hospitalized patients with HBV-related decompensated cirrhosis. Medicine. 2017 Jan;96(4):e5988.
10. Kim JH, Lee JS, Lee SH, Bae WK, Kim N-H, Kim K-A, *et al*. The Association Between the Serum Sodium Level and the Severity of Complications in Liver Cirrhosis. Korean J Intern Med. 2009 Jun;24(2):106–12.