The Egyptian Journal of Hospital Medicine (April 2023) Vol. 91, Page 3938-3944

Spontaneous Bacterial Peritonitis in Critically Ill Hepatic Patients Adverse Outcomes Detected Echocardiographically and Electro Cardiographically

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ABSTRACT

Background: Cirrhotic patients who develop Spontaneous Bacterial Peritonitis (SBP), they most likely have cirrhotic cardiomyopathy, which is characterized by diminished contractility in response to stress despite a generally normal resting cardiac output. **Objective:** Patients who developed SBP can be assessed prognosticaly by electrocardiography and echocardiography together with scoring systems this was proposed in our study.

Patients and Methods: Four hundred cirrhotic patients were included in our study admitted to our general ICU in Critical Care Medicine Department, Faculty of Medicine, Helwan University in the period from May 2020 to September 2022, all patients did not undergo transplant within the study duration and if any patients underwent liver transplant within one year of the last SBP episode were excluded. Patients were classified according to electrocardiographic parameters into low and high QT_C and echo cardiographically with tissue Doppler into low and high E/E´ Ratio with a cut off values $\geq$ 480 ms for QTc and $\geq$ 10 for E/E´ ratio.

Results: Four hundred cirrhotic patients were classified into two groups according to the QT_C and E/E´ into low QTc and low E/E´ group included 200 patients and high QT_C and high E/E´ group included the other 200 patients. Higher QT_C and higher E/E´ were associated with increased in hospital acute kidney' injury, ICU mortality and 1 year mortality. **Conclusion:** Cirrhotic patients with SBP associated with high QT_C and high E/E´ are at high risk for acute kidney injury, ICU mortality and 1 year mortality, also, high QT_C duration $\geq$ 480 ms and high E/E´ ratio of $\geq$ 10 together with diabetes mellitus, left atrial diameter and left atrial volume, were independent parameters associated with increased mortality at 1-year followup.

Keywords: SBP, Cirrhotic cardiomyopathy, QTc duration $\geq$ 480, E/E´ $\geq$10, 1-year mortality.

INTRODUCTION

Chronic liver disease, of which cirrhosis is the primary cause, is the ninth largest cause of mortality in the United States [(1)]. Spontaneous bacterial peritonitis (SBP) linked with liver is connected to a significant mortality rate of roughly 40–70% at one year. Patients with cirrhosis and this particular group in particular constitute a high-risk demographic.

After the resolution of the infection by spontaneous bacterial peritonitis, all patients became candidates for liver transplant [(2)]. For the purpose of analyzing and estimating the prognosis of cirrhotic patients, the Child-Pugh Score (CPS) and the Model for End Stage Liver Disease (MELD) score are utilized. The 3-month mortality in patients with liver disease has been found to be well predicted by the MELD score. In order to classify patients prior to liver transplantation, liver transplant hospitals in the United States have used MELD Scores since 2002 [(3)].

Patients with cirrhosis typically have significant vasodilatation of the splanchnic artery system, It stimulates the sympathetic nervous system, the renin-angiotensin system, and causes the release of anti-diuretic hormone. The overactive sympathetic state, hyperdynamic circulation, high normal to augmented cardiac output, and low degree of systemic vascular resistance are all symptoms of decompensated liver cirrhosis [(4-5)]. Nearly 50 years ago, structural anomalies on postmortem investigation by **Lunseth *et al.*** [(6)] cirrhotic patients have heart problems.

In order to describe the phenomenon of altered diastolic relaxation, suboptimal response of the heart's contractile function to physiological or pathological stressors, and electro-physiological abnormalities in the absence of known cardiac disease, **Ma and Lee** coined the term "cirrhotic cardiomyopathy" [(7)].

No matter the underlying etiology of liver disease, cirrhotic cardiomyopathy might still exist. Heart dysfunction was present in almost 50% of cirrhotic patients having liver transplants, and seven to twenty one percent of mortality following orthotopic liver transplantation are attributable to frank heart failure [(8)].

When echocardiography is performed on patients with liver cirrhosis, the ratio of relatively normal to enhanced ejection fraction might lead to a false sense of normality. In order to identify patients who are more likely to have difficulties or have a poorer prognosis, it is essential to measure cardiac function in more detail in liver transplant candidates [(9)].

In order to better understand cirrhotic patients with SBP, we concentrated on this demographic because it is a significant stressor on the cardiovascular system and may mask or exacerbate underlying heart disease.

Patients who developed SBP can be assessed prognosticaly by electrocardiography and echocardiography together with scoring systems this was proposed in our study.

Received: 11/10/2022
Accepted: 12/12/2022

PATIENTS AND METHODS

Four hundred patients with the diagnosis of liver cirrhosis associated with spontaneous bacterial peritonitis (SBP) were included in the study, which was done in the Critical Care Department, Faculty of Medicine Helwan University in the period from May 2020 to September 2022 after approval of the ethical committee of the Faculty of Medicine Helwan University and a written detailed consent from the participants. Diagnosis of cirrhosis was done by either biopsy or radiologically and patients were included irrelevant to the etiology of liver cirrhosis.

After ruling out all possible causes of secondary bacterial peritonitis, abdominal paracetesis was performed to diagnose spontaneous bacterial peritonitis. The results showed polymorphonuclear leukocytes/mm3 of more than or equal to 250 polymorphonuclear leukocytes in the Cubic millimeter of ascitic fluid, with positive fluid cultures [(10-11)].

Exclusion criteria included the following: patients who underwent liver transplantation within a year of the episode of SBP were also excluded, as were patients who were diagnosed with secondary peritonitis or cardiomyopathy (i.e., left ventricular ejection fraction (LVEF) less than 45%).

We gathered, tallied, reviewed, and processed all of the data. Age, sex, test results, clinical history of hypertension, diabetes, and dyslipidemia were all gathered. Child-Pugh Score (CPS) and Model for End Stage Liver Disease (MELD) Score were computed for each patient at the time of spontaneous bacterial peritonitis (SBP). Furthermore, echocardiograms acquired at the time of SBP were used to provide tissue Doppler-derived indices of systolic and diastolic function, in addition to conventional echocardiography. Left ventricular ejection fraction (LVEF%), left atrial diameter and volume (LAD and LAV), tissue Doppler velocities (peak early [E] velocity; E/E′ ratio, isovolumic contraction time [IVCT], isovolumic relaxation time [IVRT], and ejection time [ET], and mitral inflow velocities (peak early [E] velocity; deceleration time [DT] E/E′ ratio, by tissue Doppler and analysis of myocardial performance index (a measure of global left ventricular function [MPI] [(12)].

QTC interval was determined on an EKG at the time of the diagnosis of spontaneous bacterial peritonitis (SBP). The QT interval was electronically and manually monitored. The BAZET formula $QT_C = QT/\sqrt{RR}$ was then used to adjust QT intervals for heart rate. According to the criteria of QTC $\geq$ 480 ms and E/E′ ratio $\geq$ 10, patients were categorized.

All trial participants were monitored for the development or incidence of acute renal failure (ARF) or acute kidney injury (AKI), which was determined as either an increase in baseline creatinine of > 50% or an absolute rise in baseline creatinine of > 0.4 mg/dl.

From our follow-up data, we additionally evaluated the ICU mortality as well as the one-year mortality. With a cut off value of 480 ms for the QTC and 10 for the E/E' ratio, continuous variables were divided into high and low groups. To assess the link between mortality and other factors, such as QTC duration and E/E′ ratio, logistic regression analysis was carried out. The influence of measures of interest for various independent variables, such as E/E′ ratio $\geq$ 10 and $QT_C \geq$ 480 ms in predicting 1-year mortality, were controlled using the Cox proportional hazard model [(13)].

Ethical consent:

The study was authorised by Helwan University's Ethical Institutional Review Board. All study participants provided written informed permission after being informed of our research's goals. The Declaration of Helsinki for human beings, which is the international medical association's code of ethics, was followed during the conduct of this study.

Statistical analysis

All of the collected data was reviewed, coded, tabulated, and entered into a computer using social science statistical software (SPSS 27). The type of data collected for each parameter was suitably analyzed when the data were provided. The average and standard deviation ($\pm$ SD) for numerical data, as well as the frequency and proportion of categorical data. The Student-T test was used to assess the statistical significance of the variance between the means of the two research groups. The chi-square test was used to examine the relationship between two qualitative variables. The baseline characteristics and demographics were assessed using descriptive statistics. In order to determine statistical significance, means and standard deviation for the APACHE II score, child-pugh score, MELD score, and echocardiographic data were determined. To examine the association between the two qualitative variables, frequencies and percentages were employed for complications such acute kidney injury (AKI), ICU mortality, and 1-year death. In the examination of 1-year survival, the Kaplan Meier curve was also employed. P value less than 0.05 was regarded as significant.

RESULTS

Four hundred cirrhotic patients with SBP were classified into two hundred patients with low QT_C < 480 ms and E/E′ ratio < 10 in one group (Group I) and the other two hundred patients with high $QT_C \geq$ 480 ms and E/E′ ratio $\geq$ 10 in another group (Group II).

Table (1) showed the mean age in low QT_C and low E/E′ ratio 44.08 $\pm$ 9.52 versus 44.43 $\pm$ 9.24 in the high QT_C and high E/E′ ratio, with 113 males (56.5%) and 87 females (43.5%) in the low QT_C and low E/E′ ratio and 114 males (57%) and 86 females (43%), in high QTc and high E/E′ ratio with non-significant statistical difference. Additionally, no risk factor was statistically significant when compared between the two groups.

Table (1): Demographic data and risk factor in both groups.

		SBP with low QTC < 480 m sec and low E/E´ < 10	SBP with high QTC ≥ 480 m sec and high E/E´ ≥ 10	Test of sig.		
		Mean ± SD N(%)	Mean ± SD N(%)	Value	P Value	Sig.
AGE		44.08 ± 9.52	44.43 ± 9.24	t = -3.80	0.705	NS
Sex	Male	113 (56.5%)	114 (57%)	X^2 = 0.01	0.920	NS
	Female	87 (43.5%)	86 (43%)			
DM	No	80 (40%)	78 (39%)	X^2 = 0.04	0.838	NS
	Yes	120 (60%)	122(61%)			
HTN	No	100 (50%)	102 (51%)	X^2 = 0.04	0.841	NS
	Yes	100 (50%)	98 (49%)			
Dyslipidemic	No	110 (55%)	112 (56%)	X^2 = 0.04	0.841	NS
	Yes	90 (45%)	88 (44%)			

All scores (APACHE II, child-pugh and MELD), were non-significant statistically while the echocardiographic parameters were all significant statistically left atrial diameter (LAD) 3.5 ± 0.3 in low QT_C and a low E/E´ ratio group. Versus 4.47 ± 0.32 in the high QT_C and high E/E´ ratio. Left atrial volume 78.66 ± 5.15 Versus 97.43 ± 1.8, Deceleration time (DT) 175.57 ± 12.4 versus 124.46 ± 13.91, isovolumic relaxation time (IVRT) 94.67 ± 3.16 versus 65.26 ± 3.06, isovolumic contraction time (IVCT) 0.18 ± 0.08 versus 0.35 ± 0.09, Ejection time (ET) 0.35 ± 0.03 Versus 0.25 ± 0.3, myocardial performance index 0.78 ± 0.23 versus 1.64 ± 0.35 in the low QT_C and low E/E´ ratio versus the high QT_C and high E/E´ ratio respectively. Also ICU length of stay was shorter in the low QT_C and low E/E´ ratio 7.81 ± 1.79 versus 17.17 ± 2.3 in the high QT_C and high E/E´ ratio with a significant statistical difference (Table 2).

Table (2): APACHE II score, child pugh score, MELD score, Echocardiographic parameters and ICU length of stay when compared between both groups.

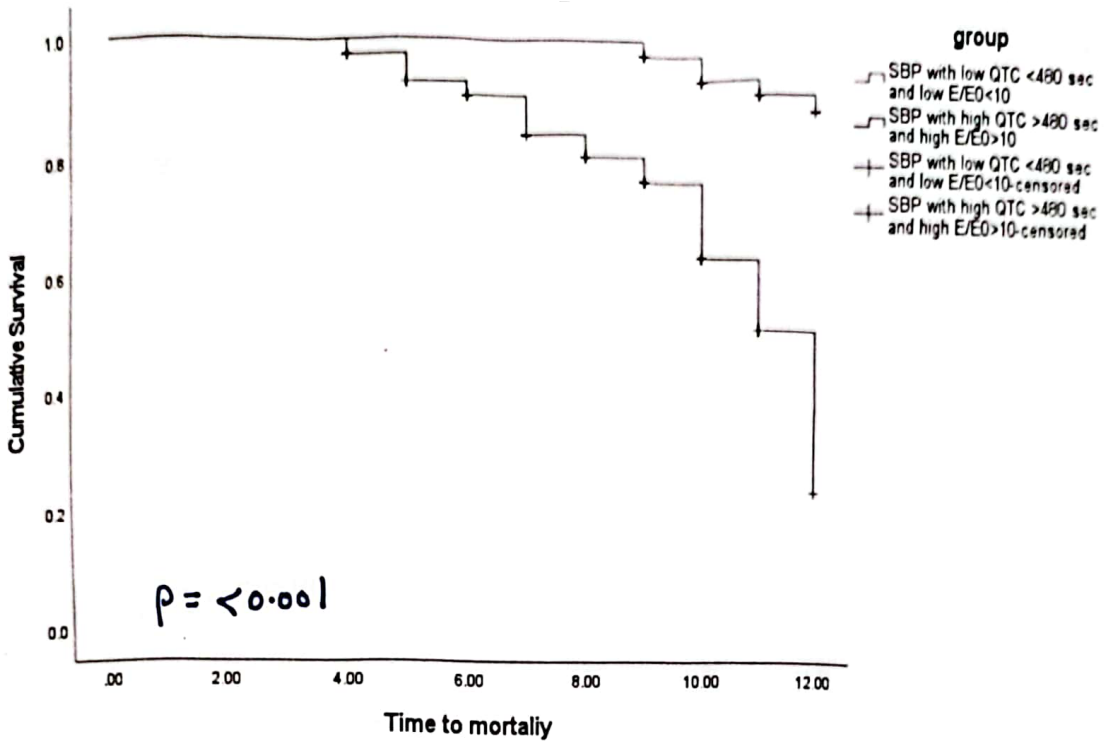
	SBP with low QTC < 480 m sec and low E/E´ < 10	SBP with high QTC ≥ 480 m sec and high E/E´ ≥ 10	Test of sig.		
	Mean ± SD N(%)	Mean ± SD N(%)	Value	P Value	Sig.
APACHE II	12.16 ± 1.49	12.19 ± 1.5	t = 0.25	0.85	NS
CPS	12.69 ± 1.73	12.65 ± 1.72	t = 0.23	0.816	NS
MELD SCORE	12.6 ± 1.13	12.48 ± 1.86	t = 0.26	0.86	NS
LAD	3.5 ± 0.3	4.47 ± 0.32	t = -30.75	<0001	S
LAV	78.66 ± 5.15	97.43 ± 1.8	t = -48.66	<0001	S
DT	175.57 ± 12.4	124.46 ± 13.91	t = 38.79	<0001	S
IVRT	94.67 ± 3.16	65.26 ± 3.06	t = 94.45	<0001	S
IVCT	0.18 ± 0.08	0.35 ± 0.09	t = -21.23	<0001	S
EJECTION TIME	0.35 ± 0.03	0.25 ± 0.03	T = 30.8	<0001	S
MPI	0.78 ± 0.23	1.64 ± 0.35	t = -29.05	<0001	S
ICU LOS	7.81 ± 1.79	17.17 ± 2.3	t = -45.42	<0001	S

Table (3) showed acute kidney injury (AKI) incidence 40 patients in the low QT_C and low E/E′ versus 110 patients in the high QT_C and high E/E′ with a significant statistical difference with more renal affection in the high QT_C and high E/E′ ratio. ICU mortality was one case in the low QT_C and low E/E′ ratio versus 26 cases in the high QT_C and high E/E′ ratio with a significant statistical difference. One-year mortality was 14 cases in the low QT_C and low E/E′ ratio versus 65 cases in the high QT_C and high E/E′ ratio group with a significant statistical difference.

Table (3): Acute kidney injury, ICU mortality and 1-year mortality when compared between both groups.

		SBP with QTC < 480 m sec and low E/E′ < 10	SBP with high QTC ≥ 480 m sec and high E/E′ ≥ 10	Chi Square test		
		Mean ± SD N(%)	Mean ± SD N(%)	X^2	P Value	Sig.
AKI	No	160 (80%)	90 (45%)	$X^2 = 52.27$	<0.001	S
	Yes	40 (20%)	110 (55%)			
ICU mortality	No	199 (99.5%)	174 (87%)	$X^2 = 24.82$	<0.001	S
	Yes	1 (0.5%)	26 (13%)			
1 Year Mortality	No	186 (93%)	135 (67.5%)	$X^2 = 41.03$	0.001	S
	Yes	14 (7%)	65 (32.5%)			

Higher QT_C and higher E/E′ ratio were independently predicted higher 1-year mortality on regression analysis, together with the risk factor diabetes mellitus and the echocardiographic parameters left atrial diameter and left atrial volume (Table 6). Acute kidney injury was diagnosed during ICU and hospital stay, assessment of etiologies of acute renal failure was 10 patient from the 40 patients (25%) who developed acute kidney injury in the low QT_C and low E/E′ ratio group were due to hepatorenal syndrome versus 90 patients out of 110 patients in the high QT_C and high E/E′ ratio (81.8%) were diagnosed as heptorenal syndrome, the rest were secondary to dehydration and shock in both groups. Usage of albumin as a plasma expander was non-significant, statistically in the two groups either with or without acute kidney injury respectively 93% vs 91.9%, p = 0.62.



Kaplan Meier survival curve.

Figure (1): Kaplan Meier Survival curve with more worse outcome in patients in the high QT_C and high E/E′ group.

Table (4) showed non-significant statistical relation to the 1-year mortality as regard demographic data & a risk factor except for diabetes mellitus which was significant statistically in relation to 1-year mortality p-value <0.001 Also group with SBP and high QTC and high E/E′ was strongly correlated to 1 year mortality.

Table (4): Demographic data, Risk factors and groups in relation to 1- year mortality

		1 Year Mortality		Chi-square test		
		No	Yes			
		N(%)	N(%)	X^2	P-Value	Sig.
Sex	Male(ref)	183 (57.01%	44(55.7%)	0.05	0.833	NS
	Female	138(42.99%)	33(44.3%)			
DM	No (ref)	148 (46.11%)	10 (12.66%)	29.68	<0.001	S
	Yes	173 (53.89%)	69 (87.34%)			
HTN	No (ref)	162 (50.47%)	40 (50.63%)	0.001	0.979	NS
	Yes	159 (49.53%)	39 (49.37%)			
Dyslipidemic	No (ref)	184 (57.32%)	38 (4.1%)	2.18	0.140	NS
	Yes	137 (42.68%)	41 (51.9%)			
Group	SBP with low QTC <480 m sec and low E/E´ <10 (ref)	186 (57.94%)	14 (17.72%)	41.03	<0.001	S
	SBP with high QTC > 480 m sec and high E/E´ >10	135 (42.06%)	65 (82.28%)			

Table (5) showed that age, sex and scoring systems APACHE II, child-Pugh score and MELD score together, with the risk factors hypertension and dyslipidemia were all non-significant statistically in relation to the 1-year mortality while echocardiographic parameters (left atrial diameter, left atrial volume, deceleration time, isovolumic relaxation time, isovolumic contraction time, ejection time, myocardial performance index), diabetes melltius, group with SBP and high QTc $\geq$ 480 m Sec and high E/E´ $\geq$ 10 together with ICU length of stay and sex in reference to male gender were all significant statistically in univariate logistic analysis in relation with 1-year mortality p-value < 0.001.

Table (5) Univariate logistic regression analysis of factors affecting 1-year mortality

	P Value	Sig.
AGE	0.477	1.01 (0.98 – 1.04)
APACHE II	0.581	1.38 (1.25 – 1.53)
CPS	0.400	0.94 (0.82 – 1.08)
MELD SCORE	0.521	1.27 (1.16 – 1.38)
LAD	<0.001	3.12 (1.95 – 4.98)
LAV	<0.001	1.1 (1.07 – 1.14)
DT	<0.001	0.97 (0.96 – 0.98)
IVRT	<0.001	0.94 (0.92 – 00.96)
IVCT	<0.001	71.25 (8.45-600.43)
EJECTION TIME	<0.001	0 (0 – 0)
MPI	<0.001	2.92 (1.8 – 4.74)
ICU LOS	<0.001	1.15 (1.09 – 1.22)
Sex (Ref: male)	<0.001	1.05 (0.64 – 1.73)
DM	<0.001	5.9 (2.94 – 11.87)
HTN	0.979	0.99 (0.61 – 1.63)
DYSLIPIDEMIC	0.141	1.45 (0.88 – 2.37)
SBP with high QTc $\geq$ 480 m sec and High E/E´ $\geq$10	<0.001	6.4 (3.45 – 11.87)

Table (6) showed that in multi-variate logistic regression analysis of variables that were studied in the univariate logistic regression analysis that diabetes mellitus, group of SBP with high QTc $\geq$ 480 m sec, E/E´ $\geq$10, left atrial diameter and left atrial volume were statistically significant as independent factors leading to 1-year mortality with p-value 0.0001, 0.002, 0.040, 0.014 respectively.

Table (6) Multivariate logistic regression analysis of factors affecting 1-year mortality

	P Value	Sig.
DM	0.0001	7% (3% - 15%)
Group of SBP with high QTc $\geq$ 480 m sec and E/E´ $\geq$10	0.002	1.49 (1.15 – 1.87)
LAD	0.040	9% (9%-9.5%)
LAV	0.014	1.07(1.01-1.3)

DISCUSSION

Researching the electrographic and echocardiographic changes and their effects on outcomes like acute kidney injury during ICU stay, ICU mortality, and 1-year mortality in cirrhotic spontaneous bacterial peritonitis, which reflects parameters leading to the diagnosis of cirrhotic cardiomyopathy and hidden cardiac status in cirrhotic spontaneous bacterial peritonitis patients Acute renal damage occurred more often among patients with high QTC and high E/E´ ratios while they were in the intensive care unit, as well as in terms of ICU mortality and 1-year mortality. It has been debated in many investigations to determine if extended QTC in cirrhotic serves as a prognostic indicator [9, 13, 14].

It was previously suggested that electrical alterations inside the cardiac myocytes and cell membranes may happen with gradual worsening of the chronic liver illness, resulting to QTC interval lengthening.

Additionally, longer QTC intervals were associated with higher child-pugh and MELD scores in earlier investigations [15].

The extended QTC interval in cirrhotics is reversible following liver transplantation, according to **Finucci *et al.*** [14] The development of acute renal damage has been observed to be associated with a greater death rate in cirrhotic patients with spontaneous bacterial peritonitis (SBP).

Patients with spontaneous bacterial peritonitis who developed acute renal failure had lower systolic blood pressures, higher cardiac outputs, and higher levels of plasma renin activity, aldosterone, and norepinephrine when compared to other patients without renal failure at the time of infection [16, 17].

This indicates that the study group has substantial circulatory dysfunction and failure. However, the worse diastolic function with high E/E′ ratio and other echocardiographic parameters, along with the progressing electrical disturbances at the cellular level as indicated by a prolonged and high QTC interval duration, can be blamed for the state of circulatory dysfunction. Ejection fraction was unaffected in either patient group who developed acute kidney injury. In our study, albumin was used at a higher rate, but it was used similarly in the groups with and without ARF.

Also, using albumin as a plasma expander in the management of SBP has been stated as an additional renoprotective effect in the treatment of spontaneous bacterial peritonitis. Additionally, we had observed that 81.8% of the high QTC and high E/E′ group and roughly 25% of the low QTC and low E/E′ group respectively experienced hepato-renal syndrome development.

Sort *et al.* [18] examined the impact of albumin on renal function in patients with cirrhosis and spontaneous bacterial peritonitis and found that almost 30% of his patients had hepatorenal syndrome (SBP).

As the Child-Pugh and MELD ratings have limitations as prognostic assessments, various other scores have been developed recently [19-20].

For a more accurate risk assessment of patients before liver transplantation, more information is required. Heart failure, which is a predictor of death, develops in about 20–25% of patients after liver donation. Pre-transplant echocardiographic data is crucial and predicts post-transplant outcome, according to numerous studies [21, 22].

In the earlier investigations, worse outcomes were related to higher levels of diastolic heart failure, high E/E′ $\geq$ 10, and larger left atrial volume index.

In several investigations, patients with high E/E′ $\geq$ 10 and left atrial volume index with advanced diastolic dysfunction without organ transplant had poorer outcomes. According to our research, left atrial volumes of 97 cc and above were linked to extremely bad outcomes.

In general, it is yet unclear how diastolic dysfunction and diastolic heart failure affect patients with cirrhosis [22, 23].

Also, earlier studies did not increase diastolic dysfunction in cirrhotic patients with spontaneous bacterial peritonitis, who are very high-risk patients. A 1-year death rate of 45.5% indicates the high-risk nature of our study groups. Univariate and multivariate regression analyses on a number of echocardiographic parameters were conducted to determine the values that positively or negatively linked with 1-year mortality. Left atrial volume and diameter had a substantial correlation with 1-year mortality and were discovered to be independent risk factors for 1-year mortality, along with group-specific SBP with high QTc $\geq$480 m sec and high E/E′ ratio and also the risk variables of diabetes mellitus.

In our study, the comparison of the LA diameter, LA volume, E/E ratio, DT, IVCT, IVRT, ejection time (ET), and myocardial performance index (MPI) between the two groups revealed statistically significant differences in all of these variables.

The effects of high-volume paracentesis on hemodynamics and cardiovascular function have been examined in a number of minor studies. Numerous investigations revealed that paracentesis increased neurohormonal activity, which was accompanied by arterial pressures fall and peripheral vasodilatation is highlighted [24, 25].

After paracentesis, the inferior vena cava is decompressed, which causes a reduction in thoracic pressures and an initial counterbalancing increase in cardiac output. This is brought on by the previously dilated splanchnic circulation being suddenly mechanically decompressed. Along with other parameters, these impacts may also be more harmful to renal function and sodium management [26, 27].

CONCLUSION

Patients with spontaneous bacterial peritonitis who have high QTC and high E/E′ ratios have a greater chance of developing acute renal damage, dying in the hospital, and dying within one year. These patients may require careful monitoring.

Additionally, there was a significant correlation between the 1-year mortality and the echocardiographic parameters of left atrial volume, and left atrial diameter.

Selecting patients with minimal risk of problems who will benefit from early transplantation requires more exact selection criteria.

IF earlier liver transplantation can revert and normalize these parameters, more follow up is needed with multi-centric large trials to further explore our findings and their relationships.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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