Echocardiographic and Electrocardiographic Predictors of Adverse Outcomes in Spontaneous Bacterial Peritonitis

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Background: Patients with cirrhosis who develop Spontaneous Bacterial Peritonitis (SBP) suffer from cirrhotic cardiomyopathy which is characterized by impaired contractility in response to stress despite a relatively normal resting cardiac output. We hypothesized that electrocardiographic and echocardiographic information would help prognosticate patients developing SBP in addition to existing scoring systems. **Methods:** Cirrhotic patients admitted to Einstein Medical Center from 01/01/2005 to 6/30/2012 for SBP, and did not receive a transplant within one year, were included. Patients were classified as QTc low vs. high, and E/E' low vs. high at cut points ≥ 480 ms for QTc and ≥ 10 for E/E' ratio. We estimated 1-year survival using Kaplan Meier curves. Regression analysis and Cox proportional hazards model were used for QTc and E/E' ratio, respectively, for assessing 1-year survival. **Results:** Among 112 patients with electrocardiogram, 78 were classified as QTc low. Among 64 patients with echocardiograms, 23 were classified as E/E' low. Higher QTc was associated with increased in-hospital acute kidney injury. QTc and E/E' ratio predicted worse 1-year survival (HR = 2.16, 95% CI 1.29–3.49; HR 2.65, 95% CI 1.31–5.35, respectively) on univariate and multivariate analysis (OR = 1.02, 95% CI 1.01–1.03; HR = 3.26, 95% CI 1.22–9.82 respectively) after adjusting for both Child Pugh stage, MELD score among other risk factors. **Conclusion:** In conclusion, cirrhotic patients with SBP who present with a prolonged QTc interval are at a greater risk for acute renal failure during hospitalization. High QTc duration and an E/E' ratio of ≥ 10 independently predict increased mortality at 1-year follow-up. (J CLIN EXP HEPATOL 2017;7:321–327)

Chronic liver diseases account for roughly 35,000 deaths annually in the United States with cirrhosis being the ninth leading cause of death.¹ Spontaneous bacterial peritonitis (SBP) in cirrhosis carries a high mortality rate of about 40–70% at one year, and this group of patients particularly represent a high-risk population. All patients with SBP need to be considered for liver transplant after resolution of the infection.^{2,3} Assessment of the Child–Pugh score (CPS) and Model for End Stage Liver Disease (MELD) score is a validated method to evaluate prognosis in cirrhotic patients. The MELD score has been shown to be an excellent marker for predicting the 3-month mortality in patients with liver disease. Since 2002, liver transplant programs in the United States use MELD scores to classify patients prior to transplantation.⁴

Cirrhotics suffer from significant vasodilation of the splanchnic arterial system resulting in the activation of the renin-angiotensin system, the sympathetic nervous system and antidiuretic hormone release. Patients with decompensated cirrhosis are in a state of sympathetic over activity with a hyperdynamic circulation characterized by high normal to elevated cardiac output and heart rate, accompanied by a low systemic vascular resistance.^{5–9} The possibility of underlying cardiac abnormalities in cirrhotic patients came to light almost 50 years ago when Lunseth et al. demonstrated structural abnormalities on post-mortem analysis.¹⁰ Cirrhotic cardiomyopathy, a term first introduced by Ma and Lee in 1996, refers to the phenomenon of a poor contractile response of the heart to physiological or pathological stressors and altered diastolic relaxation along with electrophysiological abnormalities, in the absence of known cardiac disease.^{10–14} Cirrhotic cardiomyopathy can be present irrespective of the etiology of liver disease. As many as 50% of cirrhotic patients undergoing liver transplantation show signs of cardiac dysfunction, and 7–21% of deaths after orthotopic liver transplantation result from overt heart failure.¹¹ Echocardiography in cirrhosis may reveal a relatively normal to increased ejection fraction creating a false sense of normalcy. It is important to assess the cardiac function in

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Abbreviations: ARF: acute renal failure; CPS: Child–Pugh score; MELD: Model for End Stage Liver Disease

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patients being considered for liver transplant in greater detail, and attempt to evaluate for prognostic markers to further identify patients at a higher risk for complications or worse outcomes.

We studied cirrhotic patients with SBP, as infection is a stressor on the cardiovascular system, and may unmask or exacerbate underlying cardiac dysfunction. The objective of our study was to examine the relationship between systolic and diastolic cardiac dysfunction based on echocardiographic parameters or QTc prolongation on electrocardiogram (EKG), and adverse outcomes such as acute renal failure (ARF) and one-year mortality in patients with cirrhosis and SBP.

MATERIALS AND METHODS

All cirrhotic patients who were diagnosed SBP between 01/01/2005 and 6/30/2012 at Einstein Medical Center, Philadelphia, PA were included in the study. Patients had a known diagnosis of cirrhosis either on biopsy or radiological imaging, and were included irrespective of the etiology of cirrhosis. SBP was diagnosed following abdominal paracentesis with results demonstrating ≥ 250 polymorphonuclear leukocytes/mm³ of ascitic fluid, positive fluid cultures,^{15–17} and after exclusion of all possible causes of secondary bacterial peritonitis.

Patients were excluded if they were diagnosed with secondary peritonitis, or had a prior history of coronary artery disease, moderate to severe valvular heart disease or cardiomyopathy (left ventricular ejection fraction (LVEF) < 45%). Patients who received a liver transplant within a year of the SBP episode were excluded.

Permission to conduct the study was obtained from the Institutional Review Board at Einstein Medical Center. All data collection was performed in a retrospective manner. Routine demographic data (age, race, and gender), clinical history (presence of hypertension, diabetes, and hyperlipidemia) and laboratory values were collected. CPS and MELD scores were calculated for all patients at the time of SBP.

Conventional echocardiographic and tissue Doppler-derived indices of systolic and diastolic function were obtained from echocardiograms performed at the time of SBP diagnosis. Measurements including LVEF, left atrial diameter and volume, doppler parameters of diastolic function using mitral valve inflow velocities (peak early [E] and peak late [A], E/A ratio, deceleration time [DT]), tissue doppler velocities (peak early [E'] velocity, E/E' ratio, isovolumic contraction time [ICT], isovolumic relaxation time [IRT], ejection time [ET]) and analysis of the myocardial performance index (a measure of global left ventricular function [MPI]) were obtained.¹⁸ The QTc interval was calculated on EKG at time of SBP diagnosis. The QT interval was measured manually and electronically in a sample of 50 healthy patients and then compared to

ascertain accuracy and reliability of the latter method which was eventually used for EKG measurements in the study ($R^2 = 0.96$, $P < 0.001$). QT intervals were then corrected depending on the rate using the BAZET formula: $QTc = QT/\sqrt{RR}$. Patients were grouped according to $QTc \geq 480$ ms and E/E' ratio ≥ 10 .

All patients included in the study were followed for the development of ARF or acute kidney injury (defined either as an increase in baseline creatinine of >50% or an absolute increase in creatinine ≥ 0.4 mg/dl from baseline) during the same hospitalization. We also assessed one-year mortality from the publicly available social security database.

STATISTICS

Demographics and baseline characteristics were summarized using descriptive statistics. Medians and corresponding 95% confidence intervals were calculated for continuous variables, and frequencies and percentages were displayed for categorical data. Kaplan Meier curves were used in the 1-year survival analyses. Continuous variables were dichotomized in high-low groups on the basis of cut off values as mentioned above. Logistic regression analysis was performed to assess the relationship between higher mortality and variables including QTc duration. The Cox proportional hazard model was used to control the effect of measurements of interest for different independent variables including $E/E' \geq 10$ in predicting 1-year mortality. JMP 10 (SAS, Cary, NC) was used for statistical analysis. The threshold for statistical significance was set at 0.05. We also performed exploratory analyses for all continuous variables and identified optimal cut points with the X tile software (Omicstools, Yale University, New Haven, CT) which has been described in detail elsewhere.¹⁹ Briefly, X-tile generates a series of plots to graphically illustrate the effect of a continuous variable on a time-defined outcome across the full spectrum of potential cut points.

RESULTS

From a total of 152 cirrhotic patients, 112 patients had EKG data available and 64 patients had echocardiographic data available at the time of SBP.

Electrocardiographic Analysis

Patients were classified into 2 groups based on the duration of their QTc interval at a cut off value of 480 ms. Their demographic data and baseline characteristics are shown in Table 1. Sixty-seven percent were male and 42% were African American. Thirty-four of 112 (30.3%) patients had a QTc duration of ≥ 480 ms. Patients within the high QTc group had a median QTc interval of 503.5 ms, compared to

Table 1 Differences Within the Cohort Based on QTc Duration.

Variable	Qtc duration		P value
	<480 ms	≥480 ms	
N	78	34	N/A
Median (range)	450 (274–479)	503.5 (480–597)	N/A
Age <60 years	48/78	24/34	0.35
Gender (M)	51/78	24/34	0.58
Race % (Caucasian, African American, Hispanic, others)	27, 45, 17, 11	32, 35, 15, 18	N/A
Hypertension	24/78	15/34	0.17
Diabetes mellitus	23/78	12/34	0.54
Hyperlipidemia	4/78	0/34	0.17
Acute kidney injury during hospital stay	36/77	26/34	0.0037
MELD score	20 (6–47)	27 (15–49)	0.0009
Child Pugh stage C	62/77	31/31	0.0008
<i>Etiology</i>			
Alcohol	24	12	0.62
Hepatitis	50	20	0.60
Other	13		0.80

450 ms in the low QTc group. There were no differences in baseline characteristics such as age, sex, medical history [hypertension (HTN), diabetes mellitus (DM), hyperlipidemia (HLD)] or etiology of cirrhosis between these groups. Patients in the high QTc group had statistically higher MELD scores and a larger proportion of the patients had stage C Child-Pugh scores (CPS = 10–15). There was an increased incidence of ARF during the same hospitalization in the high QTc group compared to the low QTc group ($P = 0.0037$). There were 68/112 (60.7%) deaths at 1 year in the total study population. The Kaplan Meier curve estimating 1-year survival in the two groups of patients is shown in Figure 1. Higher QTc duration independently predicted higher 1-year mortality on regression analysis as shown in Table 4.

Figure 1 Kaplan Meier curve showing a worse prognosis in patients with higher QTc interval.

Echocardiographic Analysis

A total of 64 cirrhotic patients with SBP had 2D echocardiogram data available. Sixty-two percent were male and 51% were African American. Patients were classified into high and low E/E' ratio groups. Their demographic data and baseline characteristics are shown in Table 2. From the 64 patients, 43 (67.2%) were in the high E/E' group. Patients within the high E/E' group were older and there was a trend toward an increased incidence of renal failure in that group ($P = 0.05$). The rest of the baseline characteristics were not significantly different between the two groups including the severity of liver disease as represented by the CPS and MELD scores. The Kaplan Meier curve estimating 1-year survival in the high versus low E/E' ratio group is shown in Figure 2. Patients in the higher E/E'

Figure 2 Kaplan Meier curve showing a worse prognosis in patients with higher E/E' ratio.

Table 2 Differences Within the Cohort Depending on E/E' Ratio.

Variable	E/E' ratio		P value
	<10	≥10	
N	23	41	N/A
Median (range)	7.54 (5.5–9.91)	12.4 (10–77)	N/A
Age <60 years	22/23	25/41	0.0026
Gender (M)	14/23	26/41	0.84
Race% (Caucasian, African American, Hispanic, others)	30, 56, 9, 5	22, 49, 19, 10	N/A
Hypertension	10/23	14/41	0.45
Diabetes mellitus	6/23	16/41	0.29
Hyperlipidemia	1/23	3/41	0.62
Acute kidney injury during hospital stay	10/23	28/41	0.05
MELD score	20 (11–32)	21 (6–47)	0.65
Child Pugh stage C	21/23	38/41	0.84
<i>Etiology</i>			
Alcohol	8/23	11/40	0.54
Hepatitis	17/23	24/40	0.26
Other	2/23	10/40	0.11

ratio group had a poorer survival rate ($P = 0.0078$) at one year. As shown in Table 5, E/E' ratio ≥ 10 (HR = 3.3, 95% CI 1.23–10.05) was predictive of mortality independent of age >60 years, gender, HTN, DM, HLD, Child Pugh scores, MELD scores, E/A ratio and acute kidney injury.

Other echocardiographic indices such as left atrial (LA) diameter, LA volume, E/A ratio, deceleration time (DT), isovolumic contraction time (ICT), isovolumic relaxation time (IRT), ejection time (ET) and myocardial performance index (MPI) fraction were found to have no association with the development of ARF. LVEF was not significantly different for patients who suffered from renal failure ($66 \pm 11\%$ vs. $62 \pm 10\%$ respectively; $P = 0.096$) or death at one year ($66 \pm 10\%$ vs. $62 \pm 11\%$ respectively; $P = 0.173$) compared to those who did not.

We performed X-tile analyses on the above-mentioned echocardiographic parameters to determine an association between numerical cut off values with hazard ratios generated by the program, and higher mortality as shown in Table 3.

Table 3 X-tile Program Determined Numerical Cut Off Values That Optimized Correlation With Higher Mortality at the End of One Year.

Variable	Cut off value	P value, hazard ratio (HR)
LA volume (cc)	87	0.02, HR > 1
E/A ratio	1	0.01, HR < 1
E/E' ratio	9.5	0.006, HR > 1
DT (msec)	67	0.01, HR > 1
ICT (msec)	42	0.02, HR < 1

Renal Failure

A total of 55.3% (62/112) patients were diagnosed with ARF during their hospitalization. An assessment of the etiologies for ARF revealed that a total of 27.7% (31/112) of the patients were diagnosed with hepatorenal syndrome. The rest of the patients were thought to have a combination of etiologies for AKI ranging from dehydration (14.2%) to shock (8.0%) within the study group. Use of albumin as plasma expander was similar in both groups with and without ARF, respectively (91.9% vs. 88%; $P = 0.48$).

DISCUSSION

Our study is the first to our knowledge to compare the impact of both electrocardiographic and echocardiographic changes on outcomes such as acute kidney injury during hospital stay and 1-year mortality among cirrhotic

Table 4 Regression Analysis Showing Relationship Between Risk Factors and 1-Year Mortality.

Variable	Odds ratio (95% CI)	P value
Age	12.6 (3.4–47.1)	<0.001
Hypertension	0.6 (0.2–1.8)	0.38
Diabetes	0.8 (0.2–2.4)	0.68
Hyperlipidemia	0.8 (0.1–11.4)	0.91
Child Pugh score	1.5 (1.02–2.1)	0.03
MELD score	1.1 (1.01–1.03)	0.03
QTc duration	1.02 (1.01–1.03)	0.003

Table 5 Univariate and Multivariate Analyses Assessing Relationship Between Risk Factors and 1-Year Mortality.

Variable	Univariate HR (95% CI)	Multivariate HR (95% CI) <i>n</i> = 50
Age > 60	2.03 (1.27–3.20)	1.67 (0.67–4.27)
Gender	1.29 (0.80–2.14)	0.83 (0.35–2.04)
Hypertension	1.01 (0.63–1.59)	2.25 (0.89–5.35)
Diabetes	0.97 (0.58–1.58)	1.08 (0.44–2.47)
Hyperlipidemia	1.6 (0.39–4.30)	0.73 (0.13–3.07)
Acute kidney injury	3.36 (2.08–5.56)	3.14 (1.12–9.05)
Child Pugh Score (continuous)	8.64 (2.71–52.6)	17.2 (4.04–98.55)
MELD (continuous)	1.06 (1.03–1.09)	1.07 (1.01–1.15)
E/A <1 or ≥2	2.11 (1.21–3.72)	0.54 (0.22–1.35)
E/E' (high vs. low)	2.65 (1.31–5.35)	3.3 (1.23–10.05)

patient with SBP. Patients within the higher QTc group had a greater MELD score and CPS. They experienced a higher incidence of acute kidney injury during stay and had a higher 1-year mortality on both univariate and multivariate analyses. A higher E/E' ratio of ≥ 10 was also associated with a significantly higher 1-year mortality after adjusting for additional risk factors.

Studies evaluating the role of a prolonged QTc as a prognostic marker have been controversial in cirrhotics.^{13,20,21} It is hypothesized that with progressive worsening of the underlying chronic liver disease, electrophysiological changes may occur within the cardiac myocytes, and cell membranes resulting in QTc interval prolongation. Prior studies have demonstrated higher CPS and MELD scores as seen in prior studies.²² A study by Finucci et al. in Italy found that the prolonged QTc interval in cirrhotics may, in fact, be reversible after liver transplantation.²⁰

Renal failure is a serious complication in cirrhotic patients with SBP and is associated with a higher mortality.^{23,24} A study by Ruiz-del-Arbol et al. that prospectively followed SBP patients for the development of renal failure found that patients who developed renal failure had lower systolic blood pressures, cardiac outputs, and higher levels of plasma rennin activity, aldosterone and norepinephrine when compared to patients without renal failure at onset of infection.²⁵ This was thought to be indicative of more severe circulatory dysfunction in the former group. Our study showed no difference in the ejection fraction in patients who developed renal failure but the state of circulatory dysfunction can be explained in part by worse diastolic function seen with the higher E/E' ratio and progressive electrical disturbances at the cellular level as indicated by a higher QTc duration. We found a high rate albumin use in our study population that was similar in both patient with and without ARF. Plasma expansion

with albumin in the treatment of SBP has established additional renoprotective effect in treatment of SBP. We also found that more than a quarter of all patients studied were diagnosed to have hepatorenal syndrome. Sort et al. reported a similar rate (30%) of development of hepatorenal syndrome in their study analyzing the effect of albumin on renal function in patients with cirrhosis and SBP.²⁶

The CPS and MELD scores have limitations as prognostic scores, and several alternative scores have been suggested in the recent years.^{27–34} In the current situation where there is shortage of organs, additional data is needed for better risk stratification of patients prior to liver transplantation. Heart failure occurs in almost 20–25% of patients following liver transplantation and is a predictor of mortality.^{35,36} Studies have revealed that pre-transplant echocardiographic data can also help in predicting post-transplant outcomes.^{36,37} These studies revealed worse outcome with greater degrees of diastolic heart failure including parameters such as $E/E' > 10$ and higher left atrial volume index. Though we did not include patients who received liver transplantation, our study demonstrated worse outcomes in this group of patients with more advanced diastolic function in the absence of organ replacement. Our analysis revealed left atrial volumes of 87cc and above to be associated with worse outcomes.

The role of diastolic dysfunction in general cirrhotic patients remains unclear^{36,38,39} but prior studies have not assessed patients with SBP, a very high-risk population within the cirrhotic group. A mortality rate of more than 60% at 1 year confirms the high risk nature of our study population. We performed X-tile analyses on several echocardiographic parameters to demonstrate values that correlated with 1-year mortality either positively or negatively. LA volume, E/A ratio, DT, E/E' ratio, and the ICT were found to have statistically significant cut off as represented in the results section. We intend these results to be hypothesis generating in the utilization of these parameters for further prognostication in larger studies.

The hemodynamic consequences of large volume paracentesis and their effect on cardiovascular function have been evaluated in several smaller scale studies. Studies suggest an increase in neurohormonal activity following paracentesis with concurrent accentuation of peripheral vasodilation and reduction in arterial pressures.^{40,41} The sudden mechanical decompression of an already dilated splanchnic circulation may further vasodilate this vascular bed in patients with a poorly vasoreactive bed. While these effects may have an overall negative effect of sodium regulation, and renal function among other parameters, there is an initial counterbalancing increase in cardiac output immediately following paracentesis due to decompression of the inferior cava vein and reduction of thoracic pressures.^{42,43} Intravenous administration of plasma expanders attenuates the effects of post paracentesis circulatory dysfunction. We hypothesize that patients with

co-existent diastolic failure may also suffer from a failure to appropriately enhance their cardiac output following paracentesis and may be at higher risk for circulatory dysfunction, pulmonary edema, renal failure and worse outcomes. Our study was inadequate to test this hypothesis but we did report a high rate of appropriate use of plasma expanders in this at risk population (100% in large volume paracentesis of more than 5 l). Whether there should be a lower threshold for use of plasma expanders with paracentesis in patients with diastolic dysfunction remains to be studied.

This study is subject to certain limitations. First, this is single center retrospective study. EKG and echocardiographic data were not available for all patients with cirrhosis and SBP during the study period, and hence it led to the exclusion of several patients from the final analysis. They were also unavailable for comparison post therapy in a majority of the patients. Additionally, the EKG and echocardiogram may have been obtained in SBP if there was a clinical suggestion of cardiac dysfunction, and therefore, there may be an element of inevitable selection bias in this retrospective analysis. Patients with prior known cardiomyopathy were excluded from the study. It is, therefore, possible that those with a high burden of cardiac dysfunction that was exacerbated by cirrhosis or SBP were inadvertently excluded from the study. MELD and CPS are dynamic scores and may change on a daily basis. Our study included only cirrhotic patients diagnosed with SBP and generalization of these findings to all cirrhotic patients is not advised. Patients with SBP are unique as there may be an element of septic cardiomyopathy that complicates the cirrhotic cardiomyopathy. It is very difficult to separate one from the other in these patients, and hence prospective studies with serial measurements could help us understand this relationship better.

In conclusion, SBP patients with a high E/E' ratio on echocardiography and high QTc interval on electrocardiography represent at a higher risk for mortality within 1-year and may need more aggressive care and closer follow-up. QTc interval ≥ 480 ms recognized a group of patient at higher risk for developing in-hospital acute kidney injury. Optimization of the process of identifying patients who may benefit from earlier transplantation with low risk of complications remains vital. Whether these patients do better with earlier liver transplantation remains to be seen but we encourage larger prospective studies further exploring this relationship.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

Study was performed retrospectively and informed consent was not required in accordance with the Institutional Board Review recommendations.

CONFLICT OF INTEREST

The authors have none to declare.

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