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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 $\geq$480 ms for QTc and $\geq$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 electrocardiogam, 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 $\geq$10 independently predict increased mortality at 1-year follow-up. (J Clin Exp Hepatol 2017;xx:1–7)**

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 $\geq$250 polymorphonuclear leukocytes/mm^3 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 $\geq$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 $\geq$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 $\geq$480 ms. Patients within the high QTc group had a median QTc interval of 503.5 ms, compared to

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