Longitudinal Trends, Hemodynamic Profiles, and Prognostic Value of Abnormal Liver Function Tests in Patients With Acute Decompensated Heart Failure: An Analysis of the ESCAPE Trial

MICHAEL SCHOLFIELD, MD,[1] MATTHEW B. SCHABATH, PhD,[2] AND MAYA GUGLIN, MD, PhD[1]

Tampa, Florida

ABSTRACT

Background: This study analyzed liver function abnormalities in heart failure patients admitted with severe acute decompensated heart failure (ADHF).

Methods and Results: A post hoc analysis was conducted with the use of data from the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE). Liver function tests (LFTs) were measured at 7 time points from baseline, at discharge, and up to 6 months follow-up. Survival analyses were used to assess the association between admission Model of End-Stage Liver Disease Excluding International Normalized Ratio (MELD-XI) scores and patient outcome.There was a high prevalence of abnormal baseline (admission) LFTs (albumin 23.8%, aspartate transaminase 23.5%, alanine transaminase 23.8%, and total bilirubin 36.1%). The percentage of patients with abnormal LFTs decreased significantly from baseline to 6-months' follow-up. When mean hemodynamic profiles were compared in patients with abnormal versus normal LFTs, elevated total bilirubin was associated with a significantly lower cardiac index (1.80 vs 2.1; $P < .001$) and higher central venous pressure (14.2 vs 12.0; $P = .03$). Multivariable analyses revealed that patients with elevated MELD-XI scores ($\geq$16.8) had a 2-fold (hazard ratio 2.06, 95% confidence interval 1.05−4.03) increased risk of death, rehospitalization, or transplantation after adjusting for baseline LFTs, age, sex, race, body mass index, diabetes, and systolic blood pressure.

Conclusions: Abnormal LFTs are common in the ADHF population and are a dynamic marker of an impaired hemodynamic state. Elevated MELD-XI scores are associated with poor outcomes among patients admitted with ADHF. (*J Cardiac Fail 2014;20:476−484*)

Key Words: Albumin, bilirubin, creatinine, MELD.

Most of what is understood about abnormal liver function tests (LFTs) in heart failure (HF) derives from the stable chronic HF patient population.[1,2] Recent studies have analyzed abnormal LFTs in the acutely decompensated heart failure (ADHF) patient population. Abnormalities in LFTs are common, occurring in ~70% or more of these patients, and show a vastly different distribution than those in stable HF.[3,4] Presently little is known about longitudinal trends of LFTs in patients admitted with and treated for ADHF.

Abnormal LFTs in HF patients occur with 2 hemodynamic states. Decreased cardiac output leading to impaired organ perfusion is associated with acute centrilobular hepatocellular damage, ischemic hepatic injury, and necrosis. Additionally, elevated right atrial filling pressures may lead to congestive hepatic injury and a pathologic finding described as "nutmeg liver."[5] There is growing evidence that individual biochemical markers correlate with various hemodynamic states and that the degree of hepatic injury depends on the contribution of congestion versus poor perfusion. There is substantial variability among studies, and it is still unclear if elevated liver enzymes in individuals with HF are surrogates of hemodynamics.

It is generally accepted that certain LFTs, ie, total bilirubin, are strong independent predictors of increased risk

From the [1]Department of Cardiology, University of South Florida, Tampa, Florida and [2]Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida.

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Reprint requests: Michael Scholfield, MD, University of South Florida, 2 Tampa Circle, 5th Floor Cardiology, Tampa, FL 33612. Tel: 813-361-7622; Fax: 813-259-0665. E-mail: mscholfi@health.usf.edu

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of death and poor outcomes.[1,2,4] This parallels what we understand about hepatorenal syndrome and renal dysfunction predicting multisystem involvement in HF. Multiple recent studies have used the Model of End-Stage Liver Dysfunction (MELD) scoring model, which combines markers of renal and liver function to predict outcomes in HF patients, and found it to be a powerful predictive tool. Traditionally, the MELD score is used in predicting mortality and morbidity in cirrhotic patients undergoing surgery or liver transplantation. Recently Kim et al[6] applied MELD scoring to evaluate urgency for heart transplantation in ambulatory HF patients. A modified MELD score excluding international normalized ratio, calculated as MELD-XI = (5.11 × Ln total bilirubin) + (11.76 × Ln creatinine) + 9.44, has been standardized with the large number patients on anticoagulation and is highly predictive in the HF population.[7,8] MELD-XI has been shown to predict survival following left ventricular assist device implantation and is emerging as a highly predictive composite score for multisystem dysfunction in HF.[9]

The Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) collected longitudinal LFTs at admission (baseline), discharge, and follow-up to 6 months.[10] With the use of data from ESCAPE,[10] the objective of the present analysis was to: i) explore the longitudinal changes of LFTs in patients treated for ADHF; ii) explore the effects of hemodynamic profile on various LFTs; and iii) explore the prognostic implications of MELD scoring on a broad HF population.

Methods

Study Population

This study was a retrospective analysis of the publicly available and deidentified limited-access dataset from ESCAPE provided by the National Heart, Lung, and Blood Institute (NHLBI). According to NHLBI policy, datasets from major clinical trials funded by NHLBI include the protocol and all collected variables with their descriptions and definitions. Documentation for limited-access datasets is comprehensive and sufficiently clear to enable investigators who are not familiar with a specific dataset to use it.

The original study was a multicenter trial that compared therapy guided by pulmonary artery catheters with therapy guided by clinical assessment in hospitalized patients with ADHF.[10] Patients were admitted for New York Heart Association (NYHA) functional class IV symptoms, had ≥1 earlier admission for exacerbation of HF within 6 months before randomization, and had left ventricular ejection fraction (LVEF) <30% according to contrast ventriculography, radionuclide ventriculography, or quantitative echocardiography within 1 year before randomization. For this paper, we analyzed the subset of patients that had both total bilirubin and creatinine levels available at baseline (n = 346). However, not all patients had complete LFT data for every other time point.

Liver Function Tests

Liver function tests were recorded in both arms at admission, discharge, and follow-up of 2 weeks, 1 month, 2 months, 3 months, and 6 months. For our analysis, patients without recorded baseline creatinine or total bilirubin were excluded. The prevalence of patients with abnormal total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), albumin, and creatinine (Cr) levels were calculated from admission with ADHF through the 6-month follow-up. The cutoffs for abnormal values were total bilirubin >1.0 mg/dL, AST >40 IU/L, ALT >40 IU/L, albumin <3.4 g/dL, and Cr >1.3 mg/dL.

For patients randomized to the Swan-Ganz–guided therapy arm, the following hemodynamic variables were recorded and calculated: central venous pressure (CVP), pulmonary arterial systolic, diastolic and mean pressures, pulmonary capillary wedge pressure, systemic vascular resistance, mixed venous oxygen saturation, arterial blood pressure, and cardiac index (CI). In this study we used CVP and CI values recorded at the time of admission (decompensated heart failure). The Student *t* test was used to determine if there were significant differences in mean hemodynamic profiles (CVP and CI) according to baseline LFT status (abnormal vs normal).

Statistical Analysis

The MELD-XI score was calculated with the use of the following formula: (5.11 × Ln total bilirubin) + (11.76 × Ln creatinine) + 9.44. Differences in baseline characteristics according to MELD-XI score were compared with the use of Pearson chi-square for categoric variables, and Student's *t*-test and Wilcoxon rank sum test for continuous variables. A generalized estimating equation was used to test for differences in LFT status (abnormal vs normal) from the baseline (admission) visit to the 6-month visit. Student's *t*-test was used to test for difference of mean CVP and CI according to LFT status (normal v. abnormal). Kaplan-Meier survival curves and log-rank statistics were used to assess admission (baseline) LFTs and MELD-XI score associated with a composite end point of death, rehospitalization, or heart transplantation. Cox proportional hazard models were used to estimate risk of the composite end point of death, rehospitalization, or heart transplantation for each of the baseline LFTs and MELD-XI score. The LFTs were dichotomized according to their abnormal cutoff points, as presented in Table 2, and the MELD-XI score was dichotomized at the median value. Baseline MELD-XI scores were categorized according to median value (<11.4 and ≥11.4), tertiles (<8.7, ≥8.7 to <13.9, and ≥13.9), quartiles (<6.8, ≥6.8 to <11.4, ≥11.4 to <15.5, and ≥15.5), and a classification and regression tree (CART) approach (<16.8 vs ≥16.8). CART is a nonparametric data-mining tool that can segment data into meaningful subgroups and has been adapted for failure time data with the use of the Martingale residuals of a Cox model to approximate chi-square values for all possible cutoff points (http://econpapers.repec.org/software/bocbocode/s456776.htm). We applied the CART approach to identify a potential novel cutoff point that is not based on the distribution (ie, median, tertiles, and quartiles) of the MELD-XI score. All statistical analyses were performed with the use of Stata/MP 12.1 (Statacorp, College Station, Texas).

Results

Study Population

Among the 346 patients admitted with ADHF who had both total bilirubin and creatinine levels available at