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Prognosis of Patients with Advanced Liver Disease and Positive Stress Echocardiograms: Impact of Coronary Artery Disease, Non-alcoholic Steatohepatitis, and Beta-blocker Therapy

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Abstract

Background: In the general population, a positive dobutamine stress echocardiogram (DSE) in the absence of obstructive coronary artery disease (CAD) still identifies a high risk group. DSE is a widely employed screening method in candidates for liver transplantation. We investigated the prognostic impact of a positive DSE, CAD, and clinical factors in advanced liver disease.

Methods: We obtained follow-up for cardiovascular events (angina requiring revascularization, heart failure, infarction, and cardiac death) in 61 liver transplant candidates who had positive DSE and coronary angiography. Event-free survival was compared between 22 patients with obstructive CAD (≥ 70% stenosis) and 39 patients with no obstructive CAD. Cox regression was used to identify factors associated with events.

Results: Over a mean follow-up of 27 ± 28 months, 21% (8/39) of patients with positive DSE and no CAD had events compared with 45% (10/22) of patients with positive DSE and CAD (p = 0.04). Event free survival was better in those without CAD (p = 0.014) but one year cardiac mortality was similar in those with (9%) and without CAD (8%). Multivariable analysis showed that beta blocker use (HR: 4.1, 95% CI: 1.7 – 9.9, p-value = 0.010), CAD (HR: 4.4 95% CI: 1.8– 10.8, p-value = 0.008), and non-alcoholic steatohepatitis (NASH) (HR: 4.9, 95% CI: 2.0 – 11.7, p-value = 0.04) were independently associated with events.

Conclusion: Advanced liver disease patients with positive DSE are at increased risk. CAD, beta blocker use and NASH are independently associated with cardiac events.

Keywords: Dobutamine stress echo, End-stage liver disease, Coronary artery disease

Abbreviations: ACE: Angiotensin Converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker; CAD: Coronary Artery Disease; CHF: Congestive Heart Failure; DSE: Dobutamine Stress Echocardiography; EF: Ejection Fraction; ESLD: End Stage Liver Disease; LAD: Left Anterior Descending; LV: left Ventricle; WMA: Wall Motion Abnormality

Introduction

Cardiac Complications are the leading cause of mortality after orthotopic liver transplantation [1]. Dobutamine Stress Echocardiography (DSE) is widely employed for risk stratification of end-stage liver disease (ESLD) patients who are candidates for transplantation. The American Association of Liver Disease recommends a cardiac evaluation including "an assessment of cardiac risk factors with stress echocardiography as the initial screening test…" [2]. In the general population, a positive dobutamine stress echocardiogram (DSE) in the absence of obstructive coronary disease (CAD) still identifies a high-risk group whose outcome is similar to those with positive stress exams and obstructive CAD [3,4]. At our own

institution, an increasing proportion of patients undergoing screening for liver transplantation have comorbidities including hypertension, diabetes, and hyperlipidemia which is reflected in the increasing frequency of Non-Alcoholic Steatohepatitis (NASH) [5]. These patients might be expected to be at increased risk for cardiovascular events irrespective of the presence of obstructive CAD.

In this retrospective study, we compared outcomes in ESLD patients with positive DSE who had and did not have obstructive CAD. Our hypothesis was that in ESLD patients with positive DSE those without obstructive CAD still may have similar risk to those with significant CAD. This hypothesis was based on the findings of previous investigation in the general population [3,4]. We also sought to determine clinical, echocardiographic, and stress testing factors that are associated with cardiac events in ESLD patients with positive DSE.

Methods

Patient selection

The study was approved by the Indiana University Institutional Review Board. Data was retrospectively collected and analyzed from 73 patients who had positive DSE and coronary angiography out of a total of 633 patients who had both procedures between July 2006 and December 2016. Twenty-two patients had obstructive CAD defined as $\geq$ 70% diameter stenosis of a major epicardial coronary artery by quantitative angiography. Fifty-one patients had no obstructive CAD (defined as < 70% diameter stenosis). Twelve patients who had positive DSE with prior coronary bypass grafting, intermediate grade stenoses ($\geq$50 % to < 70% diameter stenosis), or extensive prior infarction were excluded since these factors could contribute to a worse prognosis in the group defined as having no significant CAD. After exclusions, there were 39 patients in the no CAD group.

Dobutamine stress echocardiography

The methods employed for stress testing have been previously described and standard endpoints were employed [6]. Beta blockers were withheld prior to testing. Before dobutamine infusion, pre-treatment with atropine was employed in some patients as previously described [5]. Images were obtained in the parasternal long and short-axis and apical four and two-chamber views at baseline, low dose, peak dose, and early recovery. Standard two-dimensional measurements were performed using established guidelines. Echocardiographic interpretation was performed by experienced faculty blinded to the results of coronary angiography and follow-up. A positive DSE was defined as an exam demonstrating a regional wall motion abnormality at rest, with stress, or both at rest and with stress [5]. The stress ECG was defined as positive for ischemia with 1 mm or more of horizontal to down sloping ST depression in any 2 consecutive leads during stress or recovery in the setting of a normal baseline ST segment.

Coronary angiography

Quantitative coronary angiography was performed by an experienced angiographer who was blinded to the results of stress echocardiography. Significant coronary disease was defined on the basis of $\geq$ 70% stenosis of a major epicardial coronary artery or a large branch vessel.

Follow-up

Follow-up was conducted by a review of electronic medical records. Hospital admission for angina resulting in angiography and revascularization, hospitalization for heart failure (CHF), non-fatal myocardial infarction, witnessed cardiac arrest, and cardiac death defined as death due to infarction, intractable CHF, or sudden death without an obvious non-cardiac cause were considered significant events. Patients who had stable liver disease, no active non-cardiac illnesses, and were found dead within a few days of their last contact with the medical system were included as sudden cardiac deaths.

Statistical analysis

Analysis was performed using SPSS version 25 (IBM, Ammonk, New York). Categorical variables were compared with Chi-square and continuous variables were compared with unpaired t-test. Kaplan-Meier analysis with the log rank test was used to compare event-free survival (using time to the first event) between the CAD and no significant CAD groups. Cox regression analysis was used to determine variables associated with events. Variables with $p<0.10$ on univariable analysis were included in multivariable analysis which employed a forward selection method. Variables with $p<0.05$ were considered significant.

Covariates

The following clinical factors were assessed for a relationship with events: age, sex, NASH, Model of End Stage Liver Disease (MELD), hypertension, smoking history, diabetes, hyperlipidemia, BMI, family history of CAD, aspirin use, beta blocker use, statin use, ACE inhibitor or Angiotensin Receptor (ARB) blocker use. The presence of CAD by angiography and resting echocardiographic and stress testing variables were also included in the analysis.

Results

Patient population

The baseline characteristics of the 61 patients are shown in **Table 1**. Of the 61 subjects, 54 had stress-induced Wall Motion Abnormalities (WMA) (30 had normal wall motion at rest with new stress-induced abnormalities, 24 had wall motion abnormalities at rest with new or worsening wall motion abnormalities with stress). There were 7 who had resting wall motion abnormalities with no stress-induced abnormalities. There were 39 patients that had an abnormal DSE and no

Table 1: Demographics of the Patient Population.

Total Patient Population (N=61)		DSE +/CAD - (n = 39)	DSE+/CAD + (n = 22)	P Value
Age, years	59.0 ± 7.7	57.31 ± 7.4	62.09 ± 7.2	0.18
Gender, females No. (%)	40 (66)	24 (62)	17 (77)	0.22
MELD score ± std deviation	16.7 ± 6.1	16.7 ± 6.7	16.6 ± 5.0	0.90
Causes of ESLD:				
NASH (%)	24 (39)	13 (33)	11 (50)	0.21
ETOH (%)	17 (28)	14 (36)	3 (14)	0.06
Hep C (%)	9 (15)	7 (18)	2 (9)	0.36
Others (%)	11 (18)	5 (13)	6 (27)	0.16
DM (%)	35 (57)	19 (49)	16 (73)	0.07
Hyperlipidemia (%)	26 (43)	13 (33)	13 (59)	0.05
Hypertension (%)	41 (67)	24 (62)	17 (77)	0.22
BMI ± std deviation	29.3 ± 5.7	30.1 ± 6.1	28.0 ± 4.9	0.18
Smoking (%)	45 (74)	28 (72)	17 (77)	0.65
Family history of CAD (%)	31 (51)	17 (44)	14 (64)	0.14
Beta Blocker (%)	28 (46)	17 (44)	11 (50)	0.64
Aspirin (%)	11 (18)	6 (15)	5 (23)	0.48
ACEI/ARB (%)	9 (15)	2 (5)	7 (32)	**0.004**
Statin (%)	16 (26)	6 (15)	10 (45)	**0.010**
Mean resting EF% ± std deviation	61 ± 10	61 ± 10	61 ± 12	0.71
Resting Echo Abnormalities	31 (51)	17 (44)	14 (64)	0.14

Abbreviations: ACEI: Angiotensin converting Enzyme inhibitor; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; CAD: Coronary Artery Disease; DM: Diabetes Mellitus; ETOH: Ethanol; Hep C: Hepatitis C; MELD: Model for End Stage Liver Disease; NASH: Non Alcoholic Steatohepatitis; Others: refers to other causes of End stage liver disease; std: standard deviation

significant CAD and 22 patients that had an abnormal DSE and significant CAD. The mean age of all patients was 59 ± 8 years and 67% were women. NASH was the most common etiology of ESLD occurring in 39%. The only statistically significant differences in the demographics between the two groups were the use of statins and ACE inhibitors/ARBs which were both more common in the CAD group. The etiologies of liver disease were not significantly different between the two groups. There were also no differences between the two groups with respect to echocardiographic and stress testing variables (**Table 2**).

Table 2: Stress Echocardiography Variables between the two groups.

	Population (N = 61)	DSE +/CAD- (N=39)	DSE+/CAD+ (N=22)	P-value
Mean resting EF% ± std deviation	61 ± 10	61 ± 10	61 ± 12	0.71
Resting Echo Abnormalities	31 (51)	17 (44)	14 (64)	0.14
Mean LV Mass, gm	66.9 ± 24.1	67.6 ± 26.6	65.7 ± 18.9	0.78
LV Cavity Dimension, cm	4.84 ± 0.63	4.85 ± 0.67	4.80 ± 0.57	0.772
Mean LVPW Diastolic Thickness, cm	1.08 ± 0.18	1.08 ± 0.19	1.08 ± 0.14	0.96
Mean RWT, cm	0.46 ± 0.1	0.46 ± 0.11	0.45 ± 0.08	0.96
Mean IVS Diastolic Thickness, cm	1.14 ± 0.23	1.15 ± 0.25	1.12 ± 0.19	0.79
Body Surface Area, m	3.0 ± 0.5	3.0 ± 0.4	2.9 ± 0.5	0.48

Reach 85% max HR/age (%)	41 (67)	24 (62)	17 (77)	0.25
Peak Heart Rate, bpm	136 ± 15	136 ± 16	136 ± 15	0.11
Peak Blood Pressure, mm Hg	137 ± 37	143 ± 41	128 ± 27	0.11
Peak Rate Pressure Product	18554 ± 4703	19224 ± 5025	17365 ± 3898	0.14

Abbreviations: bpm: beats per minute; DSE: Dobutamine Stress Echocardiography; echo: echocardiography; EF: Ejection Fraction; HR: Heart Rate; IVS: Interventricular Septum; LV: Left Ventricle; LVPW: Left Ventricular Posterior Wall, RWT: Right Wall Thickness; std: standard.

Follow-up

Over a mean duration of 27 ± 28 months, there were 18 patients (30%) that had cardiac events. Liver transplant was performed in 17 (28%) patients, 13 in the no significant CAD group and 4 in the CAD group. Events occurred in 5 (29%) patients who had a liver transplant and in 13 (30%) patients who did not have a liver transplant (p = 0.99).

In the 22 patients with CAD, 10 (45%) had cardiac events. Six patients had single events: CHF -2, angina requiring revascularization -1, non-fatal MI -1, cardiac death -1, witnessed cardiac arrest -1. The remaining four patients each had more than one event: angina and CHF -1, CHF and non-fatal MI -1, non-fatal MI and a witnessed cardiac arrest -1, non-fatal MI and cardiac death -1.

In the 39 patients with no CAD, 8 (21%) had cardiac events. Six patients had single events: CHF -3, non-fatal MI -1, and cardiac death -2. The remaining 2 patients each had more than one event: non-fatal MI and cardiac death -1, CHF and cardiac death -1. The proportion of patients that had cardiac events was significantly higher in the group with positive DSE and CAD (10/22, 45%) compared to the positive DSE and no CAD group (8/39, 21%), p = 0.04. Of the 10 CAD patients who subsequently had events, 9 had early coronary revascularization as a result of the initial DSE. Of the 9 patients, 2 had CABG and 7 had coronary stenting. Eight of the 9 patients who had early revascularization had cardiac events within the first year of follow up. At one year of follow-up 13% (4/39) of patients with positive DSE and no obstructive CAD group had events compared to 41% (9/22) of those with positive DSE and CAD (p = 0.005). At one year of follow-up cardiac death had occurred in 8% (3/39) of patients with positive DSE and no CAD, and in 9% (2/22) of those with positive DSE and CAD.

Figure 1 shows that event free survival was substantially worse in those with positive DSE and CAD compared to those with positive DSE but no significant CAD (p = 0.014).

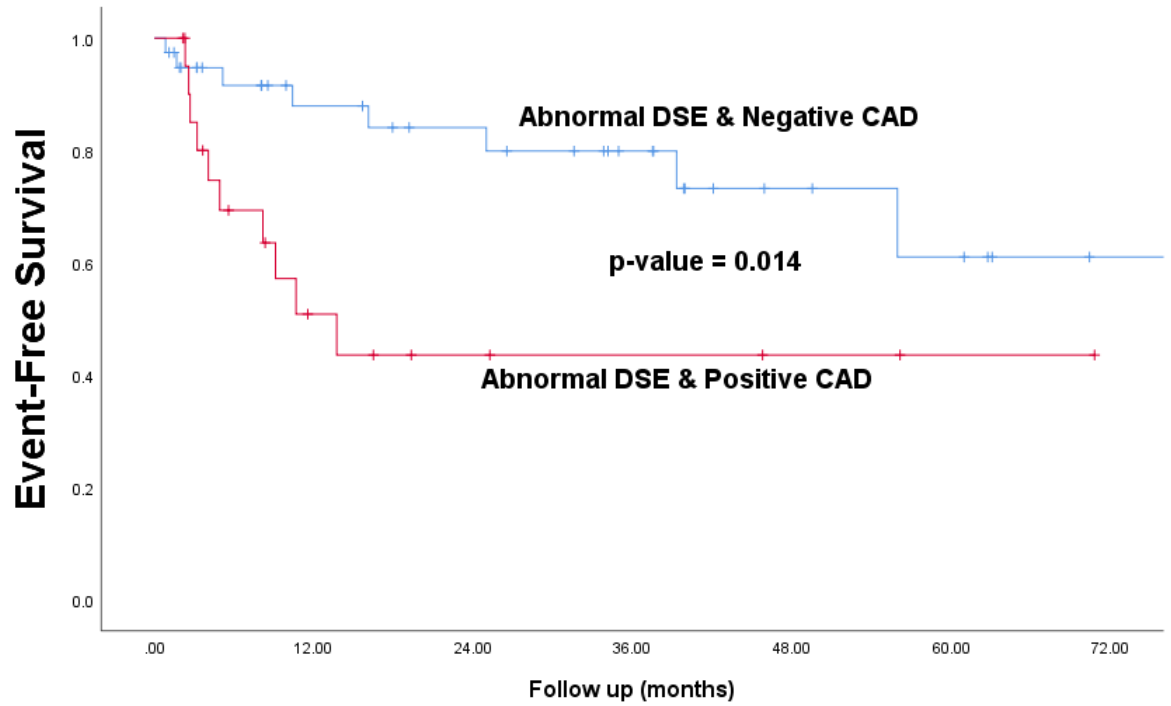

Figure 1: Event-Free Survival curves of patients with a positive DSE and no CAD and patients with a positive DSE and CAD. Event-Free Survival was significantly different and substantially worse in the CAD positive population.

Clinical, echo, and stress test variables associated with cardiovascular events

Table 3 shows the analysis of variables associated with cardiovascular events. Univariable analysis showed that NASH and CAD were significantly associated with events. Increased MELD score, the use of beta blockers, diabetes, and an ischemic ECG result trended towards significance as variables associated with events. Multivariable analysis showed that NASH, CAD, and beta blocker use (**Table 3**) were independently associated with events.

Table 3: Univariable and Multivariable Analysis in relationship to events.

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age, years	1.055 (0.984 - 1.132)	0.133		
sex, (running based on female)	0.922 (0.342 - 2.485)	0.872		
MELD score	1.074 (0.998 - 1.156)	**0.056**		
NASH vs Other Causes of ESLD	2.861 (1.123-7.286)	**0.028**	4.67 (1.65 – 13.18)	**0.004**
DM	2.801 (0.92 - 8.513)	**0.069**		
Hyperlipidemia	1.089 (0.428 - 2.770)	0.858		
Hypertension	0.740 (0.286 - 1.910)	0.538		
BMI	0.981 (0.9 -1.069)	0.657		
Smoking	1.646 (0.476 - 5.695)	0.431		
Family history of CAD	1.169 (0.460 - 2.969)	0.743		
Beta Blocker	2.418 (0.903 - 6.474)	**0.079**	3.90 (1.35 – 11.23)	**0.01**
Aspirin	1.279 (0.417 - 3.928)	0.667		
AceI/ARB	0.265 (0.035 - 1.996)	0.197		
Statin	1.725 (0.634 - 4.694)	0.286		
CAD	3.682 (1.397 - 9.702)	**0.008**	4.24 (1.46 – 12.36)	**0.008**
EF	0.991 (0.942 - 1.043)	0.740		
Resting Echo Abnormalities	2.16 (0.81 – 5.76)	0.125		
LV Mass	1.0 (0.995 - 1.023)	0.202		
LV Cavity Dimension	1.33 (0.671 - 2.661)	0.42		
LVPW Diastolic Thickness	5.7 (0.41 - 79.66)	0.197		
RWT	1.5 (0.01- 246.1)	0.874		
IVS Diastolic Thickness	1.77 (0.26 – 11.94)	0.556		
Body Surface Area	0.65 (0.22 - 1.88)	0.43		
Reached 85% of max HR	0.847 (0.327 - 2.189)	0.731		
Positive stress ECG	2.860 (0.921 - 8.887)	**0.069**		
Peak HR	0.987 (0.961 - 1.014)	0.335		
Peak BP	0.995 (0.981 - 1.009)	0.478		
DSE DP (HRXBP)	1.00 (1.00 – 1.00)	0.208		

Abbreviations: please look at tables 1 and 2 for abbreviations.

Discussion

In this study, patients with advanced liver disease with a positive DSE and no obstructive CAD had one-year cardiac mortality of 8% and an event rate of 13%. Patients with positive DSE and CAD had even worse outcomes, with 9% cardiac mortality and 41% event rate at one year with worse event-free survival over the duration of follow-up. In addition to CAD, NASH and beta blocker use were independently associated with cardiac events.

Prognosis of a positive DSE without coronary obstruction in patients with end-stage liver disease

Previous studies in general populations have shown that in the absence of obstructive CAD, patients who have a positive stress echocardiogram are at increased risk. Two studies reported one-year all-cause mortality of 6% in patients who had abnormal stress echocardiograms and no CAD [3,7]. Sicari et al. reported a 2.5% annualized mortality rate in patients with positive stress echocardiograms and no obstructive CAD [4]. In our study, cardiac mortality (8%) and cardiac event rates (13%) at one year of follow-up suggest that ESLD patients with positive DSE and no CAD may be at higher risk than general populations with positive DSE and no CAD. The increased risk of ESLD patients with positive DSE without CAD in our study may be partially attributed to a more extensive risk factor profile. In our study, nearly 50% of patients with positive DSE without CAD had diabetes which exceeds the frequency of diabetes (5 to 40%) reported in previous studies of patients with positive stress echocardiograms and no CAD. A history of tobacco use (72%) in our population was also more common than in previous studies (36 to 45%) [3,4,7]. To our knowledge, our study is the first to show that a positive DSE, in the absence of CAD, identifies ESLD patients at increased risk of cardiac events. A report from the Cleveland Clinic, found a very low rate (<1% of all exams) of positive DSE in liver transplant candidates which is a 10-fold lower rate of positive DSE compared with our institution. In their study, no patients with ischemia on DSE had early post-transplant cardiac events [8]. A study from the Mayo Clinic (Jacksonville, Fla) reported no cardiac mortality in 18 patients who had positive DSE and no obstructive CAD who underwent liver transplant and were followed a minimum of 3 years [9]. In spite of the absence of obstructive CAD, our population appears both at higher risk for inducible wall motion abnormalities and cardiac events compared with ESLD patients evaluated at other institutions.

Various causes of stress-induced wall motion abnormalities in the absence of significant CAD have been proposed including diffuse coronary narrowing, unmasking of underlying cardiomyopathy, increase in left ventricular afterload from left ventricular outflow tract obstruction, induction of stress cardiomyopathy, microvascular disease, and vasospasms.

The causes of wall motion abnormalities in ESLD patients without obstructive CAD can be linked to increased cardiac events in several ways. Microvascular disease and endothelial dysfunction in the setting of the high metabolic demand of ESLD may predispose these patients to myocardial injury. Catecholamine stress can precipitate stress cardiomyopathy and coronary spasm both of which can occur spontaneously in the setting of end stage liver disease and the transplant procedure [10,11].

Prognosis of a positive DSE with coronary obstruction in patients with end-stage liver disease

In our study, the one-year cardiac event rate was 41%. The very high-risk nature of this group was reflected in the prevalence of diabetes, hypertension, and tobacco use which were each greater than 70%. In our study, obstructive CAD was found to be independently associated with cardiac events on multivariable analysis. Prior studies have shown conflicting results about the impact of obstructive CAD on the outcome of liver transplant patients. In an early investigation, Plotkin et al. reported 50% mortality rate in liver transplant patients with coronary disease [12]. In contrast, Snipelisky et al. found no relationship between the presence of obstructive CAD and all-cause mortality [9]. In a 2013 multi-center study of 630 liver transplant patients, 151 subjects with obstructive CAD had non-inferior survival to the remaining patients who had no obstructive CAD. However, 80 of the subjects with CAD underwent revascularization prior to transplant in this study [13]. A 2016 retrospective analysis of liver transplant patients at Northwestern University showed that post-transplant cardiac events were more frequent in those with obstructive CAD (22.5%) compared to those with no or mild CAD (15.2%, $p = 0.02$) [14]. It is unclear what proportion of patients in this study underwent revascularization prior to transplant.

The role of revascularization in reducing the risk of liver transplant candidates with obstructive CAD is also uncertain. The high mortality of CAD in the study of Plotkin, et al was attributed to the lack of revascularization [12]. Coronary artery bypass grafting has been associated with increased mortality in ESLD [15]. Percutaneous intervention has a high success rate but it is unclear if this improves outcome [16]. Snipelisky found that post-liver transplant mortality was unchanged by coronary stenting in those with severe CAD [9]. Wray et al. surmised that the non-inferior survival of CAD patients in their study was due to revascularization in the majority of those subjects. However, the study had a heterogeneous subject population and insufficient sample size to compare survival of non-revascularized and revascularized patients with CAD. Patients who had coronary stenting trended towards worse survival than liver transplant patients without CAD [13]. In 2017, Salapathy et al. reported that post-transplant cardiac events were of similar magnitude in those with and without obstructive CAD (27.5% versus 25.8%). Over two-thirds of the patients with CAD in their study had revascularization before transplant. In our study, revascularization did not improve the outcome of patients with obstructive CAD, as 90% of patients with subsequent cardiac events had early revascularization.

The extensive risk factor profile of this group suggests a high likelihood of diffuse atherosclerosis which resulted in poor outcomes despite revascularization of discrete stenoses. The frequencies of tobacco use, hypertension, and diabetes in our patients with obstructive CAD were greater than the frequencies of each of these risk factors reported in recent studies assessing the prognosis of ESLD patients with CAD [14,17].

Association of NASH and beta blocker use with cardiac events

Non-alcoholic Fatty liver disease (NAFLD) has become the leading cause of chronic liver disease in the United States [18,19]. NAFLD refers to a spectrum in which pure hepatic steatosis exists on one end and conditions like nonalcoholic steatohepatitis (NASH) and cirrhosis [19] exist on the other extreme. NASH is strongly associated with cardiovascular disease through common risk factors including insulin resistance, metabolic syndrome, hypertension, dyslipidemia, and obesity. The increase in cardiovascular risk associated with NASH can also be linked to the proinflammatory process characterizing this disorder and the presence of microvascular disease. The risk factors for microvascular disease are similar to those for NASH and include dyslipidemia, obesity, metabolic syndrome, and diabetes [20]. Recent studies have demonstrated that individual risk factors for CAD may not predict the occurrence of cardiac events in liver transplant patients, but a scoring system combining a number of vascular risk factors can identify those at risk for cardiac events [14,17]. In light of this evidence, the association of NASH with cardiac events is expected.

There are conflicting studies in the literature about the use and safety of beta blockers in advanced liver disease [21,22]. Krag et al. describes a "window period" during which beta blockers improve survival. Non-selective beta blockers may worsen survival at the latter stages of liver disease. Beta blockers may cause a decrease in cardiac output in end stage liver disease where cardiac compensatory reserve is minimal and sympathetic tone is high [22]. Non-selective beta blockers have been associated with increased mortality in ESLD patients who have decreased left ventricular stroke work index [23]. ESLD patients may have underlying cardiomyopathy that is masked by systemic vasodilation and high sympathetic tone resulting in normal appearing left ventricular systolic function assessed by ejection fraction [24]. In our study population, mean ejection fraction was in the normal range and was not a predictor of outcome. However, indices of longitudinal systolic function have been shown to be more sensitive than EF for subclinical ventricular dysfunction [25]. It is possible that some of our patients had subclinical dysfunction, and beta blockers contributed to worse outcome in these patients.

Limitations & Conclusion

This was a retrospective investigation of a modest number of subjects, but to our knowledge this is the largest series of ESLD patients with positive DSE who have had assessment of cardiac outcome. Subjects were enrolled over an extended period during which the DSE protocol, image interpretation, medical management of these patients, and revascularization procedures have evolved. The findings in our study may not be directly applicable to other institutions that screen lower risk populations with DSE.

Our study showed that a positive DSE is associated with increased risk in the absence of obstructive CAD. Risk was substantially elevated in positive DSE patients by the presence of CAD. The high risk of a positive DSE and CAD was not reduced by revascularization. Larger studies are needed to define the role of revascularization in the management of ESLD patients with CAD. NASH and beta blocker use are also associated with cardiac events in patients with positive DSE.

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