American Heart Journal Plus: Cardiology Research and Practice 4 (2021) 100026

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Research paper

Clinical implications of inducible left ventricular outflow tract obstruction among patients undergoing liver transplant evaluation

Antoine Addoumieh [a], Mouin S. Abdallah [a], Jad A. Ballout [a], Lucy Thuita [c], Allan Klein [a], Wael A. Jaber [a], Reza Arsanjani [d], William Carey [b], David Majdalany [d,*]

[a] Heart and Vascular Institute, Cleveland Clinic Foundation, USA
[b] Digestive Disease Institute, Cleveland Clinic Foundation, USA
[c] Quantitative Health Science Department, Cleveland Clinic Foundation, USA
[d] Department of Cardiovascular Medicine, Mayo Clinic, Phoenix, AZ, USA

ARTICLE INFO

Keywords:
End stage liver disease
Dobutamine stress echocardiography
Left ventricular outflow tract obstruction
Liver transplant evaluation
Cirrhosis of the liver
Echocardiography
Stress imaging
Orthotopic liver transplant
Dynamic left ventricular outflow tract obstruction
Model for End Stage Liver Disease

ABSTRACT

Introduction: Patients with end stage liver disease (ESLD) have a hyperdynamic state due to decreased systemic vascular resistance and increased cardiac output. Preoperative evaluation with dobutamine stress echocardiography (DSE) is used to risk-stratify patients prior to liver transplant. We sought to identify the impact of inducible left ventricular outflow tract obstruction (LVOTO) on DSE on post-operative liver transplant outcomes.
Methods: Patients with ESLD who underwent liver transplant at Cleveland Clinic between January 2007 and August 2016 were identified. Pre-operative DSE data, and post-operative intensive care unit (ICU) data were extracted. Patients with inducible LVOTO were compared to those without LVOTO.
Results: Of the 515 patients identified who underwent DSE prior to liver transplant, 165 (30%) were female, and 95 (18%) had LVOTO. There were no major differences in baseline characteristics between the two groups. In the LVOTO group, rest gradients were 10.8 ± 3 mm Hg while peak gradients were 90 ± 48.2 mm Hg. No significant differences in ICU length of stay or duration of mechanical ventilation between both groups were noted. There were 21 deaths at 30 days. There were 2 (2.1%) deaths in the LVOTO group, versus 19 (4.5%) deaths in the non LVOTO group ($p = 0.28$). Higher Model for End Stage Liver Disease (MELD) scores predicted longer duration of mechanical ventilation and ICU length of stay.
Conclusion: Inducible LVOTO on DSE does not adversely affect the short-term outcomes post liver transplant. Presence of inducible LVOTO should not be the mere reason to deny liver transplant among patients with ESLD.

1. Introduction

More than 7000 orthotopic liver transplants (OLT) are performed each year in the United States [1], and coronary artery disease (CAD) is a significant cause of morbidity and mortality among patients undergoing transplantation [2,3]. Preoperative cardiac evaluation is routinely performed, and dobutamine stress echocardiography (DSE) is commonly used to risk stratify patients [4].

Patients with advanced liver disease have unique hemodynamics, characterized by reduced systemic vascular resistance and associated increase in cardiac output [5–7]. This hyperdynamic state causes dynamic left ventricular outflow tract obstruction (LVOTO), particularly with dobutamine infusion. Inducible LVOTO has been suggested as a predictor of future cardiac symptoms [8]. However, those results were not consistent with previous publications [9]. The clinical significance of dobutamine induced LVOTO on perioperative outcomes and management remains unclear.

In this study, we sought to evaluate the impact of dynamic LVOTO among patients undergoing DSE as part of pre-operative evaluation for OLT. We hypothesized that dynamic LVOTO would have little impact on post-operative outcome given that it is mainly driven by vasodilation related to advanced liver failure.

2. Materials and methods

2.1. Patient selection

We identified all patients at our institution, a quaternary-care

* Corresponding author at: 13400 E Shea Blvd, Scottsdale, AZ 85259, USA.
E-mail address: Majdalany.david@mayo.edu (D. Majdalany).

https://doi.org/10.1016/j.ahjo.2021.100026
Received 3 March 2021; Received in revised form 4 June 2021; Accepted 5 June 2021
Available online 24 June 2021

referral center, with end stage liver disease who underwent DSE as part of liver transplantation work up between January 2007 and August 2016. Exclusion criteria included liver transplant combined with any other organ transplant (N = 41), baseline mean aortic gradient of 15 mm Hg or more (N = 6), complete cavity obliteration on stress (N = 25), imaging not available for review, and patients with incomplete data (Fig. 1). For our final analytical cohort (N = 515), baseline characteristics including age, sex, height, weight, race, and comorbidities were recorded. This study has been approved by the Institutional Review Board (IRB) at Cleveland Clinic, OH. IRB approval number is: 16-631. No informed consent was required.

2.2. Dobutamine stress echocardiography

DSE was performed according to universal protocol. After patient's weight and height are obtained, the test began with infusion of dobutamine at 5 μg/kg/min, if there was resting wall motion abnormalities and/or severe left ventricular dysfunction, otherwise the infusion was initiated at 10 μg/kg/min. The dose was increased every 3 min until 40 μg/kg/min dose was achieved or 85% of maximum predicted heart rate (MPHR) was reached. Test was terminated if the protocol was completed, there was severe ischemia (severe angina, new wall motion abnormality or ≥2 mm ST segment depression), intolerable side effects, systolic blood pressure <100, or symptomatic hypotension, severe hypertension, atrial fibrillation, or ventricular tachycardia/ventricular fibrillation. If target heart rate was not achieved, handgrip maneuver was done especially if patient was within 10 beats/min from target. Atropine at a dose of 0.25 mg to 0.5 mg was added especially if patient used beta blockers. Recovery images were obtained when heart rate is <100–110 beats/min. If insufficient heart rate recovery occurred in 3–5 min, then esmolol or metoprolol was administered. For patients with VVI pacing and normal left ventricular ejection fraction (LVEF), resting images were obtained then the device was programmed to 85% MPHR for 3 min. If no symptoms developed and wall motion remained normal, then the device was reprogrammed to 100% MPHR. However, in patients with abnormal LVEF (EF ≤ 35% at baseline), dobutamine was initially infused at 10 μg/kg/min for 3 min, and then continued as for VVI and normal EF. For patients with DDD pacing, if pacemaker placement implantation indication was for complete heart block, then regular DSE protocol was obtained, if for SSS then same as VVI protocol. All images were read by experienced cardiologist. Outflow tract velocity was measured at peak DSE by continuous wave Doppler, and intracavitary and outflow tract gradients were calculated using modified Bernoulli equation.

2.3. Data and statistical analysis

Patients were divided into two groups, LVOTO (which included outflow tract obstruction and increased intracavitary gradients, N = 95) and non LVOTO group (N = 420). Baseline demographics, clinical characteristics between both groups, post-operative data on intensive care unit length of stay, duration of mechanical ventilation, duration of pressor/inotrope support (norepinephrine, epinephrine, vasopressin, dobutamine, dopamine, phenylephrine) were collected.

Continuous variables are summarized as mean ± standard deviation, or as equivalent 15th, 50th (median), and 85th percentiles; comparisons were made using the Wilcoxon rank-sum test. Categorical data are summarized using frequencies and percentages; comparisons were made using the χ^2 test or Fisher's exact test when frequency was less than 5.

Variables with missing values of 30% or greater were not utilized in multivariable analyses. For the remaining, we employed 5-fold multiple imputation using a Markov Chain Monte Carlo technique (SAS PROC MI and PROC MIANALYZE) [10].

To identify factors associated with LVOTO, a multivariable logistic regression analysis was performed. Variable selection, with a p value criterion for retention of variables in the model of 0.05, utilized bootstrap bagging (bootstrap aggregation) with automated analysis of 1000 resampled datasets, followed by tabulating the frequency of occurrence of both single factors and closely related clusters of factors [11]. A parsimonious model was then constructed retaining factors that occurred in 50% or more of the bootstrap models.

Having established a parsimonious model, we added other patient variables, which might be related to unrecorded selection factors (saturated model) regardless of their significance in the multivariable model. A propensity score was calculated for each patient by solving the saturated model for the probability of having LVOTO. This propensity score was used in multivariable model adjustment.

For multivariable analyses of ICU length of stay and ventilation time,

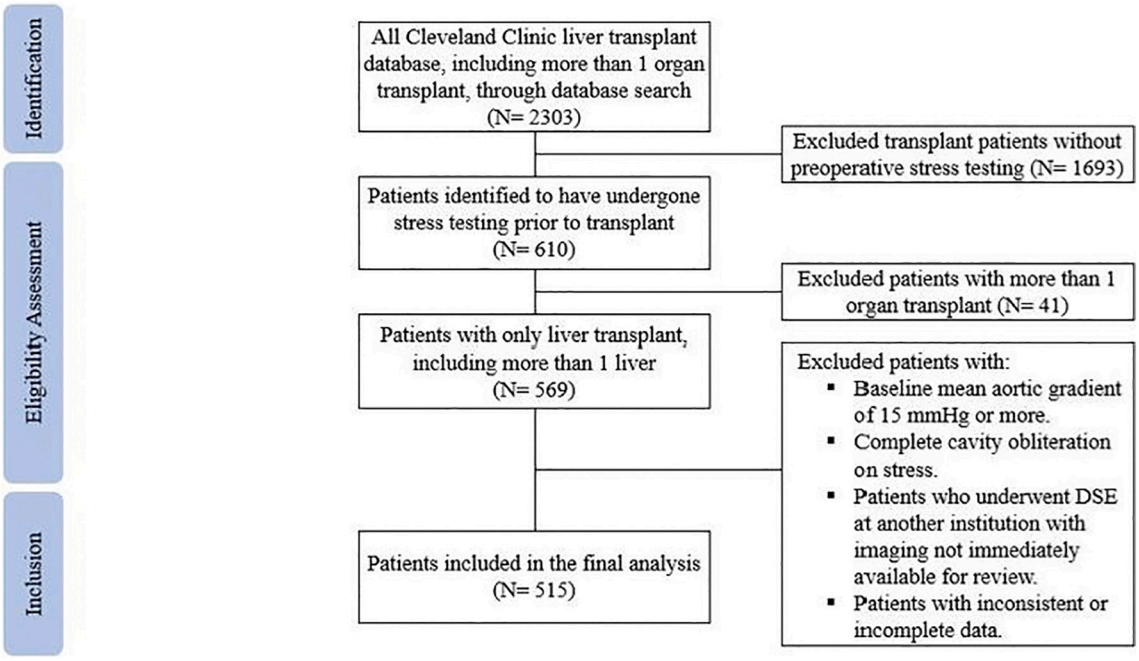

Fig. 1. Patient selection diagram with exclusion criteria.

a linear regression (PROC REG) was used. Due to skewness, ICU was transformed into an inverse scale while ventilation to a logarithmic scale. LVOTO and its propensity score were forced into each model regardless of being significant or not.

Simple descriptive statistics are used to summarize the patient baseline characteristics, stress test and echocardiographic results. Categorical data are described using frequencies and percentages; comparisons are made using chi-squared test or Fisher's exact test when frequency was less than 5. Continuous variables are presented as mean ± standard deviation. Comparisons are made using Wilcoxon rank-sum test. Multivariable logistic regression analysis was performed to identify patient characteristics mostly associated with LVOTO. Variables considered for this analysis included the following: age, sex, height, weight, body mass index, race, anemia, arrhythmias, coronary artery bypass surgery, coronary artery disease, myocardial infraction, chronic kidney disease, congenital heart disease, diabetes, hyperlipidemia, hypertension, obstructive sleep apnea, tobacco use, valvular disease, alcoholic cirrhosis, alcoholic cirrhosis with hepatitis C, chronic hepatitis B, chronic hepatitis C, non-alcoholic steatohepatitis, cryptogenic cirrhosis, hepatocellular carcinoma, primary biliary cirrhosis, primary sclerosing cholangitis, hemoglobin prior to stress test, Model for End Stage Liver Disease (MELD) score, systolic and diastolic peak pressures, resting pressures, peak heart rate, resting heart rate, ejection fraction, left ventricular inner diameter during diastole & systole, posterior wall thickness, right ventricular systolic pressure, cavity dilation, mitral valve regurgitation, and tricuspid valve regurgitation. Linear regression analysis was used to determine whether LVOTO has an impact on ICU length of stay, and duration of mechanical ventilation. All analyses were performed using SAS statistical software (SAS v9.2; SAS, Inc., Cary, NC).

3. Results

3.1. Patient demographics and baseline characteristics

A total of 2303 patients who underwent liver transplant between January 2007, and August 2016 were identified. 1693 patients were excluded because they did not undergo preoperative dobutamine stress echo. 41 patients were excluded because they underwent more than 1 organ transplant. And finally, 54 patients were excluded because they met 1 or more of the exclusion criteria (Fig. 1).

The study population consisted of 515 patients who underwent preoperative dobutamine stress echo, prior to liver transplant. Mean age of patients was 59 ± 6.7 years, of which 32% (165) were females and 87% were Caucasian. Of all patients, 95 (18%) developed dynamic LVOTO gradient during DSE. We did not observe any sex-based or race/ethnicity-based. Baseline characteristics are shown in Table 1.

Logistic regression model showed that patients who developed LVOTO were more frequently males (p = 0.005), had a diagnosis of chronic hepatitis C (p = 0.003), had higher baseline ejection fraction (p = 0.019), and smaller LV inner diameter-systole (p = 0.007). In LVOTO group, chronic hepatitis C was the most common cause of transplant (N = 25) (26%), followed by hepatocellular carcinoma (N = 24) (25%). Details about the etiology of the End stage liver disease (ESLD) are presented in Table 2.

Mean hemoglobin of patients with LVOTO was 11.5 ± 2.5 g/dL, versus 11.4 ± 2.3 g/dL in non LVOTO group (p = 0.85). The percentage of patients who achieved maximum predicted heart rate in the LVOTO group was 85.5 ± 6.5%, versus 84.8 ± 10% in the non LVOTO group (p = 0.57) Interventricular septum was significantly thicker in the LVOTO group than in the non LVOTO (1.2 ± 0.2 cm versus 1.14 ± 0.2 cm p = 0.03). Baseline ejection fraction was significantly higher in patients with LVOTO versus non LVOTO group (64.7 ± 5.6 versus 61.8 ± 5.8, p < 0.0001). No significant differences were found between the two groups with regard to baseline systolic and diastolic blood pressures, peak systolic and diastolic blood pressures, and peak heart rate (Table 3).

Table 1
Baseline characteristics.

Characteristic	Patients without LVOTO (%)	Patients with LVOTO (%)	p value
Number	420 (82)	95 (18)	
Age (years)[a]	59.5 ± 6.9	58.8 ± 6	0.39
Gender			
Male	277 (66)	73 (77)	0.04
Female	143 (34)	22 (23)	
Race			
Caucasian	88%	81%	0.11
African-American	6.6%	11%	0.19
Other (Hispanic/Asian)	5.1%	7.5%	0.39
Coronary artery disease	57 (14)	10 (11)	0.40
History of myocardial infarction	8 (2)	1 (1)	0.57
History of CABG	5 (1)	0	0.29
History of arrhythmias	25 (6)	2 (2)	0.13
Hypertension	215 (51)	49 (52)	0.94
Obstructive sleep apnea	32 (8)	7 (7)	0.94
Hyperlipidemia	120 (28)	25 (26)	0.68
Diabetes mellitus	135 (32)	33 (35)	0.61
Anemia	95 (23)	16 (17)	0.22
Chronic kidney disease	67 (16)	15 (16)	0.94
Tobacco abuse	258 (61)	64 (67)	0.29
MELD score[a]	23.7 ± 6.8	23.6 ± 6.6	0.81

CABG: coronary artery bypass graft; MELD: Model for End Stage Liver Disease.
[a] Mean ± standard deviation.

Table 2
Indications for transplant.

Causes of cirrhosis	Patients without LVOTO (%)	Patients with LVOTO (%)
Chronic hepatitis C	59 (14)	25 (26)
Hepatocellular carcinoma	108 (26)	24 (25)
Alcoholic cirrhosis	50 (12)	12 (13)
Non-alcoholic steatohepatitis	76 (18)	10 (11)
Alcoholic cirrhosis with hepatitis C	36 (9)	7 (7)
Primary sclerosing cholangitis	14 (3)	6 (7)
Chronic hepatitis B	3 (1)	3 (3)
Primary biliary cirrhosis	20 (4)	2 (2)
Cryptogenic cirrhosis	22 (5)	3 (3)
Other causes	32 (8)	3 (3)

Table 3
Cardiac and dobutamine stress echocardiography parameters.

Cardiac and dobutamine stress echocardiography results	Patients without LVOTO	Patients with LVOTO	p value
Hemoglobin at time of stress test (mg/dL)	11.4 ± 2.3	11.5 ± 2.5	0.85
Baseline ejection fraction (%)	61.8 ± 5.8	64.7 ± 5.6	0.01
Interventricular septum (cm)	1.14 ± 0.2	1.2 ± 0.2	0.03
Achieved 85% of maximum predicted heart rate (%)	85.5 ± 6.5	84.8 ± 10	0.57
Baseline systolic blood pressure (mm Hg)	128 ± 21.3	131 ± 25.8	0.86
Peak systolic blood pressure (mm Hg)	125 ± 26	119 ± 26.7	0.08
Baseline diastolic blood pressure (mm Hg)	66.4 ± 10.2	70.7 ± 9	0.10
Peak diastolic blood pressure (mm Hg)	61.1 ± 11.6	58.7 ± 12.3	0.21
Baseline heart rate (Beats/Min)	73.3 ± 12.5	72.1 ± 11.6	0.85
Peak heart rate (Beats/Min)	136 ± 16	138 ± 12	0.10
Baseline outflow tract gradient (mm Hg)		10.8 ± 3	
Peak outflow tract gradient (mm Hg)	0	90 ± 48.2	

Mean ± standard deviation, LVOTO = left ventricular outflow tract obstruction.

3.2. Length of ICU stay and mechanical ventilation

The median length of ICU stay was 2 days for both groups (15th and 85th percentile for LVOTO 1 and 7, for non LVOTO 1 and 6.6). Mean ICU length of stay was 3.8 ± 4.4 days in the LVOTO group, and 4.6 ± 7.6 days in the non LVOTO group (p = 0.7).

The median duration of mechanical ventilation in the LVOTO group was 22 h, compared to 18 h in the non LVOTO group (15th and 85th percentile of 7.2 and 54; 6 and 60, respectively). Mean duration of mechanical ventilation was 47.1 ± 103 h for patients without LVOTO, versus 32.1 ± 46.3 h in patients with LVOTO (p = 0.8). One patient from the LVOTO was on dobutamine for approximately 7 h following transplant. The mean duration of norepinephrine use in LVOTO group was 16.8 ± 15.3 h, versus 27.6 ± 33.7 h in the non LVOTO group (p = 0.03).

In multivariable analysis, higher MELD score (p < 0.0001) was associated with a longer ICU stay, and there was no significant association between ICU length of stay and LVOTO (p < 0.8). Factors associated with longer duration on mechanical ventilation were higher MELD score (p = 0.0005), and chronic kidney disease (p = 0.014), with no statistically significant association between mechanical ventilation and LVOTO (p = 0.6).

3.3. 30-day mortality

The total 30-day mortality for both groups was 21 patients. There were 2 deaths (2.1%) in the LVOTO group, compared to 19 deaths (4.5%) in the non-LVOTO group (p = 0.28) (Table 4).

Table 4
Post-transplant outcomes.

Characteristic	Patients without LVOTO	Patients with LVOTO	p value
ICU length of stay (days)	4.6 ± 7.6	3.8 ± 4.4	0.70
Duration of mechanical ventilation (h)	47.1 ± 103	32.1 ± 46.3	0.80
Norepinephrine use post-transplant (h)	27.6 ± 33.7	16.8 ± 15.3	0.03
Vasopressin use post-transplant (h)	28.9 ± 32.5	21.1 ± 23.4	0.30
Phenylephrine use post-transplant (h)		25.3 ± 39.4	
30-day mortality	19 (4.5%)	2 (2.1%)	0.28

Mean ± standard deviation.

4. Discussion

Our study suggests that in patients with end-stage liver disease undergoing orthotopic liver transplant, left ventricular outflow tract obstruction seen on pre-transplant dobutamine stress echo, does not have a significant impact on operative outcomes, namely duration on vasopressors, duration on mechanical ventilation, 30-day mortality, and ICU length of stay. Interestingly, patients with LVOTO required significantly less post-operative norepinephrine compared to patients without LVOTO.

To our knowledge, this is the largest study to date to evaluate the significance of inducible outflow tract obstruction in this subgroup of patients. These findings are important given that significant LVOTO has been a basis for denial of OLT at some centers [12], with only few existing reports showing successful transplant in patients with significant gradients [13].

The 2014 American College of Cardiology/American Heart Association guidelines on preoperative cardiovascular evaluation and management of patients undergoing non cardiac surgery, suggests that patients who are at elevated risk and have poor functional capacity should undergo noninvasive pharmacologic stress testing [14]. This is further supported by newer retrospective study evaluating the usefulness of dobutamine stress testing in OLT patients, which showed that a DSE negative for ischemia reliably predicted a low cardiac event rate post-transplant [15].

The prevalence of dynamic LVOTO during dobutamine stress test was reported to be between 17% and 43% [16–18]. These dynamic changes did not predict the presence of coronary artery disease [9,18,19], nor were they dependent on the presence of hypertrophic cardiomyopathy [18].

Patients with decompensated cirrhosis have decreased systemic vascular resistance, with arterial vasodilation owing to increased levels of Nitric Oxide, Carbon Monoxide and other mediators, as well as blood volume expansion [7]. These patients also demonstrate increased level of catecholamines triggered by baroreceptor response to low arterial blood pressure [6]. These changes contribute to increased cardiac output, and hyperdynamic circulation, which in turn may explain the prevalence of dynamic outflow tract obstruction in this population. Following successful liver transplant, liver function normalizes, leading to a decrease in cardiac output, and increase in systemic vascular resistance and arterial blood pressure [6].

Maraj et al. [17], investigated the prevalence and clinical significance of LVOTO, and found that 46 patients out of 106 (43%) undergoing DSE before OLT developed an outflow tract gradient, which was significantly associated with intraoperative hypotension, but did not affect mortality. Our study demonstrated that only 18% of patients developed LVOTO, which is closer to the prevalence seen in the general population, and was less than previously reported by Maraj et al.

The major limitation of the present study relates to its retrospective design, and to the number of patients who were not able to achieve maximum predicted heart rate. One explanation for the high number of patients not achieving maximum predicted heart rate in both groups might be related to chronotropic incompetence seen in advanced cirrhosis “cirrhotic cardiomyopathy” [20], as well as the potential high number of patients receiving non selective beta blockers for variceal bleeding prophylaxis, despite patients being instructed to hold beta blockers prior to stress testing. Another limitation is the inclusion of all patients with LVOTO irrespective of the degree of obstruction, with the concern that patients with less obstruction may be at lower risk for adverse outcomes. That said however, only few patients in the LVOTO had a peak gradient Δ <36 mm Hg, which is the value used in previous studies to describe significant LVOTO.

Finally, our study showed that LVOTO is not associated with increased short-term adverse outcomes, however, it is unknown whether LVOTO impacts long term survival and other cardiac and non-cardiac outcomes following liver transplant. Also, what is unknown, is whether the results of this study could be generalizable to other populations, given that all patients included were undergoing transplant evaluation and were deemed appropriate candidates to receive orthotopic liver transplant.

5. Conclusion

Left ventricular outflow tract obstruction induced by dobutamine stress testing in patients with ESLD is common, but is not associated with adverse perioperative events, including prolonged mechanical ventilation, ICU length of stay, and 30-day mortality. And therefore, LVOT obstruction should not be the basis for denial of liver transplantation.

Disclaimers

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

References

[1] W.R. Kim, J.R. Lake, J.M. Smith, D.P. Schladt, M.A. Skeans, A.M. Harper, et al., OPTN/SRTR 2016 annual data report: liver, Am. J. Transplant. 18 (Jan 1 2018) 172–253, https://doi.org/10.1111/ajt.14559 (Internet, cited 2018 Apr 12).

[2] W.D. Carey, J.A. Dumot, R.R. Pimentel, D.S. Barnes, R.E. Hobbs, J.M. Henderson, et al., The prevalence of coronary artery disease in liver transplant candidates over age 50, Transplantation 59 (6) (Mar 27 1995) 859–864. Available from, http://www.ncbi.nlm.nih.gov/pubmed/7701580 (Internet, cited 2017 Sep 16).

[3] J.S. Plotkin, V.L. Scott, A. Pinna, B.P. Dobsch, A.M. De Wolf, Y. Kang, Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation, Liver Transpl. Surg. 2 (6) (Nov 1996) 426–430. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9346688 (Internet, cited 2017 Sep 16).

[4] K.L. Lentine, S.P. Costa, M.R. Weir, J.F. Robb, L.A. Fleisher, B.L. Kasiske, et al., Cardiac disease evaluation and management among kidney and liver transplantation candidates, Circulation 126 (5) (2012). Available from, http://circ.ahajournals.org/content/126/5/617 (Internet, cited 2017 Sep 13).

[5] M. Bernardi, L. Fornalè, C. Di Marco, F. Trevisani, M. Baraldini, A. Gasbarrini, et al., Hyperdynamic circulation of advanced cirrhosis: a re-appraisal based on posture-induced changes in hemodynamics, J. Hepatol. 22 (3) (Mar 1 1995) 309–318. Available from, http://linkinghub.elsevier.com/retrieve/pii/0168827895802843 (Internet, cited 2017 Sep 10).

[6] S. Møller, J.H. Henriksen, Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease, Heart 87 (2002) 9–15. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766971/pdf/hrt08700009.pdf (Internet, cited 2017 Sep 16).

[7] E.M. Zardi, A. Abbate, D.M. Zardi, A. Dobrina, D. Margiotta, B.W. Van Tassel, et al., Cirrhotic cardiomyopathy, J. Am. Coll. Cardiol. 56 (7) (2010). Available from: http://www.onlinejacc.org/content/56/7/539 (Internet, cited 2017 Sep 16).

[8] B. Dawn, V.S. Paliwal, S.T. Raza, K. Mastali, R.A. Longaker, M.F. Stoddard, Left ventricular outflow tract obstruction provoked during dobutamine stress echocardiography predicts future chest pain, syncope, and near syncope, Am. Heart J. 149 (5) (May 1 2005) 908–916. Available from, http://www.ncbi.nlm.nih.gov/pubmed/15894976 (Internet, cited 2017 Sep 10).

[9] D. Luria, M.W. Klutstein, D. Rosenmann, J. Shaheen, S. Sergey, D. Tzivoni, Prevalence and significance of left ventricular outflow gradient during dobutamine echocardiography, Eur. Heart J. 20 (5) (Mar 1999) 386–392. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10206385 (Internet, cited 2017 Sep 10).

[10] D.B. Rubin, J. Wiley, N. York, C. Brisbane, T. Singapore, Multiple Imputation for Nonresponse in Surveys, 1987, https://doi.org/10.1002/9780470316696.fmatter (Internet, cited 2019 Mar 22).

[11] L. Breiman, Bagging predictors, Mach. Learn. 24 (2) (1996) 123–140, https://doi.org/10.1023/A:1018054314350 (Internet, cited 2019 Mar 22).

[12] Z. Raval, M.E. Harinstein, A.I. Skaro, A. Erdogan, A.M. Dewolf, S.J. Shah, et al., Cardiovascular risk assessment of the liver transplant candidate [cited 2017 Sep 10]; Available from: http://www.onlinejacc.org/content/accj/58/3/223.full.pdf, 2011.

[13] J.B. Cywinski, M. Argalious, T.N. Marks, B.M. Parker, Dynamic left ventricular outflow tract obstruction in an orthotopic liver transplant recipient, Liver Transpl. 11 (6) (Jun 1 2005) 692–695, https://doi.org/10.1002/lt.20440 (Internet, cited 2017 Sep 10).

[14] L.A. Fleisher, K.E. Fleischmann, A.D. Auerbach, S.A. Barnason, J.A. Beckman, B. Bozkurt, et al., 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 130 (24) (Dec 9 2014) 2215–2245. Available from, http://www.ncbi.nlm.nih.gov/pubmed/25085962 (Internet, cited 2018 May 29).

[15] D. Snipelisky, M. Levy, B. Shapiro, Utility of dobutamine stress echocardiography as part of the pre-liver transplant evaluation: an evaluation of its efficacy, Clin. Cardiol. 37 (8) (Aug 1 2014) 468–472, https://doi.org/10.1002/clc.22283 (Internet, cited 2017 Sep 10).

[16] L. Christiaens, C. Duplantier, J. Allal, E. Donal, H. Nanadoumgar, R. Barraine, et al., Normal coronary angiogram and dobutamine-induced left ventricular obstruction during stress echocardiography: a higher hemodynamic responsiveness to Dobutamine, Echocardiography 18 (4) (May 2001) 285–290, https://doi.org/10.1046/j.1540-8175.2001.00285.x (Internet, cited 2018 Mar 8).

[17] S. Maraj, L.E. Jacobs, R. Maraj, R. Contreras, P. Rerkpattanapipat, T.A. Malik, et al., Inducible left ventricular outflow tract gradient during dobutamine stress echocardiography: an association with intraoperative hypotension but not a contraindication to liver transplantation, Echocardiography 21 (8) (Nov 1 2004) 681–685, https://doi.org/10.1111/j.0742-2822.2004.03068.x (Internet, cited 2017 Sep 10).

[18] P.A. Pellikka, J.K. Oh, K.R. Bailey, B.A. Nichols, K.H. Monahan, A.J. Tajik, Dynamic intraventricular obstruction during dobutamine stress echocardiography. A new observation, Circulation 86 (5) (Nov 1 1992) 1429–1432. Available from, http://www.ncbi.nlm.nih.gov/pubmed/1423956 (Internet, cited 2018 Mar 8).

[19] M.B. Jhawar, S. Balla, M.A. Alpert, A. Chockalingam, Left ventricular outflow tract and mid-cavity obstruction may cause false-positive dobutamine stress echocardiograms, Eur. Heart J. Cardiovasc. Imaging 12 (3) (Mar 2011), E14–E14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20977996 (Internet, cited 2017 Sep 10).

[20] H. Kelbæk, A. Rabøl, I. Brynjolf, J. Eriksen, O. Bonnevie, J. Godtfredsen, et al., Haemodynamic response to exercise in patients with alcoholic liver cirrhosis, Clin. Physiol. 7 (1) (Feb 1 1987) 35–41, https://doi.org/10.1111/j.1475-097X.1987.tb00631.x (Internet, cited 2018 Mar 22).