Title

Fractional Flow Reserve in End-Stage Liver Disease

Authors

Kumar, Preetham
Kim, Juka S
Gordin, Jonathan
et al.

Publication Date

2022-03-01

DOI

10.1016/j.amjcard.2021.11.031

Fractional Flow Reserve in End-Stage Liver Disease

Preetham Kumar, MD[a], Juka S. Kim, BS[a], Jonathan Gordin, MD, MS[a], Henry M. Honda, MD[a], William Suh, MD[a], Michael S. Lee, MD[a], Marcella Press, MD, PhD[a], Ali Nsair, MD[a], Olcay Aksoy, MD[a], Ronald W. Busuttil, MD, PhD[b], Jonathan Tobis, MD[a], and Rushi V. Parikh, MD[a,*]

Fractional flow reserve (FFR) determines the functional significance of epicardial stenoses assuming negligible venous pressure (P_v) and microvascular resistance. However, these assumptions may be invalid in end-stage liver disease (ESLD) because of fluctuating P_v and vasodilation. Accordingly, all patients with ESLD who underwent right-sided cardiac catheterization and coronary angiography with FFR as part of their orthotopic liver transplantation evaluation between 2013 and 2018 were included in the present study. Resting mean distal coronary pressure (P_d)/mean aortic pressure (P_a), FFR, and P_v were measured. FFR accounting for P_v (FFR − P_v) was defined as $(P_d - P_v)/(P_a - P_v)$. The hyperemic effect of adenosine was defined as resting P_d/P_a − FFR. The primary outcome was all-cause mortality at 1 year. In 42 patients with ESLD, 49 stenoses were interrogated by FFR (90% were <70% diameter stenosis). Overall, the median model for ESLD score was 16.5 (10.8 to 25.5), FFR was 0.87 (0.81 to 0.94), P_v was 8 mm Hg (4 to 14), FFR-P_v was 0.86 (0.80 to 0.94), and hyperemic effect of adenosine was 0.06 (0.02 to 0.08). FFR-P_v led to the reclassification of 1 stenosis as functionally significant. There was no significant correlation between the median model for ESLD score and the hyperemic effect of adenosine (R = 0.10). At 1 year, 13 patients had died (92% noncardiac in etiology), and patients with FFR ≤0.80 had significantly higher all-cause mortality (73% vs 17%, p = 0.001. In conclusion, in patients with ESLD who underwent orthotopic liver transplantation evaluation, P_v has minimal impact on FFR, and the hyperemic effect of adenosine is preserved. Furthermore, even in patients with the predominantly angiographically-intermediate disease, FFR ≤0.80 was an independent predictor of all-cause mortality. **(Am J Cardiol 2022;166:122−126)**

Previous studies of patients with end-stage liver disease (ESLD) have demonstrated worse clinical outcomes in those with concomitant coronary artery disease (CAD) and improvements in long-term mortality with revascularization previous to orthotopic liver transplantation (OLT).[1−3] Fractional flow reserve (FFR) is a validated coronary pressure wire-based index that evaluates the functional significance of epicardial coronary stenoses and is commonly used to interrogate angiographically-intermediate disease.[4,5] The derivation of FFR assumes negligible central venous pressure (P_v) and microvascular coronary resistance.[6] However, these assumptions may be invalid in ESLD because of pathophysiology characterized by dynamic P_vs and marked vasodilation.[7−9] To the best of our knowledge, FFR has not been previously studied in a dedicated ESLD population. In the present study, we aimed to assess the accuracy and prognostic impact of FFR in patients with ESLD who underwent OLT evaluation.

This single-center retrospective cohort study included all adult patients with ESLD at the University of California, Los Angeles (UCLA) who underwent right-sided cardiac catheterization (RHC) and coronary angiography with FFR between 2013 and 2018 as part of their OLT evaluation. Patients aged <18 years were excluded. The study protocol was approved by the UCLA Institutional Review Board.

Hemodynamic data measured during the index procedure included resting mean distal coronary pressure (P_d)/mean aortic pressure (P_a), FFR, and central P_v. Resting P_d/P_a was defined as the ratio of P_d to P_a. FFR was defined as the P_d/P_a at maximal hyperemia during administration of adenosine, and values ≤0.80 were considered functionally significant.[10] P_v was defined as the mean right atrial pressure. We defined an adjusted FFR accounting for P_v (FFR-P_v) as $(P_d - P_v)/(P_a - P_v)$ and the hyperemic effect of adenosine as resting P_d/P_a − FFR. FFR-guided percutaneous coronary intervention (PCI) was defined as PCI of the interrogated stenosis during the index procedure or in a staged fashion (i.e., planned PCI within the following 60 days).

The primary outcome was all-cause mortality at 1 year. Secondary outcomes included nonperiprocedural myocardial infarction (MI), repeat revascularization, and the composite of all-cause mortality, MI, and repeat revascularization at 1 year (major adverse cardiovascular events [MACE]). MI was defined as an increase in troponin levels to >99th percentile of the upper reference limit in addition to either new ischemic electrocardiographic or echocardiographic changes.[11] Repeat revascularization was defined as any subsequent PCI excluding staged PCI.

[a]Division of Cardiology, Department of Medicine, University of California, Los Angeles, Los Angeles, California; and [b]Division of Liver and Pancreas Transplantation, Department of Surgery, University of California, Los Angeles, Los Angeles, California. Manuscript received July 17, 2021; revised manuscript received and accepted November 12, 2021.

See page 125 for disclosure information.

*Corresponding author: Tel: (310) 825-9011; fax: (310) 825-9012.
E-mail address: rparikh@mednet.ucla.edu (R.V. Parikh).

0002-9149/
https://doi.org/10.1016/j.amjcard.2021.11.031

Data are expressed as frequency (percentages) or median (interquartile range). Independent samples *t* tests and chi-square tests (as appropriate) were used to test for differences between groups of continuous and categorical variables, respectively, and Spearman rank correlation coefficients were used to assess the correlation between continuous variables. Time-to-event data were analyzed using Kaplan-Meier curves and log-rank tests stratified by FFR ≤0.80. Cox proportional hazards regression models including FFR ≤0.80 and key demographic, cardiovascular, and ESLD-related factors were constructed to determine independent predictors of clinical outcomes (multivariable models included factors with p <0.10 in univariable analyses). These Cox regression data are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical analyses were performed with SPSS Statistics, version 27.0 (SPSS Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant.

A total of 42 patients underwent RHC and coronary angiography with FFR as part of their OLT evaluation at UCLA from 2013 to 2018. The median age was 62 years (57.5 to 66.6), 62% were men, and the median model for ESLD (MELD) score was 16.5 (10.8 to 25.5) (Table 1). In the 42 patients with ESLD, 49 coronary stenoses were interrogated by FFR. Of these stenoses, 90% were angiographically mild or intermediate (<70% diameter stenosis on visual inspection) and 69% were located in the left main coronary artery (2%) or left anterior descending artery (67%). The median resting P_d/P_a was 0.94 (0.89 to 0.98) and the median FFR was 0.87 (0.81 to 0.94); these data indicated a median hyperemic effect of adenosine of 0.06 (0.02 to 0.08), which did not significantly correlate with MELD score ($R = 0.10$). The median P_v was 8 mm Hg (4 to 14), yielding a median FFR-P_v of 0.86 (0.80 to 0.94). There was no significant difference between FFR-P_v and FFR (p = 0.28). FFR-P_v led to the reclassification of 1 stenosis from functionally nonsignificant to functionally significant. In the 12 patients with functionally significant stenoses, 11 underwent revascularization (10 PCI and 1 coronary artery bypass grafting), whereas 1 died before planned revascularization (Table 2).

One-year outcome data were available for 41 patients; 1 patient was lost to follow-up and excluded from the

Table 1
Baseline patient characteristics

	N = 42
Age (years)	62 (57.5 − 66.6)
Male	26 (62%)
White	15 (36%)
Black	3 (7%)
Hispanic	13 (31%)
Asian	11 (26%)
Body mass index (kg/m^2)	28.1 (24.5 − 34.5)
Hypertension	30 (71%)
Hyperlipidemia	14 (33%)
Diabetes mellitus	30 (71%)
Chronic kidney disease	18 (43%)
Cerebrovascular disease	3 (7%)
Peripheral arterial disease	0 (0%)
Prior heart failure	0 (0%)
Prior myocardial infarction	2 (5%)
Prior percutaneous coronary intervention	5 (12%)
Left ventricular ejection fraction <50%	1 (2%)
Tobacco Use (current or former)	27 (64%)
Family history of coronary artery disease	5 (12%)
Stress test	
Positive	2 (5%)
Negative/equivocal	27 (64%)
None	13 (31%)
Model for End-Stage Liver Disease Score	16.5 (10.8 − 25.5)
Cause of end-stage liver disease	
Alcohol	5 (12%)
Hepatitis C virus	16 (38%)
Multifactorial	2 (5%)
Non-alcoholic steatohepatitis	9 (21%)
Other	10 (24%)

Data are presented as median (first quartile − third quartile) as appropriate.

Table 2
Hemodynamic and revascularization data

	N = 49
Stenosis degree Iinterrogated	
Mild (0-39%)	3 (6%)
Moderate (40-69%)	41 (84%)
Severe (≥ 70%)	5 (10%)
Stenosis location interrogated	
Left main	1 (2%)
Left anterior descending	33 (67%)
Left circumflex	5 (10%)
Right coronary artery	10 (21%)
P_d/P_a	0.94 (0.89 − 0.98)
Fractional flow reserve	0.87 (0.81 − 0.94)
≤ 0.80	12 (25%)*
> 0.80	37 (75%)
P_d/P_a − FFR	0.06 (0.02 − 0.08)
Venous pressure (mm Hg)	8 (4 − 14)
Right ventricular systolic pressure (mm Hg)	29.5 (22.5 − 36.8)
Right ventricular diastolic pressure (mm Hg)	7.0 (4.0 − 10.8)
Pulmonary artery systolic pressure (mm Hg)	28.0 (22.0 − 36.5)
Pulmonary artery diastolic pressure (mm Hg)	14.5 (10.0 − 19.0)
Mean pulmonary artery pressure (mm Hg)	20.0 (15.8 − 27.3)
Pulmonary capillary wedge pressure (mm Hg)	13.0 (10.0 − 17.0)
Thermodilution cardiac output (L/min)	6.7 (5.4 − 8.5)
Thermodilution cardiac index (L/min/m^2)	3.5 (3.1 − 4.8)
FFR-P_v	0.9 (0.8 − 0.9)
≤ 0.80	13 (27%)
> 0.80	36 (73%)
Reclassified as ≤ 0.80 per FFR-P_v	1 (3%)
FFR − FFR-P_v	0.01 (0.01 − 0.03)
Revascularization	
FFR ≤ 0.80	11/12 (91%)
Percutaneous coronary intervention	10 (83%)
Coronary artery bypass graft	1 (8%)
FFR > 0.80	1/37 (3%)
Percutaneous coronary intervention	1 (3%)
Coronary artery bypass graft	0
Stent Type	
Bare mental stent	10/11 (91%)
Drug eluting stent	1/11 (9%)

Data are presented as median (first quartile − third quartile) as appropriate.

* These 12 functionally significant FFR values occurred in 12 separate patients.

FFR = fractional flow reserve.

Table 3
Clinical outcomes at 1 year

	Overall(N = 41*)	FFR ≤ 0.80(N = 11)	FFR > 0.80(N = 30†)	p Value
All-cause death	13 (32%)	8 (73%)	5 (17%)	0.001
Cardiac	1 (2%)	1 (9%)	0 (0%)	0.10
Non-cardiac	12 (29%)	7 (64%)	5 (17%)	0.004
Myocardial infarction	1 (2%)	1 (9%)	0 (0%)	0.10
Repeat revascularization†	7 (17%)	4 (36%)	3 (10%)	0.04
Composite of all-cause death, myocardial infarction, and repeat revascularization	18 (44%)	10 (91%)	8 (27%)	<0.0001
Total events	21	13	8	<0.0001
Total events per person	0.51	1.18	0.27	<0.0001

* Only 1 of 42 patients was lost to follow-up.
† One patient was reclassified (FFR >0.80 but FFR-P_v ≤0.80) and experienced myocardial infarction and lesion revascularization.

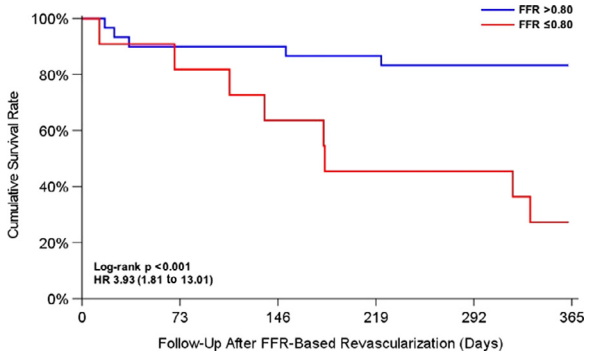

Figure 1. Association of functionally significant FFR with all-cause mortality. Kaplan-Meier analysis demonstrated that a functionally significant FFR value (≤0.80) is associated with a significantly lower rate of survival.

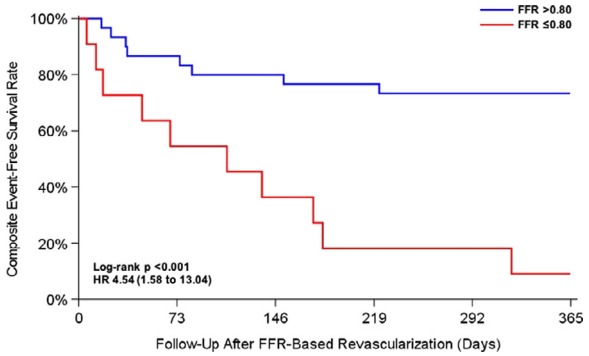

Figure 2. Kaplan-Meier estimate of composite event-free survival rate by FFR. Kaplan-Meier analysis demonstrated that a functionally significant FFR value (≤0.80) is associated with a significantly lower cumulative event-free survival rate for the composite of all-cause mortality, MI, and repeat revascularization.

analyses. The overall 1-year mortality rate was 32%, 92% of which were noncardiac in etiology (Table 3). Of note, patients with FFR ≤0.80 had largely similar baseline characteristics as those with FFR >0.80 apart from a higher rate of chronic kidney disease and hepatocellular carcinoma (Supplementary Table 1). Patients with functionally significant stenoses had significantly lower cumulative survival rates than those with functionally nonsignificant stenoses (27% vs 83%, log-rank p = 0.001, Figure 1). In addition, repeat revascularization (36% vs 10%, p = 0.04), MACE (91% vs 27%, p <0.0001, Figure 2), and total events per patient (1.08 vs 0.27, p <0.0001) occurred significantly more frequently in patients with functionally significant disease (Table 3). In multivariate Cox regression analyses, FFR ≤0.80 remained an independent predictor of all-cause mortality (HR = 3.93, 95% CI 1.81 to 13.01, p = 0.03) and MACE (HR = 4.54, 95% CI 1.58 to 13.04, p = 0.005). Finally, in the 11 patients with functionally significant stenoses who underwent revascularization, 1 was lost to follow-up, 4 received OLT (3 survived to 1 year) and 6 did not receive OLT (none survived to 1 year); 2 of the deaths were attributable to bleeding complications.

The salient findings of this retrospective study of patients with ESLD are: (1) P_v has negligible impact on FFR, and the hyperemic effect of adenosine remains preserved even in the setting of higher MELD score, a marker of liver disease extent; and (2) even in patients with predominantly angiographically-intermediate CAD, an FFR value ≤0.80 was significantly associated with all-cause mortality and MACE at 1 year. Taken together, these data suggest that FFR is a reliable physiologic index to assess the functional significance of epicardial coronary stenoses in patients with ESLD who underwent OLT evaluation and may carry significant prognostic value in this specific population.

The mathematical derivation of FFR involves 3 different variables, P_d, P_a, and P_v.[6] However, in the clinical setting, P_v is omitted because it is typically negligible relative to P_a (i.e., in a healthy patient, the mean right atrial pressure is 5 to 8 mm Hg, whereas the mean aortic pressure is 80 to 100 mm Hg), simplifying the calculation from $(P_d - P_v)/(P_a - P_v)$ to P_d/P_a. Some have questioned the influence of this simplification on the accuracy of FFR, pointing out that failing to account for P_v may yield a falsely elevated FFR value and possibly alter treatment decisions, and ultimately, patient outcomes.[12,13] This concern, together with potentially hyperdynamic P_vs in the setting of ESLD, led us to study the impact of right atrial pressure on FFR.[14,15] In the present study, P_v was 9.3 ± 6.4 mm Hg, which is consistent with previously reported values in ESLD populations. Mean FFR was 0.87 ± 0.08, and mean FFR accounting for P_v (FFR-P_v) was 0.85 ± 0.09, indicating that adjusting for P_v changed FFR values by 0.02 ± 0.02. Furthermore, FFR-P_v led to the reclassification of only 1 stenosis from functionally nonsignificant to functionally significant. Thus, these data imply that the overall impact of P_v on FFR in the

patients with ESLD is minimal and that the current practice of assuming P_v is negligible in this population is appropriate.

A fundamental assumption in the derivation of FFR is negligible microvascular resistance. The establishment of maximal hyperemia (typically intravenous or intracoronary adenosine administration), therefore, is critical for accurate FFR interrogation of epicardial coronary stenoses because it minimizes microvascular resistance. ESLD is characterized by increased circulatory flow and significant vasodilation, suggesting that this population may live in a state of maximal hyperemia and not require adenosine infusion for FFR assessment. In contrast, we found that the hyperemic effect of adenosine was indeed preserved in patients with ESLD, and most notably even in those with the highest MELD scores. This observation is consistent with previous magnetic resonance imaging-based myocardial perfusion reserve studies indicating an impaired microvascular function in patients with nonalcoholic fatty liver disease.[16]

Several case reports and small observational studies have reported coronary revascularization outcomes in patients with ESLD, but none have specifically evaluated outcomes stratified by FFR in patients with angiographically-intermediate stenoses.[17–20] In the present study of patients with ESLD with predominantly angiographically-intermediate disease, a functionally significant FFR value (≤0.80) was a significant predictor of all-cause mortality and MACE (driven by repeat revascularization) in adjusted analyses. Interestingly, in the 11 patients with an FFR ≤0.80 (all underwent revascularization), only 1 of 8 deaths was cardiac in etiology, and only 1 of 4 who successfully underwent OLT died. Taken together, these data suggest that< ischemia in the setting of even moderate CAD is a poor prognostic indicator in patients with ESLD, but may not be a mechanism of death in this high-risk population.

Several limitations warrant mentioning. First, this is a single-center, retrospective, and observational study with a small sample size, and thus the findings should be considered hypothesis-generating and may partially be because of residual confounding unaccounted for by differences between groups. Nonetheless, the study population is fairly generalizable to most OLT cohorts given the balanced demographic factors (e.g., 38% female, 31% Hispanic, 26% Asian). Second, RHC at the time of FFR interrogation was not standard protocol during the study period, which may have introduced selection bias. Third, operator variability in the FFR technique (e.g., the position of the pressure transducer in the interrogated vessel, intravenous vs intracoronary adenosine, dosage of adenosine, and others) may have impacted the FFR data. Finally, many of these patients are primarily cared for at local institutions previous to OLT, and thus some event data may not have been captured.

In conclusion, in patients with ESLD awaiting OLT, P_v has minimal impact on FFR and the hyperemic effect of adenosine is preserved, indicating that FFR is a reliable index to measure the function significance of epicardial coronary stenoses in this population. In addition, even in patients with predominantly angiographically-intermediate stenoses, an FFR value ≤0.80 was an independent predictor of all-cause mortality and MACE at 1 year.

Disclosures

Dr. Parikh reports research support from the American Heart Association, consulting fees from Abbott Vascular, and serving on the scientific advisory board (minor equity interest) of Stallion Cardio, DocVocate, and HeartCloud.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2021.11.031.

1. Plotkin JS, Scott VL, Pinna A, Dobsch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1996;2:426–430.
2. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc* 2008;40:3554–3557.
3. Maddur H, Bourdillon PD, Liangpunsakul S, Joseph Tector A, Fridell JA, Ghabril M, Lacerda MA, Bourdillon C, Shen C, Kwo PY. Role of cardiac catheterization and percutaneous coronary intervention in the preoperative assessment and management of patients before orthotopic liver transplantation. *Liver Transpl* 2014;20:664–672.
4. Pijls NH, Van Gelder B, Van der Voort P, Peels K, Bracke FA, Bonnier HJ, el Gamal MI. Fractional flow reserve. A useful index to evaluate the influence of an epicardial coronary stenosis on myocardial blood flow. *Circulation* 1995;92:3183–3193.
5. Pijls NH, De Bruyne B, Peels K, Van Der Voort PH, Bonnier HJ, Bartunek J Koolen JJ, Koolen JJ. Measurement of fractional flow reserve to assess the functional severity of coronary-artery stenoses. *N Engl J Med* 1996;334:1703–1708.
6. Pijls NH, van Son JA, Kirkeeide RL, De Bruyne B, Gould KL. Experimental basis of determining maximum coronary, myocardial, and collateral blood flow by pressure measurements for assessing functional stenosis severity before and after percutaneous transluminal coronary angioplasty. *Circulation* 1993;87:1354–1367.
7. Kowalski HJ, Abelmann WH. The cardiac output at rest in Laennec's cirrhosis. *J Clin Invest* 1953;32:1025–1033.
8. Murray JF, Dawson AM, Sherlock S. Circulatory changes in chronic liver disease. *Am J Med* 1958;24:358–367.
9. Kontos HA, Shapiro W, Mauck HP, Patterson JL Jr. General and regional circulatory alterations in cirrhosis of the liver. *Am J Med* 1964;37:526–535.
10. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, van' t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. FAME Study Investigators. Fractional flow reserve Versus angiography for guiding percutaneous coronary intervention. *N Engl J Med* 2009;360:213–224.
11. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol* 2018;72:2231–2264.
12. Perera D, Biggart S, Postema P, Patel S, Lambiase P, Marber M, Redwood S. Right atrial pressure: can it be ignored when calculating fractional flow reserve and collateral flow index? *J Am Coll Cardiol* 2004;44:2089–2091.
13. Layland J, Wilson AM, Whitbourn RJ, Burns AT, Somaratne J, Leitl G, Macisaac AI. Impact of right atrial pressure on decision-making using fractional flow reserve (FFR) in elective percutaneous intervention. *Int J Cardiol* 2013;167:951–953.
14. La Mura V, Abraldes JG, Berzigotti A, Erice E, Flores-Arroyo A, García-Pagán JC, Bosch J. Right atrial pressure is not adequate to calculate portal pressure gradient in cirrhosis: a clinical-hemodynamic correlation study. *Hepatology* 2010;51:2108–2116.

15. Parvinian A, Bui JT, Knuttinen MG, Minocha J, Gaba RC. Right atrial pressure may impact early survival of patients undergoing transjugular intrahepatic portosystemic shunt creation. *Ann Hepatol* 2014;13:411–419.
16. Nakamori S, Onishi K, Nakajima H, Yoon YE, Nagata M, Kurita T, Yamada T, Kitagawa K, Dohi K, Nakamura M, Sakuma H, Ito M. Impaired myocardial perfusion reserve in patients With fatty liver disease assessed by quantitative myocardial perfusion magnetic resonance imaging. *Circ J* 2012;76:2234–2240.
17. Carr C, Desai J. OPCAB surgery in a cirrhotic hepatocellular carcinoma patient awaiting liver transplant. *Ann Thorac Surg* 2004;78: 1460–1462.
18. Ben Ari A, Elinav E, Elami A, Matot I. Off-pump coronary artery bypass grafting in a patient with child class C liver cirrhosis awaiting liver transplantation. *Br J Anaesth* 2006;97:468–472.
19. Bizouarn P, Ausseur A, Desseigne P, Le Teurnier Y, Nougarede B, Train M, Michaud JL. Early and late outcome after elective cardiac surgery in patients with cirrhosis. *Ann Thorac Surg* 1999;67:1334–1338.
20. Marui A, Kimura T, Tanaka S, Miwa S, Yamazaki K, Minakata K, Nakata T, Ikeda T, Furukawa Y, Kita T, Sakata R. Credo-Kyoto Investigators. Coronary revascularization in patients with liver cirrhosis. *Ann Thorac Surg* 2011;91:1393–1399.