

Feasibility and Safety of Percutaneous Coronary Intervention in Patients With End-Stage Liver Disease Referred for Liver Transplantation

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Percutaneous coronary intervention (PCI) has traditionally not been an option for patients with end-stage liver disease (ESLD) and coronary artery disease (CAD). This retrospective study was designed to demonstrate the feasibility and safety of PCI in liver transplant candidates. Patients with ESLD and hemodynamically significant CAD who were otherwise deemed to be acceptable candidates for liver transplantation underwent PCI. The procedural success rates, mortality and myocardial infarction rates, and bleeding outcomes were examined. Sixteen patients with ESLD underwent PCI: 15 with bare-metal stents (1.3 stents per patient on average) and 1 with balloon angioplasty alone. The median diameter stenosis per lesion was 80%, the median platelet count was $68 \times 10^9/L$, the median international normalized ratio was 1.3, and the median Model for End-Stage Liver Disease score was 13. PCI was successful in 94% of the patients. One patient had a suboptimal residual stenosis of 50% after stenting. There were no in-hospital or 30-day deaths or myocardial infarctions, and no patients developed hematomas. One patient required a 1-U platelet transfusion, and another required 1 U of packed red blood cells. All patients remained clinically stable 1 month after PCI. Nine of the 16 patients were listed for liver transplantation, and 3 patients underwent liver transplantation. In conclusion, we have demonstrated the safety and feasibility of PCI in a small cohort of patients with ESLD and hemodynamically significant CAD, the majority of whom had significant thrombocytopenia. Larger studies are required to determine whether PCI is an effective treatment strategy for patients with ESLD and hemodynamically significant CAD who otherwise would not be candidates for liver transplantation. *Liver Transpl* 17:809-813, 2011. © 2011 AASLD.

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End-stage liver disease (ESLD) is associated with increased cardiovascular risk.¹ Although the prevalence of coronary artery disease (CAD) was previously thought to be lower in patients with ESLD versus the general population, multiple studies have demonstrated an increased prevalence of CAD in this subset of patients.²⁻⁶ The overall prevalence of CAD in patients with ESLD has been reported to be 20% to 28%, with the highest prevalence being reported in patients over the age of 50 years.^{2,6,7}

The ideal management strategy for liver transplant candidates with CAD remains unknown. The 3-year mortality rate of patients with CAD undergoing orthotopic liver transplantation (OLT) has been reported to be 26% to 50% whether medical management or surgical revascularization is pursued.^{8,9} Coronary artery bypass grafting before OLT can accelerate or exacerbate liver failure¹⁰ and has been associated with increased morbidity and mortality.¹¹ Percutaneous coronary intervention (PCI) with stenting has

Abbreviations: CAD, coronary artery disease; ESLD, end-stage liver disease; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; SPECT, single photon emission computed tomography.

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traditionally not been an option for patients with ESLD. Because of baseline thrombocytopenia and coagulopathy,¹² these patients are felt to be at increased risk for bleeding complications from the required periprocedural anticoagulation and postprocedural dual antiplatelet regimen, which consists of aspirin and a thienopyridine agent. Furthermore, many patients with ESLD have a history of gastrointestinal bleeding, which is often due to esophageal varices.¹³ Additionally, there is the potential hazard of worsening renal function with the use of contrast agents.

In this study, we sought to demonstrate the feasibility and safety of PCI in patients with ESLD and coexisting hemodynamically significant CAD who were undergoing an evaluation for OLT.

PATIENTS AND METHODS

Subjects

We identified 16 patients with ESLD who were undergoing an evaluation for OLT, were found to have hemodynamically significant CAD as part of their cardiac evaluation for OLT candidacy, and were otherwise deemed to be acceptable candidates for OLT by a multidisciplinary transplant committee. Patients with baseline platelet counts $<20 \times 10^9/L$, baseline international normalized ratios (INRs) >4.0 , hemodynamically significant left main coronary disease, and clinical evidence of active bleeding were excluded. The study was conducted with the approval of the institutional review board.

Study Design and Event Classification

Hemodynamically significant CAD was defined as (1) an angiographic diameter stenosis $\geq 70\%$, (2) a fractional flow reserve <0.75 across the culprit lesion, or (3) a minimal luminal area $<4.0 \text{ mm}^2$ in any proximal segment of an epicardial coronary artery.¹⁴ All patients underwent PCI with either bare-metal stent placement or just percutaneous transluminal coronary angioplasty (PTCA).

Bare-metal stenting was chosen as the preferred method for percutaneous revascularization in this cohort for patients with reference vessel diameters $>2.5 \text{ mm}$. Successful PTCA alone was considered an acceptable revascularization method in patients with reference vessel diameters of 2.0 to 2.5 mm .

Successful PCI was defined as angiographic, procedural, and short-term clinical success as outlined in the American College of Cardiology/American Heart Association/Society for Cardiovascular Angiography and Interventions guidelines.¹⁵ A periprocedural myocardial infarction was defined as a postprocedural increase in the creatine kinase MB levels >2 times the upper limit of normal.¹⁶

All patients were maintained on dual antiplatelet therapy with aspirin and clopidogrel for 1 month in accordance with the 2009 American College of Cardiology/American Heart Association guidelines.¹⁷ Com-

plete blood counts and platelet levels were checked on postprocedural day 1 and at 1-week intervals for a period of 4 weeks. All patients had follow-up visits at the outpatient cardiology clinic 1 week and 1 month after PCI.

Clinical bleeding was assessed with the Thrombolysis in Myocardial Infarction classification.¹⁸ Thrombocytopenia was defined as a platelet count $<150 \times 10^9/L$, and severe thrombocytopenia was defined as a platelet count $<50 \times 10^9/L$.¹⁹ Peripheral vascular complications were defined as pseudoaneurysms, arteriovenous fistulas, femoral lacerations necessitating surgical repair, retroperitoneal hematomas, significant bleeding, or any need for surgical exploration or repair. An access site hematoma was defined as significant swelling ($>5 \text{ cm}^2$) at the puncture site.²⁰

Before the procedure, the study patients did not receive any platelet transfusions, packed red blood cell transfusions, fresh frozen plasma, or cryoprecipitate. The need for packed red blood cell or platelet transfusions was determined according to the clinical judgment of the individual treating physician. Patients received packed red blood cell transfusions after the procedure if their hemoglobin levels were $<8.0 \text{ g/dL}$ or if there was any symptomatic anemia. Patients received platelet transfusions if they had active bleeding with severe thrombocytopenia or if their platelet count was $<20 \times 10^9/L$.

Complications, which included access site bleeding or hematomas, myocardial infarctions, death, and the need for a transfusion, were assessed during the hospitalization period and for 1 month after the procedure. If patients remained clinically stable at 1 month, clopidogrel was discontinued, and they received cardiac clearance for OLT.

Categorical variables are expressed as percentages, and continuous variables are expressed as medians and interquartile ranges.

RESULTS

Sixteen patients with ESLD underwent PCI: 15 with bare-metal stenting and 1 with just PTCA. Patient and lesion characteristics are summarized in Table 1. The median diameter stenosis per lesion was 80% , and 10 of the 16 patients had left anterior descending artery involvement. The median platelet count was $68 \times 10^9 \pm 49.0 \times 10^9/L$, 75% of the patients (12/16) had platelet counts $<100 \times 10^9/L$, and 38% (6/16) had severe thrombocytopenia (platelet count $\leq 50 \times 10^9/L$). The median INR was 1.3 ± 0.2 , and the median Model for End-Stage Liver Disease (MELD) score was 13 ± 5 . Sixty-three percent of the cohort was male with a median age of 57.5 ± 9.7 years. Eighty-one percent of the patients had a history of hypertension, 56% were diabetic, 19% had a history of dyslipidemia, 50% were smokers, 19% had a family history of premature CAD, and 13% had known CAD.

The procedural results, outcomes, and safety data are listed in Table 2. A femoral approach was used in all patients. The procedural success rate was 94%

TABLE 1. Baseline Characteristics of 16 Patients With ESLD Who Underwent PCI

Patient	Vessel	Stenosis (%) [*]	Platelet Count (/L)	INR	MELD Score
1	Left anterior descending artery	85	23,000	1.2	17
2	Diagonal branch artery	70	48,000	1.1	9
3	Right coronary artery, left anterior descending artery	99, 70	83,000	1.3	12
4	Left anterior descending artery	60	425,000	1	22
5	Left anterior descending artery	70	83,000	1.4	15
6	Left anterior descending artery	80	151,000	1	6
7	Left anterior descending artery, diagonal branch artery	90, 90	21,000	1.2	11
8	Left anterior descending artery	70	81,000	1.5	20
9	Left anterior descending artery, obtuse marginal artery	80, 80	60,000	1.3	15
10	Right coronary artery	70	39,000	1.3	12
11	Right coronary artery	80	135,000	1	6
12	Left anterior descending artery	70	52,000	1.2	9
13	Right coronary artery	90	31,000	1.9	22
14	Left anterior descending artery	80	84,000	1.2	15
15	Left circumflex artery	80	118,000	1.5	13
16	Left circumflex artery	95	45,000	1.5	13
Median		80	68,000	1.3	13

^{*}The average stenosis percentage was calculated with the patient's most severe lesion if more than 1 lesion was stented.

TABLE 2. Procedural Results and Clinical Outcomes for Patients Who Underwent PCI

Patient	Stents (n)	Residual Stenosis (%)	Success	In-Hospital Death or Myocardial Infarction	Bleeding or Hematoma	Transfusion	Survival to 1 Month
1	1	0	Yes	No	No	No	Yes
2	PTCA only	40	Yes	No	No	No	Yes
3	2	0	Yes	No	No	No	Yes
4	1	0	Yes	No	No	No	Yes
5	1	0	Yes	No	No	No	Yes
6	1	0	Yes	No	No	No	Yes
7	2	0	Yes	No	No	No	Yes
8	1	0	Yes	No	No	Packed red blood cells (1 U)	Yes
9	2	0	Yes	No	No	No	Yes
10	1	0	Yes	No	No	No	Yes
11	1	0	Yes	No	No	No	Yes
12	1	0	Yes	No	No	No	Yes
13	2	50	No	No	No	Platelets (1 U)	Yes
14	1	0	Yes	No	No	No	Yes
15	1	0	Yes	No	No	No	Yes
16	2	0	Yes	No	No	No	Yes
Incidence (%)			94	0	0	13	100

(15 of 16 patients), and 14 of the 15 stented patients had a residual stenosis of 0%. The average number of stents was 1.3, and all implanted stents were bare-metal stents. A single patient successfully underwent only PTCA of a diagonal branch of the left anterior descending artery. Arterial hemostasis was achieved successfully in 5 patients via a manual hold (a 6-Fr sheath in all 5 patients). In the remaining 11 patients (4 with an 8-Fr sheath and 7

patients with a 6-Fr sheath), hemostasis was achieved with an Angio-Seal device (St. Jude Medical, Minnetonka, MN).

There were no in-hospital or 30-day deaths or myocardial infarctions. There was no evidence of major or minor bleeding or hematomas (Thrombolysis in Myocardial Infarction classification). One patient was given 1 U of packed red blood cells, and another patient was given 1 U of platelets.

One patient had severe calcification of the right coronary artery and, despite the use of rotational atherectomy and aggressive balloon predilation, had a suboptimal residual stenosis of 50% after stenting. This patient underwent a repeat nuclear single photon emission computed tomography (SPECT) myocardial perfusion study 3 months after PCI, which revealed no ischemia in the territory of the right coronary artery, and a repeat angiographic examination 3 months after PCI, which revealed a stable stenosis (50%) in the stented portion of the right coronary artery. The patient received cardiac clearance on the basis of these findings.

All 16 patients received cardiac clearance for OLT 1 month after PCI; 56% of the patients (9/16) were listed for OLT, and 3 patients underwent successful OLT (50, 55, or 136 days after PCI). One patient wished to be withdrawn from consideration for OLT. One patient who had previously undergone OLT and suffered rejection was medically stabilized and was not being considered for re-OLT. One patient was completing urological clearance before listing. Four patients remained clinically stable and were not yet listed for OLT. During a median follow-up period of 14.5 months, there was 1 death. Repeat percutaneous revascularization was required for 1 of the 16 patients. Seven of the 16 patients had follow-up myocardial perfusion SPECT studies, and 2 patients underwent repeat coronary angiography within 1 year after PCI. All 7 myocardial perfusion SPECT studies were negative for any stress-induced ischemia or new infarctions. Repeat angiography in the 2 patients revealed no evidence of in-stent restenosis (diameter stenosis > 50%).

The patient who had suboptimal PCI of the right coronary artery underwent successful OLT, but he suffered an acute inferior ST elevation myocardial infarction 2 weeks after OLT and required repeat PCI of his right coronary artery. This patient has remained clinically stable since then.

DISCUSSION

The diagnosis of ESLD carries a poor prognosis. The 90-day survival is directly related to the MELD score (in our patient population, the average MELD score was 13.6 for a 90-day mortality rate of 5.6%-27%).²¹ The results of OLT are excellent: the 1-, 2-, and 5-year survival rates are 86%, 82%, and 76%, respectively.²² Patients with CAD and ESLD fare poorly with medical management alone. Plotkin et al.⁸ reported a mortality rate of 44% within 3 months of OLT and a morbidity rate of 100% for 3-year survivors. Patients with cirrhosis undergoing coronary artery bypass graft surgery fare poorly clinically²³ with an overall in-hospital mortality rate of 26%.²⁴ Simultaneous coronary artery bypass graft surgery and OLT have been proposed for patients with advanced liver disease and CAD²⁵ because of concerns about rapid hepatic decompensation after general anesthesia and cardiopulmonary bypass. Although a limited number of successful cases have been reported since 1995,^{3,25,26}

this surgical approach remains logistically and technically difficult for many centers.

Percutaneous revascularization has traditionally not been an option because of the thrombocytopenia and coagulopathy common in patients with ESLD. Pillari-setti et al.²⁷ described 43 patients with ESLD who underwent angiography for their liver transplant workup. Patients in that study received platelet transfusions for counts $<60 \times 10^9/L$ at the discretion of the cardiologist and always for counts $<30 \times 10^9/L$; fresh frozen plasma was administered to patients with INRs >1.6 . The hospital stays and the in-hospital mortality rates were similar between the patients with ESLD and the controls. Only 4 patients from the group underwent PCI, and the patients were not followed after their discharge.

Our study demonstrates that PCI with bare-metal stenting is safe and feasible in patients with ESLD, thrombocytopenia, and coexistent CAD. To the best of our knowledge, our study represents the largest experience to date with PCI in this group of patients. The procedural success rate was excellent. There were no deaths, myocardial infarctions, clinically significant bleeding events, or vascular access site complications at 1 month. Even though aspirin and clopidogrel were used in this cohort and nearly half of the patients had severe thrombocytopenia, only 1 patient required a blood transfusion. All 16 of our patients survived for at least 1 month, and the majority of our patients survived to be listed for OLT.

The limitations of our study include the relatively small sample size, the retrospective nature of the study, and the lack of long-term clinical follow-up. Our patient population may not be representative of the broader population of patients with ESLD and CAD. Because of the rare complications and the high success rate, our small population may overestimate the success rate and underestimate the rate of complications in these patients. Finally, coronary revascularization has not been demonstrated to improve clinical outcomes in patients undergoing high-risk noncardiac surgery.^{28,29} Important clinical questions that remain outside the scope of this study include the optimal timing of revascularization with respect to illness severity, the optimal antiplatelet regimen after PCI, and improvements by PCI in the long-term clinical outcomes of patients with ESLD who are undergoing OLT.

In conclusion, to the best of our knowledge, we have demonstrated for the first time the feasibility and safety of PCI in patients with ESLD and thrombocytopenia who are undergoing an evaluation for OLT. Further investigation is warranted to determine whether PCI improves clinical outcomes in patients with both ESLD and CAD.

REFERENCES

1. Ehtisham J, Altieri M, Salame E, Saloux E, Ollivier I, Hamon M. Coronary artery disease in orthotopic liver transplantation: pretransplant assessment and management. *Liver Transpl* 2010;16:550-557.

2. Carey WD, Dumot JA, Pimentel RR, Barnes DS, Hobbs RE, Henderson JM, et al. The prevalence of coronary artery disease in liver transplant candidates over age 50. *Transplantation* 1995;59:859-864.
3. Morris JJ, Hellman CL, Gawey BJ, Ramsay MA, Valek TR, Gunning TC, et al. Case 3-1995. Three patients requiring both coronary artery bypass surgery and orthotopic liver transplantation. *J Cardiothorac Vasc Anesth* 1995;9:322-332.
4. Donovan CL, Marcovitz PA, Punch JD, Bach DS, Brown KA, Lucey MR, Armstrong WF. Two-dimensional and dobutamine stress echocardiography in the preoperative assessment of patients with end-stage liver disease prior to orthotopic liver transplantation. *Transplantation* 1996;61:1180-1188.
5. Plotkin JS, Benitez RM, Kuo PC, Njoku MJ, Ridge LA, Lim JW, et al. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1998;4:253-257.
6. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Blei A, et al. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. *Am J Cardiol* 2006;98:178-181.
7. Blei AT, Mazhar S, Davidson CJ, Flamm SL, Abecassis M, Gheorghiade M. Hemodynamic evaluation before liver transplantation—insights into the portal hypertensive syndrome. *J Clin Gastroenterol* 2007;41(3 Suppl):S323-S329.
8. 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.
9. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc* 2008;40:3554-3557.
10. Keefe BG, Valantine H, Keefe EB. Detection and treatment of coronary artery disease in liver transplant candidates. *Liver Transpl* 2001;7:755-761.
11. 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.
12. Lisman T, Leebeek FW. Hemostatic alterations in liver disease: a review on pathophysiology, clinical consequences, and treatment. *Dig Surg* 2007;24:250-258.
13. Bosch J, Garcia-Pagan JC. Complications of cirrhosis. I. Portal hypertension. *J Hepatol* 2000;32(1 Suppl):141-156.
14. Tobis J, Azarbal B, Slavin L. Assessment of intermediate severity coronary lesions in the catheterization laboratory. *J Am Coll Cardiol* 2007;49:839-848.
15. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, Jacobs AK, Kern MJ, King SB III, et al. ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update the 2001 Guidelines for Percutaneous Coronary Intervention). *Circulation* 2006;113:156-175.
16. Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined—a consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. *J Am Coll Cardiol* 2000;36:959-969.
17. Kushner FG, Hand M, Smith SC Jr, King SB III, Anderson JL, Antman EM, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2009;120:2271-2306.
18. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, et al. Thrombolysis in Myocardial Infarction (TIMI) trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;11:1-11.
19. Berkowitz SD, Sane DC, Sigmon KN, Shavender JH, Harrington RA, Tchong JE, et al. Occurrence and clinical significance of thrombocytopenia in a population undergoing high-risk percutaneous coronary revascularization. Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) study group. *J Am Coll Cardiol* 1998;32:311-319.
20. Waksman R, King SB III, Douglas JS, Shen Y, Ewing H, Mueller L, et al. Predictors of groin complications after balloon and new-device coronary intervention. *Am J Cardiol* 1995;75:886-889.
21. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-470.
22. Ghobrial RM, Farmer DG, Baquerizo A, Colquhoun S, Rosen HR, Yersiz H, et al. Orthotopic liver transplantation for hepatitis C: outcome, effect of immunosuppression, and causes of retransplantation during an 8-year single-center experience. *Ann Surg* 1999;229:824-831.
23. Shaheen AA, Kaplan GG, Hubbard JN, Myers RP. Morbidity and mortality following coronary artery bypass graft surgery in patients with cirrhosis: a population-based study. *Liver Int* 2009;29:1141-1151.
24. Filsoofi F, Salzberg SP, Rahmanian PB, Schiano TD, Elsiey H, Squire A, Adams DH. Early and late outcome of cardiac surgery in patients with liver cirrhosis. *Liver Transpl* 2007;13:990-995.
25. Axelrod D, Koffron A, Dewolf A, Baker A, Fryer J, Baker T, et al. Safety and efficacy of combined orthotopic liver transplantation and coronary artery bypass grafting. *Liver Transpl* 2004;10:1386-1390.
26. Benedetti E, Massad MG, Chami Y, Wiley T, Layden TJ. Is the presence of surgically treatable coronary artery disease a contraindication to liver transplantation? *Clin Transplant* 1999;13(1 Pt 1):59-61.
27. Pillarisetti J, Patel P, Duthuluru S, Roberts J, Chen W, Genton R, et al. Cardiac catheterization in patients with end-stage liver disease: safety and outcomes. *Catheter Cardiovasc Interv* 2011;77:45-48.
28. Poldermans D, Schouten O, Vidakovic R, Bax JJ, Thomson IR, Hoeks SE, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V pilot study. *J Am Coll Cardiol* 2007;49:1763-1769.
29. Schouten O, van Kuijk JP, Flu WJ, Winkel TA, Welten GM, Boersma E, et al. Long-term outcome of prophylactic coronary revascularization in cardiac high-risk patients undergoing major vascular surgery (from the randomized DECREASE-V pilot study). *Am J Cardiol* 2009;103:897-901.