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Resources Utilization After Liver Transplantation in Patients With and Without Hepatopulmonary Syndrome: Cleveland Clinic Experience

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Background. Patients with hepatopulmonary syndrome (HPS) reportedly experience posttransplant morbidity and require more resources to care during perioperative period. The exact incremental increase of resources utilization compared with non-HPS population remains unknown. **Methods.** In this single-center retrospective investigation, we compared the perioperative resources utilization of HPS patients undergoing orthotopic liver transplant (n=28) to cohort without HPS (n=739). Potential confounding variables were adjusted in the analysis and the multivariable log-linear regression were used. **Results.** The overall hospital costs for HPS patients were about 27% higher compared with non-HPS patients (the ratio of geometric means, 1.27; 98.3% confidence interval, 1.09-1.47; $P<0$). HPS diagnosis was independently associated with both longer intensive care unit stay ($P<0.001$) and hospital stay ($P<0.001$). The odds of being discharged to extended care facility were about 15 times higher for HPS patients comparing to non-HPS patients (odds ratio, 14.9; 97.5% confidence interval, 4.98-44.29; $P<0.001$). There were no differences observed in odds of being readmitted to the hospital within 6 mo after the transplant ($P=0.75$). **Conclusions.** HPS diagnosis was associated with longer intensive care unit stay, hospital stay, and increased hospital cost, together with higher odds of being discharged to extended care facility compared with non-HPS patients.

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Orthotopic liver transplantation (OLT) remains the only definitive treatment option for the patients with end-stage liver disease. OLT requires significant resources and it is believed that significant comorbidities of transplant candidates add to the overall cost of care of the patients undergoing OLT.¹ Hepatopulmonary syndrome (HPS) is defined as poor arterial oxygenation caused by intrapulmonary vascular dilatations and intrapulmonary shunting associated with liver disease. HPS of varying severity has been found in 10%–32% of patients with cirrhosis being evaluated for liver transplantation.^{2,3} It is diagnosed by presence of arterial deoxygenation, intrapulmonary vascular dilatations, and liver disorder.² Currently, the only established treatment for HPS is OLT. To improve survival in patients with HPS, starting from 2002, HPS patients with the partial pressure of arterial oxygen < 60 mmHg are allocated extra (exception) points to model for end-stage liver disease.⁴ It seems that after this prioritization of HPS patients on the waiting list, long-term survival in HPS patients improved as compared to earlier (before 2002) HPS transplants.⁵ Interestingly survival after liver transplant was not associated with partial pressure of arterial oxygen levels at the time of HPS diagnosis.⁵ Despite established survival benefit, HPS patients undergoing OLT may require long intensive care unit (ICU) and hospital stay and extensive postoperative respiratory rehabilitation, all of which conceivably increase resource utilization.⁶ Based on the report by Gupta et al,⁶ patients with diagnosis of HPS experienced substantial posttransplant morbidity, mainly related to respiratory complications. Authors, however, did not quantify the incremental increase of resources utilization needed

to provide perioperative care for these patients as compared with non-HPS population. Our investigation is intended to fill this gap in knowledge and inform clinicians about additional resources required to provide care for HPS patients after OLT. This information may help liver transplant centers to decide if they are able and willing to provide care for these unique patient populations and expedite the referral to the centers that are capable/willing to afford needed resources.

Our primary aim was to quantify the perioperative resources utilization in HPS patients undergoing OLT and compare to matched cohort without diagnosis of HPS who were transplanted at our institution.

MATERIALS AND METHODS

This retrospective study was approved by Cleveland Clinic Institutional Review Board (number 16-992). The need for the informed consent from individual patients was waived.

Specifically, we compared overall cost of the hospital stay (the cost of ICU and hospital stay) and posttransplant hospitalization (length of post-OLT intensive unit stay and hospital stay), as well as posthospital discharge disposition and need for hospital readmissions within 6 mo after transplant. We believe that findings of this study may help transplant centers to better predict resources needed to provide perioperative care for HPS patients undergoing OLT.

We also reported graft failure and in-hospital mortality for both study groups without formal comparison.

Study Population

All adult patients (>18 y old), who underwent OLT at the Cleveland Clinic from January 1, 2005, to June 1, 2016, were included in this retrospective investigation. We obtained baseline and outcome data on 789 adult patients undergoing liver transplant from Transplant Center Database: Electronic Data

Interface for Transplantation. Intraoperative data were obtained from Perioperative Health Data System and resources utilization data were retrieved from Departmental Operating Statements.

Patients who had diagnosis of HPS at the time of the liver transplant were identified via Electronic Data Interface for Transplantation. We excluded patients who underwent multivisceral transplantation or for acute hepatic failure, retransplantations, and patients with incomplete records (Figure 1). None of the patients were on extracorporeal membrane oxygenation pretransplantation or posttransplantation. No difference existed between these patients in model for end-stage liver disease exception.

Cost primary outcome included all technical and professional as well as direct and indirect costs. We inflated the in-hospital cost of the 2009–2014 cases to 2015 US dollars. Since the cost information is confidential and proprietary for the Cleveland Clinic, we report percentage of total cost between 2 groups instead of reporting actual dollar amount.

Statistical Analysis

First, balance on potential confounding variables between HPS and non-HPS patients was evaluated by using standard univariable summary statistics as well as by using absolute standardized difference scores (absolute difference in means, mean ranking, or proportions, divided by a pooled estimate of SD among the 2 groups). Potential confounding variables exhibiting a standardized difference score of 0.10⁷ or greater are supposedly imbalanced. All the variables listed in Table 1 were used for adjustment in all subsequent analyses. SAS 9.4 statistical software, Cary, NC was used for all analyses.

Primary Analysis

A logarithmic transformation of overall in-hospital cost were performed before analysis to meet modeling assumptions. The multivariable log-linear regression were used to

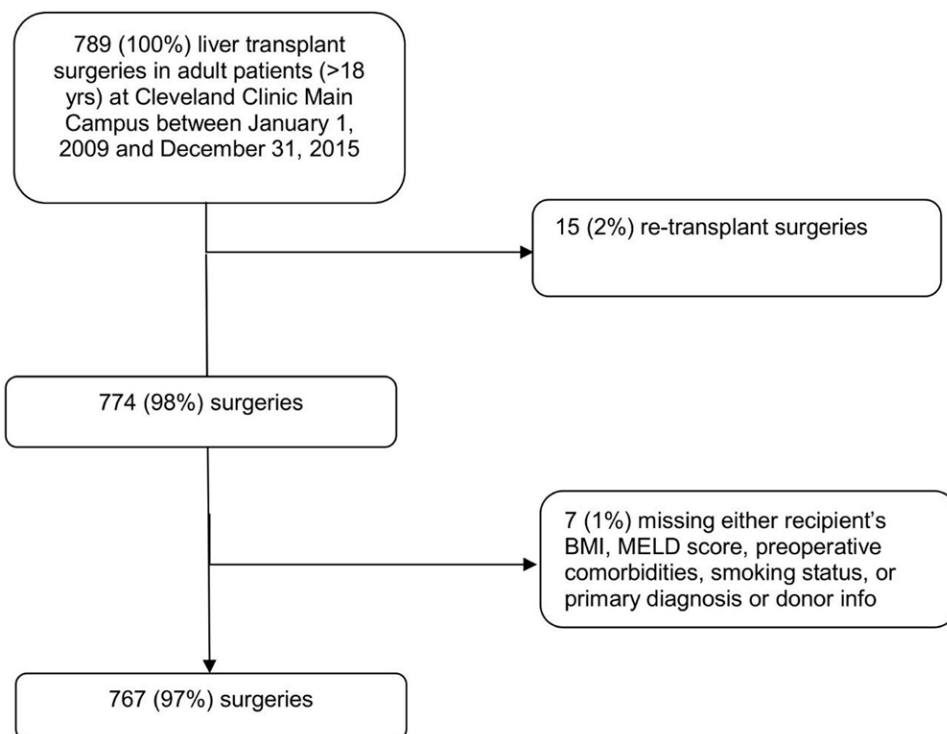


FIGURE 1. Flow chart of patient selection. BMI, body mass index; MELD, Model for End-stage Liver Disease.

TABLE 1.**The demographic, baseline, and intraoperative characteristics for patients with and without hepatopulmonary syndrome (N = 767)**

Factor	HPS group (N = 28)	Non-HPS group (N = 739)	ASD ^a
Donor info			
Donor risk index	2.7 ± 0.79	2.7 ± 0.80	0.01
Donor age, y	40 ± 16	41 ± 15	0.08
Donor height, cm	169 ± 12	172 ± 11	0.23
Donor race			0.33
White	21 (75)	597 (81)	
Black	7 (25)	118 (16)	
Other	0 (0.0)	24 (3.2)	
Donor cause of death			0.39
Anoxia	11 (39)	232 (31)	
CVA/stroke	10 (36)	214 (29)	
Head trauma	6 (21)	200 (27)	
Other	1 (3.6)	93 (13)	
Donation after circulatory death	3 (11)	84 (11)	0.02
Cold ischemic time, h	6.7 ± 1.6	6.5 ± 2.1	0.07
Whole graft (whole)	25 (89)	647 (88)	0.05
Graft location			0.16
Local	17 (61)	394 (53)	
Regional	10 (36)	306 (41)	
National	1 (3.6)	39 (5.3)	
Recipient info			
Recipient age, y	59 ± 7.5	56 ± 9.9	0.26
Recipient gender, female	10 (36)	234 (32)	0.09
Recipient BMI	29 ± 5.7	29 ± 6.8	0.01
Chemical MELD score at transplant	12 ± 3.1	20 ± 10.1	1.06
Primary diagnosis			0.64
Hepatitis induced cirrhosis	7 (25)	214 (29)	
Alcoholic cirrhosis	8 (29)	170 (23)	
NASH cirrhosis	6 (21)	137 (19)	
PSC	0 (0.0)	58 (7.9)	
PBC	1 (3.6)	39 (5.3)	
Cryptogenic cirrhosis	3 (11)	35 (4.7)	
Autoimmune cirrhosis	1 (3.6)	15 (2)	
Acute liver failure	0 (0.0)	9 (1.2)	
Others	2 (7.1)	62 (8.4)	
Medical history			
Hepatocellular carcinoma	7 (25)	252 (34)	0.20
Hypertension	17 (61)	364 (49)	0.23
Encephalopathy	20 (71)	530 (72)	0.01
Ascites	1 (3.6)	167 (23)	0.59
Hepatorenal syndrome	0 (0.0)	112 (15)	0.60
Pulmonary hypertension	7 (25)	56 (7.6)	0.49
CAD	7 (25)	127 (17)	0.20
Diabetes on insulin	4 (14)	111 (15)	0.03
Dialysis	1 (3.6)	92 (12)	0.34
Smoking	17 (61)	427 (58)	0.06
Arrhythmia	0 (0.0)	41 (5.5)	0.35
Surgery duration, min ^b	600 ± 138	604 ± 128	0.13
Surgery y			
2009	2 (2)	108 (98)	0.57
2010	6 (5)	105 (95)	
2011	2 (2)	99 (98)	
2012	5 (4)	118 (96)	
2013	6 (5)	105 (95)	
2014	6 (5)	104 (95)	
2015	1 (1)	100 (99)	
Blood loss, L	3.5 (2.0–5.5)	5.0 (2.4–10)	0.31
RBC transfused, L	1.4 (0.68–2.1)	2.1 (1.04–3.5)	0.42
FFP transfused, L	0.66 (0.0–2.0)	1.05 (0.0–2.2)	0.14
Platelets transfused, U	1.0 (0.0–3.5)	2.0 (0.0–4.0)	0.10
Cryoprecipitate, mL	0.00 (0.0–262)	0.00 (0.0–256)	0.01

^aIf ASD ≥ 0.2, 2 groups are considered as imbalanced.

^bTime period between start and end of case including anesthesia and preparation time.

Summary is presented as mean ± SD, median (1st quartile–3rd quartile), or N (%), as appropriate.

ASD, absolute standardized difference; BMI, body mass index; CAD, coronary artery disease; CVA, cerebrovascular accident; FFP, fresh frozen plasma; HPS, hepatopulmonary syndrome; MELD, Model for End-stage Liver Disease score; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; RBC, red blood cell.

compare overall in-hospital costs between HPS and non-HPS patients. The ratio of geometric means comparing HPS to non-HPS patients along with 98.3% confidence interval were reported.

The multivariable Cox proportional hazard regression⁸ was employed to assess the relationship between HPS status and hospital lengths of stay to account for patient's survival information. Discharges for patients who died in hospital were considered as failures, with time censored at the worst observation (longest length of stay) in the analysis. The hazard ratios (time to discharge alive comparing HPS to non-HPS patients) were reported along with 98.3% confidence interval.

To compare length of ICU stay for 2 study groups, the survival analysis were implemented in same manner as for hospital length of stay. Discharges for patients who died in ICU were considered as failures, with time censored at the worst observation (longest ICU stay).

A Bonferroni correction for multiple testing was applied and a significance criterion of $0.05/3 \text{ tests} = 0.017$ was used to control the overall type I error of the primary hypotheses at 5% level. Model-based Wald tests were used for formal primary hypothesis testing.

Secondary Analysis

To compare posthospital discharge dispositions (extended care facility [ECF] versus home) between 2 study groups, the multivariable logistic regression was used. The odds ratio of discharge to ECF comparing HPS and non-HPS patients along with the 97.5% confidence interval was reported.

We planned to assess the relationship between study groups and incidence of hospital readmissions within 6 mo after transplant by a logistic regression model. The odds ratio of hospital readmission comparing HPS and non-HPS patients along with the 97.5% confidence interval was planned to be reported.

Only patients discharged alive from the hospital were used for both secondary analyses. A Bonferroni correction for multiple testing was applied and a significance criterion of $0.05/2 \text{ tests} = 0.025$ was used for each secondary hypothesis to control the overall type I error of the secondary hypotheses at 5% level.

We also reported the incidence of graft failure and in-hospital mortality for HPS and non-HPS patients without formally comparing 2 study groups.

Power Consideration

We used all available patients going through the OLT between January 1, 2005, and June 1, 2016. Planning the study, we anticipated having around 1000 OLT patients that satisfy inclusion and exclusion criteria of the study with about 70 (7%) HPS patients.

The power calculation was based on the primary outcome of in-hospital cost since it is assumed to reflect longer ICU and hospital stay and utilization of additional procedures and resources. Given total sample size of 767 including 28 (3.7%) HPS patients and assuming cost coefficient of variation of 0.6 (mean/SD), we had about 92% power to identify 1.5 ratio of geometric means costs comparing HPS to non-HPS patients at 0.017 level of significance.

RESULTS

We obtained data for 767 liver transplant patients (Figure 1), including 28 patients (3.7%) with and 739 patients

(96.3%) without HPS. The summary of the recipient's demographic and baseline characteristics, intraoperative data, and donor info are reported in Table 1.

The overall hospital costs for HPS patients were about 27% higher compared with non-HPS patients (the ratio of geometric means, 1.27; 98.3% confidence interval, 1.09-1.47; $P < 0$). HPS diagnosis was independently associated with both longer ICU stay ($P < 0.001$; significance criterion of 0.017) and lengthier hospital stay ($P < 0.001$; significance criterion of 0.017) with significance criterion of 0.017 (Tables 2 and 3). Distribution of technical, professional, direct, and indirect costs in HPS and control groups is presented in Table 4.

The results on secondary analyses with supplementary outcomes are presented in Table 5. The odds of being discharge to ECF were about 15 times higher for HPS patients comparing to non-HPS patients (odds ratio, 14.9; 97.5% confidence interval, 4.98-44.29; $P < 0.001$). There were no differences observed in odds of being readmitted to the hospital within 6 mo after the transplant ($P = 0.75$). We observed 48 patients who experienced either graft failure (29) and/or in-hospital death (32) or both after liver transplant.

DISCUSSION

Medical care for the patients undergoing liver transplantation requires considerable amount of resources. Conceivably, patients with significant comorbid conditions may consume disproportionately more healthcare resources because of increased posttransplant morbidity. Although this notion is intuitively sound, there is limited data exploring the incremental increase of the resources utilization in patients with certain comorbid conditions. This information could be helpful for transplant programs to determine if they are capable to take care of more complex patients. HPS is reported to affect 10%–32% of patients with cirrhosis being evaluated for liver transplantation^{2,3}; however, there is limited data available regarding overall expanse of providing care for these patients when they undergo OLT. This investigation attempted to fill the gap in knowledge about the cost of care for HPS patients undergoing OLT relative to matched cohort. The biggest problem with estimation of the cost of care is the fact that actual dollar amount spent by individual institution is confidential, proprietary, and governed by local factors that are not publicly available. Therefore, there is paucity of publicly available reports regarding actual cost of care of medically complex organ recipients, such as patients with HPS. It is unlikely that any institution will be willing to disclose actual expense spent on taking care of HPS patients; however, analysis of proportional comparison of the total expenditure including technical, professional, direct, and indirect cost between HPS and non-HPS patients in the same institution may provide the guidance about resource utilization irrespective of the actual dollar amount.

Our analysis showed that HPS patients had significantly higher overall technical and professional, direct and indirect cost by 27% compared with non-HPS patients even after accounting for number of potential confounding factors. Essentially all cost categories were higher in HPS group; however, for majority of them, incremental increase was modest. On the other hand, nursing cost was 6 times higher as well as cost of respiratory care was 2.6 times higher for HPS patients, which was not surprising given the fact that

TABLE 2.**Primary analysis—associations between HPS status and cost (N = 767)**

Cost primary outcome	% of total cost (N = 767)	Ratio of geometric means ^a (98.3% CI) ^b (HPS vs not HPS)	P ^b
Total cost, including technical and professional, direct and indirect, in December 2015 dollars	100%	1.27 (1.09-1.47)	<0.001
Organ acquisition	37.9%	1.18 (0.93-1.51)	
Professional	18.8%	1.29 (1.09-1.53)	
Surgical services	12.7%	1.03 (0.93-1.16)	
Pathology laboratory	9.6%	1.24 (1.04-1.48)	
Nursing	8.7%	6.09 (2.38-15.62)	
Pharmacy	7.8%	1.36 (1.06-1.75)	
Respiratory pulmonary	0.7%	2.61 (1.87-3.62)	
Imaging diagnostic	0.7%	1.58 (1.15-2.16)	
Other	2.3%	1.53 (1.21-1.92)	

^aThe multivariable log-linear regression were used. All potential factors listed in Table 1 were adjusted for.

^bThe significance criterion was $P < 0.017$ (ie, 0.05/3, Bonferroni).

Raw data are reported as median (1st quartile–3rd quartile).

CI, confidence interval; HPS, hepatopulmonary syndrome.

TABLE 3.**Primary analysis—associations between HPS status and time to ICU and hospital discharge (N = 767)**

Hospital stay primary outcomes	HPS group				HR ^a (98.3% CI) ^b (HPS vs not HPS)	P ^b
	Yes (N = 28)		No (N = 739)			
	Discharge alive	Days to discharge ^c	Discharge alive	Days to discharge ^c		
ICU discharge	28 (100%)	9.5 (2–18.5)	711 (96%)	3 (2–5)	0.38 (0.23-0.63)	<0.001
Hospital discharge	27 (96%)	14 (11–28)	708 (96%)	11 (8–18)	0.38 (0.22-0.64)	<0.001

^aThe multivariable Cox proportional hazards regressions were used. All potential confounding covariables listed in Table 1 were adjusted for.

^bThe significance criterion was $P < 0.017$ (ie, 0.05/3, Bonferroni).

^cThe summary statistics were median (Q1–Q3) for patients who were discharged alive from ICU/hospital. We assessed the relationship by Cox proportional hazards regressions, in which patients dying before discharge were considered as failures in the analysis and censored at time of longest observation of any patient.

Summary is presented as N (%) or median (1st quartile–3rd quartile), as appropriate.

CI, confidence interval; HPS, hepatopulmonary syndrome; HR, hazard ratio; ICU, intensive care unit.

HPS patients required more complex medical care, longer ICU, and hospital length of stay. Importantly cost of these resources as a proportion of the overall perioperative cost was relatively low (8.7% and 7.8%, respectively), which means that although HPS patients require overall more resources, the biggest proportional increase is consumed by services with relatively low contribution to total cost of care. Our analysis demonstrated that HPS patients required longer ICU stay and lengthier hospital stay, which did translate on large increase of total expenditure as compared with non-HPS patients. It seemed that median ICU stay of HPS patients was almost 3 times longer compared with non-HPS patients, which was most likely related to more complex respiratory care, however incremental increase in median length of hospital stay was only 3 d, which may be explained by the fact that HPS patients were 15 times more likely to be discharged to ECF as opposed to home. Although we did not analyze the duration and cost of the ECF in both groups, it seems plausible that more resources needed to be allocated to cover expenses of ECF in HPS group based on the fact that 61% of these patients were discharged there.

To the best of our knowledge, this is the first report comparing resources utilization between HPS and matched non-HPS liver transplants. Although we found significantly higher

overall cost, it seems to be acceptable given complexity of these patients. Results of this analysis can be used by other institutions to aid the decision-making process when accepting HPS candidates to their programs.

We duly recognize limitations of this analysis: as with any and all retrospective studies, our ability to adjust for potential confounding factors is limited to available data. Although

TABLE 4.**Distribution of technical, professional, direct, and indirect costs in HPS and control groups**

Cost primary outcomes	% of total cost	
	HPS group	
	Yes (N = 28)	No (N = 739)
Total cost	100%	100%
Technical costs		
Direct costs	62%	65%
Indirect costs	20%	18%
Professional costs		
Direct costs	13%	13%
Indirect costs	5%	4%

HPS, hepatopulmonary syndrome.

TABLE 5.**Secondary analysis—associations between HPS status and discharge disposition and hospital readmission rate within 6 mo (N = 767)**

Outcomes	HPS group		OR ^a (97.5% CI) ^b (HPS vs not HPS)	P ^b
	Yes (N = 28)	No (N = 739)		
Secondary outcomes				
Discharge dispositions (ECF vs home)	17 (61)	205 (28)	14.9 (4.98-44.29)	<0.001
Hospital readmissions within 6 mo after transplant surgery	16 (57)	386 (52)	1.15 (0.40-2.98)	0.75
Supplementary outcomes ^c				
Graft failure	0 (0)	29 (3.9)		
In-hospital mortality	1 (3.5)	31 (4.2)		

^aThe multivariable logistic regression was used. All covariables listed in Table 1 were adjusted for.^bThe significance criterion for secondary hypotheses was $P < 0.025$ (ie, 0.05/2, Bonferroni).^cSupplementary outcomes were reported without formal comparison.

Summary is presented as N (%).

CI, confidence interval; ECF, extended care facility; HPS, hepatopulmonary syndrome; OR, odds ratio.

we accounted for potential confounding effects of 31 factors, residual bias due to uncontrolled confounding variables may remain and cannot be determined. Consequently, the associations we report should not be considered evidence of a causal relationship. We also did not consider the posthospital discharge cost of rehabilitation facilities, disposition 15 times more likely in HPS patients, which surely added to the overall cost of care. We also admit that we can investigate some factors or categorization of factors further than the current analysis, for instance, the severity of pretransplant hypoxemia correlated to the cost on HPS, or the itemized cost of each supply, for example, OpiFlow. We did not do that because a model with more variables may have less validity with this HPS patient number. Moreover, we admit the cost analysis would vary in other hospitals and healthcare systems. The generalizability of the cost in this study is a challenge. However, we cannot expose the cost structure and insurance profile, or use national Medicaid data to quantify ours because the intent of this study was to inform about incremental cost increase compared with matched non-HPS patients in our institution. In addition, we admit that cost-effectiveness analysis is a point of interest as Roberts et al⁹ reported. It is out of the intent of this study and may be in the further analysis.

CONCLUSIONS

In conclusion, we found significant association between HPS diagnosis and increased hospital cost by 27% in adult patients after having liver transplant surgery. HPS diagnosis was independently associated with longer ICU stay and

prolonged hospital stay, together with odds of being discharged to ECF 15 times higher compared with non-HPS patients. No difference in being readmitted to the hospital within 6 mo after the transplant was found.

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