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Differences in Phenotypes and Liver Transplantation Outcomes by Age Group in Patients with Primary Sclerosing Cholangitis

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Abstract

Background—There is increasing evidence for a heterogeneity of phenotypes in primary sclerosing cholangitis (PSC), but differences across the age spectrum in adults with PSC have not been well characterized.

Aims—To characterize phenotypic variations and liver transplantation outcomes by age group in adults with PSC.

Methods—The United Network for Organ Sharing database was used to identify waitlist registrations for primary liver transplantation in adults with PSC. Patients were split into three age groups: 18–39 (young), 40–59 (middle-aged), and 60 (older). Their clinical characteristics and outcomes on the waitlist and post-transplant were compared.

Results—Overall, 8272 adults with PSC were listed for liver transplantation during the study period, of which 28.9% were young, 52.0% were middle-aged, and 19.1% were older. The young age group had the greatest male predominance (70.0 vs. 66.2 vs. 65.1%, $p = 0.001$), the highest proportion of black individuals (20.0 vs. 11.0 vs. 5.5%, $p < 0.001$), and the most patients listed with concomitant autoimmune hepatitis (2.2 vs. 1.0 vs. 0.8%, $p < 0.001$). Older patients experienced the greatest waitlist and post-transplant mortality. Graft survival was greatest in the middle-aged group. Young patients were most likely to experience acute rejection (31 vs. 22.8 vs. 18.0%, $p < 0.001$) and have graft failure due to chronic rejection or PSC recurrence (47.8 vs. 42.3 vs. 17.9%, $p < 0.001$).

Conclusions—Age-related differences exist among adults with PSC and are associated with outcomes pre- and post-transplant. Young patients may have a more robust immune-related phenotype that is associated with poorer graft survival. Future studies are needed to further investigate these findings.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Keywords

Sclerosing cholangitis; Liver transplantation; Phenotype; Treatment outcome; Age factors

Introduction

Primary sclerosing cholangitis (PSC) is a chronic, cholestatic liver disease characterized by progressive biliary inflammation and fibrosis. There is currently no effective medical treatment, and many patients ultimately require liver transplantation. PSC is more common in men and is closely associated with inflammatory bowel disease (IBD), especially ulcerative colitis. It typically affects adults in middle-age, with a median age of onset of 30–40 years old, though it can occur across the age spectrum [1].

While these may be the typical features, PSC is a heterogeneous disease. There are several recognized subtypes, including overlap with autoimmune hepatitis (AIH) and involvement limited to intrahepatic small ducts, and phenotypic variations have been reported by sex, IBD diagnosis, and race [1–5]. Some differences between pediatric- and adult-onset PSC have also been observed, including a higher prevalence of overlap with AIH in children [6, 7]. Data on variations by age in adults with PSC, however, have been limited.

Characterization of the different phenotypes in PSC is important for multiple reasons, including risk stratification and the development of new therapies. The disease course of PSC is variable, and the ability to risk stratify patients to better predict prognosis and to counsel them accordingly is lacking. More precise phenotyping is critically important for the development of new therapies, as these phenotypic differences may reflect variations in disease pathophysiology that could affect patients' responsiveness to therapeutic agents.

In order to better understand age-related differences in patients with PSC, we performed this analysis using the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) database with the following objectives: to characterize phenotypic variations by age group in patients listed for transplantation and to compare the outcomes in these groups on the waitlist and post-transplant.

Methods

Study Population and Data Collection

The UNOS/OPTN database as of 9/25/2015 was used to identify all waitlist registrations for adults (18 years or older) with a primary diagnosis of PSC between 4/1/1994 and 6/30/2015. Individuals listed for repeat or multi-organ transplantation, as status 1, with acute hepatic necrosis, or with cholangiocarcinoma were excluded.

Variables extracted from the time of waitlist registration included: age, sex, race/ethnicity, IBD diagnosis, secondary diagnosis of AIH, blood type, UNOS region, primary insurance at listing, diabetes, ascites, hepatic encephalopathy, Model for End-Stage Liver Disease (MELD) score and component laboratory values (total bilirubin, creatinine, and international normalized ratio [INR]) at listing (for registrations after 2/27/2002), time on the waitlist, and

reason for waitlist removal. Complications of portal hypertension at listing were defined as the presence of ascites or hepatic encephalopathy.

Transplant recipient variables collected were primary insurance at transplant, location at transplant, mechanical ventilation, dialysis, previous abdominal surgery, ascites, hepatic encephalopathy, MELD score (post-2/27/2002), total bilirubin, creatinine, INR (available after 10/25/1999), and albumin. Complications of portal hypertension at transplant were similarly defined as the presence of ascites or hepatic encephalopathy. Donor variables included donor age (younger or older than 60), donor type (living or deceased), donation after cardiac death (DCD) donor status, and graft type (split/partial or whole).

Post-transplant variables extracted were treatment for rejection within 6 months or 1 year, graft status (functioning or failed), graft survival time (time from transplantation until graft failure), causes of graft failure, patient status (alive or deceased), patient survival time (time from transplantation until death), and causes of death.

Age Groups and Outcomes

To characterize age-related differences, patients were split into three age groups: 18–39, 40–59, and 60 and older. The clinical characteristics and outcomes on the waitlist (mortality and causes of death) and post-transplant (acute rejection, graft failure, causes of graft failure, 5-year mortality, and causes of death) were compared between these groups.

Waitlist mortality was defined as death on the waitlist or removal for being too sick for transplant. Causes of death were grouped into the following categories: infection, hemorrhage, cardiovascular, pulmonary, renal failure, multisystem organ failure, malignancy, graft failure, and other. Each patient could have one reported cause of death on the waitlist and up to three contributing causes post-transplant. One was reported for 339/888 waitlist mortalities, and at least one was indicated for 1013/1100 post-transplant mortalities.

The causes of graft failure were classified into the following categories: disease recurrence, biliary complications, vascular thrombosis, chronic rejection, acute rejection, primary nonfunction, infection, and other. The etiologies of graft failure were determined from both coded and free-text responses. This was ascertained for 805/1618 patients. Multiple etiologies could be reported, and no primary cause was indicated. Patients were therefore considered to have each reported etiology.

Acute rejection was defined as treatment for rejection within one year or graft failure due to acute rejection. These data were available for 3495/4746 transplant recipients.

Statistical Analyses

Descriptive statistics were calculated for the demographic and clinical characteristics. Comparisons were performed using Chi-square tests or Fisher exact tests for categorical variables and *t* tests or Wilcoxon rank-sum tests for continuous variables, depending on the normality of the distribution.

Competing risks analysis was performed to examine the association between age group and waitlist mortality, with transplantation treated as a competing outcome and other outcomes censored. Single predictor subhazard ratios (SHRs) were estimated by the cumulative incidence function. Predictors evaluated included age group, sex, race/ethnicity, IBD diagnosis, secondary diagnosis of AIH, blood type, UNOS region, insurance at listing, diabetes, and complications of portal hypertension at listing. Complications of portal hypertension were missing in 14.9% (1236/8272), though it was considered for inclusion in the model in order to adjust for an indicator of illness severity. A second model was performed among registrations after 2/27/2002 (4942/8272) and considered the MELD score at listing.

Graft and patient survival curves were computed using Kaplan–Meier methods and compared using log-rank tests. Cox proportional hazards regression was performed to adjust for donor and recipient factors that may affect post-transplant graft and patient survival. Covariates considered included the above variables ascertained at the time of transplantation, the location at transplant, mechanical ventilation, dialysis, previous abdominal surgery, laboratory values (bilirubin, creatinine, and albumin), and donor factors.

Predictors with $p < 0.05$ in univariate analyses were entered and retained in the multivariate models at the same level of significance using a backward selection process. The proportion of missing data was less than 5% for each variable unless otherwise specified. Models excluded cases with missing predictor variables.

All analyses were performed using SAS® Studio software, Version 3.5 (SAS Institute, Cary, NC), and a p value less than 0.05 was considered statistically significant.

Results

Clinical Characteristics at Listing and Outcomes on the Waitlist by Age Group

Overall, 8272 adults with PSC were listed for liver transplantation during the study period. The median age at listing was 48 (range 18–79; interquartile range [IQR] 37–57), and 5550 were men (67.1%). In all, 5778 (69.8%) had IBD, including 3884 (47.0%) with ulcerative colitis and 1319 (16.0%) with Crohn's disease.

Of these 8272 patients, 2392 (28.9%) were young (ages 18–39), 4299 (52.0%) were middle-aged (ages 40–59), and 1581 (19.1%) were older (ages 60 and older). The demographics and clinical characteristics at listing varied by age group (Table 1). The young age group had the greatest male predominance, the highest proportion of black individuals, and the most patients listed with a secondary diagnosis of AIH. Concomitant IBD was more common in young and middle-aged individuals due to less ulcerative colitis in the older group. The pattern of biochemical abnormalities at listing also differed between the young and older patients. The older group demonstrated greater hepatic synthetic impairment and renal dysfunction, and the young group had a more elevated bilirubin.

The older group was the sickest at listing, with the highest proportion with complications of portal hypertension and among the highest MELD scores (Table 1). They also experienced

the greatest waitlist mortality, even after adjustment for potential confounding variables (Tables 2, 3). Age group remained significantly associated with waitlist mortality after also adjusting for MELD score at listing (middle-aged vs. young: SHR 2.49, 95% confidence interval [CI] 1.98–3.14; older vs. young: SHR 3.75, 95% CI 2.92–4.78; older vs. middle-aged: SHR 1.50, 95% CI 1.27–1.78). The reported causes of death on the waitlist were overall similar.

Clinical Characteristics at Transplant and Post-transplant Outcomes by Age Group

In all, 4746 patients listed with PSC underwent transplantation during the study period, including 1451 (30.6%) young, 2478 (52.2%) middle-aged, and 817 (17.2%) older patients. Differences in demographics and clinical features by age group were also present at transplant (Table 4). The older group remained the sickest group and had the highest proportion of patients in the intensive care unit at transplant. The MELD scores at transplant were similar, though, like at listing, the patterns of biochemical abnormalities were different. The donor characteristics also differed. Patients in the young group were more likely to receive a living donor transplant or a split graft, while those in the older age group more commonly accepted a donor age 60 or older.

Post-transplant, the graft survival was greatest in the middle-aged group, even after adjusting for potential confounding recipient and donor factors (Fig. 1a, Table 3). The etiologies of graft failure varied by age group, and disease recurrence and chronic rejection were more common in the younger patients (Table 5). A total of 47.8% (159/333) of the young group, 42.3% (164/388) of the middle-aged group, and 17.9% (15/84) of the older group experienced graft failure due to either PSC recurrence or chronic rejection ($p < 0.001$). Young individuals were also most likely to experience acute rejection. Primary graft nonfunction was overall more prevalent in the older group, but this difference attenuated when limited to non-advanced age donors (younger, 17.3% [52/300] vs. middle-aged, 23.4% [74/316] vs. older, 26.6% [17/64], $p = 0.09$).

After graft failure occurred, younger patients were more likely to undergo a second transplant, and they were also more likely to die of graft failure (Table 5). The overall risk of 5-year post-transplant mortality increased with age, though the causes of death were otherwise similar (Fig. 1b). Of those who died of malignancy, young and middle-aged patients more commonly died of cholangiocarcinoma. A significantly greater proportion of mortalities among the older group occurred within 6 months of transplant compared to the younger groups (young, 15.1% [36/238] vs. middle-aged, 17.2% [98/568] vs. older, 28.6% [84/294], $p < 0.001$). The most common reported cause of death among these early mortalities in all three groups was infection (young, 27.3% [9/33] vs. middle-aged, 32.2% [29/90] vs. older, 38.0% [30/79], $p = 0.51$).

Discussion

There is increasing evidence for a heterogeneity of PSC phenotypes, but differences across the age spectrum have not been well characterized. In this study, we utilized a large national database to compare the clinical characteristics and outcomes of adults with PSC listed for

liver transplantation after stratification by age group. We found that age-related differences do exist among patients with PSC, in both phenotype and outcomes.

Younger patients were less likely to be female, more likely to have concomitant IBD, and more likely to be black, in accordance with prior studies [2–4, 8]. Young individuals were also more commonly listed with a secondary diagnosis of AIH, presumably indicating PSC/AIH overlap syndrome. This finding is consistent with prior observations of increased overlap with AIH among young adults as well as in pediatric- and adolescent-onset PSC patients, some of whom may have been listed after age 18 [6, 7, 9].

A greater proportion of older patients experienced complications of portal hypertension, and they also demonstrated more renal dysfunction and hepatic synthetic impairment, while increased bilirubin was the predominant biochemical abnormality in the young group. Taken together, these findings suggest a phenotype with more advanced fibrosis and cirrhosis in the older group, and perhaps one typified more by aggressive cholestatic disease in younger patients. Without additional data, however, it is difficult to draw any definitive conclusions, and further research to more fully characterize age-related phenotypic differences in patients with PSC prior to liver transplantation is warranted.

In addition to these phenotypic variations at listing, there were also age-related differences in outcomes on the waiting list. Waitlist mortality increased with age, independent of the severity of liver disease, consistent with previous studies [10, 11]. The causes of death on the waitlist were not thoroughly reported, and it is difficult to discern whether there were differences in liver-related and non-liver-related mortalities. We suspect, however, that this finding is due in part to uncaptured comorbid conditions or other health-related factors for which older age serves as a surrogate. Some of these factors include frailty, sarcopenia, and functional status, all of which have been found to be associated with mortality on the transplant waiting list [12–16]. We were unable to adjust for these or for many comorbidities and therefore hesitate to emphasize the impact of age alone on waitlist mortality in patients with PSC, though that it existed after adjustment for complications of portal hypertension and MELD score at listing is worth noting. Further study should be performed to identify the underlying causes for these differences in mortality on the waitlist and ways to optimize outcomes.

Outcomes after transplantation similarly varied by age group, including differences in graft survival, patient survival, and etiologies of these outcomes. As on the waitlist, the risk of mortality post-transplant increased with age. The magnitude of the difference was greatest between the older group and the two younger groups, and the decreased survival was largely due to increased short-term mortality. We were able to adjust for more indicators of illness severity than in our analysis of waitlist mortality, but there may again be unmeasured comorbidities or other factors contributing. Therefore, though these results suggest that transplantation in adults with PSC over 60 should be undertaken cautiously, our analysis may overestimate the effect of age on post-transplant mortality. Further research on ways to identify older patients with PSC more likely to experience long-term survival after transplantation should be performed.

The relationship between age and graft failure, however, differed from mortality. Graft survival was greatest in the middle-aged group, even after adjusting for recipient and donor characteristics. Increased graft loss in older transplant recipients is consistent with previous studies [17, 18]. Yet, the finding that young patients had an increased risk of graft failure compared to middle-aged individuals, such that they experienced similar graft survival to individuals over 60, has not been reported for other etiologies of liver disease. Differences in acute rejection and the reported causes of graft failure though may suggest some possible explanations.

Acute rejection has been considered to be of less consequence in livers compared to other solid organs due to older data demonstrating no impact on graft failure or mortality [19–21]. However, a recent analysis found a significant association between acute rejection and graft failure in liver transplant recipients [22]. This study also observed increased risks of acute rejection in younger individuals and in patients with PSC. We similarly found acute rejection to be most prevalent in young patients, and perhaps this partly underlies the increased risk of graft failure compared to the middle-aged group. We are unfortunately limited by the available data in further exploring this possibility, but it warrants more research. If true, these patients may benefit from a more aggressive immunosuppression regimen in order to prevent graft failure related to acute rejection. It is also possible that higher rates of noncompliance with immunosuppression contributed to the increased rejection in young patients, but we cannot discern this from the data.

Another difference between these two groups, which could also be related to acute rejection, was a greater proportion of young patients experiencing graft failure due to chronic rejection. It is important to note though that distinguishing chronic rejection from PSC recurrence is difficult, and, therefore, it is probably more appropriate to consider these processes together. The combined graft loss due to chronic rejection/recurrence was similarly greatest in the young group. If this reflects an overall increased prevalence of chronic rejection/recurrence among young recipients, rather than only among those who experienced graft failure, then it may have also contributed to the increased graft loss compared to middle-aged patients.

Previous evidence for a relationship between PSC recurrence and age has been conflicting, with some observing younger age to be a risk factor and others finding no age association [23–26]. Our analysis is somewhat different from these in that we could only assess cases of recurrence that led to graft failure, as opposed to all instances of recurrent disease. There is also the above-mentioned limitation of distinguishing recurrence from chronic rejection. Our results though suggest either increased recurrence/chronic rejection in younger transplant recipients, or, alternatively, a more aggressive disease course in these patients that more often results in graft failure. This may also reflect a more progressive disease process pre-transplant. We cannot rule out, however, that the apparent decreased recurrence in older patients is simply because they more often die before they can develop graft failure due to recurrent disease. Further research is needed to better elucidate these age-related differences in recurrence and chronic rejection in patients with PSC.

Taken together, the increased prevalence of IBD, overlap of AIH, acute rejection, and chronic rejection and recurrence as causes of graft failure suggest a more robust immune-associated phenotype in younger PSC patients. The pathophysiology of PSC remains poorly understood and is likely multifactorial, involving host genetics, immune system, gut microbiota, and environmental factors. Differences in disease phenotype may reflect differential contributions of these factors, and perhaps the immune-related component is more substantial in younger individuals. The results of our analysis remained similar after exclusion of the patients with overlap of AIH, so this apparent stronger immune-associated phenotype extends beyond a reported concomitant diagnosis of AIH. Age-related changes are known to occur in the immune system, and decreased rejection in older individuals has also been reported for transplant recipients of other solid organs and has been attributed to immunosenescence, involving alterations in the immune cell populations with age [27, 28]. In addition to affecting rates of rejection, maybe age-related changes in the immune system similarly affect the pathophysiology of PSC, resulting in a more aggressive immune-mediated disease in younger patients that is also associated with disease recurrence post-transplant. This is likely an oversimplification of a complex process, but future research to further explore these age-related differences in patients with PSC and their relationship with disease pathophysiology is warranted.

Several limitations of this study should be noted. First, this population includes only individuals listed for transplantation. Though many patients with PSC ultimately require a liver transplant, some do not, and this analysis would not be representative of those individuals, who may have their own distinct phenotypic features. Also, the age groups represent the age at listing rather than the age at diagnosis. We do not have data on these patients prior to listing and cannot know, for example, whether patients in the older age group represent predominantly a disease phenotype with later onset or one that is more slowly progressive. Similarly, the young group likely contains some individuals with pediatric- or adolescent-onset PSC.

In addition, there are inherent limitations associated with the retrospective review of administrative databases, including missing, incomplete, or potentially inaccurate data. We were particularly interested in evaluating differences in acute rejection and etiologies of graft failure, but we cannot know definitively that these were always reported or diagnosed accurately. Also, though it is difficult to compare the overall prevalence of PSC/AIH in this group to other studies due to evolving diagnostic criteria over the study period, it is lower than the typically reported 5–10% [1, 29, 30]. Therefore, a secondary diagnosis of AIH at listing may not have captured all individuals with overlap of AIH. Our results did not change with exclusion of the patients who did have reported AIH, but it is possible that increased unreported AIH in younger patients contributed to some of our findings. Despite these limitations, however, the UNOS database allowed for the analysis of pre- and post-transplant characteristics and outcomes in one of the largest cohorts of PSC patients to date. It also permitted the study of a more diverse population than many previous studies, which have largely been limited to Northern Europe.

In summary, this study adds to the literature on phenotypic variation among patients with PSC and suggests areas that warrant further investigation. We used a large dataset of a

diverse patient population and demonstrated that age-related differences exist among patients with PSC and are associated with outcomes pre- and post-transplant. We were able to corroborate some findings in studies of smaller cohorts or other populations, as well as report some potentially novel phenotypic variations and differences in outcomes by age group. Younger patients were more likely to be male, black, have concomitant IBD, have overlap of AIH, experience acute rejection, and have chronic rejection or PSC recurrence as an etiology of graft failure. Our findings suggest that young age may be associated with a subtype with more robust immune-related disease behavior, perhaps with more biliary involvement, and with poorer graft survival, while older age is associated more commonly with portal hypertension and increased waitlist and post-transplant mortality. Characterization of PSC phenotypes is important for numerous reasons, including risk stratification and the development of new therapies. In addition, as we have demonstrated, the underlying PSC phenotype may affect outcomes after liver transplantation. Future studies are needed to further characterize and understand the phenotypic variations among patients with PSC and their underlying differences in pathophysiology, and our results suggest that differences across the age spectrum deserve particular focus.

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Abbreviations

AIH	Autoimmune hepatitis
CI	Confidence interval
DCD	Donation after cardiac death
HCC	Hepatocellular carcinoma
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICU	Intensive care unit
INR	International normalized ratio
IQR	Interquartile range
MELD	Model for End-Stage Liver Disease
OPTN	Organ Procurement and Transplantation Network
PSC	Primary sclerosing cholangitis
SHR	Subhazard ratio

UNOS United Network for Organ Sharing

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Fig. 1. Kaplan–Meier curves for graft (a) and patient (b) survival of liver transplant recipients with PSC by age group. *PSC* primary sclerosing cholangitis

Table 1

Demographics and clinical characteristics by age group in patients with PSC listed for liver transplantation

	Young <i>n</i> = 2392, <i>n</i> (%)	Middle-aged <i>n</i> = 4299, <i>n</i> (%)	Older <i>n</i> = 1581, <i>n</i> (%)	<i>p</i> value
Male sex	1674 (70.0)	2847 (66.2)	1029 (65.1)	0.001
Race/ethnicity				<0.001
White	1740 (72.7)	3602 (83.8)	1408 (89.1)	
Black	478 (20.0)	473 (11.0)	87 (5.5)	
Hispanic	117 (4.9)	150 (3.5)	57 (3.6)	
Other	57 (2.4)	74 (1.7)	29 (1.8)	
Insurance				<0.001
Private	1831 (76.6)	3636 (84.6)	915 (57.9)	
Public	493 (20.6)	569 (13.2)	640 (40.5)	
Other	68 (2.8)	94 (2.2)	26 (1.6)	
Blood type				<0.001
A	866 (36.2)	1743 (40.5)	622 (39.3)	
B	323 (13.5)	516 (12.0)	162 (10.2)	
AB	97 (4.1)	121 (2.8)	63 (4.0)	
O	1106 (46.2)	1919 (44.6)	734 (46.4)	
Diabetes	104 (4.4)	395 (9.3)	249 (16.0)	<0.001
IBD	1710 (71.5)	3044 (70.8)	1024 (64.8)	<0.001
Ulcerative colitis	1144 (47.8)	2068 (48.1)	672 (42.5)	<0.001
Crohn's disease	405 (16.9)	674 (15.7)	240 (15.2)	0.26
Other	161 (6.7)	302 (7.0)	112 (7.1)	0.88
Secondary diagnosis of AIH	53 (2.2)	45 (1.0)	12 (0.8)	<0.001
Complications of portal hypertension ^a	951 (45.8)	1985 (55.2)	922 (67.6)	<0.001
Laboratory values and scores at listing ^b				
MELD score	15 (11–20)	14 (10–19)	15 (12–20)	<0.001
Bilirubin (mg/dL)	4.7 (2.0–11.0)	3.7 (1.8–8.4)	3.7 (1.7–8.6)	<0.001
Creatinine (mg/dL)	0.8 (0.6–0.9)	0.8 (0.7–1.0)	0.9 (0.8–1.2)	<0.001
INR	1.2 (1.1–1.5)	1.2 (1.1–1.4)	1.3 (1.1–1.5)	<0.001
Albumin (g/L)	3.3 (2.7–3.7)	3.1 (2.6–3.6)	3.0 (2.5–3.4)	<0.001

AIH autoimmune hepatitis, IBD inflammatory bowel disease, INR international normalized ratio, IQR interquartile range, MELD Model for End-Stage Liver Disease, PSC primary sclerosing cholangitis

^aDefined as ascites or hepatic encephalopathy at listing. Available for 2074/2392 young, 3599/4299 middle-aged, and 1363/1581 older patients

^bData expressed as median (IQR). Available for post-2/27/2002 listings (1466/2392 young, 2389/4299 middle-aged, and 1087/1581 older)

Table 2

Waitlist outcomes by age group in patients with PSC listed for liver transplantation

	Young <i>n</i> = 2392, <i>n</i> (%)	Middle-aged <i>n</i> = 4299, <i>n</i> (%)	Older <i>n</i> = 1581, <i>n</i> (%)	<i>p</i> value
Days on the waitlist ^a	299 (94–855)	299 (92–850)	196 (60–578)	<0.001
Reason for removal				
Transplanted	1607 (67.2)	2734 (63.6)	911 (57.6)	<0.001
Died or too sick	192 (8.0)	712 (16.6)	418 (26.4)	<0.001
Condition improved	81 (3.4)	139 (3.2)	53 (3.4)	0.94
Other	292 (12.2)	418 (9.7)	101 (6.4)	<0.001
Still waiting	220 (9.2)	296 (6.9)	98 (6.2)	<0.001
Causes of death ^b				
Multisystem organ failure	22 (35.5)	70 (40.0)	43 (42.2)	0.70
Infection	21 (33.9)	46 (26.3)	20 (19.6)	0.12
Cardiovascular	5 (8.1)	12 (6.9)	10 (9.8)	0.68
Hemorrhage	5 (8.1)	13 (7.4)	7 (6.9)	0.96
Malignancy	3 (4.8)	7 (4.0)	2 (2.0)	0.56
Renal failure	1 (1.6)	0	0	0.19
Pulmonary	0	5 (2.9)	1 (1.0)	0.33
Other	5 (8.1)	22 (12.6)	18 (17.6)	0.20

Number in this table removed for transplantation varies slightly from number used in post-transplant analyses due to some patients having multiple waitlist registrations. *IQR* interquartile range, *PSC* primary sclerosing cholangitis

^aData expressed as median (IQR)

^bCause of death was reported for 339/888 waitlist mortalities and was not reported for patients too sick for transplantation. Percentages are expressed as proportion of those with a reported cause of death

Table 3

Risk of waitlist mortality, graft failure, and 5-year post-transplant mortality by age group in patients with PSC

	Univariate HR (95% CI)	<i>p</i> value	Multivariate HR (95% CI)	<i>p</i> value
Waitlist mortality ^a		<0.001		<0.001
Middle-aged versus young	2.13 (1.81–2.49)		2.30 (1.84–2.87)	
Older versus middle-aged	1.75 (1.55–1.97)		1.78 (1.51–2.10)	
Older versus young	3.70 (3.12–4.41)		4.10 (3.23–5.18)	
Graft failure ^b		<0.001		0.005
Middle-aged versus young	0.87 (0.78–0.98)		0.86 (0.76–0.97)	
Older versus middle-aged	1.40 (1.23–1.60)		1.22 (1.06–1.41)	
Older versus young	1.23 (1.06–1.41)		1.05 (0.90–1.23)	
Five-year mortality ^c		<0.001		<0.001
Middle-aged versus young	1.33 (1.08–1.64)		1.28 (1.02–1.60)	
Older versus middle-aged	1.86 (1.53–2.25)		1.67 (1.36–2.07)	
Older versus young	2.47 (1.96–3.12)		2.14 (1.66–2.76)	

CI confidence interval, *DCD* donation after cardiac death, *HR* hazard ratio, *PSC* primary sclerosing cholangitis, *UNOS* United Network for Organ Sharing

^aData represent the subhazard ratio for age group in a competing risk analysis of waitlist mortality with transplantation as a competing outcome. The multivariate model was adjusted for insurance, complications of portal hypertension at listing, UNOS region, and blood type

^bFinal model also included insurance, UNOS region, diabetes, location at transplant, previous abdominal surgery, DCD donor, and donor age

^cFinal model also included insurance, UNOS region, diabetes, location at transplant, previous abdominal surgery, and albumin at transplant

Table 4

Recipient and donor characteristics at transplant by age group in patients with PSC

	Young <i>n</i> = 1451, <i>n</i> (%)	Middle-aged <i>n</i> = 2478, <i>n</i> (%)	Older <i>n</i> = 817, <i>n</i> (%)	<i>p</i> value
<i>Recipient</i>				
Male sex	1021 (70.4)	1666 (67.2)	549 (67.2)	0.10
Race/ethnicity				<0.001
White	1058 (72.9)	2103 (84.9)	730 (89.4)	
Black	290 (20.0)	261 (10.5)	41 (5.0)	
Hispanic	69 (4.8)	76 (3.1)	31 (3.8)	
Other	34 (2.3)	38 (1.5)	15 (1.8)	
Insurance				<0.001
Private	1115 (76.8)	2100 (84.8)	467 (57.2)	
Public	316 (21.8)	365 (14.7)	346 (42.4)	
Other	20 (1.4)	13 (0.5)	4 (0.5)	
Blood type				0.001
A	523 (36.0)	1046 (42.2)	320 (39.2)	
B	206 (14.2)	304 (12.3)	91 (11.1)	
AB	70 (4.8)	88 (3.6)	45 (5.5)	
O	652 (44.9)	1040 (42.0)	361 (44.2)	
Diabetes	63 (4.4)	239 (9.8)	126 (15.7)	<0.001
IBD	1024 (70.6)	1768 (71.4)	532 (65.1)	0.003
Ulcerative colitis	691 (47.6)	1203 (48.6)	362 (44.3)	0.11
Crohn's disease	245 (16.9)	407 (16.4)	109 (13.3)	0.07
Other	88 (6.1)	158 (6.4)	61 (7.5)	0.41
Secondary diagnosis of AIH	31 (2.1)	25 (1.0)	4 (0.5)	0.001
Complications of portal hypertension ^a	762 (53.0)	1493 (61.4)	627 (77.8)	<0.001
Location at transplant				0.002
Ambulatory	1140 (78.6)	1929 (77.9)	598 (73.2)	
Hospitalized	226 (15.6)	373 (15.1)	136 (16.6)	
ICU	84 (5.8)	175 (7.1)	83 (10.2)	
On mechanical ventilation	24 (1.6)	45 (1.8)	23 (2.8)	0.13
On dialysis	40 (2.8)	91 (3.7)	36 (4.5)	0.10
Previous abdominal surgery	538 (38.2)	1265 (53.2)	441 (55.8)	<0.001
Laboratory values and scores at transplant ^b				
MELD score ^c	19 (15–25)	20 (14–26)	20 (14–26)	0.42
Bilirubin (mg/dL)	7.7 (3.0–16.4)	6.0 (2.6–14.5)	6.2 (2.6–13.9)	<0.001
Creatinine (mg/dL)	0.8 (0.6–1.0)	0.9 (0.7–1.2)	1.0 (0.8–1.5)	<0.001
INR ^d	1.4 (1.2–1.8)	1.4 (1.2–1.8)	1.4 (1.2–1.8)	0.46
Albumin (g/L)	3.0 (2.5–3.5)	3.0 (2.5–3.4)	2.9 (2.5–3.3)	0.003
<i>Donor</i>				
Living donor	209 (14.4)	241 (9.7)	75 (9.2)	<0.001

	Young <i>n</i> = 1451, <i>n</i> (%)	Middle-aged <i>n</i> = 2478, <i>n</i> (%)	Older <i>n</i> = 817, <i>n</i> (%)	<i>p</i> value
DCD donor	39 (2.7)	54 (2.2)	24 (2.9)	0.39
Donor 60	110 (7.6)	302 (12.2)	168 (20.6)	<0.001
Split graft	232 (16.0)	277 (11.2)	83 (10.2)	<0.001

Number transplanted in this table varies slightly from Table 2 due to some patients having multiple waitlist registrations. *AIH* autoimmune hepatitis, *DCD* donation after cardiac death, *IBD* inflammatory bowel disease, *ICU* intensive care unit, *INR* international normalized ratio, *IQR* interquartile range, *MELD* Model for End-stage Liver Disease, *PSC* primary sclerosing cholangitis

^aDefined as ascites or hepatic encephalopathy at transplant. Available for 1438/1451 young, 2433/2478 middle-aged, and 806/817 older patients

^bData expressed as median (IQR)

^cAvailable for post-2/27/2002 transplants (970/1451 young, 1474/2478 middle-aged, and 586/817 older)

^dAvailable for transplants after 10/25/1999 (1048/1451 young, 1656/2478 middle-aged, and 632/817 older)

Table 5

Post-transplant outcomes by age group in patients with PSC

	Young, <i>n</i> (%)	Middle-aged, <i>n</i> (%)	Older, <i>n</i> (%)	<i>p</i> value
Acute rejection ^a	327 (31.2)	406 (22.8)	119 (18.0)	<0.001
Causes of graft failure ^b				
Disease recurrence	116 (34.8)	132 (34.0)	10 (11.9)	<0.001
Chronic rejection	60 (18.0)	47 (12.1)	5 (6.0)	0.006
Biliary complications	55 (16.5)	75 (19.3)	22 (26.2)	0.12
Infection	38 (11.4)	53 (13.7)	18 (21.4)	0.06
Vascular thrombosis	79 (23.7)	112 (28.9)	14 (16.7)	0.04
Primary nonfunction	61 (18.3)	84 (21.6)	27 (32.1)	0.02
Other	51 (15.3)	51 (13.1)	21 (17.1)	0.02
Retransplantation after graft failure	279 (55.7)	276 (34.2)	34 (10.9)	<0.001
Causes of death ^c				
Graft failure	36 (16.4)	54 (10.2)	16 (5.8)	<0.001
Malignancy	36 (16.4)	110 (20.9)	51 (18.6)	0.34
Cholangiocarcinoma	9 (25.0%)	25 (22.7%)	2 (3.9%)	0.008
HCC or other primary liver malignancy	0	7 (6.4%)	4 (7.8%)	0.23
Colorectal cancer	3 (8.3)	20 (18.2)	8 (15.7)	0.37
Other	18 (50.0)	40 (36.4)	27 (52.9)	0.09
Unspecified	6 (16.7)	18 (16.4)	10 (19.6)	0.87
Infection	36 (16.4)	101 (19.2)	55 (20.0)	0.56
Multisystem organ failure	32 (14.6)	69 (13.1)	25 (9.1)	0.14
Cardiovascular	19 (8.6)	57 (10.8)	32 (11.6)	0.54
Renal failure	7 (3.2)	19 (3.6)	18 (6.6)	0.10
Pulmonary	8 (3.6)	14 (2.7)	15 (5.4)	0.13
Hemorrhage	8 (3.6)	27 (5.1)	12 (4.4)	0.66

HCC hepatocellular carcinoma, *PSC* primary sclerosing cholangitis

^aDefined as treatment for rejection within one year or graft failure due to acute rejection. Data available for 1048/1451 young, 1785/2478 middle-aged, and 662/817 older patients

^bCauses of graft failure expressed as percent of those with a reported etiology (333/501 young, 388/806 middle-aged, and 84/311 older). Multiple could be reported

^cCauses of death also expressed as percent of those with a reported cause (220/238 young, 527/568 middle-aged, and 275/294 older). Up to three could be reported