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## ORIGINAL ARTICLE

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# Liver disease and transplantation in telomere biology disorders: An international multicenter cohort

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#### Abstract

**Background:** Patients with telomere biology disorders (TBD) develop hepatic disease, including hepatitis, cirrhosis, and hepatopulmonary syndrome. No specific treatment exists for TBD-related liver disease, and the role of liver transplantation (LT) remains controversial. Our study objectives were to describe the clinical characteristics, management, and outcomes in patients with TBD-related liver disease, and their LT outcomes.

**Methods:** Data from 83 patients with TBD-associated liver disease were obtained from 17 participating centers in the Clinical Care Consortium of Telomere-Associated Ailments and by self-report for our retrospective, multicenter, international cohort study.

**Results:** Group A ("Advanced") included 40 patients with advanced liver disease. Of these, 20 underwent LT (Group A<sub>T</sub>). Group M ("Mild") included 43 patients not warranting LT evaluation, none of whom were felt to be medically unfit for liver transplantation. Supplemental oxygen requirement, pulmonary arteriovenous malformation, hepatopulmonary syndrome, and higher bilirubin and international normalized ratio values were associated with Group A. Other demographics, clinical manifestations, and laboratory findings were similar between groups. Six group A patients were declined for LT; 3 died on the waitlist. Median follow-up post-LT was 2.9 years (range 0.6–13.2 y). One-year survival post-LT was 73%. Median survival post-LT has not been reached. Group A<sub>T</sub> patients had improved survival by age compared to all nontransplant patients (log-rank test  $p = 0.02$ ). Of 14 patients with pretransplant hypoxemia, 8 (57%) had improved oxygenation after transplant.

**Conclusions:** LT recipients with TBD do not exhibit excessive posttransplant mortality, and LT improved respiratory status in 57%. A TBD diagnosis should not exclude LT consideration.

## INTRODUCTION

Telomeres are repetitive sequences of DNA present on the ends of chromosomes that prevent chromosomal

degradation during the process of cell replication. Their shortening over time is key in the aging process. Telomere biology disorders (TBD) are characterized by critically short telomeres resulting from heterogenous gene mutations of

**Abbreviations:** AVM, arteriovenous malformations; HPS, hepatopulmonary syndrome; HSCT, hematopoietic stem cell transplant; LT, liver transplant; TBD, telomere biology disorder.

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telomerase or telomere maintenance proteins. TBDs have been increasingly recognized as multisystem diseases of premature aging,<sup>[1]</sup> with manifestations ranging from the prototypical dyskeratosis congenita to varying mucocutaneous, pulmonary, and hepatic involvements.<sup>[2–6]</sup>

The exact prevalence and incidence of TBD remains unclear, and long-term data is lacking. This is likely in part due to under-diagnosis, given variable and often nonspecific clinical presentation. Several genetic variants affecting the telomere complex have been identified, including, most commonly, mutations in *TERT*, *TERC*, *TINF2*, and *DKC1*.<sup>[7–9]</sup> Common clinical manifestations include the mucocutaneous triad of oral leukoplakia, reticular rash, and nail dystrophy, as well as bone marrow failure, retinopathy, and pulmonary fibrosis.<sup>[9–16]</sup>

Liver disease in telomere biology disorders is common but poorly characterized.<sup>[5,6,17]</sup> A National Institutes of Health study found hepatic involvement in 40% of adult patients with TBD.<sup>[18]</sup> In the study, which included adults aged 29–50 years, the most common laboratory findings were liver enzyme elevations and cholestasis, and the most common imaging findings were increased hepatic echogenicity and hepatomegaly. In advanced stages of liver disease, patients may develop hepatopulmonary syndrome (HPS). In 1 registry study of patients with TBDs, 42 of 150 (28%) presented only with dyspnea, and 9 were found to already have HPS at the time of TBD disease diagnosis.<sup>[19]</sup> Children with TBDs as young as 5 years of age have been reported to develop HPS.<sup>[2]</sup>

Proposed mechanisms for liver disease development include impaired regenerative ability of the liver in the setting of shortened telomeres in response to aging and/or chronic inflammatory processes. Cirrhosis in the setting of TBD is reported in at least 6% of patients with dyskeratosis congenita,<sup>[20]</sup> and patients are at risk of portal hypertensive complications. Noncirrhotic portal hypertension is also well described.<sup>[21,22]</sup>

No specific treatment exists for TBD-related liver disease, and the utility of liver transplant (LT) remains unclear. Current literature regarding the role of LT in TBDs is limited to case reports. While historically there has been a reluctance to offer LT to patients with TBDs due to uncertain prognosis and unclear risk of disease progression, reported outcomes have been largely favorable.<sup>[19,23–28]</sup>

Our objectives were to describe the clinical characteristics, management, and outcomes in a retrospective cohort of patients with TBD-related liver disease. We also sought to identify clinical or laboratory features predictive of the need for LT and specifically describe the outcomes of patients with TBD who underwent LT.

## METHODS

We performed a retrospective, multicenter cohort study in line with the strengthening the reporting of observational studies in epidemiology criteria.<sup>[29]</sup> Data were obtained from

August 2020 until December 2021 from participating centers in the Clinical Care Consortium of Telomere-Associated Ailments<sup>[30]</sup> who responded to a groupwide email soliciting interest and participation or individual patients who responded to an advertisement in a family support group (Team Telomere) for those with TBDs. Independent institutional review board approval was obtained by all centers, and all research was conducted in accordance with both the Declarations of Helsinki and Istanbul. Waivers of informed consent were obtained, and de-identified patient data were entered by each participating center into a Health Insurance Portability and Accountability Act-compliant REDCap (Research Electronic Data Capture) database hosted by the University of Cincinnati/Cincinnati Children's Hospital Center for Clinical and Translational Science and Training.<sup>[31,32]</sup> A neutral third-party Honest Broker, who was not a part of the research teams at any of the participating centers, was independently provided with 3 identifiers from each site to cross-reference and ensure that no patient was entered into the database more than once. Data were collected on 2 groups of patients: Group A ("Advanced") included patients whose liver disease severity was significant enough for their health care team to consider liver transplantation. The level of severity was determined by contributing centers at the time of data entry, for example, if the patient was considered to have decompensated cirrhosis, end-stage liver disease, or significant HPS, the team entered their data into Group A. Group M ("Mild") included patients whose liver disease was mild and was determined not to warrant liver transplantation. Our definition of liver disease was intentionally broad for the purposes of including a wide range of patients with any liver involvement, requiring, at minimum, abnormalities in liver function laboratory testing. For analysis, a subgroup of Group A was identified as A<sub>T</sub> ("Advanced with Transplant"), comprised of patients with severe liver disease who underwent liver transplantation. Our cohort included a total of 83 subjects with data entered from 17 centers, which is the largest known cohort of patients with TBD and liver involvement.

Categorical variables were analyzed using Fisher exact tests. Continuous variables across groups were compared using Wilcoxon rank sum tests. Patients with missing data were excluded from each analysis. Survival end points were analyzed using Cox proportional hazards regression. Two patients lost to follow-up were not included in survival analyses. Post hoc analyses were also conducted to determine risk factors for transplant and survival.

## RESULTS

### Demographics and clinical features

Group A was composed of 40 patients referred for LT evaluation, of whom 20 underwent LT (Group A<sub>T</sub>). Five

**TABLE 1** Demographic information and clinical features of telomere biology disorders (TBD)

	Entire cohort (n = 83)	Group A (n = 40), n (%)	Group M (n = 43), n (%)	p-value
Gender				
Female	25	12 (30.0)	13 (30.2)	1.00
Male	58	28 (70.0)	30 (69.8)	
Age at TBD diagnosis	16 y (1–71)	21.5 y (1–71)	13.0 y (1–57)	0.09
Age at liver disease diagnosis	17.9 y (1–60)	21.9 y (5–59)	17.7 y (1–60)	0.22
Age at liver transplant		29.0 y (8–66)	N/A	—
Ethnicity				
Non-Hispanic	64	34 (85.0)	30 (69.8)	0.12
Hispanic	19	6 (15.0)	13 (30.2)	—
Genes	—	—	—	0.0087
<i>ACD</i>	1	0	1 (2.3)	—
<i>CTC1</i>	2	1 (2.5)	1 (2.3)	—
<i>DKC1</i>	11	3 (7.5)	8 (18.6)	—
<i>PARN</i>	5	2 (5.0)	3 (7.0)	—
<i>RTEL1</i>	8	2 (5.0)	6 (14.0)	—
<i>TERC/hTR</i>	7	1 (2.5)	6 (14.0)	—
<i>TERT</i>	22	12 (30.0)	10 (23.3)	—
<i>TINF2</i>	14	9 (22.5)	5 (11.6)	—
<i>WRAP53</i>	2	0	2 (4.7)	—
Unknown	11	10 (25.0)	1 (2.3)	—
Telomere Length	—	—	—	0.70
Low	11	6 (15)	5 (11.6)	—
Very low	53	27 (67.5)	26 (53.7)	—
Normal	1	0	1 (2.3%) <sup>a</sup>	—
Unknown	18	7 (17.5)	11 (25.6)	—
Suspected FHx of TBD	—	—	—	0.82
Yes	34	15 (37.5)	19 (44.2)	—
No	47	24 (60)	23 (51.2)	—
Unknown	2	1 (2.5)	1 (2.3)	—

Note: Group A—advanced liver disease, evaluated for liver transplantation; Group M—mild liver disease, not evaluated for liver transplantation.

Telomere length (measured in lymphocytes) defined as low (< 10%ile), very low (< 1%ile), normal (> 10%ile).

<sup>a</sup>patient with known *TERT* mutation. Telomere biology disorder (TBD), Family History (FHx).

LT recipients included in this analysis have been previously reported in the literature.<sup>[26,33]</sup> Group M included 43 patients with mild liver disease. At the time of liver disease diagnosis, there were no significant differences between Groups A and M in age, gender, ethnicity, race, or genetic variant. The median age at diagnosis of TBD in Group A was 21.5 years (range 1–71), compared to 13 in Group M (range 1–57) ( $p = 0.093$ ). The most common gene variants overall were *TERT*, *TINF2*, and *DKC1*. Patients with *DKC1* and *RTEL1* gene variants were younger at diagnosis compared to those with variants in *TERT*. Most patients in both groups (60% in Group A and 53.5% in Group M) did not have a known or suspected family history of TBD. Several terms were used to describe patients' disease, including dyskeratosis congenita, telomeropathy, short telomere syndrome, Hoyeraal-Hreidarsson syndrome, Revesz syndrome, Coats Plus, and telomere

biology disorder.<sup>[34]</sup> Over half of the participants were diagnosed with a TBD based on telomere length (66.3%), clinical presentation (66.3%), or genetic mutation (51.8%).

Approximately 60% of patients in both groups had lymphocyte telomere lengths classified as very low for their age (< 1%ile, Table 1). There were no significant differences in telomere length, mucocutaneous triad manifestations, incidence of bone marrow failure, prior androgen use, or HSCT, between patients in Groups A and B at the time of liver disease diagnosis. Only 17 subjects (20.5%), 10 in Group A (25%) and 7 in Group M (16.3%), manifested with all 3 characteristics of the mucocutaneous triad. Nearly 70% of subjects overall experienced cytopenia of 2 cell lines or more, or hypocellular marrow. While 15 (37.5%) in Group A and 11 (26%) subjects in Group M underwent HSCT, only 1 in Group A (2.5%) and 3 in Group M had

**TABLE 2** Liver disease manifestations at time of liver disease diagnosis

	Entire Cohort (n = 83), (%)	Group A (n = 40), (%)	Group M (n = 43), (%)
Elevated liver enzymes	60 (72.3)	28 (70.0)	32 (74.4)
Abnormal imaging			
Coarse/cirrhotic liver	22 (of 65, 33.8 <sup>a</sup> )	12 (of 27, 44.4 <sup>a</sup> )	10 (of 38, 26.3 <sup>a</sup> )
Steatosis	10 (15.4)	2 (7.4)	8 (21.1)
Hepatomegaly	9 (13.8)	2 (7.4)	7 (18.4)
Splenomegaly	34 (52.3)	17 (63.0)	17 (44.7)
Nodules/discrete Lesions	7 (10.7)	5 (18.5)	2 (5.3)
Increased stiffness	6 (9.2)	3 (11.1)	3 (7.9)
HPS	33 (39.8)	31 (77.5)	2 (4.7)
Evidence of portal hypertension			
Ascites	14 (16.8)	7 (17.5)	7 (16.3)
Splenomegaly	44 (53.0)	19 (47.5)	25 (58.1)
Thrombocytopenia	52 (of 61, 85.2 <sup>a</sup> )	25 (of 27, 92.6 <sup>a</sup> )	27 (of 34, 79.4 <sup>a</sup> )
Varices	6 (7.2)	3 (7.5)	3 (7.0)
History of GI bleeds	16 (19.3)	10 (25.0)	6 (14.0)
Pruritus	1 (1.2)	1 (2.5)	0
Jaundice	6 (7.2)	3 (7.5)	3 (7.0)
Encephalopathy	3 (3.6)	3 (7.5)	0

<sup>a</sup>number of patients who underwent listed test.

Abbreviations: HPS, hepatopulmonary syndrome; GI, gastrointestinal.

undergone HSCT before the time of liver disease diagnosis. Only 1 patient in the entire cohort, in Group A, developed veno-occlusive disease/sinusoidal obstruction syndrome post HSCT. Retinopathy was diagnosed in 11% of the cohort, with 6 in Group A (15%) and 4 in Group M (9.8%). Pulmonary findings were also common in Group A: 39% in Group A had pulmonary fibrosis, compared to 19.5% in Group M ( $p = 0.088$ ), and 36.5% had been diagnosed with pulmonary arteriovenous malformations (AVMs), compared to 4.9% in Group M ( $p = 0.0007$ ). Pulmonary AVM diagnoses were entered at the discretion of participating centers. These were primarily reported to have been diagnosed with CT. One patient reportedly had AVMs diagnosed with angiography and bronchoscopy. Forty-three percent of patients in group A had supplemental oxygen requirement at the time of liver transplant evaluation. There was a high prevalence of HPS in Group A patients, discussed further below.

## Liver disease manifestations

Liver disease manifestations in our cohort are shown in Table 2. The majority of subjects (59%) were evaluated for other etiologies of liver disease, including viral hepatitis (assessed in 78% of subjects), alpha-1 anti-trypsin deficiency (63%), NAFLD (51%), autoimmune hepatitis (12%), or Wilsons disease (26%). Supplemental oxygen requirement, concern for pulmonary arteriovenous malformation or HPS, higher bilirubin, gamma-glutamyltransfe-

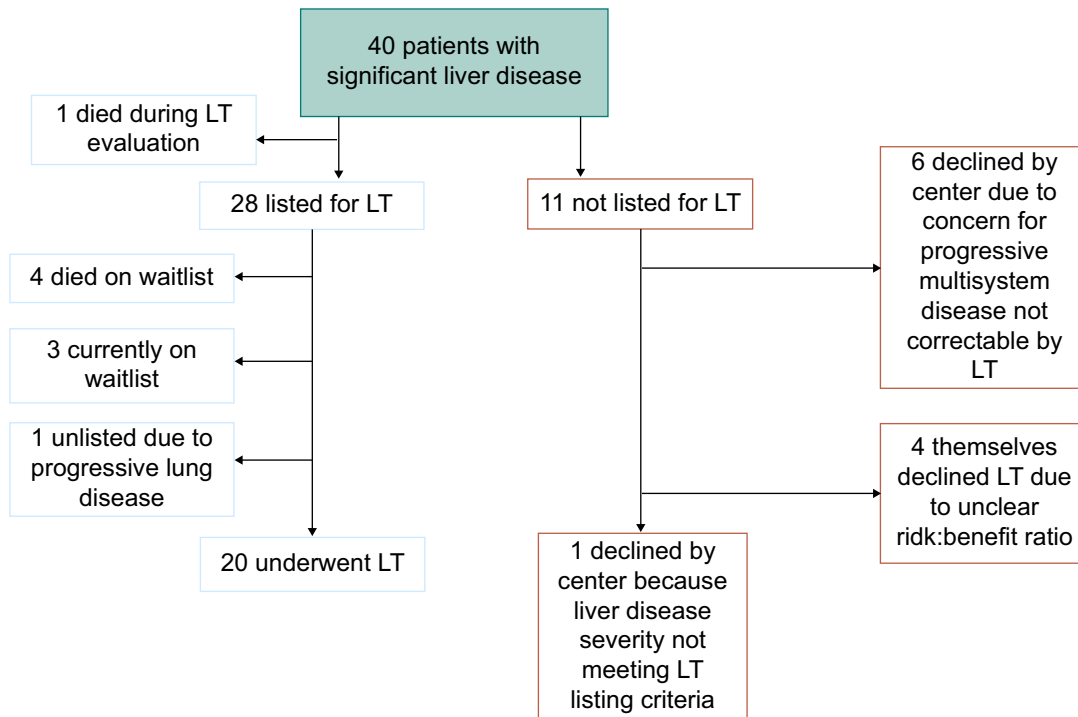
rase, and international normalized ratio were associated with being a “transplant candidate” in Group A. There were no differences in serum aminotransferase values, hematologic parameters, or ultrasound findings between groups. The most utilized imaging modality for liver assessment was ultrasound, but CT and MRI were also used by many centers. The most common imaging findings were cirrhosis or coarse echotexture and hepatosplenomegaly. Other findings included the presence of discrete nodules, varices, and steatosis.

Of the 40 patients in group A, 77.5% had features of HPS, either based on clinical signs/symptoms (platypnea, orthodeoxia, clubbing, cyanosis), imaging findings (positive bubble echocardiogram) or both, compared to 4% in group M (OR 63.6,  $p < 0.0001$ ).

## Liver transplantation

Group A patients were declined for LT by centers due to concerns for progressive multisystem disease uncorrected by LT ( $n = 6$ ), and liver disease severity not meeting LT listing criteria ( $n = 1$ , Figure 1). Four patients themselves declined liver transplant due to unclear risk-benefit ratio. Four patients died on the waitlist, and as of data collection, 3 remain on the LT waitlist. The median age of the Group A patients who declined for LT was 31.5 (range, 9–65), whereas the median age of those who themselves declined LT was 15.5 (range 15–61). Patients are increasingly being considered for a liver transplant more recently: of the





**FIGURE 1** Group A clinical course and outcomes. Abbreviation: LT, liver transplant.

43 documented discussions of LT, 30 took place from 2015 to 2020.

Listing for LT was associated with a supplemental oxygen requirement, pulmonary arteriovenous malformations, and HPS at the time of liver disease diagnosis or with higher total and direct bilirubin at the time of liver disease diagnosis ( $p < 0.001$ ).

Group A<sub>T</sub> receiving LT tended to be older than those not transplanted in Group A, with a median age of 26.5 (vs. 17,  $p = 0.29$ ) at diagnosis of a TBD, 25.2 (vs. 17.1,  $p = 0.48$ ) at liver disease diagnosis, and 26 (vs 15.5,  $p = 0.54$ ) at liver transplant discussion. There were more patients not transplanted in Group A with a *TINF2* variant (35.0% vs. 10.0%,  $p = 0.127$ ) and a history of HSCT (50% vs. 25%,  $p = 0.190$ ) than in Group A<sub>T</sub>.

Twenty patients underwent liver transplantation (Group A<sub>T</sub>, Table 3) at 15 centers. Individuals were evaluated at a median of 1 transplant center (range 1–4). Seven individuals received transplants at outside centers. The median age at transplant was 27 years (range 8–66, Supplemental Table 1, <http://links.lww.com/HCG9/A936>). Indications for liver transplant most commonly included cirrhosis and HPS. The median Model for End-Stage Liver Disease score at transplant was 31 (range 10–40), which did include 11 patients with exception points for HPS. Patients remained on the waitlist for a median of 67 days (range, 6–1470 d) and were admitted to the hospital for a median of 34.5 days (range 7–280). Of 20 LT recipients, 2 also underwent combined lung transplantation. One patient received a

living donor organ from a member of the extended family; the remainder received deceased donor organs. Induction immune suppression most commonly included steroids, basiliximab, and thymoglobulin, whereas post-LT immune suppression included steroids, tacrolimus, and mycophenolate mofetil. The most common complication of LT in these patients was infection (25%), whereas second surgery and hepatic artery thrombosis or PVT each occurred in 2 patients (10%) (Table 4). Two patients developed acute or chronic rejection (5% each).

Eight patients, all listed for HPS, had improved oxygenation after transplant, out of 14 with pretransplant hypoxemia (57%). Hypoxemia resolved completely in 3 patients, and 1 was weaned from continuous to nighttime only oxygen supplementation. The degree of improvement was unknown in the other 5 patients. Posttransplant respiratory status is unknown in the other patients listed for LT due to HPS.

Only 5 of the 20 transplanted patients were reported to have had pretransplant gastrointestinal bleeding, of whom 4 had variceal bleeding. Three of these 4 patients had no further gastrointestinal bleeding episodes after transplant.

Five patients were reported to have had hematological improvements after liver transplant, including the normalization of cell counts, reduced need for transfusions, and, in 1 patient, improved bone marrow cellularity (Figure 2). Importantly, 4 of these 5 patients had evidence of portal hypertension before transplant. Hematological status after transplant is unknown in the other 15 transplanted patients.

**TABLE 3** Liver transplant characteristics

	Median
Liver transplant recipients	20
Age at transplant	27 (range, 8–66)
Indications for transplant	Cirrhosis (9) Hepatopulmonary syndrome (14)
MELD score at transplant	31 (10–40)
Days on waitlist	67 d (6–1470)
Admission length	34.5 d (7–280)
Immune suppression	
Induction (of 15 with data), (%)	Corticosteroids 12 (80) Tacrolimus 10 (67) MMF 5 (33) Basiliximab 3 (20) Cyclosporine 2 (13) OKT3 1 (7)
Maintenance (of 15 with data), (%)	Tacrolimus 13 (87) Corticosteroids 8 (53) MMF 5 (33) Cyclosporine 1 (7)
Graft source, (%)	
Deceased donor	19 (95)
Living donor	1 (5)

Abbreviations: MELD, Model for End-Stage Liver Disease; MMF, mycophenolate mofetil.

Post-LT malignancy (skin cancer recurrence) occurred in 1 patient. No LT recipients have undergone HSCT following LT, although 5 had received HSCT before LT. Median follow-up from LT was 2.4 years (range 0.1–13.2 y). Median survival post-LT has not yet been reached. One subject with improved blood counts developed pulmonary fibrosis, and 1 subject developed severe aplastic anemia following LT.

**TABLE 4** Liver transplant outcomes

	N (%)
Liver transplant recipients	20
Combined liver-lung transplant	2 (10.0)
Adverse events	
Infection	5 (25.0)
Chronic rejection	1 (5.0)
Biliary stricture	1 (5.0)
Second surgery	2 (10.0)
Hepatic artery thrombosis/stenosis	2 (10.0)
Portal vein thrombosis	1 (5.0)
Acute liver graft rejection	1 (5.0)
Death PJP kidney failure intra-op thrombosis sepsis unknown	5 (25.0) <sup>a</sup>

<sup>a</sup>Includes 1 combined recipient.

Abbreviation: PJP, pneumocystis jiroveci pneumonia.

## Overall cohort survival

Five of 20 (25.0%) recipients of LT died from transplant-related complications (Figure 3A). Causes of death included *Pneumocystis jiroveci* pneumonia, intraoperative thrombosis, sepsis, pulmonary hemorrhage, and unknown, all within 1 year of LT. One-year overall survival for LT recipients was 73.0%. Median survival for the recipients of Group A<sub>T</sub> LT has not yet been reached. Fifteen additional nontransplanted Group A individuals (71.4%) have died, including the 4 who died awaiting LT, 4 each with progression of liver disease, lung disease, or both, 1 with renal failure, and 2 with unknown cause of death. Sixteen of 43 Group M subjects (37.2%) died. Causes of death included septic shock, pneumonitis, progression of liver disease (3), lung disease (2), or both (1), hemorrhage, arrhythmia, fungal infection, and heart and kidney failure. In summary, 12 of 31 deaths (38.7%) across both Groups A and M were related to progressive native liver disease, including 6 that occurred at institutions not reporting any liver transplants performed in this cohort.

Patients of Group A<sub>T</sub> had significantly improved survival by age compared to all nontransplant patients (Group M and un-transplanted Group A: median survival in years A<sub>T</sub> not reached, B = 40, un-transplanted A = 33, log-rank test  $p = 0.011$ ). No demographic, clinical, or laboratory characteristics at the time of liver disease diagnosis were prognostic for survival. Survival was not significantly different between patients with or without HPS (Figure 3B); however, patients with HPS who underwent LT had significantly improved survival (Figure 3C).

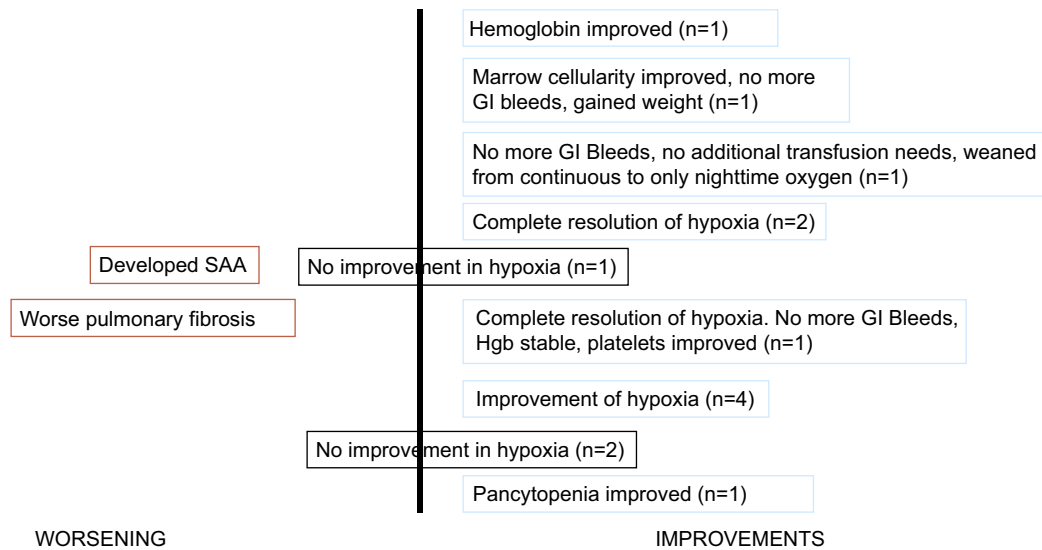
## DISCUSSION

To our knowledge, this is the largest reported cohort of patients with TBD-associated liver disease, with representative data from a multicenter, international collaboration. Our collective experience demonstrates a wide spectrum of liver disease both at diagnosis and through progression. While morbidity and mortality in patients with TBDs are primarily related to bone marrow failure, pulmonary disease, and malignancy, the high liver-related mortality (38.7%) of patients with native liver in both groups reflects the high burden of liver disease and demonstrates that liver disease can be rapidly progressive and life-threatening. HPS is common in patients with TBDs and a significant cause of morbidity and mortality, which can only be alleviated by liver transplantation.<sup>[19]</sup>

Although there are 18 known genes associated with TBDs,<sup>[9,34,35]</sup> 11 of 84 (13.1%) in this cohort remain genetically uncharacterized, and another 11 individuals had not undergone telomere length testing. Whether this is due to the limited availability of telomere length testing,



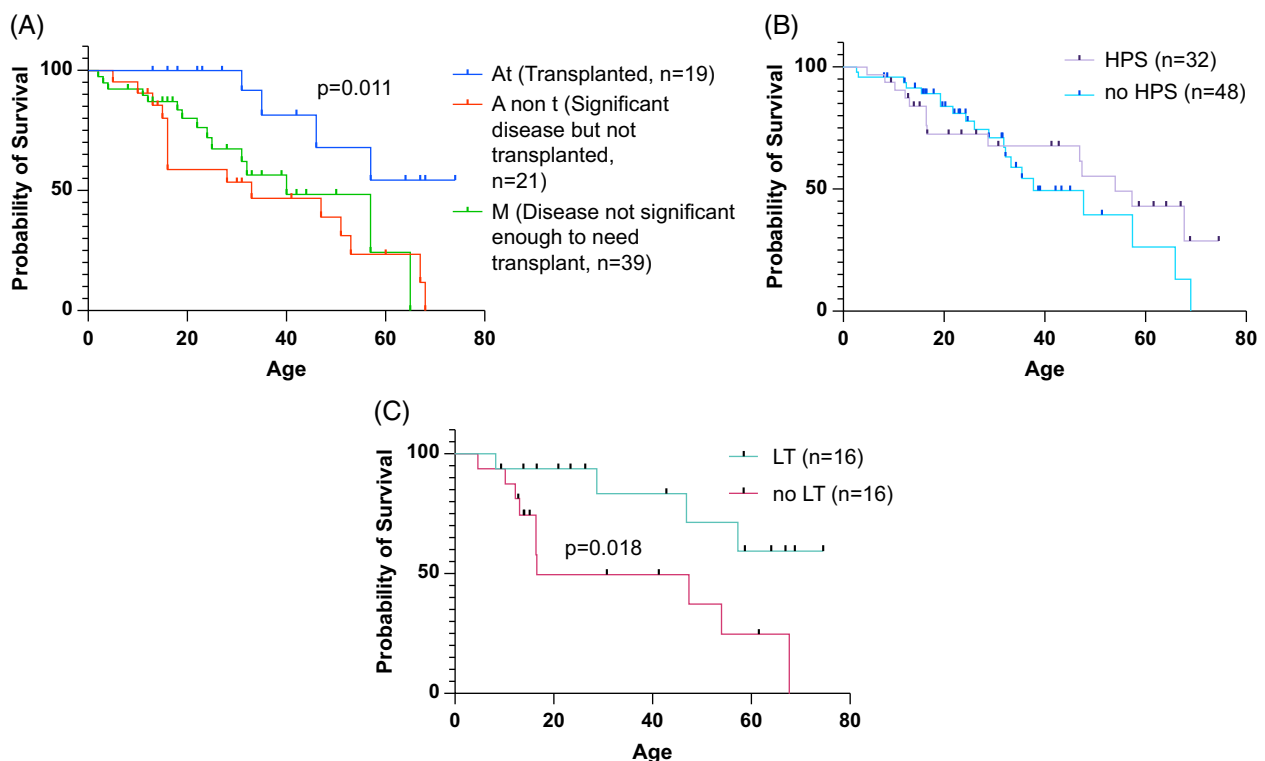
## Changes after Liver Transplant (n=14)



**FIGURE 2** Post-liver transplantation clinical course of 14 liver transplant recipients. Positive (blue boxes) and negative (red boxes) changes post-liver transplantation in individual patients. Each row represents 1 patient unless otherwise indicated by  $n = 2$  (2 patients) or  $n = 4$  (4 patients). Abbreviations: GI, Gastrointestinal; hgb, hemoglobin; SAA, severe aplastic anemia.

positive genetic testing, and resulting provider indifference, or the prohibitive cost of testing is unclear, although telomere length testing has been demonstrated to impact clinical decisions in many cases.<sup>[36]</sup> There remains no clinicopathological test; thus, the burden of including

TBDs in the differential diagnosis of liver disease in patients of any age falls largely on gastroenterology and hepatology specialists. This is made more difficult in the absence of clinical findings of TBD or family history,<sup>[37]</sup> and indeed, the rarity of this condition likely leads to



**FIGURE 3** Kaplan-Meier survival curve by (A) group assignment in entire cohort, (B) HPS status in entire cohort, and (C) LT status in cohort with HPS. Abbreviations: HPS, hepatopulmonary syndrome; LT, liver transplant.

under-diagnosis by subspecialists. Based on the high prevalence of pulmonary AVMs in patients with TBD, which is higher than in any other chronic liver disease, we recommend testing for TBD in patients with idiopathic chronic liver disease or cryptogenic cirrhosis and HPS.

The mechanisms leading to liver disease and dysfunction in patients with TBDs are not well characterized. The hepatocytes of *Tert* deficient mice fail to engage in the citric acid cycle in response to high-fat diet challenge, leading to cellular injury and steatosis.<sup>[38]</sup> In contrast, this does not occur in *Terc* deficient mice, suggesting a gene-dependent mechanism of liver disease in TBD. However, other investigators who study human embryonic stem cells demonstrated that telomere dysfunction impaired hepatocyte development and function through repression of human hepatocyte nuclear factor 4 $\alpha$ , suggesting a telomere-dependent, gene-independent mechanism of liver injury in TBD.<sup>[39]</sup>

Our cohort demonstrates a similar broad spectrum of liver involvement in earlier studies.<sup>[5,6,17–19]</sup> Elevated liver enzymes are a common manifestation seen in the majority of patients. There was a relatively high prevalence of cirrhosis in our cohort (34%). Gastrointestinal bleeding was reported in 20% of this cohort, though there was not a high proportion of variceal bleeding nor decompensating events. It is uncertain from this registry whether chronic liver disease and portal hypertension aggravate nonvariceal gastrointestinal bleeding in TBD, for instance, from intestinal AVMs. We note the high prevalence of HPS of 39.8% in the entire cohort and highlight it as the leading indication for liver transplantation.

In patients who have clinically significant, progressive liver disease, we believe our data is encouraging in support of liver transplantation for selected patients. Given that 50% of patients who died from progression of liver disease were at institutions where LT for TBD has not been performed, and 35% of LT recipients ultimately underwent transplants at outside centers, we suggest that patients diagnosed with TBD-associated cirrhosis or HPS be referred for LT at more than 1 institution. Especially among patients with HPS, we show a clear survival benefit among patients who undergo liver transplantation. Moreover, several patients have also experienced clinically significant improvements in other organ systems affected by TBD, including hematopoietic and pulmonary. While cytopenias related to hypersplenism in patients with portal hypertension would be expected to resolve post-LT, the effect of liver transplantation on TBD-related bone marrow failure remains unknown. Other published reports of liver transplant recipients have demonstrated similar improvements in cytopenias<sup>[25,40]</sup> and pulmonary function.<sup>[28,40]</sup> Whether these positive changes will be maintained remains to be seen; our own future efforts will include the re-interrogation of these outcomes in the following decades to fill this critical gap in the literature.

The prevalence of splenomegaly in this cohort is high, found in about half of subjects in both groups. Splenomegaly is not a defining characteristic of TBDs and has commonly been reported in the literature in patients with TBDs and liver disease.<sup>[2,5,18,19,21,24,25,27,41–44]</sup> We suggest, based on the frequency of splenomegaly in our cohort and prior studies, that evaluation for liver disease and resultant portal hypertension should be performed in all patients with TBDs who have splenomegaly.

HPS is emerging as an important manifestation of liver disease in patients with TBDs and was the most common indication for liver transplantation listed in this cohort, as described in prior reports.<sup>[19,23–28]</sup> Since liver transplantation is the only effective treatment of HPS, discussions regarding transplant evaluation should be initiated when HPS is diagnosed. Furthermore, measurement of oxygen saturation should be part of routine follow-up visits for patients with TBD, and even mild hypoxemia < 97%, especially if associated with orthodeoxia, should prompt assessment for liver disease.

Historically, concern for TBD-associated lung disease has been cited as a reason not to pursue liver transplantation. Of the patients who had pulmonary fibrosis in this cohort, 50% are alive and have improved respiratory status. While longer-term data are needed to confirm the effect of liver transplantation on lung disease progression in TBD, patient outcomes in this cohort do not support that pre-existing lung disease in TBD should be considered an absolute contraindication to liver transplantation.

TBD had been considered a relative contraindication for liver transplantation until recently, given the multi-system nature of the disease. Not surprisingly, 4 patients declined LT, citing concerns for prolonged suffering, unclear risk-benefit ratio, not enough known about LT outcomes in this patient group, and poor outcomes after transplant in relatives. Six patients were declined for LT listing due to center concerns about bone marrow failure, Model for End-Stage Liver Disease score “too low,” or unclear survival benefit given extrahepatic disease. An aim of our study was to re-evaluate the risks and benefits of liver transplantation for decompensated liver disease in TBD, given the increase in liver transplants for this condition since 2015 and the lack of contemporaneous cohort studies. We submit that our study data refute the notion that TBD is a contraindication for liver transplantation because of futility, given the acceptable short-term outcomes of 1-year survival after transplant of 73% and the clear survival benefit from liver transplant among patients with HPS. However, it requires longer-term prospective studies to delineate whether the benefits of decreased morbidity and mortality can be sustained and for how long after solid organ transplant.

There were no reports of any LT centers utilizing a modified protocol for patients with TBD based on underlying disease, with most centers following

standard immunosuppression protocols. Our data cannot yet determine whether there is an increased risk of infectious or immune-mediated complications in patients with TBD who are pharmacologically immunosuppressed. This would be of particular importance in patients with TBD-associated bone marrow failure who are already at risk of developing these complications, highlighted by 1 patient who developed severe aplastic anemia after liver transplant.

Patients in group M were those with liver disease (primarily abnormal liver enzymes and/or liver imaging) that was determined by participating centers to not warrant liver transplant evaluation. Reasons for this varied; some had portal hypertension but without a report of decompensating events. Importantly, 4 patients from group M (9.3%) died of a cause attributed to chronic liver disease, highlighting the difficulties in prognosticating hepatic decompensation and complications from portal hypertension in TBD. Further follow-up of this group will allow us to identify variables for risk stratification.

### Study limitations and future directions

We consider 2 significant limitations of our study: the retrospective collection of data and limited follow-up post-LT. With such a rare and potentially underdiagnosed disease entity, ongoing and real-time data aggregation would be ideal, but such efforts would require substantial resources. While patients connected to the family group Team Telomere were invited to contribute their data, the 17 participating centers were all large tertiary referral institutions spanning 4 continents, potentially selecting for more severe liver disease. We furthermore acknowledge a possible center bias relating to the group assignment of patients; for example, some centers may consider liver transplant evaluation in patients with compensated cirrhosis (assigning to Group A), but others may not. Ten of the 17 participating centers reported LTs, so this may be less likely. With a median of 3 years of follow-up after liver transplant, we are unable to confidently estimate the long-term impacts of LT, such as the lifetime malignancy risk of patients with TBD, which is known to be at least 40% by age 50.<sup>[45]</sup> The progression of bone marrow failure and later need for HSCT, or the progression of lung fibrosis and later need for a lung transplant after liver transplantation, remains unknown. Additional questions that will remain unanswered until longer-term follow-up data are available include the recurrence of TBD-associated liver disease in the allograft and what impact genotype-phenotype correlation may have on liver disease and transplant outcomes.

In conclusion, our retrospective cohort study demonstrates that liver-related morbidity, including cirrhosis

and HPS, and mortality are high in TBD. Early detection and close follow-up are needed. Splenomegaly or hypoxemia, especially if associated with pulmonary AVMs, should prompt evaluation for liver disease and portal hypertension in patients with TBD. The historical position that patients with TBD are not transplantable due to their underlying multisystem disease should be re-visited, in our opinion, on a case-by-case basis. LT is a feasible treatment option for select patients with TBD-related liver disease and should be considered in patients with HPS and gastrointestinal bleeding. Short-term outcomes of LT are acceptable, the majority of patients experience improvement in liver-related symptoms after transplant, and the survival benefit of LT among patients with HPS is unequivocal.

Patients with TBD and associated comorbidities are complex and deserve multidisciplinary attention and management. Multicenter international working groups, as formed for the purpose of this study, will be integral in optimizing transplantation protocols and outcomes in this rare group.

### AUTHOR CONTRIBUTIONS

YunZu Michele Wang and Batul Kaj-Carbaidwala collected and analyzed the data and wrote the manuscript. AL performed the formal analysis of data for the study. Suneet Agarwal, Fabian Beier, Alison Bertuch, Kristin A. Borovsky, Steven K. Brennan, Rodrigo T. Calado, Luiz Fernando B. Catto, Carlo Dufour, Christen L. Ebens, Francesca Fioredda, Neelam Giri, Nicholas Gloude, Frederick Goldman, Paula M. Hertel, Ryan Himes, Sioban B. Keel, Divya T. Koura, Christian Kratz, Sakil Kulkarni, Iris Liou, Taizo A. Nakano, Silvia Nastasio, Marena R. Niewisch, Daniel D. Penrice, Ghadir S. Sasa, Sharon A. Savage, Douglas A. Simonetto, David S. Ziegler, Alexander G. Miethke and Kasiani C. Myers collected patient data and critically revised the manuscript. Batul Kaj-Carbaidwala, Alexander G. Miethke, and Kasiani C. Myers conceptualized the study. All authors have given final approval of this manuscript.

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### CONFLICTS OF INTEREST

Suneet Agarwal consults, received grants, and owns stock in Rejuveron Telomere Therapeutics and advises Cimeio Therapeutics. Steven Brennan owns stock in

Merck. Christen Ebens consults for Elixirgen Therapeutics. Nicholas Gloude consults for Rocket Pharmaceuticals. Sioban Keel consults for Disc Medicine. Douglas Simonetto consults for Mallinckrodt, BioVie, Resolution Therapeutics, and Evive. David Ziegler consults and received grants from Accendatech and consults for Bayer, AstraZeneca, Novartis, Day One, FivePhusion, Amgen, Alexion, Norgine, and Roche. Alexander Miethke consults, advises, and received grants from Mirum. Kasiana Myers received grants Elixirgen Therapeutics and Incyte. The remaining authors have no conflicts to report.

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