Current Hematologic Malignancy Reports (2024) 19:75–81
https://doi.org/10.1007/s11899-023-00723-6

Telomere Biology Disorder: A Focus on Gastrointestinal and Hepatic Manifestations

Fatima Warsame[1] **· Douglas A. Simonetto**[2]

Accepted: 29 December 2023 / Published online: 19 February 2024

Abstract

Purpose of Review Telomere biology disorders (TBD) encompass several illnesses caused by underlying mutations in telomere maintenance leading to premature telomere attrition and telomere dysfunction. These disorders have unique features but share common disease manifestations including pulmonary fibrosis, cirrhosis, and bone marrow failure. The goals of this article are to provide an overview of the gastrointestinal and hepatic manifestations of TBD, focusing on their pathophysiology, clinical disease states, and current management strategies.

Recent Findings Telomere shortening has been observed in patients with chronic liver disease and is associated with a higher risk of progression to cirrhosis and portal hypertension. While the directionality of the association between telomere dysfunction and senescence on liver disease is not fully understood, research in TBD may provide clarity and could lead to future therapies for this increasingly prevalent disease. While treatment options remain limited in TBD-associated liver disease, recent studies point to the safety and efficacy of liver transplantation among patients with end-stage liver disease.

Keywords Telomere biology disorder · Cirrhosis · Nodular regenerative hyperplasia · Enteropathy

Introduction

The discovery of telomeres and telomerase answered the longstanding "end replication problem" by identifying how the ends of chromosomes are fully replicated [1]. Telomeres are composed of repeat DNA sequences and DNA-binding proteins. Telomerase is the tightly regulated enzyme that adds these repeat sequences to the ends of chromosomes. Even in cells with increased telomerase activity such as hematopoietic stem cells, telomeres gradually shorten during the lifespan. In somatic cells, telomerase regulation allows telomeres to gradually shorten to a critical length at which the cells stop dividing. Low telomerase activity leads to senescence and cell death while high telomerase activity may allow cancer cells to divide indefinitely [2]. Telomere biology disorders (TBD) are characterized by defective telomerase and premature telomere attrition with associated clinical syndromes. Disease severity is dependent not on the specific underlying mutations but rather on their effect on telomere length and function [3]. Further, genetic anticipation is observed in these disorders as shorter telomeres accumulate in germline cells, leading to more severe and earlier disease complications in subsequent generations [4].

Manifestations of TBD tend to occur first in fast turnover tissues such as the bone marrow and GI tract. Telomere syndromes in pediatric patients can manifest as immunodeficiency, bone marrow failure, and enteropathy. In slower turnover tissues such as the lung and liver, patients more often present in adulthood with idiopathic pulmonary fibrosis and cirrhosis or noncirrhotic portal hypertension [3]. Mutations in telomerase components were first associated with the clinical syndrome of dyskeratosis congenita (DC) which was later grouped together with other clinical syndromes such as Hoyeraal-Hreidarsson syndrome (HHS), Revesz syndrome, and Coats plus in which patients have telomere lengths below the first percentile compared to age-matched controls [5, 6••]. The clinical spectrum of TBD is broad with variable telomere component mutations and phenotypes with severe disease phenotypes manifesting as multiorgan dysfunction in the first decade of life [7].

✉ Douglas A. Simonetto
Simonetto.Douglas@mayo.edu

[1] Internal Medicine Residency, Department of Medicine, Mayo Clinic, Rochester, MN, USA

[2] Gastroenterology and Hepatology Fellowship Program, Division of Gastroenterology and Hepatology, Mayo Clinic, 200 1St SW, Rochester, MN, USA

Bone marrow failure (BMF) is a frequent presentation of TBD and can be symptomatically managed with androgen derivatives; however, most patients eventually require bone marrow transplantation [5, 8]. Idiopathic pulmonary fibrosis is another common manifestation that can be initially managed with antifibrotic regimens; however, the only curative treatment is lung transplantation. Gastrointestinal and hepatic manifestations are also common among TBDs and will be further highlighted in this review. Management of TBD is challenging as patients require dedicated multidisciplinary collaboration that may not be established outside of a few centers in the USA. Additionally, while there has been progress in understanding the genetic basis of these disorders, there are currently no known curative therapies and treatment is mostly supportive (Fig. 1).

Diagnosis of a Telomere Biology Disorder

Clinical syndromes within TBD were initially defined by classic presentations such as the "triad" of nail dystrophy, oral leukoplakia, and abnormal skin pigmentation in DC [5]. Over the last few years, quantitative methods have been developed to evaluate telomere length such as quantitative-fluorescence in situ hybridization (Q-FISH) and quantitative PCR (qPCR). Telomere length cutoffs were determined using data from patients with TBD and their families compared to healthy controls [9]. Telomere length measurement (in total leukocytes and leukocyte subsets) by Q-FISH is the most sensitive and specific screening test for TBD at this time [10]. While telomere lengths below the first percentile are suggestive of TBD, results from telomere length assays should be interpreted in association with the clinical presentation and diagnostic criteria. It is suggested that patients with the appropriate clinical presentation and telomere lengths below the tenth percentile undergo genetic testing (next-generation sequencing or exome-based genetic testing) to evaluate for telomerase mutations [11, 12].

Gastrointestinal Manifestations of Telomere Biology Disorder

The gastrointestinal (GI) epithelial tissue has one of the highest proliferation rates among all tissues. Maintaining a constant regenerative capacity is crucial for the functional integrity of the GI tract. Consequently, telomere dysfunction in TBD leads to decreased proliferation of intestinal stem cells and impaired regeneration of the gastrointestinal epithelium which results in a range of disease manifestations. Among patients enrolled in the Johns Hopkins Telomere Syndrome Registry, common GI presentations included failure to thrive, malnutrition, dysphagia, post-prandial abdominal pain, early satiety, and diarrhea [13]. On histopathology, patients were found to have esophageal strictures/webs/Schatzki's rings, atrophic gastritis, enteropathy, and enterocolitis/pancolitis. GI manifestations in TBD are commonly diagnosed in pediatric and young adult patients and can be one of the first recognized manifestations of these disorders. Due to the severe consequences on nutritional status and development, it is important to perform nutritional assessments and pursue a diagnostic and treatment strategy for underlying pathologies.

Esophageal Stenosis

Esophageal stenosis can present in infancy with poor feeding and failure to thrive or can be acquired/milder in older children and adults [14, 15]. The pathophysiology is likely similar to the other stenotic lesions seen in DC/TBD such as lacrimal duct and urethral stenosis [13]. Patients presenting with dysphagia, regurgitation, and food avoidance should undergo evaluation for structural causes such as strictures and rings/webs. Diagnostic evaluation includes esophagography, upper endoscopy with biopsies, and manometry. Once the area of stenosis is identified, endoscopic dilation can be undertaken, if feasible. In several cases, patients with

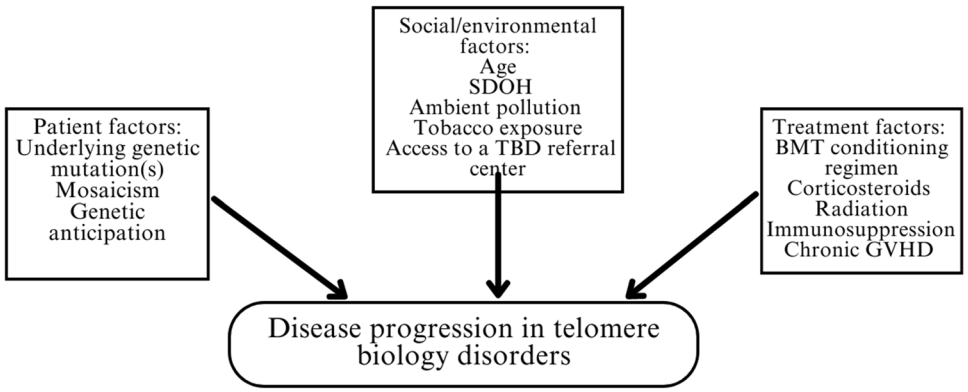

Fig. 1 Conceptual framework of potential contributors to disease progression in telomere biology disorder. Abbreviations: SDOH, social determinants of health; TBD, telomere biology disorder; BMT, bone marrow transplantation; GVHD, graft versus host disease

symptom recurrence require repeat esophageal dilations [16]. Patients with esophageal strictures refractory to dilation or esophageal dysmotility may require stent placement.

Notably, esophageal strictures can also occur after patients undergo BMT as the esophagus is one of the target organs in graft-versus-host disease (GVHD) [17]. The immunologic process in chronic GVHD can cause desquamative esophagitis that predisposes to strictures, webs, and ulceration [18]. Esophageal dilations can be undertaken in GVHD-related esophagitis; however, this should be weighed carefully against the risks of perforation.

Enteropathy and Enterocolitis

Enteropathy is one the most common lower GI manifestations of TBD and predominantly affects the small bowel. Patients can present with diarrhea, weight loss, anemia, and nutrient deficiencies related to malabsorption. Histopathology of the small intestine is characterized by villous atrophy, intraepithelial lymphocytosis, and epithelial apoptosis [13]. These features are difficult to distinguish from those seen in celiac disease and inflammatory bowel disease. Interestingly, telomere dysfunction has been associated with upregulation of immune regulators linked with inflammatory bowel disease pathogenesis [19]. The role of immune dysfunction in enteropathy among patients with TBD is not entirely clear. Based on limited data, enteropathy in TBD often does not respond to steroids or immunomodulating agents [20•].

Colitis can also be a severe and morbid manifestation of TBD. Patients may present with bloody diarrhea, abdominal pain, and failure to thrive. The pathophysiology of this condition is not entirely clear and likely also stems from epithelial defects and immune dysfunction. Colonic biopsies reveal friability, gland drop-out, and chronic inflammation. Treatment is mostly supportive including parenteral nutrition, while some patients require colectomy. There is insufficient data regarding the course of GI illnesses after BMT and it is likely that transplantation may only improve the immunologic abnormalities but not the mucosal deficits [20•].

Gastrointestinal Hemorrhage

GI bleeding is another shared gastrointestinal manifestation of TBD and can present early with significant morbidity and mortality. In a multicenter retrospective study of TBD patients treated for GI bleeding, endoscopic findings included telangiectasias, esophageal varices, gastritis, vascular dysplasia/ectasia, and "friability" [21•]. Among this cohort of patients, esophageal endoscopic findings included mucosal abnormalities of varying severity and esophageal varices. Endoscopic band ligation can be utilized in bleeding varices. In the stomach, endoscopic findings included gastritis, gastric antral variceal ectasia, and vascular dysplasia. Similarly, lesions in the colons were also described as having ectatic vasculature and increased friability.

Patients with TBD can develop portal hypertension and variceal bleeding from cirrhosis as well as noncirrhotic liver disease. Trialed interventions included proton pump inhibitors, short-acting octreotide, nonselective beta-blockers (such as nadolol, propranolol, or carvedilol), androgen therapy, endoscopic interventions, and supportive care. Therapeutic interventions include electrocauterization, radiofrequency ablation, argon plasma coagulation, and transjugular intrahepatic portosystemic shunts. Bevacizumab has been trialed in recurrent GI bleeding from vascular ectasias and its efficacy was reported in one patient requiring frequent transfusions with a sustained treatment effect [21•]. The presence of vascular anomalies in the GI tract and intrahepatic/intrapulmonary arteriovenous malformations suggests an underlying vascular process among TBDs that is yet to be fully understood [22]. Vascular telangiectasia affecting multiple organs is also seen in hereditary hemorrhagic telangiectasia and this should be excluded via genetic testing.

Hepatic Manifestations of Telomere Biology Disorder

Up to half of adults with telomere biology disorder based on telomere gene mutations and/or clinical features of the disorder have hepatic manifestations [23•]. These include persistent transaminase elevations, hepatomegaly, cirrhotic liver morphology, and portal hypertension. Liver biopsies of affected patients demonstrate steatohepatitis, cirrhosis, nodular regenerative hyperplasia (NRH), and presumed transfusion-related hemosiderosis. As opposed to pediatric patients with TBD who present predominantly with bone marrow failure, adults with TBD develop liver and lung manifestations as these slower turnover tissues develop telomere shortening. Telomere length and dysfunction have been implicated in disease progression in patients with cirrhosis [24, 25]. However, the mechanisms underlying telomere length/function and specific liver pathologies are not entirely clear [26]. Additionally, TBD patients incur more insults to the liver including transfusion-dependence, medications, and bone marrow failure which may stimulate cell proliferation and in turn accelerate the natural course of disease [27•].

Cirrhosis

Patients with TBD can have liver transaminase elevations predominantly in a cholestatic pattern, followed by hepatocellular and mixed patterns [23•, 28•]. As liver function

tests can remain normal, surveilling for hepatic fibrosis is important in this population. Although liver biopsy is the "gold standard" for assessing hepatic fibrosis, it is an invasive test with unique limitations in this population with a high prevalence of thrombocytopenia related to bone marrow failure. Noninvasive surveillance imaging can be useful for assessing hepatic fibrosis. Liver magnetic resonance elastography (MRE) is currently the most accurate noninvasive test available for assessing hepatic fibrosis [29]. Transient elastography (FibroScan) is an excellent alternative and it is more readily available, although it requires special training and carries limitations related to patient factors, such as central obesity. Surveillance for advanced liver disease may be done every 5–10 years, depending on the family history and liver test abnormalities. Once a diagnosis of cirrhosis has been established, surveillance for hepatocellular carcinoma is recommended biannually. Patients with compensated cirrhosis should be evaluated for clinically significant portal hypertension, and if present, nonselective beta-blockers are now recommended for prevention of first decompensation. Complications of cirrhosis reported in this population are inclusive of ascites, hepatic encephalopathy (HE), and variceal bleeding [30]. Cirrhosis is associated with poor overall survival and represents a negative prognostic factor in this population [31]. Patients with decompensated liver disease should undergo liver transplant evaluation. Timely listing or consideration of live donors or HCV positive donors may improve outcomes by shortening waitlist time [32].

Nodular Regenerative Hyperplasia and Hepatopulmonary Syndrome

Liver disease in TBD often also manifests as non-cirrhotic portal hypertension with or without hepatopulmonary syndrome (HPS). On liver biopsy specimens, the most common finding among patients with progressive HPS was nodular regenerative hyperplasia (NRH). NRH is a rare histopathologic abnormality that is frequently identified in patients with TBD in the absence of cirrhosis [30]. It has been suggested that NRH occurs because of an underlying vascular insufficiency [33]. NRH is complicated by noncirrhotic portal hypertension and patients may present with variceal bleeding, ascites, or HE. Among a cohort of patients in the Johns Hopkins Telomere Syndrome Registry with dyspnea, 21% had minimal or no parenchymal lung disease and their presentation was consistent with HPS [34]. Patients with hypoxia and restriction diffusion on pulmonary function testing were found to have arteriovenous fistulas, evidence of portal hypertension, and intrahepatic arterio-venous malformations. The connection between NRH and vascular malformations is yet not entirely clear but may stem from abnormal portal inflow.

While the presence of platypnea and hypoxia in a patient with liver disease is suggestive of HPS, these symptoms and the presence of a shunt can be seen in other situations including pulmonary arteriovenous malformations (PAVMs) [35]. The resolution of PAVMs after liver transplantation indicates a liver-lung interaction or an underlying vascular process in patients with non-cirrhotic portal hypertension. Further understanding regarding these complex interactions would be valuable to advance long-term management strategies [36].

The role of liver transplantation in patients with non-cirrhotic portal hypertension with HPS remains unclear. In a small case series of patients with HPS, patients' supplemental oxygen dependence completely resolved after liver transplantation [32]. Patients with HPS are eligible to receive Model for End-Stage Liver Disease (MELD) exception points which can decrease time to transplantation.

Treatment Considerations

As telomeropathies affect multiple organ systems, management considerations are complex and patients with TBD should receive multidisciplinary care in centers with expertise in these conditions (Table 1). With regard to pharmacologic management, danazol is a synthetic steroid with structural similarities to androgens that is used in patients with a variety of telomere disorders. In a prospective study of 27 patients with TBD as defined by telomere length at or below the first percentile and/or mutations in telomere maintenance and repair genes, danazol administration was associated with a reduction in the yearly telomere attrition rate [37]. Danazol was also associated with an increase in hematologic response, as measured by an increase in hemoglobin within 24 months of treatment. Liver fibrosis was noted to have improved in three of four patients with cirrhosis and worsened in one patient with ongoing alcohol use. Given limited data, danazol is not routinely used in management of liver disease among patients with TBD.

With regard to hepatic manifestations, recognition of the role of telomere dysfunction in chronic liver disease presents the possibility of targeted therapies in TBD. A potential therapeutic strategy involves telomerase activation to prevent premature telomere attrition. In a mouse model of telomerase gene delivery, this led to improvements in liver function and cirrhotic morphology [38]. Investigations using animal models have targeted multiple checkpoints to halt the senescence pathway after telomere shortening occurs [39]. The applications of telomerase-directed therapies are promising; however, there is concern regarding malignancy risks associated with

Table 1 Overview of clinical follow-up recommendations in TBD. Abbreviations: *CBC* complete blood count, *MDS* myelodysplastic syndrome, *AML* acute myeloid leukemia, *BMT* bone marrow transplantation, *Q-FISH* quantitative fluorescence in situ hybridizations, *HPV* human papillomavirus, *CT* computed tomography, *ILD* interstitial lung disease, *AVM* arteriovenous malformation

Specialty	Available diagnostic tests	Complications	Treatments reported
Hematology	CBC Bone marrow biopsy	Cytopenia Bone marrow failure MDS/AML After head and neck chemotherapy: aplastic anemia	Transfusion Androgen therapy BMT
Medical genetics	Genetic testing	Genetic anticipation	Family counseling and testing
Dermatology	Skin cancer surveillance	Skin cancer	
Dentistry	Routine dental screening	Caries Periodontal disease	Oral hygiene
Ophthalmology	Routine eye examinations	Cataract Glaucoma Retinopathy	
Gastroenterology and Hepatology	Hepatic function tests Liver magnetic resonance elastography Liver biopsy	Cirrhosis Non-cirrhotic portal hypertension	Transplantation
Gynecology	Cancer screening Related to androgen treatment: Infertility		
Primary care	Physical examination Vaccinations (HPV) Tobacco use counseling	HPV mediated cancers	
Pulmonology	Pulmonary function tests Chest computed tomography Contrast-enhanced echocardiogram	Early onset ILD Idiopathic pulmonary fibrosis Pulmonary AVM	Androgen therapy Shunt embolization Transplantation
Orthopedics	Clinical examination Radiographs	Avascular necrosis Osteoporosis	Joint replacement
Otolaryngology	Clinical examination Laryngoscopy	Head and neck cancers	
Transplantation	Comprehensive transplant evaluation	Bone marrow failure Cryptogenic cirrhosis Pulmonary fibrosis	Organ specific transplantation

halting biological checkpoints or senescence pathways. Currently, transplantation is an option for patients with TBD who develop end-stage liver disease. Prior reports with a mean follow-up of 4.1 years post-liver transplant demonstrated favorable clinical outcomes with the longest reported survival greater than 7 years post-transplant [40]. Further research to understand telomere biology and investigate the use of gene therapy is needed in this patient population.

Lastly, genetic counseling is a cornerstone of care for this patient population as family members should be counseled on disease risk and surveillance as well as the implications of genetic anticipation. Patients considering related donor transplant should undergo careful evaluation of any related donors to ensure the asymptomatic related donor is not a mutation carrier or found to have telomere lengths below the first percentile. Additionally, patients can be referred to patient-centered advocacy groups that provide information and community support [41].

Conclusion

Telomere biology disorders are associated with various GI and hepatic manifestations with underlying epithelial, vascular, and treatment-related mechanisms. Recognizing the clinical presentations of TBD-associated GI pathology is crucial as these manifestations are best treated under the framework of the entire telomere-related disease spectrum. Further advancements are needed to identify targeted and effective therapies. There are currently clinical trials investigating danazol and telomerase gene therapy. If treatment strategies aimed at increasing the activity of telomerase or increasing telomere length and function are successful and safe in this population, this would have important implications for the treatment of pathologies beyond TBD. In addition to multidisciplinary care, clinicians should consider exploring patient's concerns, treatment goals, and

priorities to best support patient-centered outcomes in this challenging disease.

Author Contribution F.W. and D.S. wrote the main manuscript text and prepared Fig. 1. All authors reviewed the manuscript.

Data Availability Not applicable.

Declarations

Competing Interests The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Corey DR. Telomeres and telomerase: from discovery to clinical trials. Chem Biol. 2009;16(12):1219–23.
2. Armanios M, Blackburn EH. The telomere syndromes. Nat Rev Genet. 2012;13(10):693–704.
3. Armanios M. Syndromes of telomere shortening. Annu Rev Genomics Hum Genet. 2009;10:45–61.
4. Armanios M. Telomeres and age-related disease: how telomere biology informs clinical paradigms. J Clin Invest. 2013;123(3):996–1002.
5. Dokal I. Dyskeratosis congenita. Hematol Am Soc Hematol Educ Program. 2011;2011:480–6.
6 ••Vieri M, Brümmendorf TH, Beier F. Treatment of telomeropathies. Best Pract Res Clin Haematol. 2021;34(2):101282 (**This review article is a useful summary of recent updates in the management of TBD for clinical practice among providers of all specialties.**).
7. Byrjalsen A, Brainin AE, Lund TK, Andersen MK, Jelsig AM. Size matters in telomere biology disorders - expanding phenotypic spectrum in patients with long or short telomeres. Hered Cancer Clin Pract. 2023;21(1):7.
8. Armanios M. Telomeres in the Clinic, Not on TV. Mayo Clin Proc. 2018;93(7):815–7.
9. Savage SA, Alter BP. Dyskeratosis congenita. Hematol Oncol Clin North Am. 2009;23(2):215–31.
10. Gutierrez-Rodrigues F, Santana-Lemos BA, Scheucher PS, Alves-Paiva RM, Calado RT. Direct comparison of flow-FISH and qPCR as diagnostic tests for telomere length measurement in humans. PLoS ONE. 2014;9(11):e113747.
11. Kam MLW, Nguyen TTT, Ngeow JYY. Telomere Biology disorders. NPJ Genom Med. 2021;6(1):36.
12. Mangaonkar AA, Ferrer A, Vairo FPE, Hammel CW, Prochnow C, Gangat N, et al. Clinical and molecular correlates from a predominantly adult cohort of patients with short telomere lengths. Blood Cancer J. 2021;11(10):170.
13. Jonassaint NL, Guo N, Califano JA, Montgomery EA, Armanios M. The gastrointestinal manifestations of telomere-mediated disease. Aging Cell. 2013;12(2):319–23.
14. Lee J, Cheeseman E, Matheus M, Kasi N. A primary gastrointestinal presentation and novel genetic variant of dyskeratosis congenita in a pediatric patient. JPGN Rep. 2022;3(3):e242.
15. Rodriguez K, Shargo R, Ekblad M, Sunkersett G, Karjoo S, Betensky M, et al. Endoscopic Assessment and serial balloon dilatation in a toddler with Dyskeratosis Congenita-Hoyeraal-Hreidarsson syndrome following bone marrow transplant: a case report. JPGN Rep. 2023;4(2):e291.
16. Yaghmai R, Kimyai-Asadi A, Rostamiani K, Heiss NS, Poustka A, Eyaid W, et al. Overlap of dyskeratosis congenita with the Hoyeraal-Hreidarsson syndrome. J Pediatr. 2000;136(3):390–3.
17. McDonald GB, Sullivan KM, Schuffler MD, Shulman HM, Thomas ED. Esophageal abnormalities in chronic graft-versus-host disease in humans. Gastroenterology. 1981;80(5 pt 1):914–21.
18. Shulman HM, Kleiner D, Lee SJ, Morton T, Pavletic SZ, Farmer E, et al. Histopathologic diagnosis of chronic graft-versus-host disease: National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: II Pathology Working Group Report. Biol Blood Marrow Transplant. 2006;12(1):31–47.
19. Chakravarti D, Lee R, Multani AS, Santoni A, Keith Z, Hsu WH, et al. Telomere dysfunction instigates inflammation in inflammatory bowel disease. Proc Natl Acad Sci USA. 2021;118(29):e2024853118.
20. Borggraefe I, Koletzko S, Arenz T, Fuehrer M, Hoffmann F, Dokal I, et al. Severe variant of x-linked dyskeratosis congenita (Hoyeraal-Hreidarsson Syndrome) causes significant enterocolitis in early infancy. J Pediatr Gastroenterol Nutr. 2009;49(3):359–63.
21• Himes RW, Chiou EH, Queliza K, Shouval DS, Somech R, Agarwal S, et al. Gastrointestinal hemorrhage: a manifestation of the telomere biology disorders. J Pediatr. 2021;230:55-61.e4 (**Case series describing the causes and management of GI bleeding with relevance across the TBD spectrum.**).
22. Higgs C, Crow YJ, Adams DM, Chang E, Hayes D Jr, Herbig U, et al. Understanding the evolving phenotype of vascular complications in telomere biology disorders. Angiogenesis. 2019;22(1):95–102.
23. Kapuria D, Ben-Yakov G, Ortolano R, Cho MH, Kalchiem-Dekel O, Takyar V, et al. The spectrum of hepatic involvement in patients with telomere disease. Hepatology. 2019;69(6):2579–85.
24• Penrice DD, Jalan-Sakrikar N, Jurk D, Passos JF, Simonetto DA. Telomere dysfunction in chronic liver disease: the link from aging. Hepatology. 2023. (Article with recent data and good follow-up duration showing favorable clinical outcomes after liver transplantations.)
25. Rattan P, Penrice DD, Ahn JC, Ferrer A, Patnaik M, Shah VH, et al. Inverse association of telomere length with liver disease and mortality in the US population. Hepatol Commun. 2022;6(2):399–410.
26. Kitada T, Seki S, Kawakita N, Kuroki T, Monna T. Telomere shortening in chronic liver diseases. Biochem Biophys Res Commun. 1995;211(1):33–9.
27. Hartmann D, Srivastava U, Thaler M, Kleinhans KN, N'Kontchou G, Scheffold A, et al. Telomerase gene mutations are associated with cirrhosis formation. Hepatology. 2011;53(5):1608–17.
28• Vittal A, Niewisch MR, Bhala S, Kudaravalli P, Rahman F, Hercun J, et al. Progression of liver disease and portal hypertension in dyskeratosis congenita and related telomere biology disorders. Hepatology. 2023. (Discusses predictors of progression to portal hypertension among patients with TBD and liver enzyme abnormalities.)

29. Hoodeshenas S, Yin M, Venkatesh SK. Magnetic resonance elastography of liver: current update. Top Magn Reson Imaging. 2018;27(5):319–33.
30. Patnaik MM, Kamath PS, Simonetto DA. Hepatic manifestations of telomere biology disorders. J Hepatol. 2018;69(3):736–43.
31. Mangaonkar AA, Ferrer A, Pinto EVF, Cousin MA, Kuisle RJ, Klee EW, et al. Clinical correlates and treatment outcomes for patients with short telomere syndromes. Mayo Clin Proc. 2018;93(7):834–9.
32. Oseini AM, Hamilton JP, Hammami MB, Kim A, Oshima K, Woreta T, et al. Liver transplantation in short telomere-mediated hepatopulmonary syndrome following bone marrow transplantation using HCV positive allografts: a case series. Liver Transpl. 2021;27(12):1844–8.
33. Wanless IR, Solt LC, Kortan P, Deck JH, Gardiner GW, Prokipchuk EJ. Nodular regenerative hyperplasia of the liver associated with macroglobulinemia A clue to the pathogenesis. Am J Med. 1981;70(6):1203–9.
34. Gorgy AI, Jonassaint NL, Stanley SE, Koteish A, DeZern AE, Walter JE, et al. Hepatopulmonary syndrome is a frequent cause of dyspnea in the short telomere disorders. Chest. 2015;148(4):1019–26.
35. Khincha PP, Bertuch AA, Agarwal S, Townsley DM, Young NS, Keel S, et al. Pulmonary arteriovenous malformations: an uncharacterised phenotype of dyskeratosis congenita and related telomere biology disorders. Eur Respir J. 2017;49(1).
36. Vettukattil JJ. Pathogenesis of pulmonary arteriovenous malformations: role of hepatopulmonary interactions. Heart. 2002;88(6):561–3.
37. Townsley DM, Dumitriu B, Liu D, Biancotto A, Weinstein B, Chen C, et al. Danazol treatment for telomere diseases. N Engl J Med. 2016;374(20):1922–31.
38. Rudolph KL, Chang S, Millard M, Schreiber-Agus N, DePinho RA. Inhibition of experimental liver cirrhosis in mice by telomerase gene delivery. Science. 2000;287(5456):1253–8.
39. Udomsinprasert W, Sobhonslidsuk A, Jittikoon J, Honsawek S, Chaikledkaew U. Cellular senescence in liver fibrosis: implications for age-related chronic liver diseases. Expert Opin Ther Targets. 2021;25(9):799–813.
40. Penrice DD, Havlichek D 3rd, Kamath PS, Simonetto DA. Outcomes following liver transplant in adults with telomere biology disorders. J Hepatol. 2022;76(1):214–6.
41. Team Telomere: TEAM TELOMERE, INC; 2022 [Available from: https://teamtelomere.org/.