ORIGINAL RESEARCH ARTICLE

Patient- and Caregiver-Reported Burden of Transfusion-Dependent β-Thalassemia Measured Using a Digital Application

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Abstract

Background and Objective Transfusion-dependent β-thalassemia (TDT) is a rare genetic disease characterized by a deficiency of functional β-globin, ultimately leading to lifelong dependence on blood transfusions. There is little patient- and caregiver-reported data with which to understand the holistic and societal impact of TDT. The objective of this study was to evaluate the patient- and caregiver-reported disease-management, symptom, and quality-of-life burden of TDT.

Methods We conducted a prospective, observational, real-world study of adults with TDT and caregivers of adolescents with TDT, in Italy, the UK, and the USA. Over 90 days, participants used a smartphone application to respond to surveys about their or their dependent's TDT, including bespoke background and disease-management surveys, the Brief Fatigue Inventory (BFI), the Transfusion-dependent Quality of life questionnaire (TranQol), and the Brief Pain Inventory Short Form (BPI-SF).

Results Eighty-five individuals participated. Mean BFI and TranQol scores on enrollment were 5.0 (0–10 scale; 10 = worst symptoms) and 51 (0–100 scale; 100 = best quality of life), respectively. Mean transfusion frequency was every 3.2 weeks. Mean time spent on TDT management was 592 min on transfusion days and 91 min on non-transfusion days (11 h per week). Mean BFI and BPI-SF "worst fatigue" and "worst pain" scores were higher in the 5 days pre-transfusion than in the 5 days post-transfusion (fatigue 5.05 vs 4.29; pain 4.33 vs 3.85; 0–10 scale; 10 = worst symptoms).

Conclusions The patient- and caregiver-reported burden of TDT is high, influenced by disease-management time, fatigue, pain, and quality-of-life impairment.

Key Points for Decision Makers

Transfusion-dependent β-thalassemia appears to place a high level of burden on individuals with the condition and their caregivers.

In our study, the burden associated with transfusion-dependent β-thalassemia was driven by a high time spent on disease management, fatigue and pain symptoms, and impairment to quality of life.

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1 Introduction

β-Thalassemia is a rare genetic disease characterized by reduced or absent production of functional β-globin necessary to form adult hemoglobin [1]. This results in impaired red blood cell function, leading in severe cases to chronic

anemia, serious morbidity, and a shortened lifespan compared with the general population [1]. Individuals with the most severe form of the disease, transfusion-dependent β-thalassemia (TDT), are reliant on regular blood transfusions [1].

The need for regular blood transfusions and daily chelation therapy to reduce transfusion-related iron overload can be burdensome for individuals with TDT and their families. This is driven by factors such as the high amount of time spent managing the condition, time spent in the healthcare setting [2, 3], out-of-pocket treatment costs [4, 5], and the management of adverse events [1].

It is important to further understand this burden to inform improvements in long-term care and health-related quality of life (HRQoL) in individuals with TDT. However, there is currently little high-quality evidence on which to act. Although multiple studies have evaluated HRQoL in TDT [6–16], only a handful have employed disease-specific instruments [13–16]. Additionally, little evidence has been collected in the real-world setting. There is, therefore, a need for real-world data on disease burden and HRQoL in individuals living with TDT.

We report on a real-world smartphone-based study exploring the burden of TDT from the patient and informal caregiver perspective. The objectives were to evaluate the real-world disease-management and symptom burden of the condition, as well as the HRQoL of individuals with TDT in Italy, the UK, and the USA.

2 Methods

2.1 Study Design

We conducted a prospective, observational, longitudinal, real-world, patient-reported outcome (PRO) study. Adults with TDT and informal caregivers of adolescents with the condition used a bespoke smartphone application (app) developed for the study, myThalLog (Vitaccess Limited, London, UK), to enter daily data about their or their dependent's TDT, its management, and its impact on their lives, over a period of 90 days. Ethics approval was granted by a central independent institutional review board (Salus Institutional Review Board, Austin, TX, USA).

2.2 Participants

Adults (aged ≥18 years) with TDT and caregivers of adolescents aged 12–17 years with TDT were eligible to participate in the study. Transfusion-dependent β-thalassemia was defined as a participant-reported diagnosis of β-thalassemia that, at the time of enrollment, was treated with a blood transfusion at least every 6 weeks. Exclusion criteria were prior receipt by the individual with TDT of an allogeneic hematopoietic stem cell transplant or participation in a gene therapy clinical trial.

2.3 Recruitment, Screening, and Enrollment

Participants were recruited from Italy, the UK, and the USA. Recruitment was community based, with potential participants made aware of the study via patient advocacy group communications, social media, and word of mouth. The myThalLog app was made available to the public in Google Play and the Apple App Store on the following dates: USA: 23 August 2018, UK: 17 October 2018, Italy: 27 November 2018. Enrollment was permitted at any time between the app launch and 90 days prior to the study closure on 30 September 2019.

Potential participants downloaded myThalLog onto their phones, before completing an in-app screening survey to check their eligibility. They then provided informed consent by reading and acknowledging their agreement with on-screen briefing and informed consent materials.

The digital app-based study approach was selected for several reasons. We hypothesized that online study promotion, and the ability for participants to enroll at home using their own devices, could drive rapid recruitment, as well as geographic and demographic diversity [17, 18]. Additionally, as smartphone apps can allow participants to enter data at times and places convenient to them, we hoped that this approach would promote data granularity and completeness, with a low impact of recall bias [18].

2.4 Data Acquisition

Participants were asked to provide data about their HRQoL, symptoms, and TDT management over a period of 90 days, via a selection of validated PRO instruments and bespoke surveys. Patient-reported outcome instrument and survey selection was based on (1) a targeted review of the literature, including previous research evaluating PROs in TDT and other indications requiring transfusions (e.g., Porter et al. [19]; Trachtenberg et al. [20]), (2) interviews with individuals who had TDT, and (3) a review of PRO-instrument databases (e.g., PROQOLID, https://www.eprovide.mapi-trust.org/). The literature review identified concepts that were important to individuals with TDT, including symptoms (e.g., pain, lack of energy/fatigue), the impact on the patient's ability to maintain their day-to-day role, and the impact on broader aspects of life, including physical, emotional, psychological, and social health [15, 21]. Ultimate selection of instruments was driven by their ability to measure these concepts of interest, and suitability for administration via a smartphone app. No instrument could be identified that adequately evaluated the burden of time

spent by patients and caregivers on TDT management. For this concept, a bespoke disease-management survey was developed, details of which are provided below. Copies of PRO instruments were evaluated for representation of the concepts of interest, evidence of content validity, and psychometric properties. The shortlist of instruments demonstrated good representation of important concepts, good psychometric measurement properties, and avoided the overlap of concepts, thus reducing respondent burden. Two TDT patient advocates reviewed the proposed instruments and provided feedback on their relevance to people with the condition. The advocates were chosen because they had strong networks of other individuals with TDT with whom they could consult on this topic, and a good understanding of the research process. Following their feedback, final instrument selection was made. Patient-reported outcome instruments and surveys presented to study participants were as follows.

2.4.1 Background Survey

A bespoke background survey asked participants about demographics, thalassemia characteristics, and the diagnosis and treatment of the individual with TDT. Participants were asked to complete the survey once, immediately following enrollment.

2.4.2 Brief Fatigue Inventory

The BFI was originally developed to assess fatigue in patients with cancer [22]. The tool has since been validated and used to assess fatigue in many indications and population groups [23–29], including people receiving blood transfusions and those with hemoglobinopathies [30, 31]. In this study, the BFI was completed by adults with TDT and by caregivers acting as proxies for their dependents. Participants were asked to compete the full BFI once, immediately following enrollment, and the "worst fatigue" question, which asks respondents to rate their fatigue at its worst in the past 24 h, daily. The "worst fatigue" question was presented to participants as part of a question pair, at the same time as the Brief Pain Inventory Short Form (BPI-SF) "worst pain" question.

2.4.3 Transfusion-Dependent Quality-of-Life Questionnaire

The Transfusion-dependent Quality of life questionnaire (TranQol) is a TDT-specific survey used to assess HRQoL across the following domains: emotional health, family functioning, career/school functioning, and physical health [15]. The TranQol was completed by adults with TDT and by caregivers acting as proxies for their dependents. Participants were asked to complete the survey once, immediately following enrollment.

2.4.4 Disease-Management Survey

A bespoke disease-management survey assessed daily time spent on TDT management. Participants were asked to report time spent on transfusion-related activities, including travel, waiting time, and transfusion duration, plus any other disease-management activities they had carried out that day. Time for these additional activities was reported by selecting the relevant activity from a list of potential tasks. Two versions of the survey were developed: adult TDT patient self-report and adolescent caregiver report. The caregiver version asked participants to report time spent by just their dependent on transfusion-related activities, and time spent by both themself and their dependent on any other disease-management activities (i.e., the total combined time for both people). Participants were asked to complete the survey daily. A copy of this is available as Electronic Supplementary Material.

2.4.5 Brief Pain Inventory Short Form

The Brief Pain Inventory (BPI) was originally developed to assess pain in patients with cancer [32]. The tool and its short-form version, the BPI-SF, have since been validated and used to assess fatigue in many indications and population groups[33–37]. Participants were asked to complete only the "worst pain" question, which asks respondents to rate their pain at its worst in the past 24 h. The question was completed by adults with TDT and by caregivers acting as proxies for their dependents. Participants were asked to complete the question daily. It was presented as part of a question pair, at the same time as the BFI "worst fatigue" question.

2.4.6 Survey Administration and Completion

Participants were asked to complete all PRO instruments and surveys at enrollment. They were then asked to complete the disease-management survey, and BFI "worst fatigue" and BPI-SF "worst pain" question pair daily over the 90-day study period. Within each data entry window, participants were able to respond to the surveys at times of their choosing and complete them in any order. Missing the data entry window, submitting an incomplete survey, or failing to complete all the required surveys on any day did not prevent continued participation.

To encourage survey completion, participants were rewarded with virtual tokens (stars and medals), which could be collected and redeemed for Amazon digital vouchers, up to a maximum value of US$450, or equivalent. The effectiveness of positive token economies in promoting and maintaining desired behavior is well established [38], with mobile app technology permitting sophisticated and effective implementation via "gamification" [39].

2.5 Statistical Analysis

Analysis was exploratory, to understand the distribution of the data, rather than to test specific hypotheses. All data were aggregated and pseudonymized prior to analysis. Participants were included in the analysis if they responded to at least one item in any survey at any time. Each survey was analyzed independently, with participants included in the analysis for a particular survey if they responded to at least one item in that survey at any required time point.

Results for the disease-management survey were calculated separately for days on which participants did or did not report receiving transfusions: transfusion days and non-transfusion days. For the BFI "worst fatigue" and BPI-SF "worst pain" questions, individual participant scores were analyzed for the period 5 days pre- and post-transfusion, as calculated from transfusion dates reported in the disease-management survey.

Patient-reported outcome instruments were scored as per their scoring manuals. Minimal clinically important differences (MCIDs) for changes in BFI "worst fatigue" and BPI-SF "worst pain" scores were based on those for similar disease populations, as disease-specific MCIDs were not available.

3 Results

3.1 Participants

Eighty-five participants responded to at least one item in any survey and were included in the analysis. Eighty-one identified as adults with TDT (β-thalassemia treated with blood transfusions at least every 6 weeks) and four identified as caregivers of adolescents with TDT. Participant flow is presented in Fig. 1.

For surveys that were presented daily during the study, participants responded on average just under half of the time (mean proportion of days completed: disease-management survey 45.1%, BFI "worst fatigue" and BPI-SF "worst pain" question pair 44.6%). Almost one-quarter of participants responded to these surveys every time they were presented (disease-management survey 24.3% of participants, BFI "worst fatigue" and BPI-SF "worst pain" question pair 23.4% of participants).
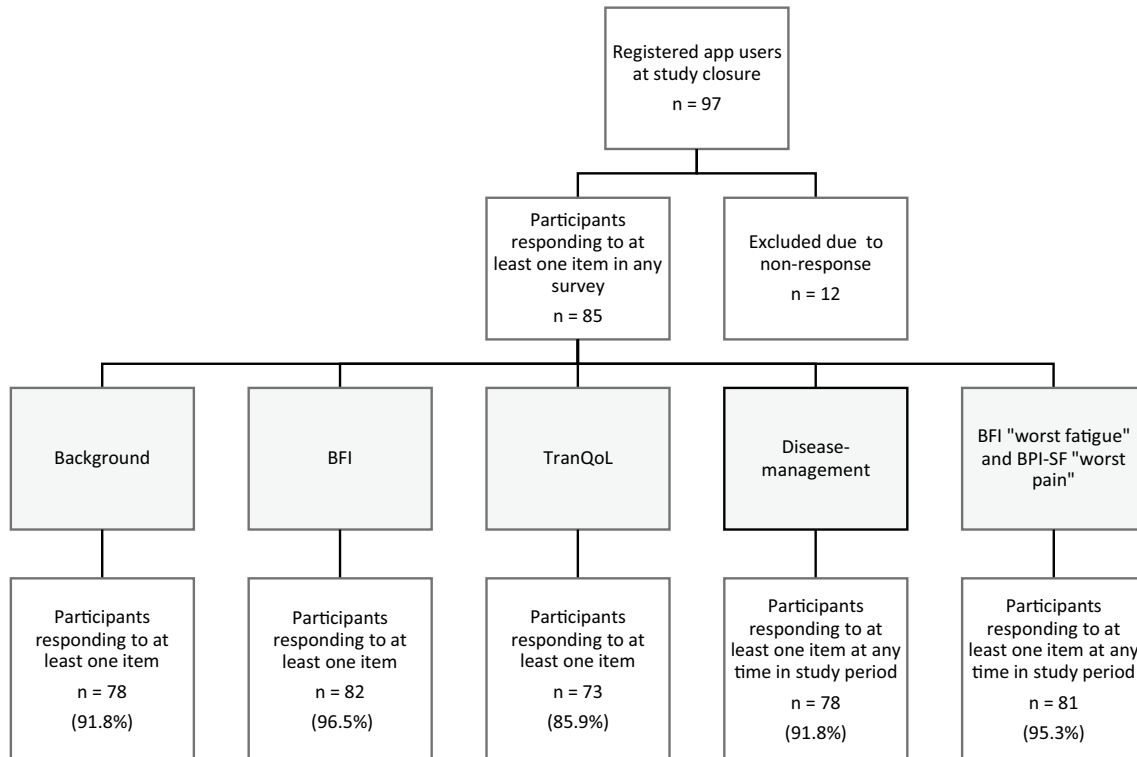
Brief Fatigue Inventory, *BPI-SF* Brief Pain Inventory Short Form, *TranQol* Transfusion-dependent Quality of life questionnaire

Fig. 1 Participant flow

3.2 Demographics

Demographic and clinical characteristics of all individuals with TDT in the overall analysis population (self-reported, $n = 81$; caregiver reported, $n = 4$) are provided in Table 1.

3.3 Brief Fatigue Inventory

Eighty-two participants responded to at least one item in the BFI. The BFI score distribution is presented in Fig. 2a. Mean BFI score at enrollment was 5.0 (standard deviation [SD] 3.0; 0–10 scale; 10 = worst symptoms).

3.4 Transfusion-Dependent Quality-of-Life Questionnaire

The TranQol score distribution is presented in Fig. 2b. Mean overall and domain scores are presented in Fig. 3. Mean TranQol score at enrollment was 51 (SD 20; 0–100 scale; 100 = best HRQoL).

3.5 Disease-Management Survey

3.5.1 Transfusion Frequency

Mean transfusion frequency during the 90-day study period was every 3.2 weeks (SD 1.5). The distribution of transfusion frequencies is presented in Fig. 2c.

3.5.2 Disease-Management Time

Daily time spent on TDT management on transfusion and non-transfusion days is presented in Table 2. On transfusion days, the mean daily time spent was 592 min (SD 349 min) or 9.8 h. The activities associated with the greatest mean time were transfusions (352 min) and organizing payments from health insurance (152 min). On non-transfusion days, the mean daily time spent on TDT management was 91 min (SD 221 min). This is equivalent to approximately 11 h per week in weeks without a transfusion. The activities associated with the greatest mean time were type- or cross-matching of blood (105 min per day) and arranging childcare (99 min).

On non-transfusion days, differences in the time spent on TDT management were seen between individuals who were receiving chelation via an infusion and those receiving oral therapy; Table 3. The mean daily time spent on TDT management by individuals receiving infused chelation and their caregivers on non-transfusion days was 336 min (SD 377 min). Over the course of a week, this equated to 39 h. For individuals receiving oral chelation and their caregivers, the mean daily time spent was 25 min (SD 49 min). Over a week, this equated to 3 h.

Table 1 Demographic and clinical characteristics of individuals with transfusion-dependent β-thalassemia

Variable	n (%)
Overall analysis population	85 (100.0)
Country of residence[a]	
UK	58 (68.2)
USA	20 (23.5)
Italy	6 (7.1)
Germany[b]	1 (1.2)
Sex	
Female	45 (52.9)
Male	32 (37.6)
Not reported	8 (9.4)
Ethnicity	
Indian	16 (18.8)
Asian	9 (10.6)
Other	9 (10.6)
Pakistani	9 (10.6)
White	9 (10.6)
Any other Asian background	6 (7.1)
Southern European	4 (4.7)
Arab	3 (3.5)
Bangladeshi	3 (3.5)
Black or African American	2 (2.4)
Chinese	2 (2.4)
African	1 (1.2)
Any other Black/African/Caribbean background	1 (1.2)
Northern European	1 (1.2)
Prefer not to answer	2 (2.4)
Not reported	8 (9.4)
Age, years	
Median	37.0
Range	13–71
Current thalassemia type	
Major	70 (82.4)
Intermedia	6 (7.1)
Unknown	1 (1.2)
Not reported	8 (9.4)
Usual transfusion frequency, weeks	
Mean	3
Standard deviation	1
Median	3
Range	1–4
Chelation therapy	
Oral	44 (51.8)
Infusion	18 (21.2)
Both oral and infusion	14 (16.5)
Don't know/can't remember	1 (1.2)
Not reported	8 (9.4)

[a]Seventy-eight of 85 participants completed at least one question in the background survey; participants not responding to certain items are labeled as 'not reported', apart from for the item 'country of residence', for which participant numbers could be derived from app download data

[b]One caregiver using the app in the UK reported their dependent's country of residence as Germany

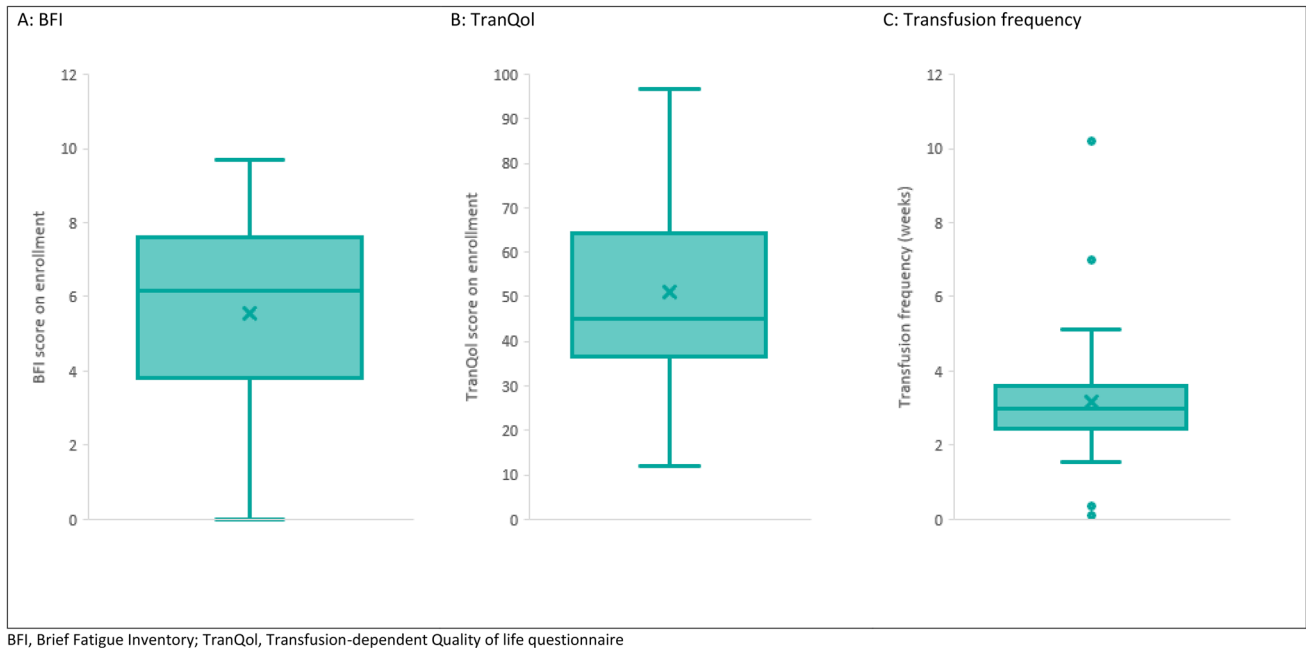BFI, Brief Fatigue Inventory; TranQol, Transfusion-dependent Quality of life questionnaire

Fig. 2 Distributions: Brief Fatigue Inventory (BFI) score, Transfusion-dependent Quality of life questionnaire (TranQol) score, and transfusion frequency
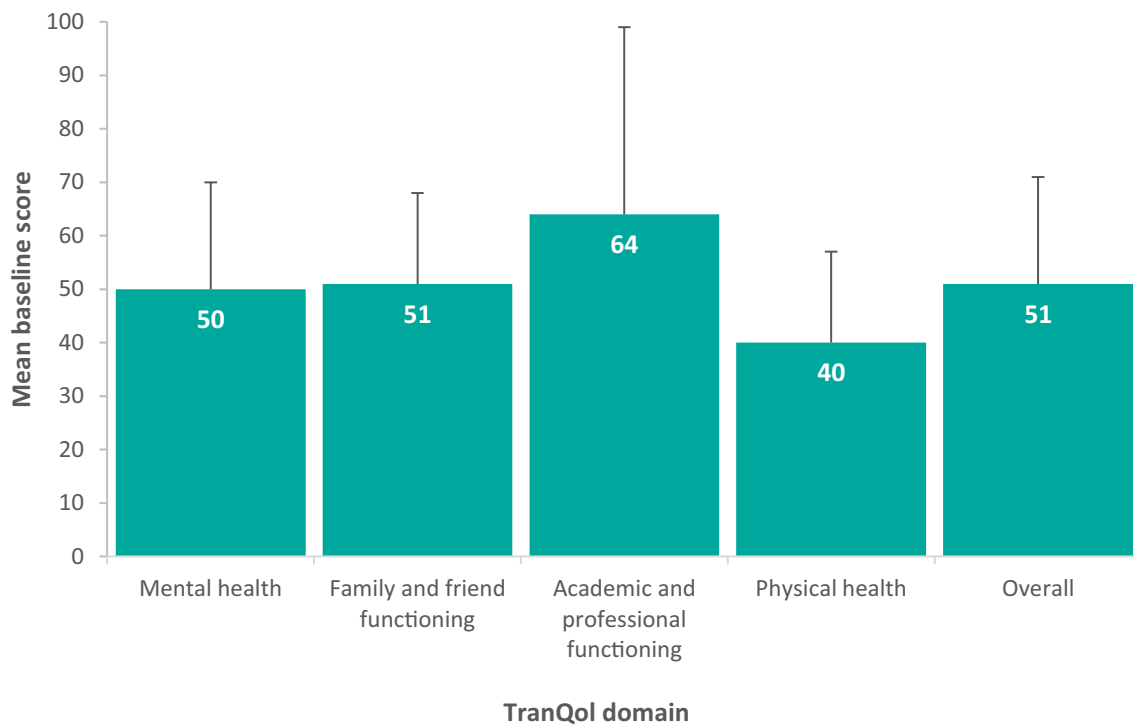

Fig. 3 Transfusion-dependent Quality of life questionnaire (TranQol) overall and domain scores. Error bars indicate standard deviation

Differences in the time spent on TDT management were also observed between participants from the UK and USA. A comparison with Italy was not feasible owing to the very low number of participants. Participants in the USA spent more time each day on TDT management than did participants in the UK (USA: mean 164 min [SD 387 min], UK: mean 107

Table 2 Daily time spent on transfusion-dependent β-thalassemia management activities: comparison between transfusion and non-transfusion days

Variable	Activity											
	Arranging childcare	Making appointments for transfusion	Blood type- or cross-matching	Preparing and taking chelators	Organizing medicines	Organizing insurance payments	Organizing time off	Traveling from transfusion	Traveling to transfusion	Waiting for transfusion	Transfusion duration	Total
Transfusion days												
Respondents, n	3	35	11	40	32	2	11	58	58	58	58	60
Daily time spent, min[a]												
Median	72	10	45	10	15	152	20	60	60	30	300	494
Range	15–188	0–780	0–200	0–960	0–360	5–300	3–300	0–960	0–1200	0–720	0–1140	0–1410
Mean	83	34	62	97	35	152	45	69	78	67	352	592
Standard deviation	64	108	61	242	62	209	73	75	98	82	237	349
Non-transfusion days												
Respondents, n	13	46	38	53	52	3	24	–	–	–	–	61
Daily time spent, min[a]												
Median	30	15	98	10	20	35	20	–	–	–	–	15
Range	0–600	0–630	0–900	0–1140	0–1020	10–60	5–480	–	–	–	–	0–1140
Mean	99	30	105	84	37	39	44	–	–	–	–	91
Standard deviation	142	58	99	225	68	19	69	–	–	–	–	221

[a]Time for each activity includes only participants who reported a time value for that activity; total time includes all participants who reported a time value for any activity

Table 3 Daily time spent on transfusion-dependent β-thalassemia management activities: non-transfusion days, comparison between infused and oral chelation

Variable	Activity							
	Arranging childcare	Making appointments for transfusion	Blood type- or cross-matching	Preparing and taking chelators	Organizing medicines	Organizing insurance payments	Organizing time off	Total
Infused chelation								
Respondents, n	2	11	5	11	11	0	7	11
Daily time spent, min[a]								
Median	120	10	120	75	20	–	30	80
Range	60–240	3–70	3–215	0–1140	3–300	–	10–120	0–1140
Mean	129	18	118	350	52	–	40	336
Standard deviation	73	20	58	383	64	–	28	377
Oral chelation								
Respondents, n	7	24	23	29	30	3	12	36
Daily time spent, min[a]								
Median	30	15	120	5	20	35	20	10
Range	0–240	0–630	2–900	0–600	0–1020	10–60	5–480	0–722
Mean	41	34	118	11	36	39	42	25
Standard deviation	54	69	111	21	76	19	76	49

[a]Time for each activity includes only participants who reported a time value for that activity; total time includes all participants who reported a time value for any activity

min [SD 250 min]). This difference was driven by higher mean time spent organizing insurance payments (USA: 57 min, UK: 0 min), traveling to, from, and waiting for transfusions (USA: 277 min, UK: 191 min), and the duration of transfusion itself (USA: 597 min, UK: 271 min).

3.6 Brief Fatigue Inventory "Worst Fatigue" and Brief Pain Inventory Short Form "Worst Pain" Questions

Across the 5-day periods pre- and post-transfusion, 63 participants responded to the BFI "worst fatigue" and BPI-SF "worst pain" question pair.

3.6.1 Brief Fatigue Inventory "Worst Fatigue"

"Worst fatigue" scores for the 5-day periods pre- and post-transfusion are presented in Fig. 4. Mean "worst fatigue" score was 5.05 (SD 2.83) in the 5 days pre-transfusion, 5.55 (SD 2.95) on transfusion days, and 4.29 (SD 2.81) in the 5 days post-transfusion (0–10 scale; 10 = worst symptoms). The difference between mean scores on transfusion days and post-transfusion met the threshold for clinical relevance; MCID: 1 point [40].

3.6.2 Brief Pain Inventory Short Form "Worst Pain"

"Worst pain" scores for the 5-day periods pre- and post-transfusion are presented in Fig. 5. Mean "worst pain" score was 4.33 (SD 2.93) in the 5 days pre-transfusion, 4.93 (SD 3.09) on transfusion days, and 3.85 (SD 2.92) in the 5 days post-transfusion (0–10 scale; 10 = worst symptoms). The difference between mean scores on transfusion days and post-transfusion did not reach the threshold for clinical relevance; MCID: 2 points [41].

4 Discussion

In this international study of adults with TDT and caregivers of adolescents with TDT, the participant-reported burden of disease was considerable. Overall fatigue levels were moderate and HRQoL was low. Time spent on disease management was high, both on transfusion and non-transfusion days. The worst levels of fatigue and pain experienced by individuals with TDT increased in the lead-up to transfusion, before dropping post-transfusion.

The daily time burden facing individuals with TDT and their caregivers was considerable and multifaceted. Mean time spent on disease management was high, particularly
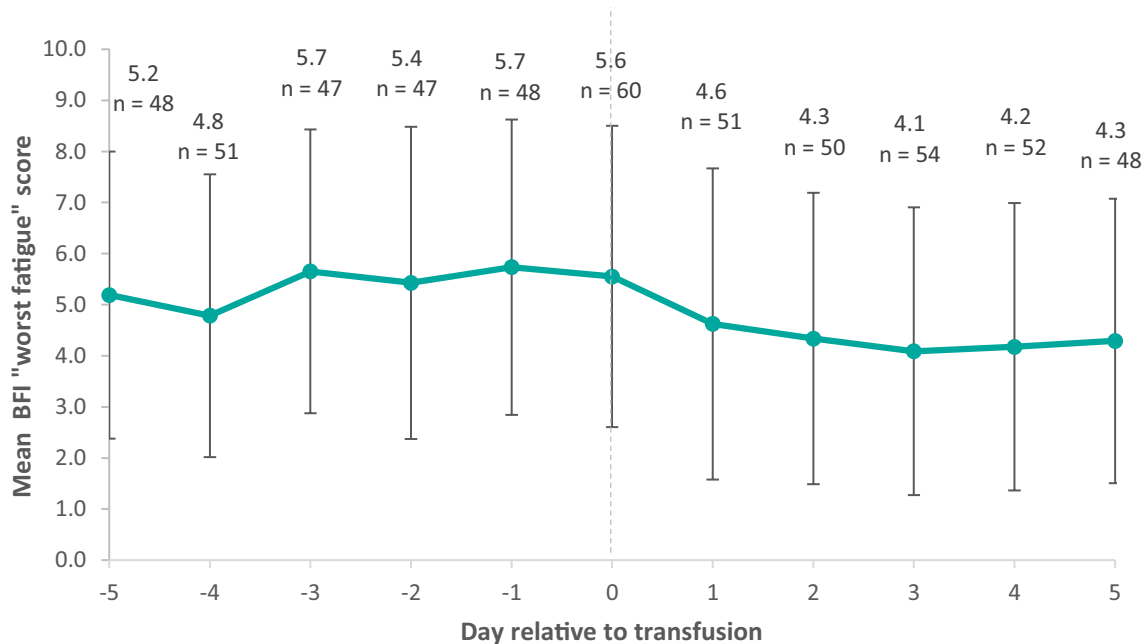
Fig. 4 Brief Fatigue Inventory (BFI) "worst fatigue" score relative to transfusion day. *Error bars indicate standard deviation*
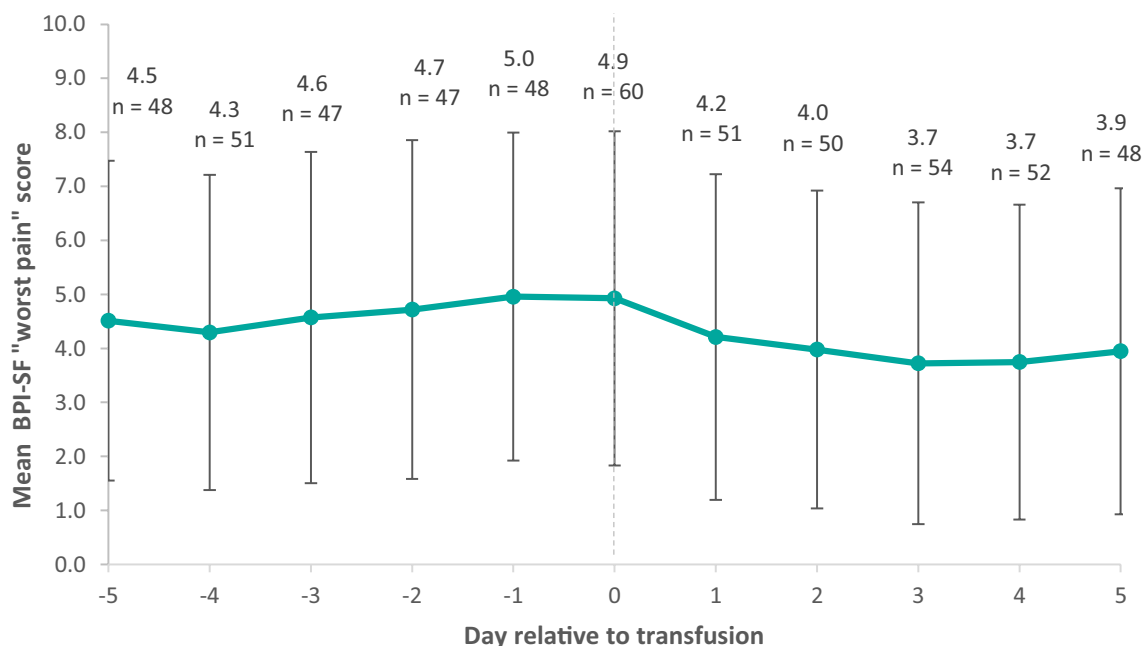

Fig. 5 Brief Pain Inventory Short Form (BPI-SF) "worst pain" score relative to transfusion day. Error bars indicate standard deviation

on transfusion days. Alongside transfusions, organizing payments from health insurance, type- or cross-matching of blood, and arranging childcare were key drivers of time burden. Few other studies have measured the time taken by people with chronic diseases to carry out a comprehensive range of health-related activities [42]. However, the available evidence is consistent with the level of burden we observed,

with one review concluding that many people with chronic diseases and their informal caregivers may both be spending at least 2 h per day on disease management, with some diseases, such as diabetes mellitus, imposing greater time burdens [42].

Overall, fatigue in individuals with TDT, as measured by the BFI, was higher than observed elsewhere in healthy

controls (5.5, compared with 2.3 for controls) [43], and similar to levels seen in other chronic diseases where time and disease burden are high, including Crohn's disease (4.2) [43], ulcerative colitis (4.1) [43], and rheumatoid arthritis (7.3) [44]. We also saw that the mean worst daily levels of fatigue experienced by individuals with TDT increased in the lead-up to transfusion, before dropping post-transfusion. Although fatigue is a common symptom of TDT, there is an absence of published studies analyzing fatigue in the condition, thus we have been unable to make meaningful comparisons of our results with those of other TDT populations.

Overall HRQoL, as measured by the TranQol, was worse than has been reported previously for TDT populations in North America (51.0, compared with 71.0 for North American patients) [15]; however, it was similar to levels reported in Middle Eastern studies (48.3–58.9) [13, 14, 16]. In our study, respondents' physical functioning domain scores were lowest, mental and family and friend functioning scores were moderate and similar, while academic and professional functioning scores were higher. These differences in domain scores could provide potential target areas for improvements in TDT care.

In our study, the mean worst daily levels of pain experienced by individuals with TDT, as measured by the BPI-SF "worst pain" score, increased in the 5-day period leading up to transfusion, before dropping in the 5-day post-transfusion period. This pattern appears to align with the known waning and rising of hemoglobin levels prior to and following transfusion [1]. Other studies evaluating BPI-SF scores in patients with thalassemia have reported similar levels of pain to those seen in our study. An analysis of North American patients with thalassemia (the majority with β-thalassemia) enrolled in the Thalassemia Clinical Research Network's Pain Survey reported mean "worst pain" scores of 5.8 over the 9-month study period [45]. In another analysis of the same population, almost half of participants cited blood transfusions as an activity that decreased pain levels [46], which supports the pattern of rising and decreasing pain pre- and post-transfusion that we observed [1].

Several limitations of our study design must be considered when interpreting the results. First, given the app-based approach, the population was restricted to confident smartphone users. This may have excluded some potential participants who were older, lacked access to a smartphone, or had difficulties with vision or dexterity.

The remote app-based approach meant that participant eligibility and accuracy of data could not be directly verified by a clinician. However, the associated risks to data quality were minimized by asking participants specific eligibility questions, setting rules for question responses, and performing checks on the data (e.g., identification and potential removal of outliers) prior to analysis.

Our study was also limited by the fact that each survey was analyzed independently, with participants included in the analysis if they responded to that particular survey, rather than if they responded to all surveys or, at a minimum, the background demographic survey. Caution must therefore be taken when making comparisons between the results of different surveys, as the populations may have been slightly different. However, as at least 73 of the 97 participants registered for the study app responded to each survey, the overlap between survey populations was high, thus this limitation is likely to have had little impact on overall conclusions.

Another factor limiting the quality of our study results was the use of a novel disease-management survey. Although the survey was reviewed by individuals with TDT during development, it was not formally validated. Analysis of survey responses identified several problems. For instance, because participants first had to select certain activities before reporting time data for them, there was no way of being certain whether an absence of data indicated no time spent, non-response to that part of the survey, or the accidental failure to select an activity in the list of available options. Additionally, participants were not asked whether they had dependent children, thus it was difficult to interpret whether the absence of time spent on childcare was because TDT had no impact on time spent, or because the participant had no children. Further refinements and validation would therefore be recommended before the survey was used in future research.

One final area of the study design that may have had undesired effects was the financial reward system used to encourage participant engagement. Financial rewards carry a risk of undermining intrinsic motivation [47], and may encourage false reporting, so must be used carefully. However, the previously mentioned efforts made to verify eligibility and ensure data accuracy reduced the risk of negative consequences.

Although the app-based approach taken in this study introduced several potential limitations, it did provide some advantages over in-person methods, which should be noted. The ease with which participants could learn about the study, enroll, and contribute data promoted a diverse and complete dataset, while digital data management and analysis reduced administrative burden and opportunities for human error.

5 Conclusions

The patient- and caregiver-reported burden of TDT is high, strongly influenced by disease-management time, fatigue and pain symptoms, and impairment to quality of life. The level of burden appears to differ across the TDT population, driven by differences in treatments received and country-specific differences in healthcare systems. It is apparent that

there remains a high unmet need in TDT caused by the burden on patients and their caregivers.

Declarations

Conflict of interest Clark Paramore is a paid employee of bluebird bio. Laurice Levine is a patient advocate who has received consulting fees from bluebird bio. Emma Bagshaw, Chengyu Ouyang, and Amber Kudlac are paid employees of Vitaccess Ltd; Mark Larkin is the CEO of Vitaccess Ltd. Vitaccess Ltd was paid by bluebird bio to run this study and develop this article. Vitaccess Ltd has also received payment from bluebird bio for consulting not directly related to this article.

Ethics approval Ethics approval for this study was granted by a central independent institutional review board (Salus Institutional Review Board, Austin, TX, USA). The study was performed in accordance with the Declaration of Helsinki.

Consent to participate All participants provided informed consent to take part in this study via the myThalLog app.

Consent for publication All participants provided consent for the publication of de-identified, aggregated data from the study.

Availability of data and material Study data are available on request by contacting Vitaccess Ltd.

Authors' contributions AK, ML, LL, and CP contributed to the design of the study and data acquisition strategy. CO and AK led the data analysis. EB assisted with the data analysis and interpretation and drafted this manuscript. All authors reviewed the manuscript, provided feedback, and approved the version to be published.

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