



Original Article

Development of a new disease severity scoring system for patients with non-transfusion-dependent thalassemia



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ABSTRACT

Background: Patients with non-transfusion-dependent thalassemia (NTDT) present with a spectrum of disease severities. Since there are multiple pathophysiologies in such patients, tailoring treatment remains essential. Therefore, one simple, reliable tool would be beneficial to assess disease severity and tailor therapy, particularly for internal medicine specialists who may treat a variety of NTDT patients with a multitude of complications. This would allow for standardization of assessments leading to timely interventions and prevention of complications. **Methods:** A working group of NTDT experts was formed to develop a new disease severity scoring system for adult and pediatric patients with NTDT, based on parameters considered to be most pertinent in defining disease severity.

Results: 20 parameters were selected for inclusion in the disease severity scoring system. An additional six parameters, largely related to growth and development, were selected specifically for pediatric patients (≤ 16 years of age). Consensus of expert opinion was used to establish the selected methods of assessment for each parameter, based on feasibility and availability of technology, cost containment, and avoidance of patient risk.

Conclusion: We propose that this new disease severity scoring system for adult and pediatric NTDT patients could be developed into a practical tool for widespread clinical use.

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1. Introduction

Thalassemias are a group of inherited hemoglobin disorders characterized by impaired erythropoiesis, anemia and hypoxia due to defective α - or β -globin chain synthesis [1–4]. There are a number of clinical phenotypes with marked differences in symptom severity and treatment requirements observed – from clinically asymptomatic thalassemia trait, to severe anemia and transfusion dependence in β -thalassemia major – as a result of varying degrees of dysfunction in globin chain production [1–4]. Falling between the phenotypes of

thalassemia trait and β -thalassemia major, non-transfusion-dependent thalassemia (NTDT) patients do not require regular transfusions for survival, but may require transfusions during periods of stress such as infection, pregnancy or surgery [5–7]. The primary forms of NTDT include β -thalassemia intermedia, hemoglobin (Hb) E/ β -thalassemia and HbH disease, which are predominant in low- and middle-income regions, including parts of Africa (β -thalassemia intermedia), Southeast Asia (HbE β -thalassemia and HbH disease), East India and Bangladesh (HbE β -thalassemia). However, as a result of population migration, an increasing prevalence of NTDT has been observed in more developed regions, such as the USA and Europe, and is therefore becoming a worldwide health problem [2,7,8].

Patients with NTDT present with a broad spectrum of severities often influenced by environmental and genetic modifiers, from mild clinical presentation to severe symptoms, such as retardation of growth and development, and skeletal deformities [2,4,9–16]. Considerable differences in the attitude of clinicians regarding when it is best to treat or when to observe these patients also exist. Morbidity in NTDT is directly linked to the severity of ineffective erythropoiesis and peripheral

Abbreviations: ALT, alanine aminotransferase; dw, dry weight; ELISA, enzyme-linked immunosorbent assay; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; LIC, liver iron concentration; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; N/A, not available; MCID, minimum clinically important difference; NTDT, non-transfusion-dependent thalassemia; NYHA, New York Heart Association; PHT, pulmonary hypertension; QoL, quality of life; RNA, ribonucleic acid; SF, serum ferritin; TRV, tricuspid regurgitation jet velocity; ULN, upper limit of normal.

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hemolysis [17]. Expansion of the erythron as a result of ineffective erythropoiesis can lead to osteoporosis and bone deformities, hepatosplenomegaly and also extramedullary hematopoietic pseudotumors [15]. Abnormalities of platelets and pathological red blood cells can lead to a hypercoagulable state with increased thrombotic risk in patients with NTD [18–20], as well as pulmonary hypertension [21,22], and leg ulcers [23,24]. Secondary to ineffective erythropoiesis, excess body iron accumulates as a result of increased gastrointestinal iron absorption alongside occasional blood transfusions, which also has a major etiological role in many complications [14–16,24–26]. Furthermore, with the progressive accumulation of iron over time, complications increase with advancing age [23], thus highlighting the importance of effective patient monitoring and early treatment intervention.

With this multiplicity of pathophysiologies and associated complications, one tool to evaluate patients on an individual basis is needed, with a view to initiating timely interventions that would prevent any further complications. A simple and reliable method of assessing disease severity would be useful in guiding management decisions in clinical practice, as summarized in Fig. 1. This would be particularly useful for internal medicine specialists who may treat a variety of NTD patients with a multitude of complications.

A disease severity scoring system expresses an integrated assessment of the burden of disease in a given patient using a defined data set to comprehensively score the patient. Groups of domains populated with non-redundant items to be included within the scoring system need to be valid and reliable. Each item also needs to be easily captured using feasible, standardized methods of assessment, and weighted based on clinical relevance, including associated morbidity and mortality. Disease severity scoring systems have been developed and implemented successfully for a number of chronic diseases, including type I Gaucher disease and rheumatoid arthritis [27–30]. Other systems for grading the severity of NTD have been proposed [31,32]; however, they were designed for use in patients with β -thalassemia intermedia or β -thalassemia/HbE disease only and were based on a limited number of parameters. Furthermore, some clinical criteria were based on the treating physician's judgment (i.e., age at first blood transfusion and requirement for regular blood transfusion), making it impractical to use when physicians employ different transfusion regimens. An accurate and comprehensive disease severity scoring system is yet to be developed and validated for patients with NTD for widespread use in routine clinical practice. Therefore, a working group of NTD experts was formed to develop a new disease severity scoring system for adult and pediatric patients with NTD. Once validated, we intend this to be developed into a practical tool for widespread clinical application. Here, we describe the methodology employed in generating this new NTD disease severity scoring system. Details regarding the testing of the

instrument for validity, reliability and feasibility will be published separately.

2. Methods

2.1. Instrument development and selection of domains

A Disease Severity Scoring System working group comprising eight global NTD experts, was formed (M. Domenica Cappellini, Ali T. Taher, Antonis Kattamis, Vip Viprakasit, John B. Porter, Khaled M. Musallam, Renzo Galanello and David J. Weatherall). The novel scoring system was constructed based on parameters thought to be most pertinent by these experts in defining disease severity in NTD patients, based on their clinical experience and expertise. The impact of each parameter on disease severity and appropriate thresholds was decided upon either according to published literature or the expertise of the group, based on an association with worse outcomes. Parameters were then assigned a severity weighting according to the extent that morbidity and mortality in that parameter contributes to disease severity in NTD patients. Temporal aspects of each parameter were also considered; for example, which are important at (or near) the time of assessment, and which are important over the course of the disease, irrespective of when they occurred. As such, parameters may indicate a more severe status if defined as 'currently active'.

The disease severity scoring system was thus developed based on group consensus comprising general parameters for all patients (adult and pediatric patients; Table 1A), with additional parameters specifically for pediatric patients only (Table 1B).

3. Results

In total, 20 parameters were finally selected by the Working Group for inclusion in the disease severity scoring system for the screening of NTD patients (Table 1A). An additional six parameters, largely related to growth and development, were selected specifically for pediatric patients (≤ 16 years of age; Table 1B). Each parameter contains two or more items that would be scored individually by the evaluating physician. The domain score would then be tabulated by summing the score for all parameters. The total score would be the sum of the domain scores, with a maximum of 52 points for adult patients and 62 points (52 + additional 10) for pediatric patients.

Consensus of expert opinion was also used to establish the selected methods of assessment for each parameter, based on feasibility and availability of technology, cost containment, and avoidance of patient risk. Thus, tools that are uniformly available, practical in terms of standard of care, and for which there is a near consensus of global standardization were selected. Patient quality of life (QoL) in particular was considered too challenging to standardize. The Working Group suggested that evaluation is usually conducted outside of standard care and therefore this domain was not included in the scoring system but may be used later for validation. Similarly, investigational parameters, such as non-transferrin-bound iron and hepcidin, were not included as they are not yet well established and methodology is not routinely available. Furthermore, factors introduced as part of physician intervention (e.g., splenectomy, transfusion, iron chelation, fetal hemoglobin induction and other methods of treatment for specific complications) were excluded from the system as the score was designed to capture only the natural history of disease; assessing its dynamic changes upon external interventions would occur in later stages of validation and development.

4. Discussion

As a result of the clinical heterogeneity and progressive accumulation of complications in patients with NTD, the management of patients cannot be simply generalized. Patients with NTD need to be

Requirements for an NTD patient evaluation tool

- ✓ Assess patient status
- ✓ Guide therapy initiation
- ✓ Monitor disease progression
- ✓ Monitor treatment response
- ✓ Classify disease subgroups
- ✓ Compare outcomes among patients with similar levels of disease severity

Fig. 1. Summary of the requirements for a tool to evaluate patients with NTD.

Table 1
Disease severity scoring system for patients with non-transfusion-dependent thalassemias.

A. All patients ^a			
Parameter	Item	Score	Remarks
<i>Hematological and iron status</i>			
Hemoglobin [16,32]	>10 g/dL	0	– Current or last available (within 3 months)
	>7 and ≤10 g/dL	1	
	>5 and ≤7 g/dL	2	
	≤5 g/dL	3	
Platelets	Normal (150,000 to 400,000/mm ³)	0	– Current or last available (within 3 months)
	<150,000/mm ³	1	
Iron overload [33,34]	>400,000/mm ³	2	
	LIC ≤ 3 mg Fe/g dw or SF ≤ 300 ng/mL	0	– Current or last available (within 6 months for LIC and within 3 months for SF)
	LIC > 3 to ≤5 mg Fe/g dw or SF >300 to ≤800 ng/mL	1	
	LIC > 5 to ≤7 mg Fe/g dw or SF >800 to ≤1500 ng/mL	2	– If both measurements (LIC and SF) are available, determination of LIC supersedes SF
	LIC > 7 to ≤15 mg Fe/g dw or SF >1500 to ≤2500 ng/mL	3	– For patients with a score of 0–3, add 1 point for any historical record of LIC > 15 mg Fe/g dw or SF > 2500 ng/mL
	LIC > 15 mg Fe/g dw or SF > 2500 ng/mL	4	
<i>Liver status</i>			
ALT	Normal (<3 × ULN)	0	– Current or last available (within 3 months)
	>3 × ULN	1	
Liver disease	Absent	0	– Current or any history
	Fibrosis	1	
	Compensated cirrhosis	2	
	Decompensated cirrhosis	3	
Hepatitis B/C	Hepatocellular carcinoma	4	
	Negative	0	– Current or last available (within 6 months)
	Positive (ELISA)	1	
Bilirubin (indirect)	Significant viral load, RNA positive	2	
	≤3 × ULN	0	– Current or last available (within 3 months)
	>3 to ≤6 × ULN	1	
	>6 to ≤10 × ULN	2	
Gallbladder	>10 × ULN	3	
	No disease	0	– Current or any history
	Cholecystectomy	1	– Apart from cholecystectomy, add 1 point if problem is active on current presentation
	Cholecystitis		
	Cholelithiasis	1	
		1	
<i>Cardiovascular status</i>			
Ejection fraction	Normal (LVEF > 55%)	0	– Current or last available (within 3 months)
	LVEF < 55%	1	
Cardiac T2* (MRI)	>20 ms	0	– Current or last available (within 3 months)
	10 to ≤20 ms	1	
	6 to <10 ms	2	
	<6 ms	3	
Heart failure	Absent	0	– Current or last available (within 6 months)
	NYHA Class I	1	
	NYHA Class II	2	
	NYHA Class III	3	
	NYHA Class IV	4	
Arrhythmias	Absent	0	– Current or any history
	Present	1	– Add 1 point if problem is active on current presentation
Thrombosis	Absent	0	– Current or any history
	Present	1	– Add 1 point if problem is active on current presentation
<i>Other comorbidities</i>			
Splenomegaly	No splenomegaly or N/A	0	– Current or last available (within 3 months)
	>2 to ≤10 cm below costal margin or 12–20 cm on ultrasound	1	
	>10 cm below costal margin or >20 cm on ultrasound	2	
Renal [35]	Normal	0	– Current or last available (within 3 months) for eGFR
	eGFR ≥ 15 to <60 mL/min/1.73 m ²	1	
	eGFR < 15 mL/min/1.73 m ² or on dialysis	2	– Current or any history for nephrolithiasis
	Nephrolithiasis	1	
PHT [36]	Normal	0	– Current or any history
	TRV > 2.5 m/s	1	
	TRV > 2.5 m/s AND symptomatic or with other echocardiographic criteria suggestive of PHT	2	– Apart from TRV > 2.5 m/s only, add 1 point if problem is active on current presentation
	TRV > 3.2 m/s or cardiac catheterization confirmed PHT	2	
Leg ulcers	Absent	0	– Current or any history
	Present	1	– Add 1 point if problem is active on current presentation

(continued on next page)

Table 1 (continued)

A. All patients ^a			
Parameter	Item	Score	Remarks
Endocrinopathies	Absent	0	– Current or any history – Score 1 if ≤ 2 abnormalities; 2 if > 2 abnormalities or insulin-dependent diabetes mellitus – Add 1 point if problem is active on current presentation
	Diabetes mellitus	–	
	Hypoparathyroidism	–	
	Hypogonadism (≥16 years)	–	
	Hypothyroidism	–	
	Adrenal insufficiency	–	
Skeletal	Growth hormone deficiency	–	– Current or any history – Score 1 if ≤ 2 abnormalities; 2 if > 2 abnormalities – Add 1 point if problem is active on current presentation
	Absent	0	
	Final height < 3rd percentile on standardized charts	–	
	Osteopenia (not osteoporosis)	–	
	Osteoporosis	–	
	Skeletal deformity	–	
	Bone pain	–	
	Pathologic fractures	–	
	Dental malocclusion	–	
Extramedullary hematopoiesis	Otitis media	–	– Current or any history – Add 1 point if currently causing clinical complications, e.g., neurological complications
	Chronic sinusitis	–	
	Absent	0	
	Present (radiologically confirmed)	1	
	Other compressed structures	2	
B. Pediatric patients (≤16 years)			
Parameter	Item	Score	Remarks
Height	Normal	0	– Current or last available (within 6 months)
	<10th percentile on standardized charts	1	
	<3rd percentile on standardized charts	2	
Activity	Normal	0	– Current or last available (within 6 months)
	Lethargic/limited	1	
	Severely affected	2	
Weight	Normal	0	– Current or last available (within 6 months)
	<10th percentile on standardized charts	1	
	<3rd percentile on standardized charts	2	
Bone age	Normal	0	– Current or last available (within 6 months)
	Delayed (>2 years)	1	
School performance	Normal or N/A	0	– Current or last available (within 6 months)
	Suboptimal	1	
Puberty	Normal or N/A	0	– Females: No thelarche at 13 years; Males: No adrenarche at 14 years – Current or any history
	Delayed	2	

^aNote: the intention is for pediatric patients to undergo scoring in both the all patients and pediatric patients sections.

ALT, alanine aminotransferase; dw, dry weight; ELISA, enzyme-linked immunosorbent assay; eGFR, estimated glomerular filtration rate; LIC, liver iron concentration; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; N/A, not available; NYHA, New York Heart Association; PHT, pulmonary hypertension; RNA, ribonucleic acid; SF, serum ferritin; TRV tricuspid regurgitation jet velocity; ULN, upper limit of normal.

assessed and treated according to their specific circumstances. As such, there is a need for an instrument to assess disease severity and monitor progression that would aid patient management by allowing for early intervention to prevent further complications. A working group of eight NTDT experts convened to assess the parameters considered most pertinent to defining NTDT syndromes and the impact of these on disease severity, based on their extensive clinical experience in treating and evaluating patients with NTDT.

A dynamic NTDT severity scoring system was thus developed for use in both adult and pediatric patients. A dynamic scoring system was required to reflect the fluctuations in disease severity often encountered throughout patients' lives. The system also needed to assess disease severity at any current presentation (since complications can also accumulate over time) but also consider past medical histories. Importantly, the score had to be able to assess changing patterns of disease severity in response to different treatment strategies, ultimately to inform optimal approaches to treatment in NTDT patients. It is also anticipated that the scoring system will be useful as a prognostic tool for disease progression. Additional parameters for pediatric patients were deemed

appropriate to encompass factors pertinent to younger patients only. By taking into consideration such specifics of NTDT syndromes, this scoring system is more detailed and potentially more beneficial than existing basic scoring systems [31,32]. However, the scoring system now needs to undergo rigorous validation to determine its utility in clinical practice, with refinement as needed.

4.1. Plans for validation and refinement

Extensive data collection is currently ongoing at participating centers in Italy, Lebanon and Greece. Initially, we intend to evaluate the ability of the Disease Severity Scoring System to differentiate patients with different clinical profiles, through correlation of the score with underlying genotypes and basic clinical phenotypes as well as management requirements. In addition, we will evaluate the ability of the score to predict future clinical morbidity or management needs, through longitudinal assessment of a retrospective cohort with over 10 years follow-up. The latter assessment will also be used to identify clinically meaningful changes with and without interventions.

In order to determine how applicable and feasible the Disease Severity Scoring System is in clinical practice, the score will initially be applied to a small group of patients followed at the centers of the experts involved in the generation of this system. This will be followed by assessment in a larger group of patients in a cross-sectional study via a combination of assessment visits and chart reviews. The aim of these two steps will be to assess how many of the parameters required for completing the scoring system will be available at the assessment visit through recent routine studies (within the time frame indicated in the score sheet), compared with how many will need to be ordered at the assessment visit specifically for incorporation into the scoring system. The scoring system will also act as a prompt to encourage physicians to actively look for some of the complications specified within the scoring system (either at current presentation or historically); difficulties may be encountered in generating a score for some complication parameters that may not have been historically assessed. This first phase of validation will help determine how applicable and feasible the scoring system will be in clinical practice, identifying the likelihood that some of the specified parameters will not be available, cannot be determined or will be missed. As well as identifying certain variables or measurements that may not be routinely available in the scheduled standard assessment of NTDT patients, the validation process should also help ascertain whether any of the definitions for the parameters listed within the scoring system should be refined. Once this first phase of the validation process is complete, an official guide to using the scoring system may be developed.

The second phase of validation will focus on examining the association between the generated score from the NTDT disease severity scoring system and a variety of elements related to treatment and/or outcomes. This may be conducted through cross-sectional studies (e.g., association between the score and a standardized QoL instrument score or association between the score and utilized intervention), and/or retrospective cohort studies (e.g., association between the score as evaluated at a certain time point and future outcomes).

The third phase of validation will determine the longitudinal changes of the score with and without intervention through cohort (retrospective or prospective) studies or inclusion in clinical trials. Thresholds for severity can be assigned once the scoring system has been tested in all or some of these phases of validation, and the minimum clinically important difference (MCID) can then be determined. The MCID is the smallest absolute difference in disease severity score that patients and physicians perceive as beneficial or detrimental and which would mandate, in the absence of troublesome adverse events and excessive cost, a potential change in a patient's management.

Following appropriate validation, we propose that the NTDT disease severity scoring system described here could be developed into a practical tool for widespread clinical application, not only to evaluate patient status and classify disease subgroups, but also to inform treatment decisions and monitor patient progress in response to therapy.

Conflict of interest statement

M.D. Cappellini reports receiving honoraria from Novartis Pharmaceuticals, Genzyme and Celgene; J.B. Porter reports consultancy, receiving research funding and honoraria from Novartis Pharmaceuticals; consultancy and honoraria from Shire; and consultancy for Celgene. J.B. Porter is supported by the NIHR University College London Hospitals Biomedical Research Centre. During development of the severity score, K.M. Musallam received honoraria and research funding from Novartis Pharmaceuticals; A. Kattamis received research funding from Novartis Pharmaceuticals and participated in a speakers' bureau for Novartis Pharmaceuticals and ApoPharma; V. Viprakasit received research grant support and lecture fees from Novartis Pharmaceuticals, Genzyme-Sanofi Co. Ltd., Sebia Co. Ltd. and Roche Diagnostics and research grant

support from Shire Co. Ltd., Sideris Co. Ltd. and Faculty of Medicine, Siriraj Hospital, Thailand; A.T. Taher reports receiving research funding and honoraria from Novartis Pharmaceuticals and consultancy for Celgene and Sidris; All opinions and conclusions expressed herein are those of the authors.

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Dr Renzo Galanello died in May 2013 but contributed significantly to the development of the NTDT disease severity scoring system.

Professor David Weatherall contributed to the Working Group discussions. The authors would like to thank him for his valuable input in the development of this NTDT disease severity scoring system.

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