

The Lancet Haematology

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--Manuscript Draft--

Manuscript Number:	thelancethaematology-D-24-00548R2
Article Type:	In Focus – Global Haematology
Keywords:	Burden estimates; Years of life lost; Years lived with a disability; disability-adjusted life years; Sickle cell disease; thalassaemia
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Manuscript Region of Origin:	ITALY

The importance of national and disease-specific characteristics to estimate disease burden in the GBD: a comparison for haemoglobin disorders in Italy.

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The Global Burden of Disease (GBD) study represents an incredible resource of information to quantify and understand the magnitude and impact of all conditions, including common and rare diseases, on patients' quality of life, mortality and morbidity [1,2]. Emerging evidence indicates that detailed national studies are needed to inform, calibrate and validate GBD estimates [3]. This need is also supported by action on local GBD network, such as the Italian GBD network (<https://www.italian-gbd-initiative.it/>), cross-talking with the global GBD network.

Thalassaemia and sickle cell disease (SCD) are haemoglobin disorders distributed worldwide and represent an increasing public health burden. These inherited disorders tend to be highly prevalent in malaria-endemic regions across sub-Saharan Africa, the Middle East and Southeast Asia, which tend to be data poor, and classified as rare diseases in Europe and North America, which are usually data rich. Furthermore, thalassaemia syndromes are caused by hundreds of different mutations in the α - and β -globin genes which leads to a wide range of clinical severity. Previous classifications (minor, intermedia and major) tend to be replaced with a new one based on transfusion requirements: transfusion-dependent and non-transfusion-dependent thalassaemia (TDT and NTDT, respectively), which is more relevant to the management of patients. These heterogeneities and changes in classification terminology represent challenges when collecting epidemiological data required to correctly estimate the burden of such conditions. For example, Brousse *et al.* [3] previously highlighted that the GDB-2021 study of SCD likely underestimated the number of patients with SCD in France and in the UK, and overestimated the number of deaths for SCD patients younger than five years of age. Although Brousse and colleagues do not get into detailed analyses of France and UK data, we believe it is important to go deeper using detailed national data especially in countries where haemoglobinopathies are endemic such as Italy. Thus, we collected detailed national data on haemoglobin disorders across Italy by 131 comprehensive specialist centres connected through the "Società Italiana

Talassemie ed Emoglobinopatie” ([SITE](#)).[4]. Here, we use SITE data to estimate the burden of thalassemia and SCD in Italy, and provide a detailed comparison of our estimates with those of the GBD-2021. Using 2019 data, our comparative indicators were: i) the number of patients; ii) the number of deaths; iii) the years of life lost (YLLs); iv) the years lived with disability (YLDs); and v) disability-adjusted life years (DALYs) for thalassaemia and SCD in Italy. Data on the number of patients were collected across the 131 SITE centres. Data on mortality and morbidity were available from eight of the largest comprehensive centres, covering about 30% of the Italian patients with haemoglobin disorders. Consistency between SITE and GBD-2021 estimates was defined as some overlap between the 95% confidence intervals of the two estimates. Further details on the data sources are available in Supplementary Methods S1.

SITE data on the number of patients were collected using specific age groups ("0-5", "6-18", "19-35", "36-50", "51-65" and "66+" years) and binary sex (male vs female). Disease severity (no-symptoms, mild-moderate and severe) was based on clinical records (see Supplementary Methods S2). Data from the survey of the eight centres were used to count the number of deaths in 2019 in these centres. Due to small numbers, we used data from the five years preceding 2019 to calculate age-specific mortality in order to extrapolate the number of deaths across the whole country, using patient counts from the 131 centres and data from the general population. The age of death attributed to each extrapolated death was the mean of the age category considered (see Supplementary Methods S3). The age-specific and the overall number of patients and deaths in Italy were directly compared with the ones reported in the GBD-2021. The GBD-2021 uses standard five-year age groups ("0-4", "5-9", ..., "90-94", "95+"). Data were therefore reprocessed to align the age groups between the two data sources. YLLs, YLDs and DALYs were calculated using the standard WHO methodology, [5] which is consistent with the GBD approach. The YLLs were calculated by multiplying the number of deaths in each age-groups by the standard loss function specifying years of life considering the deaths in that age-group (see Supplementary Methods S4). In the case of YLDs, the calculation was performed considering the patient's population divided according to the severity of the disease (see Supplementary Methods S5). A mean value of disability weight was used for each category. The disability weights were obtained by the table reported in the GBD-2021 study [6] and grouping by pathology and health state name and description. A simulation was conducted with different set of weights to identify the most likely set of parameter values equivalent to those used in the GBD-2021 estimations of YLDs. Finally, the overall DALYs were calculated by summing YLDs and YLLs.

Using the SITE data, we estimated 7,169 thalassemia patients in 2019, which overlapped with the GBD-2021 estimate of 6,497 (95%CI: 5,432-7,602). Despite the agreement in the overall number of patients, the age-specific distribution of the SITE data revealed that the Italian thalassaemic population was significantly older than estimated by GBD-2021 (**Figure 1A**) (estimated mean age: 38.1 years [95%CI: 37.7 - 38.5] for SITE population, estimated mean age: 20.7 years [95%CI: 20.2 - 21.1] for GBD-2021). The SITE estimated national

annual number of deaths (**Figure 1B**) for thalassemia was 35 (95%CI: 27-56), corresponding to 1,370 YLLs (95%CI: 1,064-2,656); while GBD-2021 estimated 30 deaths (95%CI: 25-33) and 1,247 YLLs (95%CI: 1,090-1,378) (**Figure 1C**). Using real-world national data on thalassemia severity [4], we estimated 867 YLDs (371-1,952), which is 5.8-fold greater than in GBD-2021 (149 YLDs [95%CI: 93-224]). This is likely due to the difference in the age distribution of the patients in the two datasets. Overall, the estimate of the DALYs for thalassemia in 2019 added up to 2,237 (95%CI: 1,435-4,608), which overlaps with the GBD-2021 estimates (1,396 [95%CI: 1,227-1,559]). When we accounted for the severity of thalassaemia, we estimated 5,205 TDT and 1,964 NTDT individuals. The SITE estimates of YLLs, YLDs and DALYs for TDT were 1,062 [95%CI: 821-1,528], 790 YLDs [95%CI: 369-1,750]) and 1,852 (95%CI: 1,190-3,277) respectively. For NTDT, these estimates were 309 YLLs (95% CI: 243-1,129), 76 YLDs (95%CI: 3-202) and 385 DALYs (95%CI: 245-1,331). No estimates for TDT and NTDT are currently included in the GDB.

A total of 2,348 SCD patients were estimated from the SITE survey, which was similar to GBD-2021 estimation (2,675 [95%CI: 2,354- 3,015]). The age distribution was comparable for all categories except in SCD patients younger than five years for which our estimate was substantially lower than in GBD-2021 (**Figure 1A**). The estimated number of deaths (**Figure 1B**) for SCD was 2.9 (95%CI: 0.7-13.7), corresponding to 111 YLLs (95%CI: 30-762); while the GBD-2021 estimated 3.4 (3.1-3.8) deaths and 182 YLLs (95%CI: 161-204) (**Figure 1C**). When we considered YLDs, GBD-2021 estimated 164 YLDs (120-217) for SCD. We calculated 477 YLDs (95%CI: 142-1,021) based on real-world disease severity proportions [4]. As shown in **Figure 1C**, in the GBD-2021 study, the percentage of SCD patients with a severe phenotype could not exceed 12% to 19%. This means that GBD-2021 most likely distribution was 30% of patients with no-symptoms, 55% with mild-moderate and 15% severe. The estimate of the DALYs for SCD in Italy in 2019 was 588 (95%CI: 172-1,783).

When extrapolated globally, our estimates of YLDs due to haemoglobinopathies (YLDs $2.0 \cdot 10^6$) are substantially higher than those due to other chronic disorders such as “chronic kidney disease due to diabetes mellitus type 1” ($0.28 \cdot 10^6$), “chronic kidney disease due to hypertension” ($1.36 \cdot 10^6$), “myelodysplastic, myeloproliferative, and other hematopoietic neoplasms” ($0.25 \cdot 10^6$).[7] Of note, diseases such as “other haemoglobinopathies and haemolytic anaemias” or “G6PD deficiency “might be underestimated in GBD studies, similarly to our observation on thalassaemia and SCD. This is related to the fact that “haemolytic anaemias” group different disorders such as membranopathies (e.g. hereditary spherocytosis, stomatocytosis, elliptocytosis, xerocytosis) which has a heterogeneous global distribution. Concerning G6PD deficiency, the recent revision of G6PD classification needs to be taken into consideration when we look for YLDs in patients with G6PD deficiency with/without chronic haemolysis.[8]

In conclusion, our study shows that the GBD-2021 produced reliable estimates for some indicators, but lacked precision in relation to the age distribution of patients and deaths, and specificity in relation to the severity of thalassaemia and SCD which underlines the YLD and DALY estimates. The classification of thalassaemia

into TDT and NTDT better reflects the severity of these disorders in patients. It is widely used for the management of patients and the development of new treatments, and should be incorporated into future GBD work. Although these findings are based on haemoglobin disorders in Italy, we believe that they demonstrate the ongoing need for high quality national epidemiological data in general. Furthermore, they provide valuable insights for the interpretation of the GBD estimates in other countries and for other conditions, particularly when used to guide national policies.

Data availability statement: SITE data can be requested to the corresponding author. GBD data used in this study are available through open access publication and the GBD data visualization portal (<https://vizhub.healthdata.org/gbd-compare/>).

Conflict of interest disclosure: FBP declares being on an advisory board on sickle cell disease for the Fondation Fabre; an advisory board for the development of St Jude's Global Hematology Registry; and a subject matter expert on anaemia and haemoglobinopathies for the IHME's Global Burden of Disease (GBD).

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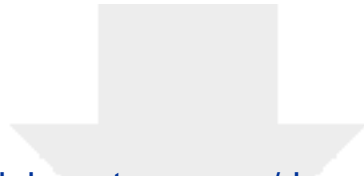
Data availability statement: SITE data can be requested to the corresponding author. GBD data used in this study are available through open access publication and the GBD data vizualization portal (<https://vizhub.healthdata.org/gbd-compare/>).

Conflict of interest disclosure: The authors declared no conflicts of interest.

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Supplementary Materials

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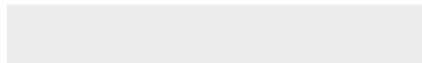
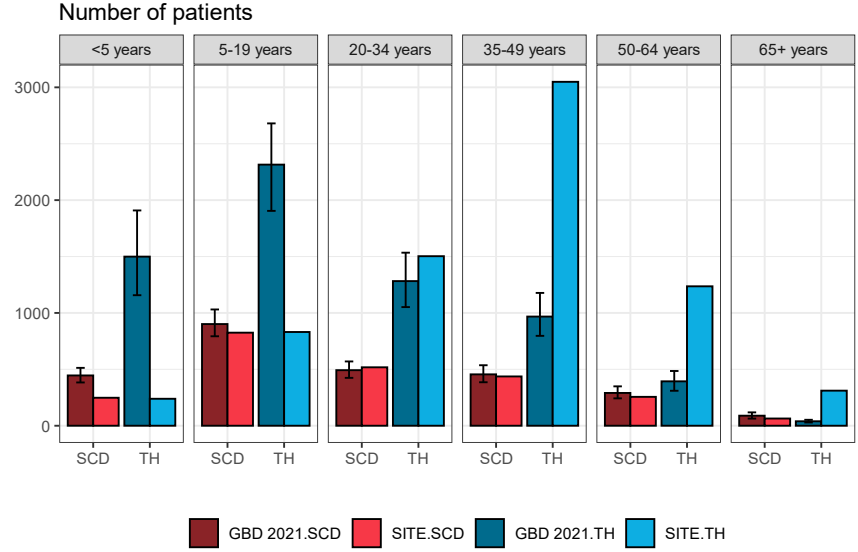
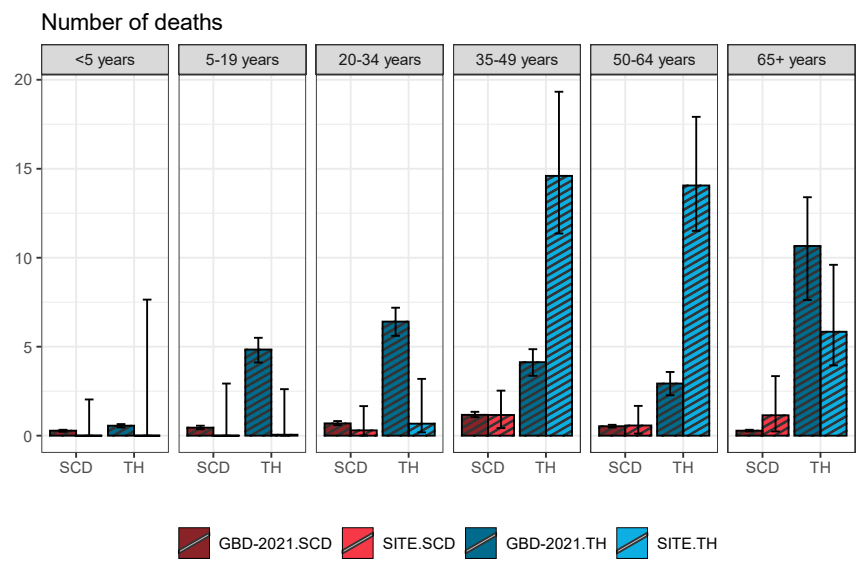


Figure 1



(B)



(C)

		SITE			GBD 2021			Difference SITE – GBD 2021
		Value	Lower	Upper	Value	Lower	Upper	
Number of patients	TH	7169			6497	5432	7602	
	TDT	5205						
	NTDT	1964						
	SCD	2348			2675	2354	3015	
Number of deaths	TH	34.5	26.8	56.4	30	25	33	
	SCD	3	0.7	13.7	3	3	4	
YLLs	TH	1370	1064	2656	1247	1090	1378	
	TDT	1062	821	1528				
	NTDT	309	243	1129				
	SCD	111	30	762	182	161	204	
YLDs	TH – 1	279	9	739	149	93	224	
	TDT	203	7	537				
	NTDT	76	3	202				
	TH – 2	867	371	1952	149	93	224	
	TDT	790	369	1750				
	NTDT	76	3	203				
	SCD – 1	19	0	53	164	120	217	
	SCD – 2	80	3	223	164	120	217	
	SCD – 3	50	2	138	164	120	217	
	SCD – 4	421	120	916	164	120	217	
	SCD – 5	477	142	1021	164	120	217	
	SCD – 6	164	37	380	164	120	217	
DALYs	TH – 2	2237	1435	4608	1396	1227	1559	
	TDT	1852	1190	3277				
	NTDT	385	245	1331				
	SCD – 5	588	172	1783	346	291	403	

TH: thalassemia; SCD: sickle cell syndromes; TDT: transfusion dependent thalassemia; NTDT: non-transfusion dependent thalassemia
TH – 1 : 100% mild-moderate; TH – 2: TDT patients 30% mild-moderate and 70% severe); NTDT 100% mild-moderate
SCD – 1: 100% no-symptoms; SCD – 2: YLD-SCD - 100% mild.moderate; SCD – 3 : YLD-SCD - 50% mild.moderate 50% no.symptom
SCD – 4 : YLD-SCD - 50% mild.moderate 50% severe; SCD – 5 : YLD-SCD - 20% no anaemia, 20% mild.moderate, 60% severe;
SCD – 6 : YLD-SCD - 30% no anaemia, 55% mild.moderate, 15% severe

Figure 1A Number of patients

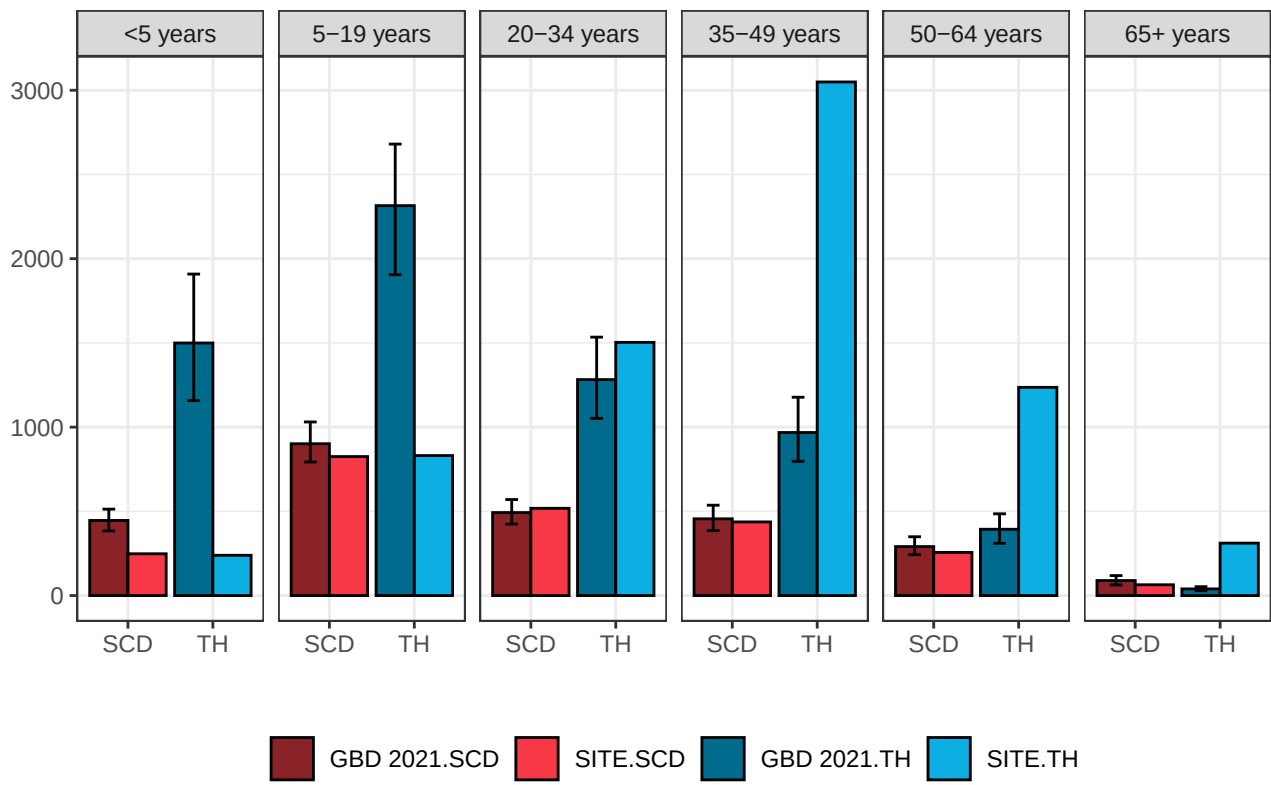


Figure 1B
Number of deaths

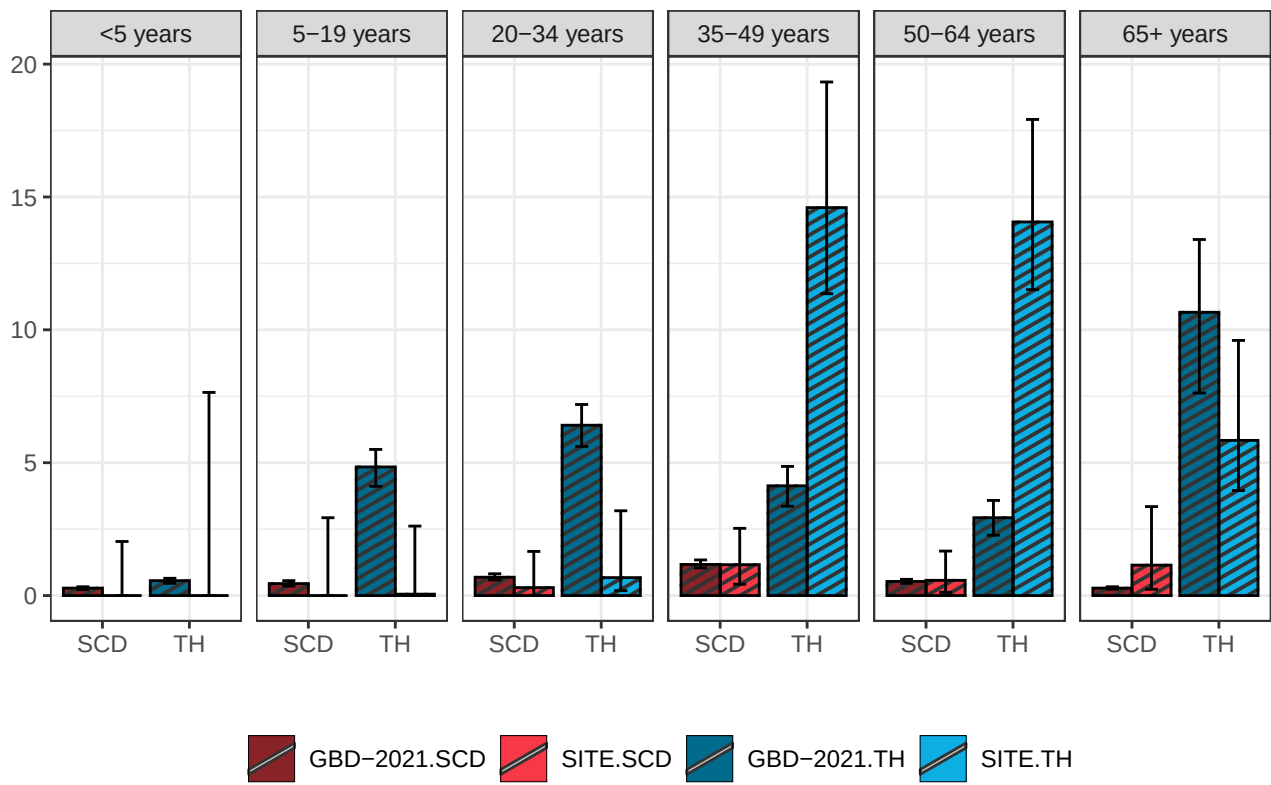
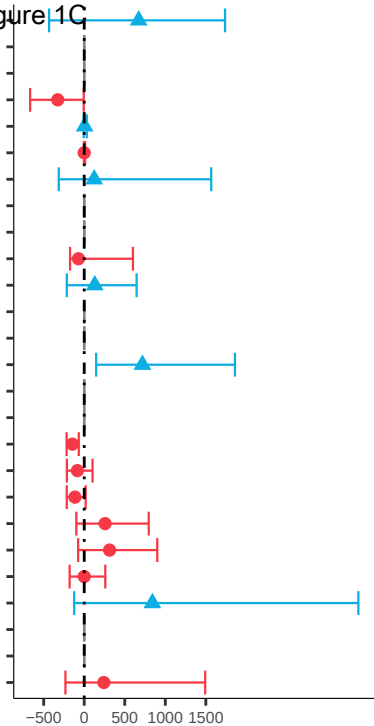


Figure 1C

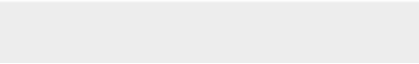


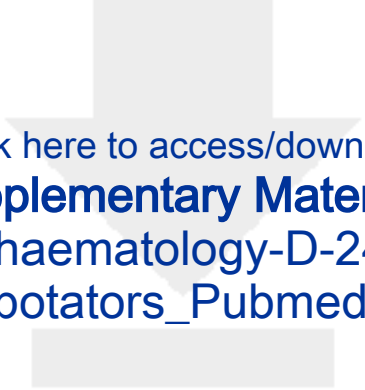


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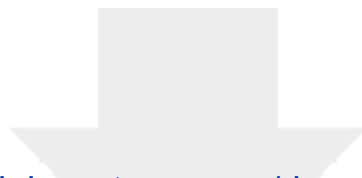
Supplementary Materials

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