The Italian multiregional thalassemia registry: Centers characteristics, services, and patients' population

Article *in* Hematology (Amsterdam, Netherlands) · February 2016

DOI: 10.1080/10245332.2015.1101971

CITATIONS
2

READS
38

18 authors, including:

Rosa Conte
Fondazione per la Ricerca Farmacologica Gia…
3 PUBLICATIONS **7** CITATIONS
SEE PROFILE

Lucia Ruggieri
Gianni Benzi Pharmacological Research Fou…
5 PUBLICATIONS **16** CITATIONS
SEE PROFILE

Arianna Gambino
CVBF - Consorzio per le Valutazioni Biologich…
3 PUBLICATIONS **9** CITATIONS
SEE PROFILE

Franco Bartoloni
CVBF - Consorzio per le Valutazioni Biologich…
7 PUBLICATIONS **25** CITATIONS
SEE PROFILE

The Italian multiregional thalassemia registry: Centers characteristics, services, and patients' population†

Rosa Conte[1], Lucia Ruggieri[1], Arianna Gambino[2], Franco Bartoloni[1], Paola Baiardi[3], Donato Bonifazi[2], Fedele Bonifazi[1], Mariagrazia Felisi[2], Viviana Giannuzzi[1], Rosa Padula[2], Alessia Pepe[4], Maria Caterina Putti[5], Giovanni Carlo Del Vecchio[6], Aurelio Maggio[7], Aldo Filosa[8], Angela Iacono[9], Laura Mangiarini[2], Adriana Ceci[1,2], on behalf of the HTA-THAL Multiregional Registry

[1]Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Via Abate Eustasio 30, 70010 Valenzano (BA), Italy, [2]Consorzio per Valutazioni Biologiche e Farmacologiche, Via L. Porta 14, 27100 Pavia, Italy, [3]Fondazione Salvatore Maugeri, Via S. Maugeri, 4, 27100 Pavia, Italy, [4]Fondazione G. Monasterio C.N.R.- Regione Toscana, Via Moruzzi 1, 56124 Pisa, Italy, [5]Azienda Ospedaliera Padova Centro Leucemie Oncoematologia Pediatrica, Via N. Giustiniani 3, 35128 Padova, Italy, [6]Azienda Ospedaliera Universitaria Consorziale Policlinico di Bari, Unità Operativa di Pediatria Generale e Specializtica "Federico Vecchio", P.zza G. Cesare, 11, 70124 Bari, Italy, [7]Azienda Ospedaliera Ospedali Riuniti Villa Sofia Cervello, Via Trabucco, 180, 90146 Palermo, Italy, [8]Azienda Ospedaliera "A. Cardarelli" UOS Talassemia Pediatrica e Emoglobinopatie Pediatriche, Via A. Cardarelli, 9, 80131 Napoli, Italy, [9]Fondazione "Leonardo Giambrone" per la Guarigione dalla Thalassemia, Via Savona, 56, 81030 Castelvolturno (CE), Italy

Objectives: The prognosis of beta-Thalassemia major and other congenital hemoglobinopathies has profoundly changed over the last decades. Moreover, only few countries in Europe provide dedicated services and the description of the measures for patients monitoring and treatment is overall very scarce. The HTA-Thal project is aimed to identify the services available in Italy and to collect epidemiological and clinical data on the thalassemic population (HTA-Thal Registry).
Methods: A map of the existing centers was created and two electronic questionnaires were completed with information on the services and patients.
Results: On 182 centers identified, 60 completed the two questionnaires. Centers resulted to be extremely heterogeneous in terms of size, age of patients in care, and services availability. The transition of pediatric patients to adult centers was not guaranteed.
Thousand eight hundred and seventy-three beta-Thalassemia major patients (of which 259 pediatrics), regularly transfused, were registered. Deferasirox is the most used chelator as monotherapy (616 patients) and its use prevails in younger patients. A higher number of patients (847 patients) use Deferoxamine, either alone (448 patients) or in combination with DFP (399 patients), while 782 patients use Deferiprone alone (383 patients) or in combination (399 patients). 31.6 and 66.6% of centers were not equipped for specialized visits or local MRI, respectively. Centers with 30–80 patients show the high percentage of patients appropriately monitored when compared to smaller or bigger centers.
Conclusions: This analysis confirms the importance of patients' registries for the collection of large datasets and the need for dedicated 'specialized centers' equipped to provide the best standard treatment to patients.

Keywords: Beta-Thalassemia, Registries, Chelation, Transfusion, MRI, Hemoglobinopathies centers

Introduction

The availability of oral chelators, with different mechanism of action (MoA) and different formulations, has allowed to tailor the treatment of Thalassemia patients according to specific therapeutic needs. At the same time, the non-invasive, T2* Magnetic Resonance Imaging (MRI) for cardiac and liver iron load

†The manuscript has been published on behalf of HTA THAL project, funded by Ministry of Health and Fondazione Giambrone and hosted by Basilicata Region.
Correspondence to: Rosa Conte, Fondazione per la Ricerca Farmacologica Gianni Benzi Onlus, Via Abate Eustasio 30, 70010 Valenzano (BA), Italy.
Email: rc@benzifoundation.org

DOI 10.1080/10245332.2015.1101971

quantification, provided the opportunity for tailoring the chelation therapy according to the level of iron accumulation in the target organs, and increasing patients' compliance to chelation and to regular iron monitoring[1–3] with consequent improvement of the prognosis.[4]

Nevertheless, these diagnostic and therapeutic tools can significantly impact on the overall management of Thalassemia only if every patient has timely access to them and if comprehensive, evidence-based therapeutic plans are made available at least at a national level. Each patient should be entitled to receive treatment in "specialized Thalassemia centers",[5] defined as clinical settings and sites in which all the tools needed for the management of the disease are present, including specialized staff and a transfusion center able to cover the specific needs of each patient. However, at present, there are only few and limited descriptions of a "standard Thalassemia center". According to Angastiniotis and Eleftheriou "the minimum throughput required to designate an expert center is not clarified",[6] while the 2008 Thalassemia International Federation Guidelines for the Clinical Management of Thalassemia state that "unless the number of patients is minimal, the unit should be dedicated, should include physicians expert in Thalassemia and should be linked to other specialists and services as indicated".[7] Reference to a minimum number of patients in a specialist centers is only present in the UK Thalassemia Society Standards for the Clinical Care of Children and Adults with Thalassemia for whom: "It is expected that a specialist Center will manage at least 20 patients on a regular basis".[8] Aguilar Martinez *et al.*, in a recent survey demonstrate that only five countries in Europe have specialized services dedicated to the management of such pathologies (Greece, Italy, Cyprus, UK, and France, and hemoglobin disorders are considered endemic only in the first three).[9] Only recently, UK is creating a Network of dedicated specialized services aimed at dealing with all the specific clinical emergencies and chronic care.[10]

In Italy, Thalassemia patients are referred to a variety of clinics (adult, pediatric, or transfusion centers or units), and a clear map of Italian structures and centers for the management of Thalassemia is not yet available. In addition, due to the lack of defined criteria for centers classification and qualification, an appropriate and cost-efficacious national distribution of centers and services is complicated by the size estimation of the Italian Thalassemia population which, to date, is still approximate.

To cover this gap, in 2008 the Minister of Health promoted a public funded project (HTA-Thal, 2008)[11] aimed at (a) creating a "Multiregional Network of Thalassemia centers", including an inventory of services and tools available at each participating center; (b) setting up a Thalassemia Registry (HTA-THAL Registry), with epidemiological and clinical data on the Thalassemia population referring to those centers. The project was co-funded by Fondazione Giambrone, and coordinated by the Region of Basilicata. Preliminary results, on the first 1000 patients included in the Registry, were published by Ceci A *et al.* in 2011.[12]

This paper details the characteristics of the Thalassemia centers adhering to the Network and of the registered patients' population with reference to the period 2010–2011.

Materials and methods

Identification of thalassemia centers

A survey aimed at identifying the operating centers (being either a therapeutic center within a hospital or a blood transfusion service), where Thalassemia patients receive regular blood transfusions and disease's therapy was developed. The following sources were consulted:

1. Lists of Centers that participated to the Registry for Controlled Use of Deferiprone (DFP)[13];
2. Regional Reference Centers as provided, after direct request, by 17 Regional Health Departments;
3. Clinical Units and Departments identified by Fondazione Giambrone (www.fondazionegiambrone.it);
4. Other websites of Thalassemia patient associations;
5. MIOT (Myocardial Iron Overload in Thalassemia) network.[14]

Data obtained from the different sources were cross-checked in order to avoid duplication. Resulting centers were verified and contacted before inclusion in the analysis.

Centers included in the "Rare Disease National Network" (Ministry Decree No. 279 of 18 May 2001)[15] available in different regional databases (i.e. *http://malattierare.regione.veneto.it/default.htm*)[16] were used as control and comparison.

Centers characteristics and available services

All the centers identified from the sources described above were invited to participate in the Multiregional Network and to complete an electronic form (Center Form) for the collection of the following information:

a) Center size by number of Thalassemia patients;
b) Availability of clinical diagnostic and monitoring services including:
    1. transfusion services, standard laboratory tests, ferritin assessment, and standard medication availability;
    2. specialized departments and laboratories (hepatology, cardiology, endocrinology, etc.);
    3. iron overload monitoring facilities (cardiac and liver MRI, liver biopsy, SQUID).

Patients' registry

In accordance with the approved protocol, criteria for including patients into the Registry were: (a) confirmed diagnosis of beta-Thalassemia major and (b) written informed consent.

A Case Report Form (Patients Form) was completed for each patient and the following information were collected:

1. demographic characteristics (age and sex);
2. information on chelation therapy;
3. information on iron overload monitoring procedures (cardiac and liver MRI, liver biopsy, SQUID) performed at the referring center or elsewhere during the last calendar year.

Ethics

In compliance with the Ministry Decree 15/07/97 providing rules for observational studies (Gazzetta Ufficiale, G.U. n. 76, 31/3/2008) and the protection and treatment of personal data decree (Legislative Decree, D.L. 196/2003), the study received approval by each competent Ethics Committee and a Consent Form was signed by each participant. For minors, consent was provided by parents or legal representative.

Electronic database governance and maintenance

The Registry was accessible on Internet (http://registro.cvbf.eu/) through a user-friendly interface. Each center was enabled to access only its own patient's data. Access for data entry was controlled by user authentication system. Standard security measures were adopted, such as password strength and auto logoff after 20 minutes of inactivity. Accesses to the system were real time monitored. Data were organized in center and patient-specific pages.

Patients' data were anonymized: name and surname were replaced by a numeric code automatically generated by the system and the key associating code to patient was securely stored in each referring center. Standardized procedures for data cleaning, double check of the data and cross-centers controls were applied to avoid duplication. Database server was accessible only through the application server and no other direct access to database was allowed. Regular database backup were automatically performed.

Data analysis

Data were summarized as frequencies and percentages for qualitative or ordinal variables, and as means and standard deviations, minimum and maximum, median values and interquartile range for quantitative variables.

Differences between groups were tested using $\chi 2$ test or Fisher exact test for categorical variables. Statistical analyzes were performed using SPSS (version 19; SPSS, Chicago, IL). The level of significance of each comparison was set to 5% ($P < 0.05$).

Results

Identification of thalassemia centers

Result of the survey

A total of 261 Thalassemia centers were identified, 60 of which were deleted because reported by multiple sources and 19 because were no longer-operating at the time of the survey. Thus, in April 2011 a total of 182 centers were considered for the analysis. Out of these, 69 were located in a blood transfusion service and 113 in a clinical unit. Among those located in clinical units, 53 were pediatric and 60 were adult units. Overall, dedicated Thalassemia units were only 34 (9 pediatrics and 25 adults).

Figure 1 shows the comparison between centers identified through the survey and the Thalassemia centers included in the "Rare Disease National Network" across the different Italian regions, and highlights that 121 centers included in our survey are not listed in the national Network list, but also that 58 centers in the national network list have not been detected by our survey.

Set up of the interregional network

All the 182 identified centers were requested to complete the electronic questionnaire. Sixty centers, representing about one-third of the total sample, completed the questionnaire. All the centers were classified as small (20 centers), medium (18 centers), large (17 centers), and very large (5 centers) if they declared a total of 1–9, 10–29, 30–79, and more than 80 patients, respectively (Table 1). Among the centers with less than 10 patients, 3 registered only 1 patient, while the largest center registered 150 patients. Out the total of the centers, 40 were clinic units (18 pediatrics and 22 adults) and 20 were blood transfusion services, while 24 were exclusively dedicated to hemoglobinopathies (HPs) or Thalassemia patients (5 pediatrics and 19 adults).

Center characteristics and available services

Type, size, and geographic distribution of the centers

The center distribution by geographic area is heterogeneous: the Registry includes 22.6% of all the survey's centers located in the North, 41.4% in the Center, 34.3% in the South, and 44.2% in the Islands with a patients/center ratio equal to 12.7, 14.4, 47.6, and 48.8, respectively, with the presence of centers with a considerably higher number of patients in the South and Islands. Overall, small and exclusively pediatric centers prevail in the North, blood transfusion services are more present in the central regions, while

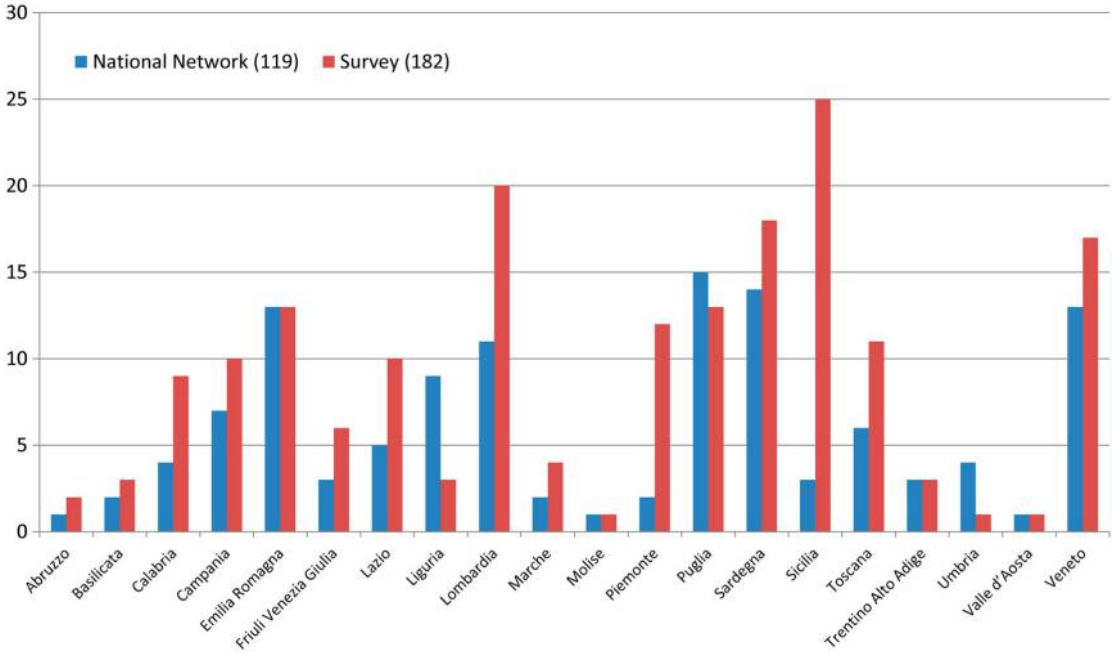

Figure 1 Comparison between centers identified in this survey and centers included in the Rare Disease National Network.

Table 1 Center size stratified by patients in care

Centers size by number of patients	Small (1–9 patients)	Medium (10–29 patients)	Large (30–79 patients)	Very large (≥80 patients)	Total
Number of centers	20 (33.3%)	18 (30%)	17 (28.3%)	5 (8.3%)	60
Number of patients	73 (3.8%)	315 (16.6%)	906 (47.7%)	605 (31.8%)	1899
Mean number of patients ±SD	3.7 ± 2.4	18 ± 6.6	53.3 ± 15.8	121 ± 28.2	31.7 ± 35.7

adult and large centers are mainly concentrated in the South and Islands (Table 2).

Availability of therapeutic, diagnostic, and iron overload monitoring services in the centers

All the centers declared to be able to provide standard care in terms of transfusion therapy, periodic visits, and standard laboratory tests (including ferritin level, liver and renal function, red and white blood cells count, etc.).

On the contrary, a total of 19 centers (31.6%, corresponding to 27.9% of all patients) declared not to be equipped for performing one or more of the specialized visits and the laboratory tests required for the management of special patient' needs (i.e. management of complications), including endocrinology (11 out 19 centers), cardiology (6 out 19 centers), fibroscan, and bone densitometry (6 out 19 centers). To cover these needs patients were referred to other centers.

The majority of centers (40 out of 60; corresponding to 66.6%), were not equipped for measuring hepatic iron concentration, while 42 centers (70%) were not equipped for performing cardiac MRI (Table 3). Our analysis demonstrated that there were no statistically significant differences among centers located in

Table 2 Type, size, and patients' population by geographical area

	North ($n = 21$)	Center ($n = 8$)	South ($n = 12$)	Island ($n = 19$)
Type				
Blood transfusion services	7 (33.3%)	5 (62.5%)	4 (30.8%)	4 (22.2%)
Adult clinical units	2 (9.5%)	3 (37.5%)	7 (53.8%)	10 (55.6%)
Pediatric clinical units	12 (57.1%)	0	2 (15.4%)	4 (22.2%)
Size				
Small centers	13 (61.9%)	4 (50%)	0	3 (16.7%)
Medium centers	7 (33.3%)	2 (25%)	5 (38.5%)	4 (22.2%)
Large centers	1 (4.8%)	1 (12.5%)	7 (53.8%)	8 (44.4%)
Very large centers	0	1 (12.5%)	1 (7.7%)	3(16.7%)

Table 3 Stratification of centers by service provision

	Size			Type			Geographic area		All centers
	Centers with < 30 patients (*n* = 38)	Centers with 30 – 80 patients (*n* = 17)	Centers with > 80 patients (*n* = 5)	Pediatric clinical centers (*n* = 18)	Adult clinical centers (*n* = 22)	Transfusion services (*n* = 20)	North-Center (*n* = 29)	South-Island (*n* = 31)	60
At least one visit/lab not available*	11/38 (28.9%)	6/17 (35.3%)	2/5 (40.0%)	3/18 (16.7%)	7/22 (31.8%)	9/20 (45%)	9 (31%)	10 (32.3%)	19/60 (31.6%)
Hepatic IOM not available†	24/38 (63.2%)	14/17 (82.4%)	2 (40.0%)	10/18 (55.6%)	16/22 (72.7%)	14/20 (70%)	17 (58.6%)	23 (74.2%)	40/60 (66.6%)
Cardiac MRI not available	27/38 (71.1%)	13/17 (76.5%)	2 (40.0%)	12/18 (66.7%)	16/22 (72.7%)	14/20 (70%)	19 (65.5%)	23 (74.2%)	42/60 (70%)

*At least one visit/laboratory test among: hematology, cardiology, endocrinology, gynecology, ophthalmology, otorinology, hepatology, orthopedy, pneumology, bone densitometry, fibroscan.
†Iron Overload Monitoring: at least one examination among: hepatic MRI, SQUID, and hepatic biopsy.

different geographic areas and among centers of different size, as well as between pediatric and adult centers or transfusion centers.

Patients' registry

Demographic characteristics

Of a total of 1899 patients in the Registry, 1873 had a confirmed diagnosis of beta-Thalassemia major and were included in the analysis. The remaining 26 were excluded from the analysis because affected by Thalassemia intermedia.

The gender distribution was balanced between males (47.5%) and females (52.5%). The overall mean age (± SD) was 30.21 ± 11.04 years. The youngest patient was 50 days-old and the oldest patient was 65 years old. Data show that 68.5% of patients aged more than 45 years were women (74 out of 108). Globally, 259 patients were pediatrics (13.8% out of the total) of which 8.1% were under 12 years of age.

The age distribution of the patient population in the adult and pediatric units was not homogeneous. On a total of 407 patients referred from pediatric units, 120 (29.5%) were pediatric, while the remaining 287 (70.5%) were adults. In contrast, the majority of pediatric patients (53.7% of the total pediatric patients) were treated in adult units.

Detailed data on the age distribution in pediatric and adult centers are provided in Fig. 2.

Chelation therapy

In terms of chelation treatment, 448 patients (23.9%) resulted to be prescribed deferoxamine (DFO), 383 (20.5%) DFP, 616 (32.8%) deferasirox (DFX), and 399 patients (21.3%) a combination of DFO and DFP administered associated (257 patients, 13.7%) or sequentially (142 patients, 7.6%). Twenty-one children, all aged less than 4 years, are not treated with any chelator (Fig. 3).

When treatment was stratified by age groups, DFO resulted to be the commonest chelator in the age group > 45 years, while DFX was the most used chelator in children and young adults (aged less than 25 years).

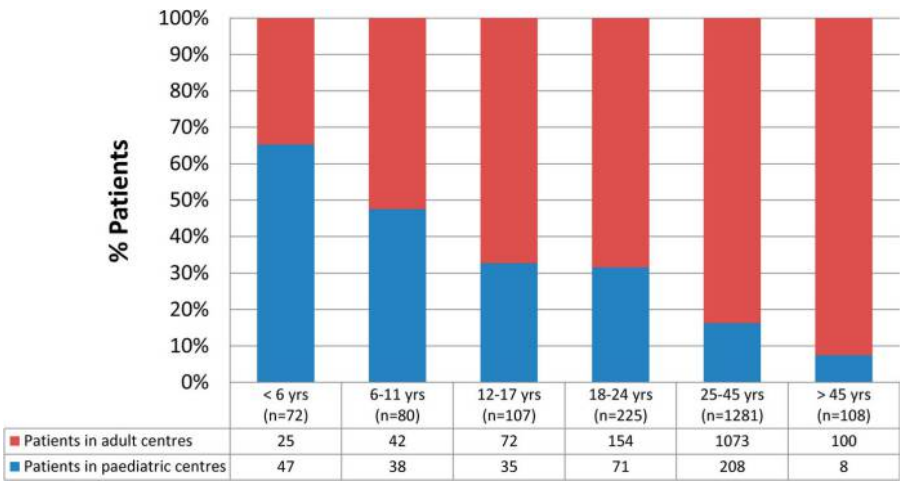

Figure 2 Patients' distribution by age.

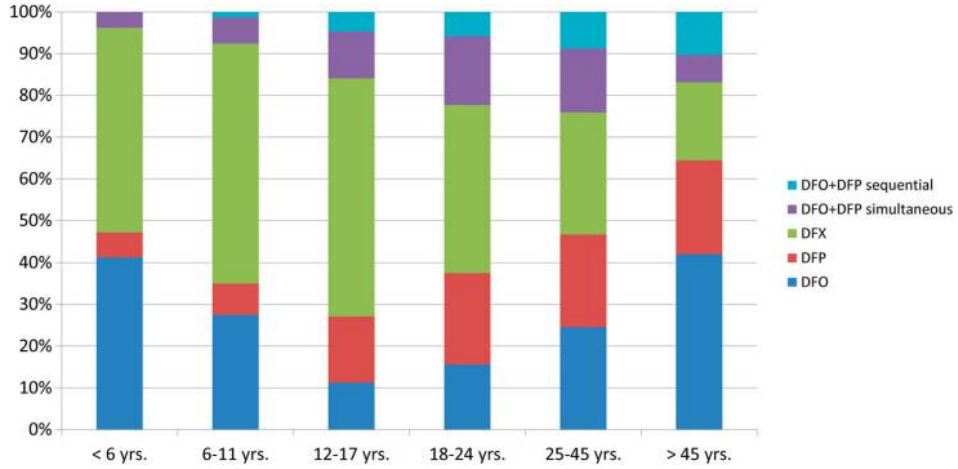

Figure 3 Percentage of patients on different chelation regimens in each age group.

Table 4 Differences in chelation prescription rate among centers

Chelation therapy	Prescription rate at 60 centers	Mean – Median
DFO	2.8–67.8%	27.4% – 20.4%
DFP	2.0–52.2%	24.2% – 14.7%
DFX	8.1–75%	37.8% – 33.3%
Combined DFO+DFP	4.8–66%	18% – 16.7%

The mean age for combined iron chelation therapy was 30.9 ± 8.6 years for associated DFO/DFP therapy and 33.1 ± 8.2 years for sequential DFO/DFP.

The analysis stratified by center shows a great variability in the prescriptive medical approach. The prescription rate for DFO varied from 2.8 to 67.8% of patients and the prescription rate for DFP monotherapy ranged from 2 to 50%, depending on the referring center. DFX was consistently used as monotherapy with a frequency as high as 75% of patients in some centers. However, the DFO/DFP combined therapy was prescribed in almost every center (Table 4). No correlation with geographic area, centers' size or other center' characteristics was identified by our analysis.

Iron overload monitoring procedures

Out of 1873 patients in this Registry, 1852 resulted receiving some kind of chelation treatment. Of these, 1082 patients (58.4%) were monitored for liver iron overload in the last calendar year, using one or more monitoring procedures among biopsy, SQUID, and T2* MRI. Remarkably, 1035 patients (55.9% of our sample) were monitored with cardiac T2* MRI. In particular, 970 patients (corresponding to 52.4% of the total) were assessed by both cardiac and liver MRI, while 770 (41.6%) and 817 (44.1%) did not receive any hepatic or cardiac iron overload monitoring, respectively. Twenty-one patients were excluded by this analysis because they were not receiving iron chelation treatment.

Table 5 indicates that the percentage of patients evaluated with MRI increases with age ($P < 0.001$), while SQUID was more frequently performed in patients aged 6–12 years.

Table 6 shows that the patients treated in large centers (with 30–80 patients in care) were monitored significantly more frequently than patients that refer to smaller (with < 30 patients) or bigger (with > 80 patients) centers.

Discussion and conclusion

Disease registries represent an important resource for epidemiological, clinical, or disease management studies.[17]

In the context of Thalassemia and other HPs, reports from the existing registries indicate how they are effective in providing information on the geographical distribution, the genetic epidemiology, the patients' clinical outcomes and/or survival[18,19] or for the evaluation of the efficacy or the weakness of the current prevention programs.[20,21] More recently, data from registries have become instrumental to guide Health Authorities and managers to set up and organize adequate Health Care Systems and treatments plans.

The inventory made in the context of this project carries some limitations such as: (1) the partial coverage of the existing Italian centers and patients particularly in the north of Italy, (2) the strict criteria defined by the approved study protocol which allow the inclusion in the data collection of only beta-Thalassemia major patients, (3) the time required to complete and to validate the data collected from such a large group of centers, which delayed the availability of these results to the public domain. Notwithstanding such limitations, the reported information significantly contribute to map the

Table 5 Iron overload monitoring procedures by age groups

Iron monitoring examination	Patients age							
	<6 years (*n* = 51)	6–11 years (*n* = 80)	12–17 years (*n* = 107)	18–24 years (*n* = 225)	25–45 years (*n* = 1281)	>45 years (*n* = 108)	Total (*n* = 1852)	*P*
Hepatic Monitoring (Total)*	12 (23.5%)	37 (46.2%)	45 (42%)	142 (63.1%)	772 (60.3%)	59 (54.6%)	1067 (62.6%)	<0.001
Hepatic T2* MRI†	7 (13.7%)	20 (25.0%)	52 (48.6%)	131 (58.2%)	737 (57.5%)	56 (51.9%)	1003 (54.2%)	<0.001
Hepatic SQUID‡	6 (11.8%)	20 (25.0%)	13 (12.1%)	13 (5.8%)	55 (4.3%)	5 (4.6%)	112 (6%)	<0.001
Cardiac T2* MRI§	6 (11.8%)	25 (31.3%)	56 (52.3%)	137 (60.9%)	756 (59%)	55 (50.9%)	1035 (55.9%)	<0.001
Hepatic and cardiac T2* MRI¶	6 (11.8%)	18 (22.5%)	49 (45.8%)	128 (56.9%)	716 (55.9%)	53 (49.1%)	970 (52.4%)	<0.001

*Significative differences between: <6years vs 18–24years, 25–45 years, >45 years; 12–17 years vs 25–45 years and >45 years.
†Significative differences between: <6years and 6–11years vs 12–17 years, 18–24years, 25–45 years, >45 years.
‡Significative differences between: 6–11years vs 18–24years, 25–45 years, >45 years; 12–17years vs 25–45years.
§Significative differences between: <6years and 6–11years vs 12–17years, 18–24years, 25–45 years, >45 years.
¶Significative differences between: <6years and 6–11years vs 12–17years, 18–24years, 25–45 years, >45 years.

Table 6 Iron overload monitoring procedures by size

	Size of patients' referring center			
	Centers with <30 patients	Centers with 30 – 80 patients	Centers with > 80 patients	*P*
Patients undergoing hepatic MRI/SQUID	226/377 (59.9%)*	585/894 (65.4%)°	271/581 (46.6%)*,°	<0.001
Patients undergoing cardiac T2* MRI	216/377 (57.3%)*	547/894 (61.2%)ᵠ	272/581 (46.8%)*,ᵠ	<0.001
Patients undergoing hepatic and cardiac T2* MRI	180/377 (47.7%)*	546/894 (61.1%)*,ᵠ	244/581 (42.0%)ᵠ	<0.001

For each row in the table statistically significant comparisons are indicated with a symbol of the same type.

Thalassemia centers (in terms of patient population, structures, and services availability) by reporting the highest number of therapeutic centers (either exclusively dedicated to Thalassemia or not dedicated) so far described in Italy by different sources.[13–15, 22–25]

In particular, this analysis indicate that therapeutic centers and services, in Italy are extremely heterogeneous in terms of age of patients in care (adult vs pediatric), typology (clinical settings versus transfusion settings), size (from very small to very large), and range of services offered to the patients (medical expertise, laboratory services, and iron overload monitoring tools).

One common characteristic across the centers is the co-presence of both pediatric and adult patients within the same setting, and generally centers that exclusively manage pediatric patients do not exist.

These data also underline that in Italy, as happens in other countries,[26,27] the transition of pediatric patients to adult care is still an unsolved issue. Several authors argue that this is because of the complexity of Thalassemia as disease as a whole, coupled with the changing organization and costs of Health care systems.[27,28] Recent guidelines [i.e. Thalassemia International Federation (TIF) Guidelines, 2008; Guidelines for the Clinical Care of Patients with Thalassemia in Canada, 2009][7,29] recognize the importance of this issue and clearly state that "the transition from pediatric to the adult care setting is a stressful time for young", claiming for "a standardized process" to ensure that "proper steps are taken to equip and prepare the individual for transition".

In relation to the size of the centers, besides many large or very large centers, also 20 very small clinical settings (with less than 10 patients) were identified in the survey and were included in the analysis as they provide information on the type of services, therapies, and diagnostic tools offered in small-scale settings which are indeed scattered across the territory. Moreover it is generally acknowledged that networking reference with peripheral or small centers often provides better care for patients living far from the larger centers. This aspect should be appropriately considered by the local and national Health Care providers when evaluating the cost-efficiency of centers, also in consideration that regular treatment and monitoring of Thalassemia patients in specialized centers is critical for their overall survival.[5]

The most concerning result of the analysis is that a large percentage of centers (ranging from 30 to 42%)

are not equipped to offer on-site services and procedures for patients' monitoring (for iron overload and/or management of complications) as recommended in the current Thalassemia management guidelines.[30–32] The insufficient availability of services, in particular of MRI equipment in validated and standardized sites[2] requires greater attention of the medical and public Health providers, since MRI-based technologies are currently considered the gold standard for monitoring iron accumulation in different organs[1,4,30,31,33] and recommended as part of routine patient care.[7,26,29–32,34]

Moreover, although the availability of MRI scans in Italy is increasing also thanks to cooperative MRI networks like MIOT.[35] the implementation of both cardiac and liver MRI assessments seems to differ from the existing recommendations[30,31] in term of thresholds for defining risk condition and starting age at which it would be appropriate to have MRI.[22,36,37] The data collected by the Registry confirm that a considerable percentage of children under 10 years of age is being monitored with cardiac and hepatic MRI, even in lack of an evidence-based consensus.

The above observations indicate the importance of defining the suitable number of MRI equipment for monitoring all the patients present on the territory, balancing the extension of the population age admitted to the procedure, the required technical characteristics of MRI equipment and the associated costs.[35,38,39]

Overall, this analysis allows several considerations:

The mean age of the patient population is 30.21 ± 11.04 years and the small age-advantage for females elsewhere described[40,41] is also confirmed in this study. On the other hand, in our sample an important segment of the population (18.6%) is aged > 40 years, and a remarkably large portion (74% of the thalassemic population) is older than 25 years. The oldest beta – Thalassemia major patient recorded in the Registry is 65 years old. This finding is in line with other epidemiological data reporting that the mean age of patients shifted from 5 years of age in 1965 to 27 years of age in 1995[2], while in the last series of patients reported by Borgna-Pignatti in 2010[42] 60% of patients were older than 30 years. More recent data also claimed for the complete eradication of the child mortality and a significant improvement of life expectancy of Thalassemia patients over the last 7–8 years.[43,44] However, despite in Italy prevention strategies (carrier screening, genetic counseling, and prenatal diagnosis) have been implemented for many years determining a dramatic reduction of affected new births,[45] an important part (13.8%) of the beta-Thalassemia population of our sample is still of pediatric age, (and 8.1% is under 12 years), showing an increase in two percentage points compared to the published interim analysis.[12] We can speculate that the reported new affected births may rather be the consequence of the increasing impact of migratory flows from countries with a higher prevalence of Thalassemia and lower attitude to prevention as also previously described in Italy and in Greece,[21] as well as of a modified reproductive attitude of the Thalassemia population.

In terms of iron chelators use, data evaluated in this patients group do not differ substantially from what reported by Ceci *et al.*, 2011.[12] The 2011 publication referred to a cohort of 981 patients and demonstrate that oral chelators are overtaking DFO. Moreover, oral chelators , mainly DFX (the most used chelator as monotherapy), are more widespread among the young population including patients aged less than 6 years, although they are not approved as first line treatment in this group of age. Nevertheless, our data also show that DFO is still an important therapeutic option for older patients and for those at high risk of iron toxicity, particularly when associated to DFP thanks to the efficacy demonstrated by the combined use of the two chelator in decreasing cardiac mortality and morbidity or, more recently, in reducing or even resolving endocrine complications.[46] This combined use is well consolidated in the Italian population where, combined data from HTA-Thal Registry and other available patients' database and publications,[22,39] estimate that not less than 25% of patients are using the DFO/DFP combination. However, different schedules and dosages are adopted in different centers and a prescription model based on the appropriate evaluation of the risk-benefit profile and the patient characteristics urgently needs to be better defined.[39]

Concluding, this analysis confirms the utility of patients' Registries for the collection of large set of data. In particular, the considerations derived from this data set highlight how the use of large, well-monitored patients' registries can guide Health Authorities and Health providers to plan cost-efficient services and to meet patients' needs and expectations. This is particularly important for the appropriate evaluation of the needs arisen by the changing population of patients affected by HPs that, for effect of the growing migration flow are living in Italy,[47] posing considerable new challenges in terms of services and tools to be provided.

Finally, as a large proportion of European and Mediterranean countries are experiencing the same progressive change in epidemiology and are facing similarly increased clinical and economic burden of the disease, the HTA-THAL Registry may represent a valuable "case study" for the definition of a useful model of multi-specialized centers for the treatment

of HPs to be applied at the European and the international level.

Disclaimer statements

Contributors All authors fulfill the authorship criteria and contributed as following described: R. Conte analyzed the data and wrote the manuscript. L. Ruggieri supported the data analysis and wrote the manuscript. A. Gambino analyzed the data and performed the statistical analysis. F. Bartoloni planned, created, and managed the electronic database. P. Baiardi performed the statistical analysis. D. Bonifazi designed the research study and commented on the manuscript. F. Bonifazi designed the research study and commented on the manuscript. M. Felisi analyzed the data and commented on the manuscript. V. Giannuzzi collaborated to research study design and commented on the manuscript. R. Padula collaborated to research study design, collected data and populated the electronic database. A. Pepe collaborated to data collection and commented on the manuscript. M.C. Putti collaborated to data collection and commented on the manuscript. G.C. Del Vecchio collaborated to data collection and commented on the manuscript. A. Maggio collaborated to data collection and commented on the manuscript. A. Filosa collaborated to data collection and commented on the manuscript. A. Iacono designed the research study and collaborated to data collection. L. Mangiarini designed the research study, analyzed the data, and wrote the manuscript. A. Ceci designed the research study, analyzed the data, and wrote the manuscript.

Funding None.

Conflict of interest The authors report no potential conflicts of interest to disclose.

Ethics approval The study received approval by each competent Ethics Committee.

References

1 Maggio A, Capra M, Pepe A, Mancuso L, Cracolici E, Vitabile S, *et al.* A critical review of non invasive procedures for the evaluation of body iron burden in thalassemia major patients. Pediatr Endocrinol Rev. 2008;6(Suppl 1):193–203. Review.

2 Tanner MA, He T, Westwood MA, Firmin DN, Pennell DJ. Thalassemia International Federation Heart T2* Investigators. Multi-center validation of the transferability of the magnetic resonance T2* technique for the quantification of tissue iron. Haematologica. 2006;91(10):1388–91.

3 Meloni A, Positano V, Ruffo GB, Spasiano A, D'Ascola DG, Peluso A, *et al.* Improvement of heart iron with preserved patterns of iron store by CMR-guided chelation therapy. Eur Heart J — Cardiovasc Imaging 2014;177(3):1012–9.

4 Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ. Improved survival of Thalassemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2008;10:42.

5 Forni GL, Puntoni M, Boeri E, Terenzani L, Balocco M. The influence of treatment in specialized centers on survival of patients with thalassemia major. Am J Hematol. 2009;84(5):317–8.

6 Angastiniotis M, Eleftheriou A. Requirements for a reference or expert Thalassemia center: the structure/model for centers dealing with chronic/hereditary blood disorders. Hemoglobin. 2009;33(Suppl 1):S204–10.

7 Cappellini MD, Cohen A, Eleftheriou A, Piga A, Porter J, Taher A. Guidelines for the Clinical Management of Thalassemia, 2nd Rev 2008. Thalassemia International Federation (TIF) Publication.

8 United Kingdom Thalassaemia Society. Standards for the clinical care of children and adults with thalassaemia in the UK (2008). 2nd Edition. Available from: http://www.hbpinfo.com/ukts-standards-2008.pdf.

9 Aguilar Martinez P, Angastiniotis M, Eleftheriou A, Gulbis B, Mañú Pereira Mdel M, Petrova-Benedict R, *et al.* Haemoglobinopathies in Europe: health & migration policy perspectives. Orphanet J Rare Dis. 2014;9:97.

10 NHS Commissioning Board (2013) 2013/14 NHS Standard contract for specialized services for haemoglobinopathy care (all ages). Available from: http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b08/.

11 Rete Interregionale per la Thalassemia: HTA dei percorsi diagnostico-strumentali e terapeutici e monitoraggio dell'accumulo di ferro (HTA-Thal) (2008) Rif. nota del Ministero della Salute n. DGRST.4/2760-P/I.9.a.b del 2.05.2007 e DGR Basilicata nn. 1591/07 e 201/08.

12 Ceci A, Mangiarini L, Felisi M, Bartoloni F, Ciancio A, Capra M, *et al.* The management of iron chelation therapy: preliminary data from a national registry of thalassaemic patients. Anemia. 2011;2011:43568. DOI:10.1155/2011/435683.

13 Ceci A, Baiardi P, Felisi M, Cappellini MD, Carnelli V, De Sanctis V, *et al.* The safety and effectiveness of deferiprone in a large-scale, 3-year study in Italian patients. Br J Haematol. 2002;118(1)330–6.

14 Meloni A, Ramazzotti A, Positano V, Salvatori C, Mangione M, Marcheschi P, *et al.* Evaluation of a web-based network for reproducible T2* MRI assessment of iron overload in thalassemia. Int J Med Inform. 2009;78(8):503–12.

15 Ministry of Health. MinistryDecree n. 279/2001 recante "Regolamento di istituzione della rete nazionale delle malattie rare e di esenzione dalla partecipazione al costo delle relative prestazioni sanitarie" ai sensi dell'articolo 5, comma 1, lettera b) del decreto legislativo 29 aprile 1998, n. 124. Gazzetta Ufficiale n. 160 Supplemento Ordinario n.180/L. 2001 Jul 12.

16 Rare Diseases Register. Rare diseases center-Venetian Region-Italy. Available from: http://malattierare.regione.veneto.it/default.htm.

17 Gliklich RE, Dreyer NA, eds. Registries for evaluating patient outcomes: a user's guide. 2nd ed. AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. 2010.

18 Thuret I, Pondarré C, Loundou A, Steschenko D, Girot R, Bachir D, *et al.* Complications and treatment of patients with β-thalassemia in France: results of the National Registry. Haematologica. 2010 May;95(5):724–9.

19 Modell B, Khan M, Darlison M, King A, Layton M, Old J, *et al.* A National register for surveillance of inherited disorders: beta thalassemia in the United Kingdom. Bull World Health Organ: Int J Public Health. 2001;79(11):1006–13.

20 Voskaridou E, Ladis V, Kattamis A, Hassapopoulou E, Economou M, Kourakli A, *et al.* A national registry of haemoglobinopathies in Greece: deducted demographics, trends in mortality and affected births. Ann Hematol. 2012;91(9):1451–8.

21 Ladis V, Karagiorga-Lagana M, Tsatra I, Chouliaras G. Thirty-year experience in preventing haemoglobinopathies in Greece: achievements and potentials for optimisation. Eur J Haematol. 2013;90(4):313–22.

22 Piga A, Longo F, Musallam KM, Cappellini MD, Forni GL, Quarta G, *et al.* Assessment and management of iron overload in β-Thalassemia major patients during the 21st century: a real-life experience from the Italian WEBTHAL project. Br J Haematol. 2013;161(6):872–83.

23 Assessorato per la Sanità, Dipartimento Attività Sanitarie e Osservatorio Epidemiologico, Regione Siciliana (2009) Registro Siciliano Talassemia ed Emoglobinopatie (RESTE) – Aggiornamento al 31/12/2009.

24 Fondazione Italiana Leonardo Giambrone per la Guarigione dalla Talassemia. La talassemia, Strutture di assistenza clinica per pazienti talassemici. Available from: http://www.fondazionegiambrone.it/la-Thalassemia.

25 Scalone L, Mantovani LG, Krol M, Rofail D, Ravera S, Bisconte MG, *et al.* Costs, quality of life, treatment satisfaction and compliance in patients with beta-thalassemia major undergoing iron chelation therapy: the ITHACA study. Curr Med Res Opin. 2008;24(7):1905–17.
26 Yardumian A, Telfer P, Constantinou G, Darbyshire P, Darlison M, Kinsey SE, *et al.* Standards for the clinical care of children and adults with thalassemia in the UK. United Kingdom Thalassemia Society 2008. Available from: http://www.hbpinfo.com/ukts-standards-2008.pdf.
27 Levine L, Levine M. Health care transition in thalassemia: pediatric to adult-oriented care. Ann N Y Acad Sci. 2010;1202:244–7.
28 Bryant R, Walsh T. Transition of the chronically ill youth with hemoglobinopathy to adult health care: an integrative review of the literature. J Pediatr Health Care. 2009;23(1):37–48.
29 Sayani F, Warner M, Wu J, Wong-Rieger D, Humphreys K, Odame I. Guidelines for the clinical care of patients with thalassemia in Canada 2009, pp.1–84. Available from: http://www.thalassemia.ca/wp-content/uploads/Thalassemia-Guidelines_LR.pdf.
30 Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanello R, *et al.* Cardiovascular function and treatment in β-thalassemia major: a consensus statement from the American heart association. Circulation. 2013;128(3):281–308.
31 Cogliandro T, Derchi G, Mancuso L, Mayer MC, Pannone B, Pepe A, *et al.* Guideline recommendations for heart complications in thalassemia major. J Cardiovasc Med (Hagerstown). 2008;9(5):515–25.
32 Angelucci E, Barosi G, Camaschella C, Cappellini MD, Cazzola M, Galanello R, *et al.* Italian Society of Hematology practice guidelines for the management of iron overload in Thalassemia major and related disorders. Haematologica. 2008;93(5):741–52.
33 Wood JC. Impact of iron assessment by MRI. Hematology Am Soc Hematol Educ Program. 2011;2011:443–50.
34 Vichinsky E, Levine L, Bhatia S, Bojanowski J, Coates T, Foote D, *et al.* Standards of care guidelines for thalassemia. Oakland, California: Children's Hospital & Research Center 2012. Available from: http://hemonc.cho.org/thalassemia/documents/SOCGuidelines2012.pdf.
35 Berdoukas V, Wood J. In search of the optimal iron chelation therapy for patients with thalassemia major. Haematologica. 2011;96(1):5–8.
36 Berdoukas V, Nord A, Carson S, Puliyel M, Hofstra T, Wood J, *et al.* Tissue iron evaluation in chronically transfused children shows significant levels of iron loading at a very young age. Am J Hematol. 2013;88(11):E283–5.
37 Borgna-Pignatti C, Meloni A, Guerrini G, Gulino L, Filosa A, Ruffo GB, *et al.* Myocardial iron overload in Thalassemia major. How early to check? Br J Haematol 2014;164(4):579–85.
38 Bonifazi F, Chiarolla E, Felisi M, Maggio A, Ceci A. MRI iron overload monitoring tools in Italy: results from the Italian Thalassemia Registry Proceedings of the 13th International Conference on Thalassemia & Hemoglobinopathies. Thalassemia International Federation (TIF) World Congress 2013 Oct 20–23; Abu Dhabi, UAE.
39 Pepe A, Meloni A, Rossi G, Cuccia L, D'Ascola GD, Santodirocco M, *et al.* Cardiac and hepaticiron and ejection fraction in thalassemia major: multicenter prospective comparison of combined deferiprone and deferoxamina therapy against deferiprone or deferoxamina monotherapy. J Cardiovasc Magn Reson. 2013;16;15(1):1. DOI:10.1186/1532-429X-15-1.
40 Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, *et al.* Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004;89(10):1187–93.
41 Marsella M, Borgna-Pignatti C, Meloni A, Caldarelli V, Dell'Amico MC, Spasiano A, *et al.* Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. Haematologica. 2011;96(4):515–20.
42 Borgna-Pignatti C. The life of patients with Thalassemia major. Haematologica. 2010;95(3):345–8.
43 Telfer PT, Coen PG, Christou S, Hadjigavriel M, Kolnakou A, Pangalou E, *et al.* Survival of medically treated thalassemia patients in Cyprus. Trends and risk factors over the period 1980–2004. Haematologica. 2006;91(9):1187–93.
44 Maggio A, Vitrano A, Capra M, Cuccia L, Gagliardotto F, Filosa A, *et al.* Improving survival with deferiprone treatment in patients with Thalassemia major: a prospective multicenter randomised clinical trial under the auspices of the Italian Society for Thalassemia and Hemoglobinopathies. Blood Cells Mol Dis J. 2009;42(3):247–51.
45 Cao A, Kan YW. The prevention of thalassemia. Cold Spring Harb Perspect Med 2013;3(2):a011775.
46 Chirico V, Rigoli L, Lacquaniti A, Salpietro V, Piraino B, Amorini M, *et al.* Endocrinopathies, metabolic disorders, and iron overload in major and intermedia thalassemia: serum ferritin as diagnostic and predictive marker associated with liver and cardiac T2* MRI assessment. Eur J Haematol. 2015;94(5):404–12.
47 Martinez A, Angastiniotis M, Eleftheriou A, Gulbis B, Del Mar Mañú Pereira M, Petrova-Benedict R, *et al.* Haemoglobinopathies in Europe: health & migration policy perspectives. Orphanet J Rare Dis. 2014;9:97. DOI:10.1186/1750-1172-9-97.