ThalassemiaNEWS

A quarterly newsletter keeping the medical and patient community in touch with thalassemia developments

Issue 3 2025

IN PROFILE

An in-depth view of an organization or individual involved in thalassemia

In this issue, we bring you excerpts from an interview with Dr Antonella Meloni of the Bioengineering Unit, Toscana Gabriele Monasterio Foundation, Pisa, and Dr Paolo Ricchi, Internist from Azienda Ospedaliera Antonio Cardarelli, Napoli, who are involved with the Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) network in Italy. The E-MIOT network has greatly benefitted from the combined skills and interests of Dr Meloni, who trained as a biomedical engineer, and Dr Ricchi's background as a hematologist.

Dr Antonella Meloni
Bioengineering Unit, Toscana Gabriele Monasterio Foundation, Pisa

Dr Paolo Ricchi
Internist from Azienda Ospedaliera Antonio Cardarelli

What was the inspiration to create E-MIOT?

The MIOT project was launched in 2006 to evaluate MRI as a possible methodology to measure hepatic and cardiac iron overload. The project was conceptualized by the Radiology department at the Toscana Gabriele Monasterio Foundation, Pisa, and thalassemia was identified as an obvious case study given the high prevalence of cardiac mortality and morbidity. MIOT has been successful because of this ongoing collaboration between leading MRI and thalassemia care centers across Italy. In 2015, the E-MIOT project was started, with the aim of adding the quantification of pancreatic iron levels.

What were the key challenges that had to be overcome?

It has taken a lot of time and effort to develop the network of 15 MRI centers and 70 thalassemia care centers that exists now. At the time we started, MRI was a relatively new technology for the assessment of iron overload, and using a network was unproven in thalassemia – so we had some skepticism to overcome, and there were many energetic discussions about the pros and cons of multislice T2* for assessing myocardial iron distribution as the methodology to use! Ensuring standardization of MRI technique across the network required us to develop detailed training protocols including visits to the MRI centers. Two areas of maintained focus are communication, and training. These help us maintain high quality standards and keep driving us forwards.

What are the main benefits you have seen from E-MIOT?

From a thalassemia perspective, the pooled data from E-MIOT centers is large enough to test hypotheses and perform meaningful analyses beyond anything that could be achieved as a single center. From a radiological perspective, E-MIOT has supported professional development through learning and applying new techniques and protocols. Together, we have learned more through this collaboration than we could have learned working alone, and we have the support of a wide network of colleagues.

What are research questions you hope to answer in the future?

The E-MIOT database contains multiple variables from a large cohort of thalassemia patients, and so there is always a long list of potential research questions! As life expectancy in thalassemia has increased, we have started to observe broader cardiac problems including atrial fibrillation, cardiac decompensation, and pulmonary hypertension. These need further evaluation. MIOT includes data from non-transfusion-dependent thalassemia patients, so we can start to compare different populations. Importantly, cardiac MRI methodology continues to evolve and develop, and we also have exciting ongoing research into measures of parietal stress.

KEY DATES

October 28th – November 1st 2025 São Paulo, Brazil
Brazilian Congress of Hematology, Hemotherapy and Cell Therapy (HEMO 2025)

November 13th–14th 2025 Paris, France
21st Global Summit on Hematology and Blood Disorders

December 6th–9th 2025 Orlando, US
67th ASH Annual Meeting and Exposition

THA-ALL-0244 / Date of preparation November 2025
The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals.
Medical writing support provided by Bright Red Fox Creative is funded by Agios.

IN-DEPTH: THALASSEMIA NETWORK IN ITALY IMPROVES PATIENT OUTCOMES

Thalassemia is a complex disease characterized by a range of non-specific symptoms, such as fatigue, and associated with a risk of developing serious comorbidities[1]. Patients with thalassemia can develop iron overload as a consequence of either the underlying pathophysiology or the frequent blood transfusions needed to manage anemia[1]. Excess iron accumulates in essential organs such as the heart and liver which can lead to serious health issues if not properly managed[1]. A ten-fold increase in mortality risk has been reported for patients with non–transfusion-dependent thalassemia with serum ferritin levels above 800 ng/mL relative to patients with lower serum ferritin levels[2], and a recent retrospective analysis highlighted the association between management of anemia and iron with morbidities and mortality, in both transfusion-dependent, and non-transfusion-dependent thalassemia[3]. Indeed, iron-induced heart failure is a leading cause of death among patients with transfusion-dependent thalassemia[4]. Regular administration of iron-chelation agents to protect organs from damaging exposure to unbound iron significantly reduces the risk of mortality[4,5]. Accurate determination of iron accumulation in the liver[6] and heart can be achieved non-invasively using T2* magnetic resonance imaging (T2* MRI), thereby facilitating the tailoring of treatment[7], but this technique is not readily available to all patients with thalassemia.

Myocardial Iron Overload in Thalassemia (MIOT) network in Italy

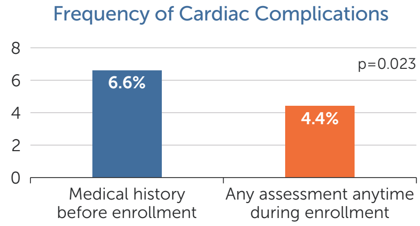
In Italy, there are more than 12,000 patients with thalassemia,[8] many of whom historically had to travel a considerable distance to undergo iron accumulation monitoring by T2* MRI. To facilitate nationwide improvement in the care of thalassemia, a collaborative network of thalassemia and MRI centers, the Myocardial Iron Overload in Thalassemia (MIOT) network, was established[9]. The MIOT network now comprises 70 thalassemia centers and 10 MRI centers evenly distributed across the country. Access to high-quality MRI monitoring of iron accumulation has consequently increased, reducing the distance patients must travel for their assessment. This has made regular T2* MRI evaluation of cardiac iron overload feasible so iron chelation therapy can be tailored according to the actual level of iron accumulation. While the original focus of MIOT was to look at the heart, T2* imaging has also been used to assess the liver and pancreas, and the technique can be expanded to the kidneys and other organs.

In addition, the MIOT network has developed a novel approach for quantifying myocardial iron distribution, in which cardiovascular magnetic resonance (CMR) imaging assesses myocardial iron overload, biventricular function, and macroscopic myocardial fibrosis in a single scan[10,11]. Data from each of the centers are being pooled in a shared database to help improve the understanding of iron accumulation in thalassemia and its management. The MIOT database has enabled numerous scientific contributions and publications since its inception and is now recognized as one of the largest thalassemia databases in the world[12]. Data collected during the first 10 years of MIOT activity have recently been analyzed and are highlighted here along with summaries of other recent MIOT publications.

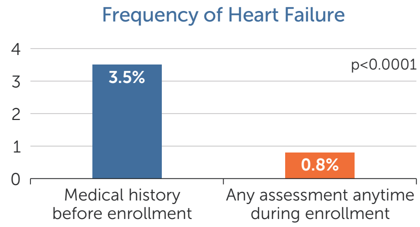
MIOT 10-year data[7]

This analysis was conducted on 1746 patients (mean age 31 years) with TDT who had received regular blood transfusions since birth, and were enrolled in the MIOT network. Myocardial iron accumulation was assessed by MRI every 18 months and iron-chelation therapy was tailored on an individual basis in line with the findings. The impact on cardiac iron levels, complications (heart failure, arrhythmia, pulmonary hypertension, myo/pericarditis, vascular diseases) and mortality were evaluated.

Ten years since the initiation of the MIOT network, the mean interval between the first and last available MRI assessments was 4.4 years. Changes from the first MRI to the last available MRI included significant reduction in cardiac iron levels, improvement in cardiac function, and lowering of cardiac complications. Myocardial iron overload was reduced in almost 70% of patients, and this was accompanied by increased cardiac efficiency.



Mean left ventricular ejection fraction had increased significantly at 18 and 36 months after the first assessment, and the frequency of heart failure decreased from 3.5 to 0.8% during the MIOT project ($p<0.0001$).



Tailoring of iron chelation treatment was implemented for almost half of patients and the authors conclude that the consequent reduction in cardiac iron overload led to the reduction in cardiac complications seen during the evaluation period.

Prospective evaluation of cardiac function[13]

Myocardial iron overload quantified by T2* MRI, biventricular function and macroscopic myocardial fibrosis were studied in 254 patients who are

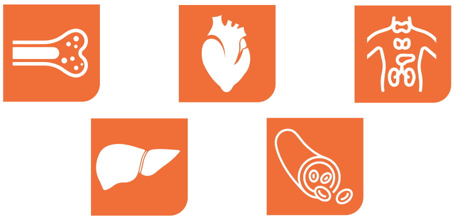
The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals.
Medical writing support provided by Bright Red Fox Creative is funded by Agios.

not regularly transfused and regularly transfused thalassemia intermedia (mean age 43 years) and were consecutively recruited to the MIOT project. Analyses revealed significant differences in patients who received regular blood transfusions compared with those who did not. Regular transfusion effectively reduced the impact of thalassemia on cardiac function (e.g., lower biventricular end-diastolic volume) and ventricular mass but was associated with a greater risk of cardiac iron accumulation.

Among those patients undergoing regular transfusion, serum ferritin level was found to be a strong predictor of global heart T2* values. However, cardiac T2* values were not associated with biventricular function. Although biventricular function was found to be similar irrespective of the presence of replacement myocardial fibrosis, myocardial fibrosis was a significant indicator of cardiac complications.

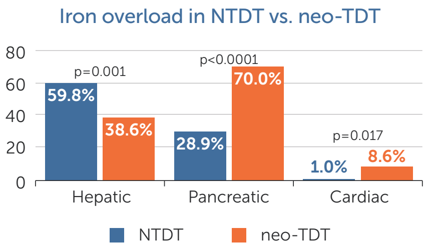
Prevalence of multi-organ iron overload and complications in non-transfusion and neo-transfusion thalassemia

Transfusion status in β-thalassemia can change over time; a recent publication by Musallam et al[14] showed an approximately 14% pheno-conversion rate over 10 years from non– to transfusion-dependent β-thalassemia. These patients that transitioned to TDT are referred to as 'neo-transfusion-dependent'[15]. Data from this population within the MIOT network has also recently been analyzed[16]. This was a cross-sectional analysis of multi-organ complications in 97 adults with NTDT and 140 adults with neo-transfusion -dependent (neo-TDT) (>4 transfusions per year) with β-thalassemia enrolled consecutively in the Extension-MIOT (E-MIOT) project. E-MIOT involves 66 thalassemia care centers and 12 MRI facilities in Italy. The analysis assessed the prevalence of bone, cardiac, endocrine, hepatic, and vascular complications.



Iron overload in different organs was assessed using MRI T2* / R2* values, and other complications were assessed using established clinical criteria.

Neo-TDT patients had significantly higher hemoglobin (mean Hb 9.55 ± 0.58 g/dL vs. 9.09 ± 1.07 g/dL, p<0.0001) and ferritin (mean serum ferritin 849.3 ± 908.5 ng/mL vs. 488.9 ± 337.4 ng/mL, p<0.0001) levels and a higher prevalence of hepatitis C virus infection (41.4% vs. 9.3%, p<0.0001) than NTDT patients. Liver iron overload was more common in NTDT patients (59.8% vs. 38.6%, p=0.001), whereas pancreatic and cardiac iron overload were significantly more frequent in the neo-TDT group.



No significant differences were observed in extramedullary hemato-poiesis, leg ulcers, hepatic cirrhosis, thrombosis, or pulmonary hypertension. Cardiac arrhythmias and impaired glucose metabolism were significantly more prevalent among neo-TDT patients. Bone disorders were the most common complication in both groups, with a significantly higher prevalence in neo-TDT (68.6% vs. 49.5%, p=0.003). The reasons for these differences are unclear, but may in part be due to patients initiating regular transfusions in response to clinical deterioration and potentially extended periods of untreated anemia.

Take home messages

- The MIOT network database is one of the largest repositories of thalassemia outcomes in the world[12].
- This national clinical and imaging network in Italy significantly increased the number of patients with TDT undergoing T2* MRI evaluation of iron overload to aid monitoring and management[7].
- Regulator monitoring has enabled tailored chelation therapy, leading to improved cardiac outcomes in patients with TDT[7].
- Regular transfusions were associated with less pronounced cardiac remodeling but an increased risk of myocardial iron accumulation[13].
- Comprehensive monitoring of cardiac and endocrine function should commence once regular transfusions are introduced[16].

1. Langer AL, Lombard L, Gilroy KS, et al. Poster 2351 Presented at the 64th ASH Annual Meeting and Exposition, December 10-13, 2022, New Orleans, LA, US.
2. Musallam KM, Vitrano A, Meloni A, et al. Am J Hematol. 2022;97:E78-80.
3. Musallam KM, Vitrano A, Inzerillo A, et al. B J Haem. 2025. https://doi.org/10.1111/bjh.70047.
4. Farmakis D, Porter J, Taher A, et al. Hemasphere 2022 Jul 29;6:e732.
5. Musallam KM, Vitrano A, Meloni, A, et al. Haematologica. 2021;106:2489-92.
6. Henninger B, Kremser C, Rauch S, et al. Eur Radiol. 2012 Nov;22:2478-86
7. Pepe A, Pistoia L, Gamberini MR, et al. European Heart Journal 2022;43:2482–92.
8. Angelucci E, Antmen A, Losi S, et al. Blood. 2017;130(suppl 1):3368.
9. Meloni A, Ramazzotti A, Positano V, et al. Int J Med Inform. 2009;78:503–512.
10. Meloni A, Maggio A, Positano V, et al. Eur Radiol. 2020;30:3217–25.
11. Pepe A, Meloni A, Rossi G, et al. Eur Heart J Cardiovasc Imaging. 2018;19:299–309.
12. Berdoukas V, Wood J. Haematologica 2011;96:5–8.
13. Meloni A, Pistoia L, Ricchi P. et al. Radiol Med. 2024;129, 879–89.
14. Musallam KH, Barella S, Origa R, et al. Am J Hematol. 2024;99:490-493.
15. Musallam KH, Cappellini MD, Viprakasit V, et al. Am J Hematol. 2021;2:E54-6.
16. Meloni A, Pistoia L, Ricchi P, et al. Blood Cells Mol Dis. 2025;115:102953. doi.org/10.1016/j.bcmd.2025.102953.

THA-ALL-0244 / Date of preparation November 2025
The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals.
Medical writing support provided by Bright Red Fox Creative is funded by Agios.

COMMUNITY RESOURCES

Discover new resources for thalassemia healthcare providers, patients, and their caregivers

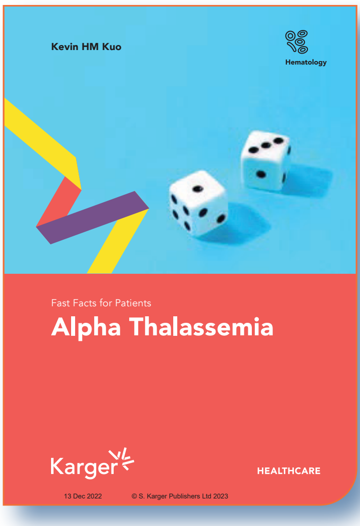
Thal Pals Podcasts

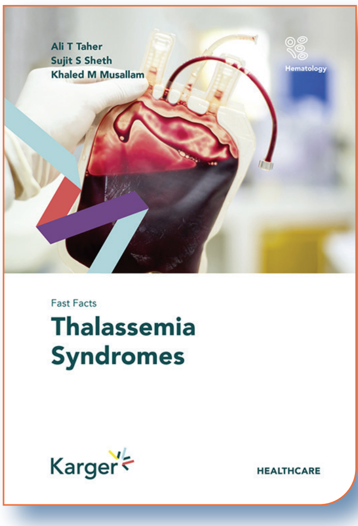
The thalassemia podcasts *Thal Pals: The Alpha Beta Revolution™* aims to facilitate ongoing collaboration between patients, caregivers, and medical experts. The monthly broadcasts feature members of the thalassemia community from around the world discussing currents topics relevant to both α- and β-thalassemia.

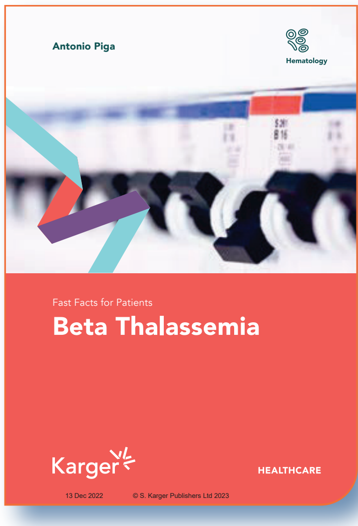
Thirty one episodes are available and can be accessed here:

Fast Facts

A series of educational booklets and information sheets written by experts for patients, families, and healthcare providers on the key topics of α-thalassemia and β-thalassemia.







Available in the following languages:

Thalassemia Syndromes: English, Arabic, Chinese, French, Italian, Spanish

Alpha-thalassemia: English, Arabic, Bengali, Chinese, French, Hindi, Italian, Spanish, Thai, Urdu, Vietnamese

Beta-thalassemia: English, Arabic, Bengali, Chinese, French, Hindi, Italian, Spanish, Urdu, Vietnamese

You can access and download the Fast Facts resources here:

THA-ALL-0244 / Date of preparation November 2025
The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals.
Medical writing support provided by Bright Red Fox Creative is funded by Agios.

CLINICAL RESEARCH UPDATE: THE ALPHA THALASSEMIA GLOBAL COHORT (AT | GC)

Sharing the latest news on clinical research in thalassemia

Until relatively recently, α-thalassemia was managed as a subtype of thalassemia, rather than the distinct condition it is now recognized to be[1]. Consequently, clinical data specific to α-thalassemia are extremely limited and treatment recommendations are typically based on expert opinion or extrapolations from β-thalassemia. Furthermore, the low incidence of α-thalassemia in many parts of the world combined with its broad spectrum of phenotypes and non-specific symptomatology, make diagnosis and treatment extremely challenging. To obtain evidence-based data that will inform effective diagnostic and treatment decisions, a global cohort study of α-thalassemia has just been approved. **The overall objective of this study is to build the evidence base for disease course, risk factors and treatment outcomes in α-thalassemia.**

This retrospective observational study will analyze pooled data for patients with a confirmed diagnosis of α-thalassemia with three gene deletions/mutations (hemoglobin H disease) registered at centers across the globe. The analysis will include clinical data collected from source documents at each participating center, from birth through December 2023.

Some of the key endpoint assessments are shown below.

Objective	Endpoints
• Evaluate genetic profiles	• Prevalence of specific deletions and mutations
• Evaluate morbidity and mortality	• Prevalence of morbidities • Morbidity-free survival • Survival rate • Age and cause of death
• Evaluate anemia course	• Change in levels of hemoglobin, lactate dehydrogenase, and bilirubin over time
• Evaluate course of iron overload	• Iron distribution in serum, heart and liver • Longitudinal changes in serum ferritin level, liver iron concentration and cardiac T2* MRI
• Evaluate management strategies in clinical practice	• Treatments received
• Evaluate healthcare resource utilization	• Number and cause of emergency room visits • Frequency and cause of hospitalisation
• Association analyses	• Correlations between evaluated risk factors and outcomes over the period of observation

Thalassemia centers are currently being invited to participate in this study. Further details of the study can be obtained from the Principal Investigator Khaled M Musallam by e-mailing
khaled.musallam@burjeelholdings.com

1. Thalassaemia International Federation. Guidelines for the Management of α-thalassaemia. 2023. Eds. Amid A, Lal A, Coates TD, Fucharoen S. ISBN 978-9963-717-28-6

EDITORIAL POLICIES & TEAM

The objective of this newsletter is to provide updates on new scientific information, resources, and activities of interest to the thalassemia medical and patient community. The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. All of these experts serve as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

- Khaled Musallam, MD, PhD
- Thomas Coates, MD
- Ali Taher, MD, PhD
- Kevin Kuo, MD
- Sujit Sheth, MD
- Vip Viprakasit, MD, DPhil
- Hanny Al-Samkari, MD
- Maria Dominica Cappellini, MD

Contact: ThalassemiaNews@agios.com

THA-ALL-0244 / Date of preparation November 2025
The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals.
Medical writing support provided by Bright Red Fox Creative is funded by Agios.