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Italian patients with hemoglobinopathies exhibit a 5-fold increase in age-standardized lethality due to SARS-CoV-2 infection

To the Editor:

Since the beginning of the COVID-19 pandemic, concerns have been expressed worldwide for patients with hemoglobinopathies and their vulnerability to SARS-CoV-2 infection. Data from Lebanon confirmed a role of underlying comorbidities on COVID-19 severity, but no deaths among a cohort of thalassemia patients.[1] Patients with sickle cell disease (SCD) displayed a broad range of severity after SARS-CoV-2 infection, spanning from a favorable outcome unless pre-existing comorbidities (UK cohort)[2] to high case mortality in US.[3] History of pain, heart, lung, and renal comorbidities was identified as risk factors of worse COVID-19 outcomes by the US SECURE-SCD Registry.[4] While Italy experienced a death rate in the general population among the highest in the world, preliminary data from the first wave of the pandemic showed a lower than expected number of infected thalassemia patients (updated up to April 10, 2020), likely due to earlier and more vigilant self-isolation compared to the general population.[5]

To explore the vulnerability to SARS-CoV-2 infection, the Italian Society for Thalassemia and Hemoglobinopathies (SITE) designed a study to compare the prevalence and mortality of COVID-19 in individuals with hemoglobinopathies and the general Italian population (EMO AER COVID-19 study). The study was approved by Institutional Review Board authorities, registered on clinicaltrials.gov (NCT04746066), and was performed in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Designed to gather data from multiple healthcare providers in Italy, it allowed for collecting relevant demographics and clinical data on a dedicated electronic Case Report Form (eCRF) (available at https://covid19.site-italia.org) by each participating center.

We enrolled patients with transfusion-dependent thalassemia (TDT), nontransfusion-dependent thalassemia (NTDT), and sickle cell disease (SCD) referred to participating centers and diagnosed with SARS-CoV-2 infection in the study period March 6, 2020 to April 7, 2021. SARS-CoV-2 infection was confirmed by either a positive swab of the upper or lower respiratory tract or serology. Patients with less than 15 days of follow-up from either the onset of symptoms or a SARS-CoV-2 positive test were excluded. Twenty-nine centers from 13 Italian Regions participated in the EMO AER COVID-19 study. These centers regularly provide care for approximately 6200 patients with hemoglobinopathies (3400 TDT, 1500 NTDT, 1300 SCD), representing 65% of the Italian population affected by these pathologies. Therefore, this sample is highly representative of Italian patients with hemoglobinopathies followed by an organized and widespread national network, providing both high coverage and high definition of data.

During the 398-day study period, a total of 345 SARS-CoV-2 infections were recorded (overall, prevalence 5.5%): 230 cases among TDT (prevalence 6.8%), 50 among NTDT (prevalence 3.3%), and 65 among SCD patients (prevalence 5.0%). In the SCD group, 49% of patients were β-Thal/HbS. Diagnosis of COVID-19 was confirmed by a positive swab in 91% of the cases and by the presence of serum IgG in 9% of the cases. Among reported cases, 52% were female. The median age at the infection was 41 years (IQR: 29–48, range: 0.75–85), with 10% of patients being pediatric (median age: 8 years, IQR: 4–11). Seventy-four percent of patients had at least one comorbidity at the time of infection. The most common were: splenectomy or functional asplenia (50%), iron overload (23%), liver disease (19%), heart disease (16%), and diabetes (8%). ABO blood groups were distributed as follows: 50% were O, 33% were A, 15% were B, and 2% of patients were AB. We observed a broad spectrum of COVID-19 severity, ranging from no symptoms (83/345, 24%) to severe manifestations (66/345, 19%) and death (7/345, 2%). The most common symptoms were fever (157/345, 46%), cough (145/345, 42%), fatigue and diffuse pain (119/345, 34%), and anosmia and ageusia (104/345, 30%). Severe symptoms, such as difficulty breathing or thoracic pain, affected 62/345 (18%) of patients; 55/345 (16%) had pneumonia; and 1 patient experienced pulmonary thromboembolism. Overall, 68 (20%) patients required hospitalization, 15 (8 TDT, 2 NTDT, 5 SCD) in high-intensity care units (ICU). Nine out of 68, all with pneumonia (1 TDT, 1 NTDT, and 7 SCD), required additional or ad hoc blood transfusions due to acute hemoglobin drop. The median hospitalization time was 11 days (IQR: 5–21, range: 1–102 days, information available for 46 patients).

Seven patients experienced fatal COVID-19 during the period of observation: 4 TDT (46/M, 48/M, 49/M, 56/F), 1 NTDT (45/M), 2 SCD (57/M, 57/F), both with the diagnosis of β-Thal/HbS. One TDT patient (57/F) and two patients (1 SCD, 52/M; 1 TDT, 57/F) died after the conclusion of the analysis and were not included in this survey. The overall lethality rate was 2.0%. The age-standardized lethality ratio (SLR) was then calculated as the ratio between the observed and the expected number of deaths, based on the age-specific rates in the Italian-COVID population. The resulting SLR was 4.8 (±3.5, 95% CI). All the fatal episodes were observed starting from November 2020. For hospital admission, age was a risk factor in TDT (OR = 1.03; CI: 1–1.1; $p = .04$) and NTDT (OR = 1.05; CI: 1–1.1; $p = .04$), but not in SCD. In TDT only, the presence of underlying lung or heart disease increased the risk to be admitted to the hospital (OR = 4.5, CI = 1.1–19.3, $p = .04$; OR = 2.9, CI = 1.0–8.0, $p = .04$). For the SCD group, chronic liver disease was associated with a higher risk of hospital admission (OR = 7.5, CI: 1.1–53.5, $p = .04$). For ICU admission and mortality, the presence of previous pulmonary disease was a risk

factor only for TDT (OR = 5.6, CI: 1.2–25.1, $p = .03$; OR = 26.6; CI: 2.3–311.4; $p = .01$, respectively).

According to our results, the prevalence of COVID-19 in hemoglobinopathies in Italy was similar to the general population (5.5% vs. 6.2%) in the first 13 months of the pandemic.

Considering the known underestimation of SARS-CoV-2 prevalence in the Italian population and the greater reliability of the same estimation in our strictly monitored patients, we speculate that the risk of infection in hemoglobinopathies was actually reduced. This hypothetical difference should be explained by the effectiveness of early recommendations from dedicated healthcare providers and the prudent attitude of the chronic patients in front of risk, as already reported from expert centers in other countries.[6]

The estimation of lethality is complex: 95.6% of the confirmed COVID-19 deaths in the Italian population have occurred in subjects in ages 60 or greater and 86.2% of the deaths in ages 70 or greater. Lethality rates for COVID-19 infected patients were 26.7% for ages 90 years or greater, 19.8% for ages 80–89 years, 9.4% for ages 70–79 years, and 2.7% for ages 60–69 years.

Our study population is significantly younger in age overall, with only 1.4% subjects infected above 70 years of age, reflecting the age-distribution of the hemoglobinopathies in Italy. The proper comparator for our population is the segment of the Italian population younger than 60 years of age, which experienced 5% of the total COVID-19 deaths, with lethality rates varying from <0.1% (age 20–29 years) to 0.6% (age 50–59 years). While no significant differences were observed in patients aged 0–30s, significantly higher lethality was observed in subjects aged 40–49 and 50–59 years, where all fatal cases were registered. Assuming for hemoglobinopathies the same lethality rates of Italians with comparable age, the number of observed deaths in hemoglobinopathies is approximately 5-fold the expected one (Figure 1). All deaths occurred in patients in the fourth to fifth decades of life, mostly obese, splenectomized, and with numerous comorbidities. Surprisingly, none of them (except one for which no recent clinical data are available) had a significant iron overload. Both deaths in the SCD group occurred in patients with β0-Thal/HbS, while there were no fatal events among patients with homozygous HbS, in agreement with the local genotype distribution that is characterized by a high prevalence of older Caucasian β-Thal/HbS patients (homozygous HbS are more frequent among younger patients).

Age was a risk factor for hospital admission due to SARS-CoV-2 infection in both TDT and NTDT, but not in SCD. Other risk factors were the presence of underlying comorbidities at the time of infection, particularly chronic lung, heart, or liver disease. In addition, chronic lung disease was a significant risk factor for ICU admission or mortality (in TDT only).

The main limitations of this work are represented by the evaluation of indirect outcomes of COVID-19 severity; in addition, not all the Italian centers taking care of these patients were involved in the study. However, the data presented here include the large majority of known patients affected by hemoglobinopathies in Italy. Another limitation of our study is the inability to consider the effects of early vaccination in this at risk cohort compared with the general population.

(A)

	All	TDT	NTDT	SCD
Number of cases (males)	345 (166)	230 (108)	50 (27)	65 (31)
Age, years Median (IQR) – [min-max]	41 (29-48) [0-85]	42 (33-47) [0-66]	43 (33-51) [8-85]	31 (12-45) [0-77]
Blood group (A/B/AB/0)	100/45/7/150	70/33/6/108	15/3/0/16	15/9/1/26
Ferritin, ng/ml Median (IQR) – [min-max]	599 (285-1200) [20-32,089]	660 (386-1348) [27-32089]	316 (218-656) [20-6000]	282 (92-1069) [22-6233]
LIC > 3 mg/g d.w., *n/N**	108/217	81/174	19/29	8/14
Heart T2* <20 ms *n/N**	23/204	17/173	2/20	4/11
Iron chelation therapy *n/N**	243/315	216/219	12/46	15/50
Hydroxyurea therapy *n/N**	42/289	7/191	8/46	27/52
Splenectomy-functional asplenia *n/N**	175/286	117/200	19/37	39/49
Hearth disease *n/N**	56/312	41/210	11/47	4/55
Pulmonary disease *n/N**	23/313	18/213	3/47	2/53
Liver disease *n/N**	65/307	56/206	4/47	5/54
Renal disease *n/N**	13/310	11/208	1/47	1/55
Diabetes type I *n/N**	28/313	28/212	0/47	0 /54
G6PD deficiency *n/N**	6/291	5/192	1/47	0/52
Obesity *n/N**	20/312	13/210	3/47	4/55
Smoke *n/N**	23/280	15/184	5/47	3/49

n: number of cases; N: number of record completed; range: min-max*
TDT: Transfusion dependent Thalassemia; NTDT: Non-Transfusion dependent Thalassemia LIC: Liver Iron Concentration; d.w.: dry weight

(C)

			95% CI			
			OR	Lower	Upper	p
Hospital admission	TDT	Pulmonary disease	4.5	1.1	19.3	0.04
	SCD	Heart disease	2.9	1.0	8.0	0.04
		Liver disease	7.5	1.1	53.5	0.04
ICU admission	TDT	Pulmonary disease	5.6	1.2	25.1	0.03
Death	TDT	Pulmonary disease	26.6	2.3	311.4	0.01

CI: confidence interval; OR: odd ratio

(B)

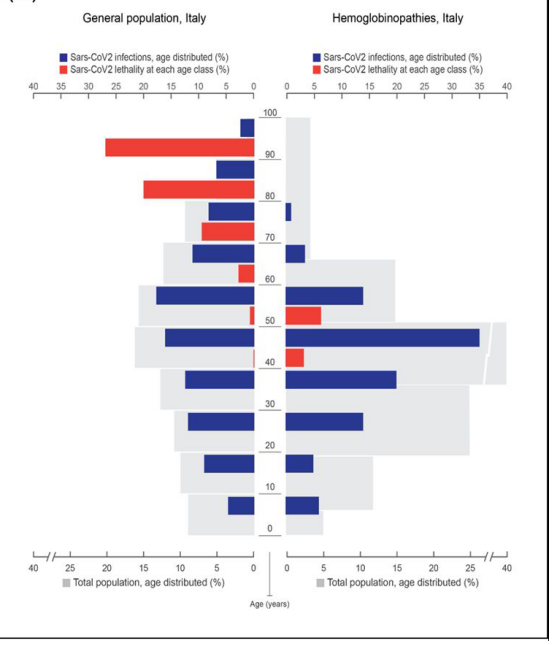

FIGURE 1 (A) Characteristics of patients with hemoglobinopathies with SARS-CoV-2. (B) The population histogram shows age distribution of total population (gray), age distribution of SARS-CoV-2 infected (blue), and lethality rate at each class (red) for Italian general population* (left) and for Italian patients with hemoglobinopathies (right). (C) The table reports pre-existing complications significantly associated with increased severity of COVID-19, that is, hospital admission, intensive care unit (ICU) admission, or death. Odds ratio (OR) was estimated for single comorbidity by a logistic regression analysis adjusted for age to investigate possible factors related to different risk levels. *https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_10-marzo-2021.pdf

Our data clearly indicate that patients affected by hemoglobinopathies have up to a five times higher likelihood of suffering lethal SARS-CoV-2. Thus, these patients should be referred to specific and expert healthcare providers. Future studies should monitor the long-term effect of COVID-19 in patients with hemoglobinopathies. More relevantly, the effectiveness of vaccines should be evaluated in these patients to address the presence of any possible difference with the general population.

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CONFLICT OF INTEREST

No conflict of interest to declare.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

Filomena Longo[1], Barbara Gianesin[2], Vincenzo Voi[1], Irene Motta[3,4], Valeria Maria Pinto[5], Andrea Piolatto[1], Anna Spasiano[6], Giovan Battista Ruffo[7], Maria Rita Gamberini[8], Susanna Barella[9], Raffaella Mariani[10], Carmelo Fidone[11], Rosamaria Rosso[12], Maddalena Casale[13], Domenico Roberti[13], Chiara Dal Zotto[14], Angelantonio Vitucci[15], Federico Bonetti[16], Lorella Pitrolo[17], Micol Quaresima[18], Michela Ribersani[19], Alessandra Quota[20], Francesco Arcioni[21], Saveria Campisi[22], Antonella Massa[23], Elisa De Michele[24], Roberto Lisi[25], Maurizio Miano[26], Sabrina Bagnato[27], Massimo Gentile[28], Valentina Carrai[29], Maria Caterina Putti[30], Marilena Serra[31], Carmen Gaglioti[1], Margerita Migone De Amicis[4], Giovanna Graziadei[4], Anna De Giovanni[4], Paolo Ricchi[6], Manuela Balocco[5], Sabrina Quintino[5], Zelia Borsellino[7], Monica Fortini[8], Anna Rita Denotti[9], Immacolata Tartaglione[13], Andrea Beccaria[26], Marco Marziali[19], Aurelio Maggio[17], Silverio Perrotta[13], Alberto Piperno[10], Aldo Filosa[6], Maria Domenica Cappellini[4], Lucia De Franceschi[14], Antonio Piga[32], Gian Luca Forni[5]

[1]*AOU San Luigi Gonzaga, Orbassano, Italy*
[2]*ForAnemia Foundation, Genoa, Italy*
[3]*Dipartimento di Scienze Cliniche e di Comunità, Università degli Studi di Milano, Milan, Italy*
[4]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[5]*E.O. Ospedali Galliera, Centro della Microcitemia e delle Anemie Congenite, Genoa, Italy*
[6]*AORN Cardarelli, Naples, Italy*
[7]*ARNAS Civico Di Cristina Benfratelli, Palermo, Italy*
[8]*Azienda Ospedaliero-Universitaria S.Anna di Ferrara, Ferrara, Italy*
[9]*SSS Talassemia Ospedale Pediatrico Microcitemico A. Cao, Cagliari, Italy*
[10]*University of Milano Bicocca, ASST-Monza, S. Gerardo Hospital, Monza, Italy*
[11]*Giovanni Paolo II, Ragusa, Italy*
[12]*AOU Policlinico "Vittorio Emanuele", Catania, Italy*
[13]*AOU Università degli Studi della Campania Luigi Vanvitelli, Naples, Italy*
[14]*Policlinico GB Rossi, Verona, Italy*
[15]*UOC Ematologia Az. Osp. Univ. Policlinico Bari, Bari, Italy*
[16]*Fondazione IRCCS Policlinico San Matteo, Pavia, Italy*
[17]*A.O.R. Villa Sofia-V. Cervello, Palermo, Italy*
[18]*Arcispedale Santa Maria Nuova, Reggio Emilia, Italy*
[19]*Policlinico Umberto I, Rome, Italy*
[20]*UOS Talassemia P.O. Vittorio Emanuele, Gela, Italy*
[21]*Azienda Ospedaliera Perugia, Perugia, Italy*
[22]*PP.OO. Siracusa, Siracusa, Italy*
[23]*Giovanni Paolo II, Olbia, Italy*
[24]*AOU OO.RR. San Giovanni Di Dio Ruggi D'Aragona, Salerno, Italy*
[25]*Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione Garibaldi, Catania, Italy*
[26]*Istituto Giannina Gaslini, Genoa, Italy*
[27]*P.O. Lentini, Siracusa, Italy*
[28]*Azienda ospedaliera di Cosenza, Cosenza, Italy*
[29]*Azienda Ospedaliero-Universitaria Careggi, Florence, Italy*
[30]*Azienda Ospedale Università Padova, Padua, Italy*
[31]*Ospedale Vato Vizzi, Lecce, Italy*
[32]*Department of Clinical and Biological Sciences, University of Torino, Turin, Italy*

Correspondence
Gian Luca Forni, Centro della Microcitemia e delle Anemie Congenite, Ospedale Galliera, Via Volta 6—16128 Genova, Italy.
Email: gianluca.forni@galliera.it

ORCID

Filomena Longo https://orcid.org/0000-0002-0434-0382
Irene Motta https://orcid.org/0000-0001-5701-599X
Maddalena Casale https://orcid.org/0000-0003-4740-2421
Massimo Gentile https://orcid.org/0000-0002-5256-0726
Giovanna Graziadei https://orcid.org/0000-0002-6801-5730
Immacolata Tartaglione https://orcid.org/0000-0003-1278-2372
Maria Domenica Cappellini https://orcid.org/0000-0001-8676-6864
Lucia De Franceschi https://orcid.org/0000-0001-7093-777X
Gian Luca Forni https://orcid.org/0000-0001-9833-1016

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Risk of mortality from anemia and iron overload in nontransfusion-dependent β-thalassemia

To the Editor:

Ineffective erythropoiesis in patients with nontransfusion-dependent β-thalassemia (NTDT) leads to chronic anemia that does not necessarily require lifelong transfusion therapy for survival.[1] Nonetheless, chronic anemia in these patients is associated with significant morbidity, especially in patients with a hemoglobin level lower than 10 g/dL.[2] Hemoglobin variations greater than 1 g/dL have also been shown to modify morbidity risk.[3] Beyond the use of transfusions in specific clinical settings, there are currently no approved agents for the management of anemia in NTDT. Ineffective erythropoiesis can also lead to considerable iron overload due to hepcidin dysregulation and increased intestinal iron absorption.[4] A serum ferritin level greater than 800 ng/mL is also associated with an increased risk of morbidity and is an indication for the use of iron chelation therapy.[5] Such clinical complications in NTDT are often serious and involve various organ systems including hepatic, endocrine, and vascular disease.[6] Despite the abundance of reports highlighting anemia and iron overload as the hallmarks of morbidity in NTDT, data on their association with long-term mortality outcomes remain limited.

For this work, we used data from an International Health Repository (IHR) formed by 13 international thalassemia reference centers from the US and seven countries in Europe, the Middle East, and Asia.[7] The IHR was established and approved on May 25, 2017 by the Italian Ethical Committee (EudraCT and Sponsor's Protocol Code Numbers: 2017-004457-17 and 143AOR2017). All data were anonymized and added to the repository following informed consent by patients or their legal representatives in case of death. The IHR database includes all β-thalassemia patients who have attended participating centers from January 1, 1997 onward. We analyzed data from all patients with NTDT (defined as previously described[8]) who had not transitioned to regular transfusion programs and who had documented hemoglobin and serum ferritin levels. Patients were historically followed from birth up to December 31, 2019, death, or loss to follow-up. For each patient, we retrieved data on age and status at the last observation, sex, splenectomy status, iron chelation status, hemoglobin level, and serum ferritin level at the last observation. Hemoglobin and serum ferritin levels represented the average of all measurements done during the year of last observation.

A total of 415 patients (48.7% females) were included in the analysis (Table S1). The median age at last observation (follow-up time) was 30.1 years (interquartile range [IQR]: 23.6–44.2). The majority were splenectomized ($n = 243$, 58.6%) and received iron chelation therapy ($n = 379$, 91.3%). The median age at the start of iron chelation therapy was 7 years (IQR: 4.3–14). At last observation, the majority of patients were on deferoxamine (49%), followed by deferiprone (23.5%), deferasirox (22.5%), and deferoxamine + deferiprone combination (4.9%) therapy. The mean hemoglobin level was 9.2 ± 1.0 g/dL (range: 6–15) with 339 (81.7%) patients having a hemoglobin level ≤ 10 g/dL. The median serum ferritin level was 960 ng/mL (IQR: 500–2843) with 235 (56.6%) patients having a serum ferritin level > 800 ng/mL. A total of 185 patients (44.6%) had both a hemoglobin level ≤ 10 g/dL and a serum ferritin level > 800 ng/mL.

Thirty-two patients died during the observation period, giving a crude mortality rate of 7.7% (95% confidence interval [CI]: 5.3–10.7). Recorded causes of death included cardiovascular disease ($n = 17$), infection ($n = 2$), hepatic failure ($n = 1$), renal failure ($n = 1$), cancer ($n = 1$), and other disease complications ($n = 10$). The median age at death was 24.1 years (IQR: 28.3–61.9; 37.5% females). Survival was significantly worse in patients with a hemoglobin level ≤ 10 g/dL than those with > 10 g/dL (Log-rank test Chi-square: 4.259, $p = .039$, Figure 1A). Survival was also significantly worse in patients with a serum ferritin level > 800 ng/mL than those with ≤ 800 ng/mL (log-rank test Chi-square: 24.379, $p < .001$, Figure 1B). Finally, survival was significantly worse in patients with both a hemoglobin level ≤ 10 g/dL and a serum ferritin level > 800 ng/mL than those with either a hemoglobin level ≤ 10 g/dL or a serum ferritin level > 800 ng/mL and those with both a hemoglobin level > 10 g/dL and a serum ferritin level ≤ 800 ng/mL (Log-rank test Chi-square: 33.728, $p < .001$, Figure 1C).

We constructed a multivariate Cox regression analysis including hemoglobin level (≤ 10 vs. > 10 g/dL), serum ferritin level (> 800 vs. ≤ 800 ng/mL), sex, splenectomy, and iron chelation status. A hemoglobin level ≤ 10 g/dL was independently associated with a 7.6-fold increase in the risk of mortality (hazard ratio [HR]: 7.632, 95% CI: 1.036–56.219, $p = .046$). A serum ferritin level > 800 ng/mL was also independently associated with a 9.8-fold increase in the risk of mortality (HR: 9.755, 95% CI: 3.368–28.257, $p < .001$).

Our study furthers our understanding of the detrimental effects of anemia and iron overload in NTDT and highlights an increased risk of mortality in patients with clinically relevant thresholds. Our work is limited by our ability to only analyze a subset of patients with documented hemoglobin and serum ferritin levels, which could have introduced a selection bias for patients with severe disease requiring regular follow-up, as is also evident from a higher and earlier mortality in this subset of patients compared to our overall cohort.[8] Prospective studies are merited in such context, as they could also assess the