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ITALIAN PATIENTS WITH HEMOGLOBINOPATHIES EXHIBIT A 5-FOLD INCREASED IN AGE-STANDARDIZED LETHALITY DUE TO SARS-COV-2 INFECTION

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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-Cov2 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-CoV2 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 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-Cov2 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 Centre.

We enrolled patients with Transfusion-Dependent thalassemia (TDT), Non-Transfusion-Dependent thalassemia (NTDT), and Sickle Cell Disease (SCD) referred to participating Centres and diagnosed with SarsCov-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 SarsCov-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 6,200 patients with hemoglobinopathies (3,400 TDT, 1,500 NTDT, 1,300 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 days study period, a total of 345 SARS-CoV2 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). 74% 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%), diabetes (8%). ABO blood groups were distributed as follows: 50% were O, 33% were A, 15% were B, 2% of patients were AB. We observed a broad spectrum of COVID19 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%), 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, one 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, 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 COVID19 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 = 0.04), NTDT (OR=1.05; CI: 1–1.1; p=0.04), 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=0.04; OR=2.9, CI=1.0–8.0, p=0.04). 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=0.04). 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=0.03; OR=26.6; CI:2.3–311.4; p=0.01 respectively).

According to our results, the prevalence of COVID-19 in hemoglobinopathies in Italy was similar to the general population (5.5% vvs6.2%) in the first 13-months of the pandemic.
Considering the known underestimation of Sars-Cov-2 prevalence in the Italian population and the greater realibility of the same estimation in our strictly monitored patients, we speculate that the risk of infection in hemoglobinopathies was actually reduced. This hypotetical 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 age 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 or greater, 19.8% for ages 80-89 y, 9.4% for ages 70-79 y, and 2.7% for ages 60-69.
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 y) to 0.6% (age 50-59 y). While no significant differences were observed for patients aged 0 to 30s, significantly higher lethality was observed in subjects age 40-49 and 50-59, 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-folds the expected one (Fig. 1). All deaths occurred in patients in the 4th-5th decade 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-CoV2 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.

Our data clearly indicate that patients affected by hemoglobinopathies have up to a 5 times higher likelihood of suffering lethal Sars-CoV2. 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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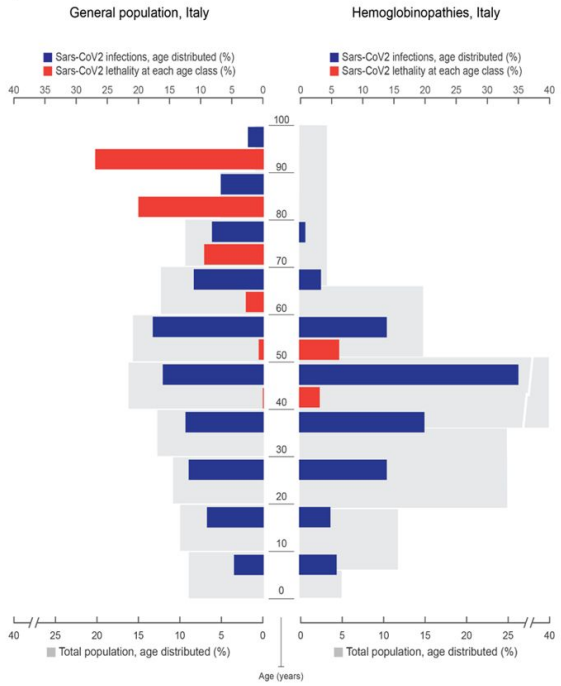
(A)

	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

(B)



(C)

			95% CI			
			OR	Lower	Upper	p
Hospital admission	TDT	Pulmonary disease	4,5	1,1	19,3	0,04
		Heart disease	2,9	1,0	8,0	0,04
	SCD	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

Figure 1. **A** Characteristics of patients with hemoglobinopathies with Sars-CoV2. **B** The population histogram shows age distribution of total population (grey), age distribution of Sars-Cov2 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, i.e. hospital admission, Intensive Care Unit (ICU) admission, or death. Odds ratio (OR) was estimated for single comorbidities 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