SARS-CoV-2 infection in beta thalassemia: preliminary data from the Italian experience.

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To the Editor:

Patients with pre-existent chronic morbidities are likely to be more severely affected by SARS-Cov2 infection, but no data are available regarding Thalassemic Syndromes (TS). TS and hemoglobin variants represent, according to WHO, one of the most frequent causes of anemia, affecting more than 7% of the world population[1]. TS are classified in either transfusion-dependent thalassemia (TDT) or non-transfusion-dependent thalassemia (NTDT). Infectious complications, mainly from bacteria, constitute a common cause of mortality and morbidity in TS. Stress erythropoiesis, iron overload, splenectomy and adrenal insufficiency among others may contribute to increase susceptibility to infection[2].

To verify the impact of SARS-CoV-2 infection on TS, we set-up a specific survey by electronic Case Report Form (eCRF)[3]. Inclusion criteria require at least 15 days of follow-up from either the onset of symptoms or SARS-CoV2 positivity. The survey was approved by Ethics Committee and eCRF was shared with the Centers of Italian Hemoglobinopathies Network. The "Società Italiana Talassemie ed Emoglobinopatie" (SITE), has estimated the presence in Italy of approximately 5000 TDT and 1900 NTDT patients[3].

As of April 10th, 2020, 11 cases of TS and COVID-19 have been collected (See Supplementary Information). All the reported patients are in Northern Italy, where the rate of infection is higher, reflecting the national epidemiology.

The mean age is 44±11 years (range 31-61 years) and 55% (6/11) are females. Ten patients are TDT, and one is NTDT. All the patients have thalassemia associated comorbidities, eight are splenectomized, and one patient (#9 in table of Supplementary Information) has pulmonary hypertension treated with sildenafil. The likely source of infection has been detected in 55% (6/11) of cases: 2 had contacts with COVID-19 positive subjects, and 4 had occupational exposure (3 are nurses working in hospital or assisted living facilities).

Three patients were asymptomatic. One patient (#3 in Supplementary Information) was admitted for high fever and bone marrow hypoplasia, lymphopenia, and agranulocytosis (on treatment with deferiprone) and tested positive at the third swab. 6/11 were hospitalized, but no one required mechanical ventilation. The patient with more severe symptoms who required more intensive ventilation support with continuous positive airway pressure (CPAP) has a history of diffuse large B-cell lymphoma treated with chemotherapy in the previous year, currently in complete remission. Of the 6 admitted to the hospital, only three received supposedly specific treatment for COVID-19: one hydroxychloroquine (HCQ), one HCQ plus ritonavir/darunavir, and one HCQ

plus anakinra. Patient #3 did not receive HCQ due to concomitant therapy with amiodarone and an increased risk of life-threatening arrhythmia. The clinical course ranged from 10 to 29 days. Ten patients have clinically recovered and are on a daily remote phone call follow-up. Splenectomy which was present in 8/11 patients did not seem to affect the clinical course. Of note, except for the patient with myelosuppression, no increase in blood requirement was observed. When luspatercept treatment was halted in the NTDT patient, hemoglobin fell from 11 to 8,2 g/dL, a value similar to the pre-luspatercept period. Neither death nor severe SARS or signs of cytokines storm, were observed in these 11 subjects. which may be surprising, taking into account the mean age and the presence of severe comorbidities.

Our data, although preliminary, do not indicate increased severity of COVID-19 in TS. A larger number of cases needs to be collected to define the impact of this new infection and its outcome in these fragile patients.

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SUPPLEMENTARY INFORMATION

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Supplementary Table 1: Clinical features of thalassemia in patients affected by the SARS-Cov2 infection

Patient	*Gender*	*Age*	*Hemoglobinopathy*	*Transfusion dependence*	*Blood group*	*Splenectomy*	*Respiratory disease*	*Cardiomyopathy*	*Renal impairment*	*Chronic hepatopathy*	*Diabetes*	*Hypothyroidism*	*Osteoporosis*	*Hypogonadism*	*Obesity*	*Others*	*Pre-infection*			*Iron chelation*		*Date of swap positive*	*Likely source*
																	Ferritin (µg/l)	*LIC (mg/g d.w.)*	*MIC (mg/g d.w.)*	*Chelator*	*Dose (mg/kg)*		
1	F	49	Beta Thalassemia	NTD	0 Rh pos										yes	Microalbuminuria, hyperparathyroidism	633	4,1	0,9	no	-	15:Mar:2020	Occupational exposure (bread counter of a supermarket)
2	F	48	Beta Thalassemia	TD	A Rh pos	yes										Previous HCV hepatitis	661	3,0	0,9	DFX	20	06:Mar:2020	Occupational exposure (nurse in elderly care facility)
3	M	31	Beta Thalassemia	TD	0 Rh pos			yes		yes	yes	yes	Yes	yes			3216	18,3	4,9	DFP+DFO	58+50	11:Mar:2020	Unknown
4	M	42	Beta Thalassemia	TD	A Rh pos	yes	allergic asthma							yes		Previous HCV hepatitis	410	1,8	1,1	DFX	18	18:Mar:2020	Unknown
5	F	33	Beta Thalassemia	TD	B Rh pos	yes						yes					1325	1,9	1,0	DFX	21	07: Mar:2020	Occupational exposure (nurse caring COVID positive patients)
6	F	59	Beta Thalassemia	TD	B Rh pos	yes	OSAS	yes	yes	yes	yes	yes	yes	yes		Off-therapy after diffuse large B cell non-Hodgkin lymphoma	5000	6,6	0,8	DFX	10	21:Mar:2020	Unknown
7	M	32	Beta Thalassemia	TD	A Rh pos	yes							yes			ALL treated by ASCT at 14 years old	514	1,1	1,1	DFX	17	09-mar-20	Occupational exposure (nurse)
8	F	61	Beta Thalassemia	TD	0 Rh pos	yes	yes	yes	yes	yes	yes		yes	yes		Sarcoidosis, Grade III renal impairment	3734	5,3	0,9	DFP	92	23:Mar:2020	Unknown
9	M	56	Beta Thalassemia	TD	0 Rh neg	yes		yes		yes			yes	yes		Pulmonary hypertension, Previous HCV hepatitis	1087	5,3	1,2	DFP	85	16: Mar:2020	Unknown
10	F	40	Beta Thalassemia	TD	A Rh pos	yes		yes		yes		yes		yes		hypoparathyroidism	1100	2,5	0,8	DFP	85	14: Mar:2020	Contact with a COVID positive relative
11	M	36	Beta Thalassemia	TD	0 Rh pos							yes					1200	6,6	0,7	DFX	18	18: Mar:2020	Contact with a COVID positive

F: female; M: male; NTD: non transfusion dependent; TD: transfusion dependent; OSAS: obstructive sleep apnea syndrome; LIC: liver iron concentration; MIC: myocardial iron concentration; DFX: deferasirox; DFP: deferiprone; DFO: deferoxamine, CPAP: continuous positive airway pressure: HCQ: hydroxychloroquine.

Empty cells correspond to the absence of the characteristics

Supplementary Table 2: Description of clinical manifestations and course of the SARS-Cov2 infection

Patient	*Signs/symptoms*								*Thickening at imaging*		*Hospital admission*	*Additional blood required*	*Treatment*	*O2/CPAP*	*Intubation*	*Specific therapy*	*Clinical course (days)*	*Outcome*
	Fever	*Cough*	*Anosmia*	*Ageusia*	*Pain*	*Fatigue*	*Diarrhea*	*Others*	*RX*	*CT*								
1	yes	yes	yes	yes	yes	yes	yes	Headache; B lines in the basal left seat at pulmonary echo	yes	-	yes low-intensity care unit	NA	yes		no	HCQ	18	Recovered
2	yes	yes	yes	yes	yes	yes			yes						no		10	Recovered
3	yes	yes	yes	yes	yes	yes		Headache, sore throat; difficulty breathing Already in hospital with febrile neutropenia.		yes	yes low-intensity care unit	yes		O2	no		25	Recovered
4	yes	yes				yes		sore throat	yes						no		21	Recovered
5		yes			yes		yes		-	-					no		29	Recovered
6	yes	yes						Difficulty breathing, sore throat	yes		yes (high intensity care unit)		yes	CPAP> O2	no	HCQ + anti IL-1	ongoing	Hospitalized (low intensity care unit)
7	yes	yes	yes	yes		yes		nausea, headache	no	-					no		28	Recovered
8					yes	yes		Difficulty breathing, glycemic decompensation	yes	yes	yes (low intensity care unit)				no		16	Recovered
9	yes	yes			yes			sore throat, Difficulty breathing	yes	yes	yes (low intensity care unit)		yes	O2	no	HCQ + ritonavir/darunavir	18	Recovered
10	yes	yes	yes	yes	yes	yes		sore throat	-	-					no		16	Recovered
11	yes	yes	yes	yes	yes	yes			yes		yes (low intensity care unit)				no		14	Recovered

F: female; M: male; NTD: non transfusion dependent; TD: transfusion dependent; OSAS: obstructive sleep apnea syndrome; LIC: liver iron concentration; MIC: myocardial iron concentration; DFX: deferasirox; DFP: deferiprone; DFO: deferoxamine, CPAP: continuous positive airway pressure: HCQ: hydroxychloroquine.

Empty cells correspond to the absence of the characteristics

Supplementary Figure 3. Graphical summary of the characteristics, the clinical manifestations and the course of the SARS-Cov2 infection reported in the Tables 1 and 2.

NTD: non transfusion dependent; TD: transfusion dependent; DFX: deferasirox; DFP: deferiprone; DFO: deferoxamine, CPAP: continuous positive airway pressure: HCQ: hydroxychloroquine.