Brief Summary of Findings on the Association Between Thalassemia and Severe COVID-19 Outcomes

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Six studies, 5 cohort[1-5], and 1 cross-sectional[6] reported data on thalassemia and severe COVID-19 outcomes and were included in this analysis.

- The evidence from some of these studies suggests but is insufficient to determine an increased risk of mortality[1,3,5,6] due to COVID-19 for people with underlying thalassemia. Limited evidence from only one study is insufficient to determine if there is an association between thalassemia and ICU admission[3]. The evidence is insufficient and inconclusive to determine if there is an association between mortality[1,4,6], ICU[2,4], intubation[2], ventilation[2,4], or hospitalization[2,4] for people with underlying non-transfusion dependent thalassemia (NTDT) compared with transfusion-dependent thalassemia (TDT).

The definitions of thalassemia, including different types, are outlined on the webpage, https://www.cdc.gov/ncbddd/thalassemia/facts.html.

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A. Methods

The aim of this review is to identify and synthesize the best available evidence on the association between underlying thalassemia and severe COVID-19 to update the U.S. Centers for Disease Control and Prevention (CDC) website on underlying conditions and add to the provider-specific website.

The methods for underlying conditions and risk factors are outlined on the webpage, https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/systematic-review-process.html. These methods were established in May 2021 and are used for conditions and risk factors where CDC conducted the review.

Below are methodologic highlights and additional methods unique to this review. For more information, please visit https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/systematic-review-process.html

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, and outcome (PECO) question. Clinical experts and library scientists were consulted to develop a robust list of search terms. These terms were then incorporated into search strategies, and these searches were performed in OVID using the COVID-19 filter for all articles from the beginning of each database until October 27, 2021. The publications span before and after the availability of vaccines. Vaccination was not a criterion for selection. The detailed search strategies for identifying primary literature and the search results are provided in Part B.1. References were included if retrieved by the literature search and reported exposures and outcomes relevant to this review.

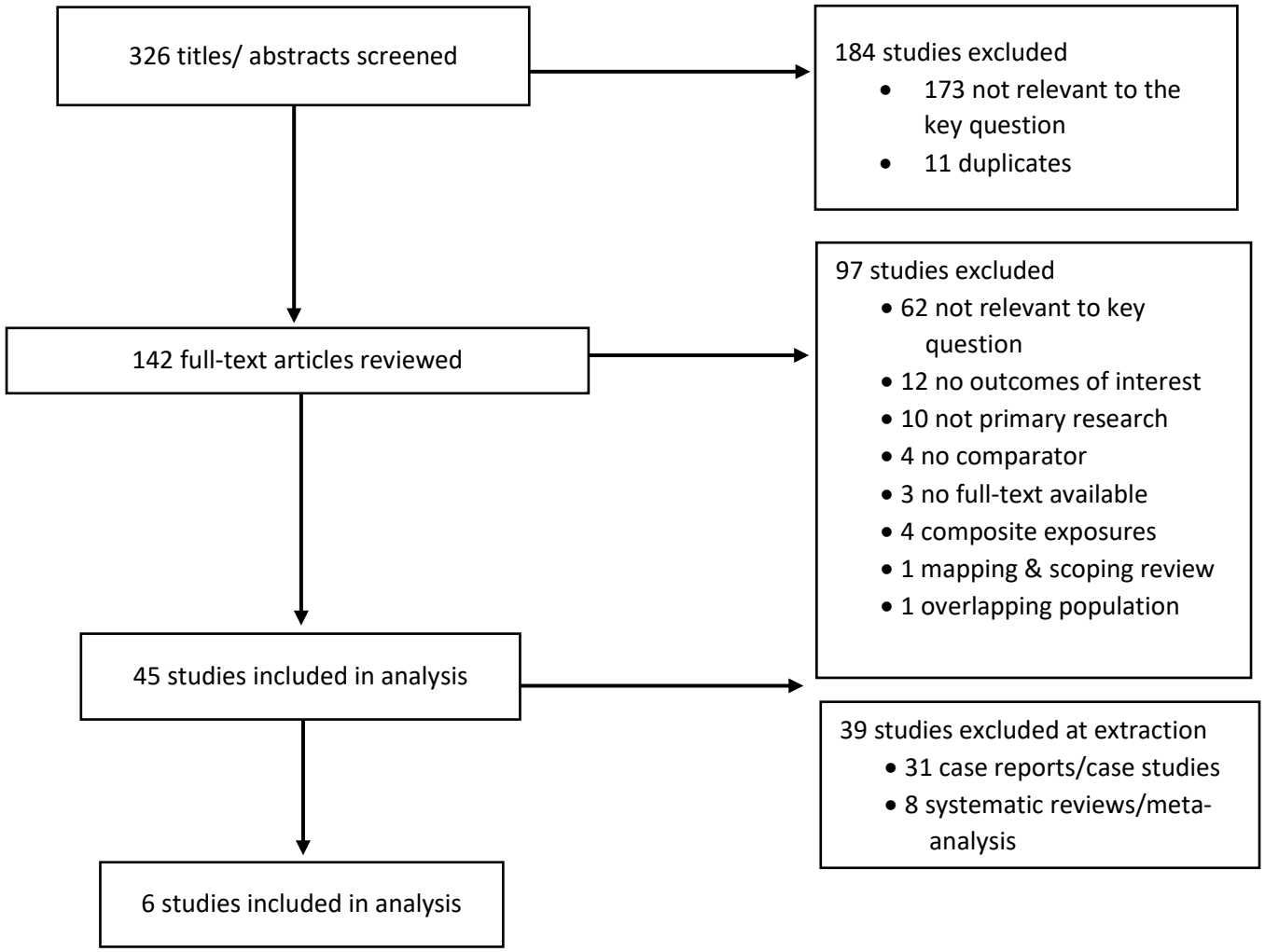
A.2. Study Selection

Titles and abstracts from references were screened by dual review (A.H., M.M., D.O.S., E.C.S, or C.N.S.) Full-text articles were retrieved if they were:

1. relevant to the PECO question;
2. primary research;
3. humans only; and
4. written in English

Part B.2 presents the full list of exclusion criteria. The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (A.H., M.M., D.O.S., E.C.S, or C.N.S.) After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with a subject matter expert. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in Figure 1.

Figure 1. Results of the Study Selection Process



A.4. Data Extraction and Synthesis

Methodologic data and results of relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review, statistical significance was defined as $p \leq 0.05$. Small sample sizes were defined as sample sizes that were less than the average sample size from all studies included.

A.5. Aggregation of the Evidence

The internal validity associated with each study was assessed using scales developed by the Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. Part B includes the questions used to assess the quality of each study design. The strength, magnitude, precision, consistency, and applicability of results were assessed for all comparators. The overall confidence in the evidence base is reported in the aggregation tables in Part B. The denominators used in the aggregation tables are of people diagnosed with COVID-19. The denominator was listed as "not reported" (NR) if the number was not given.

A.6. Reviewing and Finalizing the Systematic Review

Draft findings, aggregation tables, and evidence tables are presented to CDC subject matter experts for review and input. Following further revisions, the summary will be published on the CDC website.

B. Systematic Literature Review Results

B.1. Search Strategies and Results

Table 1 Thalassemia search conducted October 27, 2021.

Database	Strategy	Records
Medline (OVID) 1946-	Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR hemoglobin h disease OR beta-thalassemia* OR hemoglobin f disease OR Mediterranean an?emia* OR cooley* an?emia OR Hydrops fetalis OR Hb Barts OR Hb Bart syndrome OR Hb Portland OR Hb Portland syndrome OR HbH disease OR constant spring OR Southeast Asian deletion OR HBA1 OR HBA2 OR Filipino deletion OR Mediterranean deletion OR erythroblastic anemia* OR beta type microcytemia* AND Limit to COVID-19 [*valid filter*]	72
Embase (OVID) 1974	Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR hemoglobin h disease OR beta-thalassemia* OR hemoglobin f disease OR Mediterranean an?emia* OR cooley* an?emia OR Hydrops fetalis OR Hb Barts OR Hb Bart syndrome OR Hb Portland OR Hb Portland syndrome OR HbH disease OR constant spring OR Southeast Asian deletion OR HBA1 OR HBA2 OR Filipino deletion OR Mediterranean deletion OR erythroblastic anemia* OR beta type microcytemia* AND Limit to COVID-19 [*valid filter*] NOT PubMed/Medline	128 -50 Duplicates =78 unique items
Global Health (OVID)	novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov* OR sarscov OR 2019nCoV OR 2019-nCoV AND Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR hemoglobin h disease OR beta-thalassemia* OR hemoglobin f disease OR Mediterranean an?emia* OR cooley* an?emia OR Hydrops fetalis OR Hb Barts OR Hb Bart syndrome OR Hb Portland OR Hb Portland syndrome OR HbH disease	21 -15 Duplicates =6 unique items

Database	Strategy	Records
	OR constant spring OR Southeast Asian deletion OR HBA1 OR HBA2 OR Filipino deletion OR Mediterranean deletion OR erythroblastic anemia* OR beta type microcytemia* 2019 -	
PsycInfo (OVID)	novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov* OR sarscov OR 2019nCoV OR 2019-nCoV AND Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR hemoglobin h disease OR beta-thalassemia* OR hemoglobin f disease OR Mediterranean an?emia* OR cooley* an?emia OR Hydrops fetalis OR Hb Barts OR Hb Bart syndrome OR Hb Portland OR Hb Portland syndrome OR HbH disease OR constant spring OR Southeast Asian deletion OR HBA1 OR HBA2 OR Filipino deletion OR Mediterranean deletion OR erythroblastic anemia* OR beta type microcytemia* Limit English; Abstract Available; 2019 -	0
Cochrane Library	("novel coronavir*" OR "novel corona virus*" OR "2019 coronavirus" OR "coronavirus disease" OR "coronavirus 2019" OR covid19 OR "covid 19" OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR "sars cov*" OR sarscov OR 2019nCoV OR "2019 nCoV"):ti,ab AND (Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR "hemoglobin h disease" OR beta-thalassemia* OR "hemoglobin f disease" OR "Mediterranean an?emia*" OR "cooley* an?emia" OR "Hydrops fetalis" OR "Hb Barts" OR "Hb Bart syndrome" OR "Hb Portland" OR "Hb Portland syndrome" OR "HbH disease" OR "constant spring" OR "Southeast Asian deletion" OR HBA1 OR HBA2 OR "Filipino deletion" OR "Mediterranean deletion" OR "erythroblastic anemia*" OR "beta type microcytemia*"):ti,ab Limit English; Abstract Available; 2019 -	0

Database	Strategy	Records
CINAHL (EbscoHost)	(“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR “coronavirus disease” OR “coronavirus 2019” OR covid19 OR “covid 19” OR nCoV OR “novel CoV” OR “CoV 2” OR CoV2 OR sarscov2 OR sars-cov* OR sarscov OR 2019nCoV OR 2019-nCoV) AND (Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR "hemoglobin h disease" OR beta-thalassemia* OR "hemoglobin f disease" OR "Mediterranean an?emia*" OR "cooley* an?emia" OR "Hydrops fetalis" OR "Hb Barts" OR "Hb Bart syndrome" OR "Hb Portland" OR "Hb Portland syndrome" OR "HbH disease" OR "constant spring" OR "Southeast Asian deletion" OR HBA1 OR HBA2 OR "Filipino deletion" OR "Mediterranean deletion" OR "erythroblastic anemia*" OR "beta type microcytemia*") -Exclude Medline records	19 -10 Duplicates =9 unique items
Scopus	TITLE-ABS-KEY (“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR “coronavirus disease” OR “coronavirus 2019” OR covid19 OR “covid 19” OR nCoV OR “novel CoV” OR “CoV 2” OR CoV2 OR sarscov2 OR sars-cov* OR sarscov OR 2019nCoV OR 2019-nCoV) AND TITLE-ABS-KEY(Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR "hemoglobin h disease" OR beta-thalassemia* OR "hemoglobin f disease" OR "Mediterranean an?emia*" OR "cooley* an?emia" OR "Hydrops fetalis" OR "Hb Barts" OR "Hb Bart syndrome" OR "Hb Portland" OR "Hb Portland syndrome" OR "HbH disease" OR "constant spring" OR "Southeast Asian deletion" OR HBA1 OR HBA2 OR "Filipino deletion" OR "Mediterranean deletion" OR "erythroblastic anemia*" OR "beta type microcytemia*") AND NOT INDEX (Medline)	34 -28 Duplicates =6 unique items
WHO Global COVID Literature Database	Thalassemia* OR alpha-thalassemia* OR a-thalassemia* OR "hemoglobin h disease" OR beta-thalassemia* OR "hemoglobin f disease" OR "Mediterranean anemia" OR "Mediterranean anaemia" OR "cooley anemia" OR "cooley anaemia" OR "Hydrops fetalis" OR "Hb Barts" OR "Hb Bart syndrome" OR "Hb Portland" OR "Hb Portland syndrome" OR "HbH disease" OR "constant spring" OR "Southeast Asian deletion" OR HBA1 OR HBA2 OR "Filipino deletion" OR "Mediterranean deletion" OR "erythroblastic anemia" OR "beta type microcytemia"	242 -87 Duplicates =155 unique items

B.2. Study Inclusion and Exclusion Criteria

Inclusion Criteria: Studies were included at the title and abstract screen if they:

- were relevant to the key question "What is the association between thalassemia and severe COVID-19?";
    - exposures: Thalassemia, Beta Thalassemia, Mediterranean anaemia, Mediterranean anemia, Cooley's anaemia, Cooley's anemia, Beta+ thalassemia, beta+ thalassemia, beta plus thalassemia, Beta0 thalassemia, beta0 thalassemia, beta zero thalassemia, Alpha Thalassemia, Hydrops fetalis, Hb Barts, Hb Bart syndrome, Hb Portland, Hb Portland syndrome, HbH disease, --SEA (Southeast Asian deletion), -FIL (Filipino deletion), -MED (Mediterranean deletion), –α3.7 deletion (3.7-kb deletion), – α4.2 deletion (4.2-kb deletion), Constant Spring (constant spring deletion) thalassemia
    - outcomes: mortality, ICU admission, intubation, ventilation (non-invasive ventilation, mechanical ventilation, ECMO), hospitalization, and re-admission
- were primary research,
- were written in English (can be seen as [language] in title);
- examined humans only; and
- notably, descriptive data or comparative data where n < 5 with the exposure of interest were included only when comparative data were unavailable for an exposure of interest.

Exclusion Criteria: Studies were excluded at full-text review if they:

- were not available as full-text;
- did not have data available for an analysis of interest, or had no primary comparison reported;
- were a conference abstract, poster, or reply letter;
- were a systematic review, meta-analysis, mapping, or scoping review;
- reported only autopsy results;
- reported on a population that overlapped with a larger study using the same data set; and
- reported only composite outcome measures for "severe COVID-19".

B.3. Evidence Review: Thalassemia and Severe COVID-19

B.3.a. Strength & Direction of Evidence

Table 2 The Association Between Thalassemia and Severe COVID-19 Outcomes.

Outcome	Results
Mortality	Evidence from 4 studies[1,3,5,6] (N = 587) is suggestive of an increase in mortality in people with β-thalassemia or who are β-thalassemia trait carriers with hematocrit levels of 32 – 39, and COVID-19, but is insufficient to determine an association between thalassemia and mortality in COVID-19 patients. Two studies[3,6] were found to have a moderate threat to internal validity and two studies[1,5] were found to have a high threat to internal validity. • Strength of Association: One study[3] reported a measure of association of 2.79. • Precision of Association: One study[3] reported a wide confidence interval. • Consistency of Association: When reviewing the data according to the internal validity of studies, the results are consistent. • Applicability of Association: The populations and settings were applicable. Summary of Evidence: Two studies[3,6] (N = 303) reported mortality data that is suggestive of an increase in mortality in patients with β-thalassemia, or who are β-thalassemia trait carriers with hematocrit levels of 32 – 39, and COVID-19. ▪ One cohort study[3] (N = 255) examined COVID-19 positive patients in Greece and reported an increase in the adjusted odds of mortality in patients who are β-thalassemia trait carriers with hematocrit levels of 32 – 39 when compared to people without β-thalassemia [aOR: 2.79 (95% CI: 1.28 – 6.09), p = 0.01]. This study did not report the variables used in adjustment. ▪ One cross-sectional study[6] (N = 48) of people with COVID-19 in Iran reported a higher proportion of mortality among people with β-thalassemia compared to the general Iranian population [16.7% (8/48) vs. 5.7% (n/N = NR), p < 0.01]. The sample size was small, and the comparison was with uncited Iranian population data, decreasing confidence in the results. • Two studies[1,5] (N = 284) reported low numbers of deaths in patients with thalassemia and COVID-19 that, when compared with general population data, suggest no difference in mortality between these patients. ▪ One cohort study[1] (N = 275) of Italian people with thalassemia and COVID-19 suggested similar rates of mortality in people with thalassemia and COVID-19 compared to the general population [1.3% (3/227) vs. 3.4% (n/N = NR)]. The authors note that the difference in mortality rates between patients with hemoglobinopathies and the general population may be due to the younger age of patients with hemoglobinopathies. There was a low number of deaths in the study, the comparison was with uncited general population data and no statistical analyses were conducted, decreasing confidence in the results.

	▪ One cohort study[5] (N = 9) of people with thalassemia and COVID-19 in Greece suggested no difference in mortality in this population compared to the general Greek population [0.0% (0/8) vs. 1.0% (n/N = NR)]. The sample size was small, there were no deaths, the comparison was with uncited Greek population COVID-19 mortality data, and no statistical analyses were conducted, decreasing confidence in the results.
ICU admission	Limited data from only one study[3] is insufficient to determine an association between carriage of the β-thalassemia trait with hematocrit levels of 32 – 39 and ICU admission in COVID-19 patients. This study was found to have a moderate threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One study[3] (N = 255) reported a measure of association that is suggestive of an increase in ICU admission in patients with the β-thalassemia heterozygosity trait and COVID-19. ▪ One cohort study[3] (N = 255) of individuals with COVID-19 in Greece reported an increase in the adjusted odds of ICU admission among people with β-thalassemia compared to those without β-thalassemia [aOR: 1.33 (95% CI: 0.57 – 3.06), p = 0.51]. This study reported a low number of ICU admissions, and confidence intervals crossed the null, decreasing confidence in the results. This study did not report the variables used in the adjustment.

Table 3 The Association Between the Severity of Thalassemia and Severe COVID-19 Outcomes.

Outcome	Results
Mortality	Limited evidence from three studies[1,4,6] (N = 518) of people with thalassemia and COVID-19 is inconclusive to determine an association between mortality and transfusion-dependent thalassemia (TDT) compared to non-transfusion dependent thalassemia (NTDT), due to small sample sizes and a low number of deaths. TDT patients undergo regular transfusions and may be screened frequently for SARS-COV-2, which may result in earlier detection of COVID-19, possibly leading to lower mortality due to COVID-19. All studies were found to have a high threat to internal validity. • Strength of Association: No studies reported measures of association. • Precision of Association: No studies reported confidence intervals, and sample sizes were small limiting the precision. • Consistency of Association: When reviewing the data according to the internal validity of studies, the results are consistent. • Applicability of Association: The settings and populations are applicable. Summary of Evidence: • Three studies[1,4,6] (N = 518) reported proportions of mortality in COVID-19 patients with NTDT and TDT.

	▪ One cohort study[6] (N = 48) of people with COVID-19 and thalassemia in Iran, reported proportions of mortality in people with TDT and people with NTDT [11.8% (4/34) vs. 28.6% (4/14),p = NR]. 78.1% of TDT and 90.9% of NTDT patients were complicated with at least one comorbidity. There were no differences between groups for the following comorbidities except BMI (kg/m2); osteoporosis, diabetes mellitus, hypogonadism, growth failure, hypertension, kidney failure, pulmonary hypertension, heart failure, hypothyroidism, hypoparathyroidism, chronic liver disease, HCV positivity. The sample size was small, decreasing confidence in the results. ▪ One cohort study[4] (N = 195) of people with COVID-19 and thalassemia in England reported proportions of mortality in patients with TDT and people with NTDT [5% (1/20) vs. 17% (1/6), p = NR]. The study notes that the TDT patient that died had diabetes and an iron overload and the NTDT patient that died had cancer. There was a low number of deaths, decreasing confidence in the results. ▪ One cohort study[1] (N = 275) of people with COVID-19 and thalassemia in Italy, reported proportions of mortality among people with TDT and people with NTDT [1% (2/191) vs. 2.8% (1/36), p = NR]. Of the entire cohort, 72% had comorbidities. There was a low number of deaths, decreasing confidence in the results.
ICU admission	Limited data from 2 studies[2,4] (N = 217) is inconclusive to determine an association between ICU admission and TDT compared to NTDT, due to small sample sizes and a low number of ICU admissions. All studies were found to have a high threat to internal validity. • Strength of Association: No studies reported measures of association. • Precision of Association: No studies reported confidence intervals, and small sample sizes reduce precision. • Consistency of Association: The evidence is consistent. • Applicability of Association: Settings and populations are applicable. • Two studies[2,4] (N = 217) reported proportions of ICU admission among COVID-19 patients with TDT or NTDT. ▪ One cohort study[2] (N = 22) of people with COVID-19 and thalassemia in Italy reported proportions of ICU admissions among patients with TDT and patients with NTDT [5.6% (1/18) vs. 0% (0/4), p = NR]. The sample size was small and there was a low number of ICU admissions, decreasing confidence in the results. ▪ One cohort study[4] (N = 195) of people with COVID-19 and thalassemia in England reported proportions of ICU admission among patients with TDT and patients with NTDT [5% (1/20) vs. 0% (0/6), p = NR]. There was a low number of ICU admissions and the study included confirmed as well as suspected cases of COVID-19, decreasing confidence in the results.
Intubation	Limited data from only one study[2] (N = 22) is insufficient to determine an association between intubation and TDT compared to NTDT among COVID-19 patients, due to the small sample size and an absence of intubations. This study was found to have a high threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One study[2] (N = 22) reported proportions of intubation in TDT and NTDT patients with COVID-19.

	▪ One cohort[2] (N = 22) of people with COVID-19 and thalassemia in Italy reported similar proportions of intubations among people with TDT and people with NTDT [0% (0/18) vs. 0% (0/4), p = NR] The sample size was small and there were no intubations, decreasing confidence in the results.
Mechanical Ventilation	Limited data from only one study[4] (N = 195) is insufficient to determine an association between mechanical ventilation and TDT compared to NTDT among COVID-19 patients, due to the small sample size and a low number of machinal ventilations. The study was found to have a high threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One study[4] (N = 195) reported proportions of intubation in TDT and NTDT patients with COVID-19. ▪ One cohort study[4] (N = 195) of people with COVID-19 and thalassemia in England reported proportions of mechanical ventilation in patients with TDT and patients with NTDT. [5% (1/20) vs. 0% (0/6), p = NR] There was a low number of ventilations and the study included confirmed as well as suspected cases of COVID-19, decreasing confidence in the results. The sub-analysis was small
Non-invasive Ventilation	Limited data from only one study[2] (N = 22) is insufficient to determine an association between non-invasive ventilation and TDT or NTDT among COVID-19 patients, due to the small sample size and a low number of non-invasive ventilation. The study was found to have a high threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. Summary of Evidence: • One study[2] (N = 22) reported proportions of ventilation in TDT and NTDT patients with COVID-19. ▪ One cohort study[2] (N = 22) of people with COVID-19 and thalassemia in Italy reported proportions of non-invasive ventilation by CPAP in patients with TDT and patients with NTDT. [5.6% (1/18) vs. 0% (0/4), p = NR]. The sample size was small and there was a low number of ventilation, decreasing confidence in the results.
Hospitalization	Limited evidence from 2 studies[2,4] (N = 217) of people with COVID-19 is inconclusive to determine an association between hospitalization and TDT compared to NTDT, due to small sample sizes and a low number of hospitalizations. All studies were found to have a high threat to internal validity. • Strength of Association: No studies reported measures of association. • Precision of Association: No studies reported confidence intervals and both studies reported small sample sizes. • Consistency of Association: The evidence is consistent. • Applicability of Association: populations and settings are applicable. Summary of Evidence: ▪ Two studies[2,4] (N = 217) of people with COVID-19 and thalassemia reported proportions of hospitalization in TDT and NTDT patients with COVID-19.

	▪ One cohort study[2] (N = 22) of people with COVID-19 and thalassemia in Italy reported proportions of hospitalization in people with TDT and people with NTDT [27.8% (5/18) vs. 25% (1/4), p = NR]. ▪ One cohort study[4] (N = 195) of people with COVID-19 and thalassemia in England reported proportions of hospitalization in people with TDT and people with NTDT [45% (9/20) vs. 66.7% (4/6), p =NR]. There was a low number of hospitalizations and the study included confirmed as well as suspected cases of COVID-19, decreasing confidence in the results.

B.3.b. Extracted Evidence

Table 4 Extracted Studies Reporting the Association Between Thalassemia and Severe COVID-19 Outcomes.

Study	Population and Setting	Exposure	Definitions	Results
Author: Karimi[6] **Year: 2021** **Data Extractor: MM** **Reviewer: AH** **Study Design: Cross-sectional** **Study Objective: To investigate the severity of COVID-19 among thalassemia patients living in Iran.** **IVA Score: 22 (Moderate)**	**Population:** N = 48 COVID-19+ **Setting:** Comprehensive thalassemia centers **Data Source:** Electronic Medical Records **Location:** Iran **Study Dates:** January – August 2020 **Inclusion Criteria:** Thalassemia patients registered by the Iranian Ministry of Health (MOH)] with SARS-CoV-2 infection confirmed by an RT-PCR test. **Exclusion Criteria:** NR	**Medical Condition, n/N (%):** Thalassemia: 48/48 (100%) • Transfusion Dependent Thalassemia (TDT): 34/48 (71.0%) • Non-Transfusion Dependent Thalassemia (NTDT): 14/48 (29.0%) **Control/Comparison Group, n/N (%):** Iran General Population: NR	**Medical Condition(s):** *Thalassemia:* Transfusion Dependent Thalassemia (TDT) or Non-Transfusion Dependent Thalassemia (NTDT) **Severity Measure(s):** NR **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** TDT patients were regularly transfused every 2–4 weeks. The participants overlap with participants in Karimi 2020; therefore, severity data was taken from Karimi 2020.	**Severe COVID-19:** *Mortality, n/N (%)* • Thalassemia: 8/48 (16.7%) • General Iranian population: NR/NR (5.7%) • p = 0.001 **Severity Measure(s):** NR *Mortality, n/N (%)* • TDT: 4/34 (11.8%) • NTDT: 4/14 (28.6%) • p = NR **Duration of Condition:** NR **Comorbid Conditions:** All thalassemia patients who died had at least one comorbidity. **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR

Author: Longo[1] **Year: 2021** **Data Extractor: MM** **Reviewer: AH** **Study Design: Cohort** **Study Objective: To explore the hypothesis of an increased vulnerability of hemoglobinopathies to SARS-COV2 infection.** **IVA Score: 17 (High)**	**Population:** N = 275 **Setting:** 27 centers **Data Source:** Healthcare **Location:** Italy **Study Dates:** NR—February 15, 2021 **Inclusion Criteria:** Hemoglobinopathy patients with a positive swab or serology and at least 15 days of follow-up from either the onset of symptoms or SARS-COV2 positivity. **Exclusion Criteria:** NR	**Medical Condition, n/N (%):** Thalassemia: 227/275 (82.5%) Transfusion Dependent Thalassemia (TDT): 191/275 (69.5%) Non-Transfusion Dependent Thalassemia (NTDT): 36/275 (13.1%) **Control/Comparison Group, n/N (%):** General Italian Population: NR	**Medical Condition(s):** *Hemoglobinopathy:* includes TDT, NTDT, and sickle cell disease patients **Severity Measure(s):** *TDT:* ND *NTDT:* ND **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* multisystem organ failure and death *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** The authors note that the difference in mortality rates between patients with hemoglobinopathies and the general population may be due to the younger age of patients with hemoglobinopathies.	**Severe COVID-19:** *Mortality, n/N (%):* • Thalassemia: 3/227 (1.3%) • General Italian Population: n/N = NR (3.4%) • p = NR **Severity of Condition:** *Mortality, n/N (%):* • TDT: 2/191 (1.0%) • NTDT: 1/36 (2.8%) **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR
Author: Motta[2] **Year: 2020** **Data Extractor: AH** **Reviewer: DOS** **Study Design: Cohort** **Study Objective: To verify the impact of SARS-**	**Population:** N = 22 COVID-19+ **Setting:** Community **Data Source:** Electronic case report form **Location:** Italy **Study Dates:** **Inclusion Criteria:** Thalassemic syndrome	**Medical Condition, n/N (%):** β-thalassemia, 22/22 (100.0%) Transfusion-dependent thalassemia (TDT), 18/22 (81.8%) Non-transfusion-dependent thalassemia (NTDT), 4/22 (18.2%) **Control/Comparison Group, n/N (%):** NR	**Medical Condition(s):** *Thalassemic syndrome:* ND **Severity Measure(s):** *TDT:* ND *NTDT:* ND **Clinical Marker:** **Outcome Definitions:** *Mortality:* ND *ICU admission:* NR *Intubation:* ND *Ventilation:* CPAP *Hospitalization:* ND	**Severe COVID-19:** NR **Severity of Condition:** *Mortality, n/N (%):* • TDT, 0/18 (0.0%) • NTDT, 0/4 (0.0%) *ICU admission, n/N (%):* • TDT, 1/18 (5.6.0%) • NTDT, 0/4 (0.0%) *Intubation, n/N (%):* • TDT, 0/18 (0.0%) • NTDT, 0/4 (0.0%)

CoV-2 infection on thalassemia syndromes. **IVA Score: 12 (High)**	cases with at least 15 days of follow-up from either the onset of symptoms or SARS-CoV2 positivity. Cases were identified through the Centers for Italian Hemoglobinopathies Network. **Exclusion Criteria:** NR		*Non-elective readmissions*: NR **Comments:** None	*Ventilation, n/N (%):* • TDT, 1/18 (5.6%) • NTDT, 0/4 (0.0%) *Hospitalization, n/N (%):* • TDT, 5/18 (27.8.0%) • NTDT, 1/4 (25.0%) **Duration of Condition:** NR **Comorbid Conditions:** All patients have thalassemia-associated comorbidities. **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Sotiriou[3] **Year: 2021** **Data Extractor: AH** **Reviewer: MM** **Study Design: Cohort** **Study Objective: To compare the effect of age, sex, complex co-morbidities, and β-thalassemia status on clinical outcomes.** **IVA Score: 20 (Moderate)**	**Population:** N = 255 **Setting:** Tertiary referral hospital **Data Source:** Online survey **Location:** Greece **Study Dates:** October 1 – December 31, 2020 **Inclusion Criteria:** Patients admitted to the emergency department who were not vaccinated against COVID-19 with a positive SARS-CoV-2 Real-Time Polymerase Chain Reaction (RTPCR) molecular test. **Exclusion Criteria:** NR	**Medical Condition, n/N (%):** β-Thalassemia trait carriers: 45/255 (17.7%) **Control/Comparison Group, n/N (%):** No β-Thalassemia trait carriage: 210/255 (82.4%)	**Medical Condition(s):** NR **Severity Measure(s):** β-*Thalassemia trait carriers*: single gene blood disorder **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* mortality from COVID-19 *ICU admission:* ICU admission due to COVID-19 *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *aOR: Adjusted odds ratio; binary and ordinal logistic regression* *OR: Univariable (Univariate) Logistic Regression* *RR: Risk Ratio* **Severity of Condition:** *Mortality, n/N (%):* β-Thalassemia trait carriers: • aOR: 2.79 (95% CI: 1.28 – 6.09), p = 0.010 • OR: 2.56 (95% CI: 1.31 – 4.99), p = 0.005 • RR: 1.87 (95% CI: 1.24 – 2.80), p = 0.005 • Died: 20/45 (44.44%) *ICU admission, n/N (%):* β-Thalassemia trait carriers: • aOR: 1.33 (95% CI: 0.57 – 3.06), p = 0.508 • OR: 1.29 (95% CI: 0.61 – 2.77), p = 0.505 • RR: 1.22 (95% CI: 0.68 – 2.18), p = 0.51 • ICU Admission: 11/45 (24.44%) **Duration of Condition:** NR **Comorbid Conditions:** NR

				Risk Markers: NR **Long-term Sequelae:** NR
Author: Telfer[4] **Year: 2020** **Data Extractor: AH** **Reviewer: MM** **Study Design: Cohort** **Study Objective: To inform guidance on the clinical management of COVID-19 and public health policy on high risk cases of COVID-19 in hemoglobinopathy and rare inherited anemia patients.** **IVA Score: 16 (High)**	**Population:** N = 195 COVID+ **Setting:** Community **Data Source:** 14 Hemoglobinopathy Coordinating Centers (HCC) **Location:** England **Study Dates:** April 8 – May 6, 2020 **Inclusion Criteria:** Confirmed and suspected cases of COVID-19 in hemoglobinopathy and rare inherited anemia patients. **Exclusion Criteria:** NR	**Medical Condition, n/N (%):** Thalassemia: 26/195 (13.33%) • Transfusion dependent thalassemia (TDT): 20/26 (77.0%) • Non-transfusion dependent thalassemia (NTDT): 6/26 (23.0%) **Control/Comparison Group, n/N (%):** NA	**Medical Condition(s):** *Thalassemia:* ND **Severity Measure(s):** *TDT*: ND *NTDT*: ND **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* mortality from COVID-19 *ICU admission:* ICU admission due to COVID-19 *Intubation:* NR *Ventilation:* non-invasive and mechanical ventilation *Hospitalization:* hospitalization due to COVID-19 *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** NR **Severity of Condition:** *Mortality, n/N (%):* Thalassemia • TDT: 1/20 (5.0%) • NTDT: 1/6 (16.7%) *Mechanical Ventilation, n/N (%):* Thalassemia • TDT: 1/20 (5.0%) • NTDT: 0/6 (0.0%) *Non-invasive ventilation, n/N (%):* Thalassemia • TDT: 0/20 (0.0%) • NTDT: 0/6 (0.0%) *Hospitalization, n/N (%):* Thalassemia • TDT: 9/20 (45.0%) • NTDT: 4/6 (66.7%) **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Varelas[5] **Year: 2021** **Data Extractor: MM**	**Population:** N = 9 COVID+ **Setting:** Specialized Center	**Medical Condition, n/N (%):** Transfusion Dependent be β-Thalassemia (TDT): 7/9 (78.0%) **Control/Comparison Group, n/N (%):**	**Medical Condition(s):** NR **Severity Measure(s):** *TDT:* ND **Clinical Marker:** NR	**Severe COVID-19:** All Thalassemia • Thalassemia: 0/8 (0.0%) • General Greek Population: n/N = NR (1.0%) TDT (Beta)

Reviewer: AH **Study Design: Cohort** **Study Objective: To investigate the incidence and outcomes of COVID-19 in patients with hemoglobinopathies and correlate them to their coexisting comorbidities.** **IVA Score: 16 (High)**	**Data Source:** NR **Location:** Greece **Study Dates:** March — December 2020 **Inclusion Criteria:** Patients with different hemoglobinopathies consecutively monitored at the Center who were infected by SARS-COV2 during the first and second "waves" of the pandemic in Greece. **Exclusion Criteria:** NR	General Greek Population: NR	**Outcome Definitions:** *Mortality:* ND *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	*Mortality, n/N (%):* • TDT: 0/6 (0.0%) • General Greek Population: n/N = NR (1.0%) <u>HbH (Alpha)</u> *Mortality, n/N (%):* • HbH: 0/2 (0.0%) • General Greek Population: n/N = NR (1.0%) **Severity of Condition:** *Mortality, n/N (%):* • TDT: 0/6 (0.0%) • HbH: 0/2 (0.0%) • General Greek Population: n/N = NR (1.0%) *ICU Admission, n/N (%):* • TDT: 0/6 (0.0%) • HbH: 0/2 (0.0%) *Intubation, n/N (%):* • TDT: 0/6 (0.0%) • HbH: 0/2 (0.0%) *Invasive Ventilation, n/N (%):* • TDT: 0/6 (0.0%) • HbH: 0/2 (0.0%) *Hospitalization, n/N (%):* • TDT: 4/6 (66.7%) • HbH: 1/2 (50%) **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR

B.3.c. Internal Validity Assessments of Extracted Studies

Table 5 Internal Validity Assessments of Extracted Studies Reporting the Association Between Thalassemia and Severe COVID-19 Outcomes.

Author Year	**Karimi 2021[6]**	**Longo 2021[1]**	**Motta 2020[2]**	**Sotiriou 2021[3]**	**Telfer 2020[4]**	**Varelas 2021[5]**
Outcome(s)	Mortality	Mortality	Mortality, intubation, ventilation, hospitalization	Mortality, ICU admission	Mortality, ICU admission, mechanical ventilation, non-invasive ventilation, hospitalization	Mortality, ICU admission, intubation, invasive ventilation, hospitalization
Signaling question						
Study Elements: **Design appropriate to the research question**	1	1	1	0	1	1
Well described population	1	1	1	1	1	1
Well described setting	1	1	1	1	1	1
Well described intervention/ exposure	1	1	1	1	1	1
Well described control/ comparator	0	1	0	0	1	0
Well described outcome	1	1	1	1	1	1
Clear timeline of exposures/ interventions and outcomes	1	1	1	1	1	1
Selection Bias: Sampling **Randomization appropriately performed**	0	0	0	0	0	0
Allocation adequately concealed	0	0	0	0	0	0
Population sampling appropriate to study design	1	1	1	0	0	1
Selection Bias: Attrition **Attrition not significantly different between groups**	0	1	1	0	0	0
Attrition <10-15% of population	0	1	1	0	1	0
Attrition appropriately analyzed	0	1	1	0	1	0

Information Bias: Measurement and Misclassification **Measure of intervention/ exposure is valid**	1	1	0	0	0	1
Measure of outcome is valid	1	1	1	1	1	1
Fidelity to intervention is measured	0	0	0	0	0	0
Fidelity to intervention is valid	0	0	0	0	0	0
Prospective study	1	1	1	1	1	1
Adequately powered to detect result	0	0	0	0	1	0
Information Bias: Performance & Detection **Outcome assessor blinded**	0	0	0	0	0	0
Study participant blinded	0	0	0	0	0	0
Investigator/ data analyst blinded	0	0	0	0	0	0
Data collection methods described in sufficient detail	1	1	1	1	0	1
Data collection methods appropriate	1	1	1	1	0	1
Sufficient follow up to detect outcome	1	1	0	1	1	1
Information Bias: Analytic **Appropriate statistical analyses for collected data**	0	1	0	0	1	0
Appropriate statistical analyses are conducted correctly	0	0	0	0	1	0
Confidence interval is narrow	0	0	0	0	0	0
Confounding: **Potential confounders identified**	0	1	1	0	1	1
Adjustment for confounders in study design phase	0	0	0	0	0	0
Adjustment for confounders in data analysis phase	0	0	0	0	1	0
Reporting Bias: **All pre-specified outcomes are adequately reported**	1	1	1	1	1	1
Other Bias: **No other sources of bias**	1	1	1	1	1	1
COI:	1	1	0	0	1	0

Funding sources disclosed and no obvious conflict of interest						
SCORE: **Threat to internal validity**	16	22	17	12	20	16
Low, Moderate, High	High	Moderate	High	High	Moderate	High

C. References

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D. Abbreviations

Table 6 Abbreviations.

Acronym	Full
95% CI	95% confidence interval
aOR	adjusted odds ratio
CDC	Centers for Disease Control and Prevention
CI	confidence interval
COI	conflict of interest
CPAP	continuous positive airway pressure
ECMO	extracorporeal membrane oxygenation
HCC	hemoglobinopathy coordinating centers
HIC	high-income country
ICU	intensive care unit
IVA	internal validity assessments
LIC	low-income country
MIC	middle-income country
MOH	Ministry of Health
NA	not applicable
ND	not defined
NR	not reported
NTDT	non-transfusion dependent thalassemia
OR	odds ratio
PCR	polymerase chain reaction
PECO	population, exposure, comparator, and outcomes
RNA	ribonucleic acid
RR	risk ratio
RT-PCR	real-time polymerase chain reaction
SD	standard deviation
SCD	sickle cell disease
TDT	transfusion-dependent thalassemia
TF	task force

TI	thalassemia intermedia
TM	thalassemia major
WHO	World Health Organization