Incidence Rate of COVID-19 Infection in Hemoglobinopathies: A Systematic Review and Meta-analysis

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ABSTRACT
During the coronavirus-19 disease (COVID-19) pandemic, several studies were performed to determine the mortality and incidence rates of coronavirus infection among patients with hemoglobinopathies. However, there has been no systematic approach or meta-analysis to evaluate the results worldwide. This meta-analysis summarized the existing evidence of incidence and mortality rates of COVID-19 and related risk factors among patients with hemoglobinopathies with a focus on $\beta$-thalassemia ($\beta$-thal) and sickle cell disease. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Two authors independently screened the articles, extracted eligible ones, and assessed the quality of studies using the Joanna Briggs Institute (JBI) checklist. The collected data were analyzed by the Stata software. The amount of heterogeneity was demonstrated by the I\textsuperscript{2} test. The incidence of COVID-19 among patients with a hemoglobinopathy, $\beta$-thal and sickle cell disease was 4.44, 1.34, and 17.22 per 100,000 person-day, respectively, to June 15 2020. The mortality rate of COVID-19 in patients with hemoglobin (Hb) disorders was calculated as 1.07 per 1000 person-day in the same period. Our findings showed a higher incidence rate of COVID-19 in sickle cell disease patients compared to the general population. A slightly higher mortality rate was also observed in patients with hemoglobinopathies compared to the general population, possibly due to the associated risk factors and comorbidities in this vulnerable group, which underscore special care, timely diagnosis and management along with current immunization, were crucial in decreasing the frequency, disease severity and mortality of these patients.

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Introduction
During the coronavirus disease (COVID-19) pandemic, many patients with hemoglobinopathies were affected by the infection resulting in higher morbidity and mortality [1]. Coronavirus-19 presentations can vary from asymptomatic infection to severe acute respiratory syndrome [2,3]. A recent meta-analysis reported that hypertension (HTN), diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease, were the most prevalent comorbidities related to COVID-19 infection [4]. Patients with hemoglobinopathies may experience more severe symptoms through person-to-person transmission in the presence of comorbidities [5]. Thalassemia and sickle cell disease are two major and common groups of monogenic disorders that may lead to severe complications in patients affected by COVID-19 [6–9]. According to blood transfusion requirement, patients with $\beta$-thalassemia ($\beta$-thal) are categorized into two groups: transfusion dependent $\beta$-thal (TDT) and nontransfusion-dependent $\beta$-thal (NTDT) [10]. Thalassemic patients face multiple organ damage due to iron overload, ineffective erythropoiesis, chronic hemolytic anemia, and hypercoagulability [5,10]. In sickle cell disease, decreased immunity can occur due to functional asplenia and defective complement activation [11]. Indeed, both groups of patients are at risk of developing severe complications due to the COVID-19 infection [5].

During the COVID-19 pandemic, several studies were performed to determine the mortality and incidence rates of COVID-19 infections among patients with $\beta$-thal and sickle cell disease as the two major subtypes of hemoglobinopathies. However, there has been no systematic approach or meta-analysis to evaluate the results worldwide. This meta-analysis study was conducted to summarize the existing evidence of incidence and mortality rates of COVID-19 and their related comorbidities among patients with hemoglobinopathies with a focus on $\beta$-thal and sickle cell disease.

Method
This systematic review and meta-analysis has been done according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [12]. The study protocol was approved by the Ethics Committee of
Shiraz University of Medical Sciences, Shiraz, Iran [IR.SUMS.REC.1399.1281]. The review was registered at International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42021235997.

**Search strategy**

**Searched databases**

An electronic search was done in databases including Web of Science (ISI), Scopus, PubMed, and Google Scholar for articles from the initiation of the COVID-19 pandemic to January 16 2021. Combinations of the following medical subject headings (MeSH), terms and keywords, were used to conduct a comprehensive literature search: hemoglobinopathy or sickle cell disease or SCD; or transfusion-dependent thalassemia or TDT or non-transfusion-dependent thalassemia or NTDT; SARS-CoV-2 or COVID-19 or coronavirus (Supplementary Table 1). Moreover, we conducted a manual review of the reference lists of the relevant articles and previously performed reviews for additional pertinent studies.

**Inclusion and exclusion criteria**

Two authors (S. Haghpanah and M. Hosseini-Bensenjan) independently screened the articles by endnote software version 9 (https://endnote.com). The human observational studies, which reported the incidence of confirmed COVID-19 cases among patients with hemoglobinopathies, were included in this analysis. The language was limited to English. Studies such as case reports, review studies, and

![Figure 1. Flowchart of study identification and selection process.](image-url)
studies that did not have complete data for calculating incidences were excluded.

Data extraction

The same two authors independently extracted the required data from included articles using sheet form of Excel, any controversy between the data extractors was resolved by the third author (M. Sayadi). The following data were extracted: name of the first author, the timeline in which the study was conducted, duration of the study, type of study, country, the total number of hemoglobinopathies, number of cases with COVID-19, number of deaths. We also extracted the frequency of comorbidities among patients with COVID-19 and hemoglobinopathies that included DM, systemic and pulmonary HTN (PHTN), CVD, renal diseases and stroke. When there were several reports from one country, we only considered the most comprehensive meta-analysis results for incidence and mortality rates.

Study quality assessment

The quality of the included studies was assessed by two independent authors (S. Haghpanah and M. Hosseini-Bensenjan) based on Joanna Briggs Institute (JBI) checklist [13]. This checklist consists of nine items that evaluated the sampling process, data analysis process and statistical methods, study settings, measurement tools and response rate (Supplementary Table 2). The quality score of more than 5 was considered as moderate-high quality and included in meta-analysis. If there was any disagreement between assessors, it was resolved by the third author (M. Sayadi).

Statistical analyses

The collected data were entered into the Stata statistical software version 13 (https://www.stata.com). For studies with heterogeneity, we used a random effect model, while for those without significant heterogeneity, the fixed-effect model was applied [14]. The amount of heterogeneity of the selected studies was demonstrated by the I² test. The incidence rate was reported by the number of patients with hemoglobinopathies affected by COVID-19 in 100,000 person-day since the beginning of the pandemic up to June 15 2020. The mortality rate was calculated per 1000 person-day of patients with hemoglobinopathies who were affected by COVID-19 for the same duration. Subgroup analyses were carried out by type of hemoglobinopathy including sickle

| Table 1. Main characteristics of the included studies for incidence rate. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| References      | [5]            | [5]            | [5]            | [5]            | [6]            | [8]            | [16]           | [17]           | [19]           |
| Timeline        | 1/1 to 7/6     | 1/1 to 7/6     | 1/1 to 7/6     | 1/1 to 7/6     | 1/1 to 7/6     | Jan to 15/6    | 16/2 to 8/6     | to 10/4        | 8/4 to 6/5     | Feb to April    |
| Duration (days) | 158            | 158            | 158            | 158            | 158            | 166            | 82              | 100            | 28             | 60             |
| Country         | Turkey         | Azerbaijan     | Cyprus         | Oman           | Iran           | USA            | Italy           | UK             | Bahrain        |
| Study type      | cross-sectional| cross-sectional| cross-sectional| cross-sectional| cross-sectional| cross-sectional| real-time survey | cross-sectional|                |
| Total patients  | 1157           | 2033           | 319            | 2344           | 18350          | 3500           | 6900            | 13655          | 378            |
| with b-thal or  |                |                |                |                |                |                |                 |                 |                |
| Sickle cell     |                |                |                |                |                |                |                 |                 |                |
| disease (n)     | 2              | 2              | 1              | 3              | 43             | 66             | 11              | 84             | 6              |
| TDT patients    | 658            | 1304           | 247            | 300            | 15950          | NR             | 5000            | NR             | NR             |
| (n)             |                |                |                |                |                |                |                 |                 |                |
| TDT, COVID-19   | 2              | 2              | 1              | 0              | 32             | NR             | 10              | NR             | NR             |
| (n)             |                |                |                |                |                |                |                 |                 |                |
| NTDT patients   | 164            | 605            | 44             | 44             | 11             | NR             | 1               | NR             | NR             |
| (n)             |                |                |                |                |                |                |                 |                 |                |
| NTDT, COVID-19  | 0              | 0              | 0              | 0              | 11             | NR             | 1               | NR             | NR             |
| (n)             |                |                |                |                |                |                |                 |                 |                |
| Total [2]-thal  | 822            | 1909           | 291            | 344            | 18350          | NR             | 6900            | NA             | NR             |
| patients (n)    |                |                |                |                |                |                |                 |                 |                |
| [2]-Thal, COVID-19 (n) | 2 | 2 | 1 | 0 | 43 | NR | 11 | NA | NR |
| Sickle cell     | 355            | 124            | 28             | 2000           | NR             | 3500           | NR              | 13655          | 378            |
| disease patients (n) | 0 | 0 | 0 | 3 | NR | 66 | NR | 84 | 6 |
| Sickle cell     | 0              | 0              | 0              | 3              | NR             | 66             | NR              | 84             | 6              |
| COVID-19 (n)    |                |                |                |                |                |                |                 |                 |                |
| COVID-19: coronavirus disease-19; TDT: transfusion-dependent thalassemia; NR: not recorded; NA: not applicable; NTDT: non transfusion-dependent thalassemia.

| Five centers. |
| One center. |
| One center. |
| Nearly all centers. |
| Five centers. |
| National Hemoglobinopathy Registry. |

| Table 2. Main characteristics of the included studies for mortality rate. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| References      | [6]            | [16]           | [18]           | [19]           | [20]           | [21]           |
| Timeline        | Jan to 15/6     | To 10/4        | 13/3 to 16/4   | Feb to April   | 20/3 to 21/5   | 10/3 to 23/4   |
| Duration (days) | 166            | 100            | 34             | 60             | 62             | 44             |
| Country         | Iran           | Italy          | France         | Bahrain        | USA            | UK             |
| Study type      | cross-sectional| survey         | cross-sectional| cross-sectional| cross-sectional| cross-sectional|
| Disease         | [2]-thal       | [2]-thal       | sickle cell disease | sickle cell disease | sickle cell disease | sickle cell disease |
| Total affected  | 43             | 11             | 83             | 6              | 178            | 6              |
| patients by     |                |                |                |                |                |                |
| COVID-19 (n)    | 8              | 0              | 2              | 0              | 13             | 1              |
| Deceased (n)    |                |                |                |                |                |                |
| [2]Nearly all centers. |
| Twenty-four centers. |
| Twenty-two states. |
| One center. |
Figure 2. (A) Forest plot of COVID-19 incidence rate per 100,000 person-day in hemoglobinopathy patients. (B) Forest plot of mortality rate per 1000 person-day due to COVID-19 in patients with hemoglobinopathy.
cell disease, β-thal, NTDT and TDT. Moreover, pooled and individual data of the included surveys were depicted by Forest Plots. Publication bias was checked by the Egger test [15].

Results

Literature search and study characteristics

Figure 1 shows the PRISMA flowchart of the data selection process. The systematic search resulted in 474 initial records, of these 223 were excluded as duplicates and 131 as irrelevant records due to title/abstract. One hundred and twenty full-text articles were assessed for eligibility according to our inclusion criteria. Finally, nine articles (12 studies) were found to be appropriate for quantitative synthesis [5,6,8,16–21] (Figure 1). The main characteristics of the studies are summarized in Tables 1 and 2. The study designs mainly included cross-sectional methods. Publication bias was not significant according to the Egger’s test [15] (Supplementary Tables 3 and 4).

Main outcomes

Hemoglobinopathy

The total number of patients with hemoglobinopathies included in the study was 48636 [5,6,8,16,17,19]. The incidence rate of COVID-19 infection among patients with hemoglobinopathies was 4.44 (2.58-6.29) per 100,000 person-day. There was considerable heterogeneity across the included studies ($I^2 = 94.4\%$, $p < 0.001$) [Figure 2(A)].

Mortality and comorbidities

The total number of patients with hemoglobinopathies affected by the COVID-19 infection was 327 according to the included studies [6,16,18–21]. Overall death rate due to COVID-19 per 1000 person-day was 1.07 [95% confidence interval (95% CI): 0.63–1.51] and inter-study heterogeneity was acceptable ($I^2 = 0$, $p = 0.617$). For patients with TDT, the incidence rate was 1.28 (95% CI: 0.9, 1.66) per 100,000 person-day without heterogeneity ($I^2 = 0$, $p = .72$), while it was 1.55 (–0.63, 3.73) per 100,000 person-day with high heterogeneity in NTDT patients ($I^2 = 80.6$, $p = 0.023$) [Figure 3(A), 3(B) and 3(C)]. The incidence rate of infection among patients with sickle cell disease was 17.22 (95% CI: 1.81, 32.64) per 100,000 person-day with high heterogeneity ($I^2 = 97.7$, $p < 0.001$) [Figure 3(D)].

Subgroup analysis

β-thalassemia and sickle cell disease

The incidence rate of COVID-19 infection among β-thal patients was 1.34 (0.99–1.69) per 100,000 person-day without heterogeneity ($I^2 = 0$, $p = 0.617$). For patients with TDT, the incidence rate was 1.28 (95% CI: 0.9, 1.66) per 100,000 person-day without heterogeneity ($I^2 = 0$, $p = .72$), while it was 1.55 (–0.63, 3.73) per 100,000 person-day with high heterogeneity in NTDT patients ($I^2 = 80.6$, $p = 0.023$) [Figure 3(A), 3(B) and 3(C)]. The incidence rate of infection among patients with sickle cell disease was 17.22 (95% CI: 1.81, 32.64) per 100,000 person-day with high heterogeneity ($I^2 = 97.7$, $p < 0.001$) [Figure 3(D)].

Discussion

In this meta-analysis, we determined the pooled incidence and mortality rates of COVID-19 infection among patients with two major groups of hemoglobinopathies (β-thal and sickle cell disease) from the initiation of COVID-19 pandemic up to June 15 2020. The incidence rate of COVID-19 among patients with hemoglobinopathies, β-thal and sickle cell disease was 4.44, 1.34, and 17.22 per 100,000 person-day, respectively. According to the WHO reports, the incidence rate of COVID-19 was calculated as 2.89 per 100,000 person-day in the general population of the evaluated studies up to June 15 2020 [22,23].

Our meta-analysis showed that the incidence rate of COVID-19 was higher in patients with sickle cell disease compared to the general population of the evaluated countries in the specified period. It seems that sickle cell disease patients are more vulnerable to COVID-19 infection possibly due to disease-related complications, more susceptibility to viral infection and acute pulmonary illness, and possible concurrence of immunocompromised conditions [24,25].

Surprisingly, the pooled incidence rate of COVID-19 in patients with β-thal in our study was lower than the general population of participating countries in the evaluation period and it was slightly higher in NTDT compared to TDT patients. On the one hand, we were expecting a higher susceptibility of thalassemic patients to COVID-19 infection

| References | [6] | [8] | [16] | [20] | [21] |
|------------|-----|-----|-----|-----|-----|
| Country | Iran | USA | Italy | USA | UK |
| Study type | cross-sectional | cohort | survey | cross-sectional | cohort |
| COVID-19 (n) | 43 | 66 | 11 | 178 | 6 |
| Disease type | β-thal | sickle cell disease | β-thal | sickle cell disease | sickle cell disease |
| DM (n) | 11 | 6 | 6 | NR | NR |
| HTN (n) | 1 | NR | NR | NR | NR |
| Pulmonary HTN (n) | 6 | 14 | 1 | 23 | NR |
| CVD (n) | 4 | 10 | 10 | NR | NR |
| Renal disease (n) | 2 | 23 | 3 | 166 | 1 |
| Stroke (n) | 2 | 12 | NR | 32 | 1 |

COVID-19: coronavirus disease-19; DM: diabetes mellitus; NR: not recorded; HTN: hypertension; CVD: cardiovascular disease.

[a] Nearly all centers.
[b] Five centers.
[c] Twenty-two states.
[d] One center.
Figure 3. Forest plot of COVID-19 incidence rate per 100,000 person-day in (A) TDT patients. (B) Non-TDT patients. (C) β-Thalassemia patients. (D) Sickle cell patients.
was due to the occurrence of iron overload and comorbidities [6]. On the other hand, the hypothesis of β-thal immun
ity to COVID-19 infection due to the absence or decrease of β chains, was also raised as the potential target of the virus along with ineffective erythropoiesis and increased clearance of infected red blood cells by the virus [26,27], which seems to be in accordance with our results.

The overall mortality rate of COVID-19 in patients with hemoglobin (Hb) disorders was calculated as 1.07 per 1000 person-day. On the other hand, the overall mortality rate of
COVID-19 was calculated as 1.03 per 1000 person-day in the general population of the evaluated countries up to June 15 2020 [22]. The slightly higher mortality rate of COVID-19 infection in patients with hemoglobinopathies compared to the general population in our results suggests a higher likelihood of disease severity in patients with a hemoglobinopathy. However, it does not strongly support the results of the previous review [25], which introduced sickle cell disease as a known risk factor for increased disease severity in COVID-19 infections. The possible reasons for disease severity were suggested as rapidly progressive acute chest syndrome (ACS), PHTN, and functional asplenia, which increases the risk of life-threatening sepsis due to bacterial superinfection [25]. The possibility of higher disease severity in thalassemia patients affected by COVID-19 infection was also suggested due to their preexistent chronic morbidities, which resulted from ineffective erythropoiesis, chronic hemolytic anemia, and iron overload [25]. Coexistence of some risk factors, such as DM and cardiovascular disorders, were recently reported as possible disease severity risk factors in β-thal patients [3]. More updated meta-analyses with a higher number of patients are helpful in confirming the effect of sickle cell disease and β-thal on disease severity in patients affected by the COVID-19 infection.

Reported comorbidities among patients with hemoglobinopathies and COVID-19 infection in our systematic review included HTN, DM, PHTN, CVD, kidney disease and stroke [6,8,16,20,21]. According to the meta-analysis done by Fathi et al. [4], HTN, DM, CVD and kidney disease, were determined to be the most prevalent comorbidities among patients with the COVID-19 infection. Moreover, history of cerebrovascular disease (CVD) was reported as another important comorbidity related to the COVID-19 infection [28]; in our review, we had several patients with a hemoglobinopathy and COVID-19 infection with a history of stroke from USA and UK as well [8,20,21]. Although we were not able to analyze and report the most prevalent comorbidities related to COVID-19 infections in this study, the confirmed results of the above-mentioned meta-analysis [4,28] in the general population underscore the need to paying specific attention to these possible risk factors in patients with a hemoglobinopathy affected by COVID-19.

A defective health system infrastructure should be warranted especially in some countries located in the thalassemia belt in South Asian and some Mediterranean regions. Therefore, more attention should be paid to this marginalized population by national and international groups [24]. In addition, a general lack of a well-organized patients’ databases in these regions should be taken into consideration [28].

There are certain limitations in this meta-analysis. First, there was some heterogeneity due to the observational nature of the included studies. This heterogeneity may cause reduction in the statistical power for predicting the relationship between susceptibility to COVID-19 infection and subtype of the hemoglobinopathy. Second, all involved studies in the English language and other languages were not studied. Third, because the number of related articles was not sufficient, possible associated risk factors could not be evaluated in our meta-analysis. Fourth, the studies that reported the incidence rate of COVID-19 infection in hemoglobinopathies had a narrow timeline.

In conclusion, our findings suggest that patients with sickle cell disease are more prone to COVID-19 infection in comparison to the general population. The slightly higher mortality rate of COVID-19 infections in patients with hemoglobinopathies compared to the general population can also be due to associated risk factors and comorbidities. Therefore, special care, timely diagnosis and management together with current vaccine immunization, are crucial in decreasing the frequency and mortality of these patients. Further meta-analysis is required to identify the association of possible risk factors with the incidence and mortality rates of COVID-19 infections in patients with hemoglobinopathies.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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