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Research Article

**PREVALENCE AND CLINICAL FEATURES OF COVID19
AMONG HOSPITALIZED PATIENTS WITH
HEMOGLOBINOPATHY IN EASTERN PROVINCE OF SAUDI
ARABIA, CROSS SECTIONAL STUDY, 2020**

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Abstract:

Background: Patients with Hemoglobin disorders have weak immune system. Patients with sickle cell have auto-splenectomy and use hydroxyurea treatment which could cause further immunosuppression. This fact is thought to increase the risk of acquiring COVID-19 infection specially if they were older and have other co-morbid illnesses as diabetes or cancer. At April 12, 2020 Ministry of health shared the first version of Rapid Response Guidelines on COVID-19 in Sickle Cell Disease. The guideline was based on expert opinion since no studies have been published to study this special population.

Aim: To study prevalence and clinical features of hospitalized patients with hemoglobinopathies and confirmed COVID-19 in the eastern province of Saudi Arabia.

Methods: A descriptive cross-sectional study was conducted in two major hospitals in the eastern province of Saudi Arabia from March 2020 to September 2020. Data for patients with confirmed COVID-19 and hemoglobinopathy were collected from electronic medical files. descriptive and analytic inferential statistics was conducted.

Results: There were 1122 patients (700 from King Fahad Hospital in Al-Hassa and 422 from Dammam Hospital) admitted due COVID-19 from March 2020 to September 2020. Among them, 43 patients had been diagnosed with hemoglobinopathy, giving an overall prevalence rate of 3.83%. The most common type of hemoglobin disorder was sickle cell disease (53.5%) followed by sickle cell trait (27.9%). mean duration of hospital stay was 18.7 (SD 43.5) days. it was observed that the duration of hospital stay of patients who were taking antiviral medication ($p=0.009$) and hydroxychloroquine ($p=0.019$) were significantly longer.

Conclusion: Saudi Arabia showed higher prevalence of COVID-19 infection in patients with hemoglobinopathies in comparison to other countries worldwide. This is ought to the fact that Eastern province is one of the most prevalent areas for patients hemoglobinopathies. researchers found that despite a large population of patients with hemoglobinopathies in our area, COVID-19 patients with SCD or thalassemia who required hospital care, oxygenation or ICU admission were less than the non-hemoglobinopathies patients.

Key Words: Hemoglobinopathy, Covid-19, Sickle cell, Thalassemia, Saudi Arabia.

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INTRODUCTION:**COVID-19 worldwide**

On December 27, 2019, 3 adult patients presented with severe pneumonia to a hospital in Wuhan, China [1]. The 3 cases were linked to a seafood and wet animal wholesale market where circumstances were similar to severe acute respiratory syndrome coronavirus (SARS) outbreak, leading to doubts of a novel coronavirus [1]. Further testing revealed that all 3 cases had a newly identified novel coronavirus; Coronavirus disease 2019 (COVID-19) [1]. In January 2020, World Health Organization (WHO) declared an outbreak of COVID-19 which caused severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. A disease outbreak is the occurrence of disease cases in excess of normal expectancy [2]. Since its rise, cases have been found worldwide, reminiscent of SARS and Middle East

respiratory syndrome (MERS) outbreaks over the past 20 years [1]. Increasing cases globally continued to rise to a point where WHO announced COVID-19 pandemic in March, 2020 [3]. A pandemic is the worldwide spread of a new disease [2].

Number of cases of COVID-19 are rising dramatically. Since 31 December 2019 and as of 16 April 2020, 2029930 cases have been reported, including 136320 deaths [4]. This number was recorded by the Center of Disease Control and Prevention (CDC) in accordance with the applied case definitions and testing strategies in the affected countries [4]. To date, understanding of this pandemic remains limited due to its rapid expansion and obtainable data [2]. Given this fact, it is necessary that clinicians understand the initial data behind the dynamics of this disease, understand possible presentations of patients, and recognize proposed treatment modalities [5].

High risk population of severe complications from COVID-19

The COVID-19 virus infects people of all ages. However, evidence to date suggests that the two groups at a higher risk of getting severe COVID-19 disease are older people; and people of all ages with underlying medical conditions [6]. A systematic review and meta-analysis of Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19 showed that the pooled prevalence of hypertension, cardiovascular disease, smoking history and diabetes in people infected with SARS-CoV-2 were estimated as 16.37% (95%CI: 10.15%-23.65%), 12.11% (95%CI 4.40%-22.75%), 7.63% (95%CI 3.83%-12.43%) and 7.87% (95%CI 6.57%-9.28%), respectively [7]. Expert doctors in England identified specific medical conditions that could place someone at greatest risk of severe illness from COVID-19. Clinically extremely vulnerable people may include those who have cancer, those on chemo, radio or immune therapy and organ transplant. People with inborn errors of metabolism have significantly higher risk of infections (such as Severe combined immunodeficiency (SCID) and all patients with hemoglobinopathies [8]. Patients with SCD have weaker immune systems because of auto splenectomy and hydroxyurea treatment which could cause further immunosuppression. This fact increases the risk of acquiring COVID 19 infection specially if they were older and have other co-morbid illnesses as diabetes or cancer. On the other hand, very few cases have been reported in children however, children with SCD are special population that are at increased risk due to their underlying illness [9].

Hemoglobinopathies in Saudi Arabia

Hemoglobinopathies are defined as a group of blood disorders and diseases that affect red blood cells, such as sickle-cell disease and thalassemia [10]. Hemoglobinopathies are divided into two main groups: Thalassemia syndromes and abnormal hemoglobin. The condition occurs by mutation and/or deletions in the α - or β -globin genes. Both groups have many mixed combined features such as β^0/β^+ -thalassemia's, HbSC disease and HbE α -thalassemias [11-12]. Prevalence rates of β -thalassemia (β -thal) and Sickle Cell Disease (SCD) in Saudi Arabia are considered one of the highest compared to surrounding countries in the Middle East (0.05% and 4.50%, respectively) [13]. In 2004, a premarital screening program to detect hemoglobinopathies was enforced by ministry of health for people planning to get married [14]. The

screening program data base showed that the estimated prevalence from (2011-2015) for β -thalassemia trait, β -thalassemia major, Sickle cell trait and Sickle cell Disease were 12.9 per 1000, 0.7 per 1000, 5 per 1000 and 0.38 per 1000 respectively [13]. The highest rate for both β -thal and SCD was observed in the Eastern and Southern regions. The estimated prevalence rate for β -thalassemia and Sickle cell Disorder in the eastern province were 13.6 per 1000 and 48.34 per 1000 [15].

COVID-19 outbreak in Saudi Arabia

In Saudi Arabia, the first confirmed COVID-19 case was announced by ministry of health on March 2, 2020 [16]. Initially most of cases were from the eastern province [16]. The eastern province is the largest by area among the 13 provinces [17]. The capital of eastern province is Dammam city and comprises 11 governorates (Dhahran, Khobar, Al-Qatif, Hafr al-Batin, Jubail, Abqaiq, Na'iriyah, Qaryat al-Ulya) [17]. As protective measures, the government halted transport from Qatif city on 8 March 2020 [17]. Furthermore, on 6 April 2020, 24-hour curfews were implemented in most cities of Saudi Arabia including Dammam, Dhahran, Hofuf, Khobar and Qatif, with movement restricted to only essential travel between 6 a.m. and 3 p.m. [17]. In the 16th of April 2020, Ministry of Health announced total of 6,380 confirmed COVID-19 in Saudi Arabia, in which 381 were from Dammam, 198 from Qatif and 169 from AL-Hassa [18].

Rapid Response Guidelines on COVID19 in Sickle Cell, Saudi Arabia

At April 12, 2020 Ministry of health shared the first version of Rapid Response Guidelines on COVID19 in Sickle Cell Disease. The guideline was based on expert opinion since no studies have been published to study this special population. The guideline emphasized on some medications that might be useful or harmful in patients with SCD. Many SCD patients are chronically prescribed angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers [9]. Recent studies are mentioning the good contribution as treatment of these agents for COVID 19 infection [19-20]. In the other hand, NSAIDs, are suspected to aggravate COVID-19 and should be avoided [21]. No special recommendations have been mentioned in the guidelines about the use of chloroquine, hydroxychloroquine, lopinavir/ritonavir and other antibiotics.

Since very little clinical experience of infected patients with hemoglobin disorders has been recorded, we planned to contribute by studying the prevalence and clinical features of hemoglobinopathies among confirmed COVID-19 patients in the eastern province.

MATERIAL AND METHOD:

To study the prevalence and Pattern of COVID19 among patients with hemoglobinopathy in the eastern province, the study was conducted as a multicentric cross sectional study. Data for hospitalized participants was extracted from hospitals designated for COVID-19 treatment, Dammam medical complex hospital ,and King Fahad Hospital in ALHassa. Hospital records was accessed for number of total COVID-19 cases admitted from March 2020 to September 2020 (this was the denominator of prevalence of COVID19 among patients with hemoglobinopathy) . We communicated with hematology department in designated hospitals to calculate total number of patients with hemoglobinopathy and were admitted as case of Covid-19(this was the numerator of prevalence of COVID19 among patients with hemoglobinopathy).A data collection sheet was designed to study risk factors. It comprises 5 sections: A) participant's basic information, B) sociodemographic characteristics, C) chronic disease history, D) COVID-19 history and E) Hospital admission history. Prevalence of hemoglobinopathy and covid-19 , proportion of cure rate , intensive care unit admission ,ventilation use ,mortality and clinical features were calculated from our sample. The IRB was requested from Ministry of Health before starting the study. Respondents' anonymity was assured by assigning each participant

a code number, for the purpose of analysis only. All data analyses were carried out using Statistical Packages for Software Sciences (SPSS) version 21 Armonk, New York, IBM Corporation.Both descriptive and analytic inferential statistics was conducted. Categorical variables are presented as counts and proportions (%) and continuous variables are presented as mean \pm standard deviation. Two-sided significance test was used with p value <0.05 as considered statistically significant in addition to 95% confidence interval.

RESULTS:

There were 1122 patients (700 from King Fahad Hospital in ALHassa and 422 from Dammam medical complex hospital) admitted due to COVID-19 from March 2020 to September 2020. Among them, 43 patients had been diagnosed with hemoglobinopathy, giving an overall prevalence rate of 3.83%. Table 1 describes the demographic and clinical characteristics of the 43 COVID-19 patients with hemoglobinopathy. The mean age of the patients was 41.4 (SD 14.8) years with more than half were females (51.2%) and nearly two-thirds (65.1%) from King Fahad Hospital. With regards to marital status, 51.2% were married and 25.6% were single. The most common type of hemoglobin disorder was sickle cell disease (53.5%) followed by sickle cell trait (27.9%). Patients with other forms of chronic disorder constitute 56.1%, bronchial asthma was the most common among them (14%). Furthermore, 26.5% reported having one hospital admission in the past year while 17.6% had 2 or more hospital admission. The proportion of patients with a previous history of surgery was 44.7% while the proportion of patients with previous contact to positive COVID-19 case was 44.2% In addition, all patients had shown symptoms at presentation.

Table 1: Demographic and clinical characteristics of hospitalized patients with hemoglobinopathy and COVID-19⁽ⁿ⁼⁴³⁾

Study Variables	N (%)
Age in years (mean \pm SD)	41.4 \pm 14.8
Gender	
• Male	21 (48.8%)
• Female	22 (51.2%)
Name of hospital	
• King Fahad Hospital	28 (65.1%)
• Dammam Central Hospital	15 (34.9%)
Marital status	
• Single	11 (25.6%)
• Married	22 (51.2%)
• Unknown	10 (23.3%)
Type of hemoglobin disorder	
• Sickle cell disease	23 (53.5%)
• Sickle cell trait	12 (27.9%)
• Thalassemia	02 (03.7%)
• Others	06 (13.9%)
Other chronic diseases	
• Yes	23 (56.1%)
• No	18 (43.9%)
Type of other disorder	
• None	18 (41.9%)
• Bronchial asthma	06 (14.0%)
• Diabetes	02 (04.7%)
• Hypertension	04 (09.3%)
• Diabetes + Hypertension + CVD	03 (07.0%)
• Others	10 (23.3%)
Frequency of hospital admission for the past 1 year	
• No hospital admission in the past year	19 (55.9%)
• 1 hospital admission in the past year	09 (26.5%)
• 2 or more admission in the past year	06 (17.6%)
History of acute chest syndrome for the past 1 year	
• Yes	02 (06.3%)
• No	30 (93.8%)
Frequency of vassocclusive crisis for the past 1 year	
• No vassocclusive crisis for the past 1 year	16 (57.1%)
• 1 vassocclusive crisis for the past 1 year	07 (25.0%)
• 2 or more vassocclusive for the past 1 year	05 (17.9%)
History of any surgery	
• Yes	17 (44.7%)
• No	21 (55.3%)
Symptoms of presentation	
• Yes	43 (100%)
• No	0
History of contact to positive COVID-19 case	
• Yes	19 (44.2%)
• No	13 (30.2%)
• Unknown	11 (25.6%)

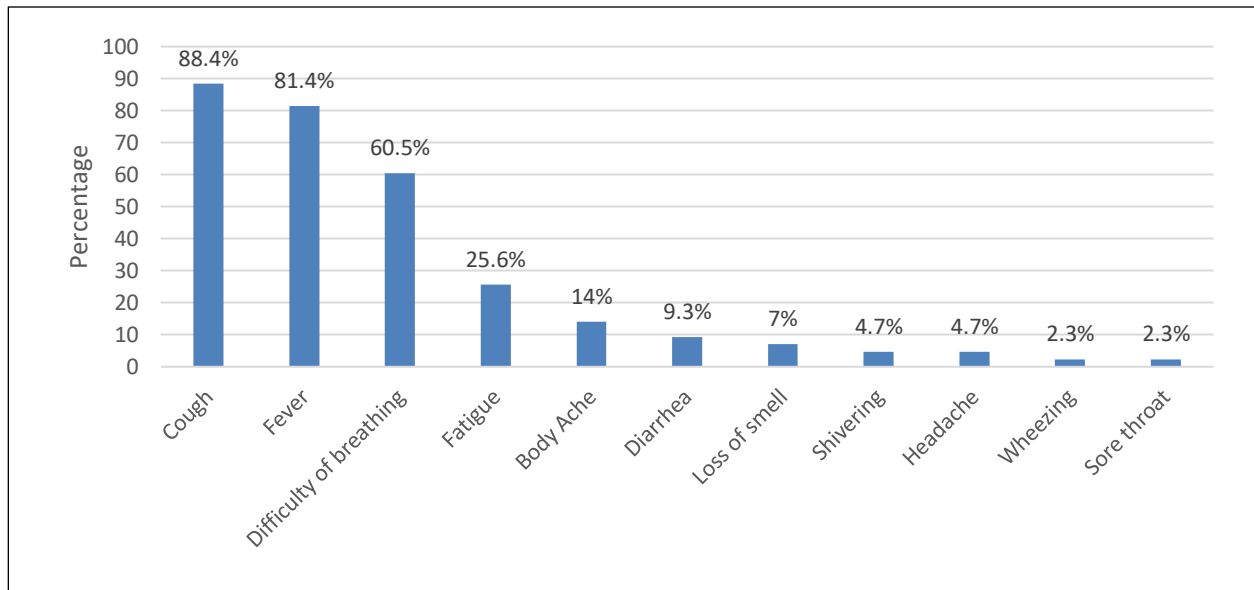
Figure 1: Symptoms on the day of admission of hospitalized patients with hemoglobinopathy and COVID-19

Figure 1 shows the symptoms on the day of admission. It was observed that cough was the most common presented symptom during admission (88.4%), followed by fever (81.4%) and shortness of breath (60.5%) while sore throat was the least common (2.3%).

Table 2: Hospital admission and treatment to hospitalized patients with hemoglobinopathy and COVID-19

Variables	N (%)
Mortality rate	
• Alive	43 (100%)
• Death	0
Hospital discharge	
• Yes	43 (100%)
• No	0
ICU admission due to COVID-19	
• Yes	02 (04.7%)
• No	39 (90.6%)
• Unknown	02 (04.7%)
Discharged from ICU	
• Yes	02 (100%)
• No	0
Complications during hospital stay	
• No complication	19 (44.2%)
• Vassocclusive crisis during hospital stay	11 (25.6%)
• Severe anemia	06 (14.0%)
• ACS + vassocclusive	03 (07.0%)
• Hemolytic anemia	02 (04.7%)
• Acute chest syndrome	01 (02.3%)
• Others	01 (02.3%)
Medications Used *	

• Antibiotics	41 (95.3%)
• Antiviral medication	22 (53.7%)
• Hydroxyurea	08 (18.6%)
• Angiotensin-converting enzyme inhibitors	06 (14.0%)
• Aspirin	05 (11.9%)
• Hydroxychloroquine	04 (09.3%)
• Angiotensin II receptor blockers	01 (02.4%)
Length of Hospital (mean \pm SD)	18.7 \pm 43.5

* Variable with multiple responses.

The characteristics of patients during hospital admission and medications used for treatment are given in table 2. Following the results, it was observed that all patients were alive and discharged. Furthermore, 2 patients had been admitted to ICU due to COVID-19 and were discharged after the treatment. The most common complication during hospital stay was vascocclusive crisis (25.6%), followed by severe anemia (14%) and Acute Chest Syndrome + vascocclusive (7%). With regards to medications used for treatment, the most commonly used were antibiotics (95.3%), followed by antiviral medication (53.7%) and hydroxyurea (18.6%). In addition, the mean duration of hospital stay was 18.7 (SD 43.5) days. In figure 2, the most commonly used antibiotic was a combination of azithromycin and ceftriaxone (39.5%), followed by Cefixime and Azithromycin (16.3%) and Ceftriaxone (16.3%) while the least of them was Imepenem and Azithromycin (4.7%).

Figure 2: Antibiotics used in hospitalize patients with hemoglobinopathy and COVID-19

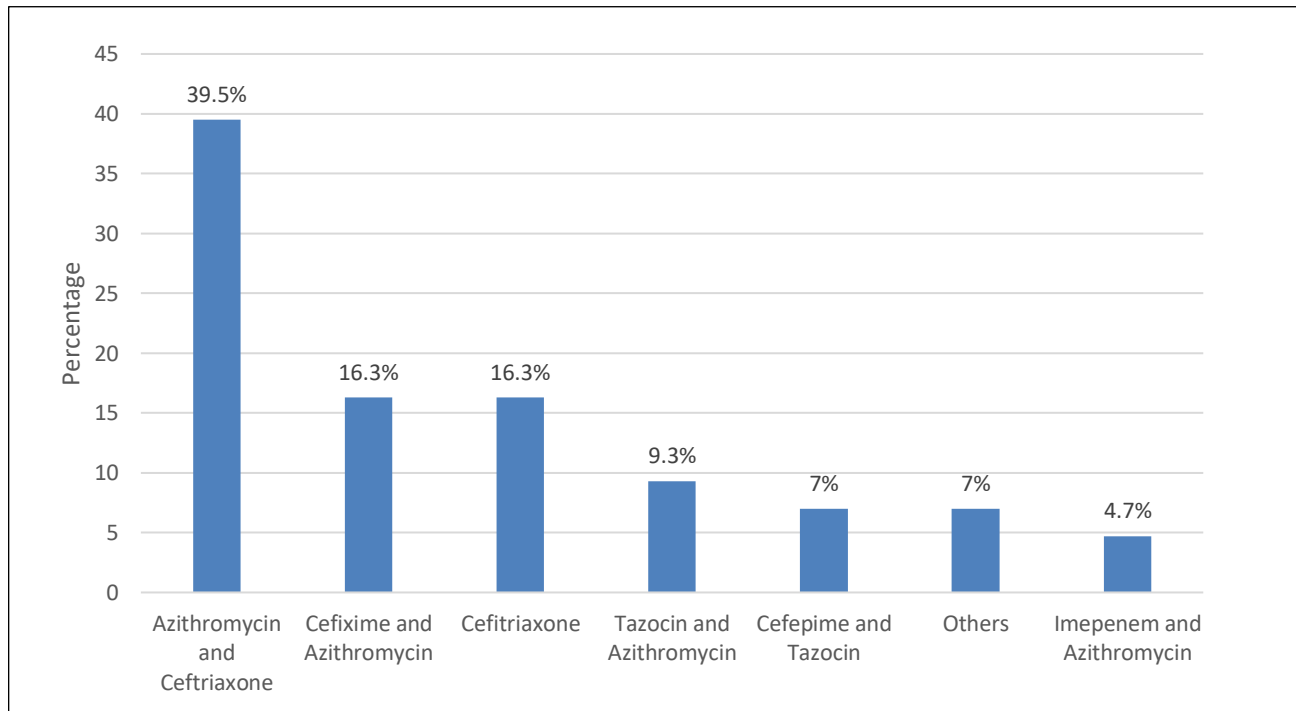
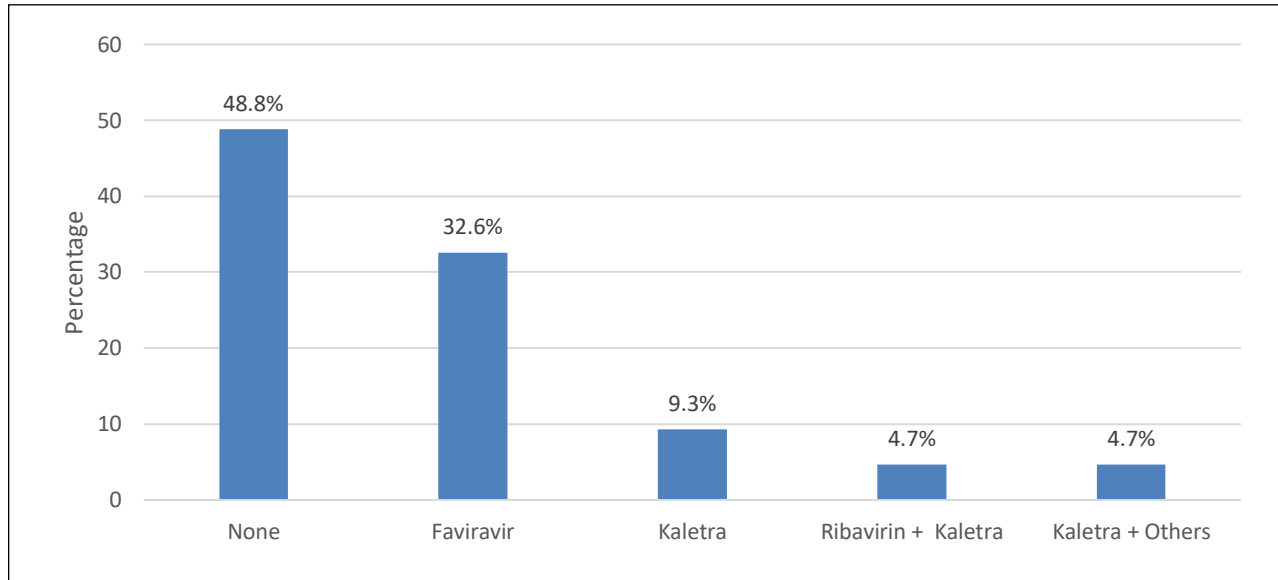


Figure 3: Antiviral medications used in hospitalize patients with hemoglobinopathy and COVID-19



In figure 3, the most frequently used antiviral medication was Faviravir (32.6%) and Kaletra (9.3%).

Table 3: Lab Investigations of hospitalize patients with hemoglobinopathy and COVID-19 during hospital, ICU admission and at discharge

Variables	Mean \pm SD
During Hospital admission	
• Hgb	9.86 \pm 2.31
• LDH	491.5 \pm 253.6
• Ferritin	422.9 \pm 747.9
• D-dimer	2.22 \pm 1.89
• Bilirubin	18.6 \pm 19.6
During ICU admission	
• Hgb	11.1 \pm 0.92
• LDH	315.0 \pm 0.0
• Total bilirubin	16.2 \pm 4.10
At Discharge	
• Hgb	9.26 \pm 2.54
• LDH	463.2 \pm 231.4
• Total bilirubin	16.6 \pm 20.1

The clinical characteristics of the patients from hospital admission until discharged were given in table 3. It can be observed that the mean values of Hgb, LDH, Ferritin, D-dimer and Bilirubin during hospital admission were 9.86, 491.5, 422.9, 2.22 and 18.6, respectively while during ICU admission, the mean values of Hgb, LDH and total bilirubin were 11.1, 315 and 16.2, respectively whereas during discharged the mean values of Hgb, LDH and total bilirubin were 9.26, 463.2 and 16.6, respectively.

Table 4: Association between Length of Hospital admission and Medications used in hospitalized patients with hemoglobinopathy and COVID-19

Treatment	Length of Hospital stay		P-value §
	≤7 days	>7 days	
	N (%)	N (%)	
Antibiotics	25 (96.2%)	16 (94.1%)	1.000
Antiviral medication	09 (36.0%)	13 (81.3%)	0.009 **
Hydroxyurea	05 (19.2%)	03 (17.6%)	1.000
Angiotensin-converting enzyme inhibitors	03 (11.5%)	03 (17.6%)	0.666
Aspirin	04 (16.0%)	01 (05.9%)	0.632
Hydroxychloroquine	0	04 (23.5%)	0.019 **
Angiotensin II receptor blockers	0	01 (05.9%)	0.405

§ P-value has been calculated using Fischer Exact test.

** Significant at $p < 0.05$ level.

We used Fischer Exact in Table 4 to determine if there are any significant differences in the length of hospital stay in relation to the used of medication. Based on the results, it was observed that the duration of hospital stays of patients who were taking antiviral medication ($p=0.009$) and hydroxychloroquine ($p=0.019$) were significantly longer.

DISCUSSION:

Prevalence:

Eastern province is known to have high prevalence of hemoglobinopathies. This fact was thought to have a significant impact upon what's happening in the world during COVID-19 pandemic. This study aimed to measure the prevalence of patients with hemoglobinopathies who had COVID-19 infection required hospital admission and special care. 1122 patients (700 from King Fahad Hospital in ALHassa and 422 from Dammam medical complex hospital admitted due COVID-19 from March 2020 to September 2020. Among these, only 43 patients are known to have hemoglobinopathy disease, giving an overall prevalence rate of 3.83%.

As far as we know no study calculated the prevalence of COVID-19 among patients with hemoglobinopathy in Saudi Arabia. A national Saudi multi-center study done between August 2020 and January 2021 under the title of COVID-19 in Saudi Patients with Sickle Cell Disease: A Retrospective Multi-Center Study evaluated 33 patients with sickle cell anemia/disease who had confirmed diagnosis of COVID-19 but they did not calculate an exact prevalence [22]. Another case report was mentioned in the literature talking about Saudi mother with SCD and two of her children[23].

Looking for comparisons worldwide, a multicenter, retrospective, cross-sectional study done in seven countries among patients with Covid-19 and hemoglobinopathies showed varied results. The highest prevalence of confirmed Covid-19 positive cases in patients with hemoglobinopathies was reported from Iran 0.41 % and Cyprus 0.4%. The lowest prevalence was seen in Oman and Azerbaijan 0.15 %. Italy and Turkey reported a percentage of 0.3%. All patients in all countries had thalassemia major except for Oman. All cases from Oman were patients with Sickle cell disease. Iran also reported having 0.32 % of cases with thalassemia intermedia. This fact ranks Iran as having the highest prevalence of total positive cases of Covid19 and hemoglobinopathy, 0.41% with thalassemia major and 0.32 % with thalassemia intermedia [24].

Another national survey of COVID19 in UK done between April 8 till May 6, 2020 for hemoglobinopathy and rare inherited anemia showed 99 of 157 confirmed cases of COVID 19 where SCD accounted for most of cases[25]. A study in Detroit USA also reported 24 patients with confirmed COVID-19 and sickle cell disease or trait who were seen at the Henry Ford Hospital of Sickle cell. Prevalence rate of 75.0% had heterozygous sickle cell trait, one was a double heterozygote for Hb S (HBB: c.20A>T)/ β^+ -thalassemia (β^+ -thal), four had sickle cell anemia (β^S/β^S) and one had Hb S/Hb C (HBB: c.19G>A) disease[26]. Another French study only reported 83 inpatients with sickle cell hospitalized with COVID19[27].

When comparing worldwide results with our study, we find that there is a difference in prevalence. Many reasons might explain this high discrepancy. Although high number of rare hemoglobinopathies are underdiagnosed especially those having a silent disease

and no symptoms, prevalence rates of β -thal and SCD in Saudi Arabia are considered one of the highest compared to surrounding countries in the Middle East (0.05% and 4.50%, respectively) [28].

Data collection methods were different among studies. In our study we only included symptomatic patients that required hospitalization and our study population was among all admitted covid 19 patients (with and without hemoglobinopathy). Other studies included all positive cases with hemoglobinopathy even those who were asymptomatic or didn't require hospitalization and their study population was among all hemoglobinopathy patients.

Sociodemographic

Looking into the sociodemographic data in this study, we can see that the mean age of patients with hemoglobinopathy and confirmed COVID- 19 was 41.4 ± 14.8 (range: 26.6-56.2); 22 (51.2%) were females. When comparing our results, we have an older mean age than the Saudi reported study where the mean age of patients was 10.75 ± 9.11 years and 48.4% of them were females [22]. International studies reported overall mean age of patients was 33.7 ± 12.3 years (range: 13-66); 9 (69.2%) were females [24]. Two other studies results were consistent with ours, where the mean age was 52.9 years (range: 24–87 years) and 33 years [25, 26]. One study revealed males, as compared to females have a higher likelihood of SARS-CoV-2 susceptibility [26].

Hospital Stay, ICU and Ventilation use

In our study the mean duration of hospital stay was 18.7 (SD 43.5) days. Furthermore, only two patients had been admitted to ICU due to COVID-19 and were discharged after the treatment and they didn't require mechanical ventilation. In comparison to the other Saudi study, they had much lower length of hospitalization with a mean of 7.6 ± 4.5 days, with only one patient requiring intensive care unit admission and assisted ventilation [22]. Inspecting literature worldwide, it was seen that 70% of symptomatic patients with hemoglobinopathies who had COVID- 19 required hospitalization with a period of 12.8 ± 5.4 days on average was measured from onset of disease to hospital discharge. out of those only one ICU admission followed by death [24]. Another study done in UK announced that 74% of patients were admitted to the hospital. Of those, 10.5% were admitted to critical care where only 4 out of 143 required mechanical ventilation [25]. In USA a percentage of 54.0% of patients with hemoglobinopathies required hospitalization, and one

patient required admission to the ICU along with mechanical ventilation and subsequently died. They also specified that SCD patients stayed in hospital at an average of 4.75 days (range 2–8 days) [26].

CONCLUSION:

Saudi Arabia showed higher prevalence of COVID-19 infection in patients with hemoglobinopathies in comparison to other countries worldwide. This is due to the fact that Eastern province is one of the most prevalent areas for patients hemoglobinopathies. researchers found that despite a large population of patients with hemoglobinopathies in our area, COVID 19 patients with SCD or thalassemia who required hospital care, oxygenation or ICU admission were less than the non-hemoglobinopathies patients. Further studies are needed in this area for guideline generation

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