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Original Article

Efficacy and Safety of Sinopharm Vaccine for SARS-CoV-2 and breakthrough infections in Iranian Patients with Hemoglobinopathies: A Preliminary Report

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Competing interests: The authors declare no conflict of Interest.

Abstract. ***Background:*** **The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to high morbidity and mortality worldwide. Vaccination against SARS-CoV-2 is a leading strategy to change the course of the COVID-19 pandemic.**
Aims of the study: **Our aim was to investigate the efficacy and side effects of the Sinopharm vaccine in patients with hemoglobinopathies in Iran and the frequency of breakthrough infection after a full course of vaccination.**
Methods: **A multicenter cross-sectional study of 434 patients with hemoglobinopathies (303 β-thalassemia major, 118 β-thalassemia intermedia, and 13 sickle-thalassemia) were conducted from March to July 2021 in IRAN. All patients have received the first dose of the China Sinopharm vaccine and received the second dose of the vaccine 28 days apart.**
Antibody testing: **Detection of immunity after vaccination was evaluated by commercial enzyme-linked immunosorbent assay (Pishtazteb ELISA commercial kit), including a surrogate virus neutralization test (sVNT), for detection of SARS-CoV-2 immunoglobulins (IgA, IgM, IgG), total neutralizing antibody (NAb).**
Results: **The mean age of patients was 35.0 ± 8.5 (from 18 to 70) years, and 55.6% were positive for the antibody. Overall, 48.2% of the studied population had at least one side effect after vaccination. The most frequent side effects were fever and chills, dizziness, and body pain. A total of 90 (20.7%) vaccinated patients developed breakthrough infections after two doses of Sinopharm vaccination. Disease severity was recorded, and it was classified as mild in 77.8%, moderate in 13.6%, and severe in 7.4% of patients. One 28-year-old woman with β-thalassemia major died eight days after diagnosing a breakthrough SARS-CoV-2 infection.**
Conclusion: **No safety concerns were identified in patients who received two doses of the Sinopharm vaccine. Its efficacy was not optimal due to the lack of effect on new variations of the virus. However, our data show that it seems to be protective against the severity of COVID-19 infection in patients with hemoglobinopathies. The frequency of breakthrough infections after two**

doses of Sinopharm vaccination supports the evolving dynamic of SARS-CoV-2 variants requiring special challenge since such infection may represent a risk for vulnerable patients.

Keywords: Hemoglobinopathies, Sinopharm vaccine, Efficacy, Safety, Adverse events, Breakthrough SARS-CoV-2 infection.

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Introduction. The coronavirus disease (COVID-19) is caused by a positive-stranded RNA virus called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), belonging to the Coronaviridae family. In humans, the virus causes COVID-19, a disease characterized by fever, shortness of breath, and pneumonia, which can be fatal in vulnerable individuals.[1] The most severe cases of COVID- 19 with admission to the Intensive Care Unit (ICU) are generally more frequent in males and the elderly, especially those with comorbidities such as diabetes mellitus, obesity, chronic cardiovascular and/or respiratory disease.[2]

The prevalence and mortality rates of SARSCOV-2 are changing on a daily basis2. According to World Health Organization (WHO), as of October 2021, the COVID-19 pandemic involved 216 countries and had affected 240,260,449 people, and that caused the death of 4,890,424.[3]

Therefore, a prophylactic approach is crucial to control the disease, although the specific management against COVID-19 is still under investigation. To date, multiple vaccines have been developed worldwide utilizing different technologies, including messenger ribonucleic acid (mRNA) vaccines and classic inactivated virus vaccines. Each vaccine exhibits a different potency and duration of efficacy, as determined by the antigen design, adjuvant molecules, vaccine delivery platforms, and immunization method. Large-scale clinical studies found that COVID-19 vaccines prevented most people from getting COVID-19 illness, but like most other vaccines, they are not 100% effective.[4-8] Sinopharm Beijing and Wuhan Institute of Biological Products have produced two inactive SARS-CoV-2 virus vaccines (CoronaVac vaccine developed by Sinovac and Sinopharm BBIBP-CorV) using chemical β-propiolactone. Both were treated with aluminum-based adjuvant to increase immunogenicity. A schedule of two doses (0/21-28-days) of the vaccine that can be stored at 2°C – 8°C is recommended to prevent SARS-CoV- 2 infection.[9]

According to China National Biotec Group Company study, more than 40,000 people in the United The Arab Emirates and Bahrain, aged 18 and above without a known history of COVID-19, participated in the trials. The vaccine showed an efficacy rate of 79% against symptomatic COVID-19 cases and reported serious adverse events (AEs) after vaccination were rare.[10,11]

On May 7, 2021, the World Health Organization (WHO) approved the vaccine, and it is used in many countries, including Iran, but the European Medicines Agency (EMA) has not yet reviewed its use for the European Union.

In Iran, a country with a population of around 85,451,701, COVID-19 affected 5,987,814 people and 127,299 mortalities were reported up to Nov. 8, 2021.

In patients with hemoglobinopathies (thalassemias and sickle cell disease), several factors (iron overload, frequent hospital visits and admissions, immunodeficiency related to the disease itself, continuous use of medications, or associated complications) could predispose subjects to an increased risk for acquiring COVID-19 and consequent complications.[12-15] Moreover, higher mortality has been reported in subjects with thalassemias than the general infected population. [12] For all these reasons, patients with hemoglobinopathies were registered as the first group to get the vaccine in Iran.

We undertook this study to determine the efficacy and side effects of the Sinopharm vaccine in patient with hemoglobinopathies in Iran, and the frequency of breakthrough infection after two doses of Sinopharm vaccination.

Patients and Methods.

Study design. This cross-sectional study was performed from March to July 2021 among 434 patients with hemoglobinopathies (303 β-thalassemia major, 118 β-thalassemia intermedia, and 13 sickle-thalassemia), followed in Shiraz (331 patients) and Tehran (103 patients) who received COVID-19 vaccine.

Patients' data. All patients were diagnosed based on their clinical and laboratory data (clinical history, complete blood count and hemoglobin electrophoresis). Patients with transfusion-dependent thalassemia (TDT) were those requiring regular lifelong blood transfusions,

starting before the age of 2 years with a hemoglobin level below 7 g/dL. Patients with non-transfusion-dependent thalassemia (NTDT) and sickle-thalassemia were Transfusions free or receiving occasional blood transfusions for a very limited period, such as surgery. All patients received two doses of Sinopharm vaccination. In subjects with a previous history of SARS-CoV-2 infection, the first Sinopharm dose was given three months after COVID-19. The interval between blood transfusion and vaccine injection was three days at least.

Patients under 18 years old, pregnant women, patients with fever and acute phase of the COVID-19 disease have not been included in the present report.

A designed questionnaire was made to collect all demographic, clinical, and laboratory data, including age, sex, age of diagnosis of a hemoglobinopathy, type of thalassemia, blood transfusion requirement (type and interval of blood transfusion), splenectomy status, serum ferritin level, preexisting comorbidities (diabetes, chronic heart failure, hypothyroidism, hypoparathyroidism, hypogonadism, cirrhosis, HCV positivity, osteoporosis, extramedullary hematopoiesis, thrombosis, liver, kidney and cardiac diseases, and pulmonary hypertension). In addition, a serum ferritin > 2,500 ng/mL was considered an indirect index of severe iron overload.

Patients' outcome and AEs after vaccination were recorded via interview or after reviewing patients' personal histories.

Breakthrough SARS-CoV-2 infection. "A breakthrough infection" was suspected in presence of clinical defined signs and diagnosed by detection of SARS-CoV-2 on reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay, two weeks or more after the second dose of Sinopharm vaccine[8] and were classified into asymptomatic/mild, moderate, and severe, according to WHO.[16]

Antibody testing. Detection of immunity after vaccination was evaluated by commercial enzyme-linked immunosorbent assay (Pishtazteb ELISA commercial kit), including a surrogate virus neutralization test (sVNT), for detection of SARS-CoV-2 immunoglobulins (IgA, IgM, IgG), total and neutralizing antibody (NAb). The assays were performed according to the manufacturer's protocol. Elisa assay has a sensitivity and specificity of 94.1% and 98.3%, respectively. A negative result can occur if the quantity of antibodies for the SARS-CoV-2 virus present in the specimen is below the assay's detection limit, or the virus has undergone minor amino acid mutation(s) in the epitope recognized by the antibody utilized in the test. The tests were performed one month after the second dose of Sinopharm vaccination.[17]

Statistical analysis. Data were analyzed by IBM SPSS version 23. Normality of data was checked by Kolmogorov-Smirnov test. Descriptive data were presented as mean, standard deviation, median, range, and percentage. Inferential analysis was performed by Student t-test or Mann-Whitney test to compare quantitative data between the two groups. Comparison of qualitative variables among different groups was made by the Chi-square test. A P-value less than 0.05 was considered statistically significant.

Ethical statement. The study protocol was approved by the Ethical Committee of Shiraz University of Medical Sciences (I.R.SUMS.REC.1400.248) which covered both centers. Written informed consent was obtained from the patients before starting the study.

Results. Four hundred thirty-four patients with hemoglobinopathies received two doses of Sinopharm vaccine up to July 2021. The mean age of patients was 35.0 ± 8.5 (range:18 - 70) years; 269 were females, and 165 were males. The demographic and clinical characteristics of the patients are summarized in **table 1**. Most of our patients got the SARS-CoV-2 infection from their parents, friends, or public areas. One hundred fifty-three patients (35.3%) SARS-CoV-2 antibody levels were checked, 85 patients (55.6%) resulted positive.

Reported post-vaccination AEs and their frequencies are summarized in **table 2**. Overall, 48.2% of enrolled patients had at least one adverse effect. The most frequent were fever and chills (18.0 %), dizziness (15.7%), and body pain (12.4%).

Ninety vaccinated patients (20.7%) developed breakthrough coronavirus infection at least one month after the second dose of the Sinopharm vaccine. In 22 out of 90 patients (24.4%), SARS-CoV-2 antibodies were checked; seven (31.8%) resulted positive.

The severity of breakthrough coronavirus infection in 81 out of 90 patients (90%) was classified as mild in 77.8%, moderate in 13.6%, and severe in 7.4%. The most common mutations of TDT were IVS-I-II and IVS-I-V with the genotype of β^0/β^0, and the most common mutations of NTDT were -101 and -92 with β^+/β^+ genotype without co-inherited α-thalassemia. The mean pre-transfusion hemoglobin levels in TDT and hemoglobin levels in NTDT and sickle-thalassemia were 9.9 ± 1.1 g/dL and 9.7 ± 1 g/dL, respectively. We did not find any relationship of COVID-19 severity disease with the severity of thalassemia itself (P=0.717), hemoglobin levels (P=0.956), and patients' genetic mutations.

A 28-year-old female with β-thalassemia major (blood group O^+, regularly transfused with washed packed red blood cells) presented with fever, dry cough, and dyspnea 120 days after the second dose of the Sinopharm vaccine. She had been compliant with

Table 1. Summary of clinical characteristics and laboratory data of vaccinated patients with hemoglobinopathies.

Parameters	Values
Age (years), Mean ± SD; Min-Max	35.0 ± 8.5 (18-70)
Sex (Male) (%)	38
Median serum ferritin level (ng/mL); Range (min-max)	968 (60-18000)
Frequency of blood transfusions (N and %)	
Regular	355(84.7)
Irregular	7 (1.7)
No	57 (13.6)
Type transfusion (N and %)	
Leukoreduced red blood cells	272 (62.7)
Leukofilter red blood cells	34 (7.8)
Washed red blood cells	28 (6.5)
Synchronous blood transfusion and vaccination (N and %)	8 (1.8)
Splenectomy (yes) (N and %)	216 (49.7)
Hemoglobin level (g/dL); Mean ± SD - Min-Max	9.8±1.1 (7.3-12.9)
Comorbidities (N. and %)	
Hypogonadism	177 (41)
Diabetes	57 (13.1)
Hypothyroidism	46 (10.6)
Pulmonary hypertension	86 (20)
Chronic heart failure	25 (5.8)
Chronic liver disease	16 (3.7)
SARS-CoV-2 infection after vaccination (N. and %)	90 (20.7)

Table 2. Adverse events (AEs) reported in order of frequency in vaccinated patients with hemoglobinopathies.

Parameters	Frequency (N. and %)
Reported AEs post-vaccination (N. and %)	
No side effect	161(51.8)
First dose	129 (41.5)
Second dose	5 (1.6)
Both doses	16 (5.1)
Fever, chills (N. and %)	78 (18.0)
Dizziness (N. and %)	69 (15.7)
Body pain (N. and %)	54 (12.4)
Headache (N. and %)	49 (11.3)
Common cold (N. and %)	17 (3.9)
Dyspnea (N. and %)	15 (3.5)
Pain at the site of injection (N. and %)	14 (3.2)
Nausea, vomiting (N. and %)	10 (2.3)
Diarrhea (N. and %)	4 (0.9)

chelation therapy with Deferasirox (dose of 20 mg/kg, based on the serum ferritin level). Moreover, the median ferritin level during the past six months was about 1,000 ng/mL, and the last recorded serum ferritin was 500 ng/mL. No relevant associated comorbidities were found, and the spleen was palpable 2 centimeters below the costal margin. The patient was hospitalized with a positive PCR COVID-19 test, and Remdesivir and thromboprophylaxis with Enoxaparin (40 mg /day) were immediately started as a severe case. Laboratory data showed that prothrombin time (PT, 15.4 Sec), International Normalized Ratio (INR, (1.12), activated partial- thromboplastin time (APTT, 31.6 Sec), D dimer (less than 500 mg/mL), fibrinogen (200 mg/dL) and platelet count (390×10^3/µL), were normal at admission.

On the 4th day of admission, she developed a severe and persistent headache requiring a brain computed tomography (CT) scan. No relevant changes were documented; however, a second brain CT scan, carried out 12 hours later, showed an intraventricular and left frontal lobe parenchymal hemorrhage with midline shift and herniation (**Figure 1**). Moreover, the CT venography detected a subarachnoid hemorrhage (**Figure 2**) without evidence of intracranial vascular thrombosis. Therefore, the patient underwent surgery due to impending herniation and midline shift. Unfortunately, a few hours after surgery, she developed hypotension and finally died. Coagulation assays (PT, INR, APTT, and platelet count) were normal prior to surgery, but PT and INR were prolonged after surgery (32.6 Sec, Control:13.8 Sec and 2.5, Reference range: 0.9-1, respectively), while PTT and platelet count were normal.

Chest CT scan showed diffuse bilateral lung involvement, typical for COVID-19 pneumonia. (**Figure 3**). The patient had no family history of bleeding tendency and was not receiving hormone replacement

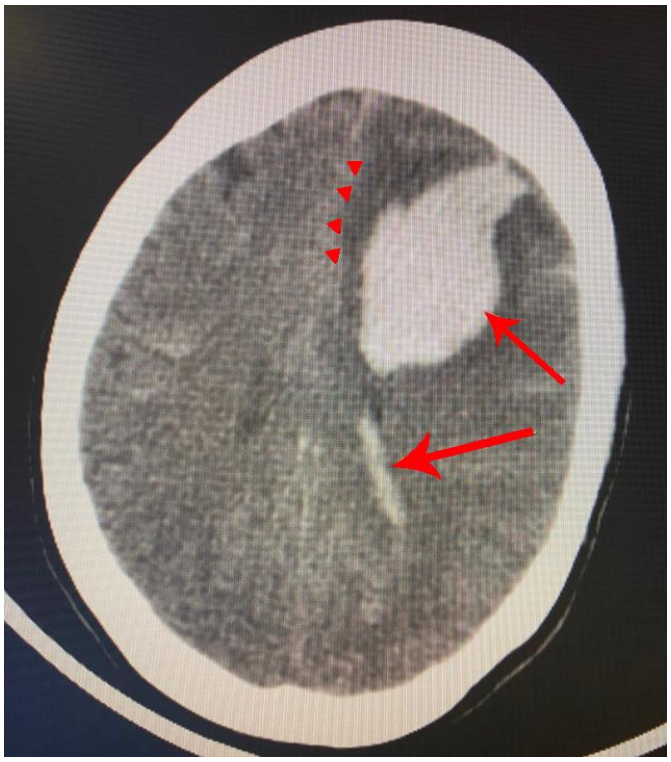

Figure 1. A SHORT ARROW SHOWS A brain CT scan without contrast: large intraparenchymal hemorrhage with surrounding edema in the left frontal lobe. Parallel arrowheads represent Subfalcine hernia and 7 mm midline shift to the right side. A tall arrow marks the intraventricular hemorrhage in body of the left ventricle.

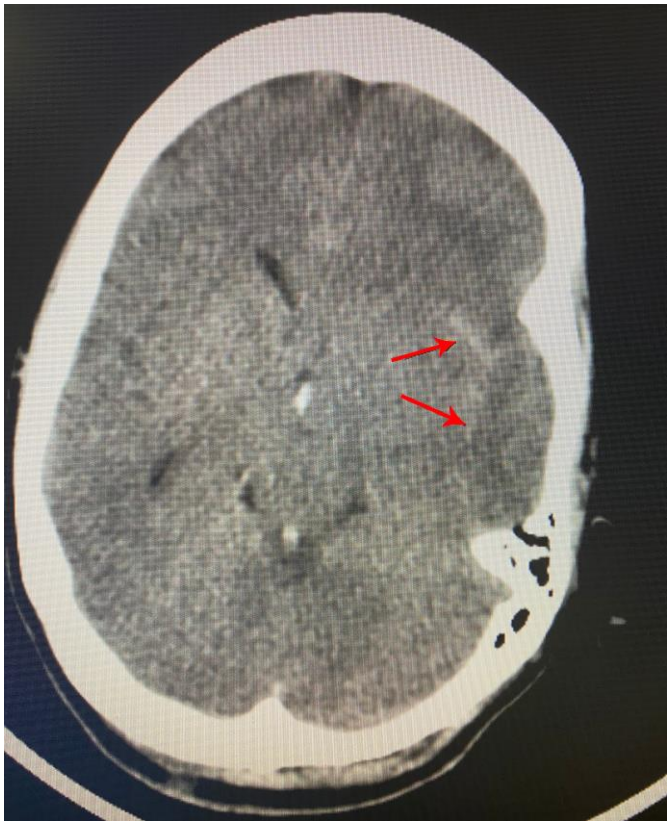

Figure 2. Brain CT scan without contrast: Subarachnoid hemorrhage is demonstrated in the left sylvian fissure associated with diffused sulci effacement secondary to increased intracranial pressure (ICP).

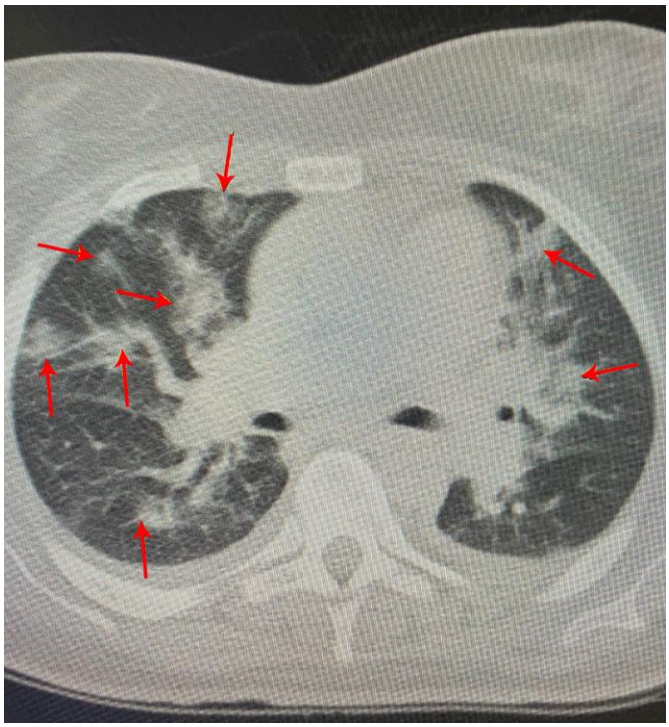

Figure 3. Low dose lung CT scan without contrast: multiple patches of ground-glass opacities and consolidations are noted diffusely in both lung parenchyma, which is predominantly distributed in peripheral regions with involvement of 70% of parenchyma.

therapy with oral estrogen/progesterone.

Table 3 shows the association of some clinical and laboratory parameters related to the antibody status of vaccinated patients. They were divided into two groups based on positive or negative antibodies. The results revealed a significantly lower incidence of breakthrough coronavirus infection after full vaccination in the positive antibody group (8.2%) compared to the negative group (22.1%; P = 0.02). The other evaluated factors were comparable between the two groups (P= >0.05).

Moreover, we evaluated the laboratory, and clinical features of post vaccinated patients with and without Sars-CoV-2 infection (**Table 4**). Only one parameter resulted statistically significant: the median of serum ferritin level in patients who developed a breakthrough coronavirus infection (**Table 4**; P = 0.013).

Discussion. Since there is no definitive therapy for COVID-19, vaccination is the only appropriate approach for controlling the disease. So, vaccines are a critical tool in managing the COVID-19 pandemic.

According to the type of vaccine, variable immune responses and side effects are seen.[6-8]

Several vaccines have been rapidly developed and approved by many countries for emergency use.

One of these vaccines is Sinopharm (Beijing Institute of Biological Products Co., Ltd, China) that is an inactive SARS-CoV-2 virus vaccine.[12] An interim recommendation for its use has been reported by the

Table 3. The relationship of antibody status of post COVID-19 vaccine with the clinical and laboratory characteristics of patients with hemoglobinopathies.

	Antibody status n=153		P value
Parameters	**Negative n = 68**	**Positive n = 85**	
Age (years) (Mean ± SD.)	35.7 ± 7.3	38.3 ± 11.4	N. S
Sex (male) (N. and %)	28 (41.2)	31(36.9)	N. S
Median serum ferritin (ng/mL) (Range)	700 (71-7961)	797 (88-12000)	N. S
Serum ferritin >2500 (ng/mL) (N. and %)	12 (19)	11 (14.1)	N. S
Hemoglobin (g/dL) Mean ± SD	9.7 ± 1.0	9.8 ± 1.1	N. S
Blood transfusion (Yes) (N. and %)	53 (80.3)	69 (83.1)	N. S
Splenectomy (N. and %)	37 (54.4)	49 (57.6)	N. S
Breakthrough coronavirus infection after full vaccination (N, and %)	15 (22.1)	7 (8.2)	**0.020***

Legend: NS not significant; * Statistically significant.

Table 4. Comparison of clinical and laboratory characteristics of patients with hemoglobinopathies who developed or not "bbreakthrough coronavirus infection" after vaccination.

Parameters	**Patients (N. 341) who did not develop "breakthrough coronavirus infection"**	**Patients (N.90) who developed "breakthrough coronavirus infection"**	**P value**
Age(year); Mean ± SD	34.8 ± 8.7	35.4 ± 8.1	N. S
Sex(male) (N. and %)	130 (38.1)	34 (37.8)	N. S
Median serum ferritin (ng/mL) Range (min-max)	875 (60-18000)	1400 (139-14000)	**0.013***
Serum ferritin >2,500 (ng/mL) (N. and %)	64(20.3)	22 (24.7)	N. S
Hemoglobin (g/dL) Mean ± SD	9.8 ± 11	9.7 ± 1.0	N. S
Blood transfusions (Yes) (N. and %)	274 (83.3)	81 (90)	N. S
Splenectomy (Yes) (N. and %)	175 (50.9)	41 (45.6)	N. S

Legend: NS not significant; * Statistically significant.

WHO Strategic Advisory Group of Experts (SAGE).

Most studies have assessed post-vaccination AEs of Pfizer–BioNTech, Moderna, and AstraZeneca vaccines,[18-21] but limited data are available on Sinopharm vaccine[22,23] knowledge no comprehensive published studies are available in subjects with hemoglobinopathies.

A cross-sectional study of 1,102 attendants (aged ≥18 years) in the UAE who received two doses of Sinopharm vaccine showed that, in general, it was tolerated, and post-vaccination AEs were mild without any serious reported adverse event.[10,11,24] Our data confirm these observations in our patients with hemoglobinopathies too.

Based on antibody assessment, the reported efficacy rate of the Sinopharm vaccine is between 73% - 86%,[11,23] but our preliminary data have shown a lower level of immunity or protection from COVID-19 (55%) after two doses of vaccine with 28 days apart. Twenty-one of vaccinated patients developed breakthrough coronavirus infection at least one month after the second dose of Sinopharm vaccine. Although in the vast majority of patients with hemoglobinopathies, who developed post-vaccine COVID-19 disease, the symptomatology was mild-moderate, in 7.4% of them, the disease was severe, and one female patient died, three months after the second dose of vaccine, for a breakthrough coronavirus infection. Therefore, the efficacy of Sinopharm against SARS-CoV-2 infection (COVID-19) seems to be partial and less protective compared to other types of vaccines, as reported in the general population.[18-23] However, specific studies are needed to assess the immunogenicity, protective efficacy, and durability of immune response in subjects with hemoglobinopathies.

A breakthrough infection post coronavirus vaccine was also observed among the positive antibody testing group, although the incidence was significantly lower (8.2%) than the negative group (22.1%), reaffirming its suboptimal immunogenicity and protective effect in our patients with hemoglobinopathies. Since several variants of SARS-CoV-2 have been described during the pandemia, only a few are considered variants of concern (VOCs) by the WHO; it is pertinent to think that one of these variants may have decreased the vaccination effectiveness.

SARS-CoV-2, like other RNA viruses, is prone to

genetic evolution while adapting to their new human hosts with the development of mutations over time, resulting in the emergence of multiple variants that may have different characteristics compared to its ancestral strains. These adaptive mutations in the viral genome can alter the virus's pathogenic potential, and even a single amino acid exchange can drastically affect a virus's ability to evade the immune system.[25,26]

One more interesting finding documented in our patients was the significantly higher median of serum ferritin level in the group of subjects with breakthrough coronavirus infection, supporting the potential role of iron overload on the immune system that may predispose patients to severe iron overload to SARS-CoV-2 infection (**Table 4**).[12-15] Therefore, the impact of iron overload and the benefit of strict adherence to iron chelation therapy should be recommended in these vulnerable patients in association to close heart monitoring, as reported in a previous study showing that heart failure and pulmonary hypertension are significant risk factors for COVID-19 severity in thalassemia patients.[27]

Nevertheless, a 28-year-old β-thalassemia major woman, with no significant past medical history of comorbidities or bleeding tendency, died during breakthrough coronavirus disease while she got the second dose of vaccine four months prior to COVID-19 infection. Hypercoagulability is a known complication of COVID-19. Although severe cases are usually reported in older populations and in those with underlying comorbidities, our case emphasizes that this may occur in young without significant medical history. Intracerebral hemorrhage (ICH) was reported in a 5-case series with COVID-19 without having an underlying vascular abnormality, as we observed in our case.

All cases were on anticoagulants, and the time between symptom onset and ICH identification was 14 to 38 days in this case series, but it was shorter in our case (one week after starting COVID-19 symptoms).[28]

The exact mechanism of COVID-19 associated ICH is not obvious at this young age case series , and our case supports the hypothesis that endothelial toxicity and disruption of the renin-angiotensin system might play a role in COVID-19-mediated ICH.[28-30]

The recent emergence of multiple variants of SARS-CoV-2 has become a significant concern for public health worldwide. New variants have been classified either as VOCs or variants of interest (VOIs) by the CDC (USA) and WHO. VOCs are associated with enhanced transmissibility or virulence, reduction in neutralization by antibodies obtained through natural infection or vaccination, the ability to evade detection, or a decrease in therapeutics or vaccination effectiveness. The common feature of these variants is that they share the N501Y mutation involving the SARS-CoV-2 spike (S) protein, which is precisely the target of most COVID-19 vaccines. Furthermore, mutations such as N501Y, E484K, and K417N in the S protein may affect viral fitness and transmissibility. However, current research on the impact of these variants on COVID-19 vaccines is still lacking.[31]

SARS-CoV-2 and its variants continue to cause great damages across the world. We advise that even fully vaccinated people continue to follow all safety precautions. Since the beginning of the pandemic, a preventive infection program has been recommended by the Iranian Ministry of Health that includes social distancing, wearing a mask, ward hospital isolation of infected patients during blood transfusion, and hand washing. Continued viral surveillance of new variants must be performed at regular intervals with viral genomic sequencing, given the possibility that more highly transmissible, more virulent variants and treatment-resistant variants could emerge.[32] Moreover, getting a booster shot may help prevent a breakthrough infection or have symptoms, as recommended by the CDC.[33]

Conclusions Although the safety concern of Astra Zeneca was evaluated in three patients with S/B^0 thalassemia,[34] the current research is the first study that has evaluated the safety and efficacy of the COVID-19 vaccine in a large population of patients with hemoglobinopathies. No safety concerns were identified in our patients who received two doses of the Sinopharm vaccine. However, its efficacy is not optimal and is associated with a relatively low level of antibodies against COVID-19 (55%), which indicates a non-full protective effect. However, it is well-tolerated and seems to reduce the risk of severe breakthrough COVID-19 infection among patients with hemoglobinopathies. The frequency of breakthrough infections after full Sinopharm vaccination supports the evolving dynamic of SARS-CoV-2 variants requiring special challenge since such infection could represent a risk for vulnerable patients.

References:

1. Atzrodt CL, Maknojia I, McCarthy RDP, Oldfield TM, Po J, Ta KTL, Stepp HE, Clements TP. A Guide to COVID-19: a global pandemic caused by the novel coronavirus SARS-CoV-2. FEBS J. 2020; 287:3633-3650. https://doi.org/10.1111/febs.15375 PMid:32446285 PMCid:PMC7283703
2. Lai CC, Shih TP, Ko WC, Tang H-J, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents. 2020; 55(3):105924. https://doi.org/10.1016/j.ijantimicag.2020.105924 PMid:32081636 PMCid:PMC7127800
3. World Health Organization (WHO). Coronavirus disease (COVID-19) outbreak situation. Available at: https://www.who.int/emergencies/diseases/novel- coronavirus-2019 cited date Oct 2021.

4. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, Chappell JD, Denison MR, Stevens LJ, Pruijssers AJ, McDermott AB, Flach B, Lin BC, Doria-Rose NA, O'Dell S, Schmidt SD, Corbett KS, Swanson PA 2nd, Padilla M, Neuzil KM, Bennett H, Leav B, Makowski M, Albert J, Cross K, Edara VV, Floyd K, Suthar MS, Martinez DR, Baric R, Buchanan W, Luke CJ, Phadke VK, Rostad CA, Ledgerwood JE, Graham BS, Beigel JH; mRNA-1273 Study Group. Safety and Immunogenicity of SARS-CoV-2 mRNA-1273 Vaccine in Older Adults. N Engl J Med. 2020;383:2427-2438. https://doi.org/10.1056/NEJMoa2028436 PMid:32991794 PMCid:PMC7556339
5. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC. COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci. 2021; 25:1663-1669.
6. Knoll M.D., Wonodi C. Oxford-AstraZeneca COVID-19 vaccine efficacy. Lancet. 2021; 397:72-74. https://doi.org/10.1016/S0140-6736(20)32623-4
7. Hotez PJ, Nuzhath T, Callaghan T, Colwell B. COVID-19 Vaccine Decisions: Considering the Choices and Opportunities. Microbes Infect. 2021; 23:104811. https://doi.org/10.1016/j.micinf.2021.104811 PMid:33744495 PMCid:PMC7968147
8. Alishaq M, Nafady-Hego H, Jeremijenko A, Al Ajmi JA, Elgendy M, Vinoy S, Fareh SB, Veronica Plaatjies J, Nooh M, Alanzi N, Kaleeckal AH, Latif AN, Coyle P, Elgendy H, Abou-Samra AB, Butt AA. Risk factors for breakthrough SARS-CoV-2 infection in vaccinated healthcare workers. PLoS ONE.2021;16(10): e0258820. https://doi.org/10.1371/journal.pone.0258820 PMid:34653228 PMCid:PMC8519462
9. Baraniuk C. What do we know about China's covid-19 vaccines? BMJ. 2021;373: n912. https://doi.org/10.1136/bmj.n912 PMid:33836994
10. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, Al Nusair M, Hassany M, Jawad JS, Abdalla J, Hussein SE, Al Mazrouei SK, Al Karam M, Li X, Yang X, Wang W, Lai B, Chen W, Huang S, Wang Q, Yang T, Liu Y, Ma R, Hussain ZM, Khan T, Saifuddin Fasihuddin M, You W, Xie Z, Zhao Y, Jiang Z, Zhao G, Zhang Y, Mahmoud S, ElTantawy I, Xiao P, Koshy A, Zaher WA, Wang H, Duan K, Pan A, Yang X. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomized Clinical Trial. JAMA. 2021; 326:35-45. https://doi.org/10.1001/jama.2021.8565 PMid:34037666 PMCid:PMC8156175
11. Saeed BQ, Al-Shahrabi R, Alhaj SS, Alkokhardi ZM, Adrees AO. Side effects and perceptions following Sinopharm COVID-19 vaccination. Int J Infect Dis. 2021; 111:219-226. https://doi.org/10.1016/j.ijid.2021.08.013 PMid:34384899 PMCid:PMC8351310
12. Haghpanah S, Hosseini-Bensenjan M, Sayadi M, Karimi M. Incidence Rate of COVID-19 Infection in Hemoglobinopathies: A Systematic Review and Meta-analysis. Hemoglobin. 2021:1-9. https://doi.org/10.1080/03630269.2021.1927751
13. Karimi M, De Sanctis V. Implications of SARS-CoV 2 infection in thalassemias: Do patients fall into the "high clinical risk" category? Acta Biomed. 2020;91:50-56.
14. Karimi M, Haghpanah S, Azarkeivan A, Zahedi Z, Zarei T, Akhavan Tavakoli M, Bazrafshan A, Shirkavand A, De Sanctis V. Prevalence and mortality in β-thalassaemias due to outbreak of novel coronavirus disease (COVID-19): the nationwide Iranian experience. Br J Haematol. 2020;190:e137-e140. https://doi.org/10.1111/bjh.16911 PMid:32484906 PMCid:PMC7300954
15. Karimi M, Haghpanah S, Zarei T, Azarkeivan A, Shirkavand A, Matin S, Tavakoli MA, Zahedi Z, De Sanctis V. Prevalence and severity of Coronavirus disease 2019 (COVID-19) in Transfusion Dependent and Non-Transfusion Dependent β-thalassemia patients and effects of associated comorbidities: an Iranian nationwide study. Acta Biomed. 2020;91(3):e2020007.
16. Son KB, Lee TJ, Hwang SS. Disease severity classification and COVID-19 outcomes, Republic of Korea. Bulletin of the World Health Organization. 2021;99:62-66. https://doi.org/10.2471/BLT.20.257758 PMid:33658735 PMCid:PMC7924894
17. Okba NMA, Müller MA, Li W, Wang C, Geurtsvan Kessel CH, Corman VM, Lamers MM, Sikkema RS, de Bruin E, Chandler FD, Yazdanpanah Y, Le Hingrat Q, Descamps D, Houhou-Fidouh N, Reusken CBEM, Bosch BJ, Drosten C, Koopmans MPG, Haagmans BL. Severe Acute Respiratory Syndrome Coronavirus 2-Specific Antibody Responses in Coronavirus Disease Patients. Emerg Infect Dis. 2020; 26:1478-1488. https://doi.org/10.3201/eid2607.200841 PMid:32267220 PMCid:PMC7323511
18. El-Shitany NA, Harakeh S, Badr-Eldin SM, Bagher AM, Eid B, Almukadi H, Alghamdi BS, Alahmadi AA, Hassan NA, Sindi N, Alghamdi SA, Almohaimeed HM, Mohammedsaleh ZM, Al-Shaikh TM, Almuhayawi MS, Ali SS, El-Hamamsy M. Minor to Moderate Side Effects of Pfizer-BioNTech COVID-19 Vaccine Among Saudi Residents: A Retrospective Cross-Sectional Study. Int J Gen Med. 2021;14:1389-1401. https://doi.org/10.2147/IJGM.S310497 PMid:33907443 PMCid:PMC8068468
19. Chapin-Bardales J, Gee J, Myers T. Reactogenicity Following Receipt of mRNA-Based COVID-19 Vaccines. JAMA. 2021;325:2201-2202. https://doi.org/10.1001/jama.2021.5374 PMid:33818592
20. Kadali RAK, Janagama R, Peruru S, Malayala SV. Side effects of BNT162b2 mRNA COVID-19 vaccine: A randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. Int J Infect Dis. 2021;106:376-381. https://doi.org/10.1016/j.ijid.2021.04.047 PMid:33866000 PMCid:PMC8049195
21. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, Sudre CH, Nguyen LH, Drew DA, Merino J, Hu C, Selvachandran S, Antonelli M, Murray B, Canas LS, Molteni E, Graham MS, Modat M, Joshi AD, Mangino M, Hammers A, Goodman AL, Chan AT, Wolf J, Steves CJ, Valdes AM, Ourselin S, Spector TD. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. Lancet Infect Dis. 2021;21:939-949. https://doi.org/10.1016/S1473-3099(21)00224-3
22. Jayadevan R, Shenoy RS, Anithadevi T. Survey of symptoms following COVID-19 vaccination in India. medRxiv. 2021.02.08.21251366 https://doi.org/10.1101/2021.02.08.21251366
23. Hatmal MM, Al-Hatamleh MAI, Olaimat AN, Hatmal M, Alhaj-Qasem DM, Olaimat TM, Mohamud R. Side Effects and Perceptions Following COVID-19 Vaccination in Jordan: A Randomized, Cross-Sectional Study Implementing Machine Learning for Predicting Severity of Side Effects. Vaccines (Basel). 2021; 9 (6) :556. https://doi.org/10.3390/vaccines9060556 PMid:34073382 PMCid:PMC8229440
24. Zahid MN, Moosa MS, Perna S, Buti EB A review on COVID-19 vaccines: stages of clinical trials, mode of actions and efficacy. Arab J Basic Appl Sci. 2021;28:225-33. https://doi.org/10.1080/25765299.2021.1903144
25. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, Tan W, Wu G, Xu M, Lou Z, Huang W, Xu W, Huang B, Wang H, Wang W, Zhang W, Li N, Xie Z, Ding L, You W, Zhao Y, Yang X, Liu Y, Wang Q, Huang L, Yang Y, Xu G, Luo B, Wang W, Liu P, Guo W, Yang X. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21:39-351. https://doi.org/10.1016/S1473-3099(20)30831-8
26. Jahromi M, Al Sheikh MH. Partial protection of Sinopharm vaccine against SARS COV2 during recent outbreak in Bahrain. Microb Pathog. 2021;158:105086. https://doi.org/10.1016/j.micpath.2021.105086 PMid:34260903 PMCid:PMC8272690
27. Karimi M, Haghpanah S, Azarkeivan A, Matin S, Safaei A, De Sanctis V. Coronavirus Disease 2019 (COVID-19) Severity in Patients with Thalassemias: A Nationwide Iranian Experience. Mediterr J Hematol Infect Dis. 2021;13(1):e2021008. https://doi.org/10.4084/mjhid.2021.008 PMid:33489047 PMCid:PMC7813286
28. Benger M, Williams O, Siddiqui J, Sztriha L. Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series. Brain Behav Immun. 2020;88:940-4. https://doi.org/10.1016/j.bbi.2020.06.005 PMid:32525049 PMCid:PMC7276127
29. Ronaldson PT, Davis TP. Mechanisms of Endothelial Injury and Blood-Brain Barrier Dysfunction in Stroke. Primer on Cerebrovascular Diseases. 2nd Ed., Elsevier; 2017; 220-6. https://doi.org/10.1016/B978-0-12-803058-5.00045-X
30. Divani AA, Andalib S, Di Napoli M, Lattanzi S, Hussain MS, Biller J, McCullough LD, Azarpazhooh MR, Seletska A, Mayer SA, Torbey M. Coronavirus Disease 2019 and Stroke: Clinical Manifestations and

Pathophysiological Insights. J Stroke Cerebrovasc Dis. 2020;29(8):104941. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104941 PMid:32689643 PMCid:PMC7214348
31. Jia Z, Gong W. Will Mutations in the Spike Protein of SARS-CoV-2 Lead to the Failure of COVID-19 Vaccines? J Korean Med Sci. 2021 May 10;36(18):e124. https://doi.org/10.3346/jkms.2021.36.e124 PMid:33975397 PMCid:PMC8111046
32. Aleem A, Akbar Samad AB, Slenker AK. Emerging Variants of SARS-CoV-2 And Novel Therapeutics Against Coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. PMID: 34033342.
33. COVID-19 Vaccine Booster Shots. www.cdc.gov/vaccines. Accessed on Jan. 19, 2022.
34. Alkindi S, Elsadek RA, Pathare AV. Safety Warning for ChAdOx1 nCov-19 Vaccine in Patients with Sickle Cell Disease. Mediterr J Hematol Infect Dis. 2021;13(1): e2021059. https://doi.org/10.4084/MJHID.2021.059 PMid:34527211 PMCid:PMC8425344