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Original article

The impact of COVID-19 on transfusion-dependent thalassemia patients of Karachi, Pakistan: A single-center experience

L'impact du COVID-19 sur les patients atteints de thalassémie transfusionnelle dépendante de Karachi, au Pakistan : une expérience dans un seul centre

S. Arshad Ali [a,*], D. Azim [a], H.M. Hassan [a], A. Iqbal [a], N. Ahmed [b], S. Kumar [a], S. Nasim [a]

[a] *Dow Medical College, Dow University of Health Sciences, Baba-e-Urdu Road, 74200 Karachi, Pakistan*
[b] *Department of Pathology, Dow Medical College, Dow University of Health Sciences, Baba-e-Urdu Road, 74200 Karachi, Pakistan*

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ABSTRACT

Objectives. – With the advent of COVID-19 in Pakistan, the already fragmented blood transfusion services (BTS) received a severe blow, putting the lives of transfusion-dependent thalassemia children on stake. This study aimed to assess the impact of the COVID-19 on blood transfusion therapy (BTT) of thalassemia patients and suggest ways to ensure safe and reliable blood supplies amid such health crises.
Material and methods. – A retrospective, cross-sectional study was conducted from October 2019 (before COVID-19) to July 2020 (during COVID-19) based on the data provided by a thalassemia center, named Help International Welfare Trust, Karachi, Pakistan. SPSS version 24.0 was used for the data analysis. Data were described in the form of means and percentages.
Results. – There was a significant reduction in the consumption of PRBCs bags after the emergence of COVID-19 ($P = 0.002$). Moreover, the number of thalassemia patients receiving BTT was dropped by 10.56% during the pandemic. There was a strong negative correlation observed between the rising cases of COVID-19 in Pakistan and the number of patients missing their therapy sessions ($r = -0.914$, $P = 0.030$). A considerable decline in the reserves of all Rhesus-negative blood groups amid the COVID-19 outbreak was also observed.
Conclusion. – The COVID-19 pandemic adversely affected the already suboptimal care catered to thalassemia patients in Karachi, Pakistan. The fear of the virus contraction coupled with the lockdown and restricted mobility has disrupted the entire transfusion chain from donor to the recipient. Collaborated efforts by the government and healthcare authorities are essential to ensure sufficient blood for thalassemia patients amid the pandemic.

Mots clés :
COVID-19
Thalassémie
Don de sang
Transfusion sanguine
Pandémies

RÉSUMÉ

Objectifs. – Avec l'avènement du COVID-19 au Pakistan, les services de transfusion sanguine (BTS) déjà fragmentés ont reçu un coup dur, mettant en jeu la vie des enfants atteints de thalassémie transfusionnelle. Cette étude visait à évaluer l'impact du COVID-19 sur la thérapie par transfusion sanguine (BTT) des patients thalassémiques et à suggérer des moyens d'assurer un approvisionnement en sang sûr et fiable au milieu de telles crises sanitaires.
Matériel et méthodes. – Une étude rétrospective transversale a été menée d'octobre 2019 (avant COVID-19) à juillet 2020 (pendant COVID-19) sur la base des données fournies par un centre de thalassémie, nommé Help International Welfare Trust, Karachi, Pakistan. La version 24.0 de SPSS a été utilisée pour l'analyse des données. Les données ont été décrites sous forme de moyennes et de pourcentages.

* Corresponding author.
E-mail address: shajeeaarshadali@gmail.com (S. Arshad Ali).

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Résultats. – Il y a eu une réduction significative de la consommation de sacs de PRBC après l'émergence du COVID-19 ($p = 0{,}002$). De plus, le nombre de patients thalassémiques recevant du BTT a diminué de 10,56 % pendant la pandémie. Il y avait une forte corrélation négative observée entre la hausse des cas de COVID-19 au Pakistan et le nombre de patients manquant leurs séances de thérapie ($r = -0{,}914$, $p = 0{,}030$). Une baisse considérable des réserves de tous les groupes sanguins Rhésus négatifs au milieu de l'épidémie de COVID-19 a également été observée.
Conclusion. – La pandémie de COVID-19 a eu un impact négatif sur les soins déjà sous-optimaux fournis aux patients thalassémiques à Karachi, au Pakistan. La peur de la contraction du virus associée au verrouillage et à la mobilité restreinte a perturbé toute la chaîne de transfusion du donneur au receveur. Les efforts concertés du gouvernement et des autorités sanitaires sont essentiels pour garantir une quantité suffisante de sang aux patients atteints de thalassémie au milieu de la pandémie.

1. Introduction

The Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China. The World Health Organization (WHO) officially declared the outbreak a global public health emergency on January 30, 2020 [1]. Despite the international efforts to curb the transmission of this virus, it spread to 113 countries that led the WHO to eventually declare it a global pandemic on March 11, 2020 [2]. As per the WHO's situation report, the first two cases of COVID-19 in Pakistan emerged from Karachi on February 27, 2020 [3]. Within a month, the total number of positive cases and associated deaths soared to 2,105 and 32, respectively [4]. The country was put under a mass lockdown to mitigate any risks of local transmission. The lockdown implied closure of businesses and restricted mobility as public transportation became less readily available [5]. While such measures were the need of the time, they disproportionately impeded the movement of potential blood donors and resulted in the cancellation of blood donation drives [6,7]. Donor attendance dwindled by 30% at Canadian Blood Services (CBS) and 10-30% in the state of Washington, United States of America (USA) [8]. The situation is even bleaker for developing countries like India and Pakistan with a pre-existing fragile healthcare system and inadequate blood transfusion services (BTS). The Indian Government has ordered prioritizing COVID-19 and emergency patients; thereby, calling off all elective transfusions. Such trends have had inevitable repercussions on patients who need regular blood transfusions therapy (BTT), for example, those suffering from myelodysplasia, nutritional anemia, or thalassemia [9].

Globally, thalassemia is the most prevalent single gene disorder [10]. It is an inherited microcytic, hemolytic anemia caused by decreased or absent production of alpha or beta-globin chain. In Pakistan, nearly 5-7% of the population has a beta-thalassemia trait, and around 100,000 people have beta-thalassemia major (BTM). Over 5,000-9,000 new cases of thalassemia major are diagnosed every year in Pakistan [10]. It is estimated that about 2.7 million blood donations are collected annually, one-fourth of which is utilized by thalassemia patients [11]. Globally, thalassemia patients have an average life expectancy ranging from 10 to 50 years [12]. However, the average life expectancy of BTM patients is less than 10 years in Pakistan, which is well below the global average [12]. Regular blood transfusions and chelation therapy are needed to ensure the survival of BTM patients. If left untreated, it may cause profound anemia, resulting in fatal outcomes in children below 3 years of age [13]. The available treatment options are unaffordable, which leads to the death of approximately 50,000–100,000 children with BTM every year in low and middle-income countries [14].

A study conducted in the twin cities of Pakistan highlighted that half of the thalassemia patients received poor quality of care when compared to the international standards [12]. Free of cost transfusions offered by non-governmental organizations (NGOs) were unavailable to 60% of the patients [12]. Hence, delayed or unavailable blood transfusion can deteriorate the health status and threaten the survival of thalassemia patients. Owing to ineffective medical care and inadequate chelation therapy, thalassemia patients often present with multiple co-morbidities such as cardiac, hepatic, and endocrine complications secondary to iron overload [15]. Consequently, the mortality rate of thalassemic patients infected with SARS-CoV-2 was 26.7%, as opposed to 6.3% in the general population, depicting a more severe clinical outcome [15].

While the pre-COVID19 situation was far from satisfactory, the pandemic was bound to create unfavorable circumstances for transfusion-dependent thalassemia patients. Even though data from previous outbreaks showed similar repercussions on blood transfusions, yet little attention was paid to the need for backup buffer stock [9]. This study aimed to assess the impact of the COVID-19 pandemic on the transfusion therapy of thalassemia major patients and suggest ways to cope up with a similar crisis in the future.

2. Materials and methods

2.1. Study design and setting

A retrospective cross-sectional study was conducted in the thalassemia center named Help International Welfare Trust, Karachi, Pakistan, between October 2019 and July 2020. The thalassemia center had 250 registered patients of thalassemia major with a mean age of 8.57 ± 4.49 years. Each patient was required to visit the center every 14th day for a complete blood count (CBC) and monitoring of their disease symptoms. The patients with a hemoglobin (Hb) level of 7-8 g/dl are transfused with packed red blood cells (PRBCs). Most of the chronically transfused patients registered in the thalassemia center were residents of rural areas who came to Karachi for free consultations and treatment.

2.2. Data collection

Data were obtained from the patient records and documentation of PRBCs bags consumption of the thalassemia center for the months of October 2019 to July 2020. The WHO confirmed the first two cases of COVID-19 in Pakistan on February 27, 2020 [3]. Based on this, data were categorized into two groups: (i) before COVID-19 (October 2019 to February 2020) period (ii) during COVID-19 (March 2020 to July 2020) period. The total number of cases of COVID-19 in Pakistan reported in WHO situation reports of 31 March, 30 April, 31 May, 30 June, and 31 July, were recorded [4].

Table 1
Data regarding consumption of PRBCs bags in a single thalassemia center of Karachi, Pakistan.

	Before COVID-19		During COVID-19	*P*-value
Mean ± SD	451.80 ± 4.82	Mean ± SD	345.60 ± 34.42	0.002*
October 2019	456	March 2020	361	
November 2019	452	April 2020	311	
December 2019	448	May 2020	307	
January 2019	457	June 2020	366	
February 2019	446	July 2020	383	

Calculated using paired samples t-test; PRBCs: packed red blood cells; SD: standard deviation; COVID-19: Coronavirus disease 2019.
* *P*-value of < 0.05 considered statistically significant.

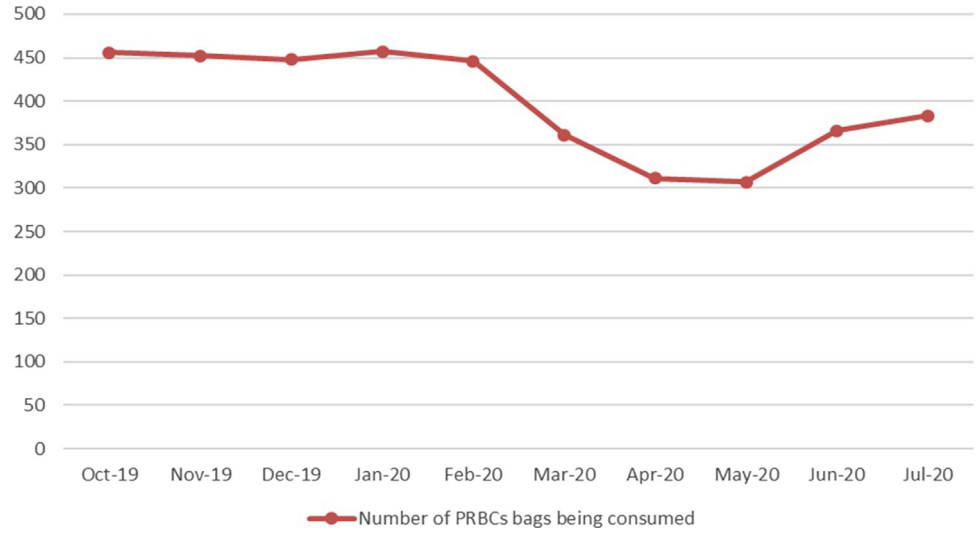

Fig. 1. Data regarding consumption of PRBCs bags in a single thalassemia center of Karachi, Pakistan. PRBCs: packed red blood cells.

Table 2
Data regarding the number of patients given BTT in a single thalassemia center of Karachi, Pakistan.

	Before COVID-19		During COVID-19	*P*-value
Mean ± SD	242.20 ± 2.59	Mean ± SD	216.60 ± 6.46	0.002*
October 2019	246	March 2020	215	
November 2019	243	April 2020	210	
December 2019	241	May 2020	212	
January 2019	242	June 2020	220	
February 2019	239	July 2020	226	

Calculated using paired samples t-test; BTT: blood transfusion therapy; SD: Standard deviation; COVID-19: Coronavirus disease 2019.
* *P*-value of < 0.05 considered statistically significant.

The data included the average consumption of PRBCs bags, the number of thalassemia patients facilitated with BTT, and the number of thalassemia patients who did not come to the center for transfusions. We further evaluated if there was unavailability or shortage of any blood group; an increase or decrease in the staff during the pandemic was also noted.

2.3. Data analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 24.0 (IBM Corp., Armonk, NY). Descriptive statistics such as mean and standard deviation (SD) were used to represent the continuous variables. The paired samples t-test was employed to analyze the difference in means of PRBCs bags, the number of patients who missed their BTT session, and the number of patients receiving therapy before and after the emergence of the COVID-19 pandemic. The Pearson's correlation coefficient denoted by "r" was used to determine the strength of association between the total number of cases of COVID-19 in Pakistan and the number of thalassemia patients who did not come for treatment. A *P*-value of < 0.05 was considered statistically significant.

3. Results

The mean ± SD number of PRBCs bags utilized per month in a single thalassemia center of Karachi, before and during the COVID-19 pandemic in Pakistan was 451.80 ± 4.82 and 345.60 ± 34.42, respectively (Table 1). With a notable drop of 23.5% of pre-COVID-19 levels, a significantly lower number ($P = 0.002$) of PRBCs bags was consumed after the advent of COVID-19 in Pakistan (Fig. 1).

With a striking drop equivalent to 10.56% of the pre-COVID-19 statistics, the mean ± SD number of thalassemia patients given BTT during the COVID-19 period was 216.60 ± 6.46, while that before the COVID-19 period was 242.20 ± 2.59 (Table 2). Thus, a significantly lower number ($P = 0.002$) of patients received their due treatment during the pandemic (Fig. 2).

Table 3 demonstrates a detailed comparison of the number of registered patients missing their transfusion sessions before and after the emergence of COVID-19 in Pakistan. We observed that

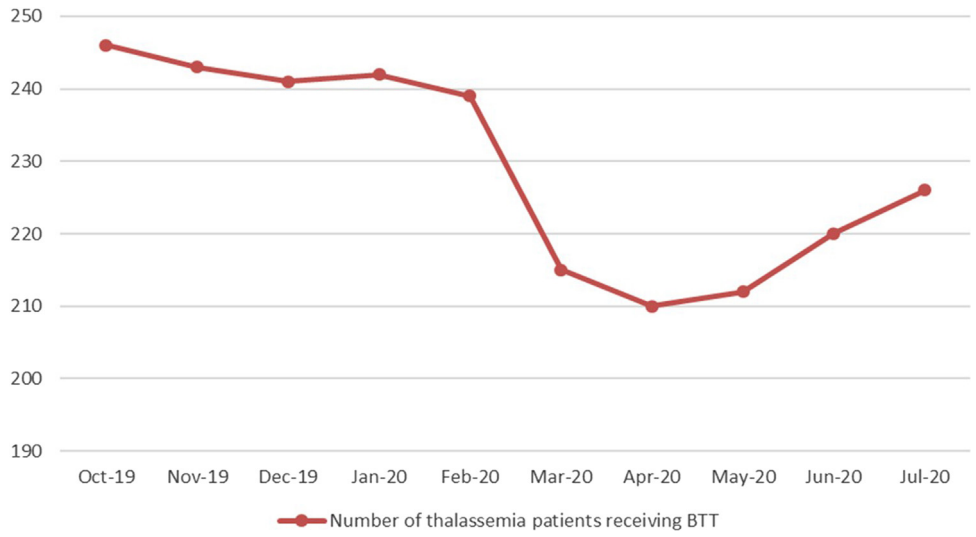

Fig. 2. Data regarding number of patients given BTT in a single thalassemia center of Karachi, Pakistan. BTT: blood transfusion therapy.

Table 3
Data regarding number of patients missing their BTT sessions in a single thalassemia center of Karachi, Pakistan.

	Before COVID-19		During COVID-19	*P*-value
Mean ± SD	7.80 ± 2.59	Mean ± SD	33.40 ± 6.46	0.002*
October 2019	4	March 2020	35	
November 2019	7	April 2020	40	
December 2019	9	May 2020	38	
January 2019	8	June 2020	30	
February 2019	11	July 2020	24	

Calculated using paired samples t-test; BTT: blood transfusion therapy; SD: standard deviation; COVID-19: Coronavirus disease 2019.
* *P*-value of < 0.05 considered statistically significant.

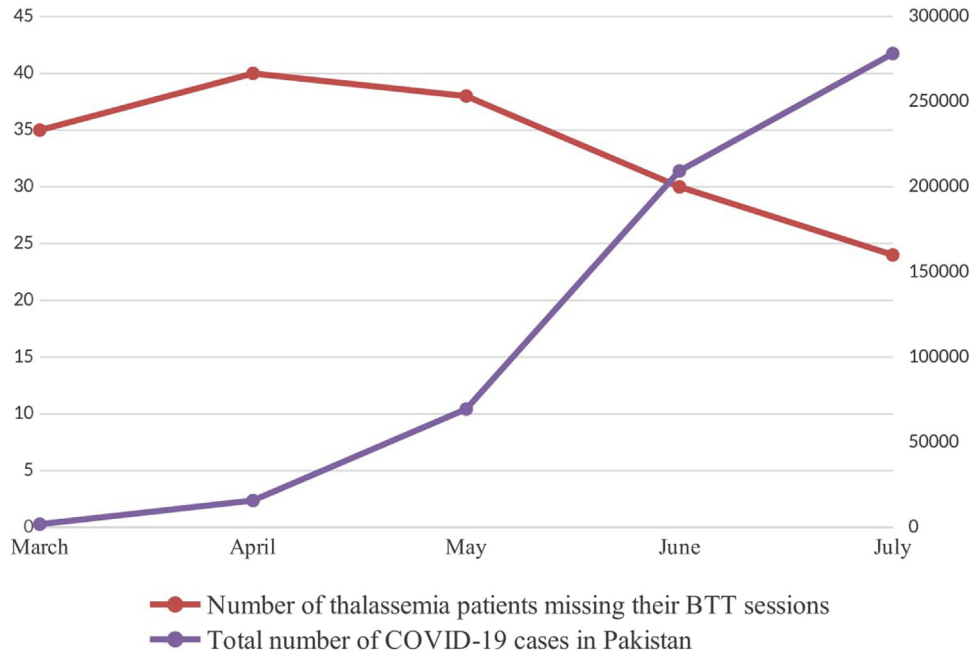

Fig. 3. Number of patients missing their BTT sessions in a single thalassemia center of Karachi, plotted against the number of rising cases of COVID-19 in Pakistan. BTT: blood transfusion therapy; COVID-19: Coronavirus disease 2019.

a significantly higher number ($P = 0.002$) of patients skipped their transfusion sessions during the COVID-19 pandemic relative to the pre-COVID-19 period. Upon plotting the number of patients not showing up for BTT after the onset of the COVID-19 pandemic against the total number of COVID-19 cases in Pakistan reported each month, we noted a strong negative correlation ($r = -0.914$, $P = 0.030$) between both the variables. Fig. 3 shows that the number of thalassemia patients skipping their therapy sessions began to rise with the emergence of COVID-19 in Pakistan. However, despite the continued rise in COVID-19 cases after May 2020, there was a

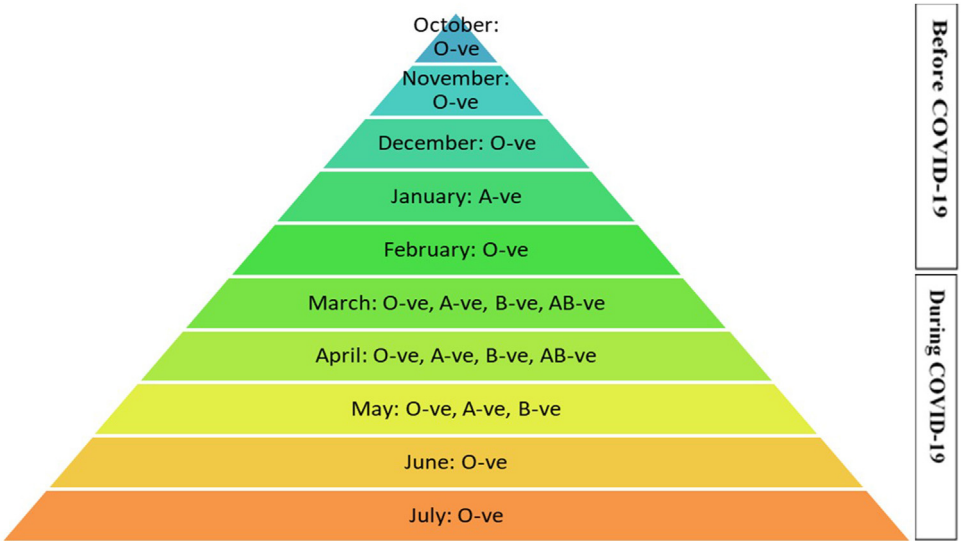

Fig. 4. Shortage of blood groups recorded in a single thalassemia center of Karachi, Pakistan during the months of October 2019 to July 2020. COVID-19: Coronavirus disease 2019.

significant decline in the number of patients skipping their therapy sessions.

The data on the inaccessibility of each blood group observed from October 2019 to July 2020 was obtained from the center. While the pre-COVID-19 period revealed a substantial shortage of O-negative blood type, there was a considerable decline in the reserves of all Rhesus (Rh)-negative blood groups in the center during the COVID-19 outbreak. Fig. 4 shows that during the months of March and April 2020, the insufficiency of all Rh-negative blood groups was recorded in the center. Moreover, we also observed a decrease in the total number of employees in the thalassemia center after the beginning of COVID-19.

4. Discussion

The current COVID-19 pandemic continues to pose an unparalleled strain on the healthcare system across the globe. Since its onset, the sole focus of the global healthcare has inevitably shifted to SARS-CoV-2, hampering the already compromised and unsatisfactory care of patients with chronic illnesses. Blood and its components constitute an essential part of routine clinical practice, providing patients with life-saving therapeutic advantages, and greatly enhance their life expectancy and quality in both acute and chronic settings [7]. BTT is, thus, an indispensable aspect of the healthcare system.

Unfortunately, the COVID-19 pandemic has significantly compromised the blood supply sustenance and its utilization, with subsequent unprecedented difficulties for thalassemia-stricken children whose lives rely solely on regular BTT. With nearly 200,000 affected children born every year, thalassemia remains one of the most common hemoglobinopathy worldwide [16]. It results in an estimated annual loss of around two million disability-adjusted life years (DALYs), causing an immense global economic burden [16,17]. Pakistan alone contributes to more than 50% of the Eastern Mediterranean region's thalassemic births, with 5000 thalassemia children born annually [13]. In Pakistan, the average number of transfusion-dependent thalassemic patients recorded is 100,000, including 18,000 in Balochistan and 25,000 in Sindh. It is believed that the number of thalassemia patients in the country is rising every day. The exact burden of the disease is, however, unknown due to the unavailability of a documentary registry in Pakistan. [11,18]. To support children affected by BTM, monthly BTT augmented with iron-chelation medication is required [19]. The estimated annual cost of iron-chelation therapy with deferoxamine is $4,400 per patient [20]. Therefore, patients who need transfusion therapy as their sole treatment option are entitled to expect reliable and safe blood reserves to fulfill their needs.

Evidence from past outbreaks also suggests that pandemics are likely to have a detrimental impact on the supply and use of blood and blood products [21–24]. Needless to say, as the COVID-19 pandemic continues to spread and cause havoc globally, many countries are facing acute blood-reserve shortages [6,25].

Our findings showed a substantial reduction in the amount of PRBCs bags consumed and the number of thalassemia patients receiving blood transfusions amid the COVID-19 outbreak compared to the pre-pandemic era ($P = 0.002$). Pakistan is a member of the International Federation of Thalassemia; however, Pakistan has not introduced standard thalassemic treatment protocols yet. Majrooh and Fatima conducted a study to determine if BTM patients are receiving optimal treatment in Pakistan. The authors found substantial gaps in personnel expertise to treat thalassemia patients, the provision of diagnostic equipment, and very poor operational cohesion [26]. In addition, a cross-sectional study conducted in Islamabad and Rawalpindi, the twin cities of Pakistan, also elucidated that almost half of the thalassemia patients were getting sub-standard treatment [12]. One possible explanation for our result stems from the fact that the COVID-19 pandemic has overwhelmed Pakistan's already vulnerable healthcare system, further undermining the sub-optimal care given to thalassemic patients. Additionally, despite no official recommendation against blood donation and transfusion, many thalassemia centers all over the country have expressed concern towards the dwindling blood supplies [18]. The constant appeal to donors and attempts by various blood banks and thalassemia centers to ensure adequate blood stores for children with thalassemia hints towards the possible drop in the number of blood donors amid the pandemic [18,27]. This may subsequently result in decreased consumption of PRBCs bags.

Another interesting finding of our study was a notable increase in the number of patients who had skipped their transfusion sessions ($P = 0.002$). While necessary to contain the virus, limited-mobility secondary to the nation-wide lockdown appears to be the primary explanation for the absenteeism of thalassemic patients. Additionally, patients' perception of the hospital environment tainted with fear of possible exposure to SARS-CoV-2 infection also explains the increased absence of thalassemia patients observed

in our study. Moreover, the fear, coupled with the misunderstanding regarding the transmission of COVID-19 through blood, further reduced patient attendance [6,7]. According to a questionnaire-based study conducted in Iran, 10% of the thalassemic patients claimed that the COVID-19 pandemic had an unfavorable impact on their BTT due to their aversion to visiting treatment centers with fear of disease contraction [15]. While SARS-CoV-2 RNA has been found in the serum or plasma of clinically ill patients, there is no precedent for COVID-19 being a transfusion-transmission viral illness. However, several international organizations suggested that blood donation be delayed for 21 days after a potential exposure to a laboratory-confirmed COVID-19 patient [28]. The increase in the number of patients skipping their due transfusion therapy also justifies the decreased consumption of PRBCs bags during the pandemic.

This study also revealed diminishing reserves of all Rh-negative blood groups in the center following the COVID-19 outbreak. Considering that O-negative is a universal donor, its shortage is relatively common. Evidence also suggests a considerable rarity of Rh-negative blood groups in the population. A retrospective study conducted in the city of Lahore, Pakistan, over a span of two years, found that 90.83% (16344) of a total of 17994 donors had Rh-positive blood type, while only 9.16% (1650) had Rh-negative blood type [29]. The study further highlighted that among Rh-negative phenotypes, blood type AB was the rarest, followed by blood groups A, B, and O [29]. Similarly, a study conducted in District Rahim Yar Khan, Pakistan, between 2008 and 2013, determined the prevalence of ABO and Rh blood groups. The findings reflected a considerable scarcity of Rh-negative blood types (6.3% vs 93.6%) in the said population [30]. The study also found a lower prevalence of Rh-negative blood types among the American and British populations, accounting for only 5% and 17%, respectively [30]. The drying stock of already-less prevalent blood groups, O-negative, A-negative, B-negative, and AB-negative, during the peak time of the COVID-19 pandemic in our study, could be attributed to prolonged containment strategies. The lack of liberty and restriction of mobility impeded the movement of voluntary blood donors putting the already dwindled Rh-negative blood reserves at stake [6,25]. While the management of common blood groups was quite challenging, the supply of Rh-negative type became farfetched. Even before the pandemic, Pakistan's blood supply depended heavily on NGOs run by students who often set up camps in universities, schools, industries, and corporate agencies. These NGOs serve as the backbone of blood collection and voluntary donor mobilization in Pakistan. With lockdowns across the country to curb the rapid spread of COVID-19, blood banks ran dry, threatening the lives of thousands of thalassemic children [31]. A study conducted at King Abdullah Hospital, Saudi Arabia, showed a 39.5% drop in donor attendance and blood supply at blood bank-based collections [32]. Similarly, the number of blood donors in Turkey dropped from 9,000 to below 2,000 per day after the advent of COVID-19 [33]. Furthermore, nearly 4,000 scheduled blood drives were postponed in the USA by March 2020 due to the closure of schools and workplaces where blood drives were usually held [34]. Blood banks in India also faced severe shortages of blood supplies as the government clamped down blood donation camps to discourage public gatherings in an attempt to eradicate the virus [25,35].

Lastly, the declining strength of employees in the thalassemia center observed in our study may have also contributed to the poor care given to the thalassemic children. While lockdown hampered donor and recipient movement, it also created commuting inconvenience for employees. Loss of subordinates, medical personnel, and technicians may render alternative procedures unviable [22]. Also, being a welfare institute, the thalassemia center is highly reliant on funds. However, the impact of the levied lockdown on Pakistan's already deteriorating economy, together with the dearth of financial capital secondary to COVID-19 created friction in the smoothly running management of the institute. Here, it is also imperative to mention the psychological ramifications of the pandemic, which may have also led to reduced employee attendance [36], further imperiling the care of the patients.

In such uncertain times, while it is imperative to concentrate all the resources towards pandemic-oriented operations, it is also crucial to not overlook the suffering of patients with chronic conditions, such as thalassemia. Patients with thalassemia are deemed vulnerable and at high risk for a more serious clinical outcome of COVID-19 since the start of the pandemic. Thus, a safe and sufficient supply of blood is vital to restore a healthy post-pandemic nation.

National health crises are well-managed in developed countries with integrated and coordinated healthcare infrastructure and blood bank network. In nations with a weak healthcare system and a dysfunctional BTS, however, the response to maintaining reliable and safe blood reserves is often ineffective [37]. Thus, a comprehensive disaster preparedness strategy to ensure blood availability is the need of the hour. The strategies should focus on establishing centralized frameworks for close surveillance of blood demand and supply, designing plans for sharing blood and its components, employing blood conservation methods, and standardizing blood management practices among blood banks. Moreover, evidence suggests that altruism is the key force that encourages people to donate blood and remain an active donor [38]. Thus, the media should also endorse the culture of blood donation by using sentiments attached to thalassemia patients and by dissolving any myths and misconceptions that may hinder the process. Following the steps undertaken by a hospital in North India, appointment letters for the voluntary blood donors should be issued by the hospitals and blood banks to counter the depleting blood stock [35]. Additionally, blood banks and hospitals must enact all the precautionary measures to lessen the risk of disease transmission to the donors, recipients, and the staff.

5. Limitations

The present study has certain limitations. Firstly, the Help International Welfare Trust did not conduct any blood drives. The PRBCs bags were supplied on demand by NGOs and renowned blood banks of Karachi. Therefore, it was not possible to assess the impact of the COVID-19 pandemic on blood donors and blood donations. Secondly, it is important to note that our study catered to a single thalassemia center in Karachi, Pakistan. Hence, our results cannot represent the impact of the pandemic on thalassemia centers all over the country. A multi-center study should be conducted in the future to draw a definitive picture of the effect of the pandemic on thalassemic patients all over the country.

6. Conclusion

In conclusion, this study highlighted the adverse effect of the COVID-19 pandemic on the already suboptimal care catered to thalassemia patients in Pakistan. Restricted mobility due to lockdown and fear of contracting the infection from hospital settings not only led to a decreased number of thalassemia patients receiving transfusion therapy but also resulted in the cancellation of blood drives and subsequent decline in the blood reserves. Moreover, shortages of staff at the center also contributed to the poor care of thalassemic patients. Collaborated efforts by the government, healthcare authorities, and mass media are essential to provide quality care to thalassemia patients and to ensure sufficient blood is available to them even in the face of a pandemic. It is hard to foretell what the future holds. It would be wise to learn from previous

experiences and work tirelessly to equip ourselves against future health crises.

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Availability of data and materials

The datasets supporting the conclusion of this article are included within the article.

CRediT authorship contribution statement

Author 1: Conceptualization, Methodology, Writing - Original Draft, Formal analysis, Visualization.
Author 2: Supervision, Writing - Original Draft, Writing - Review & Editing,
Author 3: Conceptualization, Methodology, Data Curation.
Author 4: Writing - Original Draft.
Author 5: Data Curation.
Author 6: Formal analysis, Writing - Review & Editing.
Author 7: Writing - Review & Editing.
All authors agree to be accountable for all aspects in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethical approval and consent to participate

This study requires no ethics approval due to public data- based analysis. The authors are accountable for all aspects of the work in ensuring that the question related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure of interest

The authors declare they have no competing interest.

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