

## ORIGINAL ARTICLE

# Management of children with glucose-6-phosphate dehydrogenase deficiency presenting with acute haemolytic crisis during the SARs-COV-2 pandemic

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## Abstract

**Background and Objectives:** Shortage of blood during the severe acute respiratory syndrome-COV-2 (SARs-COV-2) pandemic impacted transfusion practice. The primary aim of the study is to assess management of acute haemolytic crisis (AHC) in glucose-6-phosphate dehydrogenase(G6PD)- deficient children during SARs-COV-2 pandemic, and then to assess blood donation situation and the role of telemedicine in management.

**Methods:** Assessment of G6PD-deficient children attending the Emergency Department (ER) with AHC from 1 March 2020 for 5 months in comparison to same period in the previous 2 years, in three paediatric haematology centres. AHC cases presenting with infection were tested for SARs-COV-2 using RT-PCR. Children with Hb (50–65 g/L) and who were not transfused, were followed up using telemedicine with Hb re-checked in 24 h.

**Results:** A 45% drop in ER visits due to G6PD deficiency-related AHC during SARs-COV-2 pandemic in comparison to the previous 2 years was observed. 10% of patients presented with fever and all tested negative for COVID-19 by RT-PCR. 33% of patients had Hb < 50 g/L and were all transfused. 50% had Hb between 50 and 65 g/L, half of them (n = 49) did not receive transfusion and only two patients (4%) required transfusion upon follow up. A restrictive transfusion strategy was adopted and one of the reasons was a 39% drop in blood donation in participating centres.

**Conclusion:** Fewer G6PD-deficient children with AHC visited the ER during SARs-COV-2 and most tolerated lower Hb levels. Telemedicine was an efficient tool to support their families. A restrictive transfusion strategy was clear in this study.

## KEYWORDS

acute haemolytic crisis (AHC), glucose-6-phosphate dehydrogenase (G6PD), packed red blood cell transfusions (PRBCs), severe acute respiratory syndrome-COV-2 (SARs-COV-2)

## INTRODUCTION

The G6PD Mediterranean mutation is the commonest mutation causing G6PD deficiency in Egypt. This variant is characterized by <10% of normal G6PD activity, making it a severe form of the disease with evident need for transfusion [1–3].

Adding G6PD deficiency to the list of screening elements in a SARs-COV-2 workup if there is a high suspicion for this genetic mutation might be recommended [4]. Triggers of red cell haemolysis are the ingestion of fava beans, infection and certain drugs as hydroxychloroquine [5, 6]. There is evidence to suggest an association between G6PD deficiency and increased susceptibility to, and severity of illness with, SARs-COV-2 infection [7, 8].

Shortage of packed red blood cell (PRBCs) transfusions in blood banks during SARs-COV-2 pandemic carries a high risk to children in need of PRBCs as emergency service [9, 10]. The threshold of red blood cell transfusions showed that there was no evidence of differences in clinical outcomes over 6 months between the critically anaemic children who received immediate transfusion and those who did not [11].

A key consideration for transfusion services is maintaining the balance between supply and demand. Donor attendance might fall, as it did by 10%–30% in the state of Washington [12] and by 30% at Canadian Blood Services (Goldman M, unpublished) [13–16].

The SARs-COV-2 crisis has made telemedicine an option that should be actively considered in most patients. Real-time telemedicine consultations reduce the time of subspecialty visits, as well as risk of infection and may thereby improve visit completion [17].

Hospitals and blood centres proactively implemented blood conservation strategies as well as efforts to maintain blood donations [18]. However, not enough studies to date have provided detailed blood usage in G6PD-deficient children during SARs-COV-2 pandemic.

In the light of such shortage, physicians were urged to reconsider the management of children with G6PD. Our national guidelines necessitates transfusion if Hb <65 to 70 g/L, but in the new approach, we have accepted lower Hb levels, guided by clinical condition and longitudinal follow-up with the use of telemedicine.

The primary objective of the study was to assess the impact of SARs-COV-2 infection on management and outcome of G6PD-deficient children presenting to ER in AHC in three haematology centres in comparison to same period in the previous 2 years.

Secondary objectives were to assess the blood donation situation and role of telemedicine in follow up of G6PD-deficient children with critical presentation during the pandemic.

## METHODS

This is a prospective study to assess AHC in children with G6PD deficiency presenting to ER in three University Paediatric Haematology centres from 1 March 2020 for 5 months in comparison to same period of time in years 2019 and 2018.

### Inclusion criteria

- Children with proven or highly suspected G6PD-deficiency; with or without positive family history (confirmed as G6PD-deficient 6 weeks later).
- G6PD-deficient children in AHC presented to ER in the three participating sites (exaggerated pallor and jaundice with low Hb, high both reticulocyte count and indirect serum bilirubin).
- Parental agreement to receive blood transfusion if indicated or follow up strictly/8–12 h for 48 h by video calls if not transfused.

### Exclusion criteria

- AHC other than G6PD deficiency
- G6PD-deficient children not in AHC
- G6PD-deficient children whose families refused to sign the informed consent

Precipitating factors, PRBCs availability and transfusion decision were all assessed. Availability of blood and role of telemedicine in management were reported. The investigations stated in the protocol included CBCs, urine dipsticks, serum bilirubin (direct and indirect), blood grouping and cross matching. Quantitative G6PD assessment both at presentation and 4 weeks later was also included. A list of food, drugs and agents to be avoided was given to the parents. Blood bank guidelines did not approve requests for G6PD-deficient children in AHC with Hb >65 g/L if clinically stable.

Although the threshold of red blood cell transfusions for stable patients in AHC was Hb of <65 g/L, some children with Hb 50–65 g/L were not transfused either due to shortage of supply, parental worry from day of case admission during the SARs-COV-2 pandemic or following the haematologist decision of unnecessary transfusion.

In cases with Hb <50 g/L and PRBCs unavailability, the central National Blood Bank was notified and supplied such units. In case of parental fear, counselling was offered by both the paediatrician and haematologist that the benefit outweighs the minimal risk of SARs-COV-2 infection, which will be kept to a minimum after applying all necessary precautions.

Non-transfused patients were followed up, using telemedicine service (video call), every 8–12 h (for child activity, general appearance and urine colour). Providing service to re-check Hb daily for 2 days (if Hb dropped below 50 g/L or child became unstable, immediate referral for transfusion and blood was requested from the National Blood Bank). For all patients, a follow up Hb level at 24 and 48 h, G6PD assay for newly diagnosed patients and urinary dipstick every 12–24 h were done.

Educational material was given to all families of G6PD-deficient new patients. All cases presenting with evidence of infection were tested by nasal and throat swabs for SARs-COV-2 by RT-PCR [19].

Blood donation prospective data were obtained from donor attendance records, and blood inventory records between 1 March

and 31 July 2020 in comparison to retrospective data during the same period in previous 2 years. The data included the number and sources of donated blood units, and the number of released units for transfusion to AHC of G6PD-deficient children (Table 2). A recruitment text message for every potential blood donor during the SARs-COV-2 era in 2020 was sent out from May to July. Plans for blood donation campaigns to all registered providers were implemented.

### Laboratory methods

- CBC was done using Coulter Counter GEM-S (Beckman Coulter Inc., Miami, Florida). Reticulocyte count was determined by Brilliant Cresyl blue stain.
- Indirect bilirubin was done on Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany).
- G6PD enzyme level was assessed quantitatively using a spectrophotometer [4] at presentation to ER and 4 weeks later.

- RT-PCR using TaqPath COVID-19 CE-IVD RT-PCR Kit, 1000 reactions (Cat. No. A48067) from Thermo Fisher Scientific [20].

### Telemedicine service

There has also been a significant change in the patient pathway with more being reviewed via the means of telemedicine to reduce the risk of SARs-COV-2 exposure and transmission. Laboratory test results were shared over picture archiving and communication systems to the paediatric haematologist either before or during the appointment through live video conferencing [21].

All patients' guardians of known or suspected cases of G6PD deficiency had an access to have a video call to haematologist in ER; cases with Hb <50 g/L received transfusion immediately while those with Hb 50–65 g/L were either transfused or not.

During study, telemedicine service was mainly synchronous (real-time telephone or live audio–video interaction). We ensured the availability of smartphones for all caregivers.

**TABLE 1** Demographic data of G6PD-deficient children in AHC presenting to the three centres during 5 months of SARs-COV-2 pandemic in 2020 vs same period in 2018 to 2019

Variable	Year 2020 N = 198	Mean of year 2018 and 2019 N = 361	p-value
<b>Age at presentation</b>			
Months mean ± SD	(21.5 ± 8.1)	(22.3 ± 8.8)	
Range	9–48	10–50	
<b>Male sex</b>	178 (89.9%)	650 (mean = 325) (90%)	0.956
<b>First episode of AHC</b>	178 (89.9%)	635 (mean = 317) (87.95%)	0.448
<b>Hb (g/L)</b>			
Mean ± SD	56 ± 14	62 ± 13	<0.001
Range	2–8	2–9	
<b>Hb &lt;50 g/L</b>	66 (33.3%)	90 (25%)	0.03
<b>Hb 50–65 g/L</b>	99 (50%)	126 (35%)	<0.001
<b>Hb &gt;65 g/L</b>	33 (16.7%)	145 (40%)	<0.001
<b>Transfused (Hb ≤50 g/L)</b>	66/66 (100%)	90/90 (100%)	1
<b>Non-transfused (Hb 50–65 g/L)</b>	49/99 (49.5%)	24/126 (19%)	<0.001
PRBCs not available	19/49 (38.8%)	2/24 (8.3%)	0.007
Family decision	18/49 (36.7%)	6/24 (25%)	0.3
Haematologist decision	12/49 (24.5%)	16/24 (66.7%)	<0.001
<b>Non-transfused Hb ≥65 g/L</b>	33/33 (100%)	120/145 (83.0%)	0.01
<b>Transfused</b>	116	217	
One unit only	110/116 (94.8%)	196/217 (90.3%)	0.152
Two units	6/116 (5.1%)	21/217 (9.6%)	0.150
<b>G6PD unit/g of Hb</b>			
<i>Initial</i>			
Mean ± SD	1.6 ± 0.3	1.7 ± 0.4	0.005
Range	0.2–3.9	0.3–4.1	
<i>6 weeks later<sup>a</sup></i>			
Mean ± SD	1.52 ± 0.32	1.61 ± 0.38	0.002

Note:  $p > 0.05$ : Non-significant;  $p < 0.05$ : Significant;  $p < .01$ : Highly significant.

<sup>a</sup>G6PD level was done in 90% initially and 100% 6 weeks later.

Contact was mainly through WhatsApp or Facebook messenger (text and video call). Asynchronous and remote patient methods were not applied.

### Ethics statement

The clinical trial was conducted after approval of ethical committees of involved centres (Ain Shams, Assuit and Beni Suef Universities). Parents or guardians of all patients accepted to follow the study protocol. Parents of patients who were not transfused should be contacted regularly through video conference with the treating haematologist for fear of deterioration and were asked to respond to all queries. Parents of G6PD-deficient children with AHC accepted that strict precautions would minimize the risk of SARs-COV-2 infection.

### Statistical analysis

Statistical analyses were carried out using SPSS 17.0 software package program. The comparison between two groups with qualitative data were done using Chi-square test or Fisher exact test. Independent t-test or Mann-Whitney test were used for two independent

groups with quantitative data. Paired t-test or Wilcoxon Rank test were used for two paired groups with quantitative data. One way ANOVA or Kruskal-Wallis were used for more than two groups with quantitative data.

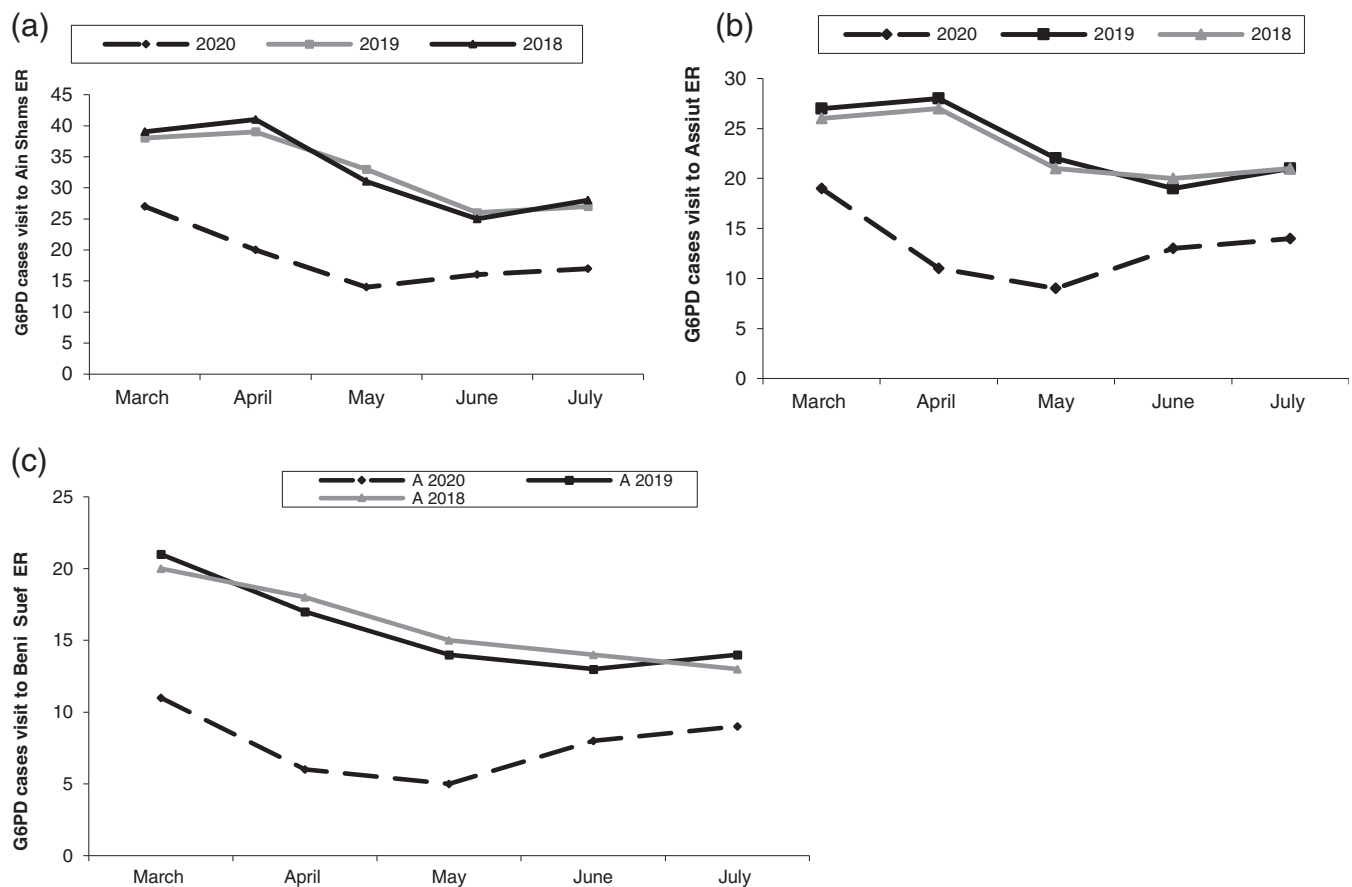
Results are considered significance if  $p$ -value  $< 0.05$  and highly sign if  $< 0.01$ .

## RESULTS

Demographic data of AHC in G6PD-deficient children attending the ER in the contributing centres during the 5 months over 3 years period 2018–2020 and transfusion service provided to them are shown in Table 1.

The number of patients were stable over last 2 years with a 45% drop in ER visits due to AHC in G6PD during SARs-COV-2 pandemic. Fear of hospital visits was the primary cause of delayed presentation in more than 70%. Families did not show any concern of SAR-COV-2 being blood-transmitted, yet all were re-assured that the virus is not blood-borne.

A maximum drop of ER visits of AHC in G6PD-deficient children was observed during May as shown in Figure 1, coinciding with the peak of the pandemic in Egypt and was compensated with the maximum drop in blood donation.



**FIGURE 1** G6PD-deficient cases in AHC visits to ER in (a): Ain shams; (b) Assiut and (c) Beni Suef for 5 months period over 3 years, 2018–2020

Ingestion of fava beans and/or derivatives were the predisposing factors of haemolysis in almost 80% and offending drug intake in 10%. Only 10% of cases presented with possible infection; however none had direct contact to active SARs-COV-2 cases and all tested negative by RT-PCR swab.

The mean Hb level at presentation during the pandemic was 56 g/L, being significantly lower in comparison to previous 2 years ( $p < 0.001$ ). Also number of patients presenting with Hb levels more than 65 g/L were significantly less than that reported over the previous 2 years. Regarding the need of transfusion, all patients presenting with Hb level less than 50 g/L were transfused as previously practiced. 100% of patients with Hb level more than 65 g/L were not transfused following a restrictive transfusion strategy during the pandemic in comparison to 83% in the previous 2 years ( $p < 0.05$ ).

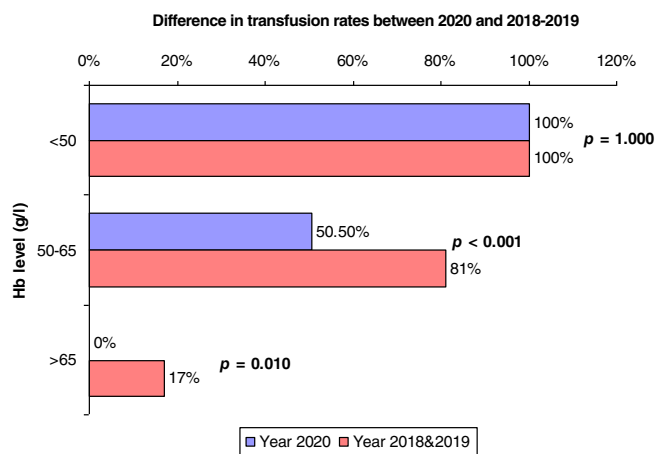
The most significant difference between COVID era and previous 2 years was in the number of non-transfused patients with Hb levels between 50 and 65 g/L. PRBC unavailability, haematologist restrictive strategy and/or parental worries were the main reasons for conservative management; however, only 4% were transfused 24 h later with the drop of Hb below 50 g/L.

Differences in transfusion rates between 2020 and previous 2 years is shown in Figure 2.

Most transfused cases received one unit but exceptionally severe cases received two units of blood in 5% during SARs-COV-2 in comparison to almost 10% in previous 2 years.

G6PD level was assessed in 90% initially and in 100% after 6 weeks from presentation or post-transfusion, a decline in level after the initial evaluation was 0%–20% (5.5%). A lower level of G6PD was detected during the pandemic.

During the outbreak of SARs-COV-2, a significant reduction in blood donations was observed in comparison to the last 2 years as shown in Table 2 and Figure 3. Females contributed less during SARs-COV-2 pandemic; however, the highly educated donors shared more. A peak reduction was noticed in May 2020 and was compensated with reduction in demand. All methods for donor recruitment were



**FIGURE 2** Differences in transfusion rates between 2020 and previous 2 years

taken with a better response in late July compared to previous months coinciding with national drop of positive SARs-COV-2 cases (Figure 3). Demographic data of donors are shown in Table 2.

Regular blood donors showed 25% increase as number and double the percentage as donors compared to previous 2 years. Family replacement was less during SARs-COV-2 and even blood campaigns stopped or slowed down during April–June and re-started to peak in July (Figure 3).

## DISCUSSION

Our results showed a marked drop in ER visits due to AHC in G6PD by 45% over 5 months during SARs-COV-2 pandemic, which could not be easily explained. The drop was observed among all severity grades of AHC; however, as expected the drop was mainly in the mild cases (75% in mild in contrast to 25% drop in severe cases) Children with mild AHC did not urge their families to visit ER.

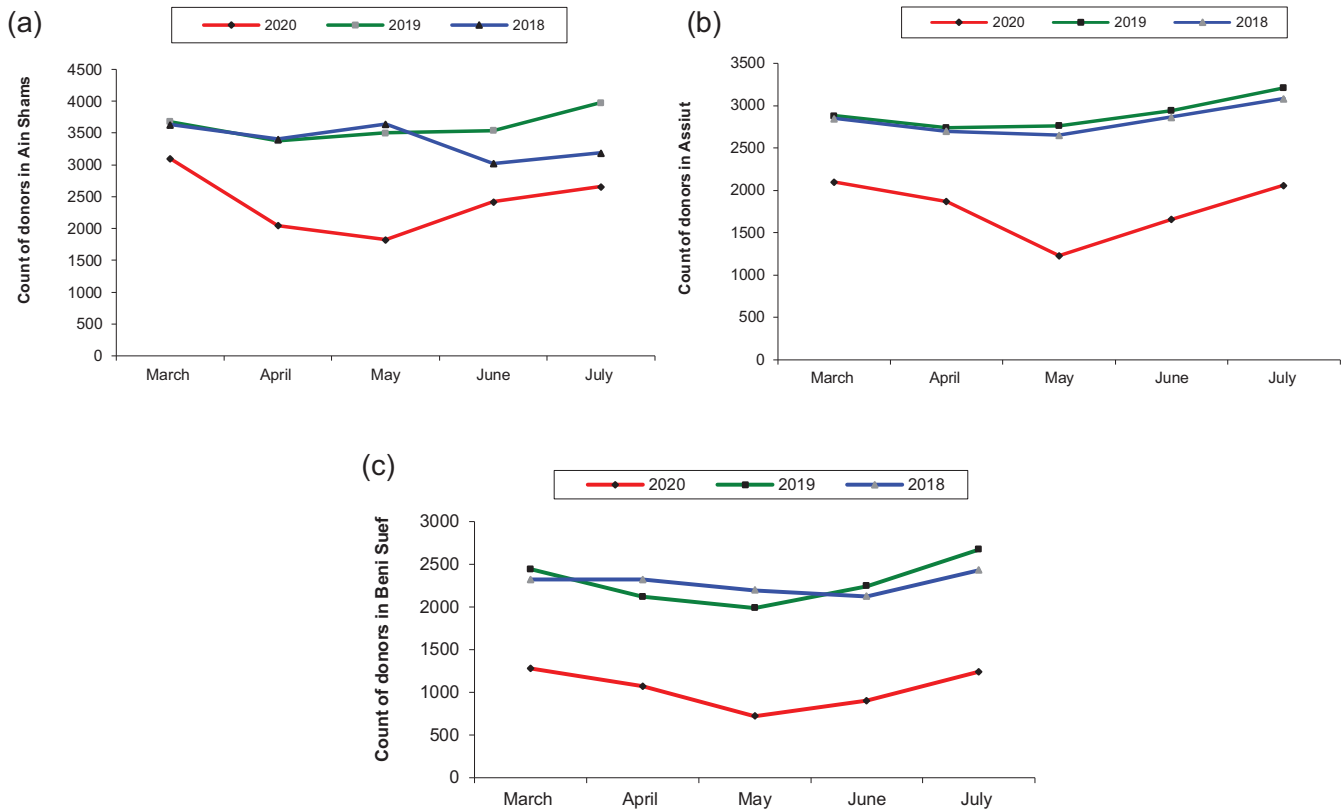
According to consensus recommendation for red blood cell transfusion [22], the need for PRBCs does depend not only on the Hb concentration but also on the overall clinical context in addition to risks, benefits and alternatives to transfusion. The three participating centres follow a transfusion strategy of Hb level of 65 g/L or less according to the clinical condition of patient and the evidence of ongoing haemolysis.

Cases with mild AHC were all stable and were not transfused according to blood bank policy during the pandemic. Parents were assured and advised to contact the haematology team through

**TABLE 2** Profile of blood donors in blood banks of the three paediatric haematology centres during March–July 2020 and 2018–2019

Blood donors	Year 2020 No = 25,989	Mean value of 2018 and 2019 No = 42,655	p value
Sex			
Females	2599 (10%)	8531 (20%)	<0.001
Males	23,390 (90%)	34,124 (80%)	
Age			
18–45 years	23,390 (90.0%)	38 389 (90%)	1.000
Education			
>12 years	18,192 (70%)	25,593 (60%)	<0.001
<12 years	7797 (30%)	17,062 (40%)	
Donation through			
Appointment	18,192 (70%)	12,797 (30%)	
Blood campaigns	2599 (10%)	17,062 (40%)	<0.001
Family replacement	5198 (20%)	12,796 (30%)	
Donor status			
Regular	5198 (20%)	4266 (10%)	<0.001
First timer	20,791 (80%)	38,389 (90%)	

Note:  $p > 0.05$ : Non-significant;  $p < 0.05$ : Significant;  $p < 0.01$ : Highly significant.



**FIGURE 3** Number of donors in (a): Ain shams; (b) Assiut and (c) Beni Suef for 5 months period over 3 years, 2018–2020

telemedicine service if the child deteriorates. Only 10% needed to re-contact the haematologist and none were transfused during follow-up.

On the other hand, in moderately-severe cases, only 50% of them were transfused in comparison to almost 90% in the previous 2 years. All non-transfused were followed up closely. Only in 4%, Hb dropped to below 50 g/L and were transfused. This may highlight the need for more restrictive transfusion strategies in clinically stable cases as long as there is adherence to follow up.

One of the main reasons for non-transfusion was parental refusal; fear of SARs-COV-2 transmission was the main reason and not the usual fear from blood-borne infections.

Severe cases presenting to ER with Hb of 50 g/L or less were all transfused, their percentage was relatively more during the pandemic. Most of them received a single unit (95%); only 5% had received two units in contrast to almost 10% in the previous 2 years, which might be related to more restrictive transfusion policy during the SARs-COV-2 era.

Blood donation services were markedly affected by the pandemic, as reported worldwide [12], with marked reduction compared to the same period in the previous 2 years. This was secondary to the governmental restrictions issued to avoid crowding and also the fear of regular donors to visit a health care facility.

A recruitment plan started few weeks after the start of SARs-COV-2 pandemic in Egypt, mainly through social media

announcements. Also text messages for regular and potential blood donors were sent out from May to July, with a significant rise in July coinciding with significant drop in reported SARs-COV-2 cases.

Regular blood donors played a great role during SARs-COV-2 time, not only they showed 25% increment in number in comparison to previous 2 years but also had higher Hb levels (data were not shown) which was mostly due to repeated advice to consume more haeme iron [23]. Surprisingly, family replacement was less during SARs-COV-2 and even blood campaigns either stopped or was less frequent through April–June and re-started to peak in July. Females contributed less during SARs-COV-2 pandemic; however, the well educated donors shared more.

Balance between shortage of PRBCs and unnecessary transfusion should be maintained well. Restrictive transfusion for stable moderate AHC cases due to G6PD deficiency should be studied more in a prospective study in unprivileged countries with shortage of blood donation. The possibility of using the same model after control of SARs-COV-2 pandemic should be well assessed.

The fate of missed cases of G6PD-deficient children with AHC who did not attend to ER to seek medical advice was unknown. We did our best to clear our retrospective data to be suitable for comparison with the prospective data. SARs-COV-2 RT-PCR screening was done only in 10% of cases who presented with evidence of infection; all were negative and chest CT was not done; however, asymptomatic

cases might be possibly missed. Telemedicine was done only for non-transfused critical cases as well as any one requesting the service, meanwhile a critical evaluation should be done in case of refusal of ER visit for border-line cases.

Telemedicine channels as Whats app and Facebook do not protect patient's privacy and personal data protection.

In conclusion, during the COVID-19 pandemic and with shortage of blood supply, a more restrictive transfusion practice for AHC in G6PD-deficient children was implemented compared to the previous 2 years. A delay in presentation to ER was noticed. It was clear that home supervision through telemedicine was a good option. Maximizing the role of regular blood donors is mandatory in Egypt and restrictive transfusion strategy should be assessed better in the future.

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M.E. is responsible for the design of the work and contributed along with all the remaining authors to:

1. The acquisition, analysis or interpretation of data for the work;
2. Drafting the work and revising it critically for important intellectual content;
3. Final approval of the version to be published;
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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