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Original Article

J Hematol. 2024;13(5):186-191

Freedom From Bleeds With Low-Dose Emicizumab Prophylaxis in Inhibitor-Positive Hemophilia A

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Abstract

Background: The real-world data on outcome of hemophilia A patients with inhibitors (HAI) is sparse, especially from developing countries. In a setting of inequitable healthcare opportunities for hemophilia patients, especially those with inhibitors, low-dose practices of emicizumab are emerging. In the present article, we describe our experience of managing HAI patients on low-dose emicizumab over a period of 56 months (from December 2019 to August 2024).

Methods: The present study reports the response of patients with inhibitor-positive severe hemophilia A (HAI) and a high annual bleed rate to two-dose schedules of emicizumab prophylaxis. All patients with HAI were previously managed with on-demand bypassing agents (BPAs) before being shifted to emicizumab. Seven patients were treated on standard dose of 3 mg/kg weekly for 4 weeks followed by once in 2 weeks, whereas 25 patients were started on low dose of 3 mg/kg once in 4 weeks with or without loading as per clinical decision. Bleed frequency, joint involvement, trough drug level and hemophilia joint health score (HJHS) were documented serially till in September 2023 (median of 16.4 months of follow-up). After September 2023, all patients were shifted to low dose of 3 mg/kg once in 4 weeks, following which 18 more patients were added, and this regimen has continued to date.

Results: Thirty-two patients were initiated on emicizumab prophylaxis between December 2019 and December 2022. The median duration of follow-up of this cohort was 16.4 months (7.7 - 27.3 months). There was a significant reduction in bleed rate and improvement in HJHS in both arms after initiation of emicizumab. During a cumulative follow-up period of 562.8 months involving the 32 patients, only one patient experienced a bleed that required treatment. At 12 months post-initiation, the median baseline HJHS improved from 9 to 0 in children who received full dose and from 12 to 4 in those who received low dose. The mean emicizumab trough level observed in September 2023 in both groups were 29.92 ± 2.53 µg/mL and 12.6 ± 3.79 µg/mL, respectively. No significant difference was noted either in treated bleeds or HJHS score between patients who received standard or low-dose emicizumab. In view of clinical equivalence, the standard-dose patients were also shifted to low dose, and 18 more patients were subsequently added to this arm since September 2023. The last date of follow-up for this analysis was 31 Aug 2024. The cost of treatment on low-dose emicizumab in India compared to on-demand BPAs modeled on a child weighing 10 kg is analyzed.

Conclusions: Emicizumab prophylaxis even in lower doses is effective in preventing bleeds and improving joint outcome in HAI with pre-existing high bleed rate and arthropathy. This opens up an avenue for providing equity in healthcare delivery for HAI in low- and middle-income countries (LMICs) such as India.

Keywords: Emicizumab; Real-world data; Prophylaxis; Hemophilia; Equity in healthcare; Inhibitor-positive hemophilia

Introduction

Patients with hemophilia need lifelong access to clotting factor concentrates, either as replacement for preventing or as episodic for treating bleeding. Factor VIII (FVIII) inhibitors develop in 25-30% of hemophilia A patients [1]. With development of inhibitors, the cost of treatment increases exponentially, and quality of life drops drastically as most families in low- and middle-income countries (LMICs) would not have access to standard treatment options, such as immune tolerance induction, bypassing agents or non-factor replacement therapies. Patients usually develop worsening of hemophilic arthropathy and succumb to life-threatening bleeding early in life. Low-titer inhibitor patients respond to higher dosage of clotting factor concentrates, whereas high-titer inhibitor patients require bypassing agents like recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrates (aPCC). Emicizumab, a bispecific monoclonal antibody which binds to factor IXa and X and activates the latter has been approved for use in patients with inhibitor-positive hemophilia A (HAI) [1, 2]. As the cost of treatment with emicizumab is high, it is used sparingly in many countries. In the current paper, we describe our experience of using emicizumab at the recommended dose and

Manuscript submitted September 6, 2024, accepted October 7, 2024
Published online October 21, 2024

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doi: https://doi.org/10.14740/jh1346

at a lower dose with similar bleeding rates and joint outcomes.

Materials and Methods

This study recorded the clinical course, factor consumption and joint status of severe hemophilia A patients with high-titer inhibitors (HAI), registered at our center and were switched from on-demand bypassing agents (BPA-OD) to emicizumab prophylaxis. All patients were registered and followed up at the Integrated Hemophilia Thalassemia Treatment Center of our institute. Ethical approval was received from the Institutional Review Board (Ethics-SSPHPGTI (CDSCO registration): ECR/1320/Inst/UP/2019-2020-24-IM-02). The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The data from treatment registers including bleeding frequency, site of bleeding, target joints and adverse events to any treatment were collected. In addition to the regular screening while on FVIII prophylaxis, patients with clinical suspicion of poor response to FVIII and frequent bleeds were screened for inhibitors. High-titer inhibitor patients were managed on aPCC or rFVIIa, often at doses lower than recommended (due to non-availability) on a bleed-to-bleed basis, prior to starting emicizumab. Emicizumab was available through state government supply, and all patients received it free of cost. The first seven patients received standard dose of 3 mg/kg weekly for four doses, followed by 3 mg/kg once in 2 weeks. The remaining 25 patients received 3 mg/kg once in 4 weeks with or without the loading dose. Loading dose was given only to children with life-threatening bleeds such as intracranial bleeding, surgery or pseudotumors. This dose was selected on the basis of data published by us and other groups which showed benefit even at lower doses [3, 4]. The dose was rounded off to the nearest vial size whenever possible. Physiotherapy consult was provided at each hospital visit, and daily home physiotherapy was advised for all patients based on their functional status. Annualized bleeding rate (ABR) and hemophilia joint health score (HJHS) [5] was calculated at baseline and at 6-month intervals. ABR was defined as the sum of bleeds observed during the study period which was annualized. HJHS version 2.1 was calculated by one of two clinicians or the physiotherapist at baseline and 6-month intervals. HJHS was not calculated in children less than 6 years of age. The cost of treatment modeled around a child weighing 10 kg while on standard and low dose was compared as per rates at which the drug is provided in India to the government sector. The trough level of emicizumab was measured using emicizumab-specific calibrators (R2 diagnostics) on an automated coagulation analyzer (Stago). Data were analyzed on SPSS 17.0, and Chi-square test was used to analyze the difference between both groups.

Results

As of August 31, 2024, 701 patients with hemophilia A were registered at our center, out of which 112 were inhibitor positive. Three of these patients were positive for low-titer inhibitors whereas the rest had high-titer inhibitors. Out of these, the data of the initial 32 patients who were compared directly between standard- and low-dose arms, followed by the addition of 18 more patients in the low-dose arm (total n = 50) since December 2019 are presented in this paper. The follow-up of these patients was done until August 31, 2024. Patients who had high bleed rates, life-threatening bleeds, pseudotumors and those with poor joint score and those with severe arthropathy who lived far from the hospital (> 150 km) were preferentially given the drug, since the supply of the drug from government could not cover all high-titer inhibitor patients. The median age of this group was 10.5 years (range: 3 - 28 years). All had severe hemophilia A, and the median inhibitor titer was 27.4 Bethesda units (BU) (range: 5.1 - 500.9). Patients were diagnosed as inhibitor positive for 1 - 22 months prior to the start of emicizumab. The median duration of follow-up until September 1, 2023, was 16.4 months (range: 7.7 - 27.3 months). The baseline ABR of patients was < 6 in two, 6 - 12 in 10, 12 - 18 in seven and > 18 bleeds per year in 13 patients. Eighty-five percent of the patients had more than two target joints at baseline. The median HJHS was 12 (range: 3 - 16, 25th percentile: 4; 75th percentile: 15), with the majority of patients having a score of more than 10 (59.2%). At baseline, five patients had to use a wheelchair, and seven had limping which impaired mobility. Five episodes of brain bleeds were reported in four HAI children and were managed with bypassing agents prior to the start of emicizumab. One child had bilateral thumb pseudotumors which were managed at another center previously with radiotherapy and on-demand rFVIIa without relief.

All doses of emicizumab were administered in hospital, and there were no significant adverse effects noted. No patient was tested for anti-drug antibodies, as there was no incidence of poor response. During this follow-up period, only two bleeds were noted: one patient had a spontaneous ankle bleed in a previous target joint, which was treated with one dose of rFVIIa (1 mg), while the other child developed an ecchymosis post trauma, which did not require treatment. The ABR reduced to 0 in all the other patients. Sixty-two percent of patients (20 patients) demonstrated complete clinical resolution of target joints, and 12 had residual contractures which improved with physiotherapy. The serial improvement in HJHS recorded every 6 months is demonstrated in Figure 1. The trough level sample was taken just prior to the next dose of the drug in September 2023. The mean drug level observed in standard-dose arm was 29.92 ± 2.53 µg/mL, and in low-dose arm it was 12.6 ± 3.79 µg/mL, respectively.

Few notable observations were absence of significant bleed or need for bypassing agents even after fracture femur or fall from 10 feet height noted in two children. One child with compartment syndrome of right forearm with neuropathy also improved without any residual deficits. The median baseline HJHS improved from 9 to 0 in children who received full dose and from 12 to 4 in those who received low dose at 12 months from initiation. On comparing the patients who received standard-dose (n = 7) vs. low-dose (n = 25) emicizumab prophylaxis, no difference was noted in the ABR or HJHS status following treatment (Table 1) despite difference in the trough levels,

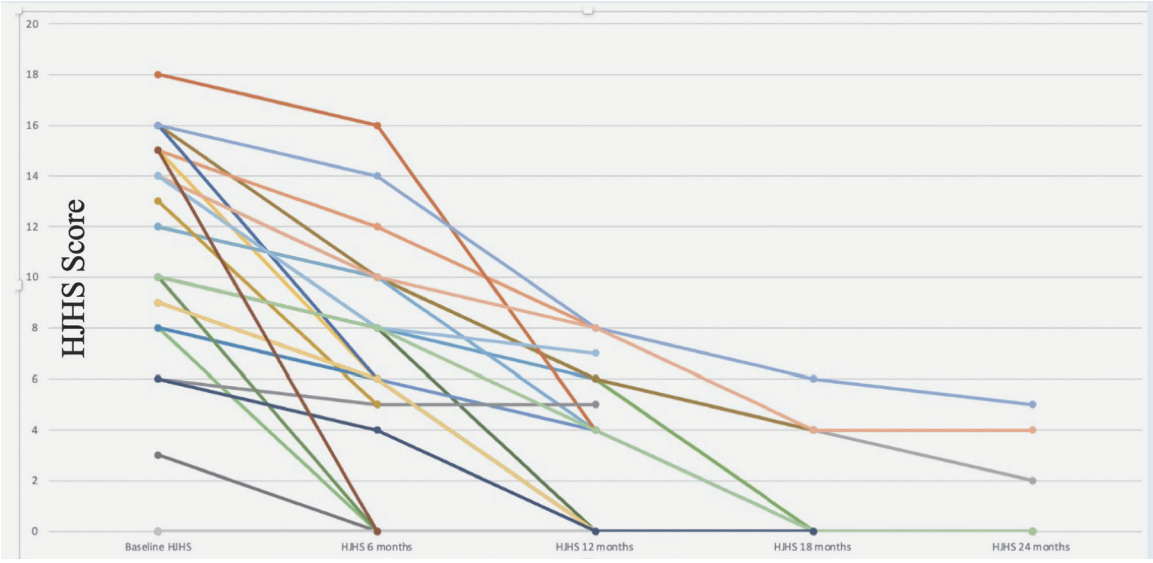

Figure 1. Improvement in HJHS recorded 6 monthly. HJHS: hemophilia joint health score.

thus demonstrating a lower hemostatic level for emicizumab which prevents spontaneous bleeding. All patients continued school regularly and participated in dancing, cycling and other activities.

Following drug level measurement in September 2023, since there was no difference noted between the two dose ranges in terms of bleeding, the standard-dose patients were also shifted to low dose. Subsequently, 18 more patients were started on low dose without loading dose and are continuing treatment for over a year. At present, a total of 50 patients are thus being continued on this low-dose arm (Fig. 2).

The drug is currently available in India through a patient access program. With the patient access program in place, the drug is available in India at $5.43 per milligram and Indian rupees (INR) 452 per milligram (INR 13,560 per 30 mg vial with patient access program). For a child weighing 10 kg, the dose calculation as per standard dose (3 mg/kg weekly for 4 weeks followed by once in 2 weeks) is compared with the lower dose (3 mg/kg once in 4 weeks without a loading dose) in Table 2. This is significantly less than aPCC, which is available currently at $312 per 500 IU vial, and rFVIIa is available at $529 for 1 mg vial. The management of a single joint bleeding for a 10 kg HAI child, with aPCC at a dose of 50 IU/kg/dose, twice a day for 4 days would cost $2,501, and with rFVIIa at 1 mg thrice a day, for 2 days would cost $3,174, both of which are more than the treatment cost for a year on low-dose emicizumab (Table 3). Moreover, bypassing agents are effective for acute care and do not offer sustained levels and benefit of prophylaxis. To add to this, over the course of time, there will be less visits to hospital emergency and rehabilitation center, less need for joint surgeries and better schooling and job opportunities. The functional independence scoring as per Pediatric Hemophilia Activities List (PedHAL), quality of life score as per Hemophilia Quality of Life (HemoQOL) and patient- and parent-reported outcomes are being documented and analyzed separately.

Discussion

Since the advent of non-factor replacement therapies, there has been a sea change in the management of hemophilia patients,

Table 1. Comparison Chart of Patients on Standard- Versus Low-Dose Emicizumab

N	Standard dose (N = 7)	Low dose (N = 25)
Median age in years (range)	8 (5 - 11)	12 (3 - 28)
Median duration of follow-up in months (range) till September 2023	27 (24.5 - 27.3)	13.5 (7.7 - 24)
Median baseline HJHS	9	12
Median post treatment HJHS at 6 months of prophylaxis (P = 0.69)	6	6
Median post treatment HJHS at 12 months of prophylaxis (P = 0.89)	0	4
Baseline ABR (median)	15	16
Treated bleeds within 6 months of starting emicizumab	0	1
Median post-treatment ABR at 12 months of prophylaxis (P = 0.96)	0	0 (1 treated bleed)

HJHS: hemophilia joint health score; ABR: annualized bleeding rate.

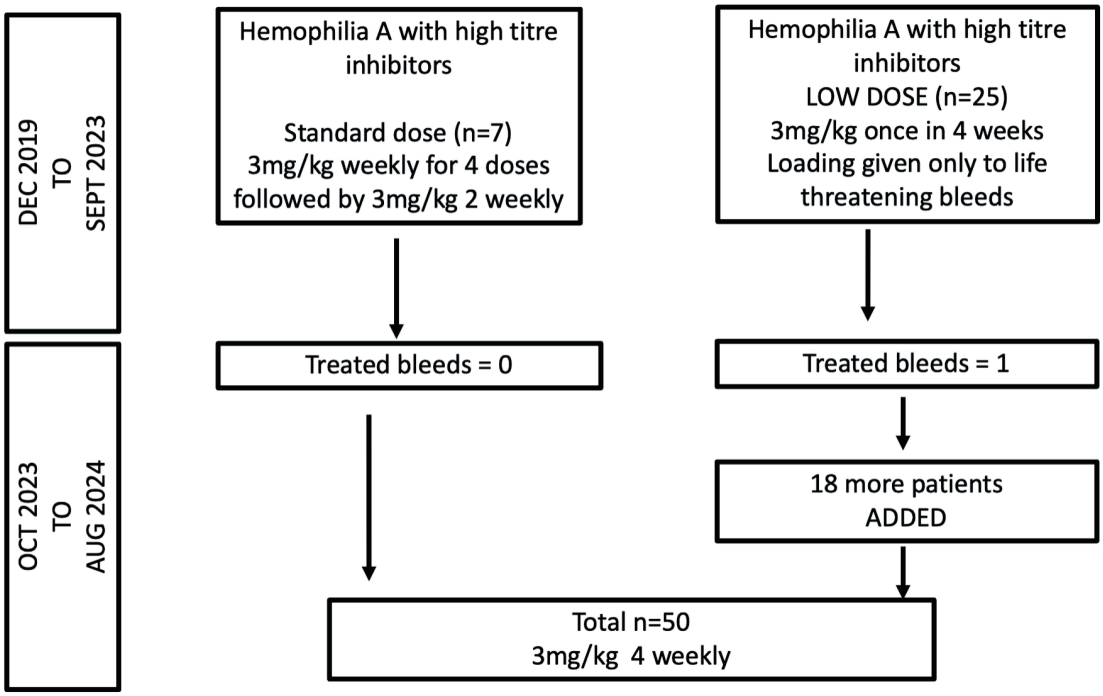

Figure 2. Follow-up of patients on both dose ranges of emicizumab. DEC: December; SEPT: September; OCT: October; AUG: August.

with or without inhibitors. Emicizumab has been available in India since April 2019, and we have previously published our initial experience with patients who received the drug [3, 4]. In the HAVEN 3 and 4 trials, zero bleed rate was documented in 50% of patients on a maintenance dose of 1.5 mg/kg, once a week, 40% on 3 mg/kg, once in 2 weeks, and 29% on 6 mg/kg, once in 4 weeks [6-8]. The drug was subsequently approved for use in hemophilia A patients with or without inhibitors. Across the consecutive HAVEN trials, almost 600 patients from infancy to adults, as well as severe to mild hemophilia, have been enrolled.

The real-world experience of efficacy of this treatment in hemophilia patients was reported by many centers subsequently [3, 9-12]. Various lower doses have subsequently been tried and few published. In our earlier limited experience of

Table 2. Cost Incurred for a 10-kg Child With HAI on Emicizumab With the Patient Access Program

	Year 1 (cost/ number of doses)	Year 2 onwards (cost/ number of doses)
Standard-dose emicizumab	$4,628	$4,269
	INR 379,680	INR 352,560
	For 28 doses	For 26 doses
Low-dose emicizumab	$2,134	$2,134
	INR 203,400	INR 203,400
	For 13 doses	For 13 doses

HAI: hemophilia A patients with inhibitors; INR: Indian rupees.

Table 3. Cost Incurred for Treating a 10 kg Child With Bypassing Agents for a Single Joint Bleed

	Average dose used for one bleed for 10-kg child	Cost per bleed
aPCC	50 IU/kg/dose twice a day, for 4 days	INR 208,000
	Modeled at cost of INR 26,000 per 500 IU vial	
rFVIIa	1 mg thrice a day for 2 days	INR 264,000
	Modeled at cost of INR 44,000 per 1 mg vial	

rFVIIa: recombinant factor VIIa; aPCC: activated prothrombin complex concentrates; INR: Indian rupees.

four patients, we reported 100% zero spontaneous bleed rate at standard and low rates [3, 4]. A recent study from India, which analyzed the bleeding profile, joint score, plasma emicizumab levels, non-activated thromboelastography and direct costs of treatment, in 10 patients on low-dose emicizumab vs. low-dose factor VIII prophylaxis, also reported all outcome measures to be significantly better in the low-dose emicizumab, compared to the FVIII prophylaxis arm. The direct cost of low-dose emicizumab was calculated to be $6,000, which was < 50% of that of the standard-dose one [12]. Another work from India involving eight patients, in which the dose was between 0.8 and 2.6 mg/kg, 4 weekly, mainly in inhibitor-positive patients, after 2 years of being on standard dose, reported bleed-free status after 1 year of reducing the dose, even with trough plasma values of between 7.3 - 11.9 µg/mL [11]. This is comparable to the value of 12.6 ± 3.79 µg/mL in 25 of our patients on low dose. These three studies from India including the present work [10, 12] with a total sample size of 68 patients on low-dose emicizumab prophylaxis, thus reliably report efficacy of the product at near 50% of the prescribed dose and trough levels, which opens up an avenue for providing care for more patients with limited resources. The use of doses as low as 0.8 - 1.6 mg/kg, once in 4 weeks without loading dose, has been reported by centers in other countries as well. It was noted to maintain the factor VIII equivalent level of 1-3% as against 15% in the standard-dose patients. The benefit was noted in quality of life, and participation in school and activities. In addition, the drug also offers an advantage of reduced hospital visits and subcutaneous injections.

We report the real-world experience of managing a very high bleeding cohort of patients who had previously no access to any drug for prophylactic use. Bypassing agents are helpful only for the acute bleed, and often most centers do not have enough drug for long-term use. It is noteworthy that only one spontaneous joint bleed was noted in 568.8 months of cumulative treatment for the initial 32 patients, followed by an additional 12 months of care for a total of 50 patients. This is significant especially in the setting of the high ABR, as evidenced by 20 patients having a bleed rate of more than 12 in this cohort prior to initiating the drug. The study demonstrates how monoclonal agents that are currently licensed as well as those in the pipeline will be the game changer in hemophilia care, offering not only the advantage of subcutaneous products and less hospital visits, but also near-zero bleeds even at lower-dose range. It offsets not only the direct costs as has been demonstrated here, but also reduces the out-of-pocket expenses of the family by reducing hospital visits and medical infrastructure costs due to subcutaneous administration, lesser or probably no need for joint replacement surgeries in the future for these children. It also offers the promise of better school and job attendance and lesser chance of disability, as well as more employment opportunities for these patients.

As per the Annual Global Survey (AGS) from World Federation of Hemophilia for 2022, 607 patients with inhibitor-positive hemophilia are reported from India [13]. Around 93 countries out of the 125 countries that submitted data to the AGS 2022 have reported usage of emicizumab. It has been reported that only around 25% of middle-income economies and < 10% of low-income economies have access to this agent despite being licensed for more than 5 years. Ironically, these are countries where the drug would have a larger impact, as the access to bypassing agents, hospitals caring for inhibitor-positive patients, and access to surgeries, etc., are limited. The World Bleeding Disorder Registry also reports that the impact of hemophilia on the productivity of the patient decreases with successively higher gross national income category, thus highlighting better access to care in higher income countries [14].

India, although not listed in this AGS report for inhibitor treatment, has availability of emicizumab since 2019, initially through direct purchase and now largely through state governmental supply. Out of 16 states that are providing support for close to 2,000 patients in India, it is refreshing to see remarkable changes in certain state states. The state of Kerala in India has started providing emicizumab prophylaxis for all children (0 - 18 years) with hemophilia who are native to this state [15]. The state of Uttar Pradesh where our center is located has also been providing treatment with emicizumab since 2020 in five of its 26 centers for hemophilia care and is currently supporting 130 patients.

In a setting of inequitable distribution of treatment support for hemophilia globally, especially inhibitor positive patients, strategies such as this, which provide the promise of supporting more patients and have emerged from low- and middle-income economies, can provide a solution for more countries to manage their difficult patients [16]. The limitation of this work is that it is not a randomized trial, and the numbers of patients on both arms (standard-dose and low-dose) are disparate. All published experience to date in this regard are also case series, and this question would benefit from a randomized trial which includes difficult bleeds, such as intracranial bleeds, pseudotumors, surgical management, etc., in both arms for a definitive answer. As the low-dose practice parameter for FVIII prophylaxis found its place in the World Federation of Hemophilia guidelines, emicizumab in low dose also can improve the access to care for over 50% more patients in any given healthcare sector without compromising efficacy.

Conclusions

This work provides the largest and longest experience of emicizumab in patients from India and other lower and middle-income economies with high-titer inhibitors with encouraging response, even at a lower than usual dose. The paper also demonstrates comparable outcome of two doses, which is substantiated by low trough levels which were 50% of the dose range demonstrated in the HAVEN trials. The study provides benefits especially for inhibitor-positive children who suffer from pre-existing arthropathy and poor joint status as a result of inequity in availability of bypassing agents. We also demonstrate that provision of non-factor replacement with physiotherapy is helpful reversing target joints and pre-existing joint morbidity and high joint scores, thus offering the possibility of reversing disability. This has translated to functional independence and better life, thus proving to be an effective strategy even for LMICs. With the available resources, the lower dose offers access to treatment for at least 50% more patients, thus opening

up a huge opportunity in the setting of extreme inequity and with the promise of reduced bleeds and a disability-free life.

Acknowledgments

The authors would wish to thank the National Health Mission, Uttar Pradesh and Government of India for their visionary support in treatment of these patients.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained.

Author Contributions

NR, SV, EPB and ArP managed patients and were involved in the manuscript and its revisions. SS and AP were involved in lab diagnosis and monitoring of all patients. All authors were involved in the preparation of the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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