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Compliance score as a monitoring tool to promote treatment adherence in children with thalassemia major for improved physical growth

Sarala Kannan, Amarjeet Singh

Abstract:

BACKGROUND/HYPOTHESIS: Creeping monotony in the treatment provides minimal motivation for children with beta-thalassemia major, leading to noncompliance for adequate blood transfusions and iron chelation therapy. This study was envisaged to formulate a clinical compliance score and correlate the score with their linear growth velocity and weight gain.

MATERIALS AND METHODS: A prospective longitudinal study among 30 thalassemia children aged between 1 and 18 years was conducted in the Department of Pediatrics, Tata Main Hospital (TMH), Jamshedpur, from July 2012 to January 2014. Relevant clinical information and investigations were recorded using a predesigned pro forma. Compliance score was calculated using pre-, post-transfusion hemoglobin and serum ferritin levels. The height velocity and weight gain were calculated. The same patients were re-assessed in January 2015.

RESULTS AND DISCUSSION: Mean age of children was 10.18 ± 4.98 years. Forty percent were females. Using the scoring table, 33% were in good category of compliance while 4% had poor compliance. The mean height velocity was significantly higher in good compliance category as compared to average or poor score category in 2014 ($P = 0.017$). Good compliance score children continued to maintain higher height velocity during the 1-year follow-up ($P = 0.02$). Average weight gain was higher in good compliance category.

CONCLUSION: This paper brings out a simple, regularly monitored scoring system to promote growth in thalassemia children through improved compliance to treatment, which incentivized them to maintain or improve their scores for better height velocity and weight gain. No such compliance score has been tabulated for thalassemia patients as of date.

Keywords:

Compliance score, ferritin, iron chelation, pretransfusion hemoglobin, thalassemia major

Introduction

The increasing mean survival age of thalassemia patient is indicative of the fact that modern therapies are generally safe and effective; however, as patients approach the age of puberty, many develop growth retardation and pubertal failure.^[1] The established treatment for beta-thalassemia major is based on regular blood transfusions (BTs) to maintain the pretransfusional hemoglobin (Hb)

level above 9 g/dl which causes iron overload. Transfusion hemosiderosis has been implicated as a major cause of growth retardation due to endocrine dysfunctions including hypothyroidism, gonadal failure, hypoparathyroidism, decreased growth hormone (GH) levels, and diabetes mellitus.^[2] Tissue damage occurs due to free radical formation and lipid peroxidation, resulting in mitochondrial, lysosomal, and sarcolemmal damage with increased collagen deposition secondary to increased activity of the iron-dependent

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Department of Pediatrics
and Neonatology,
Tata Main Hospital,
Jamshedpur, Jharkhand,
India

Address for correspondence:

Dr. Sarala Kannan,
Department of Pediatrics,
Tata Main Hospital,
Jamshedpur, No. 46,
Dindli Enclave Kadma,
Jamshedpur - 831 005,
Jharkhand, India.
E-mail: sunsar9120@
gmail.com

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protocollagen proline hydroxylase enzyme activity. Therefore, appropriate chelation therapy also is extremely important as part of thalassemia treatment to avoid the consequences of iron overload.

Repeated admissions for BTs and iron chelation create in the minds of the patients and their parents several questions regarding the physical growth prospects and life span. Creeping monotony of hypertransfusion and iron chelation in thalassemia patients provides minimal motivation, leading to noncompliance for treatment. Growth retardation and pubertal failure are often accepted as a part of the disease by most of them. To motivate patients to remain compliant to the treatment regimen for better growth, an attempt was made to keep them committed to the treatment protocol through a simple objective score understood by the child itself.

Aims and objectives

The aims of this study are as follows:

- To tabulate a compliance scoring system in regularly transfused β -thalassemia patients that incorporates pre- and post-transfusion Hb (adequate transfusions to prevent hypoxia) and serum ferritin levels (adequate chelation to prevent iron toxicity effects on tissues)
- To correlate the above compliance score to linear growth velocity and weight gain
- To establish a correlation between the growth parameters and compliance score category at 1-year follow-up.

Materials and Methods

Beta-thalassemia patients with positive Hb electrophoresis aged 1–18 years admitted to the Pediatric Ward of TMH, Jamshedpur, were included in the study. The sample size comprised 30 patients with a prerequisite of BT of at least 6/year. The study period evaluated thalassemic children over a period of 30 months from July 2012 to December 2014. The first 18 months relevant clinical information and investigations were recorded using a predesigned pro forma, which included Hb levels, details of chelation therapy, height in centimeters, and weight in kilograms. The children were assigned compliance scores, and records of their height velocity and weight gain were maintained. Over the next 12 months, the same children were reassessed for the height velocity and weight gain. Patients with other hemoglobinopathies/hemolytic anemia and comorbid diseases such as diabetes mellitus, hypothyroidism, and cardiac complications were not included in the study.

Investigations included pre- and post-transfusion Hb for every admission for BTs. Random blood sugar was done once. Serum ferritin was measured using the ferritin kit supplied by Bioplus, based on enzyme-linked

immunosorbent assay, and was done once in 6 months. GH levels were estimated once during the study.

As the mainstay of thalassemia treatment is adequate blood transfusion (posttransfusion >11 g/dl), and iron chelation (serum ferritin <1000 ng/ml), a novel approach to measure treatment compliance and motivation to improve their scores objectively was initiated and a compliance score was tabulated [Table 1].

Average pretransfusion Hb, over a period of 6 months (PreHbH1, PreHbH2, PreHbH3), and an overall average (PreHbH1+PreHbH2+PreHbH3 divided by 3) for 18 months were calculated. Similarly, average posttransfusion Hb for the same period was also calculated. The above data showed how low the Hb fell before a patient came for BT and how many units of blood he/she took to raise the Hb before getting discharged. Serum ferritin levels were measured at the 0, 9th, and 18th months of the study. Average serum ferritin was calculated (F1+F2+F3/3) and a compliance score was formulated as below. The following table shows a representative calculation.

Table 2 shows compliance score calculation of a representative patient whose average pre-BT Hb ranged between 8.1 and 9 g/dl, posttransfusion Hb between 10 and 11g/dl, and the serum ferritin between 2001 and 3000 ng/ml. This patient has been categorized as average compliance and could be motivated to be in the category of good compliance. Scores were calculated for all the patients to help them not only maintain records but also motivate them to come early for iron chelation and BT. On each visit during the study, parents and children were counseled about compliance for treatment.

Statistical analysis was done using SPSS 16 software. Comparison of means was done using independent sample *t*-test/ANOVA. Correlation was calculated using Pearson's correlation coefficient.

Results

The sample size comprised 30 patients aged ranging between 1 and 18 years (10.18 ± 4.98). Males constituted 60% of the study group. Sex distribution is shown in Table 3.

The average age of diagnosis of β -thalassemia was 10.9 ± 6.7 months and the age of first BT was 7.9 ± 2.0 months. Average frequency of BT was once every 27.4 ± 6.5 days. Average pre- and post-BT Hb levels varied in patients as described in Figures 1 and 2.

While only 13.3% of the study group took adequate BT to raise their Hb above 11 g %, 76.6% of the children

Table 1: Calculation of parameters for compliance score

Date	Pretransfusion Hb (on admission)	Posttransfusion Hb (after 24 h)	Serum ferritin
First 6 months of the study H1	Average pretransfusion Hb for H1	Average posttransfusion Hb for H1	F1 (start)
Second 6 months of the study H2	Average pretransfusion Hb for H2	Average posttransfusion Hb for H2	F2 (midway)
Third 6 months of the study H3	Average pretransfusion Hb for H3	Average posttransfusion Hb for H3	F3 (end)
Average values considered for compliance score	H1+H2+H3/3	H1+H2+H3/3	F1+F2+F3/3

Hb=Hemoglobin

Table 2: Compliance score

Compliance scoring for thalassemia patients with respect to treatment regimen (representative patient)

Average pretransfusion Hb		Average posttransfusion Hb		Oral/IV chelation to maintain average serum ferritin (ng/ml)	
Range	Points	Range	Points	Range	Points
10.1-11	5	>12	5	<2000	5
9.1-10	4	11.1-12	4	2001-3000	4
8.1-9	3	10.1-11	3	3001-4000	3
7.1-8	2	9.1-10	2	4001-5000	2
<7	1	<9	1	5001-6000	1

Scoring

3-5	Poor
6-10	Average
11-15	Good

IV = Intravenous

Table 3: Sex distribution within the age group

Sex distribution within the age group

Age group	Total patients	Male	% Of males	Female	% Of females
1-5 Years	8	5	27.8	3	25.0
6-10 Years	6	2	11.1	4	33.3
11-15 Years	10	8	44.4	2	16.7
16-18 Years	6	3	16.7	3	25.0

took BT when their Hb levels fell to around 8 g %. The average pretransfusion Hb was 8.34 ± 0.42 g/dl and posttransfusion Hb was 10.17 ± 0.79 g/dl during the study period of 18 months. Iron chelation was taken by 27 patients (90%), of whom 23 of them started iron chelation after delay, i.e., >15 BTs or serum ferritin >1000 ng/ml, while four of them had started iron chelation at the right time, i.e., serum ferritin <1000 ng/ml [Figure 3]. Fifteen patients of the study group had started iron chelation before the age of 5 years. Oral deferiprone was taken by 23 (76.6%) of them while four patients were on deferasirox. Three cases aged 2–3 years, whose serum ferritin was between 500 and 600 ng/ml, were not on chelation therapy and are on follow-up. One-third (33.3%) of the patients, in addition to the oral iron chelation therapy, were on intravenous (IV) desferrioxamine.

The average serum ferritin for the whole of the study group was 2683 ± 1478 ng/ml; the lowest being 350 ng/ml and the highest being 6275 ng/ml [Figures 4].

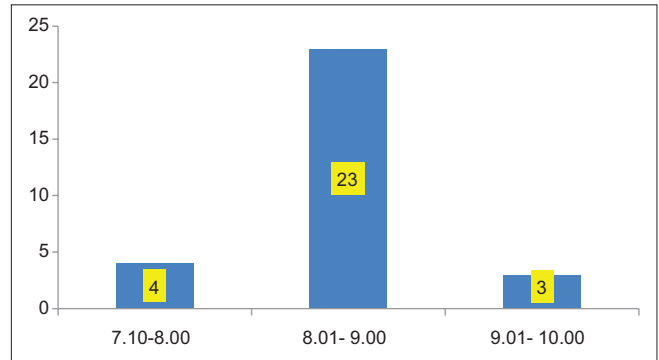


Figure 1: Average preblood transfusion hemoglobin

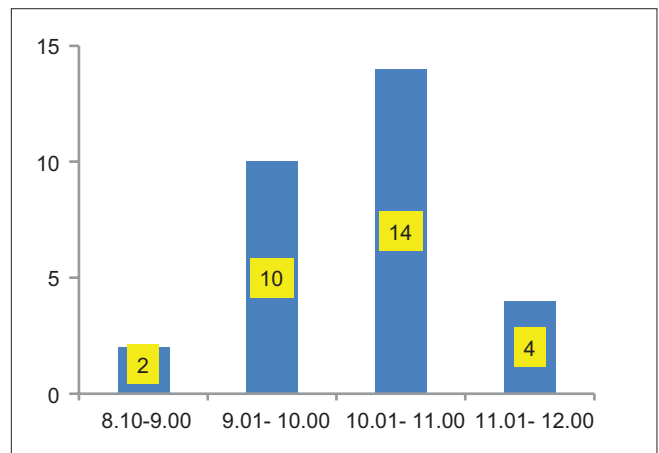


Figure 2: Average postblood transfusion hemoglobin

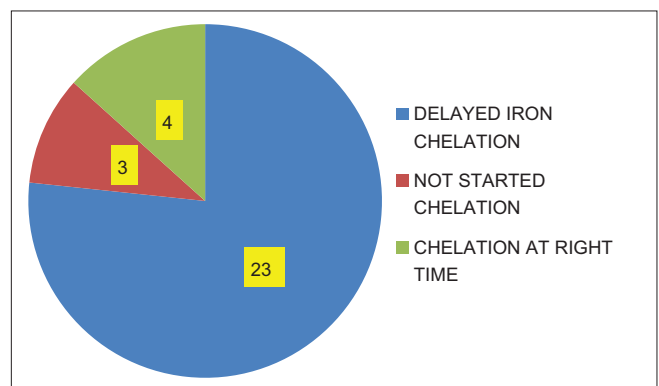


Figure 3: Iron chelation status

Compliance score for study group ranged from 4 to 13 out of a maximum of 15. Mean compliance score was 9.3 ± 2.2 . We found that 63% were in the

average compliance category, 33% categorized as good compliance, and 4% poor [Figure 5].

During the first 18 months of the study, 20 of 30 patients (66.6%) had a normal height velocity [Figure 6].

Average weight gain during the first 18 months was 2.83 kg, and it was seen that 16 children were below the average weight gain of the group [Figure 7].

Correlation of compliance score with descriptive was done as shown in Table 4; height velocity and compliance score showed moderate positive correlation (Pearson's correlation coefficient = 0.573). Higher the compliance score greater is the velocity; therefore, the good compliance category had better linear growth ($P = 0.001$). ANOVA between the three compliance category groups showed that the mean height velocity was significantly higher in good compliance category as compared to average or poor score category in 2014 ($P = 0.017$).

Weight gain and compliance score again showed moderate positive correlation (correlation coefficient = 0.396); higher the compliance score greater is the weight gain

($P = 0.03$) ANOVA between the three compliance category groups showed that the mean weight gain was significantly higher in good compliance category as compared to average or poor score category in 2014 ($P = 0.002$).

Average serum ferritin levels and height velocity showed a negative correlation ($r = -0.611$); lower the average serum ferritin, better is the height velocity, and this value for the study was statistically significant ($P = 0.000$).

Average serum ferritin and weight gain again showed negative correlation ($r = -0.274$). Weight gain is less when serum ferritin levels are high; however, this was not statistically significant in this study ($P = 0.142$).

On analyzing the average serum ferritin levels and GH between June 2012 and December 2013, the mean of average serum ferritin in low serum GH category was 4160 ng/ml, whereas in normal serum GH category, the mean of serum ferritin was 2310 ng/ml. Using the independent sample *t*-test between average serum ferritin during study period with the normal and low serum GH category, the difference was statistically

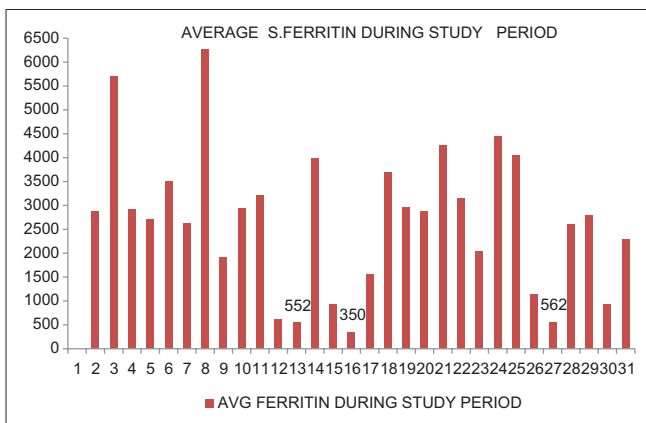


Figure 4: Average serum ferritin in the first 18 months of study

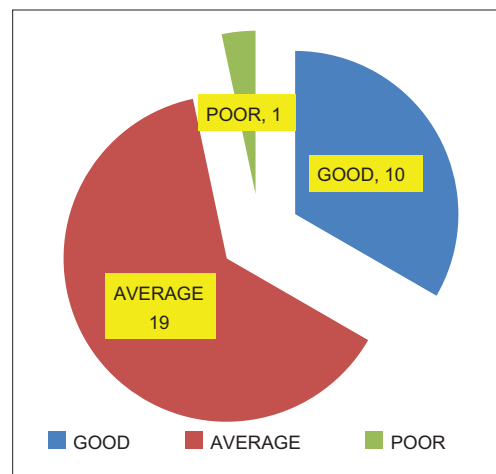


Figure 5: Compliance category among the group

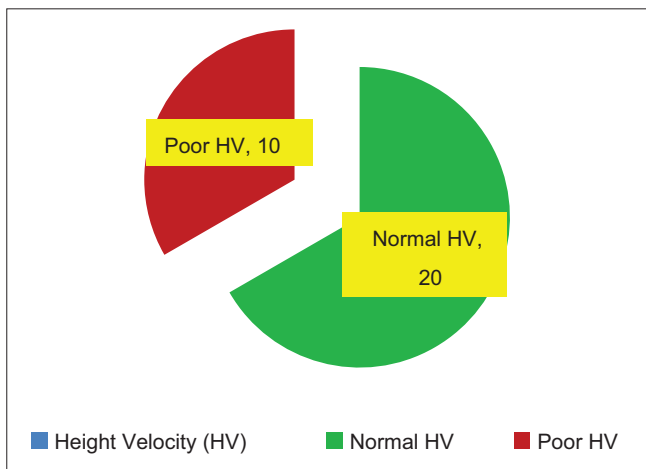


Figure 6: Height velocity of study group

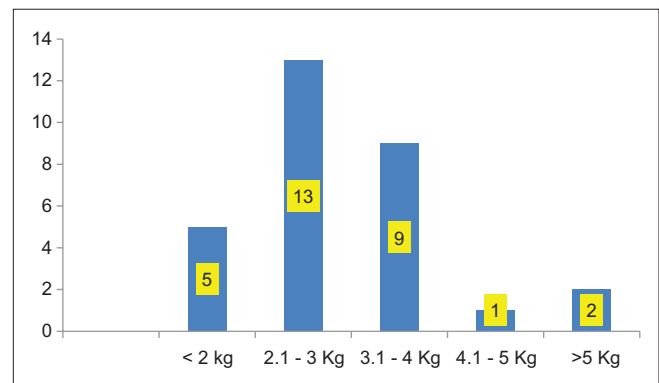


Figure 7: Weight gain of study group

Table 4: Correlation of compliance score with descriptive (first 18 months - July 2012 to December 2013)

No	Category	Pearson coeff. r value	Correlation	P	Significance	Anova
1	Height velocity and Compliance score	0.573	Moderate positive correlation	0.001	Higher the compliance score better the growth velocity	Height velocity was better in the good compliance category than the other groups ($P=0.017$)
2	Weight gain and Compliance score	0.396	Moderate positive correlation	0.03	Higher the compliance score better the weight gain	Weight gain was better in the good compliance category than the other groups ($P=0.002$)
3	Av.Serum Ferritin and Height velocity	-0.611	Strong negative correlation	0.000	Higher the ferritin lower the height velocity	NA
4	Av.Serum Ferritin and Weight gain	-0.274	Mild negative correlation	0.142	Higher the ferritin lower the weight gain	NA

significant ($t = -3.128$, $P = 0.004$). Higher the serum ferritin levels, more the GH deficiency.

Correlation of height velocity and weight gain in different compliance categories during follow-up in the last 12 months, i.e., January 2014 to December 2014, was done.

ANOVA between the three compliance category groups at follow-up again showed that the mean height velocity was significantly higher in good compliance category as compared to average or poor compliance category ($P < 0.05$).

Mean weight gain among the three compliance category groups was not statistically significant ($P > 0.05$) [Table 5].

Discussion

This study conducted at TMH situated in Jharkhand with a large tribal population has a high incidence of hemolytic anemia, namely, sickle cell anemia and thalassemia, some of them being sickle – thalassemia. In our hospital, free blood is available for thalassemia and sickle cell anemia patients; however, non entitled private patients pay for bed charges and investigations.

This being a pilot study, the significance of chronic hypoxia and suboptimal iron chelation in relation to growth retardation and short stature in thalassemia children was established through previous studies. No other study has attempted compliance scoring in thalassemia. Since, pretransfusion Hb, posttransfusion Hb, and serum ferritin levels are the sole parameters depicting hypoxia and iron overload, in this study, each of these parameters used for compliance score calculation was conclusively established from previous studies. George *et al.*^[1] reported that growth parameters were severely retarded in children with Hb level less than 8 g/dl probably, secondary to chronic hypoxia and iron overload. Hamidah *et al.*^[3] found that the prevalence of impaired growth velocity (i.e., growth velocity less than the third percentile) among the transfusion-dependent prepubertal thalassaemic was 57.7% compared to 19.2% in the control

Table 5: Height velocity and weight gain during follow-up period of study

Compliance category (n)	Mean height velocity (cm)	P	Mean weight gain (kg)	P
Good (10)	5.34	<0.05	2.76	>0.05
Average (19)	3.56		2.48	
Poor (1)	1.9		1.3	

group. Studies correlating growth in thalassemia children by Shah *et al.*^[4] and Eshghi *et al.*^[5] concluded that type of iron chelation therapy and age of beginning chelation therapy are significant. Wonke *et al.*^[6] reported that growth retardation in iron-overloaded patients is the result of GH deficiency in up to 30% of patients. All these studies emphasize the role of hypoxia and iron load on the growth of thalassemia children. Therefore, in this study, analysis was made using similar criteria.

Early discharge request due to academic, social, or financial reasons was the cause for under transfusion in our present study. In a study by Ragab *et al.*,^[7] the mean pretransfusion Hb level was 5.7 ± 1.16 g/dl, which was related to the low availability of blood due to low rate of blood donation as this blood was given to the patients free of charge. In our study, the mean pretransfusion Hb was 8.34 ± 0.42 , which is higher than the above study. Blood donation camps are frequently held in and around Jamshedpur encouraged by Tata Steel and its associated companies, and blood is freely available except during the peak summer months.

Sub-optimal iron chelation was also seen in our study which can lead to growth retardation. Strong negative correlation between average serum ferritin and height velocity was statistically significant ($P < 0.05$) as seen in Table 4. Lack of awareness and financial reasons were the prime reasons for not getting the serum ferritin done at the optimal time for starting iron chelation in our study.

Delea *et al.*^[8] and Scalone *et al.*^[9] in their studies have identified the costs of noncompliance to therapy in thalassemia children. Lee *et al.*^[10] in their study showed that the positive association between knowledge and

treatment adherence and factors of patients' knowledge indicates the need for systematic education for patients and caregivers to improve adherence to treatment. Another study by Pedram *et al.*^[11] from Iran reported that on testing compliance among three groups, it was seen that compliance adherence was achieved only in 18.2% of patients (first group) and compliance adherence was improved by close surveillance of desferrioxamine infusions and psychology intervention and social workers activity in 31.3% (second group). Despite everyday encouragement, compliance was not achieved in 48.8% (third group) and overall outcome was poor. In an online publication about increasing compliance in thalassemia treatment, Yahia^[12] showed that oral iron chelation regimens are more acceptable to patients which can increase compliance to treatment.

A thesis study for university of Toronto on methods of assessing compliance with chelation therapy in thalassemic patients was done by Dr. Pope and Dr. Koren.^[13] Measurement of patient compliance to chelation therapy was done through pill count, patient diary, and medical event monitoring systems. Biochemical methods used for measuring chelation compliance were urinary iron excretion, serum ferritin, liver iron content, etc. Vullo and Di Palma^[14] initiated a program to improve compliance, which included both physician and patient education and the administering of calendars to adolescents to help them keep track of their treatment schedule. This regulated approach revealed a decrease (20% to 3%) in the number of individuals who refused therapy over a period of 3 years.

So far, many studies have shown that improved awareness, psychotherapy, close surveillance, and oral iron chelation play a role in treatment adherence and improved compliance. However, none of the studies so far have provided an objective scoring to improve compliance in these children as done in this study. In our study, the compliance score assigned to the patient on the basis of pretransfusion Hb, posttransfusion Hb, and average serum ferritin level acts as a motivating factor to improve their growth/anthropometric parameters. This addresses the problem of inadequate chelation therapy and thereby improves compliance with chelation therapy amongst our patients. Peer comparison on the patients with better compliance scores motivates parents to bring the children for BT and iron chelation. Therefore, this study emphasizes the importance of monitoring growth parameters as a report card to improve BTs and optimize iron chelation therapy in these patients.

We presume that this can help clinicians and caretakers all over the world promote compliance to treatment regimen among patients. Though this score requires extensive validation and improvement, in this study,

we used the compliance score mainly as an objective tool to motivate the patients to get optimal BT, continue their oral iron chelators, and get admitted for IV iron chelation. This kind of compliance scoring system for thalassemia treatment has not been found in literature as yet.

Conclusion

There are no studies as yet to bring out a simple objective score to improve and motivate patients for growth in thalassemia children. Though this score may need revisions and refinement, a novel approach has been implemented for the betterment of those children. The authors would like to name the compliance score as "SARALJEET SCORE" as it is the pioneer scoring system that has been developed to honor the first author and the resident who had been instrumental in the study.

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Nil.

Conflicts of interest

During the study, Dr. Amarjeet was a student doing his DNB residency under the guidance of Dr. Sarala Kannan. After the thesis completion, the follow-up data were collected by Dr. Sarala Kannan and the paper is being sent for publication.

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