

Serum Ferritin Level as a Predictor of Disease Severity in Patients with Dengue Infection

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Abstract

Original Research Article

Background: Dengue infection is a major public health threat. The clinical spectrum of dengue infection is variable from mild fever to severe forms. Early laboratory diagnosis of dengue fever is important to provide appropriate treatment to the patients and to prevent potential complications. Although there are various biomarkers to predict the severity of dengue, they are not routinely used in clinical practice for prognostication. This study evaluated the performance of serum ferritin to predict the severity of dengue at an earlier stage as it is an inexpensive and easily accessible biomarker. **Methods:** Total 62 patients with diagnosis of dengue fever were enrolled after final selection. Serum ferritin levels of all the patients were measured on the day of admission. Patients were then divided into two groups on the basis of ferritin level. Group A comprising those with normal level and those having raised level were included in group B. Patients were then regularly followed up both clinically and biochemically during their hospital stay to see disease progression. Discharge from the hospital without complications or death of the patient during the hospital stay was the end point of the study. Every patient was managed according to the National Guideline for Clinical Management of Dengue Syndrome. **Results:** Most of the respondents (58.1%) belonged to the age group of 18-30 years with male predominance (69.4%). A significant association was found between the BMI of respondents & the groups ($p < 0.05$). Highly significant association was reported among mucosal bleed (37.1%), clinical fluid accumulation (29.0%) & liver enlargement (30.6%) with ferritin level ($p < 0.001$). A positive correlation was found between serum ferritin & hematocrit level of the respondents ($r = 0.719$; $p < 0.001$) and a negative correlation was found between serum ferritin & platelet level of the respondents ($r = -0.857$; $p < 0.001$), both of which were highly significant. Patients with high level of ferritin had severe dengue (71.4%) infection ($p < 0.05$) and stayed longer time (> 8 days) (57.1%) in hospital. **Conclusion:** Increased serum ferritin level was most commonly found in severe dengue infection patients, which helped to establish the disease severity. Therefore, serum ferritin measured during early disease course can be used as a marker to predict the severity which helps to triage and manage them appropriately.

Keywords: Serum Ferritin Level, Predictor, Dengue Infection.

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INTRODUCTION

Dengue infection poses a major health problem in tropical and subtropical countries. [1]. According to World Health Organization (WHO), around 50 to 100 million new infections are estimated to occur every year in more than 100 endemic countries across the world; of which around 500,000 people with severe dengue require hospitalization each year and about 2.5% of those affected die [2].

The burden of the disease is so much that in the year 2012 WHO classified the disease as “the most important viral disease that is transmitted by mosquitoes”. [3]. In Bangladesh, dengue fever was first

reported in 1964 but became a disease of public health significance from 2000 onwards. [4]. Bangladesh had a lower dengue prevalence than most Southeast Asian states, but recently has sustained an upsurge in dengue outbreaks; from 2769 cases in 2017 to 10,148 cases in 2018 [5].

Dhaka, the capital and most populated city in Bangladesh, had the highest number of dengue cases between 2012 and 2019. [6]. In 2019, the Directorate General of Health Services (DGHS) recorded 101,354 cases with 179 deaths, a 10-fold increase in the incidence rate of dengue from the previous year. [7]. Although in 2020, Bangladesh had reported only three

confirmed dengue-related deaths and 1,193 dengue cases, the scenario is different in 2021 and 2022. Bangladesh has witnessed 28,429 dengue cases and 105 deaths in 2021 and 16,092 cases with 55 deaths already from January to September 2022 [7].

Dengue is caused by dengue virus (DENV) serotypes 1-4 and transmitted to human beings by the bite of Aedes mosquitoes [8]. The Bangladesh Council of Scientific and Industrial Research (BCSIR) found a new variant of the dengue virus that was more infectious and deadly as the country grappled with a surge in dengue cases in 2021. [9]. DENV-1 and DENV-2 were already present in the country.

BCSIR in its genome sequencing found the presence of the DENV-3. People were becoming increasingly infected with the new dengue variant and a higher death rate was found from dengue in 2021 compared to the dengue epidemic in 2019 in Bangladesh [9].

The clinical spectrum of dengue infection is variable from mild fever to severe forms of dengue manifesting as severe thrombocytopenia with major bleeding, plasma leakage resulting in fluid accumulation, respiratory distress, shock and multi-organ dysfunction. In clinical practice, patients with dengue infection are grouped as 1) those without warning signs 2) those with warning signs and 3) severe dengue.

Around the time of defervescence, when the temperature drops to 37.5-38°C or less and remains below this level, an increase in capillary permeability in parallel with increasing hematocrit levels may occur. In addition, severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock.

Those who improve after defervescence are said to have non-severe dengue. During recovery phase patient's general well-being improves, appetite returns, gastrointestinal symptoms abate, hemodynamic status stabilizes and diuresis ensues. The hematocrit stabilizes or may be lower due to dilutional effect of reabsorbed fluid, white blood cells count and platelet count begin to rise [10].

Severe dengue results from interplay between virus related virulence factors and host factors which include inflammatory response of the host to infection with exuberant T and B cell activation, release of cytokines (cytokine storm), altered endothelial function with increased vascular permeability and nutritional status of the host [11].

MATERIALS AND METHODS

Study Design: Prospective Observational Study

Place of Study: Department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, Dhaka.

Period of Study: From April 2022 to October 2022.

Study population:

Group A: Adults with the diagnosis of dengue fever with normal serum ferritin level.

Group B: Adults with the diagnosis of dengue fever with increased serum ferritin level.

Sampling Method: Purposive sampling

Sample size: So, sample size of this study was 62.

Inclusion Criteria

- Age \geq 18 of both genders.
- Confirmed dengue cases diagnosed by positive NS1 antigen and/or dengue IgM antibody.
- Who were willing to participate.

Exclusion Criteria

- Patients presenting with severe dengue.
- History of multiple blood transfusions.

Diagnosed Cases Of

- a) Malignant Tumors
- b) Hematologic Malignancies
- c) Chronic Inflammatory Diseases
- d) Autoimmune Diseases
- e) Chronic Hemolytic Diseases
- f) Chronic Kidney Disease
- g) Chronic Liver Disease
- h) Chronic Alcoholism
- i) Covid-19 Pneumonia

STUDY PROCEDURE

Patients admitted in the department of Internal Medicine, Bangabandhu Sheikh Mujib Medical University, with the diagnosis of dengue fever on the basis of history, clinical examination and positive NS1 antigen and/or positive IgM antibodies against dengue were included in this study. Enrollments of the patients were done by meeting the inclusion and exclusion criteria after taking written informed consent.

Each of the respondents was explained about the aim, importance and purpose of the study. With the informed written consent of the respondent, data was collected with questionnaire. All necessary data including the socio-demographic data, a detailed history of the fever and associated symptoms and the findings of a thorough physical examination were collected and recorded in structured data collection sheet.

Serum ferritin level of all the patients was measured on the day of admission. With all aseptic precautions, 2 ml of blood was collected from antecubital vein and samples were then kept in screw-

capped, air-tight, de-ionized Pyrex test tubes. To prepare the serum, blood was first allowed to clot for 1 hour and then the samples were centrifuged at -4°C at 3000 rpm for 5 minutes. Clear serum was transferred into an airtight, deionized polyethylene container for estimation of serum ferritin level.

Whenever there was a delay to process it, the samples were stored at -20°C for further analysis. Finally, serum ferritin estimation was performed on the same day by an expert post-graduate clinical molecular biochemist at the Department of Biochemistry, Bangabandhu Sheikh Mujib Medical University. Quantitative determination of serum ferritin was done by sandwich chemiluminescence immunoassay technique by LIAISON[®] Analyzer following standard procedure and as per instructions set out in operating manual. Patients were then divided into two groups on the basis of ferritin levels. Group A comprising those with normal ferritin level; those having raised level were included in group B. Other necessary investigations like complete blood count, serum creatinine, serum electrolytes, ALT, AST, Chest X-ray, ultrasound of abdomen, etc. were sent according to hospital protocol.

Patients were then followed up regularly during their hospital stay to see clinical improvement or development of severe dengue. Every patient was managed according to the National Guideline for Clinical Management of Dengue Syndrome. Discharge from the hospital without complications or death during the hospital stay was the end point of study.

Data Processing and Analysis

After collection of the data these had been checked, verified and edited meticulously to reduce error and recorded for quality management. A master sheet was prepared for data analysis which included all of the variables of the study. Continuous data were expressed as mean and standard deviation and categorical data were expressed as frequency and

percentage. Comparisons were made with student t-test and chi-square test between groups for continuous and categorical variables. Correlation between continuous variables was determined using Pearson correlation coefficient. Statistical significance was set as 95% confidence level at 5% acceptable error level ($p < 0.05$). The analysis finally was done using SPSS (Statistical Package for Social Science) windows program version 24.

RESULTS

A total of 62 patients were selected aged more than 18 of both gender with confirmed dengue cases were included into two groups. In Group A (41), adults with the diagnosis of dengue fever with normal serum ferritin level & in Group B (21), adults with the diagnosis of dengue fever with increased serum ferritin level were included. Most of the respondents (58.1%) belonged to the age group of 18-30 years with male predominance (69.4%). A significant association was found between the BMI of respondents & the groups ($p < 0.05$). Abdominal pain was the most common warning sign (58.1%). Highly significant association was reported among mucosal bleed (37.1%), clinical fluid accumulation (29.0%) & liver enlargement (30.6%) with ferritin level ($p < 0.001$).

Systolic & diastolic blood pressure had a statistically significant ($p < 0.05$) association with the groups on the day of admission along with 3 days after admission to the hospital. Mean value of pulse pressure was significantly correlated with the dengue patients on the day of admission to the hospital. A positive correlation was found between serum ferritin & hematocrit level of the respondents ($r = 0.719$; $p < 0.001$) and a negative correlation was found between serum ferritin & platelet level of the respondents ($r = -0.857$; $p < 0.001$), both of which were highly significant. Patients with high level of ferritin had severe dengue (71.4%) infection ($p < 0.05$) and stayed longer time (> 8 days) (57.1%) in hospital.

Table 1: Distribution of age of the respondents with ferritin level (n=62)

Age (in years)	Group A n=41 n(%)	Group B n=21 n(%)	Total n=62 n(%)	*P value
18-30	26(63.4%)	10(47.6%)	36(58.1%)	0.233
31-40	6(14.6%)	2(9.5%)	8(12.9%)	0.570
41-50	3(7.3%)	5(23.8%)	8(12.9%)	0.067
51-60	2(4.9%)	3(14.3%)	5(8.1%)	0.198
>60	4(9.8%)	1(4.8%)	5(8.1%)	0.494

Group A: Dengue fever with normal serum ferritin level

Group B: Dengue fever with increased serum ferritin level

*P Value Was Measured By Chi Square Test

Most of the respondents (58.1%) belonged to the age group of 18-30 years. In group A 63.4% respondents & in group B, 47.6% respondents belonged

to the 18-30 years of age group. There was no significant association found between age groups of the respondents & the groups ($p > 0.05$).

Table 2: Distribution of the respondents according to their BMI (n=62)

BMI (Kg/m ²)	Group A n=41 n (%)	Group B n=21 n (%)	Total n=62 n (%)	P value
Underweight (<18.5)	12(29.3%)	1(4.8%)	13(21%)	0.025
Healthy (18.5-24.9)	14(34.1%)	4(19.0%)	18(29%)	0.215
Overweight (25-29.9)	10(24.4%)	6(28.6%)	16(25.8%)	0.722
Obese (≥30)	5(12.2%)	10(47.6%)	15(24.2%)	0.002

*P Value was Measured by Chi Square Test

In group A, out of 41 respondents, healthy respondents were found 34.1% followed by 29.3% respondents who were underweight. In group B, out of 21 respondents, most of them were obese (47.6%)

followed by overweight (28.6%). A significant association was found between the respondents who were underweight & obese along with the groups ($p < 0.05$).

Table 3: Clinical presentations among the dengue patients (n=62)

Clinical presentations	Frequency (n)	Percentage (%)
Fever	62	100
Retro-orbital pain	57	91.9
Headache	50	80.6
Photophobia	16	25.8
Skin erythema/rash	20	32.3
Muscle or joint pain	52	83.9
Anorexia	44	71
Nausea& vomiting	40	64.5
Diarrhea	24	38.7
Constipation	7	11.3

*Multiple Responses

Regarding the clinical presentations of the dengue patients, all the patients had fever (100%) and most of the respondents (91.9%) had retro-orbital pain.

Rest 83.9% had muscle or joint pain & 80.6% had headache.

Table 4: Correlation of the warning signs of dengue patients with ferritin level (n=62)

Warnings signs	Group A n=41 n(%)	Group B n=21 n(%)	Total n=62 n(%)	*P value
Abdominal pain	21(51.2%)	15(71.4%)	36(58.1%)	0.127
Persistent vomiting	17(41.5%)	11(52.4%)	28(45.2%)	0.414
Lethargy	18(43.9%)	10(47.6%)	28(45.2%)	0.781
Increase in hematocrit concurrent with rapid decrease in platelet count	14(34.1%)	8(38.1%)	22(35.5%)	0.758
Mucosal bleed	3(7.3%)	20(95.2%)	23(37.1%)	<0.001
Clinical fluid accumulation	4(9.8%)	14(66.7%)	18(29.0%)	<0.001
Respiratory distress	2(4.9%)	1(4.8%)	3(4.8%)	0.984
Liver enlargement (>2cm)	3(7.3%)	16(76.2%)	19(30.6%)	<0.001

*P Value Was Measured By Chi Square Test

According to warning signs of the dengue patient, highly significant association was reported among mucosal bleed (37.1%), clinical fluid accumulation (29.0%) & liver enlargement (30.6%) with ferritin level ($p < 0.001$), these findings were more prominent among the dengue patients who had higher

ferritin level. Abdominal pain was the most common warning sign found among 58.1% dengue patients, 45.2% respondents had both persistent vomiting & lethargy as warning sign, 35.5% respondents had increase hematocrit with rapid decrease in platelet count & only 4.8% dengue patients had respiratory distress.

Table 5: Association between serum ferritin level of the respondents & duration of hospital stay (n=62)

Hospital stays (Day)	Group A (n=41) n(%)	Group B (n=21) n(%)	Total n=62 n(%)	*P-value
3-5	21(51.2%)	4(19.1%)	25(40.3)	0.015
6-8	15(36.6%)	5(23.8%)	20(32.3)	0.308
>8	5(12.2%)	12(57.1%)	17(27.4)	<0.001

*P Value Was Measured by Chi Square Test

There was a significant association found between the serum ferritin level of dengue patient with 3-5days & more than 8 days of hospital stay ($P<0.05$). Most of the patients (57.1%) with increase serum

ferritin level (in group B) stayed more time (>8) in hospital than the patients who had normal serum ferritin level (in group A) & the result was found highly significant ($P<0.001$).

Table 6: Association of serum ferritin level with clinical variables (n=62)

Clinical variables	Group A (n=41) Mean \pm SD	Group B (n=21) Mean \pm SD	*P value
Systolic Blood Pressure			
On admission	90.15 \pm 0.82	79.67 \pm 0.58	<0.001
After 3 days	96.15 \pm 1.04	86.76 \pm 1.18	<0.001
After 5 days	104.39 \pm 1.18	98.86 \pm 1.01	0.277
On discharge	120.1 \pm 0.58	119.29 \pm 0.46	0.268
Diastolic Blood Pressure			
On admission	62.1 \pm 1.18	60.48 \pm 0.87	<0.001
After 3 days	68.68 \pm 0.65	63.71 \pm 0.46	0.036
After 5 days	72.46 \pm 0.81	70.86 \pm 1.11	0.053
On discharge	80.02 \pm 0.35	79.9 \pm 0.3	0.365
Pulse pressure			
On admission	28.05 \pm 1.30	19.19 \pm 0.98	<0.001
After 3 days	27.46 \pm 1.23	23.05 \pm 1.24	0.822
After 5 days	31.93 \pm 1.54	28 \pm 1.67	0.466
On discharge	40.07 \pm 0.68	39.38 \pm 0.59	0.196
Temperature			
On admission	103.3 \pm 0.57	103.7 \pm 0.8	0.070
After 3 days	102.9 \pm 0.4	103.1 \pm 0.54	0.078
After 5 days	102.32 \pm 0.47	102.05 \pm 0.67	0.070
On discharge	98.73 \pm 0.71	99.1 \pm 0.83	0.076

*P value was measured by Independent Samples T test

Systolic & Diastolic blood pressure had a statistically significant ($p<0.05$) association with the groups on the day of admission along with 3 days after admission to the hospital. Mean value of pulse pressure

was significantly correlated with the dengue patients on the day of admission to the hospital. Temperature of the respondents was not found statistically significant among the patients in group A & group B.

Table 7: Correlation of serum ferritin level with hematocrit, platelet, WBC and neutrophil/lymphocyte ratio (n=62)

Laboratory findings	Group A (n=41) Mean \pm SD	Group B (n=21) Mean \pm SD	*P value
Hematocrit (%)			
On admission	52.02 \pm 3.18	67.57 \pm 7.04	<0.001
After 3 days	52.55 \pm 2.98	64 \pm 4.54	<0.001
After 5 days	42.19 \pm 0.61	45.63 \pm 0.52	0.642
On discharge	36.63 \pm 1.13	38.14 \pm 0.85	0.064
Platelet (x10⁹)/L			
On admission	35.66 \pm 4.26	22.0 \pm 4.64	<0.001
After 3 days	36.56 \pm 5.11	22.24 \pm 4.21	<0.001
After 5 days	57.59 \pm 6.98	44.05 \pm 3.11	<0.001
On discharge	97.76 \pm 1.66	92.33 \pm 0.58	<0.001
WBC (x10⁹)/L			
On admission	4.39 \pm 0.86	4.83 \pm 0.95	0.064
After 3 days	6.18 \pm 0.76	6.22 \pm 0.86	0.848
After 5 days	9.48 \pm 0.99	9.76 \pm 1.16	0.337
On discharge	11.24 \pm 1.61	11.43 \pm 0.99	0.621
Neutrophil/lymphocyte ratio (%)			
On admission	6.71 \pm 2.08	7.58 \pm 1.34	0.088
After 3 days	6.49 \pm 0.93	6.97 \pm 1.11	0.080
After 5 days	4.47 \pm 1.59	4.13 \pm 1.48	0.417
On discharge	2.11 \pm 0.63	2.14 \pm 0.54	0.834

*P value was measured by Independent Samples T test

Hematocrit (%) level was found highly significant among the respondents on the day of admission & 3 days after admitted to the hospital ($p < 0.05$). Platelet ($\times 10^9$)/L level of the respondents was found in a strong significant ($p < 0.05$) relationship with

the groups on admission day, after 3 days, 5 days & on discharge from the hospital. WBC($\times 10^9$)/L & Neutrophil/lymphocyte ratio (%) was not significantly correlated with the groups ($p > 0.05$).

Table 8: Comparison of serum ferritin level with severity of dengue (n=62)

Severity of dengue	Group A (n=41) n(%)	Group B (n=21) n(%)	Total (n=62) n(%)	*P value
Without warning sign	20(48.8%)	2(9.5%)	22(35.5)	<0.001
With warning sign	15(36.6%)	4(19%)	19(30.6)	0.156
Severe	6(14.6%)	15(71.4%)	21(33.9)	<0.001

*P value was measured by Chi square test

A significant association was found between serum ferritin level with dengue severity and serum ferritin level without the warning signs of dengue (< 0.001). Most of the dengue patients (48.8%) without warning sign were found in group A. Most of the severe dengue patients (71.4%) were reported in group B who had high level of ferritin.

DISCUSSION

The aim of this study was to evaluate the serum ferritin level as a predictor of disease severity in patients with dengue infection. In India, a retrospective study by Chaudhury *et al.*, similarly documented ferritin as a surrogate marker for dengue infection [12] Suresh *et al.*, also reported serum ferritin level as a “good” predictor of diagnosis of severe dengue cases [13].

Most of the respondents of this study belonged to the age group of 18-30 years. In group A 72.2% respondents with normal serum ferritin level & in group B 27.8% respondents with increased serum ferritin level belonged to the 18-30 years of age group. There was no significant association found between age group of the respondents & the groups ($p > 0.05$). A retrospective study conducted in Dhaka; Bangladesh noted quite similar findings that the most common age group (about 74%) of their respondents was 18-40 [14].

A study conducted in India narrated similar results where most of the dengue cases were adult with largest proportion of the age group of (20-40) years [15]. A significant association was found among the dengue patients in both groups who were underweight and obese ($p < 0.05$). Similar findings were reported in a study conducted in Malaysia that obesity had a significant impact on disease severity [16].

Regarding the symptoms of the dengue patients, all respondents of current study had fever (100%) & rest (91.9%) had retro-orbital pain. A study conducted in India revealed similar findings that, the most common clinical presentation of their respondents was fever in 57 (100%) [17].

According to warning signs of the dengue patient in present study, highly significant association was reported among mucosal bleed (37.1%), clinical fluid accumulation (29.0%) & liver enlargement (30.6%) with ferritin level ($p < 0.001$) & the results were more prominent among the dengue patients who had higher ferritin level. A retrospective study included 669 dengue patients, where a significantly higher incidence of mucosal bleeding was revealed in patients with severe dengue [18]. In an Indian study, they documented liver function abnormalities in dengue patients that was correlated to present study [19].

In a study of Rathore *et al.*, they revealed serum chymase levels was associated with narrow pulse pressure and clinical warning signs such as fluid accumulation which correlate with severe dengue infection, similar to present study [20]. Abdominal pain was the most common warning sign found among 58.1% dengue patients in this study followed by 45.2% respondents who had both persistent vomiting & lethargy. In a Malaysian study, the findings were correlated that, abdominal pain/tenderness was the most common warning sign of dengue patients (49%) followed by persistent vomiting (45.1%) [16].

Among all the dengue patients, 40.3% stayed 3-5 days for their recovery from dengue infection. Patient with increase serum ferritin level (in group B) stayed more time in hospital than the patients who had normal serum ferritin level (in group A) & the result was found highly significant ($P < 0.001$). In a Bangladeshi study by Prattay *et al.*, noted similar study that average duration of hospital stay was 4.9 days and they also narrated a positive correlation between respondents recovery time from dengue cases with delayed hospitalization ($p < 0.01$) [14].

Among the respondents of present study, most of them (63%) had normal level of serum ferritin. In present study, (according to WHO 2009 dengue guideline) a significant association was found between serum ferritin level & dengue severity (< 0.001) where severe dengue patients (71.4%) were frequently reported among the respondents who had high ferritin

level & poor disease progression. Similar findings were revealed in other studies that increase serum ferritin level was associated with severity of dengue [21- 28].

Currently there is no specific drug or preventive vaccine available for Dengue infection. The mainstay of management of Dengue infected patients is supportive care and close monitoring for complications. Most of these patients recover within 5 to 7 days from onset of the febrile illness while only a small percentage progress to Severe Dengue. Severe Dengue often occurs at the end of febrile or during convalescent stage and carries a very high mortality [29]. It is very crucial to predict the severe form well in advance even prior to the appearance of warning signs by a simple diagnostic marker so that early identification and appropriate management would improve the outcome in these patients. For the purpose of early illness severity prediction in dengue virus infection, serum ferritin may be a crucial biomarker.

CONCLUSION

This study established that patients with severe dengue infection were most commonly found among elevated serum ferritin level. No significant association was found between age and gender of the respondents with serum ferritin level. However a significant association was seen with BMI, most of the patients were obese followed by overweight in patients with high ferritin level. A significant association was also found between blood pressure, pulse pressure and some warning signs like mucosal bleed, clinical fluid accumulation and liver enlargement with serum ferritin level. Laboratory investigations showed hematocrit level, platelet count and serum creatinine were highly associated with ferritin level. Also, patients with high ferritin level had longer duration of hospital stay compared to patients with normal level. Therefore, we can conclude that higher serum ferritin level on the day of admission of patients with dengue infection was associated with more severe form of the disease on follow up in hospital. So serum ferritin level can be used as a predictor of disease severity in patients with dengue infection.

Limitations of the Study

- This was a single center study
- Sample size was small
- All the biochemical parameters could not be measured regularly due to fund restriction.

Recommendations

Depending upon the study findings, following recommendations are suggested:

1. Using serum ferritin level as a predictor of disease severity in patients with dengue infection in both hospital setting and in the community.
2. Conducting mass awareness programs by the Government and health care services to alert

people about the potential socio-demographic risk factors and the common dengue symptoms.

3. Further larger multicenter studies are recommended.

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