*Original Article*

# Association between Serum Ferritin Level and Left Ventricular Function by Speckle Tracking Echocardiography in Patients with Thalassemia

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***Background***: Thalassemia is a common disease in Thailand. Most patients with thalassemia receive regular blood transfusion, resulting in iron accumulation in the body. Ferritin levels are associated with iron accumulation in vital organs of patients with thalassemia. The relationship between the ferritin levels and left ventricular (LV) function in these patients showed no relationship in most data, but all data were measured by conventional echocardiography. Currently, LV function can be measured by more advanced methods, such as the speckle tracking echocardiography, which demonstrates high accuracy in detecting early-stage LV dysfunction.

***Objective***: To investigate the association between the serum ferritin level and LV function by speckle tracking echocardiography in patients with thalassemia.

***Materials and Methods***: The present study was a cross-sectional analytic study that enrolled patients with thalassemia in the Faculty of Medicine, Vajira Hospital, between January and December 2019. Each participants provided an informed consent. Serum ferritin, conventional echocardiography, and speckle tracking echocardiography using global longitudinal strain [GLS] parameters were collected.

***Results***: Among 45 participants, 33 had transfusion-dependent thalassemia (TDT), and 12 had non-transfusion-dependent thalassemia (NTDT). Female participants accounted for 64.4% with 29 patients. The mean age was 35.51±13.81 years, and participants had no other systemic diseases. The median serum ferritin was 1,159 ng/dL with a range of 638 to 1,983. The mean values for GLS and LVEF by biplane were −22.97±2.20% and 63.90±7.62%, respectively. Serum ferritin was not significantly related to GLS (Spearman's rho 0.164, 95% CI −0.136 to 0.437, p=0.280). In the TDT group, ferritin was significantly related to GLS (Spearman's rho 0.405, 95% CI 0.072 to 0.657, p=0.019), whereas in the NTDT group, such relationship was insignificant (Spearman's rho −0.394, 95% CI 0.790 to 0.232, p=0.205).

***Conclusion***: Serum ferritin and speckle tracking echocardiography in patients with thalassemia are not significantly associated. Therefore, serum ferritin should not be a single candidate for detecting early-stage LV dysfunction. As a result, using various measurements remains the best option.

***Keywords***: Ferritin; Speckle tracking echocardiography; Thalassemia; Echocardiography

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Thalassemia is a common disease in Thailand[1]. Most patients with thalassemia undergo chronic blood transfusion, and the disease by itself increases iron absorption from the gastrointestinal system, resulting in iron accumulation in various body organs[2,3]. High serum iron level can deposit in myocardium tissue, leading to various cardiovascular complications, including cardiac arrhythmias, heart failure, and cardiomyopathy. These complications are the main causes of death among patients with thalassemia[4]. Therefore, early diagnosis of iron overload is vital to prevent serious cardiac complications.

Currently, the diagnosis of iron overload requires the use of liver biopsy or cardiac magnetic resonance imaging[5]. However, these two diagnostic options are neither routinely used in daily practice nor available in many centers. Meanwhile, echocardiography is widely and conveniently used for evaluating cardiac function. Serum ferritin, which is one of its indirect methods, is used for the diagnosis and treatment follow-up of serum iron in the body[6,7]. High serum ferritin level is associated with cardiac body deposition[8]. Inversely, the relationship between ferritin levels and left ventricular (LV) function in patients with thalassemia showed no relationship in most data[9-11]. However, all data were measured by conventional

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echocardiography. For example, one study evaluated the relationship between serum ferritin and the left ventricular ejection fraction (LVEF) among patients with thalassemia and showed no relationship (r=–0.12, p=0.48)[12]. In recent years, new methods have been developed for measuring LV function, for instance, the speckle tracking echocardiography can detect early-stage LV dysfunction, with high sensitivity and specificity[13]. According to a previous study in Taiwan, Chen et al used this measuring method to study the relationship between the ferritin levels and LV function of patients with β thalassemia and found that statistically significant relationships were found between ferritin and speckle tracking echocardiography (r=0.4, p<0.001)[14]. However, LV function measurement by speckle tracking echocardiography is still less applied in patients with thalassemia. However, such measurement is mostly conducted in patients with β thalassemia with severe disease burden. The present study aimed to examine the relationship between the ferritin levels and LV function by speckle tracking echocardiography in patients with thalassemia.

## Objective

The present study mainly aimed to determine the relationship between serum ferritin levels and LV function in patients with thalassemia by speckle tracking echocardiography. The authors also aimed to identify such relationship by using various conventional echocardiography parameters.

## Materials and Methods

### Study design

The present study was a cross-sectional analytic study and approved by the head of the Department of Internal Medicine and the Ethics Committee of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University (COA022/2562). Enrolled participants were patients diagnosed with thalassemia without systemic disease, with consideration of the study's inclusion criteria and exclusion criteria.

### Study population

The authors enrolled participants who came to the Division of Hematology of the Faculty of Medicine, in Vajira Hospital, Navamindradhiraj University between January and December 2019. The inclusion criteria were 18 years of age, diagnosis of thalassemia for at least two years, a history of continuous treatment for at least one year, and serum ferritin within six months.

The exclusion criteria were history of infection within six months, history of hepatitis or chronic liver disease, regular alcohol drinking, thyroid disease, ischemic heart disease, cardiac arrhythmia, valvular heart disease, congenital heart disease, diabetes, hypertension, hyperlipidemia, chronic kidney disease, cancer, pregnancy, autoimmune disease, thalassemia trait, and LVEF of less than 50%

### Study protocol

The study was started between January and December 2019. Data were collected from baseline demographic data and medical records, including age, gender, blood transfusion, iron-chelating agent, average ferritin levels, hematocrit levels, and hemoglobin levels. Each participant provided an informed consent. The authors also recorded patients' history and performed physical examination to exclude other systemic diseases. The serum ferritin levels were measured by COBAS e801, the normal values, or the 5 to 95 percentiles, are 15 to 332 ng/mL in men and 6 to 85 ng pre mL in women.

The researchers performed standard echocardiography (GE Vingmed Ultrasound Vivid 7 version 7.12) in the supine left lateral decubitus. Then, according to the American Society Echocardiography 2015 guideline[15], the basic structure and function of the heart was determined using the conventional echocardiography and the speckle tracking echocardiography by a cardiologist. The baseline conventional echocardiography image was gathered in 2-dimensional view parasternal long axis and apical 2- and 4-chamber views, with a good-quality endocardial border on three consecutive cardiac cycles. The image was adjusted to visualize the aortic valve closure. If the image was unclear, more than two images were excluded from the study. Furthermore, all basic qualitative echocardiography parameters, including LVEF, were analyzed by biplane Simpson method.

### Speckle-tracking for global longitudinal strain

The researchers measured the speckle-tracking using the global longitudinal strain (GLS) based on the measurement from the Practical Guidance in Echocardiographic Assessment of GLS 2015[16] and the user guide GE ECO manual[17]. The parasternal long axis, apical 2-chamber, and 4-chamber views were then selected. The frame rate was adjusted to 60 frames per second as the default was 40 to 90 frames per second. Three regions of interest, which are the two basal points and one apical points of

**Table 1.** Demographic and laboratory characteristics of patients (n=45)

| Variables | Total (n=45); n (%) | TDT (n=33); n (%) | NTDT (n=12); n (%) | p-value* |
|---|---|---|---|---|
| Demographic | | | | |
| Age (years); mean±SD | 35.51±13.81 | 34.21±13.56 | 39.08±14.46 | 0.301 |
| Sex | | | | |
| • Female | 29 (64.4) | 21 (63.6) | 8 (66.7) | 1.000 |
| Body weight (kg); mean±SD | 51.13±8.73 | 49.50±6.77 | 55.34±11.79 | 0.129 |
| BMI (kg/m$^2$); mean±SD | 20.20±3.12 | 19.70±2.91 | 21.50±3.39 | 0.089 |
| Unit of blood transfusion (unit/year); median (IQR) | 6 (2 to 12) | 6 (4 to 12) | 1 (0 to 1) | 0.010 |
| Splenectomy | 17 (37.8) | 15 (45.5) | 2 (16.7) | 0.096 |
| Smoking | | | | |
| • Never | 45 (100) | 33 (100) | 12 (100) | NA |
| Alcohol | | | | |
| • Sometime | 3 (6.7) | 2 (6.1) | 1 (8.3) | 1.000 |
| • Never | 42 (93.3) | 31 (93.9) | 11 (91.7) | |
| Iron chelating agent | | | | |
| • Deferoxamine | 1 (2.2) | 1 (3.0) | 0 (0.0) | <0.001 |
| • Deferasirox | 2 (4.4) | 2 (6.1) | 0 (0.0) | |
| • Deferiprone | 31 (68.9) | 29 (87.9) | 2 (16.7) | |
| • None | 11 (24.4) | 1 (3.0) | 10 (83.3) | |
| Laboratory investigations | | | | |
| Hct (%); mean±SD | 23.26±4.94 | 21.37±3.93 | 28.48±3.50 | <0.001 |
| Hb (g/dL); mean±SD | 6.97±1.27 | 6.54±1.13 | 8.21±0.77 | <0.001 |
| Serum ferritin level (ng/mL); median (IQR) | 1,159 (638 to 1,983) | 1,371.5 (860 to 2,603) | 321 (155.25 to 1,143.75) | 0.001 |
| • <1,000 | 21 (46.7) | 12 (36.4) | 9 (75.0) | 0.100 |
| • 1,000 to 2,000 | 14 (31.1) | 12 (36.4) | 2 (16.7) | |
| • >2,000 | 10 (22.2) | 9 (27.3) | 1 (8.3) | |

SD=standard deviation; IQR=interquartile range; TDT=transfusion-dependent thalassemia; NTDT=non-transfusion-dependent thalassemia; Hct=hematocrit; Hb=hemoglobin; NA=not available

* Comparison between TDT and NTDT; Student's t-test, Mann-Whitney U test, chi-square test and Fisher's exact test

the endocardial border were selected by automated speckle tracking. Tracing was performed along the endocardial border, starting from the left mitral annulus in the apical 4-chamber view through the continuous line that connected six to eight points along the endocardial border to the opposite mitral annulus. Then, the researchers analyzed the data and collected GLS, which was reported as percentiles, with a normal value at less than –21%. Thereafter, the authors gathered the data in a case record form.

### Statistical data analysis

Quantitative such as age, blood transfusion, and serum ferritin levels information was presented as mean and standard deviation or mean median interquartile range. Meanwhile, the qualitative data such as gender, thalassemia type, and medication history were expressed as frequency and percentage (%). The relationship between the ferritin levels and the GLS or conventional echocardiography parameter was analyzed using the Pearson test and the linear regression model, and the results with p-value less than 0.05 were considered to be statistically significant. All data were analyzed using the IBM SPSS Statistics, version 22 (IBM Corp., Armonk, NY, USA) and Microsoft Excel, version 2016.

## Results

The authors recruited 45 participants in 2019 and divided into the transfusion-dependent thalassemia (TDT) group and the non-transfusion-dependent (NTDT) group with 33 and 12 participants, respectively. The baseline characteristics are shown in Table 1. The demographic data showed that

**Table 2.** Echocardiographic measurement (n=45)

| Variables | Total (n=45); mean±SD | TDT (n=33); mean±SD | NTDT (n=12); mean±SD | p-value* |
|---|---|---|---|---|
| LVOT (cm) | 2.12±0.15 | 2.11±0.13 | 2.16±0.19 | 0.312 |
| Ao diameter (cm) | 2.70±0.40 | 2.71±0.41 | 2.67±0.37 | 0.731 |
| MPA (cm) | 2.21±0.44 | 2.22±0.48 | 2.16±0.29 | 0.642 |
| LA diameter (cm) | 3.66±0.58 | 3.70±0.60 | 3.55±0.52 | 0.455 |
| IVSd (cm) | 1.06±0.25 | 1.07±0.26 | 1.01±0.22 | 0.494 |
| LVIDd (cm) | 5.08±0.53 | 5.07±0.56 | 5.1±0.45 | 0.844 |
| LVPWd (cm) | 1.04±0.20 | 1.05±0.18 | 1.01±0.25 | 0.562 |
| IVSs (cm) | 1.34±0.30 | 1.39±0.32 | 1.19±0.23 | 0.053 |
| LVIDs (cm) | 3.20±0.57 | 3.22±0.61 | 3.16±0.49 | 0.782 |
| LVPWs (cm) | 1.42±0.26 | 1.40±0.25 | 1.45±0.31 | 0.622 |
| LVEF (Teich) (%) | 67.83±7.97 | 67.85±8.32 | 67.78±7.25 | 0.980 |
| %FS | 38.30±6.56 | 38.32±6.94 | 38.23±5.66 | 0.966 |
| LV mass index ($g/m^2$) | 155.37±42.57 | 160.45±40.58 | 141.39±46.53 | 0.187 |
| RWT | 0.41±0.10 | 0.42±0.10 | 0.40±0.10 | 0.465 |
| MV E (m/s) | 1.08±0.24 | 1.11±0.23 | 0.98±0.23 | 0.096 |
| MV DecT (msec) | 203.43±60.11 | 204.61±61.78 | 200.2±57.73 | 0.831 |
| MV A (m/s) | 0.78±0.32 | 0.81±0.36 | 0.71±0.14 | 0.377 |
| E/A (m/s) | 1.51±0.52 | 1.56±0.58 | 1.38±0.31 | 0.289 |
| E' (m/s) | 0.10±0.03 | 0.11±0.03 | 0.10±0.03 | 0.512 |
| E/E' | 11.53±5.38 | 11.94±5.94 | 10.38±3.31 | 0.394 |
| Lateral E' | 10.73±8.19 | 11.59±8.55 | 8.42±6.93 | 0.258 |
| TAPSE (cm) | 2.71±0.49 | 2.78±0.49 | 2.54±0.48 | 0.164 |
| IVC diameter (mm) | 6.95±5.43 | 6.69±5.64 | 7.66±4.98 | 0.602 |
| EF by biplane (%) | 63.90±7.62 | 62.66±7.17 | 67.30±8.10 | 0.070 |
| 50 to 60 | 13 (28.9) | 11 (33.3) | 2 (16.7) | 0.460 |
| >60 | 32 (71.1) | 22 (66.7) | 10 (83.3) | |
| GLS (%) | −22.97±2.20 | −23.03±2.17 | −22.79±2.39 | 0.749 |
| < −21 | 35 (77.8) | 27 (81.8) | 8 (66.7) | 0.418 |
| > −21 | 10 (22.2) | 6 (18.2) | 4 (33.3) | |

SD=standard deviation; IQR=interquartile range; TDT=transfusion-dependent thalassemia; NTDT=non-transfusion-dependent thalassemia; GLS=global longitudinal strain; LVEF=left ventricular ejection fraction; LV=left ventricular; RWT=relative wall thickness; TAPSE=tricuspid annular plane systolic excursion; E'=annular diastolic E wave; A=A wave; LVOT=left ventricular outflow tract; Ao=aortic; MPA=mean pulmonary artery; LA=left atrial diameter; IVSd=interventricular septum thickness in diastole; IVSs=interventricular septum thickness in systole; LVIDd=left ventricular internal end-diastolic diameter; LVIDs=left ventricular internal end-systolic diameter; LVPWd=left ventricular posterior wall in diastolic; LVPWs=left ventricular posterior wall in systolic; MV E=mitral valve E wave; MV A=mitral valve A wave; MV DecT=mitral valve deceleration time; IVC=inferior vena cava

* Comparison between TDT and NTDT; Student's t-test and Fisher's exact test

64.4% or 29 patients were female. The mean age was 35.51±13.81 years, and none had other systemic diseases. The median serum ferritin was 1,159 ng/dL with a range of 638 to 1,983. In addition, the non-transfusion dependent group tended to have lower unit blood transfusion, serum hematocrit, chelating agent, and serum ferritin levels at 321 ng/dL (all $p<0.05$). In the TDT group, 73% or 21 patients, obtained serum ferritin levels greater than 1,000 ng/dL.

The measurement of baseline echocardiography parameters is listed in Table 2. No significant difference was found between the two groups ($p>0.05$). In general, patients with thalassemia had increased LV mass index at 155.37±42.57. In addition, the mean GLS was −22.97±2.20%, whereas the mean LVEF by biplane was 63.90±7.62%.

The authors investigated the relationship between serum ferritin and various echocardiographic parameter using the Spearman's correlation coefficient and found that serum ferritin had no significant

**Table 3.** Correlation analysis (n=45)

| Variables | Spearman's rho (r) | 95% CI | p-value* |
|---|---|---|---|
| Serum ferritin level and LVEF by biplane | −0.084 | −0.369 to 0.215 | 0.582 |
| Serum Ferritin level and GLS | 0.164 | −0.136 to 0.437 | 0.280 |
| Transfusion dependent (n=33) | 0.405 | 0.072 to 0.657 | 0.019 |
| Non-transfusion dependent (n=12) | −0.394 | −0.790 to 0.232 | 0.205 |
| Serum Ferritin level and LVEF | 0.209 | −0.090 to 0.473 | 0.168 |
| Serum Ferritin level and LV mass | 0.197 | −0.102 to 0.464 | 0.194 |
| Serum Ferritin level and RWT | 0.159 | −0.145 to 0.435 | 0.302 |
| Serum Ferritin level and E/A | −0.232 | −0.492 to 0.067 | 0.126 |
| Serum Ferritin level and E/E' | 0.068 | −0.230 to 0.355 | 0.657 |
| Serum Ferritin level and lateral E` | −0.121 | −0.404 to 0.182 | 0.433 |
| Serum Ferritin level and TAPSE | 0.253 | −0.067 to 0.497 | 0.125 |

GLS=global longitudinal strain; LVEF=left ventricular ejection fraction; LV=left ventricular; RWT=relative wall thickness; TAPSE=tricuspid annular plane systolic excursion; E'=annular diastolic E wave; A=A wave

* Spearman's rank correlation analysis

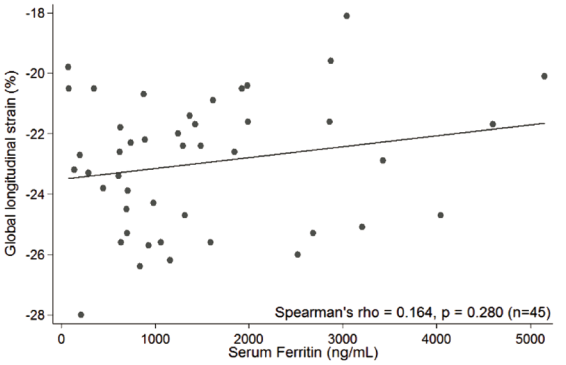


**Figure 1.** The relationship between ferritin levels and global longitudinal strain of patients with thalassemia.

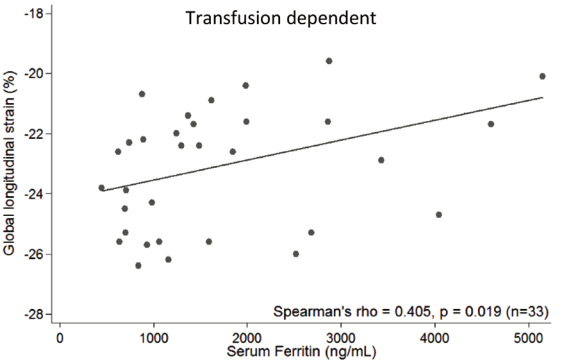


**Figure 2.** The relationship between ferritin levels in transfusion dependent group and global longitudinal strain of patients with thalassemia.

relationship with GLS (Spearman's rho 0.164, 95% CI −0.136 to 0.437, p=0.280) (Figure 1). In the TDT group, ferritin was significantly related to GLS (Spearman's rho 0.405, 95% CI 0.072 to 0.657, p=0.019) (Figure 2), whereas in the NTDT group, such relationship was not significant (Spearman's rho −0.394, 95% CI −0.790 to 0.232, p=0.205) (Figure 3). Other correlations are displayed in detail in Table 3.

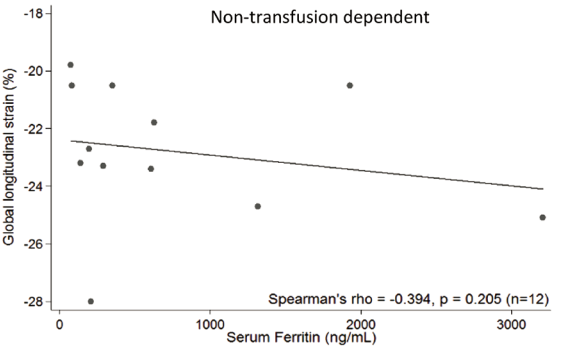


**Figure 3.** The relationship between ferritin levels in non-transfusion dependent group and global longitudinal strain of patients with thalassemia.

## Discussion

The speckle tracking echocardiography is a strong predictor of early-stage ventricular dysfunction. In the present study, the researchers evaluated the relationship of serum ferritin level and LV function by speckle tracking, which uses GLS for silent ventricular dysfunction and myocardial iron overload. The researchers found that serum ferritin had no significant relationship with GLS among patient with thalassemia. Hence, serum ferritin indicates inefficiency in predicting abnormal deposition of

cardiac iron as well as detects early-stage of LV dysfunction. Several studies have evaluated the association of various echocardiographic parameters with serum ferritin in patients with thalassemia. A study conducted by Abhathi et al also found that the ferritin level had insignificantly weak correlation with GLS (r=0.26, p=0.06), but GLS had a significantly strong relationship with cardiac T2*[18]. However, this result did not agree with the result obtained by Chen et al, in which GLS significantly correlated with ferritin in patients with β thalassemia (r=0.4, p<0.012)[14]. However, the present study obtained different demographic data and serum ferritin levels. The authors enrolled patients with thalassemia, both with TDT and NTDT. The NTDT group in the present study had lower baseline ferritin levels, blood transfusion history with one unit per year, disease burden, and regular chelating agent. On the other hand, in the TDT group of the present study, ferritin and GLS showed a positively significant correlation (Spearman's rho 0.405, 95% CI 0.072 to 0.657, p=0.019) because of slightly higher ferritin levels at more than 2,000 ng/dL, and regular blood transfusion. The positive relationship between serum ferritin and GLS might only be found in a specific patient group. Generally, a serum ferritin level greater than 1,800 ng/mL correlates with elevated cardiac iron deposition[8].

In the present study, patients had slightly increased LV mass index, in both the TDT, and the NTDT group. The systemic diseases were excluded from the present study. In the study by Bay et al, participants with thalassemia had a larger LV mass index than those without such condition[19]. However, the abnormal iron level in patients with thalassemia may be caused by a high free-radical oxidative stress responding to myocardial damage, thereby, leading to LV remodeling. On the other hand, it may result from chronic tissue hypoxia caused by chronic-anemia initiating factor, leading to subsequent injury[19]. The technique of measuring the LV diameter could also be different from each study.

Regarding the conventional echocardiography functions in the present study, the mean LVEF biplane was 63.90±7.62%, and LVEF had no relationship with serum ferritin levels. The same result was obtained between LVEF and the diastolic dysfunction parameter E/A, E/E`, and lateral E`. The candidates for predicting cardiac iron deposition in the early stage were insufficient, similar to other studies[9-12]. The mean TAPSE was 2.2 cm, implying that the right ventricular (RV) function is normal. However, TAPSE is not a gold standard measurement to evaluate RV function. More parameters, such as RV early diastolic myocardial velocity, and systolic strain of RV free wall, are needed. In one study, patients with thalassemia have RV diastolic dysfunction, and the presence of RV systolic dysfunction in these patients is related to the higher level of serum ferritin[20].

With regard to the limitation of the present study, the serum ferritin level can be disrupted by several factors such as inflammation, infection, or iron chelating agent. However, in the present study, the mean serum ferritin was measured within three months to diminish the confounding factors.

## Conclusion

No significant association exists between serum ferritin and the speckle tracking echocardiography in patients with thalassemia. Therefore, serum ferritin should not be a single candidate for detecting early-stage LV dysfunction. However, the use of various measurements remains the best option.

## What is already known on this topic?

High serum ferritin level correlates with elevated cardiac iron deposition. Diagnosis of cardiac iron overload requires the use of cardiac magnetic resonance imaging[5]. However, it is not routinely used in daily practice nor available in many centers.

## What this study adds?

In recent years, new methods of the GLS echocardiography can detect early-stage LV dysfunction. However, this study shows serum ferritin was not significantly related to GLS in thalassemia patients. In addition, in the TDT group, ferritin was significantly related to GLS.

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## Conflicts of interest

The authors declare no conflict of interest.

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