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Original Article

Kidney dysfunction in children with thalassemia

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Abstract

Background Children with thalassemia are at risk for kidney dysfunction due to chronic anemia, frequent blood transfusions, iron retention, and use of iron chelating agents. Cystatin C, an endogenous marker for assessing estimated glomerular filtration rate (eGFR), a novel biomarker for the early detection of kidney failure, has been reported to be potentially superior to the commonly used serum creatinine.

Objective To evaluate various creatinine- and cystatin C-based formulas for eGFR to detect kidney dysfunction in children with thalassemia.

Methods This was a cross-sectional study on children (age <18 years) with thalassemia. Kidney dysfunction was defined as eGFR <90 mL/minute/1.73 m^2. Hyperfiltration was defined as eGFR >150 ml/minute/1.73 m^2. This study compared the proportion of kidney dysfunction as determined using various creatinine- and cystatin C-based eGFR formulas, comprising the creatinine-based Schwartz formula, the cystatin C-based Filler formula, the creatinine-cystatin C-based New CKID formula, and the creatinine-cystatin C-based Schwartz formula.

Results The median age of the 152 study subjects was 11.0 (range 2.0-18.0) years. When using the creatinine-based Schwartz formula, none of the subjects had kidney dysfunction. Kidney dysfunction was found in 21.7% of subjects when using the cystatin C-based Filler formula, in 26.3% of subjects when using the creatinine-cystatin C-based (New CKID) formula, and 59.9% of subjects using the creatinine-cystatin C-based Schwartz formula. When using the creatinine-based Schwartz formula, 38.2% subjects experienced hyperfiltration; no hyperfiltration was found by when using other eGFR formulas. There was low correlation between creatinine and cystatin C (r=0.195; P=0.016). There was only mild agreement in eGFR between the creatinine-based Schwartz formula and the cystatin C-based Filler formula (k=0.195; P<0.001).

Conclusion The proportion of kidney dysfunction in children with thalassemia based on eGFR calculation using cystatin C- and creatinine-cystatin C-based formulas ranged from 21.7% to 59.9%. No kidney dysfunction was found using a creatinine-only-based eGFR formula, whereas hyperfiltration was a common finding. Hence, more than one parameter should be considered for early detection of kidney dysfunction in thalassemia. **[Paediatr Indones. 2025;65:337-45; DOI: https://doi.org/10.14238/pi65.4.2025.337-45**].

Keywords: *thalassemia; kidney dysfunction; eGFR; creatinine; cystatin*C

Thalassemia is a common hereditary blood disorder caused by gene mutations encoding the production of alpha-globin chains (β-thalassemia) or beta-globin chains (β-thalassemia), resulting in ineffective hematopoiesis and increased hemolysis.[1,2] Thalassemia is a global health problem, especially in countries with high frequencies of thalassemia, such as the Mediterranean, as well as regions around the equator, such as South Asia, China, and Indonesia.[3,4] Indonesia is located along the 'thalassemia belt' and is a hotspot for

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hemoglobinopathies. Three to ten percent of the population carry β-thalassemia and 2.6-11% of the population carry β-thalassemia. It is estimated that around 2,500 babies are born with β-thalassemia major each year.[5,6]

Thalassemia major is a form of thalassemia with severe clinical manifestations that require lifelong regular blood transfusions to maintain hemoglobin (Hb) levels. Repeated red blood cell transfusions increase the risk of complications due to iron overload in various organs such as the liver, heart, kidneys, lungs and endocrine glands, resulting in hemochromatosis in these organs.[7] The increased survival rate of thalassemia patients has led to the detection of various comorbidities and complication, including kidney dysfunction.[7-9]

In a study of 69 patients with β-thalassemia major, 58.8% of patients who received iron chelation had kidney dysfunction.[10] Another study of 28 pediatric thalassemia major patients in a tertiary referral hospital in Indonesia noted a decrease in eGFR in 53.6% of patients who received deferiprone. Decreased eGFR was found in 46.2% of those who received deferasirox, and 7.69% had kidney dysfunction.[11]

Early detection of kidney dysfunction may increase the life expectancy of thalassemia major patients. Creatinine is a well-known marker used to determine eGFR by the Schwartz formula.[12] Several other formulas have been developed to calculate eGFR to determine kidney dysfunction. Cystatin C, a low molecular weight protein, is a novel endogenous marker of renal function. Its serum concentration correlates better with glomerular filtration rate than creatinine.[13,14] Serum cystatin C levels have been shown to be significantly elevated in pediatric and young adult patients who receive iron chelation treatment, while creatinine eGFR results remain normal.[13] Several studies have suggested that cystatin C level is a better marker of eGFR than serum creatinine.[13,15]

There have been limited studies on kidney dysfunction in pediatric thalassemia patients. We aimed to compare the detection of kidney dysfunction in pediatric thalassemia patients using various creatinine- and cystatin C-based eGFR formulas, and to determine the agreement level and correlation among those eGFR formulas.

Methods

This observational study with cross-sectional design was conducted from October 2019 to August 2020 using primary data from laboratory results and questionnaires, as well as secondary data from medical records. Subjects were recruited consecutively.

Our study population was comprised of patients under 18 years of age with thalassemia in Mohammad Hoesin Hospital, Palembang. Inclusion criteria were all thalassemia major patients aged less than 18 years who received transfusions regularly, and whose parents provided written informed consent. Exclusion criteria were hypothyroidism, consumption of large doses of glucocorticoids (methylprednisone 500 mg/day), and history of kidney abnormalities.

Demographic data recorded included age, gender, nutritional status, age at initial diagnosis, and transfusion frequency. Laboratory results recorded included Hb level, ferritin, urea, creatinine, and cystatin C level.

The estimated glomerular filtration rate (eGFR) was calculated using several different eGFR formulas:
(1) the creatinine-based Schwartz formula for children: eGFR (mL/min/1.73 m^2)=height (cm) x constant/serum creatinine (mg/dL)[12]
(2) the cystatin C-based Filler formula: eGFR (mL/min/1.73 m^2)=91.62 x (CysC)-1.123[16]
(3) the creatinine- and cystatin C-based Schwartz formula: eGFR=39.8 [height (m)/serum creatinine (mg/dL)]0.456 x [1.8/cystatin C (mg/L)]0.418 [30/BUN (mg/dL)]0.079 [1.076]male [height (m)/1.4]0.179[17] and
(4) the creatinine- and cystatin C-based New CKID formula eGFR (mL/min/1.73 m^2)=39.1 [height (m)/serum creatinine (mg/dL)]0.516 X [1.8/cystatin C (mg/L)]0.294 [30/BUN (mg/dL)]0.169 [1.099]male [height (m)/1.4]0.188.[17]

Kidney dysfunction was defined as eGFR <90 mL/minute/1.73 m^2, while hyperfiltration was defined as eGFR >150 mL/minute/1.73 m^2. The normal reference range of cystatin C used in this study was 0.70-1.38 mg/L.[18]

Data were collected and analyzed using *SPSS version 24* for *Windows* (*IBM*, Armonk, New York, USA). The Kolmogorov-Smirnov test was used to evaluate data distribution normality. Statistical

analyses used in this study were Pearson product-moment for correlation and Cohen's Kappa for level of agreement. Correlations were considered to be strong for r values of 0.5-1.0. Agreement level was considered almost perfect for Kappa (k) values of 0.8-1.0.

Results

One hundred fifty-two patients met the inclusion criteria. Subjects' median age was 11.0 (range 2.0-18.0) years, and there were more females (56.6%) than males (43.4%). Most subjects were diagnosed at the age of 2-5 years (38.2%) and had been diagnosed for 6 years or more at the time of the study (52.6%). Median age at diagnosis was 3.0 (range 0-14) years and median time since diagnosis was 6.0 (range 1-17) years. Characteristics of subjects are shown in **Table 1**. Most patients had good nutritional status (77%), but a large proportion also had short stature (62.5%). The majority of patients had received more than 12 blood transfusions a year (86.2%). In addition, the majority of patients had been on iron chelation therapy for more than 4 years (61.8%); deferiprone was the most common agent used (63.8%). Laboratory findings showed that the majority of patients had Hb levels of 6-9 g/dL (73.7%) and ferritin levels of 1,001 to <5,000 ng/mL (59.9%). Median (range) values of urea, creatinine, and cystatin C were 19.0 (6-39.8) mg/dL, 0.5 (0.3-0.8) mg/dL, and 0.9 (0.7-1.4) mg/L, respectively.

Table 1. Characteristics of subjects

Variables	N=152
Age, n(%)	
< 2 years	0 (0.0)
2-5 years	22 (14.5)
>5 to 10 years	50 (32.9)
≥10 years	80 (52.6)
Gender, n(%)	
Male	66 (43.4)
Female	86 (56.6)
Age at diagnosis, n(%)	
<2 years	52 (34.2)
2-5 years	58 (38.2)
>5 to 10 years	29 (19.1)
≥10 years	13 (8.6)
Nutritional status, n(%)	
Severe malnutrition	1 (0.7)
Malnutrition	32 (21.1)
Normal	117 (77.0)
Overweight	2 (1.3)
Short stature, n(%)	
Yes	95 (62.5)
No	57 (37.5)
Time since diagnoses, n(%)	
<6 years	72 (47.4)
≥6 years	80 (52.6)
Transfusion frequency	
<12 times/year	21 (13.8)
≥12 times/year	131 (86.2)
Median (range), times/year	12.0 (9-18)
Iron chelation, n(%)	
Deferiprone	97 (63.8)
Deferasirox	52 (34.2)
No	3 (2.0)
Duration of iron chelation	
≥4 years	94 (61.8)
<4 years	58 (38.2)
Median (range), years	4.0 (0-14)
Hb level before transfusion, n(%)	
<6 g/dL	17 (11.2)
6-9 g/dL	112 (73.7)
>9 g/dL	23 (15.1)
Median (range), g/dL	7.8 (3.9-10.4)
Ferritin	
<1,000 ng/mL	24 (15.8)
1,001 to <5,000 ng/mL	91 (59.9)
5,000 to <10,000 1-10,000 ng/mL	33 (21.7)
≥10,000 ng/mL	4 (2.6)
Median (range), ng/mL	2,973 (237-78,760)
Median urea (range), mg/dL	19.0 (6.0-39.8)
Median creatinine (range), mg/dL	0.5 (0.3-0.8)
Median cystatin C (range), mg/L	0.9 (0.7-1.4)

Table 2 shows eGFR results based on the various formulas used, and the proportion of kidney dysfunction in study subjects. Using the creatinine-based Schwartz formula, eGFR was >90 mL/min/1.73 m^2 in all subjects, with a mean of 145.3 (SD 30.4) mL/min/1.73 m^2. Hence, no kidney dysfunction was found in any of the subjects based on this formula. However, the proportion of kidney dysfunction was 21.7% based on the cystatin C-based Filler formula [mean eGFR 101.3 (SD 14.9) mL/min/1.73 m^2]; 59.9% based on creatinine-cystatin C (Schwartz) formula [mean eGFR 87.6 (SD 9.6) mL/min/1.73 m^2]; and 26.3% based on creatinine-cystatin C (New CKID) formula [mean eGFR 96.6 (SD 12.1) mL/min/1.73 m^2)].

Furthermore, we analyzed the agreement level between the various formulas in determining kidney dysfunction (**Table 3**). The results showed that there was no agreement between the creatinine-based Schwartz formula with any of the other three formulas. There was only mild agreement between the

Table 2. Characteristics of eGFR according to various formula calculations

eGFR formula	(N=152)
Creatinine-based Schwartz formula, n(%)	
Kidney function category	
Kidney dysfunction (<90 mL/min/1.73 $m^{2)}$	0 (0.0)
Normal (90-149 mL/min/1.73 $m^{2)}$	94 (61.8)
Hyperfiltration (≥150 mL/min/1.73 $m^{2)}$	58 (38.2)
Mean (SD), nL/min/1.73 m^2	145.3 (30.4)
Median (range), nL/min/1.73 m^2	143.8 (90.11-234.42)
Cystatin C-based Filler formula, n(%)	
Kidney function category	
Kidney dysfunction (<90 mL/min/1.73 $m^{2)}$	33 (21.7)
Normal (90-149 mL/min/1.73 $m^{2)}$	119 (78.3)
Hyperfiltration (≥150 mL/min/1.73 $m^{2)}$	0 (0.0)
Mean (SD), nL/min/1.73 m^2	101.3 (14.9)
Median (range), nL/min/1.73 m^2	100.6 (64.3-143.7)
Creatinine- and cystatin C-based Schwartz formula, n(%)	
Kidney function category	
Kidney dysfunction (<90 mL/min/1.73 $m^{2)}$	91 (59.9)
Normal (90-149 mL/min/1.73 $m^{2)}$	61 (40.1)
Hyperfiltration (≥150 mL/min/1.73 $m^{2)}$	0 (0.0)
Mean (SD), nL/min/1.73 m^2	87.6 (9.6)
Median (range), nL/min/1.73 m^2	87.4 (64.1-113.0)
Creatinine- and cystatin C-based New CKID formula, n(%)	
Kidney function category	
Kidney dysfunction (<90 mL/min/1.73 $m^{2)}$	40 (26.3)
Normal (90-149 mL/min/1.73 $m^{2)}$	112 (73.7)
Hyperfiltration (≥150 mL/min/1.73 $m^{2)}$	0 (0.0)
Mean (SD), nL/min/1.73 m^2	96.6 (12.1)
Median (range), nL/min/1.73 m^2	95.9 (66.8-126.5)

cystatin C-based Filler formula and the creatinine- and cystatin C-based Schwartz Formula (k=0.124; P=0.035), but there was no agreement between the cystatin C-based Filler formula and the creatinine- and cystatin C-based New CKID formula. There was moderate agreement between the creatinine- and cystatin C-based Schwartz formula and the creatinine- and cystatin C-based New CKID formula (k=0.386; P<0.001).

We analyzed for possible correlations between creatinine-based and cystatin C-based eGFR formulas. Because the data were normally distributed, we used Pearson product-moment analysis for this purpose. There were strong positive correlations between the creatinine-based Schwartz formula and both the creatinine- and cystatin C-based Schwartz formula (r 0.757, P<0.001) and the creatinine and cystatin C-based New CKID formula (r 0.781, P<0.001). Strong positive correlations were also observed between the creatinine- and cystatin C-based Schwartz formula and the creatinine- and cystatin C-based New CKID formula (r 0.968, P<0.001). There was a moderate positive correlation between the cystatin C-based Filler formula and the creatinine- and cystatin C-based Schwartz formula (r 0.364, P<0.001), a weak negative correlation between the creatinine-based Schwartz formula and the cystatin C-based Filler formula (r -0.191, P=0.019), and a weak positive correlation between the cystatin C-based Filler formula and the creatinine- and cystatin C-based New CKID formula (r 0.201, P=0.013).

Discussion

In our study, subjects' median age was 11 (range 2.0-18.0) years, similar to a previous report of thalassemia in which the subjects' mean age was 12.28 years.[19] The majority of our patients were first diagnosed at the age of 2-5 years. A study in India similarly found that most children with thalassemia were diagnosed at the age of two.[20]

There were more females (56.6%) than males in our study (43.4%). This sex distribution is similar to that

reported in two studies of children with thalassemia, with the proportion of females being 51.6% and 53%, respectively.[21] Thalassemia is inherited in an autosomal recessive manner, independent of gender. Males and females are at similar risk of inheriting the condition from two parents who are carriers of the thalassemia trait. Such children have a 25% chance of having a normal phenotype, 50% chance of being carriers, and 25% chance of having thalassemia.[22] In our study, 77% of subjects had normal nutritional status, in contrast to an earlier study (2015) in the same center, which reported that only 57.6% of children with thalassemia had good nutritional status.[23] The improved nutritional status of children with thalassemia in our center may reflect the overall improvement of care for these patients. However, another study in done in 2015 a different region in Indonesia reported that only 23.6% of children with thalassemia were malnourished.[24]

Most of our subjects received transfusions every 3 to 4 weeks, totaling more than 12 transfusions a year. Another study in Indonesia reported that children who underwent routine transfusions had average transfusion frequency of 15.8 times per year.[25]

Most our subjects (73.7%) had pre-transfusion Hb levels <9 g/dL (range 6-9 g/dL). A previous study reported an average hemoglobin level of 5-8 mg/dL.[26] According to the recommendations of the Thalassemia International Federation (2008), pre-transfusion Hb should be maintained at 9-10.5 g/dL to slow down the onset of complications.[9] Hemoglobin below 9 g/dL might be related to diminished erythropoiesis and iron absorption in the intestines, but excess hemoglobin leads to increased viscosity and the risk of thrombosis.[27]

More than half of our subjects had ferritin levels between 1,001 and <5,000 ng/mL (91 subjects; 59.9%). Our results were consistent with those of a previous study which found a mean ferritin level of more than 3,000 ng/mL.[28] A ferritin level of >1,000 ng/mL indicates an excess concentration of serum iron, necessitating iron chelation therapy. Repeated blood transfusions could lead to hemosiderosis and/or hemochromatosis, which cause iron overload in body tissues, damaging body organs such as the liver, spleen, kidneys, heart, bones, and pancreas.[19]

Ninety-seven (63.9%) subjects used deferiprone as their chelation therapy. This finding was in line with a study conducted in a tertiary hospital in Jakarta, Indonesia, in which 53.6% of subjects used deferiprone.[11] Ninety-four (61.8%) subjects in our study used iron chelation for ≥4 years.

None of the subjects experienced kidney dysfunction based on creatinine eGFR [mean eGFR 145.3 (SD 30.4) mL/min/1.73 m^2]. These results differed from a previous study which reported that 58.8% of children with thalassemia (mean age 9 years) experienced kidney dysfunction.[10] Using the cystatin C-based Filler formula, 33 children (21.7%) had kidney dysfunction. Furthermore, using the creatinine- and cystatin C-based eGFR formulas, we found kidney dysfunction in 59.9% of subjects with the Schwartz formula, and 26.3% with the New CKID formula.

Previous studies suggested that cystatin C was superior to creatinine in detecting kidney dysfunction. Cystatin C is a specific and sensitive early marker for monitoring glomerular and tubular dysfunction. A previous study stated that 36% of thalassemia major patients experienced an increase in serum cystatin C.[13] Another study also stated that serum cystatin C was significantly increased in thalassemia patients compared to healthy subjects.[14] Ali *et al.*[29] found that children with thalassemia had significantly higher levels of cystatin C and serum creatinine, and significantly lower eGFR and creatinine clearance, compared to healthy controls. Cystatin C had a highly significant strong negative correlation with eGFR and creatinine clearance, and a higher sensitivity and specificity than serum creatinine and creatinine clearance for small changes in GFR.

Cystatin C, an endogenous marker for assessing eGFR, is relatively new and considered to be better than serum creatinine as a biomarker for detecting kidney failure.[18] This is because cystatin C levels are not affected by muscle mass, nutritional status, size, age, gender, serum protein, bilirubin or medications. Thus, in certain populations with lower muscle mass, such as children, cystatin C is very good for assessing kidney function.[30,31] After filtration in the glomerulus, cystatin C is fully catabolized in the renal proximal tubules and does not return to the blood. Therefore, the level of cystatin C in the blood is considered to represent the glomerular filtration rate.[32] Cystatin C has also been reported to be more sensitive in detecting early and intermediate renal disorders.[33]

The high frequency of glomerular dysfunction reported in several studies of thalassemia subjects, could possibly be attributed to chronic anemia, iron overload, or chelation therapy.[10,13,29] In the present study, kidney dysfunction was detected only when cystatin C was incorporated in eGFR calculations.

A limitation in this study was that we did not use inulin as the gold standard for detecting kidney dysfunction, since this would entail an invasive procedure. Inulin is freely filtered through the glomerulus and neither secreted nor reabsorbed in the renal tubules, and its urinary clearance has therefore been regarded as the gold standard for measuring GFR. However, inulin clearance is a cumbersome procedure because of the requirements for continuous intravenous infusion of the substance and timed urine collections.[35]

We used creatinine-based eGFR as a commonly used, non-invasive parameter to determine kidney function, as creatinine-based eGFR has been widely reported to have a high correlation with inulin-based eGFR. We also performed cystatin C examination and incorporated it into several methods of eGFR calculation. Several studies have been published in which GFR equations in children have been validated against renal (urinary) clearance of inulin.[35] A study in 60 children with kidney dysfunction that compared cystatin C and creatinine to the gold standard inulin found that cystatin C and creatinine were equivalent with measured eGFR via inulin clearance.[34] Another study compared cystatin C, creatinine, and inulin in 184 children with kidney disease and found a stronger correlation between cystatin C- and inulin-based eGFR than between creatinine- and inulin-based eGFR.18 Cystatin C clearance was closer to inulin clearance and was a better marker for measuring children's eGFR.[35] Furthermore, the creatinine- and cystatin C-based Schwartz formula provided eGFR estimates closest to inulin-based eGFR gold standard.[36]

Interestingly, we found 58 (38.2%) subjects with hyperfiltration (≥150 mL/min/1.73 m^2) using the creatinine-based Schwartz formula. The high proportion of hyperfiltration in this study might be the reason no kidney dysfunction was detected in our subjects when using the creatinine-based eGFR cut-off point of <90 mL/min/1.73 m^2. A study found that of 71 thalassemia subjects, 66.2% had hyperfiltration.[38] Another study reported that one-third of thalassemia patients who were not regularly transfused had abnormally high creatinine clearance (hyperfiltration)[5] Another study reported that renal hyperfiltration is common in thalassemia patients as a consequence of chronic anemia, especially in patients not regularly transfused.[5,8] Chronic anemia leads to vascular resistance resulting in reduced blood flow to the kidneys, potentially increasing the eGFR, thus causing a hyperfiltration state, as a compensation mechanism of the functioning nephrons.[8] When the number of functioning nephrons is reduced, single-nephron glomerular hyperfiltration can result in decreasing GFR.[39] Hyperfiltration can lead to decreased eGFR because of epithelial and endothelial injury.[37]

Increased GFR is well known to precede the onset of albuminuria and progressive decline of GFR in type 1 diabetes mellitus, hypertension, and obesity.[39] In a large cohort study of 55,992 healthy subjects aged ≥20 years who underwent health check-ups, a significantly higher percentage of subjects with initial renal hyperfiltration developed an eGFR decline of more than 30% or 40% during a median follow-up of 46 months compared to those without hyperfiltration.[40]

In spite of significant positive correlations among eGFR formulas, this study found no agreement in detecting kidney dysfunction between the creatinine-based Schwartz formula and cystatin C-based Filler formula. No subjects were found to have kidney dysfunction based on creatinine-only eGFR, while 21.7% of subjects had kidney dysfunction using cystatin C-only eGFR. However, hyperfiltration was detected in 38.6% of subjects using the creatinine-based Schwartz formula, while no hyperfiltration was detected using the cystatin C-based Filler formula. A previous study compared creatinine-based and cystatin C-based eGFR in assessing normal and decreased renal function and found a significant difference between the two formulas. The study found increased cystatin C clearance with concurrent normal creatinine clearance and creatinine-based eGFR, that indicated the advantages of cystatin C measurement in evaluating early changes of renal function in thalassemic patients. These findings suggest that renal dysfunction may not be detected by routine tests; therefore, the use of early markers such

as cystatin C is recommended.[13] A study at a referral hospital in Bandung, West Java, Indonesia, evaluated the agreement between creatinine and cystatin C eGFR in 21 patients with nephrotic syndrome and found that the cystatin C-based Filler formula obtained significantly lower eGFR values compared to the creatinine-based Schwartz formula.[41]

Another previous study reported that serum creatinine and creatinine clearance did not differ between children with thalassemia and controls, but urinary N-acetyl cysteine was elevated in all patients with thalassemia, showing impairment of renal tubular function.[42] The underlying mechanisms for tubular injury in patients with thalassemia include long-standing anemia, chronic hypoxia, iron overload, and iron chelating agent use. A study emphasized the role of chronic hypoxia in the tubulointerstitium as a final common pathway to end-stage renal failure.[37] Glomerular dysfunction in thalassemia is not a rare complication, so early markers such as cystatin C are useful for early detection of small changes in GFR. Periodic renal assessment of such patients is mandatory, as many of them may have hidden renal abnormalities.[14,29,42]

In conclusion, the proportion of kidney dysfunction in children with thalassemia was 21.7% when using cystatin C-based eGFR, 26.3% when using creatinine- and cystatin C-based eGFR (New CKID), and 59.9% when using creatinine- and cystatin C-based eGFR (Schwartz). However, no kidney dysfunction was detected using creatine-based (Schwartz) eGFR. There was no agreement level between creatinine-based eGFR (Schwartz) and cystatin C-based eGFR (Filler) in detecting kidney dysfunction in thalassemic children. More parameters might be needed rather than creatinine-based eGFR alone for the early detection of kidney dysfunction in children with thalassemia.

Conflict of interest

None declared.

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