

## Original Research Article

# ROLE OF SERUM CYSTATIN-C AS EARLY BIOMARKER FOR RENAL DYSFUNCTION IN CHILDREN WITH BETA THALASSEMIA MAJOR

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Received : 02/09/2026  
Received in revised form : 01/10/2026  
Accepted : 12/10/2026

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DOI: 10.70034/ijmedph.2026.4.86

Source of Support: Nil,  
Conflict of Interest: None declared

Int J Med Pub Health  
2026; 16 (4); 580-585

## ABSTRACT

**Background:** Eventhough there is advanced treatment and chelation therapy for beta thalassemia major, the unrecognized complications like renal impairment is emerging nowadays. The aim is to study the role of serum cystatin-C as the early biomarker for renal dysfunction in children with beta thalassemia major ( $\beta$ -TM).

**Materials and Methods:** The study was performed on 30 children with  $\beta$ -TM and 30 apparently healthy children matched for age and sex as a control group. For all the enrolled children, a comprehensive medical history was obtained and complete physical examination was performed, blood urea, serum creatinine, estimated glomerular filtration rate (eGFR) by original Schwartz formula and protein creatinine ratio in urine, serum cystatin-C level were measured.

**Results:** A total of 60 participants (30 cases and 30 controls) were included. Serum cystatin C levels were significantly higher in children with  $\beta$ -thalassemia major compared with controls [2.42 (2–2.9) vs. 1.02 (0.9–1.1),  $p < 0.001$ ]. Significant differences were also observed in creatinine, eGFR, urine protein, PCR, and hemoglobin levels ( $p < 0.001$ ). Serum cystatin C showed a significant positive correlation with PCR ( $\rho = 0.647$ ,  $p < 0.001$ ) and a significant negative correlation with creatinine ( $\rho = -0.593$ ,  $p < 0.001$ ). ROC analysis demonstrated excellent diagnostic performance of cystatin C with an AUC of 1.00, showing 100% sensitivity and 100% specificity at a cut-off value of 1.4 mg/L.

**Conclusion:** Cystatin-C is specific and sensitive early biomarker for monitoring glomerular and tubular dysfunction in children with  $\beta$ -TM.

**Keywords:** beta thalassemia, creatinine, sensitivity, specificity

## INTRODUCTION

Beta thalassemia is a hereditary anaemia of autosomal recessive origin which is due to either reduced or absent production of beta globin chain of hemoglobin molecule. Beta thalassemia major or homozygous beta thalassemia is the disease with complete absence of beta globin chain synthesis. These patients need blood transfusion in the first year of life usually, as the fetal hemoglobin is replaced by the adult hemoglobin during the period of 6 months to 1 year of age.<sup>[1]</sup> Even though there is advanced treatment and chelation therapy for beta thalassemia major, the unrecognized complications like renal impairment are emerging nowadays.<sup>[2]</sup>

Several factors contribute to the renal functional abnormalities in beta thalassemia major children. They are reduced life span of RBCs, increased iron turnover, tissue deposition of excess iron and nephrotoxic iron chelators.

Thalassemia major and iron overload are known to affect many organs like heart, lungs, liver, kidneys and endocrine glands.<sup>[3]</sup>

Thalassemia produces renal abnormalities like increased renal blood flow, decreased urine concentrating ability and renal tubular acidosis.<sup>[6]</sup>

Many studies on patients with beta thalassemia major are demonstrating that the anaemia and iron toxicity are the causes for renal dysfunction. Iron chelation therapy also affects renal function in these patients. The newer oral iron chelator Deferasirox causes

increase in serum creatinine, proteinuria and renal failure.<sup>[7]</sup>

Renal dysfunction is prevalent among beta thalassemia major patients which has been demonstrated by many studies which reveals proximal tubular dysfunction, proteinuria, aminoaciduria and low urine osmolarity.<sup>[8,9]</sup>

## MATERIALS AND METHODS

**Subjects:** This study was conducted on the patients attending the hematology out patient clinic of the Institute of Child Health and Hospital for Children, Egmore, Chennai during the period from January 2019 to January 2020. Two groups of children were enrolled as Group 1 and Group 2.

The group 1 includes 30 children diagnosed as beta thalassemia major on regular transfusion therapy and chelation therapy from the age 3-12 years. Their diagnosis was based on the standard criteria including high performance liquid chromatography [HPLC], regular transfusion with packed RBCs and receiving chelation therapy regularly.

The group 2 includes 30 healthy children from the age group of 3-12 years.

The inclusion criteria for the cases included the patients with beta thalassemia major regularly transfused with packed RBCs and receiving chelation therapy in regular manner from the age group of 3-12 years and the parents or care givers willing to give informed written consent.

The exclusion criteria for group 1 (cases) included patients with the history of recurrent urinary tract infections or systemic diseases which affect kidneys and history of intake of known nephrotoxic drugs and family history of renal diseases which are hereditary. The exclusion criteria for group 2 (controls) are the children with systemic diseases like anaemia, skeletal deformities, cardiovascular, liver and renal abnormalities.

**Methods:** Enrolled children are subjected to the following

1. Thorough history taking which includes the stress on the age at first transfusion, type of chelator on use, duration of chelation therapy and the patient's compliance for chelation therapy and the history of splenectomy undergone.
2. Clinical examination which includes the anthropometric measures-height, general examination and systemic examination including the clinical evidence of iron overload complication and hemosiderosis of the skin.
3. Laboratory investigations

### Sampling Methods

**Blood sample:** Venous blood 5ml was drawn from the intravenous line when it is fixed in the beta thalassemia major patients in the pretransfused stage for the purpose of blood transfusion. In the controls, the same amount of venous blood was drawn from the

antecubital vein under strict aseptic precautions and distributed as follows

1. Whole blood 1ml was drawn in an EDTA tube and mixed gently. This EDTA sample was used to measure the complete blood count.
2. Another 4ml of blood was drawn in the red capped tube with clot activator and allowed to separate the serum then centrifuged for 15 minutes at 1000×g. The serum was removed, aliquoted and stored at -20 degree Celsius.

The separated serum was used for

1. Serum urea and creatinine are measured using cobas 6000, C 501 from Roche Diagnostics by appropriate methods of chemical principles.
2. Serum cystatin-c was measured using ELISA method.

**Urine sample:** The second morning midstream urine sample of 5ml was obtained from the patients and controls and used for spot protein creatinine ratio analysis. In the anthropometric measures, the height of the cases and controls are measured

**Statistical Methods:** Statistical analysis was performed using Jamovi version 2.7.7. The normality of continuous variables was assessed using the Shapiro-Wilk test. Continuous variables were expressed as median and interquartile range (IQR) because the data were not normally distributed. Comparisons between the case and control groups were performed using the Mann-Whitney U test. Categorical variables were presented as frequency and percentage and compared using the Chi-square test. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of serum cystatin C and other renal biomarkers. The area under the curve (AUC), 95% confidence interval (CI), optimal cut-off value, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. A p-value < 0.05 was considered statistically significant.

## RESULTS

The study was conducted among 60 children aged 3-12 years. The study population consisted of two groups: Group I included 30 children with  $\beta$ -thalassemia major, while Group II included 30 healthy controls. Among the cases, 17 (56.7%) were females and 13 (43.3%) were males, whereas the control group included 16 (53.3%) females and 14 (46.7%) males. There was no statistically significant difference in gender distribution between the two groups ( $p = 0.790$ ). Similarly, no statistically significant differences were observed in age and height between cases and controls. The median age was 8 (5.4-10) years in the case group and 8 (6.3-11) years in the control group ( $p = 0.330$ ). The median height was 121 (105-128) cm among cases and 120 (107-136) cm among controls ( $p = 0.217$ ) [Table 1].

**Table 1: Socio-demographic characteristics of studied groups**

| Baseline Characteristics |        | Case (n=30)   | Control (n=30) | Test Value | p-value |
|--------------------------|--------|---------------|----------------|------------|---------|
| Gender                   | Female | 17 (56.7%)    | 16 (53.3%)     |            | 0.79    |
|                          | Male   | 13 (43.3%)    | 14 (46.7%)     |            |         |
| Age                      |        | 8 (5.4–10)    | 8 (6.3–11)     | 384        | 0.33    |
| Height                   |        | 121 (105–128) | 120 (107–136)  | 366        | 0.217   |

Clinical manifestations of the studied patients were as follows: the most presenting symptoms were moderate to severe degree of pallor and hepatomegaly in all patients 100%, jaundice in 95.5% and splenomegaly in 75.3% with splenectomy performed in 13.5% cases, the incidence of mongoloid features was 80.2%. The onset of first

blood transfusion presented early in life (mean 0.72 ± 0.42 years), age onset of iron chelation therapy was mean 2.72 ± 0.42 years and it was as follows: 56% of cases were treated by deferoxamine subcutaneous infusion, 36.5% were treated by deferasirox and 7.5% by Hydra.

**Table 2: Comparison between the studied groups regarding laboratory investigations indicating renal function tests**

| Variable         | Case (n=30) Median (IQR) | Control (n=30) Median (IQR) | Mann Whitney U Test | p-value |
|------------------|--------------------------|-----------------------------|---------------------|---------|
| Urea             | 22.5 (16.1–27.8)         | 23 (22–24.8)                | 367.5               | 0.224   |
| Creatinine       | 0.30 (0.26–0.40)         | 0.50 (0.4–0.50)             | 88                  | <0.001* |
| eGFR             | 203 (170–263)            | 145 (121–154)               | 124.5               | <0.001* |
| Urine Protein    | 19.1 (10.3–26.9)         | 7 (6–9)                     | 126                 | <0.001* |
| Urine Creatinine | 41.5 (36.5–50.8)         | 48 (42–51.5)                | 317.5               | 0.051   |
| PCR              | 0.469 (0.280–0.662)      | 0.156 (0.12–0.175)          | 34                  | <0.001* |
| Cystatin C       | 2.42 (2–2.9)             | 1.02 (0.9–1.10)             | 0                   | <0.001* |
| Hemoglobin       | 6.5 (5.5–7.1)            | 12 (11.6–12.3)              | 0                   | <0.001* |

Notes: \*significant

There were no statistically significant differences between the two groups with respect to serum urea and urine creatinine levels ( $p > 0.05$ ). The median serum urea level was 22.5 (16.1–27.8) mg/dL in cases and 23 (22–24.8) mg/dL in controls ( $p = 0.224$ ), while the median urine creatinine level was 41.5 (36.5–50.8) and 48 (42–51.5), respectively ( $p = 0.051$ ). There were statistically significant differences observed between cases and controls for serum creatinine, eGFR, urine protein, protein-creatinine ratio (PCR), serum cystatin C, and

hemoglobin (all  $p < 0.001$ ). Compared with controls, children with  $\beta$ -thalassemia major had significantly lower median serum creatinine 0.30 (0.26–0.40) vs. 0.50 (0.4–0.50) mg/dL and hemoglobin 6.5 (5.5–7.1) vs. 12 (11.6–12.3) g/dL. Conversely, the median eGFR 203 (170–263) vs. 145 (121–154), urine protein 19.1 (10.3–26.9) vs. 7 (6–9), protein-creatinine ratio 0.469 (0.280–0.662) vs. 0.156 (0.120–0.175), and serum cystatin C 2.42 (2.0–2.9) vs. 1.02 (0.9–1.1) were significantly higher in cases than in controls (all  $p < 0.001$ ).

**Table 3: Diagnostic performance of Serum Cystatin C and other renal biomarkers for the early detection of renal dysfunction in children with  $\beta$ -thalassemia major**

| Parameter        | AUC (95% CI)        | Cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | p-value |
|------------------|---------------------|---------|-----------------|-----------------|---------|---------|---------|
| Cystatin C       | 1.00 (1.00–1.00)    | 1.4     | 100             | 100             | 100     | 100     | <0.001  |
| PCR              | 0.962 (0.907–1.00)  | 0.198   | 93.3            | 100             | 100     | 93.8    | <0.001  |
| Creatinine       | 0.902 (0.827–0.978) | 0.35    | 70              | 100             | 100     | 76.9    | <0.001  |
| eGFR             | 0.862 (0.761–0.962) | 156     | 83.3            | 86.7            | 86.2    | 83.9    | <0.001  |
| Urine Protein    | 0.860 (0.757–0.963) | 12.5    | 70              | 100             | 100     | 76.9    | <0.001  |
| Urine Creatinine | 0.647 (0.503–0.792) | 41.5    | 50              | 80              | 71.4    | 61.5    | 0.046   |

Abbreviations: PPV, positive predictive values; NPV, negative predictive values.

ROC curve analysis demonstrated that Serum cystatin C had the highest diagnostic accuracy with an AUC of 1.00 (95% CI: 1.00–1.00,  $p < 0.001$ ) at a cut-off value of 1.4 mg/L, yielding 100% sensitivity, 100% specificity, 100% positive predictive value (PPV), and 100% negative predictive value (NPV). PCR also showed excellent diagnostic accuracy with an AUC of 0.962 (95% CI: 0.907–1.00,  $p < 0.001$ ) at a cut-off value of 0.198, with 93.3% sensitivity, 100% specificity, 100% PPV, and 93.8% NPV. Creatinine demonstrated good diagnostic performance with an AUC of 0.902 (95% CI: 0.827–0.978,  $p < 0.001$ ) at a cut-off value of 0.35, with 70% sensitivity and 100% specificity. Similarly, eGFR showed good diagnostic accuracy with an AUC of

0.862 (95% CI: 0.761–0.962,  $p < 0.001$ ) at a cut-off value of 156, yielding 83.3% sensitivity and 86.7% specificity. Urine protein also demonstrated good diagnostic performance with an AUC of 0.860 (95% CI: 0.757–0.963,  $p < 0.001$ ) at a cut-off value of 12.5, with 70% sensitivity and 100% specificity.

Among all parameters, urine creatinine showed the lowest diagnostic accuracy, with an AUC of 0.647 (95% CI: 0.503–0.792,  $p = 0.046$ ) at a cut-off value of 41.5, demonstrating 50% sensitivity and 80% specificity.

Combined ROC Curves

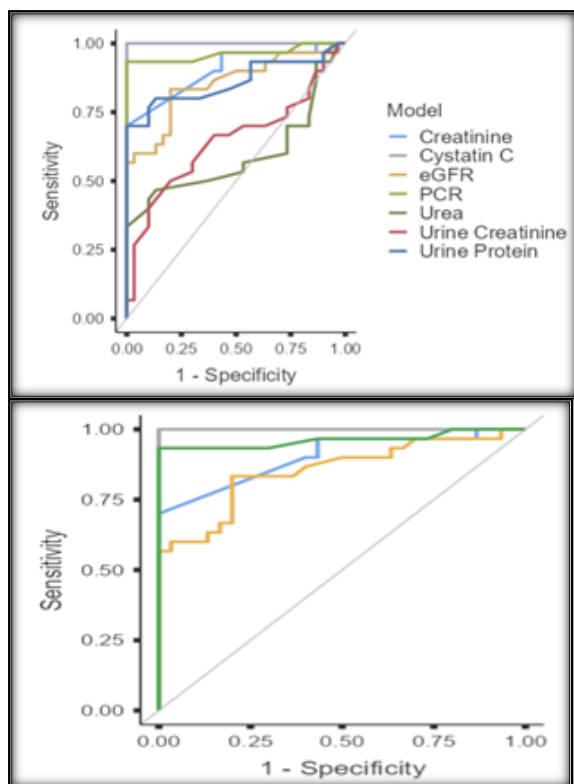


**Figure 1:** shows the combined ROC curves of serum cystatin C and other renal biomarkers. Serum cystatin C demonstrated the highest diagnostic performance, with its ROC curve closest to the upper left corner (AUC = 1.00), followed by PCR (AUC = 0.962), whereas urine creatinine showed the lowest diagnostic accuracy (AUC = 0.647).

## DISCUSSION

Chronic anaemia and iron overload are the main factors responsible for tubular damage, interstitial fibrosis, glomerulosclerosis in patients with beta thalassemia major.<sup>[20]</sup>

Hamed and Elmelegy et al. reported significant higher levels of serum cystatin -c and urine protein creatinine ratio than controls.<sup>[28]</sup>

The underlying mechanisms for tubulopathy and glomerulopathy in thalassemia major patients include

1. Long standing anaemia
2. Chronic hypoxia
3. Iron overload
4. Iron chelating drugs.<sup>[6]</sup>

In the present study, beta thalassemia major patients showed higher levels serum cystatin -C and urine protein creatinine ratio, eGFR, and lower levels of serum creatinine and blood hemoglobin than control group.

In the study of Ali and Mahmoud et al. they found that the higher levels of serumcystatin-c and urine protein creatinine ratio in the thalassemic patient group than the control group.<sup>[27]</sup>

Kacar et al found that chronic hypoxia occurs due to anemia disrupted kidney function.<sup>[29]</sup>

Koliakos et al found normal serum creatinine and creatinine clearance in thalassemia patients who received subcutaneous deferoxamine treatment.<sup>[13]</sup>

In the present study, there were Statistically significant positive correlation between cystatin c and Urine protein, and spot PCR, duration of Chelation therapy and frequency of blood Tranfusion / year and there were statistically Significant negative correlation between Cytatin C, Spot PCR and Hb.

- According to Ali and Mahmoud, they
- Concluded that in thalassemia major
- patients, glomerular dysfunction is a
- Common complication. So Cystatin C is
- an useful early biomarker for periodic
- renal assessment in those patients to
- detect the hidden renal dysfunction.<sup>[27]</sup>

Economou et al reported that 36%. of their Beta thalassemia major patients had elevated Serum Cystatin c which Suggests that cystatin c is the early and superior biomarker to serum creatinine for detection of impaired renal function in cross sectional studies.<sup>[23]</sup>

Voskaridou et al found inverse Correlation between Hb and cystatin c Levels.<sup>[37]</sup>

In the present study There were no statistically significant differences between the two groups with respect to serum urea and urine creatinine levels ( $p > 0.05$ ) The median serum urea level was 22.5 (16.1-27.8) mg/dL in cases and 23 (22-24.8) mg/dL in controls ( $p = 0.224$ ) while the median urine creatinine level was 41.5 (36.5–50.8) and 48 (42-51.5), respectively ( $p = 0.051$ )

There were statistically significant differences observed between cases and controls for serum creatinine, eGFR, urine protein, protein-creatinine ratio (PCR), serum cystatin C, and hemoglobin (all  $p < 0.001$ ) Compared with controls, children with  $\beta$ -thalassemia major had significantly lower median serum creatinine [0.30 (Q.26–0.40) vs. 0.50 (0.40-0.50) mg/dL] and hemoglobin [6.5 (5.5–7.1) vs. 12 (11.6-12.3) g/dL].

Conversely, the median eGFR [203 (170– 263) vs. 145 (121–154)], urine protein [19.1 (10.3-26.9) [0.469 (0.280-0.662) vs. 0.156 (0.120–0.175)], and serum cystatin C [2.42 (2.0-2.9) vs. 1.02 -26.9) vs. 7 (6-9)], protein-creatinine ratio (0.9–1.1)] were significantly higher in cases than in controls (all  $p < 0.001$ .)

ROC curve analysis demonstrated that Serum cystatin C had the highest diagnostic accuracy with an AUC of 1.00 (95% CI: 1.00-1.00,  $p < 0.001$ ) at a cut-off value of 1.4 mg/L, yielding 100% sensitivity, 100% specificity, 100% positive predictive value (PPV), and 100% negative predictive value (NPV). PCR also showed excellent diagnostic accuracy with an AUC of 0.962 (95% CI: 0.907–1.00,  $p < 0.001$ ) at a cut-off value of 0.198, with 93.3% sensitivity, 100% specificity, 100% PPV, and 93.8% NPV.

Similarly, eGFR showed good diagnostic accuracy with an AUC of 0.862 (95% CI: 0.761–0.962,  $p <$

0.001) at a cut-off value of 156, yielding 83.3% sensitivity and 86.7% specificity.

Urine protein also demonstrated good diagnostic performance with an AUC of 0.860 (95% CI: 0.757–0.963,  $p < 0.001$ ) at a cut-off value of 12.5, with 70% sensitivity and 100% specificity.

Narvaez-Sanches et al found that cystatin c is a very interesting option as early biomarker and Could be a replacement to serum creatinine for diagnosis and possibly monitoring kidney function in Children.<sup>[36]</sup>

Ali and Mahmoud found that AUROC for serum cystatin-C was significantly higher than that for serum creatinine (92% versus 80%). Moreover, serum cystatin-C had higher sensitivity and specificity than serum creatinine (66% versus 26%). The AUROC for serum cystatin-C was significantly higher ( $0.84 \pm 0.03$ ) than that for creatinine clearance ( $0.35 \pm 0.05$ ). Moreover, serum cystatin-C had higher sensitivity and specificity than creatinine clearance (66% versus 62% and 92% versus 65%, respectively).<sup>[27]</sup>

It is well known that cystatin-C is a valuable marker for cardiovascular morbidity and mortality in diabetes and metabolic syndrome.<sup>[30-32]</sup>

Previous studies demonstrated the relationship between arterial stiffness and renal insufficiency, including vascular structure changes, increased atherogenic lipoprotein, decreased fibrinolysis and oxidative stress; these studies demonstrated that endothelial dysfunction is the main link between renal insufficiency and cardiovascular diseases.<sup>[33-35]</sup>

This is in agreement with Filler et al who stated that the areas under the ROC curves for cystatin-C were 0.943, for  $\beta$ -2 microglobulin 0.899, and for Schwartz GFR estimate was 0.917 with no statistically significant difference ( $P > 0.05$ ), although there was a tendency toward the best area for cystatin-C. The area under the curve for creatinine (0.840) was significantly smaller than that for cystatin-C (the difference between areas, 0.103; SE, 0.031;  $P < 0.001$ ), and the Schwartz GFR estimate (the difference between areas, 0.080; SE, 0.021;  $P < 0.001$ ). The clinical sensitivities and specificities were calculated at selected decision points of the ROC curves, cystatin-C revealed higher sensitivities than cystatin c and the GFR estimate (61% versus 29%, 38%, and 31%, respectively) for reduced GFR. At the cutoff with a diagnostic specificity of 95%, cystatin-C (80%) had higher sensitivities than serum creatinine (35%).<sup>[26]</sup>

Hyperfiltration is present in patients with thalassemia major which leads to overestimated GFR by schwartz formula.<sup>[3,11,13,14]</sup>

The median eGFR<sub>203</sub>(170-263)vs.145(121-154) is seen in the present study.

Quinn et al. have found that eGFR calculated by the schwartz formula overestimated the creatinine clearance measured in their study by 30ml/min per 1.73sq.m. Most of the patients had hyperfiltration especially those with lower serum creatinine levels.<sup>[14]</sup>

Overestimation of GFR by the equations based on serum creatinine is due to low serum creatinine levels in thalassemia major patients in the present study. Many factors contribute to low serum creatinine levels urinary creatinine excretion is significantly lower than expected value.

In healthy individuals, urinary creatinine excretion is expected to equal creatinine generation.<sup>[28,29]</sup>

Lower creatinine excretion by thalassemia major patients indicates the decreased generation by the muscles. Reduced muscle mass is seen in thalassemia major patients

The hemoglobin level in 100% cases group shows the lower level compared to the controls. All controls are having normal hemoglobin level which is 100%. The comparison is done by the Mann Whitney U test which gives the p value of  $< 0.001$  which is highly significant.

In beta thalassemia major, the alpha globin chains are in excess to beta globin chains which precipitate in red cell precursors and damaging the red cell membrane leading to hemolysis and anaemia.<sup>[37]</sup>

The degree of tubular abnormalities are correlated with the severity of anaemia.<sup>[6,11]</sup> Anaemia can cause oxidative stress.<sup>[3,21]</sup> which leads to lipid peroxidation and DNA damage.<sup>[3]</sup>

Hemolysate and hemoglobin ameliorate oxidation induced DNA damage.<sup>[24]</sup> The markers of oxidative damage to tubules favour the role of anaemia and iron overload in renal dysfunction in thalassemia major patients.<sup>[11-13,20]</sup>

Elonomou et al. used cystatin-c in patients with beta thalassemia major as the marker to find the renal dysfunction.<sup>[23]</sup>

It is well known that cystatin -c is a valuable biomarker useful to evaluate cardiovascular morbidity and mortality in diabetes mellitus and metabolic syndrome.<sup>[31-33]</sup>

In the previous studies it has been demonstrated that the relationship between the arterial stiffness and renal insufficiency in which it is found that the vascular structure changes, increased atherogenic lipoprotein, to the renal decreased fibrinolysis and oxidative stress are contributing insufficiency. These studies revealed that the endothelial dysfunction is the main factor between renal insufficiency and cardiovascular diseases.<sup>[34-36]</sup>

Ali and Mahmoud, as they found significantly higher level of cystatin-C, serum creatinine, serum ferritin and albumin/creatinine ratio in the urine of thalassemic group than controls.<sup>[27]</sup>

## CONCLUSION

Cystatin c is specific and sensitive early biomarker to monitor glomerular and tubular dysfunction. Glomerular dysfunction in beta thalassemia major children is not a rare complication. So periodic renal assessment of these patients is mandatory as they may be affected by hidden renal dysfunction.

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