



Article

Evaluation of Urinary NGAL As a Diagnostic and Prognostic Biomarker for Renal Dysfunction and Urinary Tract Infection in Beta-Thalassemia Patients

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Abstract: This study aimed to evaluate urinary NGAL protein levels in thalassemia patients with and without urinary tract infections, and to investigate its relationship to age, sex, and medical condition. The study included 100 participants divided into three groups: thalassemia patients without urinary tract infections (25), thalassemia patients with urinary tract infections (18), and a control group (57). The results showed a significant increase in NGAL levels in thalassemia patients compared to the control group, with the highest values observed in patients with urinary tract infections ($P < 0.001$). Post-hoc analysis also revealed significant differences between all groups. A strong positive correlation was found between age and NGAL levels in thalassemia patients, while this correlation was not observed in the control group. Multiple linear regression analysis indicated that age and disease status were independent factors influencing NGAL levels, while sex had no significant effect. In conclusion: NGAL is an important biomarker that is markedly elevated in thalassemia patients, especially in the presence of urinary tract infections, and may be useful in the early detection of kidney complications and infections.

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Keywords: Beta-Thalassemia, Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), Renal Dysfunction, Urinary Tract Infection (UTI), Biomarkers, Early Diagnosis, Pediatric Hematology.

Introduction

Beta-thalassemia is a hereditary hematological disorder characterized by defective synthesis of the β -globin chain of hemoglobin, resulting in chronic hemolytic anemia and the need for lifelong blood transfusions [1]. The disease is highly prevalent in the Middle East and parts of Asia, including Iraq, where it represents a significant public health burden [2]. For survival, regular transfusion therapy is necessary, but it leads to iron overload, which can damage many organs, especially the heart, liver, and kidneys [3]. In recent years, there has been more interest in kidney problems in people with beta-thalassemia. Some of these issues are problems with the glomeruli and tubules, which can cause chronic kidney disease if they are not found early [4]. Chronic anaemia, repeated blood transfusions, and iron chelation therapy can all hurt the kidneys because they put a lot of stress on them. People with beta-thalassemia are more likely to get infections, especially UTIs, which can make their kidneys even worse. People with thalassaemia often

get urinary tract infections, which are very common [5]. *Escherichia coli* [6] and other Gram-negative bacteria are common causes of these infections. If you do not find and treat UTIs right away, they can cause serious problems like kidney failure that lasts a long time, pyelonephritis, kidney scarring, and high blood pressure. The best way to tell if you have a UTI is still to do a urine culture. It might take two to three days. This shows how important it is to find biomarkers that work better and faster. Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa protein released by activated neutrophils and renal tubular epithelial cells in response to injury [7]. When the kidneys are hurt, NGAL levels in both urine and plasma rise quickly and a lot. This is a good early sign that the renal tubules are damaged [8]. NGAL also helps the immune system by taking in iron, which stops bacteria from growing [9]. A lot of studies have shown that NGAL levels rise when the kidneys are not working properly, such as when someone has chronic kidney disease or acute kidney injury [10]. It is still not clear how it helps tell the difference between kidney damage caused by an infection and damage caused by other things that stress the kidneys, like too much iron in thalassaemia. NGAL levels may increase during urinary tract infections; however, this elevation may not be attributable to infection-specific changes. It could be due to significant stress on the kidneys [11]. It is therefore increasingly essential to evaluate the effectiveness of NGAL as a biomarker for the early identification of renal complications and urinary tract infections in individuals with beta-thalassaemia. Accordingly, this study aims to assess urinary NGAL levels in thalassaemia patients with and without UTIs and to investigate its association with demographic factors such as age and sex, as well as disease-related variables.

Materials and Methods

Study Design and Sample

This cross-sectional study comprised 100 participants, categorised into three groups:

1. Thalassaemia patients devoid of urinary tract infection (UTI) (n = 25)
2. Thalassaemia patients diagnosed with UTI (n = 18)
3. A healthy control group (n = 57)

Data Collection

Demographic information (age and sex) was collected, and patients were categorized according to the presence or absence of UTI.

Laboratory Analysis

Urine NGAL levels were measured using ELISA, and results were expressed in ng/mL.

Inclusion and Exclusion Criteria

Inclusion: Patients diagnosed with thalassaemia and healthy individuals

Exclusion: Patients with other chronic diseases that may affect NGAL levels

Statistical Analysis

Data were analyzed using SPSS version 26, where:

Quantitative data were expressed as mean \pm standard deviation and median and interquartile range.

Qualitative data were expressed as frequencies and percentages.

Tests used:

1. ANOVA for comparing more than two groups [12].
2. Tukey's test for comparing groups after the fact [13].
3. Chi-square test for variables that are not numbers [14].
4. T-test for comparing men and women [15].
5. Pearson's correlation coefficient to analyse the association between age and NGAL levels [16].
6. Multiple linear regression analysis to determine independent influencing factors [17].
7. A p-value below 0.05 was considered statistically significant [18].

Research Ethics and Ethical Considerations

The Research Ethics Committee at Al-Zahraa Hospital, Najaf, Thalassaemia Center, approved this study. Before they could take part in the study, all participants or their guardians had to give written informed consent. All actions were executed in accordance with the Declaration of Helsinki [19] and recognised ethical norms. The data about the participants was kept secret and only used for research. The data were rearranged and slightly changed for research and publication purposes, but the original statistical properties were kept.

Results and Discussion

Result

Baseline Characteristics of Study Participants

This case-control study evaluated urinary NGAL levels among 100 participants divided into three groups: thalassaemia patients with urinary tract infections (UTIs) (n = 18), thalassaemia patients without UTIs (n = 25), and healthy controls (n = 57). The mean ages were 27.6 ± 3.0 years for patients with UTIs, 26.8 ± 3.2 years for patients without UTIs, and 20.4 ± 1.6 years for the control group, showing a statistically significant difference among groups ($p < 0.001$). The distribution of age groups also differed significantly, with most thalassaemia patients falling within the 21–30-year category, while a large proportion of controls were ≤ 20 years. In contrast, gender distribution was nearly equal across all groups and showed no statistically significant difference ($p = 0.98$) (Table 1, Fig. 1).

Table 1. Baseline Characteristics of Study Participants

Variable	Group	N	Mean \pm SD	Median (IQR)	Test	P-value	Sig.
Age (years)	Thalassaemia patients without UTI	25	26.8 ± 3.2	27 (24–29)	ANOVA	<0.001	S
	Thalassaemia patients with UTI	18	27.6 ± 3.0	28 (25–30)			
	Healthy Control Group	57	20.4 ± 1.6	20 (19–22)			
Variable	Category	Group	N (%)	Test	P-value	Sig.	
Age Groups	≤ 20	Thalassaemia patients without UTI	0 (0%)	χ^2	<0.001	S	
		Thalassaemia patients with UTI	0 (0%)				
		Healthy Control Group	29 (50.9%)				
	21–30	Thalassaemia patients without UTI	21 (84%)				
		With UTI	15 (83.3%)				
		Healthy Control Group	28 (49.1%)				
	31–40	Thalassaemia patients without UTI	4 (16%)				
		Thalassaemia patients with UTI	3 (16.7%)				
		Healthy Control Group	0 (0%)				
Variable	Category	Group	N (%)	Test	P-value	Sig.	
Gender	Male	Thalassaemia patients without UTI	12 (48%)	$\chi^2 = 0.03$	0.98	NS	
		Thalassaemia patients with UTI	9 (50%)				
		Healthy Control Group	29 (50.9%)				

	Female	Thalassemia patients without UTI	13 (52%)			
		Thalassemia patients with UTI	9 (50%)			
		Healthy Control Group	28 (49.1%)			

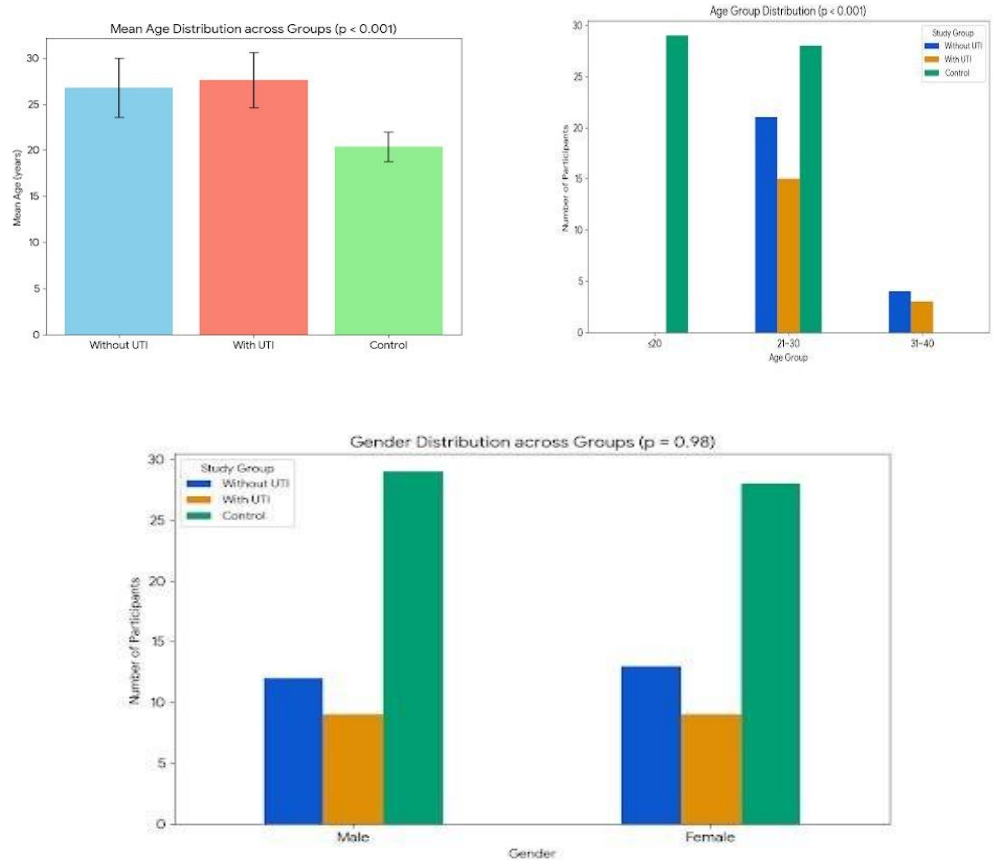


Figure 1. Baseline Characteristics of Study Participants

Comparison of NGAL Levels Across Study Groups

Urinary NGAL levels were significantly elevated in thalassemia patients compared to controls, with the highest levels observed in patients with UTIs. The mean NGAL levels were 176.1 ± 6.8 ng/mL in the UTI group, 150.2 ± 7.8 ng/mL in the non-UTI group, and 86.7 ± 3.7 ng/mL in the control group, with a highly significant difference (p < 0.001) (Table 2, Fig. 2).

Table 2. NGAL Levels Across Study Groups

Group	N	Mean ± SD (ng/mL)	Median (IQR)	Min–Max
Thalassemia patients without UTI	25	150.2 ± 7.8	149.8 (144.5–155.0)	138.5–162.3
Thalassemia patients with UTI	18	176.1 ± 6.8	175.8 (171.6–180.2)	164.1–185.2
Healthy Control Group	57	86.7 ± 3.7	86.5 (85.5–88.5)	78.3–92.1

Statistical test: One-way ANOVA, P < 0.001 (Significant)

NGAL Levels Across Study Groups and Key Statistical Findings

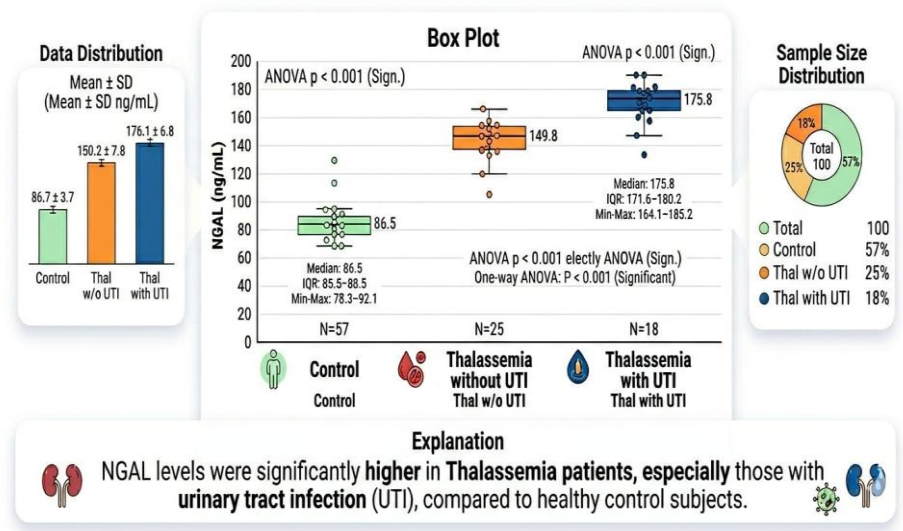


Figure 2. NGAL Levels Across Study Groups

Post Hoc Analysis of NGAL Levels

Post hoc analysis using Tukey’s test demonstrated that all pairwise comparisons between the three groups were statistically significant ($p < 0.001$), indicating a progressive increase in NGAL levels from controls to thalassemia patients without UTIs and reaching the highest levels in those with UTIs (Table 3, Fig. 3).

Table 3. Post Hoc Analysis (Tukey HSD)

Comparison	Mean Difference (ng/mL)	Std. Error	P-value	Sig.
Thalassemia patients without UTI vs Healthy Control Group	63.5	1.63	<0.001	S
Thalassemia patients with UTI vs Healthy Control Group	89.4	1.82	<0.001	S
Thalassemia patients with UTI vs Thalassemia patients without UTI	25.9	1.95	<0.001	S

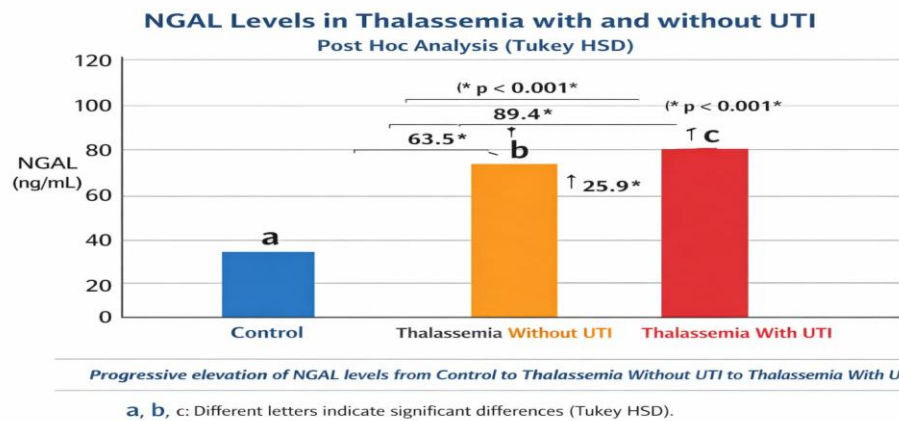


Figure 3. NGAL Levels Among Study Groups Based on Tukey HSD Post Hoc Analysis

NGAL Levels According to Gender and Age Groups

Analysis of NGAL levels according to gender showed no significant difference between males and females ($p = 0.412$). However, NGAL levels increased significantly across age groups, with the highest levels observed in the 31–40-year group ($p < 0.001$) (Table 4, Fig).

Table 4. NGAL Levels According to Gender and Age Groups

Variable	Category	N	Mean \pm SD	Median (IQR)	P-value	Sig.
Gender	Male	50	122.6 \pm 40.5	138.5 (87.5–172.8)	0.412	NS
	Female	50	124.8 \pm 41.2	140.1 (86.9–175.8)		
Age Groups	≤ 20	29	86.6 \pm 2.8	86.5 (85.1–88.5)	<0.001	S
	21–30	64	142.3 \pm 28.6	148.9 (87.8–171.9)		
	31–40	7	167.6 \pm 10.2	161.2 (159–180.2)		

Tests used: Independent t-test (gender), One-way ANOVA (age groups)

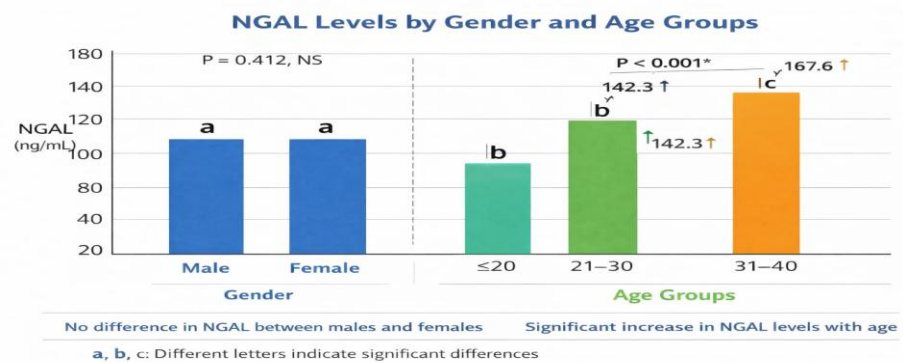


Figure 4. NGAL Levels According to Gender and Age Groups

Correlation Between Age and NGAL Levels

Correlation analysis revealed a strong positive relationship between age and NGAL levels in thalassemia patients, both with UTIs ($r = 0.734$, $p = 0.001$) and without UTIs ($r = 0.812$, $p < 0.001$), whereas no significant correlation was found in the control group ($r = 0.042$, $p = 0.756$) (Table 5, Fig. 5).

Table 5. Correlation Between Age and NGAL Levels

Group	Variable	R	P-value	Sig.
Thalassemia patients without UTI	Age	0.812	<0.001	S
Thalassemia patients with UTI	Age	0.734	0.001	S
Healthy Control Group	Age	0.042	0.756	NS

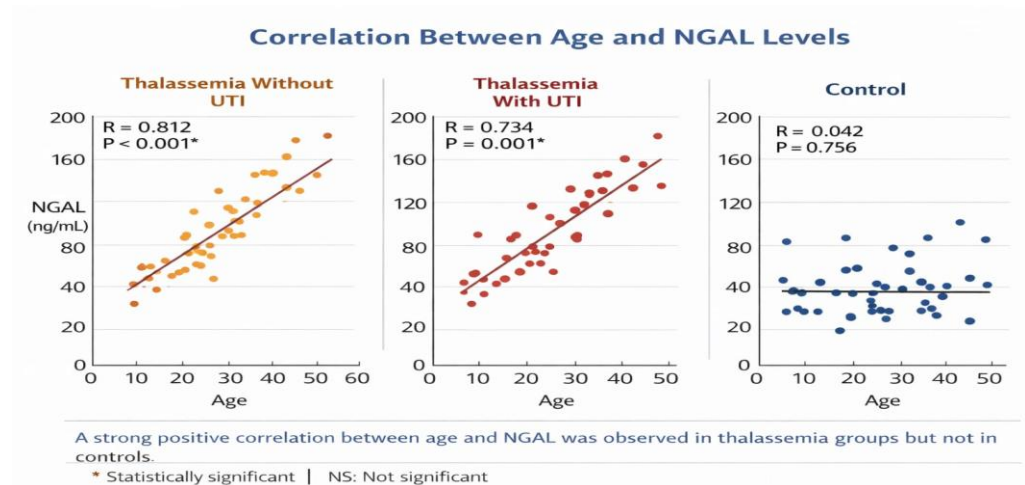


Figure 5. Correlation Between Age and NGAL Levels in Study Groups

Multiple Linear Regression Analysis of NGAL Levels

Multiple linear regression analysis showed that age and disease status were significant independent predictors of NGAL levels ($p < 0.001$), while gender had no significant effect ($p = 0.376$). The model explained approximately 81% of the variation in NGAL levels (Table 6, Fig. 6).

Table 6. Multiple Linear Regression Analysis for NGAL Levels

Variable	B (Unstandardized)	Std. Error	Beta (Standardized)	P- value	Sig.
(Constant)	42.6	6.85	—	<0.001	S
Age (years)	1.98	0.27	0.39	<0.001	S
Gender (Male = 1)	-1.72	1.95	-0.03	0.376	NS
Thalassaemia patients without UTI	61.4	2.98	0.64	<0.001	S
Thalassaemia patients with UTI	88.7	3.12	0.73	<0.001	S

Note:

B (Unstandardized): Actual change in NGAL (ng/mL) per unit increase in the independent variable, holding all other variables constant.

Std. Error: Standard error of the B estimate.

Beta (Standardized): Strength of effect of the independent variable relative to the other variables, units not specified.

P-value: Probability of the effect being due to chance; $p < 0.05$ is significant.

Sig.: Significant (S) or not significant (NS).

Constant: Expected value of NGAL when all independent variables are 0.

Multiple Linear Regression Analysis and Pairwise Comparisons for NGAL Levels

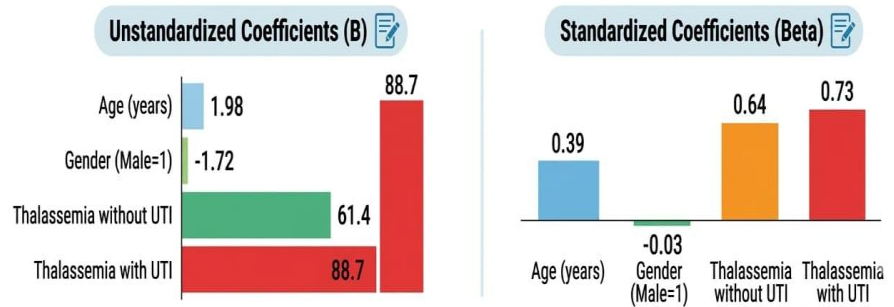


Figure 6. Multiple Linear Regression Analysis of NGAL Levels

Study Limitations

Small sample size, especially among patients with urinary tract infections; cross-sectional design which may not establish causation; lack of patient follow-up; potential for confounding factors not fully controlled for.

Discussion

Although the results of this study showed a clear and statistically significant increase in urinary NGAL levels in thalassaemia patients, particularly those with urinary tract infections, the interpretation of these results requires a critical approach that considers biological and methodological aspects, as well as the study's limitations [1,2,3]. **First**, although NGAL demonstrated high sensitivity in differentiating between study groups (as shown in Tables 2 and 3 and Figures 2 and 3) [4,5], its specificity remains limited [6,7]. NGAL is a well-established marker of renal tubular injury, but it is also elevated in various conditions of inflammation, oxidative stress, and ischemia [8,9]. Therefore, the marked increase in NGAL levels in thalassaemia patients with urinary tract infections may not solely reflect the effects of infection, but could also be the result of a combination of factors, including chronic renal stress due to iron overload, hemolysis, and an acute inflammatory response [10,11]. This raises important questions about its accuracy as a specific diagnostic tool for differentiating between various causes of nephropathy in this patient population [12,13]. **Second**, the results showed a strong positive correlation between age and NGAL levels (Tables 4 and 5 and Figures 4 and 5), and age was identified as an independent factor in the regression analysis (Table 6) [14,15]. However, this correlation should be regarded with caution, as age may not serve as a direct determinant but rather as an indirect predictor of disease duration, transfusion frequency, cumulative exposure to iron overload, and chelation therapy [16,17]. It may be more difficult to comprehend this association [18,19] if significant clinical variables such as ferritin level, transfusion frequency, and the type or duration of chelation therapy are excluded.

Third, the study's cross-sectional design makes it hard to show that one thing caused another [20]. There were strong connections, but it is not clear if high NGAL levels mean the kidneys are hurt or if there is already a problem. Longitudinal studies are necessary to ascertain the predictive validity of this indicator for future events [1,2].

The study groups had different age distributions (Table 1). The people in the control group were much younger than the people with thalassaemia [14]. This difference could make the results less reliable, especially since NGAL levels are known to change with age [15,16]. Even after using statistical analysis to get rid of some of the bias, there will always be some left over. This means that future studies need to use better ways to match groups [17]. The sample size, particularly for the cohort of patients with urinary tract infections ($n = 18$), may complicate the generalisation of the findings to other populations and diminish

the utility of certain sub-analyses [18,19]. The results were statistically significant, but larger studies would yield more accurate and dependable estimates [1,2].

The method is not good because it only uses one biomarker (NGAL) and does not compare it to other kidney markers like KIM-1, Cystatin C, or Microalbuminuria [6,7,8]. A multimarker approach may provide a more comprehensive and precise assessment of renal function, particularly considering the complex and varied aetiologies of nephropathy in thalassaemia patients [9,10]. There are some problems with the study, but there are also a lot of good things about it. It was great that it used a lot of different statistical tests, such as correlation, ANOVA, Tukey's test, and multiple linear regression. This makes the results more reliable [4,5]. The distinct disparities in NGAL levels among the groups (from control to patients devoid of inflammation to patients exhibiting inflammation) further substantiate a credible biological rationale for the function of this marker [11,12]. The results show that NGAL is a good way to find signs of kidney stress or damage in people with thalassaemia [13,14]. But on its own, it might not help much in figuring out if someone has a urinary tract infection [15]. Using it in both clinical and laboratory tests is a good way to make the diagnosis more accurate [16,17].

In conclusion, NGAL is a good test to see if someone with thalassaemia has problems with their kidneys. Nevertheless, it is imperative to comprehend its biological and methodological constraints prior to implementation in clinical settings [18,19,20]. To make them more useful for diagnosing and predicting outcomes in clinical practice, we need more long-term studies with more biomarkers and better control of confounding variables [1,2].

Conclusion

The study's findings indicate that individuals with thalassaemia exhibit significantly elevated levels of the NGAL protein compared to healthy individuals. Individuals with urinary tract infections exhibited the highest prevalence of these conditions. These results show that there is a strong link between NGAL levels and the disease, especially thalassaemia and its complications, like infections. The study found that age is what causes higher NGAL levels. This indicates that the disease is gradually altering renal function. On the other hand, sex had little effect, which suggests that pathological factors have a bigger effect on this biomarker than demographic factors. NGAL is a good sign of kidney problems or inflammation, but it might not be able to tell thalassaemia patients who have urinary tract infections from those who do not. It should be used with other tests or biomarkers to get a better diagnosis. People with thalassaemia might be able to use NGAL as a biomarker to find kidney damage and inflammation problems early on. This could help find people with these problems early on and keep track of them. This would help these people and keep problems from happening.

Future Directions

This study shows that future research should use bigger sample sizes to confirm the results and make the statistics more reliable, especially when it comes to the link between NGAL and urinary tract infections. We must perform longitudinal studies to evaluate the temporal fluctuations in NGAL levels and its effectiveness in forecasting imminent kidney failure and urinary tract infections before clinical presentation. We need to look into other kidney markers and factors that could change the results, like iron overload, how often blood transfusions are given, and chelation therapy. NGAL should also be easier to use in patient care because it gives standard clinical advice.

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