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Original article

Association Between YKL-40 and Cardiovascular Events in Hemodialysis Patients

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Abstract:

Background: YKL-40, a glycoprotein, is associated with inflammatory conditions, including endothelial dysfunction and atherosclerosis. This study aimed to assess the significance of YKL-40 levels in the serum in a hemodialysis (HD) population and investigate their connection to cardiovascular disease (CVD) development. **Methods:** A case-control study was conducted from August 2022 to January 2023, involving 80 participants (30 patients with CVD and chronic HD, 30 patients with chronic HD without CVD, and 20 apparently healthy individuals). Laboratory assessments encompassed kidney function tests (creatinine and urea), serum sodium and potassium levels, Troponin I, highly sensitive C-reactive protein (Hs-CRP), and serum YKL-40 concentrations measured using ELISA. Incidences of CVD events among the patients were documented. **Results:** Significantly elevated YKL-40 levels were observed in HD patients with CVD compared to HD patients without CVD and the control group ($p<0.001$). There was also a significant increase in YKL-40 in HD patients without CVD compared to the control group ($p<0.001$). Additionally, a significant positive correlation was found between YKL-40 and Troponin I ($p<0.001$) in HD patients, both with and without CVD. ROC analysis indicated that YKL-40, with a cutoff value of >928.4 ng/ml, could effectively differentiate between HD patients with and without CVD. Both univariate and multivariate analyses demonstrated that troponin I and YKL-40 were associated with an increased likelihood of CVD among HD patients. **Conclusion:** YKL-40 is a biomarker associated with inflammation, and it is shown to have elevated levels among patients with HD. Among those patients, our study shows that YKL-40 increases CVD risk.

Keywords: YKL-40; Prognosis; Hemodialysis; Cardiovascular Events.

Introduction

Patients undergoing hemodialysis (HD) experience higher rates of illness and death than the broader population [1]. In this group, cardiovascular (CV) incidents are the primary cause of death. Nephrologists have been diligently working to gain a deeper understanding of the origins, catalysts, and predictive elements of cardiovascular disease (CVD) in individuals grappling with chronic kidney disease (CKD) [2]. Among this demographic, both innovative and established risk factors have been connected to CV disease, yet the outcomes remain unsatisfactory, and further investigation is imperative [3, 4].

Given the hurdles in validation and recognition, numerous promising biomarkers fail to progress to the final stages of clinical application. According to a study, various obstacles exist, from the initial discovery of a biomarker to its subsequent prospective and retrospective validation [5]. In addition to proving effectiveness, substantial challenges encompass obtaining authorization from authoritative bodies and securing acceptance within the clinical community. If a biomarker is nonspecific and correlates with multiple ailments, defining its clinical utility can be perplexing. However, this scenario might also indicate that combining evidence from various disciplines can achieve a more comprehensive understanding of its exact mechanism, potential receptor kinetics, and overall impact across diseases [6].

YKL-40 serves as a prime example of such a biomarker. It has a well-established history as an indicator of chronic inflammation, and its associations extend to various medical conditions including rheumatologic disorders, arterial stiffness, atherosclerosis, stroke, and even mortality in type 2 diabetes. Additionally, it plays a significant role as a predictor of poor prognosis in different types of cancers [7].

YKL-40, is also occasionally referred to human cartilage glycoprotein-39 or chitinase-3-like protein 1, is a 40-kDa glycoprotein that is member of the family of chitinase-like proteins found in mammals. Neutrophils, macrophages, and cancer cells are attributed to YKL-40 production. It influences vascular endothelial growth factor (VEGF) and is involved in inflammatory, angiogenesis, fibrosis, and extracellular matrix restructuring [5].

Consequently, YKL-40 is associated with inflammatory diseases, endothelial dysfunction, and atherosclerosis. Serum YKL-40 levels are associated with increased mortality risks in the general population and those with chronic diseases [8]. The association between YKL-40 and HD patient mortality has been highlighted [9]. Nonetheless, additional research is required to determine whether YKL-40 is associated with CV events in this subset of HD patients and in order to ascertain other variables that modulate serum YKL-40 levels [10, 11].

This study aimed to evaluate serum YKL-40 levels in HD population and explored their association with CV events development.

Subjects and Methods

This case-control study was carried out on 80 subjects, divided into three groups as regards their HD status: Group (I) 30 chronic HD patients with CVD their age range was (56.57 ± 9.46) years, 36.7% males and 63.3% females, Group (II): 30 chronic HD patients without CVD their age range was (52.5± 11.25) years, 46.7% males and 53.3% females and Group (III): 20 apparently healthy control individuals their age range was (55.6± 11.03) years, 7% males and 13% females, HD patients attending the Nephrology Department and Renal Dialysis Unit at Benha University Hospital. Laboratory investigations were done at the Clinical and Chemical Pathological Department at Benha University Hospital from August 2022 to January 2023.This study has been approved by Local Ethical Committee of

Banha Faculty of Medicine (Ms.10.10.2022).

Inclusion criteria were patients aged >18 years and had clinical stability of HD, Patients who have not been hospitalized during the last three months.

The exclusion criteria were age < 18 years, pregnancy, known obstructive uropathy, requirement of renal replacement therapy, or renal disease (e.g., glomerulonephritis, polycystic kidney disease).

Every participant underwent a comprehensive assessment of their background information, which encompassed age, gender, CKD, the existence of hypertension, diabetes mellitus (DM), and any prior cardiovascular (CV) events such as congestive heart failure (CHF), myocardial infarction (MI), and stroke.

Physical examinations, and a thorough examination of the heart and chest alongside a series of laboratory analyses. These investigations consisted of evaluations of kidney performance (creatinine and urea levels), measurements of serum sodium and potassium levels, assessment of Troponin I levels, serum YKL-40 concentrations measurement using the ELISA technique and determination of Hs-CRP levels.

Specimen collection

Blood sample:

- Five milliliters of venous blood were aseptically collected from each participant through clean venipuncture using a disposable plastic syringe. The blood was then transferred into serum-separating tubes and allowed to clot for 30 minutes at room temperature. Afterward, it was centrifuged at 1500 rpm for 10 minutes.
- The resulting serum was separated and preserved at -20°C until analysis. It was used for conducting clinical chemistry tests, Hs-CRP, and YKL-40 measurements.

Analytical Methods

1- Serum Na, K were done using (ST 200 plus Electrolyte Analyzer, ST-902, USA)

2- Clinical chemistry tests were done using (DiALAB, S.N. 13771103, USA) which includes: Serum creatinine by modified Jaffe reaction [(12)], urea [(13)]

3- Troponin I was measured by the mini VIDAS instrument (S.N. IVD 5214732/France).

4- Highly sensitive C-reactive protein (Hs-CRP) levels were determined using the Hs-CRP ELISA kit, which employs the quantitative sandwich enzyme immunoassay method (BioSystems, CostaBrava, 30.08030 Barcelona, Spain) [(14)]. Serum YKL-40 concentrations were assessed using the Human Glycoprotein 39, Cartilage (GP39) ELISA Kit (DI develop, Catalog No: DL-GP39-HU, Canadian Chinese).

The kit contains a microtiter plate that has been precoated with a GP39-specific antibody. In order to conduct the assay, standards or samples were added to the respective wells of a microtiter plate along with a biotin-conjugated antibody targeting GP39. The wells were then incubated with Avidin conjugated to Horseradish Peroxidase (HRP). Only the wells containing GP39, the biotin-conjugated antibody, and the enzyme-conjugated Avidin changed colour when the TMB substrate solution was added. The enzymatic reaction was stopped by adding a solution of sulfuric acid, and the change in colour was measured spectrophotometrically at 450nm 10nm. By comparing the optical density (OD) of the samples to the standard curve, the concentration of GP39 in the samples was then determined.

Statistical analysis

The management of data and statistical analysis were conducted using Statistical Package for the Social Sciences (SPSS) version 21. Numerical data were summarized using means, ranges, and standard deviations, while categorical data were presented as percentages and numerical counts. The t-test was used for comparing normally distributed numerical variables between the two groups.

Disparities in categorical variables were assessed using X^2 (chi-square) tests, and Fisher's exact tests were employed when applicable. All reported p-values were based on two-sided tests, and significance was attributed to p-values less than 0.05.

Results

There were no significant differences regarding sex and age, duration of HD (years), Na level, and K level between HD patients with cardiovascular event, HD patients without cardiovascular events, and the control group. Table 1

Compared with the control, there is a statistically significant increase in urea and creatinine in HD with cardiovascular events and HD without CV event compared to the controls. Table 1

There is a significant elevation in hs-CRP levels among HD patients with CVD when compared to both HD patients without CVD and the control group ($p<0.001$). Additionally, a significant increase in hs-CRP is observed in HD patients without CVD in comparison to the control group (P-value <0.001). Table 1

Furthermore, there is a significant rise in Troponin I levels among HD patients with CVD in comparison to HD patients without CVD and the control group ($p<0.001$). Similarly, YKL-40 shows a statistically significant increase in the proportion of HD patients who also have CVD compared to HD patients who do not have CVD and the control group ($p<0.001$). As well, there is a significant increase in YKL-40 in HD patients without CVD in comparison to the control group (P-value <0.001). Table 1

Table (1) General, clinical, and laboratory findings in the studied groups .

	HD with cardiovascular events N = 30		**HD without cardiovascular events** N = 30		**Control** N = 20		**P-value**
	N	%	N	%	N	%	
Sex							
Male	11	36.7	14	46.7	7	35	0.637
Female	19	63.3	16	53.3	13	65	
Age (years)							
Mean ± SD.	56.57 ± 9.46		52.50 ± 11.25		55.65 ± 11.03		0.308
Duration of HD (years)							
Median (Range)	5.50 (1.50 – 13.0)		4.50 (0.42 – 12.0)				0.085
Urea (mg/dl)							
Median (Range)	121.0 (60.0 – 251.0) P1=0.220, P2<0.001*, P3<0.001*		138.0 (65.0 – 218.0)		19.0 (11.0 – 40.0)		<0.001*
Creatinine (mg/dl)							
Median (Range)	6.90 (1.60 – 19.0) P1=0.219, P2<0.001*, P3<0.001*		9.65 (4.55 – 17.60)		0.6 (0.3 – 1.3)		<0.001*
Na (mmol/l)							
Mean ± SD.	138.6 ± 2.93		138.5 ± 2.66		138.2 ± 3.81		0.901
K (mmol/l)							
Mean ± SD.	4.49 ± 1.13		4.10 ± 0.52		4.09 ± 1.45		0.272
hs-CRP							
Median (Range)	7.50 (1.0 – 20.0) P1<0.001*, P2<0.001*, P3=0.021*		2.0 (0.40 – 10.0)		1.0 (0.1 – 3.5)		<0.001*
Troponin I (mg/ml)							
Median (Range)	2.2 (0.3 – 20.0) P1<0.001*, P2<0.001*, P3=0.633		0.1 (0.1 – 0.6)		0.2 (0.1 – 0.4)		<0.001*
YKL-40(ng/ml)							
Mean ± SD.	1253.3 ± 338.6 P1<0.001*, P2<0.001*, P3=0.003*		766.9 ± 161.8		521.9 ± 186.3		<0.001*

P1: comparing HD with cardiovascular vs. HD without cardiovascular; P2: comparing HD with cardiovascular vs. control; P3: comparing HD without cardiovascular vs. control.

In Table 2, a significant positive correlation is shown between Troponin I and YKL-40, levels among those with and those without CVD among HD patients, with correlation coefficients of 0.906 and 0.812, respectively (P-value <0.001).

ROC analysis was done for YKL-40 to discriminate between HD patients and controls. YKL-40 showed excellent AUC (=0.923). At the best cutoff value of >570.8 (ng/ml), sensitivity was 93.33%, specificity was 80%, PPV was 93.3%, NPV was 80%, and accuracy was 90%. Figure 1- A

For discrimination between HD with cardiovascular patients and without cardiovascular, YKL-40 has a high degree of significance as a predictor for predicting CVD among HD patients at a cutoff value of >928.4 ng/ml, AUC: 0.918 (P-value <0.001). The sensitivity and specificity were 93.34% and 83.33%, respectively. PPV and NPV were 84.85% and 92.59%, respectively. The accuracy was 88.33%. Figure 1-B

Logistic Regression analysis was conducted to predict HD using gender, age, urea, creatinine, Na, K, hs-CRP, troponin I, and YKL-40 as confounders. Urea, hs-CRP, and YKL-40 were considered predictors of HD in univariate analysis. However, conducting multivariable analysis revealed that hs-CRP and YKL-40 were independent predictors of HD susceptibility. Table 3

In univariate regression analysis, troponin I and YKL-40 were significant predictors for developing CVD in HD patients (P-value <0.05). In the multivariate logistic regression model, we found that troponin I and YKL-40 were associated with increased odds of CVD among HD patients (P-value =0.028, 0.004, respectively). Table 4

Table (2) Correlation between YKL-40 and other parameters in patients' groups**.**

	YKL-40			
	HD with cardiovascular		HD without cardiovascular	
	R	P	R	P
Age (years)	-0.043	0.823	0.026	0.893
Duration of HD	0.238	0.206	-0.26	0.165
Urea	0.079	0.678	0.006	0.975
Creatinine	0.083	0.663	-0.001	0.997
Na	-0.149	0.431	0.102	0.59
K	-0.12	0.529	0.122	0.522
hs-CRP	0.176	0.352	0.024	0.9
Troponin I	0.906	<0.001*	0.812	<0.001*

Table (3) Logistic Regression analysis for prediction of HD patients.

	Univariate				Multivariate			
	P	OR	95% CI		P	OR	95% CI	
Gender	0.599	1.327	0.463	3.8				
Age	0.681	0.99	0.943	1.039				
Urea	0.002*	1.095	1.034	1.16	0.106	3.841	0.752	19.608
Creatinine	0.074	80.539	0.649	9994.2				
Na	0.654	1.04	0.877	1.232				
K	0.446	1.239	0.714	2.15				
hs-CRP	0.001*	2.897	1.55	5.416	0.047*	1.074	1.001	1.151
Troponin I	0.063	19.742	0.848	459.4				
YKL-40	<0.001*	1.009	1.004	1.014	0.024*	1.008	1.002	1.017

Table (4) Logistic Regression analysis for prediction of cardiovascular events among HD patients.

	Univariate				Multivariate			
	P	**OR**	**95% CI**		**P**	**OR**	**95% CI**	
Gender	0.433	1.511	0.538	4.244				
Age	0.137	1.039	0.988	1.094				
Urea	0.067	1.153	0.99	1.343				
Creatinine	0.258	0.993	0.981	1.005				
Na	0.792	1.007	0.954	1.064				
K	0.888	1.013	0.843	1.218				
hs-CRP	0.108	1.817	0.877	3.762				
Troponin I	<0.001*	1.863	1.348	2.575	0.028*	1.602	1.133	2.75
YKL-40	0.001*	3.402	1.616	7.158	0.004*	5.135	1.698	15.528

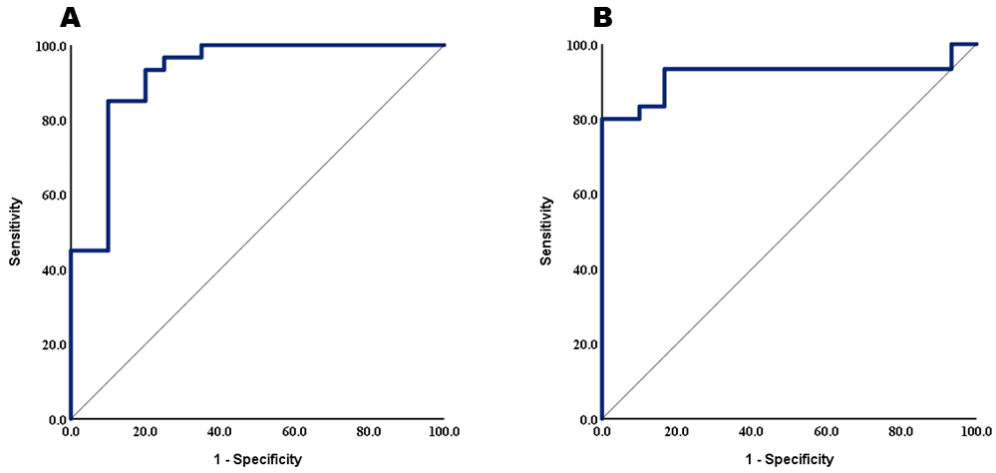

Figure (1): Validity of YKL-40 for discrimination between A) HD patients and controls; B) HD with cardiovascular patients and without cardiovascular.

Discussion

A significant proportion exceeding 50% of patients undergoing dialysis exhibit CVD, with a relative risk of mortality associated with CVD events that is shown to be twenty times more serious in HD patients comparing to the population as a whole. In fact, the prevalence of coronary heart disease and ventricular hypertrophy in patients on renal replacement therapy (RRT) has been reported to be 40% and 70%, respectively [(15)].

Over the past few years, several clinical investigations have reported a link between increased YKL-40 concentrations and mortality across various cardiovascular disorders. Research indicates that heightened YKL-40 levels can independently forecast the presence of Chronic Arterial Disease (CAD). Furthermore, one study observed a direct correlation between YKL-40 levels and the quantity of narrowed coronary arteries as determined through coronary angiography. These findings imply that YKL-40 plasma levels might serve as a quantitative marker for both the progression and existence of the disease [(16)].

This research reveals a noteworthy rise in hs-CRP levels in HD patients with CVD in contrast to those without CVD and the control group. Likewise, a statistically significant elevation in hs-CRP levels is observed in HD patients without CVD compared to the control group. In alignment with our findings, previous study also reported a statistically significant increase in serum hs-CRP

levels among HD patients when compared to a control group. Additionally, there is a statistically significant difference in the HD group when compared to the pre-HD CKD group [6]. However, [17] shown that elevated hs-CRP is independently associated with CVD among dialysis patients. Another study supports many studies stated that the high level of hs-CRP indicate who may be at risk for coronary incident, elevated level of hs-CRP is associated with other atherosclerotic vascular diseases in HD patients [18].

High-sensitivity C-reactive protein (Hs-CRP) is considered the primary acute-phase protein and is a widely recognized, non-specific marker of inflammation. Numerous epidemiological investigations have shown that Hs-CRP plays a significant role as a major risk factor in the development of atherosclerosis and coronary heart disease [19].

In this study, Troponin I demonstrated a considerable elevation in HD patients with CVD in comparison to HD patients without CVD and the control group ($p<0.001$). Furthermore, previous author documented a significant increase in Troponin I levels among HD patients who encountered cardiovascular events compared to those who did not ($p = 0.028$) [11]. The increase in troponin I levels in individuals with CKD is strongly associated with an increased risk of adverse cardiovascular events and higher overall mortality rates. Additionally, as CKD advances to more severe stages, the prognosis worsens [20].

Regarding YKL-40, this study showed a notable increase in HD patients with CVD compared to those without CVD and the control group. Additionally, there is a significant elevation of YKL-40 in HD patients without CVD when compared to the control group ($p<0.001$). These results align with the findings of other authors, who observed a substantial surge in serum YKL-40 levels in HD patients with CKD relative to HD patients without CKD, with this increase being more pronounced in HD patients without CKD than in the control group. Furthermore, another study reported a fivefold higher YKL-40 level in the HD group, particularly among those with CVD [17]. In line with these findings, a study noted elevated serum YKL-40 levels in HD patients, both with and without CVD [9].

This phenomenon can be elucidated by the discoveries of previous studies, that demonstrated that the kidney excretes YKL-40. Elevated serum YKL-40 levels may result from impaired clearance or breakdown of YKL-40 in the kidney, leading to its accumulation in the bloodstream. Consequently, increased serum YKL-40 levels were significantly linked to higher serum creatinine and urea levels in both pre-dialysis and HD patients [21, 22].

This study demonstrates a significant positive correlation between YKL-40 and Troponin I in both HD patients with and without CVD ($r=0.874$, p0.001). In a study done previously [6], where group I, composed of 40 patients with chronic kidney disease, exhibited statistically significant positive association between serum YKL-40 levels and markers including serum urea, serum creatinine, total serum cholesterol, serum triglycerides, serum LDL, and serum hs-CRP. In contrast, a significant negative correlation existed between serum YKL-40 levels and variables such as estimated glomerular filtration rate (eGFR), hemoglobin (Hb) levels, and serum HDL. In another study [9], a univariate correlation between YKL-40 and hsCRP serum levels was observed. Therefore, it is plausible that YKL-40 could serve as an indicator of localized inflammatory activity within tissues (e.g., within the vessel wall) rather from being indicative of systemic responses related to the hepatic production of inflammatory mediators [6].

In addition, a correlation between elevated serum YKL-40 levels and the likelihood of cardiovascular events occurring in stable HD patients was discovered. This is one of

the earliest studies to examine the potential of YKL-40 as a biomarker for cardiovascular events in HD [23].

Another study discovered a statistically significant positive correlation between serum creatinine and YKL-40 levels. In addition, the regression model [24] revealed that an elevated level of creatinine serves as an independent prognostic indicator for YKL-40.

This study reveals the validity of YKL-40 for discrimination between HD patients and controls; YKL-40 showed excellent AUC (=0.923) at best cut off value of >570.8 (ng/ml), sensitivity was 93.33%, specificity was 80%, PPV was 93.3%, NPV WAS 80% and accuracy was 90%. And also reveals the validity of YKL-40 for discrimination between HD with and without CVD shows a highly significant predictor for predicting CVD among HD patients at a cut off value of >928.4 ng/ml, (AUC: 0.918, P<0.001) at a sensitivity and specificity of 93.34% & 83.33%, respectively with PPV was 84.85%, NPV was 92.59% and accuracy was 88.33%. This cut off value was much higher than study by previous authors as they depend on a cut off value of >207 ng/ml for prediction of CVD in HD patients [11].

This study shows logistic regression analysis that was conducted for prediction of HD using gender, age, urea, creatinine, Na, K, hs-CRP, troponin I and YKL-40 as confounder. Urea, hs-CRP and YKL-40 were considered as a predictor of HD in univariate analysis. However, conducting multivariable analysis revealed that hs-CRP and YKL-40 were considered independent predictors of HD susceptibility.

Another study identified associations between YKL-40 and various other proinflammatory markers. They observed significant univariate correlations between YKL-40 and IL-6, hsCRP, and the chemokine IP-10, though not with MCP-1. However, after accounting for factors such as age, central venous catheters, comorbidities, and other inflammatory mediators, the correlation between YKL-40 and hsCRP was no longer significant (correlation coefficient of 0.01; p = 0.80). On the other hand, even after adjusting for age, the presence of central venous catheters, comorbidities, hsCRP, and either IP-10 or IL-6, the correlations between YKL-40 and IL-6 and IP-10 remained statistically significant. Consequently, it appears that YKL-40 may be more closely linked to inflammatory pathways that involve IL-6 or IP-10 [9].

This study reveals logistic regression analysis for prediction of CVD among HD patients shows, in univariate regression analysis, that troponin I and YKL-40 were significant predictors for developing CVD in HD patients. In multivariate logistic regression model, both Troponin I and YKL-40 were associated with increased odds of CVD among HD patients.

Other reports conducted a univariate examination and found that prior CV events, hypertension, diabetes, CRP, serum glucose levels, HbA1c, B2M, troponin T, YKL-40, and reduced prealbumin levels were linked to cardiovascular events. Subsequently, a multivariate analysis corroborated an independent association between diabetes, troponin T, YKL-40, and lower prealbumin levels with the occurrence of cardiovascular events. Kaplan–Meier analysis further validated a heightened risk of cardiovascular events in patients whose YKL-40 values exceeded the mean (log rank 7.28; p = 0.007) [11].

In the research conducted by previous reports, over a median follow-up duration of 37 months, a total of 169 patients experienced mortality. Among these, 64 cases were attributed to cardiovascular causes, while 105 were due to non-cardiovascular reasons. Additionally, 44 patients received renal transplants, and 11 patients were no longer available for follow-up assessment. Notably, cases who did not survive were disproportionately found in the upper terciles of YKL-40 (with 34, 51, and 85 cardiovascular events

per tercile, respectively). Specifically, concerning the latter group, the lower, middle, and upper YKL-40 terciles exhibited 12, 19, and 33 fatal cardiovascular events, respectively. The authors proposed that only YKL-40 and IL-6 emerged as significant predictors of non-cardiovascular mortality.

Taken together, these findings lend support to the concept that YKL-40 plays a significant role in regulating the inflammatory response. In healthy individuals, this regulation could facilitate successive tissue repair processes [25, 26].

Conversely, in the context of chronic inflammation associated with HD, elevated serum YKL-40 levels might signify unresolved, lingering inflammation and irregular local tissue restructuring, particularly within the vascular wall [27].

Furthermore, Mendelian randomization studies suggest that genetic mutations in the YKL-40 gene (CHI3L1) could result in increased marker levels but do not appear to elevate the risk of cardiovascular disease or mortality within the broader population [28, 29].

Conclusion

YKL-40 is a biomarker associated with inflammation, and it has been shown to have elevated levels among patients with HD, with even higher elevations observed in those experiencing cardiovascular events. This suggests that YKL-40 could serve as a predictor for the need for dialysis in CKD patients and as a predictor for CVD in dialysis patients.

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