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Cardiac Troponin and Homocysteine Levels in Hemodialysis Patients: Association with Dialysis Vintage and Cardiovascular Comorbidity

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Abstract

Introduction: Cardiovascular disease remains the leading cause of morbidity and mortality among patients with end-stage kidney disease (ESKD) receiving maintenance hemodialysis. Persistently elevated cardiac troponin and homocysteine concentrations are common in this population and reflect chronic myocardial injury, endothelial dysfunction, inflammation, and accelerated atherosclerosis. However, the influence of dialysis vintage on these biomarkers remains uncertain. This study investigated the association between dialysis duration, circulating troponin and homocysteine concentrations, and major cardiovascular comorbidities in patients undergoing chronic hemodialysis.

Methods: This prospective observational study included 184 adults with ESKD receiving maintenance hemodialysis at two tertiary referral centers. Patients were stratified according to dialysis vintage into three groups: <5 years (n=85), 5-10 years (n=56), and >10 years (n=42). Serum cardiac troponin was measured at baseline and after 3, 6, 9, and 12 months, while plasma homocysteine was assessed at baseline, 6, and 12 months. Subgroup analyses evaluated associations with sex, coronary artery disease (CAD), hypertension, antihypertensive therapy, lipid-lowering treatment, and folic acid supplementation.

Results: Elevated troponin concentrations (>15 pg/mL) were detected in 89.3% of patients, whereas hyperhomocysteinemia was present in 98%. Mean troponin and homocysteine concentrations were 47.28 12.80 pg/mL and 29.76 ± 12.67 μmol/L, respectively. Neither biomarker differed significantly across dialysis-vintage groups (troponin: p=0.188; homocysteine: p=0.680). Patients with established CAD had significantly higher troponin concentrations than those without CAD (p<0.001), whereas homocysteine levels were comparable (p=0.435). No significant associations were observed with sex, hypertension, antihypertensive therapy, or lipid-lowering treatment. Folic acid supplementation was independently associated with lower homocysteine (p<0.001) and troponin concentrations (p=0.009).

Conclusions: Chronic elevations of troponin and homocysteine are highly prevalent in maintenance hemodialysis patients. Dialysis vintage is not an independent determinant of either biomarker, whereas coronary artery disease is strongly associated with persistent troponin elevation. These findings support cardiac troponin as a valuable biomarker of cardiovascular burden and risk stratification in the hemodialysis population.

Keywords: Troponin; Homocysteine; Hemodialysis; Cardiovascular Disease; Chronic

Abbreviations: ESKD: End-Stage Kidney Disease; CAD: Coronary Artery Disease; SD: Standard Deviation; IQR: Interquartile Range; RHO: Rank Correlation Coefficient; CVD: Cardiovascular Disease; SD: Standard Deviation; CAD: Coronary Artery Disease

Introduction

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality among patients with end-stage kidney disease (ESKD) receiving maintenance hemodialysis, accounting for a substantial proportion of deaths despite advances in renal replacement therapy and contemporary cardiovascular care [1-

3]. The cardiovascular phenotype of ESKD differs substantially from that of the general population, as it reflects the interaction between traditional risk factors, including age, diabetes mellitus, hypertension and dyslipidemia, and kidney-specific mechanisms such as chronic inflammation, oxidative stress, endothelial dysfunction, anemia, fluid overload, vascular calcification, chronic kidney disease-mineral and bone disorder, neurohormonal activation and accumulation of uremic toxins [1-4]. These processes promote accelerated atherosclerosis, arterial stiffness, coronary microvascular dysfunction, left ventricular hypertrophy, myocardial fibrosis and uremic cardiomyopathy, resulting in markedly increased cardiovascular risk [1,3-5].

Reliable biomarkers that improve cardiovascular risk stratification in this high-risk population are therefore of major clinical interest. Cardiac troponin T and cardiac troponin I are structural proteins of the myocardial contractile apparatus and represent the biochemical standard for detecting myocardial injury [6,7]. In the general population, high-sensitivity cardiac troponin assays are central to the diagnosis of acute myocardial infarction, as reflected in the Universal Definition of Myocardial Infarction and the 2023 European Society of Cardiology guidelines for acute coronary syndromes [6,7]. However, interpretation of troponin concentrations is particularly challenging in advanced CKD and dialysis-dependent kidney failure, because chronically elevated levels are frequently observed in clinically stable patients without acute coronary syndrome [7-10].

The use of high-sensitivity assays has demonstrated that a large proportion of maintenance hemodialysis patients have troponin concentrations above the 99th percentile upper reference limit even in the absence of overt ischemic symptoms [8-11]. These elevations should not be attributed solely to impaired renal clearance. Contemporary evidence indicates that chronic myocardial injury, rather than reduced elimination alone, is the dominant mechanism underlying persistent troponin elevation in ESKD [8-12]. Recurrent subclinical ischemia, coronary microvascular disease, left ventricular hypertrophy, diffuse myocardial fibrosis, intradialytic hemodynamic stress, myocardial stunning, oxidative injury and systemic inflammation may all contribute to continuous low-grade cardiomyocyte injury and sustained biomarker release [3-5,8-12].

Beyond their diagnostic role, cardiac troponins have important prognostic value in CKD and ESKD. Persistently elevated high-sensitivity troponin concentrations have been associated with structural heart disease, heart failure, major adverse cardiovascular events, cardiovascular mortality and all-cause mortality in dialysis populations [8-12]. Accordingly, the ESC guidelines emphasize that acute myocardial infarction in patients with renal dysfunction should be diagnosed using serial changes in troponin concentrations together with symptoms, electrocardiographic findings and imaging, rather than isolated biomarker values alone [7]. Similarly, the KDIGO 2024 CKD guideline supports contextual interpretation of cardiovascular biomarkers in CKD, acknowledging the high cardiovascular risk and complexity of biomarker assessment in this population [2].

Homocysteine is another biomarker of interest in ESKD. It is a sulfur-containing amino acid generated during methionine metabolism and is normally metabolized through remethylation and transsulfuration pathways requiring folate, vitamin B12 and vitamin B6 as cofactors [13-15]. Progressive kidney dysfunction disrupts these pathways through reduced renal metabolism, impaired clearance, chronic inflammation, oxidative stress, metabolic acidosis, altered methylation capacity and nutritional deficiencies, leading to persistent hyperhomocysteinemia [13-16]. Elevated homocysteine concentrations are highly prevalent among maintenance hemodialysis patients and have been linked mechanistically to endothelial dysfunction, reduced nitric oxide bioavailability, oxidative stress, vascular inflammation, smooth muscle cell proliferation, extracellular matrix remodeling, platelet activation and thrombogenesis [13-17].

Despite this biologically plausible association with vascular injury, the clinical significance of hyperhomocysteinemia in ESKD remains controversial. Observational studies and reviews suggest that homocysteine and related one-carbon metabolites may reflect cardiovascular and metabolic risk in CKD, but its ability to independently predict cardiovascular outcomes is inconsistent [13-17]. Moreover, randomized trials and meta-analyses have shown that folic acid-based homocysteine-lowering therapy can reduce circulating homocysteine concentrations, but does not consistently reduce myocardial infarction, stroke, cardiovascular mortality or all-cause mortality in patients with kidney disease [18-20]. These findings suggest that homocysteine may function primarily as a biomarker of disturbed one-carbon metabolism and systemic uremic toxicity rather than as an isolated therapeutic target.

The influence of dialysis vintage, defined as the cumulative duration of maintenance dialysis therapy, on troponin and homocysteine concentrations remains incompletely understood. Dialysis vintage is often considered a surrogate of prolonged exposure to the uremic milieu, chronic inflammation, oxidative stress, intradialytic hemodynamic instability, mineral metabolism abnormalities and progressive cardiovascular remodeling [1-5]. However, structural cardiovascular abnormalities frequently develop before dialysis initiation, during advanced CKD stages, and may therefore determine biomarker profiles more strongly than dialysis duration itself [1-5,8-12]. Similarly, disturbances in one-carbon metabolism may become established early in advanced CKD and persist after dialysis initiation, with variability influenced by nutritional status, vitamin availability, inflammation, residual kidney function and genetic factors rather than dialysis vintage alone [13-17]. Few prospective studies have simultaneously

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evaluated cardiac troponin and homocysteine in relation to dialysis vintage and major cardiovascular comorbidities within the same hemodialysis cohort.

Most available studies have focused on one biomarker or relied on cross-sectional measurements, limiting the ability to assess chronic biomarker patterns over time. The present prospective observational study therefore aimed to investigate the association between dialysis vintage and circulating cardiac troponin and homocysteine concentrations in patients receiving maintenance hemodialysis. In addition, we evaluated the relationship between these biomarkers and major cardiovascular comorbidities and therapies, including coronary artery disease, arterial hypertension, antihypertensive treatment, lipid-lowering therapy and folic acid supplementation. We hypothesized that chronic elevations of troponin and homocysteine would be more strongly associated with underlying cardiovascular pathology and systemic metabolic disturbances than with dialysis vintage alone.

Methods

Study Design and Population

This prospective observational study was conducted in two tertiary dialysis centers in Greece. A total of 184 adult patients with ESRD undergoing maintenance hemodialysis were enrolled. The study population included 119 men (64.7%) and 65 women (35.3%) with mean age 70,81 years ± 12,01.

Inclusion Criteria:

- Age ≥18 years
- Stable maintenance hemodialysis treatment for at least three months prior to study entry.

Exclusion Criteria:

- Acute coronary syndrome
- active infection
- hospitalization within the previous month
- Active malignancy
- Incomplete laboratory follow-up

Dialysis Vintage Classification

Participants were categorized according to time on renal replacement therapy:

- Group 1: <5 years (n=85)
- Group 2: 5-10 years (n=58)
- Group 3: >10 years (n=44)

Laboratory Measurements

Serum cardiac troponin concentrations were measured at five predefined time points: baseline, 3 months, 6 months, 9 months and 12 months. Serum homocysteine concentrations were measured at baseline, 6 months and 12 months. All blood samples were obtained before the midweek dialysis session and analyzed in certified hospital laboratories using standardized methods. Elevated troponin and homocysteine levels were defined as a concentration exceeding 15 pg/mL and <15 μmol/L respectively according to institutional laboratory reference values.

Clinical Variables

Demographic and clinical data were collected from medical records. Subgroup analyses were performed according to:

- Sex
- Presence or absence of coronary artery disease
- Presence or absence of arterial hypertension
- Receiving or not antihypertensive therapy
- Receiving or not lipid-lowering therapy

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), depending on data distribution. Categorical variables were presented as frequencies and percentages. Comparisons among the three dialysis-vintage groups were performed using the Kruskal-Wallis test. Pairwise comparisons between two independent groups were conducted using the Mann-Whitney U test. Categorical variables were analyzed using Fisher's exact test. Associations between dialysis duration and biomarker concentrations were evaluated using Spearman's rank correlation coefficient (rho). All statistical tests were two-tailed. Statistical significance was defined as $p < 0.05$.

Ethical Considerations

The study was conducted according to the principles of the Declaration of Helsinki and was approved by the institutional ethics committees of the participating centers. Written informed consent was obtained from all participants before enrollment.

Results

The present study included 184 patients, 119 men (64.7%) and 65 women (35.3%), with a high prevalence of cardiovascular comorbidities. Documented coronary artery disease (CAD) was present in 49 patients (26.6%), while arterial hypertension was identified in 145 patients (78.8%). According to dialysis vintage, patients were categorized into three groups: <5 years (n=85), 5-10 years (n=56), and >10 years (n=42). The mean duration of renal replacement therapy within these groups was 3.35, 6.99, and 14.57 years, respectively. Elevated serum troponin concentrations above the reference range were observed in 89.3% of patients, with a mean overall concentration of 47.28 ± 12.80 pg/mL. Homocysteine levels were elevated in 98% of the study population, with a mean concentration of 29.76 ± 12.67 mmol/L.

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Dialysis Vintage and Biomarker Levels

Comparison of serum troponin concentrations among dialysis-vintage groups revealed no statistically significant differences (Kruskal-Walli's test, p=0.188) (Figure 1). Similarly, homocysteine concentrations did not differ significantly across dialysis-duration categories (Kruskal-Wallis test, p=0.680) (Figure 2).

Coronary Artery Disease

Patients with documented CAD exhibited substantially higher serum troponin concentrations compared with patients without CAD. This difference was highly significant (Mann-Whitney U test, p<0.001) (Figure 3), confirming a strong association between underlying ischemic heart disease and chronic troponin elevation in the hemodialysis population. In contrast, homocysteine concentrations did not differ significantly between patients with and without CAD (p=0.435), indicating that elevated homocysteine levels are highly prevalent across the entire ESRD population irrespective of established coronary disease (Figure 4).

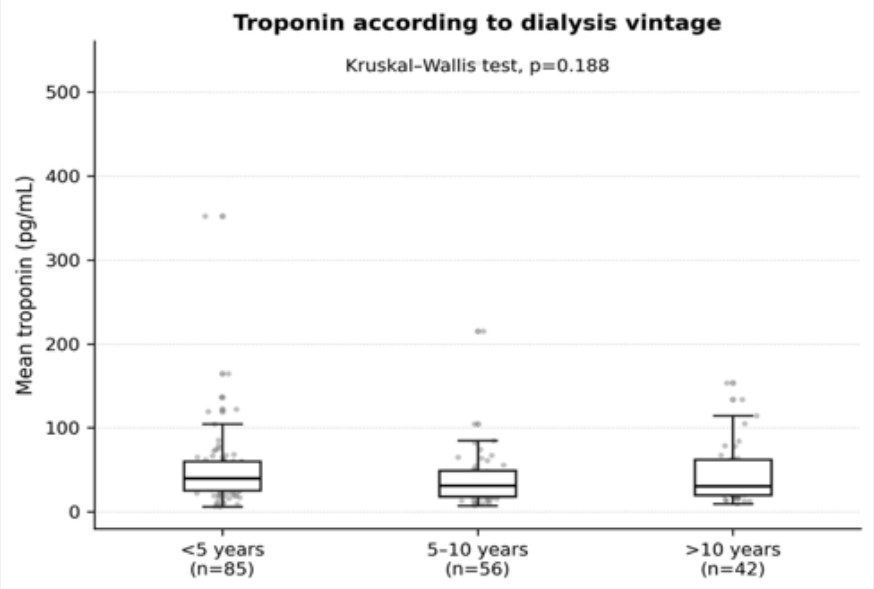

Figure 1: Troponin according to dialysis vintage.

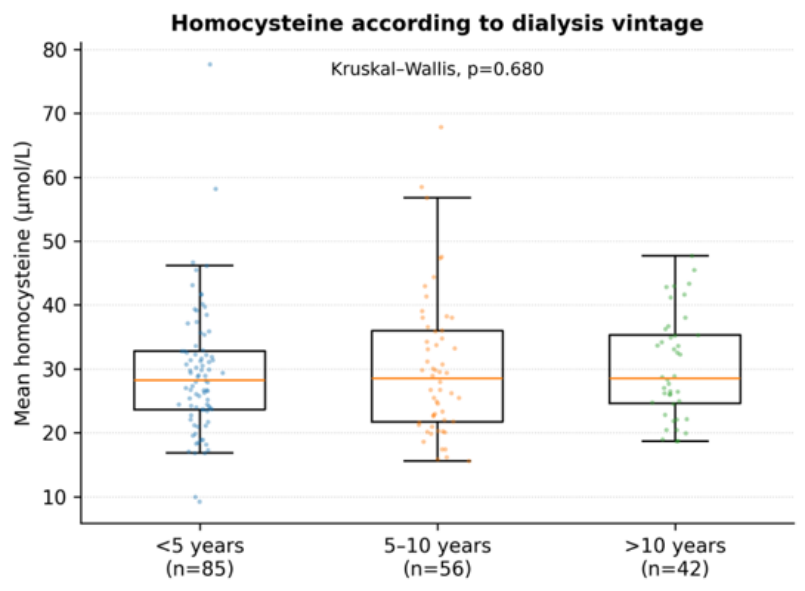

Figure 2: Homocysteine according to dialysis vintage.

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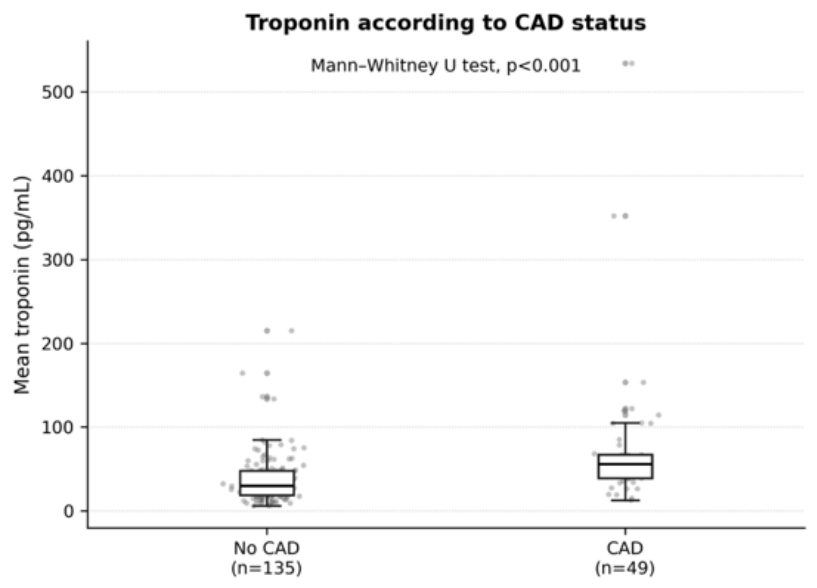

Figure 3: Troponin and CAD status.

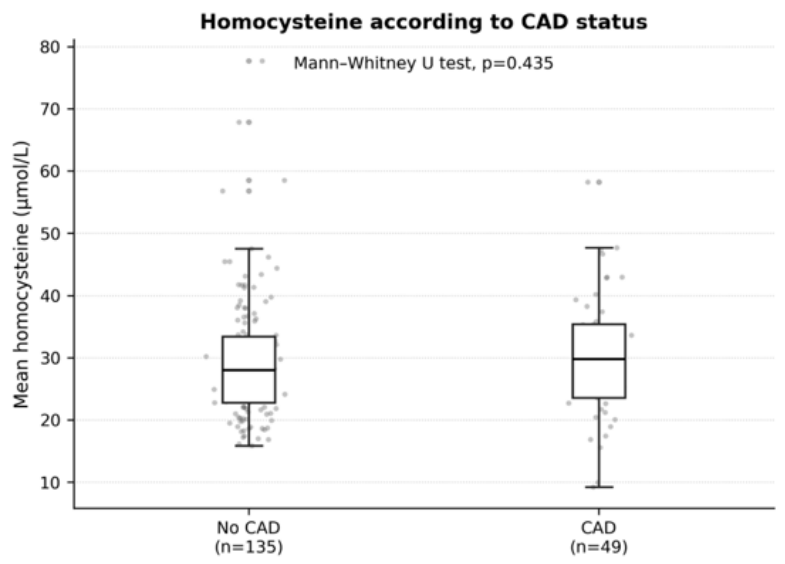

Figure 4: Homocysteine and CAD status.

Sex-Related Differences

No significant sex-related differences were observed in either biomarker. Troponin concentrations were comparable between male and female patients (Mann-Whitney U test, p=0.630) (Figure 5), while homocysteine concentrations also demonstrated no statistically significant variation according to sex (p=0.380) (Figure 6). These findings suggest that sex does not substantially influence circulating troponin or homocysteine concentrations among patients receiving long-term hemodialysis.

Arterial Hypertension

Arterial hypertension was present in many participants. Comparison between hypertensive and normotensive patients revealed no statistically significant differences in serum troponin concentrations (p=0.138) (Figure 7). Similarly, homocysteine levels were not significantly associated with hypertension status (p=0.147) (Figure 8). Therefore, despite its established role as a cardiovascular risk factor, hypertension did not appear to independently influence biomarker concentrations in this cohort.

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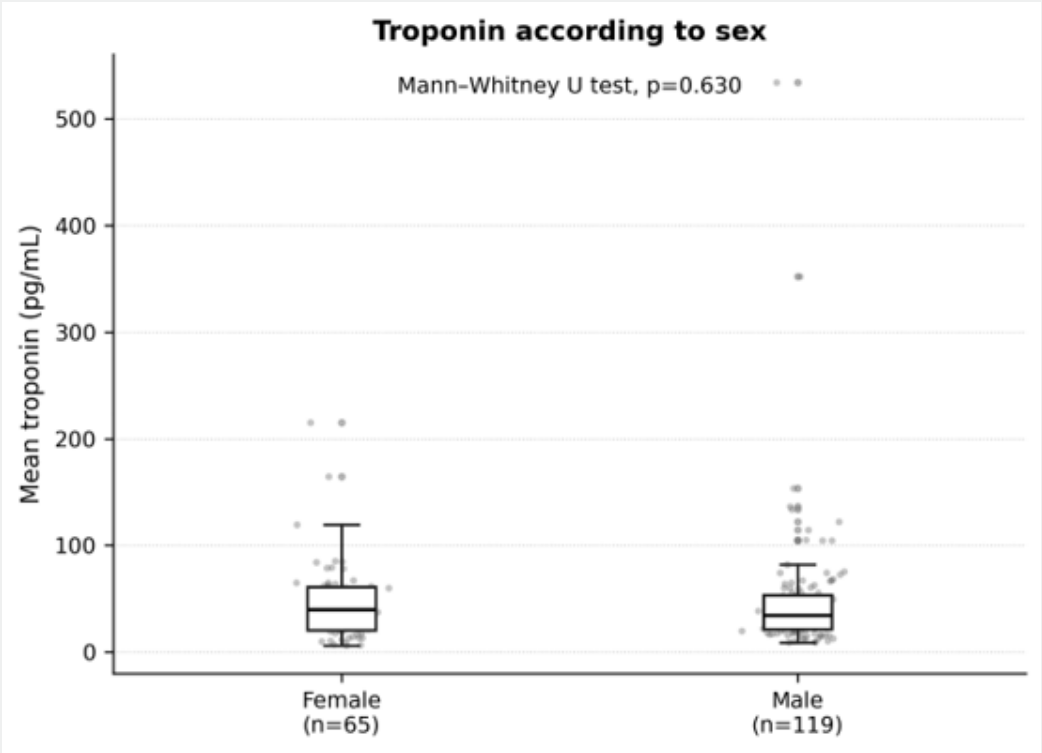

Figure 5: Correlation of troponin with sex.

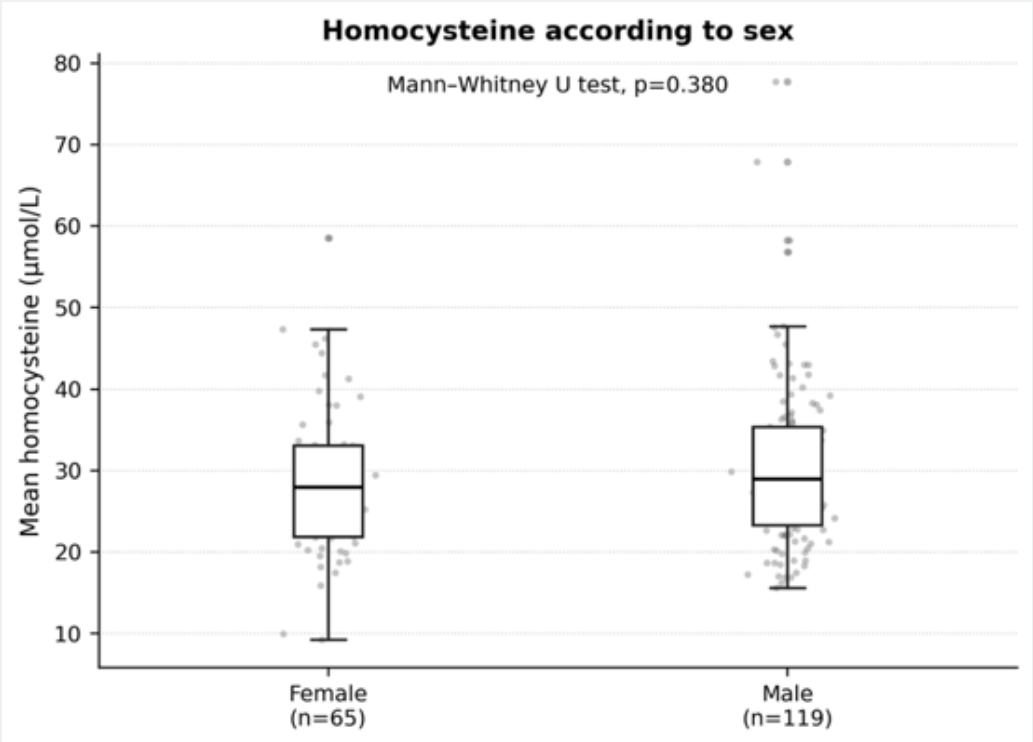

Figure 6: Correlation of homocysteine with sex.

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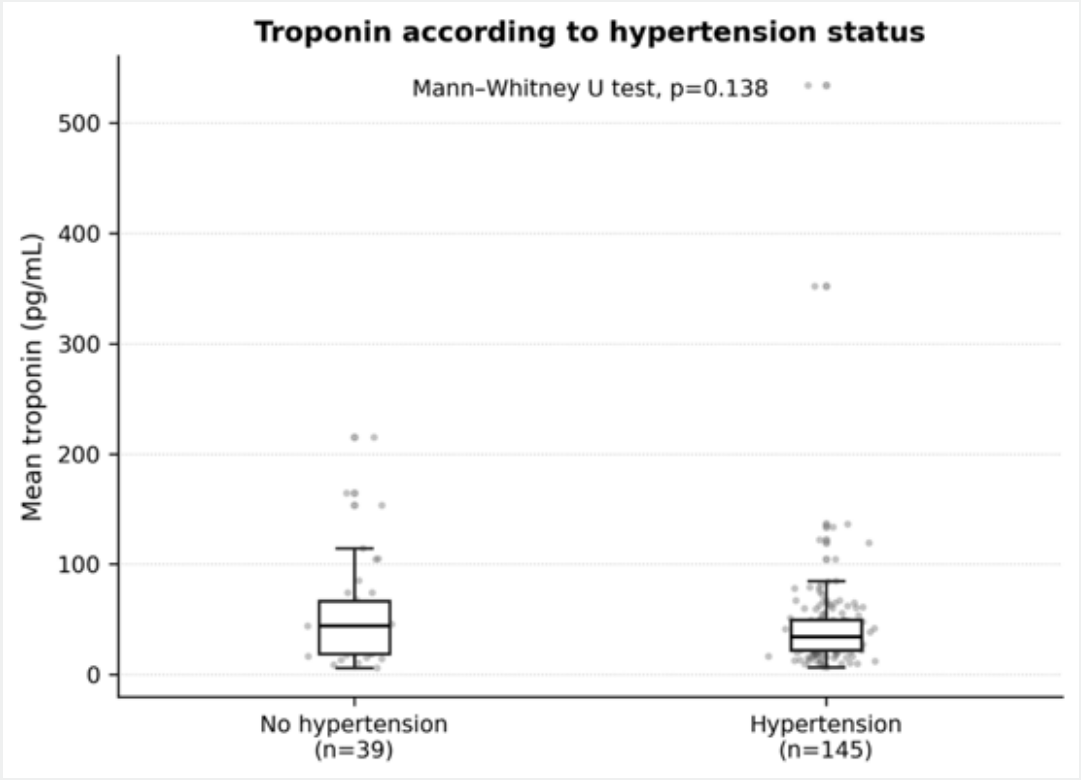

Figure 7: Troponin and hypertension status.

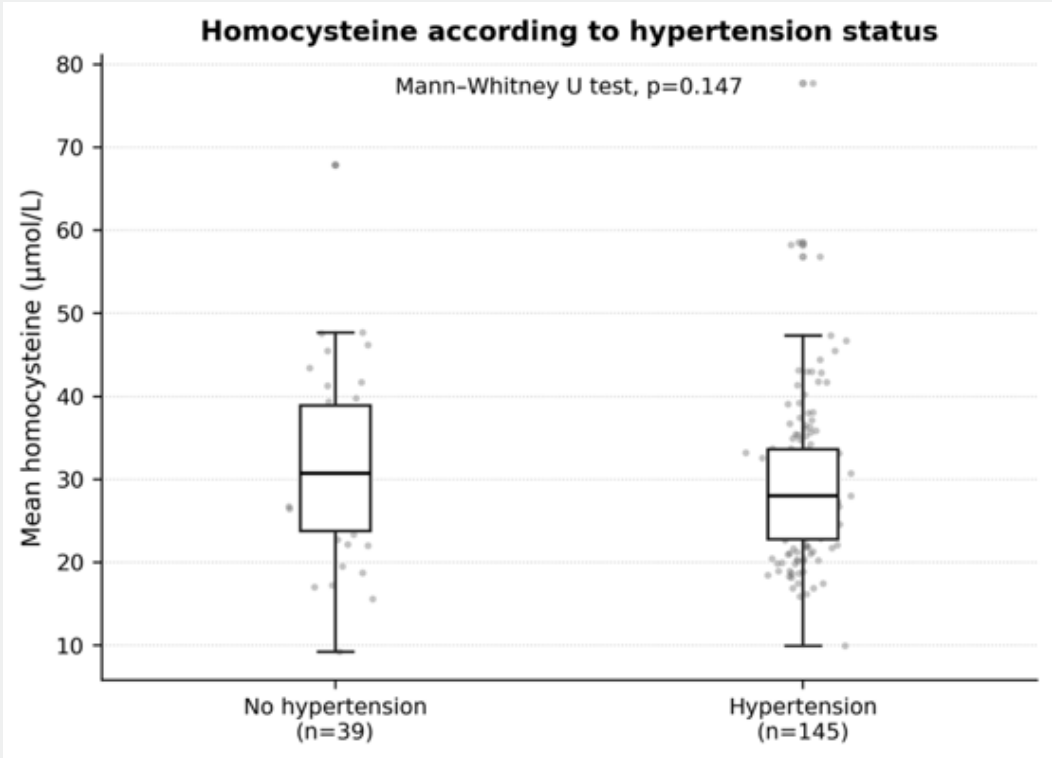

Figure 8: Homocysteine and hypertension status.

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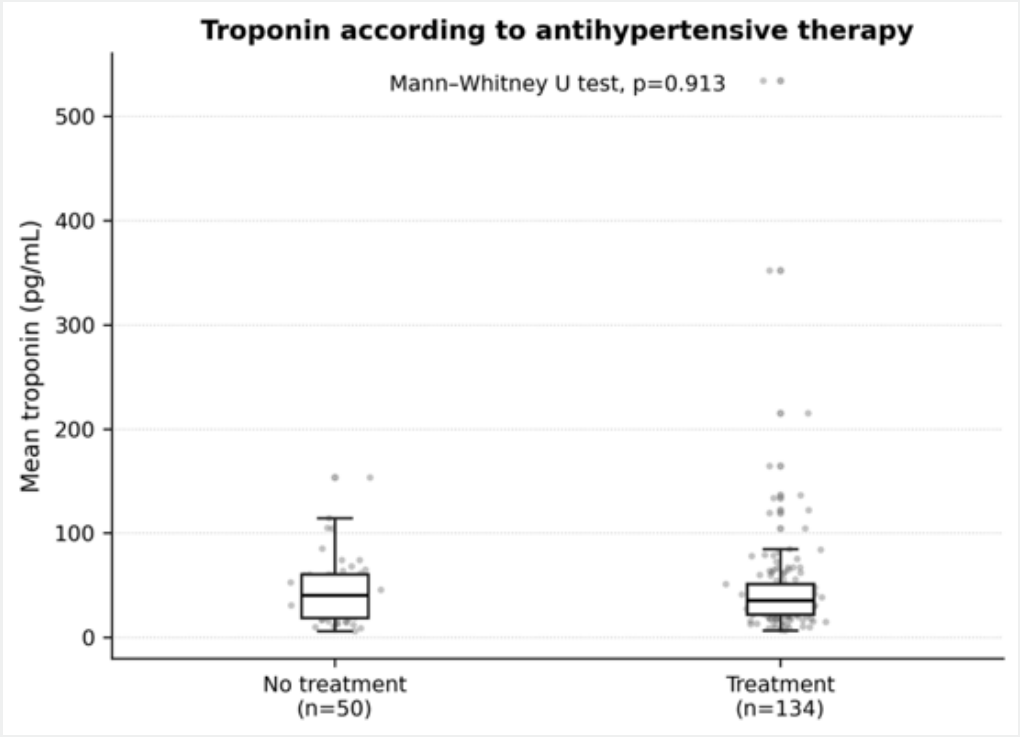

Figure 9: Troponin and antihypertensive therapy.

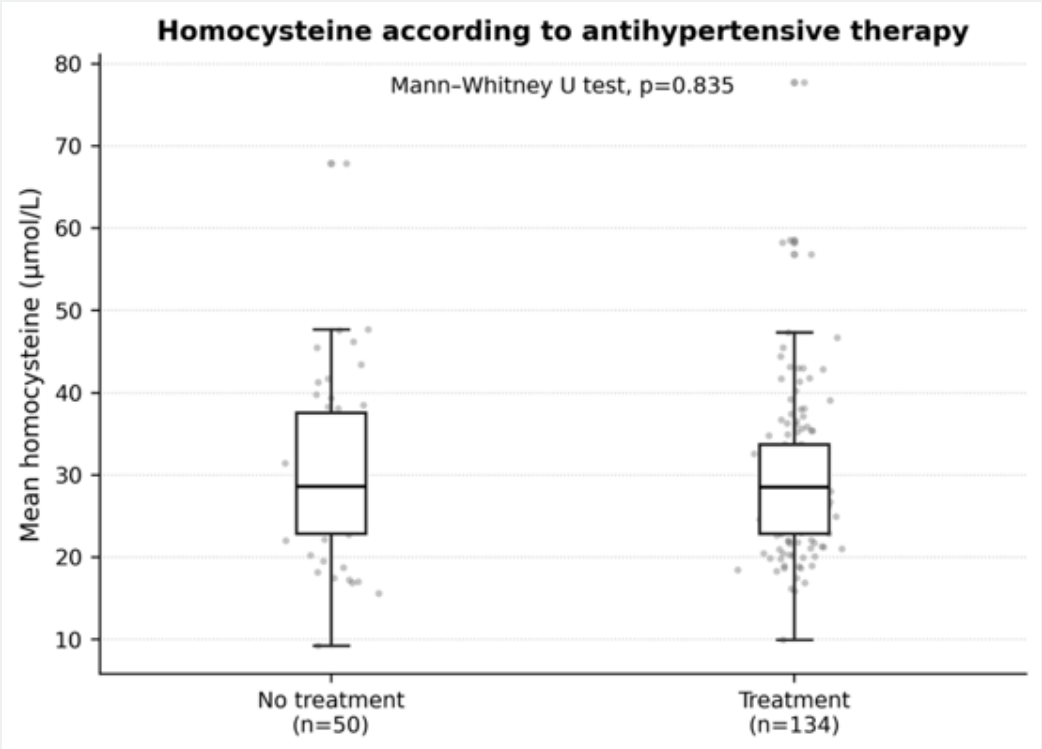

Figure 10: Homocysteine and antihypetensive therapy.

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Antihypertensive Therapy

Patients were subsequently stratified according to the use of antihypertensive medication. Troponin concentrations did not differ significantly between treated and untreated patients (p=0.913) (Figure 9). Likewise, no significant association was identified between antihypertensive therapy and homocysteine concentrations (p=0.835) (Figure 10). These findings indicate that pharmacological blood pressure control was not associated with measurable differences in either biomarker within the study population.

Lipid-Lowering Therapy

Ninety-three patients were receiving lipid-lowering treatment, whereas 91 patients were not. Troponin concentrations were comparable between the two groups (p=0.965) (Figure 11). Similarly, homocysteine concentrations tended to be lower among treated patients; however, this difference did not achieve statistical significance (p=0.202) (Figure 12). The absence of a significant association suggests that chronic troponin elevation in ESRD primarily reflects structural myocardial injury and cardiovascular disease burden rather than alterations in lipid metabolism.

Folic Acid Supplementation

Folic acid supplementation emerged as the only therapeutic variable significantly associated with biomarker concentrations. Patients receiving folic acid demonstrated significantly lower homocysteine levels compared with untreated individuals (p<0.001) (Figure 13). Interestingly, folic acid administration was also associated with significantly different troponin concentrations (p=0.009) (Figure 14). Although the observational design of the study precludes causal inference, these findings suggest that folate metabolism may contribute to the modulation of cardiovascular risk pathways in patients undergoing maintenance hemodialysis.

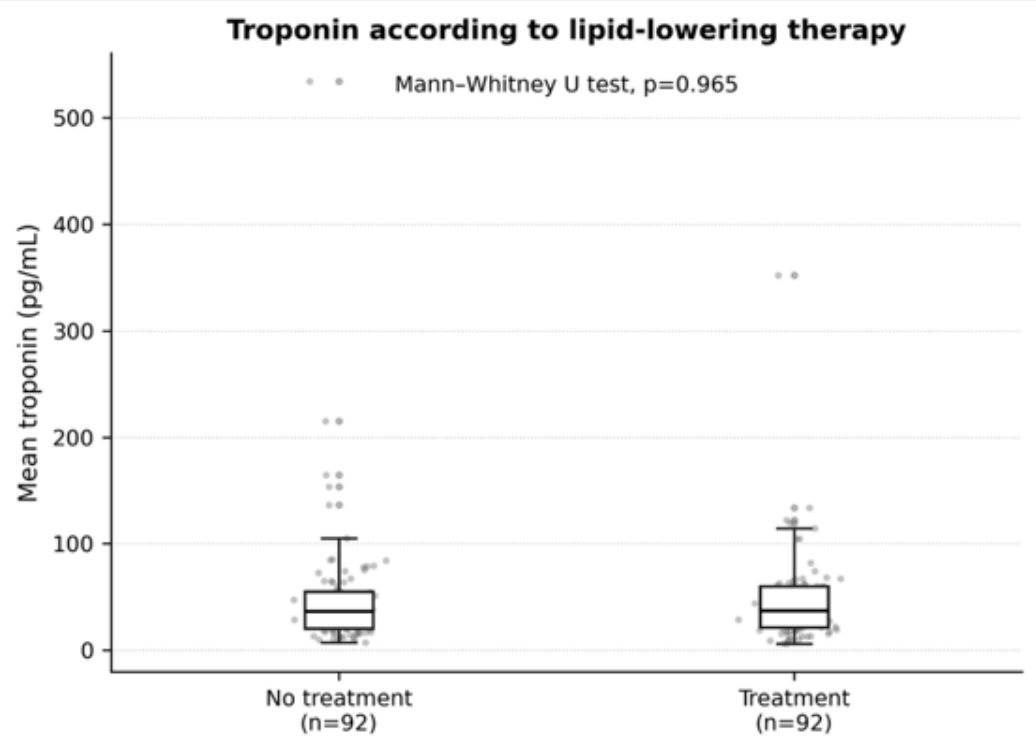

Figure 11: Troponin and lipid-lowering therapy.

Discussion

The present prospective observational study provides important insights into the determinants of chronic cardiac troponin and homocysteine elevation in patients receiving maintenance hemodialysis. Three principal findings emerged. First, elevated circulating concentrations of both biomarkers were highly prevalent, with troponin levels above the reference range in nearly 90% of patients and hyperhomocysteinemia in almost the entire cohort. Second, dialysis vintage was not significantly associated with circulating concentrations of either troponin or homocysteine. Third, established coronary artery disease was strongly associated with higher troponin concentrations, whereas homocysteine levels were not significantly different according to coronary disease status.

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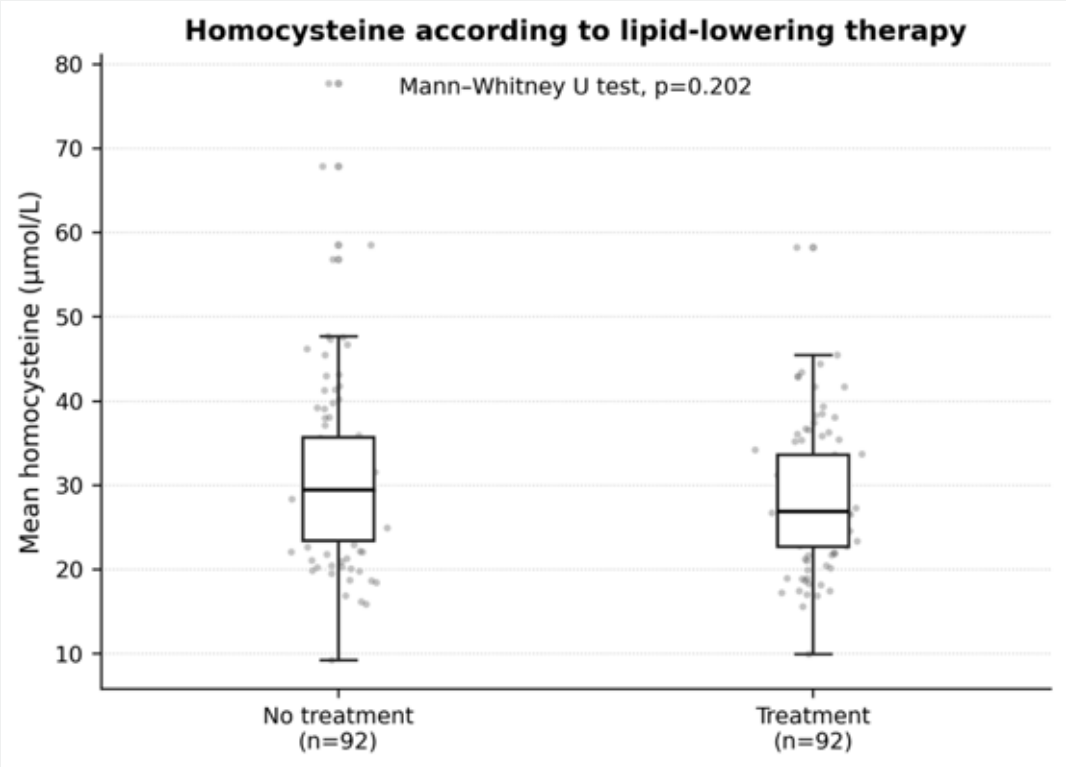

Figure 12: Homocysteine and lipid-lowering therapy.

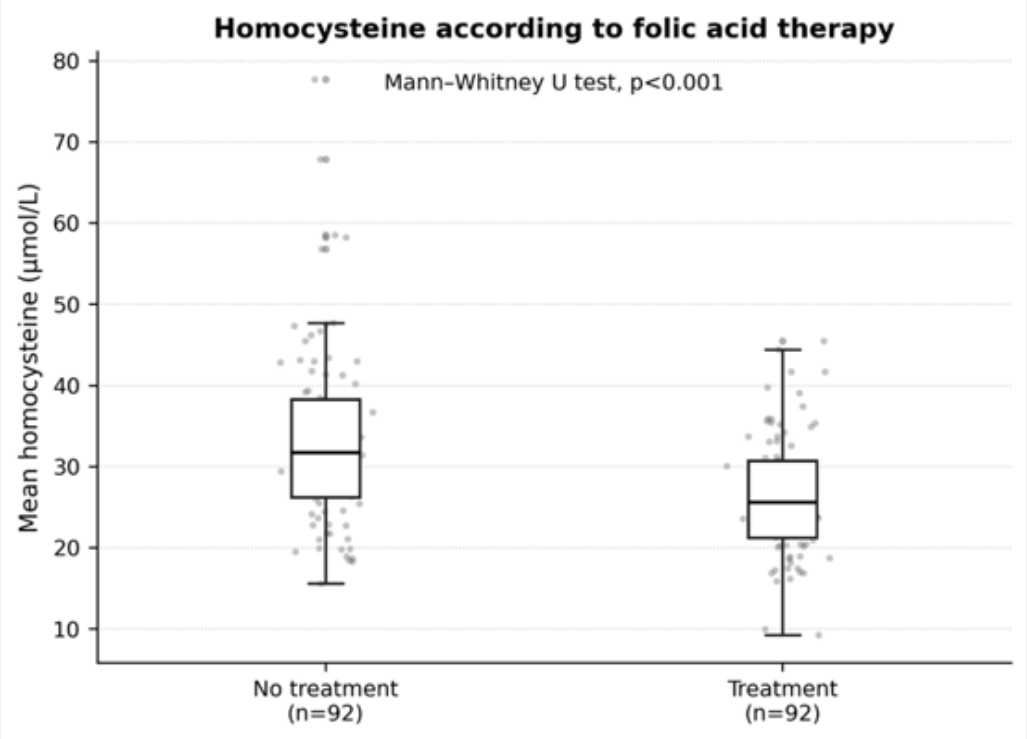

Figure 13: Homocysteine and folic acid treatment.

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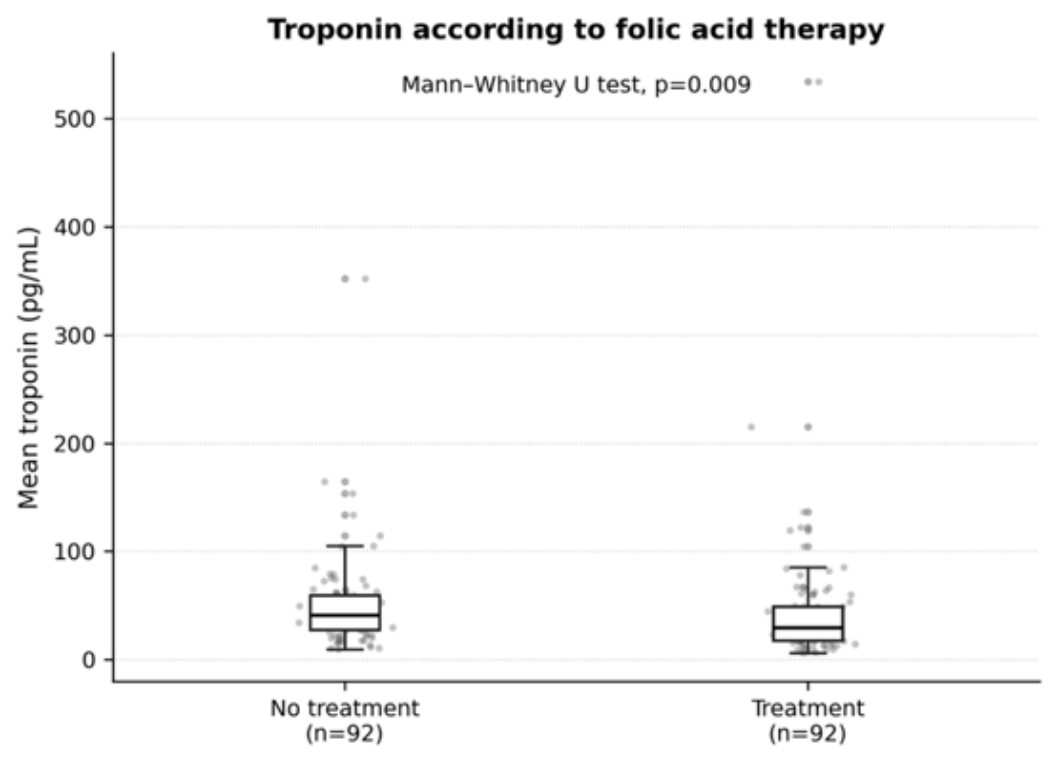

Figure 14: Troponin and folic acid therapy.

Collectively, these findings suggest that chronic troponin elevation primarily reflects underlying structural cardiovascular disease, while hyperhomocysteinemia represents a persistent metabolic consequence of end-stage kidney disease rather than a direct marker of dialysis duration. The high prevalence of elevated cardiac troponin observed in our cohort is consistent with contemporary evidence showing that chronically increased troponin concentrations are common in clinically stable dialysis patients. High-sensitivity troponin studies have demonstrated that many patients' receiving chronic dialysis have values above the conventional upper reference limit without acute coronary syndrome, and these elevations carry prognostic information rather than representing analytical noise alone [24-27]. This is clinically important because troponin interpretation in advanced chronic kidney disease is challenging; isolated elevated values should not be used as the sole diagnostic criterion for acute myocardial infarction.

Current ESC guidance emphasizes serial changes together with symptoms, electrocardiography, and imaging, while KDIGO highlights the need for contextual cardiovascular risk assessment in CKD [21,22]. The pathophysiology of chronic troponin elevation in dialysis is multifactorial. Reduced clearance of troponin fragments may contribute, but it does not fully explain the phenomenon. Chronic pressure and volume overload, left ventricular hypertrophy, diffuse myocardial fibrosis, coronary microvascular dysfunction, endothelial dysfunction, oxidative stress, systemic inflammation, and recurrent intradialytic hemodynamic stress all promote persistent low-grade cardiomyocyte injury [23,25,27,28]. Therefore, chronic troponin elevation in hemodialysis should be interpreted as an integrated biomarker of ongoing myocardial injury and adverse cardiovascular remodeling rather than simply because of kidney failure.

A central finding of this study was the absence of an independent relationship between dialysis vintage and troponin concentrations. This challenges the assumption that longer exposure to dialysis necessarily leads to progressive biomarker elevation. One plausible explanation is that cardiovascular remodeling begins before dialysis initiation, during advanced CKD. Uremic cardiomyopathy, characterized by left ventricular hypertrophy, interstitial fibrosis, impaired myocardial perfusion, and electrical instability, is driven by multiple CKD-related mechanisms, including anemia, hypertension, volume overload, neurohormonal activation, mineral metabolism abnormalities, inflammation, and oxidative stress [23,28].

By the time maintenance hemodialysis begins, substantial myocardial injury may already be established. Consequently, dialysis duration alone may be a poor surrogate for cardiovascular burden. The strong association between coronary artery disease and higher troponin concentrations further supports this

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interpretation. In our cohort, patients with documented CAD had significantly higher troponin levels than those without CAD, indicating that chronic troponin elevation reflects underlying cardiovascular pathology more strongly than dialysis duration. This finding is consistent with studies showing that elevated troponin in CKD and ESKD is associated with structural heart disease, myocardial fibrosis, heart failure, cardiovascular events, and mortality [24-27]. Clinically, persistently elevated troponin should not be dismissed as "renal troponin."

Rather, it should prompt careful assessment for occult ischemic heart disease, left ventricular hypertrophy, myocardial dysfunction, or heart failure, particularly when values are rising or accompanied by symptoms or electrocardiographic changes [22,25]. Hyperhomocysteinemia was another major finding, affecting almost all patients. This is biologically expected in ESKD because homocysteine metabolism depends on renal function, remethylation, transsulfuration, folate, vitamin B12, and vitamin B6 pathways. Kidney failure disrupts these pathways through impaired metabolism, reduced clearance, inflammation, oxidative stress, nutritional abnormalities, and altered methylation biology [29-32]. Since most circulating homocysteine is protein-bound, conventional hemodialysis removes only part of the total circulating pool, explaining why elevated levels persist despite maintenance dialysis.

The lack of association between dialysis vintage and homocysteine suggests that disturbances in one-carbon metabolism are established early in advanced kidney disease and remain relatively stable after dialysis initiation. Homocysteine levels appear to be influenced more by residual kidney function, nutritional status, vitamin availability, inflammatory burden, and genetic determinants of one-carbon metabolism than by dialysis duration alone [29-32]. This explains why homocysteine did not discriminate among dialysis-vintage groups in our cohort. Homocysteine also did not differ significantly between patients with and without CAD. Although homocysteine promotes endothelial dysfunction, oxidative stress, inflammation, smooth muscle proliferation, extracellular matrix remodeling, platelet activation, and thrombogenesis, its independent discriminatory value in ESKD may be limited [29-33].

Dialysis patients are exposed to multiple overlapping cardiovascular insults, including vascular calcification, arterial stiffness, chronic inflammation, anemia, uremic toxins, and volume overload. Within this complex milieu, homocysteine may function more as a marker of systemic metabolic disturbance than as a specific marker of established coronary atherosclerosis. A clinically relevant finding was the association between folic acid supplementation and lower homocysteine concentrations. This is biologically plausible because folate is a key methyl donor in the remethylation of homocysteine to methionine. Randomized trials and meta-analyses confirm that folic acid and B-vitamin supplementation can reduce homocysteine levels in kidney disease, but they have not consistently reduced myocardial infarction, stroke, cardiovascular mortality, or all-cause mortality [33-35]. Therefore, homocysteine should not be viewed as an isolated therapeutic target for cardiovascular risk reduction in dialysis.

The observed association between folic acid supplementation and lower troponin concentrations is intriguing but should be interpreted cautiously. Because this was an observational study, causality cannot be inferred. Potential mechanisms include improved methylation capacity, reduced oxidative stress, better endothelial function, and attenuation of vascular injury. However, residual confounding is likely, as patients receiving folic acid may differ in nutritional status, dialysis adequacy, anemia management, medication adherence, or overall quality of care. This finding should therefore be considered hypothesis-generating and requires confirmation in prospective interventional studies. Studying has several strengths. It included a clinically relevant cohort of maintenance hemodialysis patients, used serial biomarker measurements over 12 months, and simultaneously assessed two biologically distinct pathways: chronic myocardial injury and disturbed one-carbon metabolism.

Stratification by dialysis vintage, coronary artery disease, hypertension, cardiovascular therapies, and folic acid supplementation allowed clinically meaningful subgroup analyses. Several limitations should also be acknowledged. The observational design precludes causal inference. The study was conducted in two centers, which may limit generalizability. Residual confounding from dialysis adequacy, residual kidney function, nutritional status, inflammation, mineral metabolism, anemia management, and genetic variants affecting homocysteine metabolism cannot be excluded. Advanced cardiovascular imaging, including cardiac magnetic resonance, speckle-tracking echocardiography, or coronary imaging, was not systematically performed; therefore, direct correlations between biomarkers and myocardial fibrosis, ventricular remodeling, or coronary microvascular dysfunction could not be assessed.

In conclusion, chronic elevations of cardiac troponin and homocysteine are highly prevalent among patients receiving maintenance hemodialysis. Dialysis vintage was not independently associated with either biomarker, suggesting that the underlying myocardial and metabolic abnormalities are established early in advanced kidney disease and persist during long-term dialysis. By contrast, established coronary artery disease was strongly associated with higher troponin concentrations, supporting the role of troponin as a marker of structural cardiovascular injury rather than dialysis duration. Hyperhomocysteinemia appears to reflect disturbed one-carbon metabolism and systemic uremic metabolic dysfunction. Together, these findings support a multimarker approach to cardiovascular risk stratification in ESKD, integrating serial biomarkers with clinical assessment and cardiovascular imaging.

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Conclusions

These findings challenge the traditional assumption that dialysis vintage is a major determinant of chronic biomarker elevation in maintenance hemodialysis and instead highlight the predominant role of underlying cardiovascular pathology in shaping the biomarker profile of patients with end-stage kidney disease. Incorporating serial cardiac troponin measurements into routine cardiovascular assessment, alongside comprehensive clinical and imaging evaluation, may improve cardiovascular risk stratification and facilitate more personalized management of this exceptionally high-risk population.

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