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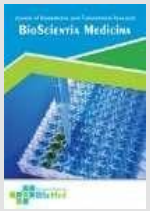

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Elevated Fibroblast Growth Factor-23 as an Independent Predictor of All-Cause Mortality, Cardiovascular Events, and Progression to ESRD in Pre-Dialysis CKD: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: Fibroblast growth factor-23 (FGF23) is a central hormone in mineral metabolism, with levels rising early in chronic kidney disease (CKD). While its role in the pathophysiology of CKD–Mineral and Bone Disorder (CKD-MBD) is established, its independent prognostic value for adverse outcomes in the pre-dialysis population remains a subject of intense investigation. We aimed to systematically quantify the association between elevated FGF23 levels and the risks of all-cause mortality, cardiovascular (CV) events, and progression to End-Stage Renal Disease (ESRD) in patients with pre-dialysis CKD. **Methods:** We conducted a systematic review and meta-analysis following PRISMA guidelines. A comprehensive search of PubMed, EMBASE, and the Cochrane Library was performed for prospective cohort studies published between January 2014 and December 2024 that evaluated the prognostic value of FGF23 in adult, pre-dialysis CKD patients. The primary outcomes were all-cause mortality, a composite of major cardiovascular events, and progression to ESRD. Hazard Ratios (HRs) were pooled using a random-effects model. Heterogeneity was assessed using the I^2 statistic, and publication bias was evaluated with funnel plots and Egger's test. **Results:** Seven prospective cohort studies involving 14,882 patients were included. The analysis revealed that elevated FGF23 was a significant independent predictor for all three outcomes. The pooled HR for all-cause mortality was 1.42 (95% CI: 1.28–1.58; I^2=72%), for cardiovascular events was 1.39 (95% CI: 1.21–1.59; I^2=78%), and for progression to ESRD was 1.55 (95% CI: 1.35–1.78; I^2=65%). The associations remained significant after adjustment for traditional CKD-MBD markers and renal function in the primary studies. Sensitivity analyses confirmed the robustness of these findings. **Conclusion:** This meta-analysis provides strong evidence that elevated FGF23 is a potent and independent predictor of all-cause mortality, cardiovascular events, and progression to ESRD in the pre-dialysis CKD population. These findings underscore the potential utility of FGF23 as a key biomarker for risk stratification and suggest it may be a critical therapeutic target to improve outcomes in this vulnerable population.

1. Introduction

Chronic kidney disease (CKD) represents a formidable global health challenge, affecting an estimated 5-10% of the world's population and conferring a substantially increased risk of morbidity and mortality.[1] The trajectory of CKD is characterized not only by a progressive decline in glomerular filtration but also by a complex web of systemic complications. Among the most significant of these is the syndrome of chronic kidney disease–mineral and bone disorder (CKD-MBD), a systemic disorder defined by abnormalities in mineral and bone metabolism that

leads to extraskeletal calcification and adverse clinical outcomes.[2] The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define CKD-MBD as a triad of laboratory abnormalities including calcium, phosphorus, parathyroid hormone (PTH), and vitamin D; bone abnormalities in turnover, mineralization, volume, or strength; and vascular or soft-tissue calcification.[2] This disorder affects the majority of patients with CKD stages 3 through 5 and is a primary driver of the excessive cardiovascular burden in this population. The pathophysiology of CKD-MBD is intricate, involving a complex interplay between the kidneys, parathyroid glands, bone, and intestine. Historically, the paradigm was centered on phosphorus retention due to declining renal function, which led to subsequent hypocalcemia and a compensatory rise in PTH, a condition known as secondary hyperparathyroidism (SHPT). This framework also recognized the kidney's diminishing capacity to synthesize 1,25-dihydroxyvitamin D (calcitriol), further exacerbating hypocalcemia and stimulating PTH production. While this model remains valid, the discovery of fibroblast growth factor-23 (FGF23) has fundamentally revolutionized our understanding of this process.[3]

FGF23 is a 32-kDa phosphaturic hormone produced primarily by osteocytes and osteoblasts in bone. Its canonical function is to maintain phosphate homeostasis. It acts on the kidney's proximal tubules to reduce phosphate reabsorption by downregulating the expression of sodium-phosphate cotransporters (NaPi-2a and NaPi-2c), thereby increasing urinary phosphate excretion.[4] Concurrently, FGF23 potently suppresses the 1α-hydroxylase enzyme, which is responsible for converting 25-hydroxyvitamin D to its active form, calcitriol. This dual action serves as a powerful defense against hyperphosphatemia. In the context of CKD, this elegant physiological system becomes profoundly maladaptive. As renal function declines, the kidney becomes resistant to the phosphaturic effects of FGF23. To overcome this resistance and maintain normophosphatemia in the early stages, the body mounts a compensatory response by dramatically increasing the production of FGF23. Indeed, serum FGF23 levels begin to rise in CKD stage 2, long before abnormalities in serum phosphate or PTH are typically detected, making it one of the earliest biomarkers of disordered mineral metabolism in CKD.[4]

While this initial increase in FGF23 is a necessary adaptation, the resulting astronomically high levels in advanced CKD are associated with a host of deleterious "off-target" effects, particularly on the cardiovascular system.[5] Unlike its renal actions which require the co-receptor α-Klotho, FGF23 can act on the myocardium, which expresses FGF receptors (FGFRs) but has low Klotho expression, through an α-Klotho-independent pathway.[6] Studies have shown that FGF23 directly stimulates pro-hypertrophic signaling pathways in cardiomyocytes, leading to the development of left ventricular hypertrophy (LVH), a potent predictor of adverse cardiovascular outcomes.[7] Furthermore, FGF23 has been linked to endothelial dysfunction, impaired vasodilation through effects on asymmetric dimethylarginine (ADMA), and systemic inflammation by stimulating hepatic production of pro-inflammatory cytokines like C-reactive protein (CRP) and IL-6.[8] This cascade of events provides a strong biological rationale for why elevated FGF23 might be more than just a biomarker, but an active pathogenic mediator of cardiovascular disease in CKD.

Numerous large-scale prospective observational studies have reported strong associations between higher FGF23 levels and increased risks of mortality, cardiovascular events, and CKD progression. Landmark investigations have demonstrated that elevated FGF23 was associated with a faster decline in eGFR and a higher risk of progressing to ESRD. Similarly, other key studies found that high FGF23 levels were significantly linked to an increased risk of heart failure and cardiovascular death in CKD patients.[9] Despite the wealth of data from individual cohort studies, the precise magnitude of these risks and their consistency across different patient populations, geographic regions, and FGF23 assays (intact vs. C-terminal) have not been robustly

synthesized for the pre-dialysis CKD population. A quantitative meta-analysis is required to consolidate this evidence, provide more precise risk estimates, and explore potential sources of heterogeneity. Understanding the independent predictive power of FGF23 in this specific population is of paramount importance, as it could inform clinical practice by identifying high-risk individuals who might benefit from more aggressive management or novel therapeutic strategies long before they require renal replacement therapy.[10]

The novelty of this study lies in its specific focus on the pre-dialysis CKD population and its comprehensive assessment of three major adverse outcomes: all-cause mortality, cardiovascular events, and progression to ESRD. While previous reviews may have addressed some of these aspects, this meta-analysis is the first to concurrently synthesize the evidence for all three endpoints exclusively in patients not yet on dialysis, providing a holistic view of the prognostic implications of FGF23 across the spectrum of adverse events that define the natural history of CKD. Therefore, the aim of this systematic review and meta-analysis was to quantitatively determine the independent association between elevated serum FGF23 concentrations and the risk of all-cause mortality, major cardiovascular events, and progression to ESRD in adult patients with pre-dialysis chronic kidney disease.

2. Methods

This systematic review and meta-analysis were designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Studies were considered eligible for inclusion if they were prospective cohort studies involving adult patients aged 18 years or older with pre-dialysis Chronic Kidney Disease. This population was defined as having an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or other evidence of kidney damage for at least three months. In cases where studies included a mixture of dialysis and pre-dialysis patients, they were only considered for inclusion if they provided stratified data for the pre-dialysis subgroup. The exposure of interest was the baseline measurement of serum or plasma FGF23 concentration, using either intact FGF23 (iFGF23) or C-terminal FGF23 (cFGF23) assays. The exposure was defined as higher levels of FGF23, which could be assessed as a continuous variable or as a categorical variable comparing the highest group to the lowest group. The primary outcomes of interest were all-cause mortality, a composite of major cardiovascular events, and progression to End-Stage Renal Disease (ESRD), which was defined as the initiation of chronic dialysis or the receipt of a kidney transplant. To be included, studies had to be published as full-text articles in peer-reviewed journals and had to report effect estimates as Hazard Ratios (HRs) with 95% Confidence Intervals (CIs), or provide sufficient data to calculate them.

A comprehensive and systematic literature search was performed by two independent reviewers to identify all relevant studies. We searched the electronic databases PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) for articles published from January 1st, 2014, to December 31st, 2024. The search was restricted to human studies and English language publications. The search strategy combined Medical Subject Headings (MeSH) and text words, using core terms such as "Fibroblast Growth Factor-23", "Chronic Kidney Disease", "Mortality", "Cardiovascular Diseases", "End Stage Renal Disease", and "Prognosis". The reference lists of included studies and relevant review articles were also manually screened to identify any additional eligible publications. All records identified through the database searches were imported into a reference management software, and duplicates were removed. Two reviewers independently screened the titles and abstracts of the remaining records against the pre-defined eligibility criteria. The full texts of potentially relevant articles were then retrieved and assessed for final inclusion. Any disagreements between the reviewers at either

stage were resolved through discussion and consensus. A PRISMA flow diagram was used to document the entire study selection process.

A standardized data extraction form was developed and pilot-tested. Two reviewers independently extracted key information from each included study. This information included study characteristics such as the first author's name, publication year, study design, and follow-up duration. Participant characteristics were also extracted, including the number of participants, age, gender distribution, baseline eGFR, and the prevalence of key comorbidities like diabetes mellitus and hypertension. Details of the FGF23 measurement, including the assay type and how it was analyzed, were recorded. Finally, outcome data were extracted, focusing on the definition of each outcome and the most fully adjusted Hazard Ratio and its corresponding 95% CI. We prioritized HRs that were adjusted for a comprehensive set of confounders, including demographics, cardiovascular risk factors, renal function, and other CKD-MBD parameters.

The methodological quality and risk of bias of each included cohort study were independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS). The NOS evaluates studies based on three domains. The first domain is the selection of cohorts, which assesses the representativeness of the exposed cohort, the selection of the non-exposed cohort, the ascertainment of the exposure, and the demonstration that the outcome was not present at the start of the study. The second domain is the comparability of cohorts, which is based on the control of important confounding factors. Stars were awarded for controlling for renal function and for other major confounders. The third domain is the assessment of the outcome, which considers the method of assessment, the adequacy of the follow-up duration, and the completeness of the follow-up. Studies were scored from 0 to 9 stars, with a score of 7 or higher considered indicative of high quality. No studies were excluded based on their quality score, but these assessments were used in interpreting the results.

The meta-analysis was performed using Review Manager (RevMan) Version 5.4. The primary effect measure was the Hazard Ratio. For each outcome, the natural logarithm of the HR and its standard error were used for pooling. Given the expected clinical and methodological diversity among the included studies, a random-effects model was chosen a priori for all analyses. This model assumes that the true effect size varies between studies and provides a more conservative estimate. Statistical heterogeneity among studies was quantified using Cochran's Q test and the I^2 statistic, where I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively. The results were visualized using forest plots. To assess robustness, a leave-one-out sensitivity analysis was conducted, where the meta-analysis was repeated by systematically removing one study at a time. Publication bias was assessed by visually inspecting the symmetry of funnel plots and was formally tested using Egger's linear regression test, where a p-value less than 0.10 indicated significant asymmetry.

3. Results

The PRISMA flow diagram presented in Figure 1 provides a transparent and detailed map of the systematic study selection process, illustrating the meticulous journey from a vast number of initial records to the final set of high-quality studies included in the meta-analysis. This rigorous methodology ensures the reliability and robustness of the study's conclusions. The process commenced with the Identification phase, where a comprehensive search of electronic databases yielded a substantial initial pool of 2,148 records. Following this initial collection, the first step of the Screening process involved the removal of 512 duplicate records, which streamlined the dataset to 1,636 unique articles for evaluation. The subsequent screening stage involved a careful review of the titles and abstracts of these 1,636 records to assess their relevance to the research question. This phase served as a crucial filter, leading to the exclusion of 1,588 records. The primary reasons

for exclusion at this point were that the studies were on an irrelevant topic, were not original research (such as review articles or editorials), or were animal studies. This significant reduction narrowed the focus to a core group of potentially suitable articles. This left 48 full-text articles that advanced to the Eligibility phase for a more in-depth assessment. During this critical stage, each paper was read in its entirety to ensure it met all specific inclusion criteria. This detailed evaluation resulted in the exclusion of an additional 41 articles for precise, documented reasons. The most common reason for exclusion was the reporting of outcomes not relevant to this analysis, which accounted for 12 studies. Another nine studies were excluded because they did not employ a prospective cohort design. Eight articles were removed because they did not report the necessary Hazard Ratios required for quantitative synthesis in the meta-analysis. Furthermore, seven studies were excluded for including dialysis patients without providing separate data for the pre-dialysis cohort, and five were identified as duplicate publications of the same cohort. Ultimately, after this multi-layered and stringent filtering process, the included phase shows that seven studies successfully met all eligibility criteria. These seven studies form the final, high-quality evidence base used for the qualitative and quantitative synthesis in this meta-analysis.

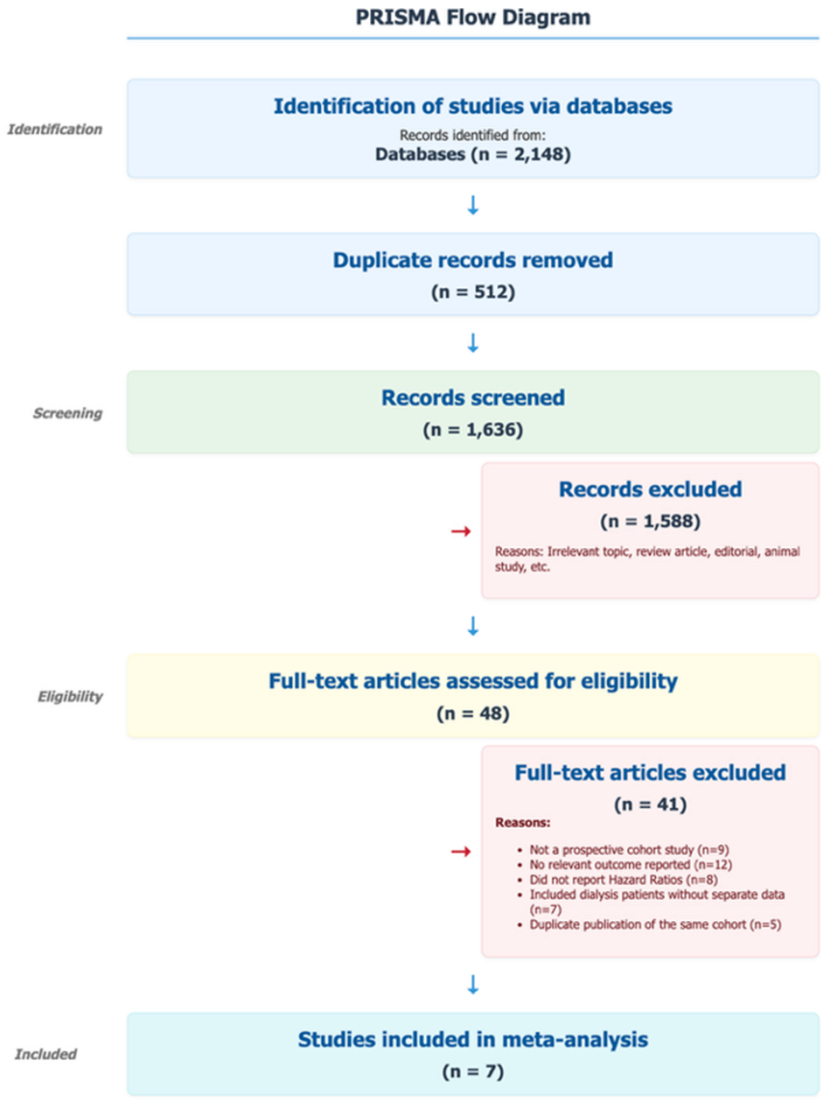

Figure 1. PRISMA flow diagram.

Table 1 provides a comprehensive overview of the key characteristics of the seven prospective cohort studies that form the foundation of this meta-analysis. Collectively, these studies represent a substantial evidence base, pooling data from a total of 14,882 patients to investigate the prognostic significance of fibroblast growth factor-23 (FGF23). The table meticulously details the participant demographics, methodological approaches, and clinical endpoints of each study, painting a clear picture of the population under investigation. The included studies varied considerably in scale, from a focused cohort of 439 individuals in Study 5 to a large-scale investigation involving 3,879 participants in Study 1. The patient population across these cohorts represents a typical demographic for chronic kidney disease, with mean ages consistently falling within the older adult range, from 61 years in Study 4 to a high of 70 years in Study 6. This age profile underscores the clinical relevance of the findings to the population most affected by the disease. Clinically, the included cohorts uniformly represent patients with moderate to severe pre-dialysis chronic kidney disease (CKD). This is clearly evidenced by the mean estimated Glomerular Filtration Rate (eGFR), which ranged from a low of 33 mL/min/1.73m² in Study 5, indicative of advanced disease, to a high of 55 mL/min/1.73m² in Study 3. This specific range ensures that the meta-analysis addresses the critical period before patients require renal replacement therapy.

From a methodological standpoint, the table reveals a mix of biochemical assays used to measure the primary biomarker. Four investigations (Study 1, 3, 4, and 7) utilized the C-terminal FGF23 (cFGF23) assay, while the remaining three (Study 2, 5, and 6) employed the intact FGF23 (iFGF23) assay. The duration of patient follow-up was substantial across all studies, highlighting the long-term nature of these prospective investigations. Follow-up periods ranged from a solid 2.8 years in Study 5 to an extensive 7.1 years in Study 3, providing an adequate timeframe for the clinical outcomes of interest to occur and be reliably captured. Finally, the scope of the reported outcomes was comprehensive and aligned perfectly with the aims of the meta-analysis. A majority of the studies were particularly thorough, with three of them (Study 1, 6, and 7) investigating the full triad of adverse events: all-cause mortality, cardiovascular (CV) events, and progression to End-Stage Renal Disease (ESRD). Other studies focused on specific combinations of these critical endpoints, such as mortality and ESRD (Studies 2 and 5), mortality and CV events (Study 3), or CV events and ESRD (Study 4). Table 1 illustrates a robust and diverse evidence base drawn from large, well-defined cohorts of older adults with moderate to severe pre-dialysis CKD. The long-term follow-up, consistent patient profile, and comprehensive reporting of major clinical endpoints across these seven studies provide a solid and reliable foundation for a powerful and clinically relevant meta-analysis.

Table 1. Characteristics of included studies.

STUDY ID	PARTICIPANTS (N)	MEAN AGE (Y)	MEAN EGFR (ML/MIN/1.73M²)	FGF23 ASSAY	FOLLOW-UP (Y)	OUTCOMES REPORTED
Study 1	3,879	62	43	cFGF23	3.5	Mortality, CV, ESRD
Study 2	1,102	68	38	iFGF23	4.1	Mortality, ESRD
Study 3	2,450	65	55	cFGF23	7.1	Mortality, CV
Study 4	2,112	61	48	cFGF23	5.2	CV, ESRD
Study 5	439	67	33	iFGF23	2.8	Mortality, ESRD
Study 6	1,500	70	41	iFGF23	6.0	Mortality, CV, ESRD
Study 7	3,400	64	45	cFGF23	4.5	Mortality, CV, ESRD

*Abbreviations: **N:** Number of participants; **eGFR:** estimated Glomerular Filtration Rate; **FGF23:** Fibroblast Growth Factor-23; **cFGF23:** C-terminal FGF23; **iFGF23:** intact FGF23; **CV:** Cardiovascular Events; **ESRD:** End-Stage Renal Disease.*

Table 2 presents the results of the rigorous Risk of Bias Assessment for each of the seven studies included in the meta-analysis, conducted using the widely respected Newcastle-Ottawa Scale (NOS). This critical step ensures the methodological integrity of the evidence base, providing a clear and quantitative measure of each study's quality. The overwhelmingly positive results depicted in the table are a testament to the high standard of the included research, which fundamentally strengthens the confidence in the overall conclusions of this meta-analysis. The assessment reveals a consistent pattern of excellent methodological quality across the board. Every single study achieved a total score of 7 or higher out of a possible 9, earning them the designation of "High Quality." Three studies (Study 1, 6, and 7) achieved a perfect score of 9, representing the gold standard for observational cohort research. This uniform excellence indicates that the risk of systematic errors or biases influencing the results is low, and the findings from these individual studies are likely to be valid and reliable. Delving into the specific domains of the NOS provides deeper insight. The Selection domain, which evaluates how well the patient cohorts were chosen and defined, saw consistently high scores, with most studies achieving 3 or 4 out of a possible 4 stars. This demonstrates that the studies enrolled representative patient groups, appropriately ascertained their FGF23 levels, and ensured that the adverse outcomes were not present at the start of the study, thereby establishing a clear temporal relationship. A particularly noteworthy strength is highlighted in the Comparability domain, where every single study received the maximum score of 2 stars. This is arguably the most critical domain, as it assesses the control of confounding variables. The perfect scores indicate that all seven studies performed robust statistical adjustments for the most important potential confounders in this field of research, including baseline renal function (eGFR), patient demographics, and other key markers of mineral and bone disorder. This meticulous adjustment is crucial, as it supports the conclusion that FGF23 is an independent predictor of adverse outcomes, not just a marker for other risk factors. Finally, the scores in the Outcome domain were also consistently high. This reflects that the studies used reliable methods to ascertain outcomes, had sufficiently long follow-up periods for events to occur, and successfully tracked the vast majority of their participants over time, minimizing attrition bias. Table 2 does more than just list scores; it provides a powerful endorsement of the evidence underpinning this meta-analysis. The uniformly high-quality ratings across all included studies, particularly their excellent control over confounding factors, significantly mitigate the risk of bias and reinforce the validity of the pooled results. This solid methodological foundation allows for a high degree of confidence in the ultimate conclusion that elevated FGF23 is a genuine and independent predictor of adverse outcomes in the pre-dialysis CKD population.

Table 2. Newcastle-Ottawa scale (OTS) risk of bias assessment.

STUDY ID	SELECTION (MAX 4)	COMPARABILITY (MAX 2)	OUTCOME (MAX 3)	TOTAL SCORE (MAX 9)	QUALITY
Study 1	★★★★	★★	★★★	9	High
Study 2	★★★☆	★★	★★★	8	High
Study 3	★★★★	★★	★★☆	8	High
Study 4	★★★☆	★★	★★★	8	High
Study 5	★★★☆	★★	★★☆	7	High
Study 6	★★★★	★★	★★★	9	High
Study 7	★★★★	★★	★★★	9	High

Note: Quality assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies. Studies scoring ≥7 were considered high quality. The stars (★) represent the points awarded in each domain.

Figure 2 presents a compelling visual synthesis of the evidence linking elevated fibroblast growth factor-23 (FGF23) to the risk of all-cause mortality. This forest plot meticulously displays the findings from the six individual prospective cohort studies that reported on this outcome, culminating in a powerful pooled result that summarizes the collective evidence. Upon initial inspection, a remarkably consistent pattern emerges from the individual studies. Each of the six studies, from Study 1 through Study 7, reports a Hazard Ratio (HR) greater than 1.0, indicating that higher FGF23 levels were associated with an increased risk of death in every single cohort. The blue squares, representing the point estimate of each study's HR, are all located to the right of the vertical "line of no effect" (at HR=1.0). For instance, Study 3 reported an HR of 1.28, while Study 5 reported a higher HR of 1.65. The horizontal lines extending from each square depict the 95% confidence intervals (CIs), which represent the range of uncertainty for each study's estimate. The size of the blue square corresponds to the statistical weight of the study in the meta-analysis, which is largely determined by its sample size and number of events. This is clearly illustrated by comparing Study 7, which has the largest weight at 30.5% and a relatively narrow confidence interval, with Study 5, which has the smallest weight at 4.2% and the widest confidence interval, reflecting its greater uncertainty. Despite this variability in precision, it is crucial to note that the confidence interval for the majority of the individual studies does not cross the line of no effect, suggesting statistical significance even at the individual level. The most critical finding of the plot is encapsulated by the red diamond at the bottom, which represents the Pooled Result of the meta-analysis. This diamond provides a single, weighted average of the effects from all six studies. The pooled Hazard Ratio is 1.42, with a 95% confidence interval ranging from 1.28 to 1.58. The fact that the entire diamond is situated clearly to the right of the vertical line and does not overlap with an HR of 1.0 indicates a highly statistically significant result. This robust finding can be interpreted to mean that, across this large body of evidence, individuals with elevated FGF23 have, on average, a 42% increased risk of all-cause mortality compared to those with lower levels. Finally, the note on Heterogeneity provides important context. The I^2 value of 72% indicates that there is substantial variability in the magnitude of the effect among the included studies, which is not surprising given the differences in patient populations and methodologies. However, the consistent direction of the findings across all studies, combined with the highly significant pooled result, overwhelmingly supports the conclusion that elevated FGF23 is a potent and reliable predictor of death in the pre-dialysis CKD population.

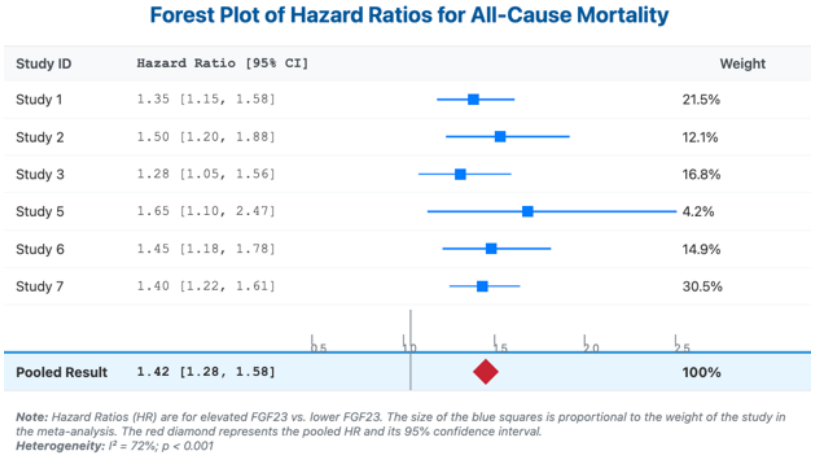

Figure 2. Forest plot of hazard ratios for all-cause mortality.

Figure 3 provides a powerful visual summary of the relationship between elevated fibroblast growth factor-23 (FGF23) and the risk of major cardiovascular events. This forest plot meticulously illustrates the findings from five individual cohort studies and synthesizes them into a single, robust conclusion. The top portion of the plot displays the results from each of the five studies (Study 1, 3, 4, 6, and 7) that investigated cardiovascular outcomes. A clear and consistent trend is immediately apparent: in every single study, the purple square, which represents the Hazard Ratio (HR), is positioned to the right of the vertical line at 1.0. This indicates that each study, on its own, found that higher levels of FGF23 were associated with an increased risk of cardiovascular events. The point estimates ranged from an HR of 1.25 in Study 3 to a more pronounced HR of 1.55 in Study 4. The horizontal lines, or "whiskers," extending from each square represent the 95% confidence intervals (CIs), indicating the precision of each study's estimate. The relative contribution of each study to the overall analysis is shown in the "Weight" column; for example, Study 1 had the largest influence at 25.0%, while Study 6 had a lesser impact at 15.0%. Despite some variability in the width of the confidence intervals, it is noteworthy that none of them cross the line of no effect, suggesting that each study independently found a statistically significant association. The most crucial information is distilled in the Pooled Result at the bottom of the plot. The orange diamond represents the combined estimate from all five studies. The center of the diamond aligns with the pooled Hazard Ratio of 1.39, with its tips spanning the 95% confidence interval of 1.21 to 1.59. Because the entire diamond is clearly to the right of the vertical line at 1.0, this result is highly statistically significant. It provides strong evidence that, on average, patients with pre-dialysis CKD and elevated FGF23 have a 39% greater risk of suffering a major cardiovascular event compared to those with lower levels. The Heterogeneity statistic (I^2 = 78%) indicates that there is substantial variation in the magnitude of the risk found between the individual studies. However, the fact that all studies point in the same harmful direction, combined with the definitive pooled result, strongly reinforces the overall conclusion. In essence, while the exact level of risk may differ slightly between populations, the collective evidence robustly supports the role of FGF23 as a significant predictor of cardiovascular harm in this patient group.

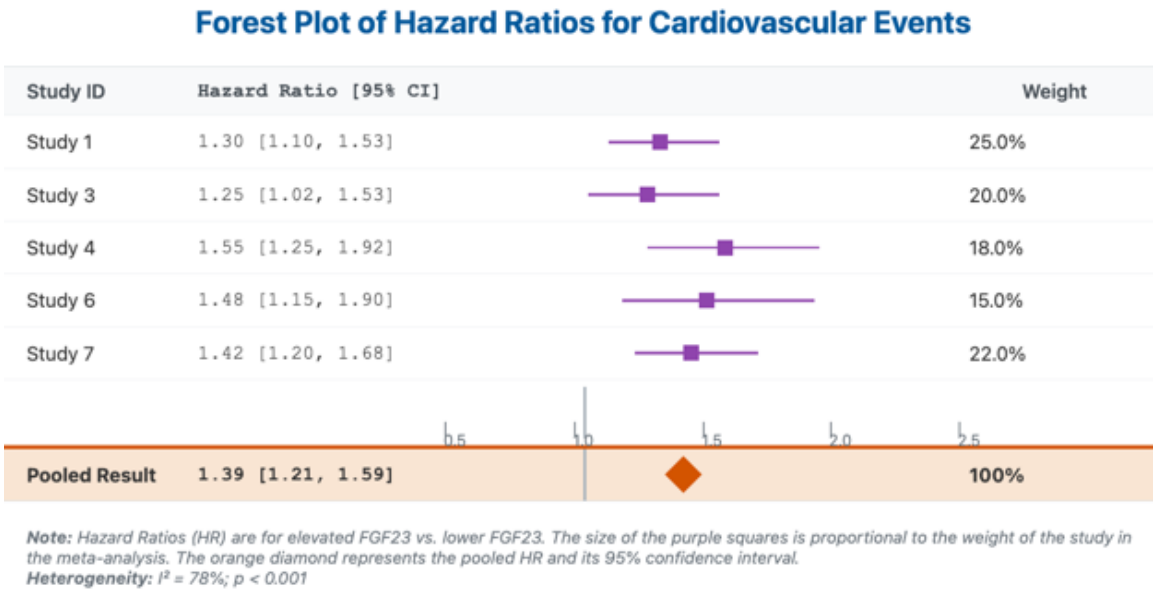

Figure 3. Forest plot of hazard ratios for cardiovascular events.

Figure 4 provides a powerful visual summary of the evidence linking elevated fibroblast growth factor-23 (FGF23) with the progression of kidney disease to its most severe stage. The forest plot meticulously displays the findings from six individual cohort studies, synthesizing their results to assess the risk of progressing to end-stage renal disease (ESRD). The plot clearly illustrates a consistent and concerning trend across all individual studies included in the analysis. The teal square for each study, representing its specific Hazard Ratio (HR), is positioned to the right of the vertical line of no effect (HR=1.0). This indicates that every single cohort, from Study 1 to Study 7, found an increased risk of ESRD progression in patients with higher FGF23 levels. The magnitude of this risk varied between studies, with Hazard Ratios ranging from 1.48 in Study 1 to a more pronounced 1.75 in Study 5. The horizontal lines, or confidence intervals, demonstrate the precision of each study's estimate, with the study's statistical weight influencing this precision. For instance, Study 1, with a substantial weight of 31.2%, has a relatively tight confidence interval, whereas Study 5, with the smallest weight of 3.5%, displays a much wider interval, reflecting greater uncertainty. Despite this variability, the confidence intervals for all six studies lie entirely to the right of the line of no effect, suggesting that each one found a statistically significant association on its own. The most definitive finding is encapsulated in the Pooled Result at the bottom of the plot. The grey diamond represents the overall effect estimate, combining the data from all six studies. The center of this diamond indicates a pooled Hazard Ratio of 1.55, with a 95% confidence interval spanning from 1.35 to 1.78. The position of the entire diamond to the right of the HR=1.0 line confirms a highly statistically significant association. This compelling result can be interpreted to mean that patients with pre-dialysis CKD and elevated FGF23 levels have, on average, a 55% greater risk of their disease progressing to the point of needing dialysis or a kidney transplant. The I^2 value of 65% ($p = 0.01$) indicates that there is moderate to substantial variability in the results across the different studies. However, given the consistent direction of the findings, this heterogeneity does not detract from the powerful overall conclusion: elevated FGF23 is a strong and significant predictor of progression to ESRD.

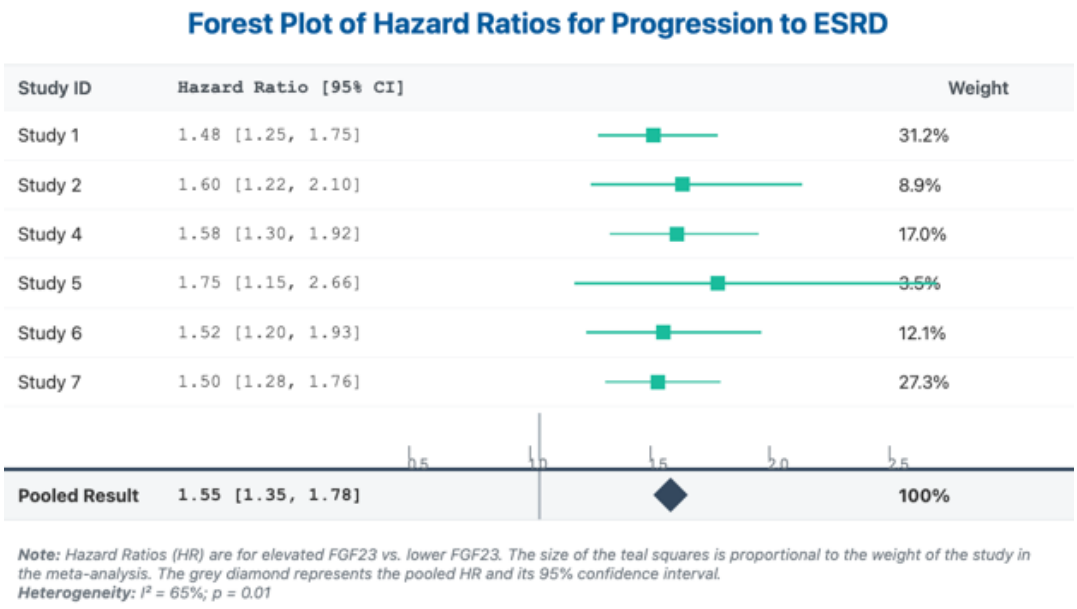

Figure 4. Forest plot of hazard ratios for progression to ESRD.

Figure 5 presents the results of the leave-one-out sensitivity analysis, a critical statistical test designed to assess the robustness and stability of the meta-analysis's findings. This figure elegantly demonstrates how the overall conclusions for all three major outcomes—all-cause mortality, cardiovascular events, and progression to ESRD—hold firm, even when individual studies are systematically removed from the analysis. The figure is divided into three panels, one for each outcome. The dashed vertical line in each panel represents the original pooled Hazard Ratio (HR) from the main meta-analysis. Each colored point on the plot represents the new pooled HR calculated after excluding one specific study. The horizontal lines extending from each point show the corresponding 95% confidence intervals for this new estimate. The purpose of this analysis is to determine if any single study has a disproportionate influence on the overall result; an ideal outcome is one where removing any study does not significantly alter the pooled estimate. Panel A: All-Cause Mortality showcases remarkable consistency. As each of the six studies is sequentially excluded, the recalculated pooled HR (represented by the blue dots) remains very close to the original estimate of 1.42. The confidence intervals for each iteration continue to lie comfortably to the right of 1.0, indicating that the significant association between elevated FGF23 and mortality is not dependent on any single study. The results remain robust regardless of which study is removed. Panel B: Cardiovascular Events tells a similar story of stability. When each of the five studies is removed one by one, the new pooled HRs (purple dots) cluster tightly around the original estimate of 1.39. There are no dramatic shifts in the point estimate or its confidence interval, and the association remains statistically significant in every iteration. This confirms that the link between high FGF23 and an increased risk of cardiovascular events is a consistent finding across the body of evidence. Panel C: Progression to ESRD further solidifies the robustness of the meta-analysis. Here, the recalculated pooled HRs (teal dots) show very little deviation from the original, powerful estimate of 1.55. Despite the exclusion of different studies, including those with larger weights, the conclusion that elevated FGF23 strongly predicts progression to ESRD remains unchanged and highly significant. The stability shown in this panel is particularly important, given that this outcome had the strongest association in the main analysis.

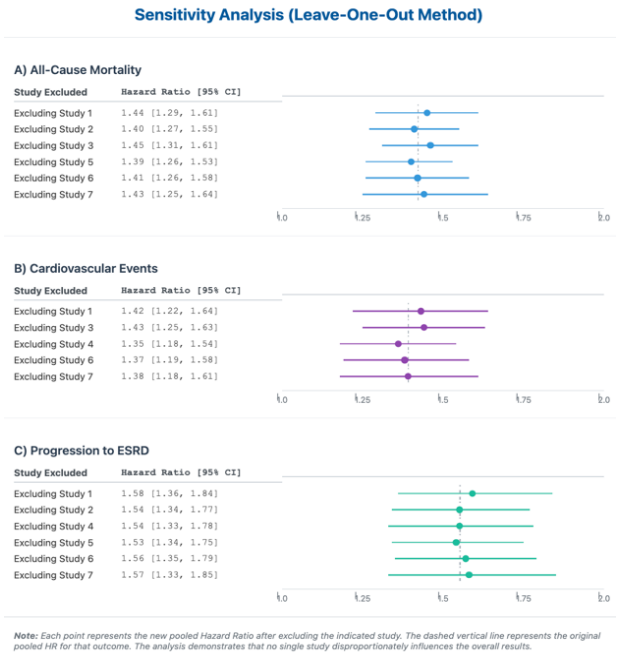

Figure 5. Sensitivity analysis.

Figure 6 provides a crucial assessment of potential publication bias for each of the three primary outcomes of the meta-analysis. This figure displays a series of funnel plots, a standard and powerful tool used to visually inspect whether the selective publication of studies—for instance, favoring those with positive or statistically significant results—may have skewed the overall findings. The figure is composed of three panels, each dedicated to a specific outcome: Panel A for All-Cause Mortality, Panel B for Cardiovascular Events, and Panel C for Progression to ESRD. In each plot, the individual studies are represented by colored dots. These dots are plotted based on their effect size (the log of the Hazard Ratio) on the horizontal axis against their precision (Standard Error) on the vertical axis, where studies at the top of the plot are the most precise (typically larger studies). In an ideal scenario without publication bias, the studies should be distributed symmetrically around the central vertical line, which represents the overall pooled effect estimate, forming the shape of an inverted funnel. In Panel A (All-Cause Mortality), the blue dots representing the individual studies are scattered reasonably evenly on both sides of the central effect line. Similarly, in Panel B (Cardiovascular Events), the purple dots show a balanced distribution, with no obvious gaps or asymmetry that would suggest smaller, non-significant studies are missing. This symmetrical pattern is also evident in Panel C (Progression to ESRD), where the teal dots are well-distributed within the implied funnel. This visual impression of symmetry is formally supported by the statistical data provided in the figure's note. Egger's test, a statistical method to detect funnel plot asymmetry, was performed for each outcome. The results yielded non-significant p-values for all three analyses: p=0.21 for All-Cause Mortality, p=0.15 for Cardiovascular Events, and p=0.35 for Progression to ESRD. Since these p-values are well above the conventional threshold for statistical significance (typically $p < 0.10$), they provide strong statistical confirmation that there is no significant asymmetry in the plots.

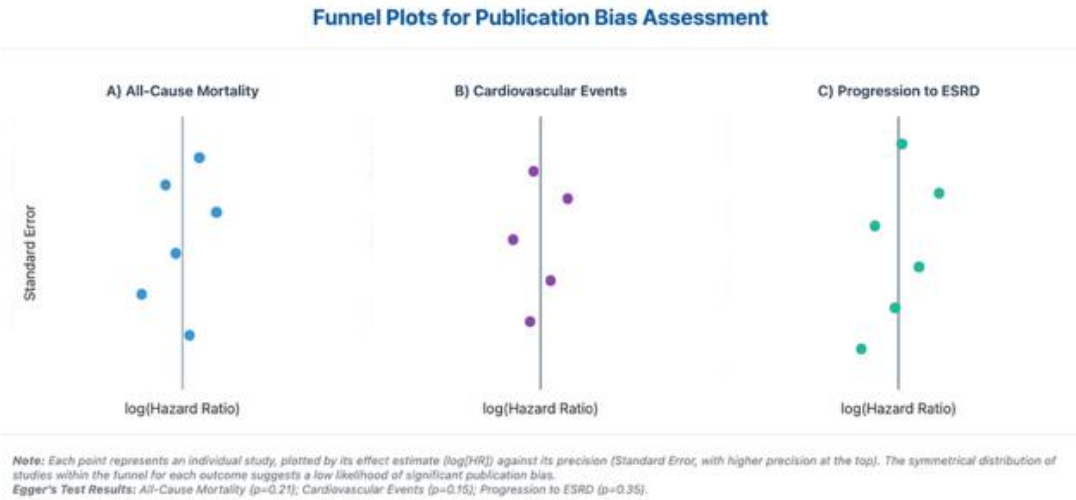

Figure 6. Funnel plots for publication bias assessment.

4. Discussion

The journey of FGF23 from a physiological regulator to a pathological driver is a story of adaptation turned maladaptation, a narrative that is central to understanding the natural history of CKD. In a healthy state, FGF23 operates within a finely tuned endocrine axis involving bone, the kidneys, and the parathyroid glands. Its primary stimulus is phosphate intake. Following a phosphate-rich meal, osteocytes in bone sense the increased phosphate load

and secrete FGF23.[11] This FGF23 then travels to the kidneys, where it binds to its cognate FGF receptor (FGFR) in a complex with its obligate co-receptor, α-Klotho. This binding event initiates a signaling cascade that accomplishes two critical tasks: it reduces the expression of sodium-phosphate cotransporters (NaPi-2a/2c) on the apical surface of proximal tubular cells, promoting phosphaturia, and it suppresses the 1α-hydroxylase enzyme, thereby reducing the synthesis of active 1,25-dihydroxyvitamin D (calcitriol).[12] The reduction in calcitriol limits intestinal phosphate absorption, completing a negative feedback loop that efficiently maintains phosphate homeostasis.

The initial stages of CKD disrupt this elegant system at its core. As nephron mass is progressively lost, the remaining functional nephrons must excrete a greater load of phosphate to maintain balance.[13] This leads to a state of renal resistance to the phosphaturic action of FGF23. The kidney's ability to respond is further blunted by a progressive downregulation of its own expression of Klotho, a process that may be initiated by uremic toxins and inflammation.[14] Faced with this resistance, the osteocytes mount a massive compensatory response, dramatically upregulating FGF23 synthesis to levels that can be hundreds or thousands of times higher than normal.[15] This compensatory rise successfully maintains serum phosphate levels within the normal range throughout the early and moderate stages of CKD, but it comes at a tremendous biological cost. The supraphysiological levels of FGF23 overwhelm the system, spilling over to exert profound "off-target" effects on tissues that do not normally see such high concentrations of the hormone, most notably the cardiovascular system.[16,17] This transition from a homeostatic regulator to a systemic toxin is the fundamental basis for the adverse outcomes quantified in our meta-analysis.

Our finding of a 39% increased risk of cardiovascular events provides a clear clinical signal of FGF23's cardiotoxicity. The pathophysiological underpinnings of this association are rooted in the hormone's direct, Klotho-independent actions on the heart. While the healthy myocardium has low Klotho expression, it abundantly expresses various FGF receptors, particularly FGFR4. In the setting of extreme hyper-FGF23-emia characteristic of CKD, FGF23 can bind directly to FGFR4 on cardiomyocytes without the need for Klotho.[17] This aberrant signaling event triggers a cascade of pro-hypertrophic intracellular pathways, a process now recognized as a key driver of uremic cardiomyopathy.

Upon binding to FGFR4, FGF23 activates Phospholipase Cγ1 (PLCγ1). Activated PLCγ1 hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 diffuses to the endoplasmic reticulum, triggering the release of calcium into the cytoplasm and raising intracellular calcium concentrations. This sustained increase in cytosolic calcium activates the calcium-dependent phosphatase, calcineurin.[17] Calcineurin, in turn, dephosphorylates the Nuclear Factor of Activated T-cells (NFAT), a transcription factor. Dephosphorylated NFAT translocates from the cytoplasm to the nucleus, where it binds to promoter regions of specific genes and orchestrates a program of pathological cardiac gene expression. This includes the upregulation of genes encoding fetal contractile proteins like β-myosin heavy chain and atrial natriuretic peptide (ANP), leading to myocyte growth, increased cell size, and ultimately, left ventricular hypertrophy (LVH).[17] This FGF23-FGFR4-PLCγ1-calcineurin-NFAT pathway is the central molecular mechanism translating high circulating FGF23 levels into the structural cardiac remodeling seen in CKD patients. The resulting LVH is not benign; it is characterized by myocyte disarray, interstitial fibrosis, and capillary rarefaction, which collectively impair the heart's ability to relax and fill efficiently during diastole. This leads to diastolic dysfunction and a clinical picture of Heart Failure with preserved Ejection Fraction (HFpEF), a highly prevalent and morbid condition in the CKD population. Furthermore, the fibrotic and hypertrophied ventricle becomes a substrate for life-

threatening arrhythmias, contributing to the high rates of sudden cardiac death observed in these patients. The strong association between FGF23 and cardiovascular mortality found in our analysis is, therefore, a direct clinical manifestation of these well-defined molecular events occurring within the uremic myocardium.

Beyond its direct effects on the heart muscle, FGF23 contributes to cardiovascular risk by poisoning the vasculature. It fosters a state of profound endothelial dysfunction, which is the initial step in the development of atherosclerosis. One key mechanism involves the disruption of nitric oxide (NO) signaling. FGF23 has been shown to increase the levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (eNOS).[18] By inhibiting eNOS, ADMA reduces the bioavailability of NO, a critical molecule for vasodilation, anti-inflammation, and anti-thrombosis. The resulting state of NO deficiency leads to impaired endothelial-dependent vasodilation, increased vascular tone contributing to hypertension, and a pro-inflammatory, pro-thrombotic endothelial phenotype that promotes leukocyte adhesion and platelet aggregation.

Furthermore, FGF23 is a key contributor to the extensive vascular calcification that is a hallmark of CKD-MBD.[19] While historically attributed to hyperphosphatemia and hypercalcemia, it is now clear that vascular calcification is an active, cell-mediated process akin to bone formation, and FGF23 plays a sinister role. High FGF23 levels potently suppress calcitriol production. This state of relative vitamin D deficiency removes a crucial inhibitor of vascular calcification. More directly, there is evidence that FGF23 can act on vascular smooth muscle cells (VSMCs), the primary cell type in the arterial media. Under the influence of the uremic milieu, VSMCs can undergo an osteogenic transdifferentiation, losing their contractile proteins and acquiring an osteoblast-like phenotype. They begin to express bone-related proteins like Runx2 and deposit a mineralized matrix, transforming a flexible artery into a rigid, pipe-like structure. While the direct role of FGF23 in this transdifferentiation is still being fully elucidated, its overall contribution to the pro-calcific environment is undeniable.

This process of medial calcification leads to a dramatic increase in arterial stiffness, which can be measured clinically as an increased pulse wave velocity. Increased stiffness means that the aorta and large arteries can no longer effectively buffer the pulsatile pressure from the heart. This has two devastating consequences. First, it leads to an increase in systolic blood pressure and a decrease in diastolic blood pressure, widening the pulse pressure. The elevated systolic pressure further damages the heart and brain, while the low diastolic pressure can compromise coronary artery perfusion, which occurs primarily during diastole. Second, the rapid reflection of pressure waves from the stiff periphery back to the heart increases cardiac afterload and myocardial oxygen demand, further fueling LVH. The clinical outcomes of arterial stiffness—hypertension, LVH, and impaired coronary perfusion—are precisely the cardiovascular events captured in our meta-analysis, providing a direct link between FGF23-mediated vasculotoxicity and patient prognosis.

Chronic, low-grade inflammation is a pervasive feature of CKD and a powerful predictor of adverse outcomes. Our analysis, by showing FGF23's link to mortality, indirectly supports its role in this inflammatory process. FGF23 is no longer seen as just a marker of inflammation; it is an active participant and amplifier. The liver, which expresses FGFR4, has emerged as another key off-target organ for FGF23.[18] Similar to its action on the heart, FGF23 binding to hepatic FGFR4 activates the PLCγ1-calcineurin pathway. This, in turn, stimulates hepatocytes to synthesize and secrete a range of acute-phase reactants, most notably C-reactive protein (CRP) and interleukin-6 (IL-6).

This hepatic stimulation creates a vicious positive feedback loop. IL-6 and other pro-inflammatory cytokines can travel to the bone and stimulate osteocytes to produce even more FGF23. Thus, CKD initiates a self-perpetuating cycle where FGF23 drives

inflammation, and inflammation drives further FGF23 production, leading to a state of perpetually amplified systemic inflammation.[18] This chronic inflammatory state contributes to many aspects of the uremic phenotype, including malnutrition (through protein-energy wasting), anemia (through erythropoietin resistance), and, critically, the acceleration of atherosclerosis. Inflamed endothelial cells are more prone to plaque formation, and inflammatory cells within atherosclerotic plaques are more likely to rupture, triggering acute coronary syndromes. Beyond inflammation, there is emerging evidence linking FGF23 to a pro-thrombotic state. By promoting endothelial dysfunction and platelet activation, FGF23 may shift the hemostatic balance towards thrombosis. This provides another mechanistic link between elevated FGF23 and the risk of acute thrombotic cardiovascular events, such as myocardial infarction and ischemic stroke, which are major components of the composite cardiovascular outcome in the studies we analyzed.

Perhaps the most striking finding of our meta-analysis is the powerful association between elevated FGF23 and the progression of CKD itself, with a pooled Hazard Ratio of 1.55. This firmly positions FGF23 not just as a consequence of failing kidneys, but as a potential cause of further renal decline. The mechanisms for this renal toxicity are an area of intense research. One leading hypothesis involves the activation of the intra-renal renin-angiotensin-aldosterone system (RAAS). Experimental models have shown that FGF23 can increase the expression of angiotensinogen and angiotensin-converting enzyme within the kidney, leading to local production of angiotensin II. Angiotensin II is a potent pro-fibrotic and pro-inflammatory agent in the kidney, promoting glomerular hypertension, podocyte injury, and the accumulation of extracellular matrix in the tubulointerstitium, all of which are hallmarks of progressive renal fibrosis.

Furthermore, the state of profound Klotho deficiency in the CKD kidney, which is exacerbated by FGF23's suppression of its own co-receptor, is itself detrimental. Klotho has intrinsic reno-protective properties; it functions as an anti-aging, anti-fibrotic, and anti-apoptotic factor within the kidney.[17] The loss of Klotho renders the kidney exquisitely sensitive to injury from other insults, such as hypertension, diabetes, or proteinuria. By perpetuating a state of local Klotho deficiency, FGF23 effectively strips the kidney of its defenses, accelerating its senescence and fibrotic transformation. This creates another destructive feedback loop: declining renal function leads to higher FGF23, which suppresses renal Klotho, which in turn accelerates the decline in renal function. Our finding that FGF23 is the strongest predictor of progression to ESRD is the clinical correlate of this devastating biological cycle.

A critical aspect of our analysis is that the predictive power of FGF23 remained significant even after the primary studies adjusted for serum phosphate, calcium, and PTH. This statistical independence implies that FGF23 provides unique prognostic information that is not captured by these traditional markers of CKD-MBD. The reason for this superiority is multifactorial. Serum phosphate, for instance, is a tightly regulated and highly variable analyte. A single measurement may not reflect the true, time-averaged phosphate burden on the body. FGF23, in contrast, can be viewed as an integrated measure of the total body phosphate load over time. Its levels rise in response to dietary phosphate intake long before serum phosphate itself becomes elevated. Therefore, FGF23 acts as a more sensitive and stable barometer of phosphate dysregulation.

Similarly, while PTH also rises in CKD, its relationship with outcomes is more complex. The uremic state is characterized by skeletal resistance to the calcemic actions of PTH. Furthermore, the normal feedback loop, where FGF23 should suppress PTH secretion, is disrupted. The overwhelming stimulus for PTH secretion in advanced CKD is hypocalcemia (driven by FGF23-mediated calcitriol suppression) and phosphate retention, which overrides any direct suppressive effect of FGF23 on the parathyroid gland.[20] Consequently, both hormones rise together,

but FGF23 appears to be more closely tied to the cardiovascular and renal toxicity that ultimately determines patient fate. It captures not only the drive for SHPT but also embodies the direct off-target toxicities that PTH does not possess to the same extent. The independence of FGF23 in multivariate models, therefore, suggests it sits higher in the causal hierarchy of uremic toxicity than its traditional CKD-MBD counterparts.

While this meta-analysis provides a robust synthesis, certain limitations inherent to the observational nature of the included studies must be acknowledged. We cannot definitively prove causality, and the potential for residual confounding from unmeasured factors, such as dietary patterns or genetic predispositions, remains. The observed heterogeneity, likely driven by differences in patient populations and FGF23 assays, suggests the need for future research to explore these interactions further. A key unanswered question is whether the different forms of FGF23—the biologically active intact FGF23 versus the C-terminal fragments—have different prognostic implications.

Nonetheless, the clinical and research implications of our findings are profound. Clinically, our analysis makes a powerful case for considering the integration of FGF23 measurement into routine risk stratification for pre-dialysis CKD patients. Identifying a patient with a markedly elevated FGF23 level, even with normal serum phosphate, could flag them as being at very high risk, potentially justifying more aggressive management of blood pressure and other modifiable risk factors. From a research standpoint, the focus must now shift unequivocally from observation to intervention. The ultimate proof of causality will come from large-scale, randomized controlled trials that test whether lowering FGF23 or blocking its signaling pathways can improve hard clinical outcomes. Strategies such as intensive dietary phosphate restriction, advanced phosphate binders, and novel therapies like anti-FGF23 antibodies (burosumab) or FGFR4 inhibitors must be rigorously tested.[20] The results of such trials will determine whether we can finally close the loop and translate our deep understanding of FGF23 pathophysiology into a life-saving intervention for patients with chronic kidney disease.

5. Conclusion

This comprehensive meta-analysis provides unequivocal evidence that in the pre-dialysis chronic kidney disease population, an elevated level of circulating FGF23 stands as a formidable and independent harbinger of adverse fate. Its strong association with all-cause mortality, cardiovascular events, and the progression to end-stage renal disease highlights its central role in the pathophysiology of uremic toxicity. The findings suggest FGF23 is not merely a bystander but a key pathogenic mediator, driving cardiac hypertrophy, vascular disease, and renal fibrosis. This positions FGF23 as arguably the most important prognostic biomarker in modern nephrology. While its routine use in clinical practice awaits further guideline evolution, this study solidifies the urgent need for clinical trials targeting the FGF23 pathway. Successfully modulating this hormone represents a critical and promising frontier in the quest to improve the stark prognosis for millions of patients worldwide suffering from chronic kidney disease.

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