This result suggests that a lower threshold of tubular YAP activation is required to cause fibrosis in the cortex. It is also surprising that there are observed sex difference, with females having an attenuated fibrotic response after MST1/2 deletion. Their results aligns with the recent findings from Harris and colleagues, where they observed that female mice with a gain of function in EGFR displayed less renal injury and fibrosis compared with their male counterparts. One could hypothesize on the basis of previous studies from the group of Harris and colleagues linking EGFR and the Hippo pathway that EGFR-mediated YAP activation in females is less detrimental. Perhaps further studies could help establish this connection.

In summary, the study by Xu et al. provides evidence for the Hippo pathway as a mediator of renal fibrosis. It will be important to reconcile with future experiments if there is a level of balance in YAP activation, whereby it plays a crucial role in renal regeneration, but overactivation might lead to renal fibrosis, possible due to maladaptive repair.

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REFERENCES


Biomarkers of CKD in Children

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The global and United States burden of CKD among children is increasing. The global prevalence of CKD in children <20 years old increased from 14,301,902.99 (uncertainty interval [UI], 12,311,407.92–16,839,916.37) in 1990 to 17,330,656.23 (UI, 14,545,431.31–20,740,504.91) in 2017. This increase outpaced that expected by population growth because the CKD prevalence rate also increased from 623.33/100,000 persons (UI, 536.57–733.94) in 1990 to 667.96/100,000 persons (UI, 560.61–799.38) in 2017. Trends are similar in the United States because prevalence has also increased from 427,925.73 (UI, 360,242.73–513,222.29) to 508,105.50 (UI, 420,435.90–613,844.54), and prevalence rate has increased from 580.62/100,000 persons (UI, 488.78–696.35) to 612.70/100,000 persons (UI, 506.99–740.21). The drivers of this increase in burden of CKD among children are not entirely clear. CKD in children is associated with serious consequences, including delayed growth and development, increased risk of cardiovascular disease, and death. Early recognition of CKD and tools to predict its progression and outcomes are important not only for risk stratification—and potentially, as a strategy to enrich enrollment in clinical trials—but also, they may contribute to a greater understanding of the underlying...
biologic mechanisms and may help identify potential therapeutic targets to halt CKD progression and reduce the burden of health loss associated with this disease.

In this issue of *JASN*, Greenberg et al.\(^2\) conducted a prospective analysis of 651 children with CKD (from the Chronic Kidney Disease in Children multicenter cohort study) to examine the relationship between kidney injury molecule 1 (KIM-1), monocyte chemottractant protein-1 (MCP-1), TNF receptor-1 (TNFR-1), TNFR-2, soluble urokinase-type plasminogen activator receptor (suPAR), and YKL-40 and the risk of CKD progression (defined as a composite end point of eGFR decline &gt;50% or incident ESKD). The median age was 11 years old (interquartile range, 8–15), and median baseline eGFR was 53 ml/min per 1.73 m\(^2\) (interquartile range, 40–67). After a median follow-up of 5.7 years, 223 children (34%) progressed to the composite end point (21% with incident ESKD and 13% with &gt;50% decline in eGFR), reflecting the unfortunate sizable toll of CKD progression among children with CKD. Children with plasma KIM-1, TNFR-1, or TNFR-2 concentrations in the highest quartile were at a significantly higher risk of CKD progression compared with those with biomarker concentrations in the lowest quartile. In analyses stratified by type of kidney disease, KIM-1 was associated with the composite outcome in children with nonglomerular causes of CKD, whereas TNFR-1 and TNFR-2 were associated with the composite outcome in children with glomerular causes of CKD. However, interaction analyses suggested that the association between each of these biomarkers and the composite outcome was not modified by type of kidney disease—suggesting that these biomarkers may not reliably serve to differentiate type of CKD. Interestingly, plasma MCP-1, suPAR, and YKL-40 were not independently associated with CKD progression in this study. Analyses of area under the curve, integrated discrimination improvement, and net reclassification improvement suggested that addition of these biomarkers (to routinely measured clinical variables, including eGFR) did not result in substantial improvement in predictive performance.

The study is notable in that it is a large longitudinal study of a well characterized cohort of children with a diverse range of CKD including over 30 primary diagnoses encompassing both glomerular and nonglomerular causes. The authors set out to evaluate potential utility of a battery of biomarkers representing several mechanistic pathways, including tubular injury (KIM-1), inflammation (MCP-1, TNFR-1, TNFR-2, and suPAR), and repair (YKL-40). The results show for the first time that elevated levels of KIM-1, TNFR-1, or TNFR-2 are independently associated with risk of CKD progression in children. The addition of these biomarkers to clinical models that also included eGFR did not improve predictive performance substantially—a reflection of both the strength of eGFR as a functional biomarker and its many limitations add to the challenges of identifying and validating novel biomarkers of CKD that can significantly improve predictive performance beyond what can be achieved with inclusion of eGFR.\(^3\)

In this specific study and as the authors indicate, the relatively small number of cohort participants may have underpowered the predictive performance of the examined biomarkers.

The findings in this pediatric cohort are generally consistent with studies in adults, including a report by Coca et al.\(^4\) in which analyses of the Action to Control Cardiovascular Risk in Diabetes trial and the Veterans Administration Nephropathy in Diabetes study of people with type 2 diabetes mellitus showed that plasma TNFR-1, TNFR-2, and KIM-1 were each independently associated with risk of eGFR decline. In the study by Coca et al.\(^4\)—which is comparatively much larger and performed in adults—addition of the three biomarkers to a prediction model that also included clinical variables improved risk prediction for eGFR decline. Also notable in this study is the finding that suPAR, plasma MCP-1, and YKL-40 were not independently associated with CKD progression. In particular, the findings on suPAR are not congruent with prior reported results, and they likely emanate from differences in assays and underlying differences in the characteristics of the study populations.

Overall, this study illustrates both the promise and the challenge of biomarkers in children with CKD. Identification and validation of CKD biomarkers have been a challenge in adults, and it is even more so in children, where cohorts are generally smaller and etiologies are vastly more diverse. The meritorious work by Greenberg et al.\(^2\) illuminates our understanding of relationship of several biomarkers and CKD in children and establishes a solid foundation for future investigations. Continued progress in biomarker discovery and validation holds great promise to improve our ability to define the disease earlier and with greater precision, risk stratify patients, and predict outcomes, and it may also aid in the identification of potential therapeutic targets.

**DISCLOSURES**

None.

**REFERENCES**


The Value of Intravenous Iron: Beyond the Cave of Speculation

Daniel W. Coyne and Steven Fishbane


See related article, “Plasma Biomarkers of Tubular Injury and Inflammation Are Associated with CKD Progression in Children,” on pages 1067–1077.

In Plato’s cave allegory, we are chained prisoners forced to look at shadows cast on a wall by the unrecognized reality behind us. We mistake the shadows for reality. When finally freed, we see the truth and comprehend our interpretative errors, but those still chained do not believe us and think we are mad. Experts saw possible harm from intravenous (IV) iron in oxidative stress; higher ferritin levels; imaging studies revealing high liver iron content; and associations of iron use to infections, cardiovascular (CV) events, and death. Experts recommended lower ferritin limits to protect patients from IV iron’s shadowy harm. In daylight, randomized, controlled trials now show that high-dose IV iron is life saving and safe. Trials validate ferritin <200–300 ng/ml as a surrogate of harmful iron deficiency.

The Proactive IV Iron Therapy in Haemodialysis Patients (PIVOTAL) trial randomized 2141 patients on hemodialysis to low-dose IV iron therapy (100–200 mg) if transferrin saturation (TSAT) is <20% or ferritin <200 ng/ml or high-dose iron (400 mg monthly) if TSAT is <40% and ferritin <700 ng/ml. This study design provided an ideal methodology for determining the relationship between IV iron and higher ferritin values with infection risk.

In this issue of JASN, Macdougall et al. provide a detailed report on infection rates in the PIVOTAL trial. Infections are the second leading cause of death in patients on hemodialysis and a major cause of hospitalizations. Iron is a growth factor for some bacteria, and iron overload can impair white cell function. Several observational studies have associated higher doses of IV iron and higher ferritin values to infections, CV events, and death in patients on dialysis.

The initial PIVOTAL trial publication demonstrated that high-dose iron significantly lowered rates of CV events, death, and transfusions compared with a low-dose iron arm. High-dose iron may mediate these benefits by treating iron deficiency and reducing erythropoiesis-stimulating agent (ESA) doses. Regardless of mechanism, these results provide an evidence-based message that iron deficiency must be avoided and that high doses of IV iron are safe, refuting previous concerns.

Macdougall et al. examine infection rates in all patients and the subgroup with catheters, and they examine whether infections were related to recent iron dose, ferritin, or TSAT values. Infections were common, with 20% of patients having an infection within 6 month and 40% having an infection by 1.5 years. Macdougall et al. found that “[i]nfection rates were identical in the high-dose and low-dose IV iron groups.” Compared with those with fistulas, patients with catheters were at greater risk for infections and fatal infections, but treatment assignment did not alter the risk; additionally, infection risk was not related to the recent dose of iron, ferritin, or TSAT.

One concern about this PIVOTAL trial report—and other trials—is that some infections may not be captured. There is no reason to think that capture rates would be lower in the high-dose iron arm. Given the strong relationship of infection to subsequent CV events, an imbalance in infections should have increased CV events and/or deaths, and both were lower in the high-dose iron arm. Additionally, placebo-controlled trials of IV iron in patients with heart failure and ferritin <300 ng/ml prior to treatment showed that iron administration reduced CV events, improved functional status, and did not increase infections. These patients, of whom 40% had CKD, received much less IV iron, and thus, they were not iron overloaded. The simplest explanation of these results is that IV iron use and iron status do not alter infection risks.

How should we use the PIVOTAL trial results in dialysis practice? Macdougall et al. noted that a recent infection increased the risk of CV events (myocardial infarction, heart failure admission, or stroke) in the next 30 days, consistent with observational data. It is unclear what drives this association, and the authors do not tell us if increased risk is evenly distributed across event types. The stress of infections might destabilize cardiac status, and therefore, clinicians and facilities should address modifiable risks, including volume control and BP management, during and after infections.

The PIVOTAL trial validates TSAT <20% and ferritin <200 ng/ml as surrogates for iron deficiency, warranting treatment. The trial results cannot substantiate that IV iron should be stopped whenever TSAT is >40% or ferritin is...