

Nephrology Times

Practical News, Trends, and Analysis

January/February 2024

VOLUME 16, NUMBER 1

NEWS

Renal Effects of GLP-1RAs in Patients With Diabetic Kidney Disease

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Urinary Epidermal Growth Factors and Decline in Kidney Function in ADPKD

As patients with autosomal dominant polycystic kidney disease (ADPKD) age, renal cysts develop and grow, gradually replacing healthy kidney tissue, resulting in impaired kidney function. Gaining a clear understanding of the molecular pathways underlying formation of cysts may result in the development of novel therapeutic interventions and biomarkers to predict disease progression in patients with ADPKD.

A pathway of particular interest is the one mediated by the epidermal growth factor receptor (EGFR) family. **Laura R. Harskamp, MD**, and colleagues conducted a study to test the hypothesis that there is an association between urinary EGFR ligands, as a reflection of EGFR activity, and decline in kidney function in patients with ADPKD, and, as the disease progresses, an indication of insufficient repair. Results of the study were reported in *Nephrology Dialysis Transplantation* [doi.org/10.1093/ndt/gfad050].

Activation of the EGFR pathway was measured via analysis of urinary excretion of two ligands of the EGFR family (EGF and heparin-binding EGF-like growth factor [HB-EGF]) and by expression of three receptors of the EGFR family (the EGFR [ErbB1/HER1], ErbB2 [HER2/neu], and ErbB4 [HER4]).

The study population included

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Estimating GFR in Patients With Heart Failure With Reduced Ejection Fraction

Among patients with heart failure (HF) and reduced ejection fraction (HFrEF), assessment of kidney function is commonly performed using serum creatinine-based estimates. However, the high prevalence of sarcopenia and malnutrition and reduced physical activity in that patient population may limit the accuracy of serum creatinine as a marker for glomerular filtration.

Cystatin C, an endogenous protease inhibitor, is less influenced by muscle mass, diet, and demographic characteristics, including race, allowing for a more accurate estimation of kidney function. When factors unrelated to kidney function are present, there

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GFR Estimation Based on Cystatin C Versus Serum Creatinine in Patients With Cancer

Appropriate dosing of renally cleared medications relies on accurate assessment of estimated glomerular filtration rate (eGFR). The most commonly used method of evaluating GFR in both clinical practice and research is measurement of serum creatinine.

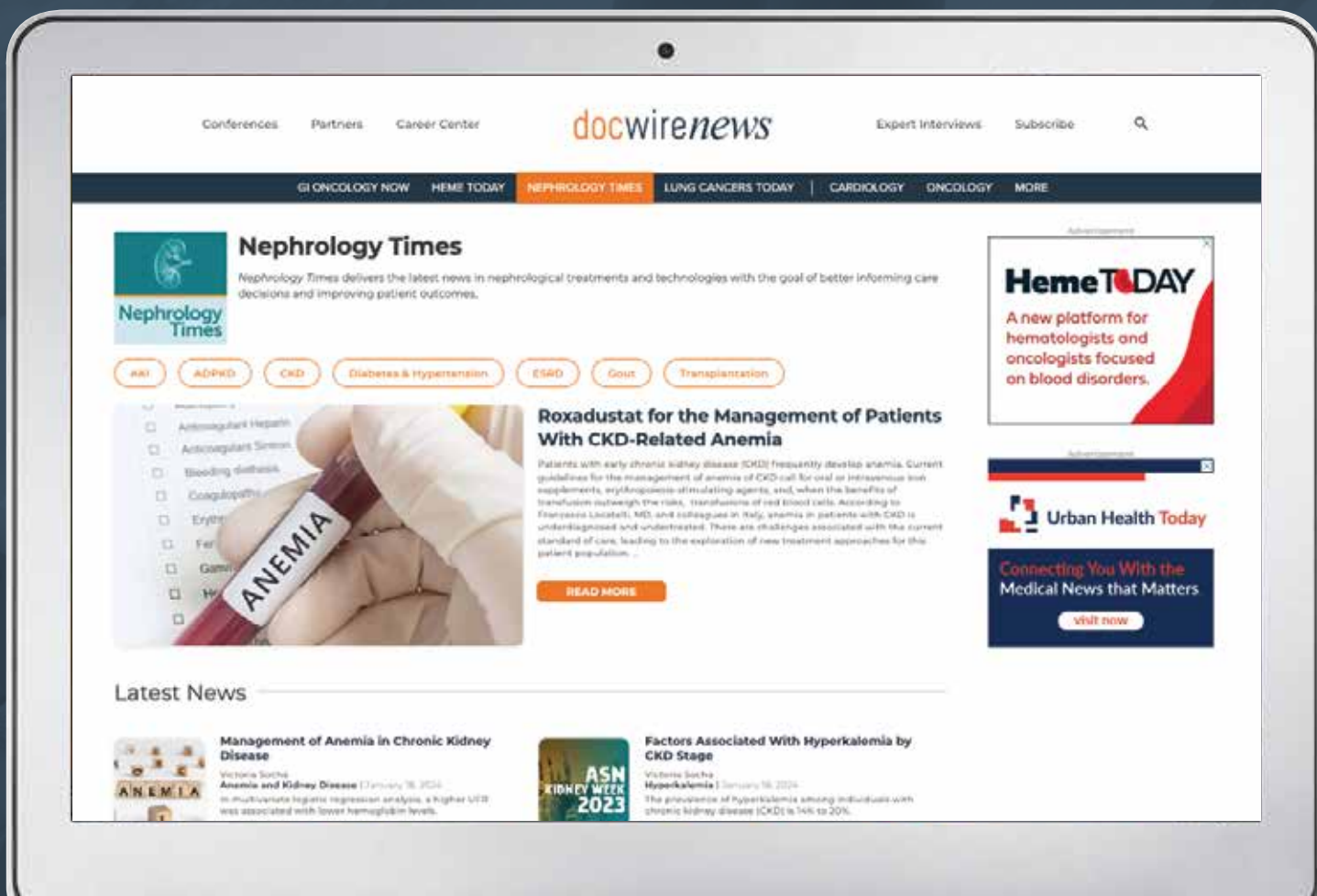
According to **Paul E. Hanna, MD**, and colleagues, despite increasing precision of eGFR equations, serum creatinine-based eGFR (eGFR_{cr}) remains inaccurate and can overestimate eGFR, particularly in patients with sarcopenia. The overestimation may result in inaccurate dosing of medications that require adjustment based on eGFR, including antibiotics, muscle relaxants, antiepileptic drugs, blood thinners, and antiarrhythmic medications.

To test the hypothesis that patients with cancer would have substantially lower eGFR based on cystatin C level (eGFR_{cys}) than based on eGFR_{cr}, the researchers recently conducted a cohort study. Results were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2023.21715].

The cohort included adult patients with cancer at two major academic cancer centers in Boston, Massachusetts. Eligible patients had creatinine and cystatin C measured on the same day between May 2010 and January 2022. The baseline

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Is Sparsentan the New Kid on the Block for Treating Glomerular Disease?



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About a year ago, there was huge excitement around the news that the US Food and Drug Administration (FDA) had granted accelerated approval to Travers for sparsentan, a dual endothelin and angiotensin receptor antagonist, in treating patients with IgA nephropathy (IgAN).¹ The interim analysis of the PROTECT study demonstrated that sparsentan reduced proteinuria by an additional 40% compared with the renin-angiotensin inhibitor irbesartan in patients with IgAN at high risk of progression (defined as a urine protein-to-creatinine ratio ≥ 1.5 g/g).² On this basis, the FDA granted accelerated approval for sparsentan in February 2023.³

On a parallel front that same year, Travers's DUPLEX study was reaching its conclusion. In the phase 3, randomized, controlled DUPLEX trial, sparsentan was evaluated in children and adults with focal segmental glomerulosclerosis (FSGS). Like the IgAN study, sparsentan was compared after maximizing renin-angiotensin-aldosterone system (RAAS) blockade with irbesartan for kidney end points, including proteinuria and kidney protection. Preliminary data from DUPLEX had demonstrated that sparsentan had a favorable benefit in proteinuria reduction relative to irbesartan.⁴

At the American Society of Nephrology Kidney Week 2023 in Philadelphia, Pennsylvania, the stage was set to hear the long-term kidney outcome data for sparsentan for both IgAN and FSGS. The excitement that two important glomerular diseases could benefit from a new nonimmunosuppressive agent was palpable. Sadly, so was the disappointment when the results were presented.

As the Dalai Lama has been quoted as saying, "Disappointment is the bridge between expectations and reality." And so it was for sparsentan. Both studies have now been published—PROTECT in the *Lancet*⁵ and DUPLEX in the *New England Journal of Medicine*.⁶ The proteinuria benefit with sparsentan was sustained over the duration of follow-up in each of the trials; however, for both IgAN and FSGS, sparsentan missed the kidney protection end point of significantly slower kidney progression using estimated glomerular filtration rate slopes.

The investigators and Travers put a brave face on regarding the results. They suggested that sparsentan could be a foundational therapy for IgAN,⁷ and that while there wasn't a statistically beneficial effect on kidney protection with sparsentan in IgAN, the benefit was clinically meaningful.⁷ Likewise, for FSGS, as others have editorialized,⁸ the reduction in proteinuria seen with sparsentan shouldn't be scoffed at. FSGS is a disease that has the potential to be devastating, especially among children. Of course, it is possible that subgroups of patients, including those with genetically versus nongenetically caused FSGS, might benefit from sparsentan.

What's the bottom line? First, the investigators, the investors, and the company, Travers, should be collectively proud of their support for sparsentan. After all, sparsentan was a castoff at Bristol Myers Squibb. Even more impressively, it was brought back from the ashes after the Martin Shkreli scandal. Doing trials for relatively rare diseases such as FSGS are hard. These studies were scientifically rigorous. They were well presented and published in high-impact journals. No mean feat!

With respect to reduction in proteinuria, the results *could be important*, especially since sparsentan was used in patients with se-

vere high-risk disease who had already been treated with high-dose RAAS blockade prior to enrollment in the trial programs. Looking at patients in subgroups will also be important.

And, while the FDA didn't advance the accelerated approval to full approval, there is the potential that, with additional data, the FDA might change its position. Missing a *P* value for efficacy doesn't mean that the drug and the therapeutic strategy are a failure. Sagan's quote, "absence of evidence is not evidence of absence," is relevant here.

The benefit-risk ratio *and* considerations about unmet need are worth considering. For FSGS, where the disease can be devastating and the options for patients very limited, especially for children, sparsentan could satisfy an unmet need. One shouldn't minimize the ease of taking sparsentan (an oral once-a-day therapy), nor its favorable safety profile. While it's important to be watchful for adverse consequences of the drug in real-world settings (for example, the potential for liver injury and drug-drug interactions), the potential liver issue was recognized as manageable when the FDA granted accelerated approval with a Risk Evaluation and Mitigation Strategy.

More broadly, sparsentan has the potential to be an important therapy in the toolbox for treating all high-risk glomerular diseases because the mechanism of action is more hemodynamic than immunological, and the beneficial effect could be applied to many glomerular diseases. Of course, more data are needed, and the FDA is correct in being deliberate in its process of approving the drug. To paraphrase Winston Churchill, success comes from stumbling from failure to failure with no loss of enthusiasm. ■

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Estimating GFR in Patients With Heart Failure

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may be discrepancies between cystatin C-based estimated glomerular filtration rate ($eGFR_{cysC}$) and serum creatinine-based $eGFR$ ($eGFR_{scr}$).

According to **Alberto Pansino, MD**, and colleagues, there are few data available of the discrepancy between $eGFR_{cysC}$ and $eGFR_{scr}$ in patients with HFrEF. The researchers conducted a post-hoc analysis of data from the PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Nephrilysin Inhibitor With Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial to examine that discrepancy. Results were reported in the *American Journal of Kidney Diseases* [2023;82(5):521-532].

The analysis included data on 1970 patients with HFrEF enrolled in PARADIGM-HF who had available baseline measurements of cystatin C and serum creatinine. The clinical outcomes of interest were the PARADIGM-HF primary end point (composite of cardiovascular mortality or hospitalization for HF), cardiovascular mortality, all-cause mortality, and decline in kidney function. Secondary outcomes included poor health-related quality of life (HRQoL), frailty, and worsening HF, defined as HF hospitalization, visit to the emergency department, or outpatient intensification of therapy between baseline and 8-month follow-up.

Clinical outcomes on baseline difference between $eGFR_{cysC}$ and $eGFR_{scr}$ ($eGFR_{diff_{cysC-Scr}}$) were regressed using Fine-Gray subdistribution hazard models and Cox proportional hazards models. The association of baseline $eGFR_{diff_{cysC-Scr}}$ with poor HRQoL and frailty was examined using logistic regression. The association of worsening HF with $eGFR_{cysC}$, $eGFR_{scr}$, and $eGFR_{diff_{cysC-Scr}}$ at 8-month follow-up was assessed using linear regression models.

Mean $eGFR_{diff_{cysC-Scr}}$ at baseline and at 8-month follow-up were -6 mL/min/ 1.73 m² and -5 mL/min/ 1.73 m², respectively. At baseline, 35.7% of patients ($n=703$) had an $eGFR_{diff_{cysC-Scr}}$ lower than -10 mL/min/ 1.73 m² (negative group), 51.3% ($n=1011$) had an $eGFR_{diff_{cysC-Scr}}$ between -10 and $+10$ mL/min/ 1.73 m² (midrange group), and 13.0% ($n=256$) had an $eGFR_{diff_{cysC-Scr}}$ higher than $+10$ mL/min/ 1.73 m² (positive group).

Compared with the midrange and positive groups, those in the negative group were older, more likely to be White, be smokers, and receive diuretic agents. They also had higher New York Heart Association (NYHA) class, heart rate, N-terminal pro-brain natriuretic peptide levels, urinary albumin-creatinine ratio, and prevalence of atrial fibrillation. They were more likely to receive beta-blockers and mineralocorticoid receptor antagonists. There were independent associations between a baseline $eGFR_{diff_{cysC-Scr}}$ lower than -10 mL/min/ 1.73 m² and older age, White race, current smoking, NYHA class III/IV, and higher heart rate.

The PARADIGM-HF primary end point, CV mortality, all-cause mortality, and decline in kidney function, occurred in 22.3% ($n=439$), 11.8% ($n=233$), 16.9% ($n=333$), and 2.6% ($n=51$) of patients, respectively.

In both crude and adjusted models, there were associations between more negative values of baseline $eGFR_{diff_{cysC-Scr}}$ and increased risk for the PARADIGM-HF primary end point (hazard ratio [HR] per 1-standard deviation [SD] decrease, 1.18; $P=.008$); CV mortality (HR per 1-SD decrease, 1.34; $P=.001$); and all-cause mortality (HR per 1-SD decrease, 1.39; $P<.001$). When baseline $eGFR_{diff_{cysC-Scr}}$ was modeled as a categorical variable, with the negative group consistently associated with higher events compared with the midrange and positive groups, the associations persisted.

Baseline $eGFR_{diff_{cysC-Scr}}$ was also associated with decline in kidney function (HR per 1-SD decrease, 1.79; $P<.001$). Following multiple adjustments, the association was attenuated (HR per 1-SD decrease, 1.31; $P=.05$). When baseline $eGFR_{diff_{cysC-Scr}}$ was modeled as a categorical variable, the risk for worsening kidney function was higher in the negative group than in the midrange and positive groups; however, statistical significance was lost in adjusted models.

Of the patients assessed at baseline, 15.5% ($n=301$) met the definition of poor HRQoL, and 67.0% ($n=1301$) were classified as frail.

There were associations between more negative values of baseline $eGFR_{diff_{cysC-Scr}}$ and higher prevalence of poor HRQoL (adjusted odds ratio [aOR] per 1-SD decrease, 1.29; $P=.001$) and frailty (aOR per 1-SD decrease, 1.17; $P=.008$). When baseline $eGFR_{diff_{cysC-Scr}}$ was modeled as a categorical variable, the prevalences of poor HRQoL and frailty were significantly higher in the negative group than in the positive group.

Worsening HF was detected in 5.7% ($n=93$) of 1631 patients who had samples available at baseline and at 8-month follow-up. There was an association between worsening HF and a decline in kidney function at 8 months when assessed using serum creatinine or cystatin C. However, changes in kidney function at 8-month follow-up were more pronounced with considering $eGFR_{cysC}$ (adjusted between-group difference, -8.08 mL/min/ 1.73 m²; 95% CI, -10.50 to -5.66 ; $P<.001$) rather than $eGFR_{scr}$ (adjusted between-group difference, -3.69 mL/min/ 1.73 m²; 95% CI, -6.06 to -1.32 ; $P=.002$). In adjusted models that included $eGFR_{diff_{cysC-Scr}}$ at baseline, there was an association between worsening HF and a change in 8-month $eGFR_{diff_{cysC-Scr}}$ of -4.67 mL/min/ 1.73 m² (95% CI, -6.94 to -2.41 ; $P<.001$).

The researchers cited some limitations to the study, including the lack of a gold-standard measure for kidney function, and the small number of patients of non-White races and NYHA class IV.

In summary, the authors said, "In a cohort of ambulatory patients with HFrEF,

more negative values of $eGFR_{diff_{cysC-Scr}}$ were associated with worse clinical outcomes, poor HRQoL, and frailty. The decline in kidney function associated with worsening HF was more marked when assessed with $eGFR_{cysC}$ than with $eGFR_{scr}$, resulting in more negative values of $eGFR_{diff_{cysC-Scr}}$. Our findings challenge the current paradigm of kidney function assessment in the HF population and call for a more widespread incorporation of cystatin C and of measures of discrepancy between those two markers in clinical practice and in future research." ■

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TAKEAWAY POINTS

- Researchers conducted a post-hoc analysis of data from a randomized trial to examine the discrepancy between estimated glomerular filtration rate based on serum creatinine ($eGFR_{scr}$) and $eGFR$ based on cystatin C ($eGFR_{cysC}$) in patients with heart failure and reduced ejection fraction.
- Discrepancies between $eGFR_{cysC}$ and $eGFR_{scr}$ were common and more negative values of differences between the two equations were associated with worse clinical outcomes.
- More negative values of the differences between $eGFR_{cysC}$ and $eGFR_{scr}$ were associated with poor health-related quality of life and frailty.

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Cystatin C Versus Serum Creatinine

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date was the date of the first simultaneous $eGFR_{cr}$ and $eGFR_{cys}$ measurement.

The primary study exposure was $eGFR$ discordance, defined as an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$. The primary outcome of interest was the risk of specified medication-related adverse events within 90 days of the baseline date: (1) supratherapeutic vancomycin trough level greater than 30 $\mu\text{g/mL}$; (2) trimethoprim-sulfamethoxazole-related hyperkalemia (>5.5 mEq/L); (3) baclofen toxic effect; and (4) supratherapeutic digoxin level (>2.0 ng/mL). The secondary outcome, assessed using a multivariable Cox proportional hazards regression model, was 30-day survival of participants with versus without $eGFR$ discordance.

A total of 1869 patients met inclusion criteria and were included in the analysis. Mean age was 66 years, 49% (n=921) were female, 51% (n=948) were male, and 80% (n=1486) identified as non-Hispanic White.

Of the overall cohort, 29% (n=543) had an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$. The reference group included patients with concordant $eGFR$. In a multivariable logistic model, the factors associated with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ included White race (adjusted odds ratio [aOR], 1.43; 95% CI, 1.05-1.95; $P=.03$), cirrhosis (aOR, 1.68; 95% CI, 1.03-2.77; $P=.04$), use of a diuretic (aOR, 1.60; 95% CI, 1.15-2.24; $P=.005$), recent corticosteroid use (aOR, 1.65; 95% CI, 1.23-2.21; $P<.001$), hypoalbuminemia, defined as serum albumin level <3.0 g/dL (aOR, 6.09; 95% CI, 4.16-8.98; $P<.001$), anemia, defined as hemoglobin level <10.0 g/dL (aOR, 1.98; 95% CI, 1.38-2.83; $P<.001$), and $eGFR_{cr-cys}$ (aOR, 0.99; 95% CI, 0.98-1.00; $P<.001$).

The most common baseline factors associated with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ were hypoalbuminemia and anemia.

Patients whose $eGFR_{cys}$ was more than 30% higher than the $eGFR_{cr}$ (n=195; 10% of the cohort) were younger, had fewer medical comorbidities, were less likely to smoke, and had higher baseline $eGFR_{cr-cys}$ than patients with concordant $eGFR$. Due to the frequent use of antiretroviral medications that inhibit secretion of creatinine, HIV infection was more common in patients with an $eGFR_{cys}$ that was more than 30% higher than the $eGFR_{cr}$.

In the multivariable logistic model, factors associated with an $eGFR_{cys}$ that was more than 30% higher than the $eGFR_{cr}$ were age (aOR per 10-year increase, 0.75; 95% CI, 0.66-0.86; $P<.001$), White race (aOR, 0.62; 95% CI, 0.43-0.89; $P=.01$), diabetes (aOR, 0.60; 95% CI, 0.40-0.89; $P=.01$), and $eGFR_{cr-cys}$ (aOR, 0.99; 95% CI, 0.99-1.00; $P=.03$).

A total of 268 patients who reported receiving vancomycin within 90 days of the baseline date had their vancomycin trough level measured. Patients with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ were more likely to have significantly elevated vancomycin trough levels than patients with concordant $eGFR$ and patients with an $eGFR_{cys}$ that was more than 30% higher than $eGFR_{cr}$ (43 of 179 [74%] vs 7 of 77 [9%]; $P=.01$).

Of the 235 patients who received trimethoprim-sulfamethoxazole within 90 days of the baseline date and had their serum potassium level checked within 30 days, grade 2 hyperkalemia was numerically higher in those with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ compared with the $eGFR$ -concordant group.

Thirty-one patients received a prescription for baclofen within 90 days of baseline. Five of the 19 patients with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ developed clinical evidence of baclofen toxic effects, prompting discontinuation of the medication compared with none of the patients with concordant $eGFR$ or with an $eGFR_{cys}$ that was more than 30% higher than the $eGFR_{cr}$.

Ninety-nine patients received a prescription for digoxin. Of those 24 had an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$. Seven of the 24 had a digoxin trough level greater than the therapeutic range compared with zero of the 10 patients in the $eGFR$ -concordant group ($P=.08$).

Seven percent of the cohort (n=126) died within 30 days and 9% (n=160) were lost to follow-up prior to 30 days. The 30-day mortality rate was significantly higher in patients with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ compared with patients with concordant $eGFR$. Following adjustment for age, sex, race and ethnicity, baseline comorbidities, laboratory studies, and medication use, patients with an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ had a 1.98-fold increased hazard of death within 30 days (95% CI, 1.26-3.11; $P=.003$). There was no increased risk of death in patients whose $eGFR_{cys}$ was more than 30% higher than the $eGFR_{cr}$ compared with patients with concordant $eGFR$.

Limitations cited by the authors included using a one-time assessment of serum creatinine and cystatin C, and the inability to identify cancer stage and measures of functional status from the electronic health record.

In conclusion, the researchers said, "In this cohort study, we found that an $eGFR_{cys}$ that was more than 30% lower than the $eGFR_{cr}$ was associated with increased renally cleared medication-related adverse events. Future prospective studies are needed to improve and personalize the approach to GFR estimation and medication dosing in patients with cancer." ■

TAKEAWAY POINTS

In patients with cancer, estimation of glomerular filtration rate (GFR) based on serum creatinine ($eGFR_{cr}$) may overestimate the GFR.

Researchers reported results of a study testing the hypothesis that having an $eGFR$ based on cystatin C ($eGFR_{cys}$) that is substantially lower than an $eGFR_{cr}$ would be common in patients with cancer.

Among patients with cancer in this study, supratherapeutic drug levels and medication-related adverse events were more common in those with $eGFR_{cys}$ more than 30% lower than their $eGFR_{cr}$.

Decline in Kidney Function

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patients who participated in the DIPKA-1 (Developing Intervention Strategies to Halt Progression of Autosomal Dominant Polycystic Disease) trial. In DIPKA-1, patients were randomized to receive the somatostatin analogue lanreotide in addition to standard of care or standard of care alone. The primary outcome of interest was the change in slope of estimated glomerular filtration rate (eGFR) during a treatment period of 2.5 years.

mean age was 49.8 years. Due to the advanced stage of disease among those patients, mean eGFR was 9.5 mL/min/1.73 m², and total kidney weight was 2704 grams.

At baseline, the researchers examined associations between excretion of urinary EGF and markers of disease severity in the patients with ADPKD. There was a positive association between urinary EGF excretion and eGFR ($R=0.54$; $P<.001$). Following adjustment for age, sex, height-adjusted total kidney volume (htTKV), PKD mutation, and urinary biomarkers (b2MG, HFABP, and MCP-1), the

decline in kidney function ($\beta=1.08$; $P<.001$).

Analyses assessing whether the association was influenced by patient characteristics such as age, sex, body mass index, blood pressure, eGFR, htTKV, urine volume, and urinary damage biomarkers did not find any influence of those factors. The use of renin-angiotensin-aldosterone system inhibitors had no impact on the level of urinary EGF excretion or any interaction with urinary EGF excretion for the outcome of decline in eGFR. There was no association between urinary EGF and percentage change in TKV during the study period.

The potential effect of unilateral nephrectomy on urinary EGF excretion was assessed in 72 healthy kidney donor controls by comparing measurements prior to and following kidney donation. On average, there were 5.5 months between those visits. Unilateral nephrectomy resulted in a decrease of 46.4% in urinary EGF excretion, and a decrease of 35.2% in eGFR and 36.8% in measured GFR (all $P<.0001$). Removing one kidney resulted in a decrease in urinary EGF from 51.0 $\mu\text{g}/24$ hours predonation to 26.3 $\mu\text{g}/24$ hours post-donation, a change of -46.4% ($P<.0001$).

The researchers cited some limitations to the study findings, including the small number of participants who were randomized to standard of care, the short follow-up period of 2.5 years, the lack of data on plasma levels of EGF and HB-EGF, and examining only the associations between EGFR ligands and ADPKD progression.

In conclusion, the authors said, “Our study shows that lower urinary EGF excretion is strongly associated with more severe disease at baseline, and with more rapid eGFR loss during follow-up. These data indicate that lower urinary EGF excretion may be a valuable biomarker to predict future kidney function decline in patients with ADPKD. We argue that lower urinary EGF excretion indicates that there is a less functional tubular mass and less regenerative capacity for repair.” ■

Unilateral nephrectomy resulted in a decrease of 46.4% in urinary EGF excretion, and a decrease of 35.2% in eGFR and 36.8% in measured GFR (all $P<.0001$).

The overall cohort in the current study included 301 patients with ADPKD who were age- and sex-matched with 72 healthy controls. The two groups were similar in baseline characteristics, with the exception of blood pressure: those in the patient group had higher systolic and diastolic blood pressure and were more likely to use blood pressure-lowering medication, compared with the control group. Patients were also more likely to have lower baseline eGFR (51.7 mL/min/1.73 m² vs 94.5 mL/min/1.73 m²).

In the group with ADPKD, excretion of urinary EGF was lower compared with healthy controls (18.6 $\mu\text{g}/24$ hours vs 51.0 $\mu\text{g}/24$ hours; $P<.0010$). The groups were similar in urinary HB-EGF excretion (176 ng/24 hours vs 170 ng/24 hours; $P=.64$). Following correction of urinary excretion of those markers for creatinine excretion, results were essentially similar (EGF 1.4 $\mu\text{g}/\text{mmol}$ vs 3.8 $\mu\text{g}/\text{mmol}$, respectively, $P<.001$; and HB-EGF 14.1 ng/mmol vs 13.9 ng/mmol, respectively, $P=.87$).

Among the subset of patients selected from the DIPAK Biobank for renal tissue ($n=19$),

association between EGF and eGFR remained significant ($R=0.49$; $P<.001$). Opposite findings were observed for HB-EGF.

Urinary HB-EGF was higher with more severe disease ($R=-.016$; $P=.007$). After adjusting for age, sex, htTKV, and PKD mutation, the association remained significant ($R=-.014$; $P=.02$). In the final model that added urinary damage biomarkers, the association disappeared ($R=-0.001$; $P=.99$).

There were no associations between urinary EGF and HB-EGF and htTKV in the ADPKD patient cohort in either unadjusted or adjusted models.

The study also examined possible associations between urinary concentrations of the EGFR ligands with decline in kidney function and TKV growth in the patients with ADPKD in the group receiving standard of care ($n=149$). During mean follow-up of 2.4 years, on average 15 eGFR values were obtained per patient, resulting in an annual rate of decline in eGFR of -3.85 mL/min/1.73 m². There was a significant association between higher baseline urinary EGF excretion and less de-

TAKEAWAY POINTS

- Researchers reported results of a study testing the hypothesis that urinary epidermal growth factor receptor (EGFR) ligands are associated with decline in kidney function in patients with autosomal dominant polycystic kidney disease.
- At baseline, there was a positive association between baseline urinary EGF, and a lower EGF was strongly associated with a more rapid decline in glomerular filtration rate (GFR).
- There was no association between heparin-binding EGF-like growth factor and a more rapid decline in GFR.

CONFERENCE COVERAGE KIDNEY WEEK 2023

Complications From COVID-19 in Kidney Transplant Recipients

Recipients of kidney transplants are immunocompromised and vulnerable to infection, and are at risk of severe disease and mortality associated with COVID-19. Emily E. Zona and colleagues at the University of Wisconsin School of Medicine, Madison, conducted an analysis to characterize the sequelae of infection among kidney transplant recipients at the center.

Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Sequelae of Severe Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Among Kidney Transplant Recipients: A Large, Single-Center Experience*.

The analysis included data on all adult kidney transplant recipients who had a first episode of COVID-19 between April 2020 and April 2022. Eligible participants had at least 12 months of follow-up (excluding those who experienced graft failure or death). The outcomes of interest were risk factors for hospitalization, all-cause mortality, and COVID-19-related mortality.

Of 979 eligible kidney transplant recipients, 39% ($n=381$) were hospitalized due to a first episode of COVID-19. At baseline, those in the hospitalized group were older at COVID-19 diagnosis than those who were not hospitalized (59.8 years vs 53.7 years; $P<.001$). Hospitalized patients were also more likely to be male (63% vs 55%; $P=.02$), non-White (28% vs 16%; $P<.001$), have diabetes mellitus as the underlying cause of end-stage kidney disease (ESKD) (33% vs 14%; $P<.001$), and less likely to have received a living donor kidney transplant (35% vs 48%, $P<.001$).

Vaccination against COVID-19 resulted in reduced risk of hospitalization [hazard ratio [HR], 0.73; 95% CI, 0.59-0.90], risk of all-cause mortality (HR, 0.52; 95% CI, 0.37-0.74), and risk of COVID-19-related mortality (HR, 0.47; 95% CI, 0.31-0.71).

In multivariable analysis, the risk factors for all-cause mortality and COVID-19-related mortality were advanced age (HR, 1.05; 95% CI, 1.03-1.07 and HR, 1.04; 95% CI, 1.02-1.05,

respectively), hospitalization (HR, 6.76; 95% CI, 3.43-13.28 and HR, 24.3; 95% CI, 6.9-85.7, respectively), and respiratory symptoms for hospital admission (HR, 2.29; 95% CI, 1.42-3.68 and HR, 2.73; 95% CI, 1.52-4.89).

Additional risk factors were being a non-White recipient (HR, 1.46; 95% CI, 1.01-2.12) and diabetes as the cause of ESKD (HR, 1.42; 95% CI, 1.00-2.01). Being a recipient of a living donor transplant had a protective effect (HR, 0.69; 95% CI, 0.48-1.00).

“Hospitalization due to COVID-19 is associated with increased mortality,” the authors said. “Vaccination against COVID-19 is a protective factor against hospitalization and mortality.”

Source: Zona EE, Gibes ML, Jain AS, et al. Sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among kidney transplant recipients: a large single-center experience. TH-P0863. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Renal Effects of GLP-1RAs in Patients With Diabetic Kidney Disease

In patients with type 2 diabetes mellitus and in those with chronic kidney disease (CKD), the leading causes of death are cardiovascular diseases. Patients with both diabetes and CKD (diabetic kidney disease [DKD]) face increased risk of end-stage kidney disease (ESKD) and the need for dialysis. The rate of cardiovascular mortality in patients with DKD is more than two-fold higher than that in patients with type 2 diabetes with preserved kidney function.

First-line medication for patients with type 2 diabetes is metformin. Recommended medications for patients with established atherosclerotic cardiovascular disease (ASCVD) or multiple risk factors for ASCVD include glucagon-like peptide-1 receptor agonists (GLP-1RAs), along with sodium-glucose cotransporter 2 inhibitors (SGLT2is). Adding GLP-1RAs to SGLT2is in patients with diabetes and heart failure has resulted in significantly reduced composite cardiovascular events.

According to **Yuan Lin, MD**, and colleagues in Taiwan, there are few data available of the effect of GLP-1RAs on cardiovascular outcomes in patients with advanced DKD (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²). The researchers conducted a cohort study to assess whether GLP-1RAs have cardiovascular and renal protective effects in patients with advanced DKD. Results were reported online in *BMC Cardiovascular Diabetology* [doi.org/10.1186/s12933-023-01793-9].

The primary outcomes of interest were composite cardiovascular outcomes, including cardiovascular death, myocardial infarction, and ischemic stroke; a composite renal outcome of a decline in eGFR >50%; progression to ESKD with dialysis; and cardiovascular death. The study cohort included patients with a first prescription for GLP-1RA or DPP-4i from January 1, 2012, to December 31, 2021.

The date of the first prescription was the index date. GLP-1RAs included liraglutide and dulaglutide, and DPP-4is included sitagliptin, vildagliptin, saxagliptin, and linagliptin. The cardiorenal protective effects in the GLP-1RA and DPP-4i groups were assessed using a Cox proportional hazard model. A propensity score matched cohort was created to compare outcomes.

A total of 125,392 patients had a first prescription during the study period and were enrolled. Following application of exclusion criteria, 759 GLP-1RA users and 8163 DPP-4i users were eligible for analysis. In the matched cohort, 212, 117, 59, and 214 patients in the GLP-1RA group were matched to 1, 2, 3, and 4 counterparts in the DPP-4i group, respectively, resulting in a total of 1479 patients in the DPP-4i group and 602 in the GLP-1RA group.

In the GLP-1RA group, the median duration to new-onset dialysis was significantly longer than in the DPP-4i group (median, 1.9 years vs 1.3 years).

Overall, mean age was 68 years and 50.6% (n=4516) were male. Mean duration of diabetes mellitus was 6.4 years and baseline hemoglobin A1c (HbA1c) was 62 mmol/mol. Compared with patients in the DPP-4is group, those in the GLP-1RA group were younger, had a higher body mass index, longer duration of diabetes mellitus, higher baseline HbA1c, less CKD stage 5 (eGFR <15 mL/min/1.73 m²), higher prevalence of diabetes mellitus retinopathy and neuropathy, hypertension, hyperlipidemia, coronary heart disease, coronary intervention and myocardial infarction, greater Charlson Comorbidity Index scores, and higher triglyceride level. Patients in the GLP-1RA group were also more likely to take thiazolidinedione, alpha glucosidase, SGLT2is, insulin, statins, and fibrates. Following matching, the two groups were similar in baseline characteristics.

In the matched cohort, mean follow-up was 2.1 years. There was no significant difference between the GLP-1RA and DPP-4i groups in the risk of composite cardiovascular outcome (13% vs 13.8%; hazard ratio [HR], 0.88; 95% CI, 0.68-1.13). The groups were also similar in the risks of myocardial infarction, ischemic stroke, and cardiovascular death.

In analyses of renal outcomes, those in the GLP-1RA group had a greater protective effect than those in the DPP-4i group,

including progression to ESKD with dialysis (23.4% vs 27.45%; subdistribution HR, 0.72; 95% CI 0.56-0.93), decline in eGFR >50%, and the composite renal outcomes. In the GLP-1RA group, the median duration to new-onset dialysis was significantly longer than in the DPP-4i group (median, 1.9 years vs 1.3 years).

In secondary outcome analyses, the GLP-1RA group had lower risk of all-cause death compared with the DPP-4i group (18.4% vs 25.2%; HR, 0.71; 95% CI, 0.57-

0.88). The risk of all-cause readmission was also lower in the GLP-1RA group. The risk of composite major adverse limb events in the GLP-1RA group was borderline significantly lower than that in the DPP-4i group.

There were no significant differences between the two groups in the common causes of death among patients with advanced DKD, including malignancy, infection, cardiovascular diseases, diabetes mellitus, and kidney disease. Other causes of death were significantly lower in the GLP-1RA group than in the DPP-4i group.

The researchers cited some limitations to the study, including the retrospective design that limited the ability to infer causal associations between GLP-1RAs and cardiovascular or kidney outcomes, background heterogeneity in the GLP-1RA and DPP-4i cohorts, the database research may have had coding errors, only including the human GLP-1-like analogues liraglutide and dulaglutide in the study, and the inability to ensure medication adherence in each patient.

“GLP-1RAs had no influence on the composite cardiovascular outcomes but reduced composite kidney events, including a decline in eGFR >50% and progression to ESKD with dialysis, all-cause mortality, and admission in patients with advanced DKD (eGFR <30 mL/min/1.73 m²) compared with DPP-4is,” the authors said. ■

TAKEAWAY POINTS

Researchers in Taiwan reported results of a study investigating the potential cardiovascular and renal protective effects of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in a population of patients with diabetic kidney disease (DKD) with moderate to severe decline in kidney function.

The study compared cardiovascular and renal outcomes in patients with DKD treated with GLP-1RAs with a matched cohort treated with dipeptidyl peptidase 4 inhibitors (DPP-4is).

GLP-1RAs had a neutral effect on composite cardiovascular outcomes but reduced composite kidney events compared with DPP-4is.

Advance Planning and End-of-Life Care Among Patients on Dialysis

Patients receiving maintenance dialysis have high rates of hospitalization and admission to nursing homes. Patients in that population also spend more time in intensive care units and are more likely to receive intensive procedures such as cardiopulmonary resuscitation (CPR), mechanical ventilation, and artificial enteral nutrition during the final months of life compared with other groups of seriously ill patients. Patients treated with dialysis are also more likely to die in the hospital and less likely to receive hospice care.

According to **Susan P. Y. Wong, MD, MS**, and colleagues, there are few data available how the value placed on longevity versus comfort affects ways patients treated with dialysis view and prepare for serious illness or care they receive near the end of life. The researchers conducted a survey designed to examine the association between patients' health care values and engagement in advance care planning and end-of-life care. Analyses of survey responses were reported in *JAMA Internal Medicine* [2023;83(5):462-469].

The survey cohort included patients receiving maintenance dialysis between 2015 and 2018 at dialysis centers in the greater metropolitan areas of Seattle, Washington, and Nashville, Tennessee, with longitudinal follow-up of decedents. Probabilities were estimated using logistic regression models. Data analysis was conducted between May and October 2022.

The study exposure was a survey question regarding the value the participant would place on longevity-focused care versus comfort-focused care if they were to become seriously ill. Survey participants were asked whether they had ever signed official documents such as an advance directive or a living will stating their preferences regarding treatment and surrogate decision-making in the event of serious illness. Spe-

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cific questions included whether they had discussed stopping dialysis and hospice if they became sicker or if their goals changed.

The survey cohort included 933 patients. Mean age was 62.6 years, 56.3% (n=525) were male, and 27.2% (n=254) identified as Black. Overall, 48.4% of the cohort (n=452) indicated they would value comfort-focused care, 19.2% (n=179) said they would value longevity-focused care, and 32.4% (n=302) said they were unsure which option they would prefer.

Compared with participants in the group that would value life prolongation and those who were unsure

about what they would value, the group that would value comfort-focused care tended to be older (mean age, 66 years vs 59 years; $P<.001$) and included a lower proportion who identified as Black (estimated probability, 41.6% [95% CI, 35.8%-47.6%] comfort focused vs 58.4% [95% CI, 52.4%-64.2%] longevity focused; $P=.002$). The comfort-focused group also had a greater proportion of participants with at least some college education or more (estimated probability, 51.5% [95% CI, 47.1%-55.9%] comfort-focused vs 48.5% [95% CI, 44.1%-52.9%] longevity focused; $P=.045$) and vascular disease (estimated probability, 54.2% [95% CI, 48.3%-

60.0%] comfort focused vs 45.8% [95% CI, 40.0%-52.7%] longevity focused; $P=.02$).

A higher proportion of participants in the group valuing comfort-focused care indicated they had a documented decision-maker compared with those in the group valuing longevity-focused care and those in the uncertain group (estimated probability, 52.3% [95% CI, 47.9%-56.8%] comfort focused vs 45.4% [95% CI, 41.0%-50.0%] longevity focused; $P=.03$).

Sixty-two percent of the overall cohort said they had not signed documents regarding their treat-

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ment preferences. Rates were significantly higher in the group that valued comfort-focused care (estimated probability, 47.5% [95% CI, 42.9%-52.1%] comfort focused vs 28.1% [95% CI, 24.0%-32.3%] longevity focused or unsure; $P < .001$). Most also indicated they had not discussed stopping dialysis or hospice (72.5%; $n=676$). Rates were higher for the group valuing comfort-based care for discussion of dialysis discontinuation (estimated probability, 33.3% [95% CI, 29.0%-37.7%] comfort focused vs 21.9% [95% CI, 18.2%-25.8%] longevity focused or unsure; $P = .001$).

END-OF-LIFE CARE

Follow-up continued through September 2020. During that time, 377 participants died. Of those, 57.3% ($n=216$) had indicated at the time of the survey they would value comfort-focused care, and 42.7% ($n=161$) that they would value longevity-focused care or were unsure of what kind of care they would value. There were no statistically significant differences among the three groups (comfort-focused care, longevity-focused care, or unsure) in the proportion who discontinued dialysis prior to death, received hospice services, or died in the hospital setting.

A total of 239 participants who died during follow-up through December 2019 had continuous Medicare Parts A and B coverage during the final month of life. Of those, 56.9% ($n=136$) had indicated they would value comfort-focused care, and 43.1% ($n=103$) had indicated they would value longevity-focused care or were unsure.

Rates of hospitalization were similar in those who valued comfort-focused care and those who valued longevity-focused care (estimated probability, 71.8% [64.0%-79.1%] comfort focused vs 76.2% [95% CI, 67.4%-84.1%] longevity focused or unsure; $P = .45$).

Results were also similar among the groups for receipt of CPR, mechanical ventilation, or an intensive procedure during the final months of life as a function of how patients had responded to the questions about values. Point estimates were generally lower for participants in the group that valued comfort-focused care.

The researchers cited some limitations to the study findings, including using a single question that was based on a discrete choice model to elicit patients' values regarding advance care planning and end-of-life care. In addition, treatments focused on comfort and those based on longevity are not mutually exclusive and some may be used to support both goals. It is also possible that the values expressed at the time of the survey may have changed at end of life. The study was conducted among English-speaking patients receiving hemodialysis primarily in dialysis centers from nonprofit and not-for-profit dialysis organizations in two metropolitan areas, possibly limiting the generalizability of the findings to the overall dialysis population. The small study sample size in the analyses of end-of-life care was also cited as a possible limitation.

In conclusion, the authors said, "In this large survey study of patients undergoing maintenance dialysis, most indicated that they would value a comfort-focused rather than longevity-focused approach to care if they were seriously ill. However, differences in how patients responded to the question about values did not translate into substantial differences in their engagement in advance care planning or the care they received at the end of life. These findings likely reflect the challenges to effective advance care planning and the presence of strong health system defaults favoring longevity-focused over comfort-focused care among members of this population. These findings also suggest important opportunities to better align the care that patients undergoing dialysis receive with their underlying values." ■

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Biomarkers as Predictors of Adverse Kidney Outcomes in COVID-19

Acute kidney injury (AKI), defined using Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria, occurs in 30% to 50% of patients hospitalized with COVID-19. Of the patients with AKI, nearly 20% require dialysis. There are associations between development of clinical AKI during hospital admission and increased need for admission to the intensive care unit, worse short-term mortality, and adverse long-term outcomes. In addition, compared with AKI due to other causes, there may be an association between COVID-19-related AKI and greater long-term decline in kidney function.

Older age, male sex, diabetes mellitus, hypertension, obesity, and heart failure have all been associated with increased risk among patients with COVID-19. Even after adjustment for those risk factors, patients with COVID-19 have a more than 40% higher risk of AKI compared with patients without COVID-19.

In previous studies in other clinical settings of AKI, **Steven Menez, MD, MHS**, and colleagues identified 26 candidate plasma biomarkers representing different biological pathways of injury, inflammation, and repair. In a recent study, the researchers sought to examine the association of plasma biomarkers with major adverse kidney events (MAKE) and assess the predictive capability of top biomarkers.

The prospective cohort study was designed to test the hypothesis that there would be a strong association between plasma biomarkers and MAKE in the setting of COVID-19, and that the biomarkers would have clinically significant predictive potential. Results of the study were reported in the *American Journal of Kidney Diseases* [2023;82(3):322-332].

The outcome of interest was MAKE, defined as KDIGO stage 3 AKI, AKI requiring dialysis, or mortality up to 60 days. The study exposure was 26 plasma biomarkers of injury, inflammation, and repair from first available blood samples collected during hospitalization.

The researchers utilized Cox proportional hazards regression to associate biomarker

level with MAKE. They also applied the least absolute shrinkage and selection operator (LASSO) and random forest regression for prediction modeling and used time-varying Cox index to estimate model discrimination.

Following application of inclusion and exclusion criteria, the study included samples from 576 patients during hospitalization for COVID-19. On admission, mean patient age was 60.3 years and 42% (n=243) were female. Mean baseline serum creatinine was 0.87 mg/dL and mean admission serum creatinine was 1.23 mg/dL.

Thirty-five percent of the patients (n=203) had diabetes mellitus, 51% (n=293) had hypertension, and 29% (n=168) had obesity, with a body mass index ≥ 30 kg/m². Thirty-percent of patients (n=52) had baseline chronic kidney disease, defined as estimated glomerular filtration rate < 60 mL/min/1.73 m². Median length of hospitalization for COVID-19 was 9 days.

Sixteen percent of patients (n=95) experienced MAKE. Of those, 60% (n=57) developed stage 3 AKI, 33% (n=31) required dialysis, and 73% (n=69) died within 60 days. Prior to biomarker measurement, 22% of patients (n=125) were treated with remdesivir, and 24% (n=140) received steroids. Sixty-seven percent of the biosamples were collected within 72 hours of hospital admission; a smaller percentage were collected between 4 and 7 days and later.

There were significant associations between 15 of the 26 candidate biomarkers and MAKE: 11 were associated with increased risk and four with decreased risk. After adjustment for clinical covariates, there was a significant association between each 1-SD increase in log₂-transformed angiotensin 1, interleukin 13, vascular endothelial growth factor A (VEGFA), and VEGFC and a lower risk of MAKE.

Of the 11 biomarkers associated with increased risk of MAKE, each 1-SD increase in either soluble tumor necrosis factor receptor 1 (sTNFR1) or sTNFR2 was associated with a greater than two-fold higher risk of 60-day MAKE (adjusted hazard ratios, 2.30; 95% CI, 1.86-2.85 and 2.26; 95% CI, 1.73-2.95, respectively).

Results were similar in subgroup analyses in a subgroup of 499 patients whose biosample collection occurred within the first week of admission, with 73 events observed. In a subset of patients who did not receive steroids prior to collection of biosample (n=436), there were 73 events. The strongest associations with MAKE were with sTNFR1 and sTNFR2.

In analyses that limited the outcome to stage 3 AKI or dialysis, the associations between sTNFR1, sTNFR2, and neutrophil gelatinase-associated lipocalin remained the most robust. Similar trends were seen for other biomarkers based on time to MAKE. In an analysis among participants with more than one plasma biomarker measurement prior to the onset of stage 3 AKI (n=70), both sTNFR1 and sTNFR2 increased in those who subsequently developed MAKE compared with those who did not develop MAKE.

The C index of sTNFR1 alone was 0.80 (95% CI, 0.78-0.84) and the C index of sTNFR2 was 0.81 (95% CI, 0.77-0.84). Using all biomarkers, LASSO and random forest regression modeling yielded C indexes of 0.86 (95% CI, 0.83-0.89) and 0.84 (95% CI, 0.78-0.91), respectively.

The researchers cited some limitations to the study, including the lack of a control group of hospitalized patients without COVID-19, and the inability to include other biomarkers such as soluble urokinase plasminogen activator receptor and cystatin-C in the analysis.

In summary, the authors said, "Increased plasma concentrations of sTNFR1 and sTNFR2 are each independently and strongly associated with MAKE in patients hospitalized with COVID-19. In particular, combining clinical variables with either sTNFR1 or sTNFR2 has very strong discrimination for predicting MAKE, and further studies should confirm these findings in COVID-19 and other hospitalized clinical settings to identify high-risk patients. These results support that those with severe disease need postdischarge care, and longer follow-up studies in a larger population are necessary to understand the full spectrum of health consequences from COVID-19." ■

TAKEAWAY POINTS

• Patients hospitalized with COVID-19 are at increased risk for long-term adverse outcomes, including major adverse kidney events (MAKE).

• Researchers examined the association between 26 candidate biomarkers with MAKE in hospitalized patients with acute kidney injury related to COVID-19 to examine the predictive value of the biomarkers.

• There were strong independent associations between both soluble tumor necrosis factor receptor 1 (sTNFR1) and sTNFR2 and MAKE in this patient population. Both biomarkers can serve as predictors of adverse kidney outcomes.

Outcomes With Metformin Use in Kidney Transplant Recipients

The leading cause of chronic kidney disease (CKD) is diabetes. For patients with diabetes and CKD that has progressed to end-stage kidney disease (ESRD), the preferred treatment is kidney transplantation. According to data from survival analyses from the US Renal Data System, patients with diabetes who receive a kidney transplant have a 73% reduction in the risk of all-cause mortality compared with patients with diabetes on the transplant wait list. Further, kidney transplant recipients without diabetes are at risk of developing post-transplantation diabetes mellitus (DM).

Metformin is the most commonly prescribed oral antidiabetic agent worldwide and is considered a first-line agent in the pharmacologic management of type 2 DM. Due to concerns regarding an increased risk of lactic acidosis, metformin use has been avoided in patients with CKD with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m².

However, according to **Soie Kwon, MD, MS**, based on recent evidence of a low incidence of lactic acidosis as well as benefits that include improved survival rate and renoprotective effects, the use of metformin has been increasingly recommended for patients with advanced CKD. A previous study also reported that metformin usage by patients with advanced CKD improved the risk of all-cause mortality and ESKD.

The researchers conducted a retrospective multicenter cohort study to test the hypothesis that the use of metformin would be beneficial in kidney transplant recipients in terms of all-cause mortality and renal outcomes, including death-censored graft failure (DCGF) and biopsy-proven acute rejection (BPAR). They also sought to assess whether there is an association between metformin usage and risk of lactic acidosis in kidney transplant recipients. Results were reported in the *American Journal of Kidney Diseases* [2023;82(3):290-299].

The study cohort included 1995 kidney transplant recipients with diabetes from six tertiary referral centers in the Republic of Korea. Metformin usage was defined as the use of metformin for more than 90 days following kidney transplantation. Of the 1995 study participants, 1193 were metformin users; the remaining 802 did not use metformin. The primary study outcome was all-cause mortality and DCGF. Secondary outcomes were

BPAR and lactic acidosis events.

In the overall cohort, 78.4% of patients (n=1565) were diagnosed with pretransplantation DM versus 21.6% (n=430) who were diagnosed with post-transplant DM. Patients in the pretransplant diabetes group tended to have fewer prescriptions for metformin than those in the post-transplant diabetes group (n=897, 57.3% vs n=296, 68.8%, respectively; $P<.001$).

In the pretransplant diabetes group, the primary cause of ESKD was DM (DM-ESKD, 83.4%, n=1305). Those patients tended to have fewer prescriptions for metformin compared with patients with ESKD from other causes. The proportion of metformin users in the DM-ESKD group was 56.6% (n=728/1305), and in the group with ESKD from other causes, the proportion of metformin users was 61.2% (n=159/260), $P<.001$.

Baseline characteristics differed between the metformin users and the non-metformin users, particularly with respect to renal function and glycemic control. Renal function was better among metformin users (higher eGFR in the third month after kidney transplantation; $P<.001$), greater proportion of living donors compared with non-metformin users ($P<.001$), and poorer glycemic control (higher hemoglobin A1C in the third month after transplantation, $P<.001$). Metformin users also had greater proportion of several oral antidiabetic agent prescriptions compared with non-metformin users. There were no differences between the two groups in insulin usage.

Mean study follow-up was 72.6 months. During follow-up, 94 of the 1995 patients died. The three leading causes of death were infection-related (44.7%, n=42/94), malignancy-related (20.2%, n=19/94), and cardiovascular/sudden death (13.8%, n=13/94). Results of Cox analyses revealed a significantly lower risk of all-cause mortality compared with non-metformin users (univariate analysis; adjusted hazard ratio [aHR], 0.39; 95% CI, 0.26-0.58; $P<.001$). In the landmark analysis, the risk of all-cause mortality was lower in metformin users compared with non-metformin users, although the difference was not statistically significant (model 3; aHR, 0.94; 95% CI, 0.32-2.76; $P=.915$).

During a mean follow-up of 64.7 months, 5.1% of patients (n=102/1995) experienced a graft failure. Metformin users had a lower risk of graft failure, even after accounting

for the competing risk of all-cause mortality. Following adjustment for time-varying confounding, hemoglobin A1c, metformin usage, and mean daily dose, the risk of DCGF remained significantly lower in metformin users compared with non-metformin users (aHR, 0.47; 95% CI, 0.23-0.96; $P=.038$).

Patients who experienced the first BPAR prior to a post-transplant diagnosis of DM were excluded from the analysis of metformin usage and BPAR. During mean follow-up of 65.6 months, BPAR was diagnosed in 11.6% of patients (n=213/1830). Following adjustment for time-fixed covariates, there was an association between metformin use and lower risk of BPAR; the association did not reach statistical significance (aHR, 0.98; 95% CI, 0.62-1.54; $P=.0924$).

The occurrence of lactic acidosis was evaluated in 90.8% of the cohort (n=1801/1995). Seventy-seven lactic acidosis events were recorded in 66 of the 1801 patients (3.67%). There was no confirmed case of lactic acidosis associated with metformin use.

In subgroup analysis, there were associations between metformin use and reduced risk of all-cause mortality, and metformin use and a lower risk of DCGF for both patients with pretransplant DM and those with post-transplant DM. Use of metformin was associated with a lower risk of BPAR in the post-transplant DM group; it was less effective in the group with pretransplant DM. There was also a correlation between a higher dose of metformin and lower risks of DCGF and BPAR.

The researchers cited some limitations to the study, including the inability to obtain data on covariates (diabetes duration prior to transplantation and diuretic usage) and outcomes (major adverse cardiovascular events); limited data on newer antidiabetic drugs such as sodium-glucose cotransporter-2 (SGLT2) inhibitors; and limited generalizability to other populations.

In conclusion, the authors said, "Metformin usage may be beneficial for kidney transplant recipients, as evidenced by its association with a reduced risk of DCGF and the absence of metformin-associated lactic acidosis events. In the future, further well-designed randomized controlled trials with post-transplant DM defined according to American Diabetes Association criteria and that account for SGLT2 inhibitor use are needed to validate our findings." ■

TAKEAWAY POINTS

- Researchers in the Republic of Korea conducted a retrospective cohort study to examine the clinical effects of metformin in kidney transplant recipients.
- There was a significant association between metformin use and a lower risk of death-censored graft failure. There was no confirmed case of lactic acidosis associated with metformin use.
- There was no significant association between metformin use and all-cause mortality or biopsy-proven acute rejection.

Deceased Donor COVID-19 Status: Use Patterns and Transplant Outcomes

At the height of the COVID-19 pandemic, there was a substantial decrease in solid organ transplant rates worldwide. Kidney transplant rates were the most affected, followed by lung, liver, and heart transplants. Kidney transplant is the most common solid organ transplant in the United States, with a record 26,228 kidney transplants performed in 2022. Following the outbreak of COVID-19, transplant surgeons and nephrologists have been faced with decisions regarding the use of kidneys from donors with SARS-CoV-2 infection.

At the outset of the COVID-19 pandemic, COVID-19-positive patients were not considered eligible to be potential living or deceased donors. Of 295 procured kidneys from SARS-CoV-2 nucleic acid amplification test (NAT)-positive donors from August 2020 to September 2021, 34.6% (n=102) were not used compared with a nonuse rate of 20.6% for kidneys from NAT-negative donors. According to **Mengmeng Ji, PhD, MBBS**, and colleagues, the uncertainty regarding the potential risk of SARS-CoV-2 transmission and the relative risk-benefit of such organs likely influenced the decision-making.

As the proportion of individuals with a previous COVID-19 diagnosis increases, there are few data available regarding national patterns in kidney use and medium-term kidney transplant outcomes among patients receiving kidneys from active or resolved COVID-19-positive donors. Dr. Ji and colleagues conducted a retrospective cohort study designed to evaluate patterns in kidney use and kidney transplant outcomes among adult recipients of kidneys from deceased donors with active or resolved COVID-19. Results were reported in *JAMA Network Open* [doi:10.001/jamanetworkopen.2023.15908].

The study exposure was donor SARS-CoV-2 NAT results. Active COVID-19 was defined as positive NAT results within 7 days prior to procurement, and resolved COVID-19 was defined as positive NAT results 1 week (>7 days) prior to procurement. The primary outcomes of interest were kidney nonuse, all-cause kidney graft failure, and all-cause patient death. Secondary outcomes were acute rejection (rejection in the first 6 months after transplant), transplant hospitalization length of stay, and delayed graft function (DGF).

Kidney nonuse, rejection, and DGF were analyzed using multivariable logistic regression models, and graft failure and all-cause death were analyzed using multivariable Cox

regression models. All models were adjusted for inverse probability treatment weighting.

During the study period of March 1, 2020, to March 30, 2023, a total of 71,334 kidneys were recovered from 35,851 deceased donors with COVID-19 test results. Of those donors, mean age was 42.5 years, 62.3% (n=22,319) were men, 37.7% (n=13,532) were women, and 66.9% (n=23,992) were White. Median time from COVID-19 diagnosis to kidney transplant was 24 days in those with resolved infection and 3 days in those with active infection.

Of the 66,831 kidneys recovered from COVID-19 negative donors, 24.2% (n=16,175) were not used, and 75.8% (n=50,656) were transplanted. Of the 2165 recovered kidneys from active COVID-19-positive donors, 29.2% (n=632) were not used, and 70.8% (n=1,533) were transplanted. Of the 2338 recovered kidneys from resolved COVID-19-positive donors, 26.3% (n=615) were not used, and 73.7% (n=17823) were transplanted.

Compared with kidneys from COVID-19-negative donors, the odds of nonuse of kidneys from active COVID-19-positive donors were 56% higher (adjusted odds ratio [aOR], 1.55; 95% CI, 1.38-1.76). The odds of nonuse of kidneys from kidneys from resolved COVID-19-positive donors were 31% higher (aOR, 1.31; 95% CI, 1.16-1.48).

In 2020, kidneys from active COVID-19-positive donors had approximately 11-fold higher odds of nonuse (aOR, 11.26; 95% CI, 2.29-55.38), 2-fold higher odds of nonuse in 2021 (aOR, 2.09; 95% CI, 1.58-2.79), and 1.5-fold higher odds of nonuse in 2022 (aOR, 1.47; 95% CI, 1.28-1.70). There was no association between kidneys from active COVID-19-positive donors procured in 2023 and higher odds of nonuse (aOR, 1.07; 95% CI, 0.75-1.63).

In 2020, kidneys from resolved COVID-19-positive donors had approximately 4-fold higher odds of nonuse (aOR, 3.87; 95% CI, 1.26-11.90), 2-fold higher odds of nonuse in 2021 (aOR, 1.94; 95% CI, 1.54-2.45), and no higher odds of nonuse in 2022 (aOR, 1.09; 95% CI, 0.94-1.28) and 2023 (aOR, 1.18; 95% CI, 0.80-1.73).

The outcome analysis included 45,912 adult kidney transplant recipients. Mean age of the recipients was 54.3 years, 60.9% (n=27,952) were male, 39.1% (n=17,960) were female, and 33.4% (n=15,349) were Black. In unadjusted analysis, there was no association between donor COVID-19 status

and graft failure over 2 years of follow-up. The median follow-up was 200 days for the active or resolved COVID-19-positive group.

Results of multivariable Cox regression analysis revealed that compared with recipients of kidneys from COVID-19-negative donors, there was no increased risk of graft failure or patient death among recipients of kidneys from donors with active COVID-19 (adjusted hazard ratio [aHR], 1.03; 95% CI, 0.78-1.37 and aHR, 1.17; 95% CI, 0.84-1.66, respectively). Likewise, there was no increased risk of graft failure or patient death among recipients of kidneys from donors with resolved COVID-19 (aHR, 1.10; 95% CI, 0.88-1.39 and aHR, 0.95; 95% CI, 0.70-1.28, respectively) compared with recipients of kidneys from COVID-19-negative donors.

There were no associations between higher risk of acute rejection within 6 months after kidney transplant among recipients of kidneys from donors with active COVID-19 (aOR, 0.99; 95% CI, 0.66-1.48) or resolved COVID-19 (aOR, 0.72; 95% CI, 0.47-1.09). There were no associations between kidneys from active COVID-19-positive donors or resolved COVID-19-positive donors and increased risk of DGF (aOR, 0.92; 95% CI, 0.79-1.05 and aOR, 1.03; 95% CI, 0.91-1.17, respectively). Hospital length of stay was 0.63 days shorter among recipients of kidneys from active COVID-19-positive donors than among recipients of kidneys from COVID-19-negative donors.

Citing limitations to the study, the researchers included the retrospective design that prohibited establishment of causation, the possibility of selection bias, and the short period (2 years) of follow-up data available.

In summary, the authors said, "This cohort study found that the likelihood of nonuse of COVID-19-positive donor kidneys decreased over time and, for kidneys procured in 2023, donor COVID-19 positivity was no longer associated with higher odds of nonuse. Transplant of kidneys from donors with resolved or active COVID-19 was not associated with increased risk of all-cause graft loss, all-cause death, acute rejection, DGF, or longer hospitalization over more than 2 years of follow-up compared with kidneys from COVID-19-negative donors. These findings suggest that the use of kidney from donors with COVID-19 is safe in the medium term. Further research is needed to assess longer-term transplant outcomes involving kidneys from COVID-19-positive donors." ■

TAKEAWAY POINTS

Researchers sought to identify national patterns in kidney use and transplant outcomes among adult recipients from deceased donors with active or resolved COVID-19.

Over time, the likelihood of nonuse of kidneys from deceased donors with active or resolved COVID-19 decreased. In 2023, there was no association between donor positivity and higher odds of nonuse.

Over 2 years of follow-up, there were no associations between donor COVID-19 status and increased risk of adverse kidney transplant outcomes.

Conference Coverage

Philadelphia, Pennsylvania | November 2-5, 2023

KIDNEY WEEK 2023

The American Society of Nephrology Kidney Week 2023 included presentations and posters highlighting the latest findings in kidney health research, as well as sessions on advances in the care of patients with kidney and related disorders. This is part two of our coverage of Kidney Week 2023.

Changes in Blood Pressure With Urate-Lowering in Uncontrolled Gout

Among patients with uncontrolled gout, the rate of hypertension is high and associated with hyperuricemia and gout. Allopurinol had little effect on blood pressure in adults; however, there were reductions in systolic and diastolic blood pressure with intensive urate-lowering with pegloticase.

Brad A. Marder and colleagues conducted an analysis of changes in blood pressure during pegloticase use in the randomized, controlled MIRROR trial. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Blood Pressure Changes With Intensive Urate Lowering in Uncontrolled Gout Patients With and Without CKD*.

Uncontrolled gout was defined as serum urate 7 mg/dL, failure of or intolerance to oral urate-lowering therapy, and one or more gout symptoms. In the MIRROR trial, patients with uncontrolled gout were randomized 2:1 to oral methotrexate (MTX; 15 mg/week) or placebo as cotherapy to pegloticase (8 mg biweekly for 52 weeks).

Following a 2-week MTX tolerance period and a 4-week MTX/placebo run-in period, patients were initiated on pegloticase plus MTX or pegloticase plus placebo (day 1). Sitting blood pressure was measured prior to MTX (baseline, week 6) and pegloticase exposure (week 4, day 1) and every 2 weeks thereafter. Data on preinfusion and on-treatment blood pressure were included. The mean change in blood pressure from baseline was examined by treatment group and baseline estimated glomerular filtrate rate (eGFR; <60 mL/min/1.73 m² vs ≥60 mL/min/1.73 m²).

The analysis included 152 patients; 80% were men, mean age was 55 years, mean history of gout was 14 years, mean gout tophi was 76%, and mean number of gout flares per year was 11. At baseline, the groups were similar in clinical characteristics, including systolic blood pressure (MTX, 133 mm Hg vs placebo, 131 mm Hg) and diastolic blood pressure (82 mm Hg vs 83 mm Hg, respectively).

In both groups, blood pressure decreased initially but decreased more in the MTX group by week 24 (change from baseline, -6 mm Hg vs -1 mm Hg). Change from baseline was sustained in patients in the MTX group through week 52 but fluctuated after week 24 in the placebo group. In the MTX group, diastolic blood pressure was below baseline through week 52. In the placebo group, diastolic blood pressure initially declined but returned to baseline by week 52.

Early in treatment, patients with baseline eGFR <60 mL/min/1.73 m² and ≥60 mL/min/1.73 m² had similar change from baseline. However, by week 24, the change from baseline was more pronounced in the group with eGFR ≥60 mL/min/1.73 m², a trend that persisted through week 52.

In summary, the authors said, "Blood pressure decreased during pegloticase therapy in chronic kidney disease (CKD) and non-CKD patients. After 6 months, patients cotreated with MTX and without CKD had more pronounced changes. These data support a possible role of urate, and potentially MTX, in regulating blood pressure, particularly in non-CKD patients with gout. Further study is needed."

Source: Marder BA, Johnson RJ, Choi H, Obermeyer KL, LaMoreaux B, Lipsky PE. Blood pressure changes with intensive urate lowering in uncontrolled gout patients with and without CKD. SA-P0505. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 4, 2023; Philadelphia, Pennsylvania. Funding for this analysis was provided by Horizon Therapeutics plc.

COVID-19 Pandemic and Anxiety Among Transplant Recipients

Solid organ transplant recipients represent a population that is immunocompromised and at high risk of infection. **Jad Fadlallah** and colleagues at the University Health Network, Toronto, Ontario, Canada, recently conducted a study to examine the impact of the COVID-19 pandemic on anxiety symptoms in that patient population.

The researchers reported results of the study during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Evaluating the Effect of COVID-19 Pandemic on Anxiety in Solid Organ Transplant Recipients*.

The analysis utilized data from a cross-sectional sample of adult kidney, kidney-pancreas, liver, and liver-kidney transplant recipients who were recruited in studies validating PROMIS (Patient-Reported Outcomes Measurement Information System) tools between 1997 and 2023. The data include patient-reported demographic data and clinical data from health records. Eligible patients completed the PROMIS-29 anxiety version 2.0 using the four-item Short Form Health Survey or the PROMIS computerized adaptive test. Patients were scored on a T-score metric where higher scores indicate more anxiety symptoms.

The primary analysis compared anxiety between patients who completed the questionnaires prior to the pandemic (PRE) with patients who completed the questionnaires following the pandemic's onset (POST). In a secondary analysis, the POST group was further stratified into those who received a solid organ transplant prior to the pandemic (POST-B) and those who received a transplant following the onset of the pandemic (POST-A).

Two-sample t-test and linear regression, adjusted for organ type, age, sex, ethnicity, education, marital status, economic disadvantage, comorbidity, time since transplant, and serum albumin and hemoglobin, were used to compare scores on the PROMIS-29 anxiety test.

The cohort included 682 participants. Of those, 62% (n=422) were male, and mean age was 53 years. In the primary analysis, those in the POST cohort had higher mean PROMIS-29 anxiety scores than those in the PRE cohort (54 vs 52; *P*=.004). In the fully adjusted regression model, anxiety scores were significantly higher (coefficient, 2.9; 95% CI, 0.9-4.9; *P*=.007).

In the secondary analysis, results of the fully adjusted regression model revealed an association between the timing of the transplant (prior to or after COVID-19 onset) status and anxiety scores (reference: PRE; POST-A, coefficient, 4.2; 95% CI, 0.8-7.6; *P*=.019; POST-B, coefficient, 2.4; 95% CI, 0.6-5.4).

"Anxiety scores collected in this sample of solid organ transplant recipients were higher after the onset of the pandemic. These findings suggest that mental health support for solid organ transplant recipients is relevant and important in the context of the pandemic. Longitudinal studies can assess the development of anxiety symptoms in the future," the authors said.

Source: Fadlallah J, Samudio AM, Groe K, Jahed M, Mucsi I. Evaluating the effect of COVID-19 pandemic on anxiety in solid organ transplant recipients. TH-P01089. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Recovery of Renal Function After Liver Transplant

Acute kidney disease (AKD) is the phase between acute kidney injury (AKI) and chronic kidney disease (CKD). AKD is a crucial window of time to initiation of therapies that may aid recovery of renal function. **Jacqueline Lee** and colleagues at Cedars-Sinai Medical Center, Los Angeles, California, conducted a study to examine the impact of the duration of AKI in patients with decompensated cirrhosis on subsequent recovery of renal function following liver transplantation.

Results of the study were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Pre-Liver Transplant Acute Kidney Disease Highlights Impaired Renal Function Recovery Phase*.

The single-center retrospective study included adults who underwent single-organ, orthotopic liver transplant from January 2015 to December 2021. AKD was defined as persistence of ZAKI for more than 7 days and up to 90 days. Cohort participants were classified by duration of pretransplant AKI and renal replacement therapy (RRT) status.

The cohort was stratified into four groups: (1) normal kidney function; (2) AKI requiring RRT within 7 days of onset (AKI-RRT); (3) AKD without RRT (AKD-noRRT); and (4) AKD with RRT (AKD-RRT). Serial measurements of estimated glomerular filtration rate before and after liver transplant were used to compare renal function

throughout the study period.

Eighty-one of 170 patients required RRT prior to liver transplant (47.6%); 41 required RRT within 7 days (24%), and 40 required RRT during the AKD phase (23.7%). The remaining participants had normal renal function (n=78; 45.8%).

Patients who initiated RRT during the AKD phase had significantly lower eGFR at 3 months and 1 year post-transplant compared with the AKI-RRT group (AKD-RRT vs AKI-RRT: 41.6 mL/min/1.73 m² vs 56.6 mL/min/1.73 m²; *P*=.05; at 3 months; and 49.7 mL/min/1.73 m² vs 59.2 mL/min/1.73 m²; *P*=.05; at 1 year). There was no significant decline in eGFR in the group with normal renal function.

In conclusion, the researchers said, "Our study findings suggest AKD is associated with significantly reduced renal function recovery at 1-year post-liver transplantation. Our study demarcates the critical phase of AKI associated with maximal renal function recovery in cirrhotic patients for orthotopic liver transplant and informs when best to initiate therapies that are linked with renal function recovery."

Source: Lee J, Huang E, Kumar S. Pre-liver transplant acute kidney disease highlights impaired renal function recovery phase. Th-P0054. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Conference Coverage

Philadelphia, Pennsylvania | November 2-5, 2023

Meta-Analysis: Long-term Safety of HIF-PHIs in Patients With CKD

Anemia associated with chronic kidney disease (CKD) can be treated with oral hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHI). **Jeffery Ha** and colleagues recently conducted a systematic review and meta-analysis designed to assess the long-term safety of HIF-PHIs in patients with CKD.

Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Long-term Safety of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors in CKD: A Systematic Review and Meta-Analysis of Randomized Trials*.

The researchers searched MEDLINE, Embase, and Cochrane databases to March 2023. Randomized trials comparing HIF-PHIs with an erythropoiesis-stimulating agent (ESA) or placebo with at least 48 weeks of follow-up were eligible for the review. Outcomes of interest were major adverse cardiovascular events (MACE), individual components of composite cardiovascular end points, thrombotic events, and non-cardiovascular adverse events. Separate analyses were conducted in those with CKD treated with dialysis and those not treated with dialysis.

A total of 25 trials representing 26,478 participants were eligible. Of those, 13 were conducted among 13,230 participants with dialysis-dependent CKD (DD-CKD), and 12 were conducted among 13,248 participants with non-dialysis-dependent CKD (NDD-CKD). There was no evidence indicating that HIF-PHIs and ESA had different effects on MACE in those with DD-CKD (relative risk [RR], 0.99; 95% CI, 0.92-1.08) and in those with NDD-CKD (RR, 1.08; 95% CI, 0.95-1.22).

Likewise, there was no evidence that HIF-PHIs and placebos had different effects on MACE in participants with NDD-CKD (RR, 1.10; 95% CI, 0.96-1.27). The lack of difference between HIF-PHIs and ESA or placebo was also seen for the individual components of MACE and for cardiovascular death.

In the DD-CKD group, the safety of HIF-PHIs for other outcomes was similar. In the NDD-CKD group, adverse events (dialysis access thrombosis, infection, hyperkalemia, and seizures) occurred more frequently in the HIF-PHI group compared with the placebo group. Esophageal or gastric erosion were more frequent with HIF-PHIs than with ESAs in the NDD-CKD group.

"The long-term effects of HIF-PHIs were similar to ESA in dialysis-dependent CKD," the researchers said. "However, HIF-PHIs increased the incidence of some adverse events in non-dialysis CKD."

Source: Ha J, Hiremath S, Jun M, et al. Long-term safety of hypoxia-inducible factor prolyl hydroxylase inhibitors in CKD: a systematic review and meta-analysis of randomized trials. TH-P0987. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Postdonation Experiences of Living Kidney Donors

Potential living kidney donors begin the donation process in good health, but they may be unprepared for possible negative outcomes following donation. Studies have shown that postdonation adverse outcomes are more prevalent among ethnic minorities. **Miriam E. Velez-Bermudez** and colleagues at the University of New Mexico Health Sciences Center, Albuquerque, conducted a study to provide an in-depth description of positive and negative outcomes among an ethnically diverse population of living donors.

Results of the study were reported during a poster session at the American Society of Nephrology Kidney Week 2023. The poster was titled *Experiences of Ethnically Diverse Living Kidney Donors*.

In-depth individual interviews with a diverse sample of donors were conducted using the DIPEX (database of individual patient experiences) method. The DIPEX method combines in-depth interviews and systematic, purposeful sampling and qualitative analysis. Interviews were conducted by a primary and secondary interviewer and analyzed by a qualitative research team.

Narrative interviews were completed by 14 donors. Of the 14 donors, nine were women, eight were White, five were Hispanic, and one was Native American.

Findings from the interviews revealed the key role of social support in validating the decision to donate and in facilitating postdonation recovery. The participants' reasons for donating focused on the desire to avoid the need for dialysis or to save the life of their recipient. Familial duties tended to motivate donation for Hispanic and Native American women, while a call to action as a healthy individual was a greater motivator among the White donors.

Thirteen of the 14 donors felt well-supported by health care providers through the predonation period. Three participants said they had erroneously been told by primary care providers that they had developed kidney disease, due to a lack of clarity regarding postdonation clinical care.

Eleven of the donors reported unanticipated outcomes following donation. Outcomes ranged from minor complications (constipation, fatigue, pain) to moderate complications (hernia, gout). Other unexpected outcomes were depression and mourning the loss of the kidney. Despite the adverse outcomes reported, all 14 participants had positive feelings about donation and did not have any regrets.

In summary, the researchers said, "Adverse outcomes postdonation did not preclude living donors' enthusiasm and support of donation; therefore, greater transparency about postdonation outcomes is warranted. An online DIPEX module presenting these diverse experiences may enhance awareness and understanding of the donation process for future living kidney donors."

Source: Velez-Bermudez ME, Brakey HR, Myaskovsky L, Unruh ML, Singh P, Pandhi N. Experiences of ethnically diverse living kidney donors. TH-P0877. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Delays in Formal Diagnosis Following Laboratory-Based Evidence of CKD

There are often delays between onset of chronic kidney disease (CKD) and formal diagnosis. According to **Satabdi Chatterjee** and colleagues, there are few data available on quantification of those delays.

The researchers conducted a retrospective cohort study designed to quantify the delay from laboratory-based physiologic detection (using estimated glomerular filtration rate [eGFR]) to diagnosis of CKD (using *International Classification of Diseases, Ninth and Tenth Revision* [[ICD 9/10] codes). Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Quantifying the Delay From Laboratory-Based Detection to Diagnosis of CKD in the United States*.

Using 2009-2020 Optum® Market Clarity data, the researchers identified individuals 18 years and older who had two laboratory records 3 to 12 months apart showing eGFR <60 mL/min/1.73 m². The second eGFR <60 mL/min/1.73 m² was defined as the index date. Exclusion criteria were a pre-existing ICD code of CKD during the 12-month preindex period (baseline) or before the first eGFR <60 mL/min/1.73 m².

Eligible participants were followed from the index date until a diagnosis of CKD or censoring (date of death, end of follow-up, or disenrollment). Study cohorts were stratified by the presence or absence of comorbid diabetes and heart failure at baseline. The factors associated with delays in diagnosis were assessed using survival analysis for the overall cohort and the stratified cohorts.

The analysis included 1.39 million adults with laboratory evidence of CKD. Mean age was 71 years, 63% were women, and 87% were White. More than 90% had Kidney Disease: Improving Global Outcomes CKD stage 2, 5% had stage 4 CKD, and 1% had stage 5 CKD. In the overall cohort, 62% did not have diabetes or heart failure, 24% had diabetes, 8% had heart failure, and 6% had both diabetes and heart failure.

Mean follow-up was 2.7 years. Mean time to CKD diagnosis in the overall cohort was 469 days. Mean time to CKD diagnosis was 537 days in the subgroup without diabetes or heart failure; 449 days in the subgroup with diabetes only; 319 days in the subgroup with heart failure only; and 270 days in the subgroup with both diabetes and heart failure. Factors associated with longer time to CKD diagnosis were absence of diabetes or heart failure, less severe CKD, younger age, female sex, and White race.

In conclusion, the researchers said, "In a large cohort of individuals with laboratory-based evidence of CKD, the time to diagnosis was delayed, on average, by over a year. In light of newer therapies that can slow kidney disease progression and reduce cardiovascular outcomes, these findings reinforce the need for early recognition of CKD that would inform optimal guideline-based treatment and improve outcomes in these patients."

Source: Chatterjee S, Levy AR, Donato BM, Zhang L, Stackland S, Kovesdy C. Quantifying the delay from laboratory-based detection to diagnosis of CKD in the United States. TH-P01041. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania. Funding was provided by Boehringer Ingelheim Pharmaceuticals, Inc.

Magnesium Levels and Cognitive Function in Elderly Patients on Dialysis

Worldwide, dementia poses a challenge for geriatric care and social welfare. Dementia is also a challenge for aging patients dependent on dialysis. Results of previous studies have suggested a potential association between cognitive function and chronic kidney disease-mineral and bone disorder (CKD-MBD).

Kazuhiko Kato and colleagues in Tokyo, Japan, conducted a cross-sectional study of patients receiving hemodialysis to identify the association between cognitive functions and serum magnesium intact parathyroid hormone (PTH), 25-hydroxyvitamin D(OHD), fibroblast growth factor(FGF)-23, and soluble α -Klotho. Results were reported during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Serum Magnesium Levels and Cognitive Function in Hemodialysis Patients: A Cross-Sectional Study*.

Cognitive function was assessed by the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). The study cohort included 390 patients, whose age ranged from 70 to 80 years (median, 74 years). Average duration of hemodialysis was 87 months. Mean serum magnesium level was 2.4 mg/dL, median intact PTH level was 157 ng/mL, and median 25-OHD level was 14.1 ng/mL. Median intact FGF-23 level was 1921 pg/mL and median soluble α -Klotho level was 381 pg/mL.

The median MoCA scores were 25 and the median MMSE scores were 28.

In multivariable adjusted analysis, MoCA and MMSE scores were significantly higher, indicating preserved cognitive function, in those with higher magnesium levels compared with lower magnesium levels (b coefficient, 0.91; 95% CI, 0.03-1.78; $P=0.043$ for MoCA and b coefficient, 0.82; 95% CI, 0.13-1.5; $P=0.019$ for MMSE). There were no significant associations between cognitive functions and the other biomarkers.

“Higher serum magnesium levels were associated with preserved cognitive function in hemodialysis patients, and avoiding hypomagnesemia may be recommended to protect cognitive function,” the authors said. “On the other hand, no significant associations were observed between cognitive functions and serum intact PTH, 25OHD, FGF-23, and soluble α -Klotho levels.”

Source: Kato K, Nakashima A, Kobayashi A, Ohkido I, Yokoo T. Serum magnesium levels and cognitive function in hemodialysis patients: a cross-sectional study. TH-P0163. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania.

Simulation of the Burden of Hyperphosphatemia in Patients on Dialysis

Patients with end-stage kidney disease (ESKD) receiving dialysis commonly develop hyperphosphatemia. The complication can lead to vascular calcification, secondary hyperparathyroidism, increased risk for fractures, and other adverse health outcomes.

To understand the role played by serum phosphate control in patients on dialysis, researchers, led by **Sandeepkumar Balabbigari**, built a decision tree model to simulate the population-level effect of reducing serum phosphate levels in adult patients in the United States with ESKD receiving in-center hemodialysis (n=480,516) over a 5-year time horizon. The model was described during a poster session at the American Society of Nephrology Kidney Week 2023 in a poster titled *Decision Tree Model Simulating the Burden of Hyperphosphatemia in US Adult Patients With ESKD on Dialysis*.

Using the US Renal Data System’s 2022 Annual Data Report, patients were assigned an initial serum phosphate level, followed by application of a reduction of 2.0 mg/dL. Based on published literature and Medicare cost data, changes in hospitalization (all-cause, cardiovascular, and fracture), parathyroidectomies, mortality, and health care costs were calculated. Direct drug costs were not addressed because the model does not specify how patients’ serum phosphate levels are reduced.

The greatest benefit seen with the modeled serum phosphate reduction was reduction in mortality, with 16,565 fewer deaths occurring over the 5-year period in the simulated population compared with a population that maintained the initial level of serum phosphate. There were 46,308 additional all-cause hospitalizations in the simulated population over the same time period, comprising the majority of an additional \$165.9 million in Medicare costs.

Limitations to the model included deriving data from older retrospective studies that may not represent the current ESKD population and the inability to simulate fluctuations in serum phosphate as they would occur in reality.

In summary, the authors said, “Simulated reduction of serum phosphate levels in patients with ESKD on dialysis decreased mortality. This pronounced effect in mortality leads to an increase in all-cause hospitalization, resulting in additional Medicare costs. However, serum phosphate control is only one component of managing patients with ESKD on dialysis; there are numerous contending comorbidities and extenuating factors. These results highlight the need to continue exploring how management of patients with ESKD can provide the best patient outcomes.”

Source: Balabbigari S, Gargano M, Benjumea DW, Doan Q, Foote B. Decision tree model simulating the burden of hyperphosphatemia in US adult patients with ESKD on dialysis. TH-P0139. Abstract of a poster presented at the American Society of Nephrology Kidney Week 2023; November 2, 2023; Philadelphia, Pennsylvania. Funding was provided by Akebia Therapeutics, Inc.



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Undocumented Immigrants With Kidney Failure Value Peer Support Group Intervention

Emergency dialysis is defined as dialysis after a patient presents as critically ill. According to **Lilia Cervantes, MD**, and colleagues, most undocumented immigrants with kidney failure rely on emergency dialysis. Patients in that population experience significant depression and anxiety and are at increased risk for death.

The researchers conducted a qualitative and single-group prospective study to test the hypothesis that culturally and language-concordant peer support group interventions may be associated with reduce depression and anxiety and may provide emotional support. Results of the study were reported in *JAMA Network Open* [doi:10.1011/jamanetworkopen.2023.19277].

The study population included undocumented immigrants with kidney failure receiving emergency dialysis at a center in Denver, Colorado, from December 2017 to July 2018. The 6-month intervention consisted of peer support group meetings in the hospital while participants were hospitalized for emergency dialysis. Data analysis was conducted from March to June 2022.

Recruitment, retention, implementation, and delivery for the intervention were tracked to assess feasibility of the program. Acceptability of the intervention was measured via structured-format interviews with participants. Themes and subthemes examining the value of peer support group intervention were identified from participant interviews and group meetings.

Of 27 individuals approached, 23 Latinix adults participated in the intervention. Nine of the 23 participants were female and 14 were male, and mean age was 47 years; recruitment rate was 85.2%. Of the 23 participants, 14 had less than a high school education, five had completed high school, and four had some college. Eleven were employed and 16 had an annual household income of <\$14,999. Mean dialysis vintage was 44 months. At baseline, six had mild depression and four had moderate-to-severe depression. Six had mild anxiety and four had moderate-to-severe anxiety.

The total intervention consisted of 12

meetings, with a mean duration of 89 minutes. At the first meeting, the participants selected topics they wanted to discuss.

Of the 23 participants, five withdrew before the meetings began, and 19 attended a mean of six meetings. Reasons for withdrawing included moving to Mexico, transitioning to a different inpatient dialysis schedule, and transitioning to outpatient scheduled dialysis. Reasons for missing a meeting included admission to the medical intensive care unit, being on isolation status, change in the date of weekly hospital admission, and admission to another hospital.

disease; (4) receiving emotional support from peers and caregivers; and (5) the role of faith and prayer in coping with the need for emergency dialysis.

The third theme expanded into four subthemes: (1) psychosocial and physical distress associated with kidney disease and kidney failure; (2) varying experiences with language-concordant care, including having to self-advocate for an interpreter; (3) dealing with emotional exhaustion from conversations regarding end-of-life care and advance directives; and (4) gratitude for clinicians and for emergency dialysis, saying

Three themes emerged: (1) camaraderie and emotional support from peers; (2) solutions to improve care and resilience; and (3) emotional and physical aspects of receiving emergency dialysis.

Three themes emerged: (1) camaraderie and emotional support from peers; (2) solutions to improve care and resilience; and (3) emotional and physical aspects of receiving emergency dialysis. The first two themes related to the acceptability of the intervention and the third related to experiences receiving emergency hemodialysis.

The camaraderie theme expanded into five subthemes: (1) peer support is vital for people newly diagnosed with kidney failure; (2) patients need a safe space to build relationships and share difficulties with peers; (3) providing peer support in the hospital setting is ideal; (4) the intervention could provide solidarity to survive and incentives to reduce financial burdens by obtaining health insurance; and (5) the desire to maintain the sustainability of the peer support group.

Subthemes associated with the solutions to improve care and resilience theme were: (1) self-advocacy as a means for participants to improve their care; (2) self-motivation and optimism; (3) the opportunity to improve participant knowledge of kidney

that in their home countries, they would have died because emergency dialysis was not available.

There were some limitations to the study cited by the researchers, including the small sample size and the single-center design; all study participants being Latinix, making the findings ungeneralizable to other racial and ethnic groups; and not collecting data on race from the participants.

In conclusion, the authors said, “In this qualitative study, undocumented immigrants with kidney failure who relied on emergency dialysis described wanting to formalize a peer support group because they reported camaraderie and learned strategies to improve their resilience, including self-advocacy and optimism. Our results suggest that group peer support may be feasible and acceptable; it may also provide a patient-centered strategy to address the need for depression, anxiety, and social support services among patients with kidney failure, especially for marginalized, uninsured populations whose members report limited English proficiency.” ■

TAKEAWAY POINTS

- Researchers sought to determine whether culturally and language-concordant peer support group interventions would be of value to undocumented immigrants with kidney failure requiring emergency dialysis.
- The intervention was shown to be feasible and had high recruitment, retention, and delivery rates.
- Participants said the intervention built camaraderie and provided peer emotional support, describing the intervention as acceptable and valued.

Monogram Health Names Chief Legal Officer

Monogram Health has named **Adam McAnaney** as chief legal officer and secretary.



Adam McAnaney

Monogram Health is a value-based provider of in-home, evidence-based care and benefit management services for patients living with chronic kidney disease (CKD) and end-stage kidney disease (ESKD).

In a recent press release, **Mike Uchirin**, Monogram Health CEO and cofounder, said, "Adam has a clear and expert understanding of the unique needs among our patients, clinicians, investors, and health plan partners, and will drive great value for Monogram Health as we continue to expand our proven in-home care delivery model across the United States."

Mr. McAnaney said, "Throughout my career, I have helped lead some of the nation's most innovative health care companies as they worked to transform the health care landscape. Monogram's value proposition was an immediate draw for me. It is a highly differentiated value-based platform with a nationally deployed team of clinicians who are making a difference every day in the lives of people impacted by CKD and ESKD. I'm proud to support both Monogram's mission and its clinicians as they deliver the highest-quality care and improve clinical outcomes for patients we serve."



NKF Launches Series on Lupus Nephritis and the Kidneys

A new four-part patient-friendly video series has been launched by the National Kidney Foundation (NKF). The animated series is designed to educate and help patients from diverse backgrounds and with varying levels of health literacy understand the link between systemic lupus erythematosus (SLE) and lupus nephritis (LN).

The one-to-two minute videos are available in English and Spanish and seek to help patients understand those conditions and how they relate to one another. Kidney disease is a common complication of SLE; LN is the most common form of kidney involvement in SLE. Patients with SLE should undergo kidney evaluations at regular intervals. Compared with patients with lupus without kidney disease, those with

kidney involvement face increased risks for morbidity and mortality.

Joseph Vassalotti, MD, chief medical officer for the NKF, said in recent press release, "SLE and LN are complicated autoimmune diseases that require many tests and kidney evaluations because a combination of steroids and antimalarial therapies may be prescribed due to the body's immune system actually attacking the body. Your doctor will help you find a treatment plan that works well for your body since everyone's body is unique."

The video series includes episodes on LN and the kidneys, lifestyle and wellness, and treatments. The series is supported by Aurinia, GSK, Kezar Life Sciences, Inc., and Novartis.

Phase 2 Trial Results for Lupus Nephritis Treatment Drug

Results of a post-hoc analysis of results from the NOBILITY phase 2 trial suggest an ability of obinutuzumab (Roche) to treat patients with lupus nephritis (LN). Reduction in the risk of developing adverse renal outcomes was 60.0% and reduction in LN flares was 57.0%. The results also demonstrated an association between administration of obinutuzumab and a reduction in declines in estimated glomerular filtrate rate.

In a press release from GlobalData, **Filippos Maniatis**, health care analyst at GlobalData, said, "The exciting results from the post-hoc analysis of the NOBILITY trial results can have a huge impact on the future of Roche in the field of LN treatment... Roche's approach of wanting to expand obinutuzumab's indications to diseases other than cancer is promising for LN patients.

"Roche's attempt to expand in the LN market may be finally closer to reality after these positive results, allowing the mapping of obinutuzumab in the LN treatment landscape as a strong drug candidate...the clinical trial results hold promise for LN patients make it an exciting pipeline to keep an eye on for the LN space."



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Advocates Attend Capitol Hill Briefing on Kidney Disease

In an effort to draw attention to the growing health crisis surrounding kidney disease and urge support of policies and guidelines that prioritize early detection and intervention, the American Kidney Fund (AKF) joined with leaders in the kidney community at a meeting on Capitol Hill. Late last year, the advocates met for a bipartisan briefing in collaboration with the Congressional Kidney Caucus, calling for the US Preventive Services Task Force (USPSTF) to update its guidance on chronic kidney disease.

In a press release, **LaVarne A. Burton**, president and CEO of AKF, said, “For more than 50 years, AKF has been focused on making meaningful changes to address the crisis in kidney disease and help people live healthier lives, with a particular focus on addressing the stark health disparities that exist.

“We thank Reps. Larry Bucshon and Suzan DelBene for their partnership as cochairs of the Congressional Kidney Caucus and for their efforts on this critically important issue that affects an estimated 37 million Americans.

“We urge the USPSTF to recommend screenings for kidney disease for every patient known to be at higher risk, and specifically populations that have been diagnosed with high blood pressure, diabetes, or cardiovascular disease.”

FDA Approves Treatment for Uncontrolled Hyperphosphatemia

In late fall 2023, the US Food and Drug Administration approved Ardelyx’s XPHOZAH® (tenapanor) as a dialysis add-on therapy in patients with inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy.

According to a press release from Ardelyx, tenapanor is the first new treatment option for this patient population in more than 30 years. The drug blocks the absorption of phosphorus and is a new option for patients with uncontrolled hyperphosphatemia.

Mike Raab, president and CEO of Ardelyx, said, “The approval of XPHOZAH is an important milestone for patients on dialysis, their families, and the nephrology care community, as it represents a new mechanism and new option for patients who, despite treatment with phosphate binders, continue to have elevated phosphorus. It is also a significant accomplishment for everyone at Ardelyx...There is a high level of anticipation and enthusiasm for the launch of XPHOZAH from the kidney community, and our world-class team will enter the marketplace well positioned with a first-in-class product.”

ImmunoFree Names Chief Medical Officer

ImmunoFree, Inc. has named **Ephraim Fuchs, MD**, as chief medical officer. Dr. Fuchs is cofounder of ImmunoFree and professor of oncology and immunology at the Johns Hopkins University School of Medicine.

“Recent clinical trial successes in patients with blood disorders have given us the scientific insight to advance the ImmunoFree tolerance protocol to safely eliminate immunosuppression for transplant recipients, Dr. Fuchs said. “I am excited to help make these medical breakthroughs available to the hundreds of thousands of

organ transplant recipients who may be challenged by the side effects of immunosuppressive medications.”

Garet Hil, cofounder and CEO of ImmunoFree and founder and CEO of the National Kidney Registry, said, “We are thrilled to have Dr. Fuchs join the ImmunoFree executive team as our chief medical officer. His deep knowledge in bone marrow transplant and his vision for the future of this treatment will be instrumental in making this technology available to all living donor and deceased donor transplant recipients.”

NKF’s Innovation Fund Supports ZeitLife™ Innovations, Inc.

The National Kidney Foundation (NKF) has announced it has invested in ZeitLife™ Transplant Innovations, Inc, a medical device company that specializes in advancing technologies to modernize kidney preservation and logistics. The investment was made through the NKF Innovation Fund.

ZeitLife’s efficient business models and routine workflows enables the modernization of the procurement and transplant system. The NKF support will enable the company’s mission to serve as a key player in supplying organs on demand.

Ron Mills, ZeitLife CEO, said, “We’re honored to have NKF’s support and encouragement. Nobody knows more about the tough challenges our customers face and the bold innovations our company offers.”

NKF CEO **Kevin Longino** said, “We are thrilled to invest in ZeitLife’s quest to modernize kidney preservation and logistics. ZeitLife’s dedication to advancing technologies and their commitment to the betterment of kidney transplantation align perfectly with NKF’s core values. With the support of the Innovation Fund, we look forward to accelerating the transformation of kidney preservation and logistics, ultimately improving the lives of countless patients waiting for kidney transplants.” ■

8000

NKR Facilitates Its 8000th Living Donor Kidney Transplant

In early December, the National Kidney Registry (NKR) announced the successful facilitation of its 8000th living kidney donor transplant, a zero-epit mismatch that was performed with a donor from the Mayo Clinic, Rochester, Minnesota, and a recipient at Hartford Hospital, Connecticut. This represents the most transplants facilitated by a single kidney paired donation registry worldwide.

The registry facilitates 22% of all living donor transplants in the United States, an increase from 20% in 2022. The registry’s first living donor kidney transplant was performed in 2008, with more than 1300 performed in 2023. The growth is driven by an increase in microsites that provide free coaching to kidney patients and a website that helps them search for a living donor.

In a press release, **Mike Lollo**, chief strategy officer at NKR, said, “The NKR is thrilled to have reached 8000 living kidney transplants facilitated. This unprecedented benchmark is a testament to the NKR’s commitment to increasing the number and quality of living donor transplants nationwide.”

The NKR 3-year death censored graft failure rate is 14% lower than all other living donor kidney transplants in the United States. The improvements in outcome are associated with a significant increase in low epit mismatch transplants, even as the NKR continues to transplant a higher percentage of the most difficult cases.

COVID-19

Remdesivir Safety in Patients With Renal Dysfunction

Journal of Infection and Chemotherapy.
doi:10.1016/j.jiac.2023.10.026

Concerns about possible toxic effects of accumulated sulfobutylether- β -cyclodextrin (SBECD) on the liver and kidneys have led to limited use of remdesivir for the treatment of COVID-19 in patients with renal dysfunction. To assess the safety of the drug, **Somi Park, MD**, and colleagues examined renal and hepatic function in renally impaired COVID-19 patients who were treated and patients who were not treated with remdesivir.

The retrospective study included 101 adult COVID-19 patients with glomerular filtration rates of <30 mL/min/1.73 m² who were admitted to a tertiary care hospital between November 2020 and March 2022. Of the 101 patients, 64 were treated with remdesivir and 37 did not receive any antiviral agent. The two groups were generally similar in baseline characteristics; the group treated with remdesivir was more likely to be infected with the Omicron variant (79.7% vs 48.6%).

Of the patients who did not initially require dialysis, 18.4% (7/38) in the remdesivir-treated group developed acute kidney injury at days 4 to 6, compared with 51.7% (15/29) in the non-remdesivir group. At days 4 to 6, liver injury worsened in 3.1% (2/64) of those in the remdesivir group compared with 5.4% (2/37) in the non-remdesivir group. There was no significant increase in AKI and liver injury over time in the patients treated with remdesivir. None of the patients treated with remdesivir discontinued treatment due to adverse reactions.

In summary, the authors said, “Concerns regarding the safety of SBECD should not lead to hasty withholding of remdesivir treatment in renally impaired patients.”

ADPKD

Predicting Renal Prognosis in Patients With ADPKD Treated With Tolvaptan

Nephrology Dialysis Transplantation.
doi:10.1093/ndt/gfad232

Patients with autosomal dominant polycystic kidney disease (ADPKD) are commonly treated with tolvaptan, a vasopressin V2 receptor antagonist. **Taro Akihisa, MD**, and colleagues conducted a single-center, prospective, observational cohort study focusing on changes in urinary osmolality (U-Osm) following initiation of tolvaptan to identify an association with the therapeutic response to tolvaptan.

The study cohort included 72 patients with ADPKD who were treated with tolvaptan. The mean value of U-Osm immediately prior to initiation of tolvaptan was 351.8 mosm/kg H₂O, which decreased to 97.6 mosm/kg H₂O in the evening. The decrease in U-Osm was

maintained in the outpatient clinic 1 month later. However, the values of U-Osm showed higher variability compared with those in the first evening of tolvaptan administration.

In multivariable analysis, there were significant correlations between baseline estimated glomerular filtration rate (eGFR), urinary protein, and initial U-Osm drop (change in the evening of the day of initial tolvaptan administration) and subsequent annual change in eGFR.

In conclusion, the researchers said, “U-Osm can be measured easily and rapidly, and U-Osm change within a short time after tolvaptan initiation may be a useful index for the renal prognosis in actual clinical practice.”

Ketogenic Dietary Interventions in Patients With ADPKD

Cell Reports Medicine. doi.org/10.1016/j.xcrm.2023.101283

Results of animal models in autosomal dominant polycystic kidney disease (ADPKD) suggested there were benefits associated with ketogenic dietary interventions. **Sadrija Cukoski, MD**, et al, reported on KETO-ADPKD, an exploratory, randomized, controlled trial designed to provide clinical translation of those findings (NCT04680780).

The study included 66 patients who were randomized to a ketogenic intervention arm (ketogenic diet [KD] or water fasting [WF]), or the control group. Both interventions induce significant ketogenesis on the basis of blood and breath acetone measurements.

In the intervention arm, 95% of those in the KD subgroup and 85% of those in the WF subgroup described the diet as feasible. KD results in significant reductions in body fat and liver volume, and is also associated with statistically nonsignificant reduced kidney volume.

At the end of treatment, the KD group exhibited improved kidney function, while the WF subgroup and the control group exhibited a progressive decline in kidney function, as is typical in ADPKD.

Adverse events (initial flu-like symptoms associated with KD) were largely mild and transient.

CHRONIC KIDNEY DISEASE

Predictive Tools for Risk of Kidney Failure in Patients With CKD

Current Opinion in Nephrology and Hypertension.
doi:10.1097/MNH.0000000000000950

In managing patients with chronic kidney disease (CKD) in routine clinical practice, informing time-sensitive decisions such as dialysis access planning or counseling patients on kidney transplant options calls for the integration of risk prediction. Several prognostic models to provide individualized evaluation of the risk of kidney failure in patients with CKD have been developed and validated.

Andrea Spasiano, MD, and colleagues reviewed the current evidence on existing

models and evaluated the various advantages and disadvantages of those tools.

Following the introduction of the Kidney Failure Risk Equation in 2011 by Tangri et al, the nephrological and scientific community has focused on enhancing available algorithms and finding new prognostic equations. Current models demonstrate high discrimination in predicting kidney failure; however, there are some unresolved questions.

“Accurately informing patients of their prognosis can result in tailored therapy with important clinical and psychological implications,” the authors said. “Over the last 15 years, the number of disease-modifying therapeutic options has considerably increased, providing possibilities to not only prevent kidney failure onset in patients with advanced CKD, but also delay progression from early stages in at-risk individuals.”

DIALYSIS

Increased Mortality Risk in Hemodialysis Patients

Nephrology Dialysis Transplantation.
2023;38(10):2248-2256

Among patients receiving maintenance dialysis, the 5-year mortality rate is more than 50%. Acute and chronic disturbances in salt and fluid homeostasis contribute to poor survival rate and are individual risk factors for mortality. According to **Julie Pinter, MD**, and colleagues, there are few data available on the interaction between those factors and mortality.

The researchers utilized the European Clinical Database 5 in a retrospective cohort analysis to examine the association between transient hypo- and hypernatremia, fluid status, and mortality risk among 72,163 hemodialysis patients in 25 countries. Patients on maintenance hemodialysis with at least one valid measurement of bioimpedance spectroscopy were followed until death or administrative censoring from January 1, 2010, to December 4, 2019.

Fluid overload was defined as >2.5 L above normal fluid status, and fluid depletion was defined as -1.1 L below normal status. When fluid status was normal, the mortality risk of hyponatremia (plasma sodium <135 mmol/L) was slightly increased (hazard ratio [HR], 1.26; 95% CI, 1.18-1.35). The risk increased by half when patients were fluid depleted (HR, 1.56; 95% CI, 1.27-1.93), and accelerated during fluid overload (HR, 1.97; 95% CI, 1.82-2.12).

In summary, the authors said, “Plasma sodium and fluid status act independently as risk factors on mortality. Patient surveillance of fluid status is especially important in the high-risk subpopulation of patients with hyponatremia. Prospective patient-level studies should examine the effects of chronic hypo- and hypernatremia, risk determinants, and their outcome risk.”

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HYPERKALEMIA

Managing Hyperkalemia With Sodium Zirconium Cyclosilicate

Journal of Nephrology. doi.org/10.1007/s40620-0223-01743-4

Patients with hyperkalemia may be treated with the potassium binder sodium zirconium cyclosilicate (SZC), a nonabsorbed nonpolymer zirconium silicate. Results of previous studies have shown that patients with hyperkalemia treated with SCZ have a higher rate of continuation of renin-angiotensin-aldosterone system (RAAS) inhibitors. However, according to **Wakana Kimura, MD**, and colleagues, there have been no studies on the effect of SCZ on continuation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) in patients with hyperkalemia, compared with that of calcium polystyrene sulfonate (CPS).

The researchers conducted a single-center, retrospective observational study that enrolled patients on ACE inhibitors or ARBs who were newly prescribed SCZ or CPS at a tertiary referral hospital between August 2020 and April 2022. The primary outcome measure was prescription for a ACE inhibitor or ARB 3 months following initiation of a potassium binder.

The total cohort included 174 patients on ACE inhibitor or ARB who were newly administered SCZ (n=62) or CPS (n=112). At 3 months following initiation of a potassium binder, the prescription rate of an ACE inhibitor or ARB was significantly higher in the SCZ group than in the CPS group (89% vs 72%, respectively).

In multivariable logistic regression models, there was an independent association between SCZ and the primary outcome of ACE inhibitor or ARB prescription (odds ratio, 2.66; 95% CI, 1.05-7.43). There was also a significant association between SCZ and the primary outcome in the propensity score-matched comparison.

In conclusion, the authors said, “Our study suggests that administering SCZ to patients with hyperkalemia allows for a higher continuation rate of ACE inhibitors or ARBs than CPS. These findings suggest that SCZ had potential benefits for patients with chronic kidney disease receiving RAAS inhibitors.”

IGA NEPHROPATHY

The IINN-PT for Predicting Risk of Progression in IgA Nephropathy

Nephrology Dialysis Transplantation. 2023;38(1):2257-2265

Gregoire Bon, MD, and colleagues conducted an analysis to validate the tool developed by the International IgA Nephropathy Network (IINN-PT) for predicting the risk of end-stage renal disease (ESRD) or a 50% decline in estimated glomerular filtration rate (eGFR) in a cohort of patients with biopsy-proven immunoglobulin A nephropathy (IgAN).

The predicted survival of the cohort was computed with IINN-PT models with or without ethnicity. The primary outcome of interest was the occurrence of either ESRD or a 50% decline in eGFR. C-statistics, discrimination, and calibration analysis were used to evaluate the performance of the models.

The cohort included 473 patients with biopsy-proven IgAN. Median follow-up was 12.4 years. Models with and without ethnicity showed areas under the curve of 0.817 (95% CI, 0.765-0.869) and 0.833 (95% CI, 0.791-0.875) and R2D of 0.28 and 0.29, respectively, and an excellent discrimination of groups of increasing predicted risk ($P < .001$).

The calibration analysis was good for both models up to 15 years after diagnosis. The model without ethnicity exhibited a mathematical issue of survival function after 15 years.

“The IINN-PT provided good performances even after 10 years post-biopsy as shown by our study based on a cohort with a longer follow-up than previous cohorts (12.4 vs <6 years),” the authors said. “The model without ethnicity exhibited better performances up to 15 years but became aberrant beyond this point due to a mathematical issue affecting the survival function. Our study sheds light on the usefulness of integrating ethnicity as a covariable for prediction of IgAN course.”

TRANSPLANTATION

Safety of Live Vaccines in Pediatric Solid Organ Transplant Recipients

JAMA Network Open. doi.10.1001/jamanetworkopen.2023.37602

Due to concern for infection in pediatric solid organ transplant recipients, live vaccines (measles-mumps-rubella [MMR] and varicella-zoster virus [VZV]) are not recommended for that patient population. However, the increasing rates of measles, mumps, and varicella put susceptible immunocompromised children at risk for those life-threatening conditions.

Amy G. Feldman, MD, MSCS, and colleagues conducted a cohort study to assess the safety and immunogenicity of live vaccines in pediatric liver and kidney transplant recipients. The study included pediatric recipients of liver and kidney transplants who had not completed their primary MMR and VZV vaccine series and/or who displayed nonprotective serum antibody levels at enrollment between January 1, 2002, and February 28, 2023.

The study exposure was receipt of a post-transplant live vaccine. Study participants received one to three doses of MMR vaccine and/or one to three doses of VZV vaccine. Safety data were collected following each vaccination, and antibody levels were obtained at 0 to 3 months and at 1 year following vaccination.

The cohort included 282 children who received a solid organ transplant at one of 18 centers. Median time from transplant to enrollment was 6.3 years. Median age at the time of the first transplant was 8.9 years. At the time of vaccination, 73% of the cohort (202/275) were receiving low-level monotherapy immunosuppression.

Following vaccination, the majority of the participants developed protective antibodies following vaccination: varicella, 72% (107/149); measles, 86% (130/152); mumps, 83% (100/120); and rubella, 99% (124/125). At 1 year following vaccination, the majority of those who initially mounted protective antibodies maintained the protection.

Five children developed clinical varicella; all resolved within 1 week. There were no cases of measles or rubella, and no episodes of graft rejection within 1 month of vaccination. There was no association between antibody response and immunosuppression level at the time of vaccination.

In conclusion, the researchers said, “The findings suggest that live vaccinations may be safe and immunogenic after solid organ transplant in select pediatric recipients and can offer protection against circulating measles, mumps, and varicella.” ■





Sarah Tolson

The Hidden Costs of “Economical” Billing Solutions



In today's evolving renal health care landscape, especially in the aftermath of COVID-19, financial prudence when running a practice or dialysis program has become paramount. With operational costs skyrocketing and reimbursements from Medicare and other insurers struggling to keep pace, it is imperative for these health care entities to tighten their belts and avoid unnecessary expenditures to stay afloat. However, the choice of a billing solution, often made under the guise of cost savings, requires a thoughtful approach.

During a recent interaction at a health care conference, I encountered a nephrology provider engaged with a billing service that exemplified cost-cutting pitfalls. The provider was initially drawn to the service for its seemingly low fees, yet these fees only covered basic claim filing. Any additional billing services demanded extra charges, placing the provider in a dilemma: either hire additional staff for comprehensive revenue cycle management or contract yet another company for these services. This approach, appearing cost-effective on the surface, ironically led to higher overall expenses compared with billing companies offering full-service revenue cycle management.

This scenario highlights an important consideration for anyone considering an inexpensive billing solution: lower-cost billing services might not have the same level of expertise or resources as more expensive options. This can lead to inaccuracies in billing and claim processing, resulting in denied or underpaid claims. Efficient and accurate claim processing is critical for maintaining steady cash flow and reducing the time and resources spent on reworking claims. Likewise, billing services that charge lower fees often do so by minimizing the effort they put into each account. This might mean less follow-up on unpaid claims or less aggressive pursuit of denials, adversely affecting your practice's collections.

Opting for more affordable billing services may also come with a trade-off in the form of reduced customer support. This limitation can become a significant source of frustration, particularly when unexpected issues crop up. Having access to knowledgeable and responsive customer service is crucial for resolving issues promptly. If billing errors occur or if patients receive incorrect statements, it can lead to dissatisfaction and complaints, potentially harming the reputation of your practice.

Medical billing services vary widely in their pricing structures. Some charge per claim or treatment, seemingly less expensive than companies charging a percentage

of collections. However, this model can lead to reduced incentive for diligent collection efforts, as their revenue isn't directly tied to the success of collections.

A trend observed in the electronic health records (EHR) domain is the integration of billing modules. While EHR firms boast benefits like seamless integration and built-in data checks, their primary expertise remains in technology, not billing. This technological focus often results in billing modules that are cumbersome and inefficient, consuming more time per claim, ultimately reducing the capacity to manage the broader spectrum of outstanding claims or conduct proactive financial analyses.

Moreover, these EHR-integrated billing solutions may falter in addressing the unique billing intricacies specific to nephrology, which can differ significantly from general physician office billing requirements. Many EHR billing combinations, while adept for basic billing tasks, may struggle with the specialized demands of renal care.

To safeguard your nephrology practice's financial interests, due diligence in selecting a billing partner is essential. Engage with existing clients of your prospective billing services to gain insights into their performance and any unforeseen costs. Consider employing an external auditor to annually review your billing, ensuring both efficacy and compliance.

In conclusion, while fiscal efficiency is undeniably crucial for nephrology practices and dialysis programs, the selection of a billing partner should be guided by comprehensive service evaluation rather than mere cost considerations. The allure of “cheap” billing solutions can be misleading, potentially leading to higher costs and reduced revenue. Practices must critically assess the full spectrum of services offered, understanding that slightly higher costs might translate into increased revenue and efficiency. By adopting this holistic view, nephrology practices can ensure their financial stability while continuing to deliver high-quality patient care in an increasingly complex health care environment. ■

Sarah Tolson is the director of operations for Sceptre Management Solutions, Inc., a company specializing in billing for outpatient ESRD dialysis programs, nephrology practices, and interventional nephrology. Your questions are welcome, and she can be reached at stolson@sceptremanagement.com, 801.775.8010, or via Sceptre's website, www.sceptremanagement.com.

Coming soon...



Watch your mailbox for the **May-June Issue** of *Nephrology Times* for coverage of selected posters and presentations from the National Kidney Foundation's

SPRING CLINICAL MEETINGS 2024