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Practical News, Trends, and Analysis

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Parathyroid Hormone Testing in Veterans with Kidney Stones and Hypercalcemia

Approximately one in 11 persons in the United States has been affected by kidney stones; among those who have experienced a kidney stone, the likelihood of recurrence is high, with up to 50% developing a recurrent stone within 10 years of the first episode. Hyperparathyroidism (PHPT) is evident in approximately 3% to 5% of patients with kidney stones and screening for PHPT is a strategy aimed at reducing the recurrence rate. Patients with kidney stones and PHPT present with hypercalcemia and hypercalciuria, raising the risk for stones by increasing urine supersaturation for calcium oxalate or phosphate.

Guidelines from the American Urological Association and the European Association of Urology call for measurement of serum calcium in patients with kidney stones, followed by the serum parathyroid level (PTH) if there is clinical suspicion for PHPT. It is unknown whether patients with kidney stones receive those recommended screenings in clinical practice. Results of a previous study suggested that fewer than one in four veterans with persistent hypercalcemia treated in the Veterans Health Administration (VHA) were screened for PHPT.

Calyani Ganesan, MD, MS, and colleagues conducted a cohort study to examine the prevalence of PTH testing in veterans with kidney stones and

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Cardiovascular Mortality Trends in Patients with Childhood ESKD

Patients with childhood end-stage kidney disease (ESKD) face a significantly diminished life expectancy compared with the general pediatric population. Among young adults treated with dialysis, mortality rates are more than 100-fold higher than their age-matched counterparts in the general population. The leading cause of death in children and adults treated with dialysis is

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Trends in Racial/Ethnic Disparities in Predialysis Nephrology Care

Patients who receive nephrology care prior to initiation of treatment for end-stage kidney disease (ESKD) experience improved survival as well as other key outcomes such as reduced hospitalizations and complications, increased quality of life, better preparation for dialysis, and greater likelihood of receiving a kidney transplant. In most cases, chronic kidney disease (CKD) is initially detected by primary care physicians who then have an important role in the decision regarding referral to a nephrologist.

Guidelines recommend referral to nephrology care for patients with an estimated glomerular filtration rate (eGFR) of >30 mL/min/1.73 m^2, severely increased albuminuria, rapid decline in eGFR, hematuria, and/or uncontrolled complications of CKD, including hypertension that requires four or more antihypertensive agents, anemia, or electrolyte abnormalities. However, according to **Tanjala S. Purnell, PhD, MPH,** and colleagues, late referral to nephrology care is common; recent reports suggest that only approximately one-third of patients with CKD receive nephrology care at least 12 months prior to initiation of ESKD therapy.

Patients with CKD who are part of a demographic group such as young adults and racial/ethnic minorities are known to experience more rapid decline in kidney function; clinicians are advised to refer those patients to a nephrologist. However, results of previous studies suggest racial/ethnic disparities in timely receipt of nephrology care.

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Print-only Content

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A New Treatment for Lupus Nephritis

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Kidney disease occurs in approximately 60% of patients with systemic lupus erythematosus (SLE). Even with treatment, between 10% and 20% progress to end-stage renal disease.[1,2] Treatment of lupus nephritis is divided into induction and maintenance phases. In induction, high doses of a steroid, either as methyl prednisone given as intravenous pulse doses or oral high dose prednisone, are administered accompanied with a cytotoxic immunosuppressive agent (usually mycophenalate mofetil [MMF]). In the maintenance phase, in addition to oral prednisone now at a low dose, cytotoxic therapy is administered (usually MMF or azathioprine). Despite treatment patients continue to have exacerbations of disease or become refractory to treatment.

A multifactorial etiology for lupus nephritis has been supported by numerous studies. All of the immune factors have been shown to play a role in initial inflammation characteristic of active nephritis. Therapies targeting T cells, B cells, cytokines and complement have been proposed, and some have shown promise.

In addition to being considered in the induction phase of lupus nephritis, it is very likely that belimumab will be considered for treating refractory disease.

Inhibiting B cells disables one part of the immune system in SLE. A key molecule critical to the activation of B cells is called B lymphocyte stimulator (BLyS), (B cell-activating factor [BAFF]). BLyS is a costimulator for B-cell survival and function (expressed by a wide variety of immune cells, including monocytes, macrophages, and dendritic cells).[3] Belimumab is a recombinant monoclonal antibody directed against BLyS that decreases B-cell survival and production of autoantibodies. Several studies have demonstrated the efficacy and safety for belimumab in SLE[4,5] and the drug was approved by the US FDA March 9, 2011, as the first targeted therapy for the treatment of SLE (as an add-on to standard therapy).[6] However, evidence has been lacking for its use in treating lupus nephritis.

A recent paper published by Furie and colleagues in the *New England Journal of Medicine*[7] tested the hypothesis that treating patients with lupus nephritis with belimumab in addition to standard therapy improves outcomes.

Furie and colleagues conducted a double-blind, placebo-controlled, randomized multicenter trial. Key eligibility criteria in the study were that patients had to have active disease: proteinuria (urine protein to creatinine ration [UPCR] ≥1), and a kidney biopsy showing either class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with or without coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis.

The study enrolled 448 patients who were then assigned to either belimumab in addition to standard therapy or placebo with standard therapy. Follow-up was 2 years. The primary end point was renal response, defined as a UPCR of ≤0.7, or an estimated glomerular filtration rate (eGFR) that was no worse than 20% below the pre-flare value or ≤60 mL/min/1.73 m^2, and no use of rescue therapy for treatment failure. In addition, there were several secondary outcomes, including a complete renal response that was defined as UPCR ≤0.5, an eGFR no worse than 10% below the pre-flare value or ≥90 mL/min/ 1.73 m^2, and no rescue therapy.

The key results from the Furie study were impressive: More patients in the belimumab group than in the placebo group met the primary end point of a positive renal response (43% vs 32%; odds ratio [OR], 1.6; 95% confidence interval [CI], 1.0 to 2.3; *P*=.03), and a complete renal response (30% vs 20%; OR, 1.7; 95% CI, 1.1 to 2.7; *P*=.02). The risk of a renal-related event or death was lower among patients who received belimumab than among those who received placebo (hazard ratio, 0.51; 95% CI, 0.34 to 0.77; *P*=.001). Belimumab's safety profile was also reassuring.

Currently, belimumab is approved for treating patients with SLE but not for lupus nephritis. It is likely that the label for the drug will be modified given the evidence from this trial. In addition to being considered in the induction phase of lupus nephritis, it is very likely that belimumab will be considered for treating refractory disease.

How should belimumab be used (once approved by the FDA)?[3] Belimumab is administered as intravenous infusion, and dosed at 10 mg/kg belimumab over 1 hour, with a gap of 2 weeks for the first three doses and then repeated every 4 weeks.[3] It is generally well tolerated, although infusion reactions have been reported. Adverse events reported include neutropenia, thrombocytopenia, infections, depression, headache, rash, diarrhea, and nausea arthralgia. In the Furie study, belimumab was administered concomitantly with steroids, MMF, cyclophosphamide and azathioprine. However, belimumab's use in children, nursing mothers, and pregnancy has not been adequately studied.

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hypercalcemia. The researchers also sought to identify the demographic, geographic, and clinical characteristics of veterans who were more or less likely to receive PTH testing. The study was designed to test the hypothesis that the frequency of PTH testing remains low despite current clinical practice guidelines and that a wide variation in screening practices is not adequately explained by patient-specific or facility-level factors. Results of the study were reported online in *JAMA Surgery* [doi:10.1001/jamasurg.2020.2423].

The study utilized VHA health records to identify patients with kidney stones and hypercalcemia who received care in one of the 130 VHA facilities across the United States from January 1, 2008, through December 31, 2013. Patients with kidney stones were those with one or more inpatient *International Classification of Diseases, Ninth Revision (ICD-9)* codes for kidney or ureteral stones, two or more outpatient ICD-9 codes for kidney or ureteral stones, or one or more *Current Procedural Terminology* codes for kidney or ureteral stone procedures within 1 year. Exclusion criteria included previous screening for PHPT, defined as those with a PTH level measurement between 6 and 30 months prior to the index stone diagnosis.

Data collection occurred from January 1, 2006, to December 31, 2014. Data analysis occurred from June 1, 2009, to January 31, 2020. The primary outcomes of interest were the proportion of patients with a serum PTH level measurement and the proportion of patients with biochemical evidence of PHPT who underwent parathyroidectomy.

A total of 157,539 unique veterans were diagnosed with kidney stones during the study period. Of those, 139,115 had a serum calcium determination within 6 months of their index stone diagnosis, and 7381 had been previously screened with a serum PTH level measurement and were excluded. Following application of exclusion criteria, the final cohort comprised 7561 patients with kidney stones and measured hypercalcemia (n=3938) or albumin-corrected hypercalcemia (n=3623). Mean age of the final cohort was 64.3 years, 94.4% (n=7139) were men, 5.6% (n=422) were women, and 75.0% (n=5673) were white. Patients with hypercalcemia compared with those with normocalcemia (n=124,173) were more likely to have diabetes (39.8% vs 29.5%), impaired kidney function, defined as estimated glomerular filtration rate <45 mL/min/1.73 m^2 (36.1% vs 15.1%), osteoporosis (4.4% vs 2.1%), and fractures (7.1% vs 4.2%).

Of the 7561 patients with kidney stones and hypercalcemia, 24.8% (n=1873) completed a serum PTH level measurement around the time of the initial stone diagnosis. In the 3938 patients with measured hypercalcemia, 34.8% (n=1369) completed a serum PHT level measurement; only 13.09% (n=504/3623) of the patients with albumin-corrected hypercalcemia did so. Of the 1873 veterans with PTH testing, 38.3% (n=717) had an elevated PTH level consistent with biochemical PHPT.

Results of multivariable logistic regression models demonstrated that the odds of PTH testing in patients with kidney stones and hypercalcemia were lower with older age (odds ratio [OR], 0.95 per decade; 95% confidence interval [CI], 0.90-1.00) and among patients with a history of metastatic cancer (OR, 0.63; 95% CI, 0.49-0.81). Patients with albumin-corrected hypercalcemia were less likely to complete PTH testing compared with patients with measured hypercalcemia (OR, 0.32; 95% CI, 0.28-0.37).

The odds of PTH testing were higher for patients who visited either a nephrologist or a urologist (OR, 1.56; 95% CI, 1.35-1.81), and much higher for those who visited both a nephrologist and a urologist (OR, 6.57; 95% CI, 5.33-8.10) compared with patients who did not visit a stone specialty clinic during the observation period.

Across the 130 VHA facilities in the United States, the prevalence of PHT testing among the veterans with kidney stones varied between 4.0% and 57.0%. The study researchers examined the composite complexity score assigned to each facility and found no association with PTH testing rate for each facility. None of the individual facility-level variables of the complexity score were associated with PTH testing across the 130 facilities. In a comparison of facilities in the top quartile versus the bottom quartile of the PTH testing, there was an association between PTH testing and the presence of stone specialty care at each facility. There was no association between PTH testing and the mean number of parathyroidectomies performed at each facility.

Study limitations cited by the authors included the high proportion of male participants, using a single definition of PHPT, and the inability to capture medical care for veterans with kidney stones who received care outside the VHA system.

In conclusion, the researchers said, "In this cohort study, a generally low rate of PTH testing was found in veterans with kidney stones and hypercalcemia, and extensive variation in PTH testing rates was found across VHA facilities in the United States. More awareness of the level or frequency of elevated serum calcium concentration may be associated with higher rates of PTH testing in patients with kidney stones. Improved screening for PHPT could increase the rates of detection and treatment of PHPT and decrease stone recurrence associated with missed or untreated PHPT." ■

TAKEAWAY POINTS

- Results of a study designed to examine the prevalence of parathyroid hormone (PTH) testing in US veterans with kidney stones and hypercalcemia and to identify the demographic, geographic, and clinical characteristics of those more or less likely to receive testing.
- The proportion of patients with kidney stones and hypercalcemia was 24.8% (1873/7561); testing rates varied widely across the 130 Veterans Health Administration facilities (range, 4% to 57%).
- Of the 717 patients with biochemical evidence of primary hyperparathyroidism, 26.4% (n=189) underwent parathyroidectomy within 2 years of a stone diagnosis.

Cardiovascular Mortality Trends

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cardiovascular disease, particularly sudden cardiac death (SCD).

There has been improvement in long-term mortality risk among children treated with dialysis in the past two decades; however, according to **Elaine Ku, MD, MAS,** and colleagues, the reasons for the improvements are unclear. Possible explanations include improvements in cardiovascular risk factor modification or infection prevention over time in that population.

The researchers conducted a retrospective cohort study to compare trends over time in mortality from CKD-related causes of death among children and adults <30 years of age who initiated dialysis between 1995 and 2015. Changes in CKD-related mortality risk were compared with changes in infection-related causes of death. The researchers also sought to compare risk factors for CVD-related causes of death in patients who initiated dialysis as children versus as young adults. Results of the study were reported in *JAMA Network Open* [2020;3(9):e2016197. doi.10.1011/jamanetworkopen.2020.16197].

The primary outcome of interest was cardiovascular cause-specific mortality. Cause-of-death data were abstracted from the Centers for Medicare & Medicaid Services death notification form that is submitted to the United States Renal Data System.

Trends in risk of different cardiovascular-related deaths were determined using Fine-Gray models. Models were adjusted for age, sex, race, neighborhood income, cause of end-stage kidney disease, insurance type, and comorbidities. Analyses were performed separately for children (age <18 years) and young adults (between ages 18 and 30 years).

The study included 80,189 children and young adults. Median age was 24 years, 45.2% (n=36,259) were women and girls, 36.8% (n=29,508) were Black, and 19.3% (n=15,516) were Hispanic White. Median follow-up was 14.3 years and the most common cause of ESKD was glomerulonephritis (37.4%). The two most common causes of death were cardiovascular disease (40.2%; n=6505/16,179) and infection-related causes (14.4%; n=2332).

Compared with the overall cohort, those who died were older at the time of initiation of dialysis (mean age, 24.3 years vs 22.5 years) and more likely to be women and girls (51.5%, n=8328) or Black (52.3%; n=8458). Patients who died were more likely to have diabetes and less likely to have glomerulonephritis as the cause of ESKD (diabetes: 4562 [28.2%] vs 11,940 [14.9%]; glomerulonephritis: 4493 [27.8%] vs 30,003 [37.4%]). In those who died, the presence of diabetes or heart failure at the time of initiation of dialysis was more common than in the overall cohort (diabetes: 5313 [32.8%] vs 14,310 [17.8%]; heart failure: 2055 [12.7%] vs 5331 [6.6%]).

Across the sequential 5-year intervals included in the analysis, age at the time of initiation of dialysis remained similar. However, over time a smaller proportion of patients initiating dialysis were Black. Generally, the prevalence of comorbid conditions at time of dialysis initiation such as heart failure or stroke were low at time of dialysis initiation and, with the exception of an increased prevalence of hypertension, did not increase over time. There was a decrease in glomerulonephritis as a cause of ESKD over time.

The overall death rate associated with cardiovascular disease was higher among patients who initiated dialysis as young adults compared with those who initiated dialysis as children. The rate of death attributed to infection-related causes was similar in the two groups. Overall, 40.2% of deaths were from causes related to cardiovascular disease (n=6506 of 16,179 patients).

Following adjustment, the rate of death related to cardiovascular disease was stable. After 2006 (vs 1995), the rate became statistically significantly lower in those initiating dialysis as children (subhazard ratio [SHR], 0.74; 95% confidence interval [CI], 0.55-1.00) or young adults (SHR, 0.90; 95% CI, 0.83-0.98).

Among deaths attributed to cardiovascular disease, SCD was 1.5 (95% CI, 1.4-1.5) per 100 person-years and up to ten times higher for children (0.9 [95% CI, 0.8-1.0] per 100 person-years) and young adults (1.5 [95% CI, 1.5-1.6] per 100 person-years compared with heart failure as the attributed cause of death (0.1 [95% CI, 0.1-0.2] per 100 person-years). Comparing 2015 to 1995, the risk for SCD improved steadily for all age groups, but to a greater degree in children.

In 2010, the risk for stroke became statistically significantly lower versus 1995 for both children (SHR, 0.40; 95% CI, 0.18-0.88) and young adults (SHR, 0.76; 95% CI, 0.59-0.99).

The authors cited some limitations to the study findings, including missing data on the cause of death in 8% of patients as well as the possibility of miscalculation of cause of death. There was also a lack of more granular data that may be needed to determine the exact reasons for changes in temporal trends in mortality over time, or changes in treatment of cardiovascular risk factors.

In conclusion, the researchers said, "Although mortality rates have improved overall in a cohort of children and young adults starting dialysis during the last 2 decades, for some outcomes risk actually increased initially only to then improve more recently, and trends varied depending on whether individuals started dialysis as children versus young adults. Given that cardiovascular disease remains the most common cause of death in this population, strategies to further improve the cardiovascular risk profile in this young population are needed to enhance survival, and modification of nontraditional cardiovascular risk factors may be needed to ensure continued improvements in outcomes for young populations starting on dialysis." ■

TAKEAWAY POINTS

- Researchers conducted a retrospective cohort study to examine the temporal trends in attributed causes of death, with an emphasis on cardiovascular-related causes, in young populations with end-stage kidney disease.
- Over the 20-year period examined in the study, the risk of death related to cardiovascular disease improved for both children and young adults.
- The improvement in the risk of sudden cardiac death improved more for children than for young adults; improvements in mortality related to stroke were slower and less pronounced.

Trends in Racial/Ethnic Disparities

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The Healthy People 2020 initiative (HP2020), coordinated by the US Department of Health and Human Services, includes 10-year targets for specific outcomes. The HP2020 CKD-specific objectives include increasing the proportion of CKD patients receiving care from a nephrologist at least 12 months prior to initiation of renal replacement therapy. One in four overarching HP2020 goals is to eliminate healthcare disparities.

Dr. Purnell et al. conducted a cross-sectional study designed to examine national trends in racial/ethnic disparities in the receipt of nephrology care at least 12 months prior to initiation of dialysis in the United States from 2005 to 2015. Results of the study were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2020.15003].

The study utilized data from the US Renal Data System, a national data system that collects, analyzes, and distributes information on ESKD in the United States. The study examined data of 1,000,390 adults who initiated maintenance dialysis from January 1, 2005, to December 31, 2015. National trends in racial/ethnic disparities in receipt of predialysis nephrology care were examined using multivariable logistic regression models with adjustments for potential confounders. The main outcome of interest was receipt of at least 12 months of predialysis nephrology care as determined by clinician-based documentation on the End Stage Renal Disease Medical Evidence Report Form CMS 2728.

Of the 1,000,390 eligible patients, 54.6% (n=546,132) were White, 27.8% (n=278,317) were Black, 14.0% (n=139,854) were Hispanic, and 3.6% (n=36,087) were Asian. Of the total cohort, 31.1% (n=310,743) received at least 12 months of nephrology care prior to initiation of dialysis. Mean age remained relatively consistent over the course of the study. Body mass index was greater in the 2005-2007 cohort versus the 2014-2015 cohort, and the prevalence of male patients was greater in the 2005-2007 cohort versus the 2014-2105 cohort. Compared with Asian and White patients, Black and Hispanic patients were younger and less likely to have private insurance. Among Black and Hispanic patients, the prevalence of ESKD attributed to hypertension or diabetes was highest; the prevalence of ESKD attributed to glomerular diseases or other causes was highest among white and Asian patients.

The unadjusted proportion of adults who received at least 12 months of predialysis nephrology care increased from the 2005 to 2007 cohort to the 2014 to 2015 cohorts by 30.1% to 39.5% among White adults, by 24.5% to 32.5% among Black adults, by 21.2% to 28.3% among Hispanic adults, and by 26.1% to 37.1% among Asian adults.

However, there was no improvement in the magnitude of racial/ethnic disparities during the study period. In the 2005 to 2007 cohort compared with receipt of at least 12 months of predialysis nephrology care among White adults, the adjusted odds ratio (aOR) was 0.82 (95% confidence interval [CI], 0.80-0.84) among Black adults, 0.67 (95% CI, 0.65-0.69) among Hispanic adults, and 0.84 (95% CI, 0.80-0.89) among Asian adults. In the 2014 to 2015 cohort, the aOR was 0.76 (95% CI, 0.74-0.78) among Black adults, 0.61 (95% CI, 0.60-0.63) among Hispanic adults, and 0.90 (95% CI, 0.86-0.95) among Asian adults.

Results of exploratory mediation analysis from incremental multivariable logistic regression models suggested adjustments for differences in health insurance type were more strongly associated with slight attenuation of racial/ethnic disparities in receipt of nephrology care at least 12 months prior to initiation of dialysis among Black patients (aORs, 0.94 [95% CI, 0.93-0.94] in the 2005-2007 cohort vs 0.93 [95% CI, 0.93-0.94] in the 2008-2010 and 2011-2013 cohorts) and Hispanic patients (aORs, 0.89 [95% CI, 0.88-0.89] to 0.88 [95% CI, 0.88-0.89] for the 2005-2007 vs 2014-2015 cohorts) than adjustments for comorbid medical conditions, type of dialysis modality, or type of vascular access. However, there was no statistically significant improvement in the magnitude of racial/ethnic disparities even in fully adjusted models.

Limitations to the study cited by the authors included the primary study outcome being subject to the accuracy of physician-provided retrospective data, the inability to further subcategorize the racial/ethnic categories available in the USRDS registry, and the inability to account for individual- or household-level patient income.

In conclusion, the researchers said, "In this national study of more than 1 million US adults with ESKD, racial and ethnic disparities in receipt of at least 12 months of predialysis nephrology care did not substantially improve from 2005 to 2015. These findings suggest that national strategies to address disparities in predialysis healthcare are needed." ■

TAKEAWAY POINTS

- Patients with chronic kidney disease who receive nephrology care at least 12 months prior to initiation of dialysis experience improved survival as well as other key outcomes.
- Researchers conducted a cross-sectional national registry study to examine national trends in racial/ethnic disparities in receipt of predialysis nephrology care at least 12 months prior to dialysis initiation.
- Using data from the US Renal Data System, the study findings suggest there was no statistically significant improvement in racial and ethnic disparities in predialysis care from 2005 to 2015.

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS

UNOS Safety Net in Kidney-Liver Transplant Access: Are there Racial Disparities?

The United Network for Organ Sharing (UNOS) implemented guidelines regarding simultaneous liver-kidney transplant in 2017. The guidelines included medical eligibility criteria as well as a safety net that provided prioritization on the kidney transplant waiting list for patients with early and persistent renal failure following liver transplant.

According to **C. Jay** and colleagues, because living donor rates are lower among African American patients, access to kidney after liver transplant is key to understanding the efficacy of the safety net. Due to limited data evaluating racial disparities in access following implementation of the safety net, the researchers conducted an analysis to compare early kidney after liver transplant and simultaneous liver-kidney transplant in a post-MELD (model for end-stage liver disease score) cohort. Results of the analysis were reported during a poster session at the virtual American Transplant Congress 2020 in a poster titled *Comparing Early Kidney after Liver Transplant (KALT) and Simultaneous Liver-Kidney Transplant (SLK): Evaluating Racial Disparities. Will Everyone Have the Same "Safety Net"?*

UNOS national data were used to compare adult recipients of simultaneous liver-kidney transplant and early kidney after liver transplant patients who underwent whole deceased donor liver transplant from 2002 to 2008. Early kidney after liver transplant was defined as 60 to 365 days between liver transplant and subsequent kidney transplant reflecting safety net criteria. Patient survival following liver transplant was compared according to race including adjustment for recipient age, sex, body mass index, MELD score, medical condition at transplant, prior liver transplant, diabetes, renal function, and kidney donor KDPI (kidney donor profile index) score.

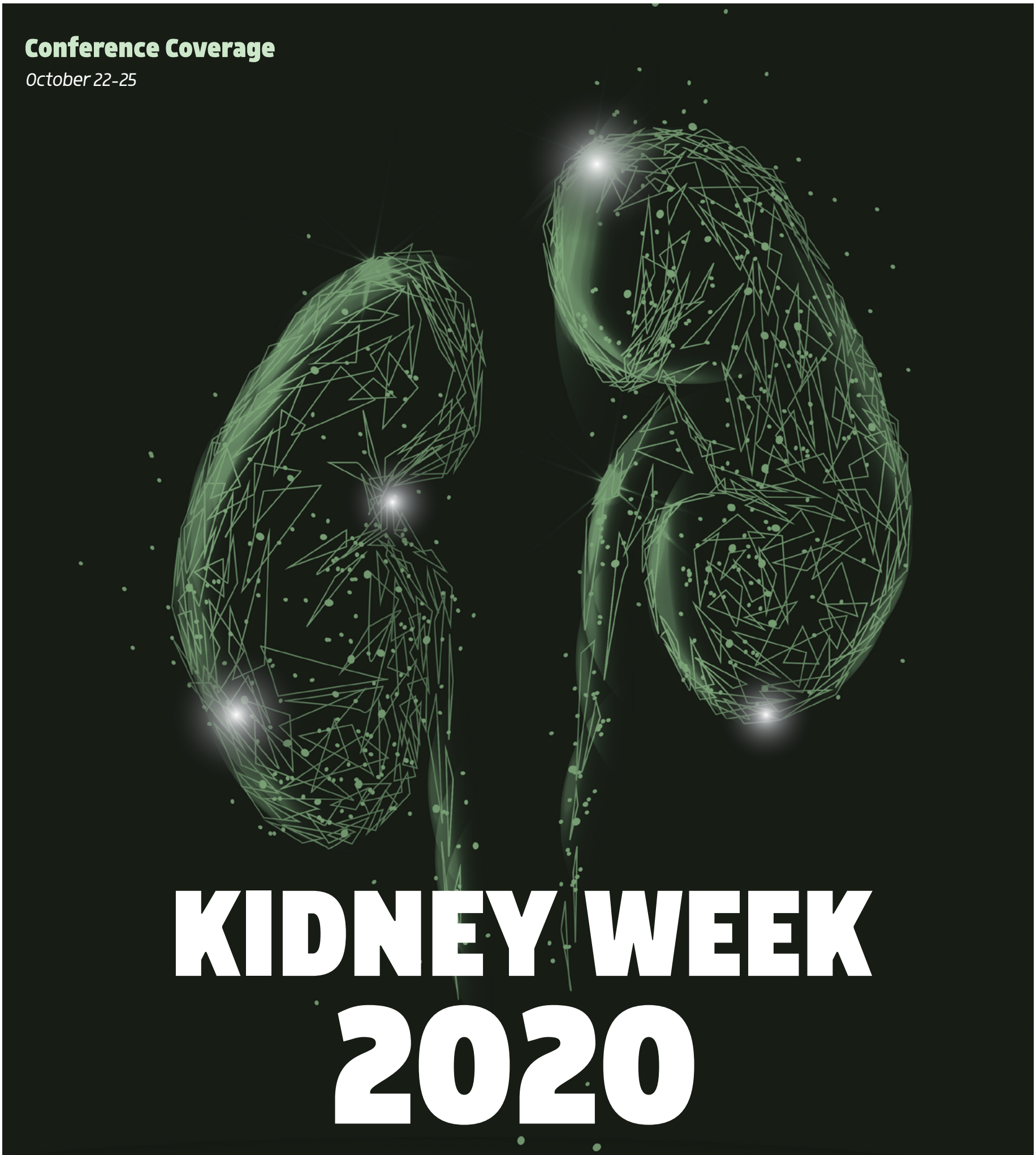
The researchers identified 6774 simultaneous liver-kidney transplants and 120 early kidney after liver transplants (77% deceased donor). For simultaneous liver-kidney transplant, 16% were African American recipients and 17% were Hispanic; however, only 7% of African American patients and 9% Hispanic patients were early kidney after liver transplant recipients ($P<.001$). After excluding living donors, the decreased proportion remained significant (deceased donor in early kidney after liver transplant: white 78%; African American 8%; Hispanic 11% vs simultaneous liver-kidney transplant: white 63%, African American 16%, Hispanic 17%; $P=.002$).

Based on recipient race, there were small but statistically significant differences in the KDPI score of simultaneous liver-kidney transplant donors: white, KDPI 38%; African American, 26%; Hispanic, 40% ($P=.007$). Differences were larger for deceased donor early kidney after liver transplant, but not statistically significant: white, 48%; African American, 58%; Hispanic, 49% ($P=.43$).

There were no significant differences in survival according to recipient age for early kidney after liver transplant. Unadjusted and adjusted survival among African Americans was worse after simultaneous liver-kidney transplant (adjusted hazard ratio [aHR], 1.23; 95% confidence interval [CI], 1.08-1.39). Following adjustment for KDPI and recipient factors, Hispanics had improved survival after simultaneous liver-kidney transplant (aHR, 0.86; 95% CI, 0.76-0.98).

"During this time, there was a lower proportion of African American and Hispanic patients undergoing early kidney after liver transplant even after excluding living donation. Higher KDPI predicted lower survival after simultaneous liver-kidney transplant, and there were minor differences in KDPI according to recipient race for simultaneous liver-kidney transplant and early kidney after liver transplant. Early kidney after liver transplant survival did not differ according to race, but African American patients had worse survival following simultaneous liver-kidney transplant after adjusting for recipient factors," the researchers said.

Source: Jay C, Stratta R, Washburn W, et al. Comparing early kidney after liver transplant (KALT) and simultaneous liver-kidney transplant (SLK): Evaluating racial disparities. Will everyone have the same safety net? Abstract of a poster presented at the virtual American Transplant Congress 2020 (Abstract LB-019), May 30, 2020.



KIDNEY WEEK 2020

The American Society of Nephrology renamed its annual meeting Kidney Week 2020 Reimagined in acknowledgment of reworking the meeting to an all-digital format. The meeting 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 one of our coverage of Kidney Week 2020 Reimagined. Part two will appear in our January/February 2021 issue.

Real-World Evidence of Tolvaptan Treatment for Patients with ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary systemic kidney disease characterized by progressive renal damage. Patients with ADPKD commonly progress to end-stage kidney disease and require renal replacement therapy. The first and only treatment to slow the progression of kidney function in adults with ADPKD at risk of rapid progression is tolvaptan.

Researchers, led by **Brett A. Maiese, PhD, MHS,** conducted a literature review to examine real-world effectiveness and safety data available on treatment with tolvaptan. Results of the review were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Global Real-World Evidence of Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD).*

The literature review was conducted in EMBASE (including MEDLINE) in January 2020 with no language, timeframe, or geography restrictions. The reviewers identified observational studies of patients with ADPKD receiving treatment with tolvaptan. Outcomes of interest were clinical effectiveness and safety, utilization of healthcare resources and costs, and quality of life.

The review identified 43 relevant publications. The studies were conducted in Canada, Japan, and Europe. Sample sizes ranged from a single case report to registry analyses of more than 1000 patients. In six studies reporting clinical results, treatment with tolvaptan slowed growth in total kidney volume and no significant changes in annual decline in estimated glomerular filtration rate over a range of 3 months to 2 years after initiation of tolvaptan. Polyuria (~10%) and liver function–related events (~9%) were commonly reported adverse events.

In six studies, 15.6% of patients discontinued tolvaptan treatment, primarily for aquaretic symptoms. In two studies, results suggested that there was no negative impact of treatment with tolvaptan on quality of life. More than 75% of patients reported little impact on daily activities.

In conclusion, the researchers said, "Patients with ADPKD receiving tolvaptan in the real world experienced improved clinical outcomes without negative impact on quality of life. Additional studies assessing real-world evidence supporting tolvaptan treatment in this population are needed."

Source: Maiese BA, Colby JA, Pareja K, et al. Global real-world evidence of tolvaptan in patients with autosomal dominant polycystic kidney disease (ADPKD). Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P01541), October 22, 2020. *Funding for this poster was provided by Otsuka Pharmaceuticals Development & Commercialization, Inc.*

AKI in Patients with Coronavirus Disease 2019: Systematic Review and Meta-Analysis

As the coronavirus disease 2019 (COVID-19) spread around the world, reports of renal involvement varied across regions. **Kam wa Chan, MD,** and colleagues at the University of Hong Kong and the London School of Hygiene and Tropical Medicine conducted a review and meta-analysis to assess the global prevalence of renal manifestations among patients with COVID-19 and identify the risk factors associated with acute kidney injury (AKI) related to COVID-19.

The researchers reported results of the analysis during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Renal Involvement in Coronavirus Disease 2019 (RECORD): A Systematic Review and Meta-Analysis.*

The researchers systematically searched six databases for peer-reviewed reports and seven data portals for grey literature for all trials, cohorts, case-control studies, and case-series reporting the prevalence of renal manifestations of COVID-19, including AKI, renal replacement therapy (RRT), proteinuria and hematuria, and their associated risk factors. Papers were screened by a minimum of two independent researchers.

Study quality was determined using National Institutes of Health assessment tools. Location, institutions, and time periods were matched to avoid duplication of patient data, and if studies overlapped, the meta-analysis only included the largest data source. The pooled prevalence of renal manifestations was obtained from studies that consecutively recruited patients from the general population and those with a clear definition of outcome. The review was prospectively registered at PROSPERO (CRD42020184621).

The search yielded 36 studies from eight countries and more than 50 cities, representing a total of 14,712 patients. Thirty-four of the studies were cohort studies and two were case-control studies. Of the 36 studies, 24 included COVID-19 patients from the general population, seven included severe/critical patients, and five reported results of patients with a history of RRT.

Overall, AKI occurred in 14.3% of COVID-19 cases, with the highest prevalence in New York City. Of hospitalized COVID-19 patients, 4.7% underwent RRT. Proteinuria and hematuria were observed in 42.5% and 26.7% of all COVID-19 cases, respectively.

The odds of mortality among COVID-19 patients with AKI were 15 times higher than among non-AKI COVID-19 patients (pooled odds ratio [OR], 16.85; 95% confidence interval [CI], 10.06-28.23; results from two cities, six studies, 9297 patients). The odds of mortality were higher in the province of Hubei, China. Increased risk of mortality was not seen in kidney transplant recipients (pooled OR, 0.95; 95% CI, 0.12-7.22; results from two studies, 30 patients).

There were associations between higher C-reactive protein, leukocyte count, serum lactate dehydrogenase, and creatinine levels on admission and AKI.

"AKI was prevalent among COVID-19 patients and significantly associated with mortality. The odds of mortality among AKI patients varied significantly between cities, which could be associated with differences in healthcare infrastructure and delayed hospitalization and treatment initiation," the researchers said.

Source: Chan Kw, Yu KY, Lee PW, Tang SC. Renal involvement in coronavirus disease 2019 (RECORD): A systematic review and meta-analysis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00661), October 22, 2020.

30-Day Hospital Readmissions in Minority Patients with ESRD

Racial/ethnic minorities are 1.5 to 4 times more likely than others to develop end-stage renal disease (ESRD). Among hospitalized patients with ESRD receiving hemodialysis, more than one-third of discharges are followed by readmission within 30 days. There are associations between 30-day readmissions and increased healthcare costs and poor health outcomes.

Dhakrit (Jesse) Rungkitwattanakul, PharmD, and colleagues at Howard University College of Pharmacy, Washington, DC, conducted a retrospective study to identify predictors within inpatient and outpatient care that contribute to 30-day hospital readmissions among minority patients with ESRD. Study participants were receiving maintenance hemodialysis at an outpatient dialysis center in the District of Columbia. Results of the study were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Predictors of 30-Day Hospital Readmission among Minority ESRD Patients Receiving Maintenance Hemodialysis.*

Data were obtained from electronic medical records for patients with an unplanned hospital admission between January 1, 2017, and August 31, 2019. The researchers conducted descriptive statistical analysis for all study variables. Identification and assessment of predictors of 30-day readmission was determined using univariate and multivariate logistic regression analysis with 30-day readmission as the dependent outcome.

The study included 96 patients. Of those, 51% (n=49) had a readmission within 30 days of the index discharge. Overall, 86.5% of the patients were Black, 29.2% were 60 to 69 years of age, and 89.6% had a diagnosis of hypertension. In multivariate analyses, there were significant associations between a diagnosis of secondary hyperparathyroidism and serum calcium <8.5 mg/dL at time of index discharge and higher rates of 30-day readmission. Rates of 30-day readmission were also higher among patients with serum parathyroid hormone <150 pg/mL at time of index discharge.

There were no associations between sex, race, weekend discharge, and serum phosphate at time of discharge and 30-day readmission.

In conclusion, the researchers said, "Overall, the study findings provide some insight into risk factors associated with 30-day readmission in minority patients receiving maintenance hemodialysis. These findings suggest that secondary hyperparathyroidism and chronic kidney disease mineral bone disorder markers predict readmissions. Identifying inpatient and outpatient strategies to mitigate risks and prevent readmission may improve outcomes in this high-risk ESRD population."

Source: Rungkitwattanakul DJ, Ohanele C, Emezienna N, Maneno MK, Daftary MN. Predictors of 30-day hospital readmission among minority ESRD patients receiving maintenance hemodialysis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020. (P01233), October 22, 2020.

Metabolic Acidosis and Progression of CKD in Racial/Ethnic Groups

Metabolic acidosis is a risk factor for progression of chronic kidney disease (CKD). There are few data available on the impact of race and ethnicity on the association between metabolic acidosis and CKD progression. **Navdeep Tangri, MD, PhD, FRCP,** and colleagues conducted an analysis to examine the relationship between metabolic acidosis and adverse renal outcomes and mortality by race and ethnicity in the United States. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Relationship Between Metabolic Acidosis and CKD Progression Is Evident Across US Racial and Ethnic Groups.*

The researchers utilized a large electronic medical record (EMR) database of >100 million patients from all 50 states in the United States and with all insurance types. The de-identified EMRs covered the period 2007 to 2019 and were used to identify patients with non-dialysis-dependent CKD stages 3-5. Eligible records had ≥2 years of post-index data or death within 2 years; records were grouped by baseline metabolic acidosis (12 to <22 mEq/L) versus normal serum bicarbonate (22 to <30 mEq/L).

The total cohort included 136,067 patients. Of those, 1328 were Asian, 15,248 were Black, 4137 were Hispanic, 111,953 were White, and 3401 were classified as other race/ethnicity. The primary end point of interest was the composite outcome of death, kidney dialysis or transplant, or a 40% decline in estimated glomerular filtration rate (eGFR) from baseline. The impact of serum bicarbonate on the composite outcome was determined using Cox proportional hazards models within each racial/ethnic group, adjusted for age, sex, eGFR, log albumin-to-creatinine ratio, diabetes, hypertension, heart failure, and Charlson Comorbidity Index score.

Of the 136,067 patients, 34.6% (n=47,032) experienced composite outcome events within 2 years: Asian, 35%; Black, 44%; Hispanic, 48%; White, 32%; and other, 48%. Serum bicarbonate was an independent predictor of the composite outcome in all racial/ethnic groups.

Adjusted hazard ratios (HR) for the composite outcome per 1 mEq/L increase in serum bicarbonate (median, 4.2 years; maximum 11.5 years of follow-up) were: Asian, 0.942 (95% confidence interval [CI], 0.917-0.968); Black, 0.976 (95% CI, 0.969-0.983); Hispanic, 0.970 (95% CI, 0.956-0.984); and White, 0.960 (95% CI, 0.957-0.963) (P<.001 for all groups).

In conclusion, the researchers said, "In a large community-dwelling US population, serum bicarbonate was independently associated with adverse kidney outcomes and deaths in Asians, Blacks, Hispanics, and Whites with CKD. Since race and ethnicity are associated with other sociodemographic factors that affect health, further exploration of the potential reasons for the observed range of HRs across these groups is warranted."

Source: Tangri N, Mathur VS, Reaven NL, Funk SE, Wesson DE. Relationship between metabolic acidosis and CKD progression is evident across US racial and ethnic groups. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00468), October 22, 2020. *Funding for this poster was provided by Tricida, Inc.*

Predictors for Renal Recovery and Mortality in Severe AKI

Critically ill patients often develop acute kidney injury (AKI), a condition that has a broad spectrum of severity. Severe AKI that requires continuous renal replacement therapy (CRRT) is associated with increased risk for morality compared with non-dialysis AKI. However, there are few data supporting consensus guidelines describing discontinuation criteria for CRRT.

Panupong Hansrivijit, MD, and colleagues conducted a meta-analysis designed to identify the clinical parameters for CRRT discontinuation as well as overall mortality in patients with AKI. Results of the meta-analysis were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *A Meta-Analysis of Clinical Predictors for Renal Recovery and Mortality in AKI Requiring Continuous Renal Replacement Therapy.*

The researchers searched Ovid MEDLINE, EMBASE, and the Cochrane Library without language restrictions up to January 2020. Inclusion criteria were patients ≥18 years of age with non-end-stage-kidney disease who required CRRT for AKI. Only studies utilizing multivariable analysis were included. Patients receiving intermittent hemodialysis were excluded. Based on primary outcomes, the analyses were divided into two cohorts: (1) renal recovery cohort and (2) overall mortality cohort.

In the renal recovery cohort (n=4497 from 14 studies), the mean effluent dose of CRRT was 24.93 mL/kg/h with a median duration of CRRT of 3.75 days. Factors that were predictive of renal recovery were increasing urine output at the time of CRRT discontinuation (per 100 mL/day) (odds ratio [OR], 1.021; 95% confidence interval [CI], 1.012-1.031), elevated initial sequential organ failure assessment (SOFA) score (per 1 score) (OR, 0.890; 95% CI, 0.085-0.984), and serum creatinine level at CRRT initiation (per 1.0 mg/dL) (OR, 0.995; 95% CI, 0.991-0.999).

In the overall mortality cohort (n=16,948 from 11 studies), the mean effluent dose of CRRT was 26.22 mL/kg/h with a median duration of 4.5 days. There were significant associations between age (per 1 year) and presence of sepsis (ORs, 1.023; 95% CI, 1.006-1.040 and 2.031; 95% CI, 1.267-3.257, respectively) with overall mortality.

All analyses remained significant through sensitivity analyses, and there was no publication bias observed.

In conclusion, the researchers said, "Urine output at CRRT discontinuation, initial SOFA score, and serum creatinine level are predictive of renal recovery and successful CRRT discontinuation. Increasing age and the presence of sepsis are independent risk factors for elevated overall mortality."

Source: Hansrivijit P, Puthenpura M, Ghahramani N, Thongprayoon C, Cheungpasitporn W. A meta-analysis of clinical predictors for renal recovery and mortality in AKI requiring continuous renal replacement therapy. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00004), October 22, 2020.

Metabolic Acidosis and Risk of Progression to Renal Replacement Therapy

Patients with advanced chronic kidney disease (CKD) commonly develop metabolic acidosis, which may be associated with CKD progression to end-stage kidney disease. Researchers, led by **Vandana S. Mathur, MD, FASN,** performed an analysis to determine the relationship between the presence of metabolic acidosis and the risk of progression of CKD to dialysis or kidney transplantation. Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Metabolic Acidosis and Progression to Renal Replacement Therapy.*

Using de-identified electronic health records (EHRs) (Optum®) from 2007 to 2017, the researchers identified patients with non-dialysis-dependent CKD stages 3-5 with two or more serum bicarbonate tests 28 to 365 days apart, three or more estimated glomerular filtration rate (eGFR) values <60 mL/min/1.73 m^2, and two or more years of post-index data or mortality within that study period. Eligible patients were divided into two groups based on index serum bicarbonate values: (1) metabolic acidosis (serum bicarbonate <22 mEq/L) and (2) normal serum bicarbonate (22-29 mEq/L).

Progression to renal replacement therapy (RRT) was defined as initiation of dialysis or kidney transplantation, identified in the EHR data by diagnosis or procedure codes, or eGFR ≤9 mL/min/1.73 m^2. Logistic regression models (2-year outcome period) and Cox proportional hazards models (up to 10 years) were used to assess the impact of baseline serum bicarbonate on RRT initiation; the models were adjusted for age, sex, race, diabetes, hypertension, heart failure, Charlson Comorbidity Index score, and baseline eGFR and log albumin-to-creatinine ratio (ACR).

A total of 51,558 eligible patients were identified; of those, 17,350 had metabolic acidosis and 34,208 had normal serum bicarbonate at baseline. The unadjusted rate of progression to RRT within 2 years was higher among patients in the metabolic acidosis group compared with those in the normal serum bicarbonate group, overall (19.6% vs 5.5%, respectively; $P<.001$) and at all baseline CKD stages ($P<.001$), with the exception of stage 5 ($P=.4$). There was an association with each 1 mEq/L increase in serum bicarbonate between 12 and 29 mEq/L and a 2.5% decrease in the 2-year risk of RRT initiation (odds ratio, 0.975; 95% confidence interval [CI], 0.965-0.985) and a 4.5% decrease in risk up to 10 years (hazard ratio, 0.955; 95% CI, 0.948-0.963).

In conclusion, the researchers said, "The presence of metabolic acidosis was associated with an increased risk of CKD progression to dialysis or kidney transplantation. This finding was independent of age, sex, race, pre-existing comorbidities, and baseline eGFR and ACR."

Source: Mathur VS, Funk SE, Reaven NL, Tangri N. Metabolic acidosis and progression to renal replacement therapy. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00467), October 22, 2020.
Funding for this poster was provided by Tricida, Inc.

Anemia Management in Incident Dialysis Patients over Three Eras in Canada

Amid safety concerns raised following trials of target hemoglobin, several jurisdictions have adopted a more conservative approach to the management of anemia in patients receiving hemodialysis. Outside of the United States, there are few data available regarding whether the conservative approach is associated with a change in outcomes.

Mark Canney, PhD, and colleagues in Canada conducted a retrospective national cohort study to examine the association between the era of anemia management and major clinical outcomes in incident dialysis patients. Results of the study were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *Temporal Trends in Anemia Management and Major Clinical Outcomes in Incident Dialysis Patients in Canada.*

The researchers utilized the Canadian Organ Replacement Register to identify 35,945 adult patients who initiated hemodialysis or peritoneal dialysis from January 1, 2007, to December 31, 2015. To capture outcomes via data linkage with hospital discharge diagnoses, the study defined time at risk starting on day 90 of dialysis and continuing for a minimum of 12 months.

Patients were categorized into three time periods anchored to landmark target hemoglobin trials and publication of anemia guidelines: Era 1 (January 2007-December 2009); Era 2 (January 2010-December 2012; and Era 3 (January 2013-December 2015). The primary outcome was a composite of acute myocardial infarction (AMI), stroke, or mortality. The association between era and the primary outcome was examined using Cox proportional hazards regression models.

There was a decrease in mean hemoglobin at initiation of dialysis from 102.9 g/L in 2007 to 95.5 g/L in 2015, corresponding with a doubling in the prevalence of hemoglobin <80 g/L (8% to 17%) and a reduction in erythropoiesis-stimulating agent (ESA) use (49% to 44%).

During 66,844 person-years of follow-up, there were 11,810 events observed. Following multivariable adjustment, Era 3 was associated with an 8% relative risk reduction in the primary outcome compared with Era 1 (hazard ratio [HR], 0.92; 95% confidence interval [CI], 0.88-0.96). The reduction in risk was driven by a reduction in all-cause mortality (HR, 0.90; 95% CI, 0.85-0.94). There was no reduction in AMI or stroke. In a model without era, hemoglobin and use of an ESA were not independent predictors of mortality.

"There have been modest declines in average hemoglobin values and ESA use among incident dialysis patients in Canada. Unlike the US, there has been no temporal reduction in stroke. Patient survival has improved over time, likely for reasons other than anemia management. An increasing number of patients are starting dialysis with a hemoglobin <80 g/L, which represents a substantial shift in practice and merits further investigation in terms of patient-centered outcomes," the researchers said.

Source: Canney M, Birks PC, Shao S, Parfrey P, Djurdjev O, Levin A. Temporal trends in anemia management and major clinical outcomes in incident dialysis patients in Canada. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00271), October 22, 2020.

Incidence Rate of Proteinuria in Patients with COVID-19 and AKI

Early data on acute kidney injury (AKI) associated with coronavirus disease 2019 (COVID-19) suggested a high prevalence of proteinuria in that patient population. If accurate, the finding may indicate an AKI pathogenesis not solely related to ischemic acute tubular injury (ATI). **Vipin Varghese, MD,** and colleagues conducted an analysis to test the hypothesis that the indications of high incidence of proteinuria in patients with COVID-19 who developed AKI resulted from observation. The researchers aimed to examine the rate of de novo proteinuria in AKI associated with COVID-19 (CoV-AKI) compared with that of AKI in the pre-COVID-19 era (non-CoV-AKI).

Results of the study were reported during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Incidence of New-Onset Proteinuria in AKI Associated with COVID-19 Is Not Greater than It Is in AKI from Other Causes.*

The study included 161 hospitalized patients with CoV-AKI and a control group of 186 non-CoV-AKI patients. The control group was identified using a database of patients with AKI who underwent urinary sediment microscopy due to suspicion of an intrinsic cause of AKI (SEDI-AKI cohort, 2018-2019). The researchers assessed the incidence of proteinuria of any degree (1+ dipstick), significant, or overt. Significant proteinuria was defined as urine protein-to-creatine ratio (UPCR) ≥0.5-3.0 g/g or 2+ dipstick; overt proteinuria was defined as UPCR ≥3.0 g/g + 3+ dipstick.

Median age in the two groups was similar: 65 years in the CoV-AKI group and 60 years in the non-CoV-AKI group. In the CoV-AKI group, 62% were female compared with 63% in the non-CoV-AKI group; 75% of the CoV-AKI group were Black compared with 35% in the non-CoV-AKI group ($P<.0001$).

In the CoV-AKI group, the presumed cause of AKI was ATI (ischemic and/or toxic) in 75% compared with 71% in the non-CoV-AKI group. The incidence of any proteinuria was 83% (n=123/148) versus 69% (n=127/184) in the non-CoV-AKI group ($P=.003$). The incidence of significant proteinuria was 66% (n=98/148) in the CoV-AKI group versus 44% (n=81/184) in the non-CoV-AKI group ($P=.0001$). The incidence of overt proteinuria in the CoV-AKI group was 10% (n=14/148) versus 13% (n=23/184) in the non-CoV-AKI group ($P=.39$).

Among patients with significant proteinuria, there was no difference in median UPCR between the two groups (0.69 vs 0.69 g/g). Using baseline UPCR when available, the rates of de novo significant and overt proteinuria were similar (46% vs 46% and 5% vs 7%, respectively). Among patients with overt proteinuria who underwent kidney biopsy, collapsing glomerulopathy was found in 75% of the CoV-AKI group compared with 0% in the control group ($P=.002$).

"The incidence rate of new onset proteinuria was not found to be increased in CoV-AKI and is consistent with that of other forms of ATI. An observed overall greater incidence in significant proteinuria in CoV-AKI may be driven by pre-existing proteinuria. While the rate of overt proteinuria is not greater in CoV-AKI, the primary cause of de novo glomerular disease may vary."

Source: Varghese V, Mohamed M, Velez JCQ. Incidence of new-onset proteinuria in AKI associated with COVID-19 is not greater than it is in AKI from other causes. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00673), October 22, 2020.

Roxadustat Efficacious and Safe in Non-Dialysis-Dependent CKD Patients with Anemia

Researchers in Japan conducted study of roxadustat, an orally active hypoxia-inducible factor prolyl hydroxylase inhibitor for the treatment of anemia in chronic kidney disease (CKD). The study was designed to examine the efficacy and long-term safety of roxadustat following conversion from darbepoetin alfa (DA), recombinant human erythropoietin (rHuEPO), or epoetin beta pegol (EBP) to roxadustat in patients with non-dialysis-dependent CKD (NDD-CKD).

The researchers, led by **Tadao Akizawa, MD, PhD,** sought to evaluate the noninferiority of roxadustat efficacy against DA. Results of the study were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *A Phase 3, Multicenter, Randomized, Open-Label, Active Comparator Conversion Study of Roxadustat in Non-Dialysis-Dependent (NDD) Patients with Anemia in CKD.*

The study cohort included adult NDD-CKD patients in Japan who were receiving DA, rHuEPO, or EBP for ≥8 weeks prior to prescreening. Patients who had received rHuEPO or DA were randomized to receive roxadustat or DA (comparative group). Patients who had used EBP were allocated to receive roxadustat (referential group).

The primary end point was the change in hemoglobin from baseline at weeks 18 to 24. The efficacy of roxadustat was confirmed if the 95% confidence interval (CI) of average hemoglobin at weeks 18 to 24 was within 10 to 12 g/dL; the noninferiority of roxadustat to DA was confirmed if the lower limit of the 95% CI of the difference between roxadustat and DA was above -0.75 g/dL. The study also examined treatment-emergent adverse events.

A total of 262 patients were randomized to the comparative groups and received one or more doses of roxadustat (n=131) or DA (n=131). Seventy patients were allocated to the referential group and received one or more doses of roxadustat.

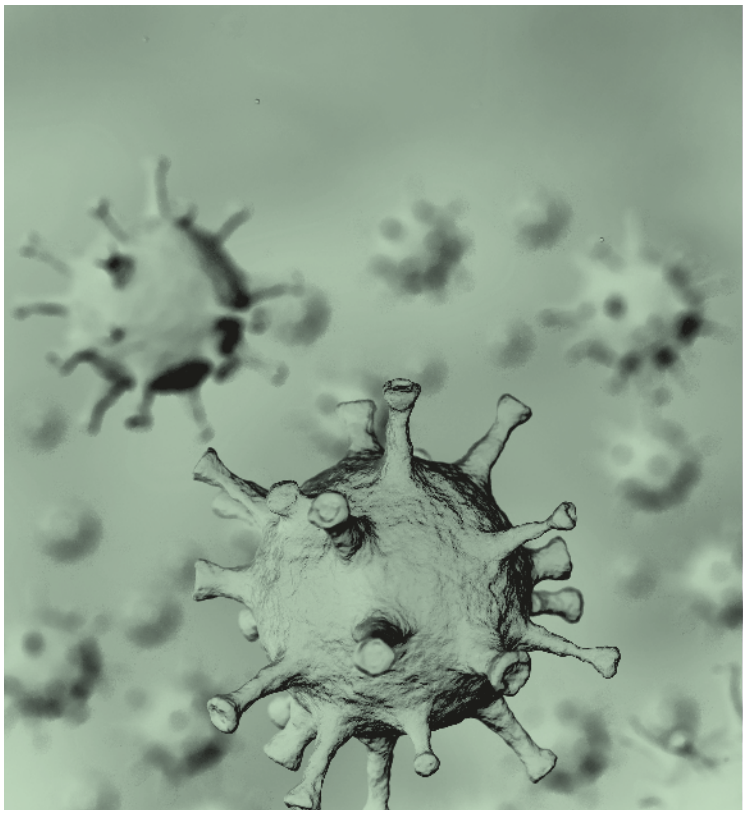
The mean (95% CI) of average hemoglobin at weeks 18 to 24 in patients in the roxadustat group was 11.14 g/dL, confirming the efficacy of roxadustat. The difference between roxadustat and DA in the change in average hemoglobin from baseline at weeks 18 to 24 was -0.07 g/dL (95% CI, -0.23 to 0.10), confirming the noninferiority of roxadustat to DA.

The incidence of treatment-emergent adverse events during the 24-week study period was 78.6% in the roxadustat group, 70.2% in the DA group, and 77.1% in the referential group. Treatment-emergent adverse events included nasopharyngitis, CKD, hyperkalemia, and hypertension; rates were comparable between the groups.

In conclusion, the researchers said, "This study confirmed the efficacy of roxadustat after conversion from DA, rHuEPO, or EBP, as well as its noninferiority to DA, in NDD-CKD patients with anemia. The safety profile of roxadustat was consistent with previous reports."

Source: Akizawa T, Iwasaki M, Otsuka T, Yamaguchi Y, Reusch M. A phase 3, multicenter, randomized, open-label, active comparator conversion study of roxadustat in non-dialysis-dependent (NDD) patients with anemia in CKD. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (PO0269), October 22, 2020.

The mean of average hemoglobin at weeks 18 to 24 in patients in the roxadustat group was 11.14 g/dL, confirming the efficacy of roxadustat.



Risk Factors for AKI in Patients with COVID-19

Patients with coronavirus disease 2019 (COVID-19) may develop acute kidney disease (AKI). The United Kingdom National Institute for Health and Care Excellence (NICE) developed guidelines for the management of AKI in patients with COVID-19. **Thomas Phillips, PhD,** and colleagues at the University Hospital Southampton NHS Foundation Trust conducted an analysis to examine the local patient-level COVID-19 Hospitalisation in England Surveillance System database to identify potential risk factors for AKI versus the guidelines. Results were reported during a virtual poster session at ASN Kidney Week 2020 in a poster titled *COVID-19 AKI: Risk factors and Markers of Disease from a Large UK Cohort.*

The analysis included data on 564 COVID-19-positive admissions between March 7, 2020, and May 24, 2020, at the University Hospital Southampton. Consistent with NICE guidance, RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) and AKIN (Acute Kidney Injury Network) criteria were used to stage AKI. Data were analyzed using X2, t-test, Mann-Whitney U test, and logistic regression.

Of the 564 patients with COVID-19, 31% (n=177) developed AKI. At peak, 61% (n=108) had stage 1 chronic kidney disease, 24% (n=42) had stage 2 AKI, and 15% (n=27) had stage 3 AKI. There were no significant differences between the cohorts in White versus non-White race/ethnicity, sex, obesity, or anti-COVID-19 treatment. Of the patients in the AKI cohort, 44% died compared with 19% in the non-AKI group ($P<.001$). There were associations between AKI and admission to the intensive care unit (ICU), (27% vs 10%; $P<.001$), the need for noninvasive ventilation (13% vs 4%; $P<.001$), and the need for invasive ventilation (14% vs 4%; $P<.001$).

In the AKI group, compared with the non-AKI group, patients more commonly had a history of diabetes (18% vs 8%), hypertension (47% vs 34%), chronic respiratory disease (25% vs 15%), and chronic heart disease (25% vs 15%). There was an association between increased age and AKI ($P=.02$), as well as a positive correlation between length of stay and AKI stage ($P<.001$).

In patients in the AKI group, and increasing with AKI stage, peak levels of ferritin, D-dimer, C-reactive protein, high sensitivity troponin-I, neutrophil count, and total white count were all significantly raised compared with the non-AKI group. In multivariable analysis of first clinical observations, the most significant predictors of AKI were neutrophil count, hemoglobin, D-dimer, and albumin: specificity 88.7%, sensitivity 43.6%.

In conclusion, the researchers said, "AKI is a frequent complication of COVID-19, and we identified similar risk factors to those in the NICE guidelines. In addition, we found hypertension and chronic respiratory disease to increase risk of AKI whilst ethnicity, gender, obesity, and COVID-19 treatments did not. Furthermore, AKI was associated with increased mortality, ICU admissions, and length of stay, concordant with previous studies. These data also point to several biomarkers as possible predictors of AKI development and severity. Further analysis of the data is ongoing."

Source: Phillips T, Leggatt G, Stammers M, et al. COVID-19 AKI: Risk factors and markers of disease from a large UK cohort. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (PO0666), October 22, 2020.

Racial Disparity in Likelihood of AKI Following PCI

Patients undergoing percutaneous coronary intervention (PCI) are at risk for acute kidney injury (AKI). There are few available data quantifying racial differences in the incidence of AKI following PCI. **Joseph Lunyera, MB-ChB,** and colleagues conducted an analysis to examine the association between self-reported race and baseline estimated glomerular filtration rate (eGFR) with the incidence of AKI at a single center between January 1, 2003, and December 31, 2013.

Results of the analysis were reported during a virtual poster session at ASN Kidney Week 2020. The poster was titled *Racial Differences in AKI Following Percutaneous Coronary Intervention.*

Patients who underwent PCI at Duke University School of Medicine, Durham, North Carolina, self-reported their race as Black, White, or other. Data were gathered in the Duke Databank for Cardiovascular Disease. AKI was defined as ≥1.5-fold increase in serum creatinine from outpatient reference value prior to PCI to the peak value within 7 days following PCI or a 0.3 mg/dL increase from the reference value within 48 hours.

The researchers utilized logistic regression adjusted for demographics, comorbidities, predisposing medications (nonsteroidal anti-inflammatory drugs, renin-angiotensin-aldosterone system inhibitors, diuretics), PCI indication (presenting with vs without acute coronary syndrome), peri-procedural prophylaxis with intravenous fluids and n-acetylcysteine, urgency of PCI, and blood pressure at the time of PCI.

The cohort included 9422 patients; median age was 63 years, 33% were female, 75% were White, 20% were Black, and 5% were other race. Nine percent of the total cohort developed AKI: 14% of Blacks, 8% of Whites, and 10% in other race groups.

Following adjustment, there was an association between Black race and greater likelihood of AKI: odds ratio (OR), in Black (vs White) patients, was 1.80 (95% confidence interval [CI], 1.49-2.18). Compared with White patients, there was no association between AKI and other race (OR, 1.31; 95% CI, 0.91-1.87). There was an association between low baseline eGFR and graded, higher likelihood of AKI: *P* for trend <.001. There was no interaction between race and baseline eGFR.

"Black patients had nearly twice the likelihood for AKI following PCI than Whites despite adjustment for baseline kidney function, prophylaxis, and procedural characteristics. Future investigations should identify other factors that predispose Black individuals to disparate AKI risk following PCI," the researchers said.

Source: Lunyera J, Clare RM, Chiswell K, et al. Racial differences in AKI following percutaneous coronary intervention. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00017), October 22, 2020.

Renal Recovery in Patients with AKI Improved with CRRT

In patients with acute kidney injury (AKI) requiring dialysis (AKI-D), the rate of adverse outcomes is high. There are few data available on modifiable factors that promote recovery of kidney function.

Five CTSA (Clinical and Translational Science Alliance) universities (University of Arkansas for Medical Science [UAMS], University of Alabama at Birmingham [UAB], University of Kentucky [UKY], Medical University of South Carolina [MUSC], and Emory) formed a consortium to identify modifiable risk factors for kidney recovery in patients with AKI-D. A retrospective analysis was conducted to compare outcomes of patients with AKI-D with those of patients who initiated treatment with intermittent hemodialysis.

The researchers, led by **John M. Arthur, MD, PhD,** provided results from the analysis during a virtual poster session at ASN Kidney Week 2020 in a poster titled *CRRT Is Associated with Improved Recovery from Dialysis-Requiring AKI in a Multicenter Retrospective Analysis.*

All patients who received dialysis while in the hospital were selected; patients with a diagnosis related to end-stage kidney disease, kidney transplantation, or chronic kidney disease stage 5 at the time of the initial renal replacement therapy (RRT) were excluded. Data on modality of dialysis, comorbidities, and outcomes were included in the analysis.

The total number of patients in the four available cohorts (UAMS, UAB, MUSC, and UKY) was 4537. Outcomes were identified at the time of hospital discharge. The primary outcomes of interest were death (n=1160, 25.6%) or alive and dialysis-free at discharge (n=1187, 26.2%). Dialysis dependence was defined as receiving dialysis within the last 4 days of hospitalization. The analysis was adjusted for sepsis, age, race, sex, quick Sequential Organ Failure Assessment score, mechanical ventilation, and levels of serum bicarbonate and serum potassium at the time of dialysis initiation. Hospital cohorts were analyzed separately.

The risk of death was higher in patients initiated on continuous RRT (CRRT) compared with patients initiated on intermittent hemodialysis. The odds ratios (ORs) and 95% confidence intervals (CIs) for death were: UAMS, 2.8; 1.9-4.2; UAB, 3.2, 2.1-4.9; MUSC, 3.7, 2.6-5.3; and UKY, 3.1, 2.3-4.2.

Of the patients who survived to discharge, those initiated on CRRT generally had a lower risk of being dialysis dependent at discharge. The ORs and 95% CIs for renal recovery were: UAMS, 0.1, 0.04-0.2; UAB, 0.3; 0.1-0.5; MUSC, 0.3, 0.2-0.5; and UKY, 0.8, 0.5-1.2.

In conclusion, the researchers said, "The odds of kidney recovery were significantly better for patients started on CRRT in three of the four cohorts examined in this study and trended toward favoring CRRT in the fourth. This has important implications for the care of patients with AKI in the intensive care unit. We believe the increased mortality in the CRRT group reflects the sicker nature of patients in that group and is not inherent to CRRT as an initial dialysis modality."

Source: Arthur JM, Neyra J, Gokun Y, et al. CRRT is associated with improved kidney recovery from dialysis-requiring AKI in a multicenter retrospective analysis. Abstract of a poster presented at the American Society of Nephrology virtual Kidney Week 2020 (P00010), October 22, 2020.

2020 ASN Lifetime Achievement Awards

Each year, the American Society of Nephrology (ASN) honors individuals who have significant accomplishments in research, education, and other areas of kidney health. The honorees for 2020 are:

The Belding Scribner Award, recognizing contributions that have direct impacts on patient care, was given to **Josef Coresh, MD, PhD, FASN.** Dr. Coresh is the George Comstock Professor of Epidemiology, Biostatistics and Medicine at The Johns Hopkins University Bloomberg School of Public Health. He is an expert in the epidemiology of kidney and cardiovascular disease and has coauthored more than 800 research articles. He leads the CKD Prognosis Consortium that includes more than 80 cohorts and more than 10 million participants from 40 plus countries.

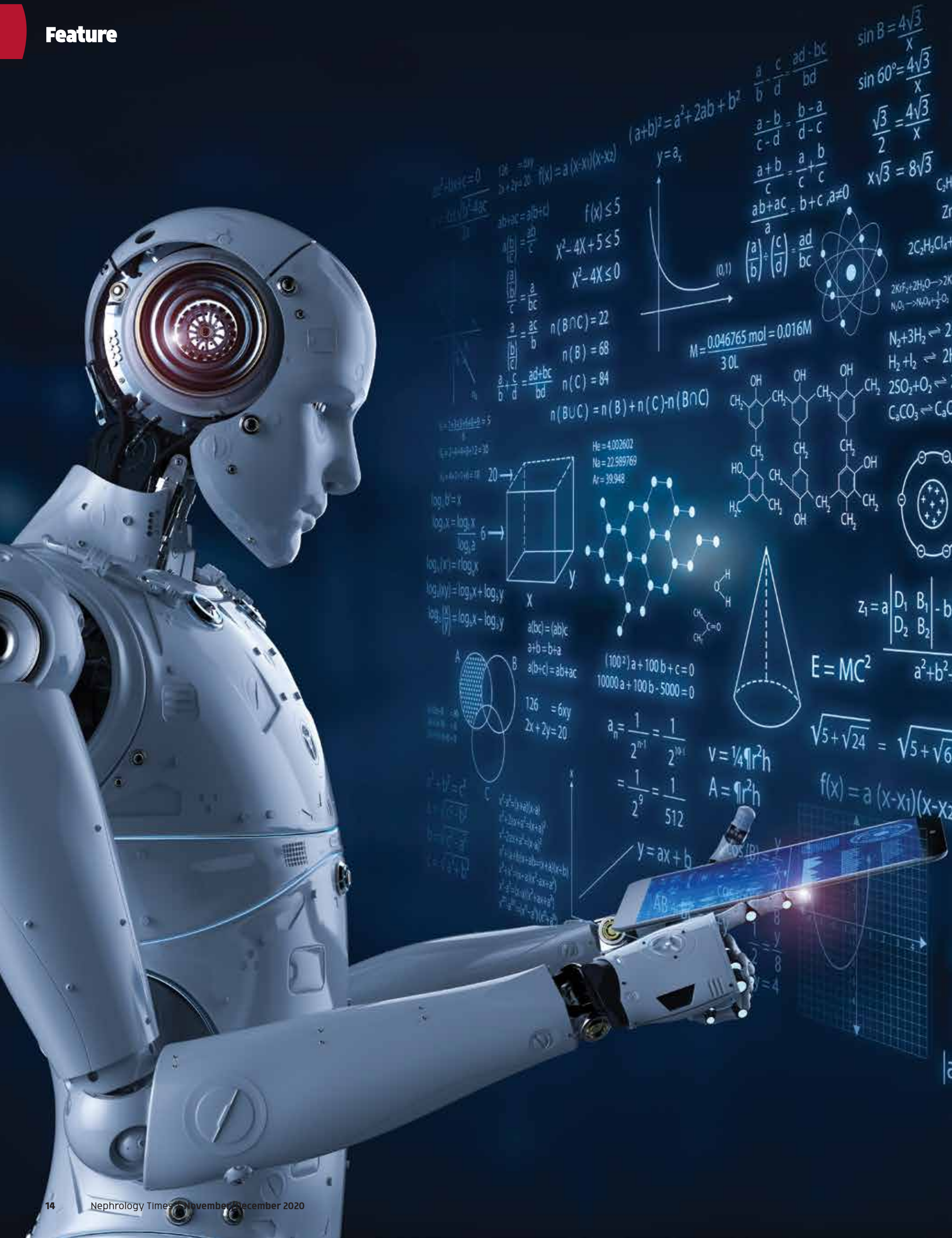
The Donald W. Seldin Young Investigator Award was presented to **Anna Greka, MD, PhD.** The award is presented to an individual with an outstanding record of achievement and creativity in basic or patient-oriented research related to the functions and diseases of the kidney. Dr. Greka is associate professor at Harvard Medical School and director of the Broad Kidney Disease Initiative and the founding director of Kidney-NExT. She has been the recipient of several previous honors, including the 2018 Seldin-Smith Award for Pioneering Research from the American Society of Clinical Investigation and a 2017 Presidential Early Career Award for Scientists and Engineers.

The Homer W. Smith Award was presented to **Sir Peter J. Ratcliffe, FRS, FMedSc.** The award recognizes contributions that affect the science of nephrology, including pathobiology, cellular and molecular mechanisms, and genetic influences on the functions and diseases of the kidney. Professor Radcliffe is a physician-scientist and nephrologist in Great Britain, studying cellular reactions to hypoxia. He is professor of clinical medicine at Oxford University and clinical research director of the Francis Crick Institute. He has received a variety of awards and honors, including the 2019 Nobel Prize in Physiology or Medicine, which he shared with William G. Kaelin, Jr., MD, and Gregg L. Semenza, MD, PhD, "for their discoveries of how cells sense and adapt to oxygen availability."

Ravi L. Thadhani, MD, MPH, received the John P. Peters Award in recognition of his contributions improving the lives of patients and furthering the understanding of the kidney in health and disease. Dr. Thadhani is professor of medicine at Harvard Medical School and chief academic officer and Harvard Medical School faculty dean for academic programs at Partners Healthcare. His research centers on preeclampsia diagnostics and therapeutics and vitamin D metabolism.

Ashita J. Tolwani, MD, MS, was awarded the Robert G. Narins Award that honors individuals who have make contributions to teaching and education. Dr. Tolwani is a professor of medicine at the University of Alabama at Birmingham and associate director of ICU nephrology. Her teaching expertise has been national and internationally recognized. She is the founder and director of the UAB Continuous Renal Replacement Therapy Academy, a national CRRT training course offering hands-on training with mannequins, providing a practical understanding of CRRT to fellows and attending physicians, critical care fellows, surgeons, nurses, and pharmacists.

The ASN President's Medal was awarded to **Gisela Deuter, BSN, MSA,** and **Priti R. Patel, MD, MPH.** Ms. Deuter helped develop, launch, and build the ASN Nephrology Self-Assessment Program, helped launch ASN Renal Weekends (now called ASN Highlights), and worked to expand educational offerings at Kidney Week. Dr. Patel serves as the dialysis activity leader within the division of healthcare quality promotion at the Centers for Disease Control and Prevention (CDC), and leads CDC's prevention, surveillance, and response activities related to dialysis patient safety.



Validation of a Machine Learning Risk Score for Acute Kidney Injury

Acute kidney injury (AKI) among hospitalized patients is associated with increased risk for morbidity and mortality. AKI is defined by either an increase in serum creatinine concentration or a decrease in urine output. Researchers have investigated biomarkers that detect AKI prior to those changes; however, to date, there has been limited large-scale validation and implementation of those prediction models.

Research into urinary and serum biomarkers is ongoing. There are also groups exploring the accuracy of electronic health record-based risk scores that identify AKI prior to changes in serum creatinine concentration. The published algorithms vary; some focus on ward and intensive care patients, others focus on postoperative AKI. The models also range from rule-based, more narrow scores to complex, machine-learning-based scores.

Matthew M. Churpek, MD, MPH, PhD, and colleagues conducted a diagnostic study designed to internally and externally validate a simplified version of an AKI score. The primary outcome of interest was the development of serum creatinine-based stage 2 AKI within 48 hours of each observation. Study results were reported in *JAMA Network Open* [doi:10.1001/jamanetworkopen.2020.12892].

The internal validation was conducted at the University of Chicago (UC) and the external validation was conducted using retrospective cohorts from independent health systems (Loyola University Medical Center (LUMC], Maywood, Illinois, and Northshore University Health System [NUS], Evanston, Illinois).

The study included prospectively collected data from the three distinct adult cohorts (≥18 years of age). The internal validation cohort from UC included all adult patients at the urban tertiary referral hospital who were part of the validation cohort (2008 to 2016) in an earlier AKI algorithm development study. The external validation cohort included all adult patients admitted to LUMC, a suburban tertiary referral hospital, from 2007 to 2017, and all adult patients admitted to NUS, a suburban 4-hospital healthcare network, from 2006 to 2016.

AKI was defined by the serum creatinine-based criteria from the Kidney Disease Improving Global Outcomes (KDIGO) consensus definition. Baseline serum creatinine concentration was defined as the admission serum creatinine value and was updated on a rolling basis for 48-hour and 7-day criteria, as per the KDIGO guidelines.

The final cohort included 495,971 adult patient admissions at six hospitals across three health systems. Mean age was 63 years, 17.7% (n=87,689) were African American, and 53.8% (n=266,866) were women. Compared with the other two cohorts, admissions from UC were more likely to be younger (mean age: LUMC, 58.6 years; NUS, 67.4 years; UC, 56.6 years; *P*<.001) and African American patients (LUMC, 22.7%; NUS, 7.3%; UC, 50%; *P*<.001).

The model provided excellent discrimination of those needing RRT within 48 hours, with AUCs of 0.95 or higher in all three cohorts.

The UC internal validation cohort included 48,463 patient admissions; of those, 14.3% (n=6935) developed at least stage 1 AKI, 3.4% (n=1664) developed stage 2 or 3 AKI, and 0.7% (n=332) required renal replacement therapy (RRT). Of the 200,613 patients in the LUMC cohort, 13.6% (n=27,352) developed at least stage 1 AKI, 2.8% (n=5722) developed stage 2 or 3 AKI, and 0.3% (n=672) required RRT. In the NUS cohort (n=246,895), 8.3% (n=20,473) developed any AKI, 1.4% (n=3499) developed stage 2 or 3 AKI, and 0.2% (n=440) required RRT.

The receiver operating characteristic area under the curve (AUC) for predicting AKI were the same or slightly higher in the UC cohort for all outcomes. The model predicted the development of stage 2 AKI within 48 hours with an AUC of 0.86 (95% confidence interval, 0.86-0.86) in the UC cohort; 0.86 (95% CI, 0.86-0.86) in the NUS cohort; and 0.85 (95% CI, 0.84-0.85) in the LUMC cohort. The model provided excellent discrimination of those needing RRT within 48 hours, with AUCs of 0.95 or higher in all three cohorts.

Following stratification by patient location, serum creatinine concentration at admission, and prior operating room status, the model had slightly higher discrimination for the prediction of stage 2 AKI for patients in the ICU compared with ward patients in the UC and LUMC cohorts, although the differences were small. In the wards in all three cohorts, the model had very similar discrimination for the prediction of AKI in the next 48 hours. The model performed better in all three cohorts in patients with higher admission serum creatinine concentrations; the model performed best among those with an admission serum creatinine concentration between 2.0 and 2.9 mg/dL. In all subgroups across all three sites, the AUC for the development of stage 2 AKI in the next 48 hours was greater than 8.0.

The AUCs for receipt of RRT within 48 hours were 0.96 (95% CI, 0.96-0.96) in the UC cohort; 0.95 (95% CI, 0.94-0.95) in the LUMC cohort; and 0.95 (95% CI, 0.94-0.95) in the NUS cohort.

The researchers cited some limitations to the study findings, including using a single definition of AKI, overprediction of the risk for the highest decile of patients, and the validation cohorts being in teaching hospitals and all in Illinois, potentially limiting the generalizability of the findings.

In conclusion, the authors said, "In this study, we internally and externally validated a novel machine learning risk score for the prediction of AKI across all hospital settings. This tool, which includes patient demographic characteristics, vital signs, laboratory values, and nursing assessments, can be used to identify patients at increased risk of the development of severe AKI and the need for RRT. Pairing this risk score with early, kidney-focused care may improve outcomes in the patients at the highest risk of the development of AKI." ■

TAKEAWAY POINTS

- Researchers conducted a multicenter diagnostic study to internally and externally validate a machine learning risk score to identify hospitalized patients at high risk of acute kidney injury (AKI).
- The machine learning algorithm had similarly high discrimination in the internal and external cohorts.
- The findings suggest that implementation of the AKI algorithm could enable early identification of patients at risk for severe AKI and decrease the incidence of preventable AKI.

Trends in Hospitalizations for AKI-D in Patients with and without Diabetes

Patients with severe acute kidney injury (AKI), defined as AKI that requires dialysis (AKI-D), have increased risk of adverse outcomes, incidence of kidney failure, in-hospital mortality, and high healthcare costs. In recent years, the incidence of AKI-D has increased worldwide, due, in large part, to the aging population and the increasing burden of acute and chronic diseases. However, there are some data that suggest a decline in morality rates associated with AKI-D.

The most common cause of kidney failure is diabetes, accounting for 46% of all new cases in the United States; diabetes has also been linked to a higher risk for AKI and AKI-related mortality. The number of adults living with diabetes is expected to increase from 42.5 million in 2017 to 629 million by 2045. In addition, type 2 diabetes is increasingly being diagnosed in young adults, exposing those patients to a longer duration of disease and an increased risk for complications.

National US data reveal a significant increase in AKI-D hospitalization rates between 2000 and 2014; the absolute increases were greater in adults with diabetes. **Jessica Lee Harding, PhD,** and colleagues conducted a cross-sectional study designed to examine three areas: (1) the current trends in the annual incidence of AKI-D hospitalizations among adults with versus without diabetes by age and sex; (2) differences in the trends in in-hospital mortality associated with AKI-D between people with and without diabetes by age and sex: and (3) the comorbid conditions associations with the increase in AKI-D in adults with and without diabetes. Results were reported in the *American Journal of Kidney Diseases* [2020;75(6):897-907].

The study utilized nationally representative data from the National Inpatient Sample and the National Health Interview Survey to generate 16 cross-sectional samples of US adults ≥18 years of age between 2000 and 2015. The study exposure was diabetes, defined using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes. The outcome of interest was AKI-D, defined using *ICD-9-CM* codes.

In adults with diabetes, the rates of AKI-D increased 55.7% during the study period from 26.4 to 41.1 per 100,000 persons (change per year, 3.3%; $P<.001$). In the cohort without diabetes, the rates increased 71.8% between 2000 and 2009 from 4.8 to 8.3 per 100,000 persons (change per year, 6.5%; $P<.001$); the increase plateaued after 2009. In 2015, the rates of hospitalization for AKI-D remained nearly five times as high in adults with diabetes compared with those without diabetes (rate ratio, 5.0; 95% confidence interval, 4.8-5.1); there was no significant increase in the excess risk between 2000 and 2015.

Trends in AKI-D rates were similar in men and women with and without diabetes. However, absolute rates remained higher in men than in women across all age groups. Absolute rates remained highest among older age groups, although the greatest relative increases were seen in the younger age groups (18 to 44 and 45 to 64 years of age).

During the study period, there was a decrease in in-hospital mortality associated with AKI-D, from 23.1 per 100 persons to 15.2, in adults with diabetes (change per year, –3.9%; $P=.01$). In the cohort without diabetes, in-hospital mortality associated with AKI-D decreased from 34.4 to 28.7 (change per year, –2.0%; $P<.001$). Trends were similar for men and women, although the decline among women with diabetes was not significant. There was significant decline in all age groups with the exception of those 18 to 44 years of age where there was no significant change seen in patients with and without diabetes.

Of AKI-D hospitalizations among patients with diabetes, there was no change over time in the proportion of hospitalizations with low to moderate comorbid conditions; there was an increase in the proportion of high-comorbid hospitalizations between 2000 and 2009 (change per year, 4.4%; $P=.02$), followed by a plateau. In the cohort without diabetes, there was a decrease in the proportion of hospitalizations with low morbidity between 2000 and 2015 (change per year, –0.8%; $P<.001$), which coincided with an increase in the proportion of high-morbidity hospitalizations (change per year, 1.7%; $P=.007$).

There were changes over time in patterns of specific comorbid conditions. In the cohort with diabetes, there were increases in the proportion of chronic pulmonary disease, liver disease (mild and moderate/severe), rheumatic disease, and kidney disease. There were declines in hypertension, myocardial infarction, congestive heart failure, and peripheral vascular disease during the study period. Throughout the study period, the proportion of men increased (from 50.6% to 57.1%; $P<.001$), and, after an initial period of decline, the proportion of cardiac procedures increased beginning in 2009.

In the cohort without diabetes, patterns of comorbid conditions were similar with the exception of (1) the proportion of men did not increase, (2) malignancies and hemiplegia or paraplegia increases and HIV/AIDS declined (compared with no change in the cohort with diabetes), and (3) there was no change in peripheral vascular disease (compared with declines in the cohort with diabetes).

Limitations to the study findings cited by the authors included a lack of laboratory data to corroborate the AKI diagnosis, the inability to distinguish whether AKI was acquired within the hospital or in a community setting, including all types of diabetes with the assumption that 90% to 95% had type 2 diabetes, and the inability to adjust for a number of possible confounders (race/ethnicity, body mass index, prior chronic kidney disease, smoking, and socioeconomic characteristics).

The researchers said, "In the United States between 2000 and 2015, hospitalization rates of AKI-D increased in adults with and without diabetes while AKI-D-associated mortality declined. However, AKI-D remained substantially higher in adults with versus without diabetes and this excess risk has not improved over time. Most alarmingly, relative increases in AKI-D were greatest among young adults with diabetes. Increases in AKI-D may be explained in part by increases in liver, renal, and rheumatic, but not cardiovascular, comorbid conditions. This study highlights the need for greater AKI risk factor mitigation above and beyond traditional cardiovascular preventions and management, especially in young adults with diabetes." ■

TAKEAWAY POINTS

- There has been substantial increase in acute kidney injury requiring dialysis (AKI-D) in the United States. Researchers conducted a cross-sectional study to examine the trends in hospitalizations in the setting of AKI-D in patients with and without diabetes.
- In the cohort with diabetes, there was an increase in AKI-D during the study period (2000–2015), with relative increases greater in younger versus older adults. There was also an increase among patients without diabetes.
- In both cohorts, there was a significant decline in AKI-D associated morality.

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Self-Management for Restriction of Dietary Sodium in Patients with CKD

TAKEAWAY POINTS

- The SUBLIME study was designed to examine the efficacy of a web-based intervention to increase self-management of sodium intake restriction in patients with chronic kidney disease.
- During the 3-month intervention period, sodium excretion decreased in the intervention group while there was no significant change in sodium excretion in the control group.
- At the end of the intervention period, systolic blood pressure decreased in the intervention group, compared with no change in the control group.

Patients with chronic kidney disease (CKD) are strongly advised to limit their intake of sodium. Results of observational studies have suggested the potential of even moderate reductions in sodium intake; for every gram in less daily sodium intake, there is an association with 15% lower risk for cardiovascular complications. There was also lower risk for kidney failure in patients with and without diabetes (15% and 10% lower risk, respectively).

According to **Jelmer K. Humalda, MD, PhD,** and colleagues, current approaches for reduction of sodium intake are largely unsuccessful. Results of an analysis of more than 10,000 patients with CKD found that average sodium intake was 164 mmol/day, even in the dedicated setting of the nephrology outpatient clinic. Other studies have found good outcomes with interventions based on self-regulation: several interventions resulted from a qualitative study of barriers and facilitators for sodium restriction.

One-to-one counseling associated with behavioral interventions is costly; e-health has the potential to improve affordability of such programs. Dr. Humalada et al. designed the SUBLIME (Sodium Burden Lowered by Lifestyle Intervention: Self-management and E-health Technology) intervention. SUBLIME included group counseling as well as a web-based self-management program, followed by a maintenance phase. The researchers evaluated the intervention for efficacy and assessed costs, and barriers, and facilitators for the implementation of SUBLIME intervention into clinical practice. Results of the assessment were reported in the *American Journal of Kidney Diseases* [2020;75(6):847-856].

SUBLIME was a randomized controlled trial conducted in nephrology outpatient clinics in four hospitals in the Netherlands. The cohort included 99 adults with CKD stages 1 to 4 or a functioning kidney transplant (defined as estimated glomerular filtration rate ≥25 mL/min/1.73 m^2), hypertension, and sodium intake >130 mmol/day.

The study compared routine care alone with routine care plus a web-based self-management intervention that included individual e-coaching and group meetings implemented over a 3-month intervention period, followed by e-coaching over a 6-month maintenance period. The primary outcomes were sodium excretion following the 3-month intervention and following the 6-month maintenance period. Secondary outcomes included blood pressure, proteinuria, costs, quality of life, self-management skills, and barriers and facilitators for implementation of the intervention.

Of the 99 patients, 52 were randomly assigned to the intervention and 47 to routine care alone (control). Five patients did not attend the baseline measurement visit. Study participants were 56.6 years of age and 44% were recipients of kidney transplantation. The control and intervention groups were similar in baseline characteristics. Five participants were lost to follow-up, and not all participants returned their 24-hour urine collection after baseline.

Results of data logs indicated that 44 of 50 participants used the program; most used the program the first 2 to 4 months. During the study period, 1647 records of daily dietary intake were made (37.4 days per participant). Participants recorded 4256 meals and 3428 snacks. Eight participants stopped recording within 1 month and 11 recorded for longer than 6 months.

In the intervention group, there was a decrease in sodium excretion from 188 mmol/day at baseline to 148 mmol/day at 3 months. Linear mixed-effects model (LMM) analyses confirmed the reduction was statistically significant, with the estimated marginal mean changing over the 3 months from 188 to 148 mmol/day ($P<.001$) for within-group difference. In the control group, there was a nominal reduction in sodium excretion that was not statistically significant. Compared with control, the effect of the intervention was –24.8 (95% confidence interval, –49.6 to –0.1) mmol/day ($P=.049$ for between group difference).

There was a concomitant decrease in both systolic blood pressure and diastolic blood pressure in the intervention group (from 140 to 131 mm Hg and 84 to 80 mm Hg, respectively). LMM confirmed the statistical significance of the change. The change in systolic blood pressure in the control group was not statistically significant.

At the end of the intervention period, 11 participants had proteinuria with protein excretion ≥1.0 g/day (six were in the intervention group and five were in the control group). Use of antihypertensive drugs decreased in one participant in the control group and increased in three; hypertensive drug use decreased in five participants in the intervention group and increased in three. The changes were not statistically significant.

During the 6-month maintenance phase, sodium excretion increased in the intervention group, but remained lower than at baseline at 160 mmol/day ($P=.01$). In the control group, sodium excretion decreased in the control group, from 174 at the end of the intervention period to 154 mmol/day ($P=.001$). Thus, there was no difference in sodium excretion between the two groups seen following the maintenance phase. There was no difference in systolic blood pressure between the groups after the maintenance phase.

Limitations to the study cited by the authors included lack of dietary data, post-randomization loss to follow-up, short-term follow-up, and the small sample size.

"In conclusion, the SUBLIME study presents a potentially effective strategy for dietary sodium restriction in CKD in clinical practice, although future larger and longer term studies are needed to test long-term efficacy," the researchers said. ■

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Intensive versus Standard Care for In-Hospital AKI

Among hospitalized patients, the incidence of acute kidney injury (AKI) ranges from 4% to 21%, making AKI one of the most common and cost-intensive acute diseases in hospitalized patients. Patients with AKI frequently develop chronic renal failure or terminal renal failure. In Germany, the estimated prevalence of chronic renal failure is 2 million individuals.

Cardiorenal complications that include death, chronic dialysis, decline in renal function, heart failure, and stroke occur more frequently following AKI than after myocardial infarction. Undetected AKI (delayed treatment) is an independent risk factor for in-hospital mortality. Specialist medical societies are recommending urgent multimodal treatment for AKI that includes prompt detection of triggering factors and complications that indicate the need to consult expert advice on treatment. According to researchers in Germany, specialized treatment for AKI, initiated in response to an early-warning system, may be beneficial compared with routine treatment.

The research team, led by **Anja Haase-Fielitz, PharmD,** and **Saban Elitok, MD,** conducted an explorative randomized controlled study to explore the variability of effect estimates and feasibility indicators of intensified treatment compared with routine care. Results were reported in *Deutsches Ärzteblatt International* [2020;117:289-296].

Patients with AKI in regular wards of a university hospital were treated either with routine care (control group) or with intensive treatment (intervention group). Patients were randomly assigned to one of the two groups. The more intensive treatment included an early warning system for a rise in serum creatinine concentration, immediate specialist consultation, and the issuance of a patient kidney passport.

The primary end point of interest was recovery of renal function after AKI during the index hospitalization. Recovery of renal function was defined as the proportion of patients who regained baseline renal function, or as the change in estimated glomerular filtration rate (eGFR) between admission and discharge during the index hospital stay. Attainment of baseline renal function was defined as an increase in eGFR to at least 90% of baseline by the time of hospital discharge. Secondary end points were renal complications and process indicators of clinical care and the time requirements of the study.

A total of 96 patients with AKI identified by the AKI early warning system were evaluated for study inclusion. Of those, 44 were excluded due to inability to consent (n=25), being treated in a nephrology or intensive care unit (n=9), participation in another study (n=3), other reasons and decline to participate (n=7). The remaining 52 patients were randomized to either the intervention group (n=26) or routine treatment (n=26). All 52 were included in the intention-to-treat analysis. The study groups were similar in demographic characteristics, comorbidities, admitting specialist department, status on admission, renal function at time of admission, AKI stage, and range of triggering factors.

Fifty percent of the patients in the intervention group and 42% of those in the control group regained baseline renal function (odds ratio with control group as reference: 1.14; 95% confidence interval, 0.5-4.0; *P*=.58). From admission to discharge, eGFR fell by 3 mL/min/1.73 m^2 in the intervention group and by 13 mL/min/1.73 m^2 in the control group (*P*=.09). Complications associated with AKI, including hyperkalemia, pulmonary edema, and renal acidosis, occurred less frequently in the intervention group than in the control group (15% vs 39%, respectively; *P*=.03); the difference was due primarily to higher incidence of hyperkalemia in the control group.

Patients in the intervention group received prompt specialist consultation more frequently than those in the control group (65% vs 4%; *P*<.001). In the intervention group, mean time of consultation was the day of AKI onset, compared with 2 days following AKI onset in the control group (*P*=.003).

The cause of AKI was more frequently identified in the intervention group compared with the control group (27% vs 4%; *P*=.05). In the intervention group, compared with the control group, drugs related to the kidney were discontinued more frequently (65% vs 31%; *P*=.01), and the diagnosis of AKI was more frequently documented in the patient's chart (58% vs 37%; *P*=.03). Triggering factors for AKI were undocumented and untreated less often in the intervention group compared with the control group (4% vs 27%; *P*=.05).

The researchers cited the explorative design of the study and the small sample size as limitations to the findings.

In conclusion, the researchers said, "Within the constraints of the study limitations, the results of this explorative randomized investigation describe the feasibility and effects of specialist-supported AKI early warning systems on regular units. Studies with sufficient power are needed to demonstrate proof of efficacy for intensified treatment." ■

TAKEAWAY POINTS

- Researchers in Germany conducted an explorative randomized controlled study to examine the efficacy of intensive treatment initiated in response to an early warning system of patients with AKI in a regular hospital ward.
- In the intervention group, 50% of patients with AKI recovered renal function, compared with 42% of those in the group that received standard care (control group), and complications were rarer in the intervention group compared with the control group (15% vs 39%; *P*=.03).
- In the intervention group, estimated glomerular filtration rate decreased from hospital admission to discharge by 3 mL/min/1.73 m^2 compared with 13 mL/min/1.73 m^2 in the control group.

Cognitive Functioning in Older Adults Nearing End-Stage Kidney Disease

In the population of older patients nearing end-stage kidney disease (ESKD), the risk for adverse health outcomes and impaired cognitive functioning is higher than among younger patients approaching ESKD. Among older patients receiving maintenance dialysis, the prevalence of impaired cognitive functioning is 30% to 87%. There is a strong association between impaired cognitive function and adverse outcomes in older patients receiving renal replacement therapy (RRT).

There are several possible pathophysiological mechanisms contributing to the high prevalence of impaired cognitive functioning, including vascular, neurodegenerative, and metabolic processes. There are few data available on the systematic assessment of patterns of cognitive functioning and their determinants in older adults approaching ESKD prior to initiation of treatment. Data on the actual brain damage seen on brain magnetic resonance imaging (MRI) are also scarce.

The COPE (Cognitive Decline in Older Patients with ESKD) study was designed to describe patterns of memory, executive function or psychomotor speed and to identify renal, geriatric, and neuroradiologic characteristics associated with cognitive impairment in older patients approaching ESKD who have not yet started RRT. **Floor J. van Deudekom, MD,** and colleagues in the Netherlands reported results of the COPE study online in *BMC Nephrology* [doi.org/10.1186/s12882-020-01764-2].

The prospective, multicenter cohort study in five hospitals in the Netherlands included 157 participants ≥65 years of age who were approaching ESKD (estimated glomerular filtration rate ≤20 mL/min/1.73 m^2) and were attending the pre-dialysis outpatient clinic between April 2014 and December 2017. As part of a routine pre-dialysis nephron-geriatric work-up the patients underwent a comprehensive geriatric assessment, (CGA) physical examination, laboratory investigation, neuropsychological testing, and a brain MRI scan.

The work-up measured kidney function, metabolic state (urea, phosphate, calcium), and measures of vascular status (blood pressure, ankle/arm index). The Modified Diet in Renal Disease or the Chronic Kidney Disease Epidemiology Collaboration was used to estimate GFR depending on the method used in different hospitals. The CGA included measures of nutrition, frailty, functional independence, and physical capacity (handgrip strength and 6-m gait speed).

Of the 157 study participants, median age was 75 years and 66% (n=103) were men. At enrollment, mean eGFR was 16.2 mL/min/1.73 m^2 and the mean decline over the previous 3 years was 9.1 mL/min/1.73 m^2. In 66% of the participants (n=99) the cause of primary kidney disease was vascular (hypertension or diabetes mellitus). Nearly half (47%, n=74) had a history of vascular disease. Using the Fried Frailty Index, 25% (n=37) were frail. Measured by the Instrumental Activities of Daily Living scale, eight participants (5%) had functional dependence (score of ≥11).

The cohort had a median Mini-Mental State Examination score of 28 of 30 points. Mean functioning on the memory test was in the 24th percentile; mean functioning on the executive function was in the 18th percentile; and mean functioning on psychomotor speed was in the 20th percentile.

In three cognitive functions of interest (memory, executive function, and psychomotor speed), there were significant associations between older age and lower educational level and cognitive impairment. Patients who performed in the lowest tertile of memory function, compared with those who performed in the highest tertile, were on average 5 years older and more often had a lower level of education.

Following adjustment for age, sex, and educational level, there was a significant association between a higher level of functional dependence and a more impaired memory function. Patients who performed in the lowest tertile of memory function were more functionally dependent compared with those who performed in the highest tertile. There was an association between a history of vascular disease and more impaired memory function; following adjustment for age, sex, and educational level, that association was no longer statistically significant. There were no associations between parameters of metabolic disturbance and impaired memory function.

Following adjustment for age, sex, and educational level, there were significant associations between higher level of functional dependence, presence of frailty, and a lower handgrip strength and a more impaired executive functioning. In the tertile with the worst executive function, the presence of frailty was higher compared with the tertile with the best executive function. There was an association between a history of vascular disease and more impaired executive function; following adjustment for age, sex, and educational level, that association was no longer statistically significant. There were no associations between parameters of metabolic disturbance and impaired executive function.

There were significant associations between a higher presence of frailty, a higher level of functional dependence, and a lower handgrip strength with impaired performance on psychomotor speed. Patients who performed in the lowest tertile of psychomotor speed had a lower handgrip strength compared with those in the highest tertile. There was an association between a history of vascular disease and an impaired performance on psychomotor speed. There were no associations between parameters of metabolic disturbance and impaired performance on psychomotor speed.

Patients who did not have a MRI were older, more frail, more functionally dependent, and had a higher history of vascular disease compared with those who did have a MRI. Among those with MRI results, following adjustment for age, sex, and educational level, there was a significant association between a higher burden of white matter hyperintensities and worse psychomotor speed. Patients who performed in the worst tertile of psychomotor speed had, on average, more white matter hyperintensities than those who performed in the best tertile. There was a trend for the association between a higher burden of white matter hyperintensities and lower executive function scores.

Citing limitations to the study findings, the researchers included the possibility of patient selection bias, the relatively small sample size, and the post hoc design of the study.

In conclusion, the researchers said, "Older patients approaching ESKD have a high prevalence of impaired memory, executive function, and psychomotor speed. The patterns of cognitive impairment and brain changes on MRI are suggestive of vascular cognitive impairment. These findings could be of potential added value in the decision-making process concerning patients with ESKD." ■

TAKEAWAY POINTS

- The COPE study examined patterns of memory, executive function, and psychomotor speed to identify characteristics associated with cognitive impairment in older patients approaching end-stage kidney disease.
- The presence of frailty and a lower handgrip strength were significantly associated with a more impaired executive functioning, and there were significant associations between presence of frailty, high level of functional dependence, and lower handgrip strength and impaired performance on psychomotor speed.
- There was a significant association between a higher burden of white matter hyperintensities and worse psychomotor speed.

Hematuria and Renal Outcomes in Patients with IgAN

Worldwide, immunoglobulin A nephropathy (IgAN) is the most common primary glomerular disease and a major cause of kidney failure requiring renal replacement therapy (RRT). The most common presentation of IgAN is hematuria; approximately 70% to 100% of patients have microscopic hematuria. However, there is some controversy regarding the role of hematuria disease progression.

In some studies, microhematuria has been shown to be a risk factor for progression of kidney disease, while others suggested that there was no association between microhematuria and the risk for kidney failure. A small study in China found a strong association between time-averaged hematuria during follow-up, using a standard urine sediment analysis in one center, and poor renal prognosis. **Gui-shen Yu, PhD,** and colleagues conducted a retrospective cohort study to examine the association of hematuria and progression of IgAN. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(1):90-99].

The cohort included 1333 patients with IgAN who were treated at a Chinese referral hospital. Median follow-up was 45 months. Microhematuria was evaluated in fresh urine using a fully automated urine particle analyzer (automated method) and urine sediment examination by a skilled examiner (manual method). Hematuria was characterized as a time-varying attribute, i.e., average hematuria level was calculated for every 6-month period for each patient during follow-up. Remission was defined as average red blood cell (RBC) count ≤5 per high-power field (HPF) using the manual method or ≤28 RBC per mL using the automated method during the first 6 months of follow-up.

The outcome of interest was a composite event of 50% decline in estimated glomerular filtration rate (eGFR) or development of kidney failure.

During follow-up, participants had 429 automated urine examinations per 100 person-years and 457 per 100 person-years using the manual method. The Oxford classification was not performed in 29 patients with fewer than eight glomeruli on kidney biopsy.

At baseline, 50.64% of the participants were men (n=675) and mean age was 35.07 years. Median eGFR was 82.2 mL/min/1.73 m^2, median protein excretion was 1.31 g/d, and mean arterial pressure (MAP) was 93.73 mm Hg. At baseline, 645 patients were hypertensive. Initial hematuria was 12.50 RBC/HPF using the manual method and 97.60 RBC/mL using the automated method. A total of 375 patients were recorded as having a history of microscopic hematuria. The distributions of M1, E1, S1, T1-T2, and C1-C2 were 39.88%, 33.05%, 62.27%, 34.51%, and 58.67%, respectively.

During the 45 months of follow-up, time-averaged hematuria was 11.31 RBC. HPF using the manual method and 68.66 RBC/mL using the automated method. For time-averaged proteinuria, median protein excretion was 0.86 g/d. Overall, 207 patients reached the composite kidney disease progression event, including 123 kidney failure events.

The two techniques for hematuria (manual and automated) displayed a strong and statistically significant linear correlation (r=0.948; *P*<.001). The conversion coefficient between the two methods was 5.6. Using the manual method, hematuria remission was defined ≤5 RBC/HPF; using the automated method, remission was defined as ≤28 RBC/mL.

During the first 6 months, there were 253 patients with ≤28 RBC/mL. Those patients showed a higher prevalence of hypertension, and lower prevalence of M1, E1, S1, C1, and C2 lesions. Using the Oxford classification, there was no significant difference in the prevalence of T lesions.

A total of 639 patients received steroids and/or other immunosuppressive agents. In the group with immunosuppressive therapy, patients had more hematuria at baseline compared with the untreated group (median values of 117.55 vs 81.20 RBC/mL; *P*<.001). Time-averaged hematuria during follow-up was similar between the treated and untreated groups.

In cause-specific hazards models, following adjustment for age, sex, time-varying proteinuria, time-varying MAP, baseline eGFR, use of steroids or other immunosuppression agents, and Oxford classification, time-varying hematuria using the automated method was an independent risk factor for the composite outcome of kidney disease progression (hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.13-1.87; *P*=.003). When hematuria was measured using the manual method, results were similar (HR, 1.46; 95% CI, 1.15-1,86; *P*=.002).

During the first 6 months, 12.3% (n=31) of patients in the hematuria remission group and 16.3% (n=176) of those in the nonremission group reached the composite kidney disease progression event (*P*=.01). There was a significant association between hematuria remission and reduced risk for the composite event (HR, 0.41; 95% CI, 0.28-0.61; *P*<.001).

In patients without proteinuria remission (protein excretion >1.0 g/d) during the first 6 months, there was significant reduction in the risk for the composite kidney disease progression event when hematuria remission during the first 6 months was treated as a time-varying covariate (HR, 0.46; 95% CI, 0.32-0.68; *P*<.001). There was no association between hematuria remission during the first 6 months and improved kidney survival in patients with proteinuria remission (HR, 0.64; 95% CI, 0.31-1.29; *P*=.2).

There were some limitations to the study cited by the authors, including the single-center design with a single ethnicity, the possibility of time-varying confounding, and not directly evaluating the predictive value of reductions in hematuria.

In conclusion, the researchers said, "In this large cohort study, we confirmed that the extent of microhematuria during follow-up was independently associated with kidney disease progression in IgAN, suggesting it should be included in the risk scoring system for predicting renal outcomes of IgAN. Hematuria remission significantly reduced the incidence of kidney disease progression events. Importantly, we found this effect much greater in patients without proteinuria remission, for whom hematuria remission during therapy may reduce the risk for kidney failure. These findings may help inform clinical management decisions. Hematuria evaluated using the fresh urine automated method had similar associations with renal outcomes as those evaluated using the manual urine sediment method. When it is confirmed as a standard and rapid method, the fresh urine automated method should be considered for IgAN clinical practice in the future." ■

TAKEAWAY POINTS

- Hematuria is the most common presentation of immunoglobulin A nephropathy (IgAN). Researchers in China conducted a retrospective cohort study to examine the association between hematuria and progression of kidney disease.
- The study utilized two methods to evaluate microhematuria: (1) a fully automated urine particle analyzer (automated method) and (2) urine sediment examination by a skilled examiner (manual method).
- There was an independent association between level of hematuria and progression of kidney disease; remission of hematuria was associated with improved kidney outcomes in IgAN in patients with persistent proteinuria. Associations with outcomes were similar with the two evaluation methods.

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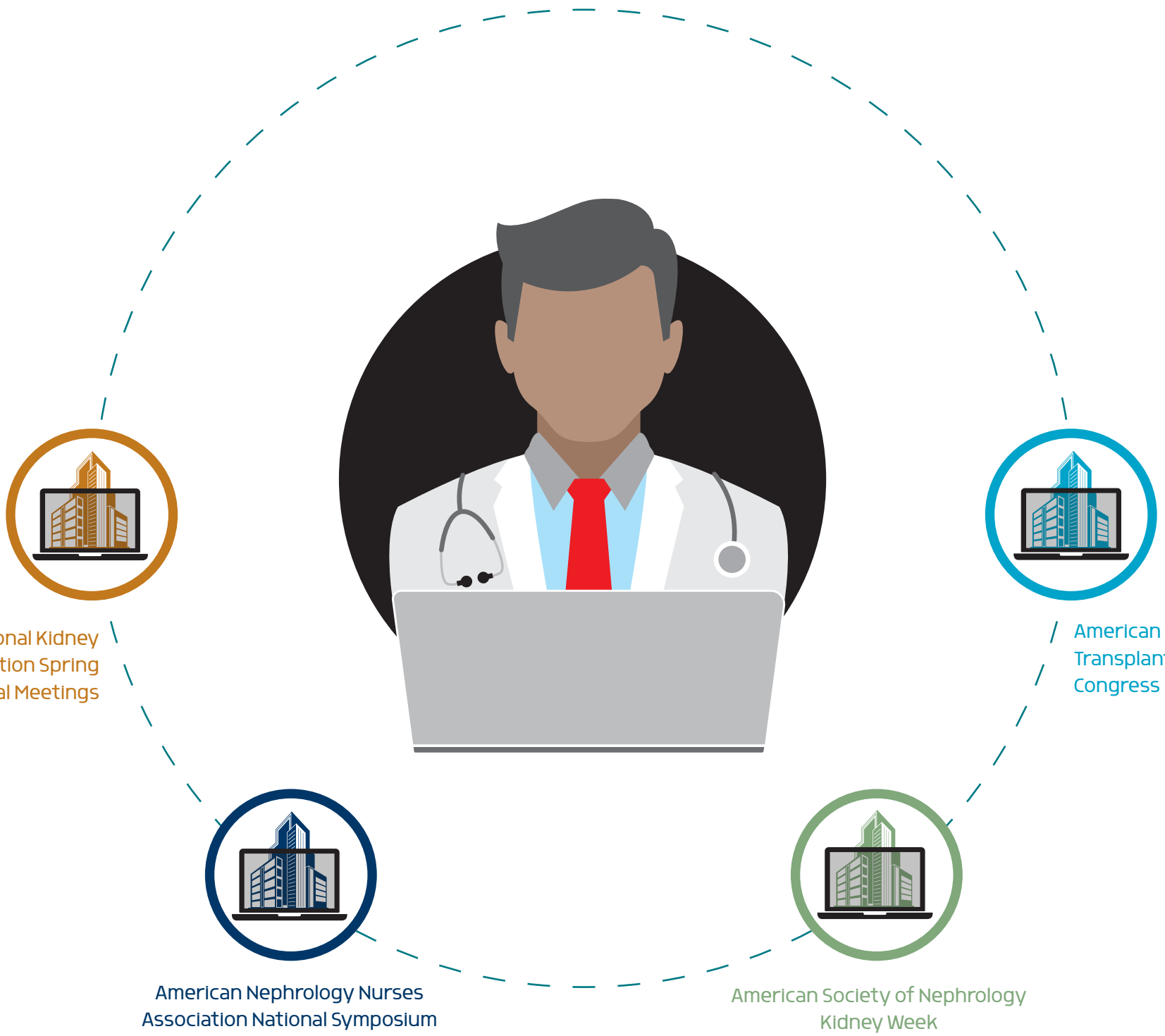

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Cognitive Function among Patients Evaluated for Kidney Transplantation

Patients with kidney failure undergoing dialysis may develop cognitive impairment; the prevalence of cognitive impairment in this patient population ranges from 10% to 80%, depending on the specific population being studied and the test used to define it. Patients with dementia are contraindicated for kidney transplantation; however, transplant candidates may have undiagnosed mild cognitive impairment. The proportion of candidates with cognitive impairment at the time of transplant evaluation and the effect on functional dependence are unknown.

Intact cognition is critical for patients undergoing evaluation for kidney transplantation; cognitive impairment may spur difficulties navigating the complex medical system associated with transplantation. Cognitive impairment also presents challenges to patients in managing chronic conditions and adherence to complex medication regimens and fluid and dietary restrictions.

TAKEAWAY POINTS

- Researchers conducted a study to estimate the burden of cognitive impairment in patients being evaluated for kidney transplantation and its association with access to transplantation and waitlist mortality.
- In a prospective cohort study of patients being evaluated for transplantation, both with and without cognitive impairment, those with cognitive impairment had a 25% lower change of being waitlisted for transplant.
- There was a nominal difference by diabetes status for the association between cognitive impairment rate and kidney transplantation rate; candidates with diabetes and cognitive impairment were at 2.47 times greater risk for waitlist mortality.

Nadia M. Chu, PhD, MPH, and colleagues conducted a two-center prospective cohort study among dialysis patients undergoing evaluation for transplantation to examine (1) the prevalence of cognitive impairment and level of functional impairment and functional dependence in those with cognitive impairment, (2) the chance of listing for kidney transplantation and the rate of kidney transplantation by cognitive impairment status at the time of evaluation, and (3) the risk for kidney transplantation waitlist mortality. The associations were also examined based on diabetes status.

Cognitive impairment was measured using the Modified Mini-Mental State Examination (3MS) at the time of kidney transplantation at the two centers. Cognitive impairment was defined as a 3MS score <80. The outcomes of interest were listing, waitlist mortality, and kidney transplantation. Results of the study were reported in the *American Journal of Kidney Diseases* [2020;76(1):72-81].

The study cohort included 3630 dialysis patients who were undergoing evaluation for kidney transplantation. Median age was 56 years, 41.2% were women, and 45.5% were Black. At the time of transplant evaluation, 6.4% of the participants were identified as having cognitive impairment. Those with cognitive impairment were more likely to be older (median age 62 vs 56 years; $P<.001$), Black (69.1% vs 43.8%; $P<.001$), have diabetes (49.5% vs 41.7%; $P=.04$), and have lower educational attainment (75.5% vs 42.3%; $P<.001$), and were less likely to be women (30.0% vs 41.9%; $P<.001$), compared with those without cognitive impairment.

There was an association between cognitive impairment at the time of kidney transplantation evaluation and functional dependence for both activities of daily living (ADLs) and instrumental activities of daily living (IADLs) (15.4% vs 7.7% in those with vs without impairment; $P<.001$, and 36.2% vs 19.4%; $P<.001$, respectively).

Of the six ADL components, four were associated with cognitive impairment: difficulty with physical ambulation (10.0% vs 5.2% in those with vs without cognitive impairment; $P=.004$), dressing (4.7% vs 1.4%; $P<.001$), bathing (6.7% vs 2.2%; $P<.001$), and toileting (1.9% vs 0.6%; $P=.03$). There was an association between cognitive impairment and all eight of the IADL components: difficulty shopping (24.3% vs 9.5%; $P<.001$), washing (19.5% vs 7.7%; $P<.001$), taking transportation (13.8% vs 5.9%; $P<.001$), managing medications (13.8% vs 3.3%; $P<.001$), managing money (13.4% vs 2.6%; $P<.001$), cooking (13.3% vs 5.3%; $P<.001$), house cleaning (11.0% vs 5.1%; $P<.001$), and using the telephone (1.0% vs 0.1%; $P=.007$).

The prevalence of cognitive impairment was 7.3% among patients with diabetes compared with 5.4% of patients without diabetes ($P=.04$). There were differences in the median scores of the different 3MS components by diabetes status: psychomotor skills (20 vs 21 points in those with vs without diabetes; $P=.001$), memory (19 vs 20 points; $P<.001$), and identification/association (23 vs 24 points; $P=.001$), There were no statistical differences in scores for orientation.

Following adjustment for age, sex, race, education, diabetes and Charlson Comorbidity Index score, cognitively impaired participants had a 25% (adjusted hazard ratio [aHR], 0.75; 95% confidence interval [CI], 0.61-0.91) lower chance of being listed for kidney transplantation, compared with participants who were not cognitively impaired. This association nominally differed by sex at a borderline level of statistical significant ($P_{interaction}=.05$): among male and female participants, aHRs for listing in those with versus without cognitive impairment were 0.55 (95% CI, 0.38-0.80) and 0.86 (95% CI, 0.68-1.08), respectively.

Following adjustment, there was no association between cognitive impairment and the risk for waitlist mortality (adjusted subdistribution HR, 1.53; 95% CI, 0.83-2.18). However, this association varied by diabetes status ($P_{interaction}=.02$). Among participants without diabetes, there was an association between cognitive impairment and a 2.47 times greater risk for waitlist mortality compared with participants without cognitive impairment. Among those with diabetes, there was no association between cognitive impairment and waitlist mortality.

Among the cohort of kidney transplantation candidates, median follow-up time following listing for transplantation was 1.6 years. There was no difference by cognitive impairment in the cumulative incidence of kidney transplantation. In both unadjusted and adjusted analyses, there was no association between the rate of kidney transplantation and cognitive impairment. However, at borderline statistical significance, there was nominal variation in the association by diabetes status: among participants with and without diabetes, adjusted incidence rate ratios for kidney transplantation in those with versus without cognitive impairment were 0.58 (95% CI, 0.36-0.93) and 1.12 (95% CI, 0.71-1.77), respectively.

Limitations to the study findings cited by the authors included the use of a single instrument to define cognitive impairment and the number of centers included in the analysis.

"Cognitive impairment is associated with a lower chance of being placed in the waitlist, and among patients without diabetes, with increased mortality on the waitlist. Future studies should investigate whether implementation of screening for cognitive impairment improves these outcomes," the researchers said. ■

Screening for Asymptomatic CAD in Waitlisted Transplant Candidates

For the majority of patients with kidney failure, kidney transplantation offers superior survival and quality of life compared with maintenance dialysis therapy. For patients with cardiovascular disease, the risk for morbidity and mortality following transplantation is high. Because early detection of asymptomatic coronary artery disease (CAD) and treatment with revascularization may prevent perioperative myocardial infarction and cardiovascular deaths, screening for CAD prior to transplantation may provide additional prognostic data and facilitate early intervention and informed allocation of resources.

Guidelines from Kidney Disease Improving Global Outcomes call for annual CAD evaluation for diabetic patients on the transplant waitlist and re-evaluation for CAD every 24 to 36 months for all other patients. Previous trials in patients without kidney failure have not shown a survival benefit for screening for CAD in asymptomatic patients, and there are no data available on the cost-effectiveness of screening for asymptomatic CAD.

Researchers are currently conducting the Canadian-Australian randomized controlled trial of screening kidney transplant candidates for CAD (CARSK [registered as ACTRN12616000736448 and NCT03674307) to test the hypothesis that after waitlist entry, no further screening for asymptomatic CAD is noninferior (with a margin of a 25% increase or 1.5% absolute difference) to regular screening for CAD in preventing major adverse cardiac events. One outcome of interest is the cost-effectiveness of regular CAD screening compared with no further screening and the subsequent economic impact of costs related to CAD from a health system perspective.

Results from the CARSK study are not expected until 2025. Researchers, led by **Tracey Ying, PhD**, conducted a cost-utility analysis to determine, prior to completion of CARSK, the cost-effectiveness of screening for asymptomatic CAD and to identify potential influential variables that may affect results of the economic evaluation in CARSK. Results of the current analysis were reported in the *American Journal of Kidney Diseases* [2020;75(5):693-704].

The researchers developed a Markov microsimulation model to replicate the natural history of a theoretical cohort of Australian kidney transplant candidates 18 to 69 years of age. The primary outcome of interest was incremental cost-effectiveness ratio (ICER), reported as cost per quality-adjusted life-year (QALY).

The analysis compared two strategies: in the no-further-screening arm, patients received no further noninvasive CAD screening following waitlist entry unless they developed CAD symptoms; in the regular screening arm, all patients commenced screening in the first year of the model. Screening tests were repeated every year in patients with diabetes mellitus and every 2 years in patients without diabetes mellitus. If a patient had a positive stress test in any given year, the test was repeated the following year. The model assumed 100% screening adherence in the regular screening group.

In the base-case model that used a single point estimate for each variable within the model, the total lifetime costs of a patient following waitlist entry were $506,092 for no further screening versus $502,288 for regular screening. No further screening accrued an average 9.38 life-years (LYs) and 7.67 QALYs compared with 8.89 LYs and 7.31 QALYs for regular screening. The ICER of no further screening compared with regular screening was $8171 per LY gained and $11,122 per additional QALY.

Among the patients in the no-further screening group, a higher proportion received a transplant after 5 years compared with patients in the regular-screening group (65% vs 63%, respectively). There was a slightly higher mortality rate at 5 years in the regular-screening arm than in the no-further-screening arm (26.0% vs 24.8%), likely due to invasive cardiac procedures and longer waitlist time.

Transportation costs in the first year and the prevalence of CAD in waitlisted candidates had the greatest effect on changes in the ICER. There was no substantial alteration in the ICER due to CAD-related expenditure items such as the cost of revascularization or the costs of screening tests. No further screening remained cost-effective until transplant costs exceeded $200,000 in the first year. CAD presence was influential in the model when tested between the ranges of 10% to 90%. The reduction in ICER was marked when the prevalence of CAD was reduced to <30%, an indication that no further screening would be very cost-effective in cohorts with low prevalence of CAD. There was no substantial increase in ICER associated with a CAD prevalence of 90%. However, when combined with changes in the cost of transportation in year 1, CAD prevalence was influential in the model.

Transportation costs in the first year and the prevalence of CAD in waitlisted candidates had the greatest effect on changes in the ICER. There was no substantial alteration in the ICER due to CAD-related expenditure items such as the cost of revascularization or the costs of screening tests.

The researchers performed two-way sensitivity analysis using the top two most influential variables to test the combined effects of a range of transportation costs in year 1 and the prevalence of CAD. When no further CAD screening was performed in a cohort with a high prevalence of CAD and health expenditure in year 1 exceeded $170,000 to $200,000, the ICER was >$50,000 per QALY gained, but remained <$100,000 per QALY gained.

Results of probabilistic sensitivity analyses showed that 94% of the simulations were cost-effective below a willingness-to-pay threshold of $50,000 per QALY gained.

In conclusion the researchers said, "By incorporating the best available evidence, our pretrial model has provided an estimate of the benefits and trade-offs of no further screening versus regular screening in asymptomatic CAD in patients on the kidney transplant waitlist. Our results challenge the belief that regular screening for asymptomatic CAD improves outcomes. The lack of randomized controlled trials among patients with kidney failure and the clinical uncertainties surrounding the efficacy of CAD screening reinforce the need for a large prospective multicenter trial." ■

TAKEAWAY POINTS

- Researchers conducted a modeled cost-utility analysis to determine the cost-effectiveness of no further screening for asymptomatic coronary artery disease (CAD) in patients on the waitlist for kidney transplantation versus regular screening.
- The incremental cost-effectiveness ratio of no further screening was $11,122 per quality-adjusted life year (QALY) gained compared with regular screening. No further screening increased survival by 0.49 LY or 0.35 QALY.
- In probabilistic sensitivity analyses, 94% of the simulations were cost-effective below a willingness-to-pay threshold of $50,000 per QALY gained.

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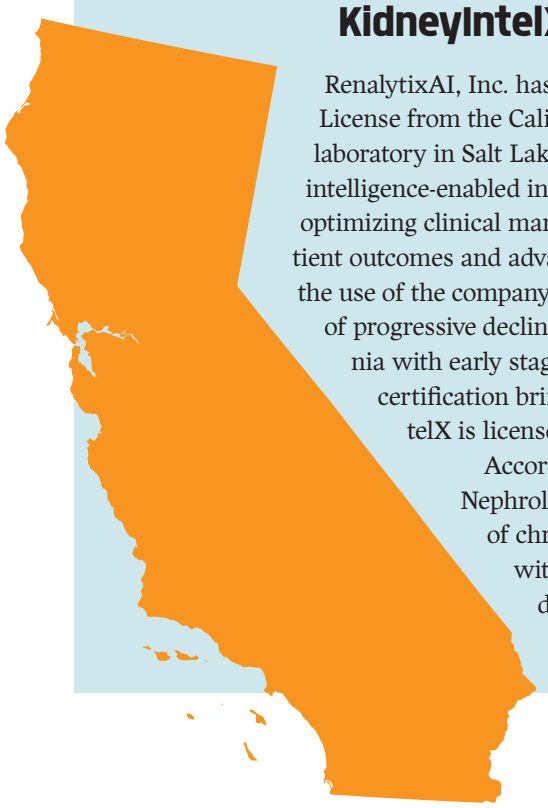

RenalytixAI, Inc. has received a California Clinical Laboratory License from the California Department of Health for its clinical laboratory in Salt Lake City, Utah. RenalytixAI is an artificial intelligence-enabled in vitro diagnostics company specializing in optimizing clinical management of kidney disease to improve patient outcomes and advance value-based care. The license enables the use of the company's KidneyIntelX™ to report risk assessment of progressive decline in kidney function for patients in California with early stage diabetic kidney disease. The California certification brings the number of states where KidneyIntelX is licensed to 49.

According to data from the American Society of Nephrology, California has one of the highest rates of chronic kidney disease in the United States, with more than 5 million patients with kidney diseases, including 94,000 patients with kidney failure and 68,000 patients on dialysis.

In August 2020, RenalytixAI announced the filing of a submission seeking clearance of KidneyItelX with the US FDA, building on the company's regulatory and commercialization program. The program included an announcement in September 2020 of the commercial launch of the KidneyIntelX clinical test reporting platform within the Mount Sinai Health System in New York.

In a press release from RenalytixAI, KidneyIntelX is described as "designed to provide potentially critical new information about the rate of disease progression and risk of progressive kidney decline in early stage kidney disease to healthcare providers, insurance payers, and population health managers in an effort to support optimization of care delivery, improve patient outcomes, and reduce the $120 billion annual cost of chronic and end-stage kidney disease to the United States healthcare system."

Nutrition in CKD Clinical Practice Guidelines Updated

The National Kidney Foundation (NFK), in collaboration with the Academy of Nutrition and Dietetics, released the 2020 Kidney Disease Outcomes Quality Initiation (KDOQI) Clinical Practice Guideline on Nutrition in Chronic Kidney Disease. The recommendations are meant to guide healthcare practitioners treating individuals with all stages of kidney disease.

KDOQI published initial guidelines on nutrition for patients with end-stage kidney disease in 2000. The current update has been expanded to include nutritional management of patients with stages 1 to 5 chronic kidney disease (CKD) as well as patients with a functioning kidney transplant. The new guidelines address six primary areas: (1) nutritional assessment; (2) medical nutrition therapy; (3) dietary protein and energy intake; (4) nutritional supplementation; (5) micronutrients; and (6) electrolytes.

In a joint press release from NKF and the academy, **Kerry Willis, PhD,** NKF chief scientific officer, said, "Global adoption and implementation of KDOQI guidelines has dramatically changed all aspects of chronic kidney disease care in the years since the original nutrition guideline was published. This guideline update reflects the numerous advances in both guideline development and dietary management of patients with chronic kidney disease over the past 20 years. We at NKF take great pride in the role KDOQI has played and will continue to play in moving the field forward and improving patient care."

The updated guideline includes practical clinical recommendations as well as insights on nutritional areas not well understood, such as the currently insufficient evidence regarding any recommendations regarding the type of protein, i.e., plant versus animal, that is best for all patients with CKD. The guideline notes that while plant-based diets may have benefits for many patients, further research is warranted to better understand the effects on clinical outcomes.

Alison Steiber, PhD, RDN, LD, chief science officer for the Academy of Nutrition and Dietetics, said, "These guidelines will be a valuable tool for registered dietitian nutritionists in administering medical nutrition therapy to patients with CKD, which will result in timely and accurate assessment of malnutrition, evidence-based nutrition interventions, and improved patient outcomes."

The international, multidisciplinary workgroup was chaired by **T. Alp Ikizler, MD,** at the Vanderbilt University Medical Center, Nashville, Tennessee, and **Lilian Cuppari, PhD,** of the Oswaldo Ramon Foundation-Hrim Federal University, Sao Paulo, Brazil.

Draft Guidance on Pharmacokinetics in Patients with Impaired Kidney Function

The US FDA has issued a draft guidance for the pharmaceutical industry titled "Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing." The draft guidance replaces the FDA guidance, "Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010)."

The current draft guidance updated recommendations on five topics: (1) when a standalone study of a drug's pharmacokinetics in subjects with impaired renal function is recommended and when it may not be needed; (2) design and conduct of pharmacokinetic studies in subjects with impaired renal function; (3) considerations for characterizing a drug's pharmacokinetics in patients undergoing intermittent or continuous dialytic therapies; (4) use of pharmacokinetic information from phase 2 and 3 studies to inform dosing recommendations for patients with impaired renal function; and (5) analysis and reporting of the results of studies that characterize the impact of impaired renal function and how these data inform dosing recommendations in labeling.

Stakeholders can provide comments to the public docket (docket number FDA-2010-D-0133) at www.regulations.gov up to 90 days following publication in the Federal Register.

Nephrology in Top Ten Specialties Adopting Telemedicine

The professional medical network, Doximity, has published its 2020 State of Telemedicine Report. The report represents an analysis of trends in telemedicine in the United States since the onset of the COVID-19 pandemic. The analysis included data from more than 2000 patients in the United States as well as an examination of online physician CVs.

The study results suggested that 20% of all medical visits will be conducted via telemedicine in 2020, accounting for more than $29.3 billion of medical services this year.

According to a press release from Doximity, of the top 10 medical specialties adopting telemedicine, nephrology is number four.

Christopher Whaley, PhD, lead author of the report, said, "This year alone, over 20% of medical office visits will likely be

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conducted via telehealth. The combination of shelter-in-place orders and the need to protect those patients most at risk from COVID-19 infection, have created a real necessity to employ alternatives to the traditional in-person office visit. Moreover, physicians have found telemedicine has served as a vital lifeline for practices negatively impacted financially by the pandemic. In our view, the rapid uptake of telemedicine has important structural implications for the US healthcare system."

NKF Partners with Moonstone Nutrition to Prevent Kidney Stones

The National Kidney Foundation (NKF) is partnering with Moonstone Nutrition to increase awareness regarding the prevalence of kidney stones and the importance of overall kidney health. The company and the foundation will develop educational materials designed to teach consumers and healthcare professionals about kidney stones. The materials will include information on symptoms and prevention options, according to a press release.

Although there are prescription treatments available for kidney stones, there are few over-the-counter (OTC) products that effectively support kidney stone prevention. Moonstone Nutrition has developed a patented formula delivering 30 mEq of alkali citrate (from citrate salts) per serving. The formula was developed by kidney stone experts.

Salim Rayes, president and CEO of Moonstone Nutrition, said "Until now, consumers only had a few OTC options. Although lemon juice and citrus-based beverages may raise urine citrate, those drinks may not be optimized for kidney stone prevention. Moonstone contains clinically significant amounts of citrate-as-alkali to increase urine citrate and pH, and may make the kidneys less hospitable to the formation of kidney stones, namely: calcium oxalate, cystine and uric acid stones. Moonstone's key ingredients have been studied and found effective in helping prevent kidney stones."

The senior vice president of strategic partnerships at the NKF, **Anthony Guciardo,** said, "We're very pleased to partner with Moonstone Nutrition to help inform our patients and healthcare professionals on ways to prevent and treat kidney stones. The informational microsite we've developed will share information on risk factors, symptoms, and what consumers can do to prevent this often-painful condition."

Fresenius Kidney Care Deploys Data Exchange Network

Fresenius Kidney Care, the dialysis services division of Fresenius Medical Care North America is deploying CommonWell health data exchange services to all of its dialysis facilities in order to enable near real-time exchange of individual patient health information. According to a press release from Fresenius Medical Care North America, "With the connection to the CommonWell Health Alliance interoperability network and its bridge to the Carequality interoperability framework, care team members can locate, exchange, and view patient health information from more than 600,000 providers and 2800 hospitals across the country."

The exchange will enable the provider network to access dialysis treatment records for any patient treated at Fresenius Kidney Care and coordinate care with the patient's other participating providers.

Mike Asselta, president of Fresenius Kidney Care, said, "Ensuring all healthcare providers have the most up-to-date records when our dialysis patients receive care is vital to providing the best treatment and

CONFERENCE COVERAGE AMERICAN TRANSPLANT CONGRESS

Long-Term Patient and Graft Survival among Pediatric Liver-Kidney Transplant Recipients

There are few data available on long-term outcomes among pediatric recipients of simultaneous liver-kidney transplantation and sequential liver and kidney transplantation (liver after kidney and kidney after liver). **K. Goli** and colleagues conducted a review of data in the United Network for Organ Sharing (UNOS) database. Results were presented at the virtual American Transplant Congress 2020 in a presentation titled *Long-Term Pediatric Outcomes of Simultaneous vs Sequential Liver-Kidney Transplantation: A Review of UNOS Database.*

The researchers queried the database for sequential and simultaneous liver and kidney transplants in patients <18 years of age between 1988 and 2018. Multivisceral listings and retransplants were excluded from the analysis. Simultaneous liver-kidney transplants were defined as occurring ≤1 day apart. Liver after kidney and kidney after liver were each defined as occurring >1 day apart. Patient survival was calculated from the time of the first transplant and graft survival was calculated from transplant of the second organ. Statistical significance was determined using log-rank tests and Meier survival analysis was used to compare simultaneous liver-kidney transplant, liver after kidney transplant, and kidney after liver transplant. Univariate analyses were performed using ANOVA and chi-square tests.

The study included a total of 389 transplant recipients: 265 simultaneous liver-kidney transplant recipients; 42 liver after kidney transplant recipients; and 83 kidney after liver transplant recipients.

There was a significant patient survival benefit for kidney after liver transplant relative to simultaneous liver-kidney transplant and liver after kidney transplant: a patient survival probability of 86% relative to 73% for simultaneous liver-kidney transplant and 56% to liver after kidney transplant at 17 years post-transplant ($P<.0001$). Following adjustment for 16 covariates, including demographic factors and total time on waiting lists, the survival benefit for kidney after liver transplant was no longer significant relative to simultaneous liver-kidney transplant ($P<.77$).

For kidney graft survival, beginning at 4.5 years following transplant, there was a significant ($P<.044$) survival benefit for simultaneous liver-kidney transplant relative to kidney after liver transplant and liver after kidney transplant. The greatest graft survival benefit for simultaneous liver-kidney transplant was seen at 17 years post-transplant: 59% versus 36% for kidney after liver transplant and 26% for liver after kidney transplant.

For liver graft survival, kidney after liver transplant conferred a significant survival benefit relative to simultaneous liver-kidney transplant and liver after kidney transplant at all time points ($P<.0001$). At 16 years after transplant, kidney after liver transplant had a 75% graft survival probability, simultaneous liver-kidney transplant showed a 56% graft survival probability, and liver after kidney transplant showed a 46% graft survival probability.

In conclusion, the researchers said, "Liver after kidney transplant has the worst outcomes, likely due to recurrent cholangitis or portal hypertension in patients who are already immunosuppressed after kidney transplant. Therefore, simultaneous liver-kidney transplant should be considered."

Source: Goli K, Rana A, Goss J, Miloh T. Long-term pediatric outcomes of simultaneous vs sequential liver-kidney transplantation: A review of the UNOS database. Abstract of a presentation at the virtual American Transplant Congress 2020 (Abstract #262), May 30, 2020.

outcomes possible. By implementing this leading national exchange, we are taking another important step toward better coordinated care for all patients living with kidney failure."

Dave Cassel, executive director of Carequality, said, "We're pleased to have Fresenius Kidney Care as part of the growing Carequality community via their participation in CommonWell. Access to health information for those treating chronic kidney patients has great potential to boost outcomes for these vulnerable patients who often have complex medical needs."

The data exchange services have been implemented in select states and dialysis centers; the services will be expanded in the coming months.

Race Removed from GFR Estimation Formula at University Health Center

In a recent press release, UW Health and University of Wisconsin School of Medicine and Public Health call for an "approach to assess kidney function devoid of race."

The formula for estimating glomerular filtration rate (GFR), developed more than 20 years ago, is widely utilized as a measure of kidney function. The formula is based on a blood test for creatinine, a protein released by muscles, and on race. Including race in creatinine-based GFR was based on observations from studies that suggested Black participants had higher GFRs compared with White participants. Possible explanations for the variation include higher average muscle mass among Black participants compared with White participants, as well as the original testing sample being comprised of primarily non-Hispanic White men.

However, according to **Arjang Djamali, MD,** professor at the UW School of Medicine and Pubic Health and UW Health nephrologist, race is a social construct rather than a biological one, and should not be used as a proxy for muscle mass or kidney function.

The use of race in the creatinine-based formula can result in overestimation of GFR to identify kidney function in patients with advanced stages of disease. Overestimation of GFR results in delays in care as well as in access to kidney transplantation for Black patients.

"Essentially, this calculation would often suggest that a Black patient's kidney function is better than what it really is," Dr. Djamali said. "These are the reasons race needs to be eliminated from the formula."

The press release noted that removal of race from the creatinine-based formula could result in the misclassification of the stage of kidney disease in approximately 10% of patients. Dr. Djamali and a multidisciplinary team suggest using a confirmatory cystatin c-based GFR test when accurate staging of kidney disease is considered. The cystatin C-based GFR test does not rely on a race-based assumption.

UW Health has begun using the cystatin C-based GFR test.

"This simple biological test, rather than a social construct, can help eliminate an element of systemic racism in medicine," Dr. Djamali said. "We strongly encourage all health systems to follow this example, and for everyone in the practice of medicine to intentionally engage in anti-racism efforts."

Walden Biosciences, Inc., Launched with Series A Financing

In a press release, Walden Biosciences, Inc., announced its launch with a $51 million Series A financing led by ARCH Venture Partners and UCB Ventures. Walden, a biotechnology company focusing on the transformation of treatment for kidney disease, seeks to develop "breakthrough medicines that reverse the progression of both rare and common forms of kidney disease and restore renal function."

The majority of current approaches to the development of renal drugs focus on reducing general physiologic stressors (hypertension, diabetes, and inflammation) that lead to chronic kidney disease. According to the press release, Walden intends to advance the treatment of renal disease by addressing kidney-specific cell types and biologic processes to produce therapies that restore renal function rather than slow its decline.

Blaine McKee, PhD, president and CEO of Walden Biosciences, said, "Kidney disease is a public health crisis and there is an urgent need to develop innovative therapies that directly target the disease and provide an alternative to dialysis or transplant. Walden seeks to revolutionize the field of nephrology and we are relentlessly focused on changing the way patients with all forms of kidney disease are treated."

The Walden team includes recognized leaders in renal disease treatment, antibody research, and company building. **Steven Gillis, PhD,** managing director at ARCH Venture Partners and chairman of the board of Walden Biosciences, said, "The team being assembled at Walden has a deep understanding of renal disease and therapeutic drug development, which will serve us well on our quest to change the way kidney disease is treated. The company is pursuing a unique approach and I look forward to seeing the potential impact Walden's first-in-class therapies will have on patients suffering from kidney disease." ■

AKF and Sanofi Genzyme Launch Campaign for Awareness of Fabry Disease

In a recent press release, the American Kidney Fund (AKF) announced an education and awareness campaign to increase visibility of Fabry disease. The campaign will include encouraging patients with chronic kidney disease (CKD) with an unknown underlying cause to get tested for Fabry disease. The campaign is being funded through a partnership with Sanofi Genzyme, a company working to support the rare disease community for more than 35 years.

Fabry disease is a genetic disorder that is diagnosed in approximately one in 40,000 people. It is caused by a mutation of the GLA gene, resulting in decreased production of an enzyme needed to break down globotriaosylceramide (GL-3) and a buildup of GL-3 in cells throughout the body. Fabry disease can lead to CKD and end-stage renal disease and is associated with damage to the heart and brain. The disease is often unrecognized or misdiagnosed. Early diagnosis can result in interventions that may delay serious complications.

LaVarne A. Burton, president and CEO of AKF, said, "For patients with a rare condition like Fabry disease, the road to a diagnosis and proper treatment can be long and painful. This partnership with Sanofi Genzyme allows us to expand our educational materials on Fabry disease, increase awareness of the condition, and empower patients with practical guides they can use when discussing their health with their doctors or families."

The campaign will use digital media, including social media, to reach and engage patients. Visit www.KidneyFund.org/fabry for more information.

EAP Launched for Treatment for Fabry Disease

Chiesi Global Rare Diseases, a business unit of Chiesi Farmaceutici S.p.A., and Protalix Bio Therapeutics, Inc., announced the launch of an Expanded Access Program (EAP) in the United States for pegunigalsidase alfa for the proposed treatment of Fabry disease. The US FDA is currently reviewing a biologics license application for pegunigalsidase alfa. The EAP will run concurrently with Protalix's ongoing phase 3 clinical program.

Marcel van Kuijck, PhD, global head of medical affairs at Chiesi Global Rare Diseases, said, "The launch of this Expanded Access Program for pegunigalsidase alfa is another example of Chiesi's and Protalix's shared commitment to support patients whose condition cannot be adequately treated by currently available FDA-approved therapies for Fabry disease."

Raul Chertoff, MD, vice president and chief medical officer at Protalix, said, "We are excited that a broader group of physicians and patients beyond those in our phase 3 program will have access to pegunigalsidase alfa, and that such support to Fabry patients in the US is available prior to FDA's final review."

According to a press release, the EAP is open to patients with a clinical diagnosis of Fabry disease who, in the opinion of the treating physician, have no comparable or satisfactory alternative treatment options with currently available FDA-approved therapies for Fabry disease. There are other eligibility criteria as well. Patients participating in the EAP will receive infusions of pegunigalsidase alfa every 2 weeks at 1 mg/kg body weight.

Jerry Walter, founder and president of the National Fabry Disease Foundation, said, "The National Fabry Disease Foundation and the Fabry community are very excited about the launch of Chiesi's Expanded Access Program for pegunigalsidase alfa for the treatment of Fabry disease. As the number of people diagnosed with Fabry disease continues to exceed predictions, access to treatment through Expanded Access Programs can play an important role in helping as many eligible patients as possible access the treatment they need."

ACUTE KIDNEY INJURY

RAS Blockers and Risk of Contrast-Induced AKI

Journal of Nephrology, doi.10.5414/CN110171

Complications following coronary angiography (AG) or percutaneous coronary intervention (PCI) include contrast-induced acute kidney injury (CI-AKI). There is an association between CI-AKI and increased morbidity and mortality. It is unclear whether renin-angiotensin system (RAS) blockers increase or decrease CI-AKI.

Takayuki Yamada, MD, and colleagues conducted a meta-analysis to examine the association between RAS blockers and CI-AKI in patients with normal kidney function or mild-to-moderate chronic kidney disease (CKD).

The researchers performed a search of PubMed, EMBASE, clinicaltrials.gov, and the Cochrane Library up to December 2019. The studies of interest assessed the association between RAS blockers and CI-AKI events following coronary AG/PCI. The primary outcome of interest was development of CI-AKI.

The analysis included five randomized controlled trials and five observational studies, representing a total of 7420 patients. Unstratified, there was a significant association between administration of RAS blockers and an increased risk of CI-AKI (pooled odds ratio [OR], 1.63; 95% confidence interval [CI], 1.19-2.25; *P*=.003). The effect was not seen in randomized controlled trials (pooled OR, 1.22; 95% CI, 0.54-2.74; *P*=.63). Results of sensitivity analysis in observational studies suggested a significant association (pooled OR, 1.77; 95% CI, 1.22-2.55; *P*=.003) with high heterogeneity and evidence of publication bias.

In summary, the researchers said, "In patients with relatively preserved renal function, the association of RAS blockers with an increased risk of CI-AKI after contrast media exposure was inconclusive, as sensitivity analysis showed conflicting results and bias. Although this study did not demonstrate significant evidence, it indicated that clinicians need to be vigilant in assessing the potential risk for RAS blockers to cause CI-AKI in low-risk patients."

CHRONIC KIDNEY DISEASE

Racial and Sex Disparities in Metformin Prescription among CKD Patients

Journal of the American Society of Nephrology. 2020;31(8):1847-1858

In 2016, the US FDA changed labeling regarding metformin contraindications in patients with diabetes and chronic kidney disease (CKD) from using thresholds based on serum creatinine to using thresholds based on estimated glomerular filtration rate (eGFR). Serum creatinine levels are affected by race and sex independently of GFR; the earlier contraindication based on serum creatinine may have caused racial and sex disparities in metformin prescription among patients with low eGFR.

Jung-Im Shin, MD, and colleagues performed an analysis to assess the association of race and sex with metformin prescription across eGFR level prior to and following the FDA label change. The analysis included data on 15,946 Black and White primary care patients with diabetes and eGFR ≥30 mL/min/1.73 m^2 in a large health system (the primary cohort). Data for a replication cohort was meta-analyzed from 36 cohorts with 1,051,723 patients from OptumLabs Data Warehouse.

Before the label change, Black patients in the primary cohort with eGFR 30 mL/min/1.73 m^2 to 44 mL/min/1.73 m^2 were prescribed metformin less often than White counterparts (adjusted prevalence ratio [aPR], 0.65; 95% confidence interval [CI], 0.52-0.82). Following the label change, the disparity was significantly attenuated (aPR, 0.90; 95% CI, 0.74-1.09), *P* for interaction by period=.04. In the replication cohorts, results were similar.

In analysis of disparities by sex, prior to the label change, men with eGFR 30 mL/min/1.73 m^2 to 44 mL/min/1.73 m^2 received prescription for metformin less often than women; the disparity was nonsignificantly attenuated after the label change. There was significant attenuation in the replication cohorts ($aPR_{pre\text{-}label}$ change, 0.76; 95% CI, 0.73-079; $aPR_{post\text{-}label}$ change, 0.85; 95% CI, 0.83-0.88; *P* for interaction by period <.001).

In conclusion, the authors said, "The metformin label change to an eGFR-based contraindication may have reduced racial and sex disparities in metformin prescription in moderate kidney dysfunction."

Surprise Question Response and Hospitalizations in Older Adults with CKD

American Journal of Nephrology. 2020;51:641-649

The risks for hospitalization and related adverse events are high among older adults with advanced non-dialysis-dependent chronic kidney disease (NDD-CKD). **S. J. Ramer, MD, MS,** and colleagues conducted a prospective cohort study of nephrology clinic patients ≥60 years of age with NDD-CKD stages 4-5.

Following an eligible patient's office visit, study staff interviewed the patient's provider regarding the patient's risk of death within the next 12 months, using the surprise question "Would you be surprised if this patient died within the next 12 months?" Responses used a scale of one to five: one, definitely not surprised to 5, very surprised. The researchers used a statewide database to determine hospitalization during follow-up.

The cohort included 488 patients. Median age was 72 years, 51% were female, 17% were Black, and median estimated glomerular filtration rate was 22 mL/min/1.73 m^2. Median follow-up was 2.1 years. During the follow-up period the rates of hospitalization per 100-person years were: 41 (95% confidence interval [CI], 34-50) in the very surprised response group; 65 (95% CI, 55-76) in the surprised response group; 98 (95% 85-113) in the neutral response group; 125 (95% CI, 107-144) in the not surprised response group; and 120 (95% CI, 94-151) in the definitely not surprised response group.

The researchers conducted a full adjusted cumulative probability ordinal regression model to determine the proportion of follow-up time spent hospitalized. Patients whose providers said they would be "definitely not surprised" if they died spent a greater proportion of follow-up in the hospital compared with patients whose providers responded they would be "very surprised" (odds ratio, 2.4; 95% CI, 1.0-5.7). Results were similar for associations for time to first hospitalization.

In conclusion, the researchers said, "Nephrology providers' responses to the surprise question for older patients with advanced NDD-CKD were independently associated with proportion of future time spent hospitalized and time to first hospitalization. Additional studies should examine how to use this information to provide patients with anticipatory guidance on their possible clinical trajectory and to target potentially preventable hospitalizations."

TRANSPLANTATION

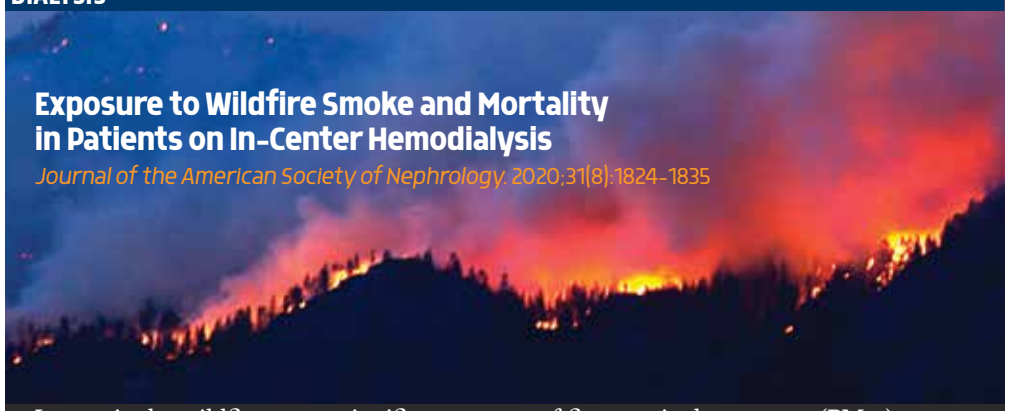
CMS Proposed New Standards for OPO Recertification

American Journal of Transplantation. 2020;20(9):2466-2480

Two new standards that must be met by organ procurement organizations (OPOs) seeking recertification were proposed by the Centers for Medicare & Medicaid Services on December 23, 2019. The standards state that (1) an OPO's organ donation rate, including deceased and potential donors and (2) the organ transplant rate, including organs transplanted and potential donors, must not fall significantly below the 75th percentile for rates among all OPOs.

Jon J. Snyder, PhD, and colleagues conducted an analysis to examine how OPOs would have fared under the proposed performance standards in 2016-2017.

DIALYSIS



Exposure to Wildfire Smoke and Mortality in Patients on In-Center Hemodialysis

Journal of the American Society of Nephrology. 2020;31(8):1824-1835

Increasingly, wildfires are a significant source of fine particulate matter ($PM_{2.5}$). Exposure to $PM_{2.5}$ is associated with adverse health effects and increased risk of mortality. Patients with end-stage kidney disease (ESKD) receiving maintenance hemodialysis are potentially susceptible to this stressor in the environment.

Yuzhi Xi, MSPH, and colleagues conducted a retrospective time-series analysis of the association between daily exposure to wildfire $PM_{2.5}$ and mortality. The analyzed data were gathered from 253 counties near a major wildfire between 2008 and 2012. Rate ratios (RRs) for all-cause mortality on the day of exposure and up to 30-days following exposure were estimated using quasi-Poisson regression models. The models adjusted for background $PM_{2.5}$, day of the week, seasonality, and heat. The analyses were stratified by causes of death (cardiac, vascular, infectious, or other) and place of death (clinical or nonclinical setting) for differential $PM_{2.5}$ exposure and outcome classification.

The analyses revealed 48,454 deaths matched to the 253 counties. There was an association between a 10-mg/m^3 increase in wildfire $PM_{2.5}$ and a 4% increase in all-cause mortality on the same day (RR, 1.04; 95% confidence interval [CI], 1.01-1.07) and a 7% increase cumulatively over 30 days following exposure (RR, 1.07; 95% CI, 1.01-1.12). The risk for deaths among patients on in-center hemodialysis occurring in nonclinical settings was elevated following exposure (RR, 1.07; 95% CI, 1.02-1.12), suggesting modification of exposure by place of death. The largest portion of deaths were attributed to causes other than cardiac, vascular, or infectious causes. Deaths due to the other causes had a strong same-day effect (RR, 1.08; 95% CI, 1.03-1.12) as well as a cumulative effect over the 30-day period following exposure. On days with a wildfire $PM_{2.5}$ contribution >10 mg/m^3, exposure accounted for 8.4% of all mortality.

"Wildfire smoke exposure was positively associated with all-cause mortality among patients receiving in-center hemodialysis," the researchers said.

The analysis used data on donors and transplants from the Organ Procurement and Transplantation Network. Detailed Multiple Cause of Death data collected by the Centers for Disease Control and Prevention were used to estimate donor potential.

In 2017, 53% of OPOs (n=31) did not meet the proposed donation rate standard, 62% (n=36) did not meet the proposed organ transplant rate standard, and 64% (n=37) failed at least one standard. Results were altered following adjustments for age, race, and Hispanic ethnicity: donation rate pass/fail status changed for eight OPOs and the proposed organ transplant standard rate pass/fail status changed for five OPOs.

The researchers said, "We conclude that the proposed new standards may result in over half of OPOs facing decertification, and risk adjustment suggests that underlying characteristics of deaths vary regionally such that decertification decisions may be affected."

State-Specific Rates of Dialysis Mortality and Transplant Outcomes

American Journal of Transplantation. doi.org/10.1111/ajt.15917

There is an association between longer pretransplant exposure and a higher risk of transplant failure. There are few data available on whether patients who receive dialysis in a region with a higher rate of dialysis mortality are at increased risk for transplant failure. **John S. Gill, MD, MS,** and colleagues conducted an analysis designed to determine adjusted state-specific hemodialysis mortality rates in 3-year intervals among prevalent dialysis patients in the United States between 1995 and 2012.

Multivariable models were used to determine the effect of state- and period-specific dialysis mortality on the association of pretransplant dialysis exposure with transplant survival through December 2017.

Dialysis mortality within states ranged from 128 deaths per 1000 patient-years to 330 deaths per 1000 patient-years. There was an association between each additional year of dialysis and a 4% higher risk of transplant failure in states in the lowest quartile of dialysis mortality, compared with an 8% higher risk in states in the highest quartile of dialysis mortality. Patients who received pretransplant dialysis treatment in states with a high rate of dialysis mortality were at higher risk for transplant failure compared with patients with the same duration of pretransplant dialysis treatment in states with a lower mortality rate.

"The findings may have implications for dialysis care in transplant candidates and the design of future outcome metrics," the authors said.

Size Mismatch and Graft Survival Modulated by Donor Age

Clinical Journal of the American Society of Nephrology. doi.org/10.2215/CJN.02310220

There is an association between small donor and/or kidney sizes relative to recipient size and a higher risk of kidney allograft failure. Graft survival is also associated with donor and recipient ages which may modulate the relationship between size mismatch and graft survival. **Fanny Lepeytre, MD,** and colleagues conducted a retrospective cohort study designed to assess whether the association between donor-recipient size mismatch and graft survival differs by donor and recipient age.

The study examined the first adult deceased donor kidney transplantations performed between 2000 and 2018 recorded in the Scientific Registry of Transplant Recipients. Multivariable Cox proportional hazards models were used to assess the association between donor-recipient body surface area ratio and death-censored graft loss, defined as return to dialysis or retransplantation. The researchers considered interactions between donor-recipient body surface area ratio and each of recipient and donor age.

A total of 136,321 kidney transplant recipients were included in the study. Of those, 17% (n=23,614) experienced death-censored graft loss over a median follow-up of 4.3 years. The three-way donor-recipient body surface area ratio by donor by recipient age interaction was statistically significant (P=.04).

The magnitude of the association between severe size mismatch (donor-recipient body surface area ratio <0.80 vs ≥1.00) and death-censored graft survival was stronger with older age and recipient age. With the exception of the youngest age category (18-30 years), in all age categories, 5- and 10-year graft survival rates were similar or better with a size-matched donor aged <40 years of age compared with a non-size-mismatched donor more than 40 years of age.

In conclusion, the researchers said, "The association of donor-recipient size mismatch on long-term graft survival is modulated by recipient and donor age. Size-mismatched kidneys yield excellent graft survival when the donor is young. Donor age was more strongly associated with graft survival than size mismatch." ■

Sarah Tolson

ESRD Treatment Choices Model Overview

In early October, I listened to a webinar in which the goal was to provide participants with a high-level overview of the recently finalized Centers for Medicare & Medicaid Services (CMS) ESRD [end-stage renal disease] Treatment Choices (ETC) Model. The presenters did a great job condensing a large amount of information into the 1-hour time slot that was allotted for the webinar. In addition to the very basic understanding I had of how the ETC Model is designed to work, I also had the distinct feeling my head may explode from trying to process so much information in one sitting. As the details of the ETC Model are many and complex, I would strongly recommend additional reading on this topic—particularly for clinicians who manage patients with kidney disease and those in the dialysis facility industry.

WHAT IS THE ECT MODEL?

The final rule for Specialty Care Models (42 CFR Part 512) states that, "The ETC Model will be a mandatory payment model focused on encouraging greater use of home dialysis and kidney transplants in order to preserve or enhance the quality of care furnished to Medicare beneficiaries while reducing Medicare expenditures."

The ETC Model encourages the use of home dialysis and kidney transplants by using two different payment adjustments—the Home Dialysis Payment Adjustment (HDPA) and the Performance Payment Adjustment (PPA). Home dialysis and home dialysis related Medicare claims from participants in the ETC Model with claim service dates from January 1, 2021, through December 31, 2023, will receive a positive adjustment, ranging from 3% to 1%, through the HDPA. This positive adjustment is intended to encourage expansion of home dialysis programs.

Payment adjustments related to PPA will be applied to claims for dialysis and dialysis-related services with claim service dates from July 1,2020, through June 30, 2026. The PPA adjustment can be either positive or negative and is based on a provider's transplant waitlisting and live donor transplant rates as well as home dialysis rates. The PPA adjustment can range from a positive 8% adjustment to a negative 10% adjustment.

In addition to the payment adjustments under the ETC Model, the Kidney Disease Education (KDE) benefit has been expanded. Social workers and nutritionists under direction of and incident to nephrologists have been added to the roster of providers that can offer KDE services. The beneficiary eligibility for the KDE benefit has been expanded from only those with stage 4 chronic kidney disease (CKD) to include beneficiaries with CKD Stage 5 or beneficiaries within six months of end-stage renal disease onset.

WHO WILL PARTICIPATE IN THE ETC MODEL?

Prior to CMS publishing the proposed rule for the ETC Model, it was thought CMS would be taking applications for this model as they have for other payment models in past years. Several of the dialysis programs we serve at Sceptre Management were eager to apply for and participate in the ETC Model. One of our clients was so eager to participate that she began working to open a new home dialysis program in a remote area. Her home program is now open, but will not be able to participate in the ETC Model due to its geographic location.

Selection to participate in the ETC Model was determined by randomly selecting Hospital Referral Regions (HRRs). Any ESRD facilities or managing clinicians located within the selected HRRs have been mandated to participate. There are several exclusions to the ETC model, including beneficiaries that are 75 years or older, have elected hospice, or reside in skilled nursing facilities. Additionally, there is a low volume provider exclusion for dialysis facilities and nephrologists with fewer than 11 attributed beneficiary years (or 132 months) in a 12-month measurement year.

Payment adjustments related to PPA will be applied to claims for dialysis and dialysis-related services with claim service dates from January 1, 2021, through June 20, 2027.

WHY IS PARTICIPATION IN THE ETC MODEL MANDATORY?

Generally speaking, CMS payment models with negative payment adjustments, such as those found in the ETC Model, have historically not been mandatory for dialysis facilities. The recent Quality Payment Program and the Merit-Based Incentive Payment System are mandatory for qualifying clinicians, but there are many tools and resources available to aid in avoiding a negative payment adjustment.

The final rule for Specialty Care Models states that the rationale for a mandatory payment model was that CMS seeks "To test the effect of payment incentives on availability and choice of treatment modality among a diverse group of providers and suppliers." Additionally, the final rule states that CMS believes that "Participation in these models by a large number of providers and suppliers with diverse characteristics will result in a robust data set for evaluating the models' proposed payment approaches."

The ETC Model feels very different from other ESRD payment models I have encountered over the past 12 years. I believe that the dialysis market in the selected HRRs will most definitely look different at the end of the ETC Model. ■

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

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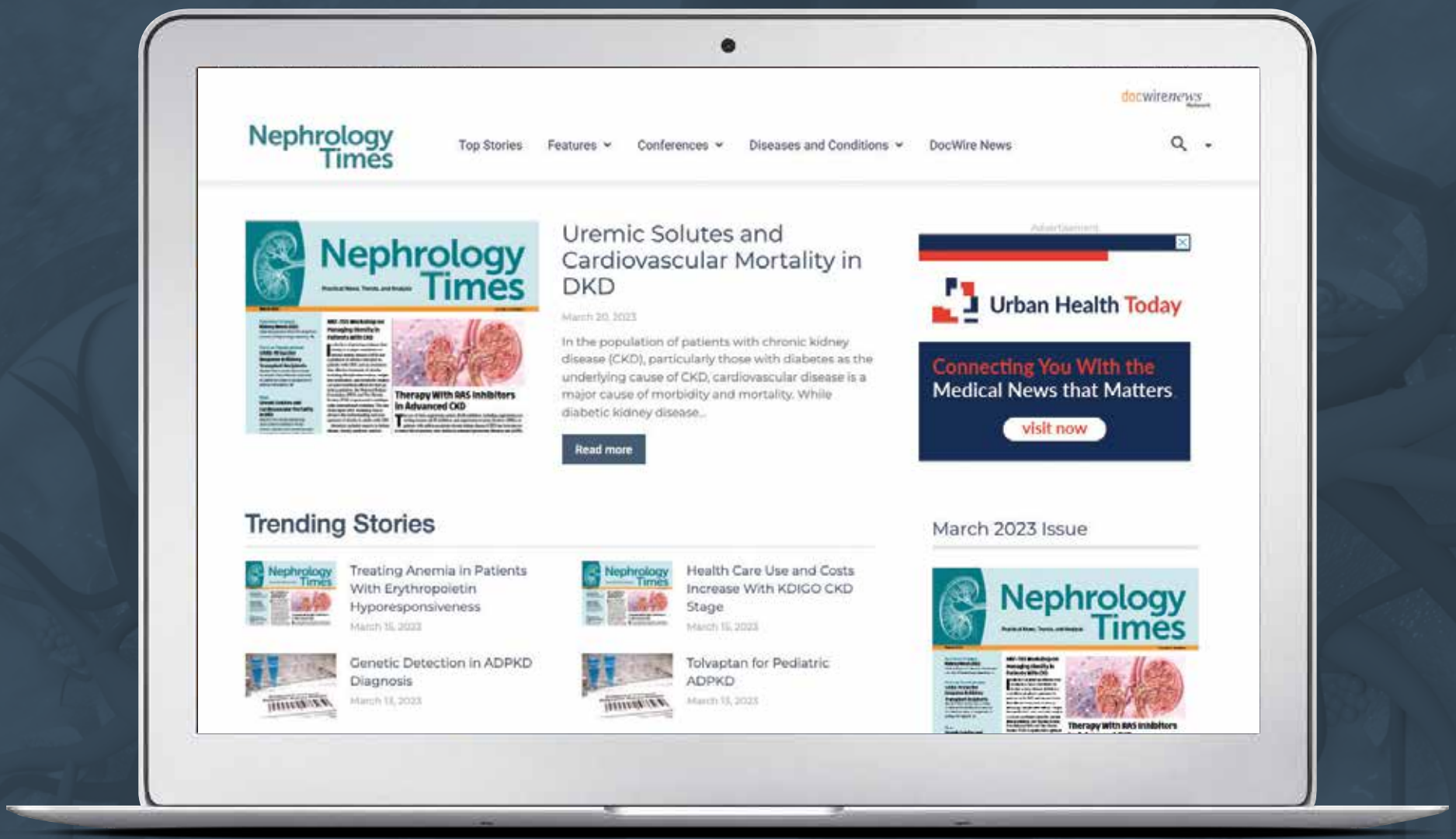

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