Sickle Cell Disease and the Kidney

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globin-related nephropathy: From sickle cell disease to sickle trait. *Expert Rev Hematol* 2017; 10:1087–1094. doi: 10.1080/17474086.2017.1395279
3. Nath KA, Hebbel RP. Sickle cell disease: Renal manifestations and mechanisms. *Nat Rev Nephrol* 2015; 11:161–171. doi: 10.1038/nrneph.2015.8
4. Guasch A, et al. Glomerular involvement in adults with sickle cell hemoglobinopathies: Prevalence and clinical correlates of progressive renal failure. *J Am Soc Nephrol* 2006; 17:2228–2235. doi: 10.1681/ASN.2002010084
5. Guasch A, et al. Evidence that microdeletions in the alpha globin gene protect against the development of sickle cell glomerulopathy in humans. *J Am Soc Nephrol* 1999; 10:1014–1019. doi: 10.1681/ASN.V1051014
6. Ashley-Koch AE, et al. MYH9 and APOL1 are both associated with sickle cell disease nephropathy. *Br J Haematol* 2011; 155:386–394. doi: 10.1111/j.1365-2141.2011.08832.x
7. Quek L, et al. Acute human parvovirus B19 infection and nephrotic syndrome in patients with sickle cell disease. *Br J Haematol* 2010; 149:289–291. doi: 10.1111/j.1365-2141.2009.08062.x
8. Abbott KC, et al. Sickle cell nephropathy at end-stage renal disease in the United States: Patient characteristics and survival. *Clin Nephrol* 2002; 58:9-15. doi: 10.5414/cnp58009
9. McClellan AC, et al. High one year mortality in adults with sickle cell disease and end-stage renal disease. *Br J Haematol* 2012; 159:360–367. doi: 10.1111/bjh.12024
10. Cecchini J, et al. Outcomes of adult patients with sickle cell disease admitted to the ICU: A case series*. *Crit Care Med* 2014; 42:1629–1639. doi: 10.1097/CCM.0000000000000316
11. Yawn BP, et al. Management of sickle cell disease: Summary of the 2014 evidence-based report by expert panel members. *JAMA* 2014; 312:1033–1048. doi: 10.1001/jama.2014.10517 [Erratums in *JAMA* 2014; 312:1932; *JAMA* 2015; 313:729].
12. National Heart, Lung, and Blood Institute, National Institutes of Health. Evidence-based management of sickle cell disease. Expert panel report, 2014. 2014. https://www.nhlbi.nih.gov/sites/default/files/publications/56-364NFULL.pdf
13. Sharpe CC, Thein SL. How I treat renal complications in sickle cell disease. *Blood* 2014; 123:3720–3726. doi: 10.1182/blood-2014-02-557439
14. Ojo AO, et al. Renal transplantation in end-stage sickle cell nephropathy. *Transplantation* 1999; 67:291–295. doi: 10.1097/00007890-199901270-00018

Overview of Onconephrology in Europe: An Essential Subspecialty with Increasing Importance

By Sheila Bermejo

Cancer is a worldwide epidemic that has increased its prevalence exponentially over the last decades. In 2020, 19.3 million new cases of cancer were diagnosed, and there were 10 million deaths from cancer worldwide (1). Cancer patients are susceptible to chemotherapy and immunotherapy treatments that can cause renal complications, such as acute kidney injury (secondary to glomerular disease, acute interstitial nephritis, or acute tubular necrosis), electrolyte disorder, proteinuria, and others (2). Additionally, a higher prevalence of cancer has been demonstrated in patients with chronic kidney disease from various types, those with a kidney transplant, and patients on kidney replacement therapy (Figure 1). Because of a lack of randomized clinical trials that test oncologic treatments in the population with renal diseases, patients with a lower glomerular filtration rate have less opportunity to receive some oncologic treatments. Thus, it is important to optimize their renal function with nephrologist intervention.

For these reasons, multidisciplinary care is important for cancer patients with diminished kidney function. Based on this idea, onconephrology was born. Onconephrology was originally considered a subspecialty that has increased in importance over the last decade, with the purpose to address accurate care of cancer patients and to diagnose and prevent complications. This increase in interest and importance of onconephrology has been evident in multiple ways (3). For example, the number of oral presentations dedicated to onconephrology topics at ASN Kidney Week has increased in the last several years. Likewise, this is also seen in Europe. During the last two European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) congresses (2020 and 2021), there has been an increase in onconephrology topics. In 2020, ERA-EDTA offered a symposium, "New immune therapies and onconephrology." In addition, a pre-congress course was dedicated to onconephrology (4). During the most recent congress in 2021 (58th ERA-EDTA Congress), there was a symposium dedicated to onconephrology with three lectures and a second symposium, entitled "AKI in special situations," in which one of the lectures was "AKI in oncology patients" (5).

The recent formation of the American Society of Onconephrology (ASON) in the United States demonstrates the advances of this subspecialty, but this type

Figure 1. The spectrum of renal diseases in cancer patients

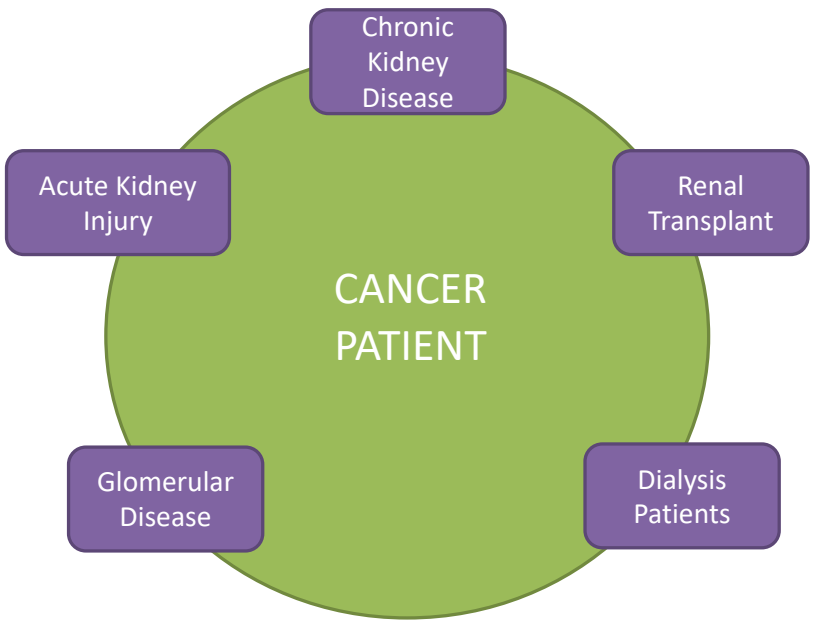
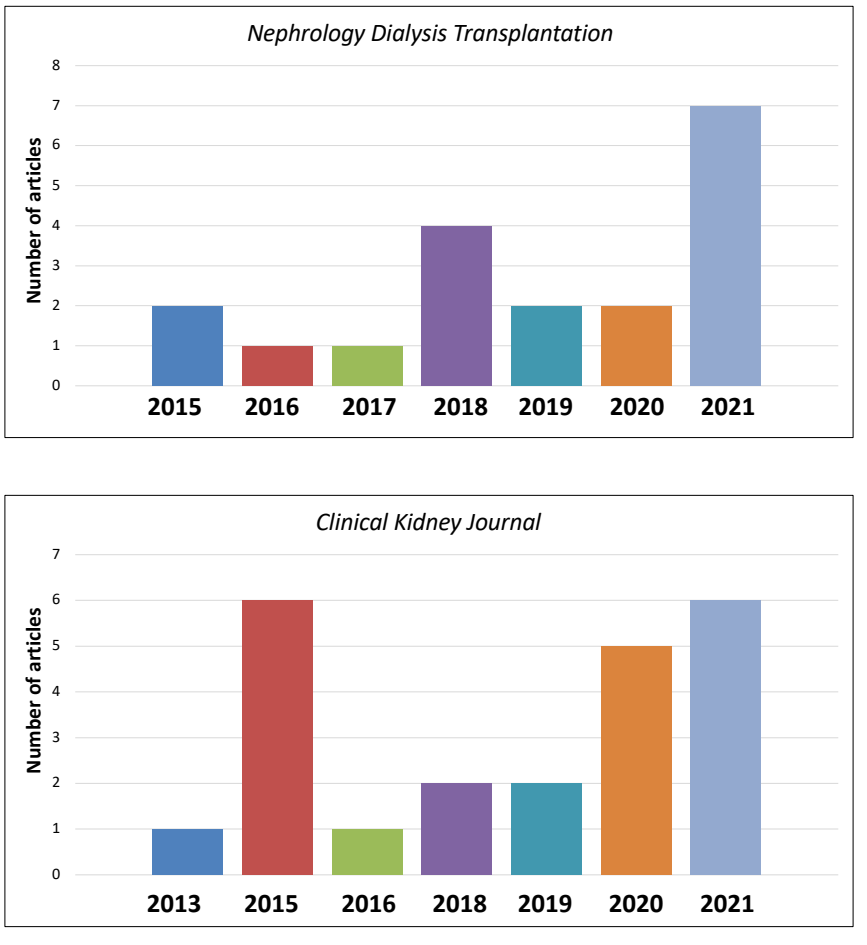


Figure 2. Distribution of onconephrology articles published in recent years in two European journals



of international society is lacking in Europe. However, this important increase in the prevalence of onconephrology is observed in the European congress and also reflected in European journals. Two major European journals, *Nephrology Dialysis Transplantation* (*NDT*) and *Clinical Kidney Journal* (*CKJ*), have published many onconephrology articles (Figure 2). In both onconephrology publications, 15 (37.5%) are reviews, 11 (27.5%) abstracts, 11 (27.5%) original articles, 5 (12.5%) editorials, 1 (2.5%) a letter, and 1 (2.5%) a meeting report.

In Spain, a working group called "Onconephrology" has been created by the Spanish Society of Nephrology. The working group holds regular meetings and multicenter collaborative projects are proposed in different hospitals with onconephrology units, as well as training courses for nephrologists in this subspecialty (6).

Recognition of the importance of onconephrology has increased recently because of the increase in the number of cancer patients with kidney impairment and the need for a multidisciplinary approach in caring for these patients. This need is reflected in the increase of onconephrology in both research and education in Europe, with an aim to optimize the care of cancer patients with kidney impairment and to improve their survival and quality of life. ■

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References

1. Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021; 71:209–249. doi: 10.3322/caac.21660
2. Salahudeen AK, Bonventre JV. Onconephrology: The latest frontier in the war against kidney disease. *J Am Soc Neprhol* 2013; 24:26–30. doi: 10.1681/ASN.2012070690
3. Thakkar J, et al. Onconephrology abstracts and publication trends: Time to collaborate. *Clin Kidney J* 2015; 8:629–631. doi: 10.1093/ckj/sfv085
4. ERA-EDTA. 57th ERA-EDTA Congress abstracts. *Nephrol Dial Transplant* 2020; 35. doi: 10.1093/ndt/gfaa139.SO003; https://academic.oup.com/ndt/search-results?page=1&q=57th%20ERA-EDTA%20Congress%20Abstracts&fl_SiteID=5333&SearchSourceType=1&allJournals=1
5. ERA-EDTA. 58th ERA-EDTA Congress abstracts. *Nephrol Dial Transplant* 2021; 36 (Suppl 1): 5–8. doi: 10.1093/ndt/gfab085.0019; https://academic.oup.com/ndt/search-results?page=1&q=58th%20ERA-EDTA%20Congress%20Abstracts&fl_SiteID=5333&SearchSourceType=1&allJournals=1
6. Alonso F, et al. Monographic consultation of onconephrology. Rationale and implementation. *Nefrologia* (*Engl Ed*) 2021; 41:154–164. doi: 10.1016/j.nefro.2020.08.008

Performance of GFR Estimating Equations in Patients with Solid Tumors

By Paul E. Hanna and Meghan E. Sise

Important decisions about diagnosing kidney disease, managing drug dosing, and considering kidney replacement therapy rely on an accurate estimation of the glomerular filtration rate (GFR), especially in patients with cancer (1, 2). Despite its continued use, the Cockcroft-Gault equation (3), originally created to assess kidney function based on serum creatinine in 1976, has significant limitations that may be even greater in patients with cancer who have sarcopenia. To address this, Costa E Silva and colleagues (4) compared the measured GFR using chromium-51-labeled ethylenediamine tetraacetic acid (^{51}Cr-EDTA) clearance in 1200 patients with solid tumors to test six GFR estimating equations. They reported both the bias (median of the differences between measured GFR and estimated GFR) and accuracy (1 minus the percentage of GFR estimates within 30% of measured GFR in mL/min/1.73 m^2 [1–P30]) of each equation (Table 1). The 2012 Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation, using both serum creatinine and cystatin C, performed the best among all equations. Among the GFR estimating equations that used serum creatinine alone, Cockcroft-Gault and 2009 CKD-EPI had the greatest bias, and Cockcroft-Gault had the least accuracy (Table 1).

Creatinine is a byproduct of muscle breakdown that lacks both sensitivity and specificity for measuring acute kidney injury (AKI) and CKD. Because creatinine is a muscle-derived biomarker, patients with advanced malignancies, who commonly exhibit muscle wasting, have 1) overestimation of their baseline estimated GFR when relying on creatinine-based equations and 2) underestimation of severity of AKI events when relying on accumulation of creatinine (9). Attempts to overcome these limitations in patients with cancer led to the development of population-specific GFR estimating equations, such as the Martin formula (10), the Wright formula (11), and the Calvert dose-determining formula (12); yet, even these did not generalize well and are not widely used (13, 14). Cystatin C is a low molecular weight protein that is released by all nucleated cells and freely filtered by the glomerulus and is used to estimate GFR. A major limitation of cystatin C is that it can be influenced by concurrent inflammation, history of smoking, obesity independent of the GFR (15), and corticosteroid therapy (16).

In subgroup analyses, the authors showed that several patient-specific factors strongly influenced the accuracy of GFR estimation. Creatinine-based equations were much more likely to overestimate GFR in women and in those with low body mass index (BMI [<25 kg/m^2]). In these populations, the CKD-EPI 2012 equation that uses cystatin C alone was most accurate. This suggests that GFR estimation could be personalized based on patient-specific factors such as BMI and sex. The authors also demonstrate that in patients with measured GFR <60 mL/min/1.73 m^2, all equa-

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Table 1. Bias and accuracy of different GFR estimating equations

Marker, equation	Bias (mGFR – eGFR) mL/min/1.73 m^2	Accuracy (1–P30)
Cr, CG (3)	–8.1 (–9.4 to –6.7)	24.9 (22.4 to 27.3)
Cr, MDRD (5)	–4.8 (–6.0 to –3.6)	18.2 (16.0 to 20.3)
Cr, CKD-EPI (6)	–8.1 (–8.9 to –7.1)	19.1 (16.8 to 21.2)
Cr, CamGFRv2 (7)	6.1 (5.3 to 6.9)	7.2 (5.7 to 8.7)
Cys, CKD-EPI (8)	4.6 (3.7 to 5.5)	12.3 (10.3 to 14.3)
Cr-Cys, CKD-EPI (8)	–2.0 (–2.6 to –1.1)	7.8 (6.3 to 9.4)

Bias and accuracy of different GFR estimating equations (eGFR) when compared with measured GFR (mGFR); data and 95% confidence intervals are presented. Cr, creatinine; Cys, cystatin C; CG, Cockcroft-Gault; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; CamGFRv2, Cambridge University Hospitals National Health Service (NHS) Foundation Trust; P30, proportion of estimates within 30% of mGFR. Adapted from Costa E Silva et al. (4).

Performance of 2012 CKD-EPI equation vs. Cockcroft-Gault equation in adults with solid tumors

KidneyNews

PROSPECTIVE

April 2015 to September 2017

58.8 years mean age

78.4 mL/min/1.73 m^2 measured GFR

n = 1200

Equation (filtration marker)	Bias (median), mL/min/1.73 m^2	Accuracy (1–P30), %
Cockcroft-Gault (CG) ($eGFR_{Cr}$)	–8.1 (–9.4 to –6.7)	24.9 (22.4 to 27.3)
CKD-EPI ($eGFR_{Cr}$)	–8.1 (–8.9 to –7.1)	19.1 (16.8 to 21.2)
CKD-EPI ($eGFR_{Cr\text{-}Cys}$)	–2.0 (–2.6 to –1.1)	7.8 (6.3 to 9.4)

Bias was defined as the median of the differences between mGFR and eGFR, whereas accuracy was defined as the percentage of estimates that differed by more than 30% from the measured GFR (1–P30).

Conclusions: The CG equation should not be preferred over the CKD-EPI equation, and $eGFR_{Cr\text{-}Cys}$ can be used as a confirmatory test in adults with solid tumors. Hence, a major policy implication would be to adopt general practice guideline-recommended methods for GFR evaluation in oncology practice and clinical trials.

Costa E Silva VT, et al. A prospective cross-sectional study estimated glomerular filtration rate from creatinine and cystatin C in adults with solid tumors. *Kidney Int* 2022; 101:607–614. doi: 10.1016/j.kint.2021.12.010

Visual Graphic by Edgar Lerma, MD, FASN