

However, we would also argue that glomerular density should not be simply viewed as a surrogate for nephron number. Certainly, this is true to some extent, as nephron number is estimated from glomerular density (calculated with stereology applied to kidney biopsy section) multiplied by cortical volume. However, we would restate this relationship in a different manner. Cortical volume can be estimated from average nephron size in the cortex (cortex per glomerulus or the reciprocal of glomerular density) multiplied by nephron number.² The interpretation of cortex per glomerulus as a measure of average nephron size is supported by its correlation with glomerular volume ($r_s=0.83$, $P<0.001$) and with mean cross-sectional tubular area ($r_s=0.66$, $P<0.001$) in our study.³ A concern with interpreting cortex per glomerulus as nephron size may be that some of the volume occupied by the cortex is not functioning nephrons but rather, interstitial fibrosis/tubular atrophy (IF/TA). However, even after excluding regions of IF/TA, the correlation of nonfibrotic cortex per glomerulus with glomerular volume ($r_s=0.84$, $P<0.001$) and cross-sectional tubular area ($r_s=0.66$, $P<0.001$) were not meaningfully different nor was the prediction of CKD progression.³

We argue that cortex per glomerulus, glomerular volume, and tubular cross-sectional area are all measures of nephron size, but there are also important differences and limitations with each. Glomerular volume does not capture the volume occupied by tubules, and only about 4% of the cortical volume is due to volume from glomeruli.² Some clinical factors, such as aging, appear to be associated with an increase in the size of tubules but not the size of glomeruli.⁴ The cross-sectional tubular area does not account for the different orientations, differing segments, and/or differing lengths of the tubules. Cortex per glomerulus may better account for the three-dimensional volume occupied by tubules in the cortex, but it does not exclude the volume occupied by vessels and IF/TA. None of these measures account for the volume occupied by nephron in the medulla. However, studying all three of these measures together may provide a more complete picture of nephron size than any alone.

Clinical characteristics can associate differently with nephron size and nephron number. In a relatively healthy population, obesity associates with larger nephrons but not with nephron number; lower GFR is not associated with nephron size but associates with lower nephron number, and family history of ESKD associates with both larger and fewer nephrons.² Both nephron number and nephron size are important to study for the prediction of outcomes. Indeed, we recently found that both low nephron number for age and larger glomerular volume in donors predicted a GFR < 45 ml/min per 1.73 m² a decade after kidney donation.⁵

DISCLOSURES

A.D. Rule reports serving as a scientific advisor or membership with the National Institute of Diabetes and Digestive and Kidney Diseases (CKD Biomarker Consortium External Expert Panel), *JASN* (Associate Editor), and Mayo Clinic Proceedings (Section Editor) and other interests/relationships with UpToDate. The remaining author has nothing to disclose.

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REFERENCES

- Seibel J, Rebibou J-M, Legendre M: Can total nephron number predict progressive CKD after radical nephrectomy? *J Am Soc Nephrol* 32: 517, 2021
- Denic A, Lieske JC, Chakkerla HA, Poggio ED, Alexander MP, Singh P, et al.: The substantial loss of nephrons in healthy human kidneys with aging. *J Am Soc Nephrol* 28: 313–320, 2017
- Denic A, Elsherbiny H, Mullan AF, Leibovich BC, Thompson RH, Ricautre Archila L, et al.: Larger nephron size and nephrosclerosis predict progressive CKD and mortality after radical nephrectomy for tumor and independent of kidney function. *J Am Soc Nephrol* 31: 2642–2652, 2020
- Denic A, Alexander MP, Kaushik V, Lerman LO, Lieske JC, Stegall MD, et al.: Detection and clinical patterns of nephron hypertrophy and nephrosclerosis among apparently healthy adults. *Am J Kidney Dis* 68: 58–67, 2016
- Merzkani MA, Denic A, Narasimhan R, Lopez CL, Larson JJ, Kremers WK, et al.: Kidney microstructural features at the time of donation predict long-term risk of chronic kidney disease in living kidney donors [published online ahead of print October 20, 2020]. *Mayo Clin Proc* 10.1016/j.mayocp.2020.08.0412020

See related letter to the editor, “Can Total Nephron Number Predict Progressive CKD after Radical Nephrectomy?” on page 517, and original article, “Larger Nephron Size and Nephrosclerosis Predict Progressive CKD and Mortality after Radical Nephrectomy for Tumor and Independent of Kidney Function,” in Vol. 31, Iss. 11, on pages 2642–2652.

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Remdesivir in COVID-19 Patients with Impaired Renal Function

In their perspective, Adamsick *et al.*¹ argue that, on the basis of its known pharmacokinetics, a 5-day course of remdesivir in patients with an eGFR of < 30 ml/min per 1.73 m² should be considered safe. Therefore, in their opinion, patients with coronavirus disease 2019 (COVID-19) who have impaired renal

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function should be offered remdesivir treatment, because this is a potentially life-saving treatment for such a vulnerable population.

We agree with the authors that accumulation of the carrier sulfobutylether- β -cyclodextrin is likely to be of no concern because there is clinical experience with other agents, such as voriconazole. However, with respect to remdesivir and its metabolite GS-441524, to our knowledge, there are no human data to claim its safety in people with impaired renal function because they were excluded from the clinical trials.² It should be emphasized that, in repeat-dose toxicity studies in rats and monkeys, the kidney (*i.e.*, tubular epithelium) was identified as the primary target organ of remdesivir toxicity.³ Furthermore, although remdesivir exhibits low renal excretion as an intact drug (<10% of the administered dose), 49% was recovered as GS-441524, and a total of 74% of a radiolabeled dose was recovered in urine.^{3,4} Not surprisingly, a recent pharmacokinetic study showed higher GS-441524 levels in a patient with renal dysfunction.⁵ Apparently, because GS-441524 will be removed by hemodialysis, toxicity of remdesivir or its metabolite will not be an issue in patients who are already on hemodialysis.⁶ In contrast, in patients with COVID-19 and CKD, it cannot be excluded that remdesivir treatment might lead to an urgent need for RRT, and that remdesivir in this patient population might even have a negative risk-benefit ratio. The recent signal on potential renal side effects of remdesivir also holds concern about its use in patients with CKD.⁷

Therefore, we would like to discourage remdesivir as routine treatment in patients with COVID-19 and CKD (eGFR of <30 ml/min per 1.73 m³). Its use should be reserved to the context of clinical trials to improve our knowledge on safety and efficacy.

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REFERENCES

- Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, et al.: Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol* 31: 1384–1386, 2020
- Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al.; ACTT-1 Study Group Members: Remdesivir for the treatment of Covid-19—Final report. *N Engl J Med* 383: 1813–1826, 2020
- European Medicines Agency: Summary on compassionate use. Remdesivir Gilead, 2020. Available at: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf. Accessed October 16, 2020

- Jorgensen SCJ, Kebriaei R, Dresser LD: Remdesivir: Review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19. *Pharmacotherapy* 40: 659–671, 2020
- Tempestilli M, Caputi P, Avataneo V, Notari S, Forini O, Scorzoloni L, et al.; COVID 19 INMI Study Group: Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19. *J Antimicrob Chemother* 75: 2977–2980, 2020
- Lê MP, Le Hingrat Q, Jaquet P, Wicky PH, Bunel V, Massias L, et al.: Removal of remdesivir's metabolite GS-441524 by hemodialysis in a double lung transplant recipient with COVID-19. *Antimicrob Agents Chemother* 64: e01521–20, 2020
- European Medicines Agency: Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 28 September - October 1, 2020, 2020. Available at: <https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-28-september-1-october-2020>. Accessed October 16, 2020

See related reply, "Authors' Reply," on pages 519–520, and original perspective article, "Remdesivir in Patients with Acute or Chronic Kidney," in Vol. 31, Iss. 7, on pages 1384–1386.

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Authors' Reply

In their letter, Gevers and colleagues¹ highlight concerns that remdesivir and its metabolite, GS-441524, may carry a risk of toxicity to the renal tubular epithelium, and that risks may be more considerable for patients with predialysis CKD. We agree that the potential risks of remdesivir and the concern for nephrotoxicity are likely greater in patients with predialysis CKD who have an eGFR of <30 ml/min per 1.73 m² compared with patients receiving dialysis.

There have been two important updates in the literature regarding coronavirus disease 2019 since we originally wrote our perspective. First, the Solidarity Trial—an unblinded, randomized trial that assigned 2750 patients to remdesivir—found that remdesivir did not reduce mortality, initiation

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