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References

1. European Centre for Disease Prevention and Control. COVID-19 pandemic [accessed 2020 Jul 21]. Available from: https://www.ecdc.europa.eu/en/covid-19-pandemic.
2. Lonergan M, Chalmers J. Estimates of the ongoing need for social distancing and control measures post-"lockdown" from trajectories of COVID-19 cases and mortality. *Eur Repir J* 2020;56:2001483.
3. Niederman MS, Richeldi L, Chotirmall SH, Bai C. Rising to the challenge of COVID-19: advice for pulmonary and critical care and an agenda for research. *Am J Respir Crit Care Med* 2020;201:1019–1022.
4. Prem K, Liu Y, Russell TW, Kucharski AJ, Eggo RM, Davies N, *et al*.; Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group. The effect of control strategies to reduce social mixing on outcomes of the COVID-19 epidemic in Wuhan, China: a modelling study. *Lancet Public Health* 2020;5:e261–e270. [Published erratum appears in *Lancet Public Health* 5:e260.]
5. Chotirmall SH, Martinez FJ, Schumacker PT, Cooke CR, Seam N, Brochard L, *et al*.; The American Thoracic Society Journal Family. Life at the editorial "COVID frontline". *Am J Respir Crit Care Med* 2020;201:1457–1459.
6. Wright DJM. Prevention of the cytokine storm in COVID-19. *Lancet Infect Dis* [online ahead of print] 7 May 2020; DOI: 10.1016/S1473-3099(20)30376-5.
7. Mehta P, Porter JC, Manson JJ, Isaacs JD, Openshaw PJM, McInnes IB, *et al*. Therapeutic blockade of granulocyte macrophage colony-stimulating factor in COVID-19-associated hyperinflammation: challenges and opportunities. *Lancet Respir Med* [online ahead of print] 16 Jun 2020; DOI: 10.1016/S2213-2600(20)30267-8.
8. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–1062. [Published erratum appears in *Lancet* 395:1038.]
9. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, *et al*.; RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med* [online ahead of print] 17 Jul 2020; DOI: 10.1056/NEJMoa2021436.
10. Remy KE, Mazer M, Striker DA, Ellebedy AH, Walton AH, Unsinger J, *et al*. Severe immunosuppression and not a cytokine storm characterize COVID-19 infections. *JCI Insight* 2020;140329.
11. Hadjadj J, Yatim N, Barnabei L, Corneau A, Boussier J, Smith N, *et al*. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* [online ahead of print] 13 Jul 2020; DOI: 10.1126/science.abc6027.
12. Mathioudakis AG, Fally M, Hashad R, Knight S, Felton T, Vestbo J. COVID-19 clinical trials: unravelling a methodological Gordian knot. *Am J Respir Crit Care Med* [online ahead of print] 7 Jul 2020; DOI: 10.1164/rccm.202005-1942ED.
13. Zuo Y, Yalavarthi S, Shi H, Gockman K, Zuo M, Madison JA, *et al*. Neutrophil extracellular traps in COVID-19. *JCI Insight* 2020;5:e138999.
14. McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, *et al*. Characterization of the inflammatory response to severe COVID-19 illness. *Am J Respir Crit Care Med* 2020;202:812–821.
15. McElvaney OJ, Zaslona Z, Becker-Flegler K, Palsson-McDermott EM, Boland F, Gunaratnam C, *et al*. Specific inhibition of the NLRP3 inflammasome as an antiinflammatory strategy in cystic fibrosis. *Am J Respir Crit Care Med* 2019;200:1381–1391.
16. UK Department of Health and Social Care. COVID-19 treatments could be fast-tracked through new national clinical trial initiative. Press release. 2020 Apr 29 [accessed 2020 Jul 20]. Available from: https://www.gov.uk/government/news/covid-19-treatments-could-be-fast-tracked-through-new-national-clinical-trial-initiative.

Subclinical Acute Kidney Injury Is Acute Kidney Injury and Should Not Be Ignored

Serum creatinine (SCr) has long been known to be an imperfect biomarker of kidney function (1). Although consensus definitions of acute kidney injury (AKI) using SCr exist, they remain limited (2). More specifically, owing to the nature of renal reserve, it often takes a significant amount of (tubular) injury to translate into a rise in SCr concentrations from baseline (3). Over the last decade, countless investigations have sought to discover and validate biomarkers of AKI that can identify patients who have early kidney injury (4). This concept of elevation in kidney injury biomarkers in the absence of changes in traditional markers (SCr and urine output [UO]) has been dubbed "subclinical AKI" (5). However, given the mounting evidence and multiple methods of detecting this injury, perhaps it needs a different name because it will not be subclinical for much longer. It is with this backdrop that, in this issue of the *Journal*, Dépret and colleagues (pp. 822–829) investigated plasma proenkephalin A (penKid), a 5-kD stable breakdown product of enkephalins that accumulates in the setting of reduced glomerular filtration (GFR) as a biomarker of subclinical AKI in critically ill patients (6).

However, this new work is not the first to look at subclinical AKI; in 2011, Haase and colleagues published a pooled multicenter analysis of prospective studies focused on NGAL (neutrophil gelatinase–associated lipocalin), an iron-binding protein that is upregulated in the setting of ischemic kidney injury (7). In a compilation of 2,322 critically ill patients, they demonstrated that patients who had elevated NGAL concentrations in the absence of changes in SCr (NGAL[+]/SCr[−]) had similar outcomes compared with those with elevations in SCr in the absence of changes in NGAL (NGAL[−]/SCr[+]). However, both these groups experienced more adverse outcomes (need for renal replacement therapy, longer length of ICU stay, and higher inpatient mortality) compared with those with no elevations in SCr or NGAL.

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These data are mirrored by other studies, including a multicenter, prospective observational study of 1,635 emergency room patients that demonstrated that patients with elevated urinary NGAL or KIM-1 (kidney injury molecule 1) and lower SCr were at increased risk for receipt of renal replacement therapy or inpatient mortality (8). On presentation, these patients with biomarker elevations in the absence of changes in SCr were also more likely to have intrinsic AKI (compared with prerenal AKI or chronic kidney disease) through a blinded adjudication process. More recently, Joannidis and colleagues demonstrated that critically ill patients with elevations in their TIMP2 × IGFBP7 (tissue inhibitor metalloprotease 2 × insulin-like growth factor binding protein 7) in the absence of changes in SCr or UO were more likely to develop stage 3 AKI or death compared with those with no changes in any biomarker. In fact, TIMP2 × IGFB7 concentrations above 2.0 were more strongly correlated with adverse outcomes compared with UO-based AKI (9). Thus, elevations in several of these biochemical biomarkers of tubular injury in the absence of changes in traditional biomarkers (SCr and UO) have been repeatedly shown to identify a cohort of patients at high risk for adverse (AKI and non-AKI) outcomes.

In this issue of the *Journal,* Dépret and colleagues conducted a *post hoc* analysis of data from two prospective observational studies, the FROG-ICU (French and European Outcome Registry in ICUs) and the AdrenOSS-1 (Adrenomedullin and Outcome in Severe Sepsis and Septic Shock 1) (6). In their analyses, they defined subclinical AKI as a penKid of more than 80 pmol/L in the absence of a change in SCr concentrations. They demonstrated that 6.2% (161 of 2587) of the population were penKid(+)/SCr(−), but these 161 subjects represented 12.6% of those previously labeled as having no AKI. Thus, in these cohorts, roughly one in every eight patients without a change in SCr actually experienced some change in kidney function as measured by penKid.

As in the prior studies, they demonstrated a stepwise increase in adverse outcomes and/or severity of illness in those with subclinical AKI compared with those without AKI. penKid(+)/SCr(−) patients were more likely to require hemodynamic support (defined as needing specific intravenous vasoactive medications) and to need support for longer duration compared with those with no AKI. Similarly, they demonstrated that 28-day survival was 93.3% in those who were penKid(−)/SCr(−) compared with 79.5% in the penKid(+)/SCr(−) cohort and 66.8% in those with SCr(+) AKI. Thus, it seems that even in the absence of a change in SCr, penKid is able to identify a cohort of critically ill adults who are at an increased risk for adverse outcomes.

It is important to note a few limitations of this work. First, UO-based criteria were not used to define AKI; although UO is often less strongly associated with adverse outcomes compared with SCr, it is still an integral part of the AKI definition. In addition, in the AdrenOSS-1 study, UO was not associated with 28-day mortality with a C-statistic of 0.49 ($P = 0.71$) (the C-statistic was slightly higher in the FROG-ICU at 0.56; $P = 0.017$). In addition, the authors chose to back-calculate baseline GFR for patients whose estimated GFRs were <75 ml/min at admission using the MDRD (Modification of Diet in Renal Disease Study) equation. Although there is no universal standard for attempting to establish a baseline SCr or baseline estimated GFR in hospitalized patients, it is not clear how this back-calculation impacted the findings through potentially erroneous designations of AKI and subclinical AKI.

Regardless of these limitations, this important work adds penKid to the growing list of clinically available tests that clearly identify at-risk critically ill patients. Because penKid accumulates early in the setting of reduced GFR, pairing it with other early biomarkers that assess tubular stress/injury may augment the ICU clinician's ability to detect AKI. We need to move beyond using SCr and UO as the sole method of assessing AKI, and AKI risk assessment should move from a static to a more dynamic/continuous process (4). At-risk patients with elevated penKid and other biomarkers in the absence of changes in SCr/UO are likely to be the ones who will benefit from early interventions such as an AKI care bundle. Recently, care bundles have been repeatedly shown to improve outcomes in patients with elevated biomarkers and in those with early SCr-based AKI (10, 11). In the near future, we hope that investigators would perform randomized trials to determine if critically ill patients with penKid (or other biomarker)-defined AKI benefit from specific interventions. ■

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References

1. Colls PC. Notes on creatinine. *J Physiol* 1896;20:107–111.
2. Group KAW. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;17:1–138.
3. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S. Renal functional reserve in humans: effect of protein intake on glomerular filtration rate. *Am J Med* 1983;75:943–950.
4. Koyner JL, Zarbock A, Basu RK, Ronco C. The impact of biomarkers of acute kidney injury on individual patient care. *Nephrol Dial Transplant* 2019;gfz188.
5. Haase M, Kellum JA, Ronco C. Subclinical AKI: an emerging syndrome with important consequences. *Nat Rev Nephrol* 2012;8:735–739.
6. Dépret F, Hollinger A, Cariou A, Deye N, Vieillard-Baron A, Fournier M-C, *et al*. Incidence and outcome of subclinical acute kidney injury using penKid in critically ill patients. *Am J Respir Crit Care Med* 2020;202: 822–829.
7. Haase M, Devarajan P, Haase-Fielitz A, Bellomo R, Cruz DN, Wagener G, *et al*. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol* 2011;57:1752–1761.
8. Nickolas TL, Schmidt-Ott KM, Canetta P, Forster C, Singer E, Sise M, *et al*. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective cohort study. *J Am Coll Cardiol* 2012;59:246–255.
9. Joannidis M, Forni LG, Haase M, Koyner J, Shi J, Kashani K, *et al*.; Sapphire Investigators. Use of cell cycle arrest biomarkers in conjunction with classical markers of acute kidney injury. *Crit Care Med* 2019;47:e820–e826.
10. Selby NM, Casula A, Lamming L, Stoves J, Samarasinghe Y, Lewington AJ, *et al*. An organizational-level program of intervention for AKI: a pragmatic stepped wedge cluster randomized trial. *J Am Soc Nephrol* 2019;30:505–515.
11. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, *et al*. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med* 2017;43:1551–1561.