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Post-Mortem Diagnostics in COVID-19 AKI, More Often but Timely

Coronavirus disease 2019 (COVID-19) is a new and devastating disease with renal involvement that deserves an intense and collaborative research effort. Golmai *et al.*¹ make use of classic autopsy with the modern modification of postmortem, fine-needle kidney biopsy. Autopsy was originally developed to investigate macroscopic, light-microscopic, postmortem, anatomic and histologic changes associated with disease. Standard autopsy is mildly time sensitive, with autolysis developing several hours after death. However, new developments in pathophysiologic diagnostics—protein, RNA, and DNA analyses—require faster sample handling and careful sample storage to prevent postmortem effects. Golmai *et al.*¹ do not describe how long after death biopsies were performed, but state the majority of samples show signs of autolysis. This precludes protein, RNA, and most DNA analyses because we would be observing mostly postmortem effects. Similar to sepsis, COVID-19 microscopic changes in the kidney are limited, with most studies showing some acute tubular necrosis, which cannot fully explain AKI. A large proportion of renal failure in patients with COVID-19 and those with sepsis seems to be attributed to functional defects without major histologic changes. Therefore, modern protein and nucleic-acid techniques might shed some light on the underlying mechanisms driving renal failure. We have shown that kidney biopsies can be performed at the bedside within 1 hour after death, and that gene expression analyses are feasible.^{2,3} Mortality of patients with COVID-19 was shown to be higher in patients with AKI.⁴ Yet, the mechanisms driving renal failure in patients with COVID-19 still remain largely unknown. Therefore, we plead for more studies to investigate postmortem renal biopsy specimens taken rapidly after death to enable the use of modern molecular diagnostics, together with classic autopsy, to investigate mechanisms of AKI induced by COVID-19.

DISCLOSURES

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See related reply, “Authors’ Reply,” on pages 255–256, and original article “Histopathologic and Ultrastructural Findings in Postmortem Kidney Biopsy Material in 12 Patients with AKI and COVID-19,” in Vol. 31, Iss. 9, 1944–1947.

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Authors’ Reply

Zijlstra *et al.*¹ question whether delay to postmortem biopsy and ensuing tissue autolysis could have interfered with our molecular diagnostics. They ask how long after death were biopsies done in our study, and suggest that studies using more rapid postmortem biopsy might be more productive. Supplemental Table 1, included in our paper,² provided the times between death and biopsy. Out of 12 cases, 11 were biopsied within 24 hours postmortem; three were performed

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within 2.5 hours. The fastest time to biopsy was 1.5 hours. A number of the cases had mild or no autolysis, as seen in Table 1. Similarly, Santoriello *et al.*³ did not find any clear evidence of viral infection of kidney in a postmortem series of 42 patients, many of whom had mild or absent autolysis. We acknowledge there remains the possibility that postmortem autolysis could interfere with the detection of the virus, although it must be emphasized that, in both of these aforementioned studies, lung specimens from autopsies used as controls were clearly positive for the virus. Corroborating our findings are two series of renal biopsy specimens in living patients with coronavirus disease 2019 included in the same issue of *JASN*.^{4,5} In these series (the majority in patients who had severe AKI), they also found no clear evidence of viral infection of the kidney, by ultrastructural examination in addition to immunohistochemical staining for viral spike and nucleocapsid proteins, and *in situ* hybridization for severe acute respiratory syndrome coronavirus 2 viral RNA. The conclusions of these four reports, two in living and two in postmortem kidneys, are consistent: it does not appear likely that direct viral infection is a primary contributor to renal dysfunction in patients with coronavirus disease 2019.

DISCLOSURES

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Complexities of eGFRs in a Study of Glomerular Physiology

In a recent article in *JASN*, Collard *et al.*¹ used a new method to indirectly determine glomerular pressures (Pglom) from renal artery pressures and flows that were measured in 28 patients undergoing angiography. Kidney function was expressed as a patient's eGFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.² After analysis, higher renal perfusion pressure, higher body mass index (BMI), and the presence of diabetes were associated with higher Pglom.

The use of eGFRs in this study may have introduced certain complexities. An eGFR is a size-indexed GFR, in milliliters per minute per 1.73 m². The ratio of GFR to body surface area (BSA) is indexed to a standard BSA of 1.73 m².² Normally, with the same eGFR, larger people have higher BSAs, BMIs, and measured GFRs (in milliliters per minute), and smaller people have the opposite. An advantage of screening with eGFRs in this study was to be sure that reasonably healthy kidneys were studied, *i.e.*, with function appropriate to body size. But when kidney function was expressed as eGFR and BMI was used as an independent variable, higher BMIs selected for higher nonindexed GFRs (in milliliters per minute). Therefore, the more fundamental association might have been between (higher) nonindexed GFR and (higher) Pglom, not (higher) BMI and Pglom. It may be relevant that, in the early days of continuous ambulatory peritoneal dialysis, we found misleading correlations when multiple size-related terms were studied in the same patient. This happened, for example, when both protein catabolic rate and dialytic clearance were normalized to body size.³ In this study, multiplying the eGFRs by each individual's BSA/1.73 to "unindex" them might help clarify the results.

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