Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

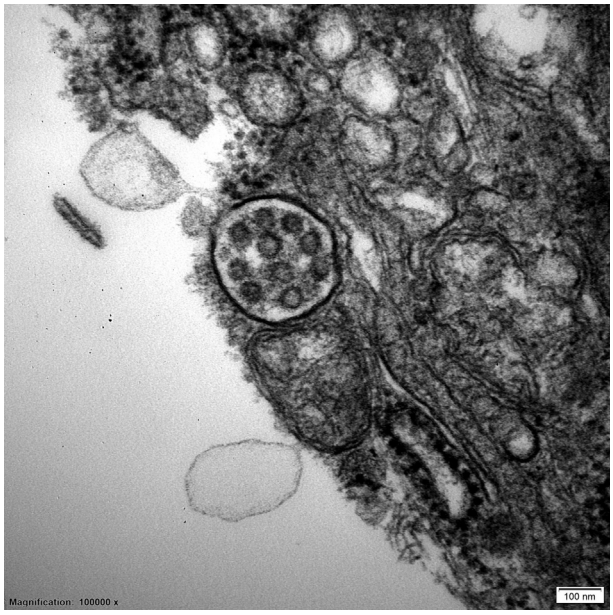

Figure 1 | Multivesicular body in a podocyte of a patient with lupus nephritis who tested negative for coronavirus disease 2019. Uranyl acetate-lead citrate, original magnification ×10,000. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

nonspecific. Endocytic vesicles may be coated by proteins, such as clathrin. The presence of coating proteins may cause an electron-dense area around these vesicles giving the appearance of a viral "corona."[4] Su *et al.*[1] found SARS-CoV nucleoprotein in renal tubules by immunohistochemistry, but the presence of a viral protein does not necessarily mean the presence of complete viral particles. Why MVBs occur so commonly in podocytes and uncommonly in tubular epithelial cells is unclear.

Transmission EM of tissue sections is not a specific or sensitive method for the detection of viral particles; there are numerous structures found by EM that resemble viruses (so-called viral-like particles), such as the well-known endothelial tubuloreticular inclusions (also called myxovirus-like particles). Therefore, caution is suggested when identifying a virus by EM in tissue sections. Immunohistochemistry may also result in nonspecific staining, particularly in renal tubules. Two recent case reports of collapsing glomerulopathy in COVID-19–positive patients failed to identify the virus in the kidney biopsy by *in situ* RNA analysis.[5,6] Another case report describing a patient with collapsing glomerulopathy also failed to find viral RNA in tissue extracted from the biopsy but demonstrated "viral particles" (with the appearance of MVBs) in podocytes.[2] Further molecular studies for the presence of the viral genome in renal parenchymal cells would be important in deciding whether SARS-CoV-2 truly infects the kidney.

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Autophagy inhibition by chloroquine and hydroxychloroquine could adversely affect acute kidney injury and other organ injury in critically ill patients with COVID-19

To the editor: We read the letter by Izzedine *et al.*[1] with great interest, especially the discussion of renal adverse effects of drug treatment options for coronavirus disease 2019 (COVID-19). We would like to draw particular attention to the potential adverse effect of chloroquine and hydroxychloroquine, the lysosomotropic antimalarial drugs that may inhibit the infection of severe acute respiratory syndrome coronavirus 2 by reducing the entry and replication of the virus. Severe acute respiratory syndrome coronavirus 2 enters cells via endocytosis by binding of its trimeric spike protein to cell surface receptors including angiotensin-converting enzyme 2. Expression of angiotensin-converting enzyme 2 is high in proximal tubular cells in the human kidney (see Supplementary Figure S1 and Supplementary References). Based on the *in vitro* observation of inhibitory effects of chloroquine and hydroxychloroquine, clinical studies of their treatment in COVID-19 patients are under way. However, we believe that these lysosomotropic agents have the potential to make acute kidney injury (AKI) and other organ failures worse due to their known effect to increase lysosomal pH and inhibit autophagy,[2] a fundamental mechanism for the survival of injured cells. Chloroquine mainly inhibits autophagy by

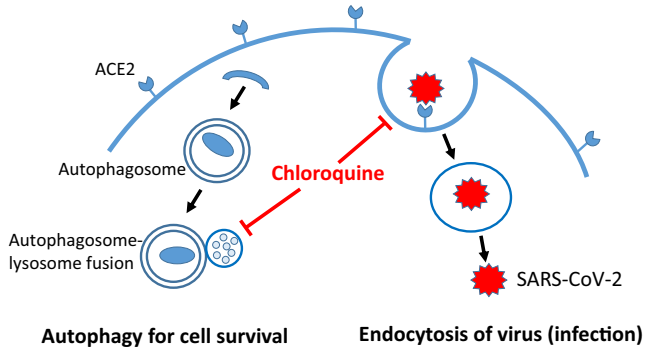

Figure 1 | Chloroquine could be a double-edged sword. Chloroquine may slow virus infection and replication early but may later potentiate tissue damage and worsen acute organ injury by inhibiting autophagy. ACE2, angiotensin-converting enzyme 2; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

impairing autophagosome-lysosome fusion and the degradative activity of the lysosome.[2] Also, chloroquine can induce an autophagy-independent severe disorganization of the Golgi and endosomal-lysosomal systems that may contribute to its effect on autophagosome-lysosome fusion.[2] Inhibition of autophagy by chloroquine results in the accumulation of damaged mitochondria due to the lack of clearance via mitophagy, which, together with attendant oxidative stress, leads to renal tubular dysfunction.[3] In patients, chloroquine increases cancer cell killing by inhibiting autophagy, an idea being tested in clinical trials.[4] In mouse models of septic AKI, autophagy protects against renal tubule injury and pharmacological inhibition of autophagy with chloroquine worsens kidney damage.[5] Chloroquine also blocks autophagic flux and worsens both ischemic and cisplatin-induced nephrotoxic AKI in mice.[6] Chloroquine has also been shown to be nephrotoxic by autophagy-dependent as well as autophagy-independent pathways, including interference with the cyclic adenosine monophosphate production and signaling in distal tubular cells.[7] In other preclinical studies, chloroquine inhibits autophagy and worsens ischemic cardiac injury[8] and sepsis-induced liver or lung injury.[9,10] Thus, chloroquine could be a double-edged sword: it may slow virus infection and replication early, but may later potentiate tissue damage and worsen acute organ injury by inhibiting autophagy (Figure 1). We write to strike a cautionary note on using chloroquine or hydroxychloroquine in COVID-19 patients with acute organ injury including AKI.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Angiotensin-converting enzyme 2 (ACE2) is the functional cellular receptor for SARS-CoV-2.

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Could ferritin help the screening for COVID-19 in hemodialysis patients?

To the editor: The screening for coronavirus disease 2019 (COVID-19) is challenging: many patients are asymptomatic, viral RNA detection in a nasopharyngeal swab is falsely negative in 30%, and a pulmonary computed tomography scan is useless in patients with no pulmonary involvement.[1,2]

In our hemodialysis center, following the Kidney Disease Improving Global Outcomes recommendations, ferritin levels are measured each month to detect iron deficiency.[3] In April 2020, there were 22 COVID-19 cases that had occurred within the 270 patients undergoing hemodialysis at our hemodialysis center. We noticed that ferritin levels were very high in these patients (Figure 1). When monthly ferritin levels were measured in April, 1 of our female patients had an unusually high ferritin level of 3806 ng/ml compared with 531 ng/ml previously. A clinical examination showed no clinical symptoms of COVID-19, but she was tested by nasopharyngeal swab and was shown to be positive.

We compared ferritin levels in patients undergoing hemodialysis who tested positive and negative for COVID-19 at our