

Clinical Characteristics,
Diagnosis, and
Outcomes of 6 Patients
With COVID-19
Infection and
Rhabdomyolysis



To the Editor: Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)¹ commonly presents with pneumonia, but there are widespread manifestations contributing to a mortality rate of 1% to 3%. Liver involvement typically manifests as mild to moderate elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels.² Rhabdomyolysis is a rare, potentially lethal systemic necrosis of skeletal muscle, often associated with inflammatory myopathies, crush injuries, extreme hyperthermia, drugs, and infection. We describe a series of 6 patients with severe rhabdomyolysis associated with COVID-19 to better understand an unusual but important manifestation of the novel disease. Rhabdomyolysis was diagnosed by previously described criteria³ and COVID-19 by nasopharyngeal swab for SARS-CoV-2 RNA. An Ovid MEDLINE search noted a single previous case report but no larger studies.⁴ Our institutional review board approved this study.

Of the 6 included patients, 5 were male with a mean age of 58 years (Table); half had no preexisting conditions. Five presented with typical symptoms of COVID-19 (including pneumonia on radiography), and all

had elevated inflammatory markers (mean C-reactive protein level, 14.9 mg/dL). The mean initial AST level was 325 U/L and the ALT level 137 U/L, with the AST/ALT ratio being 2.37. All patients had urinalysis consistent with rhabdomyolysis; 4 developed an acute renal injury, and 2 required dialysis. The initial and peak creatinine kinase levels varied widely (Supplemental Figure, available online at <http://www.mayoclinicproceedings.org>) but were closely linked to elevations in AST and ALT levels. Five patients required intensive care unit stay and intubation, all of whom received a trial drug for COVID-19, and 2 died before discharge (Supplemental Table, available online at <http://www.mayoclinicproceedings.org>).

In our series, rhabdomyolysis presented both early, along with or without the typical pneumonia syndrome, and late in the clinical course. Typically myalgias, dark urine, and recent vigorous exercise make a diagnosis of rhabdomyolysis straightforward; however, respiratory failure and multiorgan dysfunction from COVID-19 may mask the diagnosis. Additionally, treatments to improve oxygenation, including prone positioning and paralysis, may unintentionally predispose patients to rhabdomyolysis. Therefore, maintaining a high index of suspicion with prompt evaluation is necessary to avoid adding complications such as electrolyte abnormalities and renal failure to the overall morbidity of SARS-COV-2. Additional clues include normal gamma-glutamyl transferase level,² an exaggerated ratio of AST and ALT, and urinalysis with blood on the dipstick test but no red blood

cells on microscopy. Elevated aminotransferase levels are believed to be unrelated to liver toxicity, but rather released from skeletal muscle, in which AST is found in high concentrations. Management is primarily supportive, including removing causative factors, volume expansion, and dialysis, if necessary. The need for volume expansion while avoiding worsening hypoxia from pulmonary edema highlights the importance of early identification and prompt clinical decision making in COVID-19.

Our study suggests that rhabdomyolysis occurs both early and late in the COVID-19 course, with wide variation in severity and outcomes. Further studies are needed to establish prevalence and pathophysiology, but cases of COVID-19 and rhabdomyolysis are both likely underestimated in general. During the course of this study, more than half of patients hospitalized at our institution had COVID-19 and more than 1000 cases were noted in the hospital system. In that time, it is possible that many cases of rhabdomyolysis were undiagnosed or undermanaged. Many patients with COVID-19 have minimally elevated creatinine kinase, ALT, and AST levels potentially related to a viral-induced myositis, such as that described in influenza.⁵ Other possibilities including hypovolemia, prolonged immobility or medically induced paralysis, drug toxicity, and prolonged fever.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mayoclinicproceedings.org>. Supplemental

TABLE. Clinical Characteristics and Outcomes of Patients With COVID-19 and Rhabdomyolysis^{a,b}

| Characteristic | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|--|-----------------------|--------------------------|---------------------------------|----------------------------|--------------------------------|--------------------------------|
| Age at diagnosis (y) | 43 | 37 | 75 | 59 | 66 | 70 |
| Sex | Male | Male | Male | Male | Male | Female |
| Previous medical conditions | None | None | DVT | None | Hypertension | MM, CKD |
| Presenting symptoms | Myalgia, cough, fever | Fever, SOB, myalgias | Rhinorrhea, back pain, weakness | Cough, fever, diarrhea | Cough, fever, SOB | SOB, cough, malaise |
| Admission data | | | | | | |
| White blood cell count ($\times 10^9/L$) | 7.6 | 7.9 | 3.8 | 5.6 | 9.4 | 15.2 |
| Hemoglobin level (g/dL) | 16.2 | 14.5 | 16.4 | 15.2 | 14.2 | 16.2 |
| Platelet count ($\times 10^9/L$) | 237 | 314 | 182 | 178 | 38 | 127 |
| C-reactive protein level (mg/dL) | 15.6 | 7.4 | 15.7 | 20.4 | 21.3 | 9.2 |
| Lactate level (mmol/dL) | 1.40 | 1.70 | 1.20 | 2.10 | 1.30 | 5.50 |
| Ferritin level (ng/mL) | 1357 | 800 | 857 | Not drawn | 908 | >16,500 |
| D-dimer level (ng/mL) | 279 | 1454 | 394 | 237 | 790 | 2137 |
| Chest radiography findings | Bilateral pneumonia | Bilateral hazy opacities | Normal | Patchy bilateral pneumonia | Bilateral multifocal pneumonia | Bilateral multifocal pneumonia |
| Hospital course | | | | | | |
| Required ICU stay | Yes | Yes | No | Yes | Yes | Yes |
| Required intubation | Yes | Yes | No | Yes | Yes | Yes |
| Trial of prone position | Yes | No | No | No | Yes | No |
| Required vasopressors | Yes | Yes | No | Yes | Yes | Yes |
| Acute kidney injury | Yes | Yes | Yes | No | No | Yes |
| Required dialysis | Yes | No | No | No | No | Yes |
| Peak creatinine level (mg/dL) | 13.35 | 1.47 | 1.78 | 1.29 | 1.22 | 12.30 |
| Peak AST level (U/L) | 1474 | 902 | 56 | 186 | 263 | >6000 |
| Peak creatinine kinase level (U/L) | 75,240 | 82,960 | 3638 | 8310 | 10,100 | 406,300 |
| COVID-19 therapy attempted | Yes (HCQ, TCZ, MPD) | Yes (DM) | No | Yes (HCQ, RMD) | Yes (HCQ) | Yes (HCQ) |
| Survived to discharge | Yes | Yes | Yes | No | Yes | No |

^aCKD = chronic kidney disease; COVID-19 = coronavirus disease 2019; DM = dexamethasone; DVT = deep vein thrombosis; HCQ = hydroxychloroquine; MM = multiple myeloma; MPD = methylprednisolone; RMD = remdesivir; SOB = shortness of breath; TCZ = tocilizumab.

^bSI conversion factors: To convert mg/dL values to mmol/L, multiply by 0.0259; to convert g/dL values to mol/L, multiply by 0.6206; to convert ng/mL values to pmol/L, multiply by 2.247 (for ferritin); to convert U/L values to $\mu\text{kat/L}$, multiply by 0.0167.

material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.



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Association of Renin-Angiotensin System Blockers With Outcomes in Patients with COVID-19



To The Editor: Conflicting findings have been reported regarding the safety of angiotensin-converting-enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) during the COVID-19 pandemic.^{1,2} In reference to the recently published review outlining the relationship between renin-angiotensin system (RAS) and COVID-19 infection,³ we present additional data regarding the association of RAS inhibitors with outcomes in patients with COVID-19.

The COVID-19 pandemic, affecting more than 4.5 million people across the globe, has caused significant morbidity and mortality.⁴ Angiotensin-converting-enzyme 2 (ACE2) has been implicated in the entry of severe acute respiratory syndrome (SARS)-Cov-2 virus into host cells.⁵ As RAS antagonists have been suggested to upregulate ACE2 in few animal models, concerns have been raised that these drugs might be associated with increased risk of infection or severe disease from COVID-19.^{6,7} Whether such patients on ACEIs or ARBs should continue these drugs has become a matter of debate. Accordingly, we performed a meta-analysis to study the cumulative evidence for association of the use of ACEIs and ARBs with risk of mortality and severe illness with COVID-19.

A comprehensive search in electronic databases (MEDLINE and EMBASE) was performed for studies published between November 1, 2019, and May 31, 2020. The following key terms were used for search in different combinations: *coronavirus 2019, COVID-19, SARS-Cov-2, renin-angiotensin system, angiotensin-converting-enzyme, angiotensin-converting-enzyme inhibitors, ACEI, angiotensin receptor blockers, ARB, and outcomes*. Inclusion criteria were studies published in peer-reviewed journals and reporting outcomes based on use of ACEIs or ARBs in COVID-19. Two reviewers (A.G. and A.R.) screened the study titles and abstracts, followed by full manuscript evaluation. From individual studies, we collected baseline characteristics of patients including proportion of patients with hypertension and those taking ACEIs or ARBs. The primary outcome was in-hospital mortality. Secondary outcome was severe or critical illness—need for intensive care unit, invasive

mechanical ventilation, or mortality—as defined per individual study protocol. We used the Cochrane review manager 5.3 for statistical analysis. Random-effects model with Mantel-Haenszel method was used to calculate the pooled odds ratios (ORs) with 95% confidence intervals (CIs) for each end point. This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines.⁸

After initial screening and full text review, 15 studies were identified to report outcomes based on use of ACEIs or ARBs in patients with confirmed COVID-19.^{1,2,5,9-20} One study was excluded because of retraction by the authors.¹⁰ Thus, a total of 14,882 COVID-19–positive patients (n=5323 ACEI/ARB, n=9559 non-ACEI/ARB) among 14 studies were included. Compared with patients not on RAS inhibitors, patients using RAS inhibitors had similar risks for mortality (OR 1.14 [0.73-1.76]; $P=.57$) and severe illness (1.18 [0.91-1.54]; $P=0.21$) (Figure). In subanalyses restricted to patients with hypertension, use of ACEIs and ARBs was associated with significantly lower mortality (0.64 [0.45-0.89]), whereas the trend of severe or critical illness (0.76 [0.52-1.12]) remained nonsignificant compared with non-ACEI and ARB users (Supplemental Figure, available online at <http://www.mayoclinicproceedings.org>).

Currently available data from observational studies have shown contrasting findings regarding the relationship between the use of ACEIs and ARBs and outcomes in patients with COVID-19. In this context, our meta-analysis, including >14,000 patients, reconciles the findings of existing studies and shows that use of ACEIs and ARBs is not associated with