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RESEARCH LETTER

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# Serum levels of receptor-interacting protein kinase-3 in patients with COVID-19



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**Keywords:** COVID-19, Acute respiratory distress syndrome, Necroptosis, Receptor-interacting kinase 3

Dear Editor:

Patients with coronavirus disease 2019 (COVID-19) can develop acute respiratory distress syndrome (ARDS), which has been linked to poor prognosis and is a major contributor to patient death [1]. A better understanding of the pathophysiology of COVID-19-related ARDS would benefit early, precise treatment.

Cell death plays a major role in ARDS pathogenesis. While apoptosis in acute lung injury is well studied, newly identified cell death signaling has drawn attention as a potential mediator of ARDS [2]. Necroptosis, a caspase-independent form of necrosis involving receptor-interacting kinase 3 (RIPK-3), has been implicated in ARDS development with sepsis and trauma [3]. Since this highly regulated cell death signaling leads to rupture of the plasma membrane and release of damage-associated molecular patterns [4], necroptosis may be a therapeutic target for ARDS. However, the relationship between necroptosis and COVID-19-induced ARDS remains unclear.

Here, we describe serum RIPK-3 levels in COVID-19 patients measured on the first day of hospitalization. Patients were recruited from March 1 to May 30, 2020, and diagnosed as “severe” if any of the following conditions were met [5]: (1) respiratory rate > 30 breaths/min, (2) saturation of peripheral oxygen < 93% in ambient air, (3) ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen < 300 mmHg, or (4) lung infiltrates > 50% within 24–48 h. Blood samples were centrifuged within 30 min and refrigerated at 4 °C, and

plasma aliquots were frozen within 12 h. RIPK-3 levels were measured using an enzyme-linked immunosorbent assay (Wuhan Huamei Biotech, Wuhan, China).

This observational study enrolled 16 COVID-19 patients (11 males, 68.8%) (Table 1). Confirmation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was by real-time reverse transcription polymerase chain reaction of nasopharyngeal swabs. Patients’ median age was 55 years (interquartile range [IQR] 40.5–71.5 years), and the median duration from symptom onset to hospitalization was 7 days (3.25–9 days). On admission, 14 patients (87.5%) were confirmed to have COVID-19 pneumonia by chest computed tomography, 10 patients were diagnosed with severe COVID-19 and ARDS, and 6 patients were diagnosed as mild. While hospitalized, the antiviral drug favipiravir was administered to 11 patients (68.8%) in the context of a clinical trial, whereas azithromycin ( $n = 11$ , 68.8%), nafamostat ( $n = 12$ , 75%), and tocilizumab ( $n = 7$ , 43.7%) were commenced as off-label use. The median levels of serum RIPK-3 were significantly higher in severe COVID-19 cases than in mild cases (483.5 pg/mL, IQR 329.6–867.7 pg/mL vs. 139.9 pg/mL, IQR 95.37–286.8 pg/mL,  $p = 0.0075$ ) (Fig. 1). Fifteen patients recovered and were discharged, whereas three patients in the severe group were intubated due to severe acute respiratory failure and one of these patients died.

This is the first study to analyze RIPK-3 in COVID-19 patients. The higher serum RIPK-3 levels in severe patients suggest that RIPK-3-mediated signaling, such as

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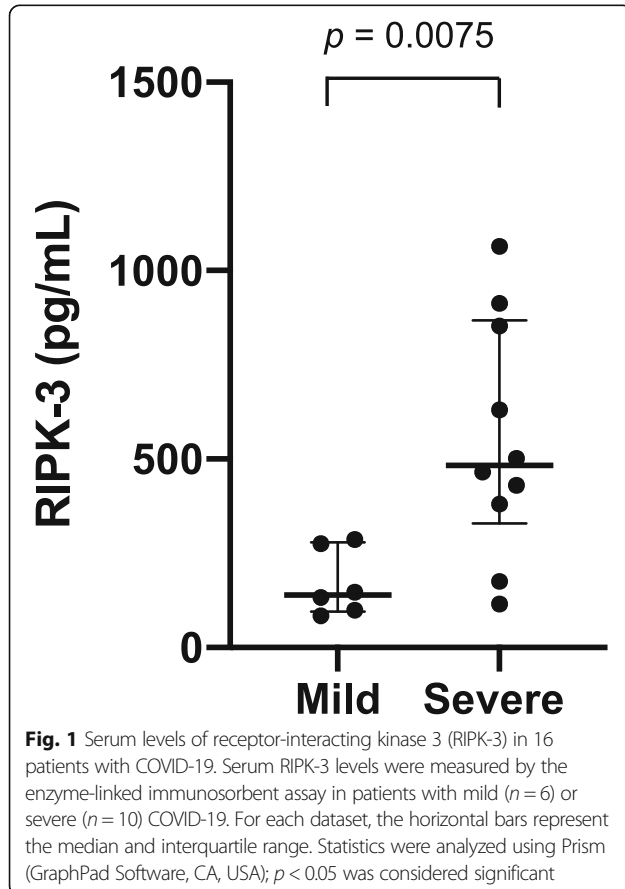


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**Table 1** Clinical characteristics of patients ( $n = 16$ )

Male	11 (68.8%)
Median age, years (IQR)	55 (40.5–71.5)
Median duration from onset of symptoms to hospitalization, days (IQR)	7 (3.25–9)
Underlying disease	
Diabetes mellitus	4 (25%)
Hypertension	2 (12.5%)
Heart disease	2 (12.5%)
Treatment	
Azithromycin	11 (68.8%)
Favipiravir	11 (68.8%)
Nafamostat	12 (75%)
Tocilizumab	7 (43.7%)
Disease severity	
Mild	6 (37.5%)
Severe	10 (62.5%)
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	
> 350	6 (37.5%)
200–300	5 (31.25%)
150–200	3 (18.75%)
< 150	2 (12.5%)

IQR interquartile range, PaO<sub>2</sub>/FiO<sub>2</sub> ratio ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen



necroptosis, might be involved in the development of acute lung injury associated with COVID-19 pneumonia. Siempos et al. reported plasma RIPK-3 levels were significantly higher in ARDS patients compared to those of non-ARDS patients [6]. Shashaty et al. demonstrated that among patients with sepsis or trauma, the change in plasma RIPK-3 levels 48 h after admission was independently associated with ARDS [3]. Because RIPK-3 mediates not only necroptosis but also other inflammatory pathways [2], the elevation of RIPK-3 does not directly indicate the execution of necroptosis. To confirm the role of RIPK-3 in COVID-19-ARDS patients, further studies are needed including a larger number of participants and histological evaluation of lung tissues, especially since RIPK-3-mediated necroptosis could be a potential therapeutic target for COVID-19-related ARDS.

#### Abbreviations

COVID-19: Coronavirus disease 2019; ARDS: Acute respiratory distress syndrome; RIPK1/3: Receptor-interacting kinase 1 and 3 (RIPK1/3); IQR: Interquartile range; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

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**Authors' contributions**

HN designed the study and had full access to all data in the study. TK and WA contributed to the laboratory work. MT and JF supervised the study and contributed to the writing of the manuscript. All authors contributed to data acquisition, data analysis, or data interpretation and reviewed and approved the final version of the manuscript.

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**Availability of data and materials**

Full de-identified data of the analyses are available upon request sent to the corresponding author.

**Ethics approval and consent to participate**

This study was approved by the ethics committee of the University of the Ryukyus for Medical and Health Research Involving Human Subjects (approval number: 1616).

**Consent for publication**

Written informed consent was obtained from all patients.

**Competing interests**

Not applicable.

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