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.

LETTER TO THE EDITOR

COVID-19 Vaccination in Immunoglobulin A Nephropathy

To the Editor:

The timely editorial from Bomback et al[1] on de novo and relapsing glomerular diseases after COVID-19 vaccination noted that immunoglobulin A nephropathy (IgAN) was one of the most frequently reported glomerulonephritides in this context. However, the absolute incidence was low, with 10 reports of de novo or relapsed IgAN, including 1 from our institution.[2] Vaccine trial safety data in IgAN are lacking in part because immunosuppressed patients, including those with glomerular diseases, were generally excluded.[3] We reviewed 145 IgAN patients diagnosed between December 2015 and March 2021 and on active follow-up, and noted that 61.4% had received at least 1 dose of messenger RNA–based COVID-19 vaccine. All patients except 1 (described in[2]) had pre-existing IgAN diagnosed before their vaccination. None of those with pre-existing IgAN who had COVID-19 vaccination reported gross hematuria at a median 28 (interquartile range, 15-50) days' follow-up. Among 29 patients with pre-existing IgAN who had kidney function, urine microscopy, and proteinuria evaluated at 11 (18-33) days after vaccination, 2 had mildly increased serum creatinine with increased hematuria and proteinuria. None required initiation or escalation of immunosuppressive therapy. The possibility of a treatable flare after vaccination should be weighed against the significantly increased risk of COVID-19-related mortality in patients with kidney disease.[4]

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RESEARCH LETTER

Outcomes From Infections With Variant Strains of SARS-CoV-2 Among Patients Receiving Maintenance Hemodialysis

To the Editor:

Even though safe and effective vaccines have been developed for SARS-CoV-2, variants of concern continue to emerge.[1,2] We present a comparison of 2 COVID-19 waves in 2 hemodialysis facilities. Patients in 1 hemodialysis facility ("wave 1") were infected by nonvariant SARS-CoV-2 between July and October 2020. Patients from the second facility ("wave 2") became ill between December 28, 2020, and January 10, 2021 and were infected by a variant SARS-CoV-2 from the B.1.362 lineage, termed IVUI-L452R (Israeli variant under investigation with L452R mutation). Genetic mutations were detected by next-generation sequencing. Detailed methods and figures showing timelines are in Item S1.

This analysis includes 33 patients, 26 from wave 1 and 7 from wave 2. Baseline clinical characteristics were similar between the groups except for a higher frequency of diabetes and heart failure among wave 1 patients (Table S1).

Table 1 and Fig 1 compare clinical presentation and disease severity. Five of 26 patients from wave 1 were asymptomatic and diagnosed by postexposure surveillance, while all patients from wave 2 were symptomatic.

COVID-19 severity was significantly worse in patients from wave 2, with more with critical COVID-19 (71% vs 8%, $P = 0.005$, Fig 1), as well as borderline statistically significantly higher need for noninvasive ventilation ($P = 0.05$), mechanical ventilation ($P = 0.05$), and hemodynamic support ($P = 0.05$). Medical treatment is detailed in Table S2.

In-hospital mortality was significantly higher among wave 2 patients (57% vs 8% in wave 1; $P < 0.005$), corresponding to an odds ratio of 16 (95% CI, 2-127.9). Overall mortality was also significantly higher for wave 2 patients (71.4% vs 15.4% for wave 1; $P < 0.001$) despite shorter follow-up (39 ± 4 vs 129 ± 54 days; $P = 0.003$).

In this retrospective study, patients infected with IVUI-L452R SARS-CoV-2 had significantly poorer outcomes and

Table 1. Clinical and Laboratory Data of Patients Infected With Nonvariant (Wave 1) and Variant (Wave 2) SARS-CoV-2

Characteristic	Wave 1 (n = 26)	Wave 2 (n = 7)	*P*
Age, y	65.8 ± 14.7	70.1 ± 12.1	0.5
Male sex	14 (54%)	5 (71%)	0.4
Dialysis vintage, mo	34.1 ± 27.7	57 ± 24.6	0.06
Clinical presentation			
Asymptomatic infection	19%	0%	0.2
Fever	62%	71%	0.9
Cough	15%	43%	0.1
GI symptoms	12%	43%	0.06
Malaise	28%	71%	0.04[a]
Confusion	4%	29%	0.05[a]
Temperature, °C	37.9 ± 0.8	38.1 ± 0.8	0.5
Heart rate	82.8 ± 14.4	86.6 ± 14.8	0.5
Systolic BP, mm Hg	146.1 ± 22.3	150.1 ± 19.7	0.7
Diastolic BP, mm Hg	70.2 ± 12.2	72.6 ± 16.3	0.7
Oxygen saturation (on room air), %	94.7 ± 10.7	93 ± 6.4	0.7
Laboratory data			
WBC count, × 10^3/μL	5.4 ± 1.8	4.0 ± 1.6	0.08
Lymphocytes, × 10^3/μL	1.0 ± 0.5	0.4 ± 0.2	0.008[a]
Neutrophils, × 10^3/μL	3.9 ± 1.6	3.2 ± 1.4	0.3
Neutrophil-lymphocyte ratio	5.1 ± 3.6	7.8 ± 3.6	0.07
Hemoglobin, g/dL	11.1 ± 1.7	11.1 ± 0.8	0.9
Platelets, × 10^3/μL	182.3 ± 73.3	164.7 ± 84	0.6
C-reactive protein, mg/dL	7.7 ± 8.4	5.3 ± 2	0.5
Total bilirubin, mg/dL	0.5 ± 0.2	0.8 ± 0.5	0.04[a]
Albumin, g/dL	3.3 ± 0.4	3.3 ± 0.3	0.9
Ferritin, μg/L	2,746 ± 2,745	1,487 ± 1,038	0.5

Abbreviations and definitions: BP, blood pressure; WBC, white blood cell; GI symptoms, gastrointestinal symptoms (nausea, vomiting, or diarrhea).
[a]Statistically significant (or, for 0.05, borderline statistically significant).

higher mortality. Variant virus–associated COVID-19 differed from onset, as all patients were symptomatic, more frequently with malaise, and had worse lymphocyte and total bilirubin levels at presentation. Since all hemodialysis patients were screened for SARS-CoV-2 following outbreaks, we believe that all cases, including asymptomatic, were diagnosed.

Concerns regarding SARS-CoV-2 variants relate to increased infectivity,[3,4] potential resistance to vaccines, and emerging data linking specific genetic mutations to virulence.[5] However, varying medical capabilities and standards between different medical centers and patient heterogenicity can significantly confound such associations. Therefore, data from specific patient populations treated at the same medical center can add meaningful information.

Patients from wave 2 were infected by SARS-CoV-2 from the B.1.362 lineage with an additional L452R mutation in the spike protein. Two other mutations associated with this variant are Q57H in the Orf3a protein, and T261I in Orf1. Both are associated with the globally prevalent viral clade 20C. IVUI-L452R is suspected by the Israeli Ministry of Health to be a potential variant of concern, and as such is currently under investigation.

The Q57H mutation in Orf3a may be associated with increased infection rates and higher mortality.[6] The L452R mutation alters the spike interface, promotes stronger virus-cell attachment through ACE2, and increases infectivity.[7] This supports plausible mechanisms that can explain the deleterious effects of infection with variant viruses.

Major limitations of this study include its retrospective nature and small sample size. Rates of heart failure and diabetes, risk factors for critical COVID-19,[8] were higher among wave 1 patients. Since this was not a controlled trial and because of continually emerging data, therapeutic approaches differed between waves. Convalescent plasma was used in wave 1 but accumulated data have failed to ascertain therapeutic benefit.[9] Glucocorticoids, which significantly reduce mortality from severe COVID-19,[8] were used more often in wave 2. Thus, differences in comorbidities and treatment were unlikely to explain differences in outcomes between the waves.

Comprehensive mutation analysis was not performed for all wave 1 patients. However, several samples tested negative for variants of concern as part of outbreak surveillance, and the mutations identified in the variant viruses were very uncommon in Israel during the wave 2 outbreak.[10] Also, the different outcomes could not be explained by variations in national morbidity and mortality rates, which were

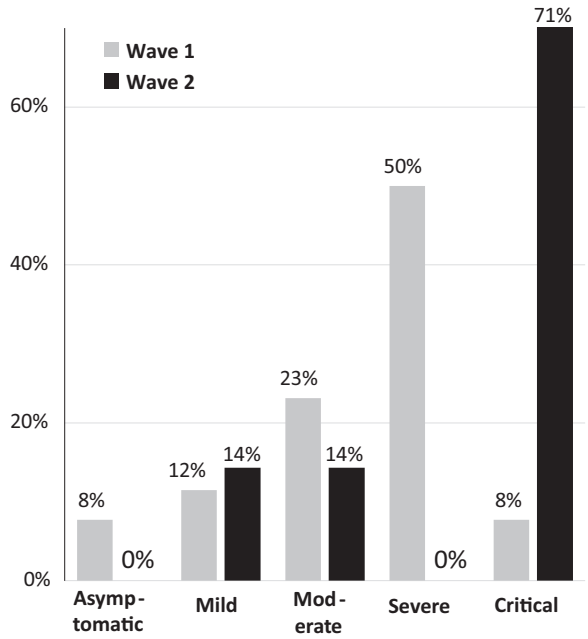

Figure 1. COVID-19 severity distribution. Severity was ranked according to National Institutes of Health guidelines as asymptomatic, mild, moderate (with clinical or radiographic evidence of lower respiratory tract disease and oxygen saturation ≥94% while breathing room air), severe (saturation <94%, respiratory rate >30/min, infiltrates over 50% of lung volume), or critical (requiring invasive or noninvasive ventilation, in shock, or with organ failure) (Item S1). Distribution of severity differed significantly between patients in wave 1 and wave 2, $P = 0.005$.

comparable between the waves (Item S1). Despite these limitations, our findings that relate viral genetic variation to clinical outcomes will inform future investigations. All patients were treated in a single medical center, which strengthens our results. Of note, no hemodialysis patients have been treated for COVID-19 in our hospital since February 2021, following nationwide vaccination that prioritized hemodialysis patients. We believe this should encourage vaccination of this population in other countries. In addition, previous reports of COVID-19 in hemodialysis patients demonstrated highly variable outcomes. We believe genetic typing of SARS-CoV-2 infection may prove important in interpreting outcomes in future studies.

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Supplementary Material

Supplementary File (PDF)

Item S1; Table S1; Table S2.

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