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SARS-CoV-2 Omicron Infections among Vaccinated Maintenance Hemodialysis Patients: Outcomes and Comparison to Delta Variant

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Keywords
Breakthrough COVID-19 infection · SARS-CoV-2 variant · BNT162b2 vaccine · Maintenance hemodialysis

Abstract

Background: Infections with B.1.1.529 (Omicron) variants of SARS-CoV-2 became predominant worldwide since late 2021, replacing the previously dominant B.1.617.2 variant (Delta). While those variants are highly transmissible and can evade vaccine protection, population studies suggested that outcomes from infection with Omicron variants are better compared with Delta. Data regarding prognosis of maintenance hemodialysis (MHD) patients infected with Omicron versus Delta variants, however, are scarce. ***Methods:*** This retrospective cohort study includes all patients with end-stage kidney disease treated with MHD in Meir Medical Center, Kfar-Saba, Israel, that were diagnosed with SARS-CoV-2 infection between June 2021 and May 2022. ***Results:*** Twenty-six subjects were diagnosed with the Delta variant and 71 with Omicron. Despite comparable age between groups and higher mean vaccine doses prior to the infection among the Omicron group ($p < 0.001$), SARS-CoV-2 infection severity was significantly worse among MHD infected with the Delta variant: 50% developed severe or critical COVID-19 versus 5% in the Omicron group ($p < 0.001$). Over half of MHD infected with Omicron (57%) were asymptomatic during their illness. The 30-day mortality rate for the whole cohort was 5.2%. It was significantly higher among MHD in the Delta group than in the Omicron group (5/26, 19.2% vs. 0/71, $p < 0.001$), as was the 90-day mortality rate (5/26, 19.2% vs. 3/71, 4.2%, $p = 0.02$). ***Conclusions:*** Infection with the SARS-CoV-2 Delta variant was associated with worse outcomes compared with Omicron, among subjects on MHD. However, despite mild disease among vaccinated MHD patients, infection with Omicron variant was still associated with the significant 90-day mortality rate.

Background

It is evident that patients' characteristics, such as age, gender, and chronic medical conditions, are significant risk factors for severe and critical coronavirus disease 2019 (COVID-19) [1]. In particular, patients on maintenance hemodialysis (MHD) are at-risk for COVID-19 and its complications. Hemodialysis attendance by itself is associated with increased exposure and infection risks

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[2]. In addition, increased morbidity and mortality was noted among MHD patients, even after adjusting for age and comorbidities [3]. Vaccination status, the immune system response to vaccination, and history of previous infection also significantly impact on the risks to acquire SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection and to develop severe COVID-19 [2, 4].

However, COVID-19 outcomes cannot be attributed only to host characteristics. Viral variants of concern may impose increased transmissibility and impact on disease severity and prognosis. MHD patients had significantly worse outcomes from infections with a SARS-CoV-2 variant from the B.1.632 lineage than from non-variants infections [5]. Breakthrough infections with the B.1.617.2 (Delta) variant among MHD patients also resulted in significant morbidity and mortality, despite previous vaccination [6]. Thus, attention to viral genotypes is important when assessing COVID-19 epidemiological and outcome studies and crucial in establishing effective public health policies.

Variants from the B.1.1.529 lineage (Omicron) has emerged and became predominant worldwide since late 2021, replacing the previously dominant Delta. While those variants are highly transmissible and can evade vaccine protection, population studies suggested that outcomes from infection with the Omicron variant are better compared with Delta [7–11]. Data regarding prognosis of MHD patients infected with Omicron versus Delta variants, however, are scarce.

Methods

This retrospective cohort study includes patients with end-stage kidney disease treated with MHD in Meir Medical Center, Kfar-Saba, Israel. The center provides chronic dialysis treatment to 150 MHD patients. Results are reported according to the STROBE statement guidelines.

Participants

Participants included adult (age ≥18 years) patients on MHD in our institution. MHD was defined as at least 3 months of hemodialysis prior to SARS-CoV-2 infection. We included consecutive MHD patients who were infected with SARS-CoV-2 from June 1st, 2021, and May 31st, 2022.

National vaccination with the BNT162b2 (Pfizer/BioNTech) mRNA vaccine began in December 2020, prioritizing MHD patients. A third vaccine dose (booster) was available and recommended from July 2021 and a fourth vaccine dose (second booster) was recommended from January 2022. Both booster doses were available for subjects who had received the previous vaccination dose at least 6 months earlier.

Diagnosis of SARS-CoV-2 Infection

The diagnosis of SARS-CoV-2 infection was ascertained by either a positive real-time reverse-transcriptase polymerase chain reaction (RT-PCR) or a positive COVID-19 lateral flow assay from nasopharyngeal swabs.

Screening for SARS-CoV-2 Infection

During the whole study period, screening for infection was performed for every MHD patient who had developed symptoms compatible with COVID-19, including fever, cough, dyspnea, nausea or vomiting, diarrhea, anosmia, or malaise. In addition, testing for SARS-CoV-2 infection was undertaken for contacts of active COVID-19 cases, including in the absence of symptoms. This surveillance protocol remained unchanged during the study period.

Study Groups

Participants were divided into two groups according to the variant of SARS-CoV-2 infection: Delta or Omicron. Categorization was performed according to the results of viral genome next-generation sequencing, when available. Otherwise, grouping according to infection time was assigned when next-generation sequencing of SARS-CoV-2 genome was not available (such as for subjects diagnosed solely based on lateral flow assays). Israel experienced a surge in COVID-19 cases related to the Delta variant from June 2021 until September 2021 ("Delta wave"). Subsequently, the Omicron variant became predominant in Israel beginning December 2021 ("Omicron wave") [12]. Thus, in the absence of sequencing data, infections, which occurred between June 1st and November 30th, 2021, were assigned to the Delta group, while those diagnosed from December 1st and onward were assigned to the Omicron group.

Measured Variables

Clinical, laboratory, and radiologic data were extracted from the participants' medical records. The day of first positive swab for SARS-CoV-2 served as day 0 of illness for the study. Baseline clinical variables included age; sex; comorbidities; dialysis vintage and adequacy parameters; baseline laboratory data. Variables related to COVID-19 included clinical findings at presentation, including COVID-19 symptoms, vital signs; laboratory findings; radiology findings from chest X-rays and computerized tomography studies when performed; treatment given for COVID-19.

Outcome Measures

We compared outcomes between study groups. The primary outcome was 30 days mortality since COVID-19 infection. Secondary outcomes included 90 days mortality since COVID-19 infection, mortality rates over time, maximal disease severity, hospital admission rates for COVID-19, rates of oxygen support and mechanical ventilation, specific treatment for COVID-19. Disease severity was ranked according to National Institute of Health (NIH) 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 lungs volume, or PaO_2/FiO_2 ratio<300), and critical (individuals who have respiratory failure requiring invasive or non-invasive ventilation, septic shock, or with multiorgan dysfunction) [13].

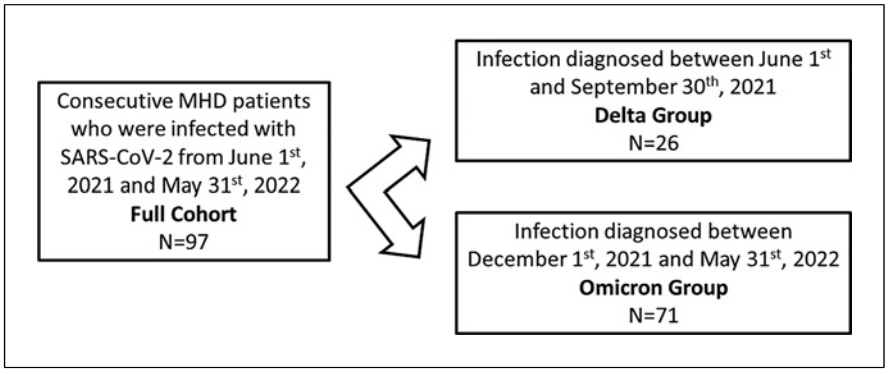

Fig. 1. Flowchart of study cohort (N = 97).

Statistical Analysis

Descriptive statistics are presented as means, medians, or percentages with standard deviations and range, as appropriate. Comparison of variables between the study groups was performed using t test, Mann-Whitney test, Fisher's exact test, or χ^2 test according to scale measured variables. A p value <0.05 was considered statistically significant. Univariate and multivariate logistic regression model was applied to estimate odds ratios of mortality. Data were analyzed with SPSS version 27 (IBM Corporation, Armonk, NY, USA).

Results

There were 97 consecutive MHD patients diagnosed with COVID-19 during the study period (Fig. 1). Twenty-six were diagnosed with the Delta variant and 71 with Omicron. All cases of Delta variant SARS-CoV-2 infection occurred between June and September 2021, while all cases of Omicron were infected since December 2021. Median age of the entire cohort was 70 years old (range 24–95), 25% were females (24 of 97), those were similar between groups.

Subjects from the Omicron group were more frequently vaccinated with 3 or 4 vaccine doses prior to infection (p < 0.001). The average interval between the last vaccine dose and infection was comparable between groups, 5.9 months for the Delta group versus 5.1 months for the Omicron group, p = 0.12. More patients in the Delta group suffered from an active hematological malignancy (15% vs. 1.5%, p = 0.008) or required chronic immunosuppressive therapy (31% vs. 6%, p = 0.002). Mean follow-up time since the day of SARS-CoV-2 infection was longer in the Delta group. The rest of the baseline clinical characteristics were comparable between the groups (Table 1). Regarding baseline laboratory parameters, subjects in the Omicron group had a lower mean lymphocyte count than those in the Delta group (1,100 cell/μL vs. 1,400 cells/μL, respectively, p = 0.03). Other laboratory findings were similar (online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000536521).

The sources of SARS-CoV-2 infections were considered nosocomial in 6/26 Delta cases (23%) and otherwise healthcare associated in additional 3/26 (11.5%). This was higher than in the Omicron group (1/71, 1.4% nosocomial, and 3/71, 4.2% healthcare associated) in which the vast majority of infection cases were considered from household contacts (67/71, 94.4%, p = 0.001, online suppl. Fig. S1).

Over half of MHD infected with Omicron (57%) were asymptomatic during their illness, while the most common symptoms of Delta infection were fever (54%) and cough (46%). COVID-19 from the Delta variant presented more often with fever or dyspnea than did infection with Omicron (Table 2). Gastrointestinal symptoms and anosmia were uncommon.

SARS-CoV-2 infection severity was significantly worse among MHD infected with the Delta variant; overall, 50% developed severe or critical COVID-19 versus 5% in the Omicron group (p < 0.001, Fig. 2). Half of the subjects infected with the Delta variant required hospital admission for COVID-19, significantly more than those infected with Omicron (28%, p = 0.04). Likewise, 50% of the Delta group required oxygen support and 12% required mechanical ventilation, versus 4% and 1% in the Omicron group (p < 0.001 and p = 0.02, respectively) (Fig. 3).

Subjects in the Delta group were more often treated with dexamethasone (46% vs. 5%, p < 0.001) or with tocilizumab (8% vs. 0, p = 0.02); usage of remdesivir or casirivimab/imdevimab was uncommon. None of the subjects were treated with baricitinib. Molnupiravir and nirmatrelvir/ritonavir were only available for subjects in the Omicron group and were administered to 6 and 1

Table 1. Baseline characteristics of study participants

	Delta (*N* = 26)	Omicron (*N* = 71)	*p* value*
Age, mean (SD), years	68.5 (16.9)	67 (14.8)	0.68
Females, *N* (%)	6 (23.1)	18 (25.4)	0.82
Dialysis vintage, mean (SD), months	27.3 (20)	28.3 (23.2)	0.86
Follow-up days, mean (SD)	256.3 (130.8)	135.9 (35.6)	<**0.001**
SARS-CoV-2 vaccine doses, *N* (%)			<**0.001**
0	2 (8)	8 (12.1)	
1	0	5 (7.6)	
2	20 (80)	13 (19.7)	
3	3 (12)	29 (43.9)	
4	0	11 (16.7)	
Comorbidities, *N* (%)			
Diabetes	14 (53.8)	40 (60.6)	0.55
Hypertension	21 (80.8)	57 (86.4)	0.50
Coronary heart disease	14 (53.8)	32 (48.5)	0.64
Heart failure	12 (46.2)	27 (40.9)	0.65
Peripheral vascular disease	2 (7.7)	10 (15.2)	0.34
Chronic lung disease	4 (15.4)	9 (13.6)	0.83
Solid malignancy	0	5 (7.6)	0.15
Hematological malignancy	4 (15.4)	1 (1.5)	**0.008**
Past malignancy	5 (20)	6 (9.1)	0.15
Immunocompromised	8 (30.8)	4 (6.1)	**0.002**

*Statistically significant differences between groups are marked in bold. Data are presented as mean (SD) or as absolute numbers (%).

Table 2. COVID-19 symptoms

	Delta (*N* = 26)	Omicron (*N* = 65)	*p* value*
Asymptomatic, *n* (%)	9 (34.6)	37 (56.9)	0.055
Fever, *n* (%)	14 (53.8)	12 (18.5)	**0.001**
Cough, *n* (%)	12 (46.2)	19 (29.2)	0.12
Dyspnea, *n* (%)	9 (34.6)	11 (16.9)	0.06
Anosmia, *n* (%)	0	1 (1.5)	0.53
Diarrhea, *n* (%)	0	2 (3.1)	0.37
Vomiting, *n* (%)	1 (3.8)	4 (6.2)	0.66
Nausea, *n* (%)	3 (11.5)	0	**0.005**
Malaise, *n* (%)	5 (19.2)	12 (18.5)	0.93

*Statistically significant differences between groups are marked in bold.

subjects, respectively (online suppl. Table S2; Fig. S2). Of note, 27% of the Delta group were treated with antibiotics for suspected or confirmed bacterial co-infection, versus 12% in the Omicron group ($p = 0.09$).

The 30-day mortality rate for the whole cohort was 5.2%. It was significantly higher among MHD in the Delta group than in the Omicron group (5/26, 19.2% vs. 0/71, $p < 0.001$), as was the 90-day mortality rate (5/26, 19.2%, vs. 3/71, 4.2%, $p = 0.02$). There was no association between comorbidities, immunosuppressive treatment, number of vaccine doses prior to infection or baseline laboratory values, and mortality.

Cox regression analysis model was developed to compare mortality rates over time between the two groups. Mortality over time was higher for MHD in the Delta group in a model which incorporated age, sex and comorbidities in addition to SARS-CoV-2 variant (Fig. 4).

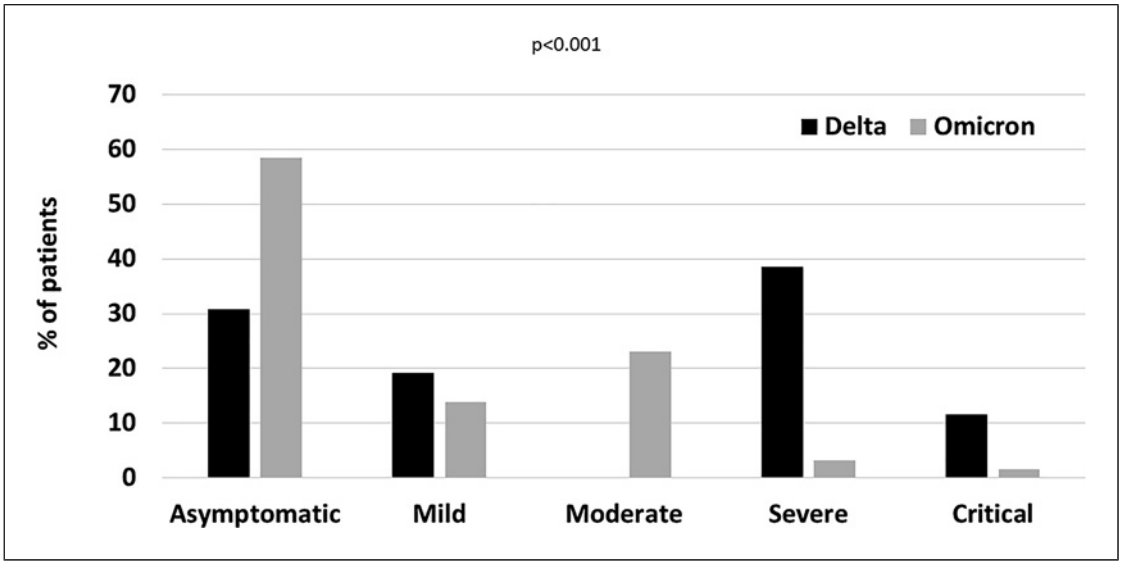

Fig. 2. Maximal COVID-19 severity. Over half of MHD infected with Omicron (57%) were asymptomatic during their illness. SARS-CoV-2 infection severity was significantly worse among MHD infected with the Delta variant; overall, 50% developed severe or critical COVID-19 versus 5% in the Omicron group ($p < 0.001$).

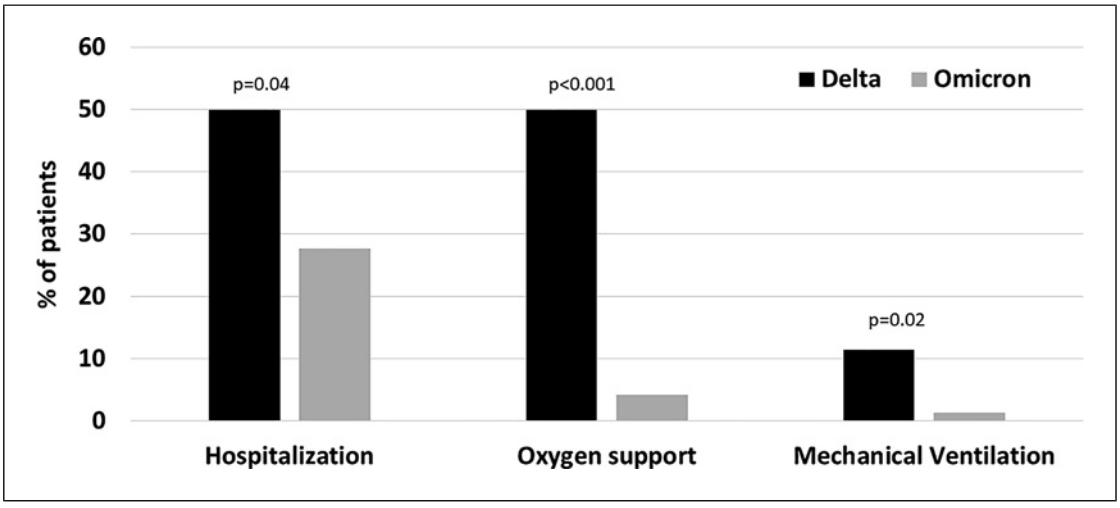

Fig. 3. Hospital admission and respiratory support. Overall, 50% of the Delta group required oxygen support and 12% required mechanical ventilation, versus 4% and 1% in the Omicron group ($p < 0.001$ and $p = 0.02$, respectively).

Discussion

In this cohort of MHD patients, infection with Delta variant SARS-CoV-2 in comparison with Omicron was associated with higher rates of symptomatic disease, worse COVID-19 severity, increased need for hospitalizations, respiratory support and specific therapy for severe illness, and increased mortality. Several studies among the general population have demonstrated different clinical presentation and improved outcomes from infection by the Omicron variant SARS-CoV-2 than from the Delta variant [7]. This includes a reduced risk for hospitalizations [9–11, 14], even among unvaccinated individuals, suggesting a reduced intrinsic disease severity

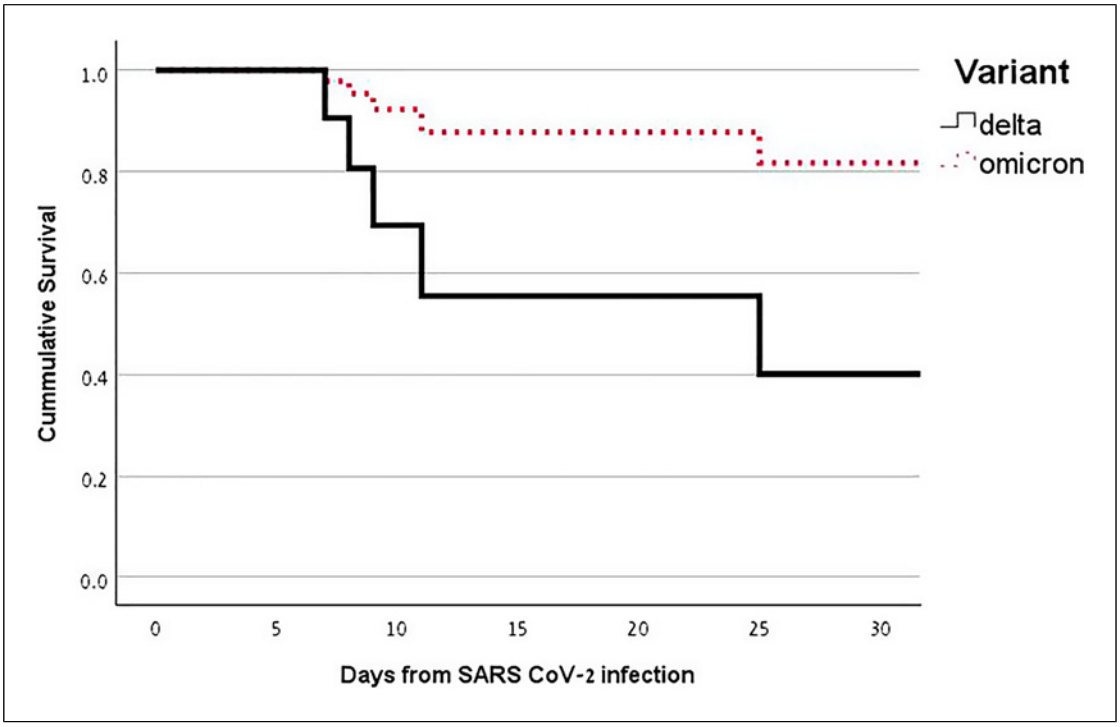

Fig. 4. Survival curves of MHD infected with SARS CoV2. Cox regression analysis model was developed to compare mortality rates over time between the two groups. Mortality over time was higher for MHD in the Delta group in a model, which incorporated age, sex and comorbidities in addition to SARS-CoV-2 variant.

of the Omicron variant [9, 10]. Risk of COVID-19-related mortality, intensive care unit admission, and mechanical ventilation is also lower for the Omicron variant [7, 14, 15]. Relative effectiveness of equivalent vaccine doses against poor COVID-19 outcomes, however, is lower for Omicron compared to Delta variant, although it is higher for 3 versus 2 doses in both cases [11, 16, 17]. This is in line with our results, in which MHD patients who were infected with the Omicron variant were mostly vaccinated with 3 or 4 vaccine doses (40/66 with available vaccination data, 61%) and indeed fared better than those infected with Delta variant.

There are less data regarding infection with different SARS-CoV-2 variants among MHD patients and the effect of vaccination. Immune system dysfunction associated with MHD, leading to an increased risk for poor COVID-19 outcomes, may attenuate the differences of clinical severity intrinsic to viral variants. In vitro assays of vaccine effectiveness (neutralizing antibodies and T-lymphocytes response) against the Omicron variant are lower than for Delta among MHD patients [18–21]. Immune response to vaccination declines over time and significantly improves with additional, booster, doses [18–22]. In addition, clinical vaccine effectiveness against severe Omicron-variant COVID-19 increases with additional doses and may correlate with antibody titers among MHD patients [2, 21, 23, 24].

A few studies regarding infection outcomes among MHD patients reported overall good prognosis in the majority of Omicron SARS-CoV-2 infection [2, 25–27]. However, those studies mostly compared outcomes with previous "historical" reports of outcome during previous COVID-19 waves and did not directly compare cohorts of MHD patients infected with different variants while considering baseline individuals' characteristics into account.

Limitations of our study include its retrospective, single-center design and modest sample size. Genomic validation of SARS-CoV-2 variants was not available in many subjects, especially within the Omicron group. However, all infections allocated to the Delta group occurred in the time period during which this variant was responsible to 97–100% of cases nationwide, and to all sequenced infections in our Medical Center, while infections in the Omicron group all occurred when this variant was identified in over 98% of cases in Israel [12]. We did not assess for different Omicron subvariants, although the clinical significance of which is still debated [11]. The two patients' groups were imbalanced in the proportion of subjects with an underlying hematological

malignancy, chronic immunosuppressive therapy, and number of vaccine doses, which may affect COVID-19 outcomes. The effectiveness of vaccination wanes over time and thus is dependent not only on the number of vaccine doses but also on the timing of vaccine. Yet there were similar time intervals between the last received vaccine dose and infection in our cohort, and we believe this would not significantly affect outcomes. Since the Omicron wave occurred after the Delta, it is possible that subjects in the Omicron group have been selected with a survival bias, such that less vulnerable subjects survived the Delta wave. However, none of the subjects in our study had been previously infected (and survived) with SARS-CoV-2. The proportion of cases, which were nosocomial or otherwise healthcare associated, was also larger in the Delta group, which could also affect outcome [28]. However, none of those variables were associated with mortality in our cohort, and the lower mortality risk with Omicron remained significant in the multivariate regression analysis models. Early therapy with antiviral medications reduces the risk for disease progression and lowers mortality among subjects with COVID-19 [29–31]. Those therapies, which were only available for subjects infected with the Omicron variant, could also bias our results. However, only a minority of patients received them, and we found no association between those antivirals and outcomes. Despite this, we cannot rule out other improvements in clinical management of COVID-19, which may have occurred between waves.

We believe that the fact that infection with the Omicron variant differed from Delta in several clinical characteristics, from subjective symptoms to "hard" outcomes such as mortality, supports an inherent reduced disease severity by this variant even among the vulnerable MHD population. Thus, attention to circulating SARS-CoV-2 variants is prudent both in clinical management and public healthcare policies among MHD patients. In conclusion, infection with the SARS-CoV-2 Delta variant was associated with worse outcomes compared with Omicron, among subjects on MHD.

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Statement of Ethics

The study was approved by the Ethics Committee and Institutional Review Board of Meir Medical Center (No. MMC 16-21). The committee waived the requirement for other participants' informed consent due to the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

The authors declare that they have no relevant financial interests.

Author Contributions

Research area and study design: Ori Wand, Naomi Nacasch, Sydney Benchetrit, and Keren Cohen-Hagai; data acquisition: Idan Drori, Ori Wand, Naomi Nacasch, Yael Einbinder, and Keren Cohen-Hagai; data analysis and interpretation: Ori Wand, Anna Breslavsky, Sydney Benchetrit, and Keren Cohen-Hagai; statistical analysis: Ori Wand and Keren Cohen-Hagai; and supervision or mentorship: Sydney Benchetrit and Keren Cohen-Hagai.

Data Availability Statement

All data generated during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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