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Clinical effectiveness of molnupiravir in patients with COVID-19 undergoing haemodialysis

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Molnupiravir is an essential oral antiviral agent against coronavirus disease 2019 (COVID-19); however, its real-world effectiveness has not been evaluated in patients undergoing haemodialysis (HD).

Methods: This multi-centre retrospective study, involving 225 patients undergoing HD with initially mild or asymptomatic COVID-19, was conducted to compare the risks of 30-day COVID-19-related acute care visits between patients receiving and not receiving molnupiravir. Patients who received molnupiravir were stratified by rapid antigen detection (RAD) test results on day 7 after disease onset to assess whether rapid molnupiravir introduction accelerated viral clearance.

Results: Thirty-day COVID-19-related acute care visits were reported in 9.41% and 21.74% of the molnupiravir and control groups, respectively, and use of molnupiravir markedly reduced the risk of acute care visits after adjusting for baseline characteristics via propensity score weighting [hazard ratio 0.218, 95% confidence interval (CI) 0.074–0.642; P=0.006]. The tolerability of molnupiravir in the enrolled patients was generally acceptable, with only 11.88% of molnupiravir users reporting mild adverse events. Moreover, rapid initiation of molnupiravir within 1 day of COVID-19 onset was an independent predictor of conversion to a negative RAD test result on day 7 after disease onset (odds ratio 6.207, 95% CI 2.509–15.358; P<0.001).

Conclusions: Molnupiravir is well tolerated and decreases the medical needs in patients with COVID-19 undergoing HD. Furthermore, the rapid initiation of molnupiravir accelerates viral clearance in patients with COVID-19 undergoing HD. These findings highlight the therapeutic role of molnupiravir for this vulnerable population.

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1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has led to more than 600 million infections and more than 6 million deaths globally as of January 2023[1]. Since 2022, the Omicron variant of SARS-CoV-2 has become the dominant strain worldwide and has resulted in extensive community spread in Taiwan[2,3]. Patients undergoing haemodialysis (HD) have a high risk of developing severe illness due to COVID-19, and a case fatality rate of up to 1% was reported within this population prior to the Omicron era[4]. Although the disease severity of COVID-19 appears to have been reduced in the Omicron era, possibly because of the attenuated virulence of the variant and pre-existing immunity derived from previous infection or vaccination, there are still concerns about its impact on vulnerable populations[5,6]. Additionally, patients undergoing HD have a remarkably high risk of viral exposure because they have to visit dialysis units regularly, where numerous patients and medical staff crowd together for hours dur-
ing each HD session [7]. Taiwan has the highest prevalence of treated end-stage renal disease (ESRD) worldwide, with 3772 cases per million people in 2020, and approximately 90% of patients with ESRD in Taiwan receive HD as a form of renal replacement therapy [8]. Considering the growing burden of ESRD and increased risk of COVID-19 in patients undergoing HD, adequate management of COVID-19 is essential within the HD population [9,10].

As most patients with COVID-19 during the Omicron era can be treated without hospitalization, molnupiravir is one of the therapeutic options [11]. Molnupiravir is an antiviral agent granted Emergency Use Authorization (EUA) in the USA and Taiwan, and is available for patients with non-severe COVID-19 who are at risk of disease progression [12,13]. Based on a phase 3 randomized controlled trial known as the MOVE-OUT study, molnupiravir can reduce the risk of COVID-19-associated hospitalization or mortality by 31% [14]. However, the mutagenic properties of molnupiravir have raised concerns about its potential to boost SARS-CoV-2 variant generation [12,15]. Despite these concerns, molnupiravir has been considered a reasonable pharmacological intervention in patients with COVID-19 undergoing HD, as its active metabolite, N-hydroxycytidine, is not substantially eliminated by the kidney [14,15]. Moreover, because of its favourable safety profile and minimal drug-drug interaction, molnupiravir is a suitable treatment option for patients with multi-morbidity and polypharmacy, which are also common in patients undergoing HD [16–18]. Nonetheless, because patients undergoing HD were excluded from the MOVE-OUT study, the clinical benefit of molnupiravir was not assessed in these patients in this landmark trial [14]. Although patients with chronic kidney disease were included in several real-world studies addressing the effectiveness of molnupiravir for COVID-19, the proportions were small (0.4–6.8%), and their dialysis status was unknown [19–22]. Furthermore, the effect of molnupiravir on accelerating viral clearance in patients with COVID-19 undergoing HD is yet to be clarified.

This multi-centre retrospective study evaluated the real-world effectiveness of molnupiravir in improving clinical outcomes and accelerating viral clearance in patients with COVID-19 undergoing HD.

2. Materials and methods

2.1. Enrolment of the study cohort

Patients were recruited from the outpatient HD units of Kaohsiung Chang Gung Memorial Hospital and Kaohsiung Municipal Feng-Shan Hospital between May and August 2022. All patients were identified from the COVID-19 registration lists of the HD units, which have been established to record all confirmed cases of COVID-19 in the HD units since January 2020 as part of hospital practice. The inclusion criteria were as follows: (1) adult patients (age ≥20 years) undergoing maintenance HD for at least 1 month before enrolment; (2) patients previously naïve to SARS-CoV-2 infection and diagnosed with COVID-19 during the study period; and (3) patients with either a mild illness or asymptomatic status at COVID-19 diagnosis. Patients who required hospitalization because of other initial causes and those who were transferred to other HD centres within 30 days of disease onset were excluded from the analysis. COVID-19 diagnosis was based on a positive SARS-CoV-2 test via either reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen detection (RAD) test on a clinical specimen (nasopharyngeal or throat swab) in compliance with the guidelines of the Taiwan Centers for Disease Control (CDC) [23]. The severity of COVID-19 was determined according to World Health Organization (WHO) guidelines [24]. The study protocol was approved by the Institutional Review Board and Ethics Committee of Chang Gung Medical Foundation, Taipei, Taiwan (IRB No. 202201346B0), and adhered to the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective study design.

2.2. Prescription of molnupiravir and follow-up schedule of RAD test for patients undergoing HD

A standardized management protocol for non-hospitalized patients with COVID-19 undergoing HD, adapted from the Taiwan CDC guidelines, has been introduced into hospital practice since April 2022 [13]. During the COVID-19 pandemic, SARS-CoV-2 diagnostic tests via either PCR or RAD were arranged for patients who had symptoms of COVID-19 or who had been in close contact with patients with COVID-19. Once the COVID-19 diagnosis was confirmed for a patient undergoing HD, an investigation of individual care requirements was conducted by healthcare workers in the HD units; these included the dates of symptom onset and positive diagnostic tests, clinical presentations, initial disease severity, and the need for point-to-point transportation services for HD during the quarantine period. The day of COVID-19 onset (day 0) corresponded to the day of symptom onset and the positive diagnostic test for symptomatic and asymptomatic patients, respectively. Patients with mild or asymptomatic COVID-19 underwent maintenance HD as per their usual schedules in the quarantine zones of HD units for at least 7 days (days 0–6). As a population at risk of disease progression, molnupiravir (Merck Sharp and Dohme, Kenilworth, NJ, USA) was offered as a treatment option for patients undergoing HD with mild or asymptomatic COVID-19, after evaluation by hospital medical teams. For patients who did not have contraindications and provided consent for molnupiravir treatment as per the regulations of the Taiwan CDC, molnupiravir was prescribed at a standard dosage of 800 mg every 12 h for 5 days [13,14]. If molnupiravir was administered by other hospitals, the initiation date was recorded. Adherence to molnupiravir was monitored by healthcare workers in the HD units. Considering the effect of molnupiravir on accelerating viral clearance in the general population [25–26], nasal RAD tests for SARS-CoV-2 were performed on days 7 and 10 in patients receiving and not receiving molnupiravir, respectively. All RAD tests employed were granted EUA by the Taiwan Ministry of Health and Welfare, and met the WHO criteria of >80% sensitivity and >97% specificity [27,28]. For infection control in HD units, patients with a positive RAD test result underwent HD in quarantine zones, and RAD tests were repeated before each HD session until a negative test result was obtained or beyond 30 days after disease onset. Patients with a negative RAD test result and clinical improvement underwent further HD sessions back in the general zones. Molnupiravir-related adverse events were investigated by the medical teams of the HD units, and categorized as either gastrointestinal or non-gastrointestinal. All treatment course data within 30 days of COVID-19 onset were recorded as part of daily practice in the HD units.

2.3. Definition of clinical outcome and collection of patient characteristics

The main outcome of interest in this study was COVID-19-related acute care visit, which was defined as a visit to an emergency room for medical management of COVID-19-related discomforts (such as aggravation of constitutional or respiratory tract symptoms) or complications (such as pneumonia, sepsis or thromboembolic events) within 30 days of disease onset. The first visit for COVID-19 diagnosis was excluded. Clinical outcomes, such as COVID-19-related hospitalization and mortality within 30 days, were also recorded. Data on COVID-19 diagnosis, initial presentation, molnupiravir prescription, follow-up RAD tests, molnupiravir-related adverse events, emergency room visits, hospitalizations and
deaths were extracted from the records in the HD units. The baseline characteristics of the enrolled patients, including age, sex, body mass index (BMI), duration of HD, smoking habits, use of immunosuppressants, and comorbidities (e.g., diabetes, hypertension, dyslipidaemia, vascular disease, heart failure, liver cirrhosis, lung disease and history of malignancy) were collected from the electronic medical record systems and HD records of the hospitals. Baseline haematological data, blood biochemical profiles, and indicators of dialysis adequacy of the enrolled patients were also collected. The details of data extraction are provided in Table S1 (see online supplementary material).

The COVID-19 vaccination status of the participants was obtained from the National Immunization Information System of Taiwan. During the study period, the SARS-CoV-2 vaccines granted EUA in Taiwan included the Oxford-AstraZeneca (ChAdOx1-S), Moderna (mRNA-1273), Pfizer-BioNTech (BNT162b2), Novavax (NVX-CoV2373) and Medigen (MVC-COV1901) SARS-CoV-2 vaccines [27]. MVC-COV1901 is a protein subunit SARS-CoV-2 vaccine that was developed domestically and granted EUA in Taiwan due to its promising immunogenicity and favourable safety profile [29,30]. Vaccination status was defined according to the latest dose of the SARS-CoV-2 vaccine administered beyond 14 days prior to disease onset.

2.4. Statistical analysis

Categorical variables are presented as numbers with percentage, and continuous variables are presented as means with standard deviations (SD). To evaluate the effect of molnupiravir in reducing the risk of COVID-19-related acute care visits, the study population was divided into two groups: patients receiving molnupiravir (molnupiravir group) and patients not receiving molnupiravir (control group). Inverse probability of treatment weighting (IPTW) for the average treatment effect on the treated (ATT) was performed to adjust the baseline differences between the molnupiravir and control groups based on propensity scores [31]. An absolute standardized mean difference (SMD) <0.10 for baseline covariates indicated a good balance between groups after IPTW-ATT. Multi-variate Cox regression analysis was conducted to adjust the effect of molnupiravir on the risk of COVID-19-related acute care visits, adjusting for baseline characteristics and vaccination status via IPTW-ATT, based on propensity scores. The vaccination status of the enrolled patients was categorized into three levels: unvaccinated, one or two doses of SARS-CoV-2 vaccines, and three or four doses of SARS-CoV-2 vaccines. Additionally, to evaluate the effect of rapid molnupiravir initiation (defined as initiating molnupiravir within 1 day of COVID-19 onset) on accelerating viral clearance, the molnupiravir group was stratified into two subgroups based on the results of the RAD test on day 7: subgroups with early conversion to a negative result (negative result on day 7) and delayed conversion to a negative result (positive result on day 7). Patient characteristics, vaccination status and timing of molnupiravir initiation were compared between subgroups. Categorical variables were analysed using the Chi-squared test, and continuous variables were examined using an independent t-test for univariate analysis. All variables with P<0.1 on univariate analyses were evaluated through logistic regression analysis using the enter method to identify the factors independently associated with early conversion to a negative RAD test result, adjusting for age, sex, BMI, duration of HD, diabetes, hypertension, use of immunosuppressants, and vaccination status. Statistical significance was set at P<0.05. The IPTW-ATT based on propensity scores and the propensity-score-weighted multi-variate Cox regression analysis were performed using R Version 4.1.2 (R Foundation for Statistical Computing, Indianapolis, IN, USA) with ‘WeightIt’ package (Version 0.13.1), ‘cobalt’ package (Version 4.4.0) and ‘survival’ package (Version 3.4-0). Statistical Product and Service Solutions (Version 22.0; IBM Corp., Armonk, NY, USA) was used for all other analyses.

3. Results

3.1. Characteristics of the enrolled patients

In the outpatient HD units of the hospitals, all patients undergoing maintenance HD were naïve to SARS-CoV-2 infection before the study period, consistent with the relatively low prevalence of COVID-19 in Taiwan before the Omicron wave since May 2022 (⟨5000 cases per million people by the end of April 2022⟩ [3]. During the study period, 247 adult outpatients undergoing HD in the hospitals experienced their first confirmed episode of COVID-19. Twenty-two patients were excluded according to the pre-specified exclusion criteria, and 225 patients were enrolled in the analysis. All enrolled patients presented with either a mild illness or asymptomatic status, and did not initially require hospitalization. The molnupiravir group consisted of 202 (89.78%) patients, whereas 23 (10.22%) patients who refused molnupiravir treatment were included in the control group (Fig. 1). The characteristics of the enrolled patients are summarized in Table 1. The mean age of the cohort was 65.37 years (SD 10.67), and women accounted for 57.33% of the study population. The mean duration of HD was 8.80 (SD 7.64) years, and 43.11% of the participants had diabetes. Twenty (8.89%) enrolled patients used immunosuppressants because of transplantation history (n=4), autoimmune diseases (n=7) or other causes (n=9). Among the enrolled patients, 77.33% had received three or four doses of SARS-CoV-2 vaccines, 23.67% had received one or two doses, and 3.04% had not received any doses of SARS-CoV-2 vaccine.

| Table 1 | Characteristics of patients with initially mild or asymptomatic coronavirus disease 2019 undergoing haemodialysis (HD) (n=225). |
|---------|---------------------------------------------------------------------------------------------------------------|
| Baseline demographic and clinical profiles | |
| Age (years), mean ± SD | 65.37 ± 10.67 |
| Female, n (%) | 129 (57.33) |
| BMI (kg/m2), mean ± SD | 23.29 ± 4.46 |
| Duration of HD (years), mean ± SD | 8.80 ± 7.64 |
| Diabetes, n (%) | 97 (43.11) |
| Hypertension, n (%) | 205 (91.11) |
| Dyslipidaemia, n (%) | 180 (80.00) |
| Vascular disease, n (%) | 90 (40.00) |
| Heart failure, n (%) | 70 (31.11) |
| Liver cirrhosis, n (%) | 23 (10.22) |
| Lung disease, n (%) | 20 (8.89) |
| Malignancy, n (%) | 60 (26.67) |
| Immunosuppressantsa, n (%) | 20 (8.89) |
| Smoking, n (%) | 20 (8.89) |
| Hb (g/L), mean ± SD | 103.70 ± 12.80 |
| BUN (mmol/L), mean ± SD | 24.70 ± 7.06 |
| Scr (µmol/L), mean ± SD | 903.11 ± 235.11 |
| Alb (g/L), mean ± SD | 39.57 ± 3.49 |
| Ca (mmol/L), mean ± SD | 2.38 ± 0.22 |
| P (mmol/L), mean ± SD | 1.68 ± 0.46 |
| K (mmol/L), mean ± SD | 4.52 ± 0.63 |
| Bilirubin (mol/L), mean ± SD | 21.64 ± 2.57 |
| ALT (U/L), mean ± SD | 14.72 ± 7.94 |
| Bil-T (µmol/L), mean ± SD | 5.61 ± 3.16 |
| Cr(T)/Creat, n (%) | 1.61 ± 0.32 |
| CTR, mean ± SD | 0.53 ± 0.08 |
| Vaccination status and use of oral antiviral agent | |
| Unvaccinated, n (%) | 24 (10.67) |
| One or two vaccine doses, n (%) | 27 (12.00) |
| Three or four vaccine doses, n (%) | 174 (77.33) |
| Molnupiravir usage, n (%) | 202 (89.78) |

Alb, serum albumin; ALT, alanine transaminase; Bil-T, blood total bilirubin; BMI, body mass index; BUN, blood urea nitrogen; Ca, blood total calcium; CTR, cardiothoracic ratio; Hb, haemoglobin; K, blood potassium; P, blood phosphorus; Scr, serum creatinine; SD, standard deviation.

a Use of immunosuppressants due to transplantation history (n=4), autoimmune disease (n=7) or other causes (n=9).
12.00% had received one or two doses of SARS-CoV-2 vaccines, and 10.67% were unvaccinated.

3.2. Clinical outcomes and molnupiravir-related adverse events in the enrolled patients

The clinical presentation of the study cohort is shown in Fig. 2A. Most enrolled patients were initially symptomatic (92.44%), including 85 (37.78%) who reported fever, while 17 (7.56%) were completely asymptomatic at diagnosis. COVID-19-related acute care visits occurred in 24 (10.67%) enrolled patients during the study period, including three deaths; the deaths were attributed to acute respiratory distress syndrome (n=1), acute myocardial infarction (n=1) and septic shock (n=1). Nineteen (19/202 cases, 9.41%) and five (5/23 cases, 21.74%) COVID-19-related acute care visits were recorded in the molnupiravir and control groups, respectively. After acute care visits, 10 patients in the molnupiravir group were further hospitalized, including two cases of mortality, whereas one patient in the control group was hospitalized and died.

Molnupiravir-related adverse events, including gastrointestinal events (n=19, such as diarrhoea, nausea and abdominal fullness) and non-gastrointestinal events (n=5, such as facial swelling, sweating and skin pruritus), were reported in 24 (11.88%) patients. All adverse events showed full recovery after conservative management, and no molnupiravir discontinuation or hospitalization-requiring adverse events were reported during the study period (Fig. 2B). In the molnupiravir group, no laboratory-confirmed viral rebound after treatment discontinuation was reported within 30 days of disease onset.

3.3. Effect of molnupiravir on reducing risk of COVID-19-related acute care visits in patients undergoing HD

To adjust for baseline differences between the molnupiravir and control groups, IPTW-ATT was performed based on propensity scores. Unweighted and weighted baseline characteristics are presented in Table 2. After weighting, all baseline characteristics and vaccination statuses were well balanced between the groups, with an absolute SMD <0.10 for all covariates. In the multi-variate Cox regression analysis adjusted for baseline characteristics and vaccination status via IPTW-ATT based on propensity scores, use of molnupiravir was associated with a remarkably lower risk of COVID-19-related acute care visits within 30 days of disease onset, with a hazard ratio of 0.218 [95% confidence interval (CI) 0.074–0.642; P=0.006] (Fig. 3).

3.4. Effect of rapid molnupiravir initiation on accelerating viral clearance in patients undergoing HD

To evaluate the effect of rapid molnupiravir initiation on accelerating viral clearance, the molnupiravir group was stratified into two subgroups: early (n=72) and delayed (n=130) conversion to a
Table 2

| Unweighted | Weighted |
|------------|----------|
| Molnupiravir (n=202) | Control (n=23) | Absolute SMD | Molnupiravir (n=67) | Control (n=23) | Absolute SMD |
| Age (years), mean ± SD | 65.88 ± 10.68 | 60.87 ± 9.58 | 0.52 | 61.34 ± 11.78 | 60.87 ± 9.58 | 0.05 |
| Female, % | 58.91 | 43.48 | 0.15 | 48.59 | 43.48 | 0.05 |
| BMI (kg/m²), mean ± SD | 23.36 ± 4.28 | 22.68 ± 5.94 | 0.11 | 22.92 ± 3.63 | 22.68 ± 5.94 | 0.04 |
| Duration of HD (years), mean ± SD | 8.96 ± 7.77 | 7.44 ± 6.33 | 0.24 | 7.79 ± 7.54 | 7.44 ± 6.33 | 0.06 |
| Diabetes, % | 42.57 | 47.83 | 0.05 | 45.01 | 47.83 | 0.03 |
| Hypertension, % | 92.08 | 82.61 | 0.09 | 85.44 | 82.61 | 0.03 |
| Dyslipidaemia, % | 79.21 | 86.96 | 0.08 | 85.77 | 86.96 | 0.01 |
| Vascular disease, % | 40.10 | 39.13 | 0.01 | 35.80 | 39.13 | 0.03 |
| Heart failure, % | 32.67 | 17.39 | 0.15 | 17.82 | 17.39 | 0.00 |
| Liver cirrhosis, % | 9.90 | 13.04 | 0.03 | 11.16 | 13.04 | 0.02 |
| Lung disease, % | 8.91 | 8.70 | 0.00 | 7.39 | 8.70 | 0.01 |
| Malignancy, % | 26.24 | 30.43 | 0.04 | 33.51 | 30.43 | 0.03 |
| Immunosuppressant, % | 9.41 | 4.35 | 0.05 | 2.73 | 4.35 | 0.02 |
| Smoking, % | 8.42 | 13.04 | 0.05 | 11.94 | 13.04 | 0.01 |
| Hb (g/L), mean ± SD | 103.80 ± 12.70 | 103.00 ± 13.80 | 0.06 | 103.40 ± 12.70 | 103.00 ± 13.80 | 0.03 |
| BUN (mmol/L), mean ± SD | 24.54 ± 6.97 | 26.11 ± 7.89 | 0.20 | 25.35 ± 7.18 | 26.11 ± 7.89 | 0.09 |
| SCr (μmol/L), mean ± SD | 897.31 ± 226.75 | 953.99 ± 300.06 | 0.19 | 930.22 ± 235.87 | 953.99 ± 300.06 | 0.08 |
| Alb (g/L), mean ± SD | 39.42 ± 3.53 | 40.90 ± 2.84 | 0.52 | 40.85 ± 3.44 | 40.90 ± 2.84 | 0.02 |
| Ca (mmol/L), mean ± SD | 2.38 ± 0.22 | 2.41 ± 0.25 | 0.11 | 2.41 ± 0.22 | 2.41 ± 0.25 | 0.02 |
| P (mmol/L), mean ± SD | 1.68 ± 0.46 | 1.63 ± 0.47 | 0.10 | 1.60 ± 0.49 | 1.63 ± 0.47 | 0.06 |
| K (mmol/L), mean ± SD | 4.51 ± 0.63 | 4.58 ± 0.65 | 0.11 | 4.57 ± 0.62 | 4.58 ± 0.65 | 0.02 |
| Bicarbonate (mmol/L), mean ± SD | 21.64 ± 2.64 | 21.59 ± 1.89 | 0.03 | 21.74 ± 2.67 | 21.59 ± 1.89 | 0.08 |
| ALT (U/L), mean ± SD | 14.71 ± 7.77 | 14.74 ± 9.51 | 0.00 | 14.87 ± 7.33 | 14.74 ± 9.51 | 0.01 |
| Bil-T (μmol/L), mean ± SD | 5.63 ± 3.23 | 5.50 ± 2.47 | 0.05 | 5.60 ± 2.66 | 5.50 ± 2.47 | 0.04 |
| KTV, mean ± SD | 1.62 ± 0.30 | 1.46 ± 0.40 | 0.39 | 1.48 ± 0.30 | 1.46 ± 0.40 | 0.04 |
| CTR, mean ± SD | 0.53 ± 0.08 | 0.50 ± 0.06 | 0.51 | 0.50 ± 0.07 | 0.50 ± 0.06 | 0.00 |
| Unvaccinated, % | 10.89 | 8.70 | 0.02 | 9.40 | 8.70 | 0.01 |
| One or two vaccine doses, % | 12.38 | 8.70 | 0.04 | 9.50 | 8.70 | 0.01 |
| Three or four vaccine doses, % | 76.73 | 82.61 | 0.06 | 81.10 | 82.61 | 0.02 |

Ahb, serum albumin; ALT, alanine transaminase; Bil-T, blood total bilirubin; BMI, body mass index; BUN, blood urea nitrogen; Ca, blood total calcium; CTR, cardiothoracic ratio; Hb, haemoglobin; HD, haemodialysis; K, blood potassium; P, blood phosphorus; SCr, serum creatinine; SD, standard deviation; SMD, standardized mean difference. An absolute SMD <0.10 for covariates indicated a good balance between groups.

* Effective sample size.

Figure 2. Initial presentations, coronavirus disease 2019-related acute care visits and molnupiravir-related adverse events in the enrolled patients. (A) Initial presentations and acute care visits in total cohort (n=225). (B) Adverse events in patients receiving molnupiravir (n=202). Twenty-four patients described molnupiravir-related adverse events, including gastrointestinal (GI) events (n=19, such as diarrhoea, nausea and abdominal fullness) and non-GI events (n=5, such as facial swelling, sweating and skin pruritus). No molnupiravir discontinuation or hospitalization-requiring adverse events were reported during the study period.

Figure 3. Effect of molnupiravir on reducing risk of coronavirus disease 2019-related acute care visits in patients undergoing haemodialysis. The multi-variate Cox regression analysis was adjusted for baseline characteristics and vaccination status using inverse probability of treatment weighting for the average treatment effect on the treated, based on propensity scores, which is provided in Table 2. CI, confidence interval; HR, hazard ratio.

negative RAD test result. The distribution of patient characteristics and vaccination statuses in the subgroups is shown in Table 3. In the subgroup with early conversion, more patients received three or four doses of SARS-CoV-2 vaccines (84.72% vs 72.31%; P=0.046) and slightly fewer patients were unvaccinated (5.56% vs 13.85%; P=0.070) compared with the subgroup with delayed conversion. Rapid molnupiravir initiation was significantly more common in the subgroup with early conversion than in the subgroup with delayed conversion (90.28% vs 63.85%; P<0.001). In the multi-variate logistic regression analysis adjusted for age, sex, BMI, duration of HD, diabetes, hypertension, use of immunosuppressants,
vaccination status, and covariables with $P<0.1$ in univariate analyses using the enter method, rapid molnupiravir initiation within 1 day of COVID-19 onset was identified as an independent predictor of early conversion to a negative RAD test result in patients undergoing HD (early vs delayed conversion, odds ratio 6.207, 95% CI 2.509–15.358; $P<0.001$) (Fig. 4).

4. Discussion

This study found that molnupiravir effectively reduced healthcare needs in patients with initially mild or asymptomatic COVID-19 undergoing HD, with a nearly 80% decline in the risk of COVID-19-related acute care visits. The tolerability of molnupiravir in the enrolled patients was generally acceptable, with only 11.88% of molnupiravir users reporting mild adverse events. Furthermore, the analysis revealed that rapid molnupiravir initiation was an independent predictor of conversion to a negative RAD test result on day 7, indicating its effect on accelerating viral clearance in the HD population. These findings in the HD population are consistent with the secondary analysis of the MOVE-OUT study, in which molnupiravir treatment decreased the risk of acute care visits by approximately 70% in the general population [32]. The incidence of molnupiravir-related adverse events was 8% in the MOVE-OUT study; these adverse events were generally mild and predominantly gastrointestinal events, and the present findings were comparable to these observations [14]. The results of the PANORAMIC trial have been published recently, and the analysis indicated that although the benefits of molnupiravir in reducing COVID-19-associated hospitalization and mortality were not demonstrated in the study population in the UK, fewer medical consultations and faster clinical recovery were observed in molnupiravir users [19]. The PANORAMIC trial and the present study were both conducted in highly vaccinated populations during the Omicron era; however, only 2% of the participants in the PANORAMIC trial had pre-existing renal disease, and the present study focused on patients undergoing HD, who are particularly vulnerable to COVID-19 [4,19]. Although molnupiravir is regarded as a reasonable treatment option for COVID-19 in patients undergoing HD, there is still a paucity of literature regarding its real-world effectiveness in this population. Two recent observational studies supported the safety and clinical benefits of molnupiravir in the HD population; however, the sample sizes were small, and the control group was not included for outcome comparison [33,34]. The present findings highlight the real-world effectiveness of molnupiravir in reducing medical needs in outpatients with COVID-19 undergoing HD, which aligns with the results of previous studies involving the general population and supports its therapeutic role in the HD population.

In this analysis, rapid initiation of molnupiravir was an independent predictor associated with early conversion to a negative RAD test result, even after adjusting for vaccination status. Molnupiravir is known to accelerate SARS-CoV-2 clearance; however, this effect is yet to be evaluated in patients undergoing HD [25,26]. In a phase 2a trial of molnupiravir in non-hospitalized patients with COVID-19, no infectious virus was isolated from nasopharyngeal swabs on day 5 in the 800-mg molnupiravir group (0/53 cases), which was significantly lower than that of the placebo.
### Independent predictor of early conversion to a negative RAD test result

| Predictor               | OR (95% CI)   | P-value |
|-------------------------|---------------|---------|
| Age (year)              | 0.999 (0.966–1.034) | 0.974   |
| Female                  | 1.929 (0.873–4.264) | 0.104   |
| BMI (kg/m²)             | 0.989 (0.911–1.074) | 0.797   |
| Duration of HD (year)   | 1.014 (0.967–1.063) | 0.572   |
| Diabetes                | 1.156 (0.547–2.443) | 0.704   |
| Hypertension            | 0.810 (0.240–2.731) | 0.733   |
| Immunosuppressant       | 1.731 (0.546–5.490) | 0.351   |
| Rapid molnupiravir initiation | 6.207 (2.509–15.358) | <0.001* |
| Vaccine doses 1–2 vs. unvaccinated | 1.424 (0.325–6.238) | 0.639   |
| Vaccine doses 3–4 vs. unvaccinated | 2.714 (0.791–9.315) | 0.112   |
| SCr (μmol/L)            | 1.001 (0.999–1.003) | 0.207   |
| P (mmol/L)              | 1.731 (0.788–3.805) | 0.172   |

Figure 4. Rapid molnupiravir initiation as an independent predictor of early conversion to a negative rapid antigen detection (RAD) test result. Multi-variate logistic regression analysis was performed to identify the independent predictors of early conversion to a negative RAD test result, adjusting for age, sex, body mass index (BMI), duration of haemodialysis (HD), diabetes, hypertension, use of immunosuppressants, vaccination status, and covariates with P<0.1 on univariate analyses using the enter method. CI, confidence interval; OR, odds ratio; P, blood phosphorus; SCr, serum creatinine. *P<0.05.

This study found that molnupiravir is well tolerated and decreases the medical needs in patients with initially mild or asymptomatic COVID-19 undergoing HD. Furthermore, the findings suggest that the rapid initiation of molnupiravir within 1 day of COVID-19 onset accelerates SARS-CoV-2 clearance in the HD population, which can reduce the healthcare burden in HD units. This study will be a valuable reference for clinicians and researchers to optimize the treatment strategies for COVID-19 in the HD population. Further large-scale research is recommended to verify these findings and elucidate the therapeutic strategies for COVID-19 in this vulnerable population.

### 5. Conclusions

The numbers of hospitalizations and deaths were limited in the enrolled patients, which precluded their further analysis in this study. While this analysis indicated the benefits of rapid molnupiravir administration on accelerating RAD test conversion in patients undergoing HD, additional research is required to determine its effects on accelerating symptom resolution (such as defervescence) and PCR conversion. Furthermore, because the first post-diagnostic RAD tests were performed on days 7 and 10 in the molnupiravir and control groups, respectively, the timing of RAD test conversion could not be compared directly between the groups. Finally, due to the observational nature of this study, drug adherence and adverse events were recorded on a patient-reported basis, and patient preference determined the allocation to the molnupiravir or control groups, which may have increased the likelihood of potential confounders.

### CRediT authorship contribution statement

**Yi-Chin Chang:** Methodology, Formal analysis, Writing – original draft, Visualization. **Yi-Chun Chen:** Methodology, Writing – review & editing. **Chiang-Chi Huang:** Investigation. **Chung-Ming Fu:** Data curation. **Yueh-Ting Lee:** Resources. **Po-Jung Wu:** Data curation. **Wen-Chin Lee:** Supervision. **Chien-Te Lee:** Resources.

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**group (6/54 cases, 11.1%) [25]. In another randomized controlled trial conducted in Hong Kong involving mainly mild cases of COVID-19 with the Omicron variant, the median time of pharyngeal SARS-CoV-2 RNA clearance was significantly shorter in the molnupiravir group than in the control group; the negative proportions of SARS-CoV-2 RNA in pharyngeal specimens on day 7 were 41% and 6% in the molnupiravir and control groups, respectively [26]. As delayed SARS-CoV-2 clearance is common and problematic in the population undergoing HD, it is important to devise strategies to improve viral clearance in vulnerable populations [35]. Previous studies on oseltamivir treatment for influenza showed that its rapid administration (within the first 12 h of fever onset) in the general population reduced the total duration of illness by 3 days [36], and administration of oseltamivir within 24 h significantly decreased the 30-day mortality rate in hospitalized patients with influenza [37]. The present study revealed the benefit of rapid molnupiravir initiation in accelerating viral clearance in patients with initially mild or asymptomatic COVID-19 undergoing HD, irrespective of vaccination status, and will provide a foundation for further studies on the clinical benefits of rapid molnupiravir administration in vulnerable populations. Furthermore, as the positivity of RAD tests correlates better with the positivity of viral culture than that of PCR tests [38,39], and as RAD tests are widely accepted for infection control in several scenarios, including determining the duration of infectiousness, RAD tests were used to determine the SARS-CoV-2 clearance status in this study [40]. Combining rapid molnupiravir administration and isolation release based on RAD test results, this study suggests a strategy that shortens the duration of isolation in HD units, thereby easing the burden on the healthcare system during the COVID-19 pandemic.

This study had some limitations. As a retrospective study based on clinical management of COVID-19 in patients undergoing HD, the molnupiravir and control groups were inherently unbalanced in sample size, and the baseline differences between the groups were adjusted using propensity score weighting [31], which might also decrease the effective sample size of the analysis. Considering the sample size and ranges of the 95% CIs, the therapeutic effects in this report should be interpreted with caution. Due to the reduced disease severity of COVID-19 during the Omicron era [5],
Competing their inal Yang Tai [13] of J yang Sigal Taiwan nCoV-19 who.int/publications/m/item/weekly- molnupiravir support Board administration, among A. Nat Centres Writing the One to and Ashby Padmanabhan, the. [23] AD, Menacho after 2022;16:102396. Menacho, they have also been called in analyses. [29] after 2023;401:281–93. to the USRDS 2023;2020:199119. on the treatment of COVID-19 in patients with end-stage renal disease on hemodialysis. PloS One 2022;17:e0273767. [9] Yachie K, Kaminuma S, Sato M, Nishiyama K, et al. Effect of CholA1 Anticoagulants 2022;60:106060. [14] Jakb Bernal A, Gomes da Silva MM, Musungabe DA, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of COVID-19 in nonhos- pitalized patients. N Engl J Med 2022;386:509–20. [15] Painter WP, Holman W, Bush JA, Almazedi F, Malik H, Erat N, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. 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