Clinical Outcome and 7-Day Virological Clearance in High-Risk Patients with Mild–Moderate COVID-19 Treated with Molnupiravir, Nirmatrelvir/Ritonavir, or Remdesivir

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ABSTRACT

Introduction: We compared the effectiveness and virological clearance (VC) at day 7 (T7) post-treatment with molnupiravir, nirmatrelvir/ritonavir, and remdesivir in SARS-CoV-2-infected patients at high risk (HR) for clinical progression.

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Methods: We conducted a retrospective study enrolling HR patients with mild-to-moderate COVID-19 (Jan–Oct 2022) treated with nirmatrelvir/ritonavir or molnupiravir or 3 days of remdesivir. We investigated clinical recovery at T7 (resolution of symptoms for ≥ 72 h or all-cause death), VC at T7 (PCR/antigenic negative nasopharyngeal swab), and median time to VC (days from symptom onset to the first negative swab). Factors associated with VC were investigated by logistic regression.

Results: In the study, 92/376 (43.8%) patients received molnupiravir, 150/376 (24.7%) nirmatrelvir/ritonavir, and 134/376 (31.5%) remdesivir. Forty-nine (13%) patients were unvaccinated or incompletely vaccinated. Patients treated with nirmatrelvir/ritonavir were younger and presented immunodeficiencies more frequently; remdesivir was used more commonly in patients hospitalized for other diseases. A high proportion of patients obtained clinical recovery without differences among the therapies (97.5% for molnupiravir, 98.3% for nirmatrelvir/ritonavir, and 93.6% for remdesivir); 12 (3.7%) patients died. Nirmatrelvir/ritonavir was associated with a higher proportion of T7 VC and a shorter time to VC compared to molnupiravir/remdesivir, also after adjustment for age

and immunodeficiency (AOR 0.445 RDV vs. NMV-r, 95% CI 0.240–0.826, $p = 0.010$; AOR 0.222 MNP vs. NMV-r, 95% CI 0.105–0.472, $p < 0.001$).

Conclusions: SARS-COV-2 antiviral treatments are an excellent therapeutic strategy in HR patients. Nirmatrelvir/ritonavir showed a higher proportion of VC as early as 7 days after treatment, confirming its likely superiority in indirect comparisons.

PLAIN LANGUAGE SUMMARY

Nirmatrelvir-ritonavir, molnupiravir, and a 3-day course of remdesivir are antiviral therapies recommended in patients with a mild-to-moderate COVID-19 disease at high risk of clinical progression. Randomized controlled trials and observational studies have shown their efficacy in reducing all-cause mortality and clinical progression. Few data are available about a direct comparison among the three drugs; furthermore, the possible role of nirmatrelvir-ritonavir in increasing viral clearance and in reducing the duration of viral shedding needs to be further elucidated. We thus investigated the effectiveness, safety, and virological clearance 7 days after treatment with these three antivirals in our retrospective cohort. We included in the analysis patients that have received these treatments from January 2022 and October 2022; we observed that patients receiving nirmatrelvir-ritonavir displayed a shorter median time from symptoms' onset to virological clearance and a higher proportion of virological clearance at day 7, also after adjustment for possible confounders, compared to molnupiravir and remdesivir. Our data might help in understanding which COVID-19 patients may benefit mostly from antiviral therapies and in the choice of antiviral therapy.

Keywords: Antiviral SARS CoV-2 treatment; COVID-19; Molnupiravir; Nirmatrelvir/ritonavir; Remdesivir

Key Summary Points

We observed a high proportion of clinical recovery in patients with a mild-to-moderate COVID-19 and at high risk of clinical progression following antiviral treatment.

No differences in clinical recovery were observed among nirmatrelvir/ritonavir, molnupiravir, and a short-course of remdesivir.

All three of the antiviral therapies are well tolerated with few adverse events.

Nirmatrelvir/ritonavir was associated with a higher proportion of virological clearance at day 7 after starting the antiviral treatment, compared to molnupiravir and a short course of remdesivir.

Nirmatrelvir/ritonavir was also associated with a shorter time to virological clearance, compared to molnupiravir and a short course of remdesivir.

INTRODUCTION

The SARS-CoV-2 pandemic has led to the introduction of new drugs and the recovery of old antiviral molecules tested for other infections, such as hepatitis C virus (HCV) or Ebola [1]. So far, the main therapeutic strategies for COVID-19 have included antiviral therapies with different mechanisms of action (remdesivir, molnupiravir, and nirmatrelvir/ritonavir) in outpatients and hospitalized individuals [2].

Antiviral treatments are recommended within 5–7 days from onset of symptoms for patients diagnosed with a mild-to-moderate COVID-19 disease and risk factors for clinical progression to severe disease. The "Agenzia Italiana del Farmaco" (AIFA) defined age > 65 years or chronic comorbidities as well as diabetes, cardiovascular diseases, chronic obstructive pulmonary disease (COPD), asthma or other chronic pulmonary diseases, immunodeficiencies, active cancers, neurological diseases and chronic liver or kidney failure as risk factors for severe disease [3].

Among antivirals, nirmatrelvir/ritonavir (NMV/r) is an oral protease inhibitor characterized by a potent pan-human-coronavirus activity in vitro; its target is the viral main protease Mpro [4]. It resulted in 89% relative risk reduction of hospitalization or death in unvaccinated symptomatic high-risk patients before Omicron era, as demonstrated by the EPIC-HR trial [5]. Furthermore, its antiviral activity does not seem to reduce in vitro against the Omicron variant [6]; in fact, observational studies report a reduction in hospitalization and mortality rates also among vaccinated patients during the Omicron era [7–14].

Similar efficacy in reducing clinical progression was observed for remdesivir (RDV), a nucleotide prodrug that is metabolized intracellularly to the active nucleoside triphosphate (ATP), which interferes with viral RNA-dependent polymerase activity [15]. This drug has been approved for emergency use since the first phase of the pandemic in hospitalized patients and afterwards also in outpatients [16–18]. The PINETREE trial, in fact, involved non-hospitalized patients who were at high risk for COVID-19 progression and demonstrated that a 3-day course of this intravenous antiviral was associated with a 87% lower risk of progression to severe disease or death than placebo; similarly, data from observational studies and real-life settings confirmed its efficacy [19–21].

Finally, a third antiviral, molnupiravir (MNP), an oral, small-molecule prodrug that is metabolized and phosphorylated to active ribonucleoside triphosphate (NHC-TP) and then incorporated into SARS-CoV-2 RNA, causing errors during viral replication with subsequent inhibition [4], was able to reduce the risk of hospitalization or death by 30% in at-risk, unvaccinated adults with COVID-19, as highlighted by the MOVe-OUT trial [22].

Retrospective data during the Omicron wave confirmed that MNP and NMV-r were associated with a significant reduction of all-cause mortality and in-hospital disease progression, while only NMV-r reduced the risk of COVID-19-related hospitalizations [23, 24].

Furthermore, in the EPIC-HR trial, NMV-r was able to reduce viral load in nasopharynx at day 5 compared to placebo [5], but similar virological data in real-life settings and data on direct comparisons of the different antiviral treatments also regarding virological efficacy are still scarce [23, 25–27].

We thus compared the effectiveness, safety, and virological clearance 7 days after the start of treatment with NMV-r, MNP, and RDV in SARS-CoV-2-infected patients at high risk of clinical progression during the Omicron era.

METHODS

Study Design and Population

We conducted a retrospective study enrolling patients with documented COVID-19 by antigen or reverse transcriptase-polymerase chain reaction (RT-PCR) test on a nasopharyngeal swab who received one antiviral treatment at the COVID-19 antiviral therapy outpatient service or during hospitalization for other reasons than COVID-19 at the San Paolo Hospital in Milan, Italy, from January 2022 to October 2022.

Inclusion criteria were mild-to-moderate disease, no need for supplemental oxygen therapy or hospitalization for COVID-19, one or more comorbidities indicated by the "Agenzia Italiana del Farmaco" (AIFA) as risk factor of developing severe COVID-19 disease, and symptoms onset within 5–7 days. Risk factors for clinical progression included body mass index (BMI) ≥ 30, primary or acquired immunodeficiencies, decompensated diabetes, cardio-cerebrovascular diseases, chronic hepatic or renal failure, chronic pulmonary or neurological diseases, or age ≥ 65 years. Mild-to-moderate disease was defined as signs and symptoms of COVID-19 and oxygen saturation ≥ 94% on room air. Patients hospitalized for COVID-19 were excluded from the analysis; patients were included irrespective of their COVID-19 vaccination status.

Study Procedures

Antiviral treatments that were available in Italy during the study period were (i) oral nirmatrelvir/ritonavir (NMV-r): 300 mg/100 mg twice daily for 5 days (or adjusted dose according to

renal glomerular filtrate rate); (ii) molnupiravir (MPN): 800 mg twice daily for 5 days; (iii) intravenous remdesivir (RDV): 200 mg day 1, followed by 100 mg on days 2–3.

Patients were referred to the outpatient clinic by their primary care physician, other specialists or the Emergency Department of San Paolo and San Carlo Hospital or were evaluated after testing positive for SARS CoV-2 infection during hospitalization for other causes. The outpatient clinic was active 7 days a week.

At the first access to the clinic, the patients were visited by an infectious disease specialist and underwent routine blood tests (complete blood count, creatinine, GOT, GPT, lactate dehydrogenase, prothrombin time, C-reactive protein).

On the same day, antiviral treatment was started; the choice of antiviral therapy was made according to AIFA recommendations by the attending physician according to the patients' clinical characteristics and drug properties (comorbidities, renal failure, drug–drug interactions, and possibility of undergoing intravenous treatment for 3 days). The patients were also evaluated 7 days after starting the antiviral treatment (T7): at T7 patients underwent medical examination, routine blood tests, and a PCR or antigenic nasopharyngeal swab, according to the first method used for diagnosis, to assess virological clearance.

For each patient we collected demographic and clinical data about age, sex, comorbidities, symptoms onset and type of symptoms, day of first SARS-CoV-2-positive test, COVID-19 vaccination status, concomitant therapy with heparin or corticosteroids, outcome at day 7. All data were recorded in an electronic dataset in an anonymous form.

The study has received approval by the Ethic Committee Milano Area 1 (no. 0000677, 01/04/2020) and all the subjects provided informed consent to participate in the study. The study has been conducted according to the World Medical Association and the Declaration of Helsinki.

Statistical Analyses

Categorical data were presented as absolute numbers and percentages, quantitative variables as median, and interquartile range (IQR). Study outcomes were: clinical recovery at day 7 (T7), defined as complete resolution of COVID-19 symptoms for at least 72 h or non-resolution of symptoms or all-cause death; virological clearance at T7, defined by a negative PCR or antigenic swab. We also collected median time to virological clearance (days from symptom onset to the first negative PCR or antigenic nasopharyngeal swab). The occurrence of adverse events was collected at T7.

Comparison among the three treatment groups (NMV-r, MNP, and RDV) were performed by non-parametric Kruskal–Wallis test, Chi-squared test, or Fisher's exact test, as appropriate. Factors associated with virological clearance at T7 were analyzed by univariable and multivariable logistic regression analyses, adjusting for possible confounders. We also performed the logistic regression analysis on outpatients, excluding patients who received the antiviral treatment during hospitalization. We also compared patients treated within the first 3 days of symptoms onset (very early treated patients) versus patients treated after the third day (early patients), as well as unvaccinated versus vaccinated patients by Mann–Whitney test, Chi-squared test or Fisher's exact test. Statistical analyses were performed by SPSS software, version 21.0.

RESULTS

Study Population

We enrolled 376 patients in the study period: 150/376 (39.9%) received NMV-r, 92/376 (24.5%) MNP, and 134/376 (35.6%) RDV. Table 1 shows the demographic and clinical characteristics of the study population.

The majority of patients were outpatients (284, 75.5%), while 92 (24.5%) were hospitalized for other reasons than COVID-19. The main reasons for hospitalization were: neurological diseases

Table 1 Demographic and clinical characteristics of patients with mild/moderate COVID-19, according to anti-SARS-CoV-2 antiviral treatment

Characteristics	Study population N 376	NMV-r N 150 (39.9%)	MNP N 92 (24.5%)	RDV N 134 (35.6%)	p value
Age [years], median (IQR)	75 (63–84)	70 (56–80)	79 (67–84)	78 (68–86)	**< 0.001**
Female sex, n (%)	167 (44.4%)	78 (52%)	33 (35.9%)	56 (41.8%)	**0.037**
COVID-19 vaccination, n (%):					**0.015**
No	29 (7.7%)	14 (9.3%)	6 (6.5%)	9 (6.7%)	
Yes	327 (87%)	121 (80.7%)	84 (91.3%)	121 (91%)	
Unknown	20 (5.3%)	15 (10%)	2 (2.2%)	3 (2.2%)	
COVID-19 vaccination, n of doses:					
Only 1 dose	4 (1.3%)	0	3 (3.6%)	1 (0.8%)	0.227
Complete first schedule	35 (10.7%)	14 (11.6%)	10 (11.9%)	11 (9.1%)	
First booster	247 (75.5%)	92 (76%)	64 (76.2%)	91 (75.2%)	
Second booster	40 (12.2%)	14 (11.6%)	7 (8.3%)	18 (14.9%)	
Unknown	1 (0.3%)	1 (0.8%)	0	0	
COVID-19 vaccination, timing, n (%):	N 293	N 100	N 80	N 113	0.661
Last vaccination > 120 days	168 (57.3%)	71 (71%)	31 (38.8%)	66 (58.4%)	
Last vaccination ≤ 120 days	125 (42.7%)	29 (29%)	49 (61.3%)	47 (41.6%)	
Calendar period:					**< 0.001**
Jan–May	176 (46.8%)	41 (27.3%)	79 (85.9%)	56 (41.8%)	
Jun–Oct	200 (53.2%)	109 (72.7%)	13 (14.1%)	78 (58.2%)	
Risk factor, n (%):					
Age ≥ 65 years	234 (62.2%)	68 (45.3%)	66 (71.7%)	100 (74.6%)	**< 0.001**
BMI ≥ 30	28 (7.4%)	11 (7.3%)	7 (7.6%)	10 (7.5%)	0.997
Cardiovascular disease	139 (37%)	34 (22.7%)	47 (51.1%)	58 (43.3%)	**< 0.001**
COPD or other respiratory disease	76 (20.2%)	33 (22%)	17 (18.5%)	26 (19.4%)	0.770
Neurological disease	35 (9.3%)	13 (8.7%)	4 (4.3%)	18 (13.4%)	0.065
Diabetes mellitus	63 (16.8%)	16 (10.7%)	16 (17.4%)	31 (23.1%)	**0.019**
Chronic kidney failure	21 (5.6%)	3 (2%)	7 (7.6%)	11 (8.2%)	**0.047**
Cancer	30 (8%)	9 (6%)	7 (7.6%)	14 (10.4%)	0.381
Immunodeficiency	49 (13%)	30 (20%)	8 (8.7%)	11 (8.2%)	**0.005**
Treatments for COVID-19, n (%):					
Heparin	59 (15.7%)	13 (8.7%)	3 (3.3%)	43 (32.1%)	**< 0.001**

Table 1 continued

Characteristics	Study population N 376	NMV-r N 150 (39.9%)	MNP N 92 (24.5%)	RDV N 134 (35.6%)	p value
Corticosteroid therapy	15 (4%)	3 (2%)	1 (1.1%)	11 (8.2%)	**0.007**
Setting, n (%):					**< 0.001**
Outpatient service	284 (75.5%)	130 (86.7%)	89 (96.7%)	65 (48.5%)	
Hospitalization because of diseases other than COVID-19	92 (24.5%)	20 (13.3%)	3 (3.3%)	69 (51.5%)	
Days from symptom onset to antiviral treatment, median (IQR)	3 (1–4)	2 (1–3)	3 (2–4)	2 (1–4)	0.161
Outcome, n (%):	N 322	N 117	N 79	N 126	0.185
Recovery	310 (96.3%)	115 (98.3%)	77 (97.5%)	118 (93.6%)	
Death	12 (3.7%)	2 (1.7%)	2 (2.5%)	8 (6.4%)	
Adverse events, n (%):	N 322	N 117	N 79		**< 0.001**
No	311 (82.7%)	108 (72%)	78 (84.8%)	125 (93.3%)	
Yes	11 (2.9%)	9 (6%)	1 (1.1%)	1 (0.7%)	
Days from symptom onset to virological clearance, median (IQR)	13 (10–17)	10 (8–15)	14 (11–18)	13 (10–19)	**0.002**
Virological clearance at day 7 from treatment start, n (%):	N 250	N 85	N 59	N 109	**< 0.001**
No	139 (37%)	32 (37.6%)	44 (74.6%)	66 (60.6%)	
Yes	111 (29.5%)	53 (62.4%)	15 (25.4%)	43 (39.4%)	

Quantitative variables are presented as median, interquartile range (1st and 3rd percentile); qualitative variables are presented as absolute numbers and percentages. Kruskal–Wallis nonparametric test and Chi-square test or Fisher's exact test were used for analyses, as appropriate

Days from symptom onset to virological clearance was defined as days from onset of symptoms to the first antigenic- or PCR-negative nasopharyngeal swab; virological clearance at day 7 was defined as patients with antigenic- or PCR-negative nasopharyngeal swab at day 7 after treatment start

NMV-r nirmatrelvir/ritonavir, *MNP* molnupiravir, *RDV* remdesivir, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease

(16/92, 17.4%), cardiological diseases (14/92, 15.2%), abdominal/urinary diseases (12/92, 13.1%), lung diseases (10/92, 10.9%), cancers (8/92, 8.7%), infectious diseases (7/92, 7.6%), kidney diseases (5/92, 5.4%), orthopedic diseases (4/92, 4.3%), hematological diseases (4/92, 4.3%), and other conditions (12/92, 13.1%).

Median age of study population was 75 years (IQR 63–84) and 167 (44.4%) were females.

High-risk criteria were more commonly older age (≥ 65 years, 62.2%), cardiovascular disease (37%) and COPD or chronic pulmonary disease (20.2%). Forty-nine patients were immunocompromised; the main immunodeficiencies were: onco-hematological diseases (22/49, 44.9%), solid organ and bone marrow transplantation (3/49, 6.1%), HIV infection (12/49, 24.5%), and autoimmune diseases (12/49, 24.5%).

About vaccination status, 87% of patients were vaccinated for SARS-CoV-2 with at least one dose; 75.5% had received their first booster, and 57.3% received the last dose of vaccine more than 120 days before SARS-CoV-2 infection.

All outpatients have a mild COVID-19 and did not receive oxygen support; 14/92 (15%) patients who were treated with a short course of RDV during hospitalization received oxygen support: low flows oxygen therapy in 11/14 (78%) patients (nasal cannula or Venturi mask) and high flows oxygen therapy in 3/14 (22%) patients (Reservoir mask).

Comparison of Demographic and Clinical Characteristics Among the Patients Receiving the Three Different Antiviral Therapies

As shown in Table 1, patients treated with NMV-r were younger and more commonly females, compared to patients treated with MNP or RDV. Furthermore, patients receiving NMV-r presented more frequently age < 65 years and immunodeficiency as risk factor for severity of COVID-19; patients suffering from cardiovascular diseases, diabetes, and chronic kidney failure received mainly MNP or RDV. Short-course RDV was more frequently used in older patients and in those hospitalized for conditions other than COVID-19.

Outcome and Safety at Day 7 Post Treatment According to Antiviral Treatment

Of 322 patients for whom post-treatment follow-up was available, 309 (96%) patients completely recovered at T7. Twelve (3.7%) patients died (two patients receiving NMV-r, two patients receiving MNP, and eight patients receiving RDV); five of 12 (41.7%) patients died from malignancy, five (41.7%) for sepsis, one (8.3%) for acute cardiovascular failure, and one (8.3%) for cerebral hemorrhage. No difference in T7 outcome was observed among the three different treatments (recovery was 98.3% in NMV-r group, 97.5% in MNP group and 93.6% in RDV group) (Table 1).

All the three therapies were well tolerated with few and mild adverse events (11/322, 2.9%). NMV-r was characterized by a higher proportion of adverse events (9, 6%), mostly dysgeusia; no serious event was displayed (Table 1). Blood tests showed higher median levels of CRP at start of treatment in patients treated with RDV (RDV: 10.9, IQR 5.4–42.3 mg/l; NMV-r: 4.9, IQR 4.9–8.3; MNP: 5.9, IQR 4.9–9.4; $p < 0.001$); no increase in GOT/GPT or creatinine was observed for any treatments between start of treatment and T7.

Virological Clearance According to Antiviral Treatment

There were 250 of 376 patients that underwent nasopharyngeal swab at day 7 (T7) after starting therapy. Virological clearance at T7 was obtained in nearly one-third of patients (111/250, 29.5%).

Interestingly, a higher percentage of patients reached virological clearance at T7 in the NMV-r group (53/85, 62.4%) in comparison with MNP (15/59, 25.4%) and RDV (43/109, 39.4%; $p < 0.001$). Patients treated with NMV-r also showed a shorter median time from symptom onset to the first negative nasopharyngeal swab compared to the other treatments (10 days, IQR 8–15 for NMV-r; 14, IQR 11–18 for MNP; 13, IQR 10–19 for RDV; $p = 0.002$) (Table 1).

The association between NMV-r and higher proportion of virological clearance at T7 was also investigated by fitting a multivariable logistic regression analysis, adjusting for possible confounders (age and immunodeficiency, which are well-known risk factors for viral persistence). Table 2 shows the results of univariable and multivariable logistic regression analyses. After correction for age and immunodeficiency, treatment with NMV-r was confirmed to be associated with a higher proportion of virological clearance (AOR 0.445 RDV versus NMV-r, 95% CI 0.240–0.826, $p = 0.010$; AOR 0.22 MNP versus NMV-r, 95% CI 0.105–0.472, $p < 0.001$). The higher probability of viral clearance following treatment with NMV-r compared to RDV and MNP was also confirmed in the analyses restricted to outpatients (Supplementary Table 1).

Table 2 Factors associated with virological clearance at T7 (negative antigenic or RNA nasopharyngeal swab at day 7 after beginning of antiviral treatment) by fitting a logistic regression analysis

Parameters	OR	95% CI	*p* values	AOR	95% CI	*p* values
Age:						
Each year more	0.978	0.963–0.994	**0.007**	0.984	0.967–1.001	0.069
Sex:		0.493–1.336	0.412			
Female	1					
Male	0.812					
Vaccination:						
> 120 days	1					
≤ 120 days	0.735	0.424–1.275	0.273			
Immunodeficiency:						
Yes	1			1		
No	0.752	0.365–1.550	0.440	1.295	0.574–2.924	0.534
Days from symptoms onset to treatment:						
Each day more	0.992	0.968–1.018	0.543			
Antiviral treatment:						
Nirmatrelvir/ritonavir	1		**< 0.001**	1		**< 0.001**
Remdesivir	0.393	0.220–0.705	**0.002**	0.445	0.240–0.826	**0.010**
Molnupiravir	0.206	0.099–0.428	**< 0.001**	0.222	0.105–0.472	**< 0.001**

Multivariable logistic regression model is adjusted for age and immunodeficiency

OR odds ratio, *AOR* adjusted odds ratio, *95%CI* 95% confidence interval

Efficacy and Safety of Antiviral Treatment According to Timing of Treatment and Vaccination Status

Two hundred and fifty-seven of 346 (74%) patients received very early antiviral treatment (within the first 3 days of symptoms onset); no difference in efficacy and safety of the three antiviral treatments was shown according to the time of treatment (very early treatment versus early treatment, i.e., at least 3 days after symptoms onset) (Table 3). Median time to virological clearance was shorter in very early treated patients, while no difference in the proportion of virological clearance at T7 was observed.

Twenty-nine of 356 (8.2%) patients were unvaccinated against COVID-19 (Table 4). Interestingly, while displaying similar clinical recovery and adverse events, unvaccinated patients showed a longer time to virological clearance.

Table 3 Comparison between very early and early-treated COVID-19 patients

Characteristics	≤ 3 days (N = 257)	> 3 days (N = 89)	p value
Age [years], median (IQR)	77 (64–84)	73 (59–81)	0.066
Female sex, n (%)	119 (46.3%)	35 (39.3%)	0.254
COVID-19 vaccination, n (%):			0.275
No	24 (9.3%)	5 (5.6%)	
Yes	233 (90.7%)	84 (94.4%)	
	N 214	N 78	0.710
Yes, last vaccination > 120 days	121 (56.5%)	46 (59%)	
Yes, last vaccination ≤ 120 days)	93 (43.5%)	32 (41%)	
Calendar period:			**0.004**
Jan–May	110 (42.8%)	54 (60.7%)	
Jun–Oct	147 (57.2%)	35 (39.3%)	
Risk factor, n (%):			
Age ≥ 65 years	174 (67.7%)	58 (65.2%)	0.661
BMI ≥ 30	20 (7.8%)	8 (9%)	0.719
Cardiovascular disease	97 (38%)	41 (46%)	0.167
COPD or other respiratory disease	58 (22.6%)	18 (20.2%)	0.645
Neurological disease	29 (11.3%)	6 (6.7%)	0.221
Diabetes mellitus	40 (15.6%)	22 (24.7%)	0.052
Chronic kidney failure	14 (5.4%)	7 (7.9%)	0.410
Cancer	21 (8.2%)	8 (9%)	0.810
Immunodeficiency	34 (13.2%)	15 (16.9%)	0.398
Treatments for COVID-19, n (%):			
Heparin	46 (17.9%)	12 (13.5%)	0.336
Corticosteroid therapy	9 (3.5%)	6 (6.7%)	0.227
Antiviral treatment:			0.095
Nirmatrelvir/ritonavir	102 (39.7%)	26 (29.2%)	
Molnupiravir	68 (26.5%)	22 (24.7%)	
Remdesivir	87 (33.9%)	41 (46.1%)	
Setting, n (%):			**0.05**
Outpatient service	187 (72.8%)	74 (83.1%)	
Hospitalization because of diseases other than COVID-19	70 (27.2%)	15 (16.9%)	

Table 3 continued

Characteristics	≤ 3 days (N = 257)	> 3 days (N = 89)	p value
Outcome, n (%):	N 225	N 84	0.260
Recovery	217 (96.4%)	81 (96.4%)	
Death	8 (3.6%)	3 (3.6%)	
Adverse events, n (%)			0.561
No	248 (96.5%)	87 (97.8%)	
Yes	9 (3.5%)	2 (2.2%)	
Days from symptom onset to virological clearance, median (IQR)	12 (9–16)	15 (11–19)	**0.002**
Virological clearance at day 7 from treatment start, n (%):	N 176	N 70	0.899
No	77 (43.8%)	30 (42.9%)	
Yes	99 (56.3%)	40 (57.1%)	

Quantitative variables are presented as median, interquartile range (1st and 3rd percentile); qualitative variables are presented as absolute numbers and percentages. Mann–Whitney nonparametric test and Chi-square test or Fisher's exact test were used for analyses, as appropriate

Days from symptom onset to virological clearance was defined as days from onset of symptoms to the first antigenic- or PCR-negative nasopharyngeal swab; virological clearance at day 7 was defined as patients with antigenic- or PCR-negative nasopharyngeal swab at day 7 after treatment start

BMI body mass index, *COPD* chronic obstructive pulmonary disease

DISCUSSION

Randomized controlled trials and observational studies have shown the efficacy and safety of antiviral treatments for SARS-CoV-2 infection also during the Omicron wave and in vaccinated patients: NMV-r, MNP, and RDV are associated with a reduced risk of clinical progression and death, especially in older patients or patients at high risk for clinical progression [5, 8, 9, 11–13, 19, 22–24, 28, 29].

In our retrospective study, we observed that antiviral treatments succeeded in obtaining a clinical cure in more than 90% of patients without differences among the three drugs; RDV has a slight non-significant minor proportion of clinical recovery, but appears also more commonly prescribed in older hospitalized patients. Few deaths were recorded and about half of patients died from complications not directly related to COVID-19, but to the underlying oncological disease.

These data confirmed results from randomized trials that were all conducted in a period before Omicron variant and in unvaccinated patients [5, 19, 22]; afterwards, observational studies including emulation trials have reported effectiveness of NMV-r, MNP, or RDV, also in vaccinated patients, in Omicron era and compared to patients that have not received any antiviral treatment [7, 8, 23, 24, 29, 30]. In fact, all three treatments retain effectiveness against the Omicron variant, as demonstrated by Vangeel et al. and other authors [6, 31]. The effectiveness of these treatments is evident despite the reduced mortality due to COVID-19 observed with the currently circulating viral variants and is in any case associated with cost savings thanks to avoided hospitalizations [32].

Among these treatments, MNP seems characterized by a lower reduction in the risk of hospitalization and mortality: in the MOVe-OUT trial its relative risk reduction was only 30% compared to placebo; likewise, no effect was observed in reducing COVID-19-associated hospital admissions or death versus standard

Table 4 Comparison between patients that received complete COVID-19 vaccination schedule and unvaccinated patients

Characteristics (*N* = 356)	Vaccinated patients *N* = 327 (91.8%)	Unvaccinated patients *N* = 29 (8.2%)	*p* value
Age [years], median (IQR)	76 (63–84)	78 (61–86)	0.946
Male sex, *n* (%)	183 (56%)	14 (48.3%)	0.425
Risk factor, *n* (%):			
Age ≥ 65 years	214 (65.4%)	20 (69%)	0.702
BMI ≥ 30	26 (8%)	2 (6.9%)	0.840
Cardiovascular disease	127 (38.8%)	12 (41.4%)	0.788
COPD or other respiratory disease	68 (20.8%)	8 (27.6%)	0.392
Neurological disease	32 (9.8%)	3 (10.3%)	0.923
Diabetes mellitus	58 (17.7%)	5 (17.2%)	0.947
Chronic kidney failure	19 (5.8%)	2 (6.9%)	0.812
Cancer	28 (8.6%)	2 (6.9%)	0.757
Immunodeficiency	46 (14.1%)	3 (10.3%)	0.577
Calendar period:			0.803
Jan–May	150 (45.9%)	14 (48.3%)	
Jun–Oct	177 (54.1%)	15 (51.7%)	
Antiviral treatment:			0.487
Nirmatrelvir/ritonavir	121 (37%)	14 (48.3%)	
Molnupiravir	84 (25.7%)	6 (20.7%)	
Remdesivir	122 (37.3%)	9 (31%)	
Setting, *n* (%):			0.388
Outpatient service	249 (76.1%)	20 (69%)	
Hospitalization for diseases other than COVID-19	78 (23.9%)	9 (31%)	
Days from symptom onset to antiviral treatment, median (IQR)	2 (1–4)	2 (1–3)	0.310
Days from symptom onset to virological clearance, median (IQR)	12 (9–17)	16 (12–21)	**0.012**
Outcome, *n* (%):	*N* 288	*N* 27	0.530
Recovery	277 (96.2%)	27 (100%)	
Death	11 (3.8%)	0	
Adverse events, *n* (%):			0.907
No	317 (96.9%)	28 (96.6%)	
Yes	10 (3.1%)	1 (3.4%)	

Table 4 continued

Characteristics (N = 356)	Vaccinated patients N = 327 (91.8%)	Unvaccinated patients N = 29 (8.2%)	p value
Virological clearance at day 7 from symptoms onset, n (%):	N = 231	N = 16	0.012
No	131 (56.7%)	9 (56.3%)	
Yes	100 (43.3%)	7 (43.8%)	

Quantitative data are presented as median, interquartile range; categorical data are presented as absolute numbers, percentages. Mann–Whitney and Chi-squared test for comparison among the three groups, as appropriate

Days from symptom onset to virological clearance was defined as days from onset of symptoms to the first antigenic- or PCR-negative nasopharyngeal swab; virological clearance at day 7 was defined as patients with antigenic- or PCR-negative nasopharyngeal swab at day 7 after treatment start

BMI body mass index, *COPD* chronic obstructive pulmonary disease

of care in PANORAMIC trial [33]. Furthermore, other trials and observational studies displayed a reduction in all-cause mortality, but not all found an effect of MNP in reduction of disease progression [29, 34, 35]. However, we observed a high proportion of clinical recovery also in MNP-treated patients, similarly to the other two therapies, in line with another Italian retrospective analysis [36].

As regards safety issues, all the three drugs were well tolerated with a very low prevalence of adverse events, confirming data from trials and real-life data [5, 7, 22, 23]. A higher proportion of adverse events was reported with NMV-r compared to MNP and RDV, but no severe adverse events and no discontinuation were observed. The prevalence of side effects was comparable to that reported by other retrospective studies and NMV-r was not associated with a higher proportion of adverse events compared to placebo in both trials and meta-analyses [4, 37, 38].

Interestingly, in our study NMV-r seemed to have a better and faster virological response: virological clearance 1 week after the start of treatment was reached in more than half of patients receiving NMV-r, but only in about a third of patients treated with MNP or RDV. NMV-r also showed a shorter time to the first negative PCR or antigenic nasopharyngeal swab. The higher proportion of viral response in a short period for NMV-r, compared to RDV and

MNP, was independent from age and immunosuppression conditions.

A faster trend of conversion from positive to negative RT-PCR RNA with NMV-r versus placebo was expected and already known [26, 39]; furthermore, the higher probability of having a negative SARS-CoV-2 swab within 10 days from the first positive one following treatment with NMV-r was previously described, also after controlling for possible confounders, but in comparison only with RDV and not MNP [36]. Nevertheless, a recent Cochrane systematic review failed to find a certain effect of NMV-r in increasing viral clearance at 7 and 14 days and other authors found that NMV-r effectively reduced viral loads, but was not able to decrease the length of virus shedding [27, 40].

Obtaining a faster virological response is crucial to shorten time of isolation and contagiousness, mainly in patients who need diagnostic procedures or the continuation of life-saving therapies.

A shorter time to viral clearance was reported also for patients treated very early after symptoms onset and for vaccinated patients, suggesting the importance of a timely initiation of antiviral treatment and the completion of vaccination schedule especially in patients who would be disadvantaged by long periods of isolation due to concomitant pathologies.

Our study has some limitations: the retrospective nature and the lack of a control

group of patients not receiving any antiviral treatment; unmeasured confounders for the association between antiviral treatment and virological clearance; the lack of daily nasopharyngeal swabs to assess the actual time to viral response; the limited sample size and losses to follow-up. This is, however, one of the first studies directly comparing three different antiviral treatments for high-risk outpatients in a real-life setting during the Omicron era.

CONCLUSIONS

In conclusion, NMV-r, MNP, and RDV have been confirmed as a therapeutic strategy for high-risk patients diagnosed with mild COVID-19 disease in order to reduce disease progression without differences among the three drugs; NMV-r was associated with a higher, but still overall low proportion, of adverse events. A possible better performance of this antiviral, compared to the other therapies, is its ability to shorten the period of viral shedding and disease transmission, which is even now essential for some categories of patients such as subjects diagnosed with hematological malignancies.

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Declarations

Conflict of Interest. Francesca Bai, Tomaso Beringheli, Virginia Vitaletti, Andrea Santoro, Francesco Molà, Alessandro Copes, Nicole Gemignani, Sofia Pettenuzzo, Roberto Castoldi, Benedetta Varisco, Riccardo Ligresti, Matteo Sala, Lorenzo Albertini, Matteo Augello, Lorenzo Biasioli, Valeria Bono, Roberta Rovito, Teresa Bini, Sabrina Passarella, Nicola Vincenzo Orfeo, Antonella d'Arminio Monforte, and Giulia Marchetti declare that the research was conducted in the absence of any commercial or financial relationships that could be interpreted as a potential conflict of interest.

Ethical Approval. The study has received approval by the Ethic Committee Milano Area 1 (n. 0000677, 01/04/2020) and all the subjects provided informed consent to participate in the study. The study has been conducted according to the World Medical Association and the Declaration of Helsinki.

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