

Prevention is better than healing. Clinical and economic implications of oral antiviral agents in COVID-19: a prospective study

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ABSTRACT

COVID-19 represents a threat for frailty patients. This study compares molnupiravir and nirmatrelvir for fragile COVID-19 patients' efficacy, safety, and cost. An observational, prospective study allowed us to evaluate molnupiravir's efficacy and safety in real life, compare it to a subgroup of patients treated with nirmatrelvir-ritonavir, and analyze its cost-effectiveness. From January to December 2022, 435 patients (225 males, 220 females; median age 72 years), were enrolled; 24 patients were unvaccinated, and 280 patients had ≥ 2 risk factors. Molnupiravir performed better clinically and economically. Compared to literature data, in these patients, hospitalization was 2.5% vs. 6.8% ($P < 0.005$), overall adverse effects 14.3% vs. 30.4% ($P < 0.0001$), severe adverse effects 2.6 vs. 6.9% ($P < 0.001$), thus involving potential total savings of about € 92.954 per patient (8% of standard of care cost). Early molnupiravir treatment helped fragile patients who partially responded to the vaccine, or with absolute contraindications to vaccination, to overcome COVID-19 without the need for hospitalization. In elderly patients with multiple pathologies and multiple drugs, molnupiravir prevents disease progression clinically and economically.

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Key words: oral antiviral agents; molnupiravir; SARS-CoV-2; COVID-19; nirmatrelvir.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Ethical approval and consent to participate: the study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee Lazio 2, number 112.22, protocol 0178316/22.

Informed consent: informed consent was obtained from all subjects involved in the study.

Received: 4 May 2024.
Accepted: 7 May 2024.

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Italian Journal of Medicine 2024; 18:1737
doi:10.4081/ijm.2024.1737

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Introduction

At the beginning of 2020, the emerging pandemic of COVID-19 represented a difficult challenge for physicians and researchers. Initially, the disease caused massive hospitalization due to severe acute respiratory syndrome, often leading to death or chronic respiratory failure.¹ This scenario forced the Countries to apply strict lockdown,² leading to the interruption of social life and severe job and financial loss. SARS-CoV-2 was implicated in 570 million infections and over 6.3 million deaths by July 27th, 2022.³ Among the several reasons for these high numbers in such a short time, both clinical and organizational reduced preparedness among health-care workers have been recognized.⁴⁻⁸

COVID-19 disease presents a wide spectrum of clinical manifestations, and it may involve any organ and system. Its symptoms range from mild cases including fever, fatigue, myalgia, rhinorrhea, coughing, and sore throat to more severe diseases that can cause acute respiratory distress syndrome, septic shock, and multi-organ failure. This severe disease is more likely in the presence of pre-existing risk factors such as: older age, chronic cardiac, pulmonary, metabolic, and kidney disease, immunosuppression, obesity, and neoplastic disease.⁹⁻¹¹

Therefore, the dramatic impact of the pandemic highlighted the need for the development of preventive measures (vaccines) and specific therapies to avoid hospital overcrowding.^{12,13}

By 2021, several therapeutic options were developed. In February 2021, the Scientific Technical Committee (CTS) of the Italian Drugs Agency (AIFA) approved, for emergency use, the first anti-SARS-CoV-2 monoclonal antibody (mAb).¹⁴ MAbs effectively reduce hospitalization in patients at risk of disease progression but have some limitations. Pri-

marily, the SARS-CoV-2 variants that spread in the last years carried mutations of those epitopes recognized by the neutralizing antibodies.¹⁵ This led to the emergence of viral resistance, with reduced efficacy and the need for new virion-binding mAbs. Moreover, mAbs are intravenous drugs that require dedicated staff and rooms, and a lot of time for preparation and administration. After a few months, the European Medicines Agency (EMA) authorized the antiviral drug remdesivir for the treatment of hospitalized patients undergoing oxygen therapy; clinical indication was then expanded in early therapy, also in non-hospitalized patients.¹⁶ Like mAbs, remdesivir is an intravenous drug; this does not facilitate quick access to therapy, especially in home care settings.¹⁷ At the end of 2021, EMA authorized Paxlovid®, (Pfizer Europe MA EEIG), an association of two protease inhibitors (nirmatrelvir-ritonavir) as the first oral antiviral treatment for COVID-19 patients at risk of disease progression.^{18,19} In a randomized, double-blind clinical trial, consisting of 3000 participants who tested positive for COVID-19, Paxlovid® was reported to be 89% effective in avoiding hospitalization of vulnerable patients.^{20,21} Nevertheless, Paxlovid®, despite having very similar eligibility criteria, is not an easily prescribed medicine due to its interaction with many drugs and the necessity for dose adjustment on kidney function, requiring the patient to undergo frequent blood tests. Before the treatment, patients should undergo a careful clinic and drug history and have a recent blood analysis. Patients with an estimated glomerular filter rate (eGFR) >60 ml/min take nirmatrelvir 150 mg 2 tablets and ritonavir 100 mg 1 tablet for 5 days. Nirmatrelvir dose needs to be halved for eGFR >30 <60 ml/min.

In the same period, the Food and Drug Administration authorized, for emergency use,²² the oral antiviral molnupiravir (Merck Sharp & Dohme) for treatment of mild-to-moderate COVID-19 in adults infected with SARS-CoV-2 and who are at high risk for progression. In the phase 3 study, molnupiravir has shown to be 31% effective in reducing hospitalization and 89% in reducing death compared with placebo.²² The drug was approved for emergency use in those patients with contraindications to alternative COVID-19 treatment options.²³

Molnupiravir was the first oral antiviral to be available in Italy; it is a small-molecule ribonucleoside prodrug of N-hydroxycytidine, which, interfering with viral RNA polymerase, misdirects viral replication thus making the virus noninfectious and unable to replicate.²⁴ This mechanism of action being independent of spike protein mutations, makes molnupiravir effective against SARS-CoV-2 variants.

Molnupiravir is a short-term oral therapy (5 days) and it is easy to administer in outpatients since it has no serious drug interaction, does not require dose adjustment up to GFR =15 ml/min,²⁴ and has been proven to be well tolerated and safe in phase 1, 2, and 3 clinical trials, at least in short-term therapy regimens.

Clinical trials and systematic reviews have shown that molnupiravir seems to have both clinical efficacy in lowering the risk of hospitalization or death for non-hospitalized patients with COVID-19 and also good safety and tolerability, reporting few and mainly low-grade adverse events.²⁵⁻²⁷

All these characteristics make the use of molnupiravir especially feasible as treatment in mild-to-moderate COVID-19 non-hospitalized frail patients undergoing multidrug chronic therapies and at risk for clinical progression. Although it was withdrawn from the market by the decision of the

EMA, molnupiravir demonstrates efficacy and safety with mild-to-moderate COVID-19 patients, especially if already COVID-19 vaccinated.²³

During the observation period (January-July 2022), the prevalence of the Omicron B.1.1.529 variant was over 99% with a constant spread of BA.5 variant in the last two months of observation, according to the national reports of Italian *Istituto Superiore di Sanità* (National Institute of Health).^{28,29}

The objectives of this study are to: i) confirm the efficacy and safety of molnupiravir use in the real world for non-hospitalized adults with mild-to-moderate, laboratory-confirmed COVID-19 patients who had at least one risk factor for severe progression of illness; ii) compare the results with those of clinical trials and to a subgroup of patients treated with the other available oral antiviral Paxlovid®; iii) perform an economic evaluation comparing the use of molnupiravir vs. Paxlovid®, to assess potential saving associated with molnupiravir use.^{30,31}

Materials and Methods

Study design

This observational, prospective monocentric study was performed according to the Declaration of Helsinki statements and was approved by the Ethics Committee Lazio 2 with number 112.22, protocol 0178316/22. The study was reported according to the STROBE guidelines.^{32,33}

Setting and population

Since April 2021, the *Ospedale dei Castelli* has hosted the COVID-19 Early Therapies Center of ASL Roma 6, which is specialized in the management of home COVID-19 patients with monoclonal antibodies and antivirals.³⁴

For treatment with molnupiravir, adult patients were selected according to the indications of AIFA's CTS.²⁴

Eligibility criteria included the positivity for a nasopharyngeal swab, mild-moderate symptoms which started no later than 5 days, no indication for hospitalization, and the presence of at least one of the following risk factors: age >65 years, severe cardiovascular disease with chronic complications, severe chronic lung disease, obesity (body mass index ≥ 30), primary or secondary immunodeficiency, neoplastic or oncohematological active disease, chronic kidney disease (eGFR >15 ml/min), diabetes mellitus with chronic damage, severe neurovascular disease, neurodegenerative diseases or neurodevelopmental pathologies.

Exclusion criteria included the absence of symptoms, the necessity to start or increase oxygen therapy, hospitalization, pregnancy, and pre-dialysis renal failure.

Patients included in the study were treated with 800 mg of molnupiravir every 12 hours for 5 days, were informed of the potential teratogenicity of the drug, and received all information on contraception timing.

From 1st January 2022 to 31st December 2022, patients were reported to the center team via e-mail by either general practitioners, specialists, or emergency department physicians.² The center team, once assessed patient eligibility, contacted them and collected the demographic, clinical, and laboratory data in a standardized and electronically filled form. The study flow is depicted in Figure 1.

According to the literature,^{23,35-43} the primary efficacy end-point was the incidence of hospitalization for any cause (defined as ≥ 24 hours of acute care in a hospital or any similar facility) or death, while the primary safety endpoint was the incidence of any adverse events during the 29 days of follow-up.

Clinical data included past and present diseases, pharmacological therapies, and self-reported vital signs (blood pressure, heart frequency, body temperature, and peripheral oxygen saturation). Laboratory data included kidney and hepatic function.

All enrolled patients received informed consent to sign, information about potential teratogenic issues, dosage and duration prescription, and their drug doses.

Patients were contacted again twice, after 7 and 29 days respectively, to record the disease course and to investigate for any adverse effects.

Furthermore, a comparison with nirmatrelvir-ritonavir-treated patients was performed.^{44,45} The *Ospedale dei Castelli* dispensed molnupiravir when nirmatrelvir-ritonavir was not allowed due to drugs interactions or clinical contraindications: eligible patients underwent a careful clinic and drug history, due to ritonavir's many interactions, and then were treated with nirmatrelvir 150 mg 2 tablets and ritonavir 100 mg 1 tablet twice a day for 5 days (eGFR ≥ 60 ml/min) or nirmatrelvir 150 mg 1 tablet and ritonavir 100 mg 1 tablet twice a day (eGFR $>30 <60$ ml/min).

Statistical analysis

Patient demographic and clinical characteristics were evaluated using descriptive analysis: frequencies and percentages for qualitative data; median and range for quantitative data. The chi-square test was used to evaluate statistically significant differences among groups. OpenEpi software, version 3.01 (Open-Source Epidemiologic Statistics for Public Health) was used.

Economic evaluation

A cost-effectiveness analysis was performed to compare the scenario in which patients were treated with molnupiravir in the absence of a standard of care. A cost-effectiveness analysis is a method of comparing the cost of a program with its expected outcomes that are qualitative in nature and it compares alternative ways to achieve a specific set of results.²⁵⁻²⁷ A "what-if" approach was followed so that the control scenario was modeled as if the patient cohort was administered a treatment without antiviral agents instead of molnupiravir. According to the literature,^{23,35-43} it was assumed a reduction of 31% in hospitalization and 89% in mortality after the administration of molnupiravir. According to the baseline characteristics of the patients included in the study, it was assumed a probability of hospitalization of 10% and an overall mortality of 0.18%. Among those hos-

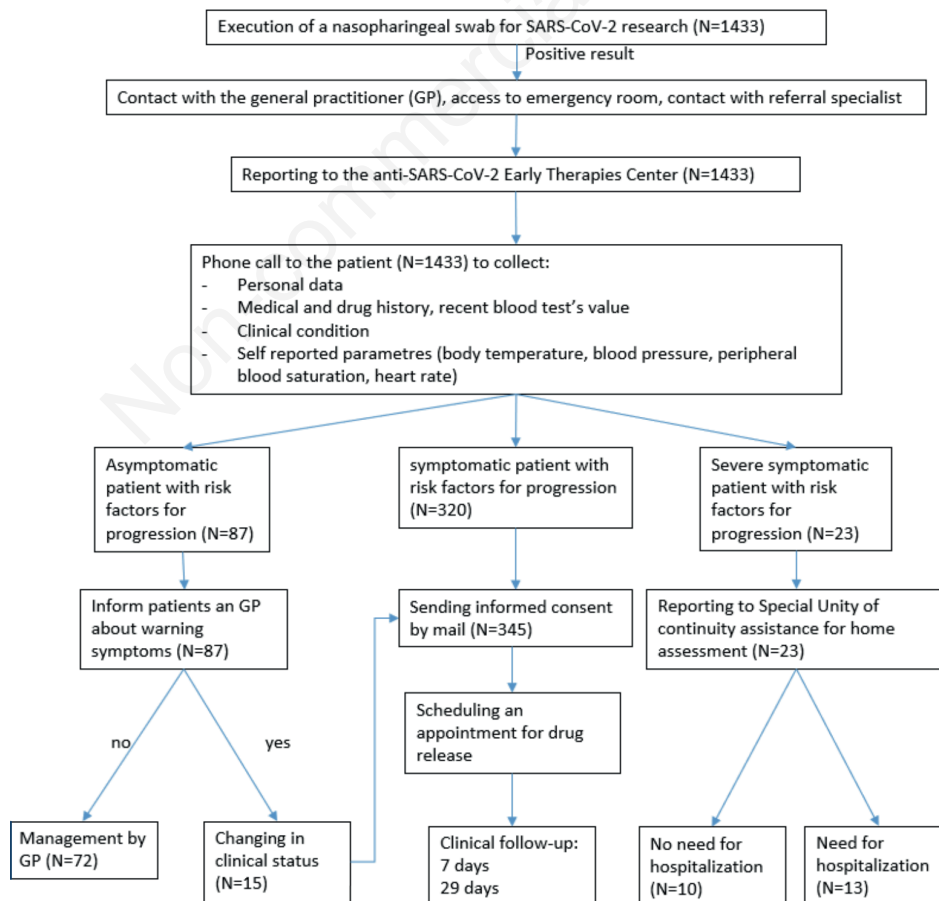


Figure 1. Patient's flow, from the first SARS-CoV-2 positive swab to the onset of therapy.

pitalized, the probability of accessing the intensive care unit (ICU) was set at 24%.

According to the estimation of the Italian Public Accounting Service (*Ragioneria Generale dello Stato*),⁴⁶ each day of hospitalization was associated with an average cost of € 674, whilst each day in ICU was assigned a tariff of €1,650. The average length of stay in the hospital was 20 days for patients admitted to the ward and 10 days for patients admitted to the ICU. Deaths were assigned an average length of stay of 8 days. Molnupiravir was associated with a cost of € 610 per patient.⁴⁷

The economic evaluation allowed us to calculate the value for money of molnupiravir compared to the standard of care. The value for money was expressed in terms of cost per avoided hospitalization.

A probabilistic sensitivity analysis within a Monte Carlo framework allowed to estimate a simulated 95% confidence interval as well as the percentile of the cumulated distribution resulting from the combination of costs and effectiveness parameters. In order to carry out the probabilistic analysis cost, data were assigned Gamma-type random vari-

ables, whilst effectiveness parameters (*i.e.*, hospitalization, treatment effectiveness, mortality rates, rate of admission in ICU) were assigned Beta-type random distributions.⁴⁸

Table 1 shows the clinical and economic inputs as well as the scale and slope parameters (alpha and beta) used to run the probabilistic sensitivity analysis.

Results

Molnupiravir

A total of 435 patients (225 males, 210 females; median age 72,9 years, 72,8 for men and 73 for women) affected by COVID-19 with mild-moderate symptoms and at least one risk factor for severe progression were enrolled in the study and treated with molnupiravir. 276 patients (63,4%) had ≥ 2 risk factors. As shown in Table 2, the main risk factor was old age (70%), followed by severe cardiovascular disease (65%), mostly chronic coronary heart disease and chronic heart fail-

Table 1. Clinical and economic parameters.

	Input	Mean	SD	α	β	Distribution
Clinical	Mortality reduction with molnupiravir	89%	18%	0.523	0.008	β
	Molnupiravir effectiveness	31%	14%	0.90478	0.074	β
	Hospitalization rate	10%	4%	0.004	0.036	β
Non-clinical	Hospitalization costs (ward)	674 €	134.8 €	25	26.96	γ
	ICU costs	1,650 €	330 €	25	66	γ
	Length of stay (ward)	20	4	25	0.8	γ
	Length of stay (ICU)	10	2	25	0.4	γ
	Length of stay (death)	8	1.6	25	0.32	γ
	Molnupiravir cost	610 €	Na	Na	Na	Deterministic

SD, standard deviation; ICU, intensive care unit; Na, not available.

Table 2. Demographic and clinical characteristics of the patients with Italian drugs agency indication for molnupiravir and nirmatrelvir-ritonavir prescription.

Patients' characteristics	Molnupiravir			Nirmatrelvir-ritonavir		
	Total (%) N=435 (100)	Females (%) N=210 (48)	Males (%) N=225 (52)	Total (%) N=124 (100)	Females (%) N=77 (62)	Males (%) N=48 (38)
Age >65 years	304 (70)	139 (66.2)	165 (72.6)	60 (48)	34 (44)	22 (45.8)
Median age (range)	72.9 (21-98)	73.0 (21-94)	72.8 (27-98)	64 years (IQR 18.5 SD 13.8)		
Non vaccinated	24 (5.5)	11 (5.2)	13 (5.8)	1 (0.8)	0	1 (2.5)
Partially vaccinated (1 or 2 doses)	29 (6.7)	10 (4.8)	19 (8.4)	15 (12)	9 (11.6)	6 (12.5)
Fully vaccinated (3 or more doses)	371 (87.8)	196 (93.3)	175 (77.8)	108 (87)	69 (90)	39 (81.2)
Severe cardiovascular disease with chronic complications	283 (65)	121 (57.6)	162 (71.3)	34 (28)	18 (23.4)	16 (33.3)
Severe chronic lung disease	182 (41.9)	90 (42.8)	92 (40.5)	39 (32)	21 (27)	18 (37.5)
Chronic kidney disease (eGFR >15 ml/min)	120 (27.6)	48 (22.8)	72 (31.7)	20 (16.8)	10 (13)	10 (20.8)
Obesity (body mass index ≥ 30)	104 (24)	30 (14.3)	74 (32.6)	48 (38.7)	45 (58.4)	3 (6.2)
Diabetes mellitus with chronic damage	91 (21)	36 (17.1)	55 (24.2)	11 (9.6)	6 (7.8)	5 (10.4)
Neoplastic or onco-hematological active disease	88 (20.2)	43 (20.5)	45 (19.8)	34 (26.4)	26 (33.7)	8 (16.6)
Primary or secondary immunodeficiency	85 (19.6)	46 (21.9)	39 (17.2)	48 (33.9)	34 (44)	14 (29.3)
Severe neurovascular disease	47 (10.8)	19 (9)	28 (12.3)	3 (2.4)	1 (1.3)	2 (4.1)
Neurodegenerative diseases or neurodevelopmental pathologies	14 (3.2)	7 (3.3)	7 (3)	11 (8.9)	5 (6.5)	6 (12.5)

IQR, interquartile range; SD, standard deviation; eGFR, estimated glomerular filter rate.

ure. Considering the numerous comorbidities, almost 70% of the patients were on poly-pharmacological therapy.

A total of 124 patients (46 males and 78 females; median age 64 years), were treated with nirmatrelvir-ritonavir (Paxlovid®) with mild-moderate symptoms. 72 (58,1%) patients had ≥ 2 risk factors. As shown in Table 2, the main risk factors were age >65 years (48%), obesity (38.8%), immunodeficiency (33.9%), and severe chronic lung diseases (32%). Almost 40% of the patients had 1 (38,4%) and 2 (39,5%) comorbidities, while 18,4% had 3-4 comorbidities, only old age 5 patients (4%).

Overall, 11 patients needed hospitalization after a few days of therapy due to disease progression; 6 after completing therapy, and 5 after partial therapy.

Out of 11, 10 hospitalized patients were dismissed after recovery; only one death was observed.

After 29 days of follow-up, survival status was confirmed for all but a single patient who died due to COVID-19, after completing a full therapy cycle. She was a 73-year-old immunocompromised patient whose clinical conditions and several comorbidities worsened 2 weeks after an apparent clinical remission. Since no autopsy was performed on the deceased patient, it is not possible to establish with certainty the cause of death.

The median time for swab negativization was 12.4 days [standard deviation (SD) 3.2] for patients treated with molnupiravir and median swab negativization was 8 days (interquartile range 3, SD 5.6) for patients treated with nirmatrel-ritonavir.

For patients in treatment with molnupiravir, residual

symptoms were complained of by 153 patients (37.1%) and 72 patients (15.9%) respectively after 7 (Table 3) and 29 (Table 4) days and the most frequently reported symptoms were fatigue and cough.

Among those in treatment with nirmatrelvir-ritonavir, after 7 days, 52 (41.6%) patients complained of residual symptoms. 60 people had ≥ 2 risk factors.

After 7 days, the most common residual symptoms were fatigue and cough, followed by myalgia, sore throat, headache, dyspnea, and nasal congestion; after 29 days, the proportions were still very close to the same (Tables 3 and 4).

After 29 days, 331 (76%) and 94 (75.8%) patients under molnupiravir and nirmatrelvir-ritonavir, respectively, had no residual symptoms (Table 4). Concerning safety, in patients treated with molnupiravir, adverse events were reported by 62 patients (14,2%); they are summarized in Table 5. The most frequently complained adverse events were gastrointestinal disorders, in agreement with data already reported in clinical trials.²³ In four patients the symptoms were so invalidating to require therapy discontinuation. Moreover, three patients did not finish therapy due to poor compliance, and five patients did not finish therapy due to hospitalization. These five patients had multiple comorbidities and required hospitalization within the first two days of therapy.

In patients treated with nirmatrelvir-ritonavir, adverse events were reported by 43 patients (34,68%); they are summarized in Table 5. The most frequently complained adverse events were dysgeusia and diarrhea, followed by nausea and vomiting.

Table 3. Efficacy: type and number of residual symptoms after 7 days in patients treated with Molnupiravir and Nirmatrelvir-ritonavir.

Type and number of residual symptoms	Molnupiravir			Nirmatrelvir-ritonavir		
	Total N=248 (%)	Females N=121 (%)	Males N=127 (%)	Total N=70 (%)	Females N=46 (%)	Males N=24 (%)
Fatigue	90 (36.3)	39 (32.2)	51 (40.2)	29 (41.4)	19 (41.3)	10 (41.6)
Cough	62 (25)	36 (29.8)	26 (20.5)	19 (27.1)	14 (30.4)	5 (20.8)
Myalgia	20 (8.1)	10 (8.3)	10 (7.9)	7 (10)	5 (10.8)	2 (8.3)
Nasal congestion	24 (9.7)	12 (9.9)	12 (9.5)	2 (2.8)	1 (2.1)	1 (4.2)
Sore throat	24 (9.7)	13 (10.7)	11 (8.7)	5 (7.1)	4 (8.4)	1 (4.2)
Dyspnea*	18 (7.3)	7 (5.9)	11 (8.7)	2 (2.8)	0	2 (8.3)
Headache	10 (4)	4 (3.4)	6 (4.7)	3 (4.3)	2 (4.2)	1 (4.2)

*The entity of the symptom was considered a severe adverse event. More symptoms can affect the same person.

Table 4. Efficacy: Type and number of residual symptoms after 29 days in patients treated with Molnupiravir and Nirmatrelvir-ritonavir.

Type and number of residual symptoms	Molnupiravir			Nirmatrelvir-ritonavir		
	Total N=104 (%)	Females N=41 (%)	Males N=63 (%)	Total N=30(%)	Females N=20 (%)	Males N=10 (%)
Fatigue	52 (50)	19 (46.3)	33 (52.4)	17 (56.6)	11 (55)	6 (60)
Cough	25 (24)	12 (29.3)	13 (20.7)	8 (26.6)	5 (25)	3 (30)
Dyspnea*	12 (11.5)	4 (9.8)	8 (12.7)	2 (6.6)	1 (5)	1 (10)
Myalgia	10 (9.6)	5 (12.2)	5 (8)	2 (6.6)	2 (10)	0
Nasal congestion	2 (1.98)	0	2 (3.2)	0	0	0
Sore throat	2 (1.98)	0	2 (3.2)	1 (3.3)	1 (5)	0
Headache	1 (.96)	1 (2.4)	0	0	0	0

*The entity of the symptom was considered a severe adverse event. More symptoms can affect the same person.

Table 6 presents a comparison between the results of this real-world clinical practice study and the results of an important clinical trial.^{22,23,49} The observed number of hospitalizations and adverse effects (overall and severe) are far lower in this study and the differences are statistically significant.

Nirmatrelvir-ritonavir: economic evaluation

Table 7 shows the results of the economic evaluation. Overall, the treatment scenario (involving the administration of molnupiravir to the 435 patients included in the study) produced a total cost of € 694,000 including treatment costs (€210,450), hospitalizations (€320,891), ICUs (€158,870) and the cost of deaths (€ 3,847).

On the other side, under the assumption that the same co-

hort of 435 patients was treated without oral antiviral agents (not involving the administration of molnupiravir), the total costs would have been € 757,012, including: €465,000 due to hospitalization inward, € 248,234 due to ICU admissions and € 43,718 due to deaths.⁵⁰

This cost structure led to a dominant result of molnupiravir vs. treatment without oral antiviral agents, thus involving a potential total savings of about € 92,954 per patient (8% of treatment without oral antiviral agents cost). The economic number-to-treat was 12.01, meaning that for each group of 12 patients treated, molnupiravir usage allows the availability of enough resources to treat an extra patient, compared to the standard of care usage.

Figure 2 shows the results of the Monte Carlo simulation, from which a simulated cost/effectiveness plan and a 95%

Table 5. Safety: Type and number of adverse events in patients treated with Molnupiravir and Nirmatrelvir-ritonavir.

Type of adverse events	Molnupiravir			Nirmatrelvir-ritonavir		
	Total N=62 (%)	Females N=25 (%)	Males N=37 (%)	Total N=43 (%)	Females N=30 (%)	Males N=13 (%)
Diarrhea	14 (22.6)	6 (24)	8 (21.6)	14 (31)	10 (40)	4 (10)
Nausea	12 (19.3)	5 (20)	7 (18.9)	6 (13)	5 (20)	1 (2.7)
Stomachache	9 (14.5)	3 (12)	6 (16.2)	0	0	0
Vomiting*	6 (9.7)	2 (8)	4 (10.8)	1 (2)	0	1 (2.7)
Dizziness*	5 (8.1)	4 (16)	1 (2.7)	0	0	0
Headache	4 (6.4)	2 (8)	2 (5.4)	0	0	0
Changes in BP*	4 (6.4)	1 (4)	3 (8.1)	0	0	0
Dry mouth	3 (4.8)	0	3 (8.1)	0	0	0
Tinnitus	2 (3.2)	1 (4)	1 (2.7)	0	0	0
Urticaria*	2 (3.2)	0	2 (5.4)	0	0	0
Lower limb cramps*	1 (1.6)	1 (4)	0	0	0	0
Dysgeusia	0	0	0	22 (48)	15 (60)	7 (15)

More events can affect the same person. *The entity of the symptom was considered a severe adverse event.

Table 6. Comparison between observed results with Molnupiravir and Nirmatrelvir-ritonavir. with literature data.

Comparison	Molnupiravir			Nirmatrelvir-ritonavir		
	Observed results N=435	Literature data* N=710	χ^2 test	Observed results N=124	Literature data** N=132	χ^2 test
Hospitalization	11 (2.5%)	48 (6.8%)	P<0.005	1 (not for SARS-CoV-2- related disease)	48 (6.8%)	P<0.001
Adverse events (overall)	62 (14.26%)	216 (30.4%)	P<0.001	45	132	P=0.099
Adverse events(severe)	9 (2.6%)	49 (6.9%)	P=0.001	20	66 (50%)	P<0.001

*Published by and by Liu *et al.*⁴⁹; **Published by Jayk Bernal *et al.*²³.

Table 7. Economic evaluation results.

Cost items	Standard of care	Molnupiravir	Difference
Specific treatment	- € *	210,450.00 €	-210,450.00 €
Hospitalization (ward)	465,060.00 €	320,891.40 €	144,168.60 €
ICU	248,234.40 €	158,870.02 €	89,364.38 €
Death	43,718.40 €	3,847.22 €	39,871.18 €
Total	757,012.80 €	694,058.64 €	62,954.16 €

*Included in the hospitalization (ward) costs. ICU, intensive care unit.

confidence interval for both incremental costs and avoided hospitalizations were extrapolated.

100% percent of simulations resulted in a saving consequent to the use of molnupiravir in non-hospitalized patients. As for the savings magnitude, a 95% confidence interval ranging from € 144,000 to € 602,000 was estimated with a 50th percentile of € 327,000 savings (circa € 750 per patient).

Concerning avoided hospitalizations, the 95% confidence interval ranged from 25 to 36 with a 50th percentile of 32 avoided hospitalizations (7.36 %).

Discussion

At present, information on the efficacy and safety of molnupiravir for the prevention of COVID-19 progression, in daily clinical practice in vaccinated non-hospitalized patients with mild to moderate COVID-19 is scarce and controversial.^{17,39,44,51-53} In literature, it is highly recommended to investigate this aspect since a good proportion of the population worldwide is currently vaccinated.^{39,44,51-53}

The percentage of hospitalizations observed in this study was 2.5% which is statistically significantly lower than that observed in the benchmark clinical trial considered (6.8%),²⁰ but very close to that observed in the study of Vena *et al.* (2.7%).⁴⁴ This latter study is a real-world study in which patient characteristics (age and comorbidities) were similar to ours, but the sample size was much smaller (only 145 vs. 435 patients).

Considering the vaccination, in the study of Vena *et al.* all patients were “fully vaccinated” but the minimum number of doses received is not specified. In our study, 87.8% of pa-

tients had three or more doses of vaccine, whereas the landmark clinical trial enrolled only unvaccinated patients.⁴⁴

For what concern safety, in this study the percentages of adverse events (overall =14.3% and serious =2.6%) were statistically lower than those observed in the benchmark clinical trial considered (30,4% and 6.9% respectively).²³ In the study of Vena *et al.*, only two patients experienced mild adverse events and nobody experienced serious ones, maybe because of the relatively low number of enrolled patients.⁴⁴

It deserves attention to point out that the lower hospitalization and occurrence of adverse events observed in our study refers to frail patients. Our cohort consists mostly of elderly patients (median age 72.9 years), with several comorbidities such as cardiovascular diseases, chronic respiratory failure and malignancies, factors that are associated with COVID-19 progression and increased risk of hospitalization.

In our experience, molnupiravir seems to be an effective treatment, thanks to its manageability especially in fragile old patients suffering from multiple pathologies and taking several drugs. Indeed, the possibility of taking molnupiravir at home and associating it with other drugs allowed patients to continue their daily routine and avoid the discomfort of the hospital. Moreover, the reported data showed how molnupiravir represents a feasible and safe alternative in those patients with contraindications to nirmatrelvir-ritonavir treatment.

The prevention of COVID-19 worsening, especially if performed in an outpatient setting, allows to relieve the pressure on medical departments and health services, representing a substantial saving for the health system. In fact, COVID-19 hospitalizations require substantial economic consumption in terms of clinical and nursing care and days of hospital stay.

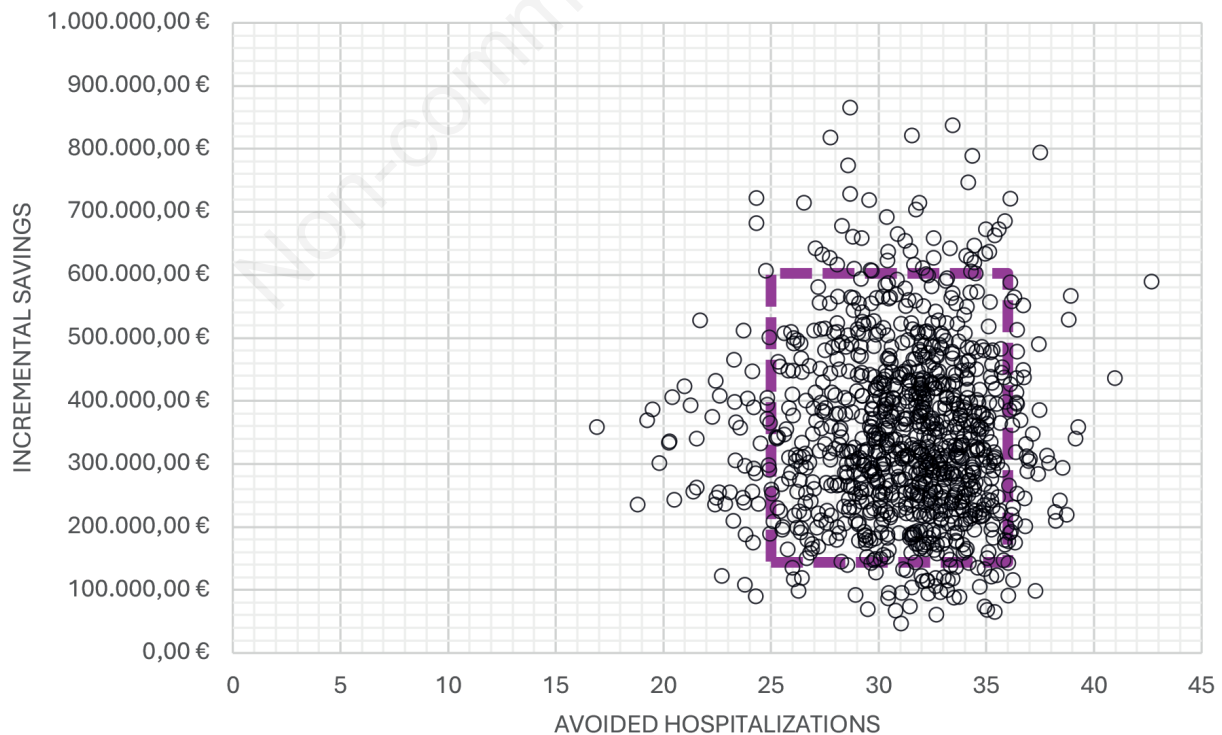


Figure 2. Monte Carlo simulations results: incremental saving vs. avoided hospitalizations. In the square, the area delimited by the 95% confidence interval boundaries.

This is without considering the additional burden in terms of organizational impact on health structures, emergency medical service usage, and costs due to prolonged care and delayed discharge.⁵⁴

Molnupiravir seems to be also an economically effective treatment. Different studies reported the cost of a single day in a COVID-19 department ranging from € 427.77 in a low-intensity ward to € 1,278.50 in a high-intensity setting.^{22,31,46} Considering that the average hospital stay in a sub-intensive care unit is 15.5 days, this means an amount of € 14,873.48. On the other hand, in Italy, the cost of molnupiravir is about € 610 for the five-day treatment, its usage resulting in a potential relief for public spending and hospital facilities burden.

Patients groups with indications for molnupiravir and for nirmatrelvir/ritonavir are not usually comparable. In this study, a comparison between molnupiravir and nirmatrelvir/ritonavir was performed because both therapeutic regimens were proposed and used against the same SARS-CoV-2 variants, and their effects on patients in terms of clinical and management impact were therefore directly comparable.

Strengths and limitations

To our knowledge, this is the largest and most updated study on clinical effectiveness and cost-efficacy of molnupiravir usage in the early onset of COVID-19 in routine clinical practice.

In analogy with a previously conducted study, its usage was favorable compared to standard supportive therapy.^{37,39,54,55} Supportive therapy is not the standard of care, because, currently, scientists do not agree on any single therapy for COVID-19 to be considered as standard of care.

The major limitation of the study lies in the usage of Monte Carlo and what-if scenarios for comparison evaluation. We believe that this limitation could only be overcome by a double-blind placebo-controlled trial, and doubts on its ethical feasibility would arise, since the usage of a placebo against a proven working molecule would represent, at least, a harsh moral hazard. Henceforth, we chose to use simulation data for comparison, instead of actual patients not treated despite clinical indication for doing so. Another limitation is that the study is a single-center design.

Conclusions

The COVID-19 pandemic represented a hard challenge for physicians and researchers. During these last two years, the scientific world has faced a heterogeneous disease with different degrees of severity. This was partially due to viral mutations and the development of new vaccines that allowed contain the disease in the vulnerable population. Moreover, the advent of specific, early treatment helped those patients who partially responded to the vaccine, or with absolute contraindications to vaccination, to overcome COVID-19 without the need for hospitalization.

In our experience, molnupiravir represented a clinically and economically effective treatment, avoiding disease progression, especially in frailty, old patients suffering from multiple pathologies and taking several medications, thanks to its manageability. Our experience confirms its efficacy as reported in the literature data.

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