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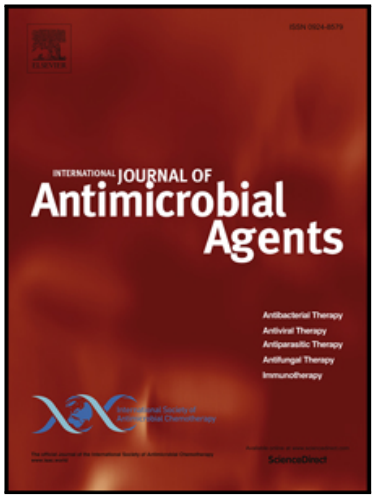


# MOLNUPIRAVIR COMPARED TO NIRMATRELVIR/RITONAVIR FOR COVID-19 IN HIGH-RISK PATIENTS WITH HAEMATOLOGICAL MALIGNANCY IN EUROPE. A MATCHED-PAIRED ANALYSIS FROM THE EPICOVIDEHA REGISTRY

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# Highlights

- Clinical management of coronavirus disease 2019 (COVID-19) has been a continuous challenge since the start of the pandemic in early 2020. Specific vaccines and drugs have been developed to prevent hospital admissions and reduce mortality rates.

- Only molnupiravir and nirmatrelvir/ritonavir are available for oral administration in patients with mild infections to prevent worsening of the patient's condition. Despite both drugs being authorised to be used in Israel, the United Kingdom, and the United States, molnupiravir can only be used in Europe in emergency settings.

- To the best of our knowledge, this is the first publication where the effectiveness of molnupiravir treatment is compared to that of nirmatrelvir/ritonavir in terms of hospitalization and mortality rates in patients with leukaemia or lymphoma.

- No statistically significant differences in hospitalization, mortality rates or survival probability on day 30, 60 and 90 after diagnosis or at last day of follow up between the two drugs have been observed.

- The results from the current research support the use of molnupiravir in patients with haematological malignancies in Europe. Our data show similar effectiveness in preventing hospitalization and death in SARS-CoV-2 infected patients in comparison to already authorised nirmatrelvir/ritonavir.

- Patients with nirmatrelvir/ritonavir-related contraindications and drug-drug interactions, who cannot benefit from the administration of a SARS-CoV-2-specific oral antiviral so far, may do now from molnupiravir intake.

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**Abstract**

***Introduction***

Molnupiravir and nirmatrelvir/ritonavir are antivirals used to prevent progression to severe SARS-CoV-2 infections, which reduce both hospitalization and mortality rates. Nirmatrelvir/ritonavir was authorised in Europe in December 2021, while molnupiravir is not yet licensed in Europe as of February 2022. Molnupiravir may be an alternative to nirmatrelvir/ritonavir, because it displays less frequent drug-drug interactions and contraindications. A caveat connected to molnupiravir derives from the mode of action inducing viral mutations. In clinical trials on patients without haematological malignancy, mortality rate reduction of molnupiravir appeared less pronounced than that of nirmatrelvir/ritonavir. Little is known about the comparative efficacy of the two drugs in patients with haematological malignancy at high-risk of severe COVID-19. Thus, we here assess the effectiveness of molnupiravir compared to nirmatrelvir/ritonavir in our cohort of patients with haematological malignancies.

***Methods***

Clinical data of patients treated either with molnupiravir or nirmatrelvir/ritonavir monotherapy for COVID-19 were retrieved from the EPICOVIDEHA registry. Patients treated with molnupiravir were matched by sex, age (±10 years), and baseline haematological malignancy severity to controls treated with nirmatrelvir/ritonavir.

***Results***

A total of 116 patients receiving molnupiravir for the clinical management of COVID-19 were matched to an equal number of controls receiving nirmatrelvir/ritonavir. In each of the groups, 68 (59%) patients were male; with a median age of 64 years (IQR 53-74) for molnupiravir recipients and 64 years (IQR 54-73) for nirmatrelvir/ritonavir recipients; 57% (n=66) of the patients had controlled baseline haematological malignancy, 13% (n=15) stable, and 30% (n=35) had active disease at COVID-19 onset in each of the groups. During COVID-19 infection, one third of patients from each group were admitted to hospital. Although a similar proportion of vaccinated patients was observed in both groups (molnupiravir n=77, 66% vs nirmatrelvir/ritonavir n=87, 75%), those treated with nirmatrelvir/ritonavir had more often received four doses (n=27, 23%) as compared to patients treated with molnupiravir (n=5, 4%, p<0.001). No differences were detected in COVID-19 severity (p=0.39) or hospitalization (p=1.0). No statistically significant differences were identified in overall mortality rate (p=0.78) or in survival probability (d30 p=0.19, d60 p=0.67, d90 p=0.68, last day of follow up p=0.68). In all patients, deaths were either attributed to COVID-19 or the infection contributed to death as per treating physician's judgement.

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***Conclusions***

In high-risk patients with haematological malignancies and COVID-19, molnupiravir showed rates of hospitalization and mortality comparable to those of nirmatrelvir/ritonavir in this matched-pair analysis. Molnupiravir appears to be a plausible alternative to nirmatrelvir/ritonavir for COVID-19 treatment in patients with haematological malignancy.

**Keywords:** molnupiravir; nirmatrelvir; ritonavir; SARS-CoV-2; COVID-19; hematology; malignancy; Treatment; antiviral

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## Introduction

Immediately after the coronavirus disease 2019 (COVID-19) pandemic was declared, [1] an unprecedented effort was undertaken to overcome the severity and mortality of this infection. First, with specific vaccines, [2,3] and later, with monoclonal antibodies [4-6] and antivirals [7-9] targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Even though the combination of both strategies led to a reduction in hospital admission and mortality, some patient populations remain at high-risk. These include, among others, patients with haematological malignancies, who are at a high-risk for severe forms of COVID-19, as they have an impaired immune system and the anti-SARS-CoV-2 vaccines may not reliably trigger an adequate immune response, as compared to healthy individuals. [10-12] Until January 2023, three antivirals have been developed: molnupiravir, [7] nirmatrelvir/ritonavir, [8] and remdesivir. [9] The first two are for oral administration, whereas the last is for intravenous injection, with the associated limitations for ambulatory use. However, not all patients in Europe can benefit from all existing drugs, as these may not have been authorised for regular administration yet, as it is the case of molnupiravir.

Molnupiravir is an oral nucleoside analogue which inhibits the SARS-CoV-2 viral replication by promoting mutations during virus replication. This mode of action has been viewed critically, as it may promote the evolution of new virus variants. [7,13,14] The target patients for this drug are adults over 18 years, with no weight restriction, who are at high-risk of developing severe COVID-19.[15] No contraindications or drug-drug interactions have yet been described. A mortality reduction of 30% was observed in clinical trials with volunteers without haematological malignancies. [7]

Nirmatrelvir/ritonavir, on the other hand, interacts with the SARS-CoV-2 protease, inhibiting viral replication. [8] Comparable to molnupiravir, nirmatrelvir/ritonavir is an oral medicine for adult patients aimed to reduce the progression from mild to severe COVID-19. [7,8] However, contraindications and drug-drug interactions have been described for nirmatrelvir/ritonavir. Clinical trials in patients without haematological malignancy found a 90% reduction of mortality rates with nirmatrelvir/ritonavir administration versus placebo. [8]

Both molnupiravir and nirmatrelvir/ritonavir are authorised for treatment administration in different geographical settings, such as in Israel, [16,17] in the United Kingdom, [18,19] or in the United States, [20,21] and recommended by experts for haematological malignancy patients. [22] Yet, unlike nirmatrelvir/ritonavir, [23] molnupiravir is not authorised in Europe. [24]

Thus, we aimed to compare the effectiveness of both oral antivirals in terms of hospitalization rates and survival rates on days 30, 60, and 90 after COVID-19 diagnosis in patients with haematological

malignancy and to determine whether molnupiravir may be an alternative to nirmatrelvir/ritonavir in European patients.

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**Methods**

This non-randomised observational analysis was performed as a routine effort with data extracted from the EPICOVIDEHA registry (NCT04733729). EPICOVIDEHA is an online registry collecting worldwide clinical data of patients with baseline haematological malignancies developing SARS-CoV-2 infection. Survey details, accessible via www.clinicalsurveys.net (EFS Summer 2021, TIVIAN, Cologne, Germany), are described elsewhere. [25] EPICOVIDEHA has its central Ethics Committee at the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). According to specific local regulation, each of the participating institutions might have their own ethical approval as appropriate.

Patients included into analysis had to fulfil the basic inclusion criteria of the EPICOVIDEHA registry: adults ≥18 years old, baseline active haematological malignancy at any point within the last five years prior to laboratory-confirmed COVID-19 diagnosis. Additionally, for this specific analysis, patients had to be treated for their COVID-19 exclusively with either molnupiravir or nirmatrelvir/ritonavir monotherapy strategies. The use of corticosteroids and/or convalescent plasma was not considered as exclusionary. No geographical or diagnosis date exclusion parameters were pre-set. However, the obtainability of each oral antiviral in the respective participating institution limited the patient recruitment to Europe, specifically from October 2021 to January 2023.

Cases receiving molnupiravir monotherapy were matched 1:1 to controls with nirmatrelvir/ritonavir. Fifty of these controls were previously described. [26] The variables selected for the matching were age, sex, and malignancy status at COVID-19 diagnosis. These variables were chosen based on the previous experience of the EPICOVIDEHA registry for mortality-associated variables, both in vaccinated and unvaccinated patients with baseline haematological malignancies. [27-30]

Categorical variables are presented with frequencies and percentages, using $X^2$ test or Fisher's exact test for proportion comparison as appropriate. Continuous variables are summarised with median, interquartile range (IQR) and range. Mann-Whitney U test is used to compare continuous variables. Patients receiving any of the oral antivirals (either molnupiravir or nirmatrelvir/ritonavir) have been matched as described above, reducing any potential selection bias. Antiviral effectiveness has been calculated with hospitalization and mortality rate comparison on days 30, 60 and 90 after SARS-CoV-2 infection diagnosis and at last day of follow up. Additionally, Kaplan-Meier survival plots are performed, with a comparison between antivirals based on the log-rank test. A $p \leq 0.05$ has been considered significative in the performed comparisons.

**Results**

As of January 2023, 338 patients documented in the EPICOVIDEHA registry received either molnupiravir (n=124, 36.7%) or nirmatrelvir/ritonavir (n=214, 63.3%) as single monotherapy for the treatment of COVID-19. From those, 116 cases receiving molnupiravir as first-line treatment were matched to an equal number of controls receiving nirmatrelvir/ritonavir. Patients were documented from all over Europe, especially Italy (n=92, 39.7%), the Czech Republic (n=35, 15.1%) and Spain (n=33, 14.2%; Table 1, Figure 1).

In both groups 68 (58.6%) patients were male. The median age for the cases was 64 years (IQR 53-74, range 21-86) and 64 years (IQR 54-73, range 18-91) for the controls. In both treatment groups almost half of the patients did not have any underlying comorbidity at SARS-CoV-2 infection onset beyond the haematological malignancy (molnupiravir n=55, 47.4%; nirmatrelvir/ritonavir n=56, 48.3%). The most prevalent comorbidity was chronic cardiopathy, in one third of the patients each (molnupiravir n=40, 34.5%; nirmatrelvir/ritonavir n=43, 37.1%), with no significant difference (p=0.784). Statistically significant differences were observed in the number of patients with baseline renal dysfunction: 11 (9.5%) patients receiving molnupiravir for the COVID-19 treatment versus 2 (1.7%) patients under nirmatrelvir/ritonavir treatment (p=0.019). Leukaemia (n=49, 42.2%) was more common in patients treated with molnupiravir than in those with nirmatrelvir/ritonavir (n=42, 36.2%). On the contrary, plasma cell disorders were more prevalent in nirmatrelvir/ritonavir controls (n=33, 30.2%) than in molnupiravir cases (n=27, 23.3%), being these differences significant (p=0.005). Malignancy status at onset was evenly distributed in both groups, as this was one of the matching criteria: 66 (56.9%) patients had a controlled malignancy, 15 (12.9%) a stable disease and 35 (30.2%) an active disease at SARS-CoV-2 infection onset. Seven (6.0%) cases and six (5.2%) controls, respectively, did not receive any malignancy treatment at any point by the time of COVID-19 diagnosis. The number of patients with neutropenia (molnupiravir n=8, 6.9%; nirmatrelvir/ritonavir n=5, 4.3%) and lymphopenia (molnupiravir n=18, 15.5%; nirmatrelvir/ritonavir n=7, 6.0%) was twice as frequent in cases than in controls. Although the differences were non-significant in neutropenia (p=0.453), they were for lymphopenia (p=0.039). The number of unvaccinated patients was similar in both comparison groups (molnupiravir n=39, 33.6%; nirmatrelvir/ritonavir n=29, 25.0%). Nevertheless, patients treated with molnupiravir had received more frequently two to three vaccine doses (n=69, 59.5%), while controls treated with nirmatrelvir/ritonavir had three to four doses (n=74, 63.8%; p<0.001). Inactivated vaccines were used as the last type of SARS-CoV-2 vaccine in 11 (9.5%) patients receiving molnupiravir and in one (0.9%) receiving nirmatrelvir/ritonavir (p=<0.001, Table 1).

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Most of the patients treated with molnupiravir (n=72, 62.1%) developed SARS-CoV-2 infection before April 2022, while 103 (88.8%) patients eventually treated with nirmatrelvir/ritonavir were infected after April 2022 (p<0.001). Although not considered a matching criterion, a similar proportion of asymptomatic/mild patients was observed in both treatment groups (molnupiravir n=53, 45.7%; nirmatrelvir/ritonavir n=48, 41.4%). Six (5.2%) cases and two (1.7%) controls had critical COVID-19 (p=0.280). One third of the patients in each comparison group (molnupiravir n=39, 33.6%; nirmatrelvir/ritonavir n=40, 34.5%) were admitted in hospital at some point during their COVID-19 episodes (p=1.000). Day of antiviral treatment start was a median one day after SARS-CoV-2 infection diagnosis (p=0.368) and duration of treatment was four days (p=0.5594, Table 1).

Similar mortality rates were reported from both groups at 30 days (molnupiravir n=6, 5.2%; nirmatrelvir/ritonavir n=2, 1.76%, p=0.280), 60 days (molnupiravir n=7, 6.0%; nirmatrelvir/ritonavir n=5, 4.3%, p=0.768), and 90 days (molnupiravir n=8, 6.9%; nirmatrelvir/ritonavir n=6, 5.2%, p=0.784) after COVID-19 diagnosis. In the Kaplan-Meier plots for survival probability no differences between drugs were observed in days 30 (p=0.190), 60 (p=0.671), and 90 (p=0.684) after SARS-CoV-2 infection diagnosis (Table 1, Figure 2).

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## Discussion

Treating COVID-19 in patients at increased risk of disease progression to severe and critical stages has become a standard clinical practice. [22,31] For logistical reasons, oral treatment options are preferred in out-patients, and the current choice is between molnupiravir and nirmatrelvir/ritonavir. [24] Comparative studies are scarce so far. [32,33] Our case-control study in patients with haematological malignancy matched both groups using well-established prognostic factors and found similar rates for clinical progression with either antiviral. Hospitalization rates and mortality rates at days 30, 60, and 90 did not differ significantly between patients receiving first-line treatment with either molnupiravir or nirmatrelvir/ritonavir.

For this analysis, cases treated with molnupiravir were matched 1:1 to controls receiving nirmatrelvir/ritonavir based on variables previously described as of major relevance for mortality in both vaccinated and unvaccinated patients with baseline haematological malignancies: age, sex, and status of the malignancy at COVID-19 diagnosis. [27-30] Thus, it was possible to analyse the sample reducing potential biases. Such bias reduction can be noticed in the lack of statistically significant differences in almost every comparison, with only certain exceptions.

One of these exceptions was the prevalence of renal dysfunction. Patients treated with molnupiravir had a significantly higher proportion of baseline kidney failure. This may be explained by one of the caveats for the use of nirmatrelvir/ritonavir: glomerular filtration rate levels. [8] Treating medical teams must scrutinize these levels in their respective patients and adjust the dose when needed to minimise and prevent any potential adverse effect. For physicians having access to molnupiravir, it may be the easier and safer alternative. [7,24]

Other observed differences between the patients receiving molnupiravir and nirmatrelvir/ritonavir were found in the vaccination scheme before SARS-CoV-2 infection. Patients with molnupiravir received a lower number of doses, mainly two to three doses, as compared to controls with nirmatrelvir/ritonavir, who received three to four. Additionally, most of the patients that had received inactivated vaccines prior to SARS-CoV-2 infection diagnosis where among those receiving molnupiravir. The fact that molnupiravir, which was made available sooner in Europe for patients at high-risk, in November 2021, [24] as compared to nirmatrelvir/ritonavir, available since December 2021, [34] can explain that the patients diagnosed with COVID-19 earlier in the course of the pandemic received more frequently molnupiravir. Additionally, the sooner the diagnosis was made, the lower the chances were to have received further doses of anti-SARS-CoV-2 vaccine, in line with evolving vaccination campaigns. [35] Regarding the difference in the type of the last vaccine received before diagnosis (i.e., mRNA-based, vector-based, or inactivated), this is associated with the

geographical setting of molnupiravir patients. The 11 patients receiving inactivated vaccines were documented from institutions in Serbia and Turkey. Of those 11 patients, ten were eventually treated with molnupiravir. In both countries there was a wider variety of vaccines available to be administered as compared to other European countries. [36-38].

Patients receiving molnupiravir had a higher prevalence of lymphopenia at SARS-CoV-2 infection onset. Larger number of patients with baseline leukaemia, together with the already reported drug-drug interactions and the associated contraindications to nirmatrelvir/ritonavir administration may have triggered the preference of physicians to administer molnupiravir in such patients instead of nirmatrelvir/ritonavir.

Both cases and controls were hospitalised at similar rates during the COVID-19 episode, probably explained by the target population of both drugs: mild infections. Although the number of patients with molnupiravir admitted to an ICU was twice as that of patients on nirmatrelvir/ritonavir, we found no evidence of a possible correlation with the outcome of our sample. Of note, only three of the seven patients admitted in the ICU had lymphocyte levels below 500 cells/µl at COVID-19 onset.

Antiviral use indications are similar both for molnupiravir and nirmatrelvir/ritonavir: treatment start within the first five days of SARS-CoV-2 infection and for a 5-day duration. [21,39] In both groups (cases and controls), our data showed that the median treatment initiation is immediately after confirmation of diagnosis, in line with current recommendations. Interestingly, for both drugs the median administration time was only four instead of the recommended five days. As previously described in an analysis of nirmatrelvir/ritonavir use in the EPICOVIDEHA registry, 50 patients of which have been included in this comparative analysis, [26] access to oral antivirals during the COVID-19 pandemic has not always been stable, neither in Europe nor in other geographical settings. Thus, an antiviral administration according to manufacturers' information is vital, but may be hampered during a pandemic.

The main goal of this work was to analyse whether there were significant differences in survival rates between molnupiravir and nirmatrelvir/ritonavir treated patients. Once having verified mortality rates and survival probabilities at 30, 60 and 90 days after SARS-CoV-2 infection diagnosis and at last day of follow up, we did not find any statistically significant difference. Considering the matched-paired nature of this analysis, and after observing the lack of major significant differences between cases and controls in factors potentially associated to mortality, the results presented support molnupiravir as an effective treatment preventing COVID-19 progression to severe forms in haematological patients. Although concerns have been raised about the mutagenicity of molnupiravir, these have not yet been confirmed. [13,40]

Limitations of our analysis comprise the retrospective nature of the EPICOVIDEHA registry and the predefined set of variables collected not being directed to drug safety information. The current administration practices for antiviral choices in Europe may be influenced by drug accessibility in certain jurisdictions or even institutions. Many participating hospitals could not access molnupiravir tablets as these were not available in their wards due to lack of authorisation. In many cases, as described by patient contributors, the only alternative for nirmatrelvir/ritonavir was intravenous remdesivir. We could not establish the reason why one drug may have been preferred over the other, which may have been interesting in settings where both oral antivirals were available. Finally, the number of patients analysed is only 338. EPICOVIDEHA was initiated in April 2020 and comprises more than 9,000 patients with haematological malignancy and COVID-19. Owing to oral antivirals becoming available only recently, the number of patients treated with new antivirals is currently still low. However, in this ongoing pandemic, we felt the medical need to share data as early as they evolve. Further analyses may also consider viral mutations, long-term complications of COVID-19 or post-acute sequelae of COVID-19.

In conclusion, patients with baseline haematological malignancies at high-risk for severe COVID-19 benefit from the administration of molnupiravir. Moreover, molnupiravir is an alternative to nirmatrelvir/ritonavir in patients with limited treatment options, for example because of baseline renal compromise or concomitant drugs with relevant drug-drug interactions.

**Declarations**

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**Competing Interests:** JSG reports speaker honoraria from Gilead and Pfizer, outside of the submitted work.

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**Ethical Approval:** EPICOVIDEHA has its central Ethics Committee at the Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). According to specific local regulation, each of the participating institutions might have their own ethical approval as appropriate.

**Sequence Information:** Not applicable

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**Author contributions**

JSG, FM, LP and OAC contributed to study design and study supervision. JSG did the statistical plan and analysis. JSG, PK and OAC interpreted the data and wrote the initial draft of the manuscript. All the authors recruited, and documented participants, critically read and reviewed, and agreed to publish the manuscript.

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## Tables

**Table 1.** Patients' characteristics.

| | Molnupiravir | | Nirmatrelvir/ritonavir | | p value |
|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | |
| **Sex** | | | | | |
| Female | 48 | 41.4 | 48 | 41.4 | 1.000 |
| Male | 68 | 58.6 | 68 | 58.6 | |
| **Age**, *in years* | 64 (53-74) [21-86] | | 64 (54-73) [18-91] | | 0.704 |
| **Comorbidities at onset** | | | | | |
| No comorbidities | 55 | 47.4 | 56 | 48.3 | |
| 1 comorbidity | 32 | 27.6 | 37 | 31.9 | 0.795 |
| 2 comorbidities | 21 | 18.1 | 17 | 14.7 | |
| 3 or more comorbidities | 8 | 6.9 | 6 | 5.2 | |
| *Chronic cardiopathy* | 40 | 34.5 | 43 | 37.1 | 0.784 |
| *Chronic pulmonary disease* | 13 | 11.2 | 9 | 7.8 | 0.502 |
| *Diabetes mellitus* | 13 | 11.2 | 14 | 12.1 | 1.000 |
| *Liver disease* | 3 | 2.6 | 4 | 3.4 | 1.000 |
| *Obesity* | 2 | 1.7 | 5 | 4.3 | 0.446 |
| *Renal impairment* | 11 | 9.5 | 2 | 1.7 | 0.019 |
| *Smoking history* | 6 | 5.2 | 8 | 6.9 | 0.784 |
| **Baseline malignancy** | | | | | |
| Leukaemia | 49 | 42.2 | 42 | 36.2 | |
| *Acute lymphoid leukemia* | 9 | 7.8 | 6 | 5.2 | |
| *Chronic lymphoid leukemia* | 17 | 14.7 | 8 | 6.9 | |
| *Acute myeloid leukemia* | 15 | 12.9 | 11 | 9.5 | |
| *Chronic myeloid leukemia* | 7 | 6.0 | 2 | 1.7 | |
| *Myelodisplastic syndrome* | 1 | 0.9 | 15 | 12.9 | |
| Lymphoma | 38 | 32.8 | 37 | 31.9 | 0.005 |
| *Hodgkin lymphoma* | 4 | 3.4 | 2 | 1.7 | |
| *Non-Hodgkin lymphoma* | 34 | 29.3 | 35 | 30.2 | |
| PH negative myeloproliferative diseases | 3 | 2.6 | 2 | 1.7 | |
| *Myelofibrosis* | 2 | 1.7 | 1 | 0.9 | |
| *Polycythemia vera* | 1 | 0.9 | 1 | 0.9 | |
| Plasma cell disorders | 27 | 23.3 | 33 | 28.4 | |
| *Multiple myeloma* | 26 | 22.4 | 32 | 27.6 | |
| *Amyloid light-chain amyloidosis* | 1 | 0.9 | 1 | 0.9 | |
| Other hematological malignancies | 0 | 0.0 | 1 | 0.9 | |
| *Aplastic anemia* | 0 | 0.0 | 1 | 0.9 | |
| **Malignancy status at onset** | | | | | |
| Controlled disease | 66 | 56.9 | 66 | 56.9 | 1.000 |
| Stable disease | 15 | 12.9 | 15 | 12.9 | |
| Active disease | 35 | 30.2 | 35 | 30.2 | |
| **Last malignancy treatment at onset** | | | | | |
| No treatment | 7 | 6.0 | 6 | 5.2 | |
| alloHSCT | 4 | 3.4 | 11 | 9.5 | |
| *In the last 6 months* | 3 | 2.6 | 2 | 1.7 | |
| *> 6 months* | 1 | 0.9 | 9 | 7.8 | |
| autoHSCT | 7 | 6.0 | 4 | 3.4 | |
| *In the last 6 months* | 6 | 5.2 | 4 | 3.4 | |
| *> 6 months* | 1 | 0.9 | 0 | 0.0 | 0.172 |
| CAR-T | 0 | 0.0 | 2 | 1.7 | |
| *In the last 6 months* | 0 | 0.0 | 2 | 1.7 | |
| *> 6 months* | 0 | 0.0 | 0 | 0.0 | |
| Conventional chemotherapy | 22 | 19.0 | 12 | 10.3 | |
| *In the last 3 months* | 21 | 18.1 | 9 | 7.8 | |
| *> 3 months* | 1 | 0.9 | 2 | 1.7 | |
| *Unknown* | 0 | 0.0 | 1 | 0.9 | |

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| | Molnupiravir | | Nirmatrelvir/ritonavir | | p value |
|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | |
| Demethylating agents | 4 | 3.4 | 8 | 6.9 | |
| *In the last 3 months* | 4 | 3.4 | 7 | 6.0 | |
| *Unknown* | 0 | 0.0 | 1 | 0.9 | |
| Immuno-chemotherapy | 39 | 33.6 | 55 | 47.4 | |
| *In the last 3 months* | 30 | 25.9 | 51 | 44.0 | |
| *> 3 months* | 9 | 7.8 | 4 | 3.4 | |
| Immunotherapy | 6 | 5.2 | 4 | 3.4 | |
| *In the last 3 months* | 6 | 5.2 | 1 | 0.9 | |
| *Unknown* | 0 | 0.0 | 3 | 2.6 | |
| Targeted therapy | 26 | 22.4 | 11 | 9.5 | |
| *In the last 3 months* | 25 | 21.6 | 11 | 9.5 | |
| *> 3 months* | 1 | 0.9 | 0 | 0.0 | |
| Supportive measures | 1 | 0.9 | 3 | 2.6 | |
| **Neutrophils** | | | | | |
| <501 | 8 | 6.9 | 5 | 4.3 | 0.442 |
| 501 - 999 | 4 | 3.4 | 2 | 1.7 | |
| >999 | 83 | 71.6 | 92 | 79.3 | |
| **Lymphocytes** | | | | | |
| <201 | 18 | 15.5 | 7 | 6.0 | 0.039 |
| 201 - 499 | 7 | 6.0 | 9 | 7.8 | |
| >499 | 66 | 56.9 | 82 | 70.7 | |
| **Anti-SARS-CoV-2 vaccination at onset** | | | | | |
| Days from last administration to onset | 155 (91-272) [14-641] | | 247 (175-318) [39-588] | | |
| Not vaccinated | 39 | 33.6 | 29 | 25.0 | |
| One dose | 3 | 2.6 | 1 | 0.9 | |
| *Days from last administration to onset* | 229 (21-488) [21-488] | | 229 (229-229) [229-229] | | |
| Two doses | 27 | 23.3 | 12 | 10.3 | <0.001 |
| *Days from last administration to onset* | 256 (160-288) [21-641] | | 300 (191-377) [39-588] | | |
| Three doses | 42 | 36.2 | 47 | 40.5 | |
| *Days from last administration to onset* | 113 (80-158) [14-319] | | 197 (134-287) [42-394] | | |
| Four doses | 5 | 4.3 | 27 | 23.3 | |
| *Days from last administration to onset* | 273 (230-407) [230-407] | | 928 (235-385) [69-439] | | |
| **Type of last anti-SARS-CoV-2 vaccine at onset** | | | | | |
| mRNA | 60 | 51.7 | 84 | 72.4 | |
| *BioNTech/Pfizer* | 60 | 51.7 | 63 | 54.3 | |
| *Moderna* | 0 | 0.0 | 21 | 18.1 | |
| Vector-based | 3 | 2.6 | 1 | 0.9 | <0.001 |
| *AstraZeneca Oxford* | 2 | 1.7 | 1 | 0.9 | |
| *Janssen* | 1 | 0.9 | 0 | 0.0 | |
| Inactivated | 11 | 9.5 | 1 | 0.9 | |
| *CoronaVac* | 2 | 1.7 | 0 | 0.0 | |
| *Sinopharm* | 9 | 7.8 | 1 | 0.9 | |
| Unknown | 3 | 2.6 | 2 | 1.7 | |
| **SARS-CoV-2 variant** | | | | | |
| Delta | 1 | 0.9 | 1 | 0.9 | 1.000 |
| Omicron | 29 | 25.0 | 29 | 25.0 | |
| Not tested | 86 | 74.1 | 86 | 74.1 | |
| **Time of SARS-CoV-2 infection diagnosis** | | | | | |
| October-December 2021 | 9 | 7.8 | 1 | 0.9 | |
| January-March 2022 | 63 | 54.3 | 12 | 10.3 | |
| April-June 2022 | 12 | 10.3 | 35 | 30.2 | <0.001 |
| July-September 2022 | 18 | 15.5 | 39 | 33.6 | |
| October-December 2022 | 14 | 12.1 | 28 | 24.1 | |
| January-March 2023 | 0 | 0.0 | 1 | 0.9 | |
| **SARS-CoV-2 infection severity** | | | | | 0.392 |

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| | Molnupiravir | | Nirmatrelvir/ritonavir | | p value |
|---|---|---|---|---|---|
| | *n* | *%* | *n* | *%* | |
| Asymptomatic | 19 | 16.4 | 19 | 16.4 | |
| Mild infection | 34 | 29.3 | 29 | 25.0 | |
| Severe infection | 57 | 49.1 | 66 | 56.9 | |
| Critical infection | 6 | 5.2 | 2 | 1.7 | |
| **Stay during SARS-CoV-2 infection** | | | | | |
| Home | 77 | 66.4 | 76 | 65.5 | |
| Hospital | 39 | 33.6 | 40 | 34.5 | 1.000 |
| *Length of stay* | 15 (8-19) [2-29] | | 7 (2-10) [1-37] | | |
| *ICU* | 6 | 5.2 | 2 | 1.7 | |
| Length of stay | 15 (13-18) [2-26] | | 5 (5-5) [5-5] | | |
| **SARS-CoV-2 infection treatment** | | | | | |
| Day of start since infection diagnosis | 1 (0-2) [0-34] | | 1 (0-2) [0-47] | | 0.368 |
| Antiviral treatment days | 4 (4-4) [2-26] | | 4 (4-5) [1-10] | | 0.559 |
| **Outcome** | | | | | 1.000 |
| Observation time | 53 (23-81) [0-310] | | 43 (17-93) [0-327] | | |
| Mortality, day 30 | 6 | 5.2 | 2 | 1.7 | 0.280 |
| Mortality, day 60 | 7 | 6.0 | 5 | 4.3 | 0.768 |
| Mortality, day 90 | 8 | 6.9 | 6 | 5.2 | 0.784 |
| Alive*, last day of follow up* | 108 | 93.1 | 110 | 94.8 | |
| *Observation time* | 55 (26-84) [0-310] | | 43 (17-94) [0-327] | | 0.784 |
| Dead*, last day of follow up* | 8 | 6.9 | 6 | 5.2 | |
| *Observation time* | 23 (13-34) [12-85] | | 38 (22-59) [14-67] | | |
| *Reason for death* | | | | | |
| COVID-19 | 5 | 4.3 | 2 | 1.7 | 0.592 |
| COVID-19 + haematological malignancy | 3 | 2.6 | 4 | 3.4 | |

alloHSCT, allogeneic hematopoietic stem-cell transplantation; autoHSCT, autologous hematopoietic stem-cell transplantation; CAR-T, chimeric antigen receptors T cell receptors; COVID-19, coronavirus disease 2019; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome causing coronavirus type 2

* Molnupiravir: 23 (19.8%) patients received molnupiravir + corticosteroids, 3 (2.6%) patients molnupiravir + plasma, and 1 (0.9%) patient molnupiravir + corticosteroids + plasma. Nirmatrelvir/ritonavir: 12 (10.3%) patients received nirmatrelvir/ritonavir + corticosteroids

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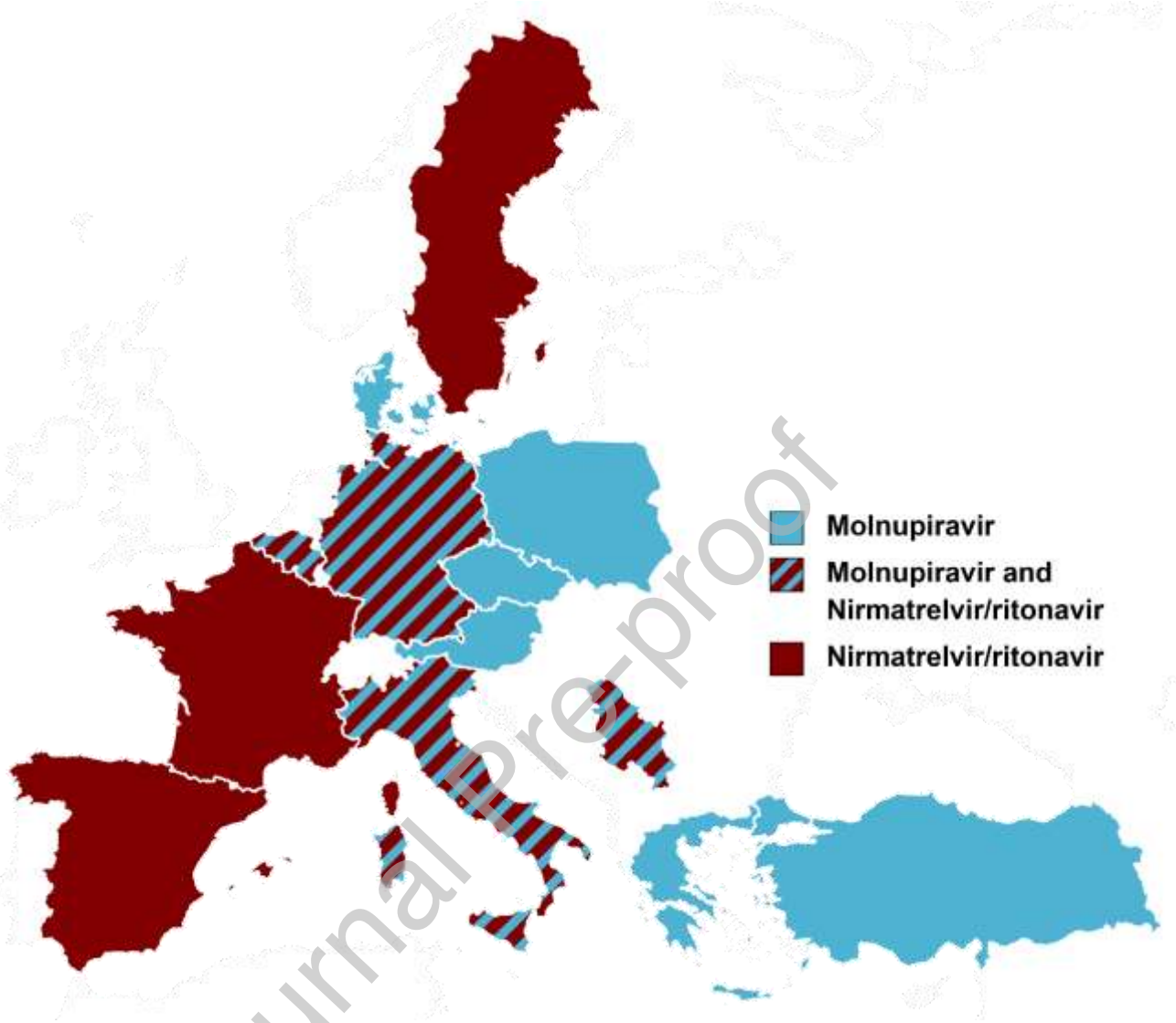
**Figures**

**Figure 1.** Geographical distribution of patients included into matched-paired analysis.




Red colour indicates patients with molnupiravir: Italy (n=38), Czech Republic (n=35), Serbia (n=19), Poland (n=11), Turkey (n=6), Austria (n=3), and Belgium, Denmark, Germany, and Greece (n=1, each). Blue colour indicates patients with nirmatrelvir/ritonavir: Italy (n=54), Spain (n=33), Belgium (n=18), Serbia (n=4), and Germany and France (n=3, each). The pattern indicates that both treatments have been administered to patients as monotherapies.

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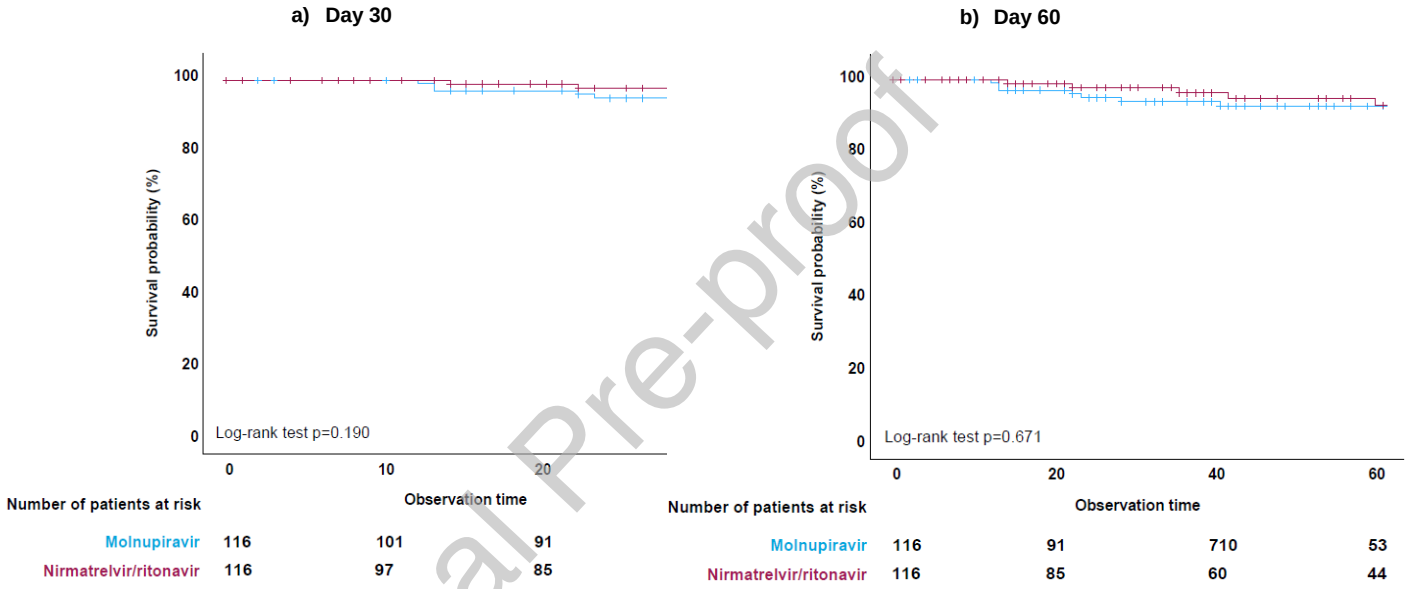
**Figure 2.** Survival probability of patients at days 30, 60 and 90 since SARS-CoV-2 infection and at last day of follow up.

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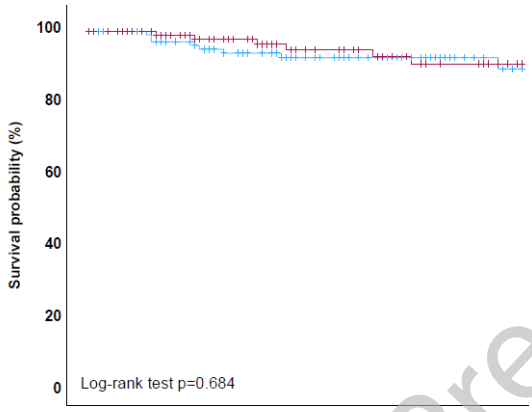
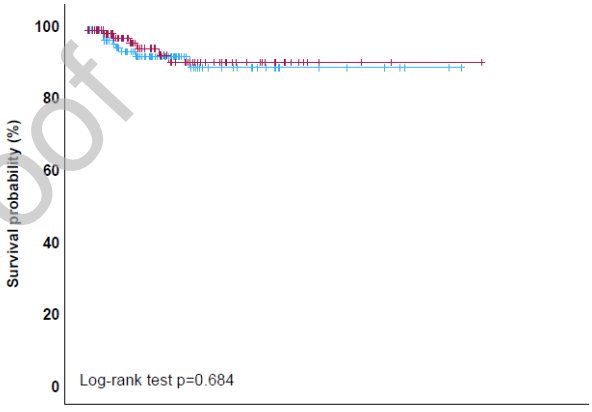
**c) Day 90**




| Number of patients at risk | Observation time | | | |
|---|---|---|---|---|
| Molnupiravir | 115 | 79 | 53 | 2 |
| Nirmatrelvir/ritonavir | 115 | 72 | 44 | 3 |

**d) Last day of follow up**




| Number of patients at risk | | | | |
|---|---|---|---|---|
| Molnupiravir | 116 | 21 | 6 | 2 |
| Nirmatrelvir/ritonavir | 116 | 26 | 2 | 1 |

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