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Nirmatrelvir/ritonavir in COVID-19 patients with haematological malignancies: a report from the EPICOVIDEHA registry

Jon Salmanton-García,[a,b,c,bv,*] Francesco Marchesi,[d,bv] Maria Gomes da Silva,[e] Francesca Farina,[f] Julio Dávila-Valls,[g] Yavuz M. Bilgin,[h] Andreas Glenthøj,[i] Iker Falces-Romero,[j,k] Jaap Van Doesum,[l] Jorge Labrador,[m,n] Caterina Buquicchio,[o] Shaimaa El-Ashwah,[p] Verena Petzer,[q] Jens Van Praet,[r] Martin Schönlein,[s] Michelina Dargenio,[t] Gustavo-Adolfo Méndez,[u] Stef Meers,[v] Federico Itri,[w] Antonio Giordano,[x] László Imre Pinczés,[y] Ildefonso Espigado,[z] Zlate Stojanoski,[aa] Alberto López-García,[ab] Lucia Prezioso,[ac] Ozren Jaksic,[ad] Antonio Vena,[ae] Nicola S. Fracchiolla,[af] Tomás José González-López,[ag] Natasa Colović,[ah] Mario Delia,[ai] Barbora Weinbergerová,[aj] Monia Marchetti,[ak] Joyce Marques de Almeida,[al] Olimpia Finizio,[am] Caroline Besson,[an,bu] Monika M. Biernat,[ao] Toni Valković,[ap,aq,ar] Tobias Lahmer,[as] Annarosa Cuccaro,[at] Irati Ormazabal-Vélez,[au] Josip Batinić,[av,aw] Noemí Fernández,[ax] Nick De Jonge,[ay] Carlo Tascini,[az] Amalia N. Anastasopoulou,[ba] Rémy Duléry,[bb] Maria Ilaria Del Principe,[bc] Gaëtan Plantefeve,[bd] Mario Virgilio Papa,[be] Marcio Nucci,[bf] Moraima Jiménez,[bg,bh] Avinash Aujayeb,[bi] José-Ángel Hernández-Rivas,[bj,bk] Maria Merelli,[az] Chiara Cattaneo,[bl] Ola Blennow,[bm] Anna Nordlander,[bm] Alba Cabirta,[bg] Gina Varricchio,[be] Maria Vittoria Sacchi,[ak] Raul Cordoba,[ab] Elena Arellano,[bn] Stefanie K. Gräfe,[b,bo,bp,bq] Dominik Wolf,[q] Ziad Emarah,[p] Emanuele Ammatuna,[l] Ditte Stampe Hersby,[i] Sonia Martín-Pérez,[g] Raquel Nunes Rodrigues,[e] Laman Rahimli,[b,bq] Livio Pagano,[x,br,bw] and Oliver A. Cornely,[a,b,c,bs,bt,bw,**] on behalf of the EPICOVIDEHA registry

[a]University of Cologne, Faculty of Medicine, and University Hospital Cologne, Chair Translational Research, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
[b]University of Cologne, Faculty of Medicine, and University Hospital Cologne, Department I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany
[c]German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Cologne, Germany
[d]Hematology and Stem Cell Transplant Unit, IRCCS Regina Elena National Cancer Institute, Rome, Italy
[e]Portuguese Institute of Oncology, Lisbon, Portugal
[f]IRCCS Ospedale San Raffaele, Milan, Italy
[g]Hospital Nuestra Señora de Sonsoles, Ávila, Spain
[h]Department of Internal Medicine, ADRZ, Goes, the Netherlands
[i]Department of Hematology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark
[j]La Paz University Hospital, Madrid, Spain
[k]CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain
[l]University Medical Center Groningen, Groningen, the Netherlands
[m]Department of Hematology, Research Unit, Hospital Universitario de Burgos, Burgos, Spain
[n]Facultad de Ciencias de la Salud, Universidad Isabel I, Burgos, Spain
[o]Ematologia con Trapianto, Ospedale Dimiccoli Barletta, Barletta, Italy
[p]Oncology Center, Mansoura University, Mansoura, Egypt
[q]Department of Hematology and Oncology, Comprehensive Cancer Center Innsbruck (CCCI), Medical University of Innsbruck (MUI), Innsbruck, Austria
[r]Department of Nephrology and Infectious Diseases, AZ Sint-Jan Brugge-Oostende AV, Brugge, Belgium
[s]Department of Oncology, Hematology and Bone Marrow Transplantation with Section of Pneumology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[t]Hematology and Stem Cell Transplant Unit, Vito Fazzi, Lecce, Italy
[u]Hospital Escuela de Agudos Dr. Ramón Madariaga, Posadas, Argentina
[v]AZ KLINA, Brasschaat, Belgium
[w]San Luigi Gonzaga Hospital - Orbassano, Orbassano, Italy
[x]Hematology Unit, Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Rome, Italy
[y]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[z]Department of Hematology, University Hospital Virgen Macarena - University Hospital Virgen del Rocío, Instituto de Biomedicina de Sevilla (IBIS / CSIC), Universidad de Sevilla (Departamento de Medicina), Seville, Spain

*Corresponding author. University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne Excellence, Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany.
**Corresponding author. University of Cologne, Faculty of Medicine and University Hospital Cologne, Cologne Excellence, Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany.
E-mail addresses: jon.salmanton-garcia@uk-koeln.de (J. Salmanton-García), oliver.cornely@uk-koeln.de (O.A. Cornely).
[bv]Shared junior authorship.
[bw]Shared senior authorship.

[aa]University Clinic of Hematology, Skopje, North Macedonia
[ab]Fundacion Jimenez Diaz University Hospital, Health Research Institute IIS-FJD, Madrid, Spain
[ac]Hospital University of Parma - Hematology and Bone Marrow Unit, Parma, Italy
[ad]Department of Hematology, University Hospital Dubrava, Zagreb, Croatia
[ae]Ospedale Policlinico San Martino, Genoa, Italy
[af]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
[ag]Department of Hematology, Hospital Universitario de Burgos, Burgos, Spain
[ah]University Clinical Center Serbia, Medical Faculty University Belgrade, Belgrade, Serbia
[ai]Hematology and Stem Cell Transplantation Unit, AOUC Policlinico, Bari, Italy
[aj]Department of Internal Medicine - Hematology and Oncology, Masaryk University Hospital Brno, Brno, Czech Republic
[ak]Azienda Ospedaliera Nazionale SS. Antonio e Biagio e Cesare Arrigo, Alessandria, Italy
[al]Istituto Oncologico della Svizzera Italiana, Bellinzona, Switzerland
[am]UOC Hematology, AORN Cardarelli, Naples, Italy
[an]Centre Hospitalier de Versailles, Le Chesnay, France
[ao]Department of Haematology, Blood Neoplasms, and Bone Marrow Transplantation, Wroclaw Medical University, Wroclaw, Poland
[ap]University Hospital Centre Rijeka, Rijeka, Croatia
[aq]Croatian Cooperative Group for Hematological Diseases (CROHEM), Croatia
[ar]Faculty of Medicine and Faculty of Health Studies University of Rijeka, Rijeka, Croatia
[as]Medizinische Klinik II, Klinikum rechts der Isar, TU München, Munich, Germany
[at]Hematology Unit, Center for Translational Medicine, Azienda USL Toscana NordOvest, Livorno, Italy
[au]Complejo Hospitalario de Navarra, Iruña-Pamplona, Spain
[av]University Hospital Centre Zagreb, Zagreb, Croatia
[aw]School of Medicine University of Zagreb, Zagreb, Croatia
[ax]Hospital Universitario Marqués de Valdecilla, Santander, Spain
[ay]Amsterdam UMC, Location VUmc, Amsterdam, the Netherlands
[az]Azienda Sanitaria Universitaria del Friuli Centrale, Udine, Italy
[ba]Laikon Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[bb]Service d'Hématologie Clinique et de Thérapie Cellulaire, Hôpital Saint Antoine, Assistance Publique-Hôpitaux de Paris, Sorbonne Université, Inserm UMRs 938, Paris, France
[bc]Hematology, Department of Biomedicine and Prevention, University of Rome Tor Vergata, Rome, Italy
[bd]Head ICU and CRC, Centre Hospitalier Victor DUPOUY, Argenteuil, France
[be]Azienda Ospedaliera Sant'Anna e San Sebastiano, Caserta, Italy
[bf]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil
[bg]Department of Hematology, Vall d'Hebron Hospital Universitari, Experimental Hematology, Vall d'Hebron Institute of Oncology (VHIO), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
[bh]Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain
[bi]Northumbria Healthcare, Newcastle, United Kingdom
[bj]Hospital Universitario Infanta Leonor, Madrid, Spain
[bk]Departmento de Medicina, Universidad Complutense de Madrid, Madrid, Spain
[bl]Hematology Unit, ASST-Spedali Civili, Brescia, Italy
[bm]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
[bn]Department of Hematology, University Hospital Virgen Macarena, Seville, Spain
[bo]I. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[bp]III. Department of Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[bq]University of Cologne, Faculty of Medicine, and University Hospital Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany
[br]Hematology Unit, Università Cattolica del Sacro Cuore, Rome, Italy
[bs]University of Cologne, Faculty of Medicine, and University Hospital Cologne, Center for Molecular Medicine Cologne (CMMC), Cologne, Germany
[bt]University of Cologne, Faculty of Medicine, and University Hospital Cologne, Clinical Trials Centre Cologne (ZKS Köln), Cologne, Germany
[bu]Université Paris-Saclay, UVSQ, Inserm, Équipe "Exposome et Hérédité", CESP, Villejuif, France

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Summary

Background **Nirmatrelvir/ritonavir treatment decreases the hospitalisation rate in immunocompetent patients with COVID-19, but data on efficacy in patients with haematological malignancy are scarce. Here, we describe the outcome of nirmatrelvir/ritonavir treatment in a large cohort of the latter patients.**

Methods **This is a retrospective cohort study from the multicentre EPICOVIDEHA registry (NCT04733729) on patients with haematological malignancy, who were diagnosed with COVID-19 between January and September 2022.**

Patients receiving nirmatrelvir/ritonavir were compared to those who did not. A logistic regression was run to determine factors associated with nirmatrelvir/ritonavir administration in our sample. Mortality between treatment groups was assessed with Kaplan–Meier survival plots after matching all the patients with a propensity score. Additionally, a Cox regression was modelled to detect factors associated with mortality in patients receiving nirmatrelvir/ritonavir.

Findings A total of 1859 patients were analysed, 117 (6%) were treated with nirmatrelvir/ritonavir, 1742 (94%) were treated otherwise. Of 117 patients receiving nirmatrelvir/ritonavir, 80% had received ≥1 anti-SARS-CoV-2 vaccine dose before COVID-19 onset, 13% of which received a 2nd vaccine booster. 5% were admitted to ICU. Nirmatrelvir/ritonavir treatment was associated with the presence of extrapulmonary symptoms at COVID-19 onset, for example anosmia, fever, rhinitis, or sinusitis (aOR 2.509, 95%CI 1.448–4.347) and 2nd vaccine booster (aOR 3.624, 95%CI 1.619–8.109). Chronic pulmonary disease (aOR 0.261, 95%CI 0.093–0.732) and obesity (aOR 0.105, 95%CI 0.014–0.776) were not associated with nirmatrelvir/ritonavir use. After propensity score matching, day-30 mortality rate in patients treated with nirmatrelvir/ritonavir was 2%, significantly lower than in patients with SARS-CoV-2 directed treatment other than nirmatrelvir/ritonavir (11%, p = 0.036). No factor was observed explaining the mortality difference in patients after nirmatrelvir/ritonavir administration.

Interpretation Haematological malignancy patients were more likely to receive nirmatrelvir/ritonavir when reporting extrapulmonary symptoms or 2nd vaccine booster at COVID-19 onset, as opposed to chronic pulmonary disease and obesity. The mortality rate in patients treated with nirmatrelvir/ritonavir was lower than in patients with targeted drugs other than nirmatrelvir/ritonavir.

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Keywords: Nirmatrelvir; SARS-CoV-2; Haematology; Malignancy; COVID-19

Research in context

Evidence before this study

Nirmatrelvir/ritonavir is a new antiviral targeting the SARS-CoV-2 3Cl protease. It is widely recommended for patients with mild symptoms to prevent severe episodes of COVID-19. A web search was performed on November 12th for articles in English, French, German, Italian, or Spanish using strings combining the terms "haemato*, "hemato*", "nirmatrelvir*", "paxlovid" with "administration", "mortality", "outcome", and "treatment". No studies focusing specifically on nirmatrelvir/ritonavir administration in haematological patients were found. Single publications targeting the general population or immunosuppressed patients were retrieved, but provided no detailed information on patients with haematological malignancy.

Added value of this study

To the best of our knowledge, this is the first publication describing the factors associated with nirmatrelvir/ritonavir administration and investigating factors associated with mortality in patients with haematological malignancy. Our results show that nirmatrelvir/ritonavir was administered more frequently to patients with extrapulmonary symptoms and those who had received a 2nd vaccine booster dose against SARS-CoV-2. On the contrary, patients with chronic pulmonary disease or obesity were less likely to receive nirmatrelvir/ritonavir. Mortality was significantly lower than in patients with other directed treatments.

Implications of all the available evidence

Clinical management of COVID-19 patients with baseline haematological malignancies remains challenging two years after onset of the pandemic. Although vaccines prevent hospitalization and reduce mortality rates, patients with haematological malignancy may not mount protective immune response. In this vulnerable immunosuppressed patient group nirmatrelvir/ritonavir treatment results in lower mortality rates as compared to other treatment approaches. Still not all patients qualifying for nirmatrelvir/ritonavir received that treatment. Reasons for underuse remain unclear at this point.

Introduction

Since the coronavirus disease 2019 (COVID-19) pandemic was declared in March 2020,[1] unprecedented efforts by all stakeholders led to effective treatment options that can ameliorate the disease. Vaccines have proved to be a most effective method preventing

hospitalisation and mortality.[2,3] Immunocompromised patients, for instance those with haematological malignancy, have been at increased risk for severe courses of COVID-19 and fatal outcome. Because of impaired immune response to vaccination, they are still at high-risk and need other approaches than current vaccines.[4–6]

Such approaches have been implemented with the antivirals molnupiravir,[7] nirmatrelvir/ritonavir,[8] and remdesivir,[9] and with the monoclonal antibodies targeting viral antigens.[10–14] The common goal of these drugs is reducing rates of hospitalisation, severe disease, and death. Approved for administration in 2022,[15,16] during the initial moments of the *omicron* wave, nirmatrelvir/ritonavir is an oral protease inhibitor administered in high-risk patients with mild symptoms early in the course of COVID-19.[15,16] Although the phase 3 development programme addressed high-risk patients, only few patients with cancer were enrolled.[8] Current consensus guidelines recommend nirmatrelvir/ritonavir in patients with haematological malignancy,[17] although there is a lack of available data on this patient group.[18]

This EPICOVIDEHA study compares epidemiology and outcome of patients with haematological malignancy receiving nirmatrelvir/ritonavir treatment versus those who did not.

Methods

All data included in this analysis were exported from the EPICOVIDEHA registry. EPICOVIDEHA (NCT04733729) is an online registry open for patients with haematologic malignancy and SARS-CoV-2 infection. Cases from various regions of the world are documented in an electronic case report form (eCRF) accessible via www.clinicalsurveys.net (EFS Summer 2021, TIVIAN, Cologne, Germany). The eCRF comprises epidemiological data, such as baseline pre-COVID-19 conditions, previous clinical management of the haematologic malignancy, anti-SARS-CoV-2 vaccination history, COVID-19 diagnosis and management, and outcome. All patients are included in a validation process for data coherence and completeness performed by experts in haematologic malignancy and infectious diseases.[19] In this validation process, data missing completely at random were reduced as possible, contacting contributors were to solve pending queries. Exclusions from the database only happened if a patient was not fulfilling all the inclusion criteria (no haematological malignancy, not active within the last 5 years prior to COVID-19, no adult, no laboratory-based COVID-19 diagnosis).

For the present analysis, patients needed to fulfil all inclusion criteria to be eligible: active haematologic malignancy within the last five years prior to COVID-19, including patients at onset or watch and wait; age ≥18 years; SARS-CoV-2 infection confirmed by either polymerase chain reaction (PCR) or antigen test; and SARS-CoV-2 diagnosis between January 1st and September 30th, 2022.

Selected patients were grouped according to treatment specifically received for COVID-19. Thus, we formed the following categories: patients treated with nirmatrelvir/ritonavir ± other directed or non-directed treatments, patients receiving other SARS-CoV-2 directed antivirals or monoclonal antibodies ± other non-directed treatments, and finally patients receiving neither directed antivirals or monoclonal antibodies, nor corticosteroids or convalescent plasma.

Statistical analysis

Consecutive data from participating institutions were summarised with frequencies and percentages for categorical variables and with median, interquartile range (IQR) and absolute range for continuous variables. Proportion comparisons were performed using Fisher's exact or Pearson's chi (X) squared tests, respectively. Logistic regression was utilised to determine which independent variables were associated with subsequent nirmatrelvir/ritonavir administration. For comparison analyses, patients were matched with a propensity score based on a logistic regression. The model included the variables sex, age (±10 years), baseline haematological malignancy, haematological malignancy status at COVID-19 onset, and origin continent (Europe). In order to determine the power and robustness of the performed propensity score, variables used for the matching were confronted with a median difference (age), Phi coefficient (sex and origin continent [Europe]), or Cramér's V (baseline haematological malignancy and haematological malignancy status at COVID-19 onset), as appropriate (Supplementary Table S1). A log-rank test was used to compare the survival probability of the patients based on the treatment received for COVID-19, which was graphically represented with a Kaplan–Meier survival plot. Additionally, Cox regression was used to analyse which factor could be associated with mortality both in every patient and in nirmatrelvir/ritonavir recipients who had data on duration of follow up. Variables with a p value < 0.1 in the univariable models were considered for the respective multivariable model. P value < 0.05 was considered statistically significant.

Ethics statement

The central ethics committee is at Fondazione Policlinico Universitario Agostino Gemelli - IRCCS, Università Cattolica del Sacro Cuore of Rome, Italy (Study ID: 3226). Additionally, each participating institution may also have a local approval for the research initiative as appropriate. The anonymized data that do not contain any personally identifiable information from any sources implies that the informed consent is not applicable.

Role of the funding source
The funders had no role in the study design, the collection, analysis, and interpretation of data, writing of the report and the decision to submit for publication. JSG, FM, LP, and OAC had access to and verified all raw data sets and made the decision to submit the manuscript.

Results
This EPICOVIDEHA data set comprises 1859 patients with haematological malignancy from 84 centres in 28 countries, who were diagnosed with COVID-19 between January and September 2022 (Fig. 1A).

Overall cohort
Almost 60% of the patients were male (n = 1070, 57.6%), and often with no other comorbidities (n = 766, 41.2%) besides haematological malignancy. Non-Hodgkin lymphoma (n = 602, 32.5%) was the most frequent haematological malignancy, followed by multiple myeloma (n = 337, 18.1%). Only one in four documented patients (n = 501, 26.9%) had active malignancy when COVID-19 was diagnosed. Overall, 69.0% (n = 1282) had received antineoplastic treatment within the preceding three months, or hematopoietic stem-cell transplantation or chimeric antigen receptor T cell administration within the last six months before COVID-19 diagnosis. The overall vaccination rate was 76.9% (n = 1430). Of 1118/1859 (60.1%) patients receiving directed treatment for COVID-19, 117/1118 (10.5%) received nirmatrelvir/ritonavir, either as monotherapy (n = 93/117, 79.5%) or in combination with other recommended drugs (n = 24/117, 20.5%), while 1001/1118 (89.5%) patients received treatment schemes without nirmatrelvir/ritonavir. A total of 741/1859 (39.9%) patients did not receive SARS-CoV-2 directed treatment. In total, intensive care was delivered to 148 (8.0%) patients (Table 1, Table 2).

In univariable logistic regression, nirmatrelvir/ritonavir treatment was associated with a patient without history of chronic pulmonary disease (odds ratio [OR] 0.341, 95% confidence interval [CI] 0.136–0.852), without obesity (OR 0.110, 95% CI 0.015–0.796), with extrapulmonary (i.e., anosmia, fever, rhinitis, or sinusitis) symptoms at COVID-19 onset (OR 2.102, 95% CI 1.278–3.457), and receipt of a second booster/4th dose (OR 3.434, 95% CI 1.674–7.045). In the multivariable model, patients with extrapulmonary symptoms (aOR 2.509, 95% CI 1.448–4.347) and those having received a 4th vaccine dose (aOR 3.624, 95% CI 1.619–8.109) were more likely to be treated with nirmatrelvir/ritonavir, while patients with chronic pulmonary disease (adjusted OR [aOR] 0.261, 95% CI 0.093–0.732) and obesity (aOR 0.105, 95% CI 0.014–0.776) were not (Table 3).

After matching the patients from the three treatment groups by sex, age (±10 years), baseline haematological malignancy, haematological malignancy status at COVID-19 onset, and origin continent (Europe), the day-30 mortality rate was 2.0% (n = 2/102) after nirmatrelvir/ritonavir administration, 10.8% (n = 11/102) after the administration of directed treatment options other than nirmatrelvir/ritonavir, and 5.9% (n = 6/102) in patients without treatment administration (p = 0.036, Table 4, Supplementary Table S2). Survival probability was significantly higher in patients treated with nirmatrelvir/ritonavir as compared to those with directed treatment options other than nirmatrelvir/ritonavir (p = 0.008, Fig. 2A and B).

Sensitivity analyses we performed to determine which factors were associated to mortality in all the matched patients. Thus, we could observe how, in the univariable analyses, administration of directed drugs other than nirmatrelvir/ritonavir was associated with an increased mortality (p = 0.046), as compared to nirmatrelvir/ritonavir. Nevertheless, the factor more greatly associated with mortality in the analysed patients, either in the univariable or in multivariable analyses was the hospital, especially to ICU (Supplementary Tables S3 and S4). Nirmatrelvir/ritonavir administration remained as a protective factor in the coupled multivariable analyses performed considering the COVID-19 treatment and the variables observed to have a $p < 0.1$ in the univariable models when including in couples COVID-19 treatment and age, comorbidities, neutrophils, status of the malignancy at COVID-19 onset and symptoms at COVID-19 onset, respectively (Supplementary Tables S5 and S6).

Nirmatrelvir/ritonavir recipients
The majority of the 117 patients receiving nirmatrelvir/ritonavir was male (n = 61, 51.7%). Non-Hodgkin lymphoma (n = 37/117, 31.6%) and multiple myeloma (n = 25/117, 21.4%) were the baseline haematological malignancy in more than half of the patients, 24.8% (n = 29/117) of which had active malignancy at COVID-19 onset. Immuno-chemotherapy (n = 49/117, 41.9%), targeted therapy (n = 23/117, 19.7%) and conventional chemotherapy (n = 16/117, 13.7%) were the most common HM treatment strategies administered immediately before infection diagnosis. Only 3.4% (n = 4/117) of the patients received no haematological malignancy treatment any time before COVID-19, all due to a contemporaneous diagnosis of malignancy and infection (Table 1).

In the unmatched populations, the proportion of patients without any additional comorbidity at COVID-19 onset was higher in patients with nirmatrelvir/ritonavir (n = 53/117, 45.3%) than in those receiving other directed drugs (n = 371/1001, 37.1%, p = 0.007), with no difference between nirmatrelvir/ritonavir patients and those with no treatment/non-SARS-CoV-2 directed treatment (n = 342/741, 46.2%, p = 0.618). Among the patients with at least one comorbidity, chronic cardiopathy was the most frequent (n = 48/117, 41.0%), similar

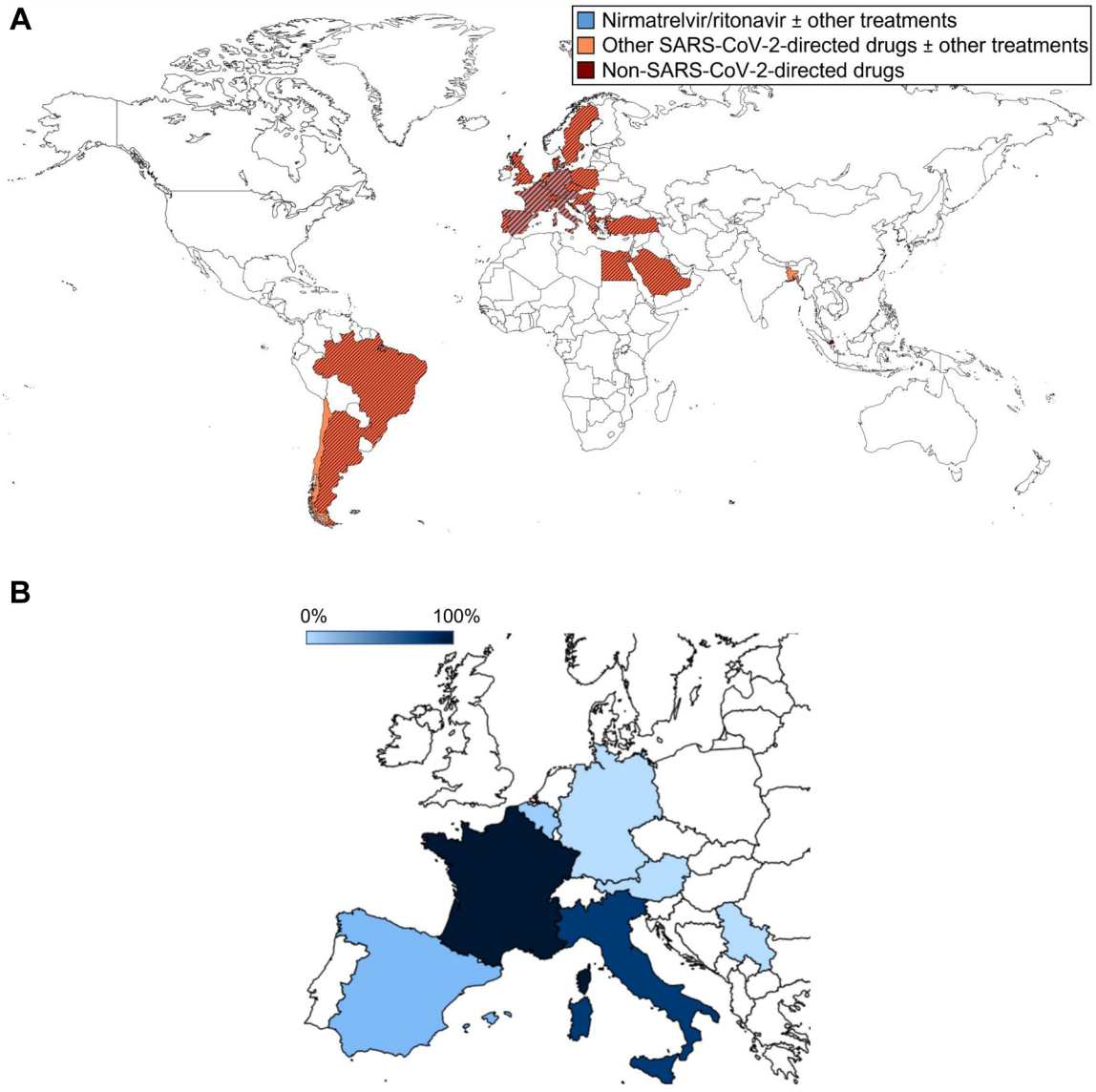


Fig. 1: **Geographical distribution of patients documented in 2022 in EPICOVIDEHA according to the treatment received for COVID-19.** A) Overall sample. This figure includes patients from institutions worldwide. Countries with patterns of more than one colour indicate that more than one type of treatment has been administered in the respective country. Blue indicates patients with nirmatrelvir/ritonavir ± other treatments: Italy (n = 59), Spain (n = 31), Belgium (n = 13), Germany (n = 7), France (n = 5), and Austria and Serbia (n = 1, each). Orange indicates patients with other SARS-CoV-2-directed drugs ± other treatments: Italy (n = 284), Spain (n = 162), Denmark (n = 73), Netherlands (n = 59), Germany (n = 51), Croatia (n = 36), Egypt (n = 33), Hungary (n = 32), Austria (n = 31); Belgium and France (n = 29, each), North Macedonia (n = 23), Serbia (n = 20), Czech Republic (n = 19), Greece (n = 18), Argentina, Poland, and Portugal (n = 16, each), Switzerland (n = 13), United Kingdom (n = 11), Sweden (n = 8), Turkey (n = 7), Brazil and Saudi Arabia (n = 6, each), and Bangladesh, Chile, and Hong Kong SAR (n = 1, each). Brown indicates patients with non-SARS-CoV-2-directed drugs: Spain (n = 192), Italy (n = 166), Netherlands (n = 105), Portugal (n = 80), Belgium (n = 35), Croatia (n = 26), France (n = 23), Argentina (n = 20), Austria (n = 15), Egypt (n = 14), Hungary (n = 11), Germany (n = 10), North Macedonia (n = 9), Switzerland (n = 7), Brazil (n = 6), Greece (n = 5), Turkey (n = 4), Serbia (n = 3), Denmark, Poland, and Sweden (n = 2, each), and Czech Republic, Saudi Arabia, Singapore, and United Kingdom (n = 1, each). B) Proportional ambulatory administration of nirmatrelvir/ritonavir. This figure includes patients from European institutions. The darker the blue, the higher proportion of patients receiving ambulatory nirmatrelvir/ritonavir: France (5/5) 100.0%, Italy (48/59) 81.4%, Spain (5/29) 17.2%, Belgium (1/13) 7.7%, and Austria (0/1), Germany (0/7), and Serbia (0/1) 0.0%, each.

	Directed treatment other than N/R		p value N/R vs other directed treatment	N/R		p value N/R vs no/other non-directed tx	No treatment/non-SARS-CoV-2 directed treatment		Overall	
	n	%		n	%		n	%	n	%
Sex			0.112			0.618				
Female	400	40.0		56	47.9		333	44.9	789	42.4
Male	601	60.0		61	51.7		408	55.1	1070	57.6
Age	66 (53–75) [18–95]		0.858	66 (55–75) [22–88]		0.165	63 (51–74) [19–97]		65 (52–75) [18–97]	
Comorbidities at COVID-19 onset										
No comorbidities	371	37.1	**0.007**	53	45.3	0.618	342	46.2	766	41.2
1 comorbidity	320	32.0		40	34.2		248	33.5	608	32.7
2 comorbidities	192	19.2		22	18.8		102	13.8	316	17.0
3 or more comorbidities	118	11.8		2	1.7		49	6.6	169	9.1
Chronic cardiopathy	405	40.5	0.921	48	41.0	0.176	255	34.4	708	38.1
Chronic pulmonary disease	116	11.6	**0.017**	5	4.3	0.077	70	9.4	191	10.3
Diabetes mellitus	130	13.0	0.187	10	8.5	0.623	77	10.4	217	11.7
Liver disease	44	4.4	0.469	3	2.6	0.789	28	3.8	75	4.0
Obesity	73	7.3	**0.005**	1	0.9	0.072	33	4.5	107	5.8
Renal impairment	67	6.7	**0.039**	2	1.7	0.298	31	4.2	100	5.4
Smoking history	136	13.6	0.387	12	10.3	0.472	60	8.1	208	11.2
Baseline malignancy at COVID-19 onset			0.432			0.635				
Leukemia	393	39.3		49	41.9		282	38.1	724	38.9
Acute myeloid leukemia	152	15.2		17	14.5		62	8.4	231	12.4
Chronic myeloid leukemia	15	1.5		4	3.4		36	4.9	55	3.0
Acute lymphoid leukemia	58	5.8		8	6.8		35	4.7	101	5.4
Chronic lymphoid leukemia	107	10.7		5	4.3		97	13.1	209	11.2
Myelodisplastic syndrome	58	5.8		14	12.0		50	6.7	122	6.6
Hairy cell leukemia	3	0.3		1	0.9		2	0.3	6	0.3
Lymphoma	392	39.2		38	32.5		257	34.7	687	37.0
Hodgkin lymphoma	39	3.9		1	0.9		45	6.1	85	4.6
Non-Hodgkin lymphoma	353	35.3		37	31.6		212	28.6	602	32.4
PH negative myeloproliferative diseases	28	2.8		5	4.3		51	6.9	84	4.5
Essential thrombocythemia	2	0.2		0	0.0		19	2.6	21	1.1
Myelofibrosis	20	2.0		3	2.6		15	2.0	38	2.0
Polycythemia vera	4	0.4		1	0.9		14	1.9	19	1.0
Systemic mastocytosis	2	0.2		1	0.9		3	0.4	6	0.3
Plasma cell disorders	179	17.9		25	21.4		143	19.3	347	18.7
Multiple myeloma	175	17.5		25	21.4		137	18.5	337	18.1
Amyloid light-chain amyloidosis	4	0.4		0	0.0		6	0.8	10	0.5
Other hematological malignancies	9	0.9		0	0.0		10	1.3	19	1.0
Aplastic anemia	9	0.9		0	0.0		10	1.3	19	1.0
Status malignancy at COVID-19 onset			0.234			0.065				
Controlled disease	473	47.3		64	54.7		397	53.6	934	50.2
Stable disease	188	18.8		19	16.2		175	23.6	382	20.5
Active disease	314	31.4		29	24.8		158	21.3	501	26.9
Unknown	26	2.6		5	4.3		11	1.5	42	2.3
Last haematological malignancy treatment immediately before COVID-19 onset										
No treatment	85	8.5		4	3.4		95	12.8	184	9.9
alloHSCT	65	6.5		6	5.1		32	4.3	103	5.5
In the last 6 months	32	3.2		1	0.9		14	1.9	47	2.5
>6 months	32	3.2		5	4.3		18	2.4	55	3.0
Unknown	1	0.1		0	0.0		0	0.0	1	0.1

(Table 1 continues on next page)

	Directed treatment other than N/R		p value N/R vs other directed treatment	N/R		p value N/R vs no/other non-directed tx	No treatment/non-SARS-CoV-2 directed treatment		Overall	
	n	%		n	%		n	%	n	%
(Continued from previous page)										
autoHSCT	16	1.6		5	4.3		5	0.7	26	1.4
In the last 6 months	13	1.3		3	2.6		4	0.5	20	1.1
>6 months	3	0.3		2	1.7		1	0.1	6	0.3
CAR-T	11	1.1		1	0.9		3	0.4	15	0.8
In the last 6 months	4	0.4		0	0.0		2	0.3	6	0.3
>6 months	7	0.7		1	0.9		1	0.1	9	0.5
Conventional chemotherapy	300	30.0		26	22.2		209	28.2	535	28.8
In the last month	129	12.9		10	8.5		82	11.1	221	11.9
In the last 3 months	146	14.6		13	11.1		92	12.4	251	13.5
>3 months	20	2.0		3	2.6		35	4.7	58	3.1
Unknown	5	0.5		0	0.0		0	0.0	5	0.3
Demethylating agents	57	5.7		7	6.0		41	5.5	105	5.6
In the last month	43	4.3		5	4.3		34	4.6	82	4.4
In the last 3 months	11	1.1		0	0.0		6	0.8	17	0.9
>3 months	3	0.3		0	0.0		1	0.1	4	0.2
Unknown	0	0.0		2	1.7		0	0.0	2	0.1
Immuno-chemotherapy	351	35.1		49	41.9		238	32.1	638	34.3
In the last month	229	22.9		34	29.1		156	21.1	419	22.5
In the last 3 months	42	4.2		5	4.3		24	3.2	71	3.8
>3 months	79	7.9		10	8.5		57	7.7	146	7.9
Unknown	1	0.1		0	0.0		1	0.1	2	0.1
Immunotherapy	46	4.6		1	0.9		34	4.6	81	4.4
In the last month	25	2.5		1	0.9		17	2.3	43	2.3
In the last 3 months	10	1.0		0	0.0		6	0.8	16	0.9
>3 months	9	0.9		0	0.0		11	1.5	20	1.1
Unknown	2	0.2		0	0.0		0	0.0	2	0.1
Supportive measures	16	1.6		5	4.3		19	2.6	40	2.2
In the last month	3	0.3		1	0.9		1	0.1	5	0.3
In the last 3 months	2	0.2		0	0.0		0	0.0	2	0.1
>3 months	1	0.1		0	0.0		0	0.0	1	0.1
Unknown	10	1.0		4	3.4		18	2.4	32	1.7
Targeted therapy	183	18.3		23	19.7		147	19.8	353	19.0
In the last month	138	13.8		21	17.9		116	15.7	275	14.8
In the last 3 months	19	1.9		0	0.0		9	1.2	28	1.5
>3 months	17	1.7		0	0.0		16	2.2	33	1.8
Unknown	9	0.9		2	1.7		6	0.8	17	0.9
Neutrophils at COVID-19 onset			0.704			0.708				
<501	91	9.1		8	6.8		29	3.9	128	6.9
501–999	58	5.8		6	5.1		33	4.5	97	5.2
>999	758	75.7		91	77.8		459	61.9	1308	70.4
Lymphocytes at COVID-19 onset			**0.044**			0.180				
<201	124	12.4		9	7.7		22	3.0	155	8.3
201–499	166	16.6		12	10.3		57	7.7	235	12.6
>499	618	61.7		84	71.8		436	58.8	1138	61.2
SARS-CoV-2 vaccination status at COVID-19 onset										
Overall days from last dose administration to COVID-19 onset	127 (73–203) [2–532]		**<0.001**	174 (121–235) [14–482]		**<0.001**	116 (70–191) [3–372]		126 (75–201) [2–532]	
Number of doses			**0.003**			**0.040**				
Not vaccinated	258	25.8		23	19.7		148	20.0	429	23.1
One dose	32	3.2		3	2.6		27	3.6	62	3.3
Days from last dose administration to COVID-19 onset	231 (123–275) [5–461]			110 (23–394) [23–394]			163 (108–247) [6–368]		195.5 (110–258) [5–461]	

(Table 1 continues on next page)

	Directed treatment other than N/R		p value N/R vs other directed treatment	N/R		p value N/R vs no/other non-directed tx	No treatment/non-SARS-CoV-2 directed treatment		Overall	
	n	%		n	%		n	%	n	%
(Continued from previous page)										
Two doses	208	20.8		15	12.8		165	22.3	388	20.9
Days from last dose administration to COVID-19 onset	233 (161–276) [8–425]			305 (166–365) [39–482]			198 (141–244) [7–355]		212 (153–267) [7–482]	
Three doses	454	45.4		61	52.1		351	47.4	866	46.6
Days from last dose administration to COVID-19 onset	97 (57–134) [2–532]			155 (111–190) [14–286]			90 (56–123) [3–372]		98 (59–135) [2–532]	
Four doses	49	4.9		15	12.8		50	6.7	114	6.1
Days from last dose administration to COVID-19 onset	188 (155–216) [94–297]			234 (197–260) [104–295]			197 (164.5–234) [84–293]		193 (161–234) [84–297]	
Type of last vaccine										
mRNA	683	68.2		92	78.6		547	73.8	1322	71.1
BioNTech/Pfizer	548	54.7		75	64.1		408	55.1	1031	55.5
Moderna COVE	135	13.5		17	14.5		139	18.8	291	15.7
Vector-based	38	3.8		1	0.9		39	5.3	78	4.2
AstraZeneca Oxford	29	2.9		1	0.9		18	2.4	48	2.6
Sputnik	5	0.5		0	0.0		6	0.8	11	0.6
J&J - Janssen	4	0.4		0	0.0		15	2.0	19	1.0
Inactivated	18	1.8		1	0.9		5	0.7	24	1.3
CoronaVac | Sinovac	5	0.5		0	0.0		1	0.1	6	0.3
Sinopharm	13	1.3		1	0.9		4	0.5	18	1.0

This table includes patients from institutions worldwide. alloHSCT, allogeneic hematopoietic stem-cell transplantation; autoHSCT, autologous hematopoietic stem-cell transplantation; CAR-T, chimeric antigen receptor T cells; COVE, coronavirus efficacy; COVID-19, coronavirus 2019 disease; J&J, Johnson and Johnson; mRNA, messenger ribonucleic acid; N/R, nirmatrelvir/ritonavir; PH, Philadelphia; tx, treatment. Reasons for no vaccination in nirmatrelvir/ritonavir: unknown (n = 23, 100.0%). Reasons for no vaccination in other SARS-CoV-2-directed drugs: unknown (n = 216, 83.7%), patient refusal (n = 24, 9.3%), ongoing malignancy treatment (n = 14, 5.4%), and other reasons (n = 4, 1.6%). Reasons for no vaccination in non-SARS-CoV-2-directed drugs: unknown (n = 129, 87.2%), patient refusal (n = 14, 9.5%), ongoing malignancy treatment (n = 4, 2.7%), and other reasons (n = 1, 0.7%).

Table 1: **Baseline characteristics of EPICOVIDEHA patients after licensing of nirmatrelvir/ritonavir.**

proportion to other patients (other directed drugs n = 405/1001, p = 0.921; no targeted drugs n = 255/741, p = 0.176). As compared to patients receiving other directed drugs against SARS-CoV-2, patients receiving nirmatrelvir/ritonavir had a lower proportion of chronic pulmonary diseases (n = 5/117, 4.3% versus n = 116/1001, 11.6%, p = 0.017), obesity (n = 1/117, 0.9% versus n = 73/1001, 7.3%, p = 0.005) and renal impairment (n = 2/117, 1.7% versus n = 67/1001, 6.7%, p = 0.039). No significant differences were observed between patients with nirmatrelvir/ritonavir and those with no treatment/non-SARS-CoV-2 directed treatment. Up to 80.3% (n = 94/117) had received at least one anti-SARS-CoV-2 vaccine dose preceding infection onset, a higher frequency than the 74.2% (n = 743/1001) in patients with other directed drugs (p = 0.003). Compared to patients with no treatment/non-SARS-CoV-2 directed treatment, patients with nirmatrelvir/ritonavir had received more frequently four vaccine doses (n = 15/117, 12.8% versus n = 50/741, 6.7%, p = 0.040, Tables 1 and 2). After matching, statistically significant differences were observed between patients in lymphocyte levels at COVID-19 onset (p < 0.001), number of vaccine doses (p = 0.047), and symptoms at COVID-19 onset (p = 0.001, Table 4, Supplementary Table S2).

COVID-19 was diagnosed after a median of 174 days (IQR 121–235) since last vaccination. Thirteen (11.1%) patients out of 117 remained asymptomatic during the entire COVID-19 episode, whereas 38/117 (32.5%) had mild symptoms, 60/117 (51.3%) progressed to severe disease, and 6/117 (5.1%) to a critical condition (Table 2).

In unmatched patients with directed drugs other than nirmatrelvir/ritonavir, there were similar percentages of asymptomatic (n = 145/1001, 14.5%) and severely sick patients (556/1001, 55.5%), but fewer mild infections (176/1001, 17.6%) and more critical evolutions (124/1001, 12.4%) (p < 0.001). Patients with no treatment or no SARS-CoV-2 directed drugs, had a higher rate of asymptomatic courses (n = 211/741, 28.5%), and lower rates of mild (n = 185/741, 25.0%), severe (n = 327/741, 44.1%) and critical infections (n = 18/741, 2.4%) than patients with nirmatrelvir/ritonavir (p < 0.001). After matching the patients by sex,

	Directed treatment other than N/R		p value N/R vs other directed treatment	N/R		p value N/R vs no/other non-directed tx	No treatment/non-SARS-CoV-2 directed treatment		Overall	
	n	%		n	%		n	%	%	n
SARS-CoV-2 variant of concern			0.139			1.000				
Wild type	1	0.1		0	0.0		1	0.1	2	0.1
Delta	7	0.7		0	0.0		1	0.1	8	0.4
Omicron	479	47.9		44	37.6		281	37.9	804	43.2
Not tested	514	51.3		73	62.4		458	61.8	1045	56.2
Symptoms at COVID-19 onset			**0.001**			**<0.001**				
Pulmonary	145	14.5		34	29.1		220	29.7	399	21.5
Pulmonary + extrapulmonary	176	17.6		32	27.4		121	16.3	329	17.7
Extrapulmonary	556	55.5		38	32.5		178	24.0	772	41.5
Screening	124	12.4		13	11.1		222	30.0	359	19.3
COVID-19 infection			**<0.001**			**<0.001**				
Asymptomatic	145	14.5		13	11.1		211	28.5	369	19.8
Mild infection	176	17.6		38	32.5		185	25.0	399	21.5
Severe infection	556	55.5		60	51.3		327	44.1	943	50.7
Critical infection	124	12.4		6	5.1		18	2.4	148	8.0
Stay during COVID-19 episode			**<0.001**			**<0.001**				
Home	264	26.4		59	50.4		554	74.8	877	47.2
Hospital	736	73.5		56	47.9		182	24.6	974	52.4
Overall days of hospital stay	12 (7–21) [1–135]		**<0.001**	8 (1–15) [1–57]	0.975	7 (2–15) [1–118]	11 (6–20) [1–135]			
ICU admission	124	12.4	**0.021**	6	5.1	0.124	18	2.4	148	8.0
Overall days in ICU	9 (5–14) [1–68]		0.609	7 (3–11) [2–32]		0.323	3 (2–11) [1–24]		9 (4–14) [1–68]	
COVID-19 treatment										
Days under COVID-19 treatment	2 (1–4) [1–34]			4 (4–5) [1–24]				4 (1–4) [1–34]		
Days under nirmatrelvir/ritonavir treatment				4 (4–5) [1–10]					4 (4–5) [1–10]	
Days from COVID-19 onset to nirmatrelvir/ritonavir treatment				1 (0–3) [0–151]					1 (0–3) [0–151]	
Type of treatment										
No treatment administered	0	0.0		0	0.0		741	100.0	741	39.9
Antiviral + monoclonal antibody ± corticosteroids ± plasma	141	14.1		0	0.0		0	0.0	141	7.6
Antiviral ± corticosteroids ± plasma	293	29.3		0	0.0		0	0.0	293	15.8
Corticosteroids	242	24.2		0	0.0		0	0.0	242	13.0
Monoclonal antibodies ± plasma ± corticosteroids	305	30.5		0	0.0		0	0.0	305	16.4
Nirmatrelvir combination therapy ± corticosteroids ± plasma	0	0.0		24	20.5		0	0.0	24	1.3
1st line	0	0.0		7	6.0		0	0.0	7	0.4
Other line	0	0.0		17	14.5		0	0.0	17	0.9
Nirmatrelvir monotherapy ± corticosteroids ± plasma	0	0.0		93	79.5		0	0.0	93	5.0
1st line	0	0.0		93	79.5		0	0.0	93	5.0
Plasma ± corticosteroids	20	2.0		0	0.0		0	0.0	20	1.1
Outcome			**0.027**			**0.016**				
Days from COVID-19 onset to final day of follow up/death	26 (12–47) [0–219]			35 (16–64) [0–191]			27 (12–46) [0–214]		27 (13–48) [0–219]	
Alive	853	85.2	**0.023**	109	93.2	0.666	701	94.6	1663	89.5
Dead	148	14.8		8	6.8		40	5.4	196	10.5
Days from COVID-19 onset to final day of follow up	29 (14–51) [0–219]			35 (15–63) [0–191]			28 (13–46) [0–214]		29 (14–50) [0–219]	
Days from COVID-19 onset to death	16 (8–28) [0–109]			48.5 (28.5–83) [14–156]			12 (4–25) [0–127]		16 (7–30) [0–156]	

(Table 2 continues on next page)

	Directed treatment other than N/R		p value N/R vs other directed treatment	N/R		p value N/R vs no/other non-directed tx	No treatment/non-SARS-CoV-2 directed treatment		Overall	
	n	%		n	%		n	%	%	n
(Continued from previous page)										
Reason for death			0.177			0.588				
COVID-19	84	8.4		2	1.7		17	2.3	103	5.5
COVID-19 + hematological malignancy	46	4.6		4	3.4		11	1.5	61	3.3
Hematological maligancies +/– other reasons	14	1.4		2	1.7		9	1.2	25	1.3
Other reasons	4	0.4		0	0.0		3	0.4	7	0.4

This table includes patients from institutions worldwide. COVID-19, coronavirus 2019 disease; ICU, intensive care unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 2: **Characteristics of COVID-19 episodes.**

age (±10 years), baseline haematological malignancy, haematological malignancy status at COVID-19 onset, and origin continent (Europe), those with directed drugs other than nirmatrelvir/ritonavir remained with a higher prevalence of critical COVID-19 episodes ($p < 0.001$, Table 1, Table 2, Table 4, Supplementary Table S2).

Overall, nirmatrelvir/ritonavir was administered with similar frequencies to hospital in-patients (n = 59/117, 50.4%) and out-patients (n = 56/117, 47.9%). However, when analysing results by country, this significantly differed, being more common for outpatients in Italy (n = 48/59, 81.4%) versus (n = 11/59, 18.6%) in-patients rather than in Spain (24/29, 82.8% hospital versus n = 5/29, 17.2% home, $p < 0.001$, Fig. 1B). Of the 56/117 (47.9%) patients admitted to hospital, 6/117 (10.7%) required intensive care. In patients with other directed drugs, both hospitalization (n = 736/1001, 73.5%, $p < 0.001$) and intensive care (n = 124/1001, 12.4%, $p = 0.02$) were significantly more frequent. On the contrary, patients with no treatment/non-SARS-CoV-2 directed treatment were less frequently in-hospital (n = 182/741, 24.6%, $p < 0.001$), although similarly treated in intensive care (n = 18/741, 2.4%, $p = 0.12$, Table 2, Table 4, Supplementary Table S2).

Nirmatrelvir/ritonavir treatment commenced the day after COVID-19 diagnosis (median 1, IQR 0–3) and lasted a median of 4 days (IQR 4–5). Among the 24/117 (20.5%) patients receiving nirmatrelvir/ritonavir in combination with other drugs (9/24 with other antivirals, 7/24 with monoclonal antibodies and 8/24 with both) only 17/24 received it as salvage treatment (Table 2).

The overall mortality rate in nirmatrelvir/ritonavir recipients was 6.8% (n = 8/117), death was attributed to COVID-19 in 5.1% (n = 6/8) cases. In the Cox regression models, no factor stood out to be associated with mortality after administration of nirmatrelvir/ritonavir (Table 2, Table 5).

Discussion

Of 1859 patients with haematological malignancy registered in EPICOVIDEHA since the licensing of nirmatrelvir/ritonavir, 117 (6.3%) received the drug to prevent complicated courses of COVID-19.[8] Patients with extrapulmonary symptoms at COVID-19 onset and those who had received a 2nd booster dose of an mRNA vaccine were more likely to receive nirmatrelvir/ritonavir. Recipients of nirmatrelvir/ritonavir had a significantly lower mortality rate than patients with other treatment approaches. Additionally, we aimed to discover factors associated with mortality in patients receiving nirmatrelvir/ritonavir for the COVID-19 treatment, although none was observed as significant, potentially linked to the reduced sample size and overall mortality rate.

Patients with chronic pulmonary diseases and obesity were less likely to receive nirmatrelvir/ritonavir, although precisely these are patients at risk of developing more severe COVID-19,[20] and therefore being the most appropriate candidates for nirmatrelvir/ritonavir administration even in the absence of haematological malignancy.[15–17] This apparent underuse of nirmatrelvir/ritonavir may have multiple reasons explaining such results: lack of stock in hospital pharmacies and clinical practices,[21] unawareness on when and how to administer it, unidentified obstacles in prescription, or already described adverse events, such us dysgeusia, diarrhoea or emboli, or drug–drug interactions.[8,22] The performance of a similar analyses once the drug has been longer available may show broader use and may provide results more in line with the drug recommendations. In parallel, the presence of only extrapulmonary symptoms at COVID-19 was associated with nirmatrelvir/ritonavir use, following the prescription recommendations regarding target patients: mild COVID-19 episodes with high-risk for SARS-CoV-2 progression.[15–17] Those fully vaccinated including a 2nd booster dose were more likely to receive nirmatrelvir/ritonavir. Interpretations

	Univariable analysis				Multivariable analysis			
	p value	OR	95% CI		p value	OR	95% CI	
			Lower limit	Upper limit			Lower limit	Upper limit
Sex								
Female	–	–	–	–				
Male	0.101	0.725	0.494	1.065				
Age	0.521	1.004	0.992	1.016				
Comorbidities at COVID-19 onset								
Chronic cardiopathy	0.906	1.024	0.694	1.511				
Chronic pulmonary disease	**0.021**	0.341	0.136	0.852	**0.011**	0.261	0.093	0.732
Diabetes mellitus	0.173	0.626	0.319	1.228				
Liver disease	0.356	0.572	0.175	1.873				
Obesity	**0.029**	0.110	0.015	0.796	**0.027**	0.105	0.014	0.776
Renal failure	0.050	0.242	0.059	1.003	0.071	0.265	0.063	1.120
Smoking history	0.316	0.727	0.389	1.357				
No comorbidity	0.261	1.250	0.847	1.845				
Neutrophils at COVID-19 onset								
<501	–	–	–	–				
501–999	0.774	1.177	0.388	3.565				
>999	0.418	1.366	0.642	2.905				
Lymphocytes at COVID-19 onset								
<201	–	–	–	–	–	–	–	–
201–499	0.993	0.996	0.407	2.438	0.672	1.219	0.487	3.052
>499	0.085	1.873	0.917	3.824	0.050	2.080	1.000	4.329
Status malignancy at COVID-19 onset								
Controlled disease	–	–	–	–				
Stable disease	0.289	0.747	0.436	1.281				
Active disease	0.105	0.683	0.430	1.083				
Unknown	0.487	1.421	0.527	3.833				
Baseline malignancy at COVID-19 onset								
Leukaemia	–	–	–	–				
Lymphoma	0.269	0.777	0.498	1.215				
PH negative myeloproliferative diseases	0.480	1.432	0.529	3.881				
Plasma cell disorders	0.665	1.120	0.671	1.871				
Other haematological malignancies	0.999	0.000	0.000	–				
Symptoms at COVID-19 onset								
Pulmonary	–	–	–	–	–	–	–	–
Pulmonary + extrapulmonary	0.908	0.970	0.585	1.611	0.995	1.002	0.570	1.762
Extrapulmonary	**0.003**	2.102	1.278	3.457	**0.001**	2.509	1.448	4.347
Screening	0.357	0.732	0.376	1.423	0.740	0.888	0.441	1.789
SARS-CoV-2 vaccination status at COVID-19 onset								
Not vaccinated	–	–	–	–	–	–	–	–
One dose	0.937	1.052	0.299	3.700	0.654	0.706	0.154	3.233
Two doses	0.539	0.809	0.412	1.590	0.292	0.673	0.322	1.406
Three doses	0.110	1.507	0.911	2.493	0.081	1.618	0.942	2.780
Four doses	**<0.001**	3.434	1.674	7.045	**0.002**	3.624	1.619	8.109

This table includes patients from institutions worldwide. CI, confidence interval; COVID-19, coronavirus 2019 disease; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3: **Factors associated with a potential nirmatrelvir/ritonavir administration.**

range from pockets of patients with access to all management options being very well taken care of (patients receiving nirmatrelvir/ritonavir were concentrated in Western Europe, as opposed to a wider geographical spread of patients in the other groups), to effects of different vaccination schemes alleviating COVID-19 course.[4,6,23]

We observed an overall vaccination rate of 76.9%; 80.3% in patients receiving nirmatrelvir/ritonavir, 80.0% in those with no treatment/non-SARS-CoV-2

	Directed treatment other than N/R		N/R		No treatment/non-SARS-CoV-2 directed treatment		p value
	n	%	n	%	n	%	
Sex							1.000
Female	44	43.1%	44	43.1%	44	43.1%	
Male	58	56.9%	58	56.9%	58	56.9%	
Age	66 (57–74) [21–89]		67 (56–75) [22–88]		67 (58–75) [22–89]		0.913
Comorbidities at COVID-19 onset							
No comorbidities	39	38.2%	46	45.1%	36	35.3%	0.429
1 comorbidity	32	31.4%	33	32.4%	35	34.3%	
2 comorbidities	22	21.6%	21	20.6%	24	23.5%	
3 or more comorbidities	9	8.8%	2	2.0%	7	6.9%	
Chronic cardiopathy	41	40.2%	42	41.2%	38	37.3%	0.874
Chronic pulmonary disease	15	14.7%	5	4.9%	12	11.8%	0.062
Diabetes mellitus	9	8.8%	10	9.8%	9	8.8%	1.000
Liver disease	8	7.8%	3	2.9%	7	6.9%	0.397
Obesity	5	4.9%	1	1.0%	5	4.9%	0.245
Renal impairment	9	8.8%	2	2.0%	5	4.9%	0.097
Smoking history	9	8.8%	10	9.8%	16	15.7%	0.281
Baseline malignancy at COVID-19 onset							1.000
Leukemia	43	42.2%	43	42.2%	43	42.2%	
Acute myeloid leukemia	12	11.8%	15	14.7%	11	10.8%	
Chronic myeloid leukemia	3	2.9%	3	2.9%	8	7.8%	
Acute lymphoid leukemia	9	8.8%	8	7.8%	5	4.9%	
Chronic lymphoid leukemia	9	8.8%	4	3.9%	9	8.8%	
Myelodisplastic syndrome	10	9.8%	13	12.7%	10	9.8%	
Hairy cell leukemia	0	0.0%	0	0.0%	0	0.0%	
Lymphoma	34	33.3%	34	33.3%	34	33.3%	
Hodgkin lymphoma	2	2.0%	1	1.0%	4	3.9%	
Non-Hodgkin lymphoma	32	31.4%	33	32.4%	30	29.4%	
PH negative myeloproliferative diseases	3	2.9%	2	2.0%	7	6.9%	
Essential thrombocythemia	0	0.0%	0	0.0%	0	0.0%	
Myelofibrosis	2	2.0%	2	2.0%	3	2.9%	
Polycythemia vera	1	1.0%	0	0.0%	1	1.0%	
Systemic mastocytosis	0	0.0%	0	0.0%	3	2.9%	
Plasma cell disorders	21	20.6%	21	20.6%	21	20.6%	
Multiple myeloma	19	18.6%	21	20.6%	19	18.6%	
Amyloid light-chain amyloidosis	2	2.0%	0	0.0%	2	2.0%	
Other hematological malignancies	0	0.0%	0	0.0%	0	0.0%	
Aplastic anemia	0	0.0%	0	0.0%	0	0.0%	
Status malignancy at COVID-19 onset							1.000
Controlled disease	62	60.8%	62	60.8%	62	60.8%	
Stable disease	13	12.7%	13	12.7%	13	12.7%	
Active disease	27	26.5%	27	26.5%	27	26.5%	
Last hematological malignancy treatment immediately before COVID-19 onset							
No treatment	12	11.8%	4	3.9%	11	10.8%	
alloHSCT	10	9.8%	5	4.9%	5	4.9%	
In the last 6 months	5	4.9%	1	1.0%	3	2.9%	
>6 months	5	4.9%	4	3.9%	2	2.0%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
autoHSCT	2	2.0%	5	4.9%	1	1.0%	
In the last 6 months	2	2.0%	3	2.9%	0	0.0%	
>6 months	0	0.0%	2	2.0%	1	1.0%	

(Table 4 continues on next page)

	Directed treatment other than N/R		N/R		No treatment/non-SARS-CoV-2 directed treatment		p value
	n	%	n	%	n	%	
(Continued from previous page)							
CAR-T	0	0.0%	1	1.0%	0	0.0%	
In the last 6 months	0	0.0%	0	0.0%	0	0.0%	
>6 months	0	0.0%	1	1.0%	0	0.0%	
Conventional chemotherapy	12	11.8%	14	13.7%	16	15.7%	
In the last month	10	9.8%	8	7.8%	10	9.8%	
In the last 3 months	2	2.0%	3	2.9%	0	0.0%	
>3 months	0	0.0%	3	2.9%	6	5.9%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
Demethylating agents	10	9.8%	6	5.9%	6	5.9%	
In the last month	8	7.8%	4	3.9%	6	5.9%	
In the last 3 months	2	2.0%	0	0.0%	0	0.0%	
>3 months	0	0.0%	0	0.0%	0	0.0%	
Unknown	0	0.0%	2	2.0%	0	0.0%	
Immuno-chemotherapy	38	37.3%	43	42.2%	37	36.3%	
In the last month	27	26.5%	29	28.4%	27	26.5%	
In the last 3 months	5	4.9%	4	3.9%	5	4.9%	
>3 months	6	5.9%	10	9.8%	5	4.9%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
Immunotherapy	0	0.0%	1	1.0%	4	3.9%	
In the last month	0	0.0%	1	1.0%	3	2.9%	
In the last 3 months	0	0.0%	0	0.0%	1	1.0%	
>3 months	0	0.0%	0	0.0%	0	0.0%	
Unknown	0	0.0%	0	0.0%	0	0.0%	
Supportive measures	0	0.0%	5	4.9%	0	0.0%	
In the last month	0	0.0%	1	1.0%	0	0.0%	
In the last 3 months	0	0.0%	0	0.0%	0	0.0%	
>3 months	0	0.0%	0	0.0%	0	0.0%	
Unknown	0	0.0%	4	3.9%	0	0.0%	
Targeted therapy	17	16.7%	18	17.6%	24	23.5%	
In the last month	15	14.7%	17	16.7%	22	21.6%	
In the last 3 months	2	2.0%	0	0.0%	1	1.0%	
>3 months	0	0.0%	0	0.0%	1	1.0%	
Unknown	0	0.0%	1	1.0%	0	0.0%	
Neutrophils at COVID-19 onset							0.866
<501	4	3.9%	6	5.9%	3	2.9%	
501–999	4	3.9%	5	4.9%	3	2.9%	
>999	88	86.3%	80	78.4%	76	74.5%	
Lymphocytes at COVID-19 onset							<0.001
<201	15	14.7%	8	7.8%	0	0.0%	
201–499	21	20.6%	11	10.8%	9	8.8%	
>499	60	58.8%	72	70.6%	73	71.6%	
SARS-CoV-2 vaccination status at COVID-19 onset							
Overall days from last dose administration to COVID-19 onset	112 (47–173) [2–425]		173 (121–235) [14–482]		104 (57–170) [6–368]		<0.001
Number of doses							0.003
Not vaccinated	27	26.5%	20	19.6%	15	14.7%	0.047 §
One dose	2	2.0%	2	2.0%	4	3.9%	
Days from last dose administration to COVID-19 onset	175 (112–237) [112–237]		67 (23–110) [23–110]		191 (55–323) [6–368]		
Two doses	21	20.6%	14	13.7%	20	19.6%	
Days from last dose administration to COVID-19 onset	235 (83–276) [20–425]	–482	304 (166–364) [39]		208 (135–238) [7–272]		
Three doses	49	48.0%	52	51.0%	58	56.9%	
Days from last dose administration to COVID-19 onset	81 (37–125) [2–250]		154 (110–189) [14–286]		84 (51–113) [10–260]		

(Table 4 continues on next page)

	Directed treatment other than N/R		N/R		No treatment/non-SARS-CoV-2 directed treatment		p value
	n	%	n	%	n	%	
(Continued from previous page)							
Four doses	3	2.9%	14	13.7%	5	4.9%	
Days from last dose administration to COVID-19 onset	152 (125–161) [125–161]		231 (197–260) [104–295]		189 (158–193) [127–196]		
Type of last vaccine							
mRNA	74	72.5%	80	78.4%	81	79.4%	
BioNTech/Pfizer	58	56.9%	65	63.7%	59	57.8%	
Moderna COVE	16	15.7%	15	14.7%	22	21.6%	
Vector-based	0	0.0%	1	1.0%	5	4.9%	
AstraZeneca Oxford	0	0.0%	1	1.0%	4	3.9%	
Sputnik	0	0.0%	0	0.0%	0	0.0%	
J&J - Janssen	0	0.0%	0	0.0%	1	1.0%	
Inactivated	1	1.0%	1	1.0%	0	0.0%	
CoronaVac | Sinovac	0	0.0%	0	0.0%	0	0.0%	
Sinopharm	1	1.0%	1	1.0%	0	0.0%	
SARS-CoV-2 variant of concern							0.147
Wild type	1	1.0%	0	0.0%	0	0.0%	
Delta	1	1.0%	0	0.0%	0	0.0%	
Omicron	50	49.0%	38	37.3%	40	39.2%	
Not tested	50	49.0%	64	62.7%	62	60.8%	
Symptoms at COVID-19 onset							0.001
Pulmonary	35	34.3%	28	27.5%	25	24.5%	
Pulmonary + extrapulmonary	21	20.6%	30	29.4%	15	14.7%	
Extrapulmonary	21	20.6%	34	33.3%	30	29.4%	
Screening	25	24.5%	10	9.8%	32	31.4%	
COVID-19 infection							<0.001
Asymptomatic	20	19.6%	10	9.8%	29	28.4%	
Mild infection	22	21.6%	34	33.3%	32	31.4%	
Severe infection	41	40.2%	52	51.0%	40	39.2%	
Critical infection	19	18.6%	6	5.9%	1	1.0%	
Stay during COVID-19 episode							<0.001
Home	29	28.4%	53	52.0%	72	70.6%	
Hospital	73	71.6%	48	47.1%	29	28.4%	
Overall days of hospital stay	14 (7–28) [1–135]		8 (1–15) [1–57]		6 (1–11) [1–52]		<0.001
ICU admission	19	18.6%	6	5.9%	1	1.0%	<0.001
Overall days in ICU	14 (9–20) [3–54]		7 (3–11) [2–32]		(–) [-]		0.160
COVID-19 treatment							
Days under COVID-19 treatment	2 (1–4) [1–10]		4 (4–5) [1–24]				
Days under nirmatrelvir/lopinavir treatment			4 (4–5) [1–10]				
Days from COVID-19 onset to nirmatrelvir/lopinavir treatment			1 (0–3) [0–151]				
Type of treatment							
No treatment administered	0	0.0%	0	0.0%	102	100.0%	
Antiviral + monoclonal antibody ± corticosteroids ± plasma	20	19.6%	0	0.0%	0	0.0%	
Antiviral ± corticosteroids ± plasma	31	30.4%	0	0.0%	0	0.0%	
Corticosteroids	21	20.6%	0	0.0%	0	0.0%	
Monoclonal antibodies ± plasma ± corticosteroids	27	26.5%	0	0.0%	0	0.0%	
Nirmatrelvir combination therapy ± corticosteroids ± plasma	0	0.0%	23	22.5%	0	0.0%	
1st line	0	0.0%	6	5.9%	0	0.0%	
Other line	0	0.0%	17	16.7%	0	0.0%	
Nirmatrelvir monotherapy ± corticosteroids ± plasma	0	0.0%	79	77.5%	0	0.0%	
1st line	0	0.0%	79	77.5%	0	0.0%	
Plasma ± corticosteroids	3	2.9%	0	0.0%	0	0.0%	

(Table 4 continues on next page)

	Directed treatment other than N/R		N/R		No treatment/non-SARS-CoV-2 directed treatment		p value
	n	%	n	%	n	%	
(Continued from previous page)							
Outcome							
Days from COVID-19 onset to final day of follow up/death	28 (10–30) [1–30]		30 (16–30) [0–30]		28 (12–30) [0–30]		0.197
Day 30 mortality rate	11	10.8%	2	2.0%	6	5.9%	0.036
Days from COVID-19 onset to alive	30 (14–30) [1–30]		30 (16–30) [0–30]		30 (13–30) [0–30]		
Days from COVID-19 onset to death	10 (6–16) [1–28]		18 (14–22) [14–22]		13 (10–19) [7–21]		

This table includes patients from European institutions. § Sensitivity analyses on vaccination coverage proportions after propensity score-based matched paired analyses are depicted in Supplementary Table S2. alloHSCT, allogeneic hematopoietic stem-cell transplantation; autoHSCT, autologous hematopoietic stem-cell transplantation; CAR-T, chimeric antigen receptor T cells; COVE, coronavirus efficacy; COVID-19, coronavirus 2019 disease; ICU, intensive care unit; J&J, Johnson and Johnson; mRNA, messenger ribonucleic acid; N/R, nirmatrelvir/ritonavir; PH, Philadelphia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; tx, treatment.

Table 4: **Characteristics of patients and COVID-19 episodes after matching by propensity score.**

directed treatment, and 74.2% in patients with directed drugs other than nirmatrelvir/ritonavir. These vaccination rates are similar to those in the general population.[24] In line with previous experiences in immunosuppressed settings,[25] the absence of vaccination in our patients was related to an ongoing haematological malignancy treatment or to patient refusal. However, in the majority of them it was unknown the rationale. Specific studies analysing the vaccination coverage in patients with an increased risk for COVID-19-associated mortality could help to understand and overcome this situation, facilitating a close-to-full vaccination in haematological malignancy patients. With these data, one could elucidate that the variables included in the propensity score-based matching performed in our analysis (sex, age (±10 years), baseline haematological malignancy, haematological malignancy status at COVID-19 onset, and origin continent [Europe]) has made the treatment groups very homogeneous and comparable, not only in the matching variables, but also in the vaccination coverage. Additionally, the fact that all the patients were diagnosed in 2022 has facilitated a higher coverage. In order to see more detailed reasons, we may need to look patient to patient and thus, the heterogenicity of the results to be potentially obtained could have a very poor significance. Further analysis may need to focus on this aspect and we will definitely keep in mind in our prospective research.

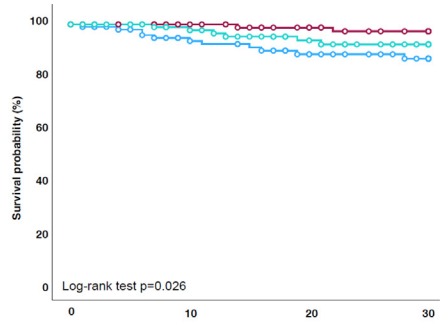
Surprisingly, the patients in our sample received nirmatrelvir/ritonavir for a median of only four days, one day less than the manufacturer recommendations, which may hint towards general shortage of the drug.[15,16] Other potential reasons may be drug–drug interactions,[26,27] adverse effects[22] or prompt recovery of symptoms. Additionally, storage and supply restrictions,[21] which can potentially end in a distribution of available doses among more patients than recommended, and difficulties in the access to the compound,[28] might have interfered with the correct number of administration days.

A retrospective study from Israel analysed factors associated with mortality in patients with high-risk of COVID-19 progression after receiving nirmatrelvir/ritonavir.[29] Immunosuppressed patients showed increased mortality, adjusted by different comorbidities (i.e., cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes mellitus, malignancy in the prior year, or neurological disease), but the authors did not differentiate haematologic malignancy from other causes of immunosuppression. Interestingly we did not identify factors associated with mortality. The high rate of vaccinated patients may have reduced death rates even in our immunosuppressed population. The 6.8% mortality rate in nirmatrelvir/ritonavir recipients, much lower than in previously reported populations without vaccination (31.2%)[5] or including pre-nirmatrelvir/ritonavir cases[4] (9.2%), jeopardises the performance of further mortality analyses.

Our study has some limitations. The retrospective design may intrinsically yield lower data quality, and the sample size is large by comparison to published studies, but still too small to allow additional subgroup comparisons. We do not capture the actual antineoplastic treatment days and doses limiting analyses of drug–drug interactions with ritonavir.[26] Finally, we have been unable to detect which factors are associated with mortality. Further analyses with a larger sample size collecting more variables, including laboratory values, might overcome these limitations.

In conclusion, patients with extrapulmonary symptoms at COVID-19 onset and a 2nd vaccine dose are more prone to receive nirmatrelvir/ritonavir as opposed to those with chronic pulmonary disease and obesity. Despite mortality in patients with nirmatrelvir/ritonavir is lower as compared to that in other treatment schemes, no statistical significance was observed. Thus, further analyses are needed to depict the factors associated to this observation.

A

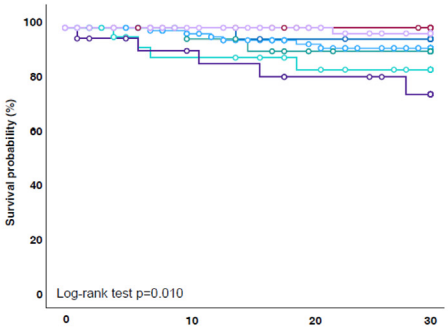


Number of patients at risk				
Directed treatment other than nirmaltrevir/ritonavir	102	79	60	49
No treatment/non-SARS-CoV-2 directed treatment	102	83	62	48
Nirmatrelvir/ritonavir	102	85	73	61

This figure includes patients from European institutions.

Log-rank test p value	Directed treatment other than nirmatrelvir/ritonavir	Nirmatrelvir/ritonavir
Nirmatrelvir/ritonavir	**0.008**	
No treatment/non-SARS-CoV-2 directed treatment	0.208	0.120

B



Number of patients at risk				
No treatment administered	102	83	62	48
AVs + MoAbs ± corticosteroids ± plasma	20	15	11	9
AVs ± corticosteroids ± plasma	31	22	18	14
Plasma ± corticosteroids	24	19	14	11
MoAbs ± plasma ± corticosteroids	27	23	17	15
Nirmatrelvir combi ± corticosteroids ± plasma	23	23	21	20
Nirmatrelvir mono ± corticosteroids ± plasma	79	62	52	41

This figure includes patients from European institutions.

Log-rank test p value	No treatment/non-SARS-CoV-2 directed treatment	Antiviral + monoclonal antibody ± corticosteroids ± plasma	Antiviral ± corticosteroids ± plasma	Plasma ± corticosteroids	Monoclonal antibodies ± plasma ± corticosteroids	Nirmatrelvir combination therapy ± corticosteroids ± plasma	Nirmatrelvir monotherapy ± corticosteroids ± plasma
Antiviral + monoclonal antibodies ± corticosteroids ± plasma	0.288						
Antiviral ± corticosteroids ± plasma	0.165	0.088					
Plasma ± corticosteroids	**0.021**	**0.039**	0.498				
Monoclonal antibodies ± plasma ± corticosteroids	0.816	0.245	0.412	0.171			
Nirmatrelvir combination therapy ± corticosteroids ± plasma	0.572	0.419	0.186	0.053	0.528		
Nirmatrelvir monotherapy ± corticosteroids ± plasma	0.112	**0.641**	**0.006**	**<0.001**	0.112	0.534	

Fig. 2: **Survival probability by COVID-19 treatment strategy.** A) Summarised treatment strategies. This table includes patients from European institutions. B) Detailed treatment strategies. This table includes patients from European institutions.

	Univariable analysis				Multivariable analysis			
	p value	HR	95% CI		p value	HR	95% CI	
			Lower limit	Upper limit			Lower limit	Upper limit
Sex								
Female	–	–	–	–				
Male	0.234	2.644	0.533	13.116				
Age	0.332	1.029	0.972	1.089				
Comorbidities at COVID-19 onset								
Chronic cardiopathy	0.063	7.479	0.900	62.169	0.092	6.761	0.731	62.532
Chronic pulmonary disease	0.619	0.044	0.000	.				
Diabetes mellitus	0.056	5.001	0.957	26.126	0.167	4.229	0.547	32.698
Liver disease	0.720	0.046	0.000	.				
Obesity	.	.	.	.				
Renal failure	0.799	0.048	0.000	.				
Smoking history	0.626	0.044	0.000	.				
No comorbidity	0.122	0.191	0.023	1.555				
Neutrophils at COVID-19 onset								
<501	–	–	–	–				
501–999	0.642	0.512	0.030	8.614				
>999	0.172	0.210	0.022	1.970				
Lymphocytes at COVID-19 onset								
<201	–	–	–	–				
201–499	0.640	0.563	0.051	6.249				
>499	0.149	0.266	0.044	1.607				
Status malignancy at COVID-19 onset								
Controlled disease	–	–	–	–	–	–	–	–
Stable disease	0.980	0.000	0.000	.	0.950	0.000	0.000	.
Active disease	0.064	4.721	0.915	24.354	0.311	2.462	0.431	14.060
Unknown	0.993	0.000	0.000	.	0.995	0.000	0.000	.
Baseline malignancy at COVID-19 onset								
Leukaemia	–	–	–	–				
Lymphoma	0.837	0.863	0.213	3.492				
PH negative myeloproliferative diseases	0.989	0.000	0.000	.				
Plasma cell disorders	0.971	0.000	0.000	.				
Symptoms at COVID-19 onset								
Pulmonary	–	–	–	–				
Pulmonary + extrapulmonary	0.966	0.968	0.212	4.419				
Extrapulmonary	0.305	0.299	0.030	3.001				
Screening	0.988	0.000	0.000	.				
SARS-CoV-2 vaccination status at COVID-19 onset								
Not vaccinated	–	–	–	–				
One dose	0.940	.	0.000	.				
Two doses	0.920	.	0.000	.				
Three doses	0.924	.	0.000	.				
Four doses	0.980	1735.991	0.000	.				
ICU admission	0.106	3.614	0.760	17.178				
Nirmatrelvir/ritonavir line								
Other line	–	–	–	–				
First line	0.997	1.003	0.188	5.349				
Days from COVID-19 onset to nirmatrelvir/ritonavir treatment	0.771	1.003	0.980	1.027				
Stay during COVID-19 episode								
Home	–	–	–	–				
Hospital	0.171	4.387	0.528	36.477				

This table includes patients from European institutions. CI, confidence interval; COVID-19, coronavirus 2019 disease; HR, hazard ratio; ICU, intensive care unit; PH, Philadelphia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 5: **Factors associated with mortality in patients with nirmatrelvir/ritonavir administration.**

Contributors

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

Data sharing statement

Data are available upon reasonable request to the corresponding authors Dr. Jon Salmanton-García (jon.salmanton-garcia@uk-koeln.de) or Prof. Dr. Oliver A. Cornely (oliver.cornely@uk-koeln.de).

Declaration of interests

The authors do not declare conflicts of interest related to the submitted manuscript. The funder of the study had no role in study design, data analysis, interpretation, or writing of the report. All authors had full access to the data and had final responsibility for the decision to submit for publication.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101939.

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