

Clinical outcomes, safety and predictors of disease progression in high-risk COVID-19 outpatients treated with nirmatrelvir/ritonavir: an Italian multicenter retrospective cohort study (PRIMA study)

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Abstract

Background Widespread vaccination, hybrid immunity following natural infection, and the Omicron variant altered COVID-19 severity, challenging oral antiviral benefits in immunocompetent populations. We characterized real-world clinical outcomes, tolerability, and predictors of disease progression among high-risk, non-hospitalized Italian adults treated with nirmatrelvir/ritonavir (N/r).

Methods This multicenter retrospective cohort study included symptomatic outpatients from 15 centers meeting high-risk criteria, who initiated N/r within five days of symptom onset. The primary outcome was 30-day all-cause hospitalization or death.

Results Among 3,916 patients (median age 66; median three vaccine doses), the 30-day composite outcome (defined as hospital admission or all-cause death) occurred in 0.9% (0.7% hospitalization, 0.4% mortality). In adjusted multivariable analyses (backward selection model), solid neoplasms (OR 6.32, 95% CI 1.91–20.87), lymphoma (OR 14.33, 95% CI 5.15–39.88) and leukemia (OR 5.81, 95% CI 1.24–27.37) emerged as the strongest independent predictors of the composite outcome. Adverse events occurred in 10.7% (mainly dysgeusia and gastrointestinal symptoms), with a 0.7% toxicity-related discontinuation rate.

Conclusions In a largely triple-vaccinated, frail outpatient cohort, early N/r was associated with few adverse events and very low rates of severe outcomes. However, patients with active solid or hematologic malignancies remain at higher risk, requiring intensified preventive and therapeutic strategies.

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Keywords COVID-19 · Nirmatrelvir/ritonavir · SARS-CoV-2 · Hematologic malignancies · Real-world study · Antiviral agents

Introduction

The clinical history of COVID-19 has changed substantially since the pandemic's outset, firstly due to widespread vaccination and secondly to accumulated hybrid immunity in immunocompetent populations, and to a lesser extent in some immunocompromised individuals. Moreover, since late 2021, the emergence of the Omicron variant (generally less virulent than earlier strains) led to even lower rates of severe disease and death in the general population [1].

Despite these advances, vulnerable populations (including immunocompromised individuals, patients with comorbidities, and older adults) remain at risk of disease progression; consequently, early administration of antiviral agents is recommended for these groups to mitigate this risk [2].

Nirmatrelvir/ritonavir (N/r) is an oral protease inhibitor regimen that received emergency use authorization based on impressive efficacy in the pivotal EPIC-HR trial with a reduction of the relative risk of COVID-19-related hospitalization or death by 89% compared to placebo among high-risk unvaccinated outpatients [3].

However, real-world evidence on the effectiveness and safety of nirmatrelvir/ritonavir (N/r) in high-risk, vaccinated patients remains limited. Moreover, the most recent randomized data have raised questions about the magnitude of its benefit in this population [4]. To address this gap, we conducted a multicenter study with two prespecified objectives: to describe the real-world clinical outcomes and tolerability of N/r, and to identify baseline predictors of severe outcomes, in a broad cohort of high-risk adults with SARS-CoV-2 infection managed in routine clinical practice.

Methods

Study design and population

We performed the PRIMA (Protease-inhibitor Real-world Italian Multicenter Analysis) study, a multicenter, retrospective cohort study that included all consecutive adult outpatients seen at 15 Italian centers between December 2021 and November 2023 who met the following criteria: (i) symptomatic COVID-19 confirmed by a validated SARS-CoV-2 antigen or PCR test, with N/r initiated within 5 days of symptom onset; (ii) no need for supplemental oxygen or hospitalization for COVID-19 at the time of first administration of oral antivirals (OAs); and (iii) high risk of disease progression, defined as age > 65 years and/or at least one of the following comorbidities: active onco-hematologic disease; chronic kidney disease with estimated glomerular filtration rate (eGFR) < 30 mL min⁻¹; Child–Pugh class A or B liver disease; severe chronic lung disease; primary or acquired immunodeficiency; body-mass index (BMI) ≥ 30 kg m⁻²; severe cardiovascular disease; hemoglobinopathy; neurodevelopmental or neurodegenerative disorder; or uncontrolled diabetes mellitus.

Data collection and definitions

We collected information on patients' demographic characteristics (age, sex), comorbid conditions (such as hypertension, heart disease, diabetes mellitus, lung disease, renal disease, neurological disease, immunodeficiency) computing the Charlson Comorbidity Index, vaccination status, time from last vaccination to infection and time from infection to therapy. Patients were classified as vaccinated if they had received at least two doses of a COVID-19 vaccine. For each patient, we calculated the Monoclonal Antibody Screening Score (MASS),

originally developed to rapidly identify and stratify patients to be prioritized for receiving monoclonal antibody according to their risk of hospitalization [5].

Outcomes

The primary outcome was a composite of hospital admission or all-cause death. Secondary outcomes were all-cause death and hospitalization considered separately. In addition, adverse events and treatment discontinuations recorded during follow-up were summarized descriptively to characterize drug tolerability. The identification of baseline predictors of the composite outcome and of its individual components was a prespecified objective, addressed through the regression models described below. The follow-up duration was 30 days from symptom onset or the first positive test for SARS-CoV-2.

Statistical analysis

In this study, categorical variables were reported as numbers and percentages, while continuous variables are presented as median values and interquartile ranges (IQRs). The Mann-Whitney U test was used to determine differences in baseline characteristics between groups for continuous variables, and Pearson's χ^2 test was used for categorical variables. Risk factors for the composite outcome, as well as for all-cause mortality and hospitalization separately, were analyzed performing a univariable analysis and using a logistic regression model after imputing missing values. To account for missing data, multivariate imputation by chained equations under fully conditional specification with predictive mean matching, under the missing at random assumption, was carried out. Imputed datasets included all variables in the analytic models and the outcome indicators, and regression estimates were combined using Rubin's rules. The number and proportion of missing values per variable, before imputation, are reported in Supplementary Table S1 and visualized in Supplementary Figure S1. After imputation, univariable analyses were performed. Then, two different models were presented: a multivariable one including all the predictors of interest (Method A), and another one refined via an automatic backward stepwise approach (Method B). All analyses were performed using SPSS version 29.0.1 and R, version 4.1.0 (R Core Team), with the following packages: *finalfit*, *mice*, *StepReg*.

Ethics

The study was approved by the ethics committee of University Federico II and Cardarelli Hospital of Naples (protocol number 14372).

Results

We enrolled 3,916 patients (see Table 1). The median age of the cohort was 66 years (interquartile range (IQR) 54–75), and the median number of SARS-CoV-2 vaccine doses received was 3 (IQR 2–3). The median time elapsed between the last vaccination and confirmed SARS-CoV-2 infection was 169 days (IQR 114–243), whereas the time from symptom onset to the first dose of N/r was 3 days (IQR 2–4). The cohort's median BMI was 25 (IQR 22–29), the median Charlson Comorbidity Index was 3 (IQR 1–4), and the median Monoclonal Antibody Screening Score (MASS) was 2 (IQR 0–3). Across the entire study population, 420 patients (10.7%) experienced at least one adverse event during N/r treatment, most commonly dysgeusia ($n=370$), diarrhea ($n=64$), nausea ($n=36$), and headache ($n=15$). A total of 91 patients (2.3%) discontinued therapy, 27 (0.7%) of them due to drug-related adverse events.

Within 30 days of symptom onset, the primary composite outcome (hospitalization or all-cause death) occurred in 36 patients (0.9%). Considered separately, 26 patients (0.7%) were hospitalized and 15 (0.4%) died.

Table 1 Baseline features of the cohort ($N=3916$)

N	3916
Age (years) [median, IQR]	66 [54–75]
Number of SARS-CoV-2 vaccine doses received [median, IQR]	3 [2–3]
Time between last vaccination and COVID-19 (days) [median, IQR]	169 [114–243]
BMI [median, IQR]	25 [22–29]
Charlson comorbidity index [median, IQR]	3 [1–4]
MASS Score [median, IQR]	2 [0–3]
Time between symptoms and first N/r administration [median, IQR]	3 [2–4]
Hematological Neoplasms (n, %)	283 (7.2%)
Adverse drug reaction (n, %)	420 (10.7%)
Headache	15 (0.4%)
Dysgeusia	370 (9.4%)
Nausea	36 (0.9%)
Vomit	13 (0.3%)
Diarrhea	64 (1.6%)
Abdominal pain	20 (0.5%)
Elevation of liver enzymes	1 (0.1%)
Drug discontinuation	91 (2.3%)
Drug discontinuation for adverse events	27 (0.7%)
Hospitalization (n)	26 (0.7%)
Death (n)	15 (0.4%)
Hospitalization or Death (n)	36 (0.9%)

IQR: interquartile range; BMI: body mass index

A descriptive comparison of baseline and clinical variables across outcome groups is reported in Supplementary Table S2. Because of missing data, multiple imputation was then performed before univariable (Supplementary Table S3) and multivariable logistic regression analyses.

At univariable analysis (Supplementary Table S3), several factors were significantly associated with the outcomes. For the composite outcome, lymphoma (odds ratio [OR] 5.94, 95% confidence interval [CI] 2.50–12.6; $p<0.001$), hematologic neoplasms (OR 5.08, 95% CI 2.31–10.3; $p<0.001$), Charlson Comorbidity Index (OR 1.34, 95% CI 1.12–1.60; $p=0.001$), MASS (OR 1.31, 95% CI 1.13–1.51; $p<0.001$), and delay in therapy (OR 1.09, 95% CI 1.02–1.17; $p=0.014$) were significantly associated with a higher likelihood of hospitalization or death. Considered separately, for hospitalization a hematologic neoplasm (OR 5.84, 95% CI 2.38–13.1; $p<0.001$), lymphoma (OR 7.64, 95% CI 2.95–17.6; $p<0.001$), and delays in treatment initiation (OR 1.12, 95% CI 1.04–1.19; $p=0.001$) emerged as strong predictors, whereas for mortality solid neoplasms (OR 6.64, 95% CI 2.06–18.8; $p<0.001$), hematologic neoplasms (OR 4.72, 95% CI 1.30–13.9; $p=0.008$), higher Charlson Comorbidity Index (OR 1.72, 95% CI 1.33–2.19; $p<0.001$), higher MASS (OR 1.31, 95% CI 1.14–1.51; $p<0.001$), and later administration of N/r (OR 1.09, 95% CI 1.02–1.17; $p=0.014$) were all significantly associated with an increased risk.

In the full multivariable model (Method A; Supplementary Table S4), solid neoplasms were the only variable that reached statistical significance, for the composite outcome (OR 5.47, 95% CI 1.21–24.7; $p=0.027$) and for death (OR 33.7, 95% CI 4.78–237; $p<0.001$), whereas no variable remained significantly associated with hospitalization. For lymphoma, leukemia and hematologic neoplasms, Method A failed to converge because of data sparseness and complete separation in some strata, producing unstable point estimates with non-informative confidence intervals (Supplementary Table S4); for these variables, results are interpretable only through the parsimonious backward model (Method B; Table 2).

In the parsimonious backward stepwise model (Method B; Table 2), the composite outcome was significantly predicted by solid neoplasms (OR 6.32, 95% CI 1.91–20.87; $p=0.002$), lymphoma (OR 14.33, 95% CI 5.15–39.88; $p<0.001$), and leukemia (OR 5.81, 95% CI 1.24–27.37; $p=0.025$). Considered separately, hospitalization was independently associated with lymphoma (OR 17.68, 95% CI 6.02–51.9; $p<0.001$) and leukemia (OR 7.32,

Table 2 Multivariable assessment after backward analysis for imputed dataset

N=3916	Hospitalization			Death			Composite outcome		
	OR ¹	95% C.I. ¹	p-value	OR ¹	95% C.I. ¹	p-value	OR ¹	95% C.I. ¹	p-value
Sex	2.56	0.87, 7.56	0.088	-	-	-	2.09	0.80, 5.44	0.128
Solid Neoplasia	3.70	0.77, 17.77	0.101	22.79	4.60, 112.80	<0.001	6.32	1.91, 20.87	0.002
Leukemia	7.32	1.49, 35.94	0.014	-	-	-	5.81	1.24, 27.37	0.025
Lymphoma	17.68	6.02, 51.9	<0.001	-	-	-	14.33	5.15, 39.88	<0.001
Hematologic Neoplasia	-	-	-	7.65	1.30, 44.76	0.023	-	-	-
Drug discontinuation	-	-	-	9.21	0.99, 85.02	0.051	-	-	-

OR: odds ratio; CI: confidence interval

95% CI 1.49–35.94; $p=0.014$), and all-cause mortality with solid neoplasms (OR 22.79, 95% CI 4.60–112.80; $p<0.001$) and hematologic neoplasms (OR 7.65, 95% CI 1.30–44.76; $p=0.023$). Figure 1 summarizes the significant multivariable predictors of severe outcomes across both models.

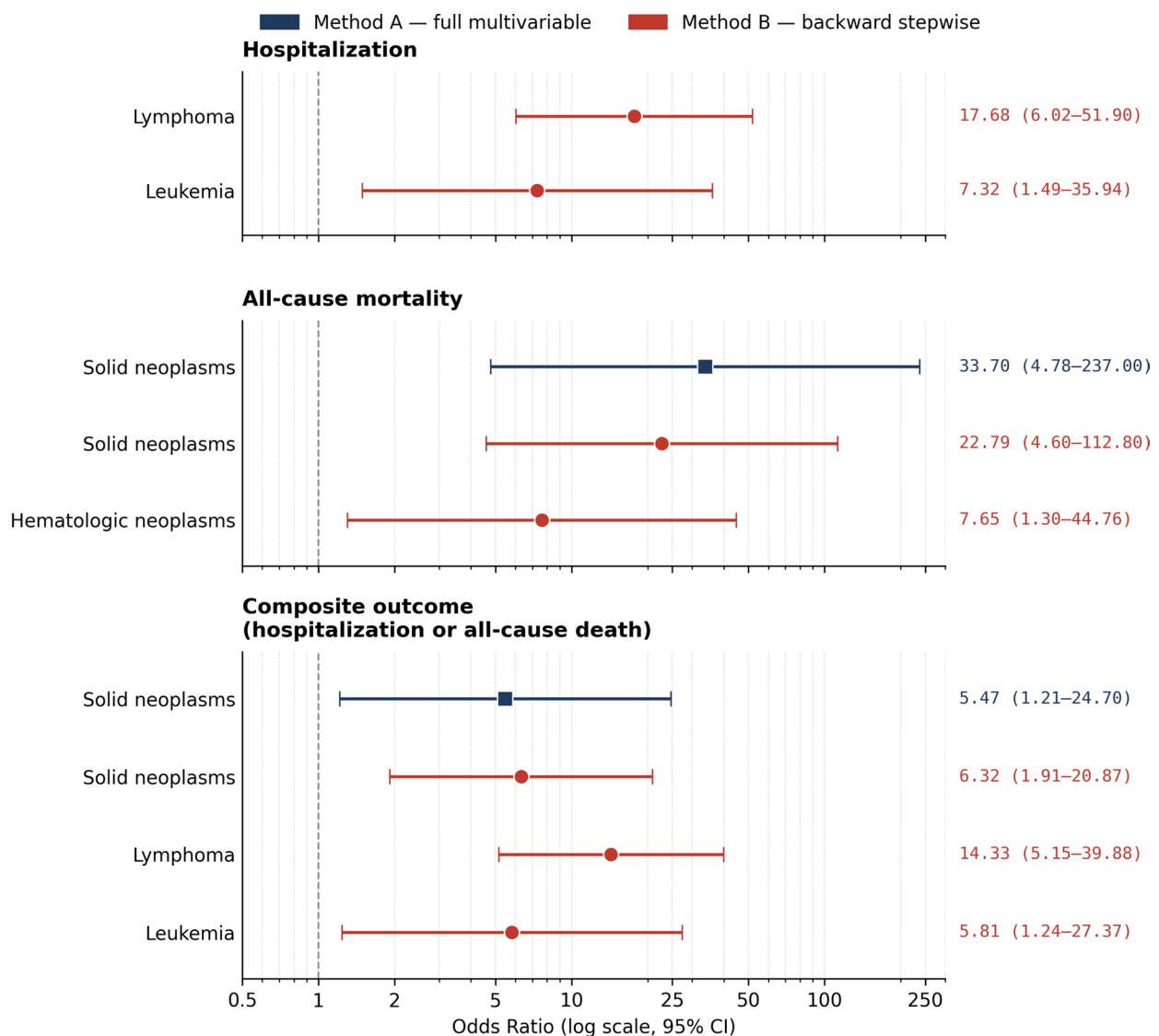
Discussion

In this multicenter real-world study, we described clinical outcomes, tolerability and predictors of severe disease in a large cohort of high-risk COVID-19 outpatients treated with nirmatrelvir/ritonavir (N/r) during the Omicron-predominant period. Our analysis was designed to describe clinical outcomes and to identify risk factors for disease progression in a vaccinated, frail outpatient population, rather than to estimate the absolute treatment effect of N/r, which would require a controlled comparator. Overall, the incidence of severe outcomes was remarkably low, with only 0.7% hospitalized and 0.4% experiencing death within 30 days of symptom onset. Our findings highlight the considerably reduced morbidity and mortality among vaccinated populations, consistent with recent literature underscoring the protective role of vaccination against severe disease outcomes. For instance, Nyberg et al. reported a significantly lower risk of hospitalization and death in vaccinated individuals compared to unvaccinated ones, especially during the Omicron variant predominance [6].

While pivotal clinical trials demonstrated impressive efficacy of N/r in unvaccinated, high-risk cohorts [3], recent studies have reported less pronounced effects in vaccinated individuals without significant risk factors. This has raised questions about the generalizability of those results to today's immunocompetent, vaccinated populations. More definitively, a recent randomized trial in a cohort of outpatients, the majority of whom were vaccinated, demonstrated that N/r did not significantly improve clinical outcomes compared to placebo [7]. However, roughly half of the enrolled were “standard-risk” and therefore without any of the traditional risk factors for severe COVID-19. More recently, two open-label platform trials in higher-risk vaccinated outpatients (PAN-ORAMIC in the United Kingdom and CanTreatCOVID in Canada) similarly did not demonstrate a reduction in hospitalization or death with N/r compared with usual care [4].

However, in a large full-matched case-control study, Gentile et al. [8] recently reported a significant reduction in mortality among patients treated with N/r regardless of vaccination status, further demonstrating that the greatest benefit occurs among unvaccinated individuals, but significant benefits remain for vaccinated patients as well. Our cohort, composed mainly of patients with a high Charlson Comorbidity Index and substantial vaccine coverage (median of 3 doses), also experienced a low absolute rate of severe outcomes, potentially reflecting hybrid immunity (vaccination combined with prior exposure) combined with early antiviral administration.

Another intriguing finding of our study concerns the timing of N/r initiation. In univariable analyses, each additional day of delay after symptom onset was associated with higher odds of hospitalization (OR 1.12, 95% CI 1.04–1.19) and of the composite outcome (OR 1.09, 95% CI 1.02–1.17). The association with all-cause death alone was unstable given the small number of deaths and should be interpreted with caution. Patients who remained event-free had started therapy a mean of 2.68 (± 1.91) days after symptoms, whereas those who



Significant multivariable predictors of severe outcomes — PRIMA study.
Method A: full multivariable model (Supplementary Table S4). Method B: backward stepwise model (Table 2).
Reference line at OR = 1 (no association).

Fig. 1 Significant multivariable predictors of severe outcomes in the PRIMA study. Forest plot showing odds ratios (OR) with 95% confidence intervals (logarithmic scale) for the variables independently associated with hospitalization, all-cause mortality, and the composite outcome (hospitalization or all-cause death). For each outcome, estimates are reported from both the full multivariable model (Method A; Supplementary Table S4) and the parsimonious backward stepwise model (Method B; Table 2). The vertical dashed line indicates OR = 1 (no association)

progressed waited $3.57 (\pm 5.14)$ days, a statistically significant difference ($p=0.001$, Supplementary Table S2). Although the association was attenuated in fully adjusted multivariable models, where malignancy-related immunosuppression dominated risk, the temporal association is biologically plausible: SARS-CoV-2 replication peaks early, and delaying protease-inhibitor exposure permits additional viral cycles that may overwhelm host defenses before therapeutic levels are reached. A possible explanation is that in onco-hematologic patients, the underlying immunosuppression and the malignancy itself may substantially diminish the effectiveness of currently available COVID-19 therapies, thereby mitigating any advantage conferred by early initiation of antiviral treatment.

In fact, in our study, despite the low rate of progression, hematologic malignancies and solid neoplasms were identified as strong predictors of hospitalization and death. This was particularly apparent from the refined multivariable model that selected a parsimonious set of covariates, while recognizing the exploratory nature of model selection in the setting of sparse outcome events. The persistence of substantial mortality among patients with active malignancies despite early antiviral therapy may reflect either treatment failure (pointing to the need for intensified strategies such as combination therapy) or a limited net antiviral benefit in some highly vulnerable subgroups; this interpretation remains hypothesis-generating and should be viewed in the context of recent randomized evidence showing no overall reduction in hospitalization or death among vaccinated higher-risk outpatients treated with N/r [4].

These findings corroborate prior studies demonstrating a higher rate of progression in oncologic and onco-hematologic patients, underscoring the need to prioritize these populations for early SARS-CoV-2 prophylaxis and treatment [2, 9–12].

Some studies have explored the effectiveness of antivirals in immunocompromised patients. A large cohort study in Hong Kong examined approximately 39,000 hospitalized COVID-19 patients (including 2,217 immunocompromised individuals) during the Omicron era. Among immunocompromised patients, N/r use was associated with a 42% reduction in post-acute mortality (HR 0.58) but this effect was significantly less pronounced than in immunocompetent patients [13]. Moreover, a report from the multicenter EPICOVIDEHA registry, based on a cohort of 1,859 patients with hematologic malignancies and SARS-CoV-2 infection, demonstrated a significantly lower 30-day mortality rate after propensity score matching in patients treated with N/r, compared to those receiving other specific COVID-19 agents or no treatment (2% vs. 10.8% and 5.9%, respectively; $p = 0.036$). It is noteworthy that in this study, N/r use was associated with a higher rate of vaccination/booster administration and the presence of extrapulmonary symptoms at COVID-19 onset [14].

In short, our findings are consistent with prior evidence suggesting that immunocompromised patients may benefit from antiviral therapy, while also showing that their residual risk of severe COVID-19 remains higher despite treatment. This diminished efficacy has been attributed to factors like high viral loads, harboring of resistant variants, and the lack of robust immune “backup” to aid antiviral drugs in clearing infection.

Given the insufficient protection conferred by vaccines and standard antivirals in onco-hematologic patients, researchers are exploring the possibility of employing combination therapies to improve outcomes [15–20].

With respect to tolerability, adverse events were observed in 10.7% of patients and toxicity-related discontinuation in 0.7%, in line with other observational reports [21, 22]. Dysgeusia, diarrhea, and nausea were the most common adverse reactions in our study, consistent with findings from other studies that also documented these symptoms as frequently reported, but typically mild and transient [23, 24].

Despite important strengths, such as its large, multicenter, real-world design, reflecting clinical practice across diverse settings, thus enhancing the generalizability of our findings, several limitations should be acknowledged.

Firstly, the observational nature of the study inherently includes potential biases and residual confounding despite multivariable adjustments. Secondly, missing data required multiple imputations, which could have introduced additional variability. Lastly, the absence of a control group limits definitive conclusions regarding treatment effectiveness, highlighting the need for further randomized controlled trials. In addition, by design this study did not collect direct pharmacodynamic markers of antiviral activity (e.g., viral clearance time, time to sustained symptom resolution, overall illness duration); accordingly, our findings should be interpreted as a description of clinical outcomes and risk stratification under routine N/r use, rather than as a measure of antiviral efficacy. Adverse events were recorded as binary occurrences (presence/absence) without information on severity grading, time to onset, management strategy or resolution; this limits the depth of the safety characterization. Selection and information bias cannot be excluded, because treated patients may have differed in access to care, clinical monitoring, and prescribing suitability, including drug–drug interaction management. SARS-CoV-2 variants were not individually sequenced, and the study period should therefore be interpreted as Omicron-predominant rather than variant-confirmed. Hospitalizations and deaths were analyzed as all-cause outcomes and were not centrally adjudicated as COVID-19-related versus attributable to underlying disease or competing conditions.

Finally, because the number of outcome events was small ($n=36$ composite events; $n=15$ deaths), multivariable estimates are vulnerable to sparse-data bias, complete separation and overfitting, and should be interpreted as exploratory risk-stratification signals rather than precise effect-size estimates.

Conclusions

This study aimed to characterize real-world clinical outcomes and to stratify the residual risk of severe disease in a large, well-vaccinated, frail Italian outpatient cohort treated with N/r, rather than to provide a direct estimate of absolute treatment efficacy. In conclusion, our multicenter real-world study recorded few adverse events and rare toxicity-related discontinuation, and was associated with low rates of severe COVID-19 outcomes, as demonstrated by the low absolute rates of hospitalization and death observed in this high-risk, well-vaccinated population. Although patients with solid or hematologic malignancies had a significantly higher residual risk, the absolute incidence of hospitalization and death within these subgroups remained low.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1186/s12879-026-14363-7>.

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Data availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the ethics committee of University Federico II and Cardarelli Hospital of Naples (protocol number 14372, approved on July 21, 2022). Informed consent was obtained from all individual participants included in the study whenever possible; for the remaining cases, a waiver of informed consent was granted by the ethics committee due to the retrospective nature of the study.

Consent for publication Informed consent for data collection and publication was obtained from all enrolled subjects in accordance with the ethics committee's requirements. For cases in which individual consent could not be obtained, a waiver was granted by the ethics committee due to the retrospective nature of the study.

Competing interests The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Andrea Antinori (AA): Received consultancy fees from AstraZeneca, Bavarian Nordic, Gilead Sciences, GSK, Janssen-Cilag, Merck, Moderna, Pfizer, and ViiV Healthcare; and institutional research grants from AstraZeneca, Gilead Sciences, and ViiV Healthcare. Anna Maria Cattelan (AMC): Received fees for advisory boards and travel grants from Angelini, Gilead Sciences, Janssen, MSD, and ViiV Healthcare. Ivan Gentile (IG): Served as a consultant for AbbVie, Angelini, Gilead Sciences, GSK, MSD, Nordic, Pfizer, and SOBI; and received departmental/project funding from Gilead Sciences. Lichtner: Reports financial relationships with AbbVie, AstraZeneca, Gilead Sciences, InfectoPharm, Menarini, Merck, and ViiV Healthcare. Mastroianni: Reports financial relationships with AbbVie, AstraZeneca, Gilead Sciences, GSK, Menarini, Pfizer, and Shionogi. Valentina Mazzotta (VM): Received support for conference participation from AstraZeneca and GSK; served as a paid consultant for AstraZeneca, Gilead Sciences, GSK, Pfizer, Viatris, and ViiV Healthcare; and received institutional research funding from Gilead Sciences. Emanuele Nicastrì (EN): Received travel grants from Gilead Sciences and PharmaMar; serves on the advisory boards for Valneva and Takeda; and received presentation and consultation fees from Gilead Sciences and Roche. The remaining authors declare that they have no conflict of interest.

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