Oral Nirmatrelvir and Ritonavir in Non-hospitalized Vaccinated Patients with Covid-19

Sarju Ganatra MD[1*], Sourbha S. Dani, MD, MSc,[1*] Javaria Ahmad, MD[1], Ashish Kumar, MD[2], Jui Shah, MD[1], George M. Abraham, MD, MPH[3], Daniel P. McQuillen, MD[5], Robert M. Wachter, MD[5], Paul E. Sax, MD[6]

*Authors have contributed equally.

1. Division of Cardiovascular Medicine, Department of Medicine, Lahey Hospital and Medical Center, Beth Israel Lahey Health, Burlington, MA, USA
2. Department of Medicine, Cleveland Clinic Akron General, Akron, OH, USA
3. Division of Infectious Disease, Department of Medicine, Saint Vincent Hospital, Worcester, MA, USA
4. Division of Infectious Disease, Department of Medicine, Lahey Hospital and Medical Center, Beth Israel Lahey Health, Burlington, MA, USA
5. Department of Medicine, University of California San Francisco, San Francisco, CA, USA
6. Division of Infectious Disease, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Corresponding author:

Sarju Ganatra, MD
Landsman Heart and Vascular Center
Division of Cardiovascular Medicine
Lahey Hospital and Medical Center
Beth Israel Lahey Health
41 Mall Road, Burlington, MA 01805, USA
Email: Sarju.Ganatra@Lahey.org
Twitter: SarjuGanatraMD

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Abstract

Background

Treatment of coronavirus disease-2019 (Covid-19) with nirmatrelvir plus ritonavir (NMV-r) in high-risk non-hospitalized unvaccinated patients reduced the risk of progression to severe disease. However, the potential benefits of NMV-r among vaccinated patients are unclear.

Methods

We conducted a comparative retrospective cohort study using the TriNetX research network. Patients ≥18 years of age who were vaccinated and subsequently developed Covid-19 between December 1, 2021, and April 18, 2022, were included. Cohorts were developed based on the use of NMV-r within five days of diagnosis. The primary composite outcome was all-cause emergency room (ER) visit, hospitalization, or death at a 30-days follow-up. Secondary outcomes included individual components of primary outcomes, multisystem symptoms, Covid-19 associated complications, and diagnostic test utilization.

Results

After propensity score matching, 1,130 patients remained in each cohort. A primary composite outcome of all-cause ER visits, hospitalization, or death in 30 days occurred in 89 (7.87%) patients in the NMV-r cohort as compared to 163 (14.4%) patients in the non-NMV-r cohort (OR 0.5, CI 0.39-0.67; $p<0.005$) consistent with 45% relative risk reduction. A significant reduction in multisystem symptom burden and subsequent complications such as lower respiratory tract infection, cardiac arrhythmia, and diagnostic radiology testing were noted in NMV-r treated patients. There was no apparent increase serious complications between days 10 to 30.

Conclusion

Treatment with NMV-r in non-hospitalized vaccinated patients with Covid-19 was associated with a reduced likelihood of emergency room visits, hospitalization, or death. Complications and overall resource utilization were also decreased.

Keywords

Nirmatrelvir plus Ritonavir (NMV-r), Paxlovid, Covid-19, Vaccination, Rebound symptoms

Introduction:

As cases of coronavirus disease-2019 (Covid-19) continue to increase globally, antiviral agents may play an increasingly important role in reducing the severity of illness. Currently approved outpatient management options include the antivirals nirmatelvir plus ritonavir (NMV-r),[1] molnupiravir,[2] remdesivir,[3] and the monoclonal antibody bebtelovimab.[4] A major advantage of NMV-r and molnupiravir is oral administration. In clinical trials among unvaccinated high-risk people with Covid-19, both agents significantly reduced the risk of hospitalization or death compared to placebo. Because NMV-r was associated with a greater reduction in the primary endpoint (89% vs. 30%)[1,2] than molnupiravir and lacks molunpiravir's association with teratogenicity and mutagenicity, treatment guidelines list NMV-r as the preferred outpatient therapy for patients at high risk of progressing to severe disease.[5]

Importantly, this recommendation to use NMV-r in high-risk people with mild-to-moderate Covid-19 applies to both vaccinated and unvaccinated patients, even though data on the efficacy of the drug in vaccinated patients are incomplete. An interim analysis of a study in standard-risk patients demonstrated a trend toward improved clinical outcomes;[6] however, this study has been subsequently modified to exclude people who are vaccinated, and also stopped early due to failure to meet its primary endpoint.[7,8]

To close this data gap, we sought real-world experience with NMV-r in vaccinated people with Covid-19. With approximately 75% of the United States population ≥ 12 years of age vaccinated [9] and close to a million courses of NMV-r prescribed to both vaccinated and unvaccinated people,[10] this is an important clinical question. In addition, with increased anecdotal reports of rebound of both symptoms and antigen test positivity after treatment,[11] we wanted to investigate whether follow-up of treated patients would show evidence of reduced benefits. To

address the knowledge gaps about the role of NMV-r in the treatment of vaccinated patients with Covid-19, we took advantage of electronic health records (EHR) based, curated real-world data of the TriNetX research network.[12]

Methods

Study Oversight

Data were analyzed and interpreted by the authors. All authors reviewed the manuscript and affirmed the accuracy and completeness of the data. Institutional review board (IRB) approval was exempted by Lahey Clinic IRB, given aggregate de-identified data was used from a research network database. These study findings are reported per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for cohort studies.

Data Source

We utilized the TriNetX Analytics Network database – Research Network. TriNetX is a multicenter federated health research network aggregating anonymized data from electronic health records (EHRs) from participating healthcare organizations, including academic medical centers, specialty physician practices, and community hospitals covering ~250+ million patients from more than 120 health care organizations (HCO). The research network contains data on >88 million patients from 59 HCO. While the data are in aggregate de-identified form, the built-in analytics allow for the generation of patient-level data for cohort selection and matching, analyzing incidence and prevalence of events in a cohort, and comparing characteristics and outcomes between matched cohorts. More information on the database can be found online.[12]

Study Population and Design

TriNetX research network was searched, and data curation was performed on May 22, 2022. We conducted a comparative retrospective cohort study, including. non-hospitalized patients ≥18 years of age who were vaccinated and subsequently developed Covid-19 at least one month after vaccination and between December 1, 2021, and April 18, 2022. Key exclusion criteria were treatment with a monoclonal antibody, convalescent plasma, or molnupiravir for the index case of Covid-19. Patients were further categorized based use of NMV-r within five days of diagnosis. Validated diagnostic, procedure, and laboratory codes were utilized to define the vaccination status and Covid-19 diagnosis. Patients with NMV-r were identified using the National Library of Medicine RxNorm terminology. The Supplementary Appendix provides additional inclusion and exclusion criteria and information. Cohorts were matched using propensity score matching (PSM), a technique that attempts to adjust for confounding by selecting a control sample from the untreated population as similar as possible to the treatment group. Primary and secondary outcomes were analyzed 30-days after the index diagnosis of Covid-19 in the control cohort or after initiation of NMV-r in the treatment cohort.

Study Endpoints

Primary Composite Endpoint

The primary composite endpoint of this study was all-cause emergency room (ER) visits, hospitalization, or death at a 30-days follow-up.

Secondary endpoints

Secondary endpoints included individual components of composite primary endpoints: all-cause ER visits, hospitalization, and death.

Additionally, pre-specified secondary outcomes included the prevalence of various systemic and nonspecific symptoms (constitutional, cardio-respiratory, gastrointestinal, nervous system and musculoskeletal symptoms, smell–taste alteration), systemic complications (cardiovascular, respiratory, gastrointestinal, mood disorders), and diagnostic testing utilization (radiologic diagnostic tests, cardiovascular diagnostic tests [echocardiogram and heart rhythm monitors]) within 30 days of diagnosis of Covid-19. These outcomes were identified based on the ICD-10 codes. (Supplemental Appendix)

Finally, to explore rebound or prolonged Covid-19 symptoms or complications, we assessed all outcomes between 10 to 30-days following the diagnosis of Covid-19 or initiation of NMV-r.

Statistical Analysis

Non-hospitalized vaccinated patients who subsequently developed Covid-19 were divided into two cohorts based on their use of NMV-r within five days of diagnosis: NMV-r and non-NMV-r cohorts. We compared the cohorts using independent-sample t-tests for continuous variables, which are reported as mean (range). Categorical variables are reported as counts (%) and compared using the Chi-square ($\chi 2$) test. To control for baseline differences in the patient cohorts, 1:1 PSM was performed for characteristics of clinical relevance leveraging a built-in algorithm that uses the greedy nearest-neighbor algorithm with a caliper of 0.1 pooled standard deviations. Any characteristic with a standardized mean difference between cohorts lower than 0.1 was considered well-matched. After propensity matching, odds ratios with 95% confidence intervals were calculated for primary and secondary outcomes using the $\chi 2$ for the measures of association. Relative risk reduction was calculated as the division of the absolute risk reduction between the treatment (NMV-r) and control (non-NMV-r) cohorts by the absolute risk of the control group. The survival analysis was performed by plotting Kaplan-Meier curves with log-

rank tests and calculating hazard ratio (HR) to compare the two cohorts. Statistical significance was set at a two-sided p-value <0.05. Statistical analyses were completed using the TriNetX online platform using R for statistical computing.

As a sensitivity analysis, we measured the E-value, a measure to check for robustness against bias from unmeasured confounding or omitted covariates in the observational studies, for both primary and secondary outcomes.[13] A higher E value implies a stronger unmeasured confounder would be needed to negate the effect estimate for the covariate and increases the likelihood of causality.

Results

Study Population

A total of 111,588 non-hospitalized vaccinated patients with Covid-19 were identified during the study period. Of the total vaccinated, 1,131 patients received NMV-r within five days of the diagnosis, and 110,457 did not receive NMV-r. After PSM, 1,130 patients remained in each cohort and were included in our study (Figure 1).

Patient characteristics

Baseline characteristics of patients are as in Table 1. Patients treated with NMV-r were older (mean age 57.6±16.3 vs. 49.3±17.6 years; SD 0.485). Females comprised 63% of the study population. African-Americans were 9.7% in the NMV-r cohort vs. 17.8% in the non-NMV-r group before propensity matching. Patients receiving NMV-r were predominantly White adults (81.9%). Furthermore, patients on NMV-r had a higher prevalence of cardiovascular risk factors, established CVD (and be on medications for CVD), neoplasms, and chronic lower respiratory

disease. However, after PSM, baseline characteristics in the two groups were similar, and no residual imbalance was found (standard difference <0.1 for included covariates).

Study Outcomes

Primary Outcome

A primary composite outcome of all-cause ER visits, hospitalization, or death in 30 days occurred in 89 (7.87%) patients in the NMV-r cohort and 163 (14.4%) patients in the non-NMV-r cohort (OR 0.5, CI 0.39-0.67; p<0.005), consistent with 45% relative risk reduction (Table 2, Figure 3). Furthermore, patients on NMV-r had a higher probability of event-free survival at 30-days (88.15% vs. 84.16%, HR 0.67 (CI 0.52, 0.87); p=0.002) (Figure 2).

The E value of the Odds ratio of the primary outcome was 3.36 and the lower confidence interval was 2.37, both of which supported stronger association of NMV-r treatment leading to these observed differences in outcomes.

Secondary Outcomes

All-cause ER visits (82 vs. 142, OR 0.55, CI 0.41-0.73, p<0.05) and hospitalization (10 vs. 23), OR 0.43, CI 0.2-0.9; p=0.02) were significantly lower in Covid-19 patients who received NMV-r. Ten deaths were noted, all in the non-NMV-r cohort, whereas no deaths occurred (p<0.05) in the group receiving NMV-r (Table 2). Patients on NMV-r had fewer constitutional, cardio-respiratory, gastrointestinal, nervous, and musculoskeletal symptoms. No significant difference was noted in reported smell-taste alteration between the two cohorts. Overall, systemic complications, such as lower respiratory tract infections, arrhythmias, and anxiety/mood disorders, were seen less frequently in the NMV-r cohort than in the non-NMV-r cohort. No difference was noted in the occurrence of gastroenteritis, colitis, or diarrhea. Further, patients

receiving NMV-r had lower utilization of radiologic diagnostic testing than those who did not receive NMV-r. Cardiovascular diagnostic testing was similar in both cohorts (Table 2, Figure 3).

Sensitivity analysis with E-values is reported in Table 2, suggesting stronger association of NMV-r on observed outcomes and a low likelihood that differences in the outcomes are due to unmeasured confounders.

An exploratory secondary analysis of outcomes between 10 to 30-days following the diagnosis of Covid-19 or NMV-r initiation showed that patients in the NMV-r cohort continued to have overall fewer symptoms and complications (Table 3). Overall symptom burden was reduced in both the cohorts over time and became similar for nervous, musculoskeletal, and constitutional symptoms. However, cardio-respiratory and gastrointestinal symptoms, anxiety/mood disorder, and all-cause ER visits, hospitalization, or death remained lower in the NMV-r cohort at 30 days (Table 3). In addition, the occurrence of smell-taste alteration, which was similar in both the cohorts for the entire 30-days follow-up, was significantly less frequent in the NMV-r cohort between 10 to 30-days follow-up.

Discussion

In vaccinated, non-hospitalized patients with Covid-19, our real-world data demonstrate a strong association between treatment with nirmatrelvir with ritonavir (NMV-r) and improved outcomes. The study shows that when NMV-r was administered within five days of Covid-19 diagnosis, there was a 45% relative risk reduction in the occurrence of subsequent emergency room (ER) visits, hospitalizations, or deaths compared to a group receiving no treatment. We also report

reduced symptom burden (constitutional, cardio-respiratory, gastrointestinal, nervous system, and musculoskeletal symptoms) and complications such as lower respiratory tract infection or cardiac arrhythmia. While a virologic rebound is known to occur in some treated patients,[11] our findings demonstrate that, even if a rebound did occur in some, it did not negate the benefit of NMV-r treatment. Indeed, we found no late increase in complications among those with treatment compared to no treatment, although our study likely would have missed cases of transient or mild rebound occurring between 10 and 30 days after diagnosis. As we await further prospective data on NMV-r, our data strongly support the clinical effectiveness of NMV-r in vaccinated patients and the current NIH guidelines [5] listing this as the preferred therapy for mild-moderate Covid-19 in those at high risk of severe disease.

EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients) compared NMV-r to placebo in unvaccinated, non-hospitalized adults with mild-moderate Covid-19 at high risk for progression to severe disease.[1] This randomized controlled trial also excluded people with a known prior history of Covid-19. The study demonstrated an 89% reduction in the risk of hospitalization or death with NMV-r compared to placebo, with 0 vs. 7 deaths, respectively. Given this high efficacy, NMV-r was granted Emergency Use Authorization (EUA) in the United States in December 2021 for treatment of mild-moderate Covid-19 in people at high risk of severe disease.[14]

Since the EUA, clinicians have prescribed NMR-r for millions of individuals, many of whom are vaccinated, or have a prior history of Covid-19, or both. Since this group with pre-existing immunity to Covid-19 typically experiences milder disease than those who are immunologically naïve,[15,16] whether NMV-r would lead to comparable benefits in this population with other risk factors for severe disease remains unknown and motivated this analysis. An interim

evaluation of NMV-r in lower-risk individuals (including some who were vaccinated) failed to demonstrate a benefit in the primary outcome of time to symptom resolution, prompting the cessation of this study.[6,8] An ongoing randomized study of NMV-r in the United Kingdom is also evaluating efficacy in both vaccinated and unvaccinated people with Covid-19.[17] These two studies will provide more precise estimates of the benefits of this treatment in various patient populations.

Differences between the study population of EPIC-HR and the present analysis include older age (57 vs. 46 years) and a higher proportion of females (62-63% vs. 48-49%) in this study. Our data captured a higher proportion of White adults, possibly reflecting differences in access to healthcare in the United States. Our study also had a higher burden of comorbid conditions, which is likely due to the specifics of the EUA for NMV-r, which specify inclusion of only people at high-risk of progression to severe disease.[1]

While the 45% relative risk reduction in an all-cause ER visit, hospitalization, or death in those who received NMV-r is lower than the 89% reported in EPIC-HR, this result still implies substantial clinical benefits over and above those provided by vaccination. These are further reflected in our secondary outcomes, with a 72% relative risk reduction in the subsequent development of pneumonia and 50% reduction in arrhythmia in patients treated with NMV-r. Furthermore, treatment was associated with fewer clinical complaints at 30-days, specifically cardio-respiratory, gastrointestinal, nervous system, and musculoskeletal and constitutional symptoms. With lower rates of these complications, not surprisingly, we also observed additional evidence of reduced resource utilization, with a significant relative reduction in diagnostic radiology testing (45%) in NMV-r treated patients.

While reports of rebound were unusual in the controlled trial, in real-life use, there have been many reports of Covid-19 symptoms rebounds several days after completing the 5-day therapy with NMV-r.[11] Our analysis does not have sufficiently detailed patient-level data to describe the frequency of such relapses, especially if mild in clinical severity. However, follow-up between 10 to 30 days in our study continues to show the benefits of treatment, implying that such relapses, when they occur, rarely precipitate emergency room visits, hospitalization, or death.

Patients with Covid-19 commonly report alterations in smell and taste. A different phenomenon is the taste disturbance associated with NMV-r treatment, reported in 6% of study participants in the EPIC-HR trial (and, anecdotally, more commonly in real-life use). Our study found EHR documentation of smell-taste alteration in < 1% of patients, with similar fractions in the two cohorts. Notably, reports of gastrointestinal symptoms were significantly lower within the NMV-r cohort.

Our study has several limitations. Most importantly, despite our efforts to carefully control for baseline differences in the treated versus non-treated populations using propensity matching, unmeasured confounding could influence the outcomes. Hence, we performed a sensitivity analysis, the results of which indicate that the findings are highly unlikely to be due to an unmeasured confounder. Retrospective data curated from an EHR are not always accurate, although we did have access to more-objective laboratory testing results. It is possible that clinical data, including receipt of vaccines or clinical outcomes, could have occurred in some patients outside of participating healthcare organizations in this research network. If so, such patients may have been misclassified. However, this limitation presumably would apply to both the treated and untreated groups. Unlike the EPIC-HR study, which addressed hospitalizations

directly related to Covid-19, here we assessed all-cause hospitalization, ER visits, and mortality rather than a cause-specific outcome. It is possible that these outcomes may have occurred in some patients due to non-Covid-related illnesses, though even in clinical practice it can be difficult to assess whether Covid-19 contributes to hospitalization or is an incidental finding, especially in patients with medical comorbidities in whom viral infections are known to precipitate medical instability. Since ER visits may be influenced by primary care access, and in some cases may have been where patients received prescriptions for NMV-r, our sensitivity analysis looking at only hospitalization or death showed a comparable benefit of NMV-r.

In summary, this evaluation of NMV-r in vaccinated patients at high risk for Covid-19 complications shows a strong association between treatment and a reduced risk of emergency room visits, hospitalizations, and death. With cases of Covid-19 continuing to occur despite widespread vaccination, these data support administering antiviral therapy to this vulnerable group, vaccination status notwithstanding. Ongoing prospective clinical trials of NMV-r in a variety of patient populations will more precisely define the benefits and risks of treatment.

NOTES

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Doctors Company; serves on board of directors of Second Wave Delivery Solution (for which he receives stock options) and the scientific advisory boards for Teladoc a large telemedicine provider (ended 2021), Amino.com, Curai Health, and EarlySense (stock options); consults with Commure (stipend and stock options), Forward (stock options), and Notable (stock options); received honoraria as a speaker at conferences for many (>150) healthcare organizations, medical societies, hospitals (vast majority non-profit; for-profit entities since 2017 include Nuance, GE, Health Catalyst, AvaCare, Siemens, and Voalte)); has given >200 talks (a few to for-profit entities including Nuance, GE, Health Catalyst, Siemens, AvaCare and the Governance Institute) for which he has received honoraria; and holds the Benioff Endowed Chair in Hospital Medicine from Marc and Lynne Benioff and the Holly Smith Distinguished Professorship in Science and Medicine at UCSF.

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1 **Table 1. Baseline Characteristics**

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	Before Propensity Matching			After Propensity Matching		
Baseline Characteristics	**Nirmatrelvir-Ritonavir N=1131 (%)**	**No Nirmatrelvir-Ritonavir N=110457 (%)**	**SD**	**Nirmatrelvir-Ritonavir N=1130 (%)**	**No Nirmatrelvir- Ritonavir N=1130 (%)**	**SD**
Demographics						
Mean Age	57.6 +/- 16.3	49.3 +/- 17.6	0.485	57.5 +/- 16.3	57.7 +/- 16.3	0.012
Female	713 (63.0%)	71,017 (64.3%)	0.026	712 (63.0%)	724 (64.1%)	0.022
White	926 (81.9%)	71,081 (64.4%)	0.403	925 (81.9%)	941 (83.3%)	0.037
African American	110 (9.7%)	19,646 (17.8%)	0.236	110 (9.7%)	103 (9.1%)	0.021
Non-Hispanic/Latino	878 (77.6%)	70,377(63.7%)	0.309	877 (77.6%)	857 (75.8%)	0.042
BMI ≥ 30	237 (21%)	27629 (25%)	0.09	237 (21%)	208 (18%)	0.06
Comorbidities						
Hypertension	591 (52.3%)	45,616 (41.3%)	0.221	590 (52.2%)	578 (51.2%)	0.021
Hyperlipidemia	651 (57.6%)	42,811 (38.8%)	0.383	650 (57.5%)	661 (58.5%)	0.020
Diabetes Mellitus	250 (22.1%)	21,640 (19.6%)	0.062	250 (22.1%)	249 (22.0%)	0.002
Chronic Lower Respiratory Disease	342 (30.2%)	28,159 (25.5%)	0.106	342 (30.3%)	339 (30%)	0.006

Chronic Kidney Disease	91 (8.0%)	10,512 (9.5%)	0.052	91 (8.1%)	80 (7.1%)	0.037
Atrial Fibrillation/Atrial Flutter	59 (5.2%)	7,010 (6.3%)	0.048	59 (5.2%)	82 (7.3%)	0.084
Ischemic Heart Disease	172 (15.2%)	14,810 (13.4%)	0.051	172 (15.2%)	155 (13.7%)	0.043
Heart Failure	52 (4.6%)	7,831 (7.1%)	0.106	52 (4.6%)	54 (4.8%)	0.008
Ischemic Stroke	51 (4.5%)	4,502 (4.1%)	0.021	51 (4.5%)	53 (4.7%)	0.008
Malignancy	512 (45.3%)	36,169 (32.7%)	0.259	512 (45.3%)	524 (46.4%)	0.021
Demyelinating Disease	21 (1.9%)	988 (0.9%)	0.083	21 (1.9%)	21 (1.9%)	<0.001
Systematic Connective Tissue Disorder	90 (8.0%)	4,975 (4.5%)	0.143	90 (8.0%)	67 (5.9%)	0.080
Medications						
Beta Blockers	410 (36.3%)	32,702 (29.6%)	0.142	409 (36.2%)	399 (35.3%)	0.018
Diuretics	346 (30.6%)	29,860 (27.0%)	0.079	346 (30.6%)	334 (29.6%)	0.023
ACE inhibitors	208 (18.4%)	19,032 (17.2%)	0.030	208 (18.4%)	208 (18.4%)	<0.001
Angiotensin Receptor Blocker	230 (20.3%)	15,783 (14.3%)	0.160	229 (20.3%)	228 (20.2%)	0.002
Aspirin	308 (27.2%)	25,020 (22.7%)	0.106	308 (27.3%)	318 (28.1%)	0.020
Anticoagulants	305 (27.0%)	29,278 (26.5%)	0.010	305 (27.0%)	272 (24.1%)	0.067
Statins	465 (41.1%)	34,326 (31.1%)	0.210	465 (41.2%)	476 (42.1%)	0.020

Immune Suppressants	53 (4.7%)	5,650 (5.1%)	0.020	53 (4.7%)	60 (5.3%)	0.028
Antineoplastics	137 (12.1%)	11,796 (10.7%)	0.045	137 (12.1%)	133 (11.8%)	0.011
Antidepressants	458 (40.5%)	42,023 (38.0%)	0.050	458 (40.5%)	515 (45.6%)	0.102
Anticonvulsants	282 (24.9%)	26,693 (24.2%)	0.018	282 (25.0%)	327 (28.9%)	0.090
Laboratory Tests						
Creatinine (mg/dL)	0.88 +/- 0.2 (n= 1,068)	0.98 +/- 1.9 (n= 75,270)	0.071	0.88 +/- 0.2 (n= 1,068)	0.92 +/- 0.5 (n= 1018)	0.093
Hemoglobin (g/dl)	13.6 +/- 1.5 (n= 1023)	13.3 +/- 1.8 (n= 85,080)	0.148	13.6 +/- 1.5 (n= 1022)	13.6 +/- 1.7 (n= 1005)	0.013
Lymphocytes (percentage leukocytes)	28.0 +/- 10.4 (n= 938)	27.3 +/- 10.6 (n= 74,697)	0.068	28.0 +/- 10.4 (n= 937)	27.1 +/- 10.4 (n= 897)	0.085
Platelets (per microliter blood)	253.8 +/- 76.2 (n= 1,023)	257.8 +/- 77.3 (n= 84,769)	0.053	253.8 +/- 76.2 (n= 1022)	250.6 +/- 70.7 (n= 1005)	0.043
C reactive protein >10 mg/L	92 (8.1%)	6324 (5.7%)	0.094	92 (8.1%)	72 (6.3%)	0.068
Ferritin (micrograms/L)	181.5 +/- 427.8 (n= 283)	218.4 +/- 676.6 (n= 21,899)	0.065	181.5 +/- 427.8 (n=283)	172.3 +/- 274.9 (n=273)	0.025
Total Cholesterol (mg/dL)	183.4 +/- 40.9 (n=902)	178.9 +/- 42.6 (n= 65,344)	0.107	183.4 +/- 40.9 (n= 901)	181.3 +/- 43.4 (n= 908)	0.050
LDL (mg/dL)	103.5 +/- 34.1 (n= 941)	102.7 +/- 35.6 (n= 67,443)	0.023	103.5 +/- 34.1 (n=940)	103.6 +/- 36.2 (n= 939)	0.004
Hemoglobin A1c	6.1 +/- 1.7 (n= 799)	6.1 +/- 1.6 (n= 51,351)	0.007	6.1 +/- 1.7 (n= 798)	6.0 +/- 1.4 (n= 779)	0.080

Left Ventricular Ejection Fraction (LVEF) (%)	61.3 +/- 10.7 (n= 167)	58.9 +/- 11.9 (n= 7,178)	0.212	61.3 +/- 10.8 (n= 166)	60.5 +/- 9.5 (n= 143)	0.082

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2 Abbreviations: SD: standard difference, LDL: low-density lipoprotein

Table 2. Outcomes comparison at 30-days

Outcomes	Nirmatrelvir-Ritonavir N=1130 (%)	No Nirmatrelvir-Ritonavir N=1130 (%)	Risk difference	Relative Risk Reduction	Odds ratio	E value of Odds ratio	E value for lower confidence interval of Odds ratio	P-value
Primary Composite Outcomes								
All-cause ER visit, hospitalization or death	89 (7.87%)	163 (14.4%)	-0.065 (-0.091, -0.040)	45%	0.507 (0.386, 0.666)	3.36	2.37	<0.001
Secondary Outcomes								
Individual components of primary outcomes								
All-cause ER visit	83 (7.34%)	142 (12.5%)	-0.052 (-0.077, -0.028)	41%	0.552 (0.415, 0.733)	3.02	2.07	<0.001
All-cause hospitalization	10 (0.8%)	23 (2%)	-0.012 (-0.021, -0.002)	60%	0.430 (0.204, 0.907)	4.08	1.44	0.023
30-day mortality	0	10 (0.8%)	-0.009 (-0.014, -0.003)	100%	-	-	-	0.002
Symptoms								
Constitutional symptoms	72 (6.3%)	146 (12.9%)	-0.065 (-0.090, -0.041)	50%	0.459 (0.341, 0.616)	3.78	2.63	<0.001
Cardio-respiratory symptoms	153 (13.5%)	309 (27.3%)	-0.138 (-0.171, -0.105)	51%	0.416 (0.336, 0.516)	4.24	3.29	<0.001

Gastrointestinal symptoms	38 (3.3%)	89 (7.87%)	-0.045 (-0.064, -0.026)	57%	0.407 (0.276, 0.601)	4.35	2.71	<0.001
Nervous system and musculoskeletal symptoms	10 (0.8%)	25 (2.2%)	-0.013 (-0.023, -0.003)	59%	0.395 (0.189, 0.826)	4.5	1.72	0.011
Smell-taste alteration	10 (0.8%)	10 (0.8%)	0 (-0.008, 0.008)	0	1 (0.415, 2.412)	1	1	1
Complications								
Lower respiratory tract infection	27 (2.38%)	92 (8.14%)	-0.058 (-0.076, -0.039)	72%	0.276 (0.178, 0.428)	6.71	4.1	0.000
Arrhythmia	22 (1.9%)	43 (3.8%)	-0.019 (-0.032, -0.005)	50%	0.502 (0.298, 0.845)	3.4	1.65	0.008
Gastroenteritis/Colitis/Diarrhea	12 (1%)	13 (1.1%)	-0.001 (-0.010, 0.008)	8%	0.922 (0.419, 2.030)	1.39	1	0.841
Anxiety/mood disorder	64 (5.6%)	114 (10%)	-0.044 (-0.066, -0.022)	44%	0.535 (0.389, 0.735)	3.14	2.06	0.000
Diagnostic Testing Utilization								
Radiology diagnostic tests	90 (7.9%)	164 (14.5%)	-0.065 (-0.091, -0.040)	45%	0.510 (0.388, 0.669)	3.33	2.35	<0.001
CV tests (Echocardiogram and heart monitors)	10 (0.88%)	13 (1.1%)	-0.003 (-0.011, 0.006)	25%	0.767 (0.335, 1.757)	1.93	1	0.530

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2 Abbreviations: CV: cardiovascular, ER: emergency room

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Table 3. Outcomes comparison between 10 to 30-days

Outcomes	Nirmatrelvir-Ritonavir N=1130 (%)	No Nirmatrelvir-Ritonavir N=1130 (%)	Risk difference	Relative Risk Reduction	Odds ratio	P-value
Primary Composite Outcome						
All-cause ER visit, hospitalization, or death	23 (2.03%)	56 (4.95%)	-0.029 (-0.044, -0.014)	58%	0.398 (0.243, 0.652)	<0.001
Secondary Outcomes						
Individual components of primary outcomes						
All-cause ER visit	18 (1.59%)	34 (3.01%)	-0.014 (-0.026, -0.002)	47%	0.522 (0.293, 0.930)	0.025
All-cause hospitalization	10 (0.88%)	24 (2.12%)	-0.012 (-0.022, -0.002)	57%	0.411 (0.196, 0.864)	0.016
30-day mortality	0	10 (0.88%)	-0.009 (-0.014, -0.003)	100%	-----	0.002
Symptoms						
Constitutional symptoms	23 (2.03%)	35 (3.09%)	-0.011 (-0.024, 0.002)	35%	0.650 (0.382, 1.107)	0.11
Cardio-respiratory symptoms	49 (4.33%)	83 (7.34%)	-0.030 (-0.049, -0.011)	41%	0.572 (0.398, 0.822)	0.002
Gastrointestinal symptoms	23 (2.03%)	43 (3.80%)	-0.018 (-0.032, -0.004)	47 %	0.525 (0.314, 0.877)	0.012

Nervous system and Musculoskeletal symptoms	10 (0.88%)	14 (1.24%)	-0.004 (-0.012, 0.005)	33%	0.712 (0.315, 1.609)	0.412
Smell-taste alteration	0	10 (0.88%)	-0.009 (-0.014, -0.003)	100%	—	0.002
Complications						
Lower respiratory tract infection	14 (1.24%)	32 (2.83%)	-0.016 (-0.028, -0.004)	57%	0.430 (0.228, 0.811)	0.007
Arrhythmia	12 (1.06%)	27 (2.39%)	-0.013 (-0.024, -0.003)	54%	0.438 (0.221, 0.870)	0.015
Gastroenteritis/Colitis/Diarrhea	10 (0.88%)	10 (0.88%)	0 (-0.008, 0.008)	0 %	1 (0.415, 2.412)	1
Anxiety/mood disorder	36 (3.18%)	74 (6.54%)	-0.034 (-0.051, -0.016)	52%	0.470 (0.313, 0.706)	<0.001
Diagnostic Testing Utilization						
Radiology diagnostic tests	48 (4.24%)	71 (6.23%)	-0.020 (-0.039, -0.002)	32%	0.662 (0.454, 0.964)	0.03
CV tests (Echocardiogram and heart monitors)	10 (0.88%)	14 (1.24%)	-0.004 (-0.012, 0.005)	33%	0.712 (0.315, 1.609)	0.412

Abbreviations: CV: cardiovascular, ER: emergency room

Figure Legends

Figure 1: Consort diagram.

This figure illustrates the proportion of vaccinated non-hospitalized patients who tested positive for SARS-CoV-2 infection or were diagnosed with Covid-19 stratified by use of nirmatrelvir plus ritonavir (NMV-r).

Figure 2: Efficacy of Nirmatrelvir plus Ritonavir (NMV-r) in Vaccinated Patients Preventing Covid-19–Related ER visit, hospitalization or death.

This figure illustrates the survival analysis with a cumulative percentage comparison of an all-cause ER visit, hospitalization, or death among patients treated with or without nirmatrelvir plus ritonavir for Covid-19 within five days of diagnosis. The cumulative percentage was estimated for each treatment group using the Kaplan–Meier method.

Figure 3: Primary and Secondary Outcomes of Nirmatrelvir plus Ritonavir (NMV-r) in Vaccinated Patients

This forest plot demonstrates the odds ratios with 95% confidence intervals for primary and secondary outcomes in vaccinated patients treated with Nirmatrelvir plus Ritonavir (NMV-r).

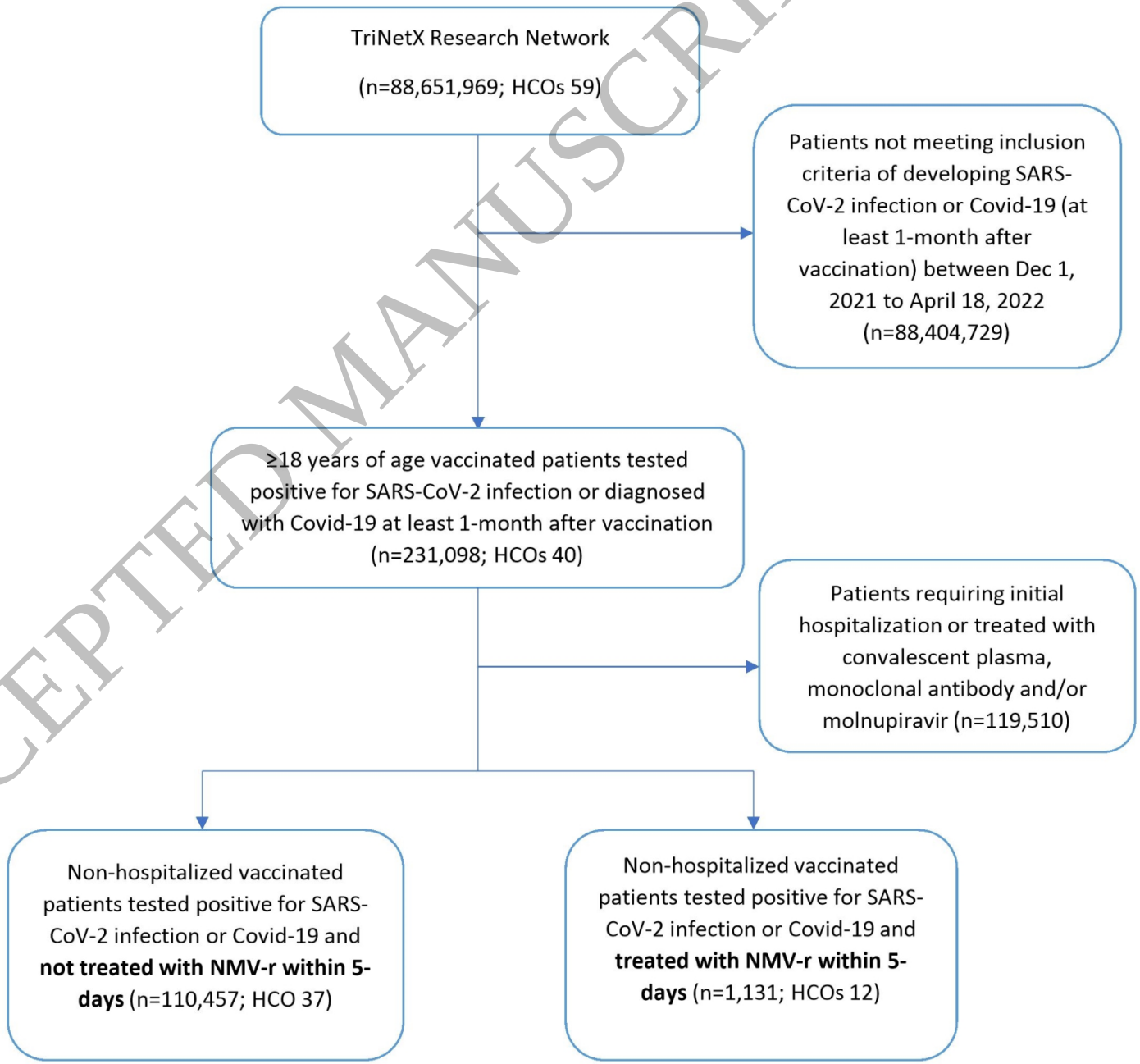


Figure 1
187x176 mm (.12 x DPI)

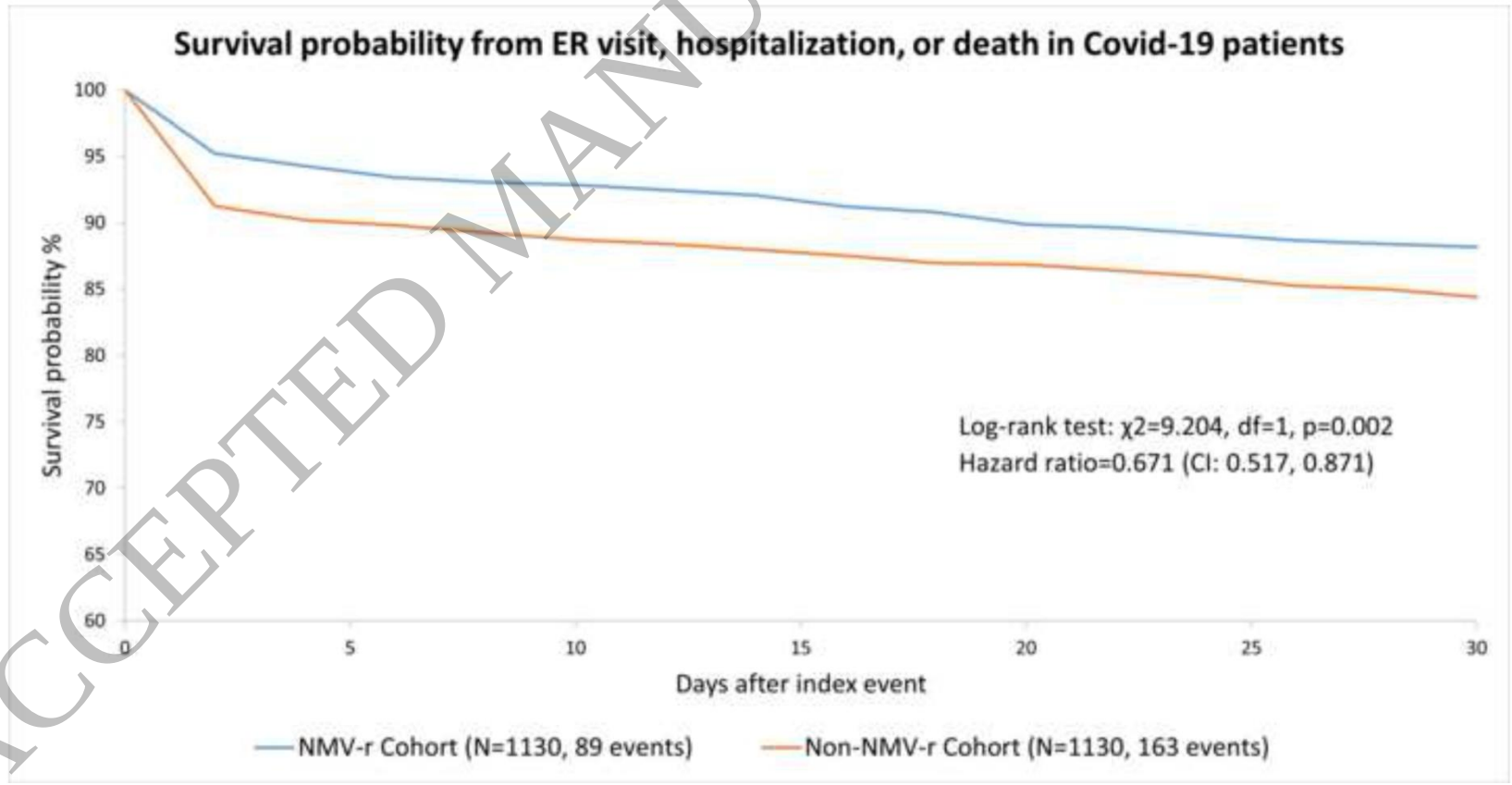
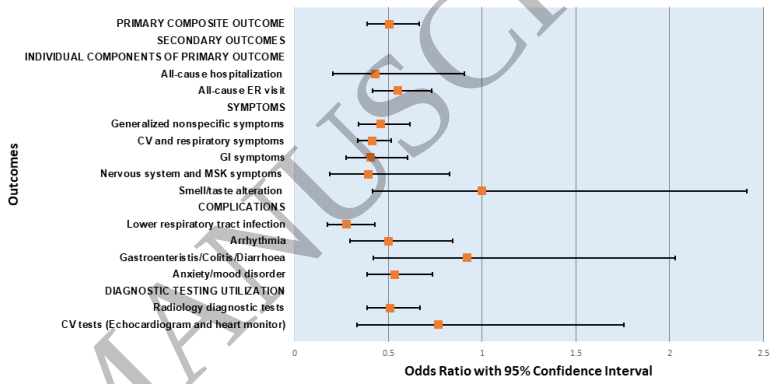


Figure 2
229x118 mm (.12 x DPI)



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2 **Figure 3**
3 **108x61 mm (.12 x DPI)**