Capstone Project (Winter-Spring 2024)

Manish Kumar

Studying the Efficacy of Nirmatrelvir and Ritonavir (Paxlovid) for Outpatient Treatment of COVID-19 in the Pediatric Population Using Real-World Data from the National COVID Cohort Collaborative (N3C).

Abstract

Background: Since the onset of COVID-19 pandemic, multiple therapeutics have been used for treatment. Nirmatrelvir and Ritonavir (NMV-r; Paxlovid) is one such medication that has undergone clinical trials in the adult population but since then has been authorized for use in patients at least 12 years of age and weight above 40 kg. This study attempts to analyze the efficacy of NMV-r using real life data from a large nationwide COVID-19 data repository.

Methods: We conducted this study using data from The National COVID Cohort Collaborative (N3C) data repository on patients between 12-18 years of age diagnosed with COVID-19 during or after December 2021 (the authorization date of NMV-r). We identified all the patients who had received NMV-r treatment, as well as those who had not received the treatment, along with associated patient characteristics including demographics, associated co-morbid conditions, and clinical outcomes such as hospitalization within 30 days, emergency room visits, and mortality. A study cohort comprising of treated and untreated groups was constructed using nearest neighbor propensity score matching using various patient characteristics. Clinical outcomes were then compared between the two groups. IRB approval was obtained from OHSU. All analysis were performed on N3C platform though NCATS N3C Data Enclave (https://covid.cd2h.org and N3C Attribution & Publication Policy. This research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists who have contributed to the on-going development of this community resource.

Results: A total of 436,593 cases of COVID-19 during the study period and between 12-18 years were identified on N3C. A total of 3,879 cases treated with NMV-r were matched to 3,879 untreated cases. The results show a 74% relative risk reduction ($p<0.001$) in hospitalization for patient treated with NMV-r. Similarly, 14% relative risk reduction ($p<0.001$) was seen in emergency department visits between treated and untreated groups.

Discussion: This study is the largest retrospective study using real-world data to evaluate the effectiveness of NMV-r in the age group 12-18 years. The study shows the effectiveness of NMV-r in preventing hospitalization and ED visits following infection with COVID-19. Since this is a retrospective study using propensity matching, unmeasured confounders could lead to bias in the study.

Introduction:

Since the start of pandemic, COVID-19 has impacted more than 776 million people and has caused significant morbidity and mortality.[1] The infection has mostly affected the adult population, but about 11 percent of all cases in US have been reported in pediatric population.[2] Consequently, most of the clinical trials for therapeutics have been directed towards the adult population, with very few enrolling pediatric patients.[3] There is growing advocacy for increased enrollment of children in clinical trials for COVID-19 therapeutics.[4] The treatment of COVID-19 in pediatric patients had relied on extrapolation from adult studies and small descriptive reports.[5]

Nirmatrelvir and Ritonavir (NMV-r; Paxlovid) is one such medication that has undergone clinical trials in adults who are 18 years of age or older[6], but its clinical usage has been extended to those 12 years of age and older and at least 40 kg in weight under emergency authorization from FDA.[7] So far, no clinical trials have been conducted to demonstrate the efficacy of NMV-r in pediatric population between 12-18 years of age. Moreover, pediatrics cases have been milder and required less hospitalization, making it challenging to extrapolate adult data to this age group.

This study aims to estimate the efficacy of NMV-r in pediatric population between 12-18 years age group, using real life data from The National COVID Cohort Collaborative (N3C).

N3C provides a secure platform for analysis of EHR-based clinical data collected on more than 22.5-million individuals, and 8.7 million with confirmed COVID-19 from 84 partner health organizations across the US for clinical research purposes. The data within N3C is curated into a unified format for analysis across different healthcare settings and providers. Sidky et al. examined the use of Remdesivir in adults using N3C data and reported positive benefits of employing such a large-scale data model.[8] Xiao et al., studied the drug-drug interaction of NMV-r using N3C data in adults.[9] Additionally , large scale validation can be achieved across multiple health institutions, providing particularly useful tool in studying outcomes with low prevalence, like pediatric morbidity and mortality due to COVID-19.

Due to the limited availability NMV-r during the pandemic as well as other factors such as lack of provider and public awareness, many patients who were eligible for the medication did not receive it. This situation created two distinct groups: one that received NMV-r and another that did not. The study uses propensity score matching in a retrospective study to estimate the efficacy of NMV-r in a pediatric population using N3C data.

Methods:

<u>Study Design</u>

This cohort is comprised of all individuals from age 12 to 18 years diagnosed with COVID-19 during or after December of 2021 (the authorization date of NMV-r). For each individual only

the first instance of COVID-19 during the study period was considered. COVID-19 was defined as presence of a positive COVID-19 diagnostic test or having COVID-19 ICD-10 code documented in the EHR. Additional patient characteristics collected included demographics, associated co-morbid conditions and prescription of NMV-r. The selected co-morbidities included those recommended at any time by the National Institutes of Health as an indication for NMV-r in children.[10] The primary outcome was hospitalization within 30 days, secondary outcomes included emergency department visits, numeric severity score (range: 0-4 where 0 represents no need for ED or hospital care and 4 represents death) and markers of severe disease (invasive mechanical ventilation, extra-corporeal membrane oxygenation or death).

The treatment group was selected as those patients who were COVID-19 positive and treated with NMV-r within 5 days of diagnosis. In order to correct for confounding, we selected the untreated group using nearest neighbor propensity score matching derived from a logistic regression model for probability of NMV-r treatment using multiple variables (day of COVID-19 diagnosis, demographics, BMI, presence of specific risk factors for severe COVID-19 and contributing data partner). The ratio of 1:1 between treated and control group was used.[11]

Statistical analysis

Mean values and percentages were calculated for clinical features and outcomes of the treated and untreated cohorts before and after propensity score matching. Statistical significance was calculated using a two-sided T-test for continuous variables and using the chi-squared or Fisher's exact test for categorical variables.

N3C platform

All analyses were performed on N3C's secure cloud-computing Palantir platform using Python (3.7), Pandas(1.2.5) and Scikit-learn packages.[12-14] The analyses described in this report were conducted with data or tools accessed through the NCATS N3C Data Enclave https://covid.cd2h.org and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NCATS Contract No. 75N95023D00001. This research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists who have contributed to the on-going development of this community resource.[15]

IRB approval was obtained from OHSU by all authors.

Results:

A total of 436593 cases of COVID-19 infection were identified among the 12-18 years old pediatric population out of which 3879 received treatment and 432714 did not receive treatment with NMV-r. The cohort was comprised of 44% males and 56% females. The racial distribution was 60% White, 17% Black or African American, 3% Asian 1% native Hawaiian or Other Pacific Islander, with other and unknown being 13%. Rates of previously diagnosed comorbidities varied from 18% of the cohort (obesity) to 0.05% (Down Syndrome). The number

of individuals contributed by each individual clinical source (data partner) varied widely, with the most heavily represented site contributing 18% of the cohort (Table 1).

Variable	All	Untreated	Treated
Total N	436593	432714 [99.99%]	3879 [0.009%]
Day of COVID-19 diagnosis (# of days after Jan 1, 2020)***	954.65 [744.00-1084.00]	953.34 [744.00-1083.00]	1100.74 [931.00-1310.50]
Age_at_COVID-19 (y)***	15.15 [13.00-17.00]	15.15 [13.00-17.00]	15.68 [14.00-17.00]
Gender Male**	191491 [44.0]	189686 [44.0]	1805 [47.0]
Gender Female**	244598 [56]	242525 [56]	2073 [53]
Gender Unknown**	504 [0.0]	503 [0.0]	<20
Race white***	264034 [60.0]	261730 [60.0]	2304 [59.0]
Race Black or African American***	74881 [17.0]	74264 [17.0]	617 [16.0]
Race Asian***	13288 [3.0]	13119 [3.0]	169 [4.0]
Race American Indian or Alaska Native***	3757 [1]	3703 [1]	54 [1]
Race Native Hawaiian or Other Pacific Islander***	1752 [0.0]	1732 [0.0]	20 [1.0]
Race Other***	20320 [5.0]	20212 [5.0]	108 [3.0]
Race Unknown***	58561 [13.0]	57954 [13.0]	607 [16.0]
Ethnicity Not Hispanic or Latino***	310153 [71.0]	307473 [71.0]	2680 [69.0]
Ethnicity Hispanic or Latino***	84346 [19]	83439 [19]	907 [23]
Ethnicity Unknown***	42094 [10.0]	41802 [10.0]	292 [8.0]
Maximum recorded BMI pre-COVID_19***	15.42 [0.00-25.00]	15.34 [0.00-25.00]	24.95 [19.00-32.00]
Obesity***	78422 [18.0]	76966 [18.0]	1456 [38.0]
Asthma***	56785 [13.0]	55551 [13.0]	1234 [32.0]
Primary Immunodeficiency***	8523 [2.0]	8333 [2.0]	190 [5.0]
Diabetes Mellitus***	6271 [1.0]	6104 [1.0]	167 [4.0]
Chronic Kidney Disease	5470 [1.0]	5424 [1.0]	46 [1.0]
Cancer***	3883 [1.0]	3816 [1.0]	67 [2.0]
Rheumatologic Diagnosis***	2371 [1.0]	2310 [1.0]	61 [2.0]
Sickle Cell Disease***	1747 [0.0]	1710 [0.0]	37 [1.0]
Congenital Heart Disease**	1290 [0.0]	1269 [0.0]	21 [1.0]
Solid organ or Hematopoietic Stem Cell Transplant*	619 [0.0]	619 [0.0]	0 [0.0]
Medical Device Dependance	749 [0.0]	743 [0.0]	<20
Prematurity	513 [0.0]	504 [0.0]	<20
Down Syndrome	201 [0.0]	197 [0.0]	<20
Data Partner 1***	78942 [18.0]	78938 [18.0]	<20
Data Partner 2***	30641 [7]	30420 [7]	221 [6]
Data Partner 3***	27718 [6.0]	27017 [6.0]	701 [18.0]

Data Partner 4***	23422 [5.0]	22984 [5.0]	438 [11.0]
Data Partner 5***	16069 [4.0]	15835 [4.0]	234 [6.0]
Data Partner 6***	15729 [4.0]	15557 [4.0]	172 [4.0]
Data Partner 7***	13723 [3.0]	13723 [3.0]	0 [0.0]
Data Partner 8***	12686 [3.0]	12543 [3.0]	143 [4.0]
Data Partner 9***	11966 [3.0]	11910 [3.0]	56 [1.0]
Data Partner 10***	10854 [2.0]	10722 [2.0]	132 [3.0]
Data Partner 11***	10378 [2.0]	10306 [2.0]	72 [2.0]
Data Partner 12***	9176 [2.0]	8944 [2.0]	232 [6.0]
Data Partner 13***	9044 [2.0]	8965 [2.0]	79 [2.0]
Data Partner 14***	8599 [2.0]	8589 [2.0]	<20
Data Partner 15***	7348 [2.0]	7289 [2.0]	59 [2.0]
Data Partner 16***	6664 [2.0]	6664 [2.0]	0 [0.0]
Data Partner Other***	143634 [33.0]	142308 [33.0]	1326 [34.0]

Table 1. Pre-matched table showing baseline characteristics of patients who were 12-18 years of age and diagnosed with COVID-19 in N3C database. [] represents percentages for categorical variables and interquartile range for continuous variables. * - $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2 shows the composition of the cohort after 1:1 propensity matching with the number of treated patients 3879 matching the untreated 3879 patients. Other patient characteristics such as BMI, gender, race, and diagnosis matching up closely with the treated group. Close approximation was achieved between different data partner institutions.

Variable	All	Untreated	Treated
Total N	7758	3879[50%]	3879[50%]
Day of COVID-19 diagnosis (# of days after Jan 1, 2020) ***	1111.29 [925.00-1336.00]	1121.85 [910.00-1369.50]	1100.74 [931.00-1310.50]
Age_at_COVID-19 (y)	15.66 [14.00-17.00]	15.64 [14.00-17.00]	15.68 [14.00-17.00]
Gender Male	3548 [46.0]	1743 [45.0]	1805 [47.0]
Gender Female	4208 [54]	2135 [55]	2073 [53]
Gender Unknown	<20	<20	<20
Race white	4542 [59.0]	2238 [58.0]	2304 [59.0]
Race Black or African American	1284 [17.0]	667 [17.0]	617 [16.0]
Race Asian	322 [4.0]	153 [4.0]	169 [4.0]
Race American Indian or Alaska Native	102 [1]	48 [1]	54 [1]
Race Native Hawaiian or Other Pacific Islander	34 [0.0]	<20	20 [1.0]
Race Other	239 [3.0]	131 [3.0]	108 [3.0]
Race Unknown	1235 [16.0]	628 [16.0]	607 [16.0]
Ethnicity Not Hispanic or Latino	5395 [70.0]	2715 [70.0]	2680 [69.0]
Ethnicity Hispanic or Latino	1786 [23]	879 [23]	907 [23]

Ethnicity Unknown	577 [7.0]	285 [7.0]	292 [8.0]
Maximum recorded BMI pre-COVID_19	24.86 [19.00-32.00]	24.76 [19.00-32.00]	24.95 [19.00-32.00]
Obesity	2857 [37.0]	1401 [36.0]	1456 [38.0]
Asthma	2418 [31.0]	1184 [31.0]	1234 [32.0]
Primary Immunodeficiency	390 [5.0]	200 [5.0]	190 [5.0]
Diabetes Mellitus	324 [4.0]	157 [4.0]	167 [4.0]
Chronic Kidney Disease	104 [1.0]	58 [1.0]	46 [1.0]
Cancer	134 [2.0]	67 [2.0]	67 [2.0]
Rheumatologic Diagnosis	104 [1.0]	43 [1.0]	61 [2.0]
Sickle Cell Disease	70 [1.0]	33 [1.0]	37 [1.0]
Congenital Heart Disease	39 [1.0]	<20	21 [1.0]
Solid organ or Hematopoietic Stem Cell Transplant	0 [0.0]	0 [0.0]	0 [0.0]
Medical Device Dependance	<20	<20	<20
Prematurity	<20	<20	<20
Down Syndrome	<20	<20	<20
Data Partner 1	<20	<20	<20
Data Partner 2	415 [5]	194 [5]	221 [6]
Data Partner 3*	1336 [17.0]	635 [16.0]	701 [18.0]
Data Partner 4	898 [12.0]	460 [12.0]	438 [11.0]
Data Partner 5*	515 [7.0]	281 [7.0]	234 [6.0]
Data Partner 6	339 [4.0]	167 [4.0]	172 [4.0]
Data Partner 7	0 [0.0]	0 [0.0]	0 [0.0]
Data Partner 8	305 [4.0]	162 [4.0]	143 [4.0]
Data Partner 9	117 [2.0]	61 [2.0]	56 [1.0]
Data Partner 10	261 [3.0]	129 [3.0]	132 [3.0]
Data Partner 11	159 [2.0]	87 [2.0]	72 [2.0]
Data Partner 12*	415 [5.0]	183 [5.0]	232 [6.0]
Data Partner 13	152 [2.0]	73 [2.0]	79 [2.0]
Data Partner 14	<20	<20	<20
Data Partner 15	128 [2.0]	69 [2.0]	59 [2.0]
Data Partner 16	0 [0.0]	0 [0.0]	0 [0.0]
Data Partner Other	2696 [35.0]	1370 [35.0]	1326 [34.0]

Table 2. Post-matched table showing patient characteristics between the treated and untreated groups. [] shows percentage for categorical variables and interquartile range for continuous variables. * - $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3 shows the primary and secondary outcomes of the treated and untreated groups before and after propensity matching. Hospitalization shows a decrease of 5.78% (absolute risk reduction) and a relative risk reduction of 74% in the treated group with a significance of

p<0.001. Similarly, absolute risk of ED visit decreased 2.53% in the treated group (14% reduction in related risk reduction) (p<0.001). The mean severity score also shows significant difference (0.136633, p<.001) between the treated and untreated groups, suggesting NMV-r may reduce risk of severe disease in high-risk children with COVID-19. Some of the other variables such as ECMO within 30 days, invasive ventilation within 30 days and death were so rare in either group that it did not achieve any statistically significant result.

Variable	Unmatched Untreated	Unmatched Treated	Matched Untreated	Matched Treated
N	432714	3879	3879	3879
Hospitalization	24497[5.66]***	78[2.01]***	302[7.79]***	78[2.01]***
ED visit	79299[18.33]***	620[15.98]***	718[18.51]**	620[15.98]**
Invasive Ventilation within 30 days	1593[0.37]*	<20*	<20	<20
ECMO within 30 days	109[0.03]	0[0.00]	<20	0[0.00]
Death	216[0.05]	0[0.00]	<20	0[0.00]
Severity Score (Mean)	0.292681***	0.197216***	0.333849***	0.197216***
Severity Score = 0	332328[76.80]	3197[82.42]	2908[74.97]	3197[82.42]
Severity Score = 1	75826[17.52]	604[15.57]	667[17.20]	604[15.57]
Severity Score = 2	23075[5.33]	73[1.88]	287[7.40]	73[1.88]
Severity Score = 3	1269[0.29]	<20	<20	<20
Severity Score = 4	216[0.05]	0[0.00]	<20	0[0.00]

Table 3. Final outcome table between matched untreated and treated with NMV-r. [] represents percentages, * - p < 0.05, ** p < 0.01, *** p < 0.001

Discussion:

This study is the largest real-world retrospective study to evaluate the effectiveness of NMV-r in the age group 12-18 years. To date, study of this medication in children has been limited by low rates of use in children and low rates of hospitalization and severe outcomes in children. Our retrospective study estimated a 74% reduction in hospitalization (p-value < 0.001). The primary prospective randomized trial of NMV-r in adults showed a comparable a 89% reduction in likelihood of hospitalization or death.[6] Additionally, the study also exhibits a more modest, but statistically significant 14% reduction in emergency department visits for matched treated group (p-value <0.01) as compared to matched untreated group. Furthermore, the mean severity score was also significantly lower in the match treated group as compared with the matched treated group (p-value <.001). Taken together, this suggests that NMV-r has utility in reducing the risk of severe COVID-19 in high-risk children, despite their low rate of severe outcomes relative to adults. Severe outcomes such as patients requiring ECHO and invasive ventilation during hospitalization, or pediatric deaths, were very rare and therefore did not achieve statistical significance.

Multiple smaller pediatric studies have been published that evaluate the effectiveness of NMV-r in children, but to our knowledge, this is the largest study to date. Wong et al. evaluated the effectiveness of NMV-r on 345 patients between 12-17 years of age, and reported a smaller absolute (0.23%) and relative (34%) risk reduction.[16] This difference may be accounted for by differences in cohort population. The Wong study focused on a territory-wide population in Hong Kong, while in this study the population was enriched for medically fragile children more likely to seek care at an academic medical center, consistent with our relatively high rates of ED and hospital visits. Yan et al. reported NMV-r study with five subjects (all of which had favorable outcomes)[17] and similar studies and case reports has been published where the sample size was less than twenty five.[18] Several large studies that have used regional clinical registries or hospital electronic health records have included only patients that are over 18 years of age.[19, 20] Our study uses the N3C which is the largest EHR-based data set of COVID-19 patients allowing for analysis the efficacy of NMV-r in the pediatric population. Due to the low number of children severely affected with COVID-19, large scale, multi-institutional studies are needed for accurate assessments. Such studies would be difficult without the support from federal institutions such as NIH and NCAT which manages N3C.

This study is subject to several important limitations. As a retrospective study using propensity matching, we cannot control unmeasured confounders, which could lead to bias. We note that the risk of hospitalization was lower in the treated group, even before propensity matching, which is somewhat unexpected given the likelihood of confounding by indication in this cohort. It is also notable that the calculated risk of hospitalization (2-7%) and ED visits (15-18%) are relatively high for the pediatric population. We suspect that this is due to the enrichment of this cohort for medically complex children cared for at academic medical centers more likely to join the N3C. The identity of individual study sites is blinded, so we have little insight into the reasons NMV-r was provided to individual children (underlying risk, provider choice, health inequities, etc.). Finally, this analysis is dependent on the use of ICD-10 codes for COVID-19 and co-morbidity diagnosis, which is subject to error or inconsistency, and cannot distinguish between hospitalization due to COVID-19 and unrelated hospitalizations with coincident COVID-19.

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