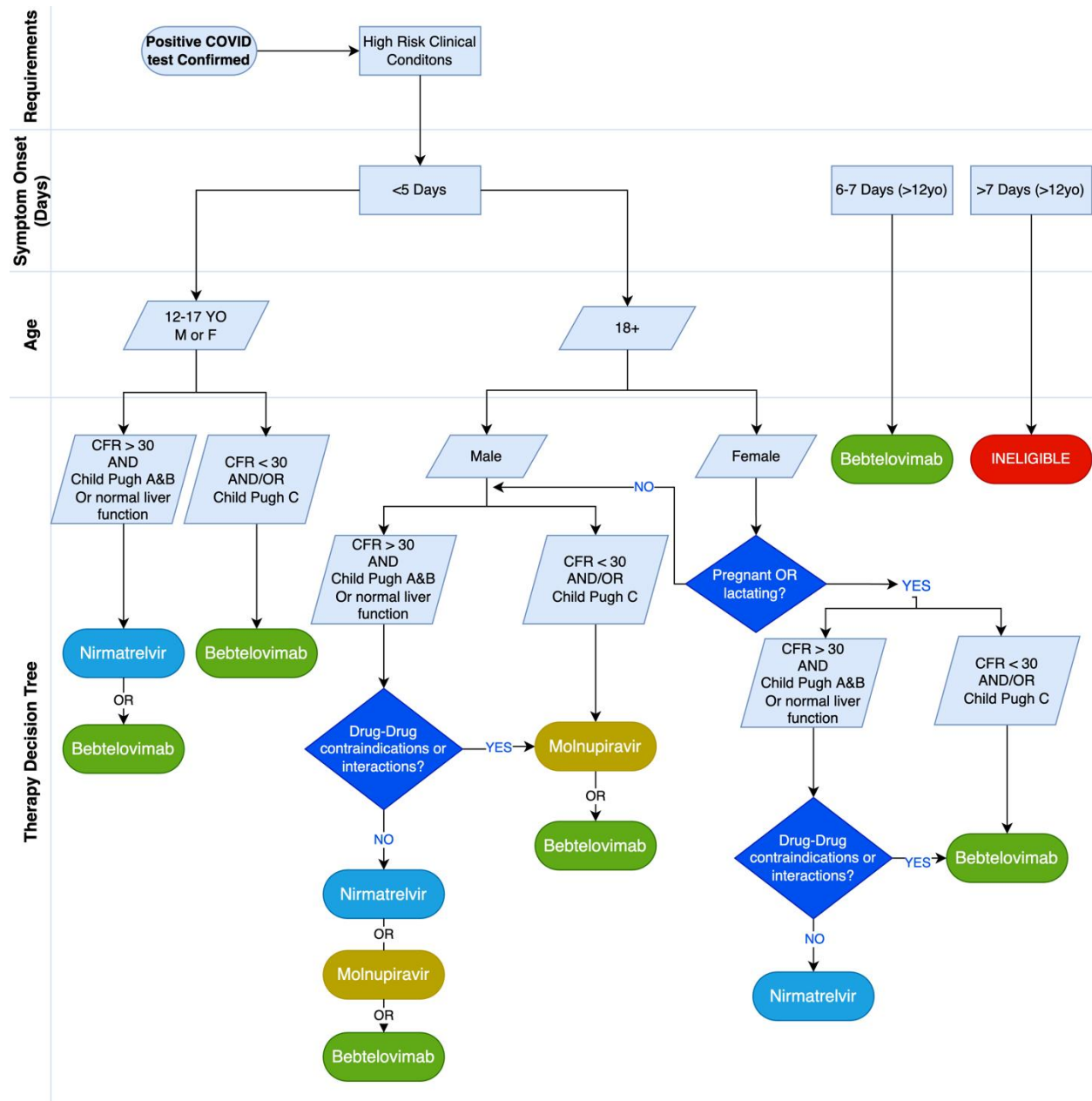


Supplemental Online Content

Lin DY, Abi Fadel F, Huang S, et al. Nirmatrelvir or molnupiravir use and severe outcomes from Omicron infections. *JAMA Netw Open*. 2023;6(9):e2335077. doi:10.1001/jamanetworkopen.2023.35077

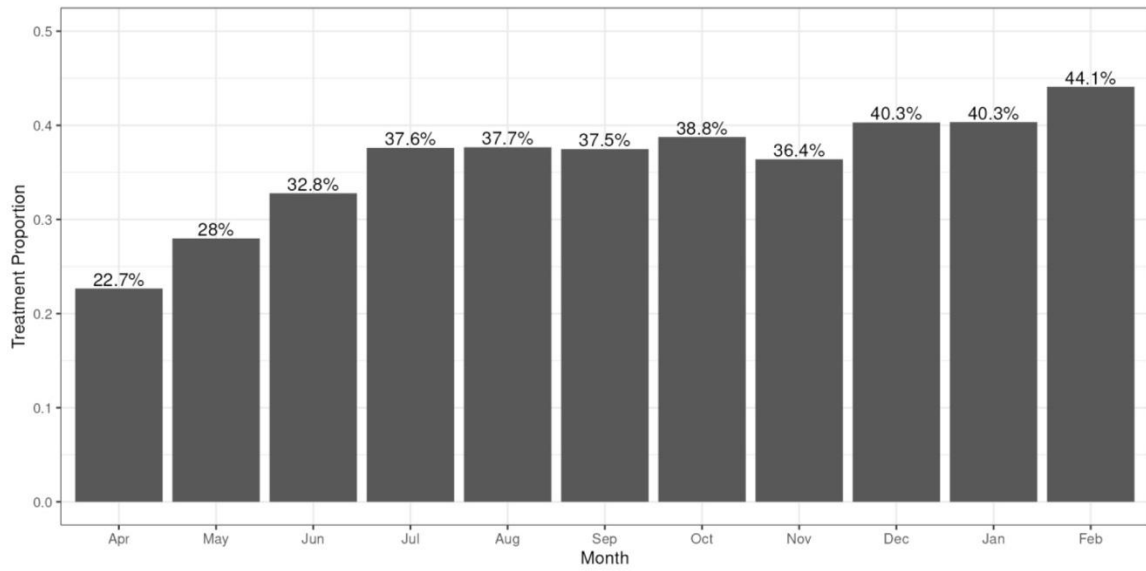
- eFigure 1.** Outpatient Covid-19 Therapeutic Decision Tree at Cleveland Clinic
- eFigure 2.** Proportions of Patients Receiving Treatments Over Time
- eFigure 3.** Cumulative Incidence of Death After Omicron Infection by Treatments for Patients 65 Years of Age or Older
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- eTable 6.** Adjusted Hazard Ratios of Hospitalization or Death After Omicron Infection for Treatments by Subgroup

This supplemental material has been provided by the authors to give readers additional information about their work.

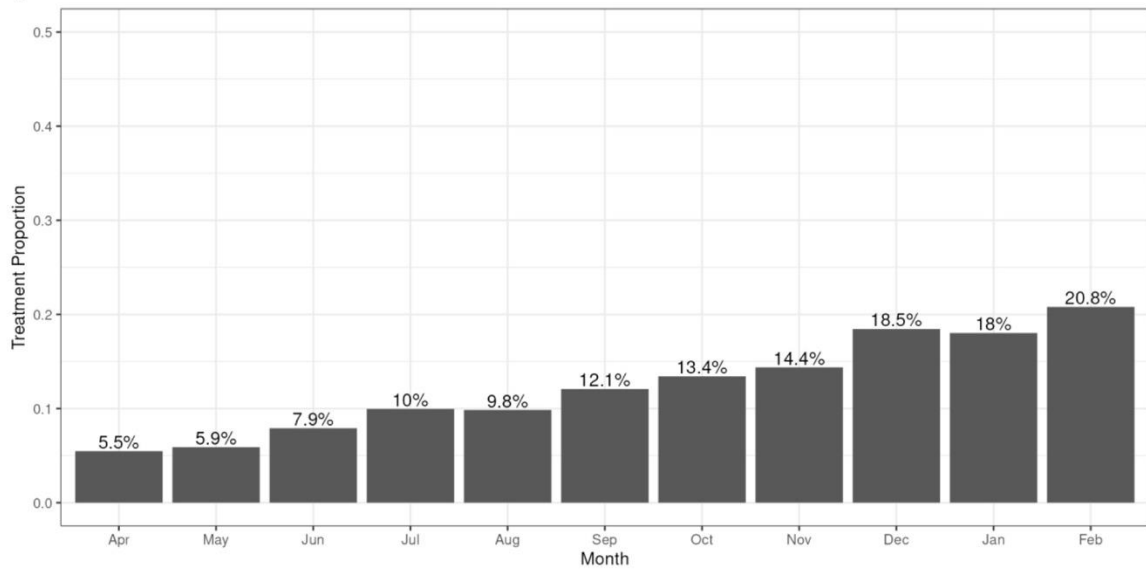


eFigure 1. Outpatient Covid-19 Therapeutic Decision Tree at Cleveland Clinic.

A Nirmatrelvir

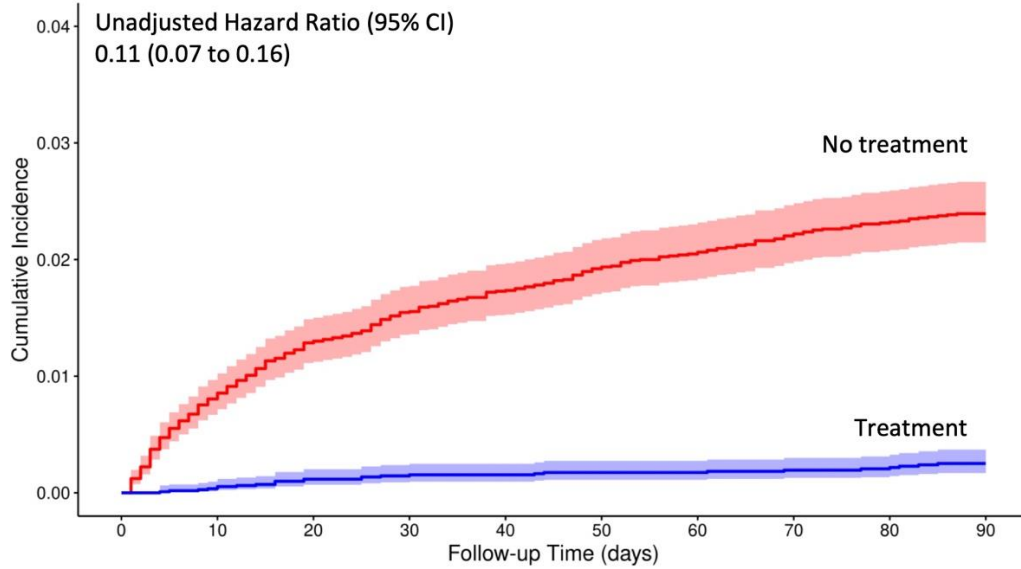


B Molnupiravir



eFigure 2. Proportions of Patients Receiving Treatments Over Time

A Nirmatrelvir

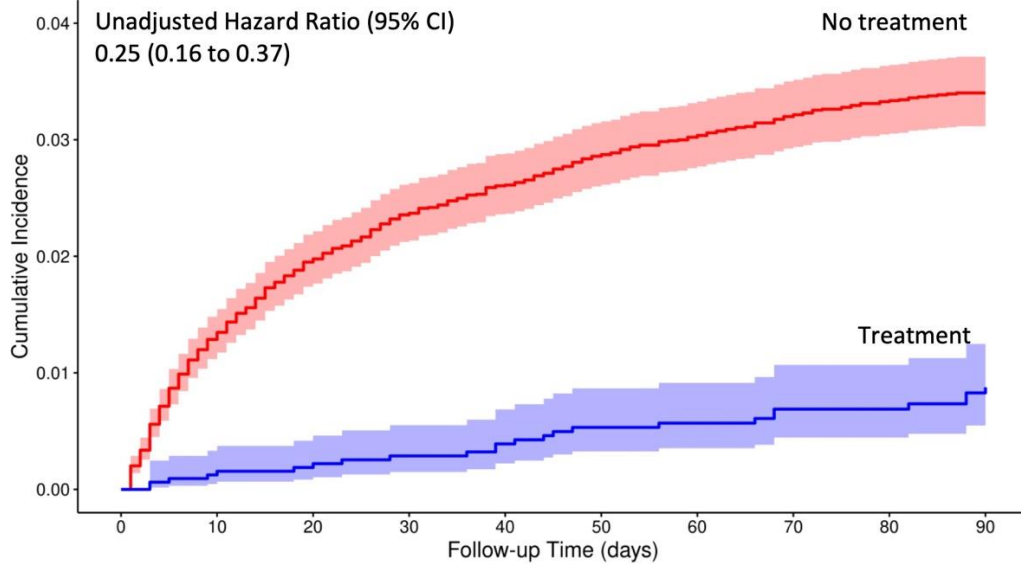


No. at Risk

(Cumulative No. of Events)

No Treatment	13,934	13,733	13,386	13,114	12,858	12,566	12,152	11,693	11,214	10,760
	(0)	(119)	(180)	(214)	(238)	(264)	(280)	(299)	(311)	(319)
Treatment	11,303	11,186	10,866	10,614	10,407	10,164	9,865	9,344	8,856	8,422
	(0)	(6)	(13)	(17)	(17)	(19)	(19)	(21)	(23)	(26)

B Molnupiravir



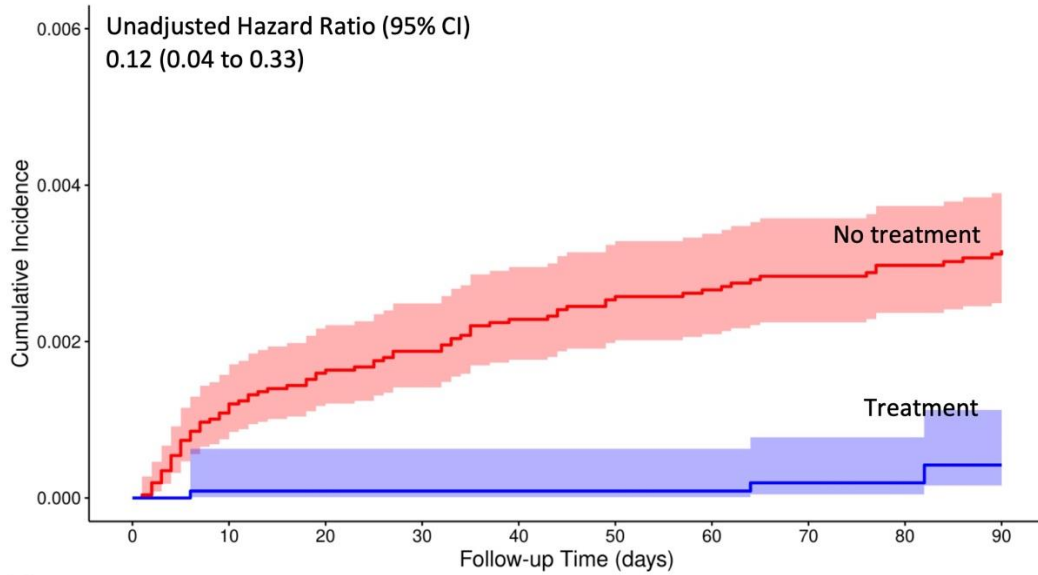
No. at Risk

(Cumulative No. of Events)

No Treatment	14,857	14,566	14,165	13,851	13,565	13,245	12,796	12,299	11,785	11,300
	(0)	(200)	(292)	(348)	(382)	(418)	(440)	(463)	(478)	(486)
Treatment	3,226	3,178	3,055	2,961	2,869	2,776	2,638	2,415	2,231	2,063
	(0)	(5)	(7)	(9)	(12)	(16)	(17)	(20)	(20)	(24)

eFigure 3. Cumulative Incidence of Death After Omicron Infection by Treatments for Patients 65 Years of Age or Older.

A Nirmatrelvir

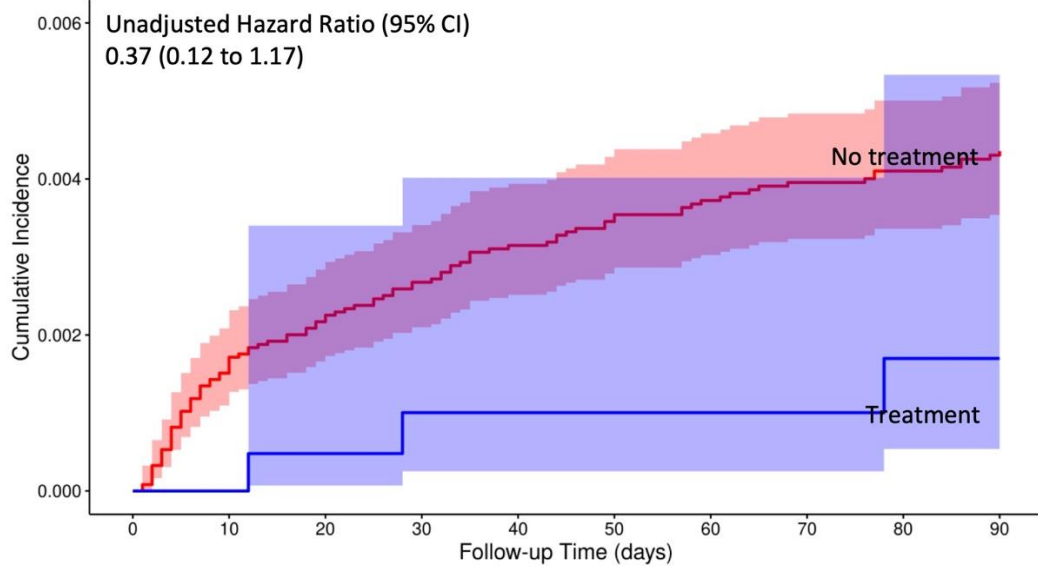


No. at Risk

(Cumulative No. of Events)

No Treatment	25,796	25,666	25,165	24,675	24,256	23,769	23,132	22,236	21,324	20,413
	(0)	(31)	(42)	(48)	(58)	(65)	(67)	(71)	(74)	(78)
Treatment	11,291	11,210	10,883	10,561	10,344	10,127	9,837	9,342	8,849	8,412
	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(2)	(2)	(4)

B Molnupiravir

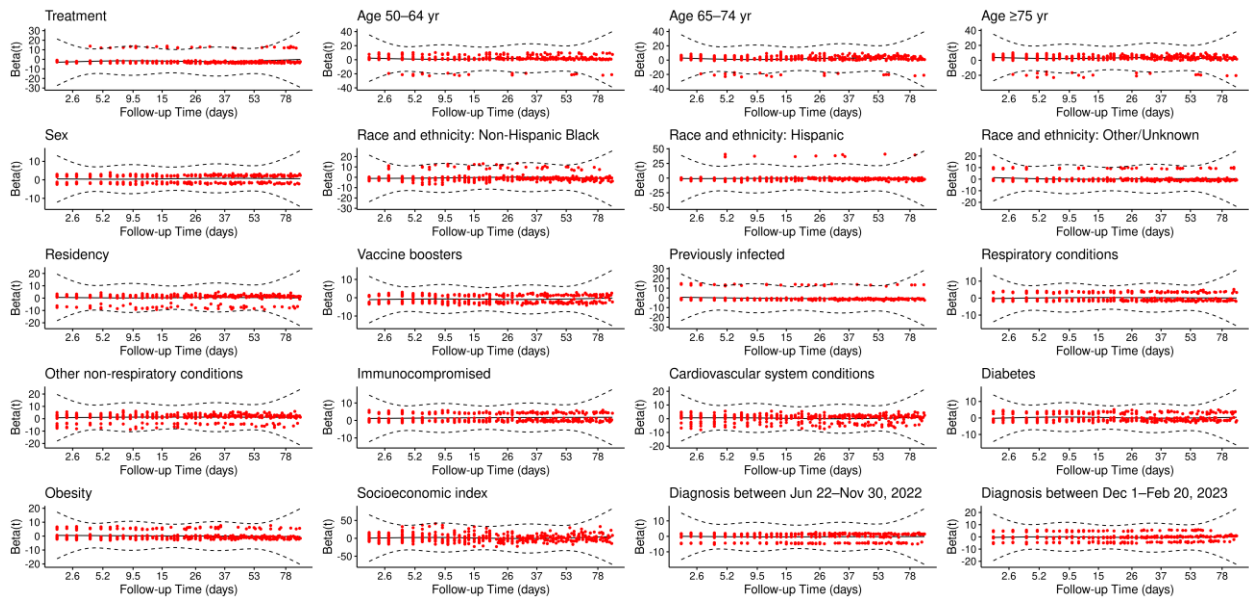


No. at Risk

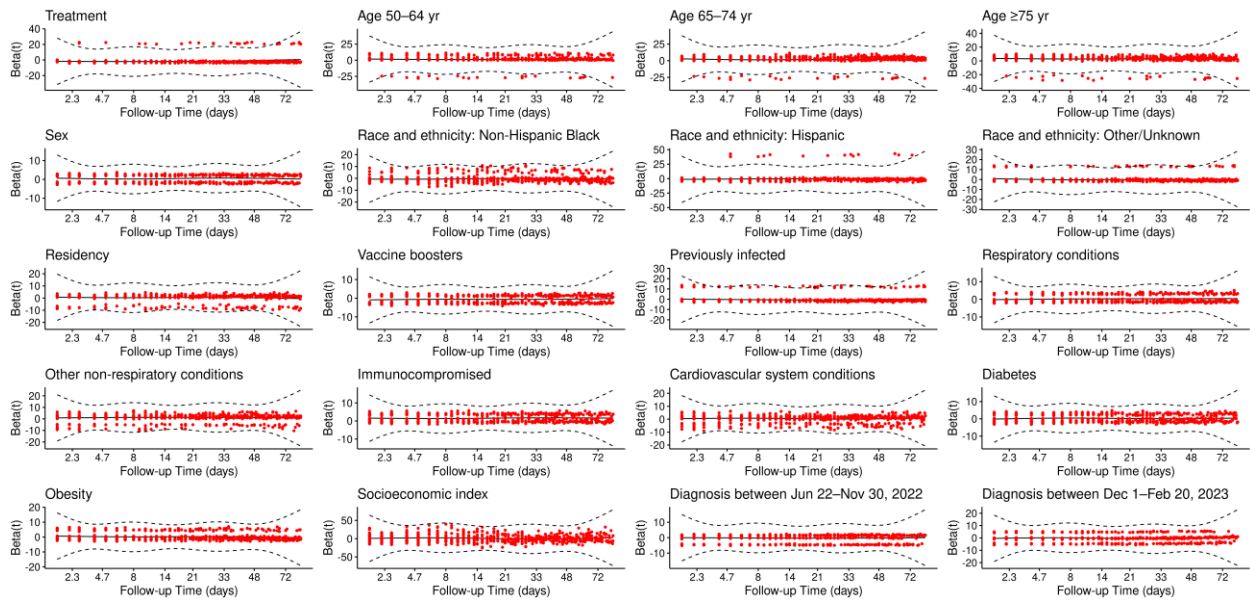
(Cumulative No. of Events)

No Treatment	24,494	24,457	23,873	23,401	23,002	22,523	21,902	21,029	20,160	19,296
	(0)	(42)	(55)	(65)	(76)	(85)	(89)	(94)	(97)	(102)
Treatment	2,085	2,085	1,966	1,886	1,823	1,754	1,689	1,546	1,422	1,316
	(0)	(0)	(1)	(2)	(2)	(2)	(2)	(2)	(3)	(3)

eFigure 4. Cumulative Incidence of Death After Omicron Infection by Treatments for Patients Less Than 65 Years of Age.



eFigure 5. Estimates of Time-Varying Hazard Ratios for Time to Death in the Cox Regression Analysis of Nirmatrelvir Treatment.



eFigure 6. Estimates of Time-Varying Hazard Ratios for Time to Death in the Cox Regression Analysis of Molnupiravir Treatment.

eTable 1. ICD-10 Codes for the Underlying Conditions of Covid-19 Patients at High Risk of Progressing to Severe Disease.

Conditions	ICD-10 diagnosis code
Overweight (BMI>30) and obesity	E66
Diabetes mellitus	E08-E13
Pregnancy, childbirth and the puerperium	O00-O9A
Glomerular diseases	N00-N08
Renal tubulo-interstitial diseases	N10-N16
Acute kidney failure and chronic kidney disease	N17-N19
Diseases of the circulatory system	I00-I99
Diseases of the respiratory system	J40-J99
Sickle-cell disorders	D57
Diseases of the nervous system	G00-G99
Congenital malformations of the nervous system	Q00-Q07
Artificial opening status	Z93
Neutropenia	D70
Functional disorders of polymorphonuclear neutrophils	D71
Certain disorders involving the immune mechanism	D80-D89
Long term (current) use of systemic steroids	Z79.52
Human immunodeficiency virus [HIV] disease	B20
Autoinflammatory syndromes	M04-M04
Inflammatory polyarthropathies	M05-M14
Systemic connective tissue disorders	M30-M36
Myositis	M60
Ankylosing spondylitis	M45
Other inflammatory spondylopathies	M46
Lupus erythematosus	L93
Other localized connective tissue disorders	L94
Vasculitis limited to skin, not elsewhere classified	L95
Neoplasms	C00-D49
Encounter for antineoplastic radiation therapy	Z51.0
Encounter for antineoplastic chemotherapy and immunotherapy	Z51.1
Encounter for antineoplastic chemotherapy	Z51.11
Encounter for antineoplastic immunotherapy	Z51.12

eTable 2. Categories of Comorbidities for Covid-19 Patients.^a

Respiratory conditions	Chronic pulmonary disease Pulmonary circulation disease
Immunocompromised conditions^b	Human immunodeficiency virus Pneumocystosis Malignant neoplasm associated with transplanted organ Other malignant immunoproliferative diseases
Cardiovascular system conditions	Congestive heart failure Valvular disease Peripheral vascular disease Hypertensive disease Ischemic heart disease Cerebrovascular disease
Diabetes conditions	Diabetes without chronic complications Diabetes with chronic complications
Obesity conditions	Obesity
Other non-respiratory conditions	Paralysis Other neurological disorders Hypothyroidism Renal failure Liver disease Peptic ulcer Disease x bleeding Lymphoma Metastatic cancer Solid tumor w/out metastasis Rheumatoid arthritis/collagen vas Coagulopathy Fluid and electrolyte disorders Chronic blood loss anemia Deficiency Anemias Alcohol abuse Drug abuse Psychoses Depression

a. The Elixhauser Comorbidity Software, Version 3.7 was used to extract the comorbidity variables. The comorbidity was based on diagnosis within 30 days of the COVID diagnosis date and followed the definition from “The AHRQ Elixhauser Comorbidity index. Med Care. 2017 Jul; 55(7):698-705”. The definitions and ICD-10 codes of the comorbidity variables can be found at <https://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp>

b. The full list of immunocompromised states is available at https://www.qualityindicators.ahrq.gov/Downloads/Modules/PSI/V60-ICD10/TechSpecs/PSI_Appendix_1.pdf

eTable 3. Differences of Demographic and Clinical Characteristics Between Treated and Untreated Patients

Variable	Mean Difference (95% CI)	
	Nirmatrelvir	Molnupiravir
Age	7.86 (7.59 to 8.14)	9.99 (9.56 to 10.43)
Female sex (%)	-3.09 (-3.88 to -2.29)	-9.45 (-10.89 to -8.01)
Race and ethnicity (%)		
Hispanic	-2.32 (-2.69 to -1.96)	-3.03 (-3.58 to -2.48)
non-Hispanic Black	-8.95 (-9.44 to -8.46)	-10.13 (-10.88 to -9.38)
Non-Hispanic White	12.87 (12.19 to 13.55)	15.13 (14.05 to 16.21)
Ohio residency (%)	0.39 (-0.17 to 0.95)	1.44 (0.47 to 2.41)
SARS-CoV-2 immunity status (%)		
Vaccine boosters	25.27 (24.52 to 26.02)	27.51 (26.29 to 28.73)
Previously infected	-4.88 (-5.36 to -4.39)	-4.40 (-5.23 to -3.58)
Coexisting conditions (%)		
Respiratory	-1.52 (-2.16 to -0.89)	3.83 (2.61 to 5.04)
Immunocompromised	0.17 (-0.22 to 0.55)	10.73 (9.66 to 11.81)
Cardiovascular system	4.89 (4.08 to 5.69)	17.53 (16.10 to 18.96)
Diabetes	1.06 (0.49 to 1.63)	7.97 (6.78 to 9.17)
Obesity	0.17 (-0.41 to 0.75)	2.43 (1.35 to 3.50)
Other non-respiratory	-0.26 (-1.08 to 0.55)	11.99 (10.57 to 13.41)
Socioeconomic index	-0.03 (-0.03 to -0.03)	-0.03 (-0.03 to -0.03)
Covid-19 diagnosis (%)		
Apr 1– Jun 21, 2022	-7.48 (-8.13 to -6.83)	-11.60 (-12.59 to -10.61)
Jun 22 – Nov 30, 2022	2.90 (2.09 to 3.71)	-3.16 (-4.60 to -1.71)

eTable 4. Kaplan-Meier Estimates and 95% Confidence Intervals for the Cumulative Incidence of Death After Covid-19 Diagnosis

	30 Days		60 Days		90 Days	
	Treatment	No Treatment	Treatment	No treatment	Treatment	No treatment
Nirmatrelvir						
All Patients	0.08%	0.67%	0.09%	0.90%	0.15%	1.05%
	(0.05 to 0.13)	(0.59 to 0.75)	(0.06 to 0.14)	(0.81 to 0.99)	(0.10 to 0.21)	(0.95 to 1.15)
≥65 yrs	0.15%	1.57%	0.17%	2.08%	0.25%	2.42%
	(0.10 to 0.25)	(1.36 to 1.77)	(0.11 to 0.27)	(1.84 to 2.32)	(0.17 to 0.37)	(1.15 to 2.67)
<65 yrs	0.01%	0.19%	0.01%	0.27%	0.04%	0.32%
	(0.001 to 0.06)	(0.14 to 0.25)	(0.008 to 0.06)	(0.21 to 0.34)	(0.02 to 0.11)	(0.25 to 0.40)
Molnupiravir						
All Patients	0.21%	1.07%	0.39%	1.39%	0.60%	1.57%
	(0.12 to 0.39)	(0.96 to 1.17)	(0.25 to 0.61)	(1.26 to 1.50)	(0.41 to 0.88)	(1.43 to 1.68)
≥65 yrs	0.29%	2.40%	0.57%	3.08%	0.88%	3.46%
	(0.15 to 0.55)	(2.14 to 2.63)	(0.35 to 0.91)	(2.77 to 3.33)	(0.59 to 1.31)	(3.12 to 3.71)
<65 yrs	0.10%	0.27%	0.10%	0.37%	0.17%	0.44%
	(0.03 to 0.40)	(0.21 to 0.34)	(0.03 to 0.40)	(0.30 to 0.46)	(0.05 to 0.54)	(0.36 to 0.53)

eTable 5. Adjusted Hazard Ratios of Hospitalization or Death After Omicron Infection for Treatments and Confounding Variables

Variable	Hazard Ratio (95% CI)	
	Nirmatrelvir (N=62,324)	Molnupiravir (N=44,662)
Treatment	0.63 (0.59 to 0.68)	0.59 (0.53 to 0.66)
Age group		
50–64 yr	1.10 (1.01 to 1.20)	1.20 (1.09 to 1.32)
65–74 yr	1.20 (1.10 to 1.31)	1.39 (1.26 to 1.53)
≥75 yr	1.54 (1.40 to 1.68)	1.78 (1.62 to 1.96)
Male sex	0.99 (0.93 to 1.05)	1.06 (1.00 to 1.13)
Race and ethnicity		
Hispanic	0.86 (0.74 to 1.00)	0.88 (0.76 to 1.03)
Black, non-Hispanic	0.87 (0.79 to 0.95)	0.89 (0.81 to 0.98)
Other/Unknown	1.04 (0.93 to 1.17)	1.01 (0.89 to 1.14)
Ohio residency	1.62 (1.46 to 1.81)	1.41 (1.28 to 1.57)
SARS-CoV-2 immunity status		
Vaccine boosters	0.82 (0.77 to 0.87)	0.79 (0.74 to 0.84)
Previously infected	0.95 (0.87 to 1.04)	0.96 (0.87 to 1.05)
Coexisting conditions		
Respiratory	1.38 (1.29 to 1.47)	1.32 (1.23 to 1.41)
Immunocompromised	2.24 (2.07 to 2.43)	2.39 (2.22 to 2.57)
Cardiovascular system	1.57 (1.47 to 1.69)	1.65 (1.53 to 1.78)
Diabetes	1.12 (1.04 to 1.20)	1.10 (1.03 to 1.19)
Obesity	1.44 (1.34 to 1.54)	1.44 (1.34 to 1.55)
Other non-respiratory	2.42 (2.26 to 2.59)	2.52 (2.33 to 2.73)
Socioeconomic index	0.54 (0.40 to 0.74)	0.64 (0.47 to 0.88)
Covid-19 diagnosis		
Jun 22 – Nov 30, 2022	1.06 (0.98 to 1.14)	1.09 (1.00 to 1.18)
Dec 1– Feb 20, 2023	1.21 (1.11 to 1.32)	1.24 (1.13 to 1.36)

eTable 6. Adjusted Hazard Ratios of Hospitalization or Death After Omicron Infection for Treatments by Subgroup.

	Nirmatrelvir		Molnupiravir	
	No. treated/N	Hazard Ratio (95% CI)	No. treated/N	Hazard Ratio (95% CI)
Age				
12–64 yr	11,291/37,087	0.67 (0.61 to 0.75)	2,085/26,579	0.58 (0.48 to 0.70)
≥65 yr	11,303/25,237	0.60 (0.55 to 0.66)	3,226/18,083	0.60 (0.53 to 0.68)
Race and ethnicity				
Non-Hispanic White	18,571/46,113	0.63 (0.59 to 0.68)	4,499/31,878	0.60 (0.54 to 0.67)
Others	4,023/16,211	0.61 (0.52 to 0.73)	812/12,784	0.54 (0.41 to 0.71)
Vaccine boosters				
Yes	16,966/36,761	0.63 (0.58 to 0.69)	4,162/24,174	0.59 (0.52 to 0.66)
No	5,628/25,563	0.58 (0.51 to 0.66)	1,149/20,488	0.56 (0.45 to 0.71)
Previous infection				
Yes	1,816/6,947	0.70 (0.56 to 0.86)	444/5,467	0.75 (0.55 to 1.02)
No	20,778/55,377	0.63 (0.58 to 0.67)	4,867/39,195	0.57 (0.51 to 0.64)
Respiratory disorders				
Yes	3,994/11,623	0.71 (0.62 to 0.80)	1,242/8,938	0.63 (0.53 to 0.76)
No	18,600/50,701	0.60 (0.56 to 0.66)	4,069/35,724	0.57 (0.50 to 0.65)
Immunocompromised disorders				
Yes	1,339/3,627	0.54 (0.45 to 0.66)	960/3,849	0.48 (0.39 to 0.58)
No	21,255/58,697	0.65 (0.60 to 0.70)	4,351/40,813	0.66 (0.58 to 0.75)
Cardiovascular system disorders				
Yes	9,472/24,187	0.60 (0.55 to 0.66)	3,045/18,708	0.56 (0.50 to 0.64)
No	13,122/38,137	0.69 (0.62 to 0.78)	2,266/25,954	0.71 (0.57 to 0.87)
Diabetes				
Yes	3,263/8,579	0.65 (0.57 to 0.76)	1,215/7,080	0.52 (0.43 to 0.63)
No	19,331/53,745	0.63 (0.58 to 0.68)	4,096/37,582	0.63 (0.55 to 0.71)
Obesity				
Yes	3,255/8,911	0.56 (0.48 to 0.64)	901/6,622	0.54 (0.43 to 0.66)
No	19,339/53,413	0.66 (0.60 to 0.71)	4,410/38,040	0.61 (0.54 to 0.69)
Other non-respiratory disorders				
Yes	10,200/28,240	0.62 (0.57 to 0.67)	3,143/21,713	0.56 (0.50 to 0.63)
No	12,394/34,084	0.68 (0.59 to 0.77)	2,168/22,949	0.76 (0.60 to 0.96)
Covid-19 diagnosis				
Apr 1– Jun 21, 2022	3,762/13,349	0.66 (0.56 to 0.78)	649/10,023	0.62 (0.46 to 0.83)
Jun 22 – Nov 30, 2022	13,190/35,231	0.65 (0.60 to 0.71)	2,778/24,603	0.59 (0.51 to 0.68)
Dec 1– Feb 20, 2023	5,642/13,744	0.57 (0.49 to 0.65)	1,884/10,036	0.57 (0.47 to 0.68)