

Figure S1: Covid-19 Variants in Analyzed Sequences in Israel

Obtained by GISAID via CoVariants.org – at 1st of October, 2022

During the study period, more than 99% of the sequenced cases are Omicron sublineages (21K till end of February, then 21L till early June and then 22B till the end of the study).

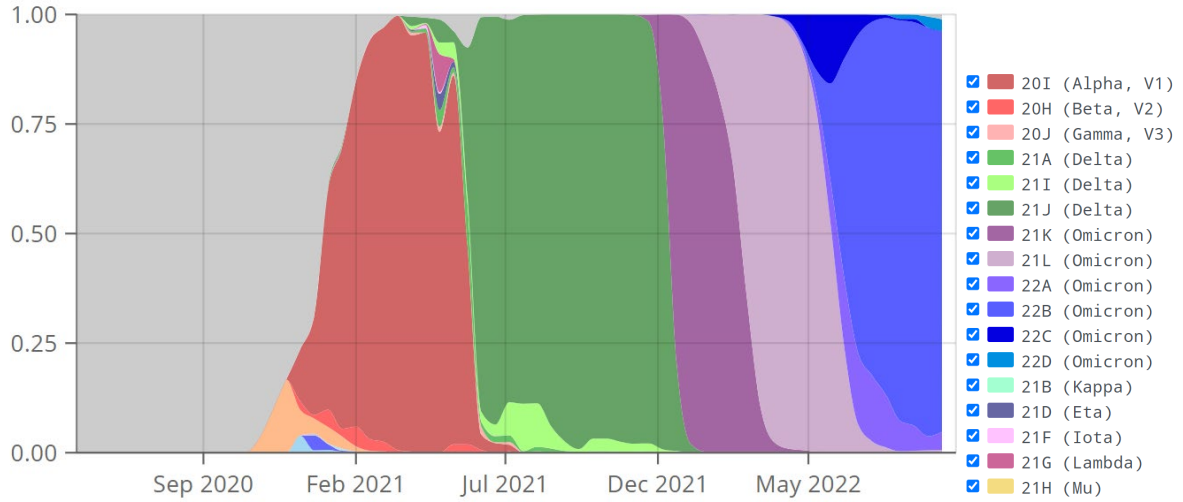


Figure S2: The cumulative percentage of patients with Covid-19–related hospitalization (Panel A) and death of any cause (Panel B) estimated using of the Kaplan–Meier model. Treatment with Nirmatrelvir is associated with a lower hospitalization rate (p-value=0.0088) and mortality rate (p-value<0.001). To improve clarity, the Y-axis has been zoomed in to the range of 0 to 15%

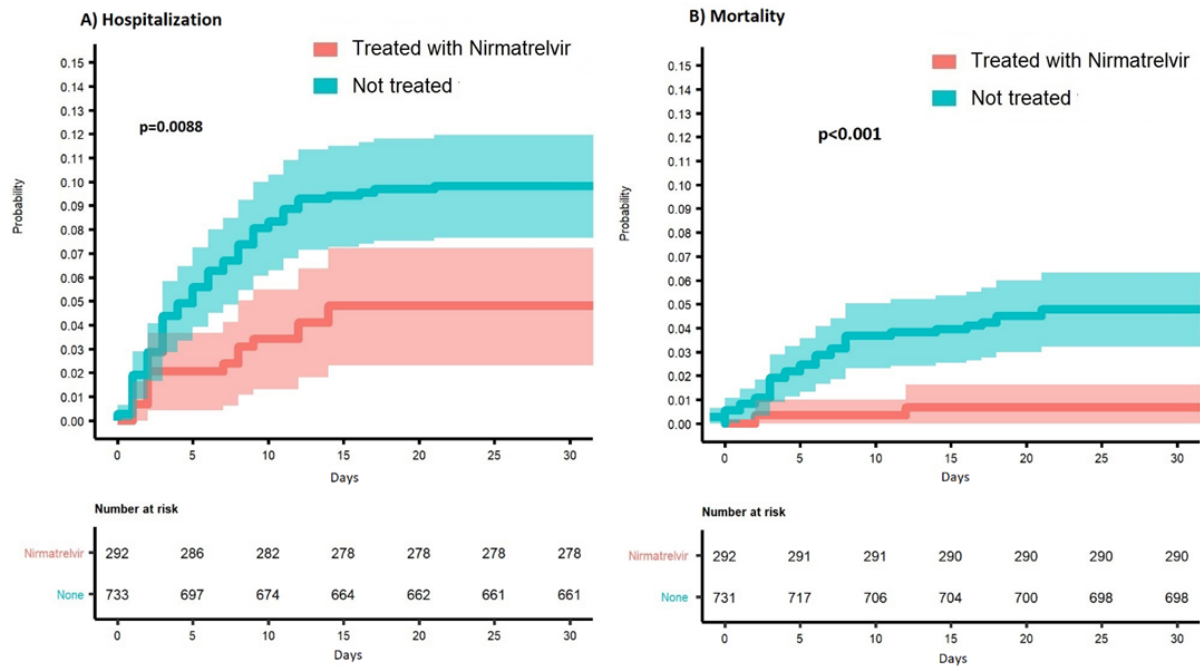


Figure S3: Repeating the cumulative Hazard Ratio analysis presented in Figure 1B, when time zero is set to the time at which each patient had received a positive Covid-19 PCR for both treated and untreated patients. To improve clarity, the Y-axis has been zoomed in to the range of 0 to 15%

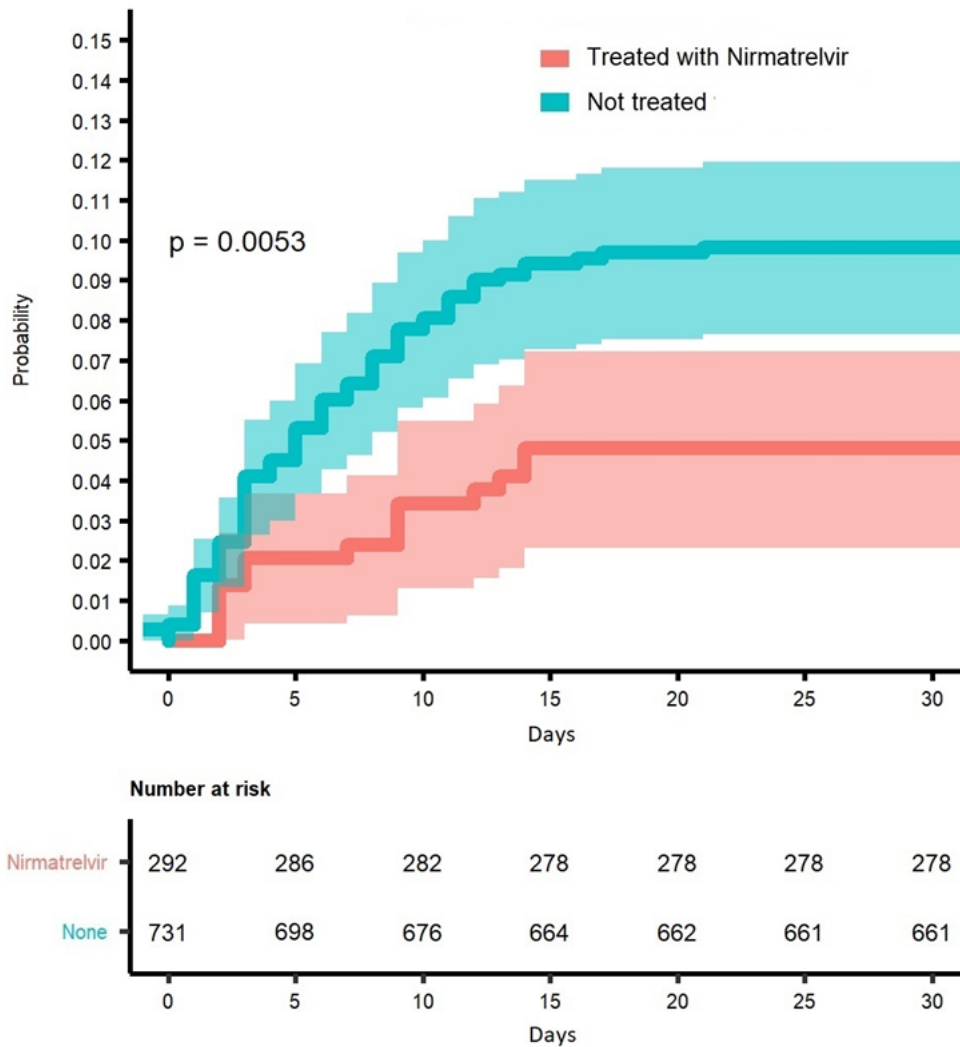


Figure S4: Cumulative Hazard Ratio by Covid-19 anti-viral therapy, showing that the outcome of Molnupiravir group can't be distinguished from untreated group. To improve clarity, the Y-axis has been zoomed in to the range of 0 to 30%

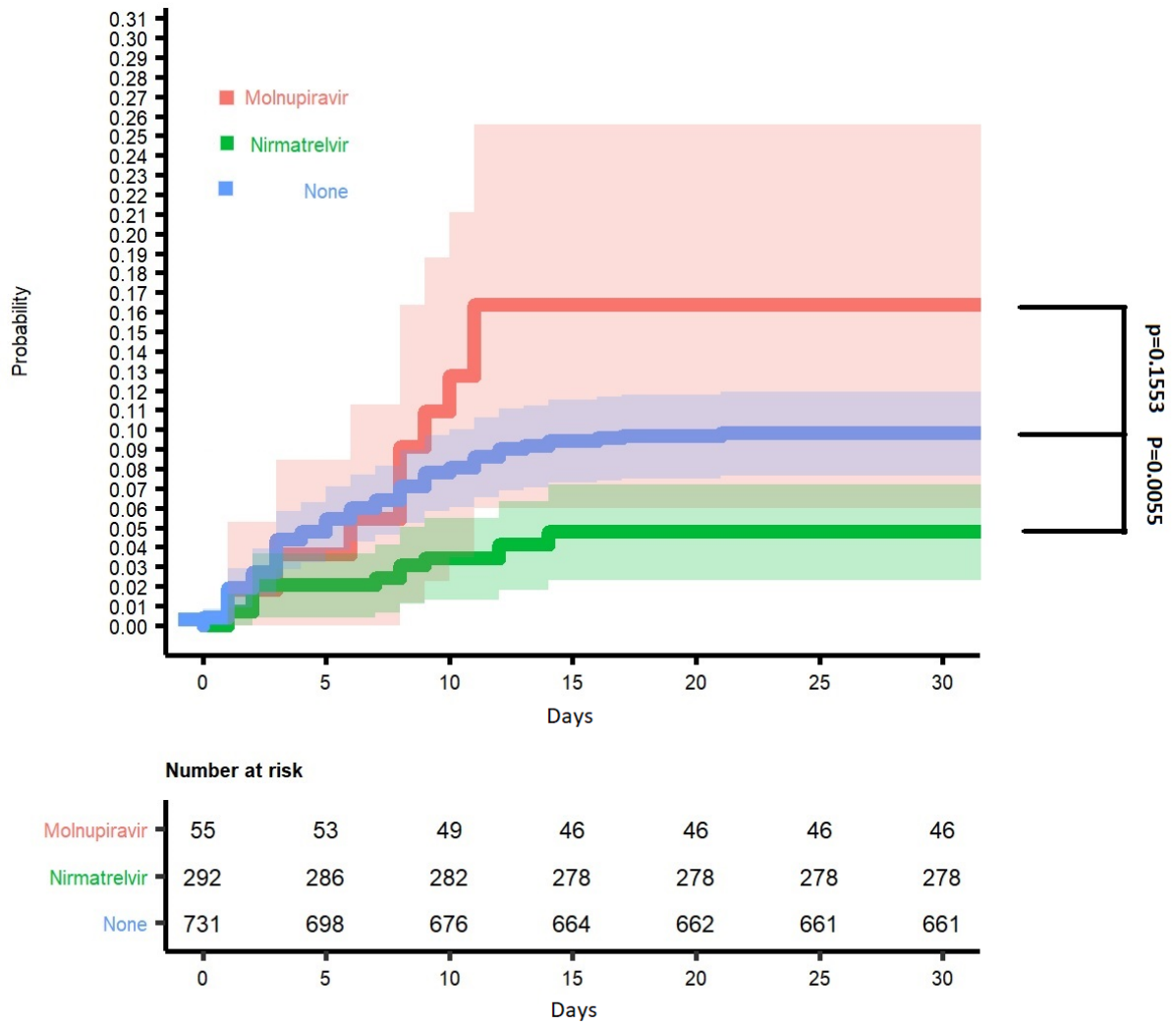


Figure S5: Cumulative Hazard Ratio by Covid-19 any anti-viral therapy, showing that the outcome of treated group can't be distinguished from untreated group. To improve clarity, the Y-axis has been zoomed in to the range of 0 to 20%

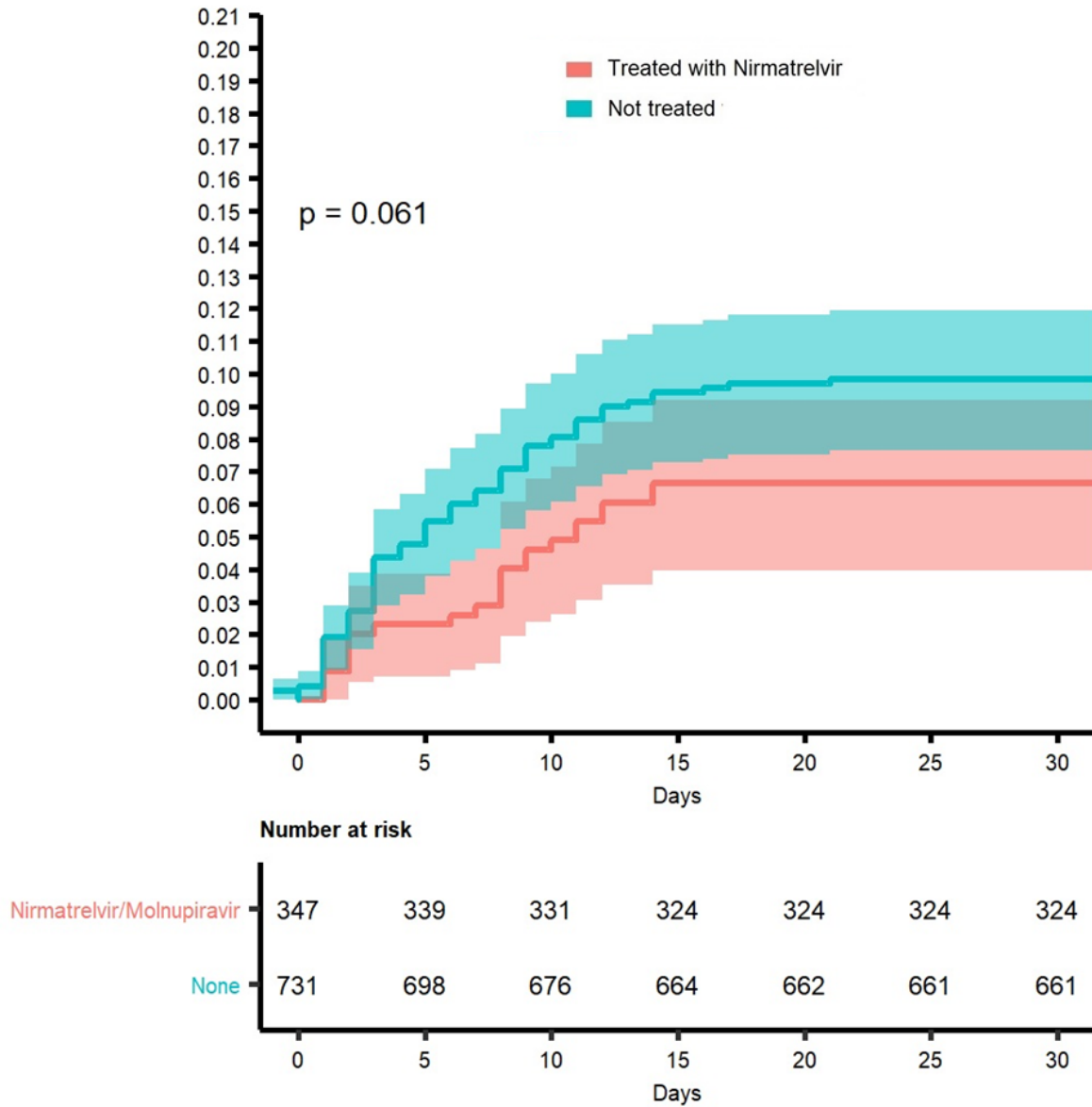


Table S1: Demographic and Clinical Characteristics of the Patients (Full Analysis Population). P values indicate if anti-viral therapy varies considerably by factor. The first p-value refers to all three treatment options (No therapy, Molnupiravir, Nirmatrelvir) the second p-value compare only the Nirmatrelvir group to the Molnupiravir group.

		Molnupiravir (N=55)	Nirmatrelvir (N=292)	None (N=733)	Total (N=1080)	p value	p-value Molnupiravir vs. Nirmatrelvir3
Demographic							
Age	Median (Q1, Q3)	73 (67, 78)	71 (65, 77)	70 (61, 77)	71 (62, 77)	0.012	0.14
	<65	10 (18.2%)	81 (27.7%)	262 (35.7%)	353 (32.7%)		
	≥65	45 (81.8%)	211 (72.3%)	471 (64.3%)	727 (67.3%)		
Gender	Female	19 (34.5%)	132 (45.2%)	313 (42.7%)	464 (43.0%)	0.332	0.144
	Male	36 (65.5%)	160 (54.8%)	420 (57.3%)	616 (57.0%)		
Ethnic Group	Arabic	1 (1.8%)	4 (1.4%)	21 (2.9%)	26 (2.4%)	0.259	0.452
	Former USSR	7 (12.7%)	16 (5.5%)	91 (12.4%)	114 (10.6%)		
	Moderate Orthodox	0 (0.0%)	11 (3.8%)	16 (2.2%)	27 (2.5%)		
	General Jew	46 (83.6%)	258 (88.4%)	575 (78.4%)	879 (81.4%)		
	Orthodox Jew	1 (1.8%)	3 (1.0%)	30 (4.1%)	34 (3.1%)		
Socioeconomic Score	Median (Q1, Q3)	8 (5, 9)	8 (7, 9)	7 (5, 9)	7 (5, 9)	< 0.001	0.121
CLL Status and Therapy							
Treatment Status	Treatment Naïve	26 (47.3%)	171 (58.6%)	548 (74.8%)	745 (69.0%)	< 0.001	0.062
	Off Therapy	12 (21.8%)	66 (22.6%)	118 (16.1%)	196 (18.1%)		
	On Therapy	17 (30.9%)	55 (18.8%)	67 (9.1%)	139 (12.9%)		
Number of CLL Treatments	Median (Q1, Q3)	1 (0, 2)	0 (0, 1)	0 (0, 1)	0 (0, 1)	< 0.001	0.019
Current Treatment	BTki	14 (25.5%)	41 (13.9%)	48 (6.5%)	103 (9.5%)	0.865	0.665
	Ven	3 (5.5%)	12 (4.1%)	15 (2.0%)	30 (2.8%)		
Time since last Anti-CD20 therapy	<12 mo	6 (10.9%)	18 (6.2%)	34 (4.6%)	58 (5.4%)	0.565	0.295
	≥12 mo	12 (21.8%)	65 (22.3%)	101 (13.7%)	178 (16.4%)		
IVIg Treatment		6 (10.9%)	35 (12.0%)	48 (6.5%)	89 (8.2%)	0.013	0.821
Frequent Comorbidities and Risk Factors							
Diseases of the Circulatory System							
	Cardiac arrhythmia	18 (32.7%)	98 (33.6%)	212 (28.9%)	328 (30.4%)	0.321	0.904
	Heart Failure	2 (3.6%)	18 (6.2%)	57 (7.8%)	77 (7.1%)	0.39	0.461
	Hypertension	33 (60.0%)	189 (64.7%)	450 (61.4%)	672 (62.2%)	0.575	0.504
	Other Cerebrovascular Disease	1 (1.8%)	23 (7.9%)	46 (6.3%)	70 (6.5%)	0.228	0.105
	Other Heart Disease	6 (10.9%)	54 (18.5%)	148 (20.2%)	208 (19.3%)	0.225	0.173
	Stroke	1 (1.8%)	21 (7.2%)	54 (7.4%)	76 (7.0%)	0.298	0.134
Endocrine And Metabolic Diseases							
	Diabetes Mellitus	16 (29.1%)	87 (29.8%)	237 (32.3%)	340 (31.5%)	0.678	0.917
	Disorder Of Thyroid	13 (23.6%)	65 (22.3%)	187 (25.5%)	265 (24.5%)	0.544	0.823
	Disorders of lipid metabolism	39 (70.9%)	192 (65.8%)	517 (70.5%)	748 (69.3%)	0.315	0.458
	Obesity	17 (30.9%)	123 (42.1%)	295 (40.2%)	435 (40.3%)	0.298	0.12
	Other Metabolic Disorders	4 (7.3%)	36 (12.3%)	79 (10.8%)	119 (11.0%)	0.512	0.282
Hematological diseases							
	ALL	1 (1.8%)	16 (5.5%)	39 (5.3%)	56 (5.2%)	0.51	0.249
	AML	2 (3.6%)	0 (0.0%)	13 (1.8%)	15 (1.4%)	0.031	0.001
	CML	7 (12.7%)	46 (15.8%)	111 (15.1%)	164 (15.2%)	0.847	0.568
	Diseases Of the Blood and Blood Forming Organs	30 (54.5%)	142 (48.6%)	375 (51.2%)	547 (50.6%)	0.642	0.422
	Hodgkin	2 (3.6%)	2 (0.7%)	14 (1.9%)	18 (1.7%)	0.194	0.06
	Lymphadenopathy	27 (49.1%)	98 (33.6%)	281 (38.3%)	406 (37.6%)	0.071	0.028
	Myeloproliferative diseases	1 (1.8%)	13 (4.5%)	33 (4.5%)	47 (4.4%)	0.639	0.363
	NHL	18 (32.7%)	69 (23.6%)	204 (27.8%)	291 (26.9%)	0.24	0.154
	Other Haematological Malignancies	20 (36.4%)	81 (27.7%)	230 (31.4%)	331 (30.6%)	0.335	0.197
	Splenomegaly	4 (7.3%)	20 (6.8%)	64 (8.7%)	88 (8.1%)	0.593	0.91
Kidney diseases							
Chronic Kidney Disease	-A (GFR above 90 and proteinuria)	1 (1.8%)	4 (1.4%)	19 (2.6%)	24 (2.2%)	0.028	0.008
	-A1 (GFR 60 to 89 and proteinuria)	2 (3.6%)	14 (4.8%)	40 (5.5%)	56 (5.2%)		
	-B (GFR 30 to 59)	31 (56.4%)	110 (37.7%)	266 (36.3%)	407 (37.7%)		
	-C (GFR 15 to 29)	3 (5.5%)	3 (1.0%)	14 (1.9%)	20 (1.9%)		
	-D (GFR below 15 or dialysis)	1 (1.8%)	0 (0.0%)	2 (0.3%)	5 (0.3%)		
	Other Renal Failure	5 (9.1%)	43 (14.7%)	97 (13.2%)	145 (13.4%)	0.513	0.268
Liver diseases							
	Hepatic disease	15 (27.3%)	74 (25.3%)	181 (24.7%)	270 (25.0%)	0.902	0.764
	Hepatomegaly	1 (1.8%)	4 (1.4%)	18 (2.5%)	23 (2.1%)	0.547	0.798
Mental Disorders							
	Nonpsychotic Mental Disorders	24 (43.6%)	111 (38.0%)	292 (39.8%)	427 (39.5%)	0.706	0.433
Neurologic diseases							
	Neurologic disease	3 (5.5%)	21 (7.2%)	63 (8.6%)	87 (8.1%)	0.582	0.642
Other Malignancy							
	Calculus Of Kidney And Ureter	9 (16.4%)	62 (21.2%)	176 (24.0%)	247 (22.9%)	0.316	0.412
	Melanoma	4 (7.3%)	16 (5.5%)	32 (4.4%)	52 (4.8%)	0.515	0.601
	Non-Melanoma Skin Malignancy	20 (36.4%)	115 (39.4%)	240 (32.7%)	375 (34.7%)	0.127	0.674
	Other Malignancy	19 (34.5%)	72 (24.7%)	184 (25.1%)	275 (25.5%)	0.281	0.127
	Other Malignancy In Situ or Pre Cancer	12 (21.8%)	60 (20.5%)	159 (21.7%)	231 (21.4%)	0.919	0.831
Respiratory System							
	Asthma	1 (1.8%)	12 (4.1%)	29 (4.0%)	42 (3.9%)	0.713	0.412
	COPD	4 (7.3%)	32 (11.0%)	59 (8.0%)	95 (8.8%)	0.306	0.412
Recent Infection Events	Median (Q1, Q3)	2 (1, 4)	1 (0, 3)	1 (0, 3)	1 (0, 3)	0.203	0.07
Recent hospitalizations		31 (56.4%)	102 (34.9%)	304 (41.5%)	437 (40.5%)	0.008	0.003
Previous Covid Infection	Yes	5 (9.1%)	44 (15.1%)	83 (11.3%)	132 (12.2%)	0.196	0.244

Table S2: The association between Nirmatrelvir or Molnupiravir therapy and Covid-19–related hospitalization or death was estimated with the use of a multivariate Cox proportional-hazards regression model after adjustment for confounding factors. Variables that met the testing criteria and were significantly associated with the outcome served as the inputs for the multivariate regression analysis. ¹ recent refers last three years. ² Number of doses counts both mRNA-based vaccines (mainly Pfizer) and passive vaccines (75 patients received Tixagevimab and Cilgavimab)

Variable	Hazard Ratio for Covid-19 related Hospitalization or Death	p value
Age	1.05 [1.03-1.07]	< .001***
Number of Prior CLL Treatments	1.33 [1.12-1.59]	0.0015 **
Recent Hospitalizations ¹	1.84 [1.2-2.83]	0.0052 **
IVIG Treatment	1.77 [1.09-3.16]	0.041 *
Nirmatrelvir	0.48 [0.26-0.86]	0.0144 *
Molnupiravir	1.58 [0.83-3.02]	0.1655
Previous Covid-19 Infection	0.25 [0.09-0.68]	0.0072 **
Doses of Covid-19 Vaccine ² pre infection	0.75 [0.65-0.87]	< .001***
Recent Melanoma ¹	1.73 [1.09-2.78]	0.0213 *
Recent Other Malignancy ¹	0.41 [0.2-0.85]	0.0167 *
Asthma	2.48 [1.14-5.41]	0.0219 *
Myeloproliferative diseases	3.01 [1.51-6.06]	0.0019 **
Chronic kidney disease status	1.02 [0.57-1.78]	0.82