THE LANCET

Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Wong CKH, Au ICH, Lau KTK, et al. Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study. *Lancet* 2022; **400:** 1213–22.

Appendix 2

Supplementary Table 1. Baseline characteristics of non-hospitalized patients with COVID-19 in (a) molnupiravir and respective control groups, and (b) nirmatrelvir/ritonavir and respective control groups before 1:10 propensity score matching

Baseline characteristics	Before 1:10 matching								
	Molnupiravir (n=5,383)		Control (n=923,783)		SMD	Nirmatrelvir/ritonavir (n=6,464)		Control (n=922,702)		SMD
	N	%	N	%		N	%	N	%	
Age, years										
18-60	574	(10.7%)	667,030	(72.2%)	1.60	875	(13.5%)	666,729	(72.3%)	1.47
>60	4,809	(89.3%)	256,753	(27.8%)		5,589	(86.5%)	255,973	(27.7%)	
Sex					0.03					0.00
Male	2,552	(47.4%)	426,198	(46.1%)		2,988	(46.2%)	425,762	(46.1%)	
Female	2,831	(52.6%)	497,585	(53.9%)		3,476	(53.8%)	496,940	(53.9%)	
Time of COVID-19 diagnosis										
February to March 2022	4,367	(81.1%)	886,850	(96.0%)	0.48	3,962	(61.3%)	887,255	(96.2%)	0.94
April to June 2022	1,016	(18.9%)	36,933	(4.0%)		2,502	(38.7%)	35,447	(3.8%)	
Charlson's Index										
0-4	4,709	(87.5%)	918,229	(99.4%)		6,159	(95.3%)	916,779	(99.4%)	
5-6	471	(8.8%)	3,823	(0.4%)	0.50	251	(3.9%)	4,043	(0.4%)	0.26
7-14	203	(3.8%)	1,731	(0.2%)		54	(0.8%)	1,880	(0.2%)	
Fully vaccinated*	803	(14.9%)	498,090	(53.9%)	0.90	1,923	(29.7%)	496,970	(53.9%)	0.50

Notes: NA = not applicable; SMD = standardized mean difference

* Fully vaccinated patients were defined as those with at least 2 doses of BNT162b2 (Comirnaty) or 3 doses of COVID-19 Vaccine (Vero Cell), Inactivated (CoronaVac).

Supplementary Table 2. Characteristics of case and control groups for outcomes of all-cause mortality, hospitalization, and in-hospital disease progression outcome after matching

Baseline characteristics	All-cause mortality				Hospitalization				In-hospital disease progression			
	Case (n=1,006)		Control (n=9,675)		Case (n=2,041)		Control (n=18,833)		Case (n=719)		Control (n=6,831)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age, years												
18-60	81	(8.1%)	496	(5.1%)	1,211	(59.3%)	11,023	(58.5%)	113	(15.7%)	981	(14.4%)
>60	925	(92.0%)	9,179	(94.9%)	830	(40.7%)	7,810	(41.5%)	606	(84.3%)	5,850	(85.6%)
Sex												
Male	598	(59.4%)	5,611	(58.0%)	900	(44.1%)	8,372	(44.5%)	417	(58.0%)	3,906	(57.2%)
Female	408	(40.6%)	4,064	(42.0%)	1,141	(55.9%)	10,461	(55.5%)	302	(42.0%)	2,925	(42.8%)
Time of COVID-19 diagnosis												
February to March 2022	953	(94.7%)	9,281	(95.9%)	1,887	(92.5%)	16,831	(89.4%)	688	(95.7%)	6,454	(94.5%)
April to June 2022	53	(5.3%)	394	(4.1%)	154	(7.6%)	2,002	(10.6%)	31	(4.3%)	377	(5.5%)
Charlson's Index												
0-4	567	(56.4%)	6,298	(65.1%)	1,736	(85.1%)	17,936	(95.2%)	233	(32.4%)	2,838	(41.6%)
5-6	259	(25.8%)	2,052	(21.2%)	251	(12.3%)	816	(4.3%)	314	(43.7%)	2,596	(38.0%)
7-14	180	(17.9%)	1,325	(13.7%)	54	(2.7%)	81	(0.4%)	172	(23.9%)	1,397	(20.5%)
Fully vaccinated*	226	(22.5%)	2,028	(21.0%)	815	(39.9%)	8,322	(44.2%)	244	(33.9%)	2,474	(36.2%)

Notes: NA = not applicable; SMD = standardized mean difference

* Fully vaccinated patients were defined as those with at least 2 doses of BNT162b2 (Comirnaty) or 3 doses of COVID-19 Vaccine (Vero Cell), Inactivated (CoronaVac).

Supplementary Table 3. Odds ratios of outpatient molnupiravir and nirmatrelvir/ritonavir exposure between cases and controls after matching in case-control study design

All-cause mortality	Case (N=1,006)	Control (N=9,675)	OR	95% CI	P-value
Non-users	964 (95.8%)	8,719 (90.1%)		(reference)	
Molnupiravir users	35 (3.5%)	679 (7.0%)	0.47	(0.33, 0.66)	<0.0001
Nirmatrelvir/ritonavir users	7 (0.7%)	277 (2.9%)	0.23	(0.11, 0.49)	0.0001

Hospitalization	Case (N=2,041)	Control (N=18,833)	OR	95% CI	P-value
Non-users	1,930 (94.6%)	17,311 (91.9%)		(reference)	
Molnupiravir users	70 (3.4%)	662 (3.5%)	0.95	(0.74, 1.22)	0.68
Nirmatrelvir/ritonavir users	41 (2.0%)	860 (4.6%)	0.43	(0.31, 0.59)	<0.0001

In-hospital disease progression	Case (N=719)	Control (N=6,831)	OR	95% CI	P-value
Non-users	656 (91.2%)	5,914 (86.6%)		(reference)	
Molnupiravir users	42 (5.8%)	609 (8.9%)	0.62	(0.45, 0.86)	0.0039
Nirmatrelvir/ritonavir users	21 (2.9%)	308 (4.5%)	0.61	(0.39, 0.96)	0.034

Notes: OR = Odds ratio; CI = confidence interval

Supplementary Table 4. Post-hoc sensitivity analyses of treating oral antiviral use as time-varying covariate in Cox regression model

Outcomes	Molnupiravir vs Control			Nirmatrelvir/ritonavir vs Control		
	HR†	95% CI	P-value	HR†	95% CI	P-value
All-cause mortality	0.78	(0.63, 0.97)	0.025	0.35	(0.23, 0.54)	<0.0001
Hospitalization	1.11	(1.02, 1.21)	0.020	0.85	(0.75, 0.97)	0.018
In-hospital disease progression	0.60	(0.45, 0.80)	0.00039	0.60	(0.40, 0.91)	0.015

Notes: HR = hazard ratio; CI = confidence interval

† HR >1 (or <1) indicates oral antiviral users had higher (lower) risk of outcome compared to the matched control group.

Supplementary Table 5. Subgroup analyses of outcomes for (a) outpatient molnupiravir users versus matched controls, and (b) outpatient nirmatrelvir/ritonavir users versus matched controls by vaccination status and age groups

Outcomes	Molnupiravir (N=4,983)			Control (N=49,234)			Molnupiravir vs Control			
	Crude incidence rate (Events / 100,000 person-days)			Crude incidence rate (Events / 100,000 person-days)						
	Estimate	95% CI	Person-days	Estimate	95% CI	Person-days	HR†	95% CI	P-value	P_{int}
All-cause mortality	17.9	(14.3, 22.0)	492,995	22.1	(20.9, 23.4)	5,134,524	0.76	(0.61, 0.95)	0.013	
With full SARS-CoV-2 vaccination	2.6	(0.3, 9.3)	77,321	3.9	(2.6, 5.6)	768,346	0.66	(0.16, 2.77)	0.57	0.72
Without full SARS-CoV-2 vaccination	22.9	(18.5, 28.0)	415,417	25.4	(23.9, 27.0)	4,281,002	0.85	(0.70, 1.05)	0.13	
Age ≤60	7.4	(2.0, 19.0)	54,037	3.0	(1.8, 4.9)	560,530	2.31	(0.77, 6.90)	0.13	0.047
Age >60	19.9	(15.9, 24.5)	438,221	25.4	(23.9, 26.9)	4,494,192	0.75	(0.60, 0.93)	0.0076	
Hospitalization	107.6	(98.2, 117.6)	450,697	104.0	(101.1, 107.0)	4,740,249	0.98	(0.89, 1.06)	0.58	
With full SARS-CoV-2 vaccination	27.8	(17.2, 42.6)	75,412	42.5	(37.9, 47.5)	741,323	0.66	(0.42, 1.02)	0.063	0.059
Without full SARS-CoV-2 vaccination	126.0	(114.9, 137.9)	375,286	117.9	(114.6, 121.4)	3,913,988	1.01	(0.93, 1.10)	0.76	
Age ≤60	87.7	(63.7, 117.7)	50,171	71.5	(64.4, 79.1)	528,872	1.15	(0.84, 1.59)	0.38	0.12
Age >60	108.4	(98.5, 119.1)	401,121	117.5	(114.2, 120.9)	4,103,751	0.89	(0.81, 0.97)	0.0067	
In-hospital disease progression	10.2	(7.5, 13.4)	491,635	16.8	(15.7, 18.0)	5,115,217	0.57	(0.43, 0.76)	0.00011	
With full SARS-CoV-2 vaccination	2.6	(0.3, 9.4)	77,223	4.4	(3.1, 6.2)	766,475	0.58	(0.14, 2.43)	0.46	0.85
Without full SARS-CoV-2 vaccination	13.5	(10.2, 17.6)	413,914	19.2	(17.9, 20.6)	4,263,643	0.67	(0.51, 0.87)	0.0029	
Age ≤60	5.6	(1.1, 16.3)	53,845	4.5	(2.9, 6.6)	558,668	1.18	(0.35, 3.98)	0.79	0.23
Age >60	11.0	(8.1, 14.6)	437,115	19.0	(17.8, 20.3)	4,475,352	0.55	(0.42, 0.73)	<0.0001	

Outcomes	Nirmatrelvir/ritonavir (N=5,542)			Control (N=54,672)			Nirmatrelvir/ritonavir vs Control			
	Crude incidence rate (Events / 100,000 person-days)			Crude incidence rate (Events / 100,000 person-days)						
	Estimate	95% CI	Person-days	Estimate	95% CI	Person-days	HR†	95% CI	P-value	P_{int}
All-cause mortality	4.2	(2.6, 6.3)	528,328	11.6	(10.8, 12.6)	5,471,588	0.34	(0.22, 0.52)	<0.0001	
With full SARS-CoV-2 vaccination	0.6	(0.0, 3.3)	169,612	2.3	(1.6, 3.2)	1,683,420	NA	NA	NA	NA

Without full SARS-CoV-2 vaccination	7.1	(4.6, 10.4)	353,876	15.1	(13.9, 16.4)	3,664,797	0.44	(0.30, 0.66)	<0.0001	
Age ≤60	0.0	NA	72,254	1.2	(0.5, 2.3)	752,585	NA	NA	NA	NA
Age >60	5.2	(3.3, 7.8)	443,793	10.5	(9.6, 11.5)	4,447,743	0.48	(0.32, 0.74)	0.00069	
Hospitalization	48.5	(42.6, 54.9)	507,655	61.0	(58.9, 63.2)	5,221,023	0.76	(0.67, 0.86)	<0.0001	
With full SARS-CoV-2 vaccination	20.4	(14.1, 28.5)	166,753	28.3	(25.8, 31.0)	1,644,167	0.71	(0.51, 1.01)	0.056	0.77
Without full SARS-CoV-2 vaccination	60.6	(52.6, 69.5)	336,624	76.0	(73.1, 78.9)	3,460,742	0.76	(0.66, 0.87)	0.00012	
Age ≤60	25.4	(15.1, 40.2)	70,793	46.9	(42.0, 52.1)	727,665	0.50	(0.31, 0.81)	0.0050	0.071
Age >60	51.5	(44.9, 58.8)	425,314	63.8	(61.4, 66.3)	4,228,069	0.80	(0.69, 0.91)	0.0011	
In-hospital disease progression	4.6	(2.9, 6.8)	526,844	7.5	(6.8, 8.3)	5,462,351	0.57	(0.38, 0.87)	0.0083	
With full SARS-CoV-2 vaccination	1.2	(0.1, 4.3)	169,422	2.0	(1.4, 2.8)	1,681,789	0.58	(0.14, 2.41)	0.45	0.75
Without full SARS-CoV-2 vaccination	7.4	(4.8, 10.8)	352,506	9.5	(8.5, 10.6)	3,657,771	0.73	(0.49, 1.09)	0.13	
Age ≤60	0.0	NA	72,254	1.6	(0.8, 2.8)	751,775	NA	NA	NA	NA
Age >60	5.7	(3.7, 8.3)	442,233	7.8	(7.0, 8.7)	4,438,436	0.71	(0.47, 1.06)	0.096	

Notes: HR = hazard ratio; CI = confidence interval; NA = not applicable; P_{int} = P-value for interaction

† HR >1 (or <1) indicates oral antiviral users had higher (lower) risk of outcome compared to the matched control group.

HR were estimated only when the number of events in both groups were more than or equal to 2.

Supplementary Table 6. STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7-8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	Fig 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9-10
		(*b*) Describe any methods used to examine subgroups and interactions	10

			(*c*) Explain how missing data were addressed	NA
			(*d*) If applicable, explain how loss to follow-up was addressed	NA
			(*e*) Describe any sensitivity analyses	10
Results				
Participants		13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Fig 1
			(b) Give reasons for non-participation at each stage	Fig 1
			(c) Consider use of a flow diagram	Fig 1
Descriptive data		14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11, Table 1
			(b) Indicate number of participants with missing data for each variable of interest	NA
			(c) Summarise follow-up time (eg, average and total amount)	11, Table 2
Outcome data		15*	Report numbers of outcome events or summary measures over time	11-12, Table 2
Main results	16		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12, Table 2
			(*b*) Report category boundaries when continuous variables were categorized	NA
			(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17		Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, Supp Tables 3-5
Discussion				
Key results	18		Summarise key results with reference to study objectives	13
Limitations	19		Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16

Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10, 18

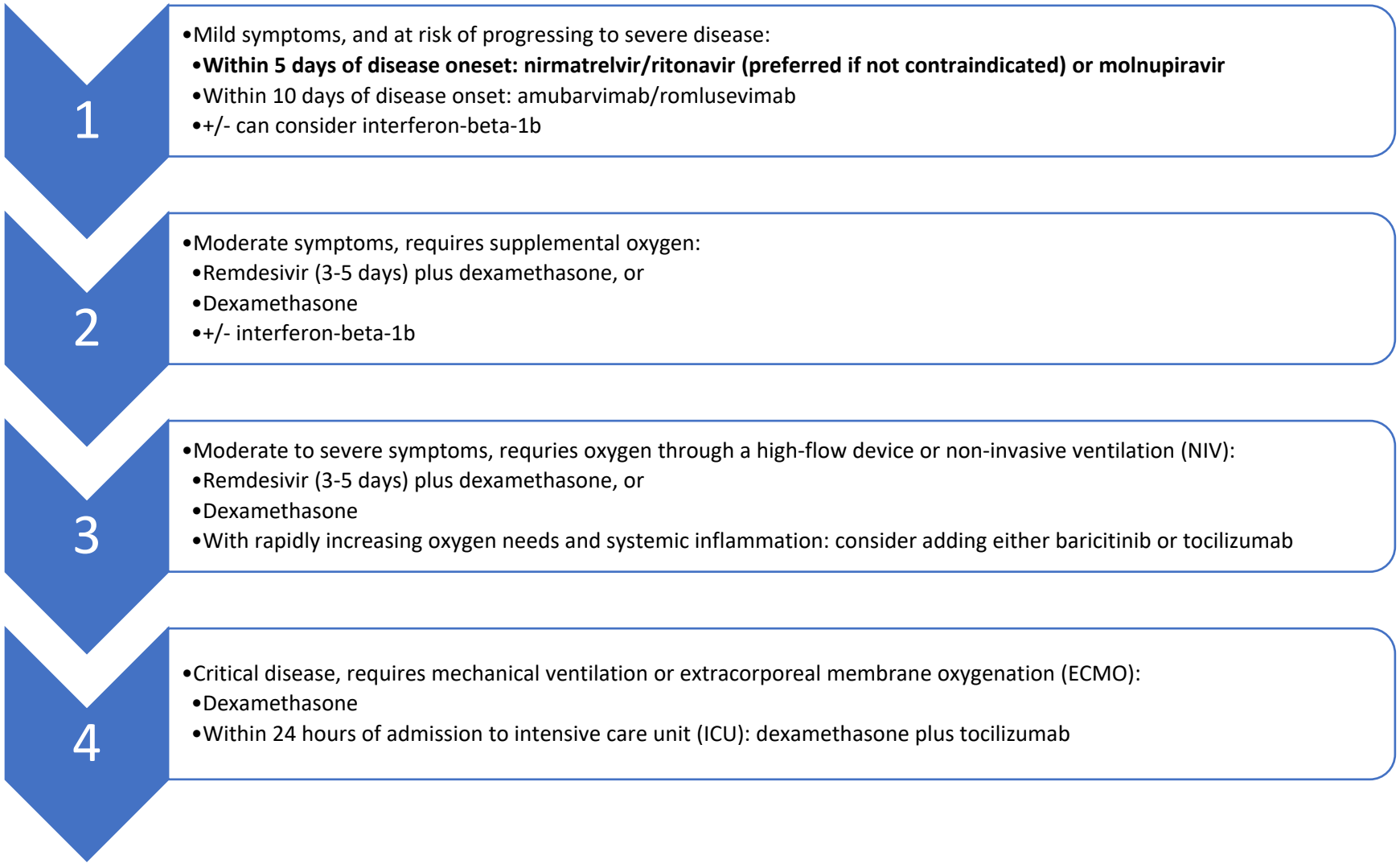
*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting.

The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/).

Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Supplementary Figure 1. Proposed therapeutic management of adults with COVID-19 based on disease severity as recommended by the Hospital Authority



Supplementary Figure 2. Distribution of propensity-score in oral antiviral and control groups before and after the propensity-score matching