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Early-Phase Oral Antiviral Use and Post–COVID-19 Condition in Outpatients

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Abstract

IMPORTANCE Post–COVID-19 condition (PCC) contributes substantially to long-term morbidity after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Information about the effectiveness of oral antivirals in preventing PCC in outpatient populations remains limited.

OBJECTIVE To evaluate the association between early oral antiviral use and PCC risk among outpatients with COVID-19, with and without risk factors for severe disease.

DESIGN, SETTING, AND PARTICIPANTS Prospective, nationwide, multicenter, registry-based cohort study conducted at 51 acute-care hospitals across Japan during the predominance of Omicron sublineages JN.1 and KP.3. Outpatients aged 12 years or older with laboratory-confirmed COVID-19, symptom onset of 5 days or less before enrollment, and no recent anti–SARS-CoV-2 treatment were enrolled between February and October 2024, with follow-up through February 2025. The primary analysis population included participants with complete baseline covariates and valid day 28 and day 84 assessments.

EXPOSURES Oral antiviral use (ensitrelvir, nirmatrelvir, or molnupiravir) at enrollment vs no antiviral use.

MAIN OUTCOMES AND MEASURES The primary outcome was PCC, defined as persistence of 1 or more of 5 prespecified symptoms (cough, shortness of breath, malaise, smell disorder, or taste disorder), with the same symptoms reported on both days 28 and 84. Exploratory outcomes included failure to return to usual health by day 84.

RESULTS Among 7699 participants (2181 receiving antivirals: 1131 [51.9%] male; median [IQR] age, 58.0 [41-71] years; and 5518 without antivirals: 2928 [53.1%] female; median [IQR] age, 45.0 [29-57] years), most had mild COVID-19 (7599 participants [98.7%]) and received 2 or more vaccine doses (6902 participants [89.6%]). Participants receiving antivirals were older and had more comorbidities; other baseline characteristics were similar between groups. After prespecified adjustment, antiviral use was associated with a lower risk of PCC (adjusted risk ratio [aRR], 0.86; 95% CI, 0.78-0.93). Results were consistent for ensitrelvir (aRR, 0.86; 95% CI, 0.79-0.95) and molnupiravir (aRR, 0.81; 95% CI, 0.67-0.98). Failure to return to usual health by day 84 was less common among participants receiving antivirals than among participants without antivirals (9.9% vs 12.9%; aRR, 0.77; 95% CI, 0.67-0.89).

CONCLUSIONS AND RELEVANCE In this cohort study of outpatients with COVID-19, early oral antiviral use was associated with a lower risk of PCC. These findings suggest that early antiviral treatment may help mitigate long-term consequences of SARS-CoV-2 infection.

Key Points

Question Is early oral antiviral use associated with a lower risk of post–COVID-19 condition (PCC) among outpatients with COVID-19?

Findings In this cohort study including 7699 outpatients, early oral antiviral use was associated with a significantly lower risk of PCC in the primary adjusted analysis. Participants receiving antivirals were less likely to fail to return to usual health by day 84.

Meaning These findings suggest that early oral antiviral use may help reduce the risk of PCC and support recovery in outpatients with COVID-19.

+ Supplemental content

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Introduction

Since late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused recurrent waves of coronavirus disease 2019 (COVID-19) worldwide.[1] Although vaccination, oral antivirals, and lower-virulence Omicron variants have reduced severe outcomes, immune waning and viral evolution continue to pose public health challenges.[2]

Beyond the acute phase, post–COVID-19 condition (PCC), also known as long COVID or postacute sequelae of SARS-CoV-2 infection, is increasingly recognized as a substantial contributor to long-term morbidity.[3-6] PCC is characterized by persistent symptoms, such as fatigue, respiratory complaints, and olfactory or gustatory disturbances, that impair daily functioning.[3-7] Although its mechanisms remain unclear, proposed pathways include viral persistence, dysregulated immune responses, and chronic inflammation, and no established pharmacologic therapies exist.[7,8]

Early antiviral treatment may reduce PCC risk by limiting viral replication and downstream inflammation.[8] Post hoc analyses of randomized trials of ensitrelvir and retrospective electronic medical record (EMR)–based studies for ritonavir-boosted nirmatrelvir (hereafter nirmatrelvir) have suggested potential reductions in postacute outcomes.[9-11] However, evidence remains inconsistent and largely derived from retrospective analyses of high-risk or hospitalized Western populations.[11-13] Prospective clinical data from younger, lower-risk Asian outpatients during the Omicron era remain limited.

In Japan, 3 oral antivirals, ensitrelvir, nirmatrelvir, and molnupiravir, are available for COVID-19 treatment.[14-20] In clinical practice, nirmatrelvir and molnupiravir are prescribed primarily to patients at high risk of severe disease, such as those of older age or with comorbidities, consistent with their regulatory approvals based largely on global trials in high-risk unvaccinated populations.[15-19] In contrast, ensitrelvir was evaluated predominantly in Asian patients infected with Omicron variants and is indicated regardless of risk factors.[20-22] Clinical evidence on the prevention of PCC remains scarce, particularly in nonhospitalized Asian populations. Japan's universal, free-access health care system enables the inclusion of a broad outpatient population across diverse risk strata.

We therefore conducted a prospective, nationwide, registry-based cohort study (of outpatients with COVID-19 in Japan during the Omicron era.[23] We evaluated the association of early oral antiviral use, overall and by agent, with the risk of PCC in routine clinical practice.

Methods

Study Design and Setting

The ANCHOR study (a prospective nationwide COVID-19 health care outcomes registry) is a prospective, nationwide, multicenter, registry-based cohort study of acute SARS-CoV-2 infection in Japan. This analysis (ANCHOR-01) evaluated the association between early oral antiviral use and PCC risk in outpatients.

Participants were consecutively enrolled from 51 geographically diverse acute-care hospitals within the Tokushukai Medical Group across Japan (eTable 1 in Supplement 1). These hospitals are distributed across 22 of Japan's 47 prefectures, spanning from Hokkaido to Okinawa. Enrollment occurred between February 1 and October 31, 2024, during the predominance of Omicron sublineages JN.1 and KP.3,[23] with follow-up through February 16, 2025.

The protocol and subsequent amendments, including an extension of the recruitment period before data lock, were approved by the Tokushukai Group Ethics Committee. All participants provided written informed consent. The study adhered to the Declaration of Helsinki and relevant Japanese ethical guidelines and followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines. It was registered in the University Hospital Medical Information Network Clinical Trials Registry in Japan (UMIN000053506).

Participants and Data Sources

Eligible participants were consecutive outpatients aged 12 or more years with symptomatic laboratory-confirmed COVID-19, symptom onset of 5 or fewer days, and no anti–SARS-CoV-2 treatment in the preceding 30 days. Exclusion criteria included previous study participation, concurrent interventional trials, or planned use of protocol-prohibited therapies (eMethods 1 in Supplement 1).

Demographic and clinical data were integrated from the Tokushukai Medical Database and an electronic patient-reported outcome (ePRO) system, including telephone-assisted entries when needed. All data were anonymized before analysis.

Procedures

Participants who received ensitrelvir, nirmatrelvir, or molnupiravir at enrollment were classified as the antiviral group, and those who did not were classified as the no antiviral group. Additional antiviral use after enrollment and symptomatic treatments were permitted at the clinician's discretion. Treatment decisions were made in routine clinical practice, generally following the Japanese COVID-19 clinical management guidelines (version 10.1).[21] Antiviral regimens are described in eMethods 2 in Supplement 1.

Assessments

Baseline data included demographic characteristics, comorbidities, vaccination status, and COVID-19–related clinical characteristics (eTable 2 in Supplement 1). Race was self-reported using investigator-defined categories (Japanese and other; the other category includes all non-Japanese individuals [including Asian, Black, and White participants] and those of mixed heritage). Acute symptom severity was assessed for 14 symptoms using a standardized 0 to 3 scale (0-2 for smell and taste disorders), and a composite severity score was calculated.

At days 28 and 84 after enrollment, participants completed a structured ePRO assessing 27 symptoms experienced in the preceding 4 weeks (0-3 scale) (eTable 3 in Supplement 1), standardizing symptom assessment and reducing interviewer bias. Symptoms were selected based on the World Health Organization (WHO) clinical case definition of PCC and the section on post–COVID-19 symptoms in the Japanese COVID-19 clinical management guidelines.[6,21] Symptoms deemed unrelated to COVID-19 were excluded from PCC classification. Additional antiviral use after enrollment through day 28 was ascertained from EMR and ePRO responses. On day 84, participants reported return to usual health compared with the preinfection state (yes or no), using a closed-ended format to reduce response variability.

Outcomes

The prespecified primary outcome was the proportion of participants who developed PCC. PCC was defined as persistent reporting of the same prespecified symptom (cough, shortness of breath [difficulty breathing], malaise [fatigue], smell disorder, or taste disorder) on both day 28 and day 84. Symptoms were selected based on prevalence and clinical specificity, and were required to be reported at both time points to approximate the WHO criterion of symptom persistence for 2 months or longer.[6] Exploratory outcomes included the proportion of participants reporting each symptom considered possibly related to COVID-19 on day 28, day 84, or both, and that of participants reporting failure to return to usual health by day 84.

Statistical Analysis

A prespecified blinded interim analysis was conducted for participants enrolled by October 2024 (eMethods 3 in Supplement 1). The final analysis used complete follow-up data through February 2025.

The full analysis population included all eligible participants without missing prescription or baseline medication data and without any protocol-prohibited medications. The primary analysis population (PAP) included participants with complete baseline covariates and valid outcome data at

days 28 and 84. Exploratory analyses were conducted using participants with complete data for each end point. Continuous variables are presented as median (IQR). For age, ranges are also reported. Categorical variables are presented as number and percentage.

Associations were estimated as risk ratios (RRs; modified Poisson) and risk differences (RDs; modified least-squares regression) with 95% CIs using generalized estimating equations specified at the participant level with an independent working correlation structure and robust (sandwich) standard errors. Models were adjusted for prespecified baseline covariates selected using directed acyclic graph principles, including baseline symptom severity and other clinical factors (eTable 4 in Supplement 1), with no antiviral use as the reference group. The overall association for antiviral use was estimated by combining the agent-specific associations using weights proportional to the number of participants in each antiviral group. Baseline characteristics of participants excluded from the primary analysis because of missing outcome data were summarized to assess potential attrition bias.

Prespecified subgroup analyses for the primary end point included age, time from COVID-19 symptom onset to study enrollment, high-risk status defined using a modified US Centers for Disease Control and Prevention list,[24] sex, and baseline symptom severity (eMethods 4 and eTable 5 in Supplement 1). These subgroup variables were prespecified based on their potential clinical relevance to acute COVID-19 severity, treatment timing, and baseline symptom burden. Associations were estimated within each stratum without formal interaction testing. Diabetes (type unspecified), a component of the high-risk definition, was additionally evaluated as a post hoc subgroup because of its clinical relevance.

A 2-sided $P < .05$ was considered statistically significant. Exploratory analyses were not adjusted for multiplicity and were interpreted cautiously based on the consistency and direction of effects. Numbers needed to treat (NNTs) were calculated post hoc from adjusted RDs (aRDs) (eMethods 5 in Supplement 1). Analyses were performed using SAS version 9.4 or SAS Viya 4.0 (SAS Institute).

Results

Study Population

Among 8657 participants in the full analysis population, 7699 were included in PAP (antiviral: 2181; no antiviral: 5518) (**Figure 1**). Most exclusions were due to missing outcome data (934 participants). Age, comorbidities, and vaccination history differed between participants included in the PAP and those with missing outcome data (eTable 6 in Supplement 1). However, the proportions of participants excluded because of missing outcome data were similar between the antiviral (266 participants [10.9%]) and no antiviral groups (692 participants [11.1%]). Baseline characteristics of the PAP were largely similar between the groups, including comparable COVID-19 symptom severity scores (median [IQR], antiviral: 10.0 [7.0-13.0]; no antiviral: 10.0 [7.0-14.0]) (**Table**), although participants receiving antivirals were older and had more comorbidities. The age range was broad (12-98 years). Most participants had mild COVID-19 at baseline (7599 participants [98.7%]), with pneumonia being uncommon (antiviral: 19 participants [0.9%]; no antiviral: 23 [0.4%]). Fever was common, with similar median (IQR) maximum body temperatures in the antiviral and no antiviral groups (38.2 [37.6-38.8] °C vs 38.3 [37.7-38.8] °C). Most participants had received 2 or more vaccine doses (antiviral: 2002 participants [91.8%]; no antiviral: 4900 [88.8%]) (Table). Baseline symptom distributions by antiviral status and individual antiviral agent are shown in eTable 7 in Supplement 1. Additional antiviral use after enrollment through day 28 was uncommon (antiviral: 10 participants [0.5%]; no antiviral: 26 [0.5%]).

Primary Outcome: PCC

In the PAP, adjusted analyses showed that the estimated PCC risk was 21.5% among participants receiving antivirals and 25.1% among those not receiving antivirals; accordingly, antiviral use was associated with a lower risk of PCC than no antiviral use. In PAP, antiviral use was associated with a

lower risk of PCC than no antiviral use (adjusted RR [aRR], 0.86; 95% CI, 0.78 to 0.93; *P* < .001), with an aRD of −4.14 percentage points (pp) (95% CI, −6.34 to −1.94 pp; *P* < .001) and an NNT of 24.2 (**Figure 2**; eTable 8 in Supplement 1).

Individual Antiviral Agents

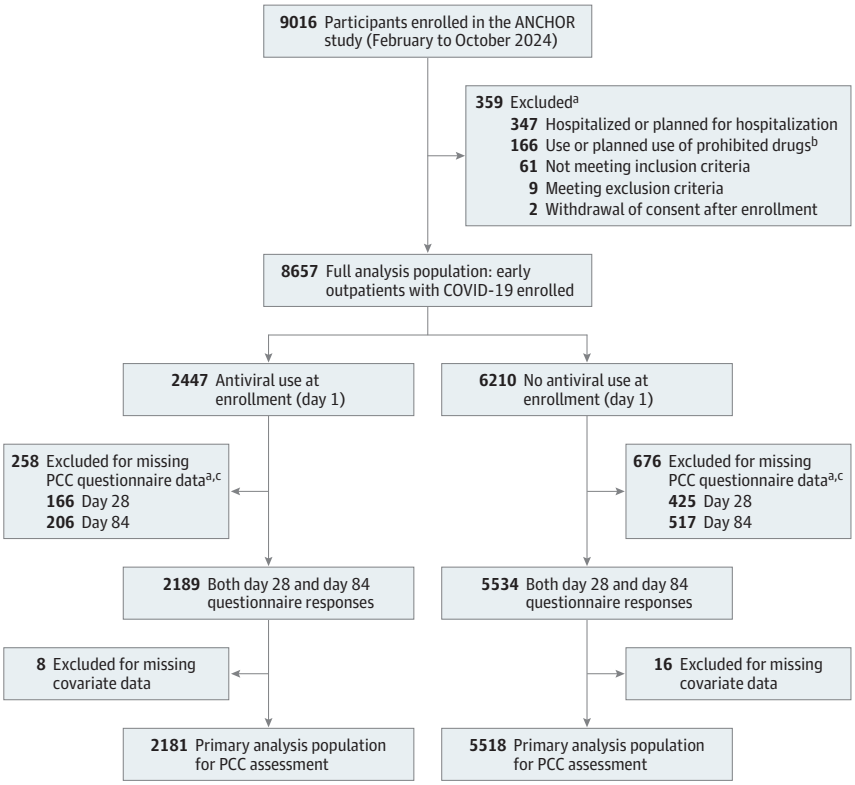
When individual antivirals were compared separately against the no antiviral group, ensitrelvir and molnupiravir were associated with a lower risk of PCC (1698 participants receiving ensitrelvir: aRR, 0.86; 95% CI, 0.79 to 0.95; *P* = .002; aRD, −3.85 pp; 95% CI, −6.19 to −1.50 pp; *P* = .001; NNT, 26.0; 385 participants receiving molnupiravir: aRR, 0.81; 95% CI, 0.67 to 0.98; *P* = .03; aRD, −5.58 pp; 95% CI, −10.22 to −0.93 pp; *P* = .02; NNT, 17.9). For nirmatrelvir, point estimates favored nirmatrelvir use, but the association did not reach statistical significance (98 participants receiving nirmatrelvir; aRR, 0.88; 95% CI, 0.63-1.24; *P* = .47; aRD, −3.53 pp; 95% CI, −12.13 to 5.07 pp; *P* = .42) (Figure 2; eTable 8 in Supplement 1).

Subgroup Analyses

The direction of associations was consistent across all prespecified subgroups (**Figure 3**). Among participants aged 12 to 39 years (antiviral: 516 participants; no antiviral: 2299), aRD was −3.96 pp (95% CI, −7.53 to −0.38 pp; *P* = .03), although an aRR could not be estimated because of model nonconvergence. Among participants aged 40 to 59 years (antiviral: 649 participants; no antiviral: 2049), antiviral use was associated with a lower risk of PCC (aRR, 0.81; 95% CI, 0.71 to 0.94; *P* = .004). A similar association was observed among those aged 60 years or older (antiviral: 1016 participants; no antiviral: 1170), although it did not reach statistical significance (aRR, 0.91; 95% CI, 0.80 to 1.05; *P* = .20).

Statistically significant associations between antiviral use and a lower risk of PCC were also observed among participants who enrolled 1 to 3 days after symptom onset, among both male and

Figure 1. Flowchart of Participants and Dispositions in the ANCHOR-01 Study



Participant flow and disposition through screening, enrollment, exclusions, and analysis populations. PCC indicates post–COVID-19 condition.

[a] Participants could be excluded for more than 1 reason.

[b] Protocol-prespecified prohibited concomitant drugs were remdesivir, casirivimab-imdevimab, sotrovimab, tixagevimab-cilgavimab, dexamethasone, baricitinib, and tocilizumab.

[c] Including participants who withdrew consent.

Table. Baseline Characteristics of Outpatients With COVID-19 in the Primary Analysis Population by Treatment Group

Characteristic	Participants, No. (%)	
	Antiviral (n = 2181)	No antiviral (n = 5518)
Age, median (IQR) [range], y	58.0 (41.0-71.0) [12.0-97.0]	45.0 (29.0-57.0) [12.0-98.0]
Age, y		
12-39	516 (23.7)	2299 (41.7)
40-59	649 (29.8)	2049 (37.1)
≥60	1016 (46.6)	1170 (21.2)
Sex		
Male	1131 (51.9)	2590 (46.9)
Female	1050 (48.1)	2928 (53.1)
Race		
Japanese	2163 (99.2)	5469 (99.1)
Other[a]	18 (0.8)	49 (0.9)
BMI, median (IQR)[b]	22.8 (20.4-25.6)	22.5 (20.2-25.3)
Smoking history		
No	1295 (59.4)	3466 (62.8)
Yes	886 (40.6)	2052 (37.2)
Comorbidities[c]		
Any	1059 (48.6)	1545 (28.0)
Hypertension	619 (28.4)	778 (14.1)
Dyslipidemia	357 (16.4)	480 (8.7)
Diabetes (type unspecified)	250 (11.5)	294 (5.3)
Cardiovascular disease	236 (10.8)	234 (4.2)
Respiratory disease	125 (5.7)	233 (4.2)
Malignant tumor	184 (8.4)	167 (3.0)
Mental illness	63 (2.9)	108 (2.0)
Hepatic disease	20 (0.9)	31 (0.6)
Chronic kidney disease on dialysis	22 (1.0)	14 (0.3)
Genetic disorder	9 (0.4)	8 (0.1)
Immunodeficiency[d]	3 (0.1)	3 (<0.1)
Maximum body temperature, °C		
Median (IQR)	38.2 (37.6-38.8)	38.3 (37.7-38.8)
<37 °C	187 (8.6)	487 (8.8)
≥37 °C	1994 (91.4)	5031 (91.2)
COVID-19 severity[e]		
Mild	2130 (97.7)	5469 (99.1)
Moderate I	51 (2.3)	49 (0.9)
COVID-19 symptom severity score		
Median (IQR)	10.0 (7.0-13.0)	10.0 (7.0-14.0)
Score categories[f]		
<Median	1049 (48.1)	2567 (46.5)
≥Median	1132 (51.9)	2951 (53.5)
Days from COVID-19 symptom onset to enrollment		
<1	216 (9.9)	399 (7.2)
1-<3	1644 (75.4)	3823 (69.3)
≥3	321 (14.7)	1296 (23.5)

(continued)

Table. Baseline Characteristics of Outpatients With COVID-19 in the Primary Analysis Population by Treatment Group (continued)

Characteristic	Participants, No. (%)	
	Antiviral (n = 2181)	No antiviral (n = 5518)
Time from most recent SARS-CoV-2 vaccination to enrollment		
<6 mo	72 (3.3)	119 (2.2)
6 mo-<1 y	474 (21.7)	786 (14.2)
≥1 y	1476 (67.7)	4080 (73.9)
Not vaccinated	159 (7.3)	533 (9.7)
No. of SARS-CoV-2 vaccinations received		
0	159 (7.3)	533 (9.7)
1	20 (0.9)	85 (1.5)
2	271 (12.4)	1025 (18.6)
≥3	1731 (79.4)	3875 (70.2)
Participants with pneumonia[g]		
No	2162 (99.1)	5495 (99.6)
Yes	19 (0.9)	23 (0.4)
Antiviral use		
Ensitrelvir	1698 (77.9)	0
Nirmatrelvir	98 (4.5)	0
Molnupiravir	385 (17.7)	0
Symptomatic medication	1420 (65.1)	3373 (61.1)

Abbreviation: BMI, body mass index

[a] Race was self-reported by participants. The other category includes all non-Japanese individuals (including other Asian, Black, and White) and those of mixed heritage.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Multiple responses were allowed.

[d] Immunodeficiency was defined as HIV infection, a history of solid-organ or hematopoietic stem-cell transplantation, or primary immunodeficiency disorders.

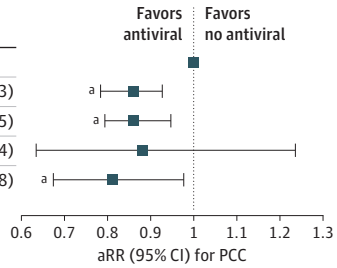
[e] Categorized according to the Japanese COVID-19 clinical management guidelines, version 10.1, as follows: mild, no oxygen desaturation; moderate I, oxygen desaturation without the need for oxygen therapy; moderate II, requiring oxygen therapy; severe, requiring mechanical ventilation or intensive care unit admission.

[f] Median (IQR) value for the total population was 10.0 (7.0-14.0).

[g] Pneumonia was assessed based on clinical indication, without routine radiological screening for all participants.

Figure 2. Forest Plot Showing Proportion of Participants With Post–COVID-19 Condition (PCC) and Adjusted Risk Ratios

Treatment group	No./total No.	Proportion of participants with PCC (%)		aRR (95% CI)
		Unadjusted	Adjusted	
No antiviral	1443/5518	26.2	25.1	1 [Reference]
Antiviral (overall)	530/2181	24.3	21.5	0.86 (0.78-0.93)
Ensitrelvir	412/1698	24.3	21.7	0.86 (0.79-0.95)
Nirmatrelvir	25/98	25.5	22.2	0.88 (0.63-1.24)
Molnupiravir	93/385	24.2	20.4	0.81 (0.67-0.98)



aRR indicates adjusted risk ratio; PCC, post–COVID-19 condition.

[a] Statistically significant at $P < .05$. Estimates were adjusted for predefined covariates, with overall antiviral estimates additionally weighted for group size.

female participants, among those without risk factors for severe disease, and among those with baseline symptom severity scores at or above the median (Figure 3). In post hoc analysis, the direction of association was consistent regardless of diabetes status, with similar associations observed among participants with diabetes (antiviral: 250 participants; no antiviral: 294; aRR, 0.91; 95% CI, 0.69 to 1.18) and those without diabetes (antiviral: 1931 participants; no antiviral: 5224; aRR, 0.85; 95% CI, 0.77 to 0.93).

Failure to Return to Usual Health

Among participants who completed the day 84 questionnaire (antiviral: 2232 participants; no antiviral: 5676), antiviral use was associated with a lower risk of failure to return to usual health (9.9% vs 12.9%; aRR, 0.77; 95% CI, 0.67 to 0.89; $P < .001$; aRD, −3.19 pp; 95% CI, −4.87 to −1.51 pp; $P < .001$; NNT, 31.4). Among individual antiviral agents, ensitrelvir was associated with a lower risk of failure to return to usual health (1736 participants; 9.7% vs 12.9%; aRR, 0.75; 95% CI, 0.64 to 0.88;

P < .001; aRD, −3.49 pp; 95% CI, −5.25 to −1.73 pp; *P* < .001; NNT, 28.6). There were no associations for other agents (eTable 9 in Supplement 1).

Symptom-Specific Outcomes

Several symptoms reported as possibly related to COVID-19 were common at day 28, although most declined by day 84. The proportions of participants in the no antiviral group reporting the 5 PCC-defining symptoms on days 28 and 84, along with the aRRs representing associations between antiviral use and each symptom, are shown in eFigure 1 and eFigure 2 in Supplement 1.

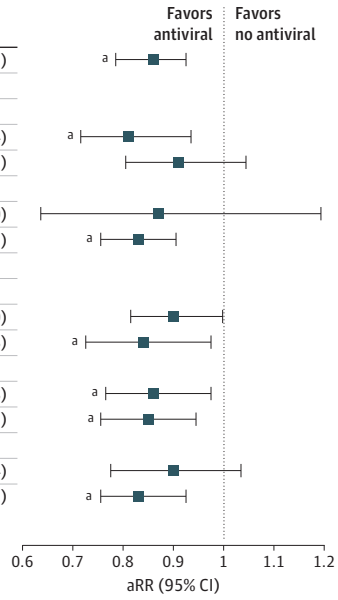
Only cough and malaise (fatigue) were reported by 10% or more of participants at both day 28 and day 84 (**Figure 4**); other symptoms were less frequent (eFigure 3 in Supplement 1). Antiviral use was consistently associated with lower proportions of participants reporting symptoms relatively specific to COVID-19, such as smell disorder (aRRs of 0.52; 95% CI, 0.46 to 0.58 at day 28, 0.57; 95% CI, 0.45 to 0.71 at day 84, and 0.43; 95% CI, 0.32 to 0.58 for symptoms reported on both days) and taste disorder (aRRs of 0.61; 95% CI, 0.55 to 0.67 at day 28, 0.71; 95% CI, 0.57 to 0.89 at day 84, and 0.59; 95% CI, 0.45 to 0.78 for symptoms reported on both days) (Figure 4; eFigure 1 and eFigure 2 in Supplement 1). NNT estimates for all 5 prespecified symptoms at day 28, day 84, and both days are provided in eTable 10 in Supplement 1.

Discussion

In this large, nationwide prospective cohort in Japan, early oral antiviral use was associated with a lower risk of PCC during the Omicron JN.1– and KP.3–predominant periods. In adjusted analyses, the estimated PCC risk was 21.5% among participants receiving antivirals and 25.1% among those not

Figure 3. Forest Plot Showing Subgroup Analysis of Participants With PCC

Subgroup	Unadjusted: Antiviral No./total No.	Unadjusted: Antiviral No. With PCC, %	Unadjusted: No antiviral No./total No.	Unadjusted: No antiviral No. With PCC, %	Adjusted: Antiviral	Adjusted: No antiviral	aRR (95% CI)
All participants	530/2181	24.3	1443/5518	26.2	21.5	25.1	0.86 (0.78-0.93)
Age, y							
12-39	83/516	16.1	446/2299	19.4	NA	NA	NC[b]
40-59	178/649	27.4	662/2049	32.3	25.6	31.4	0.81 (0.71-0.94)
≥60	269/1016	26.5	335/1170	28.6	24.9	27.3	0.91 (0.80-1.05)
Days from COVID-19 symptom onset to enrollment							
<1	46/216	21.3	92/399	23.1	18.6	21.3	0.87 (0.63-1.20)
1-<3	391/1643	23.8	1004/3823	26.3	20.9	25.3	0.83 (0.75-0.91)
≥3	93/322	28.9	347/1296	26.8	NA	NA	NC[b]
Risk factors, including age ≥60 years[c]							
Yes	381/1439	26.5	708/2366	29.9	25.7	28.5	0.90 (0.81-1.00)
No	149/742	20.1	735/3152	23.3	18.9	22.5	0.84 (0.72-0.98)
Sex							
Male	253/1131	22.4	624/2590	24.1	20.0	23.2	0.86 (0.76-0.98)
Female	277/1050	26.4	819/2928	28.0	22.8	26.9	0.85 (0.75-0.95)
Symptom severity score at enrolment[d]							
<Median	208/1049	19.8	526/2567	20.5	17.8	19.9	0.90 (0.77-1.04)
≥Median	322/1132	28.5	917/2951	31.1	25.3	30.3	0.83 (0.75-0.93)



aRR indicates adjusted risk ratio; NA, not applicable; NC, not calculable; PCC, post–COVID-19 condition.

[a] Statistically significant at *P* < .05. Estimates were adjusted for predefined covariates, with overall antiviral estimates additionally weighted for group size.

[b] Covariate-adjusted risk ratios could not be calculated because of model nonconvergence in the subgroup defined by age 12 to 39 years and in the subgroup with time from COVID-19 symptom onset to study enrollment of 3 days or longer. Adjusted risk differences were −3.96 (95% CI −7.53 to −0.38; *P* = .03) and −0.91 (95% CI −6.63 to 4.81; *P* = .76), respectively.

[c] High-risk status was defined by the presence of high-risk factors for severe COVID-19.

[d] Median values for the antiviral and no antiviral groups were 10.

receiving antivirals (aRR, 0.86). In addition, failure to return to usual health by day 84 occurred in 9.9% of participants receiving antivirals and 12.9% of those not receiving antivirals. These findings suggest that persistent symptoms remain common even in the contemporary Omicron era with widespread vaccination. This cohort included outpatients across a wide age range and both with and without risk factors for severe disease, reflecting routine clinical practice. As an observational study, these results indicate an association rather than causation but were consistent across analyses.

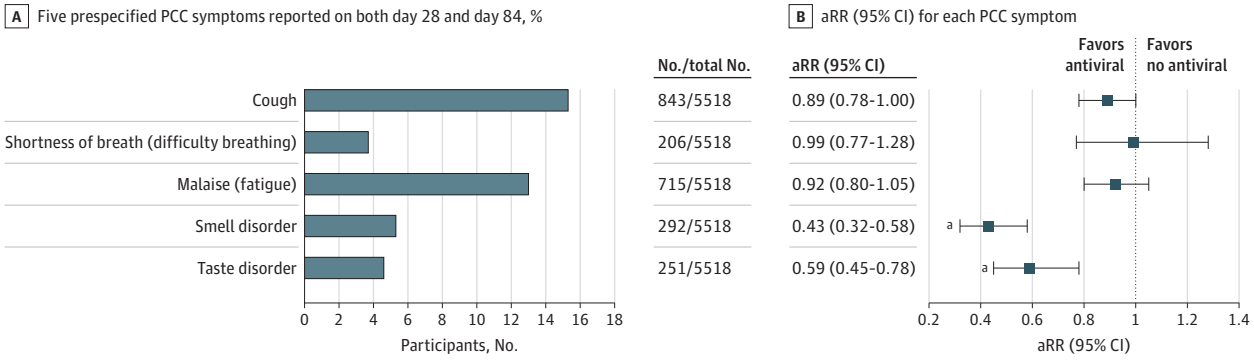
Among specific agents, ensitrelvir (aRR, 0.86) and molnupiravir (aRR, 0.81) were associated with a lower PCC risk. The finding for nirmatrelvir (aRR, 0.88) was inconclusive, with CIs overlapping the null value of 1.00, possibly reflecting the small sample size. This study was not designed for head-to-head comparisons among antivirals. These findings complement those of earlier retrospective studies, which were often inconsistent and focused primarily on high-risk or hospitalized patients.[9,11-13] The prospectively collected symptom and health data from a large outpatient population also help address limitations of prior studies that relied mainly on administrative data.

Prompt antiviral treatment can reduce the duration and severity of COVID-19 symptoms, decrease SARS-CoV-2 viral load, prevent progression to severe disease, and lower the risk of developing PCC in patients with risk factors for severe disease.[5,10,11,25] In this study, with participants enrolled within 5 days of symptom onset, early antiviral use was associated with a lower risk of PCC across a broad outpatient population, including younger participants and those without risk factors for severe disease.

Our findings differ from those of recent trials evaluating treatment for established PCC, which did not demonstrate a benefit of antiviral therapy.[26,27] This difference may reflect intervention timing, suggesting that treatment during the acute phase could influence PCC development, whereas later-stage viral suppression may have limited impact once symptoms are established. Although viral load was not evaluated in this study, the lower proportions of smell and taste disorders, hallmark symptoms of COVID-19,[3,4,28] in participants receiving antivirals are consistent with findings from previous reports of accelerated viral clearance and symptom recovery with ensitrelvir.[10,20] Because olfactory dysfunction is often underestimated and may contribute to neurocognitive sequelae, these results, together with accumulating evidence linking COVID-19–related olfactory dysfunction to structural and functional brain alterations, raise the possibility that early antiviral treatment may have broader clinical implications.[28-30]

Subgroup analysis by age showed associations with lower PCC risk among younger and participants aged less than 60 years. Although a similar direction of association was seen in those aged 60 years and older, the estimate did not exclude the null, potentially reflecting limited statistical

Figure 4. Bar Chart Showing Participants in the No Antiviral Group Reporting Each of the 5 Post–COVID-19 Condition (PCC) Symptoms and Forest Plot Showing Adjusted Risk Ratios (aRRs)



[a] Statistically significant at $P < .05$. Estimates were adjusted for predefined covariates, with overall antiviral estimates additionally weighted for group size.

power and the higher burden of nonspecific symptoms unrelated to COVID-19 in the context of age-related comorbidities. Furthermore, aging-associated immune dysfunction (immunosenescence)[31] may attenuate the association between early antiviral treatment and PCC risk by impairing viral clearance and inflammatory resolution. These considerations suggest that the magnitude of association may differ by age, although antiviral treatment remains clinically important for preventing severe COVID-19 in this population.

Strengths and Limitations

Study strengths include the large-scale, nationwide prospective design using clinical ePRO data, which captured comprehensive baseline information across a wide age range (12-98 years) regardless of risk status. Rigorous data management and proactive follow-up resulted in high data completeness and low attrition. Although definitions of PCC vary across studies, we used a prespecified set of 5 symptoms assessed at both day 28 and day 84 to improve specificity and reduce misclassification of transient symptoms. Because our assessment focused on 5 common and relatively specific symptoms and required the same symptom to be present at both time points, PCC prevalence may have been underestimated given the heterogeneous and fluctuating nature of PCC and its broader manifestations.

Several limitations should be considered. First, the observational design precludes causal inference, and residual confounding, including confounding by indication, cannot be excluded despite adjustment for prespecified baseline covariates. Baseline characteristics differed in age and comorbidity burden, which may have influenced the observed associations. Second, participants who did not complete follow-up were older, had more comorbidities, and were more likely to be unvaccinated than those included in the PAP. Although loss to follow-up was low and similar across the exposure groups, attrition bias cannot be excluded. Third, self-reported ePRO data may introduce nondifferential measurement bias, and symptom assessments, although structured and guideline-aligned, were not based on formally validated multidimensional PCC instruments. Fourth, the 3-month follow-up does not capture longer-term trajectories of PCC. Finally, the predominantly Japanese study population may limit generalizability to other populations.

Conclusions

This large prospective cohort study provides clinical evidence that early oral antiviral use is associated with a lower risk of PCC among outpatients with COVID-19. While the observational design precludes causal inference or direct comparisons between specific agents, similar directions of associations across subgroups suggest that early antiviral use may help mitigate the long-term burden of COVID-19. Further studies are warranted to confirm longer-term effectiveness and evaluate these associations in diverse populations.

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SUPPLEMENT 1.

SUPPLEMENT 2.