

Real-world Impact of Early Outpatient COVID-19 Antiviral Treatment on Post- COVID-19 Condition: The ANCHOR-01 Study

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KEY MESSAGE

- Acute-phase oral antiviral treatment in COVID-19 outpatients was associated with a reduced risk of post–COVID-19 condition (PCC).
- This reduction in PCC risk was observed across all age groups, regardless of the presence or absence of risk factors for severe disease.
- Persistent taste and smell disorders, hallmark COVID-19 symptoms, were also less frequent with antivirals, highlighting their potential to reduce long-term impacts.

BACKGROUND

- Since its emergence in late 2019, coronavirus disease 2019 (COVID-19) has caused widespread infections and deaths globally and continues to challenge public health systems despite progress in vaccination and antiviral therapies.^{1,2}
- Many people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experience prolonged and sometimes debilitating symptoms, referred to as long COVID or post–COVID-19 condition (PCC). This condition, present for at least 3 months and affecting one or more organ systems, has a global prevalence of about 36% among COVID-19-positive individuals and significantly impacts quality of life and productivity.^{3–6}
- The use of oral antivirals such as ensitrelvir and nirmatrelvir has shown promise in reducing the risk of PCC, but existing studies mainly focus on high-risk or hospitalized populations.^{7–10}
- A nationwide observational study in Japan aimed to fill this gap by evaluating the real-world effectiveness of oral antiviral use in preventing PCC among outpatients with COVID-19 during the JN.1 and KP.3 epidemic in Japan.

METHODS

- **Study design:** ANCHOR-01 (UMIN-CTR ID: UMIN000053506) was a prospective, multi-institutional, nationwide, registry-based cohort study conducted in Japan to evaluate the impact of oral antivirals on PCC in outpatients.
- **Participants:** Outpatients aged ≥12 years with confirmed symptomatic SARS-CoV-2 infection were enrolled between February and October 2024 and followed up until January 2025.
- **Treatment groups:** Patients were classified into antiviral and no antiviral groups based on clinical decisions by treating physicians that were aligned with national COVID-19 guidelines; oral antivirals included ensitrelvir, nirmatrelvir/ritonavir, and molnupiravir.
- **Data collection:** Patient-reported outcomes related to PCC were collected via electronic questionnaires on Days 28 and 84, with telephone follow-ups conducted when necessary.
- **Endpoint/Outcome:** The primary endpoint included the incidence of PCC in the antiviral and no antiviral groups, defined as persistence of any of five pre-specified symptoms (fatigue, cough, dyspnea or respiratory distress, smell disorder, taste disorder) on both Days 28 and 84, excluding symptoms not attributed to COVID-19.
- **Statistical analysis:** Risk ratios (RRs) and risk differences (to assess overall and individual effects) were estimated using modified Poisson and least squares regression models, adjusted for baseline characteristics. Comparison between the antiviral treatment group and the no-antiviral group was performed after applying weighting based on the number of cases associated with each antiviral drug.

RESULTS

Study population

- The antiviral group had a higher median age (58.0 vs 45.0 years) and more underlying comorbidities, though other baseline characteristics were generally balanced between the groups.

Baseline demographic and clinical characteristics of outpatients with COVID-19: comparison between the no antiviral and antiviral treatment groups		
Characteristics	Antiviral group (n=2181)	No antiviral group (n=5518)
Age, years, Median (range)	58.0 (12–97)	45.0 (12–98)
Sex, Male, n (%)	1,131 (51.9)	2,590 (46.9)
BMI (kg/m²), Median (range)	22.8 (13.6–65.8)	22.5 (13.3–55.8)
Smoking history, Yes, n (%)	886 (40.6)	2052 (37.2)
Maximum body temperature, ° C, Median (range)	38.2 (35.8–41.0)	38.3 (35.5–42.1)
Patients with pneumonia, Yes, n (%)	19 (0.9)	23 (0.4)
Number of patients receiving ensitrelvir, n (%)	1698 (77.9)	0
Number of patients receiving molnupiravir, n (%)	385 (17.6)	0
Number of patients receiving nirmatrelvir, n (%)	98 (4.5)	0
Comorbidities, n (%)		
Hypertension	619 (28.4)	778 (14.1)
Dyslipidemia	357 (16.4)	480 (8.7)
Diabetes	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)
Liver disease	20 (0.9)	31 (0.6)
Chronic kidney disease	22 (1.0)	14 (0.3)
Genetic disease	9 (0.4)	8 (0.1)
Immunodeficiency	3 (0.1)	3 (0.1)
COVID-19 severity*, n (%)		
Mild	2130 (97.7)	5469 (99.1)
Moderate I	51 (2.3)	49 (0.9)
COVID-19 severity score†, median (range)	10.0 (0–32)	10.0 (0–34)
Time from symptom onset to study enrolment		
<1 day	216 (9.9)	399 (7.2)
≥1 to <3 days	1644 (75.4)	3823 (69.3)
≥3 days	321 (14.7)	1296 (23.5)
Number of SARS-CoV-2 vaccinations received, n (%)		
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)

*Categorized according to the Japanese guidelines for the treatment of COVID-19, 10th edition, as follows: mild, no oxygen desaturation; moderate I, oxygen desaturation without the need for oxygen therapy.
†Median for the total population was 10 (range, 0–34). COVID-19 severity score is calculated as the sum of individual symptom scores on Day 1, where malaise (fatigue), myalgia or body pain, headache, chills/sweating, fever (pyrexia), runny nose or nasal congestion, sore throat, cough, shortness of breath (dyspnea), nausea, vomiting, and diarrhea are each rated on a 4-point scale (0: none, 1: mild, 2: moderate, 3: severe), and dysgeusia and dyschromia are rated on a 3-point scale (0: same as usual, 1: weaker than usual, 2: not feeling).

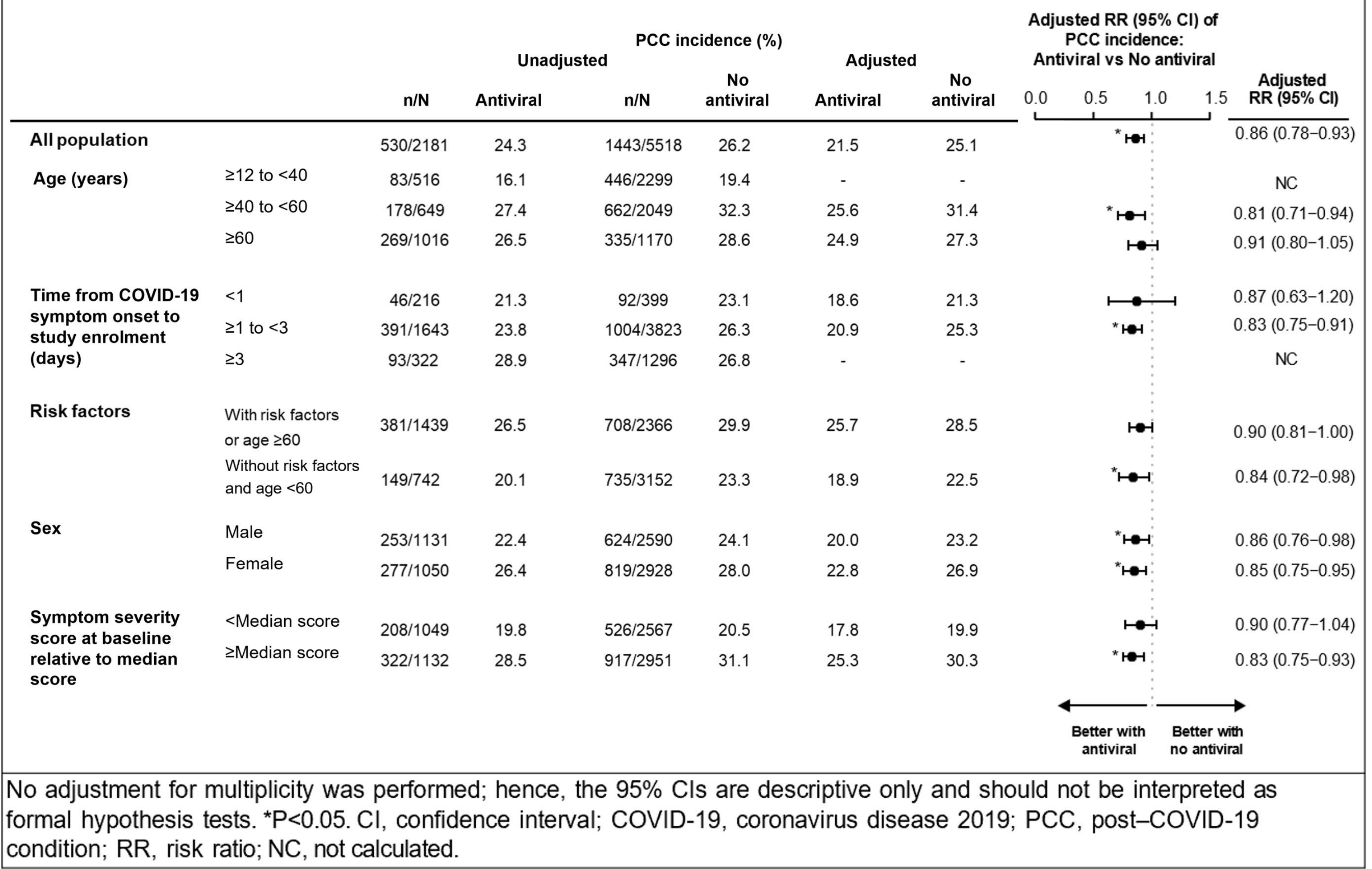
Incidence of PCC (Figure 1)

- In the no antiviral group, 26.2% of patients developed PCC, compared to 24.3% of patients in the antiviral group.
- After adjusting for covariates, the risk of developing PCC was significantly lower in the antiviral group, with an RR of 0.86 (95% confidence interval [CI]: 0.78–0.93) and risk difference of -4.14 percentage points (95% CI: -6.34 to -1.94), both with a P-value <0.001.

Antiviral-specific analysis (Figure 2)

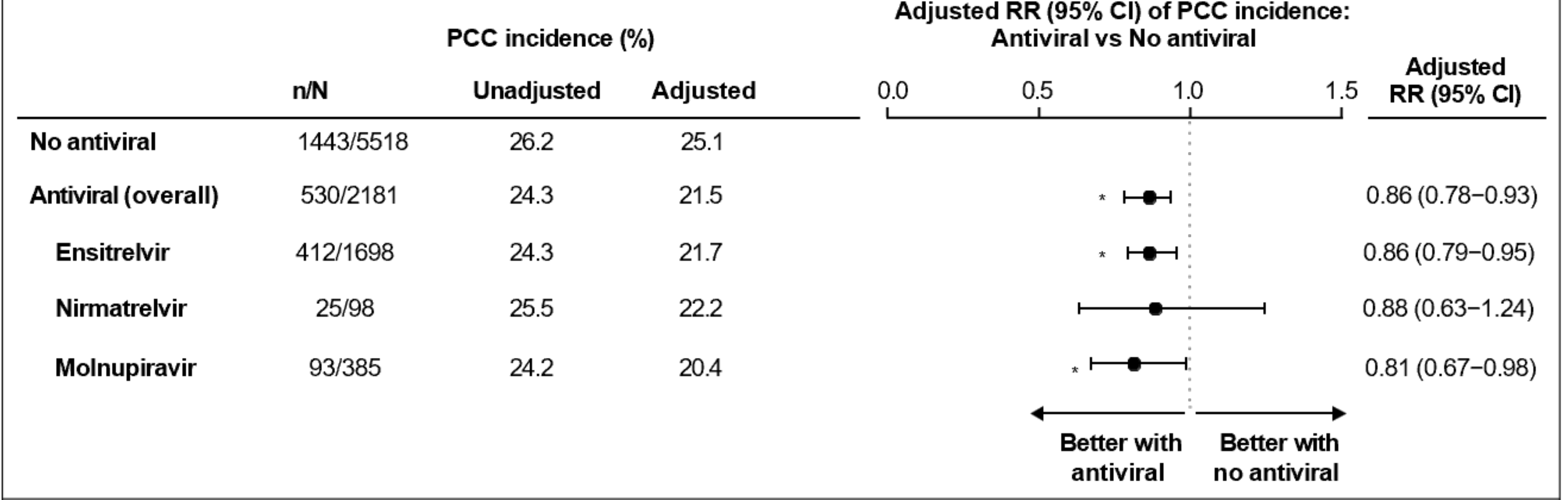
- Both ensitrelvir and molnupiravir significantly reduced the incidence of PCC compared to the no antiviral group, with covariate-adjusted RRs of 0.86 and 0.81, respectively, indicating a meaningful treatment effect.

Figure 1. Incidence of PCC according to prespecified subgroups



No adjustment for multiplicity was performed; hence, the 95% CIs are descriptive only and should not be interpreted as formal hypothesis tests. *P<0.05. CI, confidence interval; COVID-19, coronavirus disease 2019; PCC, post–COVID-19 condition; RR, risk ratio; NC, not calculated.

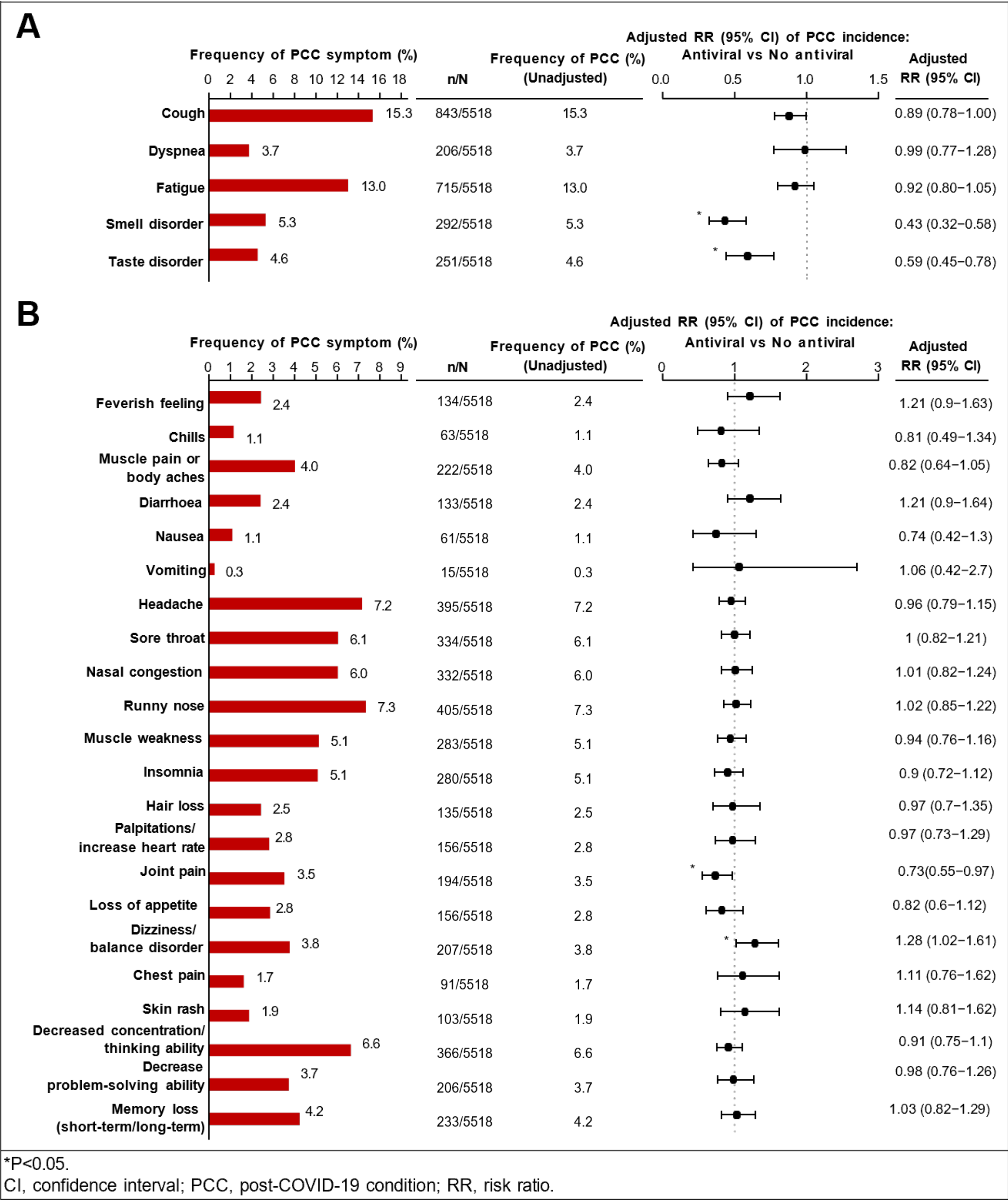
Figure 2. Unadjusted and adjusted incidence of PCC according to antiviral treatments



*P<0.05. CI, confidence interval; PCC, post-COVID-19 condition; RR, risk ratio.

- Prevalence of each of the 27 individual symptoms at both Day 28 and Day 84 (Figure 3)
- Among the prespecified five symptoms, the risks of smell and taste disorders were significantly reduced in the antiviral group, while cough and fatigue exhibited a tendency toward reduction.

Figure 3. Incidence of (A) five prespecified and (B) 22 remaining PCC symptoms persisting from Day 28 to 84 in patients without antivirals, and their RR in the antiviral versus no antiviral groups



*P<0.05. CI, confidence interval; PCC, post-COVID-19 condition; RR, risk ratio.

CONCLUSION

The ANCHOR-01 analysis provides real-world evidence from Japanese patients showing that oral antiviral treatment, especially ensitrelvir and molnupiravir, is significantly associated with lower PCC risk in outpatients with COVID-19. The antiviral treatment appears promising for mitigating COVID-19’s long-term impact.

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CONFLICTS OF INTEREST

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