Association of nirmatrelvir–ritonavir with post-acute sequelae and mortality among patients who are immunocompromised with COVID-19 in Hong Kong: a retrospective cohort study

Guozhang Lin, Yuchen Wei*, Huwen Wang, Christopher Boyer, Katherine Min Jia, Chi Tim Hung, Xiaoting Jiang, Conglu Li, Carrie Ho Kwan Yam, Tsz Yu Chow, Yawen Wang, Shi Zhao, Zihao Guo, Kehang Li, Aimin Yang, Chris Ka Pun Mok, David S C Hui, Ka Chun Chong, Eng Kiong Yeoh*

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See Comment page e77

*Authors contributed equally

School of Public Health and Primary Care (G Lin MSc, Y Wei PhD, H Wang MPhil, Prof C T Hung MBBS, X Jiang MSc, C Li MSc, C H K Yam PhD, T Y Chow BSc, S Zhao PhD, Z Guo MSc, K Li MSc, K C Chong PhD, Prof E K Yeoh MBBS), **Department of Medicine & Therapeutics, Faculty of Medicine** (A Yang PhD), **Li Ka Shing Institute of Health Sciences** (C K P Mok PhD), **SH Ho Research Centre for Infectious Diseases** (Prof D S C Hui MBBS), **Chinese University of Hong Kong, Hong Kong, China; Center for Communicable Disease Dynamics, Department of Epidemiology, Harvard TH Chan School of Public Health, Harvard University, Boston, MA, USA** (C Boyer PhD, K M Jia MSc); **Division of Landscape Architecture, Department of Architecture, Faculty of Architecture, The University of Hong Kong, Hong Kong, China** (Y Wang PhD); **School of Public Health, Tianjin Medical University, Tianjin, China** (S Zhao)

Correspondence to: Dr Ka Chun Chong, School of Public Health and Primary Care, The Chinese University of Hong Kong, Hong Kong, China **marc@cuhk.edu.hk**

Summary

Background The effect of nirmatrelvir–ritonavir on post-COVID-19 outcomes for individuals who are immunocompromised is understudied. We aimed to examine the association of nirmatrelvir–ritonavir with post-acute sequelae and mortality among patients who are immunocompromised and admitted to hospital with COVID-19.

Methods We did a retrospective cohort study using territory-wide electronic health records from the Hong Kong Hospital Authority and Hong Kong Department of Health. Eligible patients were adults aged 18 years or older who tested positive for SARS-CoV-2 during the study period (March 11, 2022, to Nov 9, 2023) and were admitted to hospital with COVID-19. Four exposure groups were formed based on immune status (immunocompromised or immunocompetent) and nirmatrelvir–ritonavir status (yes or no). The primary outcome was post-acute inpatient death, starting from 21 days after the positive RT-PCR date. Standardised mortality ratio weighting with doubly robust adjustment was applied to control for confounders. Cox models were used to estimate hazard ratios (HRs) for the outcomes.

Findings Between March 11, 2022, and Nov 9, 2023, there were 89 772 individuals with positive RT-PCR tests, of whom 39 923 met eligibility criteria and were included in the study cohort. 19 914 (49·9%) of 39 923 patients were female, 20 009 (50·1%) were male and the median age was 75·0 years (IQR 63·0–85·0). 846 (38·2%) of 2217 patients who were immunocompromised and 14 586 (38·7%) of 37 706 patients who were immunocompetent were prescribed nirmatrelvir–ritonavir. Among the patients who were immunocompromised, those patients who received nirmatrelvir–ritonavir had significantly lower risk of post-acute inpatient death (HR 0·58, 95% CI 0·45–0·74; p<0·0001) and hospitalisation for acute respiratory distress syndrome (0·43, 0·20–0·90; p=0·024) than those who did not. A significant negative interaction was found between immune status and nirmatrelvir–ritonavir on post-acute all-cause hospitalisation (relative excess risk due to interaction –0·84, 95% CI –1·30 to –0·37; p=0·0004).

Interpretation Nirmatrelvir–ritonavir was associated with reduced risk of post-acute inpatient death among patients who were immunocompromised and admitted to hospital with COVID-19. However, the effectiveness of nirmatrelvir–ritonavir on post-acute hospitalisation outcomes was less pronounced in patients who were immunocompromised than in patients who were immunocompetent.

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Introduction

The persistent presence of newly identified variants of concern, characterised by variable levels of virulence and transmissibility, remains a crucial factor contributing to the mortality and morbidity associated with post-COVID-19 condition. This condition, also referred to as long COVID or post-COVID sequelae, includes a range of prolonged health effects in individuals following their initial recovery from COVID-19. According to WHO, post-COVID condition affects around 10–20% of people infected by SARS-CoV-2 and includes symptoms such as fatigue, shortness of breath, and cognitive dysfunction.[1] The development of post-COVID condition has been suggested to be multifactorial and follow the dysregulation of multiple body organs and systems in response to a trigger.[2] Risk factors for post-COVID condition include age, comorbidity burden, and glucocorticoid use among patients with systemic autoimmune rheumatic diseases.[3]

The orally administered antiviral drug nirmatrelvir–ritonavir (Paxlovid) specifically targets a crucial protease enzyme of the SARS-CoV-2 virus. In a phase 3 randomised clinical trial,[4] nirmatrelvir–ritonavir was showed

Research in context

Evidence before this study

We searched PubMed for the published studies from database inception to June 2, 2024, using search terms ("paxlovid" or "nirmatrelvir") and ("post COVID" or "long COVID" or "post-acute sequelae") and ("immunocompromised" or "immunosuppressed") without language restrictions. One review was found on COVID-19 management in patients including immunocompromised populations. Immunocompromised populations are highly susceptible to SARS-CoV-2 infection and at a greater risk of mortality and complications during hospitalisation than are immunocompetent populations, with rapid and severe disease pathogenesis. Nirmatrelvir–ritonavir is associated with lower risks of all-cause death and disease progression. However, there remains a research gap on the effectiveness of nirmatrelvir–ritonavir in preventing post-acute sequalae and mortality among patients who are immunocompromised.

Added value of this study

To our knowledge, this is the first real-world study to examine the relationship between nirmatrelvir–ritonavir and post-COVID health outcomes specifically in immunocompromised individuals. Our results suggest that nirmatrelvir–ritonavir is associated with reduced risk of post-acute inpatient death in patients who are immunocompromised and admitted to hospital with COVID-19. In terms of post-acute all-cause hospitalisation, our results indicate that nirmatrelvir–ritonavir might not be as effective at reducing post-acute death and all-cause hospitalisation for patients who are immunocompromised as for patients who are immunocompetent. Although at risk of SARS-CoV-2 infection and severe COVID-19 outcomes, immunocompromised populations have been under-represented in randomised clinical trials in COVID-19. Our study assessed the real-world effectiveness of nirmatrelvir–ritonavir in this population and compared with the immunocompetent population, thus revealing the potential impact of immune status on the effectiveness of nirmatrelvir–ritonavir in reducing post-acute mortality and sequelae.

Implications of all the available evidence

Early initialisation of nirmatrelvir–ritonavir was associated with significant reductions in risks of post-acute inpatient death and admission to hospital with acute respiratory distress syndrome in individuals who are immunocompromised and admitted to hospital with COVID-19. However, the effectiveness of nirmatrelvir–ritonavir on post-acute hospitalisation outcomes was less apparent in patients who are immunocompromised than in patients who are immunocompetent. Given the less pronounced association and higher risks of mortality and complications, additional research is warranted to explore more effective treatment options in immunocompromised patient population.

to be effective in lowering the risk of progression to severe COVID-19 outcomes by day 28 after infection. Large observational cohort studies further support the effectiveness of nirmatrelvir–ritonavir in mitigating acute severity across different SARS-CoV-2 variants, including Omicron.[5] In late 2021, an emergency use authorisation was issued for nirmatrelvir–ritonavir,[6] targeting outpatients with mild-to-moderate COVID-19 at high risk, including patients with immunocompromised conditions without respiratory failure.

In general, individuals who are immunocompromised have an increased risk of severe presentation, hospitalisation, and mortality associated with COVID-19.[7,8] In some populations, such as transplant recipients, the response to vaccination can be greatly compromised, leading to a higher vulnerability to COVID-19, prolonged viral shedding, and the development of severe complications.[9] Short-term benefits (within 28 days) of nirmatrelvir–ritonavir have been reported in individuals who are immunocompromised.[10] For instance, outpatient treatments, including nirmatrelvir–ritonavir, were found to be associated with reduced mortality and admission to hospital in the acute phase among patients with systemic autoimmune rheumatic diseases.[11] However, no studies have specifically shown the protective effect of nirmatrelvir–ritonavir on post-COVID-19 sequelae in this population, despite several observational studies reporting the extended benefits of nirmatrelvir–ritonavir on post-COVID-19 conditions in the general population.[12,13] In a previous study,[14] we showed that nirmatrelvir–ritonavir was associated with reduced risks of post-acute inpatient death, cardiovascular complications, and respiratory complications among patients admitted to hospital with COVID-19. Given the distinct clinical characteristics of individuals who are immunocompromised compared with the general population, we planned a separate study to examine the effects of nirmatrelvir–ritonavir in people who are immunocompromised.

Individuals who are immunocompromised are often underrepresented in randomised controlled trials in COVID-19 and are typically excluded from assessments of antiviral interventions.[15] Large observational studies, which allow for an evaluation of real-life effectiveness of interventions, can help complement the findings from trials. In this study, we used real-world data to investigate the relationship between nirmatrelvir–ritonavir and post-acute mortality, and admission to hospital due to post-acute sequelae in individuals who were immunocompromised and admitted to hospital in Hong Kong.

Methods

Study design

We did a retrospective cohort study investigating the risk of selected post-acute health outcomes of SARS-CoV-2

infection among four exposure groups of patients admitted to hospital with COVID-19. The exposure groups were formed based on immune status (immunocompromised or immunocompetent) and the use of nirmatrelvir–ritonavir (yes or no). The effect of nirmatrelvir–ritonavir was studied separately in patients who were immunocompromised and patients who were immunocompetent to assess the difference in effect sizes between the two groups. We also analysed the potential interaction between immune status and nirmatrelvir–ritonavir in the entire study population.

Real-world territory-wide data were provided by the Hong Kong Hospital Authority and the Department of Health. The Hospital Authority is a statutory authority managing all public hospitals in Hong Kong. Its services are accessible to over 7·3 million Hong Kong residents, encompassing approximately 80% of regular hospital admissions and all patients with COVID-19 in the territory.[16] The Hospital Authority maintains a centralised electronic database, which has been widely used in high-quality studies including pharmacological research related to COVID-19.[16] The extensive electronic records from this database were linked to population-based vaccination records from the COVID-19 vaccination registry of the Department of Health. The diagnoses and procedures were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Both data sources used anonymised pseudo numbers to protect patient confidentiality. Data on ethnicity were not available.

The study followed the STROBE reporting guideline. Ethics approval was obtained from the Joint CUHK-NTEC Clinical Research Ethics Committee (2023.006).

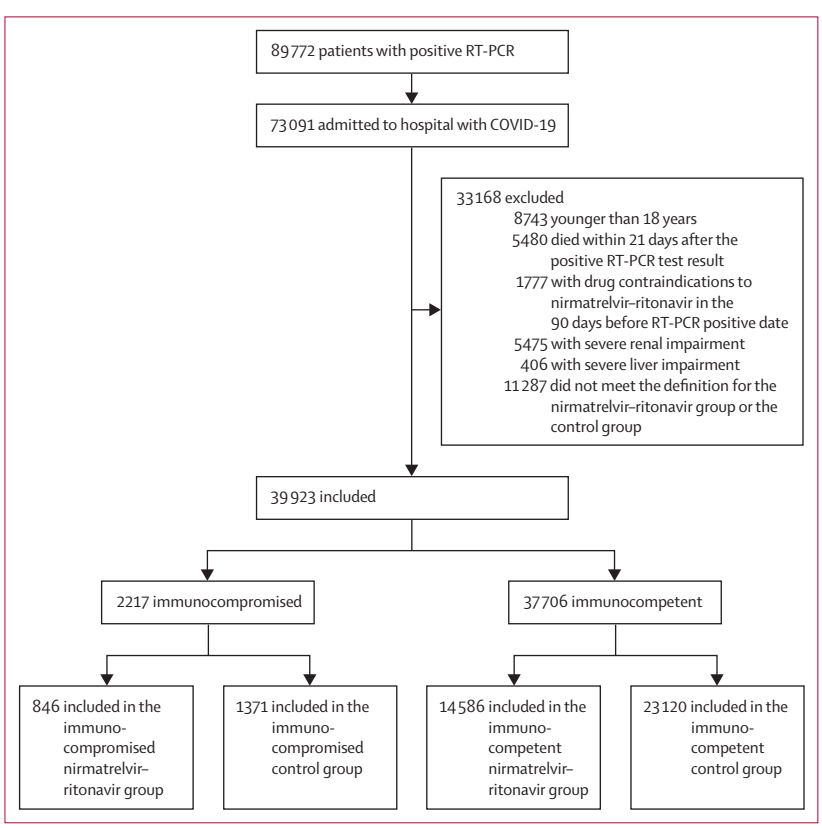


Figure 1: **Patient inclusion and exclusion**

Participants

The inclusion criteria included a positive RT-PCR test result for SARS-CoV-2 between March 11, 2022 (5 days before the availability of nirmatrelvir–ritonavir in Hong Kong), and Nov 9, 2023 (21 days before the end of data availability [Nov 30, 2023]), during which the Omicron variant was the predominant variant and monoclonal antibodies used to neutralise SARS-CoV-2 were not available as an outpatient treatment option (for individuals with more than one positive test result in this period, only the first instance was included); and an admission record within 3 days before or after the index date (the positive RT-PCR date).[14] These patients were considered hospitalised with COVID-19.

Exclusion criteria were age younger than 18 years; death within 21 days after the positive RT-PCR test result;[13] contraindications to nirmatrelvir–ritonavir due to drug interaction (dispensing history of amiodarone, apalutamide, carbamazepine, ivosidenib, lumacaftor-ivacaftor, phenobarbital, phenytoin, primidone, rifampicin, rifapentine, or St John's Wort within 90 days before the index date); severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m², dialysis, or renal transplantation); severe liver impairment (cirrhosis, hepatocellular carcinoma, or liver transplantation); or not meeting the criteria of the nirmatrelvir–ritonavir group or the control group.[5,17]

As this study was a retrospective analysis using secondary data without any personal information, the requirement for obtaining informed consent was waived and approved by the Joint CUHK-NTEC Clinical Research Ethics Committee.

Procedures

Patients were included in the nirmatrelvir–ritonavir group if they had dispensing history of nirmatrelvir–ritonavir within five days after the positive RT-PCR test result and did not have dispensing history of molnupiravir within 21 days after the positive RT-PCR test result.[14] Patients were included in the control group if they did not have any dispensing history of nirmatrelvir–ritonavir or molnupiravir within 21 days after the positive RT-PCR test result.

Patients were identified as immunocompromised if they were diagnosed with HIV at any time before the index date, had a haematological malignancy in the year before the index date, an immune-mediated rheumatic disease at any time before the index date, other haematological conditions in the year before the index date, other immune conditions in the year before the index date, had

a solid organ transplant at any time before the index date, or a bone marrow or stem cell transplant in the 2 years before the index date.[10,18,19] The ICD-9-CM codes for these conditions and procedures are provided in the appendix (p 4). Patients were also identified as immunocompromised if they had a dispensing history or remaining supply of a monoclonal antibody in the past 3 months, an oral immunosuppressive drug in the past month, an oral glucocorticoid (20 mg/day of prednisone equivalent taken on an ongoing basis) in the past month, or had a dispensing history of an immunosuppressive infusion or injection in the 3 months before the index date (appendix pp 5–6; defined based on WHO Anatomical Therapeutic Chemical classes).[10,20] Patients that were not identified as immunocompromised were classified as immunocompetent in this study.

Confounders were selected based on previous studies.[5,21] The confounders controlled for were age; sex; previous SARS-CoV-2 infection; vaccination status (unvaccinated, 1–2 doses of vaccine, or ≥3 doses of vaccine; incomplete doses, defined as the doses received less than 14 days before the index date, did not count towards the total number of vaccine doses); week of the index date; intensive care unit admission on the index date; initiation of concomitant pharmacological treatments (dexamethasone, prednisolone, interferon, baricitinib, tocilizumab, or remdesivir) on the index date; and Charlson Comorbidity Index calculated based on the diagnosis before the index date (appendix p 3). In the analysis of the effectiveness of nirmatrelvir–ritonavir among patients who were immunocompromised, the aforementioned immune-related conditions, procedures, and medication use (ie, HIV, haematological malignancy, immune-mediated rheumatic disease, other haematological conditions, other immune conditions, solid organ transplant, bone marrow or stem cell transplant, and the use of each class of the immunosuppressive medications) were also controlled for with the same time ranges applied.

Outcomes

The primary outcome was post-acute inpatient death occurring between 21 days and 365 days after the index date. More than 90% of deaths in Hong Kong occurred in hospitals, especially public hospitals.[22]

Secondary outcomes were post-acute all-cause hospital admission and post-acute cause-specific hospital admission, with causes including chronic pulmonary disease, acute respiratory distress syndrome, coronary artery disease, congestive heart failure, chronic kidney disease, and acute kidney injury. These conditions were selected based on previous literature,[16,23] with the aim to compare post-COVID-19 pulmonary, cardiovascular, and renal functions in patients with different immune status and nirmatrelvir–ritonavir use status (appendix p 4). Individuals with a history of the condition of interest before the index date were excluded from the corresponding analysis.

	Immunocompromised		Immunocompetent	
	No nirmatrelvir–ritonavir	Nirmatrelvir–ritonavir	No nirmatrelvir–ritonavir	Nirmatrelvir–ritonavir
Total	1371	846	23120	14586
Age, years	69·0 (60·5–76·0)	66·0 (59·0–74·0)	75·0 (59·0–86·0)	76·0 (67·0–85·0)
Sex				
Female	679 (49·5%)	499 (59·0%)	11815 (51·1%)	6921 (47·4%)
Male	692 (50·5%)	347 (41·0%)	11305 (48·9%)	7665 (52·6%)
History of SARS-CoV-2 infection	23 (1·7%)	11 (1·3%)	242 (1·0%)	99 (0·7%)
Intensive care unit admission	35 (2·6%)	6 (0·7%)	591 (2·6%)	116 (0·8%)
Vaccination status				
Unvaccinated	369 (26·9%)	118 (13·9%)	6065 (26·2%)	2194 (15·0%)
1–2 doses	467 (34·1%)	214 (25·3%)	6968 (30·1%)	2695 (18·5%)
≥3 doses	535 (39·0%)	514 (60·8%)	10087 (43·6%)	9697 (66·5%)
Concomitant pharmacological treatments				
Dexamethasone	254 (18·5%)	37 (4·4%)	4052 (17·5%)	461 (3·2%)
Prednisolone	170 (12·4%)	92 (10·9%)	309 (1·3%)	188 (1·3%)
Interferon	2 (0·1%)	0	35 (0·2%)	5 (<0·1%)
Baricitinib	7 (0·5%)	2 (0·2%)	75 (0·3%)	23 (0·2%)
Tocilizumab	3 (0·2%)	0	46 (0·2%)	1 (<0·1%)
Remdesivir	194 (14·2%)	13 (1·5%)	2932 (12·7%)	244 (1·7%)
Charlson Comorbidity Index	2·0 (0·0–3·0)	2·0 (1·0–3·0)	0·0 (0·0–1·0)	0·0 (0·0–0·0)
Myocardial infarction	15 (1·1%)	5 (0·6%)	436 (1·9%)	139 (1·0%)
Congestive heart failure	52 (3·8%)	16 (1·9%)	1100 (4·8%)	290 (2·0%)
Peripheral vascular disease	19 (1·4%)	6 (0·7%)	204 (0·9%)	76 (0·5%)
Cerebrovascular disease	54 (3·9%)	19 (2·2%)	1511 (6·5%)	707 (4·8%)
Dementia	5 (0·4%)	2 (0·2%)	385 (1·7%)	96 (0·7%)
Chronic pulmonary disease	58 (4·2%)	32 (3·8%)	1244 (5·4%)	488 (3·3%)
Connective tissue disease	163 (11·9%)	84 (9·9%)	0	0
Peptic ulcer disease	33 (2·4%)	19 (2·2%)	310 (1·3%)	182 (1·2%)
Mild liver disease	51 (3·7%)	36 (4·3%)	459 (2·0%)	192 (1·3%)
Diabetes without complications	148 (10·8%)	64 (7·6%)	1711 (7·4%)	856 (5·9%)
Diabetes with complications	25 (1·8%)	5 (0·6%)	250 (1·1%)	77 (0·5%)
Hemiplegia or paraplegia	13 (0·9%)	2 (0·2%)	156 (0·7%)	56 (0·4%)
Renal disease	80 (5·8%)	4 (0·5%)	527 (2·3%)	88 (0·6%)
Malignancy	600 (43·8%)	510 (60·3%)	748 (3·2%)	486 (3·3%)
Moderate to severe liver disease	4 (0·3%)	2 (0·2%)	31 (0·1%)	10 (0·1%)
Metastatic solid tumour	195 (14·2%)	173 (20·4%)	219 (0·9%)	132 (0·9%)
HIV	8 (0·6%)	5 (0·6%)	0	0
Immune conditions in specified time range				
Haematological malignancy	203 (14·8%)	118 (13·9%)	..	..
Immune-mediated rheumatic disease	209 (15·2%)	97 (11·5%)	..	..
Rheumatoid arthritis	86 (6·3%)	45 (5·3%)	..	..
Systemic lupus erythematosus	45 (3·3%)	26 (3·1%)	..	..
Others	90 (6·6%)	30 (3·5%)	..	..
Other haematological conditions	58 (4·2%)	43 (5·1%)	..	..
Other immune conditions	16 (1·2%)	3 (0·4%)	..	..

(Table continues on next page)

	Immunocompromised		Immunocompetent	
	No nirmatrelvir–ritonavir	Nirmatrelvir–ritonavir	No nirmatrelvir–ritonavir	Nirmatrelvir–ritonavir
(Continued from previous page)				
Transplantation status				
Bone marrow or stem cell transplant	10 (0·7%)	7 (0·8%)	..	..
Solid organ transplant	58 (4·2%)	3 (0·4%)	..	..
Immunosuppressive medications				
Anthracycline	40 (2·9%)	44 (5·2%)	..	..
Azathioprine	69 (5·0%)	38 (4·5%)	..	..
Calcineurin inhibitor	75 (5·5%)	4 (0·5%)	..	..
Checkpoint inhibitor	55 (4·0%)	44 (5·2%)	..	..
Cyclophosphamide	67 (4·9%)	54 (6·4%)	..	..
Interleukin inhibitor	19 (1·4%)	8 (0·9%)	..	..
Janus kinase inhibitor	12 (0·9%)	4 (0·5%)	..	..
Mycophenolic acid*	206 (15·0%)	52 (6·1%)	..	..
Protein kinase inhibitor	150 (10·9%)	96 (11·3%)	..	..
Rituximab	62 (4·5%)	34 (4·0%)	..	..
Oral glucocorticoid	30 (2·2%)	11 (1·3%)	..	..
Targeted cancer therapy	127 (9·3%)	101 (11·9%)	..	..
TNF inhibitor	30 (2·2%)	9 (1·1%)	..	..
Other cancer therapies	531 (38·7%)	460 (54·4%)	..	..
Other selective immunosuppressants	103 (7·5%)	53 (6·3%)	..	..

Data are n (%) or median (IQR). Distribution of covariates by immune status and the use of nirmatrelvir–ritonavir before weighting. *Mycophenolic acid includes mycophenolate, mycophenolate sodium, and mycophenolate mofetil.

Table: **Baseline characteristics**

See Online for appendix

The outcomes were assessed starting from 21 days after the index date. The 21-day timeframe was one of the common definitions of the post-acute phase based on previous studies.[16] Every patient was followed up for up to 365 days from the index date. The follow-up ended at inpatient death, the occurrence of the health outcome in the corresponding analysis, 365 days after the index date, or the end of data availability (Nov 30, 2023), whichever came first.

Statistical analysis

Standardised mortality ratio weighting was applied to balance the confounders.[24] The propensity scores were obtained from logistic regression models. Truncation at the 1st and 99th percentiles was applied in the case of extreme weights. We used the absolute value of the standardised mean difference to assess covariate balance before and after weighting. Covariates with standardised mean difference 0·1 or greater after weighting were considered imbalanced and were included in the corresponding models for doubly robust adjustment.[25]

To examine the effect of nirmatrelvir–ritonavir, Cox proportional hazards models were used to estimate the risk of the outcomes in weighted samples. The Huber sandwich estimator was adopted to obtain robust standard errors. Plots of scaled Schoenfeld residuals were used to assess the model assumption of proportional hazards.

With regards to the relevance of additive interaction for both clinical decisions and public health,[26] we evaluated both additive interaction and multiplicative interaction in the analysis for the interaction between immune status and nirmatrelvir–ritonavir (appendix p 7).

To explore potential effect modifiers, in the immunocompromised cohort, we conducted subgroup analyses by age groups (<65 or ≥65 years), vaccination status (unvaccinated, 1–2 doses of vaccine, or 3 doses of vaccine), and the recent use of any cancer therapy (yes or no), where recent was defined as fulfilling the same above-mentioned timeframe requirements of the immunosuppressive medications for the criteria of patients who were immunocompromised, and a cancer therapy was defined as any one of anthracycline, checkpoint inhibitor, cyclophosphamide, protein kinase inhibitor, rituximab with malignancy diagnosis, targeted cancer therapy, or other cancer therapies[20] (appendix pp 5–6). We did two sensitivity analyses, in which we ascertained the outcomes starting from 30 and 60 days after the index date, instead of 21 days in the main analysis. The same standardised mortality ratio weighting method with doubly robust adjustment was used in both the subgroup and sensitivity analyses. All analyses were done using R (version 4.3.2).

Role of the funding source

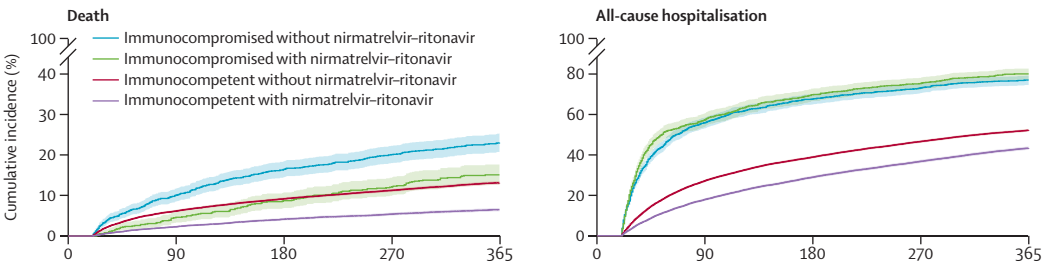
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

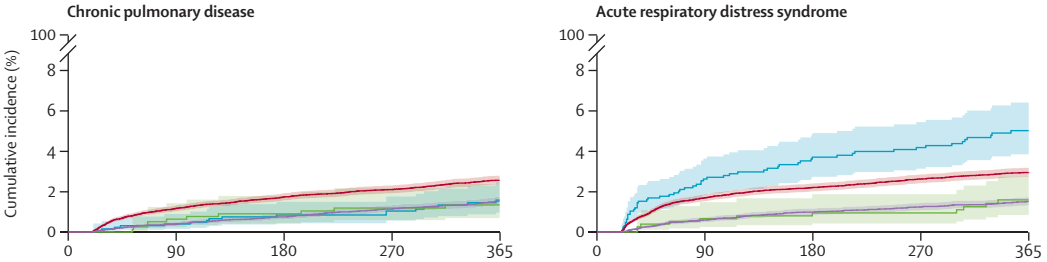
Of 89772 patients with positive RT-PCR tests between Mar 11, 2022, and Nov 9, 2023, 73091 patients were admitted to hospital with COVID-19, of whom 39923 patients met the eligibility criteria and were included in the study cohort (figure 1). 19914 (49·9%) of 39923 patients were female, 20009 (50·1%) were male, and the median age was 75·0 years (IQR 63·0–85·0). The median follow-up time was 365·0 days (IQR 344·0–365·0). Of the 2217 patients who were immunocompromised, 846 (38·2%) met the definition of the nirmatrelvir–ritonavir group, and 1371 (61·8%) met the definition of the control group. Of the 37706 patients who were immunocompetent, 14586 (38·7%) met the definition of the nirmatrelvir–ritonavir group, and 23120 (61·3%) met the definition of the control group (table).

Figure 2: **Cumulative incidence of outcome by immune status and use of nirmatrelvir–ritonavir**

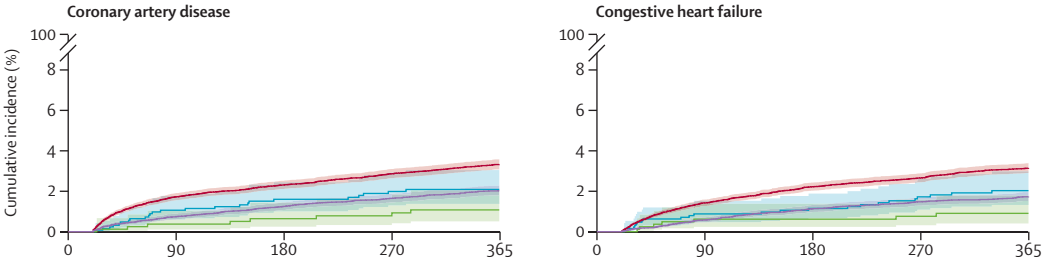
Unadjusted cumulative incidences are stratified by immune status and the use of nirmatrelvir–ritonavir for each outcome, without adjusting for covariates.



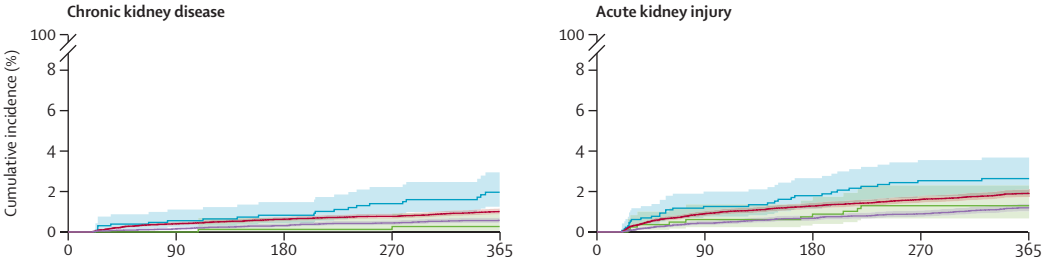
Number at risk (number of events)										
Immunocompromised without nirmatrelvir–ritonavir	1371 (0)	1227 (137)	1125 (85)	1068 (48)	810 (40)	1371 (0)	557 (734)	402 (144)	336 (65)	222 (50)
Immunocompromised with nirmatrelvir–ritonavir	846 (0)	799 (38)	751 (33)	710 (28)	480 (25)	846 (0)	356 (478)	248 (100)	200 (46)	122 (38)
Immunocompetent without nirmatrelvir–ritonavir	23120 (0)	21589 (1416)	20792 (687)	20186 (474)	15264 (415)	23120 (0)	16233 (6077)	13533 (2571)	11760 (1679)	8198 (1208)
Immunocompetent with nirmatrelvir–ritonavir	14586 (0)	14173 (330)	13832 (267)	13579 (176)	9637 (159)	14586 (0)	11830 (2570)	10188 (1559)	9033 (1100)	5913 (922)



Number at risk (number of events)										
Immunocompromised without nirmatrelvir–ritonavir	1313 (0)	1172 (5)	1075 (5)	1017 (2)	768 (5)	1272 (0)	1134 (32)	1045 (10)	991 (7)	744 (8)
Immunocompromised with nirmatrelvir–ritonavir	814 (0)	763 (5)	715 (2)	675 (2)	455 (1)	774 (0)	729 (5)	688 (1)	653 (1)	445 (4)
Immunocompetent without nirmatrelvir–ritonavir	21876 (0)	20302 (246)	19518 (112)	18917 (75)	14292 (83)	22682 (0)	21042 (372)	20261 (107)	19656 (84)	14873 (65)
Immunocompetent with nirmatrelvir–ritonavir	14098 (0)	13672 (54)	13319 (49)	13050 (51)	9241 (47)	14425 (0)	13979 (85)	13638 (54)	13373 (34)	9480 (34)



Number at risk (number of events)										
Immunocompromised without nirmatrelvir–ritonavir	1307 (0)	1159 (13)	1057 (6)	1001 (3)	758 (2)	1319 (0)	1173 (11)	1073 (3)	1016 (5)	765 (4)
Immunocompromised with nirmatrelvir–ritonavir	818 (0)	771 (3)	723 (2)	685 (1)	458 (2)	830 (0)	781 (5)	734 (0)	693 (1)	471 (1)
Immunocompetent without nirmatrelvir–ritonavir	21944 (0)	20255 (366)	19459 (119)	18834 (105)	14220 (87)	22020 (0)	20389 (302)	19585 (161)	19005 (85)	14363 (94)
Immunocompetent with nirmatrelvir–ritonavir	14100 (0)	13623 (102)	13263 (68)	12997 (53)	9180 (49)	14296 (0)	13842 (81)	13473 (75)	13208 (47)	9369 (32)



Number at risk (number of events)										
Immunocompromised without nirmatrelvir–ritonavir	1317 (0)	1168 (7)	1068 (3)	1006 (6)	757 (5)	1329 (0)	1183 (16)	1083 (6)	1026 (7)	774 (2)
Immunocompromised with nirmatrelvir–ritonavir	844 (0)	797 (0)	749 (1)	709 (0)	479 (1)	834 (0)	786 (5)	739 (1)	697 (4)	470 (0)
Immunocompetent without nirmatrelvir–ritonavir	22640 (0)	21097 (88)	20314 (46)	19728 (30)	14917 (44)	22749 (0)	21159 (197)	20355 (81)	19766 (63)	14940 (60)
Immunocompetent with nirmatrelvir–ritonavir	14512 (0)	14087 (21)	13736 (23)	13478 (18)	9563 (17)	14449 (0)	14008 (62)	13669 (33)	13400 (30)	9510 (38)

In patients who were immunocompromised, and before standardised mortality ratio weighting, the nirmatrelvir–ritonavir group had a lower median age (66·0 years *vs* 69·0 years), a smaller proportion of male patients (347 [41·0%] of 846 *vs* 692 [50·5%] of 1371), a larger proportion of patients who had completed at least three doses of vaccine (514 [60·8%] *vs* 535 [39·0%]), and smaller proportions of patients given dexamethasone (37 [4·4%] *vs* 254 [18·5%]) and remdesivir (13 [1·5%] *vs* 194 [14·2%]), than did the control group (table). The differences between the nirmatrelvir–ritonavir group and the control group among patients who were immunocompetent were similar to those among the patients who were immunocompromised, except that the patients who were immunocompetent in the nirmatrelvir–ritonavir group had a higher median age and a larger proportion of male patients (table). The medications most commonly used by the patients with immune-mediated rheumatic diseases are listed in the appendix (p 6).

We plotted cumulative incidence curves with risk tables stratified by the four exposure groups without adjusting for the covariates (figure 2). For the same immune status, patients in the control group had higher unadjusted cumulative incidences than the patients in the nirmatrelvir–ritonavir group for most of the outcomes at most of the times, including inpatient death, acute respiratory distress syndrome, cardiovascular conditions, and renal conditions, but not all-cause hospitalisation or chronic pulmonary disease.

After standardised mortality ratio weighting, the covariates were well balanced with a standardised mean difference of less than 0·1 (appendix pp 8–31) except for week of the index date, which was included in the

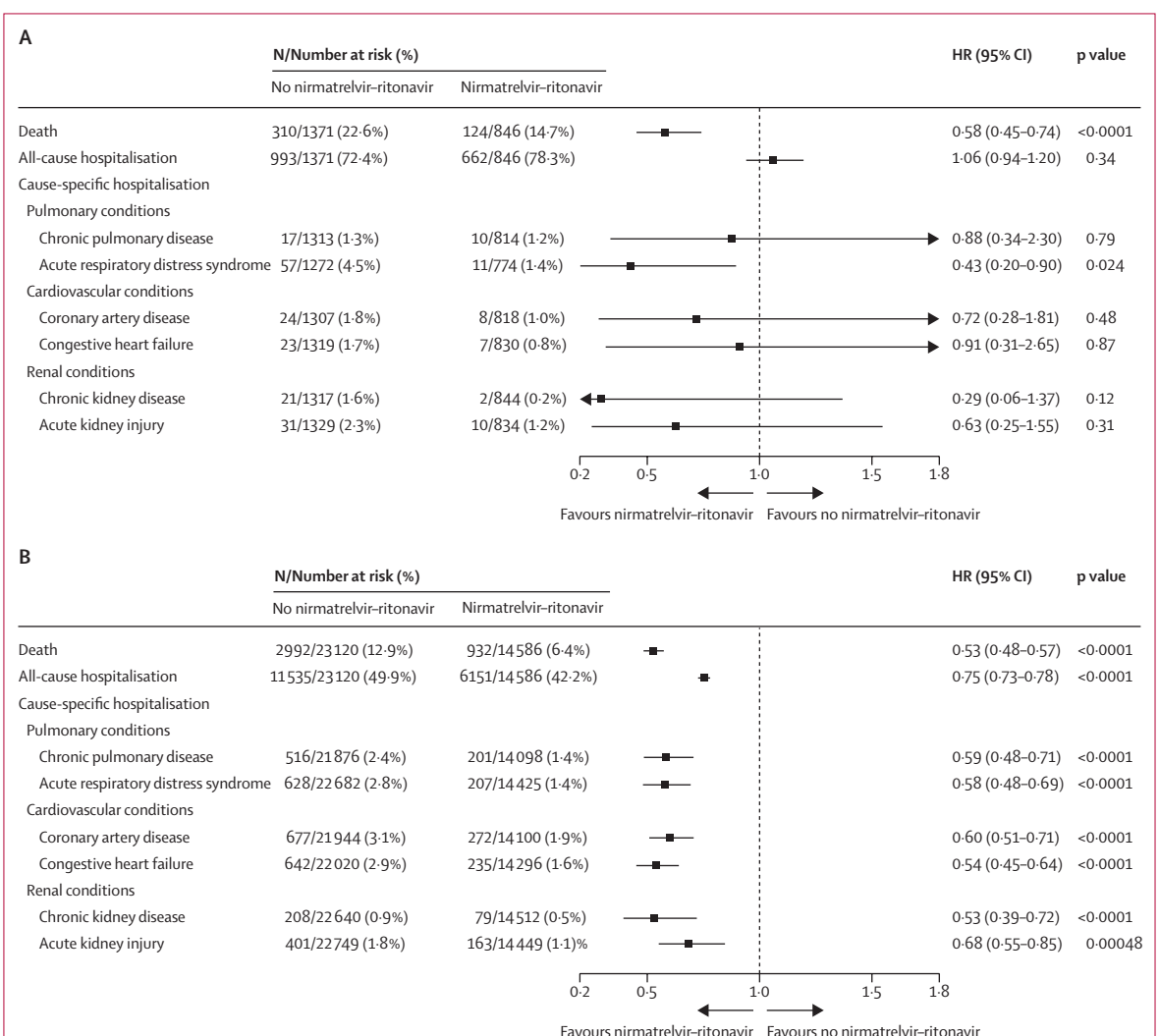


Figure 3: **Effect of nirmatrelvir–ritonavir on outcomes by immune status**
(A) Patients who were immunocompromised. (B) Patients who were immunocompetent. The effect of nirmatrelvir–ritonavir on each outcome is stratified by immune status after standardised mortality ratio weighting was applied.

corresponding models for doubly robust adjustment. The plots of scaled Schoenfeld residuals did not show clear evidence of the violation of the proportional hazards assumption (appendix pp 32–33).

Among patients who were immunocompromised, Cox models showed significantly lower risks of post-acute inpatient death (hazard ratio [HR] 0·58, 95% CI 0·45–0·74; p<0·0001) and hospital admission for acute respiratory distress syndrome (0·43, 0·20–0·90; p=0·024) in the nirmatrelvir–ritonavir group compared with the control group (figure 3A). No significant differences were observed for all-cause hospitalisation or hospitalisation due to cardiovascular or renal conditions (figure 3). Patients who were immunocompetent in the nirmatrelvir–ritonavir group had significantly lower risks for all outcomes compared to those in the control group, including inpatient death (HR 0·53, 95% CI 0·48–0·57; p<0·0001, a larger effect size than the immunocompromised cohort), and all-cause hospitalisation (0·75, 0·73–0·78; p<0·0001, which was not significant in the immunocompromised cohort; figure 3).

The measures used to evaluate the interaction between immune status and nirmatrelvir–ritonavir are listed in appendix (p 7). For all-cause hospitalisation, we detected significant negative additive (relative excess risk due to interaction –0·84, 95% CI –1·30 to –0·37; p=0·0004) and negative multiplicative interactions (exponential of the coefficient of the interaction term in the cox model 0·64, 95% CI 0·55 to 0·74; p<0·0001, appendix p 7), indicating that nirmatrelvir–ritonavir was significantly less effective in preventing post-acute all-cause hospitalisation for patients who were immunocompromised than for patients who were immunocompetent.

Some key findings of the subgroups analysis in the immunocompromised cohort are described in the appendix (pp 34–36). HR of inpatient deaths was 0·47 in patients younger than 65 years (95% CI 0·30–0·73, p=0·0009) and 0·65 in patients aged 65 years or older (0·48 to 0·87, p=0·0038). Patients with recent use of any cancer therapy were also found to have a larger HR of post-acute inpatient death (HR 0·59, 95% CI 0·44–0·78; p=0·0002) than those without (0·42, 0·21–0·83; p=0·013). Sensitivity analyses showed similar results to those from the primary analyses (appendix p 37).

Discussion

Our study examined the association of nirmatrelvir–ritonavir on post-acute mortality and hospitalisation due to post-acute sequelae in patients who were immunocompromised and admitted to hospitals in Hong Kong, most of whom had COVID-19 during the Omicron epidemic. We showed that prescribing nirmatrelvir–ritonavir during the acute phase of COVID-19 was associated with a reduced risk of post-acute death in patients who were immunocompromised, compared with patients who did not receive nirmatrelvir–ritonavir. Our study showed that the effect size of nirmatrelvir–ritonavir in reducing the risk of post-acute death was slightly smaller in patients who were immunocompromised than that in patients who were immunocompetent. Although, to our knowledge, no previous studies have specifically examined the effect of nirmatrelvir–ritonavir on post-acute outcomes in patients who are immunocompromised, our estimated effect size aligns with a similar investigation among the patients admitted to hospital with COVID-19 regardless of immune status.[14] Our findings suggest that patients who are immunocompromised could still benefit from antiviral use, although they had a higher COVID-associated mortality than individuals who are immunocompetent.[7]

Among the post-acute sequelae, nirmatrelvir–ritonavir was associated with a reduced risk of hospitalisation due to acute respiratory distress syndrome in patients who were immunocompromised. The effect size of the reduced risk was similar to that observed in patients who were immunocompetent. This finding echoes another retrospective study from the USA, which showed that nirmatrelvir was associated with a reduced risk of pulmonary embolism and shortness of breath.[13] Furthermore, the severity of COVID-19 during the acute phase has been suggested to be associated with post-acute occurrence of several respiratory diseases.[16] Alveolar type II epithelial cells are one of the primary target cell types for SARS-CoV-2. When they are infected by SARS-CoV-2, the epithelial repair mechanisms can be disrupted, leading to incomplete repair, scarring, and fibrosis.[27] By reducing the viral load,[4] nirmatrelvir–ritonavir might help alleviate the impairment of alveolar type II cells and thus lower the risks of pulmonary damage (eg, acute respiratory distress syndrome) during the post-acute phase of COVID-19. However, we were unable to demonstrate a significant relationship with cardiovascular and renal conditions in patients who were immunocompromised, possibly due to a smaller number of events in both the control and exposure groups compared with those admitted to hospital with acute respiratory distress syndrome.

In our study, nirmatrelvir–ritonavir was associated with a lower risk of post-acute all-cause hospitalisation in patients who were immunocompetent but not in patients who were immunocompromised. Our data analysis further suggested a negative interaction effect between immune status and nirmatrelvir–ritonavir. It has been shown that immunocompromised individuals are generally more prone to severe and persistent SARS-CoV-2 infection.[28] Thus, this might result in a worse outcome of post-acute hospitalisation compared with individuals who are immunocompetent.

Patients who are immunocompromised are often understudied in experimental studies of COVID-19. For example, although the causal relationship between nirmatrelvir–ritonavir and COVID-19 mortality was

established in the EPIC-HR trial,[4] only a few individuals who were immunocompromised were enrolled in that trial. Therefore, our real-world investigation serves as a valuable complement to the scarce randomised controlled trial findings in immunocompromised populations. Although observational studies are subject to residual confounding,[29] this retrospective cohort study used registry data with a large sample size. The registry data allowed the assessment of outcomes related to post-COVID condition that required long follow-up periods. The findings from this study call for further randomised controlled trials to gather more robust evidence and establish causal relationships between nirmatrelvir–ritonavir and post-acute outcomes in immunocompromised populations.

This real-world investigation has a notable strength in that it used data highly representative of patients admitted to hospital with COVID-19. The data was collected from all public hospitals in Hong Kong and accounted for approximately 80% of all routine hospitalisations and all patients with COVID-19.[16] The data are also representative of patients who are immunocompromised, because most of the immunocompromised population use services provided by public hospitals due to subsidisation in the public health-care system in Hong Kong. Additionally, in the public hospital system, patients' medical records were digitally documented, which strengthened the validity of disease diagnoses and prescription information. Nevertheless, there are several limitations of this study. First, we did not use the post COVID condition defined by WHO, which primarily focuses on symptoms such as fatigue and shortness of breath,[1] due to a lack of corresponding diagnoses in the electronic health system. Instead, we specifically targeted post-acute sequelae that are typically documented in a standardised manner using ICD codes within the health-care system in Hong Kong. These ICD codes have often been used in similar studies investigating post-COVID condition.[16] Second, the participants enrolled in this study were predominantly infected with Omicron sub-lineages BA.2 and BA.5, while the proportion of patients infected with sub-lineage XBB was small, suggesting that caution is needed when extrapolating our findings to other variants and sub-lineages. Third, since most of the study population was prescribed nirmatrelvir–ritonavir, we did not investigate the use of other antiviral medications such as molnupiravir.[12] Fourth, our retrospective observational design is subject to possible residual confounding. For instance, unmeasured clinical characteristics during the acute phase of infection and socioeconomic factors could introduce bias. Fifth, individuals who are immunocompromised are a very heterogeneous population, and their COVID-19 outcomes vary greatly across different immunocompromised categories, such as transplantation and HIV.[7,30] Due to the limited number of outcome events in this study, we were only able to carry out subgroup analyses on the malignancy group who had recent use of cancer therapy.

In conclusion, we demonstrated the benefits of nirmatrelvir–ritonavir in reducing post-acute mortality and hospitalisation due to acute respiratory distress syndrome among patients who were immunocompromised. Nirmatrelvir–ritonavir has been recommended for treating COVID-19 in individuals who are immunocompromised and who are considered to be at a high risk of COVID-19 progression, irrespective of previous vaccination or infection status.[29] Our study additionally documented the long-term benefit, further reinforcing the recommendation for using nirmatrelvir–ritonavir in this population. Nevertheless, our study also revealed that the effectiveness of nirmatrelvir–ritonavir on post-acute hospitalisation outcomes was less pronounced in patients who were immunocompromised than in individuals who were immunocompetent. Considering this, longer courses of nirmatrelvir–ritonavir or combination therapies might be warranted for the treatment of SARS-CoV-2 infection in patients who are immunocompromised to achieve long-term clinical benefits, although existing evidence from randomised controlled trials is scarce.[28]

Contributors

Study design and conceptualisation: GL, HW, YWei, CB, and KCC. Data collection and pre-processing: GL, YWei, CHKY, TYC, ZG, and EKY. Data analysis and interpretation: GL, HW, YWei, YWang, and KCC. Writing–original draft: GL, HW, CTH, KMJ, XJ, CL, SZ, CKPM, DSCH, and KCC. Writing–review and editing: CB, CHKY, TYC, KL, AY, EKY. EKY and KCC have accessed and verified all the data. All authors critically reviewed the manuscript and gave final approval for publication.

Declarations of interests

We declare no competing interests.

Data sharing

Patient surveillance data and medication records were extracted from electronic records in the system managed by the Hong Kong Hospital Authority. The vaccine history was extracted from the COVID-19 surveillance database provided by the Department of Health in Hong Kong. Restrictions apply to the availability of these data.

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