QJM: An International Journal of Medicine, 2026, **119(2)**, 117–127
https://doi.org/10.1093/qjmed/hcaf218
Advance Access Publication Date: 22 September 2025
Original Article

Development and validation of age-specific predictive models on the risk of post-acute mortality within 1 year of COVID-19 infection

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Abstract

Background: The existing risk prediction models for COVID-19 associated mortality have not considered the differences in risk factors across different age groups of patients.

Aim: To develop age-specific prediction models to forecast the risk of all-cause mortality in patients recovering from COVID-19 infection.

Design: Population-based, retrospective cohort study.

Methods: Patients with COVID-19 between 1 April 2020 and 31 July 2022 survived beyond the acute phase of infection were stratified into separate age cohorts (<45, 45–64, ≥65) and followed-up for 1 year. Backward stepwise logistic regression and four statistical and machine learning algorithms were employed to develop age-specific models on the risk of post-acute mortality following COVID-19 infection, based on a comprehensive set of clinical parameters including demographics, COVID-19 vaccination status, pre-existing comorbidities and laboratory-test findings.

Results: Of the 891 246 patients with COVID-19 identified, 13 578 (1.05%) died within 1 year of the index date. Age, COVID-19 vaccination status and history of acute respiratory syndrome prior infection were identified as predictors in the models for separate age groups. The model for patients aged ≥65 exhibited excellent prediction performance with an AUROC of 0.87 (95% CI: 0.87, 0.88), followed by the model for patients aged 45–64 [AUROC = 0.83 (95% CI: 0.81, 0.85)] and those aged <45 [AUROC = 0.79 (95% CI: 0.72, 0.86)].

Received: 12 June 2025. **Revised (in revised form):** 25 August 2025.

Conclusion: The age-specific models accurately predicted the risk of post-acute mortality in their corresponding age groups of patients, providing valuable asset in optimizing clinical strategies and resource allocation in the management of the global burden of Long COVID.

Introduction

Since the outbreak of the COVID-19 pandemic in 2019, there have been over seven billion confirmed cases and seven million deaths reported worldwide, with most of these recorded among older adults.[1] Whilst many patients recover from the acute phase of the illness, as much as 80% of patients continue to experience persistent and newly developed symptoms or adverse clinical outcomes beyond the acute infection. The current literature referred post-acute sequelae of SARS-CoV-2 (PASC), also known as Long COVID, as clinical presentation which persists or develops 30 days following the initial COVID-19 infection.[2–5] The constellation of signs and symptoms of PASC could range from mild symptoms including fatigue, shortness of breath and cognitive impairment to severe complications including acute respiratory distress syndrome (ARDS), sepsis and multi-organ failure, which could lead to mortality in severe cases.[3,6] Despite the milder disease severity associated with the dominant Omicron variant and the gradual reduction in the spread COVID-19, over 16 000 new cases of infection continued to be reported worldwide every week.[1] Previous studies have reported an approximately 4-fold increase in risk of post-acute all-cause mortality amongst patients with COVID-19 compared to their matched non-COVID-19 controls.[7] The considerable risk increase and the large population of patients with COVID-19 at risk of developing post-acute sequelae following infection raise the need for more effective strategies to identify individuals at high risk of poor clinical prognosis and subsequent death following their infection.

Emerging evidence throughout the course of the pandemic has demonstrated the association of age, certain comorbidities and severe COVID-19 conditions with various post-acute adverse outcomes of COVID-19 including hospital admission or death.[8–10] Nevertheless, physiological changes and dysregulation in the immune system and inflammatory response associated with aging have led to the speculation on the variations in the associated risk factors across patients of different age.[11–13] Building on the current knowledge of the risk factors associated with poorer prognosis of COVID-19 infection, various prognosis predictive models with the aim of predicting the risk of Long COVID, hospital admission and mortality amongst patients with COVID-19 have been devised and implemented to support clinical decisions in hospital settings.[14–17] Nonetheless, existing prediction models have focused mainly on the prediction of the risk of adverse clinical outcomes after COVID-19 during the earlier acute phase of infection. Besides, the risk prediction based on the same factors across patients of different age could compromise the accuracy of previous models. Lastly, laboratory measurements, such as elevated levels of inflammatory markers and lower cycle threshold (CT) value, which have been identified as important predictors of disease severity of infection, were not included in previous prediction models for the post-acute outcomes of patients with COVID-19.

This study aims to develop age-specific prediction models on the risk of post-acute mortality following COVID-19 infection drawing on a diverse range of clinical parameters, including demographic information, pre-existing medical conditions, COVID-19 vaccination history and laboratory measurements. Robust statistical models devised based on key predictive risk factors serve as a valuable tool for identifying high-risk patients in clinical settings.

Materials and methods

Data source

The study extracted patient's electronic medical records from the Hong Kong Hospital Authority (HKHA) database. As a statutory body, HKHA is responsible for managing all public hospitals and ambulatory clinics in Hong Kong. The healthcare service is accessible to more than 7.3 million HK residents, covering around 80% of all routine hospital admissions and all patients diagnosed with COVID-19. The electronic medical records in the HKHA database comprised disease diagnoses recorded during planned or unplanned doctor consultations, hospital visits and emergency visits. This facilitates the prompt recording of medical records for all users of public health services in HK. Vaccination records were provided by the Department of Health, the Government of Hong Kong Special Administrative Region. Death records were obtained from the Hong Kong Deaths Registry. The database has been used in previous studies on the long-term sequelae of COVID-19 infection, COVID-19 vaccines, oral antiviral safety surveillance and effectiveness evaluation.[7,18–24]

Study design and population

The base population for this study was defined as patients aged 18 years or above with a SARS-CoV-2 infection (confirmed by either rapid antigen test [RAT] adopted for self-testing or polymerase chain reaction [PCR] test in throat swab, nasopharyngeal aspirate or deep throat sputum specimens conducted in hospital and community testing centres) between 1 April 2020 and 31 July 2022. For patients with multiple records of positive COVID-19 screening test, the date of the first record of positive result from either PCR or RAT were taken as the date of their COVID-19 infection. Patients were stratified by age into under 45, 45–64 and 65 or over representing young adults, middle-age and older adults, respectively.[25,26] Patients who survived the acute phase of infection (30 days post-infection) were eligible as study population for prediction model development. The index date of patients was defined as 30 days after COVID-19 infection. Each patient was followed-up from the index date until their death or 12 months from the index date (the last record was on 31 August 2023), whichever occurs the earliest. This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guideline for prognostic studies.[27]

Outcome

The outcome of this study was post-acute all-cause mortality within 1 year of index date.

Predictors

A comprehensive range of predicting variables was selected based on the risk factors for poor prognosis following COVID-19 infection including patients' characteristics, comorbidities and laboratory-test parameters. Specific patient's characteristics included age, sex, history of COVID-19 vaccination (2/+ doses), history of disease diagnoses involving multiple organ systems defined by the International Classification of Diseases, Ninth

Revision, Clinical Modification (ICD-9-CM; Supplementary Table S1) were selected as potential predictors. These variables were measured on index date whilst laboratory testing results were obtained within 14 days infection to capture the rapid onset of changes following COVID-19 infection. The specific disease diagnoses and laboratory-test results selected for model development were further described in Supplementary Method S1.

Statistical analysis

Before model construction, univariate analysis adjusting for age and sex only was conducted to assess the association between each candidate predictor and all-cause mortality. The significant predictors were then included in a multivariable regression model and were examined by variance inflation factors (VIFs). Predictors with a VIF above 3 were excluded to avoid multi-collinearity between variables.[28] Descriptive characteristics were summarized using counts and percentages for categorical variables and mean and standard deviation for continuous variables.

The cohort of individuals from each age strata were divided randomly into training set and validation set in the ratio of 7:3. To develop age-specific prediction models for post-acute 1-year all-cause mortality, logistic regression with backward selection and four statistical and machine learning algorithms were performed in different age groups using training sets. The predictors selected by backward logistic regression were determined by Bayesian Information Criterion (BIC).[29,30] In the developed model, we further tested the multicollinearity assumption by VIF and linearity assumption by the Box–Tidwell test and plotting the numerical parameters (i.e. age) and the log odds of the outcome (Supplementary Figure S1).[31] The squared age term was included in the prediction model for patients over 65 to satisfy the linearity assumption of the model. Stepwise Cox proportional hazards regression with backward selection by BIC was also conducted, however, due to the violation of the proportional hazard assumption and the relatively short followed-up of 1 year, logistic regression with backward selection was chosen for the current analysis (Supplementary Table S2). Four additional statistical and machine learning algorithms represent a spectrum of modelling strategies ranging from penalized regression, Least Absolute Shrinkage and Selection Operator (LASSO) to tree-based ensemble methods, random forest, eXtreme Gradient Boosting (XGBoost) and Light Gradient-Boosting Machine (LightGBM) were employed to cross-validate the findings in ensuring the robustness of findings and independence on the choice of a single algorithm.[32–34] These models, which do not demand adherence to statistical assumptions typically required by conventional models, are merited for their capability to consider complex, nonlinear interactions in clinical data.[35] Detailed description on the development and hyperparameters tuning of the statistical and machine learning models were provided in Supplementary Method S2 and Table S3.

Model performance in the testing sets was evaluated by examining discrimination and calibration. Discrimination was assessed by the area under receiver operating characteristic curve (AUROC) and the area under precision recall curve (AUPRC). The precision–recall curve can be more informative in imbalanced datasets.[36] The reference value for AUPRC was the prevalence of all-cause mortality in each age group (0.06% in those under 45; 0.47% in patients aged 45–64; 4.56% in patients over 65), whereas the reference value for AUROC was 0.5. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and *F*1 score of the models were also reported at different predicted probability cutoffs. Calibration was graphically depicted in calibration plot between the predicted probability and observed probability, and measured by calibration slope, calibration-in-the-large (i.e. intercept in the calibration plot) and the Hosmer–Lemeshow goodness-of-fit test. The 95% confidence interval (CI) of performance measures was estimated by bootstrapping using the percentile method.

Further sensitivity analyses were conducted by including only (i) patients hospitalized during the acute phase of COVID-19 and (ii) individuals screened positive by PCR testing. Data cleaning and logistic regression analyses were conducted by R version 3.6.3, and statistical and machine learning were conducted by Python (version 3.9.13) and PyCharm 2022 (Professional Edition).

Results

A total of 901 801 patients with COVID-19 between 1 April 2020 and 31 July 2022 were identified, in which 891 246 patients survived the acute phase and were included in prediction model development. Of the 891 246 COVID-19 survivors, 13 578 (1.05%) died within 1 year of the index date. These patients were stratified into three age groups: <45 ($n = 306\,338$), 45–64 ($n = 324\,085$), ≥65 ($n = 260\,823$). Patients aged ≥65 had a highest rate of all-cause mortality within 1 year of 4.56%, followed by patients aged 45–64 and <45 with 0.47% and 0.06%, respectively (Table 1). The cumulative number of deaths after COVID-19 infection was plotted in Supplementary Figure S2. The univariate analysis adjusting for age and sex showed that older patients, males, with less than two doses of vaccination, existing chronic diseases (except for psychotic disorder, Bell's palsy, hypertension and anxiety), developed ARDS during the acute phase and abnormal levels of biomarkers shortly after the infection were associated with increased risk of mortality within 1 year after COVID-19 infection (Supplementary Table S4). The statistically significant factors were included in a multivariable logistic model and tested for multicollinearity, where five correlated factors with high collinearity were excluded in feature selection process. A total of 27 candidate predictors were eventually selected, taking into account the VIF estimated (Supplementary Table S5).

Figure 1 illustrates the performance of different prediction models in each age group against the testing sets. Models developed by separate statistical and machine learning model exhibit comparably high predictive performance. Given the parsimonious and greater clinical interpretability of model developed by the logistic regression, the model based on logistic regression was identified as the preferred model for clinical application (Supplementary Tables S6–S8). Models developed for patients aged over 65 achieved the highest predictive performance [AUROC: 0.87 (95% CI 0.87, 0.88); AUPRC: 0.29 (95% CI 0.27, 0.30)], followed by the model for patients aged 45–64 [AUROC: 0.83 (95% CI 0.81, 0.85); AUPRC: 0.10 (95% CI 0.07, 0.13)] and those aged <45 [AUROC: 0.79 (95% CI 0.72, 0.86); AUPRC: 0.02 (95% CI 0.01, 0.04)]. Table 2 and Supplementary Table S9 present the performance measures at different probabilities cutoffs for age-specific models. All models were well calibrated with intercepts and slopes of the calibration plots close to 0 and 1, respectively (Figure 2 and Supplementary Figure S3).

The odds ratios of selected predictors estimated are summarized in Table 3. The prediction model for 1-year all-cause mortality varied across different age groups. Age, sex, receipt of two doses of vaccination, ARDS before infection and lymphocyte were found to be significant predictors across all the models, while the model for patients aged 45–64 years additionally included ARDS during acute phase of COVID-19, heart failure, ESKD, type 2 diabetes, seizure, DVT and CT; the model for those

Table 1 Demographics, medical history and clinical laboratory parameters of study population

	Age < 45			Age 45–64			Age ≥ 65		
Variable	**Alive**	**Dead within 1 year**	**P[a]**	**Alive**	**Dead within 1 year**	**P[a]**	**Alive**	**Dead within 1 year**	**P[a]**
Demographic characteristics									
Number of patients	306 155	183		322 571	1514		248 942	11 881	
Male (*n*, %)	138 932 (45.4)	110 (60.1)	<0.001	136 998 (42.5)	938 (62.0)	<0.001	122 442 (49.2)	6684 (56.3)	<0.001
Age in years (mean, SD)	33.26 (6.94)	36.90 (6.11)	<0.001	55.18 (5.75)	57.63 (5.26)	<0.001	74.39 (8.10)	84.45 (9.60)	<0.001
Vaccinate 2+ doses (*n*, %)	247 653 (80.9)	108 (59.0)	<0.001	274 374 (85.1)	768 (50.7)	<0.001	164 390 (66.0)	3342 (28.1)	<0.001
Diagnosis (*n*, %)									
Myocardial infarction	126 (<0.1)	2 (1.1)	<0.001	1843 (0.6)	56 (3.7)	<0.001	4169 (1.7)	842 (7.1)	<0.001
Heart failure	172 (0.1)	4 (2.2)	<0.001	1223 (0.4)	105 (6.9)	<0.001	7484 (3.0)	1996 (16.8)	<0.001
Stroke	589 (0.2)	1 (0.5)	0.803	6186 (1.9)	143 (9.4)	<0.001	24 039 (9.7)	2967 (25.0)	<0.001
Atrial fibrillation	158 (0.1)	0 (0.0)	–	1789 (0.6)	47 (3.1)	<0.001	11 632 (4.7)	1933 (16.3)	<0.001
Deep vein thrombosis	110 (<0.1)	4 (2.2)	<0.001	380 (0.1)	28 (1.8)	<0.001	781 (0.3)	178 (1.5)	<0.001
Psychotic disorder	199 (0.1)	0 (0.0)	–	103 (<0.1)	1 (0.1)	0.984	25 (<0.1)	0 (0.0)	–
Encephalitis and encephalopathy	89 (<0.1)	1 (0.5)	0.054	73 (<0.1)	3 (0.2)	<0.001	78 (<0.1)	9 (0.1)	0.020
Bell's Palsy	46 (<0.1)	0 (0.0)	–	135 (<0.1)	0 (0.0)	–	167 (0.1)	8 (0.1)	1.000
Interstitial lung disease	1 (<0.1)	0 (0.0)	–	21 (<0.1)	2 (0.1)	<0.001	96 (<0.1)	24 (0.2)	<0.001
Chronic pulmonary disease	2416 (0.8)	8 (4.4)	<0.001	3923 (1.2)	48 (3.2)	<0.001	10 899 (4.4)	1534 (12.9)	<0.001
ARDS before infection	264 (0.1)	11 (6.0)	<0.001	1081 (0.3)	133 (8.8)	<0.001	2629 (1.1)	733 (6.2)	<0.001
ARDS during acute phase	19 (<0.1)	3 (1.6)	<0.001	110 (0.0)	32 (2.1)	<0.001	405 (0.2)	331 (2.8)	<0.001
Pancreatitis	167 (0.1)	3 (1.6)	<0.001	454 (0.1)	7 (0.5)	0.003	925 (0.4)	121 (1.0)	<0.001
Liver injury	91 (<0.1)	1 (0.5)	0.058	208 (0.1)	5 (0.3)	<0.001	277 (0.1)	32 (0.3)	<0.001
End-stage kidney disease	41 (<0.1)	2 (1.1)	<0.001	188 (0.1)	37 (2.4)	<0.001	502 (0.2)	168 (1.4)	<0.001
Acute kidney injury and failure	205 (0.1)	6 (3.3)	<0.001	727 (0.2)	65 (4.3)	<0.001	3055 (1.2)	1014 (8.5)	<0.001
Type 1 diabetes	239 (0.1)	1 (0.5)	0.346	325 (0.1)	12 (0.8)	<0.001	389 (0.2)	35 (0.3)	<0.001
Type 2 diabetes	3776 (1.2)	12 (6.6)	<0.001	38 962 (12.1)	382 (25.2)	<0.001	73 724 (29.6)	4245 (35.7)	<0.001
Hypertension	6650 (2.2)	21 (11.5)	<0.001	71 338 (22.1)	454 (30.0)	<0.001	132 081 (53.1)	7532 (63.4)	<0.001
Anxiety	1046 (0.3)	4 (2.2)	<0.001	1833 (0.6)	11 (0.7)	0.518	1884 (0.8)	77 (0.6)	0.199
Post-traumatic stress disorder	2838 (0.9)	8 (4.4)	<0.001	2662 (0.8)	21 (1.4)	0.024	1608 (0.6)	140 (1.2)	<0.001
Seizure	1907 (0.6)	7 (3.8)	<0.001	1896 (0.6)	80 (5.3)	<0.001	1914 (0.8)	351 (3.0)	<0.001
Clinical laboratory parameters (*n*, %)									
COVID CT			<0.001			<0.001			<0.001
Missing	268 554 (87.7)	118 (64.5)		283 162 (87.8)	762 (50.3)		203 080 (81.6)	4659 (39.2)	
<20	16 653 (5.4)	25 (13.7)		19 666 (6.1)	371 (24.5)		22 681 (9.1)	3576 (30.1)	
≥20	20 948 (6.8)	40 (21.9)		19 743 (6.1)	381 (25.2)		23 181 (9.3)	3646 (30.7)	
C-reactive protein			<0.001			<0.001			<0.001
Missing	297 688 (97.2)	150 (82.0)		313 493 (97.2)	1073 (70.9)		228 152 (91.6)	6475 (54.5)	
≤15 mg/l	6919 (2.3)	12 (6.6)		6177 (1.9)	123 (8.1)		9469 (3.8)	1353 (11.4)	
>15 mg/l	1548 (0.5)	21 (11.5)		2901 (0.9)	318 (21.0)		11 321 (4.5)	4053 (34.1)	
WBC (TLC) count			<0.001			<0.001			<0.001
Missing	294 843 (96.3)	130 (71.0)		308 513 (95.6)	860 (56.8)		219 513 (88.2)	5104 (43.0)	
$\leq 10 \times 10^9$/l	10 199 (3.3)	38 (20.8)		12721 (3.9)	501 (33.1)		24 651 (9.9)	4962 (41.8)	
$>10 \times 10^9$/l	1113 (0.4)	15 (8.2)		1337 (0.4)	153 (10.1)		4778 (1.9)	1815 (15.3)	
Absolute neutrophil count			<0.001			<0.001			<0.001
Missing	295 673 (96.6)	132 (72.1)		309 545 (96.0)	885 (58.5)		221 501 (89.0)	5383 (45.3)	
$\leq 7.5 \times 10^9$/l	9572 (3.1)	38 (20.8)		11 832 (3.7)	467 (30.8)		22 485 (9.0)	4481 (37.7)	
$>7.5 \times 10^9$/l	910 (0.3)	13 (7.1)		1194 (0.4)	162 (10.7)		4956 (2.0)	2017 (17.0)	
Platelet count			<0.001			<0.001			<0.001
Missing	294 846 (96.3)	130 (71.0)		308 528 (95.6)	860 (56.8)		219 538 (88.2)	5109 (43.0)	

(continued)

Table 1 (continued)

Variable	Age < 45			Age 45–64			Age ≥ 65		
	Alive	Dead within 1 year	P[a]	Alive	Dead within 1 year	P[a]	Alive	Dead within 1 year	P[a]
$<150\times10^9$/l	864 (0.3)	16 (8.7)		1613 (0.5)	130 (8.6)		5794 (2.3)	1480 (12.5)	
$\geq150\times10^9$/l	10 445 (3.4)	37 (20.2)		12 430 (3.9)	524 (34.6)		23 610 (9.5)	5292 (44.5)	
Procalcitonin			<0.001			<0.001			<0.001
Missing	305 678 (99.8)	179 (97.8)		321 602 (99.7)	1418 (93.7)		246 639 (99.1)	11 151 (93.9)	
≤0.25 ng/ml	385 (0.1)	0 (0.0)		715 (0.2)	39 (2.6)		1389 (0.6)	351 (3.0)	
>0.25 ng/ml	92 (<0.1)	4 (2.2)		254 (0.1)	57 (3.8)		914 (0.4)	379 (3.2)	
Serum ferritin			<0.001			<0.001			<0.001
Missing	304 183 (99.4)	170 (92.9)		319 971 (99.2)	1355 (89.5)		242 699 (97.5)	10 157 (85.5)	
≤400 ng/ml	1573 (0.5)	5 (2.7)		1421 (0.4)	60 (4.0)		3060 (1.2)	712 (6.0)	
>400 ng/ml	399 (0.1)	8 (4.4)		1179 (0.4)	99 (6.5)		3183 (1.3)	1012 (8.5)	
Lactate dehydrogenase			<0.001			<0.001			<0.001
Missing	297 960 (97.3)	148 (80.9)		313 915 (97.3)	1126 (74.4)		230 515 (92.6)	7329 (61.7)	
<245 U/l	7345 (2.4)	16 (8.7)		6647 (2.1)	182 (12.0)		11 452 (4.6)	2137 (18.0)	
≥245 U/l	850 (0.3)	19 (10.4)		2009 (0.6)	206 (13.6)		6975 (2.8)	2415 (20.3)	
Lymphocyte			<0.001			<0.001			<0.001
Missing	295 673 (96.6)	132 (72.1)		309 545 (96.0)	885 (58.5)		221 501 (89.0)	5383 (45.3)	
$<1.0\times10^9$/l	2666 (0.9)	31 (16.9)		3938 (1.2)	339 (22.4)		11 654 (4.7)	3587 (30.2)	
$\geq1.0\times10^9$/l	7816 (2.6)	20 (10.9)		9088 (2.8)	290 (19.2)		15 787 (6.3)	2911 (24.5)	
Neutrophil-lymphocyte ratio (NLR)			<0.001			<0.001			<0.001
Missing	295 673 (96.6)	132 (72.1)		309 545 (96.0)	885 (58.5)		221 501 (89.0)	5383 (45.3)	
≤3	9647 (3.2)	45 (24.6)		11 638 (3.6)	560 (37.0)		23 688 (9.5)	5553 (46.7)	
>3	835 (0.3)	6 (3.3)		1388 (0.4)	69 (4.6)		3753 (1.5)	945 (8.0)	
Erythrocyte sedimentation rate (ESR)			<0.001			<0.001			<0.001
Missing	295 673 (96.6)	132 (72.1)		309 545 (96.0)	885 (58.5)		221 501 (89.0)	5383 (45.3)	
Male: ≤age/2 Female: ≤(age + 10)/2	9647 (3.2)	45 (24.6)		11 638 (3.6)	560 (37.0)		23 688 (9.5)	5553 (46.7)	
Male: >age/2 Female: >(age + 10)/2	835 (0.3)	6 (3.3)		1388 (0.4)	69 (4.6)		3753 (1.5)	945 (8.0)	

SD, standard deviation.

[a] The characteristics between alive persons and dead persons were compared using the Chi-squared test for categorical variables, and *t*-test for continuous variables.

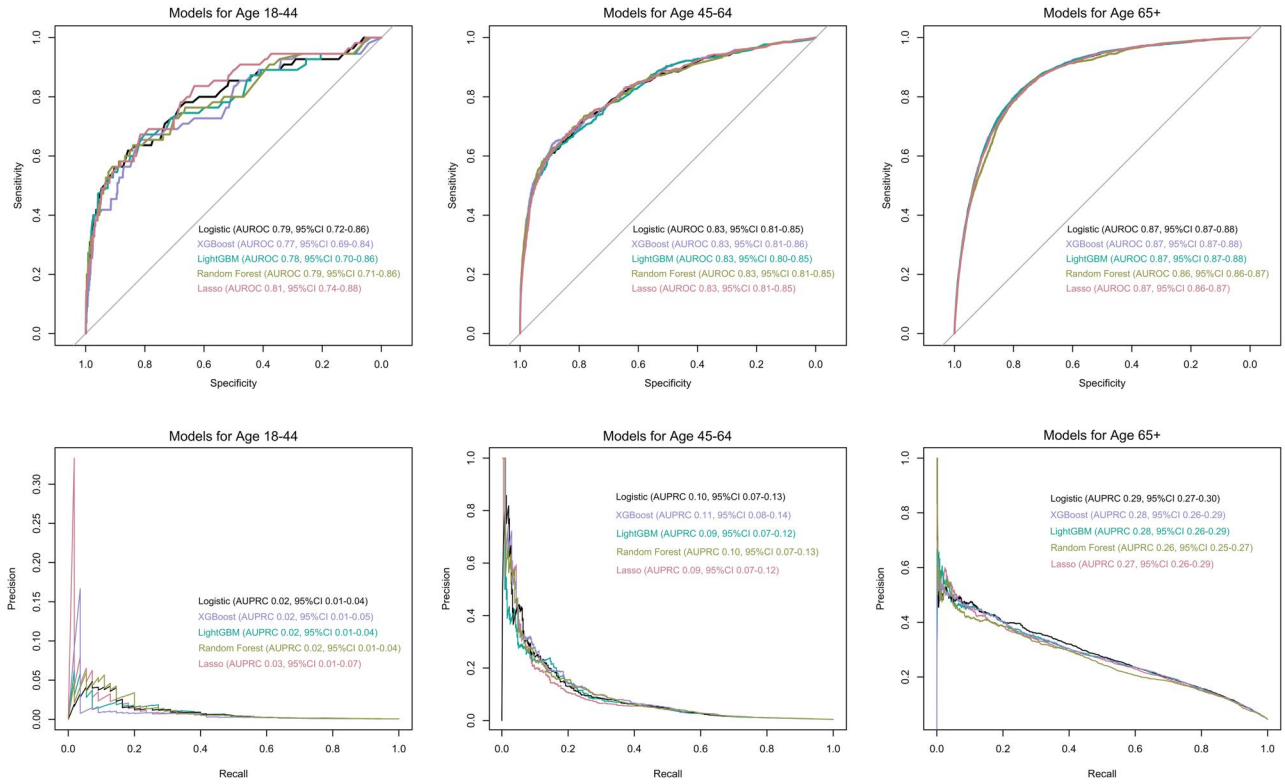

Figure 1. Comparison of AUROCs and AUPRCs of different prediction models against the testing sets in separate age groups.

Table 2 Performance of logistic regression model against testing sets in each age groups at different predicted probability cut-offs

Risk cut-offs	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	F1 (%)
Model 18–44					
0.05%	78.18 (67.27, 88.89)	66.28 (65.98, 66.56)	0.14 (0.10, 0.19)	99.98 (99.97, 99.99)	0.28 (0.20, 0.37)
0.1%	54.55 (42.01, 67.21)	90.58 (90.38, 90.76)	0.35 (0.23, 0.48)	99.97 (99.96, 99.98)	0.69 (0.46, 0.95)
0.2%	34.55 (22.58, 47.30)	97.66 (97.56, 97.75)	0.88 (0.54, 1.27)	99.96 (99.95, 99.97)	1.71 (1.05, 2.46)
Model 45–64					
0.2%	88.33 (85.28, 91.26)	48.90 (48.58, 49.22)	0.77 (0.70, 0.85)	99.89 (99.86, 99.92)	1.54 (1.39, 1.68)
0.5%	64.99 (60.72, 69.34)	85.54 (85.32, 85.76)	1.99 (1.76, 2.22)	99.82 (99.79, 99.84)	3.86 (3.43, 4.30)
1%	53.32 (48.73, 58.08)	94.06 (93.92, 94.20)	3.89 (3.38, 4.41)	99.78 (99.75, 99.80)	7.26 (6.35, 8.18)
Model 65+					
2%	91.10 (90.18, 92.09)	63.95 (63.61, 64.29)	10.66 (10.31, 11.03)	99.35 (99.28, 99.42)	19.09 (18.52, 19.68)
4%	81.18 (79.85, 82.48)	79.17 (78.87, 79.45)	15.55 (15.02, 16.05)	98.89 (98.81, 98.97)	26.10 (25.31, 26.83)
5%	76.23 (74.82, 77.56)	82.95 (82.68, 83.22)	17.43 (16.81, 18.01)	98.66 (98.57, 98.75)	28.38 (27.49, 29.21)

PPV: positive predictive value; NPV: negative predictive value.
The values denote the estimates (and 95% confidence interval).

aged ≥65 years included the addition of ARDS during acute phase of COVID-19, heart failure, ESKD, seizure, myocardial infarction, stroke, atrial fibrillation, DVT, CPD, CT and serum ferritin. Increased age and fewer than two doses of vaccination showed similar adverse effects on 1-year all-cause mortality across age groups, while the adverse effects of ARDS before infection decreased with age from OR of 21.63 (95% CI: 8.82, 53.02) for patients aged <45, 6.72 (95%CI: 5.15, 8.75) for patients aged 45–64, to 2.61 (95% CI: 2.32, 2.94) for patients aged ≥65. For patients aged between 45 and 64, the adverse effect of ARDS during acute phase of COVID-19 [OR 4.70 (95% CI 2.82, 7.83)] was lower than ARDS before infection, whereas in patients aged over 65, ARDS during acute phase became to exhibit higher risk [OR 3.72 (95% CI 3.04, 4.55)] than ARDS before infection at the same age group. In addition, all morbidities included in the models were associated with higher risk of all-cause mortality. Of the laboratory parameters, lymphocyte $<1.0 \times 10^9$/l and serum ferritin >400 ng/ml was associated with higher risk of all-cause mortality, while the absence of laboratory variables constituted to a lower risk of all-cause mortality.

Patients requiring hospital admission following SARS-CoV-2 infection incurred a higher rate of mortality ($N = 6753$ [12.91%]), with a more complete record of laboratory parameters (Supplementary Table S10) Models developed among hospitalized patients identified comparable predictors and consistent direction for risk factors associated with mortality, with the absence of laboratory variables shown to constitute to a greater risk of all-cause mortality (Supplementary Tables S11 and S12). As routine blood tests are typically performed for hospitalized patients, missing laboratory data may reflect distinct comorbidity profiles or early mortality before testing. Given the uncertainty surrounding the absence values in this group of patients,

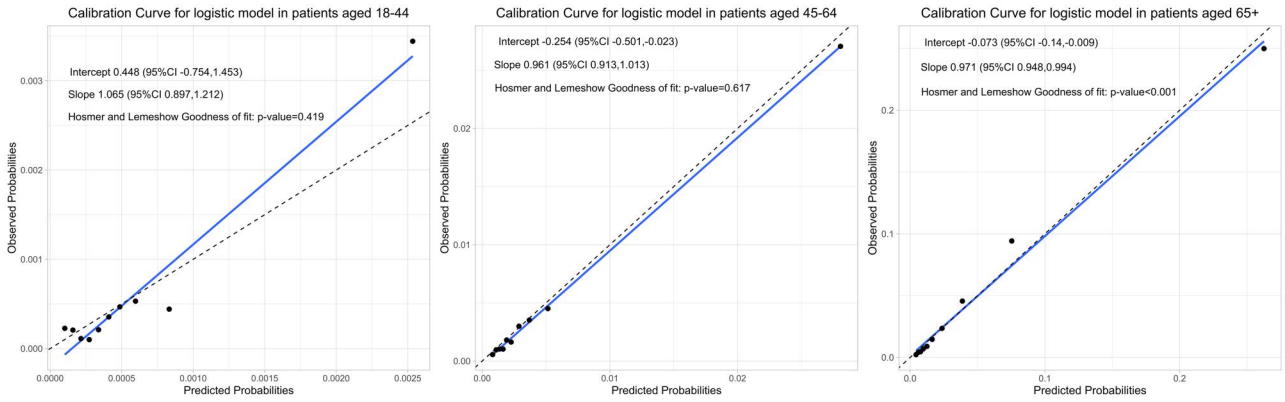

Figure 2. Calibration plots for logistic models against the testing sets in separate age groups.

the findings should be interpreted cautiously and not over-interpreted. The characteristics of patients with COVID-19 identified through either a positive PCR and RAT screening test were presented and compared in Supplementary Table S13. Prediction models for patients with PCR developed demonstrated largely consistent findings in the predictors identified in the main analysis (Supplementary Tables S14 and S15 and Figures S4 and S5).

Discussion

This study reported age-specific risk prediction models for all-cause mortality within 1 year of post-acute COVID-19 infection accounting for variations in risk factors associated with poor disease prognosis among patients as they age. Advancing age, incomplete COVID-19 vaccination, reduced lymphocyte count and history of ARDS were significant predictors contributing to an increased risk of mortality across patients of all age groups. The model for middle-age and older adults further included existing comorbidities including heart failure, end-stage renal diseases, diabetes and other laboratory variables including CT value, and absolute neutrophil count as predictors. All models demonstrated excellent predictive capability with AUROC of 0.8 or above; in particular, the model for patients aged ≥65 achieved an AUROC of 0.9. The variation in the predictors identified along with the potential physiological differences associated with aging highlighted the clinical benefit in the enhanced predictive accuracy of age-specific models reported compared to existing models. Through adopting robust statistical modelling techniques, the findings provided further understanding on the various risk factors associated with post-acute mortality identified through the current data-driven process. The evidence generated serve as crucial step in the research roadmap address the intricate challenges posed by Long COVID.[37]

Our risk prediction model identified several key clinical parameters which could influence the risk of all-cause mortality within one year of acute COVID-19 infection across all age groups of patients. Firstly, the associated increased risk with advanced age highlighted the greater susceptibility for severe COVID-19 infection and clinical manifestations in older adult, emphasizing the need for focused care amongst these patients.[38,39] Secondly, complete vaccination with two or more doses of COVID-19 vaccines was observed to confer a protective effect against mortality within 1 year of infection, supporting the effectiveness of COVID-19 vaccines in reducing the risk and persistence in risk of PASC including all-cause mortality.[2,40]

The development of ARDS, whether prior to or during acute COVID-19 infection, was associated with increased post-acute mortality across all age groups. Given that the respiratory system serves as the primary target for SARS-CoV-2 infection, viral pneumonia caused by severe ARDS could impair alveolar gas exchange and perfusion, resulting in subsequent irreversible damage to the vital organs.[39,41–43] Notably, this study identified an age-dependent pattern where ARDS during the acute phase posed a greater risk in older adults, likely due to diminished recovery capacity and pulmonary reserve, suggesting the acute respiratory deterioration from acute infection may be a more critical prognostic factor than chronic respiratory condition in this age group of patients. Furthering to the existing evidence indicating the association between cardiovascular and renal disorder with poorer prognosis following COVID-19 infection, this study identified specific patient groups with certain conditions that may face an elevated risk of mortality during the post-acute phase of COVID-19.[10,44,45] These insights provide essential guidance for clinical decision-making.

Beyond the common parameters affecting the risk of mortality in patients across all age, several clinical and haemological abnormalies were found to be associated with increased risk of mortality in different age groups of patients. Firstly, a reduced lymphocyte counts was identified as a significant predictor across all the age groups whilst an elevated level of ferritin was associated increased risk of mortality among older patients aged 65 or above. Given the correlation between lymphopenia with COVID-19 severity, our current findings provided further insight into the pathophysiology of PASC attributed to the irreversible organ damage associated with severe condition of COVID-19, resulting in subsequent mortality beyond the acute infection.[46,47] Secondly, an increased CT values indicating a low viral load was not associated with a greater risk of post-acute mortality. The absence of the biological markers and CT value measurements amongst the general population of patients could indicate cases of milder disease severity, where testing was deemed unnecessary by clinical judgment or in patients managed in community settings where RT-PCR testing were performed less regularly. This lower severity constituted to a lower risk of mortality over the long-term. Whilst abnormal levels of laboratory parameters were often observed in severe COVID-19 disease, physiological changes in the immune systems levels of inflammatory cytokines and biomarkers associated with aging could lead to variation in the composition of cells and soluble mediators involved in both innate and adaptive immune responses within lymphoid and non-lymphoid peripheral tissues. These changes determine not only the susceptibility to infections, but also the disease progression and subsequent clinical outcome, thus implicating the need for considering specific parameters in forecasting the risk of

Table 3 Summary of predictors selection from logistic regression against the training sets in each age groups

Variable	Age < 45 model			45 ≤ Age ≤ 64 model			Age ≥ 65 model		
	Coefficient	OR (95% CI)	P-value	Coefficient	OR (95% CI)	P-value	Coefficient	OR (95% CI)	P-value
(Intercept)	−9.390		<0.001	−7.101		<0.001	−5.520		<0.001
Age	0.087	1.09 (1.06, 1.12)	<0.001	0.064	1.07 (1.05, 1.08)	<0.001			
Age^2							0.001	1.001 (1.000, 1.001)	<0.001
Male	0.702	2.02 (1.41, 2.88)	<0.001	0.603	1.83 (1.61, 2.08)	<0.001	0.469	1.60 (1.52, 1.68)	<0.001
Vaccinate 2+ doses	−0.729	0.48 (0.33, 0.71)	<0.001	−1.029	0.36 (0.31, 0.41)	<0.001	−0.735	0.48 (0.45, 0.51)	<0.001
ARDS before infection	3.074	21.63 (8.82, 53.02)	<0.001	1.904	6.72 (5.15, 8.75)	<0.001	0.963	2.62 (2.33, 2.95)	<0.001
ARDS during acute phase				1.547	4.70 (2.82, 7.83)	<0.001	1.312	3.71 (3.04, 4.54)	<0.001
Heart failure				1.427	4.16 (3.11, 5.57)	<0.001	0.505	1.66 (1.53, 1.79)	<0.001
End stage kidney disease				1.651	5.21 (3.19, 8.51)	<0.001	0.636	1.89 (1.46, 2.45)	<0.001
Type 2 diabetes				0.359	1.43 (1.23, 1.67)	<0.001			
Seizure				0.710	2.03 (1.47, 2.82)	<0.001	0.643	1.90 (1.63, 2.23)	<0.001
Myocardial infarction							0.367	1.44 (1.30, 1.61)	<0.001
Stroke							0.284	1.33 (1.25, 1.41)	<0.001
Atrial fibrillation							0.160	1.17 (1.09, 1.27)	<0.001
Deep vein thrombosis				1.416	4.12 (2.37, 7.15)	<0.001	0.630	1.88 (1.49, 2.36)	<0.001
Chronic pulmonary disease							0.238	1.27 (1.17, 1.37)	<0.001
Acute kidney injury and failure							0.624	1.87 (1.69, 2.07)	<0.001
COVID CT < 20				Ref			Ref		
COVID CT—missing				−0.840	0.43 (0.35, 0.53)	<0.001	−0.534	0.59 (0.54, 0.64)	<0.001
COVID CT ≥ 20				−0.148	0.86 (0.72, 1.04)	0.119	−0.055	0.95 (0.89, 1.01)	0.107
Lymphocyte ≥1.0 × 10^9/l	Ref			Ref			Ref		
Lymphocyte—missing	−1.208	0.30 (0.16, 0.56)	<0.001	−1.237	0.29 (0.23, 0.36)	<0.001	−0.802	0.45 (0.41, 0.49)	<0.001
Lymphocyte < 1.0 × 10^9/l	1.640	5.16 (2.54, 10.45)	<0.001	0.559	1.75 (1.42, 2.15)	<0.001	0.338	1.40 (1.31, 1.51)	<0.001
Serum ferritin ≤ 400 ng/ml							Ref		
Serum ferritin—missing							0.014	1.01 (0.91, 1.14)	0.761
Serum ferritin > 400 ng/ml							0.314	1.37 (1.19, 1.58)	<0.001

OR: odds ratio; CI: confidence interval.

post-acute mortality in different age groups of patients as well as emphasizing the need for the age-stratified models reported in clinical settings.[11,12,48,49] By leveraging the extensive clinical features present in our electronic health record (EHR) data, models reported this study, especially that developed based on hospitalized patients with a lower proportion of missing measurements of laboratory-based predictors, were able to account for the variations in physiology and risk factors across patients of different ages comprehensively as well as provide more accurate prediction on the risk of post-acute mortality compared to existing models.

While prior research has aimed to facilitate patient-level risk assessment for adverse outcomes of COVID-19, existing prediction models are susceptible to biases arising from studies conducted on highly-selective cohorts and limited transparency.[50] As illustrated by the Supplementary Figure S1, the nonlinear relationship between age and post-acute mortality could undermine the accuracy of the existing prediction models developed for patients of all age. The extensive clinical features, including laboratory-based measurements and coverage of patient's medical records within the territory-wide hospital database provided a comprehensive and reliable source for the development of individualized prediction models taking into consideration of the age-specific physiology to enhance the accuracy in the risk prediction generated through our current models. The stepwise logistic regression adopted in the development of models for separate age groups also ensures the accuracy and selection of the most relevant predictors for the separate patient cohorts compared to existing models developed for the general population. The highly consistent findings in the predictors identified through different statistical modelling approaches further emphasized the robustness of our prediction model.

Nevertheless, this study is subjected to several limitations. Firstly, the current logistic model did not include complex terms such as nonlinear relationships and interactions between variables. However, statistical and machine learning models which took these complex relationships into account achieved comparable predictive performance, suggesting a low degree of interactions between predictors and the lack of significant nonlinear association between predictors and outcomes. To facilitate the ease of clinical application, such complex terms were not included to maintain simplicity of the prediction model. Secondly, the variant of COVID-19 was not considered in the models reported owing to data availability. However, owing to the success in containing the Alpha and Delta variants through its zero COVID policy, it is expected that the majority of cases of COVID-19 included in our current study were caused by the Omicron variant.[51] Thirdly, the comorbidity profile of patients within our study population could change over the course of the follow-up. However, given the relatively short follow-up period of 1 year, any significant change in patient's chronic health conditions affecting its survivability is considered unlikely. Fourthly, mild diseases and symptoms such as fatigue and shortness of breath were not included as parameters in our prediction model. However, such mild symptoms presented following COVID-19 infection were unlikely to result in a severe COVID-19 condition or subsequent mortality, thus should not greatly affect the accuracy of this model. Furthermore, the inclusion of laboratory-based parameters such as inflammatory markers and biomarkers provided a more accurate data indicating the severity of COVID-19 of individual patients in predicting patient's prognosis. Lastly, lifestyle factors including smoking, drinking and exercise habits were not considered due to the lack of relevant data. Nevertheless, the comprehensive laboratory parameters and the disease diagnosis incorporated would reflect on the health status of individual patients.

Conclusion

This study reported age-specific risk prediction models for all-cause mortality within 1 year beyond the acute phase of COVID-19 infection based on a comprehensive range of patient demographics, clinical diagnosis and laboratory-based parameters. Models developed for separate age group demonstrated high prediction performance. Given the vast number of individuals with a history of COVID-19 infection and the limited healthcare resources available, the findings from this study may assist clinicians in identifying patients at higher risk of mortality following COVID-19 infection, optimizing clinical strategies and resource allocation to alleviate the global burden of Long COVID.

Acknowledgements

The authors thank the Hospital Authority for the generous provision of data for this study. This work was supported by HMRF Research on COVID-19, The Hong Kong Special Administrative Region (HKSAR) Government (Principal Investigator: EWYC; Ref No. COVID1903011); Collaborative Research Fund, University Grants Committee, the HKSAR Government (Principal Investigator: ICKW; Ref. No. C7154-20GF); and Research Grant from the Health Bureau, the HKSAR Government (Principal Investigator: ICKW; Ref. No. COVID19F01). The funders did not have any role in design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the article and decision to submit the article for publication. I.C.K.W. and F.T.T.L. were partially supported by the Laboratory of Data Discovery for Health ($D^2$4H) funded by the AIR@InnoHK administered by Innovation and Technology Commission.

Author contributions

I.C.H.L., J.Z., W.L. and E.Y.F.W. had the original idea for the study, contributed to the development of the study, extracted data from the source database, constructed the study design and the statistical model, reviewed the literature and act as guarantors for the study. I.C.H.L., J.Z., W.L. and E.Y.F.W. accessed and verified the data, performed statistical analysis. I.C.H.L., J.Z., W.L. and E.Y.F.W. wrote the first draft of the manuscript. I.C.K.W. is the principal investigator and provided oversight for all aspects of this project. K.K.C.M., Q.Z., H.L., C.K.H.W., C.S.L.C., F.T.T.L., X.L., E.W.Y.C., E.Y.F.W. and I.C.K.W. provided critical input to the analyses, study design and discussion. I.C.H.L., R.Z., E.Y.F.W. and I.C.K.W. had full access to and accessed all underlying data in this study. All authors contributed to the interpretation of the analysis, critically reviewed and revised the article and approved the final article to be submitted. All authors had final responsibility for the decision to submit for publication.

Supplementary material

Supplementary material is available at *QJMED* online.

Conflict of interest: F.T.T.L. has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative

Region, outside the submitted work. C.S.L.C. has received grants from the Health Bureau of the Hong Kong Government, Hong Kong Research Grant Council, Hong Kong Innovation and Technology Commission, Pfizer, IQVIA and Amgen; and personal fees from PrimeVigilance; outside the submitted work. X.L. has received research grants from the Health Bureau of the Government of the Hong Kong Special Administrative Region; research and educational grants from Janssen and Pfizer; internal funding from the University of Hong Kong and consultancy fees from Merck Sharp & Dohme, unrelated to this work. C.K.H.W. reports the receipt of General Research Fund, Research Grant Council, Government of Hong Kong SAR; EuroQol Research Foundation; AstraZeneca and Boehringer Ingelheim, all outside the submitted work. I.C.K.W. reports grants from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK and Novartis, the Hong Kong RGC, and the Hong Kong Health and Medical Research Fund in Hong Kong, National Institute for Health Research in England, European Commission, National Health and Medical Research Council in Australia, consulting fees from IQVIA and World Health Organization, payment for expert testimony for Appeal Court of Hong Kong and is a non-executive director of Jacobson Medical in Hong Kong and Therakind in England, outside of the submitted work; no other relationships or activities that could appear to have influenced the submitted work. E.W.C. reports grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda and Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region; honorarium from Hospital Authority; outside the submitted work. E.Y.F.W. has received research grants from the Excellent Young Scientists Fund (Hong Kong and Macau), National Natural Science Foundation of China (NSFC), Health Bureau of the Government of the Hong Kong Special Administrative Region and the Hong Kong Research Grants Council, outside the submitted work.

Funding

This work was supported by Health and Medical Research Fund Research on COVID-19, The Hong Kong Special Administrative Region (HKSAR) Government (Principal Investigator: EWYC; Ref No. COVID1903011); Collaborative Research Fund, University Grants Committee, the HKSAR Government (Principal Investigator: ICKW; Ref. No. C7154-20GF) and Research Grant from the Health Bureau, the HKSAR Government (Principal Investigator: ICKW; Ref. No. COVID19F01). I.C.K.W. and F.T.T.L. were partially supported by the Laboratory of Data Discovery for Health (D24H) funded by the AIR@InnoHK administered by Innovation and Technology Commission. The funders did not have any role in design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the article and decision to submit the article for publication.

Data access

EYFW had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Data availability

The data contain confidential information and hence cannot be shared with the public due to third-party use restrictions.

Codes availability

The codes used to derive the current findings are made available in https://github.com/Jiayiz2222/LongCovid_prediction to ensure transparency and reproducibility of the findings reported.

Ethical approval

Ethical approval for this study was granted by the Institutional Review Board of the University of HK/HA HK West Cluster (UW20-556 and UW21-149) and Department of Health, HK (L/M21/2021 and L/M175/2022) with an exemption for informed consent from participants as patients' confidentiality was maintained in this retrospective cohort study.

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QJM: An International Journal of Medicine, 2026, 119, 117–127
https://doi.org/10.1093/qjmed/hcaf218
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