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Long-term effects of coronavirus disease 2019 on diabetes complications and mortality in people with diabetes: Two cohorts in the UK and Hong Kong

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Abstract

Aim: To evaluate the long-term associations between coronavirus disease 2019 (COVID-19) and diabetes complications and mortality, in patients with diabetes.

Materials and Methods: People with diabetes diagnosed with COVID-19 infection (exposed group), from 16 March 2020 to 31 May 2021 from the UK Biobank (UKB cohort; $n = 2456$), and from 1 April 2020 to 31 May 2022 from the electronic health records in Hong Kong (HK cohort; $n = 80\,546$), were recruited. Each patient was randomly matched with participants with diabetes but without COVID-19 (unexposed group), based on age and sex (UKB, $n = 41\,801$; HK, $n = 391\,849$). Patients were followed for up to 18 months until 31 August 2021 for UKB, and up to 28 months until 15 August 2022 for HK. Characteristics between cohorts were further adjusted with Inverse Probability Treatment Weighting. Long-term association of COVID-19 with

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multi-organ disease complications and all-cause mortality after 21 days of diagnosis was evaluated by Cox regression.

Results: Compared with uninfected participants, patients with COVID-19 infection with diabetes were consistently associated with higher risks of cardiovascular diseases (coronary heart disease [CHD]: hazard ratio [HR] [UKB]: 1.6 [95% confidence interval {CI}: 1.0, 2.4], HR [HK]: 1.2 [95% CI: 1.0, 1.5]; and stroke: HR [UKB]: 2.0 [95% CI: 1.1, 3.6], HR [HK]: 1.5 [95% CI: 1.3, 1.8]), microvascular disease (end stage renal disease: HR [UKB]: 2.1 [95% CI: 1.1, 4.0], HR [HK]: 1.2 [95% CI: 1.1, 1.4]) and all-cause mortality (HR [UKB]: 4.6 [95% CI: 3.8, 5.5], HR [HK]: 2.6 [95% CI: 2.5, 2.8]), in both cohorts.

Conclusions: COVID-19 infection is associated with long-term increased risks of diabetes complications (especially cardiovascular complications, and mortality) in people with diabetes. Monitoring for signs/symptoms of developing these long-term complications post-COVID-19 infection in the infected patient population of people with diabetes may be beneficial in minimizing their morbidity and mortality.

KEYWORDS

cardiovascular complications, COVID-19, diabetes, infection, microvascular complications, SARS-CoV-2

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection causing coronavirus disease 2019 (COVID-19) is linked to increased disease severity in patients with diabetes,[1] which may possibly result in persistent symptoms potentially leading to long-term complications postrecovery.

Several studies have reported a higher prevalence of severe COVID-19 in patients with diabetes, estimated at 9.5% by a recent meta-analysis.[2] Further, diabetes was one of the most common co-morbidities among hospitalized COVID-19 patients.[3,4] Moreover, COVID-19–infected patients with diabetes were more probable to require intensive care unit (ICU) admission and mechanical ventilation, and develop severe complications, including acute respiratory distress syndrome and cardiac injury after COVID-19 infection.[5] Because the persistence of COVID-19 symptoms termed as 'Post-acute Sequelae of COVID-19' (PASC) or 'long COVID' (reportedly a systemic disease associated with multi-organ impairment[6]) was also first reported in hospitalized patients requiring mechanical ventilation (correlated with increased disease severity in the acute phase of infection), it is possible that infected patients with diabetes may be more probable to develop persistent long-term effects of COVID-19, leading to postacute complications.[7] Indeed, COVID-19 has been reported to induce long-term systemic vascular complications, particularly cardiovascular diseases (especially in severe COVID-19 cases),[8] as well as microvascular diseases, including neuropathy, retinopathy and nephropathy,[9] while poorly controlled diabetes is already established as causing the aforementioned cardiovascular[10,11] and microvascular complications.[12] Hence, analysing potential accelerations of such disease complications/outcomes in COVID-19–infected patients with diabetes over the long term may highlight the relationship between COVID-19 (particularly long COVID) and diabetes complications. Indeed, one study reported that, among COVID-19 patients, those with diabetes showed increased cardiovascular complications compared with those without diabetes.[13] Altogether, these findings suggest the possibility of patients with both diabetes and COVID-19 facing an aggregated enhanced risk of cardiovascular disease compared with the risks posed to patients with only one of these conditions.[14] A narrative review supports this hypothesis by suggesting the possibility of a bidirectional relationship between diabetes and COVID-19 as the underlying explanation for this enhanced risk of cardiovascular disease.[14]

Previously, a limited number of studies have attempted to evaluate the difference in risks of cardiovascular and microvascular complications in people with diabetes, infected with or without COVID-19, in the postacute phase of infection. Hence, by identifying two patient cohorts comprising people with diabetes, with COVID-19 infection (exposed group) and without COVID-19 infection (unexposed group) from two different populations and healthcare systems (UK and Hong Kong) with the intent of minimizing potential biases, this study aimed to evaluate the associations between the long-term effects of COVID-19 with the risks of cardiovascular and microvascular complications and mortality in people with diabetes. These findings may be beneficial in facilitating the monitoring and management of the long-term effects of COVID-19, particularly cardiovascular events, in this population.

2 | MATERIALS AND METHODS

2.1 | Study design and population

This study recruited two cohorts of participants with diabetes from the UK Biobank (UKB) and Hong Kong (HK). The Supplements (see the supporting information) present the details of the cohorts.

The inclusion period for participant recruitment was from 16 March 2020 to 31 May 2021 for the UKB cohort, and from 1 April 2020 to 31 May 2022 for the HK cohort. Patients with diabetes with a positive diagnosis of COVID-19 (Supplements) during the inclusion period were selected. For the HK cohort, most of the COVID-19–infected participants were from the fifth wave of infection, as the emergence of the Omicron variant from January 2022 onwards led to the highest numbers of infections and deaths in Hong Kong compared with previous waves,[15] whereas the infected participants from the UKB cohort encompassed the first and second waves of infection (before the emergence of the Omicron variant in the UK).[16] To evaluate the long-term effects, only those infected participants surviving the acute phase of infection (the 21-day period postdiagnosis) were identified as the 'exposed group'. Hence, the index date was defined as 21 days after the date of first diagnosis with COVID-19 during the inclusion period, and outcomes were defined as those occurring after the index date.[17] Participants without a positive COVID-19 test result were selected as unexposed group for analyses in the HK. Patients without a positive COVID-19 test result COVID-19 diagnosis and/or record of COVID-19–related mortality until 18 October 2021 (the date of the last valid record related to COVID-19 infection) in the UKB cohort were deemed as 'uninfected' or the 'unexposed group'. To ensure similar baseline characteristics of age and sex between the exposed and unexposed groups, participants in the unexposed groups were randomly selected and matched to participants in the exposed groups based on the distribution of age and sex. In addition, each of the matched unexposed patients with diabetes was further assigned to a corresponding exposed patient with diabetes with identical index date to ensure similar follow-up periods. All participants were followed until the first date of occurrence of an outcome; event of mortality; or until 31 August 2021 for the UKB cohort and until 15 August 2022 for the HK cohort, whichever occurred first.

2.2 | Outcome measures

The outcomes included (a) coronary heart disease (CHD); (b) stroke; (c) heart failure; (d) neuropathy; (e) retinopathy; (f) nephropathy; (g) end stage renal disease (ESRD); and (h) all-cause mortality. All outcomes were defined using the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) for the HK cohort, and the International Classification of Diseases, tenth revision (ICD-10-CM) for the UKB cohort, identified from inpatient and outcome settings (Table S1).

2.3 | Baseline characteristics

The baseline characteristics included age, sex, Charlson Comorbidity Index,[18] history of heart failure, CHD, stroke, neuropathy, retinopathy, nephropathy and ESRD, and latest vaccination status. For the UKB dataset, the dm + d codes were used to identify vaccination records for the COVID-19 vaccines (ChAdOx1 [39114911000001105] and BNT162b2 [39115611000001103]).[19] For the HK cohort, vaccination records for the two types of COVID-19 vaccine available to the public—BNT162b2 and CoronaVac—were identified for this study. In addition, the HK cohort also included history of medication as a baseline characteristic for all participants (based on drug records for usage of renin-angiotensin-system agents, beta blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, insulins, antidiabetic drugs, oral anticoagulants, antiplatelets and immunosuppressants). All the disease definitions of baseline characteristics are listed in Table S1.

2.4 | Ethical approval

Ethical approval for UK Biobank was given by the North-West Multicentre Research Ethics Committee. Written consent was provided by all participants in this study, and participants were removed from our analysis if they withdrew from the study. The Application number under UKB Resource used in this research is 65 688. The ethical approval for Hong Kong Hospital Authority (HKHA) 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).

2.5 | Statistical analysis

To reduce the impact of confounders, weighting was conducted by the Inverse Probability Treatment Weighting (IPTW) methodology based on age, sex, Charlson Comorbidity score, history of cancer, chronic kidney disease, respiratory disease, diabetes and cardiovascular disease, and the latest vaccination status before index date. In addition to these confounders, for all HK-cohort participants, a history of medication was incorporated as an additional confounder for weighting. After weighting, the baseline characteristics were summarized using descriptive statistics. The standard mean differences (SMDs) between the exposed group and the two unexposed groups were described. An SMD of less than 0.2 was considered as a sufficient balance between the exposed and unexposed groups.[20]

Incidence of outcomes was observed in the follow-up period. Incidence rates and their corresponding 95% confidence intervals (CIs) were assessed based on their Poisson distribution. The association between COVID-19 infection and each outcome, compared with the unexposed group, was evaluated using univariable Cox proportional hazard regression for both cohorts. For each outcome, its incidence and incident rates were calculated after excluding

TABLE 1 Health characteristics of COVID-19 and non-COVID-19 groups after weighting

Baseline characteristics	COVID-19 ($N = 470\,981$) (HK) N/Mean (%/SD)	Non-COVID-19 ($N = 472\,541$) (HK) N/Mean (%/SD)	SMD[b]	COVID-19 ($N = 44\,099$) (UKB) N/Mean (%/SD)	Non-COVID-19 ($N = 44\,259$) (UKB) N/Mean (%/SD)	SMD[b]
Age, y[a]	69 (12)	69 (12)	0.013	70 (7.5)	70.31 (7.9)	0.004
Sex, male	230 618 (49)	229 893 (49)	0.006	25 478 (58)	25 614 (58)	0.011
Charlson Comorbidity Index[a]	3.79 (1.8)	3.80 (1.8)	0.004	5.69 (2.7)	5.76 (2.8)	0.026
Pre-existing morbidities						
Myocardial infarction	9933 (2.1)	8300 (1.8)	0.026	4941 (11)	5117 (12)	0.014
Congestive heart failure	14 483 (3.1)	14 192 (3.0)	0.004	1612 (3.6)	1381 (3.1)	0.028
Peripheral vascular disease	3406 (0.7)	3347 (0.7)	0.002	3681 (8.3)	3892 (8.8)	0.018
Cerebrovascular disease	45 540 (9.7)	45 371 (9.6)	0.002	5334 (12)	5946 (14)	0.043
Chronic obstructive pulmonary disease	18 438 (3.9)	15 977 (3.4)	0.028	11 385 (26)	12 277 (28)	0.048
Dementia	6076 (1.3)	3509 (0.7)	0.055	1037 (2.3)	3618 (8.2)	0.265
Paralysis	2524 (0.5)	2287 (0.5)	0.007	1320 (3.0)	1866 (4.2)	0.067
Diabetes without chronic complication	380 558 (81)	373 217 (79)	0.045	40 042 (91)	40 861 (93)	0.080
Diabetes with chronic complication	26 401 (5.6)	26 736 (5.7)	0.002	12 550 (28)	11 990 (27)	0.026
Chronic renal failure	22 519 (4.8)	23 986 (5.1)	0.014	8803 (20)	8657 (20)	0.006
Mild liver disease	1789 (0.4)	1591 (0.3)	0.007	5261 (12)	5857 (13)	0.042
Moderate–severe liver disease	1282 (0.3)	1049 (0.2)	0.010	356 (0.8)	444 (1.0)	0.021
Ulcers	11 707 (2.5)	10 239 (2.2)	0.021	3122 (7.1)	3283 (7.4)	0.015
Rheumatoid arthritis and other inflammatory polyarthropathies	1404 (0.3)	1479 (0.3)	0.003	3118 (7.0)	3391 (7.7)	0.025
Acquired immune deficiency syndrome	NA	NA	NA	150.4 (0.3)	98.8 (0.2)	0.022
Malignancy	22 006 (4.7)	22 033 (4.7)	< 0.001	7904 (18)	7287 (17)	0.035
Metastatic solid tumour	3237 (0.7)	3327 (0.7)	0.002	1231 (2.8)	987 (2.2)	0.035
Major CVD	97 302 (21)	98 996 (21)	0.007	14 787 (33)	15 144 (34)	0.020
CHD	50 780 (11)	50 949 (11)	< 0.001	11 564 (26)	11 604 (26)	0.004
Stroke	47 958 (10)	47 760 (10)	0.003	2648 (6.0)	2771 (6.3)	0.013
Heart failure	15 290 (3.2)	15 045 (3.2)	0.004	3910 (8.8)	4002 (9.1)	0.009
Neuropathy	4875 (1.0)	4863 (1.0)	0.001	10 524 (24)	10 432 (24)	0.003
Retinopathy	17 853 (3.8)	17 464 (3.7)	0.005	15 045 (34)	14 932 (34)	0.003
ESRD	7683 (1.6)	7472 (1.6)	0.004	1920 (4.3)	1920 (4.4)	0.001
Nephropathy	63 594 (14)	62 776 (13)	0.006	9787 (22)	9757 (22)	0.001
T1D	4350 (0.9)	3413 (0.7)	0.022	11 079 (25)	9258 (21)	0.096
T2D	468 197 (99)	467 530 (99)	0.022	33 181 (75)	34 841 (79)	0.096
Pre-existing prescription						
Renin-angiotensin-system agents	242 966 (52)	243 705 (52)	< 0.001	-	-	-
Beta blockers	124 563 (26)	124 917 (26)	< 0.001	-	-	-
Calcium channel blockers	267 706 (57)	269 555 (57)	0.004	-	-	-
Diuretics	45 240 (9.6)	45 088 (9.5)	0.002	-	-	-
Nitrates	26 630 (5.7)	26 681 (5.6)	< 0.001	-	-	-
Lipid-lowering agents	327 050 (69)	328 687 (70)	0.003	-	-	-
Insulins	62 549 (13)	48 161 (10)	0.096	-	-	-
Antidiabetic drugs	330 710 (70)	316 063 (67)	0.072	-	-	-

TABLE 1 (Continued)

Baseline characteristics	COVID-19 (*N* = 470 981) (HK) N/Mean (%/SD)	Non-COVID-19 (*N* = 472 541) (HK) N/Mean (%/SD)	SMD[b]	COVID-19 (*N* = 44 099) (UKB) N/Mean (%/SD)	Non-COVID-19 (*N* = 44 259) (UKB) N/Mean (%/SD)	SMD[b]
Oral anticoagulants	12 843 (2.7)	12 914 (2.7)	< 0.001	-	-	-
Antiplatelets	97 164 (21)	96 981 (21)	0.003	-	-	-
Immunosuppressants	3055 (0.6)	3069 (0.6)	< 0.001	-	-	-
Doses of COVID-19 vaccines received			0.008	-	-	0.015
Without vaccination record	87 422 (19)	86 790 (18)	-	38 020 (86)	37 685 (86)	-
First dose	56 283 (12)	55 773 (12)	-	5640 (13)	5730 (13)	-
Second dose	191 006 (41)	193 373 (41)	-	600 (1.4)	666 (1.5)	-
Third/fourth dose	136 271 (29)	136 605 (29)	-	-	-	-

Abbreviations: CHD, coronary heart disease; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; ESRD, end stage renal disease; HK, Hong Kong; SD, standard deviation; SMD, standard mean difference; T1D, type 1 diabetes; T2D, type 2 diabetes; UKB, UK biobank.

[a]Age and Charlson Comorbidity Index are presented as mean ± SD.

[b]SMD < 0.2 is considered a good balance between cohorts.

those with a history of that particular outcome, and the association analysis for each outcome was conducted independently in the corresponding subgroups of participants, postexclusion. Further, tests to evaluate the interaction effects of age (stratified by < 65, ≥ 65 years), Charlson Comorbidity score (stratified by ≤ 4, > 4) and vaccination status before index date (stratified by ≥ 2, < 2 doses), were conducted. A second interaction effect test to evaluate the interaction of COVID-19 disease severity (stratified by the severe COVID-19 exposed group and the non-severe COVID-19 exposed group) was conducted. The severe COVID-19 exposed group was identified as patients with records of receiving specific types of ventilation support or admission to an ICU within 7 days after first diagnosis of COVID-19 infection, using the ICD-9-CM code for the HK dataset and Classification of Interventions and Procedures version 4 (OPCS-4) for the UKB dataset (Table S2). Details of the type of ventilation support to define severe COVID-19 are summarized in Table S2. Further, four sensitivity analyses were employed for analysis: (1) defining the index date as 30 days after the first diagnosis date of COVID-19 infection, and each exposed patient with diabetes was randomly matched with an unexposed patient with diabetes, and the same procedures as the main analysis were followed; (2) conducting a competing risk Cox regression using the Fine-Grey proportional hazards regression model[21] method to adjust for mortality as a competing risk while evaluating associations; (3) excluding participants with type 1 diabetes; and (4) selecting the confounders as those baseline characteristics with an SMD of 0.2 or higher and adjusting those confounders by weighting (for the HK cohort: vaccination status; for the UKB cohort: age, history of dementia and vaccination status).

Results from the study were analysed by adopting two-tailed tests, with a *P* value of .05 or less interpreted as a statistically significant result. Two investigators (RZ and BW) conducted the statistical analyses independently for quality assurance. STROBE—Strengthening the Reporting of Observational Studies in Epidemiology—statement checklists were followed to guide transparent reporting of the cohort study. All statistical analyses were conducted using Stata version 15.1 and R version 4.0.3 (www.R-project.org).

3 | RESULTS

Patients with diabetes diagnosed with COVID-19 infection (exposed group) from the UKB ($n = 2456$) and HK ($n = 80\,546$) cohorts, matched with uninfected (non-COVID-19) people with diabetes (unexposed group) (UKB: $n = 41\,801$; HK: $n = 391\,849$), were identified. The median follow-up period for the UKB and HKHA was 244.5 and 145 days, respectively. Table 1 summarizes the baseline characteristics after weighting, while the baseline characteristics before weighting are shown in Table S3. The characteristics between the exposed group and unexposed group after weighting were well balanced (SMD < 0.2).

The incidence rate and hazard ratio (HR) with 95% confidence interval (CI) for each of the outcomes among patients with and without a COVID-19 diagnosis, 21 days after infection, are summarized in Table 2, and HRs are depicted in Figure 1. Infected patients displayed higher incidence rates (per 1000 person-years) of developing cardiovascular diseases, particularly CHD and stroke, as well as all-cause mortality, compared with the uninfected unexposed group in both cohorts, while for microvascular diseases, a higher incidence rate of ESRD was observed. Similar results were identified after adjustment in the regression analysis. Compared with uninfected participants with diabetes, patients with diabetes and with COVID-19 infection were consistently associated with higher risks of cardiovascular diseases (CHD: HR [UKB]:1.6 [95% CI:1.0, 2.4], HR [HK]:1.2 [95% CI:1.0, 1.5]; and stroke: HR [UKB]: 2.0 [95% CI: 1.2, 3.6], HR [HK]: 1.5 [95% CI:1.3, 1.8]), ESRD (HR [UKB]: 2.1 [95% CI:1.1, 4.0], HR [HK]:1.2 [95% CI:1.1, 1.4]) and all-cause mortality (HR [UKB]: 4.6 [95% CI: 3.8, 5.5], HR [HK]: 2.6 [95% CI: 2.5, 2.8]), in both cohorts.

TABLE 2 Postacute phase incidence rate and HR of outcomes in non-COVID-19 and COVID-19 groups after weighting (main analysis)

	UK Biobank				Hong Kong			
	COVID-19		Non-COVID-19 (REF)				COVID-19	
Outcome	Event	Incidence per 1000 person-years (95% CI)	Event	Incidence per 1000 person-years (95% CI)	Event	Incidence per 1000 person-years (95% CI)	Event	Incidence per 1000 person-years (95% CI)
CHD	608	27.6 (25.5, 29.9)	433	17.7 (16.1, 19.4)	849	5.2 (4.8, 5.5)	718	4.2 (3.9, 4.5)
Stroke	351	12.5 (11.2, 13.9)	193	6.2 (5.3, 7.1)	1191	7.2 (6.8, 7.6)	808	4.7 (4.4, 5.1)
Heart failure	488	18.0 (16.4, 19.7)	456	15.0 (13.7, 16.5)	872	4.9 (4.6, 5.2)	519	2.8 (2.6, 3.1)
Neuropathy	333	14.7 (13.2, 16.4)	258	10.1 (8.9, 11.5)	105	0.6 (0.5, 0.7)	97	0.5 (0.4, 0.6)
Retinopathy	1102	56.1 (52.8, 59.5)	767	35.2 (32.8, 37.8)	516	2.9 (2.7, 3.2)	477	2.6 (2.4, 2.8)
Nephropathy	543	23.4 (21.5, 25.5)	555	21.5 (19.8, 23.4)	3662	23.0 (22.3, 23.8)	3111	18.9 (18.2, 19.5)
ESRD	161	5.6 (4.8, 6.5)	89	2.8 (2.2, 3.4)	1537	8.5 (8.1, 8.9)	1270	6.8 (6.4, 7.2)
All-cause mortality	2819	93.7 (90.2, 97.2)	670	20.0 (18.6, 21.6)	11 161	60.8 (59.7, 61.9)	4386	23.0 (22.4, 23.7)

Note: The HR was obtained by Cox regression adjusted with weighting.
Abbreviations: CHD, coronary heart disease; CI, confidence interval; COVID-19, coronavirus disease 2019; ESRD, end stage renal disease; HR, hazard ratio; REF, reference group.

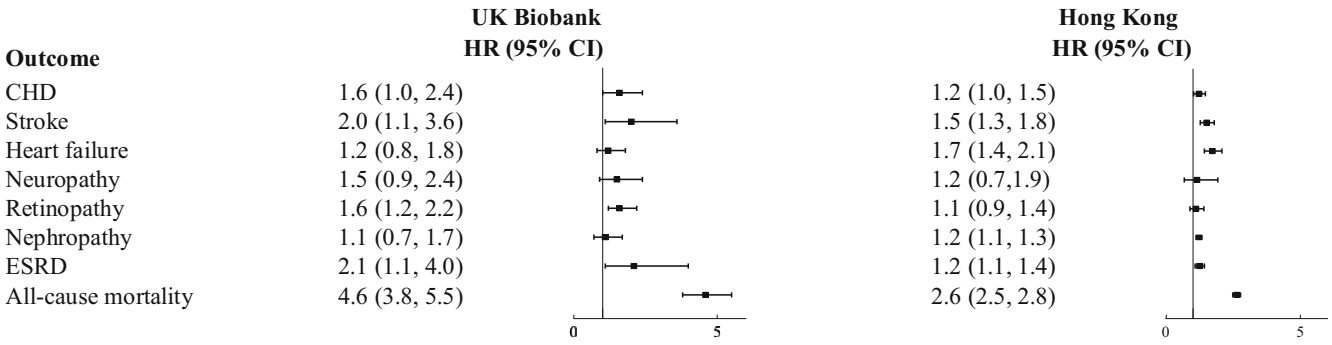

FIGURE 1 Hazard ratio of post-acute COVID-19 composite outcomes compared to the unexposed groups in the diabetes population. The Hazard ratio was obtained by Cox regression adjusted with weighting. CHD, coronary heart disease; CI, confidence interval; COVID-19, coronavirus disease 2019; ESRD, end stage renal disease; HR, hazard ratio.

Figure 2 provides the results from the subgroup analyses. In both cohorts, results largely consistent with the main analysis were observed for different subgroups. Moreover, patients who are female; aged older than 65 years; identified with severe COVID-19 infection; received less than two doses of COVID-19 vaccines; or with Charlson Comorbidity scores of 4 or more, were more probable to develop PASC than their opposing subgroup of patients. Tables S4–S6 summarize the results from the sensitivity analysis and these remain consistent with the main analysis.

4 | DISCUSSION

This study provides evidence on the long-term effect of COVID-19 associated with people with diabetes. Particularly, the findings of this study identify increased long-term risks associated with cardiovascular complications and mortality in the postacute phase of COVID-19 infection in infected people with diabetes compared with uninfected people with diabetes. These findings are found to be highly consistent, shown by obtaining consistent results from conducting identical analyses in two different patient cohorts with differing dominant strains of COVID-19 infection, recruited from two different patient databases (UKB and HK) of diverse ethnic backgrounds to compensate for potential biases in different genetic populations, healthcare systems and COVID-19 policies. Notably, compared with uninfected patients with diabetes, COVID-19–infected patients with diabetes were associated with a 2-fold increase in the risk of stroke and ESRD, as well as a 60% increase in risk of CHD in the UKB cohort. Similarly, in the Omicron-dominant HK cohort, infected patients with diabetes were 20%, 50% and 70% more probable to develop CHD and ESRD, stroke and heart failure, respectively, than uninfected people with diabetes. In addition, they faced a 4.6-fold (UKB) and a 2.6-fold (HK) higher likelihood of all-cause mortality than uninfected people with diabetes. The difference in risks of mortality between the two

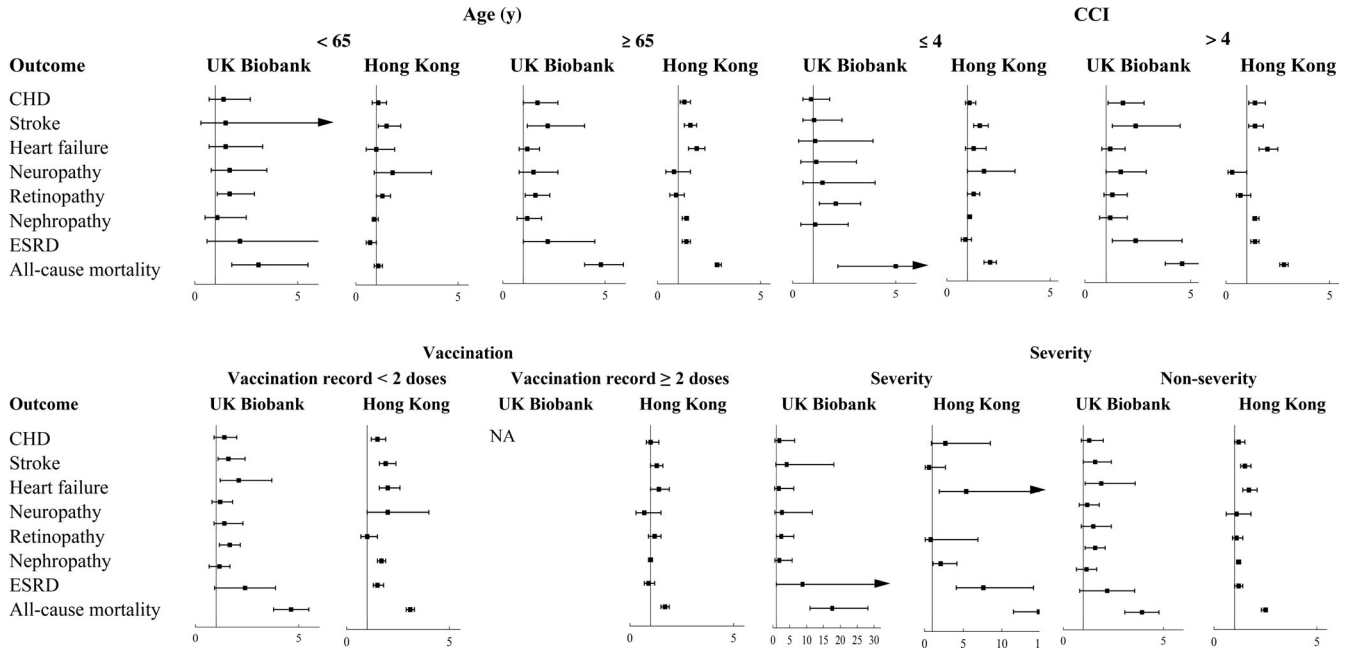

FIGURE 2 Hazrd ratio of postacute COVID-19 composite outcomes compared with the unexposed groups in different subgroups by interaction test. Severity: patients with records of ICU admission or ventilation support within 7 days after COVID-19 infection. The Hazard ratio was obtained by Cox regression adjusted with weighting. CCI, Charlson Comorbidity Index; CHD, coronary heart disease; COVID-19, coronavirus disease 2019; ESRD, end stage renal disease; HR, hazard ratio; ICU, intensive care unit; NA, not available because of insufficient number.

cohorts may possibly be attributed to the original virus and Delta variant (UKB cohort) being much more severe than Omicron-dominant infections (HK cohort), leading to a higher likelihood of mortality in the UKB patient cohort.[22] Further, patients that were female; aged 65 years or older; identified with severe COVID-19; had received less than two doses of vaccine; or with more co-morbidities, were identified as especially vulnerable and associated with even higher risks of these disease complications over the long term, consistent with previous studies reporting these as risk factors for developing postacute COVID-19 complications.[23,24] Altogether, these findings suggest that continuous monitoring for signs and symptoms of cardiovascular and microvascular complications postinfection and up until at least 1 year postrecovery may be especially beneficial for COVID-19–infected patients with diabetes, possibly reducing COVID-19–associated cardiovascular morbidity and mortality in the long term.

Previously, COVID-19 has been reported to cause worsened glycometabolic control (yielding poor diabetes control), progression of prediabetes to diabetes, as well as incident diabetes,[25] in the short and long term after infection,[26,27] which may subsequently lead to clinical deterioration, including the development of cardiovascular complications like cardiovascular diseases and microvascular complications.[28] However, a study discussing the short-term mortality and incidence of first hospitalizations for cardiovascular events within 6 months of COVID-19 reported that the co-presence of COVID-19 and diabetes did not lead to any additional risk in terms of both cardiovascular events and mortality,[29] although infection with COVID-19 and having diabetes were both independently associated with higher risks of all-cause mortality and first hospitalizations for cardiovascular events, respectively, in infected patients. Another case control study concluded that diabetes was not a risk factor for long COVID[30] after finding no significant differences in persistent post-COVID-19 symptoms between 145 recovered COVID-19 patients with diabetes compared with 144 matched infected patients without diabetes, with persistent symptoms. The discrepancy of these results compared with our findings may be explained by the first study being limited by a short follow-up period of 6 months and the second study being restricted by a small sample size of patients, both of which may lead to an insufficiency to analyse the risks of cardiovascular events after COVID-19, because cardiovascular diseases may require a longer period of time to develop and progress, or because of the inadequacy of the statistical power for finding significant differences in risks.

Currently, the mechanism behind the effects of COVID-19 on cardiovascular risks with diabetes can be divided into the indirect effect of COVID-19 via worsened glycaemic control and exacerbated immune response, and a direct effect via COVID-19–induced viral damage. Firstly, COVID-19 disrupts glycaemic control, subsequently predisposing patients to diabetes complications, including cardiovascular diseases. Several hypotheses have been postulated to explain the link between COVID-19 and glycometabolic control, including direct infection and destruction of pancreatic β-cells by SARS-CoV-2,[31] induction of cytokine storm including interleukin-6 and tumour necrosis factor-α leading to inflammation,[32,33] and consumption of angiotensin-converting enzyme 2 for SARS-CoV-2 cellular entry causing increased angiotensin II levels that induce vasoconstriction and reduce blood flow to the pancreas.[14,34] Therefore, glycaemic control could be altered by COVID-19, eventually increasing the risk of

diabetes complications, including cardiovascular diseases. Further, uncontrolled diabetes leading to organ damage including vascular injury, along with the inherent chronic low-grade inflammatory state of diabetes subjects associated with insulin resistance,[35] may increase the risk of long COVID in such patients by predisposing them to elicit exaggerated immune responses upon COVID-19 infection.[36,37] Because long COVID is further associated with multi-organ damage and subsequent dysfunction, including cardiovascular and microvascular damage, it is hypothesized that diabetes patients with persistent infection may be even more probable to develop such outcomes over the long term.[7] Secondly, SARS-CoV-2 may directly affect the cardiovascular system by hypoxia, systemic inflammation and dysregulation of the renin-angiotensin-aldosterone system,[14,38] leading to an increased cardiovascular disease risk after COVID-19. Moreover, COVID-19 may lead to significant stress and other psychosocial consequences, which are known to be associated with cardiovascular diseases and risk factors such as hypertension.[39] In addition, a bidirectional link between diabetes and COVID-19 has been proposed, which may further amplify the already increased cardiovascular disease risk following COVID-19, given that diabetes itself has been shown to predispose patients to severe COVID-19, in which complications including cardiovascular disease are more common.[14] Therefore, increased cardiovascular disease risks after COVID-19 among people with diabetes may be explained by both indirect and direct effects of COVID-19, which may be enhanced by the interaction between COVID-19 and diabetes in the short and long term.

In addition to cardiovascular disease, an increased likelihood of ESRD (~2-fold [UKB] and 1.2-fold [HK]) was observed following COVID-19 in people with diabetes, indicating that the long-term management postdiagnosis with COVID-19 in such patients should not only focus on cardiovascular, but also on microvascular, disease. Previously, some studies also reported risks associated with long COVID for decline in kidney function (nephropathy) leading to ESRD[40] and long-term ocular damage in COVID-19 survivors, leading to diabetic retinopathy.[41] Although statistically significant risks were associated with a few microvascular complications in this study, like retinopathy (HR [UKB]: 1 [95% CI: 1.2, 2.2]) and nephropathy (HR [HK]: 1.2 [95% CI: 1.1, 1.3]), others did not always reach statistical significance, possibly because of the small sample size of patients developing these complications. Another reason may be the diagnosis for microvascular diseases going undetected in patients with onset of these diseases during the pandemic. The early stages of retinopathy and neuropathy are usually asymptomatic; hence, the detection and consequent diagnosis is only made during regular screening of patients with other complications. With disruptions in the routine healthcare services during this period, regular screenings and check-ups for non-COVID–related diseases were often suspended, therefore microvascular diseases may have gone undiagnosed and consequently unreported in hospital data.[42] Further, disruptions in care for patients with non-COVID-19–related problems may also stem from avoidance/delay of medical attention, because of fear of transmission within hospitals and/or reduced availability of manpower resulting from healthcare services being overwhelmed.[43] Evidently, a multinational survey for healthcare professionals concluded that diabetes was the chronic condition most affected by COVID-19 resulting from disruptions in care.[44] Hence, compared with cardiovascular complications, comparatively fewer urgent diseases like microvascular complications may not have been well identified during the COVID-19 pandemic period. Further study is warranted to confirm the risk of retinopathy and neuropathy.

The primary strength of this study stems from addressing the paucity of long-term evidence linking COVID-19 to cardiovascular and microvascular complications (common complications of diabetes) and mortality, in people with diabetes. We designed two different study cohorts (compensating for potential biases in different healthcare systems and genetic populations) to investigate incident vascular complications and mortality post-COVID-19 infection and found largely consistent results, while following up to investigate these complications in patients spanning different waves of infection/dominant strains. Indeed, while the COVID-19–infected participants from the HK cohort encompassed the fifth wave of infection, leading to the highest numbers of infections and deaths in Hong Kong compared with previous waves, marked by the emergence of the Omicron variant from January 2022 onwards, the infected participants from the UKB cohort encompassed the first and second waves of infection (before the emergence of the Omicron variant in the UK). Nevertheless, our study has some specific limitations. Firstly, being an observational study, only the association between COVID-19 infection and risks for the specific disease outcomes can be established, rather than causality. Some potential confounders, such as different quality of care/ICU availability/burden on healthcare systems in the Hong Kong and UK; lifestyle factors including body mass index, abdominal adiposity and others, may have been overlooked/were unavailable for this study, although we used matching and weighting by age, sex, a comprehensive list of co-morbidities, vaccination status and drug records (for the HK cohort) to minimize selection and confounding biases. Secondly, a difference in weighting criteria between the two cohorts may affect the comparability of the findings, although both cohorts yielded largely consistent findings and only one additional variable (i.e. history of medication) was included in the HK cohort analysis compared with the UKB cohort analysis. Thirdly, because the exposed group was distinguished from the unexposed group based on the latter not having a positive COVID-19 PCR test result and not being hospitalized with a COVID-19–related diagnosis admission code, there remains the possibility of asymptomatic COVID-19–infected participants, who could not be diagnosed, being included in the control groups. Moreover, while existing studies suggest a difference in risks of COVID-19 between patients with type 1 diabetes and type 2 diabetes,[45] because of the limited number of patients with a diagnosis of type 1 diabetes in the dataset, the statistical power was insufficient to analyse the risks in patients stratified by type of diabetes. Lastly, because of the limited sample size of COVID-19 patients with diabetes, especially those with severe disease, associated risks identified for certain disease complications may be affected by low event rates and high CIs. In addition, future studies are warranted to overcome these limitations and validate these findings in even larger cohorts of people with diabetes and among different subtypes of diabetes.

5 | CONCLUSION

In conclusion, this study found that COVID-19–infected patients with diabetes are associated with increased risks of cardiovascular complications and mortality than uninfected people with diabetes, even for Omicron-dominant infections. Continuous monitoring for signs/symptoms of cardiovascular and microvascular complications postinfection and up until at least 1 year postrecovery may be especially beneficial for these patients.

AUTHOR CONTRIBUTIONS

Concept and design by EYFW and ICKW. Acquisition by EYFW and ICKW. Analysis or interpretation of data by EYFW, RZ, SM, AHYL, BW, VKCY, FTTL, CSLC, XL, CKHW, CLC, EWYC, KCBT and ICKW. Drafting of the manuscript by EYFW, SM and AHYL. Critical revision of the manuscript for important intellectual content by all authors. Statistical analysis by EYFW, RZ, BW and VKCY. Administrative, technical or material support by EYFW and ICKW. Supervision by EYFW and ICKW. EYFW and ICKW are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as the patients privacy.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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