JACC: ADVANCES VOL. 2, NO. 6, 2023

ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Emergency Visits or Hospitalizations for Cardiovascular Diagnoses in the Post-Acute Phase of COVID-19

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ABSTRACT

BACKGROUND Prior studies of COVID-19 cardiovascular sequelae include diagnoses made within 4 weeks, but the World Health Organization definition for "postacute phase" is >3 months.

OBJECTIVES The purpose of this study was to determine which cardiovascular diagnoses in the postacute phase of COVID-19 are associated with SARS-CoV-2 infection.

METHODS Retrospective cohort study of all adults in Alberta who had a positive SARS-CoV-2 reverse transcription polymerase chain reaction test between March 1, 2020 and June 30, 2021, matched (by age, sex, Charlson Comorbidity score, and test date) with controls who had a negative reverse transcription polymerase chain reaction test.

RESULTS The 177,892 patients with laboratory confirmed SARS-CoV-2 infection (mean age 42.7 years, 49.7% female) were more likely to visit an emergency department (5.7% vs 3.3%), be hospitalized (3.4% vs 2.1%), or die (1.3% vs 0.4%) within 1 month than matched test-negative controls. After 3 months, cases were significantly more likely than controls to have an emergency department visit or hospitalization for diabetes mellitus (1.5% vs 0.7%), hypertension (0.6% vs 0.4%), heart failure (0.2% vs 0.1%), or kidney injury (0.3% vs 0.2%). In the 6,030 patients who had survived a hospitalization for COVID-19, postacute phase risks were substantially greater for diabetes mellitus (9.5% vs 3.0%, adjusted odds ratio [aOR]: 3.16 [95% CI: 2.43-4.12]), hypertension (3.5% vs 1.4%, aOR: 2.89 [95% CI: 1.97-4.23]), heart failure (2.1% vs 0.7%, aOR: 3.16 [95% CI: 1.88-5.29]), kidney injury (3.1% vs 0.8%, aOR: 2.70 [95% CI: 1.71-4.28]), bleeding (1.5% vs 0.5%, aOR: 3.40 [95% CI: 1.83-6.32]), and venous thromboembolism (0.8% vs 0.3%, aOR: 3.60 [95% CI: 1.59-8.13]).

CONCLUSIONS Clinicians should screen COVID-19 survivors for diabetes mellitus, hypertension, heart failure, and kidney dysfunction in the postacute phase. (JACC Adv 2023;2:100391) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received November 18, 2022; revised manuscript received March 7, 2023, accepted April 3, 2023.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100391

ABBREVIATIONS AND ACRONYMS

AbSPORU = Alberta Strategy for Patient Oriented Research Support Unit

aOR = adjusted odds ratio

ED = emergency department

RT-PCR = reverse transcription polymerase chain reaction

WHO = World Health Organization

More than 670 million individuals have survived COVID-19 thus far. The World Health Organization (WHO) defines long COVID as having persistent symptoms more than 3 months after acute SARS-CoV-2 infection which cannot otherwise be explained and have lasted for at least 2 months.[1] While estimates of the frequency of long COVID symptoms vary depending on the duration of follow-up, a recent systematic review of 41 studies found that 54% of COVID hospitalization survivors and 34% of nonhospitalized COVID survivors report at least 1 persistent symptom 3 months after their infection.[2] However, there is debate about which of the more than 50 symptoms described by patients with long COVID are actually related to their prior infection and which are merely commonly experienced by individuals of that age/sex regardless of whether or not they had prior SARS-CoV-2 infection.[3-5]

While a recent analysis of U.S. claims data reported that 15% of adults younger than 65 and 32% of those older than 65 years infected with SARS-CoV-2 developed physician-diagnosed clinical sequelae that required medical care more than 3 weeks after their acute infection,[6,7] an analysis from the Veterans Affairs system suggested lower incidence rates (1.5% hypertension, 0.8% diabetes, 0.4% kidney injury, and 0.4% heart failure).[8] However, it should be noted that all of these studies defined the "postacute" phase as beginning 3 to 4 weeks after the initial infection, which conflates early and later events and is inconsistent with the current WHO definition. Thus, the question of which physician-assigned diagnoses are most common in the postacute phase (ie, after 3 months) of COVID-19 remains uncertain.

Thus, we designed this study to examine the frequency of physician-assigned diagnoses in the postacute phase of SARS-CoV-2 infection (ie, more than 3 months after initial infection) and to determine which were associated with COVID-19 we matched COVID-19 cases with contemporaneous controls who had a negative reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 done in the same timeframe.

METHODS

STUDY DESIGN AND STUDY SAMPLE. We conducted a retrospective cohort study of all adults in the Canadian province of Alberta who had a positive SARS-CoV-2 RT-PCR test between March 1, 2020 and June 30, 2021, and matched (by age, sex, and Charlson Comorbidity Index score) each case with a population control who had a negative SARS-CoV-2 RT-PCR test within 30 days of the case's test date. For patients tested multiple times during our study, we only examined the data related to their first positive SARS-CoV-2 test.

DATA SOURCES. Alberta has a publicly funded, universal access health care system without point of care user fees. As previously described,[9] we used several health care databases for this study and linked records deterministically via encrypted unique health identifier number to create our study sample. The Discharge Abstract Database records all acute care hospitalizations with up to 25 diagnoses and admission/discharge dates; the Ambulatory Care Database captures all emergency department (ED) visits and hospital-based physician office visits with up to 10 diagnostic codes; the Healthcare Provider Claims Database captures all physician visits (including those shadow-billed by salaried physicians) with up to 3 diagnoses; Alberta Precision Laboratory data store the results of SARS-CoV-2 tests; the Alberta Immunization Database captures COVID-19 vaccination status (with each case defined as fully vaccinated 2 weeks after the second dose of an approved COVID-19 vaccine); and the Alberta Health Care Insurance Program Central Stakeholder Registry holds demographic data including home address and date of emigration or death.

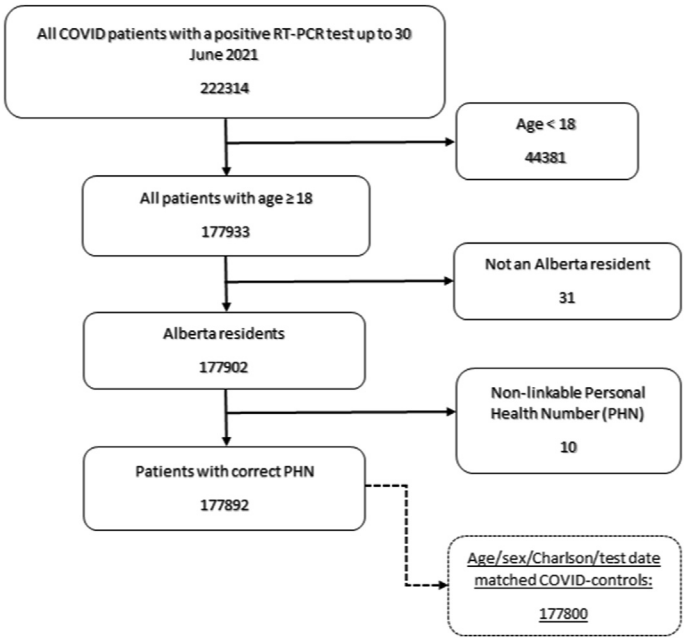
COMORBIDITIES AND OUTCOMES. We used previously validated International Classification of Diseases-9th Revision and International Classification of Diseases-10th Revision based case definitions from the hospitalization, ED, and provider claims datasets to identify baseline comorbidities in the 2 years prior to (and including) the index (ie, polymerase chain reaction test) date as well as the outcomes of interest (ED visits or hospitalizations for the diagnoses listed in Supplemental Table 1). For the outcomes, we followed all patients for 9 months and report events (ED visits or hospitalizations with a primary diagnosis for any of the diagnoses listed in Supplemental Table 1) occurring within 3 months of the acute SARS-CoV-2 infection (defined as the "acute phase" of COVID-19) but our analyses focused only on those events occurring after 3 months ("postacute phase"). Our outcome definitions included incident (new) and prevalent diagnoses (ie, patients with a prior history of that condition who had an ED visit or hospitalization for that condition again after

COVID-19), but in a sensitivity analysis we examined only new diagnoses (incident cases). We used case definitions for the comorbidities and outcomes previously validated in the Alberta datasets.[9] For mortality, we followed all patients until March 31, 2022.

STATISTICAL ANALYSIS. We report patient characteristics, care patterns, baseline comorbidities, and subsequent outcomes, comparing patients who tested positive vs controls who tested negative for SARS-CoV-2 infection. To compare outcome rates between those with/without COVID, we calculated adjusted odds ratios (aORs) for each of the outcomes, using logistic regression analyses and including age, sex, Pampalon deprivation index (which also controls for geography since it is based on postal code), the Charlson Comorbidity score, and vaccination status as covariables and modeling death as a competing risk. Since cases and controls were matched, propensity score analysis was not needed. We generated Kaplan-Meier curves to explore the incidence of each physician-assigned clinical sequelae statistically significantly associated with COVID-19 in the post-acute phase amongst those cases and controls who were alive at 3 months after their index test date—of note, follow-up was censored at the time of death for any cases or controls who died during the postacute phase. All statistical analyses were done using SAS v.9.4 (R Foundation for Statistical Computing, Vienna, Austria) (SAS Institute, Cary, NC) and figures were generated using R 4.1.2. As we were comparing event rates for 25 different outcomes between cases and controls, we adjusted the *P* value for significance to 0.002 per the Bonferroni correction.

ETHICS AND DATA AVAILABILITY. This study was approved by the Health Ethics Review board at the University of Alberta (Pro00101096), with waiver of individual patient signed informed consent as we analyzed deidentified health care administrative data. All analyses were done within the Data and Research Services Platform of the Alberta Strategy for Patient Oriented Research Support Unit (AbSPORU). To comply with Alberta's Health Information Act, the dataset used for this study cannot be made publicly available. The dataset from this study is held securely in coded form within the AbSPORU Data and Research Services Platform. While legal data sharing agreements between the investigators, AbSPORU, and Alberta Health Services/Alberta Health prohibit us from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.absporu.ca.

FIGURE 1 Study Flowchart



RT-PCR = reverse transcription-polymerase chain reaction.

RESULTS

Our study cohort (Figure 1) included 177,892 patients ("cases") with laboratory confirmed SARS-CoV-2 infection (mean age 42.7 years, 49.7% female) and 177,800 matched controls (median age 42.2, 49.7% female) with laboratory confirmed negative SARS-CoV-2 tests (Table 1). Cases had higher material/social deprivation scores and Charlson Comorbidity Index scores than controls and although a higher proportion of cases had prior comorbidities than controls (Table 1), the proportions in either group having specific comorbidities at baseline were <1% for all but diabetes mellitus (4.5% vs 2.0%), hypertension (2.5% vs 1.7%), chronic obstructive pulmonary disease (1.9% vs 1.0%), and anxiety/depression (2.2% vs 2.2%). Reflecting the timeframe of our study (COVID vaccination roll out in Alberta began in early 2021 and initially prioritized long-term care residents, health care workers, indigenous peoples, and immunosuppressed individuals and thus most cases/controls enrolled prior to the spring of 2021 would not have had an opportunity to have been vaccinated), <6,000 patients in our study had had

TABLE 1 Characteristics of Cases and Controls

	COVID-19 Cases (n = 177,892)	RT-PCR Test Negative Controls (n = 177,800)
Female	88,484 (49.7%)	88,369 (49.7%)
Age, y	42.69 ± 16.86	42.19 ± 16.84
Material/social deprivation		
1 (least deprived)	24,846 (14.0%)	29,727 (16.7%)
2	32,893 (18.5%)	36,296 (20.4%)
3	38,650 (21.7%)	34,772 (19.6%)
4	30,233 (17.0%)	28,625 (16.1%)
5 (most deprived)	40,558 (22.8%)	34,341 (19.3%)
Charlson Score	0.18 ± 0.75	0.10 ± 0.59
Medical history (based on all encounters in 2 y prior to index date)		
Myocardial infarction	782 (0.4%)	467 (0.3%)
Congestive heart failure	1,372 (0.8%)	751 (0.4%)
Peripheral vascular disease	456 (0.3%)	366 (0.2%)
Cerebrovascular disease	1,016 (0.6%)	674 (0.4%)
Dementia	1,637 (0.9%)	728 (0.4%)
Chronic pulmonary disease	3,434 (1.9%)	1,779 (1.0%)
Rheumatic disease	750 (0.4%)	489 (0.3%)
Peptic ulcer disease	439 (0.2%)	290 (0.2%)
Mild liver disease	1,084 (0.6%)	539 (0.3%)
Diabetes without complications	4,983 (2.8%)	2,092 (1.2%)
Diabetes with complications	3,080 (1.7%)	1,414 (0.8%)
Paraplegia and hemiplegia	285 (0.2%)	165 (0.1%)
Renal disease	1,099 (0.6%)	595 (0.3%)
Cancer	1,692 (1.0%)	1,223 (0.7%)
Moderate or severe liver disease	206 (0.1%)	116 (0.1%)
Metastatic carcinoma	432 (0.2%)	364 (0.2%)
AIDS/HIV	104 (0.1%)	42 (0.0%)
Hypertension	4,398 (2.5%)	3,043 (1.7%)
Pulmonary hypertension	105 (0.1%)	60 (0.0%)
Cardiac arrhythmia	288 (0.2%)	252 (0.1%)
Deep vein thrombosis (DVT)	676 (0.4%)	549 (0.3%)
Pulmonary embolism (PE)	592 (0.3%)	413 (0.2%)
Bleeding	1,782 (1.0%)	1,364 (0.8%)
Anxiety disorder	2,475 (1.4%)	2,277 (1.3%)
Depression diagnosis	1,505 (0.8%)	1,617 (0.9%)
Interstitial lung disease	119 (0.1%)	64 (0.0%)
Vaccination status at date of RT-PCR test		
Fully vaccinated	611 (0.3%)	1 (0.0%)
Partially vaccinated	5,369 (3.0%)	6 (0.0%)
Unvaccinated	171,912 (96.6%)	177,793 (100.0%)
Outcomes within 30 d of RT-PCR test		
Emergency department visit	10,108 (5.7%)	5,792 (3.26%)
Hospitalization	6,966 (3.4%)	3,711 (2.09%)
Death	2,357 (1.32%)	671 (0.38%)

Values are n (%) or mean ± SD.
RT-PCR = reverse transcription-polymerase chain reaction.

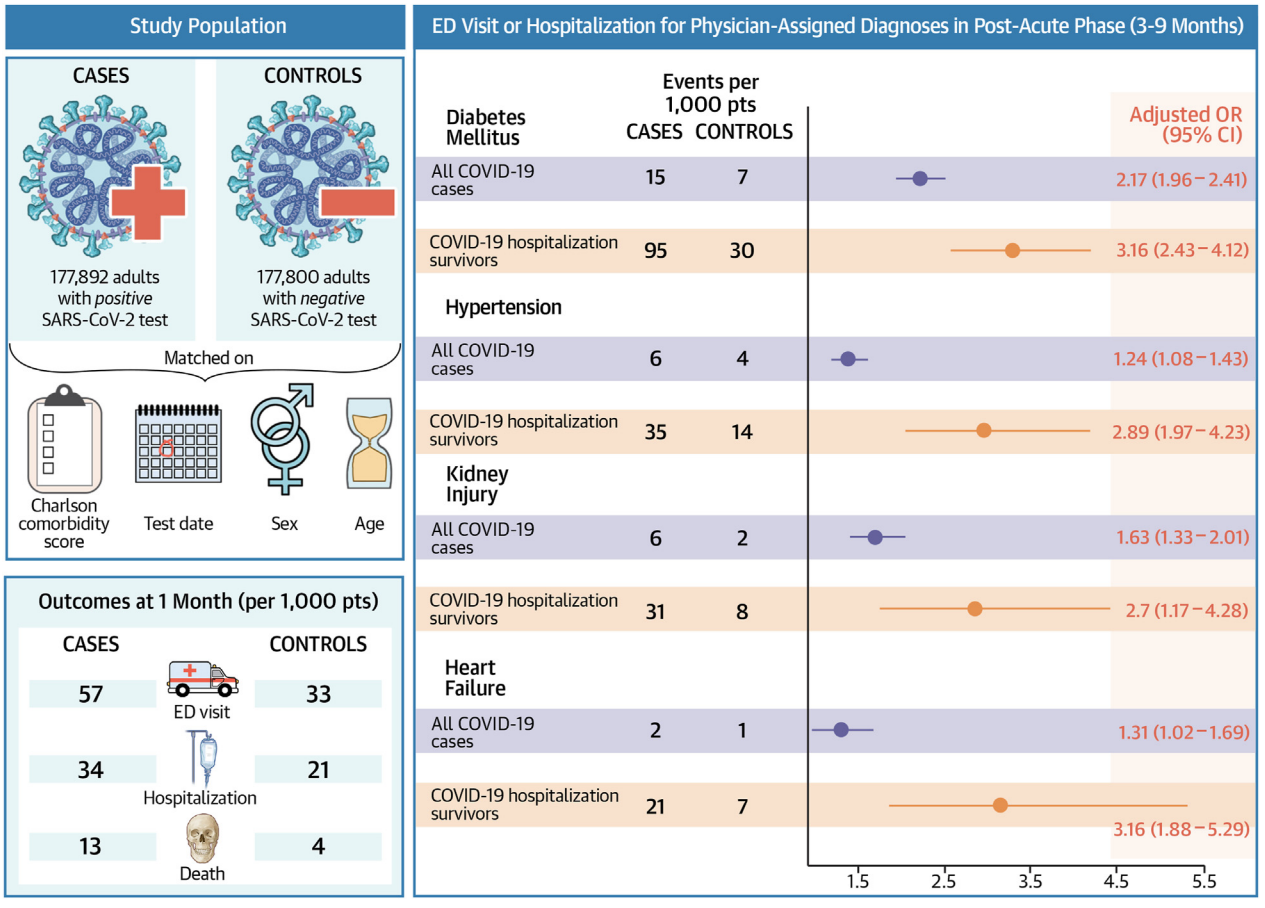
at least 1 COVID vaccination by their index date (Table 1). Cases were significantly (all $P < 0.001$) more likely to visit an ED (5.7% vs 3.3%), be hospitalized (3.4% vs 2.1%), or die (1.3% vs 0.4%) within a month of their RT-PCR tests (Central Illustration).

Cases were significantly (all $P < 0.001$) more likely than controls to have an ED visit or hospitalization in the postacute phase (months 3-9 after index date) for diabetes mellitus (1.5% vs 0.7%), hypertension (0.6% vs 0.4%), heart failure (0.2% vs 0.1%), or kidney injury (0.3% vs 0.2%) (Table 2). Although bleeding, tachycardia, pulmonary hypertension, and interstitial lung disease were also more common amongst cases in the postacute phase, they did not meet our Bonferroni-corrected limit for statistical significance. We did not find an excess risk of acute coronary syndrome (0.1% vs 0.1%, $P = 0.61$) or stroke (0.1% vs 0.1%, $P = 0.91$) in the postacute phase. While venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) was significantly more common amongst cases in the acute phase (0.3% vs 0.2%, $P = 0.0002$) (Table 2), the excess risk in the postacute phase did not achieve statistical significance (0.2% vs 0.1%, $P = 0.23$) (Table 2). Of note, although controls were more likely to have ED visits or hospitalizations for acute coronary syndrome, stroke, heart failure, hypertension, cardiac arrhythmias, bleeding, or kidney injury in the acute phase of COVID-19 (Table 2) this reflects ascertainment and collider bias since the vast majority of these events were within 7 days of the RT-PCR testing date (Supplemental Table 2) and all patients presenting with any of these diagnoses during the COVID-19 pandemic were tested at time of admission to exclude SARS-CoV-2 infection.

To focus on new diagnoses during the postacute phase, we excluded any ED visits or hospitalizations for physician-assigned diagnoses in the postacute phase if that patient had an ED visit or hospitalization for that diagnosis in the acute COVID phase (first 3 months) or the prior 2 years. This sensitivity analysis confirmed that cases were statistically significantly more likely than controls to have an ED visit or hospitalization in the postacute phase (months 3-9 after index date) for a new diagnosis of diabetes mellitus, hypertension, heart failure, or new kidney injury (Table 2).

After adjusting for age, sex, Charlson score, deprivation score, and vaccination status, SARS-CoV-2 infection remained associated with significantly increased risks of ED visits or hospitalizations for diabetes mellitus (aOR: 2.17; 95% CI: 1.95-2.41), hypertension (aOR: 1.24; 95% CI: 1.08-1.43), heart failure (aOR: 1.31; 95% CI: 1.02-1.69), or kidney injury (aOR: 1.63; 95% CI: 1.33-2.01) in the postacute phase (Table 3, Figure 2). When we restricted our analyses to only those 6,030 COVID-19 cases who were hospitalized (and their matched controls), the absolute risks (Table 4) and relative associations (Table 3) were even stronger. For example, in the 3 to 9 months after they

CENTRAL ILLUSTRATION **Emergency Visits or Hospitalizations for Cardiovascular Diagnoses After COVID-19 Recovery**



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survived a hospitalization for COVID-19, patients had substantially higher risks of an ED visit or hospitalization for diabetes mellitus (9.5% vs 3.0%, aOR: 3.16 [95% CI: 2.43-4.12]), hypertension (3.5% vs 1.4%, aOR: 2.89 [95% CI: 1.97-4.23]), heart failure (2.1% vs 0.7%, aOR: 3.16 [95% CI: 1.88-5.29]), kidney injury (3.1% vs 0.8%, aOR: 2.70 [95% CI: 1.71-4.28]), bleeding (1.5% vs 0.5%, aOR: 3.40 [95% CI: 1.83-6.32]), and venous thromboembolism (0.8% vs 0.3%, aOR: 3.60 [95% CI: 1.59-8.13]), but not acute coronary syndrome (0.5% vs 0.4%, aOR: 1.30 [95% CI: 0.55-3.05]) or atrial fibrillation (1.0% vs 0.6%, aOR: 1.58 [95% CI: 0.85-2.93]).

DISCUSSION

Our study demonstrated a significant increase in ED visits or hospitalizations for physician-assigned diagnoses of diabetes mellitus, hypertension, heart failure, or kidney injury during the postacute phase (ie, more than 3 months after acute infection) of COVID-19. This finding was robust even if we restricted our analysis to only new diagnoses of each condition and the associations were strongest in those patients who had been hospitalized for their COVID-19. Indeed, some additional associations, such as increased risk of venous thromboembolic disease or bleeding during the postacute phase, were only seen in those COVID-19 survivors who had been hospitalized for their infection. After excluding events in the first 3 months, we did not find excess risk of other commonly cited sequalae of SARS-CoV-2 infection when compared to test negative age/sex/comorbidity matched controls such as acute coronary syndrome, stroke, or atrial fibrillation. This is important information that can help inform the debate around which symptoms reported or

TABLE 2 ED Visits or Hospitalizations for Physician-Assigned Diagnoses in All Survivors of COVID-19 of Any Severity

ED Visit or Hospitalization With Diagnosis of:	Acute Phase (<3 mo)			Post-Acute Phase (Months 3-9)			New Post-Acute Events (Excluding Those Subjects With Same Diagnosis in the Acute Phase)		
	Cases (n = 177,892)	Controls (n = 177,800)	*P* Value	Cases (n = 175,184)	Controls (n = 176,810)	*P* Value	Cases (n = 175,184)	Controls (n = 176,810)	*P* Value
Diabetes mellitus	2,175 (1.2%)	1,400 (0.8%)	<0.0001	2,675 (1.5%)	1,297 (0.7%)	<0.0001	1,958 (1.1%)	874 (0.5%)	<0.0001
Hypertension	790 (0.4%)	1,187 (0.7%)	<0.0001	1,020 (0.6%)	794 (0.4%)	<0.0001	941 (0.5%)	699 (0.4%)	<0.0001
Kidney injury	454 (0.3%)	857 (0.5%)	<0.0001	531 (0.3%)	338 (0.2%)	<0.0001	484 (0.3%)	290 (0.2%)	<0.0001
Heart failure	231 (0.1%)	501 (0.3%)	<0.0001	330 (0.2%)	243 (0.1%)	0.0002	280 (0.2%)	189 (0.1%)	<0.0001
Pulmonary hypertension	18 (0.0%)	41 (0.0%)	0.003	29 (0.0%)	15 (0.0%)	0.03	27 (0.0%)	11 (0.0%)	0.017
Cardiac arrhythmia	36 (0.0%)	89 (0.1%)	<0.0001	66 (0.0%)	78 (0.0%)	0.34	64 (0.0%)	76 (0.0%)	0.33
Atrial fibrillation	236 (0.1%)	503 (0.3%)	<0.0001	286 (0.2%)	294 (0.2%)	0.82	258 (0.1%)	259 (0.1%)	0.95
Postural orthostatic tachycardia syndrome	12 (0.0%)	27 (0.0%)	0.02	21 (0.0%)	36 (0.0%)	0.050	19 (0.0%)	34 (0.0%)	0.04
Myocarditis	13 (0.0%)	15 (0.0%)	0.70	11 (0.0%)	10 (0.0%)	0.81	11 (0.0%)	10 (0.0%)	0.81
Myocardial infarction	81 (0.0%)	283 (0.2%)	<0.0001	119 (0.1%)	112 (0.1%)	0.60	115 (0.1%)	111 (0.1%)	0.74
Acute coronary syndrome	124 (0.1%)	363 (0.2%)	<0.0001	178 (0.1%)	170 (0.1%)	0.61	172 (0.1%)	164 (0.1%)	0.60
Cardiogenic shock	7 (0.0%)	34 (0.0%)	<0.0001	9 (0.0%)	8 (0.0%)	0.79	9 (0.0%)	8 (0.0%)	0.79
Any venous thromboembolic event	455 (0.3%)	348 (0.2%)	0.0002	276 (0.2%)	251 (0.1%)	0.23	262 (0.1%)	241 (0.1%)	0.2982
Deep vein thrombosis	191 (0.1%)	160 (0.1%)	0.10	162 (0.1%)	155 (0.1%)	0.63	153 (0.1%)	152 (0.1%)	0.89
Pulmonary embolism	290 (0.2%)	229 (0.1%)	0.008	129 (0.1%)	109 (0.1%)	0.171	122 (0.1%)	102 (0.1%)	0.16
Bleeding	275 (0.2%)	368 (0.2%)	0.0002	469 (0.3%)	404 (0.2%)	0.02	449 (0.3%)	382 (0.2%)	0.014
Any stroke	94 (0.1%)	245 (0.1%)	<0.0001	140 (0.1%)	143 (0.1%)	0.91	139 (0.1%)	135 (0.1%)	0.7506
Ischemic stroke	66 (0.0%)	184 (0.1%)	<0.0001	108 (0.1%)	117 (0.1%)	0.59	108 (0.1%)	109 (0.1%)	0.99
Hemorrhagic stroke	32 (0.0%)	66 (0.0%)	0.0006	33 (0.0%)	27 (0.0%)	0.42	32 (0.0%)	27 (0.0%)	0.49
Anxiety disorder	489 (0.3%)	463 (0.3%)	0.40	626 (0.4%)	592 (0.3%)	0.26	571 (0.3%)	555 (0.3%)	0.53
Depression	210 (0.1%)	381 (0.2%)	<0.0001	363 (0.2%)	394 (0.2%)	0.31	337 (0.2%)	366 (0.2%)	0.33
Post-traumatic stress disorder	33 (0.0%)	63 (0.0%)	0.002	54 (0.0%)	63 (0.0%)	0.43	50 (0.0%)	59 (0.0%)	0.41
Chronic kidney disease	128 (0.1%)	201 (0.1%)	<0.0001	145 (0.1%)	126 (0.1%)	0.22	122 (0.1%)	104 (0.1%)	0.21
Respiratory failure	72 (0.0%)	93 (0.1%)	0.10	37 (0.0%)	26 (0.0%)	0.155	35 (0.0%)	23 (0.0%)	0.11
Interstitial lung disease	49 (0.0%)	48 (0.0%)	0.92	30 (0.0%)	18 (0.0%)	0.08	20 (0.0%)	10 (0.0%)	0.064

Values are n (%).
ED = emergency department.

conditions detected in survivors of COVID-19 are actually associated with the prior infection and which are merely common in individuals of that age/sex regardless of whether or not they had prior SARS-CoV-2 infection. It is now well recognized that SARS-CoV-2 targets all angiotensin-converting enzyme 2-expressing cells and not just pulmonary alveolar epithelial cells—the direct impacts of infection on pancreatic β-cells and renal proximal tubular podocytes are postulated to cause organ dysfunction leading to the increases in cardiovascular, cardiometabolic, and cardiorenal disease that we found.[10]

While other recent studies[6-8,11-19] have also reported associations between cardiovascular sequelae and prior COVID-19, only 1 (looking at diabetes and heart failure)[11] examined events after 3 months without including earlier events (thus conforming to the WHO definition of post-3 months for postacute COVID-19, like we did). This is an important distinction since studies that included earlier events reported very high effect estimates for excess risk, but closer examination revealed most of those events occurred within the first 3 months, and often within the first 30 days.[19] For example we found that venous thromboembolism (deep vein thrombosis and/or pulmonary embolism) was significantly more common amongst patients with COVID-19 within 3 months of infection (consistent with other recent studies),[6-8,11,18-21] but the excess risk was attenuated in the postacute phase compared to matched controls (and only detectable in those who had been hospitalized for their COVID-19). Although studies which defined the post-acute phase as beginning 30 days after COVID-19 infection reported an excess risk of atherosclerotic events,[6-8,13,19] we did not find an excess risk of acute coronary syndrome or stroke in the WHO-defined postacute phase of COVID-19

TABLE 3 Multivariable Analyses for Risks of ED Visits or Hospitalizations for Physician-Assigned Diagnoses, Adjusted for Age, Sex, Charlson Comorbidity Index Score, Deprivation Index, and Vaccination Status

ED Visit or Hospitalization With Diagnosis of:	Post-Acute Phase (Months 3-9) for All COVID-19 Survivors		Post-Acute Phase (Months 3-9) for COVID-19 Hospitalization Survivors	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Diabetes mellitus	2.08 (1.94-2.22)	2.17 (1.95-2.41)	3.44 (2.9-4.09)	3.16 (2.43-4.12)
Hypertension	1.29 (1.17-1.41)	1.24 (1.08-1.43)	2.57 (1.99-3.32)	2.89 (1.97-4.23)
Kidney injury	1.57 (1.37-1.8)	1.63 (1.33-2.01)	3.69 (2.7-5.04)	2.70 (1.71-4.28)
Heart failure	1.36 (1.15-1.6)	1.31 (1.02-1.69)	3.14 (2.2-4.49)	3.16 (1.88-5.29)
Pulmonary hypertension	1.93 (1.04-3.6)	1.92 (0.75-4.92)	6.00 (1.34-26.83)	7.76 (1.21-49.82)
Cardiac arrhythmia	0.85 (0.61-1.17)	0.85 (0.52-1.40)	5.00 (1.10-22.83)	2.85 (0.37-22.05)
Atrial Fibrillation	0.97 (0.83-1.14)	1.07 (0.84-1.38)	1.61 (1.07-2.42)	1.58 (0.85-2.93)
Postural orthostatic tachycardia syndrome	0.58 (0.34-1.00)	0.81 (0.36-1.80)	4.00 (0.45-35.77)	3.65 (0.19-70.29)
Cardiomyopathy	1.55 (0.99-2.43)	1.72 (0.87-3.42)	2.50 (0.78-7.97)	3.39 (0.63-18.34)
Myocarditis	1.10 (0.47-2.59)	1.33 (0.38-4.68)	-	-
Myocardial infarction	1.06 (0.82-1.37)	0.96 (0.65-1.41)	1.10 (0.59-2.06)	1.27 (0.48-3.34)
Acute coronary syndrome	1.05 (0.85-1.30)	1.09 (0.79-1.50)	1.21 (0.70-2.08)	1.30 (0.55-3.05)
Cardiogenic shock	1.12 (0.43-2.91)	1.30 (0.31-5.41)	-	-
Any venous thromboembolic event	1.10 (0.93-1.30)	1.18 (0.91-1.54)	2.89 (1.63-5.10)	3.60 (1.59-8.13)
Deep vein thrombosis	1.04 (0.84-1.30)	1.24 (0.88-1.74)	2.20 (1.04-4.65)	3.31 (1.12-9.78)
Pulmonary embolism	1.18 (0.92-1.53)	1.16 (0.79-1.70)	4.17 (1.71-10.18)	3.88 (1.13-13.35)
Bleeding	1.16 (1.02-1.33)	1.44 (1.17-1.77)	3.32 (2.17-5.07)	3.40 (1.83-6.32)
Any stroke	0.98 (0.78-1.24)	0.88 (0.62-1.26)	2.00 (1.05-3.81)	2.20 (0.84-5.75)
Ischemic stroke	0.92 (0.71-1.20)	0.84 (0.57-1.24)	2.18 (1.07-4.46)	1.58 (0.54-4.62)
Hemorrhagic stroke	1.22 (0.73-2.03)	0.93 (0.44-1.99)	1.67 (0.40-6.97)	5.55 (0.93-33.11)
Anxiety disorder	1.06 (0.94-1.18)	1.27 (1.07-1.50)	5.13 (2.60-10.11)	5.83 (2.29-14.84)
Depression diagnosis	0.92 (0.80-1.06)	1.46 (1.17-1.82)	2.78 (1.59-4.84)	2.92 (1.27-6.71)
PTSD	0.86 (0.60-1.23)	1.09 (0.64-1.89)	6.00 (0.72-49.84)	16.25 (1.20-220.82)
Chronic kidney disease	1.15 (0.91-1.46)	1.30 (0.90-1.88)	2.92 (10.75-4.85)	2.65 (1.25-5.62)
Respiratory failure	1.42 (0.86-2.35)	1.27 (0.60-2.71)	16.02 (20.12-120.85)	11.26 (1.00-127.17)
Interstitial lung disease	1.67 (0.93-2.99)	1.63 (0.69-3.87)	3.00 (1.09-8.26)	4.06 (1.01-16.42)

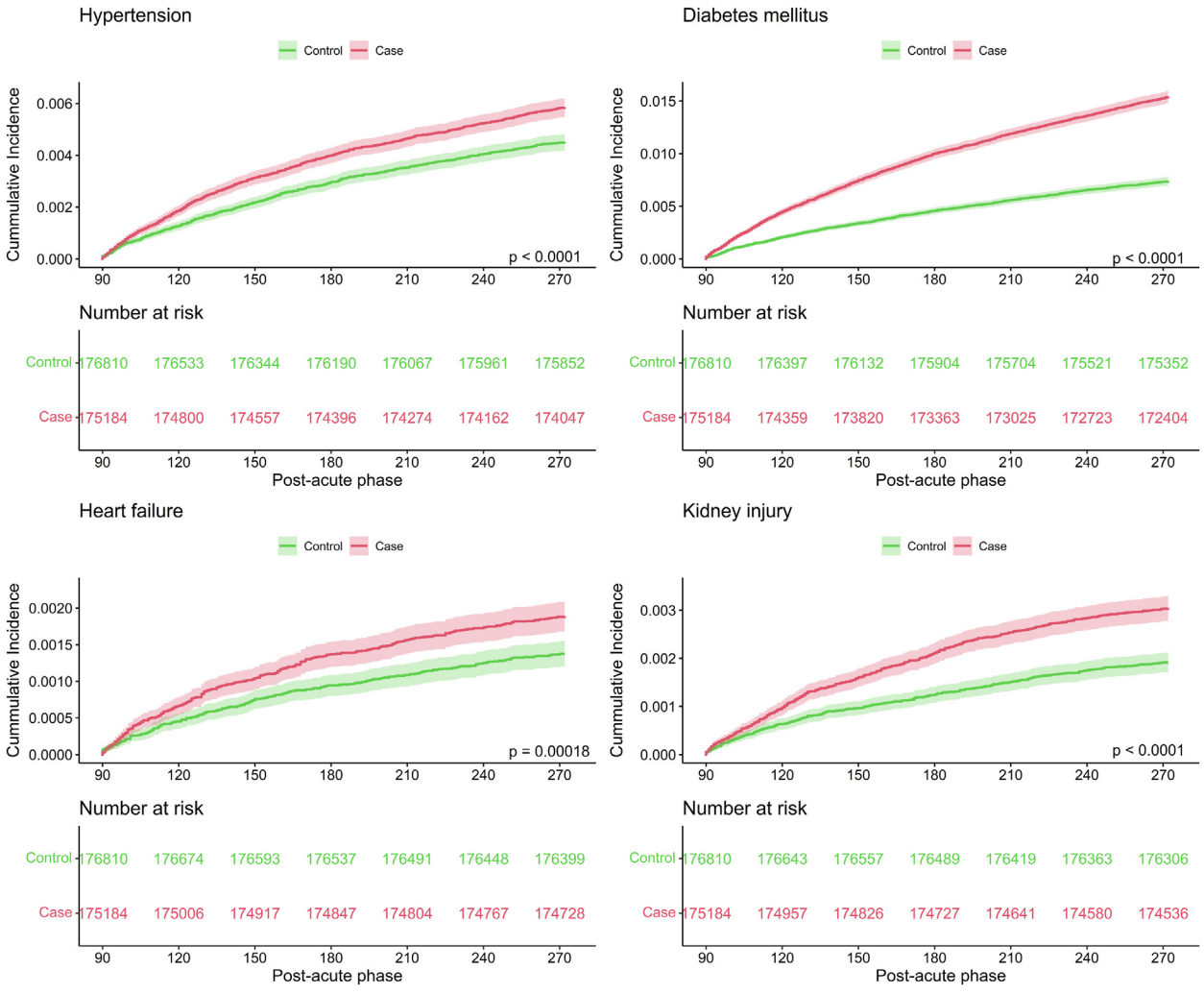
aOR = adjusted odds ratio; ED = emergency department; OR = odds ratio; PTSD = post-traumatic stress disorder.

(consistent with a recent study from the United Kingdom which reported outcome data for the post-3-month timeframe).[11]

Although we know vaccination decreases the risks of infection, hospitalization, and death from COVID-19, there is debate about whether vaccination reduces the risk of post-COVID sequelae. Unfortunately, due to the low rates of vaccination prior to our cohort's index dates (since the majority of infections and matched testing dates were prior to the spring of 2021 in Alberta), our data were under-powered to investigate this issue. A recent systematic review (6 studies, n = 17.3 million) found that patients who were fully vaccinated prior to an acute SARS-CoV-2 infection reported fewer long COVID symptoms (with odds reduced by 10%-89% depending on the symptom).[22] However, most patients in those studies were infected within a month of being vaccinated, follow-up was <3 months in most of the studies, patients with varying severities of COVID-19 were pooled for analyses, and none of the studies employed the WHO definition for long COVID. In addition, as the studies were based on patient self-report they were all subject to healthy volunteer bias and recall bias (an important issue in light of studies suggesting that many symptoms reported by patients with long COVID were found to also be common in patients without evidence of prior COVID).[4,5] Although a recent Korean study reported 58% fewer hospitalizations for stroke or acute myocardial infarction in vaccinated patients 1 to 4 months after SARS-CoV-2 infection,[23] a study from the U.S. Food and Drug Administration Sentinel System found that the risk of stroke or acute myocardial infarction after COVID-19 was not influenced by availability of vaccination.[18] Thus, the question of whether vaccination prevents cardiovascular clinical sequelae after COVID-19 remains uncertain.

We found that the majority of individuals with COVID-19 in Alberta during the first 15 months of the

FIGURE 2 **Occurrence of ED Visits or Hospitalizations for Physician-Assigned Cardiovascular Diagnoses in the Postacute Phase of COVID-19**



ED = emergency department.

pandemic were young (mean age 43 years, <15% older than 60 years) and relatively healthy. In line with other reports of the epidemiology of COVID-19,[24-26] we found that even though we matched by age, sex, and date of RT-PCR test (thereby accounting for differences in population prevalence over time), patients who tested positive for SARS-CoV-2 infection had higher material/social deprivation scores and Charlson Comorbidity Index scores than those who tested negative.

We were able to match nearly 178,000 patients with COVID-19 to contemporaneous controls with negative RT-PCR tests done around the same time (who presumably had symptoms which precipitated the testing), thus improving comparability between our cases and controls as opposed to study designs where COVID cases are just matched to population-based controls who had not undergone testing. We also followed all patients for at least 9 months, and adjusted for currently recognized risk factors for long COVID (including female sex, socioeconomic deprivation, comorbidities, and severity of the acute infection) in multivariable models.[25,27] However, there are some limitations to our study. For one, although outpatient visits with familiar physicians are known to reduce ED visits and

TABLE 4 ED Visits or Hospitalizations for Physician-Assigned Diagnoses in 6,030 COVID-19 Hospitalization Survivors and Their Matched Controls

ED Visit or Hospitalization With Diagnosis of:	Acute Phase (<3 mo)			Post-Acute Phase (Months 3-9)			New Post-Acute Events (Excluding Those Subjects With Same Diagnosis in the Acute Phase)		
	Cases (n = 6,030, 3.4%)	Controls (n = 6,023, 3.4%)	*P* Value	Cases (n = 6,030, 3.4%)	Controls (n = 6,023, 3.4%)	*P* Value	Cases (n = 6,030, 3.4%)	Controls (n = 6,023, 3.4%)	*P* Value
Diabetes mellitus	907 (15.0%)	238 (4.0%)	<0.0001	572 (9.5%)	178 (3.0%)	<0.0001	256 (4.2%)	112 (1.9%)	<0.0001
Hypertension	409 (6.8%)	161 (2.7%)	<0.0001	209 (3.5%)	83 (1.4%)	<0.0001	160 (2.7%)	67 (1.1%)	<0.0001
Kidney injury	302 (5.0%)	125 (2.1%)	<0.0001	184 (3.1%)	51 (0.8%)	<0.0001	150 (2.5%)	45 (0.7%)	<0.0001
Heart failure	132 (2.2%)	95 (1.6%)	0.0135	124 (2.1%)	40 (0.7%)	<0.0001	91 (1.5%)	31 (0.5%)	<0.0001
Pulmonary hypertension	12 (0.2%)	7 (0.1%)	0.252	12 (0.2%)	2 (0.0%)	0.0075	10 (0.2%)	2 (0.0%)	0.021
Cardiac arrhythmia	9 (0.1%)	12 (0.2%)	0.5106	10 (0.2%)	2 (0.0%)	0.021	9 (0.1%)	2 (0.0%)	0.0349
Atrial fibrillation	120 (2.0%)	73 (1.2%)	0.0007	61 (1.0%)	38 (0.6%)	0.0206	50 (0.8%)	30 (0.5%)	0.0252
Postural orthostatic tachycardia syndrome	3 (0.0%)	3 (0.0%)	0.9989	4 (0.1%)	1 (0.0%)	0.18	3 (0.0%)	1 (0.0%)	0.3178
Myocarditis	7 (0.1%)	0 (0.0%)	0.0082	4 (0.1%)	0 (0.0%)	0.0456	4 (0.1%)	0 (0.0%)	0.0456
Myocardial infarction	43 (0.7%)	36 (0.6%)	0.4325	21 (0.3%)	19 (0.3%)	0.7542	18 (0.3%)	19 (0.3%)	0.8664
Acute coronary syndrome	56 (0.9%)	44 (0.7%)	0.2305	29 (0.5%)	24 (0.4%)	0.4939	25 (0.4%)	23 (0.4%)	0.7755
Cardiogenic shock	3 (0.0%)	4 (0.1%)	0.7042	2 (0.0%)	0 (0.0%)	0.1575	2 (0.0%)	0 (0.0%)	0.1575
Any venous thromboembolic event	210 (3.5%)	34 (0.6%)	<0.0001	46 (0.8%)	16 (0.3%)	0.0001	42 (0.7%)	15 (0.2%)	0.0003
Deep vein thrombosis	68 (1.1%)	13 (0.2%)	<0.0001	22 (0.4%)	10 (0.2%)	0.0339	19 (0.3%)	10 (0.2%)	0.0949
Pulmonary embolism	157 (2.6%)	24 (0.4%)	<0.0001	25 (0.4%)	6 (0.1%)	0.0006	23 (0.4%)	5 (0.1%)	0.0007
Bleeding	87 (1.4%)	40 (0.7%)	<0.0001	92 (1.5%)	28 (0.5%)	<0.0001	80 (1.3%)	25 (0.4%)	<0.0001
Any stroke	43 (0.7%)	42 (0.7%)	0.9176	28 (0.5%)	14 (0.2%)	0.0308	28 (0.5%)	13 (0.2%)	0.0191
Ischemic stroke	32 (0.5%)	30 (0.5%)	0.8025	24 (0.4%)	11 (0.2%)	0.028	24 (0.4%)	10 (0.2%)	0.0164
Hemorrhagic stroke	13 (0.2%)	13 (0.2%)	0.9976	5 (0.1%)	3 (0.0%)	0.4804	5 (0.1%)	3 (0.0%)	0.4804
Anxiety disorder	102 (1.7%)	17 (0.3%)	<0.0001	51 (0.8%)	10 (0.2%)	<0.0001	40 (0.7%)	10 (0.2%)	<0.0001
Depression	84 (1.4%)	16 (0.3%)	<0.0001	47 (0.8%)	17 (0.3%)	0.0002	38 (0.6%)	17 (0.3%)	0.0046
Post-traumatic stress disorder	15 (0.2%)	0 (0.0%)	0.0001	6 (0.1%)	1 (0.0%)	0.0589	3 (0.0%)	1 (0.0%)	0.3178
Chronic kidney disease	88 (1.5%)	41 (0.7%)	<0.0001	58 (1.0%)	20 (0.3%)	<0.0001	43 (0.7%)	17 (0.3%)	0.0008
Respiratory failure	54 (0.9%)	13 (0.2%)	<0.0001	16 (0.3%)	1 (0.0%)	0.0003	14 (0.2%)	1 (0.0%)	0.0008
Interstitial lung disease	35 (0.6%)	9 (0.1%)	<0.0001	15 (0.2%)	5 (0.1%)	0.0254	9 (0.1%)	2 (0.0%)	0.0349

Values are n (%).
ED = emergency department.

hospitalizations,[28,29] we do not have any data on follow-up frequency or continuity for our cases or controls. Second, we cannot comment on the frequency of cardiovascular diagnoses after infections with variants of concern as the majority of our patients were infected with the ancestral Wuhan strain given the timing of our study. Early reports from the United Kingdom of lower risks for long COVID after omicron compared to delta infections is encouraging in this regard.[30] Third, in the timeframe we studied the vast majority of patients with COVID-19 were unvaccinated and thus we could not examine the frequency of cardiovascular outcomes after breakthrough infections in vaccinated individuals or after repeat infections, although at least 1 recent study has done so.[31] Fourth, we relied on administrative data to define comorbidities and outcomes using previously validated case definitions for all health care encounters in the prior 2 years (including physician billing claims and not just ED visits or hospitalizations) but lack the clinical details needed to fully delineate illness severity (such as glycosylated hemoglobin, left ventricular ejection fraction, creatinine clearance, blood pressure levels) and acknowledge that we may have undercaptured comorbidities in individuals who had not sought medical care in those 2 years. Fifth, we were unable to account for the undoubted heterogeneity in management practices during the first 15 months of the pandemic when therapy evidence was sparse and outpatient resources to assist COVID-19 patients were still being developed. In particular, the increased use of the efficacious therapies identified later in the pandemic may influence future risk of postacute COVID-19 sequelae. Moreover, it is possible that some therapies used to treat COVID-19 in these patients may have contributed to increased rates of diabetes or renal dysfunction. Finally, as with any observational study, there is always the possibility of bias due to misclassification (false negative or false positive RT-PCR tests) or

unknown confounders and there could be physiologic differences in the control group that made them both less likely to contract COVID and reduced their susceptibility to cardiovascular sequelae.

CONCLUSIONS

We have demonstrated the absolute and relative risks of cardiovascular diagnoses requiring ED visits or hospitalizations in the postacute phase after SARS-CoV-2 infection which will help inform planning around future healthcare needs and what conditions survivors of COVID-19 should be screened for. However, further research is needed to examine differences across variants of concern, particularly the omicron variant which has been dominant since December 2021, and to determine whether vaccination (with/without booster doses) impacts cardiovascular outcomes in the postacute phase of COVID-19.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The Alberta SPOR Support Unit is funded by the Canadian Institute of Health Research, Alberta Innovates, and the University Hospital Foundation. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In the postacute phase of COVID-19 (3 or more months after testing positive for SARS-CoV-2 infection), patients were more likely to have an ED visit or hospitalization with diabetes mellitus, hypertension, heart failure, or kidney injury than in matched controls, and risks were even higher in those who were hospitalized for their COVID-19. COVID-19 survivors should be screened for these conditions in the postacute phase.

TRANSLATIONAL OUTLOOK: As these data are from the first 18 months of the pandemic, it is unknown whether these risks differ across variants of concern and whether vaccination (with or without booster doses) impacts cardiovascular outcomes in the postacute phase of COVID-19.

REFERENCES

1. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV, WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis*. 2022;22:e102-e107.

2. Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. *J Infect Dis*. 2022;226:1593-1607.

3. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep*. 2021;11:16144.

4. Brightling CE, Evans RA. Long COVID: which symptoms can be attributed to SARS-CoV-2 infection? *Lancet*. 2022;400:411-413.

5. Matta J, Wiernik E, Robineau O, et al. Association of self-reported COVID-19 infection and SARS-CoV-2 serology test results with persistent physical symptoms among French adults during the COVID-19 pandemic. *JAMA Intern Med*. 2022;182:19-25.

6. Daugherty SE, Guo Y, Heath K, et al. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2021;373:n1098.

7. Cohen K, Ren S, Heath K, et al. Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ*. 2022;376:e068414.

8. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature*. 2021;594:259-264.

9. McAlister FA, Nabipoor M, Chu A, et al. The impact of shifting demographics, variants of concern and vaccination on outcomes during the first 3 COVID-19 waves in Alberta and Ontario: a retrospective cohort study. *CMAJ Open*. 2022;10:E400-E408.

10. Lau D, McAlister FA. Implications of the COVID-19 pandemic for cardiovascular disease and risk-factor management. *Can J Cardiol*. 2021;37:722-732.

11. Rezel-Potts E, Douiri A, Sun X, Chowienczyk PJ, Shah AM, Gulliford MC. Cardiometabolic outcomes up to 12 months after COVID-19 infection. A matched cohort study in the UK. *PLoS Med*. 2022;19:e1004052.

12. Bowe B, Xie Y, Xu E, Al-Aly Z. Kidney outcomes in long COVID. *J Am Soc Nephrol*. 2021;32:2851-2862.

13. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022;28:583-590.

14. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol*. 2022;10:311-321.

15. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. *Diabetologia*. 2022;65:949-954.

16. Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 years - United States, March 1, 2020-June 28, 2021. *MMWR Morb Mortal Wkly Rep*. 2022;71:59-65.

17. Salah HM, Fudim M, O'Neil ST, Manna A, Chute CG, Caughey MC. Post-recovery COVID-19 and incident heart failure in the National COVID Cohort Collaborative (N3C) study. *Nat Commun*. 2022;13:4117.

18. Lo Re V 3rd, Dutcher SK, Connolly JG, et al. Association of COVID-19 vs influenza with risk of arterial and venous thrombotic events among hospitalized patients. *JAMA*. 2022;328:637-651.

19. Raisi-Estabragh Z, Cooper J, Salih A, et al. Cardiovascular disease and mortality sequelae of COVID-19 in the UK Biobank. *Heart*. 2022;109:119-126.

20. Katsoularis I, Fonseca-RodrÃguez O, Farrington P, et al. Risks of deep vein

thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. *BMJ*. 2022;377:e069590.

21. Knight R, Walker V, Ip S, et al. Association of COVID-19 with major arterial and venous thrombotic diseases: a population-wide cohort study of 48 million adults in England and Wales. *Circulation*. 2022;146:892-906.

22. Notarte KI, Catahay JA, Velasco JV, et al. Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: a systematic review. *EClinicalMedicine*. 2022;53:101624.

23. Kim YE, Huh K, Park YJ, Peck KR, Jung J. Association between vaccination and acute myocardial infarction and ischemic stroke after COVID-19 infection. *JAMA*. 2022;328:887-889.

24. Udell JA, Behrouzi B, Sivaswamy A, et al. Clinical risk, sociodemographic factors, and SARS-CoV-2 infection over time in Ontario, Canada. *Sci Rep*. 2022;12:10534.

25. de Lusignan S, Dorward J, Correa A, et al. Risk factors for SARS-CoV-2 among patients in the Oxford Royal College of General Practitioners Research and Surveillance Centre Primary Care Network: a cross-sectional study. *Lancet Infect Dis*. 2020;20:1034-1042.

26. Khan SU, Hagan KK, Javed Z. Disproportionate impact of COVID-19 among socially vulnerable patients. *Circ Cardiovasc Qual Outcomes*. 2022;15:e009294.

27. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med*. 2022;10:761-775.

28. Elliott MN, Adams JL, Klein DJ, et al. Patient-reported care coordination is associated with better performance on clinical care measures. *J Gen Intern Med*. 2021;36:3665-3671.

29. McAlister FA, Bakal JA, Green L, Bahler B, Lewanczuk R. The effect of provider affiliation with a primary care network on emergency department visits and hospital admissions. *CMAJ*. 2018;190:E276-E284.

30. Antonelli M, Pujol JC, Spector TD, Ourselin S, Steves CJ. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. *Lancet*. 2022;399:2263-2264.

31. Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med*. 2022;28:1461-1467.

KEY WORDS COVID-19, diabetes mellitus, heart failure, hypertension

APPENDIX For supplemental tables, please see the online version of this paper.