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Risk factors for COVID-19 hospitalization after COVID-19 vaccination: a population-based cohort study in Canada

Héctor A. Velásquez García[1,2,*], Prince A. Adu[1,2], Sean Harrigan[1], James Wilton[1], Drona Rasali[1], Mawuena Binka[2], Hind Sbihi[1], Kate Smolina[1,2], Naveed Z. Janjua[1,2,3,*]

[1] Data and Analytic Services, British Columbia Centre for Disease Control, Vancouver, Canada
[2] School of Population and Public Health, University of British Columbia, Vancouver, Canada
[3] Centre for Health Evaluation & Outcome Sciences, St. Paul's Hospital, Vancouver, Canada

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ABSTRACT

Objectives: With the uptake of COVID-19 vaccines, there is a need for population-based studies to assess risk factors for COVID-19-related hospitalization after vaccination and how they differ from unvaccinated individuals.

Methods: We used data from the British Columbia COVID-19 Cohort, a population-based cohort that includes all individuals (aged ≥18 years) who tested positive for SARS-CoV-2 by real-time reverse transcription-polymerase chain reaction from January 1, 2021 (after the start of vaccination program) to December 31, 2021. We used multivariable logistic regression models to assess COVID-19-related hospitalization risk by vaccination status and age group among confirmed COVID-19 cases.

Results: Of the 162,509 COVID-19 cases included in the analysis, 8,546 (5.3%) required hospitalization. Among vaccinated individuals, an increased odds of hospitalization with increasing age was observed for older age groups, namely those aged 50-59 years (odds ratio [OR] = 2.95, 95% confidence interval [CI]: 2.01-4.33), 60-69 years (OR = 4.82, 95% CI: 3.29, 7.07), 70-79 years (OR = 11.92, 95% CI: 8.02, 17.71), and ≥80 years (OR = 24.25, 95% CI: 16.02, 36.71). However, among unvaccinated individuals, there was a graded increase in odds of hospitalization with increasing age, starting at age group 30-39 years (OR = 2.14, 95% CI: 1.90, 2.41) to ≥80 years (OR = 41.95, 95% CI: 35.43, 49.67). Also, comparing all the age groups to the youngest, the observed magnitude of association was much higher among unvaccinated individuals than vaccinated ones.

Conclusion: Alongside a number of comorbidities, our findings showed a strong association between age and COVID-19-related hospitalization, regardless of vaccination status. However, age-related hospitalization risk was reduced two-fold by vaccination, highlighting the need for vaccination in reducing the risk of severe disease and subsequent COVID-19-related hospitalization across all population groups.

1. Introduction

As of July 24, 2022, over 560 million confirmed cases of COVID-19 have been reported worldwide, with over 6 million deaths. Almost four million confirmed cases, including 42,215 deaths, have been reported in Canada alone [1]. In British Columbia (BC), Canada's third largest province by population size, over 370, 000 cases have been recorded, with over 3,855 deaths as of July 24, 2022 [2]. Although vaccination roll-out and uptake have reduced COVID-19 disease burden in many jurisdictions, prompting the opening of economies and a return to normalcy, the effects of COVID-19 are far from over.

Hospitalization is commonly used as a measure of COVID-19 severity. Since the beginning of the pandemic, there has been an emergence of a growing number of studies assessing the risk factors of COVID-19 hospitalization. These studies have established certain key risk factors; prominent among them are age, sex, and certain comorbidities. However, most of these studies were hospital-based [3–5], with few population-based studies involving all diagnosed patients in a jurisdiction. Vaccination has resulted in

* Corresponding authors.
E-mail addresses: Hector.Velasquez@bccdc.ca (H.A. Velásquez García), Naveed.janjua@bccdc.ca (N.Z. Janjua).

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the prevention of severe disease that would lead to hospitalization, intensive care unit (ICU) admission, and mortality [6,7]. However, it was not very well established during the time of high vaccine effectiveness, which population groups remained at the risk of hospitalization, and whether these risk factors and the magnitude of association differed by vaccination status. These data could identify candidates for additional interventions, such as pharmacotherapy, to reduce the risk of hospitalization and severe disease. In addition, this evidence will help improve health outcomes and maintain health system capacity. Therefore, the aim of this study was to assess COVID-19-related hospitalization risk by vaccine status and age among confirmed COVID-19 cases during the period of high vaccine effectiveness.

2. Materials and methods

2.1. Study design and data sources

We used data from the BC COVID-19 Cohort (BCC19C; https://a4ph.med.ubc.ca/projects-and-initiatives/bc-covid-19-cohort/]), a population-based data platform that has been established as a public health surveillance system under the BC Centre for Disease Control's public health mandate [8]. The BCC19C integrates data on all individuals tested for COVID-19 in BC, with data on COVID-19 hospital and ICU admissions, medical visits, hospitalizations, emergency room visits, chronic conditions, prescription drugs, and mortality (see Appendix A of the Supplementary file).

2.2. Study population

This analysis included all adult individuals (aged 18 or older) who tested positive for SARS-CoV-2 by real-time reverse transcription-polymerase chain reaction from January 01, 2021 to December 31, 2021. During this period, vaccination coverage (at least two doses) for all eligible ages ranged from 2% as of January 2021 to 80% as of December 2021 [9]. We excluded from the analysis the individuals who reside in long-term care facilities because these individuals are very different from the general population with respect to their exposure risk and disease severity, given their comorbidity profile and characteristics. In addition, the transfer of these patients to hospitals was irregular over time and across local regions.

2.3. Outcome and exposures

The outcome of interest for the study was hospitalization or ICU admission with a positive SARS-CoV-2 test within 14 days before or up to 3 days after hospitalization. We excluded nosocomial cases flagged in notifiable disease reporting systems and SARS-CoV-2-positive cases with specimen collection >3 days after hospital admission [6].

The following comorbidities and risk factors were assessed using medical visits, hospitalization, and/or prescription drugs: Alzheimer's disease/dementia, asthma, chronic heart disease: acute myocardial infarction, angina, heart failure, ischemic myocardial infarction, chronic obstructive pulmonary disease (COPD), cirrhosis, chronic kidney disease (CKD), depression, diabetes (categorized as no diabetes, non-insulin dependent, and insulin), epilepsy, gout, hypertension, stroke (ischemic, hemorrhagic, transitory ischemic attack), mood and anxiety disorders, osteoarthritis, osteoporosis, Parkinsonism, rheumatoid arthritis, substance use disorder, injection drug use (IDU), problematic alcohol use, cancer, immunosuppression, intellectual and developmental disabilities, and schizophrenia and psychotic disorders (SZP).

Other factors taken into account for this analysis were age, vaccination status (categorized as not vaccinated or based on the timing of infection relative to receipt of dose as follows: partially vaccinated: ≥14 days after first dose or vaccinated: ≥14 days after second dose), and variant of concern (VOC; details about genomic sequence analysis can be found elsewhere) [10]. Variable definitions and diagnostic codes used to identify comorbidities are presented in Appendix B of the Supplementary file.

2.4. Statistical analysis

We compared the demographic characteristics and comorbidities among the overall analytic sample, those requiring ambulatory care, and those requiring hospitalization (Table 1). We also summarized the distribution of characteristics among unvaccinated adult cases (Table 2) and among vaccinated adult cases (Table 3). Age was summarized in terms of median and interquartile range (IQR) and categorized for the analyses. Categorical variables were summarized as frequencies and percentages.

We assessed the risk factors associated with hospital admission by estimating odds ratios (ORs) through multivariable logistic regression models and then stratified our analysis by vaccination status. These results are presented in Figure 1 and the tables for these models, as well as the analyses stratified by age groups, are presented in Tables S2-S10 of Appendix C of the Supplementary file. We also performed additional sensitivity analyses to examine the potential waning effect of vaccination by stratifying our analyses by time since full vaccination status. The results of these analyses are presented in Tables S11-S14 of Appendix C of the Supplementary file.

3. Results

3.1. Demographic characteristics

The characteristics of the study population are presented in Table 1. Of the 162,509 cases included in the analysis, 153,963 (94.7%) were ambulatory cases and the remaining 8,546 (5.3%) were hospital admissions. Although the male sex represented only a slightly greater proportion of the overall confirmed COVID-19 cases (50.2%), it represented an even greater proportion (57.2%) of the hospitalized cases. The overall median age of COVID-19 cases was 38 years (IQR: 28-52); the median age of hospitalized cases was 60 years (IQR: 45-72). The highest proportion of ambulatory cases was in the 20-29 years age group (27.5%), but the highest proportion of cases requiring hospitalization admission was in the 60-69 years age group (20.3%).

3.2. Risk factors

We found a higher proportion of comorbidities among hospitalized cases than ambulatory cases; respectively, asthma (18.3% vs 13.3%), cirrhosis (2.7% vs 0.3%), COPD (10.3% vs 1.4%), obesity (5.6% vs 2.7%), myocardial infarction (4.7% vs 0.7%), chronic heart disease (19.1% vs 3.6%), heart failure (7.9% vs 0.8%), hypertension (40.1% vs 11.3%), ischemic heart disease (16.5% vs 3.3%), problematic alcohol use (14.0% vs 5.4%), immunosuppression (6.6% vs 2.3%), depression (38.8% vs 24.8%), intellectual and developmental disability (1.2% vs 0.6%), epilepsy (1.9% vs 0.8%), Parkinsonism (0.6% vs 0.1%), rheumatoid arthritis (3.2% vs 1.0%), and SZP (5.5% vs 1.4%). Also, there was a higher proportion of individuals with IDU among hospitalized cases than ambulatory cases (13.8% vs 5.4%). The Delta variant represented 25.0% of the ambulatory cases but a greater percentage of hospital admissions (37.2%). Although 58.6% of ambulatory cases were unvaccinated, an even greater proportion (76.2%) of the hospitalized cases were unvaccinated individuals. Vaccinated individuals represented only 10.6% of the hospitalized cases compared with 30.9% among the ambulatory cases (Table 1).

Table 1
Distribution of characteristics in confirmed (lab-tested) COVID-19 adult cases during 2021, British Columbia COVID-19 Cohort.

		Ambulatory (N = 153,963)	Hospitalized (N = 8546)	Overall (N = 162,509)	*P*-value
Sex	Female	77,213 (50.2%)	3,656 (42.8%)	80,869 (49.8%)	<0.001
	Male	76,750 (49.8%)	4,890 (57.2%)	81,640 (50.2%)	
Age (years)	Median (Q1-Q3)	37 (27-50)	60 (45-72)	38 (28-52)	<0.001
Age group	<20 Years	5852 (3.8%)	41 (0.5%)	5,893 (3.6%)	<0.001
	20-29 Years	42,304 (27.5%)	533 (6.2%)	42,837 (26.4%)	
	30-39 Years	37,305 (24.2%)	1003 (11.7%)	38,308 (23.6%)	
	40-49 Years	27,722 (18.0%)	1,114 (13.0%)	28,836 (17.7%)	
	50-59 Years	21,223 (13.8%)	1,534 (18.0%)	22,757 (14.0%)	
	60-69 Years	12,939 (8.4%)	1,739 (20.3%)	14,678 (9.0%)	
	70-79 Years	4925 (3.2%)	1,465 (17.1%)	6,390 (3.9%)	
	80+ Years	1693 (1.1%)	1,117 (13.1%)	2,810 (1.7%)	
Health authority	Fraser	69,169 (44.9%)	3,542 (41.4%)	72,711 (44.7%)	<0.001
	Interior	25,138 (16.3%)	1,703 (19.9%)	26,841 (16.5%)	
	Northern	11,781 (7.7%)	1,143 (13.4%)	12,924 (8.0%)	
	Vanc. Coastal	34,369 (22.3%)	1,546 (18.1%)	35,915 (22.1%)	
	Vanc. Island	12,283 (8.0%)	603 (7.1%)	12,886 (7.9%)	
	Unknown	1,223 (0.8%)	9 (0.1%)	1232 (0.8%)	
Income (quintile, 1 = low - 5 = high)	1st	28,991 (18.8%)	2,579 (30.2%)	31,570 (19.4%)	<0.001
	2nd	29,034 (18.9%)	1,785 (20.9%)	30,819 (19.0%)	
	3rd	28,296 (18.4%)	1,503 (17.6%)	29,799 (18.3%)	
	4th	28,433 (18.5%)	1,285 (15.0%)	29,718 (18.3%)	
	5th	25,721 (16.7%)	1,021 (11.9%)	26,742 (16.5%)	
	Unknown	13,488 (8.8%)	373 (4.4%)	13,861 (8.5%)	
Material deprivation index (quintile, 1 = less deprived - 5 = more deprived)	1st	25,338 (16.5%)	983 (11.5%)	26,321 (16.2%)	<0.001
	2nd	28,965 (18.8%)	1,345 (15.7%)	30,310 (18.7%)	
	3rd	27,316 (17.7%)	1,583 (18.5%)	28,899 (17.8%)	
	4th	27,585 (17.9%)	1,805 (21.1%)	29,390 (18.1%)	
	5th	25,605 (16.6%)	25,605 (16.6%)	27,494 (16.9%)	
	Unknown	19,154 (12.4%)	941 (11.0%)	20,095 (12.4%)	
Social deprivation index (quintile, 1 = less deprived - 5 = more deprived)	1st	31,012 (20.1%)	1,552 (18.2%)	32,564 (20.0%)	<0.001
	2nd	29,379 (19.1%)	1,486 (17.4%)	30,865 (19.0%)	
	3rd	23,983 (15.6%)	1,306 (15.3%)	25,289 (15.6%)	
	4th	23,595 (15.3%)	1,345 (15.7%)	24,940 (15.3%)	
	5th	26,840 (17.4%)	1,916 (22.4%)	28,756 (17.7%)	
	Unknown	19,154 (12.4%)	941 (11.0%)	20,095 (12.4%)	
Asthma		20,521 (13.3%)	1,568 (18.3%)	22,089 (13.6%)	<0.001
Cirrhosis		538 (0.3%)	230 (2.7%)	768 (0.5%)	<0.001
Cancer, lymphoma		706 (0.5%)	172 (2.0%)	878 (0.5%)	<0.001
Cancer, solid		15,917 (10.3%)	1,799 (21.1%)	17,716 (10.9%)	<0.001
Cancer, metastatic		2,903 (1.9%)	459 (5.4%)	3362 (2.1%)	<0.001
Chronic kidney disease		4,230 (2.7%)	1605 (18.8%)	5,835 (3.6%)	<0.001
Chronic obstructive pulmonary disease		2,107 (1.4%)	876 (10.3%)	2983 (1.8%)	<0.001
Diabetes	No diabetes	144,493 (93.8%)	6412 (75.0%)	150,905 (92.9%)	<0.001
	Non-insulin dependent	7,817 (5.1%)	1,487 (17.4%)	9,304 (5.7%)	
	Insulin- dependent	1,653 (1.1%)	647 (7.6%)	2,300 (1.4%)	
Obesity		4,219 (2.7%)	479 (5.6%)	4698 (2.9%)	<0.001
Malnutrition		2,283 (1.5%)	427 (5.0%)	2,710 (1.7%)	<0.001
Myocardial infarct (acute)		1,124 (0.7%)	399 (4.7%)	1,523 (0.9%)	<0.001
Chronic heart disease (combined)		5,538 (3.6%)	1,630 (19.1%)	7,168 (4.4%)	<0.001
Heart failure		1,276 (0.8%)	671 (7.9%)	1,947 (1.2%)	<0.001
Hypertension		17,415 (11.3%)	3,430 (40.1%)	20,845 (12.8%)	<0.001
Ischemic heart disease (combined)		5,037 (3.3%)	1,408 (16.5%)	6,445 (4.0%)	<0.001
Problematic alcohol use		8,276 (5.4%)	1,200 (14.0%)	9,476 (5.8%)	<0.001
Injection drug use		8,328 (5.4%)	1179 (13.8%)	9,507 (5.9%)	<0.001
Immunosuppression		3,513 (2.3%)	561 (6.6%)	4,074 (2.5%)	<0.001
Alzheimer/dementia		234 (0.2%)	155 (1.8%)	389 (0.2%)	<0.001
Depression		38,208 (24.8%)	3,315 (38.8%)	41,523 (25.6%)	<0.001
Intellectual & developmental disability		895 (0.6%)	106 (1.2%)	1,001 (0.6%)	<0.001
Epilepsy		1,186 (0.8%)	160 (1.9%)	1,346 (0.8%)	<0.001
Parkinsonism		85 (0.1%)	51 (0.6%)	136 (0.1%)	<0.001
Rheumatoid arthritis		1,466 (1.0%)	273 (3.2%)	1,739 (1.1%)	<0.001
Schizophrenia & psychotic disorders		2,150 (1.4%)	466 (5.5%)	2,616 (1.6%)	<0.001
Variant of concern	Non-variant of concern	9,353 (6.1%)	556 (6.5%)	9,909 (6.1%)	<0.001
	Alpha	17,270 (11.2%)	1003 (11.7%)	18,273 (11.2%)	
	Beta	98 (0.1%)	7 (0.1%)	105 (0.1%)	
	Gamma	12,827 (8.3%)	1,083 (12.7%)	13,910 (8.6%)	
	Delta	38,540 (25.0%)	3,180 (37.2%)	41,720 (25.7%)	
	Omicron	6,958 (4.5%)	100 (1.2%)	7,058 (4.3%)	
	Not sequenced	68,917 (44.8%)	2,617 (30.6%)	71,534 (44.0%)	
Vaccination status	Not vaccinated	90,252 (58.6%)	6,508 (76.2%)	96,760 (59.5%)	<0.001
	Partially vaccinated	16,063 (10.4%)	1,136 (13.3%)	17,199 (10.6%)	
	Vaccinated	47,648 (30.9%)	902 (10.6%)	48,550 (29.9%)	

Vanc. = Vancouver

Table 2
Distribution of characteristics in confirmed (lab-tested) COVID-19 unvaccinated adult cases during 2021, British Columbia COVID-19 Cohort.

		Ambulatory (N = 90,252)	Hospitalized (N = 6508)	Overall (N = 96,760)	*P*-value
Sex	Female	43,140 (47.8%)	2,797 (43.0%)	45,937 (47.5%)	<0.001
	Male	47,112 (52.2%)	3,711 (57.0%)	50,823 (52.5%)	
Age (years)	Median (Q1-Q3)	36 (27-49)	57 (43-70)	37 (27-51)	<0.001
Age group	<20 Years	26,285 (29.1%)	437 (6.7%)	26,722 (27.6%)	<0.001
	20-29 Years	3,825 (4.2%)	35 (0.5%)	3,860 (4.0%)	
	30-39 Years	22,419 (24.8%)	857 (13.2%)	23,276 (24.1%)	
	40-49 Years	15,835 (17.5%)	955 (14.7%)	16,790 (17.4%)	
	50-59 Years	11,918 (13.2%)	1,253 (19.3%)	13,171 (13.6%)	
	60-69 Years	6889 (7.6%)	1,338 (20.6%)	8227 (8.5%)	
	70-79 Years	2,410 (2.7%)	1,010 (15.5%)	3420 (3.5%)	
	80+ Years	671 (0.7%)	623 (9.6%)	1,294 (1.3%)	
Health authority	Fraser	42,259 (46.8%)	2,745 (42.2%)	45,004 (46.5%)	<0.001
	Interior	15,074 (16.7%)	1,310 (20.1%)	16,384 (16.9%)	
	Northern	7,491 (8.3%)	910 (14.0%)	8,401 (8.7%)	
	Vanc. Coastal	19,603 (21.7%)	1,118 (17.2%)	20,721 (21.4%)	
	Vanc. Island	5,481 (6.1%)	420 (6.5%)	5,901 (6.1%)	
	Unknown	344 (0.4%)	5 (0.1%)	349 (0.4%)	
Income (quintile, 1 = low - 5 = high)	1st	17,930 (19.9%)	1,870 (28.7%)	19,800 (20.5%)	<0.001
	2nd	17,924 (19.9%)	1,370 (21.1%)	19,294 (19.9%)	
	3rd	16,373 (18.1%)	1,177 (18.1%)	17,550 (18.1%)	
	4th	15,659 (17.4%)	998 (15.3%)	16,657 (17.2%)	
	5th	13,163 (14.6%)	782 (12.0%)	13,945 (14.4%)	
	Unknown	9,203 (10.2%)	311 (4.8%)	9,514 (9.8%)	
Material deprivation index (quintile, 1 = less deprived - 5 = more deprived)	1st	12,901 (14.3%)	716 (11.0%)	13,617 (14.1%)	<0.001
	2nd	15,363 (17.0%)	1,027 (15.8%)	16,390 (16.9%)	
	3rd	15,490 (17.2%)	1,225 (18.8%)	16,715 (17.3%)	
	4th	16,873 (18.7%)	1,416 (21.8%)	18,289 (18.9%)	
	5th	17,199 (19.1%)	1,426 (21.9%)	18,625 (19.2%)	
	Unknown	12,426 (13.8%)	698 (10.7%)	13,124 (13.6%)	
Social deprivation index (quintile, 1 = less deprived - 5 = more deprived)	1st	18,749 (20.8%)	1,207 (18.5%)	19,956 (20.6%)	<0.001
	2nd	16,844 (18.7%)	1,132 (17.4%)	17,976 (18.6%)	
	3rd	13,403 (14.9%)	1,008 (15.5%)	14,411 (14.9%)	
	4th	13,437 (14.9%)	1,031 (15.8%)	14,468 (15.0%)	
	5th	15,393 (17.1%)	1,432 (22.0%)	16,825 (17.4%)	
	Unknown	12,426 (13.8%)	698 (10.7%)	13,124 (13.6%)	
Asthma		11,293 (12.5%)	1,123 (17.3%)	12,416 (12.8%)	<0.001
Cirrhosis		299 (0.3%)	144 (2.2%)	443 (0.5%)	<0.001
Cancer, lymphoma		339 (0.4%)	97 (1.5%)	436 (0.5%)	<0.001
Cancer, solid		8525 (9.4%)	1,214 (18.7%)	9739 (10.1%)	<0.001
Cancer, metastatic		1544 (1.7%)	289 (4.4%)	1833 (1.9%)	<0.001
Chronic kidney disease		2,082 (2.3%)	983 (15.1%)	3065 (3.2%)	<0.001
Chronic obstructive pulmonary disease		1,045 (1.2%)	516 (7.9%)	1,561 (1.6%)	<0.001
Diabetes	No diabetes	85,162 (94.4%)	5,087 (78.2%)	90,249 (93.3%)	<0.001
	Non-insulin dependent	4,271 (4.7%)	1,005 (15.4%)	5276 (5.5%)	
	Insulin dependent	819 (0.9%)	416 (6.4%)	1235 (1.3%)	
Obesity		2170 (2.4%)	357 (5.5%)	2,527 (2.6%)	<0.001
Malnutrition		1,245 (1.4%)	271 (4.2%)	1,516 (1.6%)	<0.001
Myocardial infarct (acute)		587 (0.7%)	263 (4.0%)	850 (0.9%)	<0.001
Chronic heart disease (combined)		2,838 (3.1%)	1,038 (15.9%)	3,876 (4.0%)	<0.001
Heart failure		635 (0.7%)	383 (5.9%)	1,018 (1.1%)	<0.001
Hypertension		9,152 (10.1%)	2,298 (35.3%)	11,450 (11.8%)	<0.001
Ischemic heart disease (combined)		2,588 (2.9%)	903 (13.9%)	3,491 (3.6%)	<0.001
Problematic alcohol use		5,353 (5.9%)	885 (13.6%)	6,238 (6.4%)	<0.001
Injection drug use		5,550 (6.1%)	888 (13.6%)	6,438 (6.7%)	<0.001
Immunosuppression		1,925 (2.1%)	344 (5.3%)	2,269 (2.3%)	<0.001
Alzheimer/dementia		115 (0.1%)	78 (1.2%)	193 (0.2%)	<0.001
Depression		21,716 (24.1%)	2,456 (37.7%)	24,172 (25.0%)	<0.001
Intellectual & developmental disability		576 (0.6%)	83 (1.3%)	659 (0.7%)	<0.001
Epilepsy		701 (0.8%)	109 (1.7%)	810 (0.8%)	<0.001
Parkinsonism		43 (0.0%)	24 (0.4%)	67 (0.1%)	<0.001
Rheumatoid arthritis		779 (0.9%)	174 (2.7%)	953 (1.0%)	<0.001
Schizophrenia & psychotic disorders		1,424 (1.6%)	339 (5.2%)	1763 (1.8%)	<0.001
Variant of concern	Non-variant of concern	8,432 (9.3%)	474 (7.3%)	8,906 (9.2%)	<0.001
	Alpha	14,393 (15.9%)	789 (12.1%)	15,182 (15.7%)	
	Beta	83 (0.1%)	<5 (0.1%)	87 (0.1%)	
	Gamma	10,243 (11.3%)	792 (12.2%)	11,035 (11.4%)	
Delta	Delta	18,580 (20.6%)	2,341 (36.0%)	20,921 (21.6%)	
	Omicron	442 (0.5%)	15 (0.2%)	457 (0.5%)	
	Not sequenced	38,079 (42.2%)	2,093 (32.2%)	40,172 (41.5%)	

Vanc. = Vancouver

Table 3
Distribution of characteristics in confirmed (lab-tested) COVID-19 vaccinated[a] adult cases during 2021, British Columbia COVID-19 Cohort.

		Ambulatory (N = 47,648)	Hospitalized (N = 902)	Overall (N = 48,550)	*P*-value
Sex	Female	25,757 (54.1%)	368 (40.8%)	26,125 (53.8%)	<0.001
	Male	21,891 (45.9%)	534 (59.2%)	22,425 (46.2%)	
Age (years)	Median (Q1-Q3)	39 (29-52)	70 (56-80)	39 (29-53)	<0.001
Age group	<20 Years	11,699 (24.6%)	38 (4.2%)	11,737 (24.2%)	<0.001
	20-29 Years	1,416 (3.0%)	<5 (0.4%)	1420 (2.9%)	
	30-39 Years	11,345 (23.8%)	62 (6.9%)	11,407 (23.5%)	
	40-49 Years	9,131 (19.2%)	55 (6.1%)	9,186 (18.9%)	
	50-59 Years	7,082 (14.9%)	114 (12.6%)	7,196 (14.8%)	
	60-69 Years	4,627 (9.7%)	177 (19.6%)	4,804 (9.9%)	
	70-79 Years	1,677 (3.5%)	210 (23.3%)	1,887 (3.9%)	
	80+ Years	671 (1.4%)	242 (26.8%)	913 (1.9%)	
Health authority	Fraser	20,076 (42.1%)	333 (36.9%)	20,409 (42.0%)	<0.001
	Interior	6,720 (14.1%)	200 (22.2%)	6,920 (14.3%)	
	Northern	2,941 (6.2%)	116 (12.9%)	3,057 (6.3%)	
	Vanc. Coastal	11,459 (24.0%)	157 (17.4%)	11,616 (23.9%)	
	Vanc. Island	5621 (11.8%)	95 (10.5%)	5,716 (11.8%)	
	Unknown	831 (1.7%)	<5 (0.1%)	832 (1.7%)	
Income (quintile, 1 = low - 5 = high)	1st	7,664 (16.1%)	312 (34.6%)	7,976 (16.4%)	<0.001
	2nd	7,920 (16.6%)	183 (20.3%)	8,103 (16.7%)	
	3rd	9,048 (19.0%)	129 (14.3%)	9,177 (18.9%)	
	4th	9,923 (20.8%)	140 (15.5%)	10,063 (20.7%)	
	5th	10,137 (21.3%)	112 (12.4%)	10,249 (21.1%)	
	Unknown	2956 (6.2%)	26 (2.9%)	2,982 (6.1%)	
Material deprivation index (quintile, 1 = less deprived - 5 = more deprived)	1st	10,024 (21.0%)	125 (13.9%)	10,149 (20.9%)	<0.001
	2nd	10,663 (22.4%)	143 (15.9%)	10,806 (22.3%)	
	3rd	9,018 (18.9%)	153 (17.0%)	9,171 (18.9%)	
	4th	7,784 (16.3%)	162 (18.0%)	7,946 (16.4%)	
	5th	5451 (11.4%)	192 (21.3%)	5,643 (11.6%)	
	Unknown	4,708 (9.9%)	127 (14.1%)	4,835 (10.0%)	
Social deprivation index (quintile, 1 = less deprived - 5 = more deprived)	1st	9,127 (19.2%)	138 (15.3%)	9,265 (19.1%)	<0.001
	2nd	9,560 (20.1%)	153 (17.0%)	9,713 (20.0%)	
	3rd	7,990 (16.8%)	130 (14.4%)	8,120 (16.7%)	
	4th	7,676 (16.1%)	132 (14.6%)	7,808 (16.1%)	
	5th	8,587 (18.0%)	222 (24.6%)	8,809 (18.1%)	
	Unknown	4,708 (9.9%)	127 (14.1%)	4,835 (10.0%)	
Asthma		6,879 (14.4%)	205 (22.7%)	7,084 (14.6%)	<0.001
Cirrhosis		165 (0.3%)	43 (4.8%)	208 (0.4%)	<0.001
Cancer, lymphoma		269 (0.6%)	43 (4.8%)	312 (0.6%)	<0.001
Cancer, solid		5,523 (11.6%)	303 (33.6%)	5826 (12.0%)	<0.001
Cancer, metastatic		1,011 (2.1%)	100 (11.1%)	1,111 (2.3%)	<0.001
Chronic kidney disease		1,509 (3.2%)	302 (33.5%)	1,811 (3.7%)	<0.001
Chronic obstructive pulmonary disease		770 (1.6%)	191 (21.2%)	961 (2.0%)	<0.001
Diabetes (treatment)	No diabetes mellitus	44,686 (93.8%)	578 (64.1%)	45,264 (93.2%)	<0.001
	Non-insulin dependent	2,388 (5.0%)	205 (22.7%)	2,593 (5.3%)	
	Insulin dependent	574 (1.2%)	119 (13.2%)	693 (1.4%)	
Obesity		1555 (3.3%)	61 (6.8%)	1616 (3.3%)	<0.001
Malnutrition		748 (1.6%)	82 (9.1%)	830 (1.7%)	<0.001
Myocardial infarct (acute)		376 (0.8%)	71 (7.9%)	447 (0.9%)	<0.001
Chronic heart disease (combined)		1900 (4.0%)	295 (32.7%)	2195 (4.5%)	<0.001
Heart failure		441 (0.9%)	161 (17.8%)	602 (1.2%)	<0.001
Hypertension		5,889 (12.4%)	530 (58.8%)	6,419 (13.2%)	<0.001
Ischemic heart disease (combined)		1,722 (3.6%)	246 (27.3%)	1,968 (4.1%)	<0.001
Problematic alcohol use		1,843 (3.9%)	122 (13.5%)	1,965 (4.0%)	<0.001
Injection drug use		1,612 (3.4%)	103 (11.4%)	1,715 (3.5%)	<0.001
Immunosuppression		1,174 (2.5%)	108 (12.0%)	1,282 (2.6%)	<0.001
Alzheimer/dementia		68 (0.1%)	42 (4.7%)	110 (0.2%)	<0.001
Depression		11,974 (25.1%)	369 (40.9%)	12,343 (25.4%)	<0.001
Intellectual & developmental disability		202 (0.4%)	12 (1.3%)	214 (0.4%)	<0.001
Epilepsy		354 (0.7%)	23 (2.5%)	377 (0.8%)	<0.001
Parkinsonism		30 (0.1%)	14 (1.6%)	44 (0.1%)	<0.001
Rheumatoid arthritis		474 (1.0%)	53 (5.9%)	527 (1.1%)	<0.001
Schizophrenia & psychotic disorders		401 (0.8%)	38 (4.2%)	439 (0.9%)	<0.001
Variant of concern		27 (0.1%)	<5 (0%)	27 (0.1%)	NA
	Alpha	72 (0.2%)	2 (0.2%)	74 (0.2%)	
	Beta	0 (0%)	0 (0%)	0 (0%)	
	Gamma	69 (0.1%)	<5 (0.4%)	73 (0.2%)	
	Delta	14,008 (29.4%)	573 (63.5%)	14,581 (30.0%)	
	Omicron	6442 (13.5%)	82 (9.1%)	6524 (13.4%)	
	Not sequenced	27,030 (56.7%)	27,030 (56.7%)	27,271 (56.2%)	

[a] 14 days or more after second vaccine dose.Vanc. = Vancouver

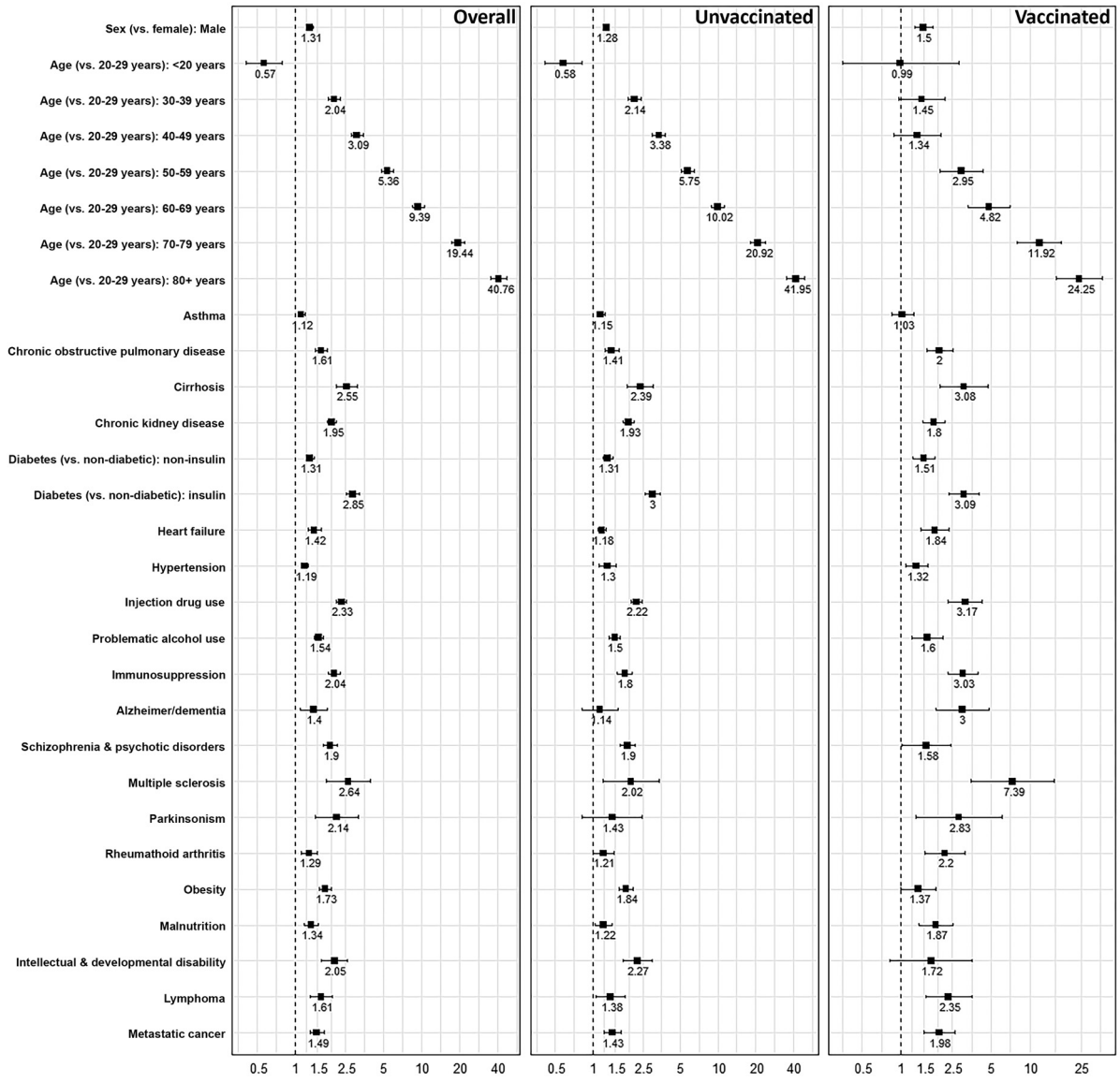

Figure 1. Factors associated with hospitalization status in multivariable logistic regression analysis among confirmed COVID-19 adult cases during 2021, BC COVID-19 Cohort. *Odds ratios adjusted for the variables presented in the figure, as well as Health Authority, income (dissemination area level), and variant of concern. In addition, odds ratios for the "overall" are adjusted for vaccination status.

In the adjusted logistic regression model (Table S2; Figure 1), age (*P*-trend <0.001 across age groups with increasing risk with older age [adjusted OR (aOR), age 30-39 years = 2.04; 95% CI: 1.83-2.27, to aOR age >80 years = 40.76; 95% CI: 35.50-46.79 compared with age 20-29 years), male sex (aOR = 1.31; 95% CI: 1.25-1.38), asthma (aOR = 1.12; 95% CI: 1.05-1.20), COPD (aOR = 1.61; 95% CI: 1.45, 1.78), cirrhosis (aOR = 2.55; 95% CI: 2.11-3.08), CKD (aOR = 1.95; 95% CI: 1.80-2.11), diabetes (non-insulin dependent), aOR = 1.31; 95% CI: 1.22-1.42, insulindependent aOR = 2.85; 95% CI: 2.54-3.20), hypertension (aOR = 1.19; 95% CI: 1.12-1.27), heart failure (aOR = 1.42; 95% CI: 1.26-1.60), IDU (aOR = 2.33; 95% CI: 2.13-2.56), problematic alcohol use (aOR = 1.54; 95% CI: 1.41-1.68), immunosuppression (aOR = 2.04; 95% CI: 1.83-2.29), Alzheimer disease/dementia (aOR = 1.40; 95% CI: 1.09-1.78), SZP (aOR = 1.90; 95% CI: 1.68-2.16), multiple sclerosis (aOR = 2.64; 95% CI: 1.77-3.96), Parkinsonism (aOR = 2.14, 95% CI: 1.43-3.19), rheumatoid arthritis (aOR = 1.29, 95% CI: 1.11-1.51), obesity (aOR = 1.73, 95% CI: 1.55-1.94), weight loss (aOR = 1.34, 95% CI: 1.18-1.52), intellectual and developmental disability (aOR = 2.05, 95% CI: 1.62-2.59), lymphoma (aOR = 1.61, 95% CI: 1.31-1.97), and metastatic cancer (aOR = 1.49, 95% CI: 1.32-1.69) were significantly associated with increased hospitalization.

Also, compared with non-VOC lineage, the Delta (aOR = 3.22; 95% CI: 2.90-3.59), Alpha (aOR = 1.65, 95% CI: 1.46-1.86), Gamma (aOR = 3.09, 95% CI: 2.74-3.49), Omicron (aOR = 2.41; 95% CI: 1.90-3.07), and nonsequenced variants (aOR = 1.25; 95% CI: 1.12-1.39) were significantly associated with increased hospitalization. In addition, compared with no vaccination, full vaccination (aOR = 0.15; 95% CI: 0.14-0.17) and partial vaccination (aOR = 0.52; 95% CI: 0.49-0.57) were associated with reduced odds of hospitalization (Table S2).

3.2.1. Risk factors by vaccination status

The proportion of males in the unvaccinated group was higher than in the vaccinated group (52.5% vs 46.2%). The proportion of males who received ambulatory care was larger in the unvaccinated group than in the vaccinated group (52.2% vs 45.9%). Otherwise, the distribution of characteristics was similar across vaccination status (Table 2 and Table 3).

For vaccinated individuals (Table S4 and Figure 1), an increased odds of hospitalization by increasing age was only observed for older age groups, 50-59 years (aOR = 2.95, 95% CI: 2.01-4.33), 60-69 years (aOR = 4.82, 95% CI: 3.29, 7.07), 70-79 years (aOR = 11.92, 95% CI: 8.02- 17.71), and ≥80 years (aOR = 24.25, 95% CI: 16.02, 36.71). However, for unvaccinated adult cases (Table S3 and Figure 1), there was a graded increase in the odds of hospitalization with age, starting at age group 30-39 years. In addition, the magnitude of association of each age was much stronger among unvaccinated individuals than among vaccinated individuals (Figure 1).

Although the comorbidity risk factors for hospitalization were similar among vaccinated and unvaccinated individuals, the magnitude of association (aORs) for many of the risk factors were higher among vaccinated individuals than unvaccinated individuals: COPD (2.00 vs 1.41), cirrhosis (3.08 vs 2.39), IDU (3.17 vs 2.22), immunosuppression (3.03 vs 1.80), multiple sclerosis (7.39 vs 2.02), rheumatoid arthritis (2.20 vs 1.21), weight loss (1.87 vs 1.22), lymphoma (2.35 vs 1.38), and metastatic cancer (1.98 vs 1.43), respectively. CKD (aORs = 1.80 vs 1.93), obesity (1.37 vs 1.84), and SZP (1.58 vs 1.90) were the only conditions whose magnitude of association were higher among unvaccinated individuals than vaccinated individuals. Furthermore, asthma was a significant risk factor among unvaccinated individuals but not for vaccinated individuals (Table S3 and Table S4).

3.2.2. Risk factors by age group

The magnitude of association (aORs) for most of the comorbidities was highest for the youngest age group (18-49 years) than the two older age groups (50-69 years and ≥80 years): COPD (2.88 vs 1.80 vs 1.76), cirrhosis (3.73 vs 2.56 vs 1.71), CKD (2.48 vs 2.44 vs 1.84), non-insulin dependent diabetes (2.23 vs 1.38 vs 1.17), insulin-dependent diabetes (3.85 vs 3.17 vs 2.03), heart failure (2.11 vs 1.38 vs 1.55), hypertension (1.79 vs 1.33 vs 1.12), problematic alcohol use (1.62 vs 1.36 vs 1.52), immunosuppression (2.08 vs 1.88 vs 1.92), SZP (2.17 vs 1.51 vs 1.89), intellectual and developmental disability (1.48 vs 2.28 vs 0), lymphoma cancer (2.09 vs 1.46 vs 1.57), and metastatic cancer (1.67 vs 1.71 vs 1.30), respectively (Table S6, Table S8, and Table S10).

Although being vaccinated was associated with reduced odds of hospitalization across the three stratified age groups, the benefit of being vaccinated appeared to be greatest among the 50-69 years age group (aOR = 0.13; 95% CI: 0.11, 0.15), followed by the 18-49 years age group (aOR = 0.15; 95% CI: 0.13, 0.18), and then ≥70 years age group (aOR = 0.20; 95% CI: 0.17, 0.23) (Table S6, Table S8, and Table S10).

3.3. Sensitivity analyses

The sensitivity analyses did not provide evidence to show that there was a difference by the analyzed vaccination strata, suggesting that there was no significant waning effect of vaccination (Tables S11-S14 of Appendix C of the Supplementary file).

4. Discussion

In this large population-based study, we assessed the risk factors for COVID-19 hospitalization after breakthrough infection among individuals who received vaccination and those who did not receive vaccination using data from 162,509 confirmed COVID-19 adult cases collected from January 1, 2021 to December 31, 2021 in the Canadian province of BC. In our analysis, we found many patient characteristics and comorbidities to be associated with hospitalization. However, the magnitude of association of these characteristics differed between vaccinated and unvaccinated individuals. Older age was the strongest risk factor for hospitalization overall and had a bigger relative impact in unvaccinated than in vaccinated individuals. Indeed, the odds of hospitalization only increased with increasing age from 50-59 years and older in vaccinated individuals, whereas there was a graded increase with increasing age in unvaccinated individuals. The association of various comorbidities was similar or, in some cases, slightly higher among vaccinated individuals for some comorbidities. We also found that compared with non-VOC lineage, the Delta, Alpha, Gamma, and Omicron variants were significantly associated with higher hospitalization risk, which was consistent with other studies [11–14].

We found age to be the strongest independent risk factor for hospitalization, which was consistent with findings from our previous study [8]. A recent rapid review also found age to be the most significant risk factor for severe outcomes, noting that adults aged >60 years may have a five-fold increase in hospitalization and mortality from COVID-19 compared with individuals aged <45 years [15]. Our stratified analysis by vaccination status found that for vaccinated individuals, age as an independent risk factor was only significant for older age groups (>50 years). However, for unvaccinated adults, the increased odds of hospitalization were significant across all the age groups, with a graded increase in the odds of hospitalization with age. Furthermore, the magnitude of association was much higher among unvaccinated individuals than vaccinated individuals, similar to findings from Ontario Province in Canada [16]. This highlights the need for additional interventions among unvaccinated individuals to reduce the risk of severe disease, such as treatment with antiviral agents (e.g., nirmatrelvir/ritonavir). It also highlights the success of vaccination in reducing the increased risk of hospitalization associated with increasing age.

In younger age groups (18-49 years age group), the magnitude of association was higher for many comorbidities than in older age groups. We also found that for most of the comorbidities that we assessed, the magnitude of association between these comorbidities and hospitalization was higher among vaccinated individuals than unvaccinated individuals. The risk of hospitalization present among vaccinated individuals with certain comorbidities, such as cancers, immunosuppression, and rheumatological diseases, have been noted in other studies [17,18]. This may be the result of the underlying immune dysfunction in these conditions or could also be related to the fact that the vaccination roll-out was prioritized for older individuals and individuals with comorbidities [8,19].

A major strength of our study is its large sample size, which enabled us to produce more precise estimates of effect sizes and also increased the representativeness of our findings. Our use of population-based cases rather than hospital or selected cases also reduced potential selection bias and ensured that our findings are generalizable to the general population. In addition, we objectively identified infection status using polymerase chain reaction and assessed VOC through whole genome sequencing. Furthermore, we ascertained vaccination status with the records from the Provincial Immunization Registry, which contains the records for all administered vaccines in BC. Likewise, we were able to assess a wide range of comorbidities and other risk factors using validated algorithms.

Our findings should be interpreted in light of the following limitations. First, there is a possibility for misclassification of patient characteristics and morbidities because of the use of administrative data. Second, the COVID-19 assessment was based on BC testing guidelines, which not only varied over the pandemic period but could also differ from the guidelines of other jurisdictions, thereby limiting the generalizability of our findings to other contexts. Also, even though we considered many variables in our analyses, there is still a potential for unmeasured confounders, which could not be accounted for. In addition, this analysis is limited to those who sought health care/testing and thus may not be representative of the whole population of BC. Also, the testing rates may differ by

vaccination status; however, this was not accounted for. Given that not many people had received booster doses at the time of our study, future studies should focus on disentangling the specific impact of booster doses on COVID-19-related outcomes.

5. Conclusion

To the best of our knowledge, this is one of the largest population-based studies examining the risk factors for hospitalization among patients with COVID-19 after vaccination. Given the higher risk of hospitalization among vaccinated older individuals and those with certain comorbidities, our findings also highlight the need for adding additional layers of protection from severe disease among those at higher risk, with improved access to antiviral treatments, such as nirmatrelvir/ritonavir, and the need for further vaccine booster doses.

Declaration of competing interest

N.Z.J. participated in advisory boards for AbbVie and has spoken for AbbVie and Gilead not related to the current work. The other authors have no competing interests to declare.

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Ethical approval

This study was reviewed and approved by the Research Ethics Board of the University of BC (approval # H20-02097).

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Author contributions

Conceptualization: H.A.V.G. and N.Z.J.; writing-original draft preparation: P.A.A.; methods: H.A.V.G. and N.Z.J.; analysis: H.A.V.G. and P.A.A.; writing - review and editing: P.A.A., H.A.V.G., S.H., J.W., D.R., M.B., H.S., K.S., and N.Z.J.; supervision and project administration: N.Z.J.; funding acquisition: N.Z.J.; all authors have read and agreed to the published version of the manuscript.

Data availability statement

The study is based on data contained in various provincial registries and databases. Access to the data could be requested through the BC Centre for Disease Control Institutional Data Access for researchers who meet the criteria for access to confidential data. Requests for the data may be sent to datarequest@bccdc.ca.

Disclaimer

All inferences, opinions, and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the Data Steward(s).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.12.001.

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