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Outcomes of coronavirus disease 2019 (COVID-19) and risk factors associated with severe COVID-19 in patients with mature B-cell non-Hodgkin lymphomas: A US electronic health record cohort study

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Abstract

Objectives: The objectives of this study were to assess the risk of severe coronavirus disease 2019 (COVID-19) outcomes in patients with mature B-cell non-Hodgkin lymphoma (mature B-cell NHL) compared with other cancers and to identify risk factors associated with severe COVID-19.

Methods: This study used Optum's electronic health record database. Risk factors were evaluated using multivariable logistic regression.

Results: Patients with mature B-cell NHL were more likely to be hospitalized or die from COVID-19 (age- and sex-standardized risk: 15.6%, 2.1%, respectively) than those without cancer (9.5%, 1.2%), or with solid tumors (9.7%, 1.3%). In patients with mature B-cell NHL, factors associated with severe COVID-19 outcomes included: greater age (75–84 years, adjusted odds ratio, 1.6 [95% CI, 1.3–2.0]; ≥85, 2.6 [2.0–3.4]), male sex (1.4 [1.2–1.6]), chronic kidney disease (1.4 [1.1–1.7]), chronic obstructive pulmonary disease (1.3 [1.0–1.6]), type 2 diabetes (1.3 [1.1–1.5]), and receiving treatment for NHL (1.5 [1.1–2.1]).

Conclusions: These data suggest that patients with mature B-cell NHL are at a higher risk of severe COVID-19 than patients with solid tumors or without cancer and that risk factors are largely consistent with those in the general population.

KEYWORDS

COVID-19, epidemiology, hematology, hospitalization, lymphoma, mortality, neoplasms, observational study

Novelty Statements

What is the NEW aspect of your work?

This study evaluated the risk factors associated with severe COVID-19 in the largest known cohort of patients with mature B-cell NHL and COVID-19.

What is the CENTRAL finding of your work?

Patients with mature B-cell NHL are more susceptible to severe COVID-19 outcomes than those with solid tumors or without cancer, and the risk factors for developing severe COVID-19 (greater age, male sex, chronic kidney disease, diabetes mellitus type 2, chronic obstructive pulmonary disease, public health insurance) are similar to those reported in the overall population.

What is (or could be) the SPECIFIC clinical relevance of your work?

This study highlights the importance of using demographics and clinical characteristics to assess COVID-19-related risks of severe disease faced by patients with mature B-cell NHL.

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in approximately 6.3 million deaths worldwide between December 2019 and July 2022.[1] In the general population, risk factors for developing severe COVID-19 include older age, obesity, certain comorbidities (e.g., hypertension, type 2 diabetes mellitus [DM]), and a compromised immune system.[2] Given their weakened immune status and treatment with various cytotoxic and immunomodulatory regimens, patients with cancer are considered to be at increased risk of severe COVID-19 outcomes compared with the general population.[3,4]

Patients with mature B-cell non-Hodgkin lymphoma (mature B-cell NHL) are typically of advanced age, have inherent immune dysfunction, have a high comorbidity burden, and often receive long-term anti-cancer treatments.[5] However, few studies have evaluated the risk of developing severe COVID-19 in patients with mature B-cell NHL. These patients have an increased risk of severe outcomes from COVID-19, and assessing risks factors in this patient population with high comorbidities was important to evaluate. The impact of COVID-19 on this population has been predominantly assessed within studies of patients with various hematological malignancies,[6–10] and as noted in those publications, the studies that did focus on COVID-19 in patients with mature B-cell NHL have been limited by their small sample sizes.[11–16] The objective of this large, retrospective study of electronic health records (EHRs) was to assess the risk of severe COVID-19 outcomes in patients with mature B-cell NHL compared with patients with no cancer or other cancers and to identify the risk factors of severe COVID-19 outcomes in those with mature B-cell NHL.

2 | METHODS

2.1 | Study design and data sources

This retrospective cohort study was conducted using patient-level data from a nationwide Optum de-identified COVID-19 EHR database (Optum, Eden Prairie, MN, USA) collected from January 1, 2007, through April 28, 2021, and included patients diagnosed with COVID-19 between February 1, 2020, and March 31, 2021. The Optum COVID-19 EHR database contains longitudinal patient care data from healthcare provider organizations comprising more than 700 hospitals and 7000 clinics in the United States and captures point-of-care COVID-19-specific diagnostic data, including patient-level and clinical results from both inpatient and ambulatory settings. It includes patients from all 50 US states with all types of health insurance (i.e., Medicare, Medicaid, commercial insurance, self-insurance, and no insurance). The data include patient demographics, comprehensive laboratory test results, and medications prescribed and administered. The Optum EHR database included records for polymerase chain reaction (PCR)-based and antigen-based testing results (verified by a team of medical terminologists and clinicians via manual review) and/or a clinical diagnosis for COVID-19. The patients with COVID-19 without PCR or antigen tests include transferred patients whose confirmatory diagnosis was outside of the treating hospital. These patients are all diagnosed by physicians and assigned the international classification of diseases (ICD) codes per the centers for disease control and prevention (CDC) Coding and Reporting Guidelines.[17] These patients underwent PCR or antigen tests in the pharmacies, clinics, or hospitals that were not in the Optum system.

2.2 | Compliance with ethics guidelines

The authors affirm that this retrospective database analysis did not collect, use, or transmit patient-identifiable data. Based on US Department of Health and Human Services code 45CFR46.104(d)(4) (Existing Data and Specimens—No Identifiers),[18] this study is exempt from the requirement for institutional review board approval. The study is compliant with data security requirements of the Health Insurance Portability and Accountability Act of 1996.

2.3 | Study population

The study included individuals aged ≥18 years who had a COVID-19 diagnosis per ICD (10th Revision) diagnostic codes U07.1 or U07.2[19] or a positive result of a laboratory molecular test (polymerase chain reaction, PCR) or antigen diagnostic test between February 1, 2020, and March 31, 2021. The index date was defined as the first COVID-19 diagnosis date or the first positive molecular or antigen test date, whichever came first. All participants were required to have at least 15 months of continuous enrollment prior to the COVID-19 diagnosis (index date) and 30 days of follow-up after the index date. Patients with missing age or sex data were excluded from the analysis. Eligible

patients with COVID-19 were divided into four cohorts based on their diagnosis prior to COVID-19 infection: (1) patients without cancer, (2) patients with solid tumors, (3) patients with non-mature B-cell NHL, and (4) patients with mature B-cell NHL. Patients with mature B-cell NHL were classified into different subtypes based on ICD-10 codes and World Health Organization classification,[20] including diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), multiple myeloma (MM; a plasma malignancy), primary mediastinal B-cell lymphoma, marginal zone lymphoma, mantle cell lymphoma, and Waldenström macroglobulinemia; the full list of malignancy types for both mature B-cell and non-mature B-cell NHL is listed in Table S1. Only one diagnosis code was required, and the conditions of interest were considered mutually exclusive. Patients with both mature B-cell NHL and another oncologic diagnosis (solid tumor or hematological malignancy, including non-mature B-cell NHL) were included only in the mature B-cell NHL cohort. The follow-up period was at least 30 days after the index date or until a censoring event (i.e., end of active EHR, last date of data capture [April 28, 2021]) or death had occurred (Figure S1).

2.4 | Study variables

Demographic characteristics included age, sex, race, region of residence (Midwest, Northeast, South, and West), insurance type, and time of COVID-19 diagnosis measured on the index date. Comorbidities included cardiovascular diseases, chronic kidney disease, chronic liver diseases, chronic lung diseases, type 2 DM, obesity, and neurological diseases. The Charlson comorbidity index was calculated for a quantitative evaluation of the overall disease burden.[21,22] For patients with mature B-cell NHL, we captured histological subtypes: chronic CLL, SLL, MM, diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, and Waldenström macroglobulinemia. History of mature B-cell NHL treatment at time of COVID-19 diagnosis was also determined and included chemoimmunotherapy, immunotherapy, chemotherapy, Bruton's tyrosine kinase-targeted therapy, and various novel therapies.

2.5 | Outcomes and healthcare utilization

The primary outcome was a composite measure consisting of severe COVID-19 outcomes (hospitalization, intensive care unit admission, acute respiratory insufficiency [ARI], or death) within 30 days of COVID-19 diagnosis.

2.6 | Statistical analyses

Patient demographics and clinical characteristics were summarized using descriptive statistics. Standardized mean difference was used to evaluate the differences in baseline variables (age, sex, race, region of residence, insurance type, comorbidities) between the four cohorts and between patients with mature B-cell NHL who did and did not have severe COVID-19. An absolute standardized mean difference of >0.1 indicates a notable difference between patients with and without severe outcomes. Age- and sex-standardized risks of death, hospitalization, and ARI were calculated by directly standardizing those risks to the age and sex distribution in the general population of the United States in 2010, and the 95% confidence interval was provided.[23]

Univariate analyses were performed to assess the covariate effect of risk factors and severe COVID-19 outcomes. Multivariable logistic regression was performed for the subgroup of patients with mature B-cell NHL to estimate the independent effects of variables, such as age, sex, type of insurance, histological subtype, month of COVID-19 diagnosis, individual comorbidities, and NHL treatments within 30 days prior to COVID-19 diagnosis on the primary outcome. Results were expressed as adjusted odds ratio (aOR) with 95% CI. The analyses were conducted using SAS Studio 3.81 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Patient characteristics

A total of 487 642 individuals with a COVID-19 diagnosis or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were identified (without cancer, $n = 431\,659$; with solid tumors, $n = 48\,609$; with non-mature B-cell NHL, $n = 3781$; with mature B-cell NHL, $n = 3593$) (Figure S2). The majority of SARS-CoV-2 infections were confirmed with laboratory testing results (334 470 [68.6%] with positive PCR tests and 14 798 [3.0%] with positive antigen tests), while the remaining infections (28.4%) were identified based on clinical diagnosis (Figure S3). Demographic and clinical characteristics are summarized in Table 1, and lists of malignancies in different cohorts are included in Table S1. Patients with cancers, especially those with mature B-cell NHL, were significantly older than those without cancer (mean age, 68 years and 48 years, respectively). At least one comorbidity was recorded in 95% of patients with mature B-cell and non-mature B-cell NHL, 92% of patients with solid tumors, and 67% of patients without cancer (Table S2).

In the subset of patients with mature B-cell NHL, 54% were men, 80% were White, and the most common subtypes of mature B-cell NHL were CLL/SLL (27%) and MM (22%) (Table 1). The most common comorbidities were hypertension (60%) and neurological disease (52%) (Table S2).

The baseline demographics and clinical characteristics of patients with mature B-cell NHL, with or without COVID-19-related severe outcomes, are shown in Table 2. Most patients with mature B-cell NHL did not experience severe COVID-19 outcomes (64%). Patients with mature B-cell NHL who had severe COVID-19 outcomes differed from patients with mature B-cell NHL without severe COVID-19 outcomes in terms of mean age (72 years for patients with severe outcomes and 65 years for patients without severe outcomes), sex distribution (men 59% and 51%, respectively), race

TABLE 1 Baseline demographics and clinical characteristics of patients with COVID-19

Characteristic	Patients with COVID-19, *N* (%)							
	Without cancer diagnosis (1)	Solid tumors (2)	Non-B-cell NHL (3)	mB-cell NHL (4)	SMD[a] 1 vs. 4	SMD[a] 2 vs. 4	SMD[a] 3 vs. 4	SMD[a] 1 vs. 2 + 3 + 4
Number of patients	431 659	48 609	3781	3593				
Age, years					**1.19**	**0.35**	**0.31**	**0.86**
Mean ± SD	48 ± 18	63 ± 16	63 ± 16	68 ± 15				
Median (IQR)	48 (28)	63 (21)	64 (21)	69 (20)				
Range	18–89	18–89	18–89	18–89				
Age group, years					**1.19**	**0.37**	**0.34**	**0.86**
18–29	79 109 (18)	1510 (3)	118 (3)	76 (2)				
30–39	74 233 (17)	3069 (6)	222 (6)	102 (3)				
40–49	74 118 (17)	5131 (11)	362 (10)	185 (5)				
50–59	82 158 (19)	9546 (20)	721 (19)	543 (15)				
60–64	37 922 (9)	6455 (13)	504 (13)	463 (13)				
65–69	27 084 (6)	5830 (12)	484 (13)	456 (13)				
70–79	34 002 (8)	9638 (20)	796 (21)	938 (26)				
80+	23 033 (5)	7430 (15)	574 (15)	830 (23)				
Sex					**0.23**	**0.23**	**0.25**	0.02
Female	249 372 (58)	28 016 (58)	2211 (59)	1664 (46)				
Male	182 287 (42)	20 593 (42)	1570 (42)	1929 (54)				
Race					**0.22**	0.05	0.09	**0.27**
White	309 717 (72)	40 072 (82)	3010 (80)	2865 (80)				
Black	53 558 (12)	4619 (10)	407 (11)	390 (11)				
Asian	8803 (2)	627 (1)	63 (2)	48 (1)				
Other/unknown	59 581 (14)	3291 (7)	301 (8)	290 (8)				
Region of residence					**0.18**	**0.14**	**0.12**	**0.12**
Midwest	207 723 (48)	24 250 (50)	1850 (49)	1576 (44)				
Northeast	107 522 (25)	13 531 (28)	1081 (29)	1171 (33)				
South	75 615 (18)	6750 (14)	534 (14)	571 (16)				
West	25 959 (6)	2959 (6)	237 (6)	195 (5)				
Unknown	14 840 (3)	1119 (2)	79 (2)	80 (2)				
Insurance type					**0.74**	**0.25**	**0.24**	**0.52**
Commercially insured only	190 120 (44)	14 482 (30)	951 (25)	809 (23)				
Medicaid covered only	26 227 (6)	1600 (3)	182 (5)	88 (2)				
Medicare beneficiary	35 989 (8)	9182 (19)	811 (21)	930 (26)				
Commercial and Medicaid	9694 (2)	525 (1)	50 (1)	51 (1)				
Commercial and Medicare	17 837 (4)	4575 (9)	325 (9)	414 (12)				
Medicare and Medicaid	3859 (1)	614 (1)	54 (1)	67 (2)				
Commercial, Medicare, and Medicaid	1624 (0.4)	293 (1)	37 (1)	34 (1)				
Uninsured	9584 (2)	406 (1)	29 (1)	21 (1)				
Unknown	136 725 (32)	16 932 (35)	1342 (36)	1179 (33)				
Month of COVID-19 diagnosis					**0.10**	0.08	0.06	0.06
Jan–Mar 2020	8591 (2)	923 (2)	89 (2)	74 (2)				
Apr–Jun 2020	66 316 (15)	7201 (15)	605 (16)	620 (17)				
Jul–Sep 2020	77 953 (18)	7632 (16)	631 (17)	536 (15)				
Oct–Dec 2020	190 246 (44)	22 334 (46)	1616 (43)	1540 (43)				
Jan–Mar 2021	88 553 (21)	10 519 (22)	840 (22)	823 (23)				

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; mB-cell, mature B-cell; NHL, non-Hodgkin lymphoma; SMD, standardized mean difference.

[a]SMDs with an absolute value ≥0.1 (in bold) indicate a significant between-group difference.

TABLE 2 Baseline demographics and clinical characteristics of patients with mature B-cell NHL and with or without COVID-19-related severe outcomes

Characteristic	Patients with mB-cell NHL with severe outcomes, *N* (%)	Patients with mB-cell NHL without severe outcomes, *N* (%)	SMD[a]
Number of patients	1290	2303	
Age, years			**0.498**
Mean ± SD	72 ± 13	65 ± 15	
Median (IQR)	74 (18)	66 (20)	
Range	20–89	18–89	
Age group, years			**0.512**
18–29	10 (1)	66 (3)	
30–39	17 (1)	85 (4)	
40–49	41 (3)	144 (6)	
50–59	121 (9)	422 (18)	
60–64	143 (11)	320 (14)	
65–69	154 (12)	302 (13)	
70–79	383 (30)	555 (24)	
≥80	421 (33)	409 (18)	
Sex			**0.172**
Female	527 (41)	1137 (49)	
Male	763 (59)	1166 (51)	
Race			**0.166**
White	982 (76)	1883 (82)	
Black	179 (14)	211 (9)	
Asian	15 (1)	33 (1)	
Other/unknown	114 (9)	176 (8)	
Region of residence			**0.240**
Midwest	520 (40)	1056 (46)	
Northeast	389 (30)	782 (34)	
South	277 (22)	294 (13)	
West	75 (6)	120 (5)	
Unknown	29 (2)	51 (2)	
Insurance type			**0.567**
Commercially insured only	216 (17)	593 (26)	
Medicaid covered only	33 (3)	55 (2)	
Medicare beneficiary	436 (34)	494 (22)	
Commercial and Medicaid	22 (2)	29 (1)	
Commercial and Medicare	221 (17)	193 (8)	
Medicare and Medicaid	42 (3)	25 (1)	
Commercial, Medicare, and Medicaid	18 (1	16 (1)	
Uninsured	3 (0)	18 (1)	
Unknown	299 (23)	880 (38)	
Month of COVID-19 diagnosis			**0.240**
Jan–Mar 2020	51 (4)	23 (1)	
Apr–Jun 2020	260 (20)	360 (16)	
Jul–Sep 2020	191 (15)	345 (15)	
Oct–Dec 2020	496 (38)	1044 (45)	
Jan–Mar 2021	292 (23)	531 (23)	
Body mass index (kg/m^2)			**0.194**
<18.5 (underweight)	26 (2)	28 (1)	
18.5–24.9 (normal)	289 (22)	469 (20)	
25.0–29.9 (overweight)	353 (27)	706 (31)	
30.0–34.9 (obesity class I)	257 (20)	513 (22)	
35.0–39.9 (obesity class II)	118 (9)	247 (11)	
≥40 (obesity class III)	108 (8)	159 (7)	
Unknown	139 (11)	181 (8)	
Charlson Comorbidity Index, mean ± SD	5.0 ± 3.6	4.1 ± 3.1	**0.259**
Underlying medical conditions			
Chronic kidney disease	359 (28)	343 (15)	**0.320**
Chronic kidney disease, without dialysis	328 (25)	324 (14)	**0.288**
End-stage renal disease, with dialysis	65 (5)	45 (2)	**0.169**
Chronic liver disease	120 (9)	219 (10)	0.007
Chronic lung disease	324 (25)	451 (20)	**0.133**
Asthma	127 (10)	233 (10)	0.009
Emphysema	74 (6)	91 (4)	0.083
COPD	215 (17)	237 (10)	**0.188**
Tuberculosis	2 (0)	1 (0)	0.036
CVD/serious heart condition	1033 (80)	1624 (71)	**0.223**
Hypertension	872 (68)	1298 (56)	**0.233**
Heart failure/ cardiomyopathy	308 (24)	360 (16)	**0.208**
Cerebrovascular disease	174 (13)	214 (9)	**0.132**
Valvular heart diseases	257 (20)	309 (13)	**0.175**

(Continues)

TABLE 2 (Continued)

Characteristic	Patients with mB-cell NHL with severe outcomes, *N* (%)	Patients with mB-cell NHL without severe outcomes, *N* (%)	SMD[a]
Cardiac arrhythmia/ conduction disorders	445 (34)	492 (21)	**0.296**
Ischemic heart disease	449 (35)	533 (23)	**0.259**
Other CVD	572 (44)	825 (36)	**0.175**
Neurological disease	725 (56)	1147 (50)	**0.128**
Dementia	159 (12)	141 (6)	**0.216**
Seizure disorders	41 (3)	53 (2)	0.054
Other neurologic conditions	691 (54)	1117 (49)	**0.101**
Diabetes mellitus (type 2)	470 (36)	597 (26)	**0.228**
Immunosuppression	1118 (87)	2000 (87)	0.005
Rheumatologic or autoimmune condition	263 (20)	429 (19)	0.044
Immunosuppressive condition (e.g., solid organ transplant, HIV infection, cancer with chemotherapy receipt or stem cell transplant)	1079 (84)	1901 (83)	0.029
Immunosuppressive medications	464 (36)	758 (33)	0.064
Psychiatric condition	480 (37)	859 (37)	0.002
Blood disorder	793 (61)	1115 (48)	**0.265**
Medication used for treating NHL within 30 days prior to COVID-19 diagnosis	86 (7)	100 (4)	**0.102**
Chemoimmunotherapy only[b]	47 (4)	66 (3)	
BTK inhibitor[c]	9 (1)	9 (<1)	
Other novel therapy[d]	30 (2)	25 (1)	

Abbreviations: BTK, Bruton's tyrosine kinase; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; CVD, cardiovascular disease; IQR, interquartile range; mB-cell, mature B-cell; NHL, non-Hodgkin lymphoma; SMD, standardized mean difference.

[a]SMDs with an absolute value ≥0.1 (in bold) indicate a significant between-group difference.

[b]Chemoimmunotherapy, chemotherapy, or immunotherapy without BTK inhibitor or novel therapy.

[c]BTK inhibitor (ibrutinib, acalabrutinib, zanubrutinib) with/without chemoimmunotherapy.

[d]Novel therapy (idelalisib, duvelisib, venetoclax, dinaciclib, vidaza, ublituximab, umbralisib, pembrolizumab, nivolumab, copanlisib, bortezomib) with/without other therapy.

(Black 14% and 9%), region of residence (South 22% and 13%), and mean Charlson comorbidity index score (5.0 and 4.1). Active anti-cancer treatment for NHL was being received by 5% of the patients with mature B-cell NHL within 30 days of a COVID-19 diagnosis. A slightly higher percentage of patients with severe COVID-19 outcomes were receiving anti-cancer treatment compared with those that did not have severe COVID-19 outcomes (Table 2; Table S3). The most common comorbidities in patients with severe COVID-19 outcomes were cardiovascular disease or serious heart conditions (80%), neurological diseases (56%), and type 2 DM (36%). Patients with coexisting chronic kidney disease, chronic lung disease, serious heart condition, neurological disease, and type 2 DM were at a significantly higher risk of developing severe COVID-19 outcomes (Table 2, Figure 1).

3.2 | Standardized risk of severe COVID-19

The age- and sex-standardized risks of hospitalization and death were 9.5% (95% CI, 9.4%–9.6%) and 1.2% (95% CI, 1.2%–1.2%), respectively, for patients without cancer diagnosis (Figure 2). The risks of ARI and death were doubled for patients with mature B-cell NHL compared with the cohort without cancer (3.7% [95% CI, 2.8–5.5%] vs. 1.8% [95% CI, 1.7%–1.8%], 2.1% [95% CI, 1.8%–3.6%] vs. 1.2% [95% CI, 1.2%–1.2%], respectively). The standardized risks of hospitalization, ARI, and death varied among groups with different cancer types and were higher in patients with mature B-cell NHL, who had higher hospitalization, mortality, and ARI risk than patients with solid tumors. The standardized risk of hospitalization and death was similar between patients with non-mature B-cell NHL (15.4% [95% CI, 13.3–17.9%] and 2.2% [95% CI, 1.8–2.9%], respectively) and patients with mature B-cell NHL (15.6% [95% CI, 13.7–18.0%] and 2.1% [95% CI, 1.8–3.5%], respectively) (Figure 2).

3.3 | Outcomes and healthcare resource utilization among different mature B-cell NHL histologies

Overall, in the mature B-cell NHL cohort, 36% ($n = 1290$) of patients developed severe COVID-19, 32% ($n = 1155$) were hospitalized, 8% ($n = 280$) were admitted to an intensive care unit, and 9% ($n = 314$) died. Among histologies within mature B-cell NHL, patients with CLL/SLL and MM had the highest frequencies of severe COVID-19 outcomes (40% and 42%, respectively), hospitalizations (35% and 39%), and deaths (11% and 10%) (Figure 3). Additional details related to COVID-19 outcomes and mature B-cell NHL histologies are shown in Table S4.

3.4 | Risk factors associated with severe COVID-19 in patients with mature B-cell NHL

Multivariable logistic regression showed that patients infected between January and March 2020 were approximately four times

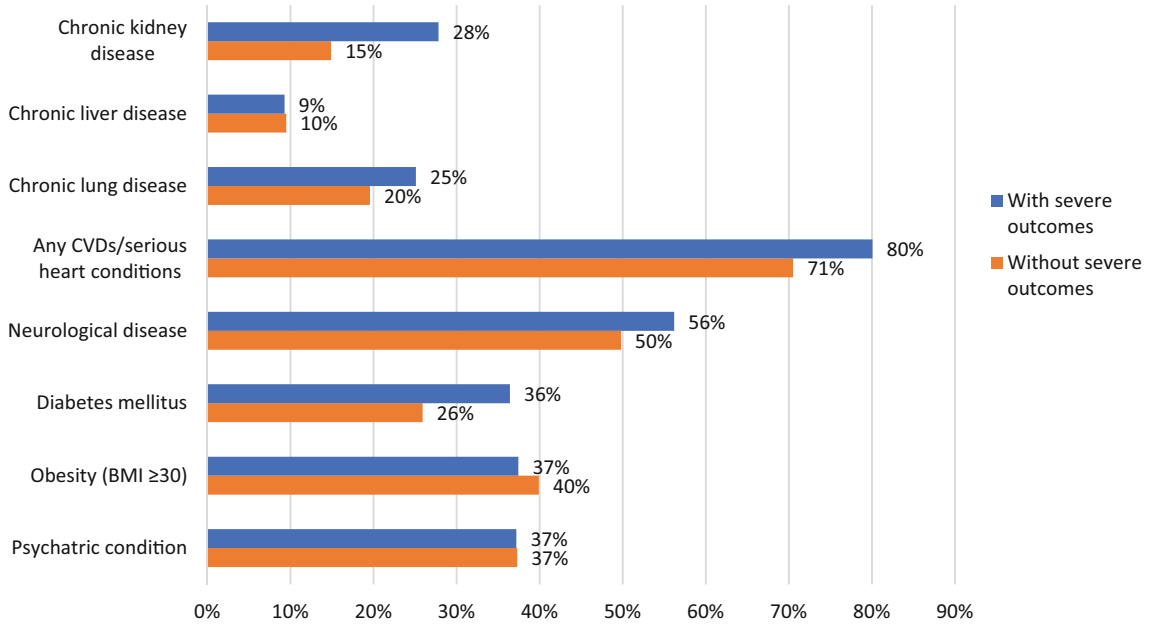

FIGURE 1 Comorbidities for patients with mature B-cell NHL and with COVID-19, stratified by occurrence of severe COVID-19 outcomes. BMI, body mass index; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; NHL, non-Hodgkin lymphoma

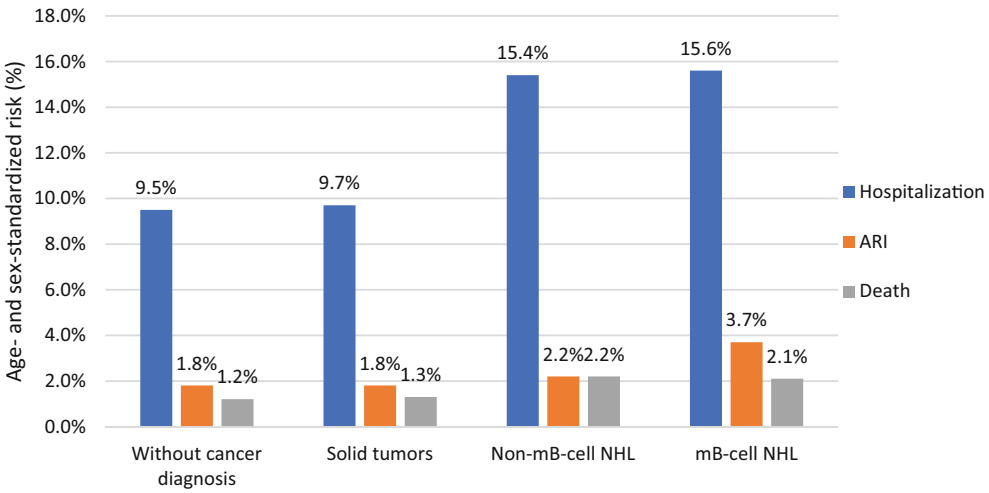

FIGURE 2 Age- and sex-standardized risk of COVID-19-related hospitalizations, ARI, and death. Standard population is the 2010 US Census population.[28] ARI, acute respiratory insufficiency; COVID-19, coronavirus disease 2019; mB-cell, mature B-cell; NHL, non-Hodgkin lymphoma

more likely to develop severe COVID-19 than patients infected in January and March 2021 (aOR 4.2; $p < .0001$) (Figure 4). The odds of developing severe COVID-19 were higher in men than women (aOR 1.4; $p < .001$) and more than twice as high in patients aged ≥85 years than in those aged <65 years (aOR 2.6; $p < .0001$). Patients with public health insurance (Medicaid or Medicare) were twice as likely to develop severe COVID-19 compared with those with commercial insurance only (aOR 2.1 for Medicaid and 1.7 for Medicare; both $p < .0001$). Patients with chronic kidney disease (aOR 1.4; $p = .001$), chronic obstructive pulmonary disease (aOR 1.3; $p = .02$), cardiac arrhythmia or conduction disorders (aOR 1.3; $p = .005$), or type 2 DM (aOR 1.3; $p = .002$) had higher odds of developing severe COVID-19 than those without these conditions. Additionally, patients receiving active treatment for NHL within 30 days prior to COVID-19 diagnosis were 1.5-times as likely to develop severe COVID-19 than those without active treatment ($p = .010$). No significant difference was observed between histologies, regardless of whether patients with MM, a plasma cell malignancy rather than B cell lymphoma, were included (Figure 4) or excluded (Figure S4) from the analysis.

4 | DISCUSSION

In this nationwide study of one of the largest EHR databases, we found evidence that severe COVID-19 outcomes are more common in patients with mature B-cell NHL than in those with other cancer types or no cancer and are similar to those of patients with non-mature B-cell NHL. We also identified demographic and clinical

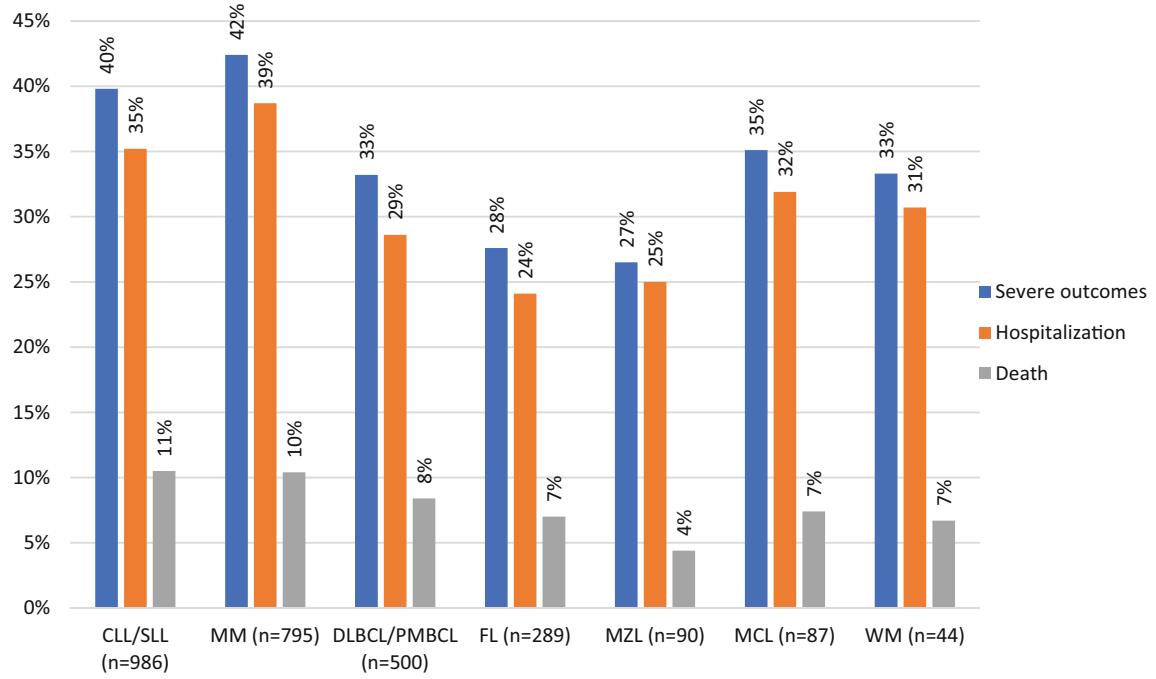

FIGURE 3 Outcomes for patients with COVID-19 and mature B-cell NHL, stratified by histological subtypes. Severe outcomes include hospitalization, intensive care unit admission, acute respiratory insufficiency, and death. CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; SLL, small lymphocytic lymphoma; WM, Waldenström macroglobulinemia

characteristics that could be used as potential predictors of severe COVID-19 outcomes among patients with mature B-cell NHL. These findings are consistent with previous studies.[8,24–26] For example, a high likelihood of poor COVID-19 outcomes has been shown for patients with cancer, especially those with hematologic malignancies such as leukemia or NHL.[8] Many independent risk factors for a higher susceptibility to severe COVID-19 outcomes that were identified in our study (e.g., older age, male sex, certain comorbidities) were previously reported, but only in the context of the general population.[27–32]

An increased susceptibility to severe COVID-19 outcomes in patients with hematologic cancers is hypothesized to be a consequence of the decreased levels of anti-SARS-CoV-2 antibodies during infection, as well as of defects in CD4-positive T- and B-cells, as compared to patients with solid tumors.[33,34] More severe outcomes in patients with mature B-cell NHL who contracted SARS-CoV-2 infection earlier in the pandemic could be explained by the substantial improvements in COVID-19 treatment options and greater availability of diagnostic testing for patients with mild or no symptoms during the later periods of the pandemic.

Our finding that active treatment for mature B-cell NHL is associated with severe COVID-19 outcomes has also been shown in other studies, which have revealed an association between active neoplastic treatment and higher COVID-19-related mortality in patients with hematologic malignancies.[16,35] We did not, however, investigate the associations of specific therapies with the COVID-19 outcomes in this study. The available evidence suggests that in patients with mature B-cell NHL, bendamustine and anti-CD20 were generally associated with worse COVID-19 outcomes,[16,35,36] whereas Bruton's tyrosine kinase inhibitors had either a neutral or protective effect.[13–15,35]

The strength of this study lies in the use of one of the largest nationwide EHR databases, which contains relevant clinical information from a large network of providers and hospitals as well as longitudinal care data for patients with COVID-19. We were able to obtain a large sample size of patients with mature B-cell NHL without needing to pool heterogeneous data from different databases and studies. The large sample size improved the accuracy of the assessment of risk of severe COVID-19 outcomes. In addition, clinical information from the EHR allows for accurate identification of SARS-CoV-2-positive patients because it includes professionally reviewed diagnostic laboratory test results, in addition to diagnosis code information. Indeed, 72% of the patients in the study cohort were identified by a positive diagnostic test result, and the rest of the study population was identified based on recorded clinical diagnosis. Moreover, our data set was payer-agnostic and therefore less influenced by changes in patient eligibility resulting from socioeconomic impacts of the COVID-19 pandemic, such as loss of employer-based health insurance.[37]

This work has several limitations, including EHRs not being suited for capturing hospitalizations if diagnostic sites are outside the healthcare delivery network. Comorbidities in EHRs can be underreported,[38] and centers contributing to the Optum EHR database may not be fully representative of the general US population. Although this bias might affect the absolute risk assessment, it should have only a minimal

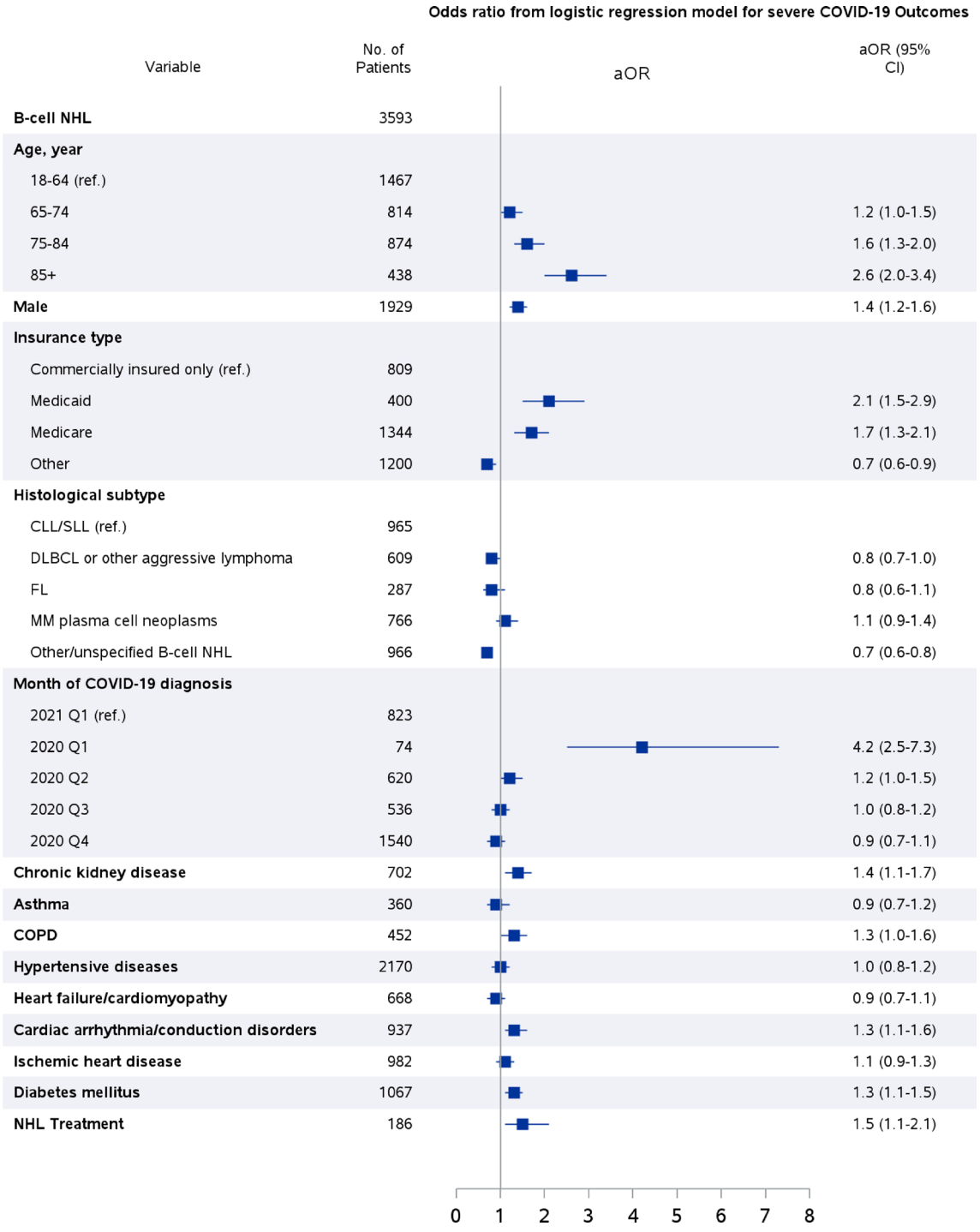

FIGURE 4 Multivariable regression analysis of patients with mature B-cell NHL with severe COVID-19. NHL treatment (including chemoimmunotherapy, immunotherapy, chemotherapy, Bruton's tyrosine kinase [BTK] inhibitors) within 30 days prior to COVID-19 infection. aOR, adjusted odds ratio; CLL, chronic lymphocytic leukemia; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio; Q, quarter; SLL, small lymphocytic lymphoma

effect on relative risk estimates between patient cohorts. It is important to note that the effect of COVID-19 vaccination was not evaluated in this study and it may have influenced both the number of included patients and their outcomes.[39] Since the US Food and Drug Administration approval of COVID-19 vaccines in mid-December 2020,[40] through all available data (28 April 2021), only 28 681 (5.7%) patients had records for receiving at least one dose of vaccine while the national coverage was estimated at 57% in May 2021, which may suggest under-capturing of vaccination status in this EHR database. Moreover, we did not evaluate the effect of COVID-19 therapies and treatments on the COVID-19 outcomes, because the available therapies during that period of pandemic were limited and not specific for

COVID-19 infection. The risks factors associated with reinfection with COVID-19 were not evaluated. A total of 22 445 (4.6%) patients got COVID-19 twice, and 2296 (0.5%) patients were infected more than twice during the study period. Given these low numbers, it is unlikely to significantly change our findings since the vast majority of the study population were only infected once.

In conclusion, this EHR-based study, which, to the best of our knowledge includes the largest cohort of patients with mature B-cell NHL and COVID-19 analyzed to date, suggests that mature B-cell NHL diagnosis confers no significant additional risks of severe COVID-19 outcomes when compared with other hematologic diagnoses, including non-mature B-cell NHL. It also suggests that demographic and clinical predictors of severe COVID-19 outcomes in patients with mature B-cell NHL are similar to those in the general population. These results highlight the importance of using demographics and clinical characteristics in fully assessing COVID-19-related risks faced by patients with mature B-cell NHL. Further prospective studies are needed to identify specific actions to improve COVID-19 outcomes in this group of patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version of the manuscript. Xiaomeng Yue, Yangyang Liu, Annie McNeill, and James P. Dean contributed to the study conception and design. Xiaomeng Yue, David Hallett, Yangyang Liu, Elisa Basa, Annie McNeill, and James P. Dean contributed to the acquisition of data. Xiaomeng Yue, David Hallett, Yangyang Liu, Elisa Basa, Annie McNeill, and James P. Dean contributed to the analysis and interpretation of data.

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CONFLICT OF INTEREST

Xiaomeng Yue: employment and stock ownership in AbbVie. David Hallett: employment at AbbVie. Yangyang Liu: employment and stock ownership in AbbVie. Elisa Basa: employment and stock ownership in AbbVie, immediate family member with leadership role and consulting in San Francisco Healthcare & Rehab, and consulting for Greenhills Manor. Annie McNeill: employment and stock ownership in AbbVie. James P. Dean: employment and stock ownership in Pharmacyclics LLC, an AbbVie Company.

DATA AVAILABILITY STATEMENT

Not applicable.

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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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