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Risks of Severe COVID-19 Outcomes Among Patients With Diabetic Polyneuropathy in the United States

Wen-Jan Tuan, DHA, MS, MPH; Robert P. Lennon, MD, JD; Alice Zhang, MD; Ajay Macherla; Aleksandra E. Zgierska, MD, PhD

ABSTRACT

Context: Diabetic neuropathy (DN) affects more than 50% of diabetic patients who are also likely to have compromised immune system and respiratory function, both of which can make them susceptible to the SARS-CoV-2 virus.

Objective: To assess the risk of severe COVID-19 illness among adults with DN, compared with those with no DN and those with no diabetes.

Setting: The analysis utilized electronic health records from 55 US health care organizations in the TriNetX research database.

Design: A retrospective cohort study.

Participants: The analysis included 882 650 adults diagnosed with COVID-19 in January 2020 to June 2021, including 16 641 with DN, 81 329 with diabetes with no neuropathy, and 784 680 with no diabetes.

Outcome Measures: The presence of health care utilization (admissions to emergency department, hospital, intensive care unit), 30-day mortality, clinical presentation (cough, fever, hypoxemia, dyspnea, or acute respiratory distress syndrome), and diagnostic test results after being infected affected by COVID-19.

Results: The DN cohort was 1.19 to 2.47 times more likely than the non-DN cohorts to utilize care resources, receive critical care, and have higher 30-day mortality rates. Patients with DN also showed increased risk (1.13-2.18 times) of severe symptoms, such as hypoxemia, dyspnea, and acute respiratory distress syndrome.

Conclusions: Patients with DN had a significantly greater risk of developing severe COVID-19–related complications than those with no DN. It is critical for the public health community to continue preventive measures, such as social distancing, wearing masks, and vaccination, to reduce infection rates, particularly in higher risk groups, such as those with DN.

KEY WORDS: COVID-19, diabetic neuropathy, electronic health records

Diabetes mellitus (DM) is one of the most frequently observed comorbidities in COVID-19 patients, found in more than 58% of patients with coronavirus infection in the United States.[1,2] Individuals with diabetes are 2 to 4 times more likely to experience severe COVID-19 complications than their nondiabetic counterparts.[3] The SARS-CoV-2 virus causes damage to the pancreatic islet cells of diabetic patients, resulting in insulin deficiency and hyperglycemia.[4] Hyperglycemia further triggers the release of a large number of inflammatory mediators and cytokines in a short amount of time, leading to organ damage or failure.[5,6] Yet, little is known about the impact of COVID-19 on people experiencing neurological issues, such as diabetic neuropathy (DN). The large scale of this pandemic has raised challenges to our health care practice and the need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for patients with diabetes and its complications.

Diabetic neuropathy, a type of nerve damage affecting sensory and motor functions, has been found in more than 50% of diabetic patients.[7,8] Nerve damage can potentially lead to a dysregulation of the inflammatory reflex in the nervous system,

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The authors declare no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (http://www.JPHMP.com).

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DOI: 10.1097/PHH.0000000000001587

resulting in a heightened proinflammatory state and elevated cytokines in patients with DN infected by COVID-19.[9] Moreover, patients with DN who have impaired lung function, particularly abnormalities in bronchial neuroadrenergic innervation,[10] can be more susceptible to severe COVID-19 due to a vulnerable respiratory system. Although the risk of increasing morbidity and mortality from SARS-CoV-2 infection among individuals with certain chronic conditions has been identified and incorporated into outcome prediction models,[11] the relationship between DN and SARS-CoV-2–related morbidity and mortality has not been assessed.

Because of the impaired immune response and lung function, patients with DN infected by COVID-19 may have more severe adverse health outcomes. Given the high prevalence of DN among diabetic patients, more research is urgently needed to investigate DN as a pathway to severe COVID-19. This study aims to assess the risks of developing severe outcomes or increased health care utilization for COVID-19 patients with DN compared with individuals who have no diabetes or have diabetes with no the history of DN. Understanding these risks may help clinicians counsel their patients with DN to adhere to public health recommendations to avoid SARS-CoV-2 infection, as well as to develop more effective care guidelines for treating COVID-19 patients with DN.

Methods

Study design and data source

The study applied a retrospective, longitudinal cohort design utilizing electronic health records (EHR) from 55 health care organizations sourced from the TriNetX research network database in the United States (Cambridge, Massachusetts). TriNetX is a federated health research network that provides researchers with access to de-identified, aggregated EHR data (demographics, diagnoses, procedures, medications, and laboratory tests) of more than 80 million patients from participating health care organizations. All the data queries were performed in the TriNetX online portal, and the results contained only aggregated counts and statistical summaries. Data in the TriNetX database have been shown referential integrity and be reliable.[12] The coding information of the research data also underwent extensive curation and was mapped to common clinical terminologies to ensure high usability and consistency with the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines criteria.[13] Because there were no patient-level identifiable data involved or accessed in the analysis, this research was determined to be exempt from the institutional review board oversight.

Study population

The study population consisted of adults (aged 18 years and older) diagnosed with COVID-19 from January 1, 2020, through June 30, 2021, based on the presence of *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes and positive laboratory test results.[14] Diabetic neuropathy was determined on the basis of *ICD-10* diagnosis codes that contained various DN types, including mononeuropathy, polyneuropathy, autonomic neuropathy, and nonspecific neurological complications.[15] Three nonoverlapping cohorts were constructed in the analysis. The cohort of primary interest (DN cohort) comprised diabetic adults (type I or II) with DN who preceded their COVID-19 infection. Adults with diabetes (type I or II) but with no DN diagnoses (DM/non-DN cohort) and those with no either diabetes or DN diagnoses (non-DM cohort) served as two comparator cohorts. The study population excluded individuals who had cancers, or living in nursing homes, hospice, or palliative care facilities. The Figure 1 is a cohort selection flowchart. Detailed information for diagnostic codes is provided in the online Supplemental Digital

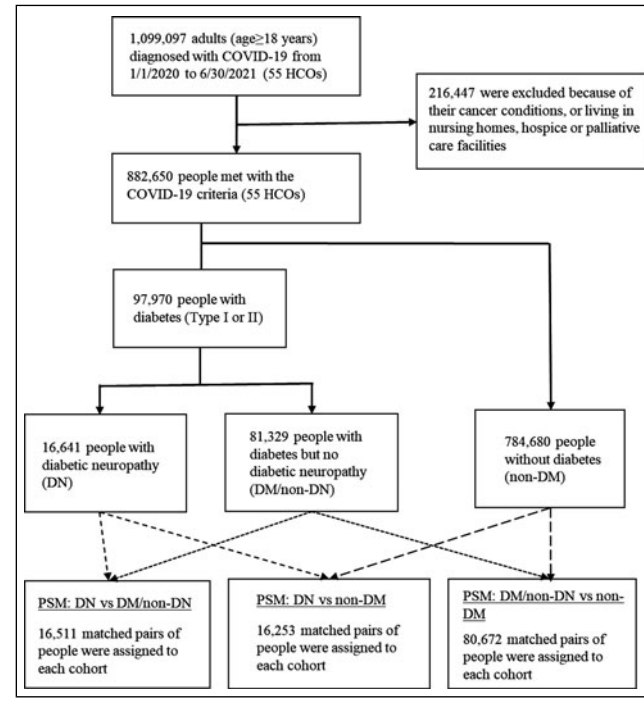

FIGURE 1 Flowchart of the Study Cohort Selection Process
Abbreviations: DM/non-DN, diabetes with no diabetic neuropathy; DN, diabetic neuropathy; HCOs, health care organizations; Non-DM, no diabetes and no diabetic neuropathy; PSM, propensity score matching.

Content Table S1, available at http://links.lww.com/JPHMP/B11.

Outcome measures

Infection severity was assessed through 3 areas: health care utilization/mortality, clinical presentation, and diagnostic test results. Health care utilization measures included the indicators (yes/no) of admission to the emergency department (ED), admission to the inpatient ward, admission to the intensive care unit, placement on mechanical ventilation, and vasopressor treatment, within 30 days of COVID-19 infection. Mortality was defined as deaths within 30 days after COVID-19 infection. Clinical presentation measures were presence (yes/no) of cough, fever, hypoxemia, dyspnea, or acute respiratory distress syndrome (ARDS) after being infected by COVID-19. Diagnostic test results included common biomarkers, such as serum creatinine, blood urea nitrogen, and C-reactive protein (CRP) levels, which were identified as severity indicators of COVID-19 infection in both inpatients and outpatient settings.[11,14] These measures were based on the first observations recorded within 1 and 7 days immediately after COVID infection. Diagnosis and laboratory test codes for outcome measures are available in the online Supplemental Digital Content Table S1, available at http://links.lww.com/JPHMP/B11.

Statistical analyses

Baseline characteristics including patient characteristics (age, sex, race and ethnicity) and comorbidities (obesity, hypertension, chronic pulmonary conditions, and cardiovascular diseases) were accounted for as confounding variables. To account for potential mediating effects of the socioeconomic condition, we further included diagnoses that may indicate increased risk due to socioeconomic and psychosocial circumstances (education and literacy, employment, housing, lack of adequate food or water, or exposure to occupational hazards). The study applied a 1:1 propensity score matching (PSM) technique to balance the baseline characteristics by creating matched pair of patients with similar propensity scores between the DN and its 2 comparator cohorts. The PSM method was performed using logistic regression and nearest neighbor algorithms with a caliper width of 0.1 pooled standard deviation, ensuring that matched pairs have similar baseline characteristics. Risk ratios with 95% confidence intervals (95% CI) for the likelihood of experiencing each outcome were calculated, and a 2-sided P value of <.05 was defined a priori for statistical significance. All data queries and statistical analyses were performed on the TriNetX portal.

Results

Overall population

A total of 882 650 adults diagnosed with COVID-19 met the study criteria between January 1, 2020, and June 30, 2021, in the EHR database, including 16 641 patients with DN (DN cohort), 81 329 patients with DM with no DN (DM/non-DN cohort), and 784 680 patients with no either DM or DN (non-DM cohort) (see the Figure). The demographic characteristics and comorbid conditions of the cohort populations at the baseline, both before and after PSM analysis, are shown in Supplemental Digital Content Tables S2a-c, available at http://links.lww.com/JPHMP/B12. Before PSM, individuals in the DN cohort generally had a higher average age, a greater percentage of non-Hispanics and Blacks, and a higher prevalence of comorbidity conditions than their DM/non-DN and non-DM counterparts. More male patients were found in the DN cohort than the non-DM cohort, but there was no difference in the gender proportion between the DN and the DM/non-DN cohorts. In addition, patients with DN had higher average hemoglobin A_{1C} values than non-DN patients, indicating worse diabetes control at baseline.

The PSM identified 16 511 matched pairs of patients for the DN versus DM/non-DN analysis, 16 253 matched pairs of patients for the DN versus non-DM analysis, and 80 672 matched pairs of patients for the DN versus non-DN analysis. After PSM, there were no baseline differences between the DN and comparator cohort characteristics, suggesting that the demographic characteristics and comorbid conditions were well balanced between the cohorts. Moreover, absolute standardized differences for all measured baseline characteristics were less than 10%, further indicating similar distributions of the baseline characteristics between the PSM-matched samples.[16]

Health care utilization and 30-day mortality

COVID-19 patients with DN consistently showed greater utilization of various health care resources than COVID-19 patients with no DN (Table 1). Patients with DN were 1.19 times (95% CI: 1.15-1.24, $P < .001$) more likely to have ED visits, and 1.24 times (95% CI: 1.19-1.3, $P < .001$) more likely to be hospitalized than the DM/non-DN cohort. The DN cohort also showed greater risks of receiving intensive care (risk ratio [RR] = 1.39, 95% CI: 1.27-1.52, $P < .001$), mechanical ventilation (RR = 1.24, 95% CI: 1.12-1.37, $P < .001$), and vasopressors (RR = 1.22, 95% CI: 1.03-1.45, $P = .03$) than the DM/non-DM

TABLE 1

Health Care Utilization, 30-Day Mortality, and Clinical Presentation Among COVID-19 Patients: After Propensity Score Matching[a]

	Diabetic Neuropathy (DN) Versus Diabetes With No Diabetic Neuropathy (DM/Non-DN) (N = 16 511)			Diabetic Neuropathy (DN) Versus Nondiabetes (non-DM) (N = 16 253)			Diabetes With No Diabetic Neuropathy (DM/non-DN) Versus Nondiabetes (non-DM) (N = 80 672)		
	DN, n (%)	DM/ Non-DN, n (%)	Risk Ratio (95% CI)	DN, n (%)	Non-DM, n (%)	Risk Ratio (95% CI)	DM/ Non-DN, n (%)	Non-DM, n (%)	Risk Ratio (95% CI)
Health care utilization and 30-d mortality									
ED visits	4566 (27.65)	3822 (23.15)	1.19[b] (1.15-1.24)	4468 (27.49)	3169 (19.5)	1.41[b] (1.35-1.47)	14 386 (17.83)	12 112 (15.01)	1.19[b] (1.16-1.21)
Hospitalization	3597 (21.79)	2896 (17.54)	1.24[b] (1.19-1.3)	3508 (21.58)	2179 (13.41)	1.61[b] (1.53-1.69)	11 963 (14.83)	7520 (9.32)	1.59[b] (1.55-1.63)
ICU	1067 (6.46)	769 (4.66)	1.39[b] (1.27-1.52)	1027 (6.32)	511 (3.14)	2.01[b] (1.81-2.23)	3261 (4.04)	1662 (2.06)	1.96[b] (1.85-2.08)
Mechanical vent	836 (5.06)	674 (4.08)	1.24[b] (1.12-1.37)	805 (4.95)	362 (2.23)	2.22[b] (1.97-2.51)	3208 (3.98)	1439 (1.78)	2.23[b] (2.1-2.37)
Vasopressor	292 (1.77)	239 (1.45)	1.22[c] (1.03-1.45)	282 (1.74)	114 (0.7)	2.47[b] (1.99-3.07)	1133 (1.4)	542 (0.67)	2.09[b] (1.89-2.31)
Death (30 d)	988 (5.98)	821 (4.97)	1.20[b] (1.1-1.32)	954 (5.87)	621 (3.82)	1.54[b] (1.39-1.7)	3409 (4.23)	2241 (2.78)	1.52[b] (1.44-1.6)
Clinical presentation									
Fever	833 (5.05)	563 (3.41)	1.48[b] (1.33-1.64)	809 (4.98)	514 (3.16)	1.57[b] (1.41-1.75)	2411 (2.99)	1864 (2.31)	1.29[b] (1.22-1.37)
Cough	1664 (10.08)	1472 (8.92)	1.13[b] (1.06-1.21)	1629 (10.02)	1326 (8.16)	1.23[b] (1.15-1.32)	5283 (6.55)	5107 (6.33)	1.03 (1.00-1.07)
Dyspnea	3360 (20.35)	2865 (17.35)	1.17[b] (1.12-1.23)	3269 (20.11)	2553 (15.71)	1.28[b] (1.22-1.34)	9741 (12.07)	8508 (10.55)	1.14[b] (1.11-1.18)
Hypoxemia	1275 (7.72)	1083 (6.56)	1.18[b] (1.09-1.27)	1234 (7.59)	801 (4.93)	1.54[b] (1.41-1.68)	3829 (4.75)	2577 (3.19)	1.49[b] (1.41-1.56)
ARDS	286 (1.73)	207 (1.25)	1.38[b] (1.16-1.65)	277 (1.7)	127 (0.78)	2.18[b] (1.77-2.69)	1067 (1.32)	457 (0.57)	2.33[b] (2.09-2.6)

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; ED, emergency department; ICU, intensive care unit.

[a] *N: total number of patients in the cohort; n: number of patients with the health outcome.*

[b] $P < .01$.

[c] $P < .05$.

cohort. Compared with the non-DM cohort, patients with DN were 1.41 times (95% CI: 1.35-1.47, $P < .001$) and 1.61 times (95% CI: 1.53-1.69, $P < .001$) more likely to be admitted to ED and hospital, respectively, and more likely to use intensive care (RR = 2.01, 95% CI: 1.81-2.23, $P < .001$), mechanical ventilation (RR = 2.22, 95% CI: 1.97-2.51, $P < .001$), and vasopressors (RR = 2.47, 95% CI: 1.99-3.07, $P < .001$). The DM/non-DN cohort had greater likelihoods than the non-DM cohort to be admitted to ED (RR = 1.19, 95% CI: 1.16-1.21, $P < .001$) and hospital (RR = 1.59, 95% CI: 1.55-1.63, $P < .001$) and require intensive care (RR = 1.96, 95% CI: 1.85-2.08, $P < .001$), mechanical ventilation (RR = 2.23, 95% CI: 2.10-2.37, $P < .001$), and vasopressors (RR = 2.09, 95% CI: 1.89-2.31, $P < .001$).

Patients in the DN cohort experienced significantly greater 30-day post-COVID-19 diagnosis mortality rates than those in the DM/non-DN (RR = 1.20, 95% CI: 1.10-1.32, $P < .001$) and those in the non-DM (RR = 1.54, 95% CI: 1.39-1.70, $P < .001$) cohorts. The 30-day mortality rate was also about 1.5 times higher (RR = 1.52, 95% CI: 1.44-1.60, $P < .001$) in the DM/non-DN cohort than in the non-DM cohort.

Clinical presentation–related outcomes

Overall, the DN cohort was likely to experience severe COVID-19–related complications compared with both the DM/non-DN and the non-DM cohorts (see Table 1). Patients in the DN cohort were approximately 1.13 to 1.57 times ($P < .01$) more likely to present with fever and cough, and 1.17 to 1.54 times ($P < .01$) more likely to present with dyspnea and hypoxemia than those in the non-DM and non-DN cohorts. The DN cohort also showed a higher risk of ARDS diagnoses than the DM/non-DN cohort (RR = 1.38, $P < .01$) and the non-DM cohort (RR = 2.18, $P < .01$). Similarly, the DM/non-DN cohort was 1.14 to 2.33 times ($P < .01$) more likely to experience most of the aforementioned COVID-19 complications than nondiabetic patients, except for cough diagnoses, which did not differ between these 2 cohorts.

Laboratory tests

Mixed results were found in laboratory tests (see Table 2) commonly assessed in patients with COVID-19 and that can be predictive of the disease severity. Although patients in the DN cohort had significantly lower diastolic blood pressure levels than DM/non-DN (72.8 vs 74.2 mm Hg, $P < .01$) and non-DM (72.8 vs 75.5 mm Hg, $P < .01$) patients, the absolute difference in the diastolic pressure was less than 4 mm Hg, and no statistical differences were found in systolic blood pressure between the cohorts. The lymphocyte count of DN patients was lower than those of DM/non-DN (22.5 vs 23.1 per 100 leukocytes, $P < .01$) and non-DM (22.6 vs 23.6 per 100 leukocytes, $P < .01$) patients, with a small absolute difference.

The DN cohort also had greater elevation in serum creatinine (1.7 vs 1.3 mg/dL, $P < .01$ against DM/non-DN; 1.7 vs 1.2 mg/dL, $P < .01$ against non-DM), blood urea nitrogen (24.3 vs 22.1 mg/dL, $P < .01$ against DM/non-DN; 24.3 vs 19.7 mg/dL, $P < .01$ against non-DM), alkaline phosphatase (99.6 vs 90.4 units/L, $P < .01$ against DM/non-DN; 99.5 vs 84.9 units/L, $P < .01$ against non-DM), and CRP (48.0 vs 47.7 mg/L, $P < .01$ against DM/non-DN; 47.4 vs 38.5 mg/L, $P < .01$ against non-DM).

Among patients with no DN, the DM/non-DN cohort showed lower lymphocyte count and greater elevation in serum creatinine (1.2 vs 1.1 mg/dL, $P < .001$), blood urea nitrogen (20.4 vs 18.8 mg/dL, $P < .01$), alkaline phosphatase (89.4 vs 83.4 units/L, $P < .001$), and CRP (46.0 vs 40.4 mg/L, $P < .001$) compared with the non-DM cohort. In addition, patients in the DM/non-DN cohort also had elevated platelet counts (259.5 vs 253.8 K/μL, $P < .001$), aspartate aminotransferase (52.9 vs 42.9 units/L, $P < .001$), and serum ferritin (50.0 vs 40.4 ng/mL, $P < .001$).

Discussion

The COVID-19 pandemic has posed significant public health challenges for chronically ill populations, especially among patients with diabetes, which has been recognized as a risk factor for worse COVID-19 outcomes.[3,17] This study confirmed that, in general, diabetic patients suffer from more severe COVID-19 complications than nondiabetic patients.[3,5] It also presented new evidence that patients with DN are at a greater risk of COVID-19 complications, including death, and higher health care utilization compared with both nondiabetic and diabetic cohorts of individuals with no neuropathy. The results are consistent with existing literature showing that diabetic patients with DN are more susceptible to lung damage and respiratory dysfunction.[10,18] Combined with the findings from the present study, patients with COVID-19 and DN might benefit from more intensive monitoring and management than their counterparts, and from early physical therapy to improve respiratory function[19] and nutrition management for better long-term lung recovery.[20]

The vital signs assessed as a part of this study showed that, although DN patients had lower diastolic blood pressure than DM/non-DN patients

TABLE 2
Laboratory Test Results Among COVID-19 Patients: After Propensity Score Matching[a]

	Diabetic Neuropathy (DN) Versus Diabetes With No Diabetic Neuropathy (DM/Non-DN)			Diabetic Neuropathy (DN) Versus Non-Diabetes (Non-DM)			Diabetes With No Diabetic Neuropathy (DM/Non-DN) Versus Non-Diabetes (Non-DM)		
	DN Mean ± SD (n)	DM/Non-DN Mean ± SD (n)	*P*	DN Mean ± SD (n)	Non-DM Mean ± SD (n)	*P*	DM/Non-DN Mean ± SD (n)	Non-DM Mean ± SD (n)	*P*
Systolic blood pressure	130.06 ± 22.69 (10 980)	130.29 ± 21.44 (10 704)	.44	130.08 ± 22.63 (10 807)	130.08 ± 20.45 (9490)	.98	128.36 ± 21.43 (47 769)	129.31 ± 19.88 (40 015)	<.001
Diastolic blood pressure	72.78 ± 13.5 (11 149)	74.22 ± 13.35 (10 822)	<.001	72.83 ± 13.49 (10 971)	75.46 ± 13 (9607)	<.001	73.98 ± 13.67 (48 385)	75.84 ± 12.67 (40 500)	<.001
Leukocytes	8.22 ± 4.9 (9721)	8.7 ± 50.02 (9362)	.34	8.21 ± 4.89 (9571)	11.17 ± 121.99 (7903)	.02	8.69 ± 39.81 (39 038)	8.67 ± 57.94 (32 738)	.96
Lymphocytes	22.5 ± 11.38 (9008)	23.1 ± 11.51 (8604)	<.001	22.56 ± 11.38 (8849)	23.59 ± 11.53 (7175)	<.001	23.36 ± 11.76 (34 865)	24.2 ± 11.85 (29 249)	<.001
Platelets	246.95 ± 94.8 (10 130)	247.46 ± 88.89 (9804)	.70	247.25 ± 94.72 (9954)	246.36 ± 86.36 (8285)	.51	259.53 ± 98.19 (40 158)	253.83 ± 88.93 (34 005)	<.001
Serum creatinine	1.69 ± 3.29 (11 143)	1.33 ± 1.46 (10 849)	<.001	1.68 ± 3.3 (10 961)	1.22 ± 3.26 (8888)	<.001	1.23 ± 1.91 (44 273)	1.11 ± 2.25 (35 305)	<.001
Blood urea nitrogen	24.39 ± 18.53 (9774)	22.16 ± 17.46 (9689)	<.001	24.29 ± 18.51 (9610)	19.7 ± 13.96 (7809)	<.001	20.43 ± 15.99 (38 953)	18.77 ± 13.83 (29 759)	<.001
Lactate dehydrogenase	372.76 ± 734.9 (2960)	381.65 ± 575.15 (2525)	.62	365.7 ± 646.19 (2895)	382.87 ± 604.03 (1806)	.36	403.38 ± 755.61 (10 362)	393.45 ± 935.1 (7202)	.44
Alanine aminotransferase	36.46 ± 193.72 (9555)	40.59 ± 194.92 (9222)	.15	35.93 ± 191.99 (9394)	37.72 ± 209.32 (7413)	.57	42.91 ± 206.46 (37 251)	39.8 ± 204.32 (29 504)	.05
Aspartate aminotransferase	49.68 ± 453.98 (9555)	52.27 ± 462.53 (9254)	.70	48.74 ± 453.07 (9394)	43.53 ± 342.15 (7408)	.41	52.94 ± 505.69 (37 134)	42.87 ± 317.43 (29 501)	.003
Alkaline phosphatase	99.61 ± 80.9 (9532)	90.37 ± 54.21 (9216)	<.001	99.55 ± 82 (9372)	84.92 ± 42.25 (7376)	<.001	89.42 ± 58.57 (36 745)	83.42 ± 47.01 (29 125)	<.001
Serum ferritin	729.53 ± 2726.97 (4319)	789.13 ± 4968.44 (3681)	.50	727.34 ± 2747.87 (4232)	648.16 ± 2443.77 (2665)	.22	804.36 ± 4033.09 (14 541)	709.1 ± 3079.83 (10 287)	.04
Troponin I	0.65 ± 5.48 (2053)	0.55 ± 4.27 (1707)	.55	0.66 ± 5.56 (1985)	0.39 ± 4.25 (1264)	.14	0.7 ± 9.05 (5677)	0.51 ± 4.89 (4395)	.19
C-reactive protein	48 ± 68.93 (4170)	44.67 ± 62.92 (3396)	.03	47.44 ± 68.28 (4081)	38.5 ± 59.21 (2670)	<.001	45.97 ± 64.25 (14 070)	40.37 ± 60.72 (10 547)	<.001

[a]*Measurement unit: leukocytes in 1000/μL; platelets in number/volume; serum creatinine in mg/dL; C-reactive protein (CRP) in mg/L; lymphocytes, neutrophils in cells/μL; blood urea nitrogen in mg/dL; serum ferritin, troponin I in ng/mL; lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase in units/liter.*

and non-DM patients, with no difference in systolic pressures and an absolute difference less than 4 mm Hg, this is of doubtful clinical significance. COVID-19 like other infections is expected to impact immune and inflammatory responses. Lower lymphocyte count was found in the DN population; this could be viewed as suggesting a lower (worse) immune function in DN patients that was described previously in the literature.[21] Moreover, our study showed considerably higher CRP in patients with DN than in patients with no diabetes (without a significant difference between DN and non-DN patients—both with diabetes), suggesting more severe inflammation experienced by diabetic patients after COVID-19 infection.[22] Elevated CRP is also a prognostic indicator of severe COVID-19,[11] consistent with higher dyspnea and ARDS in DN compared with non-DM and non-DN patients.

Prior research has documented signs of kidney injury among patients with severe cases of COVID-19. It is consistent with our findings of elevated creatinine and blood urea nitrogen levels in patients with diabetes and DN. Kidney function impairment in COVID-19 patients has been also associated with increased risk of dialysis[23] and death.[24] Elevated serum creatinine can be prognostic of severe COVID-19,[11] underscoring the importance of close monitoring of renal function in patient with DN throughout their COVID-19 infection. Our findings demonstrate the importance of diligent counseling to encourage patients with DN to adhere to public health COVID-19 mitigation recommendations and suggest a need for close monitoring and follow-up of renal function in those patients who become infected with SARS-CoV-2.

Implications for Policy & Practice

- Adults with DN are more likely to experience severe COVID-19 complications than those with diabetes but with no neuropathy, or those with no diabetes.
- DN should be considered a potential prognosticator for worse COVID-19 outcomes. Generally accepted treatment modalities should be made readily available to patients with DN to optimize care outcomes.
- Based on prior literature, these might include close monitoring of renal function to reduce the risk of acute kidney injury and failure and offering early therapy to improve respiratory functions for better long-term lung recovery.
- Policy interventions should emphasize on promoting prevention strategies, including masking, physical distancing, handwashing, and vaccination, to reduce subsequent morbidity and mortality.

Strengths and limitations

There are several limitations in the study common to all research utilizing EHR data. First, EHR data lack relevant sociodemographic information that could affect the risk of severe COVID-19 outcomes. This study was unable to include socioeconomic indicators, such as education attainment, employment status, or rural residence[25] in statistical analysis. Although we did use socioeconomic and psychosocial diagnoses as proxies, these diagnoses were often not recorded. Second, diagnostic results including COVID-19 tests or other laboratory studies completed outside the participating research network may not be captured in the EHR, potentially resulting in sampling incompleteness. However, using a large national database enabled us to develop balanced and comparable cohorts to assess DN effects on selected COVID-19 outcomes, increasing the generalizability of results. Third, although the study found significantly greater risk of requiring critical care services or death after COVID-19 infection in patients with DN, absolute differences in the number and percentage of those events between DN and their comparators were rather less and should be cautiously interpreted when considering applications to clinical practice. Finally, the study did not address the differences between specific types of DN, such as peripheral, autonomic, proximal, and focal neuropathy. Patients with a type of DN might have experienced different severity of illness from patients with another type of DN.[26]

Conclusions

Adults with DN who have COVID-19 are at a greater risk of severe complications and intensive care utilization than those with no DN. As researchers continue to develop and test effective treatments for COVID-19, and glycemic management may not be effective in alleviating COVID-19 complications among patients with DN,[27,28] it is incumbent on clinicians and public health officials to encourage patients with DN to strictly adhere to public health COVID-19 mitigation recommendations and to provide more intensive monitoring and clinical management of patients with DN who are infected with SARS-CoV-2. Further research is warranted to determine optimal ways for effective prevention and treatment approaches to reduce morbidity, mortality, and health care utilization in this population.

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