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Long-term Neurologic Sequelae Among Patients with Varying COVID-19 Severity: An Administrative Claims Database Analysis

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BACKGROUND & OBJECTIVE

BACKGROUND:

- Data showed over 600 million confirmed cases of COVID-19 and over 6 million related deaths.[1]
- Prior studies have reported wide range of neurologic manifestations among hospitalized COVID patients[2,3] and during the post acute phase lasting 180 days.[4]
- There is limited data on the incident neurologic sequelae post COVID, and over a longer time to follow up.

OBJECTIVE:

- To examine the long-term incident neurologic sequelae, post COVID recovery and assess relationship with COVID severity using real-world data.

METHODS

STUDY DESIGN AND DATABASE

- A retrospective cohort study was conducted using Optum Research Database during 01July2019 to 30Sep2022
- Neurologic conditions were identified using International Classification of Diseases, Tenth edition (ICD-10) diagnosis codes
- Individuals were followed a minimum of 12 months post COVID to identify neurologic sequalae

PATIENT SELECTION CRITERIA

- Patients were ≥18 years of age with COVID-19 diagnosis between 01Jan2020 and 31Oct2020. First diagnosis during the identification (ID) period was defined as the Index date.
- Continuous enrollment with medical and pharmacy benefits 6 months before (baseline) and ≥12 months after (follow-up) the index date. Patients with less than 12 months of follow up due to death were excluded
- No evidence of neurologic sequelae during the baseline period
- No missing demographics, insurance type and geographic region; no evidence of pregnancy during the study period

STUDY COHORTS

- The following cohorts were created. Patients were assigned to the most severe cohort, if multiple were present.
  - Mild COVID (index diagnosis)
  - Moderate COVID (evidence of hospital inpatient admission within 15 days of index diagnosis)
  - Severe COVID (evidence of acute respiratory distress including mechanical ventilation, intensive care unit admission, or supplemental oxygen within 15 days of diagnosis).

STUDY OUTCOMES

- Any neurologic sequelae in follow up (Persistent headache, migraine, anosmia, sleep disturbance, cognitive dysfunction, post-traumatic stress disorder, suicidality, anxiety, depression, attention deficit hyperactivity disorder, cerebrovascular disease/stroke, fatigue/pain/myalgia and tremors)
- Number of neurologic sequelae
- Other covariates (baseline):
  - Patient demographics (Age, gender, insurance type, geographic region)
  - Clinical characteristics (Charlson comorbidity score and categories, comorbid conditions)

STATISTICAL ANALYSIS

- All study variables, including baseline and outcome measures, were analyzed descriptively
- Results were stratified by COVID severity cohorts
- Incident rate ratios (IRR's) were calculated using neurologic events during follow up per 10,000 person-years at risk.
- Kaplan–Meier (KM) analysis was used to estimate the fraction of patients with neurologic sequelae at 6, 12, 18 and 24 months.
- A Cox proportional hazards model was used to assess the incident neurologic sequelae adjusting for baseline demographics and comorbid conditions

RESULTS

STUDY OUTCOMES

- A total of 534,843 patients were identified with COVID-19 during the ID period. Of those,107,656 met the study inclusion criteria (Mild 96,637; Moderate 3,371; Severe 7,648).
- Patients in the mild cohort were younger and had fewer comorbidities compared with patients in the moderate and severe cohorts (Table 1). Mean (SD) age was 47.8 (18.6), 65.0 (16.1) and 65.2 (14.4) in the mild, moderate and severe cohorts, respectively.
- About 78% of patients had commercial coverage in the mild cohort compared with 38% in both the moderate and severe cohorts.
- In all the study cohorts, most patients were Caucasian and from the South.
- Median follow up time was 750, 774 and 768 days in the mild, moderate and severe cohorts, respectively.
- Mean Charlson score was 0.3 (0.8) in the mild cohort, 0.9 (1.4) in moderate and 0.8 (1.6) in the severe cohort.
- Overall and within the cohorts, most prevalent comorbid conditions in the baseline were overweight/obesity (12.1% overall) followed by thyroid disorders (6.7% overall) and chronic kidney disease (5.7% overall) (Table 2)

Table 1 Demographics and clinical characteristics of study population, by COVID severity levels

Demographics/ Clinical Characteristics	Mild (n=96,637)	Moderate (n=3,371)	Severe (n=7,648)
Age, mean (SD)	47.8 (18.6)	65.0 (16.1)	65.2 (14.4)
Age group, n (%)			
18 to 44	43,461 (45.0%)	429 (12.7%)	762 (10.0%)
45 to 64	31,257 (32.3%)	915 (27.1%)	2,225 (29.1%)
65+	21,919 (22.7%)	2,027 (60.1%)	4,661 (60.9%)
Gender, n (%)			
Female	45,686 (47.3%)	1,480 (43.9%)	3,110 (40.7%)
Male	50,951 (52.7%)	1,891 (56.1%)	4,538 (59.3%)
Insurance type, n (%)			
Commercial	75,119 (77.7%)	1,295 (38.4%)	2,921 (38.2%)
Medicare	21,518 (22.3%)	2,076 (61.6%)	4,727 (61.8%)
Region, n (%)			
Midwest	16,142 (16.7%)	491 (14.6%)	843 (11.0%)
Northeast	23,202 (24.0%)	853 (25.3%)	1,991 (26.0%)
South	43,242 (44.8%)	1,795 (53.3%)	4,020 (52.6%)
West	14,051 (14.5%)	232 (6.9%)	794 (10.4%)
Race, n (%)			
African American/Black	9,629 (10.6%)	706 (21.9%)	1,479 (20.4%)
Asian	3,450 (3.8%)	101 (3.1%)	252 (3.5%)
Caucasian	55,423 (60.9%)	1,683 (52.3%)	3,580 (49.3%)
Hispanic	17,921 (19.7%)	616 (19.1%)	1,663 (22.9%)
Other/Unknown	4,660 (5.1%)	114 (3.5%)	288 (4.0%)
Follow up days, median	750	774	768
Charlson Score, mean (SD)	0.3 (0.8)	0.9 (1.4)	0.8 (1.4)
Charlson score category, n(%)			
0	82,527 (85.4%)	2,010 (59.6%)	4,621 (60.4%)
1 to 2	11,159 (11.6%)	982 (29.1%)	2,174 (28.4%)
3 to 4	2,265 (2.3%)	275 (8.2%)	681 (8.9%)
5+	686 (0.7%)	104 (3.1%)	172 (2.3%)

Table 2 Top ten comorbid conditions in baseline, by COVID severity levels

Top ten comorbid conditions in baseline	Mild (n=96,637)	Moderate (n=3,371)	Severe (n=7,648)
Comorbid Conditions n(%)			
Overweight/obese	10,760 (11.1%)	657 (19.5%)	1,619 (21.2%)
Thyroid disorders	6,092 (6.3%)	378 (11.2%)	784 (10.3%)
Chronic kidney disease	4,192 (4.3%)	627 (18.6%)	1,284 (16.8%)
Smoking	2,841 (2.9%)	263 (7.8%)	640 (8.4%)
Cancer	2,886 (3.0%)	301 (8.9%)	538 (7.0%)
Chronic obstructive pulmonary disease	1,650 (1.7%)	174 (5.2%)	700 (9.2%)
Liver Disease	1,316 (1.4%)	119 (3.5%)	214 (2.8%)
Asthma	833 (0.9%)	25 (0.7%)	74 (1.0%)
Substance use disorder	722 (0.8%)	66 (2.0%)	80 (1.1%)
Immunocompromised state	298 (0.3%)	41 (1.2%)	52 (0.7%)

NEUROLOGIC SEQUELAE

- The mean (SD) count of neurologic sequelae was 1.1 (1.2) in mild, 1.9 (1.5) in moderate and 1.9 (1.5) in the severe cohort.
- About 13% of patients in the mild, 28% in moderate and 30% in the severe cohort experienced ≥3 neurologic sequelae during the follow-up period. (Figure 1)
- A significantly higher incidence of any neurologic sequelae was observed in moderate and severe cohorts compared with the mild cohort (IRR 3.1 for both; p<0.001). (Table 3)
- Cognitive dysfunction (moderate IRR 5.4, severe IRR 5.7; p<0.001), and CVD (moderate IRR 4.8, severe IRR 4.0; p<0.001) were the most commonly occurring manifestations in moderate and severe cohorts compared with the mild cohort. (Table 3)
- In KM analysis, the difference in the occurrence of any neurologic sequelae between the mild, moderate and severe cohorts was statistically significant over the variable follow-up period (p<0.001).(Figure 2)
- Patients in mild cohort had a lower adjusted hazard of any neurologic event compared with the moderate (HR = 2.155, 95% CI: 2.074-2.240) and severe cohorts (HR = 2.152, 95% CI: 2.094-2.212). (Table 4)
- Moreover, age 45 to 64 years, female gender, Medicare coverage, baseline Charlson comorbidity scores of 1-2 and 3+ had a higher risk of any neurologic sequelae. (Table 4)

Figure 1 Count of neurologic sequelae during variable follow-up

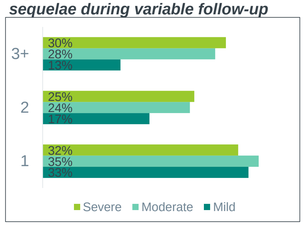

Figure 2 KM curve: Any neurologic sequelae during variable follow-up

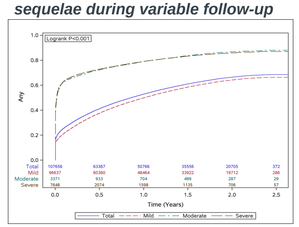

Table 3 IRR: Neurologic sequelae during variable follow-up

Neurologic sequelae during follow-up	Moderate vs Mild		Severe vs Mild		Severe vs Moderate	
	Ratio	p-value	Ratio	p-value	Ratio	p-value
Neurologic conditions						
Any	3.1	<0.001	3.1	<0.001	1.0	0.76
Headache	1.1	0.002	1.0	0.321	0.9	0.047
Anosmia	0.6	<0.001	0.7	<0.001	1.0	0.814
Migraine	0.8	0.02	0.8	<0.001	1.0	0.945
Sleep disturbance	2.0	<0.001	2.9	<0.001	1.4	<0.001
Cognitive dysfunction	5.4	<0.001	5.7	<0.001	1.0	0.343
PTSD	1.3	0.19	1.4	0.008	1.1	0.684
Suicidality	4.2	<0.001	1.9	<0.001	0.5	0.001
Anxiety disorders	1.4	<0.001	1.5	<0.001	1.1	0.023
Depressive disorders	2.0	<0.001	2.1	<0.001	1.1	0.303
Cerebrovascular disease/stroke	4.8	<0.001	4.0	<0.001	0.8	0.003
ADHD	0.4	<0.001	0.2	<0.001	0.5	0.019
Fatigue/Pain/myalgia	2.7	<0.001	2.5	<0.001	0.9	0.004
Tremors	3.2	<0.001	3.0	<0.001	1.0	0.772

Table 4 Proportional hazards model for any neurologic sequelae- adjusted

Independent Variables	Any neurologic sequelae			
	HR	Lower 95% CI	Upper 95% CI	p-value
COVID severity cohort				
Mild (ref)	ref.	–	–	–
Moderate	2.155	2.074	2.240	<0.001
Severe	2.152	2.094	2.212	<0.001
Covariates				
Age group				<0.001
18 to 44 (ref)	ref.	–	–	–
45 to 64	1.110	1.090	1.131	<0.001
65+	1.004	0.967	1.043	0.833
Gender				
Female (ref)	ref.	–	–	–
Male	0.791	0.779	0.803	<0.001
Race				<0.001
Black	0.999	0.974	1.023	0.914
Asian	0.876	0.840	0.915	<0.001
Caucasian (ref)	ref.	–	–	–
Hispanic	1.012	0.992	1.032	0.250
Other/Unknown/Missing	0.967	0.942	0.992	0.010
Insurance type				
Commercial (ref)	ref.	–	–	–
Medicare	1.253	1.208	1.299	<0.001
Region				<0.001
Northeast	0.991	0.969	1.013	0.416
Midwest	0.988	0.969	1.007	0.225
South (ref)	ref.	–	–	–
West	0.901	0.880	0.922	<0.001
Baseline Charlson comorbidity score (categorical)				<0.001
0 (ref)	ref.	–	–	–
1-2	1.175	1.144	1.206	<0.001
3+	1.395	1.327	1.467	<0.001

Proportional hazards test (overall - log(time) with Schoenfeld residuals): p-value=<0.001
Proportional hazards sub-test (log(time) with Schoenfeld residuals): p-value=<0.001
Adjusted for COVID severity cohort, age, gender, race/ethnicity, insurance, geographic region, index month, baseline Charlson score (categorized), baseline comorbidities (asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, HIV, immunocompromised state, interstitial lung disease, liver disease, overweight/obese, smoking, solid organ or blood stem cell transplant, substance use disorder, thyroid disorders)

LIMITATIONS

- As with all retrospective studies with claims data, there is a potential of bias from misclassification and misinformation since claims were collected for the purpose of payment.
- A 6-month baseline period may not eliminate the existing neurologic conditions and the IRR may be overestimated.
- Cohorts based on inpatient visits may have been more likely to have outcomes identified, given that they were already interacting with the health system; while patients in the mild population may have been less likely to visit their provider during the follow-up period. COVID diagnosis may also have been incidental to the hospitalization that assigned the index date.

CONCLUSIONS

- These results highlight the need for long-term monitoring and preventative strategies for neurologic conditions post COVID recovery that might impair quality of life and increase overall healthcare burden in the U.S.

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Disclosure: This study was exclusively for research purposes and all authors declare no conflict of interest.

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