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Long-Term Metabolic Sequelae of COVID-19, by Severity Levels

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BACKGROUND & OBJECTIVE

BACKGROUND:

- An estimated 6 million deaths have occurred worldwide since the start of pandemic in January 2020, attributed mainly to pulmonary damage and resulting comorbid conditions.[1]
- Prior studies have assessed post-acute sequelae of COVID, usually for a shorter time period post COVID.[2]
- A range of metabolic conditions have been reported among patients beyond the acute phase of COVID. These may be an aggravation of an existing condition or a new onset symptom or disease[3]; however, the evidence is limited.

OBJECTIVE:

- To estimate the long-term metabolic sequelae after COVID diagnosis 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
- Metabolic 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 metabolic sequalae

PATIENT SELECTION CRITERIA

- Patients were ≥18 years of age with COVID-19 diagnosis between 01Jan2020 and 31Oct2020. The 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 metabolic sequelae during the baseline period
- No missing demographics, insurance type and geographic region; or evidence of pregnancy during the study period

STUDY COHORTS

- The following cohorts were created. Patients were assigned to the most severe cohort, if multiple types 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 Metabolic sequelae in follow up including (acute myocardial infarction/stroke (MI), cardiomyopathy, heart failure (HF), myocarditis, pericardial disease (PCD), conduction disorders, coronary artery disease, thrombolytic/hemolytic disorders (TH), hypotension (HYP), diabetes, pulmonary heart disease (PHD), hemolytic-uremic syndrome, other heart diseases, and bowel-ischemia)
- Number of metabolic sequelae, time to first metabolic sequelae
- Other covariates (baseline):
  - Patient demographics (Age, gender, insurance type, geographic region)
  - Clinical characteristics (Charlson comorbidity score, 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 metabolic events during follow up per 10,000 person-years at risk.
- Kaplan–Meier (KM) analysis was used to estimate the fraction of patients with metabolic sequelae at 6, 12, 18 and 24 months.
- A Cox proportional hazards model was used to assess the incident metabolic 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, 146,718 met the study inclusion criteria (Mild 134,134; Moderate 4,119; Severe 8,465) .
- 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 46.9 (18.1), 61.5 (17.2) and 62.4 (15.2) in the mild moderate and severe cohorts, respectively.
- About 79% of patients had commercial coverage in the mild cohort compared with nearly 45% in both the moderate and severe cohorts.
- In all the study cohorts, most patients were Caucasian and from the South census region.
- Median follow up time was 750, 771 and 767 days in the mild, moderate and severe cohorts, respectively.
- Mean Charlson score was 0.3 (0.8) in the mild cohort, 0.7 (1.3) in moderate and 0.6 (1.1) in the severe cohort.
- Overall and within the cohorts, the most prevalent comorbid conditions in the baseline were overweight/obesity (13.8% overall) followed by thyroid disorders (7.9% overall) and chronic kidney disease (4.2% overall) (Table 2)

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

Demographics/ Clinical Characteristics	Mild (n=134,134)	Moderate (n=4,119)	Severe (n=8,465)
Age, mean (SD)	46.9 (18.1)	61.5 (17.2)	62.4 (15.2)
Age group, n (%)			
18 to 44	62,613 (46.7%)	737 (17.9%)	1,180 (13.9%)
45 to 64	44,967 (33.5%)	1,313 (31.9%)	2,920 (34.5%)
65+	26,554 (19.8%)	2,069 (50.2%)	4,365 (51.6%)
Gender, n (%)			
Female	71,126 (53.0%)	2,146 (52.1%)	3,966 (46.9%)
Male	63,008 (47.0%)	1,973 (47.9%)	4,499 (53.2%)
Race/Ethnicity, n (%)			
African American/Black	12,459 (9.9%)	702 (17.9%)	1,345 (16.8%)
Asian	4,221 (3.3%)	113 (2.9%)	243 (3.0%)
Caucasian	80,254 (63.4%)	2,279 (58.0%)	4,401 (54.9%)
Hispanic	23,104 (18.3%)	682 (17.4%)	1,686 (21.0%)
Other/Unknown	6,506 (5.1%)	155 (3.9%)	337 (4.2%)
Region, n (%)			
Northeast	21,822 (16.3%	586 (14.2%)	955 (11.3%)
Midwest	31,949 (23.8%)	1,050 (25.5%)	2,203 (26.0%)
South	60,279 (44.9%)	2,145 (52.1%)	4,319 (51.0%)
West	20,084 (15.0%)	338 (8.2%)	988 (11.7%)
Insurance type, n (%)			
Commercial	106,227 (79.2%)	1,885 (45.8%)	3,775 (44.6%)
Medicare	27,907 (20.8%)	2,234 (54.2%)	4,690 (55.4%)
Follow up days, median	750	771	767
Charlson Score, mean (SD)	0.3 (0.8)	0.7 (1.3)	0.6 (1.1)
Charlson score category, n (%)			
0	113,995 (85.0%)	2,753 (66.8%)	5,666 (66.9%)
1 to 2	16,334 (12.2%)	1,045 (25.4%)	2,221 (26.2%)
3 to 4	3,037 (2.3%)	242 (5.9%)	467 (5.5%)
5+	768 (0.6%)	79 (1.9%)	111 (1.3%)

Table 2 Top ten comorbid conditions, by COVID severity levels

Top ten comorbid conditions in baseline	Mild (n=134,134)	Moderate (n=4,119)	Severe (n=8,465)
Comorbid Conditions n (%)			
Overweight/obese	17,524 (13.1%)	835 (20.3%)	1,830 (21.6%)
Thyroid disorders	10,227 (7.6%)	460 (11.2%)	927 (11.0%)
Smoking	6,010 (4.5%)	511 (12.4%)	901 (10.6%)
Chronic kidney disease	4,834 (3.6%)	456 (11.1%)	870 (10.3%)
Cancer	3,982 (3.0%)	366 (8.9%)	540 (6.4%)
Chronic obstructive pulmonary disease	2,966 (2.2%)	248 (6.0%)	945 (11.2%)
Substance use disorder	2,942 (2.2%)	233 (5.7%)	283 (3.3%)
Liver Disease	2,774 (2.1%)	200 (4.9%)	318 (3.8%)
Asthma	1,667 (1.2%)	54 (1.3%)	135 (1.6%)
Immunocompromised state	556 (0.4%)	56 (1.4%)	72 (0.9%)

METABOLIC SEQUELAE

- Any metabolic sequelae were observed in about 20% of patients in the mild cohort, 59% in moderate and 67% in the severe cohort during follow up. The mean (SD) count of metabolic sequelae was 0.4 (0.9) in mild, 1.4 (1.7) in moderate and 1.8 (1.9) in the severe cohort.
- ≥3 sequelae were observed in 3.9% of patients in mild cohort, 21% in moderate and 29% in severe cohort. (Figure 1)
- At follow-up, moderate and severe cohorts had 5.0- and 7.1-times increased risk (IRR) of any metabolic sequelae compared to the mild cohort (p<0.001). Severe patients had 1.4 times higher risk of any metabolic sequelae versus moderate cohort (p<0.001). (Table 3)
- PHD, HYP, MI, HF, PCD and TH disorders were the most common metabolic manifestations in both moderate and severe cohorts (all IRR>5 vs. mild cohort; p<0.001). (Table 3)
- In KM analysis, the difference in the occurrence of any metabolic sequelae between the mild, moderate and severe cohorts was statistically significant (p<0.001).(Figure 2)
- In the Cox model, the adjusted hazard ratio of any metabolic sequelae was 2.9 and 3.8 times higher in patients with moderate and severe COVID respectively, than in those with mild COVID (Table 4).

Figure 1 Count of metabolic sequelae during variable follow-up

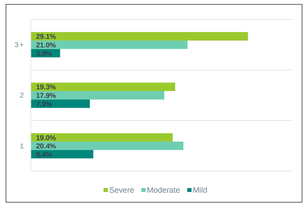

Figure 2 KM curve: Any metabolic sequelae during variable follow-up

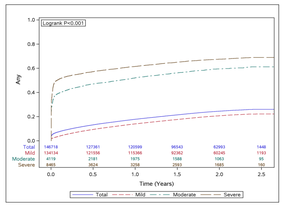

Table 3 IRR: metabolic Sequelae during Variable Follow-up

Metabolic Sequelae during follow-up	Incident Rate Ratio					
	Moderate vs Mild		Severe vs Mild		Severe vs Moderate	
	Ratio	p-value	Ratio	p-value	Ratio	p-value
Metabolic conditions						
Any	**5.0**	**<0.001**	**7.1**	**<0.001**	**1.4**	**<0.001**
Acute MI/Cardiac arrest/Stroke	6.8	<0.001	8.9	<0.001	1.3	<0.001
Cardiomyopathy	4.5	<0.001	7.1	<0.001	1.6	<0.001
Heart conduction disorders	4.0	<0.001	4.9	<0.001	1.2	<0.001
Heart failure	5.5	<0.001	7.9	<0.001	1.4	<0.001
Myocarditis	4.0	<0.001	4.5	<0.001	1.1	0.713
Pericardial disease	5.5	<0.001	5.7	<0.001	1.0	0.83
Coronary artery disease	3.7	<0.001	4.1	<0.001	1.1	0.083
Other heart disease	4.0	<0.001	5.2	<0.001	1.3	0.004
Pulmonary heart/vessel disease	6.2	<0.001	10.8	<0.001	1.7	<0.001
Thrombotic/hemolytic disorders	5.5	<0.001	6.5	<0.001	1.2	<0.001
Hypotension	6.9	<0.001	8.1	<0.001	1.2	0.002
Diabetes	2.7	<0.001	3.9	<0.001	1.4	<0.001
Diabetes - type 2	2.7	<0.001	3.9	<0.001	1.4	<0.001
Hemolytic-uremic syndrome	–	1	–	1	–	1
Bowel ischemia	3.5	0.002	2.7	0.003	0.8	0.515

Table 4 Proportional hazards model for any metabolic sequelae- adjusted

Independent Variables	Any metabolic sequelae			
	Hazard ratio	Lower 95% CI	Upper 95% CI	p-value
COVID severity cohort				
Mild (ref)	ref.	–	–	–
Moderate	2.853	2.734	2.977	<0.001
Severe	3.760	3.647	3.876	<0.001
Covariates				
Age group				<0.001
18 to 44 (ref)	ref.	–	–	–
45 to 64	2.518	2.440	2.599	<0.001
65+	3.094	2.951	3.242	<0.001
Gender				
Female (ref)	ref.	–	–	–
Male	1.145	1.120	1.170	<0.001
Race				<0.001
African-American/Black	1.246	1.206	1.288	<0.001
Asian	1.063	0.998	1.133	0.058
Caucasian (ref)	ref.	–	–	–
Hispanic	1.084	1.053	1.117	<0.001
Other/Unknown/Missing	1.066	1.027	1.106	<0.001
Insurance type				
Commercial (ref)	ref.	–	–	–
Medicare	1.670	1.604	1.738	<0.001
Region				<0.001
Northeast	1.196	1.161	1.231	<0.001
Midwest	0.997	0.969	1.025	0.826
South (ref)	ref.	–	–	–
West	0.899	0.868	0.931	<0.001
Baseline Charlson comorbidity score (categorical)				<0.001
0 (ref)	ref.	–	–	–
1-2	1.235	1.196	1.276	<0.001
3+	1.448	1.363	1.537	<0.001

Proportional hazards test (overall - log(time) with Schoenfeld residuals): p-value=<0.001
Adjusted for age, gender, race, insurance, geographic region, index month, baseline Charlson score, and baseline comorbidities (asthma, cancer, chronic kidney disease, chronic obstructive pulmonary disease, HIV, immunocompromised state, interstitial lung disease, liver disease, overweight/obese, smoking, solid organ/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 metabolic 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

- The study provides early insights into long-term metabolic sequelae among COVID patients using large claims database highlighting the need for continuous monitoring and evaluation of moderate-to-severe COVID patients to prevent newer metabolic conditions.

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

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