Long COVID is a Multisystem Disorder: Assessment of the National Academies Definition

922

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BACKGROUND:

- Long COVID was recently defined by the National Academies of Science Engineering and Medicine (NASEM): An infection-associated chronic condition occurring after SARS-CoV-2 infection. Can manifest as one or multiple symptoms or diagnosable conditions.[1]
- We evaluated the new NASEM Long COVID definition.

METHODS

- We reviewed hospital admissions from 5/1/20 – 9/30/22 in electronic health records (EHR) from a multistate healthcare system (Providence Health & Services).
- The COVID+ group had first SARS-CoV-2 lab test or encounter diagnosis between 30 days before to 5 days after admission, and the non-COVID group was admitted with no prior or current SARS-CoV-2 test or diagnosis.

Table 1:

Feature:	COVID+ Admissions (n=46,841)	Non-COVID Admissions (n=426,047)
Age, mean (SD):	61.2 (19.2)	57.9 (21.3)
Male Sex:	21,798 (46.5%)	158,187 (37.1%)
Race:		
White	33,123 (70.7%)	319,924 (75.1%)
Black	1,798 (3.8%)	14,796 (3.5%)
Other	11,920 (25.4%)	91,327 (21.4%)
Ethnicity:		
Hispanic	9,202 (19.6%)	51,898 (12.2%)
Not Hispanic	32,420 (69.2%)	321,734 (75.5%)
Other	5,219 (11.1%)	52,415 (12.3%)
Commercial Insurance	9,667 (20.6%)	117,658 (27.6%)
CCI, mean (SD)	1.5 (2.1)	1.2 (1.9)
Immunocompromised	195 (0.4%)	1,158 (0.3%)
Variant Era:		
Origin	19,804 (42.3%)	245,472 (57.6%)
Delta	10,854 (23.2%)	78,520 (18.4%)
Omicron	16,183 (34.5%)	102,055 (24.0%)
Fully Vaccinated	12,678 (27.1%)	142,561 (33.5%)
Steroid Use, mean (SD) *	697.3 (2737.3)	324.8 (6824.2)
Admission WHO OSS:		
Non-severe	33,214 (70.9%)	354,182 (83.1%)
Severe	11,484 (24.5%)	62,167 (14.6%)
Critical	2143 (4.6%)	9,698 (2.3%)

CCI = Charleston Comorbidity Index; * prednisone equivalents

Long COVID is multisystem disorder per the *new* ***NASEM definition***. Incident diagnoses across multiple organ systems were evident after COVID-19 hospitalization compared to all other hospitalizations in EHR data from a large health system.

METHODS (continued):

- The populations were balanced with overlap weights based on a high-dimensional propensity score of pre-specified variables and the top 100 comorbidities differing between the groups.[2]
- Hazard ratios (HR) were calculated for the combined primary outcome including any of the individual secondary outcomes or U09.9 (Post-Covid Conditions).
- Secondary outcomes included 29 individual incident diagnoses 90 to 360 days after admission.
- To account for multiplicity on secondary outcomes, a Bonferroni-corrected p-value < 0.0017 was considered significant.

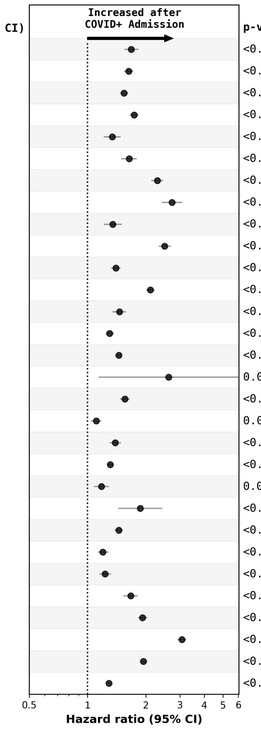
RESULTS

- Admissions included 45,065 persons with and 417,268 persons without COVID-19 during the study period. Mean age: 58 years, 62% female, 25.4% non-white, and 13% Hispanic (**Table 1**).
- After weighting, SMD was < 0.01 for age, sex, race, ethnicity, insurance, vaccination, variant era, WHO ordinal scale, steroid use, immunocompromised status and 100 clinical features.
- In the COVID+ and non-COVID groups 16,945 (37.6%) and 122,201 (29.3%) met the combined primary outcome, respectively.
- The HR for the primary outcome after weighting was 1.29 (95%CI 1.27, 1.32), p < 0.00001.
- Of the individual secondary outcomes, all but 1 outcome (post-exertional malaise) had significantly elevated HR in the COVID+ vs. non-COVID groups, after adjustment for multiplicity (**Figure 1**).
- Incident diagnoses with strong associations (HR > 2) included thromboembolism, hair loss, diabetes mellitus, obesity, and hypoxia.
- Anosmia/dysgeusia was associated with prior COVID admission, but wide confidence intervals reflected few charted diagnoses.

Figure 1:

Organ System	Outcome	Hazard ratio (95% CI)	p-value
Cardiovascular	Acute coronary syndrome †	1.68 (1.55, 1.83)	<0.0001
	Arrythmias †	1.63 (1.54, 1.72)	<0.0001
	Chest pain	1.54 (1.47, 1.62)	<0.0001
	Heart failure †	1.74 (1.65, 1.83)	<0.0001
	Palpitations	1.34 (1.21, 1.48)	<0.0001
	Tachycardia	1.64 (1.49, 1.79)	<0.0001
Coagulation	Thromboembolism †	2.29 (2.13, 2.46)	<0.0001
Dermatological	Hair loss	2.73 (2.42, 3.08)	<0.0001
	Skin rash	1.35 (1.21, 1.50)	<0.0001
Endocrine	Diabetes mellitus †	2.50 (2.33, 2.69)	<0.0001
	Hyperlipidemia †	1.40 (1.32, 1.48)	<0.0001
	Obesity †	2.11 (2.00, 2.22)	<0.0001
Gastrointestinal	GERD †	1.46 (1.34, 1.58)	<0.0001
	GI symptoms †	1.30 (1.24, 1.37)	<0.0001
General	Fatigue	1.45 (1.39, 1.51)	<0.0001
	Post-exertional malaise	2.62 (1.14, 6.04)	0.024
Kidney	Kidney dysfunction †	1.56 (1.47, 1.65)	<0.0001
Mental health	Anxiety/Depression †	1.11 (1.04, 1.18)	0.0016
	Sleep disorder †	1.39 (1.30, 1.49)	<0.0001
Musculoskeletal	Joint/Muscle pain	1.31 (1.26, 1.36)	<0.0001
	Muscle weakness	1.18 (1.08, 1.29)	0.00034
Neurological	Anosmia/Dysgeusia	1.87 (1.44, 2.43)	<0.0001
	Brain fog	1.45 (1.38, 1.52)	<0.0001
	Dysautonomia	1.20 (1.13, 1.28)	<0.0001
	Headache	1.23 (1.15, 1.32)	<0.0001
	Ischemic Stroke/TIA †	1.67 (1.53, 1.81)	<0.0001
Respiratory	Cough	1.92 (1.82, 2.03)	<0.0001
	Hypoxia †	3.07 (2.91, 3.23)	<0.0001
	Shortness of breath	1.94 (1.86, 2.03)	<0.0001
Multisystem	Long Covid	1.29 (1.27, 1.32)	<0.0001

† Baseline condition excluded anytime prior; Otherwise: excluded in the 1 year prior.



CONCLUSIONS

- Manifestations of Long COVID at population scale are detectable as routine symptoms and clinical diagnoses in the EHR after admissions for COVID-19, compared with all other admissions.
- Some features of Long COVID not well coded in EHR:
  - Post-exertional malaise (ICD-10 diagnosis codes not well mapped to this symptom).
  - Anosmia/dysgeusia not commonly coded in medically attended visits.
- The NASEM Long COVID definition is a useful construct for observational research in that multiple symptoms or diagnosable conditions are detectable in a COVID+ versus non-COVID hospitalized populations.

ADDITIONAL KEY INFORMATION

- References: [1] National Academies, doi:10.17226/27768. [2] Al-Aly, Nature, 2021 PMID: 33887749.
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