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# Characterization of Long COVID Phenotypes and Associated Clinical Phenotypes in Administrative Claims Data

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## BACKGROUND

- Real-world data (RWD) are being employed to understand post-acute sequelae of COVID-19, or long COVID
- Numerous RWD studies have utilized different data sources to identify clinical phenotypes of long COVID[1-4]
- A study by Zhang et al used a machine learning approach to electronic health record (EHR) data, resulting in 4 clinical phenotypes: cardiac and renal (CR); respiratory, sleep, and anxiety (RSA); musculoskeletal and nervous (MN); and digestive and respiratory (DR)[4]
- Efforts to understand the characteristics of patients diagnosed with long COVID using RWD are necessary as more people experience the lasting effects of COVID-19

## OBJECTIVE

- To map EHR-based clinical phenotypes to administrative claims data for the estimation of the rate of symptoms and conditions following a diagnosis of long COVID within each phenotype

## METHODS

### Study Design

- This retrospective observational cohort study used open and closed medical and pharmacy claims identified in the HealthVerity database

### Study Population

- Patients were eligible if they had evidence of long COVID:
  - ICD-10 diagnosis code of U09.9, post COVID-19 condition, unspecified, or B94.8, sequelae of other specified infectious and parasitic diseases, with a diagnosis code for COVID-19 (U07.1) in the 365 days prior
- The first date of a long COVID claim was defined as the index date

### Additional Inclusion Criteria

- Patient must have had ≥365 days of prior medical and pharmacy benefits enrollment with a 60-day allowable gap before the index date, as well as valid age (≥18 years) and sex data
- Phenotype subgroups were not mutually exclusive and were defined based on evidence of predetermined diagnosis codes falling into 1 of the specified categories occurring within 90 days before the long COVID index date through 90 days after the long COVID index date
  - Phenotypes were identified within this window to capture pre-existing conditions that may have been exacerbated by long COVID as well as conditions that were new onset following a long COVID diagnosis

### Primary Analysis

- Baseline characteristics were assessed from the start of all available data through 1 day before the index date, including long COVID symptoms and general clinical characteristics
- The distribution of phenotype subgroups, as well as overlap, was described across the study population
  - Each non-mutually exclusive phenotype subgroup was defined based on evidence of relevant ICD-10 diagnosis codes for the condition(s) within 90 days prior through 90 days following the long COVID index diagnosis date
- Within each phenotype subgroup, the distribution of individual clinical conditions was described (eg, the proportion of patients in the CR subgroup who had a cardiac diagnosis only, a renal diagnosis only, or both diagnoses)
- Rates of diagnosed conditions were estimated per 100,000 person-years during follow-up
- Patients were censored on the earliest occurrence of the condition of interest, end of enrollment, or end of available data (August 31, 2022)
  - An outcome-specific washout was applied from the start of all available data through 90 days before the index date

## RESULTS

### Baseline Characteristics

- The median age among the study population was 51 years (interquartile range [IQR]: 38, 61), and most were female (**Table 1**)
  - Patients in the CR subgroup were slightly older, with a median age of 56 years (IQR: 46, 64)
- The mean Charlson-Quan comorbidity score and prevalence of baseline comorbidities was highest among patients in the CR subgroup (mean: 2.34; standard deviation: 2.50)
- Additional baseline characteristics are presented in **Supplemental Table 1** and **Supplemental Figures 1-3**

**Table 1. Baseline[a] Demographic and Clinical Characteristics Among Patients Diagnosed With Long COVID Between January 1, 2021, and August 31, 2022**

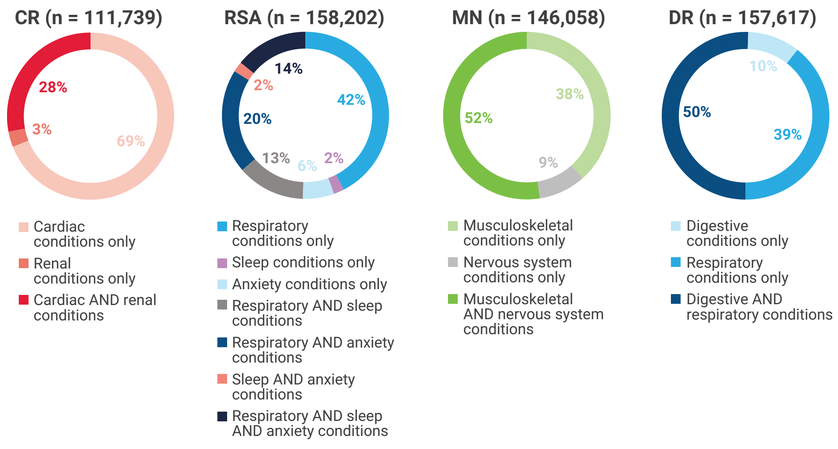
| | All Adult Patients[a] | Adult Clinical Phenotype Subgroups | | | |
|---|---|---|---|---|---|
| | Adult patients with a diagnosis of long COVID n = 188,232 | CR subgroup n = 111,739 | RSA subgroup n = 158,202 | MN subgroup n = 146,058 | DR subgroup n = 157,617 |
| **Demographics (on index date)** | | | | | |
| **Continuous age, years** | | | | | |
| Median [IQR] | 51 [38, 61] | 56 [46, 64] | 51 [39, 61] | 51 [40, 61] | 51 [39, 61] |
| **Age categories, years, n (%)** | | | | | |
| 18-24 | 10,563 (5.6) | 2309 (2.1) | 8326 (5.3) | 6882 (4.7) | 8225 (5.2) |
| 25-49 | 79,163 (42.1) | 34,076 (30.5) | 65,762 (41.6) | 59,404 (40.7) | 64,866 (41.2) |
| 50-64 | 68,601 (36.4) | 48,257 (43.2) | 58,141 (36.8) | 54,279 (37.2) | 57,817 (36.7) |
| ≥65 | 29,905 (15.9) | 27,097 (24.3) | 25,973 (16.4) | 25,493 (17.5) | 26,709 (16.9) |
| **Sex, n (%)** | | | | | |
| Female | 124,854 (66.3) | 69,502 (62.2) | 105,560 (66.7) | 99,449 (68.1) | 105,370 (66.9) |
| **Insurance type, n (%)** | | | | | |
| Commercial | 90,538 (48.1) | 47,926 (42.9) | 73,159 (46.2) | 66,565 (45.6) | 71,974 (45.7) |
| Medicare | 22,439 (11.9) | 19,738 (17.7) | 19,692 (12.4) | 19,219 (13.2) | 20,155 (12.8) |
| Medicaid | 70,993 (37.7) | 41,376 (37.0) | 61,600 (38.9) | 56,802 (38.9) | 61,806 (39.2) |
| Missing | 4262 (2.3) | 2699 (2.4) | 3751 (2.4) | 3472 (2.4) | 3682 (2.3) |
| **Comorbidity Indices** | | | | | |
| **Charlson-Quan score (365-day baseline)[b]** | | | | | |
| Median [IQR] | 1 [0, 2] | 2 [0, 3] | 1 [0, 2] | 1 [0, 3] | 1 [0, 3] |
| **Frailty score (365-day baseline)** | | | | | |
| Median [IQR] | 0.14 [0.11, 0.18] | 0.17 [0.13, 0.22] | 0.15 [0.12, 0.19] | 0.15 [0.12, 0.20] | 0.15 [0.11, 0.19] |

CR, cardiac and renal; DR, digestive and respiratory; IQR, interquartile range; MN, musculoskeletal and nervous; RSA, respiratory, sleep, and anxiety; SD, standard deviation.
[a]Median days of follow-up time [IQR] irrespective of outcome rates: 196 [87, 262]. Follow-up time did not differ by phenotype subgroup.
[b]The baseline period began at the start of all data and ended 1 day before the cohort index date (long COVID diagnosis). All patients were required to have a minimum of 365 days of continuous baseline enrollment with a 60-day allowable gap.

### Symptom Overlap Within Phenotypes

- Among 188,232 patients identified with long COVID, 84.0% were in the RSA subgroup, 83.7% in the DR subgroup, 77.6% in the MN subgroup, and 59.4% in the CR subgroup (**Figure 1**)
  - The RSA subgroup included mostly patients with a respiratory diagnosis (42%)
  - Half of the patients in the DR subgroup had both a digestive and respiratory diagnosis; 10% of patients had only a digestive-related condition
  - The MN subgroup largely consisted of patients with both a musculoskeletal and nervous system diagnosis (52%)
  - The CR subgroup included mostly patients with a cardiac diagnosis only (69%) followed by patients with both a cardiac and renal diagnosis (28%)

**Figure 1. Overlap of Conditions Within Phenotype Subgroups Among Those Diagnosed With Long COVID Between January 1, 2021, and August 31, 2022**

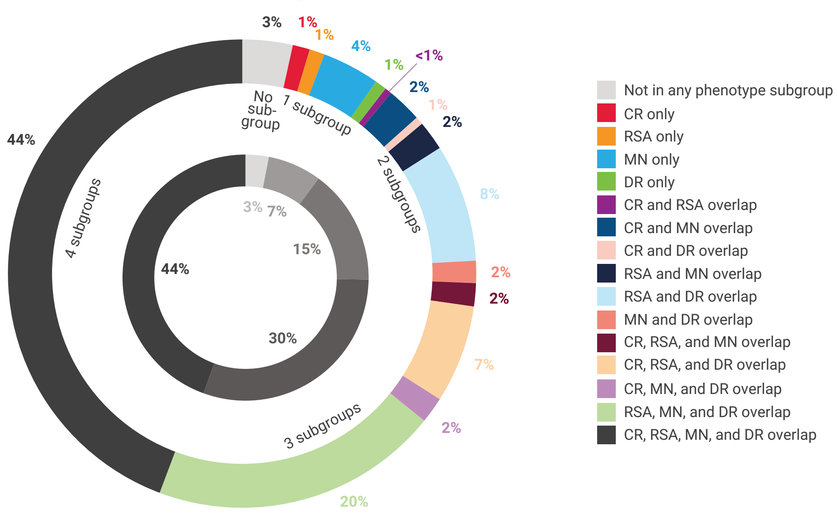



CR, cardiac and renal; DR, digestive and respiratory; MN, musculoskeletal and nervous; RSA, respiratory, sleep, and anxiety.

### Overlap Within Phenotype Subgroups

- Most adults (96.6%) were classified as being in ≥1 phenotype subgroup, and 45.9% qualified for all 4 phenotype subgroups (**Figure 2**)
- Approximately 3.0% of patients were not in any subgroup and 7.0% were in a single subgroup, while 44% qualified for entry into all 4 phenotype subgroups
  - Among patients who qualified for 1 subgroup, most qualified for the MN subgroup only (4%)

**Figure 2. Overlap Between Phenotype Subgroups Among Those Diagnosed With Long COVID Between January 1, 2021, and August 31, 2022**

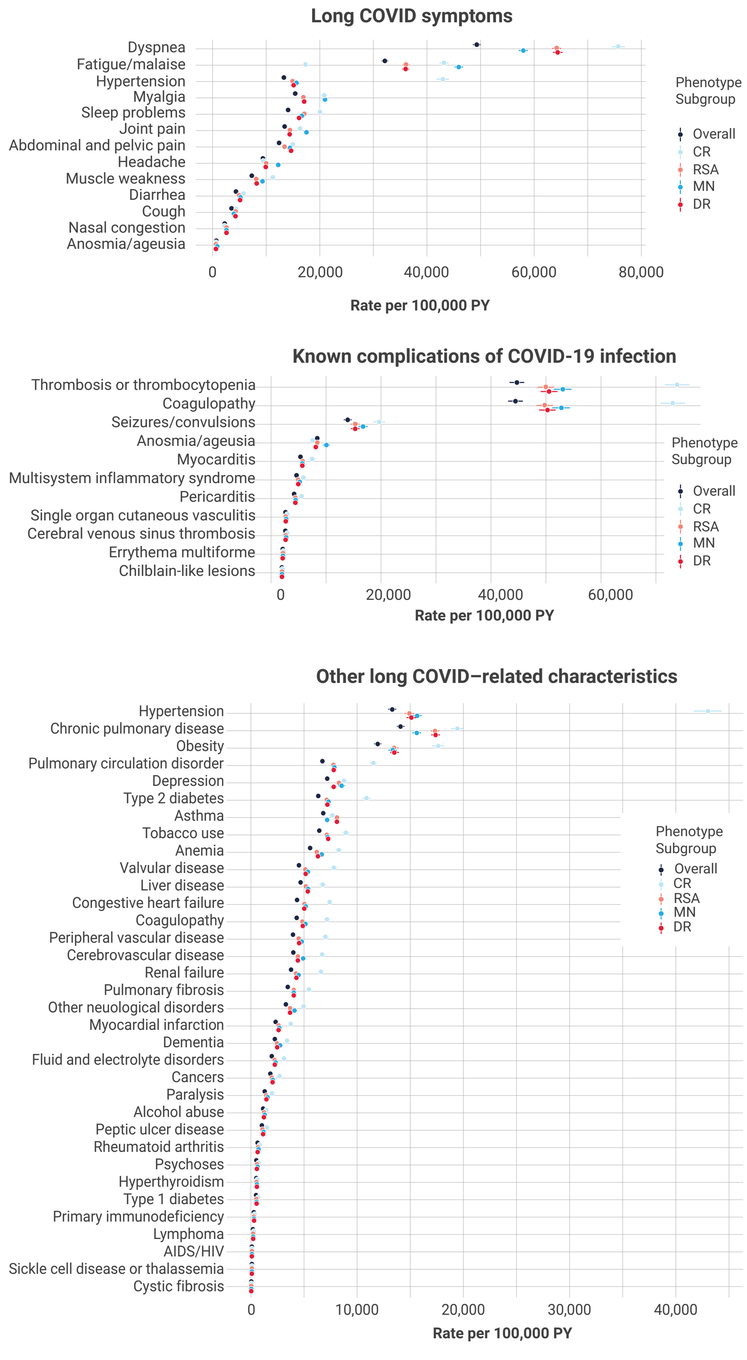



CR, cardiac and renal; DR, digestive and respiratory; MN, musculoskeletal and nervous; RSA, respiratory, sleep, and anxiety.

### Rates of Symptoms by Phenotype Subgroup

- Rates of dyspnea and fatigue/malaise ranked among the highest of conditions assessed (**Figure 3**)
- Rates of newly coded long COVID symptoms were highest among patients in the CR subgroup
- Rates of long COVID symptoms were similar among other subgroups. Observed trends in incidence rates were generally consistent within sex and phenotype subgroups

**Figure 3. Rates of Clinical Characteristics Stratified by Phenotype Subgroup**




CR, cardiac and renal; DR, digestive and respiratory; MN, musculoskeletal and nervous; PY, person years; RSA, respiratory, sleep, and anxiety.

## CONCLUSIONS

- Most patients with long COVID qualified for inclusion in ≥1 phenotype subgroup
  - The broad nature of the phenotypes subgroup inclusion criteria resulted in substantial overlap between the subgroup conditions
  - However, differences in long COVID symptoms were observed between clinical phenotypes, particularly among patients with cardiovascular or renal conditions
- Patients with pre-existing or newly developing cardiovascular or renal conditions demonstrate a greater risk of developing long COVID symptoms, which aligns with reports from EHR

### References

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4. Zhang H, et al. *Nat Med*. 2023;29(1):226-235.

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### Disclosures

BK, JS, MI, and KEM are employees at Aetion, Inc. BK and KEM are stock option holders of Aetion, Inc. AMR, SSL, DM, and DBE are employees of Moderna, Inc., and hold stock/stock options in the company.

## ADDITIONAL INFORMATION

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