The appraisal of WHO definition of post COVID-19 condition (Long COVID): an international network cohort and meta-analysis study

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Background: Epidemiological estimates of the post-COVID condition (PCC) are hampered by the lack of objective diagnostic biomarkers, thus they largely rely on clinical definitions and provide estimates based on pre-specified symptom lists. The WHO Delphi consensus group was unable to agree on a minimum number of symptoms to establish the PCC diagnosis.

Objective: We critically appraised the WHO PCC symptom list to identify which symptoms better discriminate PCC from test-negative controls, and propose a shorter symptom list that may be prioritised for future research of PCC.

Methods: We conducted a population-based retrospective study across an international network of 7 cohorts with observational health data mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM) from Europe (United Kingdom, Netherlands, Estonia, Spain, France) which covers both primary care and hospital settings. The study period spanned from September 1, 2020 to the end of available data (variable by data source, up to late 2022). We curated two denominator cohorts: a SARS-CoV-2 infection cohort, characterized by the presence of a positive PCR or LFT test result or a clinical diagnosis of COVID-19, with the index date defined as the first confirmed infection date; and a test-negative benchmarking cohort, identified by the initial PCR or LFT negative testing event. The numerator cohorts consisted of 25 post-acute symptoms, as issued by the World Health Organization (WHO). We followed individuals among the denominator cohorts from the index date to the occurrence of the outcome, death, loss of database coverage, or the end of the study, whichever occurred first. In accordance with the WHO guidelines, we exclusively considered symptoms manifesting >90 and 365 days post-index. Moreover, we implemented a 180-day washout period preceding the index to minimize the risk of recurrent coding of prior symptoms. We calculated the incidence rate (IR) for each outcome and derived the respective incidence rate ratio (IRR) by dividing the IR in the infection cohort by the IR in the test-negative cohort. Finally, we conducted a meta-analysis across multiple databases and ranked the 25 symptoms based on their IRR values.

Results: Compared with the test-negative cohort, the infection cohort showed significantly elevated incidences for most of the examined symptoms, with the most prominent being altered smell taste (IRR: 5.19 95% CI 3.97-6.79), dyspnea (2.87 95% CI 2.31-3.56), and cough (1.98 95% CI 1.57-2.51). Over the calendar years, the IRR were particularly pronounced for infections in the last quarter of 2020 and gradually declined throughout 2021 and 2022 (Figure 1).

Conclusion: Definition and diagnosis of PCC using altered smell taste, dyspnea, fatigue, cough, intermittent fevers can provide more accurate assessments of the PCC for epidemiological, pathogenesis and therapeutic research.

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