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Letter to the Editor

Is the number of long-term post-COVID symptoms relevant in hospitalized COVID-19 survivors?

Dear editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing the coronavirus disease-2019 (COVID-19) is associated with heterogeneous symptoms at its acute phase but also at post-acute phase. Current evidence suggests that 50% of survivors experience post-COVID symptoms the following months after the acute infection [1,2]. The presence of post-COVID symptoms is associated with worse quality of life [3]. In fact, up to 50 diffferent post-COVID symptoms have been described, and patients usually exhibit more than one symptom [4]. Similarly, the number of symptoms at onset is also heterogeneous, and patients can exhibit several number of symptoms. It has been found that a higher number of onset symptoms at the acute phase (high viral load) is associated with a greater number of post-COVID symptoms [5]. Previous studies focussing on post-COVID symptoms did not use machine learning analysis. Here we present the use of a network analysis for investigating the associations between COVID-19 onset symptoms at hospital admission and the presence of post-COVID symptoms at a long-term follow-up in previously hospitalised COVID-19 survivors recruited from different hospitals.

The LONG-COVID-EXP-CM is a multicenter cohort study including COVID-19 survivors hospitalized during the first wave of the pandemic (from March 10 to May 31, 2020) in five urban hospitals of Madrid (Spain). From all patients hospitalized during the first wave with a positive diagnosis of COVID-19 by RT-PCR technique and radiological findings, a sample of 400 subjects from each hospital was randomly selected by electronic softwares. The Ethics Committees of all the hospitals approved the study (HCSC20/495E, HSO25112020, HUFA 20/126, HUIL/092–20, HUF/EC1517). All participants provided their informed consent before their inclusion.

Demographic (age, sex, height, weight), clinical (pre-existing medical comorbidities), COVID-19 associated onset symptoms at hospital admission, and hospitalization (days in hospital, intensive care unit [ICU] admission) data were collected from hospital medical records. Patients were scheduled for a telephone interview conducted by trained health care professionals one year after hospital discharge and were systematically asked about the presence of post-COVID symptoms that experienced at the time of study (multiple symptoms could be selected by the same patient).

Statistical analyses were conducted using the R software v.4.1.1 for Windows 10. Additionally, the qgraph v.1.6.9 and glasso v.1.11 (for network estimation), igraph v.1.2.6 (for community detection), huge v.1.3.5 (for variable transformation), bootnet v.1.4.3 (for stability analysis), CINNA v.1.1.54 (for harmonic centrality measurement) and mgm v. 1.2–12 (for estimating k-order mixed graphical models) packages were used.

This network was composed by 33 nodes (6 continuous and 27 categorical variables). The edges represented the magnitude of strength (width of lines) and direction (green and red for positive and negative correlations respectively for continuous variables and gray for those including categorical variables which sign is not defined) of partial correlations between two nodes. The dataset as well as the related two vectors specifying the type ("g" for Gaussian, "p" for Poisson, "c" for categorical) and the number of levels for each variable was provided. The mgm was estimated for $k = 2$ to only take pairwise interactions into account, using least absolute shrinkage and selection operator (LASSO, ℓ1-regularization) that seeks to maximize specificity (aims to include as few false positives as possible). The LASSO tuning parameter λ selection was performed by minimization of Extended Bayesian Information Criterion (EBIC) to control the level of sparsity and minimize the number of spurious edges while maximizing the number of edges [6].

Since not all nodes in a network are equally important for determining the structure, centrality was assessed by calculating strength centrality (defined as the sum of weights of edges), betweenness centrality (defined as the total number of shortest paths that passes through the target node, moderated by the total number of shortest paths existing between any couple of nodes in the graphs) and harmonic centrality (defined as the sum of inverted distances of shortest paths of the target node from all other nodes in the network) [7].

Finally, to get an overview of the variability of the centrality indices, participant-dropping subset bootstrap (1000 iterations 95% confidence interval) was utilized. The CS-coefficient (correlation stability) reflects the maximum proportion of data that can be dopped to retain with 95% certainty a correlation of at least 0.7 with the original centrality indices [8]. Ideally, it has been suggested that this coefficient should be above at least 0.25.

From 2000 participants randomly selected from the involved hospitals and invited to participate, a total of 1593 (mean age: 61.5, SD: 16 years, 46.5% women) individuals were assessed at hospital admission and 13.2 (range 11 to 15) months after hospitalization The most common symptoms at hospital admission were fever (74.8%), dyspnea (30.4%), myalgia (30.3%), and cough (27.8%) (Table 1).

The node with the highest strength centrality and the highest betweenness centrality was the number of long-term post-COVID symptoms (node 19, Fig. 2). The node with the highest harmonic centrality was age (node 1, Suppl. Fig. 1). The betweenness ($CS_{cor=0.7}$ =0.50) and strength ($CS_{cor=0.7}$ =0.750) measures of the network were stable (Suppl. Fig. 2).

The application of network analysis in a large population of COVID-19 survivors from different hospitals supports the relevance of the number of long-term post-COVID symptoms at one-year follow-up after discharge. No association between onset symptoms at hospital admission and post-COVID symptoms was found. Fatigue and dyspnea were the long-term post-COVID symptoms showing higher correlations with the total number of post-COVID symptoms.

Table 1

Demographic and clinical data of the sample ($n = 1593$).

Age, mean (SD), years	61.5 (16)
Gender, male/female (%)	854 (53.5%) / 739 (46.5%)
Weight, mean (SD), kg.	74.5 (15)
Height, mean (SD), cm.	165 (17)
Number of onset symptoms at hospital admission	2.2 (0.8)
Main Symptoms at hospital admission, n (%)	
Fever	1193 (74.8%)
dyspnea	484 (30.4%)
Myalgia	483 (30.3%)
Cough	443 (27.8%)
Headache	266 (16.7%)
Vomiting	172 (10.8%)
Anosmia	130 (8.1%)
Ageusia	114 (7.1%)
Dizziness	55 (3.4%)
Stay at the hospital, mean (SD), days	11 (10.5)
Intensive Care Unit (ICU) admission	
Yes/No, n (%)	95 (5.9%) / 1498 (94.1%)
Stay at ICU, mean (SD), days	12 (11)
Number of long-term post-COVID symptoms	1.5 (1.4)
Post-COVID symptoms at 12 months, n (%)	
Fatigue	879 (55.2%)
dyspnea at exertion	787 (49.4%)
Musculoskeletal pain	603 (37.8%)
dyspnea at rest	233 (14.6%)
Memory loss	200 (12.5%)
Brain fog/Cognitive Blurring	85 (5.4%)
Ocular/Vision Disorders	77 (4.8%)
Concentration Loss	75 (4.7%)
Gastrointestinal Disorders	72 (4.5%)
Skin Rashes	58 (3.6%)
Loss hair	57 (3.5%)
Tachycardia-Palpitations	50 (3.2%)
Anosmia	49 (3.1%)
Ageusia	28 (1.8%)
Throat pain Voice problems	31 (1.9%)
	12 (0.7%)

According to the current network analysis, the number of post-COVID at one-year follow-up seems to play a relevant role in previously hospitalized COVID-19 survivors since this variable exhibited the highest centrality indices. A high number of post-COVID symptoms, particularly fatigue and dyspnea, could explain why some patients are not able to return to work several months after hospital discharge [9]. Interestingly, fatigue and dyspnea were the nodes showing the highest correlation with the numner of post-COVID symptoms one year after hospitalization in this study Fig. 1.

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Surprisingly, the number of symptoms at hospital admission was not significantly associated with the number of post-COVID symptoms at one-year when using a network analysis, as previously suggested [5]. Differences in statistical analyses and follow-up period could explain these discrepancies. It is possible that the association between onset symptoms (COVID-19 symptoms load) with the number of post-COVID symptom (post-COVID symptoms load) would be lower with longer follow-up periods. Indepedently of an association or a lack of with the number of onset symptoms at hospital admission, monitoring the heterogeneous expression of long-term post-COVID symptomatology may alert clinician of a broader afectaction by SARS-CoV-2 virus.

Although this is a large multicentre cohort study using network analysis and a one-year follow-up period, it should be recognized that only hospitalised COVID-19 survivors from the first wave were included. Second, the assessment of post-COVID symptoms at one-year was conducted by telephone. Third, the severity of the disease was not collected.

In conclusion, this multicenter study using a network analysis in a large population of COVID-19 survivors supports the relevance of the number of post-COVID symptoms at one-year after hospital discharge. No association with COVID-19 associated symptoms at hospital admission was observed.

Author contributions

All authors contributed to the concept and design. CFdlP and SFN conducted literature review. UV and JAVC did the statistical analysis. All authors recruited participants and collected data. SPC supervised the study. All authors contributed to interpretation of data. All authors contributed to drafting the paper, have revised the text for intellectual content and have read and approved the final version of the manuscript.

Consent to participate

Participants provided informed consent before collecting data.
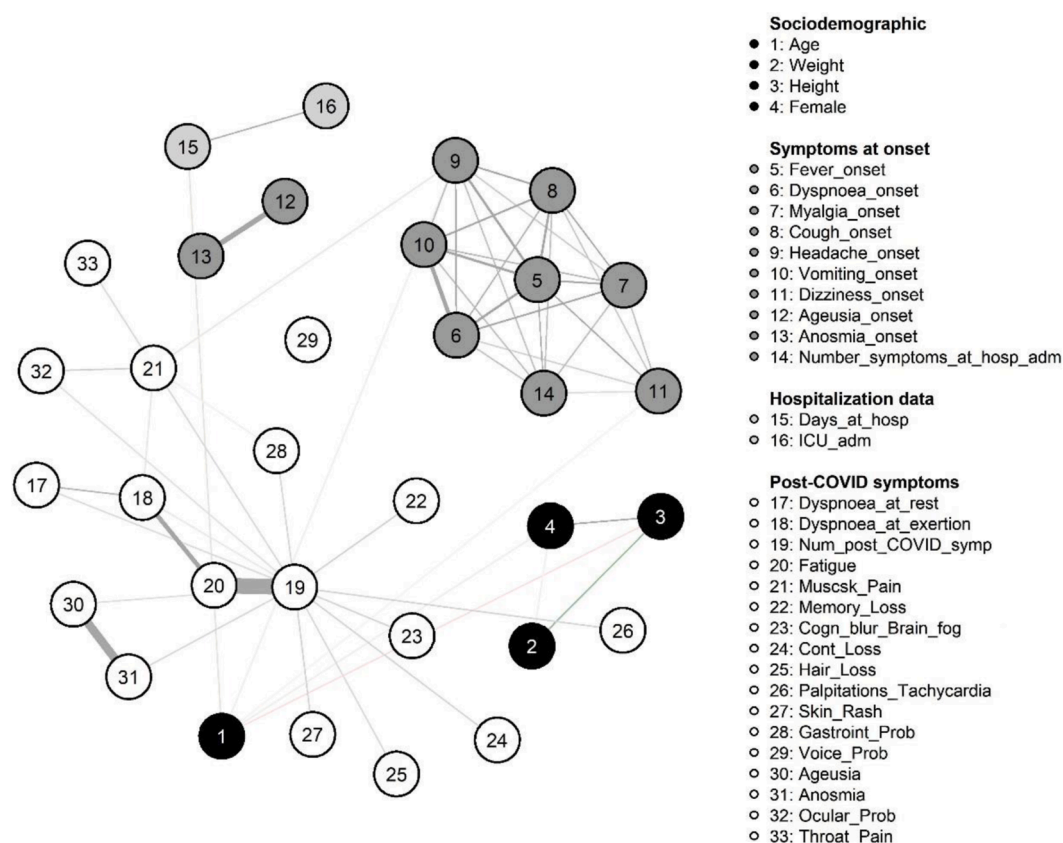
**Role of the funding source**

Declaration of Competing Interest

No conflict of interest is declared by any of the authors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.02.013.

Fig. 1. Network analysis of the association between demographic, hospitalization data, COVID-19 symptoms at hospital admission and long-term post-COVID symptoms. Edges represent connections between two nodes and are interpreted as the existence of an association between two nodes, adjusted for all other nodes. The thickness of an edge denotes its weight (the strength of the association between two nodes).
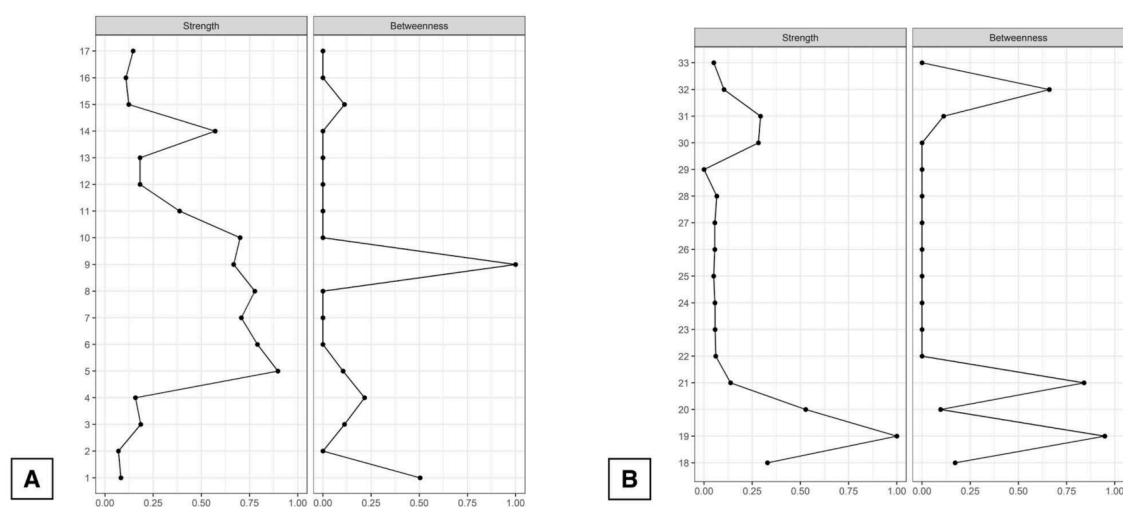
Fig. 2. Centrality measures of Strength and Betweenness of each node in the network. Centrality value of 1 indicates maximal importance, and 0 indicates no importance.

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