Acta Neurologica Belgica (2022) 122:1093–1095
https://doi.org/10.1007/s13760-022-01998-x

LETTER TO THE EDITOR

The relevance of headache as an onset symptom in COVID-19: a network analysis of data from the LONG-COVID-EXP-CM multicentre study

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Received: 8 May 2022 / Accepted: 1 June 2022 / Published online: 7 June 2022

To the Editor,

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus primary affects the respiratory system; however, a multiorganic affection is evident. Neurological symptoms are frequent at the acute- and post-acute phases after infection [1]. Headache is a neurological symptom experienced as a COVID-19-onset symptom associated with a more benign course of the disease [2]; however, it has been also associated with a higher prevalence of post-COVID headache [3].

During the acute COVID-19 phase, headache often co-exists with other neurological symptoms, e.g., anosmia or ageusia [4]. The presence of anosmia as an onset symptom is also associated with lower mortality rate and a less severe disease, although it seems that patients with anosmia and ageusia represent a different group than those with headache [5]. In this letter, we applied a network analysis to determine the relevance of COVID-19-onset symptoms, including headache, as well as pre-existing medical co-morbidities in a sample of previously hospitalised COVID-19 patients.

The LONG-COVID-EXP-CM is a multicentre cohort study including individuals with a diagnosis of SARS-CoV-2 infection by RT-PCR technique and/or radiological findings hospitalised during the first wave of the pandemic in five hospitals of Madrid (Spain). Among all patients hospitalised during the first wave, a sample of 400 from each hospital was randomly selected. The Ethics Committee of all the hospitals approved the study (HCSC20/495E, HSO25112020, HUFA20/126, HUIL/092-20, HUF/EC1517). Verbal informed consent was obtained from participants for the use of their data in this analysis. Demographic data, pre-existing medical comorbidities, COVID-19 symptoms at hospital admission, days at hospital, and intensive care unit (ICU) admission were collected from hospital records.

The network included 28 nodes linked by edges weighted by partial correlation coefficients. 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 (or categories) for each variable is provided. The mgm was estimated for order = 2 to only take pairwise interactions into account, using least absolute shrinkage and selection operator (LASSO, $\ell 1$-regularisation) that seeks to maximise specificity (to include as few false positives as possible) with rule = "AND" (which specifies whether the two estimates for an edge are combined with an "AND" or an "OR" rule). Since not all nodes in a network are equally important, 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 pass through the target node, moderated by the total number of shortest paths existing between any couple of nodes in the graph) and closeness centrality (defined as the inverse sum of the distances of shortest of the target node from all other nodes in the network).

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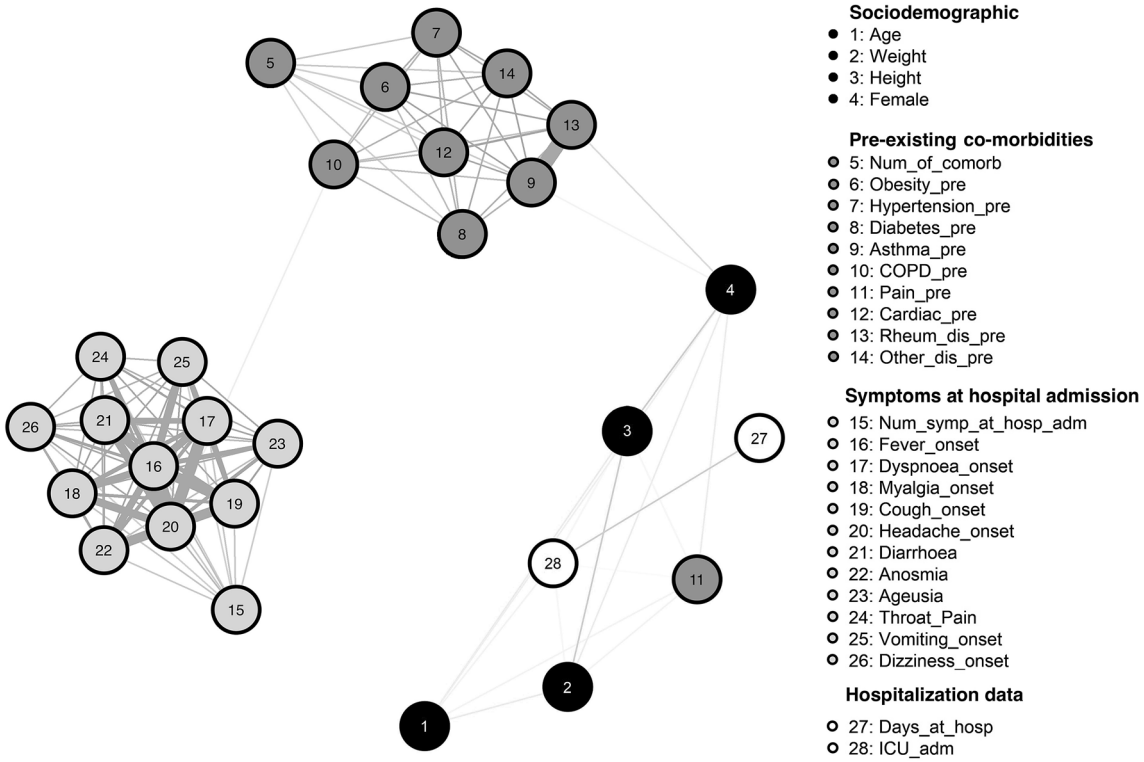

Fig. 1 Network analysis of the association between demographic, pre-existing medical co-morbidities, hospitalisation data and COVID-19-onset symptoms at hospital admission. Edges represent connections between two nodes and are interpreted as the existence of an association between two nodes, adjusted for all other nodes. The thickness of an edge denotes its weight (the strength of the association between two nodes)

Two thousand ($n = 2000$) patients were randomly selected and invited to participate. A total of 1969 (age:61 ± 16 years, 46.4% women) were included. The most common symptoms at hospital admission were fever (74.6%), dyspnoea (31.5%), myalgia (30.7%) and cough (27.9%). The network identified one group of variables grouping all COVID-19-onset symptoms at hospitalisation, and a second one grouping all pre-existing medical co-morbidities (Fig. 1). Multiple positive correlations between the variables in each group were found. The highest correlation (ρ:5.87) in the medical co-morbidity group was between asthma (node 9) and rheumatological diseases (node 13). Within the COVID-19-onset symptoms group, headache (node 20) had several high correlations with fever (node 16, ρ:5.981), dyspnoea (node 17, ρ:5.617), anosmia (node 22, ρ:5.2276 and ageusia (node 23, ρ:4.660). No correlations between both groups of variables were seen. In the group of COVID-19-onset symptoms, headache was the node showing the highest strength centrality, highest betweenness centrality and highest closeness centrality (node 20, Fig. 2).

The application of network analysis in a large population of COVID-19 survivors from five different hospitals supports the relevance of headache as an onset symptom at the acute COVID-19 phase, in agreement with previous studies. The SARS-CoV-2 virus exhibits neurotropic properties leading to an invasion of the central nervous system through potential direct mechanisms (e.g., haematogenous dissemination or neuronal retrograde dissemination) or others. These mechanisms could activate the trigeminal nerve pathways, contributing to the development of headache and anosmia. Monitoring headache at the acute phase may alert clinicians of an early potential invasion of the central nervous system or of a systemic inflammatory response caused by the SARS-CoV-2 virus. The better prognosis of patients reporting headache during the acute COVID-19 phase could be also linked to a stronger immune response against the SARS-CoV-2 virus.

Although this is the largest multicentre cohort study focusing on headache as a COVID-19-onset symptom using a network analysis, it should be considered that we only included hospitalised COVID-19 survivors, and we did not characterise the semiological features of headache as an onset symptom.

In conclusion, this multicentre study using a network analysis in a large population of COVID-19 survivors supports the relevance of headache as a key onset symptom at the acute COVID-19 phase.

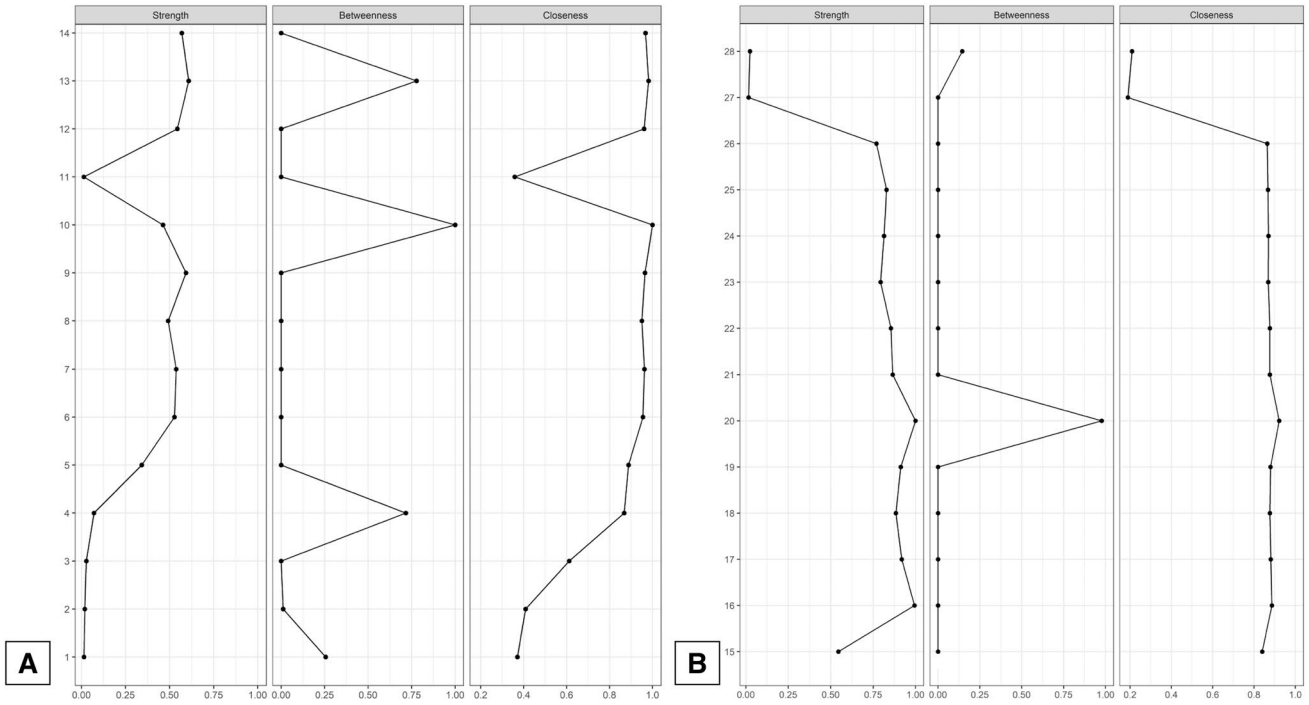

Fig. 2 Centrality measures of strength, betweenness and closeness of each node in the network. Centrality value of 1 indicates maximal importance, and 0 indicates no importance

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

Funding The LONG-COVID-EXP-CM is supported by a grant from Comunidad de Madrid y la Unión Europea, a través del Fondo Europeo de Desarrollo Regional (FEDER), Recursos REACT-UE del Programa Operativo de Madrid 2014–2020, financiado como parte de la respuesta de la Unión a la pandemia de COVID-19. The sponsor had no role in the design, collection, management, analysis or interpretation of the data, draft, review or approval of the manuscript or its content. The authors were responsible for the decision to submit the manuscript for publication, and the sponsor did not participate in this decision.

Declarations

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

Ethics approval The procedures used in this study adhere to the tenets of the Declaration of Helsinki. The Ethics Committee of all the hospitals approved the study (HCSC 20/495E, HUFA 20/126, HSO25112020, HUIL/092-20, HUF/EC1517).

Consent to participate Informed consent was obtained from all individual participants included in the study.

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