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Trajectory of anxiety/depressive symptoms and sleep quality in individuals who had been hospitalized by COVID-19: The LONG-COVID-EXP multicenter study

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ABSTRACT

Objective: To apply Sankey plots and exponential bar plots for visualizing the evolution of anxiety/depressive symptoms and poor sleep in previously hospitalized COVID-19 survivors.
Methods: A sample of 1266 subjects who were hospitalized due to a SARS-CoV-2 from March–May 2020 were assessed at 8.4 (T1), 13.2 (T2) and 18.3 (T3) months after hospitalization. The Hospital Anxiety and Depression Scale was used to determine anxiety (HADS-A) and depressive (HADS-D) symptoms. The Pittsburgh Sleep Quality Index (PSQI) evaluated sleep quality. Clinical features, onset symptoms and hospital data were collected from medical records.
Results: Sankey plots revealed that the prevalence of anxiety symptomatology (HADS-A $\geq$ 8 points) was 22.5% (n = 285) at T1, 17.6% (n = 223) at T2, and 7.9% (n = 100) at T3, whereas the prevalence of depressive symptoms (HADS-D $\geq$ 8 points) was 14.6% (n = 185) at T1, 10.9% (n = 138) at T2, and 6.1% (n = 78) at T3. Finally, the prevalence of poor sleep (PSQI$\geq$8 points) decreased from 32.8% (n = 415) at T1, to 28.8% (n = 365) at T2, and to 24.8% (n = 314) at T3. The recovery curves show a decrease trend visualizing that these symptoms recovered the following years after discharge. The regression models did not reveal medical records associated with anxiety/depressive symptoms or poor sleep.
Conclusion: The use of Sankey plots shows a fluctuating evolution of anxiety/depressive symptoms and poor sleep during the first years after the infection. In addition, exponential bar plots revealed a decrease prevalence of these symptoms during the first years after hospital discharge. No risk factors were identified in this cohort.

1. Introduction

Although coronavirus disease 2019 (COVID-19) is mainly considered a primary respiratory disease, the heterogeneous symptoms associated with this condition suggests a multiorgan pathology. Symptoms associated with a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) acute infection can affect respiratory (cough, throat pain, dyspnoea), gastrointestinal (diarrhoea, vomiting), or neurological (headache, anosmia, ageusia) system. This biological symptomatology is intrinsically related to the trophism of SARS-CoV-2; however, psychological symptoms (anxiety, depression, or poor sleep) have also raised as a worldwide health care problem [1], since the pandemic has provoked a deleterious impact on mental health in the general population [2]. Liu et al. observed the presence of depressive or anxiety symptoms in 40% and poor sleep quality in up to 50% of subjects hospitalized due to a SARS-CoV-2 infection [3]. An umbrella review [n = 14 meta-analyses] showed a pooled prevalence of depression in 31% (95% CI 25% to 38%) of people hospitalized due to COVID-19 but with a high heterogeneity [4]. Therefore, evidence supports the presence of psychological symptoms at the acute phase of infection, particularly in

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hospitalized patients; however, this associated symptomatology can be also long-lasting after the acute phase.

The presence of long-lasting symptoms after SARS-CoV-2 infection has received different terms, but long-COVID [5] and post-COVID-19 condition [6] are probably the most commonly used. >100 post-COVID symptoms have been described [7]. The presence of post-COVID symptoms, particularly fatigue and dyspnea, is associated with worse quality of life [8]. The Global Burden of Disease Long COVID study (which included 1.2million of subjects who experienced an acute symptomatic SARS-CoV-2 infection) reported that 15.1% of patients still experience symptoms one-year after [9]. In addition to post-COVID symptoms biologically associated to SARS-COV-2, the presence of psychological disturbances represents a challenge for affected individuals since these symptoms could promote and perpetuate health burden. Several meta-analyses reported prevalence rates ranging from 12% to 25% for depression, from 20% to 30% for anxiety and from 30% to 45% for poor sleep the first 3–9 months after an acute SARS-CoV-2 infection [10–12]. A recent meta-analysis has identified that anxiety, depression and sleep problems are still present in 13.4%, 18% and 21% of COVID-19 survivors, respectively, two-years after SARS-COV-2 infection [13].

It is important to note that most studies investigating the presence of anxiety or depressive symptoms have used cross-sectional designs since they just assessed these symptoms once and also included follow-ups no longer than one-year [10–12]. It seems that anxiety/depressive levels appearing during the COVID-19 outbreak [14] or appearing after COVID-19 [15] usually improve over time. Johnson et al. analyzed the evolution of anxiety, depression or insomnia in a small cohort of COVID-19 survivors and observed a stable or slightly decreased tendency of the symptoms [16]. The LONG-COVID-EXP study analyzes the prevalence of anxiety and depressive symptoms as well as poor sleep from the onset of the infection up to the first year after hospital discharge in a large cohort of hospitalized COVID-19 survivors [17]. Better understanding long-term evolution of psychological symptoms appearing after COVID-19 could have potential implications for optimizing diagnosis, counselling and management strategy for these patients [18]. We present here the complete analysis of the LONG-COVID-EXP study by including data from the onset of infection, up to 6, 12 and 18 months after their hospitalization. In addition, we present Sankey plots and exponential bar plots as novel way to visualize a fluctuating evolution of anxiety and depressive symptoms as well as sleep quality.

2. Methods

2.1. Participants

The LONG-COVID-EXP is a multicenter study analyzing a cohort of patients who had been previously hospitalized by an acute SARS-CoV-2 infection confirmed at hospitalization by real-time reverse transcription-polymerase chain reaction (RT-PCR) assay of nasopharyngeal/oral swab samples and clinical symptoms during the first wave of the pandemic (March–May 2020) in five public urban hospitals of Madrid (Spain). As previously described, from all patients hospitalized in these hospitals (n = 7150) during the first wave of the pandemic, a randomly selected sample of 400 subjects from each hospital was invited to participate [17]. The Ethics Committee of all hospitals approved the study (HUFA20/126, HUF/EC1517, HUIL/092–20, HCSC20/495E, HSO25112020). Verbal informed consent was obtained from all the participants before collecting data.

2.2. Procedure

Participants were scheduled for a telephone interview conducted by healthcare professionals at six (T1), twelve (T2) and eighteen (T3) months after hospitalization. In such an interview, the Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI) were used to assess anxiety/depressive symptoms and sleep quality, respectively, since these questionnaires can be properly evaluated by telephone interview [19]. Briefly, the HADS consists of 7 items assessing anxiety symptoms (HADS-A) and 7 items assessing depressive symptoms (HADS-D) [20]. Each item is scored on a 4-point Likert scale (0–3) providing a maximum of 21 points for each scale. The HADS has shown good validity and reliability in the general population [21] and more recently in individuals with long-COVID [22]. A cut-off score of ≥8 points on each scale has shown good sensitivity and specificity for identifying anxiety or depressive symptoms [23].

The PSQI evaluates sleep quality over the previous month by including 19 self-rated questions assessing the usual bed-time, usual wake time, number of hours slept, and number of minutes to fall asleep [24]. Questions are answered on a 4-point Likert-type scale (0–3). All answers are transformed into a global score ranging from 0 to 21 points where higher scores indicate worse sleep quality. A score ≥ 8 points is indicative of poor sleep quality [24]. The PSQI has shown good internal consistency and reliability [25].

Finally, clinical and hospitalization data were collected from hospital medical records.

2.3. Sankey plots

Sankey plots were used as a method for visualization of the fluctuating evolution of the patients over time [26]. The X axis represents each follow-up (six, twelve or eighteen months after hospital discharge). The Y axis represents the percentage of individuals reporting (or not) a particular symptom (anxiety, depression, or poor sleep). The vertical bars show the percentage of subjects with or without the symptom at that time-point. The arcs depict the flows of individuals positive or negative on a symptom with a width that is proportional to the percentage (from the sample) of subjects in that flow [26].

2.4. Exponential bar plots

Exponential bar plots were the second method for visualization of the trajectory of psychological symptoms and were created with Matplotlib 3.3.4. The curve slope was fitted according to the following formula $y = Ke^{ct}$, where y represents the modeled prevalence of the symptom (anxiety, depression, poor sleep) at a time t (in months) and K and c are the parameters of the model.

2.5. Statistical analysis

Finally, multivariate logistic regressions were performed to identify those variables collected at hospital admission (COVID-10 onset) associated with the development of anxiety/depressive symptoms or poor sleep at six (T1), twelve (T2), and eighteen (T3) months after the infection by using Python's library statsmodels 0.11.1. Adjusted odds ratio (OR) with their respective confidence intervals (95%CI) were calculated. A priori, the level of significance was set at 0.05.

3. Results

From a sample of 2000 subjects who need hospitalization due to SARS-COV-2 infection from March–May 2020, a total of 1266 (45.6% women, age: 61, SD: 16 years) were evaluated at all follow-up periods: T1 (mean: 8.4, range 6 to 10), T2 (mean: 13.2, range 11 to 15) and T3 (mean: 18.3, range 16 to 21) months after hospitalization. Table 1 summarizes COVID-19 associated symptoms at hospital admission and comorbidities of the sample.

The prevalence of anxiety symptoms (HADS-A ≥ 8 points) was 22.5% (n = 285) at T1, 17.6% (n = 223) at T2, and 7.9% (n = 100) at T3 (Fig. 1). Looking the Sankey plots of anxiety, 33% of subjects (n = 94/285) self-reporting anxiety symptoms at T1 did not report it at T2 (7.74% arc from true at T1 to false at T2). Thus, 16.1% (n = 36/223) of subjects not experiencing anxiety at T1 started to experience this

Table 1
Demographic and clinical data of the sample ($n = 1266$).

Age, mean (SD), years	61 (16.5)
Female (%)	578 (45.6%)
Weight, mean (SD), kg.	74.5 (14.5)
Height, mean (SD), cm.	165 (19.0)
COVID-19 associated Symptoms at hospital admission, n (%) - T0	
Fever	948 (74.9%)
Dyspnoea	361 (28.5%)
Myalgia	374 (29.5%)
Cough	360 (28.4%)
Headache	135 (16.7%)
Diarrhoea	105 (8.3%)
Anosmia	105 (8.3%)
Ageusia	66 (7.0%)
Throat Pain	66 (5.2%)
Vomiting	39 (3.0%)
Medical co-morbidities	
Hypertension	336 (26.5%)
Other (Cancer, Kidney Disease)	207 (16.3%)
Diabetes	158 (12.5%)
Cardiovascular Disease	141 (11.2%)
Asthma	85 (6.7%)
Obesity	57 (4.5%)
Chronic Obstructive Pulmonary Disease	47 (3.7%)
Rheumatological Disease	16 (1.3%)
Stay at the hospital, mean (SD), days	10.5 (10.8)
Intensive Care Unit (ICU) admission	78 (6.2%)

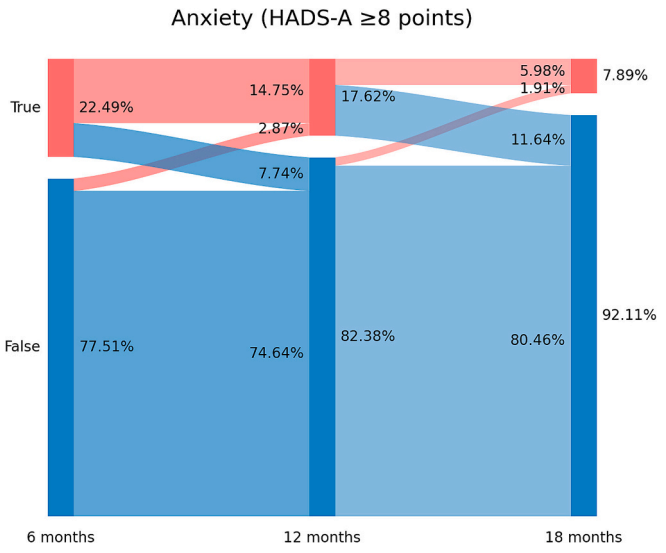

Fig. 1. Sankey plots of anxiety symptomatology (HADS-A ≥ 8 points) during THE LONG-COVID-EXP study (from left to right): T1 (8.4 months after hospital discharge), T2 (13.2 months after hospital discharge), and T3 (18.3 months after hospital discharge).

symptom at T2 (2.9% arc from false at T1 to true at T2). Overall, Sankey plots revealed that 75 individuals (6.0% of the sample) experienced anxiety symptoms throughout all the study.

The prevalence of depressive symptoms (HADS-D ≥ 8 points) was 14.6% ($n = 185$) at T1, 10.9% ($n = 138$) at T2, and 6.1% ($n = 78$) at T3 (Fig. 2). The Sankey plot revealed a similar tendency than with anxiety. As it can be observed, 52.9% of subjects ($n = 98/185$) experiencing depressive symptoms at T1 did not report it at T2 (7.7% arc from true at T1 to false at T2). Again, 37% ($n = 51/138$) of individuals not experiencing depressive symptoms at T1 started to experience it at T2 (4.1% arc from false at T1 to true at T2). The same tendency was observed between T2 and T3. Fig. 2 revealed that 52 patients (4.2% of the sample) reported depressive symptomatology during all the follow-up periods.

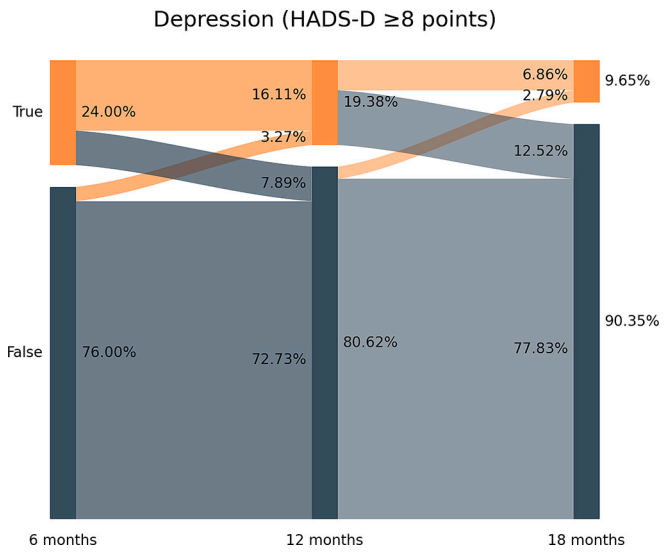

Fig. 2. Sankey plots of depressive symptomatology (HADS-D ≥ 8 points) during THE LONG-COVID-EXP study (from left to right): T1 (8.4 months after hospital discharge), T2 (13.2 months after hospital discharge), and T3 (18.3 months after hospital discharge).

The prevalence of poor sleep (PSQI ≥8 points) decreased from 32.8% ($n = 415$) at T1, to 28.8% ($n = 365$) at T2, and to 24.8% ($n = 314$) at T3. Fig. 3 visualizes the Sankey plots of poor sleep and graphs that 30.1% of subjects ($n = 125/415$) experiencing poor sleep at T1 did not report it at T2 (9.8% arc from true at T1 to false at T2). Showing a similar tendency than anxiety/depressive symptoms, 20.3% ($n = 74/365$) of subjects not experiencing poor sleep at T1 experienced it at T2 (5.8% arc from false at T1 to true at T2). The Sankey plot graphed that 240 individuals (19.0% of the sample) reported poor sleep quality during all the follow-up periods.

Fig. 4 graphs the fitted exponential curves visualizing a decreased prevalence trend in anxiety/depressive symptomatology and poor sleep during the following years after hospitalization. Vertical bars represent the percentage of those patients reporting anxiety (light orange) or depressive (light green) symptoms or poor sleep (dark green).

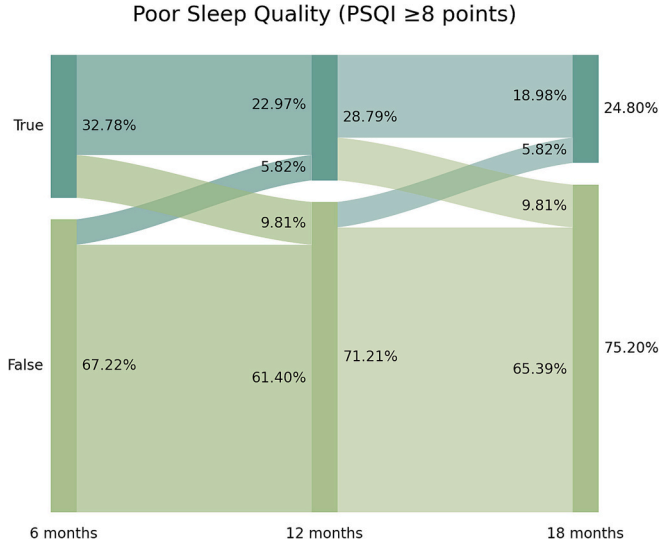

Fig. 3. Sankey plots of poor sleep quality (PSQI≥8 points) during THE LONG-COVID-EXP study (from left to right): T1 (8.4 months after hospital discharge), T2 (13.2 months after hospital discharge), and T3 (18.3 months after hospital discharge).

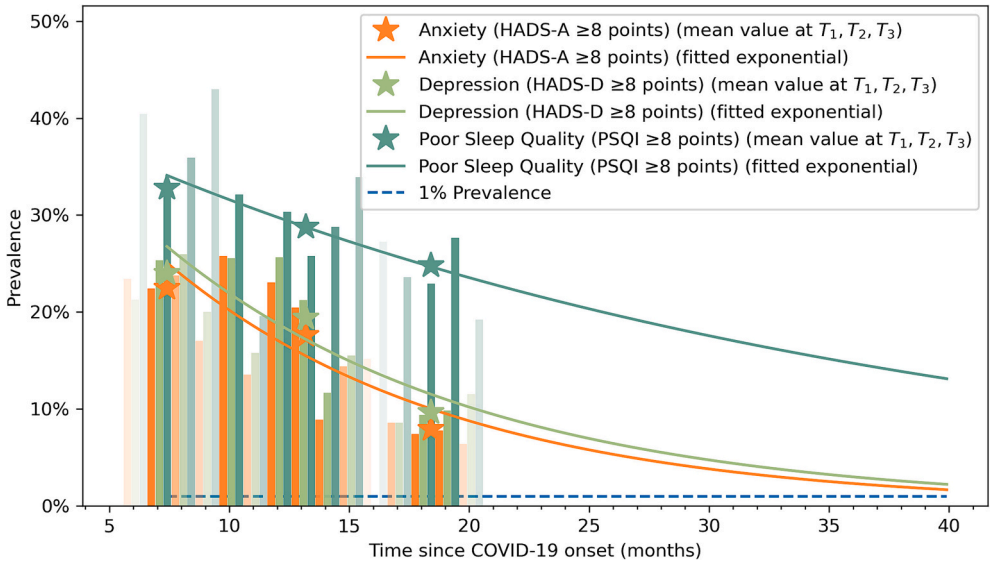

Fig. 4. Exponential bar plots of anxiety symptoms (light orange), depressive symptoms (light green) and poor sleep quality (dark green). Opacity approximately indicates the sample size at that follow-up time. Asterisks represent mean values at T0, T1, T2 and T3 follow-ups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The regression models did not reveal any symptom at hospitalization associated with the development of anxiety/depressive symptoms or poor sleep quality at long-term follow-up periods.

4. Discussion

This is the first study using Sankey plots and exponential bar curves, as two novel visualization approaches, for assessing the trajectory of anxiety or depression, as well as sleep quality in individuals who had been previously hospitalized due to SARS-CoV-2. The Sankey plots revealed a fluctuating nature of anxiety/depressive symptoms or poor sleep after COVID-19. Thus, exponential bar plots revealed a tendency decrease in the prevalence of these symptoms during the first four years after the infection.

Previous meta-analyses including cross-sectional studies had reported an overall prevalence of anxiety symptomatology ranging from 20% to 30% for anxiety, from 12% to 25% for depression, and from 30% to 45% for poor sleep the first 3–9 months after an acute SARS-CoV-2 infection [9–11]. The current study showed similar prevalent rates of these symptoms at the first follow-up period with a progressive tendency with longer follow-ups. It is important to note that prevalence of psychological symptoms and sleep disorders in COVID-19 survivors is heterogeneous due to differences in designs (cross-sectional vs. longitudinal), follow-ups (three or six or twelve months after), population (hospitalized vs. non-hospitalized cohort) or collection procedures (self-reported or use of patient-reported outcome measure-PROM). The use of Sankey plots revealed that the prevalence of anxiety/depressive symptoms and poor sleep is fluctuating during the first years after hospitalization and has also permitted to identify the following situations:

1, new-onset symptomatology: subjects experiencing anxiety, depression or poor sleep starting soon after the infection (e.g., 22.4% at T1 on Fig. 1 for anxiety),

2, delayed-onset symptomatology: subjects reporting anxiety, depression or poor sleep at a longer follow-up period, i.e., with a delayed in time, in relation to the infection (2.9% arc from false at T1 to true at T2 on Fig. 1 for anxiety symptoms),

3, persistent symptomatology: subjects experiencing anxiety, depression or poor sleep throughout all follow-up period and starting soon after the acute infection (6.0% being positive from T1 to T3 on Fig. 1 for anxiety symptoms).

By definition, new-onset and persistent symptomatology can be easily attributable to SARS-CoV-2 if the symptom started no later than three months after [6]. The case of delayed-onset symptomatology is more difficult to attribute to the acute infection since it appears months after. This is relevant considering that psychological symptoms can be considered as COVID-19 associated-factors rather than direct post-COVID symptoms since anxiety or depressive symptoms are also present in individuals who had not been infected by SARS-CoV-2. Thus, evidence supports a bidirectional relationship between psychological symptomatology and COVID-19. For instance, the presence of pre-existing depressive symptoms before COVID-19 has been associated with higher infection rate, hospitalization, intensive care unit admission and mortality rate [27]. Thus, psychological factors can also promote the development of post-COVID symptoms [28], since the presence of depressive symptoms the first month after SARS-COV-2 infection strongly predicts the presence of post-COVID fatigue one-year after [29]. Similarly, the presence of sleep disorders combined with other post-COVID symptoms has been associated with worse quality of life [8]. This association could be explained since anxiety/depressive symptoms or poor sleep can potentiate and shares its underlying mechanism (mainly related to the peripheral immune-inflammatory response associated with SARS-CoV-2 trophism) with other post-COVID symptoms such as fatigue or cognitive impairments [30,31]. Thus, the presence of mood disorders and poor sleep can act as psychological stressors leading to long-term perpetuation of any post -COVID symptom.

The exponential bar plots used in the current study visualized that the prevalence of anxiety/depressive symptoms can last up to 5 years after the infection. Therefore, early identification of risk factors associated with these symptoms could help to prevent long-lasting perpetuation. We did not find any potential risk factor from hospitalization for psychological symptomatology in our cohort of previously hospitalized COVID-19 survivors. It has been previously found that female sex, the number of COVID-19 onset symptoms at hospital admission, and the days at hospital were factors associated with the presence of anxiety and depressive symptoms eight months after the infection [32]. It has been proposed that factors such as fear, immobilization, isolation, stigmatization, or medication-related side effects in the context of hospitalization can increase the risk of poor sleep or psychological symptoms within the following months after the infection. However, the prevalence of anxiety/depressive symptomatology and poor sleep quality observed in COVID-19 survivors seven months after hospitalization was similar than in the general population during the main outbreak [33]. It

is possible that hospitalization risk factors have less influence in the development of psychological symptoms with longer follow-up periods such as those included in our study. It is also plausible that potential factors not included in our study such as differences in neuro-inflammation biomarkers could be more associated with the presence of anxiety or depressive symptoms as well as poor sleep quality in previously hospitalized patients.

Although the current study used two novel methods for visualizing anxiety and depressive symptoms and poor sleep, results should be considered attending potential limitations. First, the cohort just included previously hospitalized COVID-19 survivors. We do not know of similar results will be find in a cohort of non-hospitalized COVID-19 survivors. Second, although we used specific PROMs for evaluating the presence of anxiety/depressive symptomatology and poor sleep, they were collected by telephonic interview which could has a potential bias. However, the use of telephonic interviews is the only way to assess large cohorts (over 1000 of patients during long-term follow-up periods) like in our study. Further, it should be considered that prevalence rates reported are based on cut-off scores established for the HADS and PSQI questionnaires. In fact, determining cut-off values of the different PROMs is key for increasing the validity and the transparency of studies investigating psychological disturbances in individuals with long-COVID. We used cut-off scores of 8 points since these values have obtained good sensitivity and specificity (HADS-A $\geq$ 8points, sensitivity 0.89 / specificity 0.75; HADS-D $\geq$ 8 points sensitivity 0.80 / specificity 0.88) [23]. In addition, although the suitability of the HADS for diagnosing depression and anxiety pathology has been questioned [34], it continues to be the most used screening instrument for assessing depressive and anxiety symptomatology in population studies. Third, although this longitudinal study included different follow-up periods after hospitalization, we did not collect anxiety or depressive symptoms and sleep quality of patients during their hospitalization or before infection. Accordingly, we do not know pre-infection psychological status of our sample. Finally, other psychological (e.g., post-traumatic stress disorder - PTSD), social (e.g., isolation, stigmatization), and familiar (e.g., death of a familiar) stressors which may influence the presence of anxiety/depressive symptoms and poor sleep quality, were not evaluated.

5. Conclusion

This study revealed, by using Sankey plot, a fluctuating evolution of anxiety and depressive symptomatology as well as poor sleep quality during the first years after the hospitalization due to acute SARS-CoV-2 infection. The use of exponential bar plots showed a decrease in the prevalence of these symptoms the first years after hospital discharge. No associated risk factors were identified.

Consent to participate

Participants provided informed consent before collecting data.

Consent for publication

No personal info of any patient is provided in the text.

Role of the funding source

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CRediT authorship contribution statement

César Fernández-de-las-Peñas: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing. **José A. Arias-Navalón:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Writing – original draft, Writing – review & editing. **José D. Martín-Guerrero:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Writing – review & editing. **Oscar J. Pellicer-Valero:** Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Margarita Cigarán-Méndez:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

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