Psychoneurological symptoms and inflammatory markers in patients with glioma in China: a network analysis

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Research Article

Keywords: Glioma, Psychoneurological symptoms, Inflammation, Network analysis

Posted Date: January 11th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2454827/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Supportive Care in Cancer on July 3rd, 2023. See the published version at https://doi.org/10.1007/s00520-023-07873-6.

Abstract

Purpose Anxiety, depression, sleep disorder, fatigue, and pain develop as common psychoneurological symptoms in patients with glioma, and their occurrence and development are potentially related to inflammatory factors. However, this theory has not been proven within the context of glioma. This study aimed to estimate interconnections among psychoneurological symptoms and inflammatory biomarkers by a network analysis.

Patients and methods We selected 203 patients with stage - glioma from a tertiary A hospital in China using convenient sampling method. Patients completed the self-made questionnaires, Hamilton anxiety scale-14 (HAMA-14), Hamilton Depression Scale-24 (HAMD-24), Pittsburgh Sleep Quality Index (PSQI), Multidimensional Fatigue Inventory-20 (MFI-20), and Numerical Rating Scale (NRS). The plasma inflammatory cytokines were examined. Partial correlation network analysis was performed to illustrate interactions of symptoms and inflammatory biomarkers.

Results Among the 203 included patients, all psychoneurological symptoms, except for depression and pain, exhibited significant connections with each other. Depression, anxiety, fatigue, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) with higher strength centrality indices were identified as the most central node within the symptom-biomarker networks.

Conclusion Depression, anxiety, fatigue, IL-6, and TNF-α play a significant role in the symptom-biomarker network in patients with glioma. Medical staff should strengthen the dynamic evaluation of the involved symptoms and inflammatory cytokines, and take effective measures to alleviate the burden of symptoms and improve the quality of life of patients.

Introduction

Gliomas account for 80% of primary malignant brain tumors in adults, and they are generally related to poor clinical outcomes irrespective of treatment [1]. Anxiety, depression, sleep disorder, fatigue and pain are the most common and distressing psychoneurological symptoms that occur and cluster together among glioma survivors [2]. Between 56% and 88% of patients with grade II–IV glioma experience psychoneurological symptoms during cancer treatment [3], and approximately 30% of them report a persistent high severity of anxiety, depression and fatigue throughout the disease trajectory [4]. Present studies have proposed these multiple co-occurring symptoms also affect each other internally [5]. A follow-up study on 65 glioma patients asserted that baseline fatigue severity was strongly associated with depression [6]. According to another study, sleep disorder were also general causes of depression and fatigue of patients with glioma to a certain extent [7]. Choi and colleagues [8] defined this series of simultaneous and interrelated symptoms as “symptom clusters”, such that certain symptoms in the clusters were probably side effects controlling other symptoms. These psychoneurological symptoms do not only reduce one’s capacity to return to work and resume socializing normally, but also reduces the therapeutic effect, negatively influencing the quality of life and shortening the survival of patients [9]. In

clinical practice, medical workers generally pay more attention to the neurological symptoms, such as headache, epilepsy and hemiplegia, while psychological and behavioral changes tend to be ignored [10, 11]. This makes it extremely difficult to reach an accurate diagnosis of psychoneurological symptoms and hinders the effective symptom management in glioma patients. Therefore, further identification of the concrete symptom-symptom associations among five psychoneurological symptoms and exploration of the potential biological mechanism of symptoms in glioma patients is critically important for improvement of the patients' quality of life.

The co-occurrence of multiple psychoneurological symptoms with the onset of cancer has led researchers to investigate what common mechanisms may underlie these symptoms. Recently, more and more scholars have proposed the contention that inflammatory cytokines released by inflammatory activation play a crucial role in the psychoneurological symptoms of cancer patients [12, 13]. Glioma is closely linked with inflammation, as it leads to the development and progression of inflammation due to pathophysiological changes [14]. Therefore, it can be speculated that psychoneurological symptoms is also partly triggered by inflammatory cytokines in glioma patients. Previous studies in cancer patients demonstrated that worse psychoneurological symptoms are concerned with a higher level of inflammatory markers [15–17]. Specifically, in diagnosed lung, and head and neck cancers patients, robust relations were established between fatigue and higher levels of interleukin-6 (IL-6) [18] as well as c-reactive protein (CRP) [19], and between pain and a higher level of CRP [20]. Hypothetically, psychoneurological symptoms and inflammatory biomarkers may influence each other by providing positive or negative feedback.

Although a lot of studies illustrated significant connections between psychoneurological symptoms and inflammatory cytokines, the concrete associations among these elements were not identified in patients with glioma. Hence, further exploration of this topic is beneficial to formulate targeted management strategies. Network analysis is used increasingly in mental health research, which is a novel approach to examine and visualize symptom-symptom interactions and allows us to quantify the overall importance of symptoms. Each symptom was defined as "node" and relationships between two nodes were defined as "edges". The thickness of the edges represents the magnitude of the relationships. The key nodes are placed centrally within the network structure, which is especially important for established networks as their activation would be followed by the activation of other symptoms. Early interventions should be implemented to alleviate the key symptoms, which may further prevent episodes of a disorder [21]. Consequently, we used this innovative approach to describe the relationships between psychoneurological symptoms (anxiety, depression, sleep disorder, fatigue, and pain), and inflammatory markers (interleukin-1beta (IL-1β), IL-6, interleukin-4 (IL-4), interleukin-10 (IL-10), tumor necrosis factor-alpha (TNF-α), and CRP) among patients with glioma.

Based on previous literature, we hypothesized that: (I) positive associations among psychoneurological symptoms internally (i.e., anxiety, depression, sleep disorder, fatigue, and pain are positively connected with each other) (II) positive associations between psychoneurological symptoms and inflammation markers (i.e., worse psychological symptoms are connected with higher inflammatory cytokines).

Methods

Participants

A total of 203 patients diagnosed with glioma who were hospitalized in the Neurosurgery Department of Affiliated Cancer Hospital of Shandong First Medical University from December 2020 to 2021 were enrolled in the study. The following inclusion criteria were used: (a) age between 18 and 70 years, (b) normal language expression, good comprehension and clear consciousness, (c) volunteering to take part in the study. Patients were excluded if: (a) the existence of severe systemic disorders or history of disease that affects the immune system, (b) cognitive dysfunction, (c) administration of immunocompromised and antipsychotic drugs.

Ethical approval was obtained from the Ethics Review Board of School of Nursing and Rehabilitation, Shandong University (2020-R-071), and all patients provided informed consent prior to the study.

Data collection and questionnaires

Baseline information

Clinical and demographic features were determined from the patients' self-reporting or electronic medical records, including age, gender, body mass index (BMI), KPS, smoking history, alcohol consumption, pathological grading, tumor location, etc. Among these characteristics, age [22] and BMI [23] were taken as covariates into the final network model as they were related to higher inflammation biomarkers.

Anxiety

The patients' anxiety was measured by the Hamilton anxiety scale-14 (HAMA-14) [24]. The HAMA-14 is a well-verified questionnaire for evaluating the severity of neurotic anxiety symptoms. It includes 14 each rated using a five-point Likert scale (range = 0-4), such that 0 represents never and 4 represents extremely often. The higher the score, the greater the anxiety. HAMA-14 was shown to be a reliable tool in this study (Cronbach's α= 0.94).

Depression

The Hamilton Depression Scale-24 (HAMD-24) [25] was used to assess depressive symptoms. It includes seven dimensions: weight, anxiety/somatization, diurnal variation, cognitive disturbance, hopelessness, sleep disturbance and retardation. The score is determined as the sum of the seven domain scores, such that a higher score reflects more severe depression. HAMD-24 exhibited good validity and reliability in this study (Cronbach's α= 0.90).

Sleep quality

The Pittsburgh Sleep Quality Index (PSQI), compiled by Buysee in 1989 [26], was used for subjective assessment of sleep disturbance and quality within the last month. It consists of 4 write-in items and 15

multiple-choice items, which produce the scores for 7 subscales: sleep disturbance, duration of sleep, day dysfunction, sleep latency, sleep efficiency, sleep medications and overall sleep quality. Each item is rated on a 0-3-point scale, and the 7 subscale scores are summed to generate a global score (range = 0-21 points); a higher score indicates poorer sleep quality. The PSQI is one of the most widely used instruments among Chinese glioma patients and has previously shown good validity (Cronbach's α= 0.83) [27].

Fatigue

The Multidimensional Fatigue Inventory-20 (MFI-20) was employed for measuring fatigue. It is a 20-item self-report measure with 5 dimensions: physical fatigue, general fatigue, reduced activity, reduced motivation and mental fatigue [28]. Each dimension contains four items ranging within 0–5, and the four items are summed to produce the score for each dimension. Finally, the five dimensions are summed to generate the total score of MFI-20. Higher scores indicate more fatigue. The MFI-20 has excellent reliability and validity in glioma patients in China [29].

Pain

We performed the patients' self-reported Numerical Rating Scale (NRS) to evaluate the mean pain and the intensity of the most severe pain. The NRS is rated on a zero- (none-mild) to ten-point (most severe) scale to capture different levels of pain. The NRS has been proven to be effective and reliable to measure the intensity of pain [30].

Laboratory measures

Sample collection

On the morning of the day prior to the questionnaire evaluation, blood samples were withdrawn into chilled ethylenediaminetetraacetic acid (EDTA) tubes from a venipuncture, and then kept at 4 ℃. After centrifugation, the specimens were stored at −80 °C until performing batched inflammatory biomarker assay.

Inflammatory biomarkers

We concentrated on seven inflammatory biomarkers that have been related to psychoneurological symptoms in previous studies, including IL-1β, IL-6, IL-4, IL-10, CRP and TNF-α, using the Human High Sensitivity Cytokine Base Kit. Plasma concentration of each inflammatory cytokine was determined using a multiplex enzyme-linked immunosorbent assay (ELISA), following the manufacturer's instructions (ESUN BIO, CHINA). All specimens were assessed in duplicate, and mean level was applied in the last results. The inter- and intra-coefficients of variation were reliably <10%.

Statistical analysis

Descriptive statistics were employed for analyzing clinical and demographic data. Categorical variables were presented frequency (N) and percentage (%), whereas continuous variables were expressed as mean with standard deviation. The symptom scores were standardized using *z* scores and transformed to *t* scores for visualization. Given that our data are continuous variables, we estimated Gaussian Graphical Models (GGMs) and performed a partial correlation network analysis by using the *Estimate Network* feature of the *R* package 'bootnet' and 'qgraph'. In such network model, variables are considered 'nodes' (i.e., the nodes of each network corresponded to the list of psychoneurological symptoms, inflammatory markers and covariates, respectively). The 'edges' between nodes are conditional dependence relations that can be understood as partial correlations, and blue edges represent positive conditional dependence relations among variables, red edges depict negative relations. To avoid false-positive findings, we used the least absolute shrinkage and selection operator (LASSO) that shrinks all edge-weights toward zero and sets small weights to exactly zero, thus leading to a sparse network structure. The strength of the penalty is controlled by a parameter λ, which we selected using the Extended Bayesian Information Criterion (EBIC). To gain insight into the structural importance of the nodes in the network, we calculated three centrality indices: strength (i.e., the sum of all edges of a given node to all other nodes), closeness (i.e., the average distance from one node to all other nodes) and betweenness (i.e., the number of times a node being the shortest path among nodes) [31]. Of note, recent studies indicated that the closeness centrality and betweenness centrality estimates tend to be unstable [32]. Therefore, we focused on the node strength and its accuracy and stability in this study.

We examined the accuracy and stability of the network model by assessing the stability of edge weights and the stability of centrality indices [33]. First, edge stability was estimated using non-parametric bootstrapping procedures, and bootstrapped confidence intervals were employed to gauge the certainty of edge weights and test for the significant differences between edges to check if a given edge is significantly larger than other edges. We determined the 95% confidence intervals (CIs) for each edge, using 2000 bootstraps. Second, we took the correlation stability (CS)-coefficient to assess the strength centrality index, which indicates the maximum proportion of the data that can be dropped while the centrality indices remain highly correlated (>0.70) to the original centrality indices. The CS coefficients should be at least 0.25 for the centrality to be acceptable, preferably above 0.5 [33]. All statistical tests were conducted with R (version 4.2.2), and two-tailed $P<0.05$ was deemed statistically significant.

Results

Baseline information

The demographic and clinical features of the participants are depicted in Table 1. A total of 203 glioma patients, the average age was 54.10 years (S.D. = 14.1) and half of the patients were men (50.7%). Mean BMI was 24.54 (S.D. = 3.6). Most participants had a KPS score > 60 (82.8%), had no history of tobacco use (85.7%), had no history of alcohol use (88.2%), diagnosed with high grade glioma (68.5%), received surgery (68.5%), and did not receive concurrent radiotherapy (64.0%) and chemotherapy (63.1%). Mean symptom severity *t* scores of all patients are presented in Fig. 1.

Network Estimation

The network analysis of correlations between psychoneurological symptoms and inflammatory cytokines without covariates and with covariates (age and BMI) were demonstrated in Fig. 2a and Fig. 2b. Blue edges represented positive partial correlations among variables, and red edges represented negative relations. In network **2a**, all psychoneurological symptoms, except for depression and pain, exhibited significant connections with each other, with the highest regularized partial correlation between anxiety and pain (0.41), followed by the correlation between anxiety and depression (0.36). In addition, most symptoms, except for anxiety, were positively related to IL-6. When corrected for covariates of age and BMI in **2b**, the relationship between anxiety and pain (0.38) were attenuated. Fatigue (0.20) and IL-6 (0.06) were positively related to age, depression was negatively related to BMI (-0.05). The corresponding weighted adjacency matrices for the network of symptoms and inflammatory biomarkers without and with covariates were summarized in Online Resource Table **S1** and **S2**, respectively. Online Resource Fig. **S1** showed the results of bootstrapped difference test of each edge weight, and no significant association could be established between anxiety and pain vs. anxiety and depression ($P < 0.05$). The edge weight of the association between IL-6 and depression was higher than the weight of the association between IL-6 and sleep disorder and pain (P 0.05).

Network Inference

Centrality indices of all nodes were displayed in Fig. 3. Based on strength centrality indices, three nodes with the highest node strength were depression (1.32), anxiety (1.08), fatigue (0.84), while, the least central node, which had the few and weak connections with other nodes, was BMI (0.05). Besides, IL-6 (0.64) and TNF-α (0.58) also showed greater strength. The node strength of psychoneurological symptoms, inflammation markers, and covariates of the fitted network were depicted in Online Resource Fig. **S2**.

Network Accuracy And Stability

The edge weights in the current sample were consistent with the bootstrapped sample, which seems to suggest that the network structure was accurate (Online Resource Fig. **S3**). It's worth noting that there were no unambiguous cut-offs yet to explain the bootstrapped 95%CIs for each edge, which makes it challenging to explain them. In our consequences, the order of the edge weights could only be explained with caution as 95%CIs appear to be quite large and overlapping.

Further stability tests revealed that the edge stability coefficient was 0.438, which can be interpreted as acceptable. Besides, the case dropping subset bootstrap procedure demonstrated the values for strength, closeness, and betweenness was still stable while dropping up to 75% of the participant. Among them, the strength centrality stability coefficient was relatively high (0.517), which can be considered as good (Fig. 4). After dropping large portions of the sample, the order of the variables in strength remained

related to the original network (r = 0.70). Therefore, we concentrated on the interpretation of variable strength on the basis of our network analysis.

Discussion

This research is the first to examine the correlations between psychoneurological symptoms and biomarkers of inflammation within networks and evaluate for age and BMI associated with symptom-biomarker networks in patients with glioma. In our network model, all psychoneurological symptoms, except for depression and pain, were associated with each other; in addition to anxiety, other symptoms were related to IL-6 in the expected directions: the more severe the symptoms, the higher the levels of inflammatory cytokines, which enhances our understanding of the interconnections among five psychoneurological symptoms and identifies depression, anxiety, fatigue, IL-6, and TNF-α as the most core position in the symptom-biomarker network model.

The key position of depression, anxiety and fatigue in the model reveals their significance among other psychoneurological symptoms. In general, clinicians often blame anxiety and depression on disease or treatment, worrying that antidepressants are likely to lead to potential delirium and seizures early after surgery, which indicates that psychological change in glioma patients is underdiagnosed and could not be effectively treated. Therefore, medical workers are supposed to focus on mental health and strengthen the dynamic evaluation of the psychological status. Lavender aromatherapy combined with emotional freedom techniques (EFT) and mindfulness based cognitive therapy (MBCT) can be considered to alleviate the patients' mood disorders [34]. Based on previous study, fatigue has been proved both as a cause as well as a consequence of psychological distress in cancer patients [35]. Meagan and colleagues [36] also revealed that various symptoms co-occur during cancer treatment for breast cancer. These findings indicated that psychoneurological symptoms did not exist separately, but they influenced and promoted each other. Besides, various symptoms were combined into clusters, jointly affecting the quality of life and functional status of cancer patients. As such, medical workers should also consider psychotherapy, exercise or cognitive and behavioral strategies, which would presumably yield better results. Barsevick [37] demonstrated that the "intersectional" intervention strategy had an obvious effect on symptom clusters.

We discovered that advanced age appeared to be positively connected with fatigue in glioma patients, so we speculate that that in addition to declined physical function, older patients suffer from vulnerable social support, slender income and inexpressible loneliness, which provided a reasonable opportunity for physical and psychological fatigue [38]. Thus, medical staff should pay more attention to the changes of elderly patients, to timely identify patients with negative emotion, carry out targeted care and mobilize social and family resources to reduce the occurrence of fatigue and improve the patient prognosis.

In our models, depression, sleep disorder, fatigue, and pain were linked with IL-6, and anxiety, depression, and fatigue were associated with TNF-α in an unadjusted model (Fig. 2a). When corrected for age and BMI, the link with IL-6 and TNF-α was relatively reduced but remained significant (Fig. 2b). The results of

our research were consistent with the outcomes in head and neck, and breast cancer [39, 40], manifesting that IL-6 and TNF-α played a critical role in psychoneurological symptoms. IL-6 and TNF-α serve as multifunctional cytokine capable of inducing the proliferation and differentiation of immune cells, which can be released by the tumor cells themselves and immune cells surrounding the tumor [41]. Albulescu and colleagues [42] discovered altered inflammatory biomarkers including IL-6 and TNF-α that were closely related to brain tumor behavior in patients with glioma. IL-6 and TNF-α could enhance the blood brain barrier (BBB) permeability [43], while dysfunctional BBB accelerated the infiltration of peripheral immune cells and inflammatory mediators into the CNS, thereby triggering behavioral abnormality as well as psychological disorders [44]. Of note, depression shared unique associations with CRP and IL-10 after age and BMI adjustment. CRP is an acute phase protein, possessing both anti- and pro-inflammatory effects, and in addition to activating monocytes and neutrophils and triggering the secretion of TNF-α [45], it can also stimulate the release of the anti-inflammatory cytokine IL-10 [46]. IL-10 has been proven to be equipped to inactivate a variety of cells, reducing endothelial cell damage, improving vascular dysfunction, and limiting inflammation [47]. We assumed that IL-10 exerted a protective role in the progression of depression due to its negatively correlation with depression. Paolucci and colleagues [48] found that moderate-intensity aerobic exercise and strength training could promote mental health by effectively decreasing the levels of inflammatory cytokines, which is a critical reminder for medical staff to use exercise in psychoneurological distress treatment. Future research using time-series data on the relationships between inflammatory cytokines and psychoneurological symptoms are urgently needed in the future to develop targeted measures that act on mechanistic pathways and effectively alleviate the agony of patients.

In summary, more attention should be paid to the exploration of the pathophysiological mechanisms underlying cancer psychoneurological symptoms clusters, which is beneficial to clarify the ambiguous relationships among diverse symptoms. Besides, it helps to identify genetic predisposition for long-term symptoms development, finally developing innovative therapeutic strategies aiming at symptom clusters.

Strengths And Limitations

The advantages of our research were that we used representative and commonly available inflammatory biomarkers and psychoneurological symptoms. In addition, it is easy to interpret the relationship between symptoms and inflammatory markers by network analysis, providing a theoretical basis for clinical work to develop feasible prevention and treatment strategies.

Our study had some limitations. First, we did not take treatments or medications into account, which should be collected in future research (e.g., use of opioid or antidepressant). Besides, anxiety and depression examination were dependent on scales instead of professional diagnosis, which to some extent restricted the generalization to clinical anxiety and depression. Third, we measured plasma inflammatory cytokines levels only in the early morning, and biomarkers levels may vary throughout the day. Finally, our speculations should be considered with caution, owing to the nature of the cross-

sectional survey, which was not able to provide rigorous control of psychosocial factors and inflammatory biomarkers. In brief, further exploration in longitudinal research is needed to validate our findings.

Conclusions

We focused on distinctively issue the associations of anxiety, depression, sleep disorder, fatigue, pain, and inflammatory markers in patients with glioma. We discovered that depression, anxiety, fatigue, IL-6 and TNF-α played the most critical role in these complex interconnections by a network analysis. Our discoveries may assist future research in disentangling the effect of inflammation and psychoneurological symptoms in the progression of glioma-related outcomes over time and provide a theoretical foundation to develop innovative strategies to cure the psychoneurological symptoms. In future work, we plan to recruit more participants and conduct multi-center prospective studies to further explore the inflammatory mechanisms of the symptom clusters in cancer patients.

Declarations

Acknowledgements Thanks for the guidance and help from Shandong Cancer Hospital and Institute.

Author contribution All authors contributed to the study conception and design. Feng Li: conceptualization, project administration, and writing—review and editing. Huayu Li: investigation, methodology, software and writing—original draft preparation. Xiaohan Shi: data collection supervision, formal analysis, and writing assisting. Jing Li: data collection supervision, software, and methodology. Xinrui Zhang: investigation, formal analysis, and methodology. All authors have read and agreed to the published version of the manuscript.

FundingThis research was supported by the Key Technology Research and Development Program of Shandong (2017GSF218028).

Data availability The original information supporting our consequences can be gettable upon request.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki and approved by the Ethics Review Board of School of Nursing and Rehabilitation, Shandong University (protocol code 2020-R-071).

Consent to participate All patients provided informed consent prior to the study.

Consent to publish The authors declare that all content of the article can be published.

Conflict of interest No conflict of interest was disclosed for each author.

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Table

Table 1 Demographic and clinical characteristics of patients (N=203)

Characteristics	Mean (S.D.) or No. (%)
Mean Age years (S.D.)	54.10 (14.1)
Mean BMI, kg/m^2 (S.D.)	24.54 (3.6)
Sex	
Male	103 (50.7)
Female	100 (49.3)
KPS score	
≤60	35 (17.2)
>60	168 (82.8)
Income level	
Less than 1000	44 (21.7)
1000-3000	84 (41.4)
3000-5000	48 (23.6)
5000-10000	23 (11.3)
More than 10000	4 (2.0)
Smoking history	
Yes	29 (14.3)
No	174 (85.7)
Alcohol history	
Yes	24 (11.8)
No	179 (88.2)
Surgery	
Yes	139 (68.5)
No	64 (31.5)
Radiotherapy	
Yes	73 (36.0)
No	130 (64.0)
Chemotherapy	

Yes	75 (36.9)
No	128 (63.1)
WHO glioma grade	
Low (-)	64 (31.5)
High (-)	139 (68.5)
Lobe	
Temporal	31 (15.3)
Frontal	71 (35.0)
Occipital	9 (4.4)
Parietal	23 (11.3)
Other	69 (34.0)

BMI, body mass index; KPS, Karnofsky Performance Status; Income level, the unit is ¥/month.

Figures

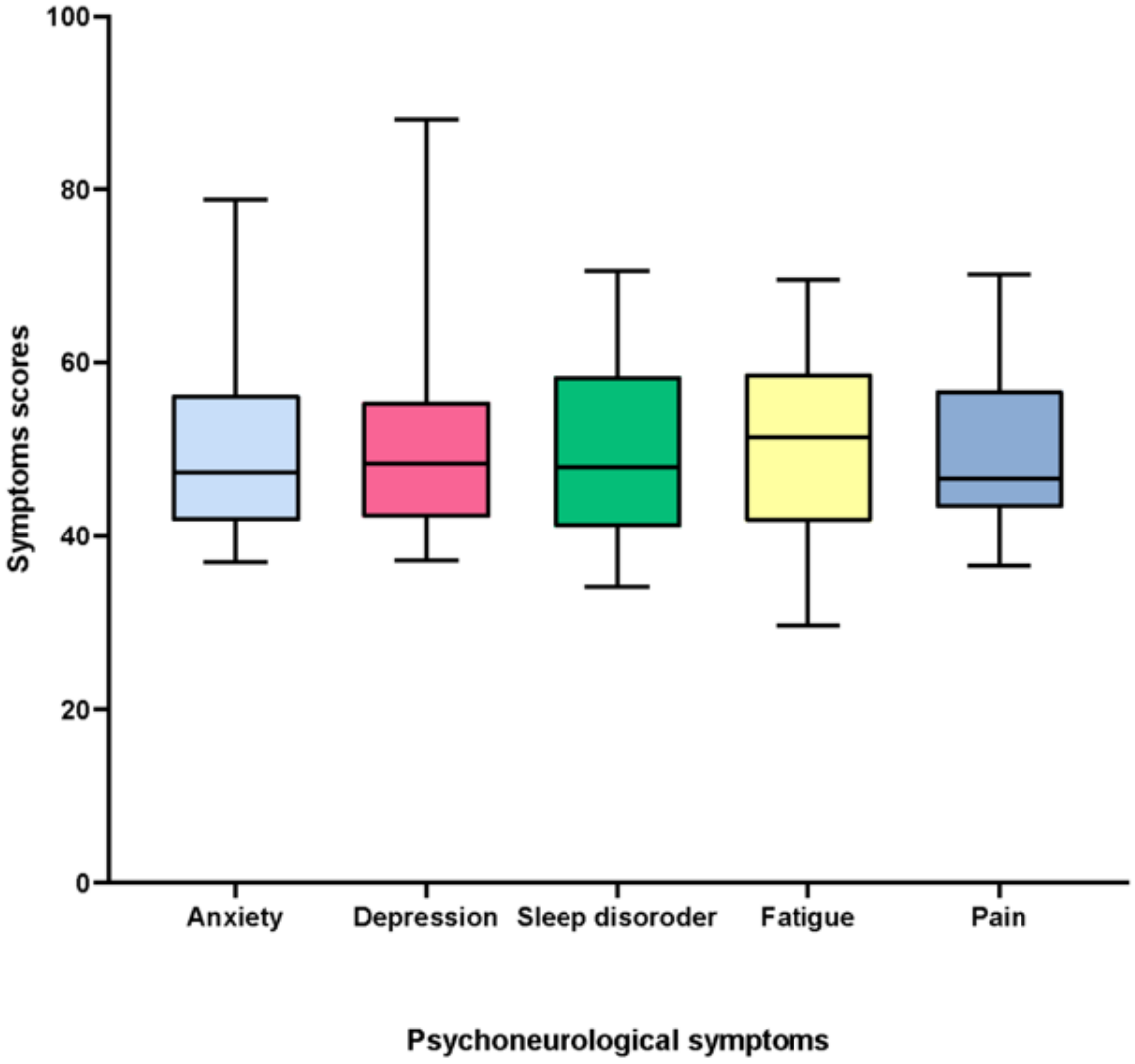

Figure 1

Mean symptom severity *t* scores of 203 glioma patients

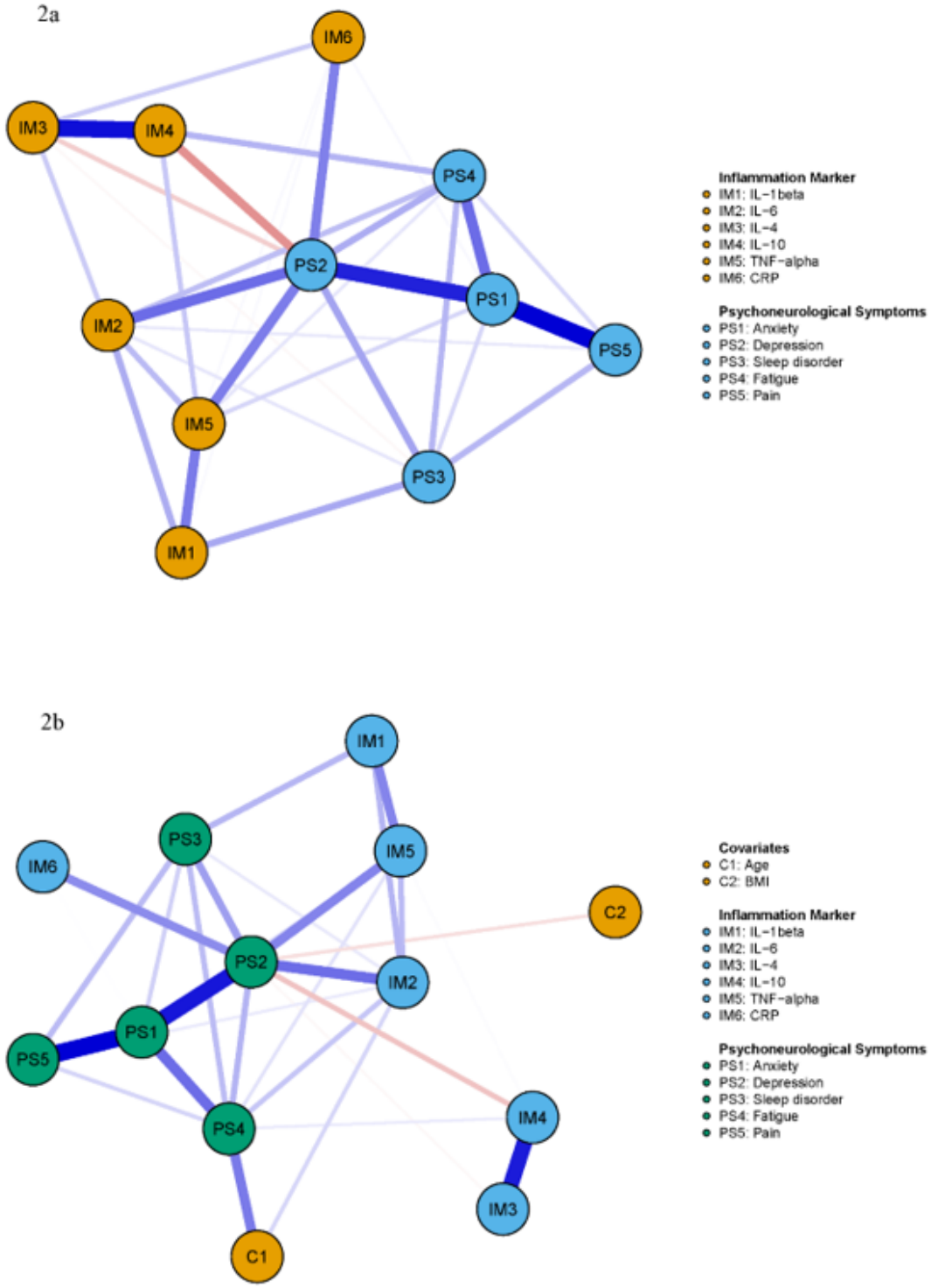

Figure 2

Network displaying the relationship between psychoneurological symptoms and inflammatory markers before (**2a**) and after controlling for covariates (**2b**). Note: Blue edges constitute positive partial correlations between variables, red edges constitute negative partial correlations

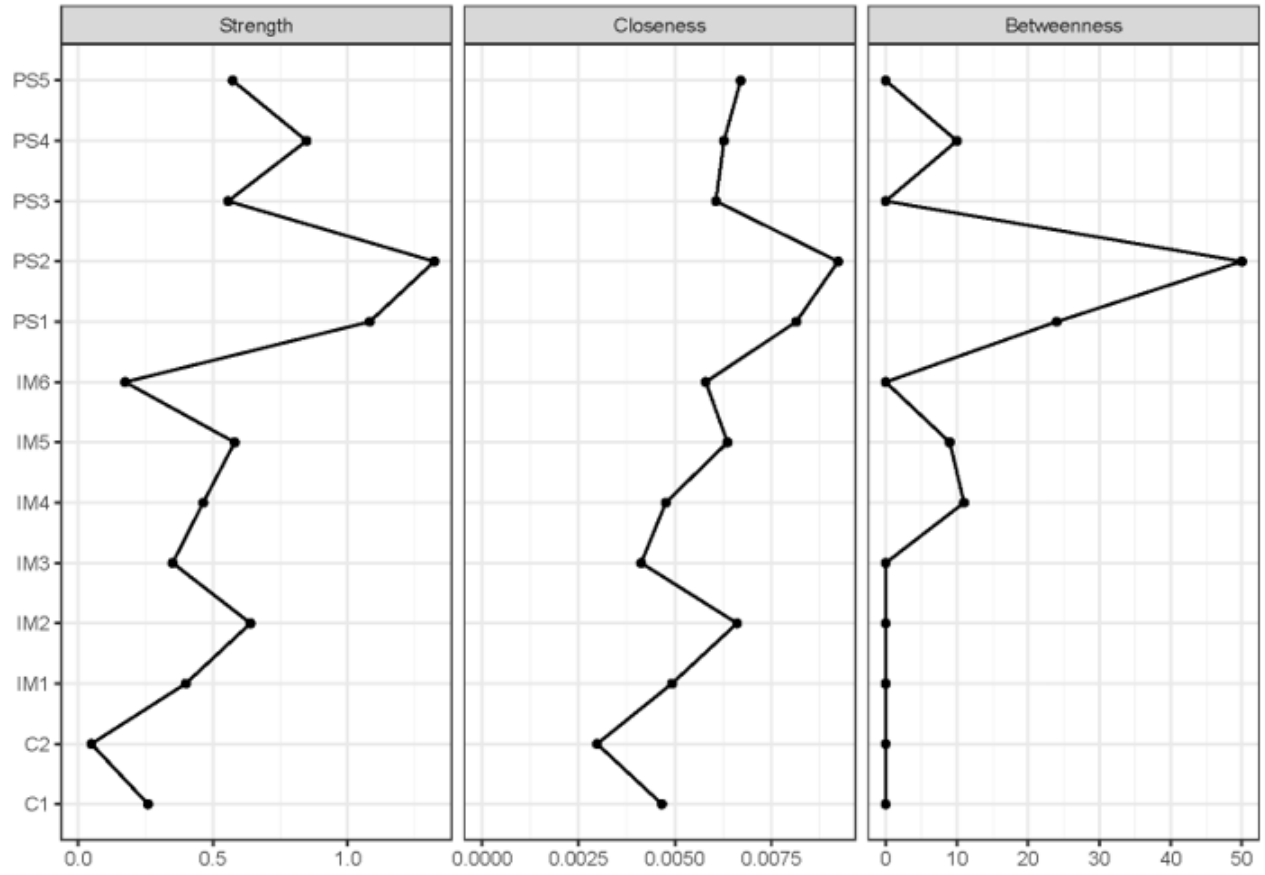

Figure 3

Centrality indices for psychoneurological symptoms, inflammatory markers, and covariates within the networks. Note: C1, age; C2, body mass index (BMI); IM1, interleukin-1beta (IL-1β); IM2, interleukin-6 (IL-6); IM3, interleukin-4 (IL-4); IM4, interleukin-10 (IL-10); IM5, tumor necrosis factor-alpha (TNF-α); IM6, c-reactive protein (CRP); PS1, anxiety; PS2, depression; PS3, sleep disorder; PS4, fatigue; PS5, pain

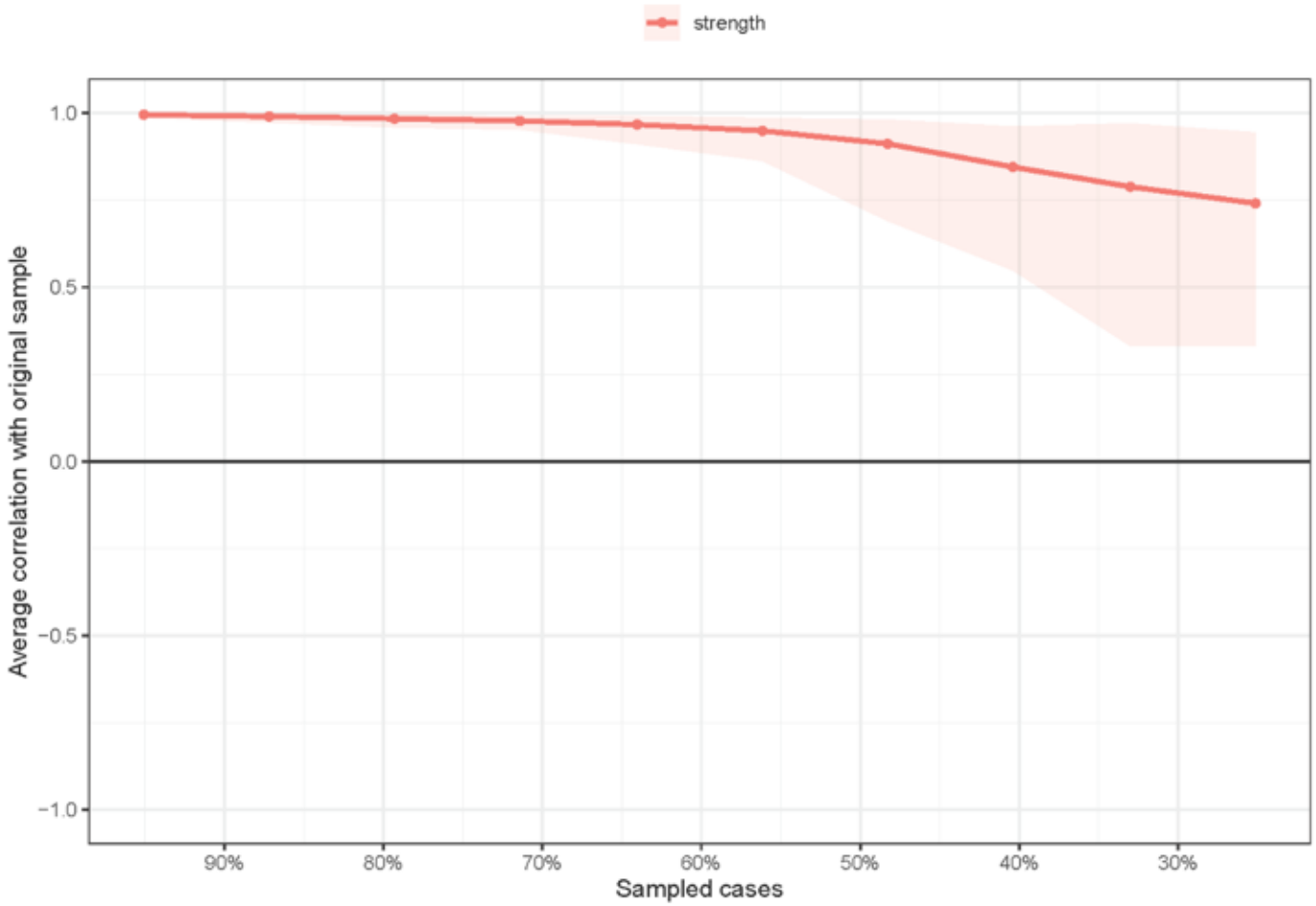

Figure 4

Correlations of the centrality of nodes in the original network with the centrality of bootstrapped networks sampled while dropping participants. Note: The X-axis represents the proportion of sampled case at each step, while the Y-axis represents the mean correlations between the original strength indices and the subset expected influence indices. Colorful areas represents 95% CI

Supplementary Files

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- Supplementaryfile.docx