

Alleviating Excessive Worries Improves Co-Occurring Depression and Pain in Adolescent and Young Adult Cancer Patients: A Network Approach

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Objective: Anxiety, depression, and pain are highly interactive with each other in adolescent and young adult (AYA) cancer patients. This study aims to map out the connectivity between anxiety, depression and pain symptoms amongst Chinese AYA cancer patients from the perspective of a network model.

Methods: Two hundred and eighteen AYA patients, aged between 15 and 39 years at diagnosis; completed the Patient Health Questionnaire (PHQ), Generalized Anxiety Disorder (GAD), and McGill Pain Questionnaire-Visual Analogue Scale (MPQ-VAS). Network analyses were performed.

Results: In all, 38.07% (95% CI = 31.58–44.57%) of the participants reported depression, 30.73% (95% CI = 24.56–36.91%) reported anxiety, and 14.22% (95% CI = 9.55–18.89%) reported current pain. The generated network illustrated that anxiety, depression and pain community were well connected. In the network, “having trouble relaxing” (GAD4, node strength = 1.182), “uncontrollable worry” (GAD2, node strength = 1.165), and “sad mood” (PHQ2, node strength = 1.144) were identified as the most central symptoms, while “uncontrollable worry” (GAD2, bridge strength = 0.645), “guilty” (PHQ6, bridge strength = 0.545), and “restlessness” (GAD5, bridge strength = 0.414) were the key bridging symptoms that connected different communities.

Conclusion: Anxiety, depression and pain symptoms are highly interactive with each other. Alleviating AYA cancer patient's excessive worries might be helpful in improving the patient's co-occurring anxiety, depression and pain symptoms.

Keywords: adolescent, anxiety, cancer, depression, network, pain, young adult

Introduction

Cancer is the leading cause for disease-related deaths in adolescents and young adults (AYAs).¹ AYA cancer patients, defined as age 15–39 years by the National Cancer Institute,² face a crucial period in their lives due to the inevitable changes in their physiology, social situation, and psychological well-being.¹ In China, the prevalence of cancer has been estimated to be around 87.56 per million person-years among AYAs.³ A cancer diagnosis can lead to psychological distress, and AYA patients with

cancer are specifically vulnerable to psychological distress due to the intersection of disease and young age.⁴ Consequently, AYA cancer patients are more likely to report treatment disengagement, lower quality of life, and even suicidality.^{5,6}

Psychological disturbances are common in AYA cancer patients.^{1,7,8} A meta-analysis indicated that approximately 32% of cancer patients experience some type of psychological distress during active treatment,⁹ and a review reported a significant association between younger age and greater psychological distress during cancer trajectory.¹⁰ In China, a study found that about 75% of the AYA cancer patients reported anxiety, and 90% of them reported depression.¹¹ Emotional disturbances can compromise cancer patients' emotional and role functioning,¹² lower their quality of life, and may lead to higher risk of mortality.^{13–15}

As a complex symptom, pain is prevalent in cancer population.^{16,17} A recent cross-sectional study found that 66% of the cancer patients reported moderate-to-severe pain,¹⁸ while another study showed that 42.1% of the adult cancer patients reported pain.¹² Previous studies have found that age, gender, genetic predisposition, and cognitive and/or emotional process around pain could significantly affect one's perceived pain level.^{19,20} Inappropriate management of pain could result in negative consequences for patients' emotions and cognitive function, and their quality of life.²¹

Anxiety, depression, and pain are prevalent, and highly interactive with each other in AYA cancer patients.²² Individuals with comorbid anxiety and depression tend to respond more slowly to treatment and have a higher probability of suicide and recurrences.²³ Moreover, pain often co-occurs with anxiety and depression, and together leads to considerable social and economic burden.²⁴ The pain related to the oncological process may be accompanied by anxiety about medical procedures and hospitalization, separation anxiety and psychological stress.²² The presence of pain is also associated with more depressive symptoms and worse outcome, such as lower quality of life, poorer work performance, and higher health service utilization.¹⁹

In a randomized controlled trial, patients with increased pain were more likely to report higher levels of anxiety, fatigue, and depression.²⁵ On the other hand, fatigue, anxiety and depression also have significant influence on pain in patients with cancer.²⁵ A previous study showed that compared to non-depressed patients with pain, patients with comorbid depression and pain tend to experience more pain-related complaints, more severe pain symptoms, and greater impairments.²⁶ Subsequently, even though anxiety, depression, and pain are prevalent, and highly interactive with each other, the interaction amongst these conditions has not been fully investigated. To the best of our knowledge, no study has examined the comorbidity of anxiety, depression and pain in cancer population from the perspective of network analysis.

Network analysis is an alternative novel approach to examine the comorbidity of two or more disorders.²⁷ In network analysis, it is believed that comorbidity occurs when symptoms from different disorders are directly linked to each other.²⁸ It estimates the unique associations between each pair of measured symptoms while controlling for all other symptoms and shrinking potentially spurious associations to zero.²⁹ In this study, 1) network analysis was applied to assess the connectivity between anxiety, depression and pain symptoms in a Chinese AYA cancer sample; 2) the prevalence of anxiety, depression and pain in AYAs was also investigated.

Methods

Participants

This study's participants were consecutively seen at the outpatient units of Southern Medical University Nanfang Hospital and Guangdong Provincial People's Hospital. Participants were recruited from 1 January 2018 to 30 November 2018. To be eligible, patients needed to: 1) have a cancer diagnosis within the last 6 months; 2) have ages between 15 and 39 years; 3) be able to understand Chinese. Those with disturbances of consciousness were excluded.

Study Procedure

This study was performed in accordance with the Helsinki standard and the study protocol was approved by the Nanfang Hospital Ethics Committee (ref No: NFEC-2018-038) and Guangdong Provincial People's Hospital Research Ethics Committee (ref No. 2018295H(R1)). All participants were approached in the waiting room by trained research assistants. For those patients (adults), showing an interest in participating; were asked to provide a written informed consent form. Simultaneously, approval was also required from a parent/legal guardian for participants under the age of 18 years. All recruited participants were asked to complete a personal information collection form and a set of scales after which they

were sent back to the research assistants immediately. The recruitment and assessment procedure was supervised by a licensed psychiatrist.

Measures

Basic Demographic and Clinical Data

Participants' basic demographic and clinical data (such as, gender, age, cancer site, comorbidities, and family cancer history) were collected using a specially designed case record form.

Patient Health Questionnaire (PHQ-9)

The PHQ is a self-rating scale that measures depression-related symptoms of patients. PHQ contains 9 items, each item uses a four-level score of 0 to 3, with a total score of 0 to 27. A total score of 5 or more indicates depressive symptoms.³⁰ The Chinese PHQ-9 showed good psychometrics properties,³¹ and the internal consistency of PHQ-9 was 0.802 in Chinese AYA cancer patients.³²

Generalized Anxiety Disorder (GAD-7)

The GAD is a 7-item self-report scale used to assess an individual's anxiety symptoms. Response options available are rated from 0 to 3, and a total score of 5 or more indicates anxiety symptoms.³³ The Chinese GAD-7 showed satisfactory psychometrics properties,³⁴ and the Cronbach's alpha of GAD-7 was 0.883 among Chinese AYA cancer patients.³²

McGill Pain Questionnaire-Visual Analogue Scale (MPQ-VAS)

The McGill Pain Questionnaire-Visual Analogue Scale (MPQ-VAS) is one of the most widely used tests for the measurement of pain,³⁵ and has been validated in the Chinese language in 2013.³⁶ The score for VAS ranges from 0 (no pain) to 100 (worst possible pain), and a total score of 40 or more indicates that the patient is currently suffering from pain.³⁶

Sample Size Estimation

The sample size (N) was calculated with the formula: $N = Z_{\alpha}^2 P(1 - P)/d^2$ ³⁷ where Z is the statistic of the significance test, alpha is the significance level, P is the prevalence, and d is the allowable error. In this study, alpha was set at 0.05, Z_{α} was set at 1.96, and d was 0.1P. Based on a previous finding that about 75% of the AYA cancer patients reported anxiety, and 90% of them reported depression in China.¹¹ We, therefore, assume the prevalence as 75% and to enable further analyses, we increased the expected sample size by 50%. Finally, at least 192 participants were recruited in this study.

Statistical Analysis

Network Analysis

First, we estimated the network using the R "bootnet" and "qgraph" packages,³⁸ with "EBICglasso" (ie, the Extended Bayesian Information Criterion combined with the Graphical Least Absolute Shrinkage and Selection Operator method) as the default method.²⁹ A network is a graphical representation of variables (nodes), and their correlations are depicted as edges.³⁹ In the network, thicker and more saturated edges represent stronger correlations, green lines represent positive correlations, and red lines represent negative correlations.

Secondly, to quantify the importance of each node in the network, we computed the centrality indices of *Strength*, *Betweenness*, and *Closeness*. Higher centrality index values are representative of greater importance within the network, and symptoms with high centrality measures might be important as potential targets for further treatment interventions.⁴⁰ Additionally, to identify the bridge symptoms that connect different communities, we computed the bridge centrality (*Bridge Strength*, *Bridge Betweenness*, and *Bridge Closeness*). Recent studies have recommended that both *Betweenness*, *Bridge Betweenness*, *Closeness*, and *Bridge Closeness* indices might not be robust in psychological networks.⁴¹ Therefore, in the subsequent network analysis, we mainly focused on *Strength*⁴² and *Bridge Strength*.^{43,44} *Strength* means the sum of the absolute value of a node's correlations with other nodes in the structure, while *Bridge Strength* refers to the sum of absolute edge weight values of all intercommunity edges.^{43,44} Centrality plots were created to represent these indices.

Thirdly, to examine the stability and accuracy of the networks,²⁹ a case-dropping bootstrap procedure was performed to compute the correlation stability coefficient (CS-C). The CS-C is required to be above 0.25.²⁹ Also, a non-parametric

bootstrapping method was used to estimate the accuracy of edge-weights by computing confidence intervals (CIs). This means that larger CIs indicated poorer precision in the estimation of edges, while narrower CIs indicated a more trustworthy network.⁴² Additionally, to examine the possible influence of age and gender on cancer patient's emotional disturbances, the network model and the local structure indexes were re-estimated, after controlling for age and gender.

Results

Patient Characteristics

Demographic and clinical characteristics of the included participants are reported in [Table 1](#). The study sample consisted of 218 patients with complete data on the 17 variables (7 anxiety nodes, 9 depression nodes, and 1 pain node) used to construct the network. Comparison of patients with complete data vs the rest of the recruited sample ($n = 31$) revealed no significant differences in sex and age, which indicates that the subgroup of participants included in the network analysis can be considered to be representative of the overall sample. The mean age of the AYA patients was 30.22 years ($SD = 4.82$). In total, 38.07% (95% CI = 31.58–44.57%) of the participants reported depression, 30.73% (95% CI = 24.56–36.91%) reported anxiety, and 14.22% (95% CI = 9.55–18.89%) reported current pain.

Network Analysis

[Figure 1](#) presents the association network. The generated network illustrated that the anxiety, depression and pain community were well connected (with no isolated node). Out of 136 edges, 87 (63.97%) of them were estimated to be non-zero. This model and edge weight matrix revealed that the edges between “excessive worry” and “trouble relaxing” (GAD3 - GAD4, edge weight = 0.3031), “nervousness” and “uncontrollable worry” (GAD1 - GAD2, edge weight = 0.2676), and “anhedonia” and “sad mood” (PHQ1 - PHQ2, edge weight = 0.2671) were the strongest positive edges in the model.

Three important bridges between anxiety and depression communities emerged to be: “afraid” and “guilty” (GAD7 - PHQ6, edge weight = 0.1965), “restlessness” and “concentration difficulties” (GAD5 - PHQ7, edge weight = 0.1784), and “uncontrollable worry” and “appetite change” (GAD2 - PHQ5, edge weight = 0.1548). Additionally, there were three bridges between pain and depression: “pain” - “guilty” (PHQ6) (edge weight = 0.0894), “pain” - “motor change” (PHQ8) (edge weight = 0.0452), and “pain” - “sleep problems” (PHQ3) (edge weight = 0.0326). The only bridge that links the pain and anxiety community was “pain” - “restlessness” (GAD5) (edge weight = 0.0576).

Central Symptoms and Bridging Symptoms

[Figure 2](#) shows the network centrality indices, and [Figure 3](#) shows the network bridge centrality indices. The node “having trouble relaxing” (GAD4, node strength = 1.182), was the most central node within the network, followed by “uncontrollable worry” (GAD2, node strength = 1.165), and “sad mood” (PHQ2, node strength = 1.144). Additionally, “uncontrollable worry” (GAD2, bridge strength = 0.645) was also the strongest bridge symptom in the network that connected the anxiety, depression, and pain clusters, followed by “guilty” (PHQ6, bridge strength = 0.545), and “restlessness” (GAD5, bridge strength = 0.414) ([Table 2](#)).

Network Stability

[Supplementary Figure 1](#) shows the results of the case-dropping subset bootstrapping test. The CS-coefficient for *Strength* and *Bridge Strength* was 0.518, and 0.284, both exceeding the recommended threshold of 0.25. This indicates that the network model is relatively robust. The bootstrapped 95% CIs for the estimated edge-weights were relatively narrow, suggesting that the estimates were accurate ([Supplementary Figure 2](#)). The edge weight matrix is presented in [Supplementary Table 1](#). After controlling for age and gender, the network model and local structure indexes were re-estimated. When compared with the original network model, an almost identical network was obtained with respect to magnitude ($r = 0.986$ [0.971, 0.996]), and strength ($r = 0.994$ [0.970, 0.998]) of edges.

Table I Demographic and Clinical Characteristics of the Study Sample

	N	%
Gender		
Male	75	34.4
Female	143	65.6
Cancer Site		
Breast	121	55.5
Leukemia	67	30.7
Colorectal	20	9.2
Nasopharynx	10	4.6
Physical comorbidities		
No	41	18.8
Yes	177	81.2
Current Smoker		
No	215	98.6
Yes	3	1.4
Daily Exercise Time		
None	27	12.4
Less than 60min	171	78.4
More than 60min	20	9.2
Childhood Adversity Experience (eg, bullying)		
None	204	93.6
Yes	14	6.4
Family Cancer History		
None	167	76.6
Yes	51	23.4
Depression		
Negative (PHQ total score <5)	135	61.9
Positive (PHQ total score \geq 5)	83	38.1
Anxiety		
Negative (GAD total score <5)	151	69.3
Positive (GAD total score \geq 5)	67	30.7
Current Pain		
Negative (VAS total score <40)	187	85.8
Positive (VAS total score \geq 40)	31	14.2

Abbreviations: GAD, General Anxiety Disorder Questionnaire; PHQ, Patient Health Questionnaire.

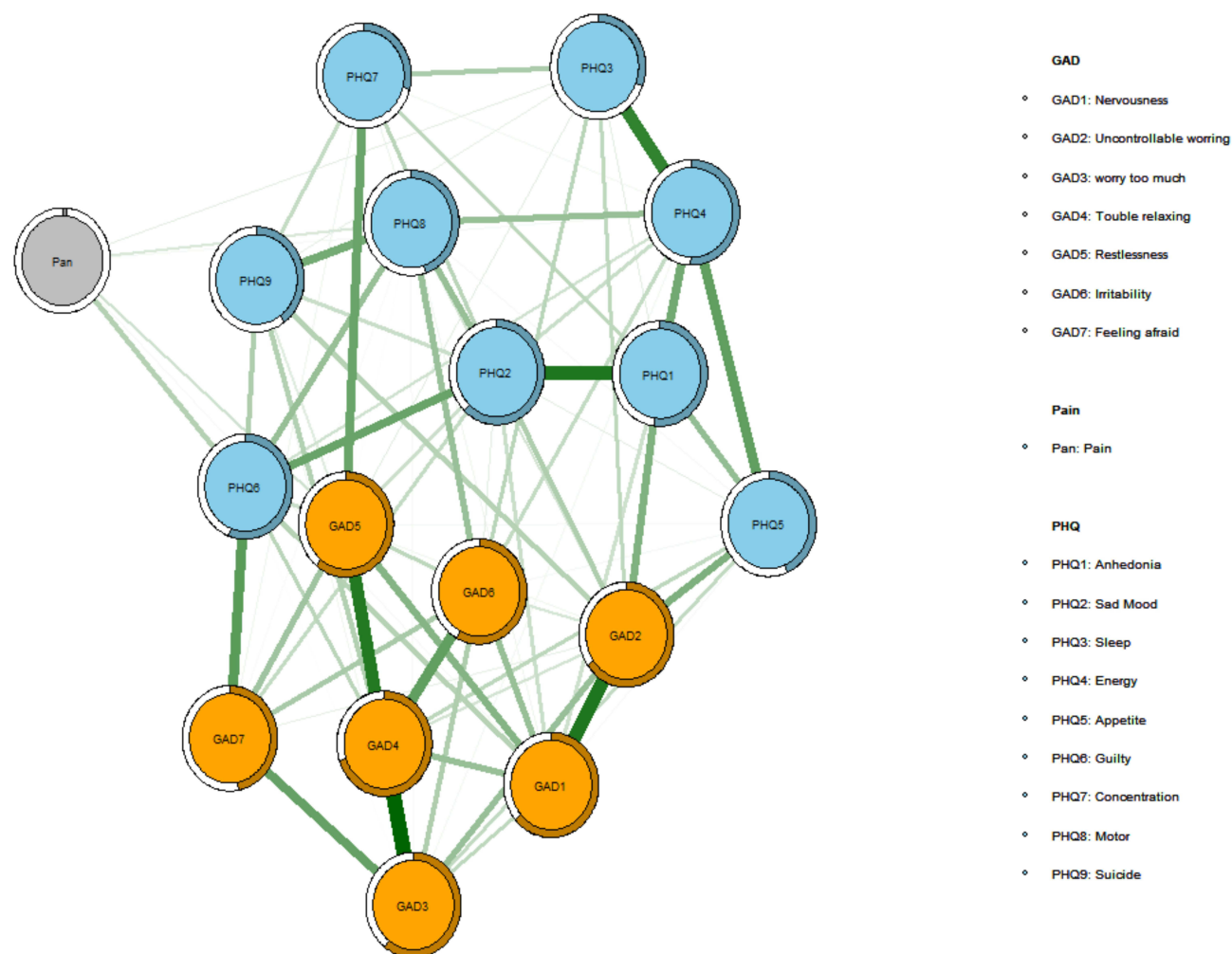


Figure 1 Network structure of anxiety, pain and depression.

Notes: In the diagram, orange nodes represent anxiety symptoms, light blue nodes represent depression symptoms, and grey node represents pain symptom. Nodes with stronger correlations are closer to each other. The thickness of an edge indicates the strength of the correlation. Green lines represent positive connections.

Abbreviations: PHQ, Patient Health Questionnaire; GAD, General Anxiety Disorder.

Discussion

This was the first study that explored the connectivity between anxiety, depression and pain symptoms in Chinese AYA cancer patients, using a network approach. In this study, we found that the prevalence of depression (38.07%) and anxiety (30.73%) in AYA cancer patients is lower than that in a previous AYA study in China.¹¹ However, the prevalence found in the current study is significantly higher than that in Chinese general cancer population.³ A recent investigation has reported that about 13.9% and 15.1% of the Chinese cancer patients have significant symptoms of depression and anxiety, respectively.³ Although several relevant studies have been conducted in China, generalizations to the larger population cannot be made due to several limitations, such as small sample sizes and single-site study designs. In addition, we found that around 14.22% of the AYA patients reported being in current pain. A previous study revealed that about 81.8% of the AYA cancer survivors reported some pain,⁴⁵ while another study reported that 36.2% of the AYA cancer survivors reported pain.⁴⁶ The difference in results could be partially explained by the difference in study sample, patient's sociocultural background, cancer type, and the use of various measurement tools and cutoff values.

In this study, we found that the three communities (ie, anxiety, depression, and pain) were well connected with each other, particularly anxiety and depression. Previous studies have consistently proved that anxiety and depressive symptoms are highly correlated with each other in different populations,^{39,47–49} including cancer patients.³² Anxiety and depression often share a high degree of comorbidity amongst cancer patients.^{7,50} The possible underlying

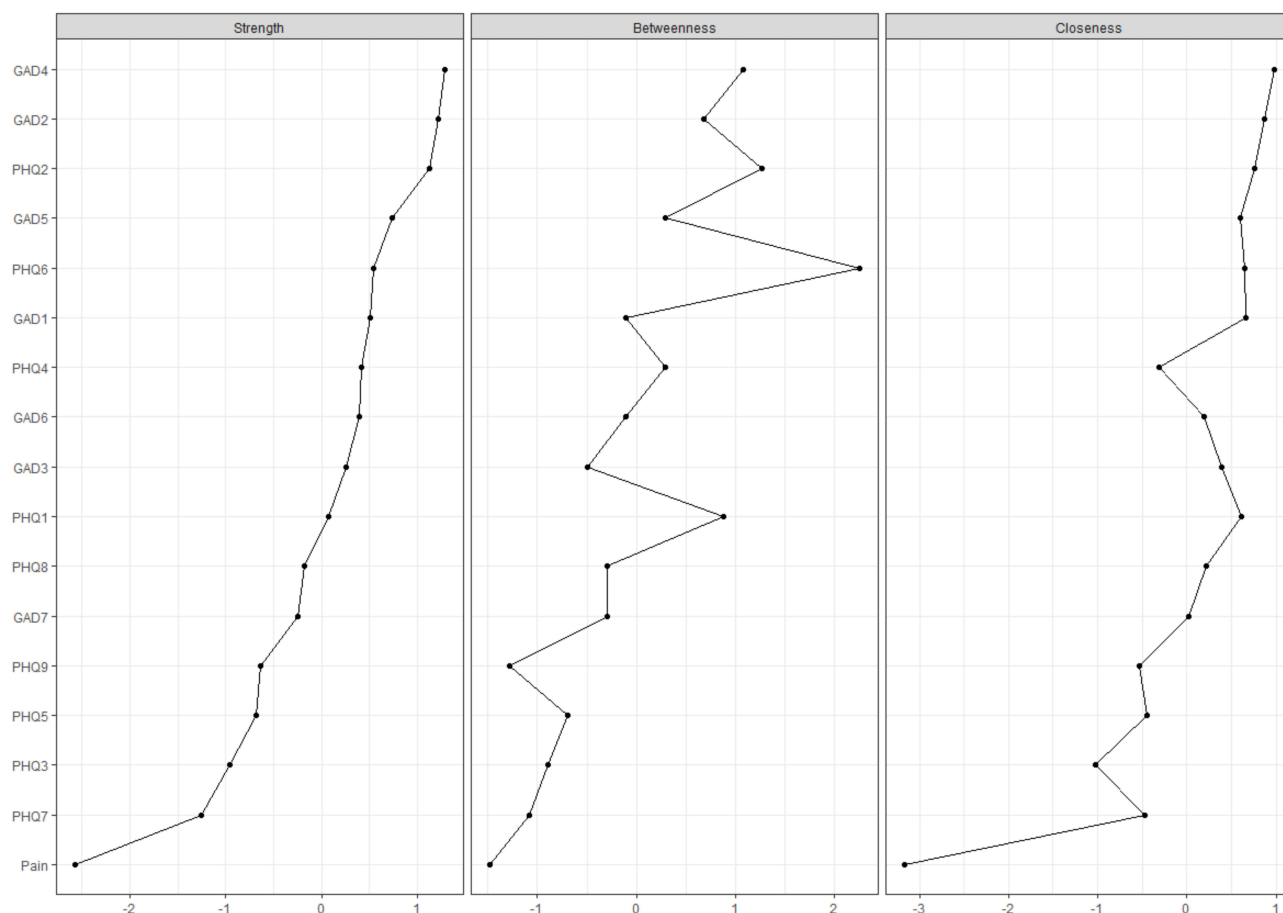


Figure 2 Centrality Indices of all symptoms within the network.

Abbreviations: PHQ, Patient Health Questionnaire; GAD, General Anxiety Disorder.

mechanisms behind the anxiety–depression interaction could be the polymorphic variation at the serotonin 1-A receptor gene,⁵¹ or the alteration of activation and connectivity of amygdala and ventral cingulate.⁵²

Besides the strong associations between anxiety and depression, several positive edges were identified between pain and anxiety/depression. In the network model, pain was positively linked to “guilty”, “motor change”, “sleep problems”, and “restlessness”. Pain is recognized to have both a sensory dimension (ie intensity) and an affective dimension, such as, unpleasantness, anxiety, sadness, and annoyance.⁵³ It has a profound impact on a patient’s physical, psychological, and social quality of life.⁵⁴ The network model confirmed results from previous studies that emotional disturbances significantly influence the prognosis and treatment of pain, and vice versa.^{19,53} For example, studies have proved that depression, anxiety, and fear of cancer progression play important roles in the association between objective pathophysiology and patient’s subjective experience of pain.⁸ Simultaneously, the presence of pain is associated with worse psychological and health-related outcomes, such as higher depression, poorer work performance, and lower quality of life.¹⁹ Meanwhile, our findings are in accordance with previous studies which indicated that insomnia at baseline predicted the development of pain, and anxiety symptoms partially mediated that association between insomnia and pain.⁵⁵ As suggested by the biopsychosocial models, an increasing number of researchers have delineated psychosocial variables to be important correlates of pain.

In this study, the node “having trouble relaxing” was the most central node within the network, followed by “uncontrollable worry” and “sad mood”. Our findings were consistent with previous similar studies which identified “persistent worrying or anxiety”, and “inability to relax” as core symptoms for the diagnosis of generalized anxiety disorder, and “sad mood” as the hallmark symptom of major depressive disorder.^{39,48} Also, “uncontrollable worry” was the strongest bridging symptom in the network. Previous studies have indicated that the activation of bridging symptoms

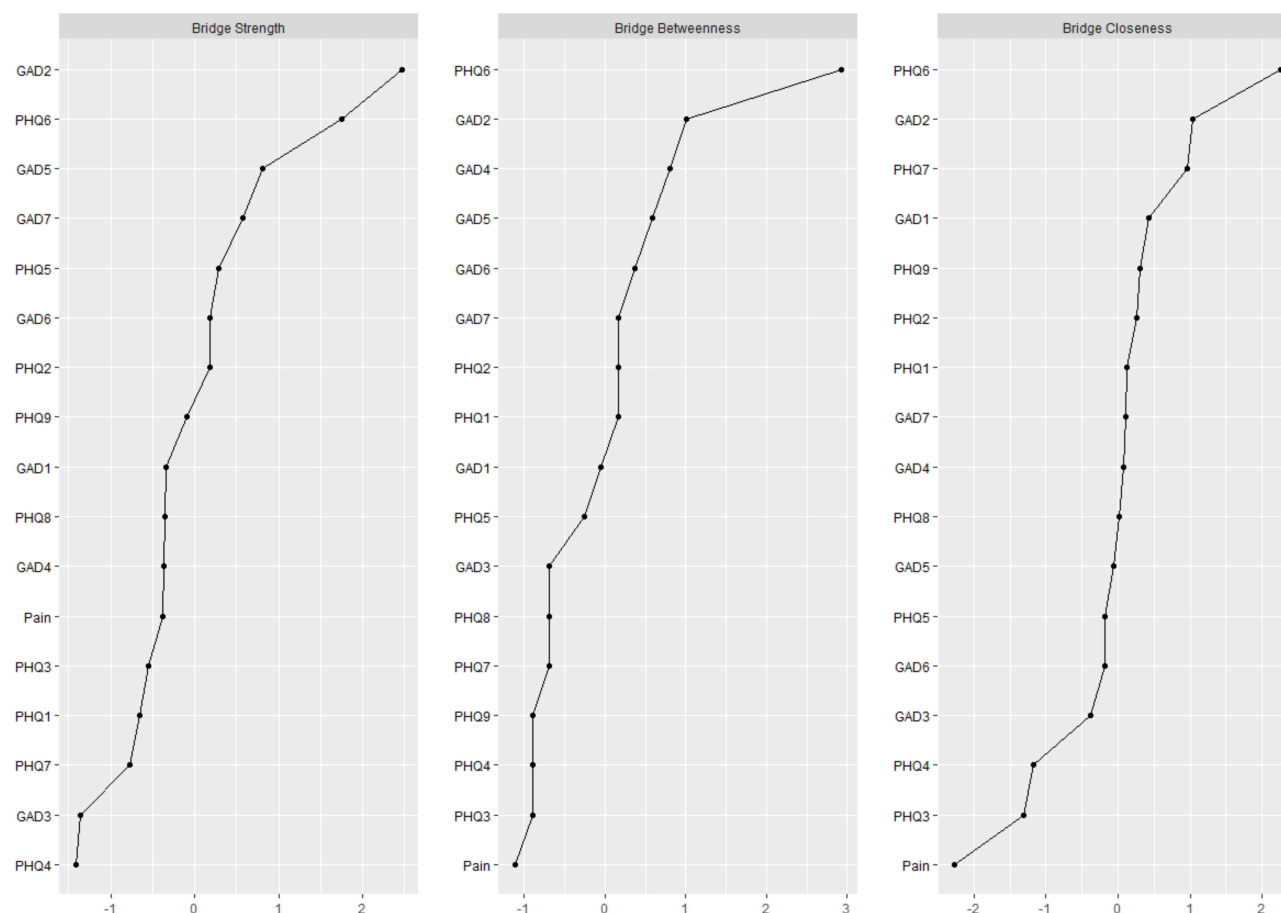


Figure 3 Bridge Centrality Indices of all symptoms within the network.

Abbreviations: PHQ, Patient Health Questionnaire; GAD, General Anxiety Disorder.

is likely to result in the development and maintenance of different disorders.⁵⁶ Therefore, “uncontrollable worry”, “guilty”, and “restlessness”, which were the key bridging symptoms that linked one cluster to other clusters in the current study, should be considered as potential targets for future intervention. In particular, in this study, “uncontrollable worry” acts as both central symptom and bridging symptom, indicating that alleviating cancer patient’s excessive worries might be helpful in improving the patient’s co-occurring anxiety, depression and pain symptoms.

This study contributes to the literature in several ways. First, we specifically targeted the AYA population, as they have unique biological and psychological needs. However, health care services in this population have not shown any significant improvement in over two decades, and in China, AYA cancer patients are often ignored.³² The current study helped fill the gap between pediatric and adult psycho-oncology. Second, this was the first study that examined the connectivity between anxiety, depression and pain symptoms in Chinese AYA cancer population. Pain and emotional distress (eg, anxiety, and depression) have been considered as the fifth and sixth vital signs for a cancer patient’s well-being, along with signs of blood pressure, heart rate, temperature, and respiration. Thus, investigating the connectivity between emotional distress and pain provided us better insights into the AYA population. Third, this study used sophisticated network analysis approach, which is a novel approach to examine the comorbidity of two or more disorders.

Study Limitations

There are several limitations that should be acknowledged, however. First, due to the cross-sectional design of the study, no causal relationship could be derived. Second, the sample size of the current study was relatively small; thus, our findings may not be generalizable to the entire AYA population in China. In addition, the sample size calculation formula for cross-sectional study might not be applicable to network analysis. Third, cancer pain was assessed by one-item

Table 2 Centrality and Bridge Centrality Estimates of Nodes in the Network

	Centrality				Bridge Centrality			
	Strength	Betweenness	Closeness	Expected Influence	Predictability	Strength	Betweenness	Closeness
Pain	0.249	0	0.003	0.045	0.016	0.249	0	0.046
PHQ1	0.888	12	0.005	0.888	0.520	0.212	6	0.066
PHQ2	1.144	14	0.005	1.144	0.620	0.327	6	0.068
PHQ3	0.639	3	0.004	0.573	0.310	0.227	1	0.054
PHQ4	0.972	9	0.004	0.949	0.504	0.106	1	0.055
PHQ5	0.705	4	0.004	0.705	0.435	0.342	4	0.064
PHQ6	1.003	19	0.005	1.003	0.559	0.545	19	0.085
PHQ7	0.566	2	0.004	0.566	0.293	0.196	2	0.074
PHQ8	0.829	6	0.005	0.738	0.450	0.254	2	0.066
PHQ9	0.718	1	0.004	0.718	0.402	0.290	1	0.068
GAD1	0.993	7	0.005	0.969	0.635	0.255	5	0.069
GAD2	1.165	11	0.005	1.165	0.651	0.645	10	0.074
GAD3	0.933	5	0.005	0.933	0.604	0.114	2	0.062
GAD4	1.182	13	0.005	1.182	0.696	0.252	9	0.066
GAD5	1.050	9	0.005	1.050	0.609	0.414	8	0.065
GAD6	0.967	7	0.005	0.967	0.577	0.328	7	0.064
GAD7	0.812	6	0.005	0.812	0.471	0.382	6	0.066

Abbreviations: GAD, General Anxiety Disorder Questionnaire; PHQ, Patient Health Questionnaire.

question, and anxiety and depression symptoms were measured by self-rating scales, thus, recall bias and measurement bias may exist. Fourth, certain factors that may influence an individual's anxiety, depression and pain, such as, family/social support, time since diagnosis, disease severity, and substance use were not examined in this study. A further multicenter, large-sample, longitudinal investigation using validated objective instruments is needed.

Clinical Implications

This is the first network study to assess the bridge symptoms/items that mediate the interaction among different disorders/syndromes (eg, anxiety, and depression) in AYA cancer populations. Examining patient's anxiety, depression, and pain symptoms as dynamic systems may provide new insights into the maintenance of these psychosomatic problems. As "uncontrollable worry" was the strongest bridge symptom that linked one symptom cluster to other symptom clusters, this finding suggested that interventions aimed at alleviating patients' worries and fostering a sense of control (eg, Acceptance – commitment therapy and Mindfulness – base stress reduction) might have utility. Further longitudinal studies could also help to better understand the directionality of these bridge pathways.

Conclusion

In conclusion, anxiety, depression, and pain are highly interactive with each other in Chinese adolescent and young adult cancer patients. In the anxiety-depression-pain network model, "having trouble relaxing", "uncontrollable worry", and "sad mood" were identified as the most central symptoms, while "uncontrollable worry", "guilty", and "restlessness"

were the key bridging symptoms that linked one cluster to other clusters. Alleviating AYA cancer patient's excessive worries might be helpful in improving a patient's co-occurring anxiety, depression and pain symptoms.

Data Sharing Statement

The dataset supporting the conclusions of this article is included within the article and its additional file.

Ethical Approval and Consent to Participate

This study was performed in accordance with the Helsinki standard, and the study's protocol was approved by the Nanfang Hospital Ethics Committee (ref No: NFEC-2018-038) and Guangdong Provincial People's Hospital Research Ethics Committee (ref No. 2018295H(R1)). The informed consent was obtained from all subjects and/or their legal guardian(s).

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Disclosure

The authors declare that they have no competing interests.

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