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Using network analysis to identify central symptoms of depression and anxiety in different profiles of infertility patients

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Abstract

Background Depression and anxiety were not only common but also with serious consequence in infertility patients. The current study endeavors to define distinct depression and anxiety profiles of infertility patients and identify central symptoms within different profiles to facilitate targeted interventions.

Method The research employed K-means Clustering to delineate the depression and anxiety profiles, followed by a repetition of the analysis using Latent Class Analysis (LCA). Furthermore, network analysis was utilized to identify central symptoms within the various profiles.

Result K-means Clustering identified Cluster 1 (16.15%), Cluster 2 (37.08%) and Cluster 3 (46.77%), while LCA yielded the low-risk group (47.23%), the mild-risk group (34.46%) and the high-risk group (18.31%). A majority of patients in the three clusters were predominantly in a single LCA-derived patient class (88.38–100%). Network analysis revealed that connections within each symptom in PHQ-9 and GAD-7 were stronger than those between symptoms. Furthermore, PHQ 2 ("*sad mood*"), GAD 1 ("*nervousness*") and GAD 2 ("*uncontrollable worry*") were identified as the central symptoms in Cluster 1 GAD 3 ("*excessive worry*"), GAD 2 ("*uncontrollable worry*") and GAD 5 ("*restlessness*") emerged as the central symptoms in Cluster 2) Additionally, PHQ 4 ("*fatigue*"), GAD 6 ("*irritability*") and GAD 3 ("*excessive worry*") were identified as the central symptoms in Cluster 3.

Conclusions We defined three distinct depression and anxiety profiles among infertility patients and pinpointed central symptoms within each profile. These findings underscore the importance of directing research towards those central symptoms within each profile in order to develop targeted intervention strategies.

Keywords Infertility, Depression, Anxiety, K-means clustering, Latent class analysis, Network analysis

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Introduction

Infertility represents a global public health concern, profoundly impacting the personal, social, and economic aspects of individuals and families alike [1, 2]. The enormous pressure from traditional ideals, families, and society substantially affects the psychological well-being of infertility patients, resulting in prevalent depression and anxiety [3–8]. Studies have revealed pooled prevalence rates of depression and anxiety among infertile women to be 44.32% and 54.24% in low- and middle-income countries, and 28.03% and 25.05% in high-income countries, respectively [9, 10]. The overall prevalence of depression in infertile men was 18.30% [11]. In China, the prevalence of depression, anxiety, and a combination of both psychological symptoms in the infertile men was 20.8%, 7.8%, and 15.4%, respectively [12]. Another study showed that the prevalence rates of depression at 9.4% and 7.9%, and anxiety at 13.5% and 8.7% in female and male partners undergoing assisted reproductive technology (ART) treatment, respectively [3]. Furthermore, severe depression has been associated with reduced pregnancy rates during infertility treatment [5], and depression and anxiety also produce adverse effects on semen quality, with men experiencing anxiety showing lower final total motile sperm counts (fTMSC) in in-vitro fertilization (IVF) procedures, compared to men without anxiety [13].

Depression and anxiety were not only common but also with serious consequence in infertility patients. A better understanding of the characteristics and needs of these patients is of great significance in order to develop effective interventions and deliver appropriate services. Ideally, prevention interventions would be tailored to the differing needs of distinct infertility patient profiles rather than treating all as a homogeneous group, which would allow resources to be more effectively allocated. Although a considerable body of literature is available on profile identification, most studies in this field have been conducted using a single method of classification [14–16]. Given the lack of a gold standard for statistically validating data clustering results, single methods may introduce subjectivity, thereby clouding the validation, applicability, and stability of identification results [17, 18]. Therefore, employing two or more grouping methods with differing principles could allow for the mutual verification of results, potentially furnishing an opportunity to confirm the accuracy and stability of the findings, hence reducing subjectivity. K-means Clustering and Latent Class Analysis (LCA) have been widely used as grouping methods in previous studies [19, 20], and each confers its own unique analytical slant. K-means used an arbitrary distance measure to identify clusters and separates the study units into different clusters, whereas LCA estimates the probability that a given study unit belongs to each of the different latent classes [21, 22]. To data, only one exploratory study defined distinct student anxiety profiles through latent profile analysis and k-means clustering method [23]. However, as far as we know, no previous study described anxiety and depression symptoms among infertility patients via K-means Clustering and LCA. As such, the primary objective of the current exploratory study is to outline distinct depression and anxiety profiles of infertility patients through K-means Clustering and subsequently verify its stability through LCA.

Furthermore, it is known that depression and anxiety comprise several different symptom dimensions. While existing studies often employ sum or mean scores to represent the degree of depression and anxiety that assign equal weight to all symptoms, there exists the risk of overlooking significant differences between specific symptoms [24, 25]. In response, network analysis, which permits the assessment of symptom-symptom interactions and facilitates the identification of central symptoms, offers a promising approach [24]. Central symptoms, characterized by strong correlations with a large number of other symptoms, may play a major role in the onset and/or maintenance of psychiatric syndrome, making them potential targets for more efficient preventive measures and interventions [26, 27]. By analyzing depression and anxiety symptoms through the lens of network analysis, it becomes feasible to transcend the current mean level of symptoms and discern the particular centrality of specific symptoms in the experience of depression and anxiety. Thus, the second aim of this study is to identify central symptoms of depression and anxiety in different profiles of infertility patients.

In light of these considerations, the current study endeavors to define distinct depression and anxiety profiles of infertility patients and identify central symptoms within different profiles to facilitate the development of targeted interventions. The study departs from the following hypotheses: (a) Infertility patients form a heterogeneous group with different depression and anxiety profiles; and (b) central symptoms differ within each profile.

Methods

The setting of the study

This study was conducted in Dalian, a coastal city at the southern tip of Liaodong Peninsula in Liaoning Province, China. It is located to the south of the Bohai Sea and north of the Yellow Sea [28]. In this study, patients were recruited by Dalian Women and Children's Medical Group, located in the main city, which is the largest public general hospital for women and children in Northeast China.

Participants
The cross-sectional study involved the participation of individuals presenting infertility as their primary concern at the Department of Reproductive Center. As for female, eligibility inclusion criteria included: (1) not been pregnant for at least 12 months prior their participation in this study; (2) childbearing age, defining as women aged between 20 and 49 years in this study; (3) agreed participation. As for male, eligibility inclusion criteria included: (1) men from infertile couples; (2) agreed participation.

The exclusion criteria were applied: (1) past history of psychotic disorders; (2) voluntary withdrawal or incomplete information.

The study was carried out from November 2022 to December 2023, during which period doctors and nurses received professional training for the collection of questionnaires. Following clinical diagnosis, each participant was escorted to a private treatment room for the survey. Participants were assured that all data would solely be utilized for the purpose of this study and their involvement was entirely voluntary. Then, the electronic "Questionnaire Star" tool (https://www.wjx.cn/) was used to send questionnaire to the participants. Ethical approval was obtained from the Ethical Review Board of the Dalian Women and Children's Medical Group (internal file number: 2024002). Paper detailing the findings from the recruitment procedure has been published [29].

Ultimately, a total of 658 questionnaires were collected, of which 650 were deemed valid, resulting in an effective rate of 98.78%.

Measurements
The nine-item patient health questionnaire (PHQ-9)
The Patient Health Questionnaire depression module (PHQ-9) is a widely used self-administered instrument comprising nine items, designed to detect depression and assess its severity [30]. Within a 2-week time frame, each symptom is evaluated using a 4-point rating scale, ranging from 0 for "*not at all*" to 3 for "*nearly every day*" [31]. The PHQ-9 has undergone extensive testing for depression screening, demonstrating its efficacy as a brief, user-friendly measure of depressive symptoms with robust psychometric properties, making it suitable for routine use in patients with infertility [32, 33]. In the general Chinese population, the Chinese version of the PHQ-9 is a valid and efficient tool for screening depression, with a recommended cutoff score of 7 or more [34]. In this study, the Cronbach's alphas was 0.953, indicating good internal consistency.

The generalized disorder scale (GAD-7)
The GAD-7 is composed of seven self-report items focused on assessing the severity of anxiety symptoms, with participants rating the frequency of these symptoms over the past week on a scale from 0 (*not at all*) to 3 (*nearly every day*) [35]. Previous studies have demonstrated the GAD-7 to be an efficient, easy-to-use, and valid measure of anxiety severity, aiding in subsequent clinical diagnosis [36]. Additionally, it has been noted to be sensitive in detecting changes in psychopathology over the course of treatment [37]. The Chinese version GAD-7 was shown to have good reliability and validity in general hospital outpatients, with a proposed cutoff score of 10 [38]. In the current sample, the reliability was satisfactory as indicated by a high Cronbach's alphas of 0.969.

Statistical analyses
In conducting the statistical analysis, first, we employed basic descriptive statistics to describe the participants' demographic characteristics. Then, we implemented two independent analytic strategies (K-means Clustering, Latent Class Analysis) to define distinct infertility patient profiles. Last, based on the results of K-means Clustering, a chi-square test was conducted to compare the three clusters on demographic variables and then we applied network analysis as we attempted to identify central symptoms in different profiles.

K-means clustering
The K-means Clustering is a method to use data to uncover natural groupings within a heterogeneous population [15], which was used to identify the depression and anxiety profiles of infertility patients who would be classified most frequently in the same cluster. The method has worked by finding the difference between initial group means and in a process, moving around these means until these distances are minimized [39]. The optimal cluster number solution was determined by the elbow test. The elbow method ran K-means Clustering on the data set for a range of values for K and calculated the sum of squared errors (SSE) for each value of K [17]. The underlying assumption with this method is that increasing the number of clusters beyond the elbow position will not further reduce SSE substantially [40]. The optimal number is the elbow position [19]. K-means was performed by python 3.9.

Latent class analysis, LCA
Latent Class Analysis is an iterative, maximum likelihood method that estimates how patterns in patient characteristics can be summarized into a finite number of groups, or latent classes, by providing a probability distribution over the cluster assignment for each patient [14, 18]. The scientific goal of LCA-based Clustering was to arrive at a solution that represented the most parsimonious and interpretable set of classes [18]. We assumed that each patient belonged to one of a set of n latent classes, the number or size of which were unknown a priori. We

explored models that would identify 2–5 classes, assessing each respective model's performance using Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), adjusted Bayesian Information Criterion (BIC) and entropy, and compared models using the Lo-Mendell-Rubin (LMRT) and bootstrap likelihood ratio test (BLRT) [14, 17]. Moreover, it should be noted that the interpretability and practical implications for practitioners were also considered in the determination of the final model [23]. The statistical analysis software utilized was Mplus Editor, version 6.

Network analysis

To address the potential overlap between redundant nodes, we utilized the "goldbricker" function (threshold: 0.25) from the "networktools" R package and found no reduction of nodes was suggested in this study [41, 42]. Therefore, all items from PHQ-9 and GAD-7 were included in the network analysis. Then, the R package qgraph was used to calculate and visualize the networks of depression and anxiety symptoms [43]. Networks consist of two building blocks: nodes and edges. Nodes are usually visualized as circles and represent variables. Edges are lines that connect these nodes, and represent relationships [26]. Expected influence (EI) indices was used to identify highly influential nodes in the network that may play a prominent role in the treatment. A higher EI of a node indicates that it is a more central symptom, and targeting these central symptoms through preventive measures and interventions may prove more efficient [44–46].

Table 1 Demographics of survey participants ($n = 650$)

Variable	Frequency	Percentage (%)
Gender		
Male	223	34.31
Female	427	65.69
Residence		
City	553	85.08
Township	52	8.00
Village	45	6.92
Monthly family income/RMB		
≤ 4000	184	28.31
4000–7000	249	38.31
7000–10,000	127	19.54
≥ 10,000	90	13.85
Only child status		
Yes	331	50.92
No	319	49.08
Only child status of the partner		
Yes	368	56.62
No	282	43.8
Birth history		
Yes	52	8.00
No	598	92.00

Note: Based on a currency exchange rate of 7.2745 RMB to $1.00 in December 5, 2024

Results

Sample characteristics

There were 223 males (34.31%) and 427 females (65.69%), with a mean age of 34.66 years (SD = 4.55 years, range = 25–53). The great majority were from city (85.08%). A total of 66.62% of their monthly family income were below 7000 RMB. 50.92% were only children and 56.62% had only-child partners. Only 8% reported had birth history. The mean years of marriage was (4.87 ± 3.31) years, the mean year of infertility was (3.66 ± 2.70) years, and the mean year of treatment was (1.58 ± 2.25) years (Table 1). Additionally, the overall mean PHQ-9 and GAD-7 scores were (6.67 ± 6.49) and (5.17 ± 5.28), respectively. The questionnaire assessment determined that 42.31% of patients scored above the cut off for depression symptoms, and 15.85% scored above the cut off for anxiety symptoms.

Results of K-means clustering and LCA

The elbow test, as depicted in Fig. 1(a), indicated that the most significant decrease in slope for SSE across sequential clusters occurred from *k*2-3 to *k*3-4, signifying that the optimal number of clusters was three. Subsequently, the K-means Clustering method was used to identify three relatively homogeneous clusters. These were characterized as follows: Cluster 1 ($N = 105$, 16.15%) with higher depression and anxiety; Cluster 2 ($N = 241$, 37.08%) with mild depression and anxiety; and Cluster 3 ($N = 304$, 46.77%) displaying lower depression and anxiety than other clusters, as illustrated in Fig. 1(b).

In the context of LCA, models with two to five classes were compared in order to determine the optimal number (Table 2). The 2-class model was initially excluded due to the largest AIC, BIC, and aBIC values, while the entropy value of the 5-class model indicated its inferiority, compared to others. Subsequently, although the 4-class model demonstrated better statistical indicators, the 3-class model, from a general practice perspective, was deemed more concise and interpretable. Therefore, the 3-class model was finalized as the optimal choice.

Grouping the patients based on depression and anxiety symptoms resulted in three distinct classes: the low-risk group ($N = 307$, 47.23%), the mild-risk group ($N = 224$, 34.46%), and the high-risk group ($N = 119$, 18.31%), as exemplified in Fig. 1(c). Notably, no crossing was observed among the three lines, indicating differences in symptom classes among groups. Furthermore, ANOVA demonstrated significant differences in scores across all PHQ-9 and GAD-7 domains among the three groups, further validating the latent classes, as indicated in Table 3.

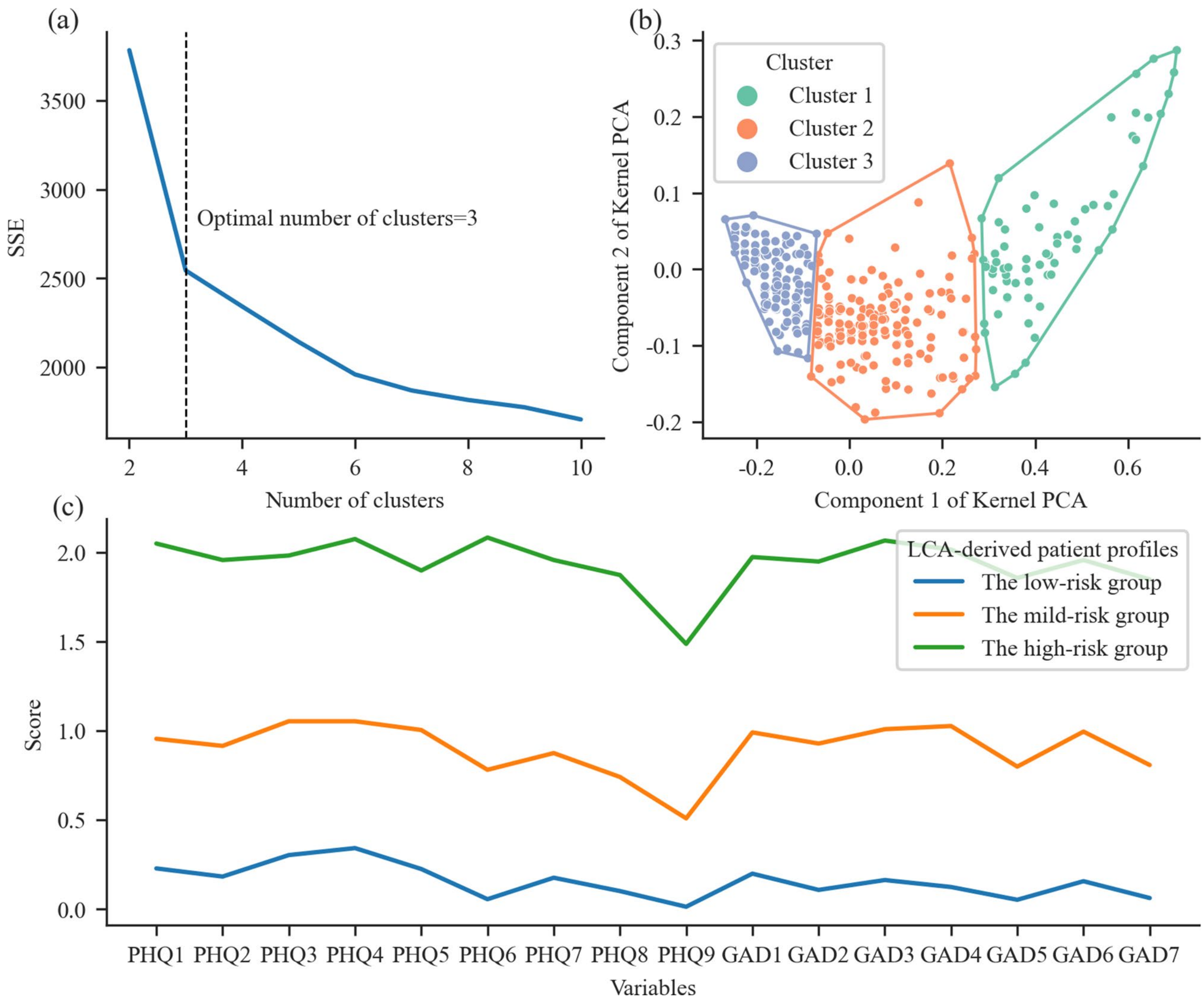

Fig. 1 Results of K-means Clustering and LCA. Notes: (**a**) elbow test; (**b**) k-means clustering. The variability between each individual pair is evaluated along two principal components, which are the orthogonal axes along which the data have the most variability. (**c**) latent class analysis; Abbreviations: SSE, sum of squared errors; PHQ-9 symptoms: PHQ 1, anhedonia; PHQ 2, sad mood; PHQ 3, sleep; PHQ 4, fatigue; PHQ 5, appetite; PHQ 6, guilt; PHQ 7, concentration; PHQ 8, motor; PHQ 9, suicide. GAD-7 symptoms: GAD 1, nervousness; GAD 2, uncontrollable worry; GAD 3, excessive worry; GAD 4, trouble relaxing; GAD 5, restlessness; GAD 6, irritability; GAD 7, feeling afraid

Table 2 Model fit statistics for LCA models specifying two to five classes

Models	AIC	BIC	aBIC	Entropy	LMR, *p* value	BLRT, *p* value	Mixing ratios
2-class	16,826.789	17,261.055	16,953.082	0.976	0.000	0.000	48.15%/51.85%
3-class	14,172.997	14,826.635	14,363.088	0.980	0.761	0.000	18.31%/47.23%/34.46%
4-class	13,291.998	14,165.007	13,545.886	0.983	0.831	0.000	4.31%/33.54%/46.77%/15.39%
5-class	12,467.045	13,559.427	12,784.731	0.974	0.773	0.000	4.46%/14.92%/20.15%/28.00%/32.46%

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; aBIC, adjusted Bayesian information criterion; LMR, Lo-Mendell-Rubin; BLRT, Bootstrapped Likelihood Ratio test. Lower values of AIC, BIC and aBIC indicated better model fit, while higher values of entropy indicated better classification quality. As for LMR and BLRT, a significant *p* value indicated that the class was better

Comparison of K-means clustering results with LCA results

The investigation into the alignment between patients assigned to the three clusters and the three classes derived from the LCA revealed that the majority of patients were predominantly associated with a singular LCA-derived patient profile. Specifically, all patients in Cluster 1 ideally matched the high-risk group of LCA. Additionally, 88.38% of patients in Cluster 2 were in the mild-risk group of LCA, while 96.38% of patients in

Table 3 Mean comparisons across three groups based on LCA

Items	high-risk group Mean ± SD	mild-risk group Mean ± SD	low-risk group Mean ± SD	F
Depression symptoms (PHQ-9)				
PHQ 1 anhedonia	2.05 ± 0.61	0.96 ± 0.52	0.23 ± 0.54	493.50**
PHQ 2 sad mood	1.96 ± 0.64	0.92 ± 0.39	0.18 ± 0.43	643.93**
PHQ 3 sleep	1.98 ± 0.77	1.05 ± 0.57	0.30 ± 0.63	310.74**
PHQ 4 fatigue	2.08 ± 0.69	1.05 ± 0.47	0.34 ± 0.63	378.51**
PHQ 5 appetite	1.90 ± 0.77	1.00 ± 0.53	0.22 ± 0.52	382.78**
PHQ 6 guilt	2.08 ± 0.62	0.78 ± 0.47	0.06 ± 0.27	981.94**
PHQ 7 concentration	1.96 ± 0.77	0.88 ± 0.56	0.18 ± 0.56	381.82**
PHQ 8 motor	1.87 ± 0.81	0.74 ± 0.50	0.10 ± 0.38	501.27**
PHQ 9 suicide	1.49 ± 0.96	0.51 ± 0.53	0.10 ± 0.14	341.33**
Total	17.37 ± 4.35	7.89 ± 2.45	1.63 ± 2.55	1267.98**
Anxiety symptoms (GAD-7)				
GAD 1 nervousness	1.97 ± 0.69	0.99 ± 0.34	0.20 ± 0.45	637.63**
GAD 2 uncontrollable worry	1.95 ± 0.70	0.93 ± 0.33	0.11 ± 0.35	821.62**
GAD 3 excessive worry	2.07 ± 0.62	1.01 ± 0.33	0.16 ± 0.40	882.62**
GAD 4 trouble relaxing	2.02 ± 0.65	1.03 ± 0.39	0.12 ± 0.41	785.10**
GAD 5 restlessness	1.86 ± 0.74	0.80 ± 0.48	0.05 ± 0.31	639.60**
GAD 6 irritability	1.96 ± 0.67	1.00 ± 0.40	0.16 ± 0.42	670.57**
GAD 7 feeling afraid	1.85 ± 0.81	0.81 ± 0.47	0.06 ± 0.31	586.96**
Total	13.67 ± 3.98	6.56 ± 1.46	0.86 ± 1.84	1408.10**

Note: ***p* value < 0.00

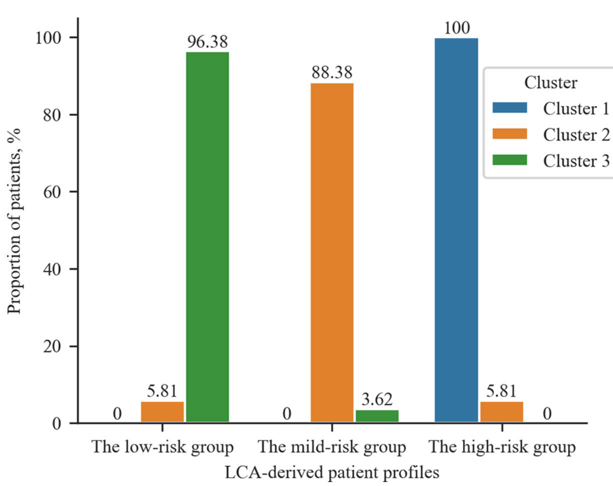

Fig. 2 The overlap of K-means clustering results with LCA results

Table 4 The comparison of three clusters with demographic variables

Items	Cluster 1 *n* (%)	Cluster 2 *n* (%)	Cluster 3 *n* (%)	*P*
Gender				
Male	33 (14.80%)	79 (35.43%)	111 (49.78%)	0.524
Female	72 (16.86%)	162 (37.94%)	193 (45.20%)	
Residence				
City	82 (14.83%)	204 (36.89%)	267 (48.28%)	0.165
Township	13 (25.00%)	18 (34.62%)	21 (40.38%)	
Village	10 (22.22%)	19 (42.22%)	16 (35.56%)	
Monthly family income/RMB				
≤ 4000	48 (26.09%)	65 (26.10%)	71 (38.59%)	0.000
4000–7000	36 (14.46%)	94 (37.75%)	119 (47.79%)	
7000–10,000	12 (9.45%)	43 (33.86%)	72 (56.69%)	
≥ 10,000	9 (10.00%)	39 (43.33%)	42 (46.67%)	
Only child status				
Yes	54 (16.31%)	128 (38.67%)	149 (45.02%)	0.632
No	51 (15.99%)	113 (35.42%)	155 (48.59%)	
Only child status of the partner				
Yes	65 (17.66%)	141 (38.32%)	162 (44.02%)	0.233
No	40 (14.18%)	100 (35.46%)	142 (50.35%)	
Birth history				
Yes	6 (11.54%)	15 (28.85%)	31 (59.62%)	0.152
No	99 (16.56%)	226 (37.79%)	273 (45.65%)	

Cluster 3 were in the low-risk group of LCA, as demonstrated in Fig. 2.

Network structure and EI centrality in different profiles of infertility patients

Based on the results of K-means Clustering, a chi-square test was conducted to compare the three clusters on demographic variables (Table 4). The analysis revealed a significant relationship between monthly family income and clusters ($P < 0.01$), indicating that higher monthly income is associated with lower depression and anxiety. No significant relationships were found between other variables and clusters.

Then, the study conducted an analysis of the network structure and centrality within three profiles of infertility patients. The analysis revealed that connections within each symptom in PHQ-9 and GAD-7 were more prominent than connections between symptoms, as demonstrated in Fig. 3(a-c). Furthermore, within each profile, specific symptoms exhibited elevated EI centrality.

In Cluster 1, the node PHQ 2 ("*sad mood*") displayed the highest EI centrality, followed by the nodes GAD 1 ("*nervousness*") and GAD 2 ("*uncontrollable worry*"). In Cluster 2, the node GAD 3 ("*excessive worry*") had the highest EI centrality, followed by the nodes GAD 2 ("*uncontrollable worry*") and GAD 5 ("*restlessness*"). In Cluster 3, the node PHQ 4 ("*fatigue*") had the highest EI

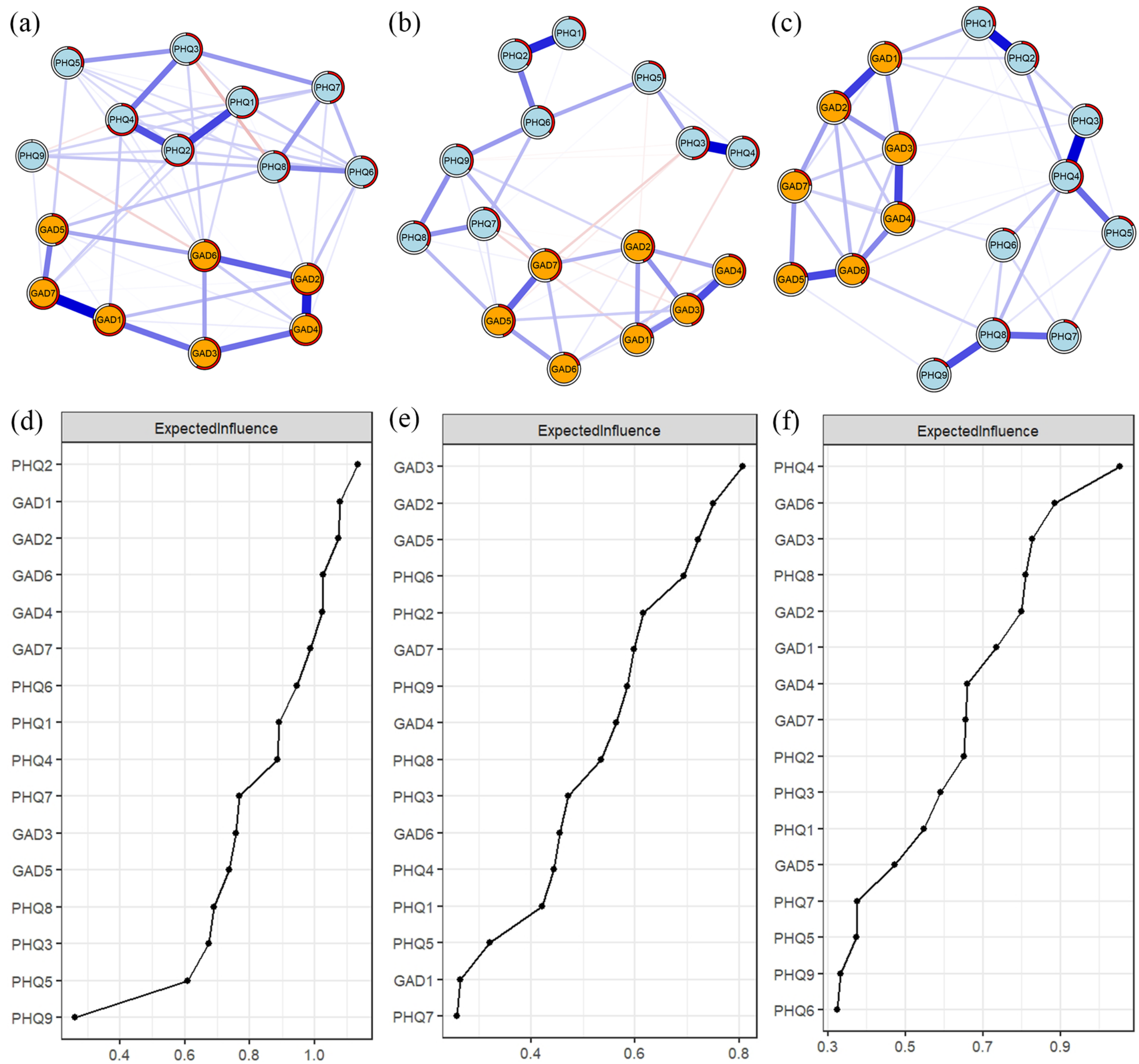

Fig. 3 The network structure and EI centrality in three profiles of infertility patients. Notes: (**a-c**): The network structure of Cluster 1, Cluster 2, and Cluster 3, respectively. The blue circle represents PHQ-9 symptoms, while the yellow one represents GAD-7 symptoms. Blue and red edges reflect positive and negative associations, respectively. (**d-f**): The EI centrality of Cluster 1, Cluster 2, and Cluster 3, respectively. The y-axis represents each symptom of PHQ-9 and GAD-7. The x-axis represents the node standardization results of EI

centrality, followed by the nodes GAD 6 ("*irritability*") and GAD 3 ("*excessive worry*") (Fig. 3(d-f)).

Discussion

To data, as we know, this study represents the first empirical attempt to define distinct depression and anxiety profiles among infertility patients, while identifying central symptoms within each profile simultaneously. Through the application of K-means Clustering and subsequent validation using LCA, three unique depression and anxiety profiles were identified. Furthermore, in the aid of the K-means Clustering results, we came up with the EI centrality within each profile. The above findings hold the potentiality to offer tailored interventions to addressing depression and anxiety symptoms among infertility patients.

The rationality for grouping

To circumnavigate the "one size fits all" approach to management strategies, increasing researchers are turning to analytic algorithms that allow the use of multiple indicators to identify homogeneous profiles within these heterogeneous populations [21]. The markedly different principles underlying the K-means Clustering and LCA methodologies allow for the mutual verification of their results. In our study, based on items from the PHQ-9 and GAD-7, K-means clustering identified three clusters, and LCA showed low, mild, and high risk groups, which was in line with the broader goal of identifying biotypes in psychiatric disorders. Taken as a whole, two independent analytic strategies both characterized the profiles based on symptom severity. In addition, the study found substantial overlap (88.38–100%) between the results of K-means Clustering and those of LCA, which exceeded the overlap observed in other studies as noted by Grant et al. and Liu et al. [17, 18]. It verified the reasonability to yield three profiles of infertility patients based on depression and anxiety symptoms, to a certain degree. The results aligned with the first hypothesis, that is, infertility patients represent a heterogeneous group and can indeed be differentiated on the basis of various depression and anxiety profiles.

The central symptoms found in different profiles of infertility patients

Based on the results of K-means Clustering, a chi-square test was conducted to compare the three clusters on relevant demographic variables to explore potential differences between clusters. The analysis revealed that higher monthly income is associated with lower depression and anxiety. ART is a long and expensive process, and the cost of ART needs to be borne by the patients themselves in China [47]. To a certain extent, better economic conditions can reduce the psychological burden. Additionally, no significant trend relationships were found between other variables and clusters.

In the analysis of the central symptoms of depression and anxiety within different profiles of infertility patients, the study sought to identify key indicators that could play a crucial role in the development, persistence, and remission of mental disorder networks as advocated by Robinaugh et al. [46]. This could lend support to locating targeted key interventions in each profile. The findings were consistent with the second hypothesis, which posited that central symptoms differ across distinct depression and anxiety profiles.

Specifically, in Cluster 1, "*sad mood*", "*nervousness*" and "*uncontrollable worry*" had the highest EI centrality. "*Sad mood*" was also the most central symptom across from a large psychiatric sample and stroke survivors [24, 48]. Sad mood has been shown to outperform other depression symptoms, and in some cases even the sum of all depression symptoms, in predicting depression diagnosis [49]. Undoubtedly, Cluster 1 was characterized by higher depression and anxiety, these infertility patients experience more serious psychological burden. Additionally, "*nervousness*" and "*uncontrollable worry*" were other central symptoms. Infertility treatment such as IVF is costly, lengthy, invasive, and has unpredictable success rates, all these may increase patients' nervousness and worry.

In Cluster 2, "*excessive worry*", "*uncontrollable worry*" and "*restlessness*" had the highest EI centrality. Infertility patients equated the period before the results of the pregnancy test were released to waiting for a death sentence [50]. This feeling of anxiety and worry continues until a healthy baby is born successfully [25]. In turn, too much worry leads to some physical symptoms, such as restlessness.

In Cluster 3, "*fatigue*", "*irritability*" and "*excessive worry*" had the highest EI centrality. We noticed that "fatigue" and "irritability" were common and mild symptoms, even in the general population (e.g., Chinese female nursing students) [27]. However, we cannot afford to ignore them because this could be a sign of prodrome period.

The practical significance of study

The current findings carry several clinical implications. The grouping results demonstrated the need for tailored intervention strategies to address the specific needs of distinct profiles of infertility patients. Thus, resources can be prioritized for high-risk patients. Moreover, addressing the central symptoms might have the most significant impact on reducing overall symptom severity within each profile.

As for Cluster 1, it is recommended to integrate psychological counseling or intervention within infertility treatment to effectively address the identified emotional and psychological burdens. In cases of significant distress, patients are encouraged to seek the aid of a psychiatrist to further locate the root cause, followed by targeted therapy aimed at addressing the specific psychological challenges associated with this cluster's central symptoms. As for Cluster 2, focused interventions targeting anxiety symptoms are recommended over depression symptoms. To be concise, providing additional health education, social support or psychological counseling, with a specific emphasis on reducing worry, is possible to effectively reduce anxiety levels within this profile. As for Cluster 3, patients were encouraged to take adequate rest, perform relaxation training and strengthen self-regulation.

Additionally, the study advocates that strategies should be developed to address shared needs across groups, such as interventions targeting "*uncontrollable worry*" and "*excessive worry*", given its centrality across multiple profiles.

Strengths and limitations

A main strength of the current study lies in its use of both K-means and LCA to cross-validate patient profiles, which increases reliability of the findings and aligns with the broader goal of identifying biotypes in psychiatric disorders. Then, network analysis identified the most central symptoms within each profile in infertility patients. The approach enhanced the specificity and targeting of interventions to addressing depression and anxiety symptoms among infertility patients.

There are some limitations in our study. Firstly, the cross-sectional design of the study resulted in undirected estimated networks, and centrality estimates did not provide information on whether a symptom actively triggers other symptoms or whether a symptom is mostly triggered by other nodes [51]. Thus, we cannot clarify the causality between the most central symptom and other symptoms. In this light we suggest that future studies could use intensive longitudinal data to investigate the causality of these symptoms [27, 48].

Secondly, the patients were recruited from the same reproductive hospital, which limits the generalizability of the findings. Further studies might want to remedy this weakness.

Thirdly, there is also the concern of the sample's heterogeneity issue, with the psychological impact of infertility may vary depending on the stage of assisted reproductive treatment. To remedy this heterogeneity issue, future longitudinal studies should ascertain specific treatment stages (before-, after-, immediately after- and post) so as to provide better tailored interventions [29].

Additionally, while two clustering methods were employed, the absence of independent sample validation is a notable limitation, which may affect the robustness of findings. Independent replication or cross-validation in a separate cohort would strengthen the conclusions, and we aim to address in future research.

Conclusion

In conclusion, this explorative study is significant as it has developed three distinct depression and anxiety profiles among infertility patients and, on the basis of the profiles, it has identified central symptoms. The findings underscore the significance of research focusing on the central symptoms in each profile for the ultimate purpose of enhancing targeted interventions. Highly central items within each profile could become prime candidates for future longitudinal and experimental research efforts to confirm their causal role and to identify their genetic, neurological, and cognitive underpinnings.

Abbreviations

ART	Assisted reproductive technology
fTMSC	final total motile sperm counts
IVF	In-vitro fertilization
LCA	Latent class analysis
PHQ-9	The nine-item patient health questionnaire
GAD-7	The generalized disorder scale
SSE	Sum of squared errors
AIC	Akaike's information criterion
BIC	Bayesian information criterion
BIC	adjusted bayesian information criterion
LMRT	Lo-mendell-rubin
BLRT	Bootstrap likelihood ratio test
EI	Expected influence

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Author contributions

Fang Liu: Conceptualization, Writing- original draft. Wei Qiao: Supervision. Wenju Han: Conceptualization, Data curation, Investigation. Xueming Fan: Writing-review & editing. Yingbo Chen: Data curation. Ruonan Lu: Data curation. Yujie Zhai: Data curation. Tianci Pan: Data curation. Xiuxia Yuan: Project administration. Xueqin Song: Project administration, Supervision, Writing-review & editing. Dongqing Zhang: Supervision, Writing-review & editing.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Review Board of Dalian Women and Children's Medical Group (internal file number: 2024002). All participants gave informed consent to participate and they have the right to refuse and terminate the survey at any time. Moreover, all data were collected anonymously and treated with absolute confidentiality.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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