



Review Article

Symptom Clusters in Patients with HCC: A Systematic Review

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Abstract: Background HCC patients suffering from various symptoms during palliative care. Effective symptom management can reduce patient's painful symptom experience and improve their quality of life. The researches on symptom management have shifted from single symptom to multiple symptoms occurring simultaneously. Meanwhile, different studies varied considerably on the symptom clusters and its composition. Objectives The aim of this systematic review was to summarize the compositions, measures, and analytical techniques of symptom clusters in patients with HCC. Method We conducted a comprehensive search to identify published studies about symptom clusters in patients with HCC. Databases including National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database (VIP), Wanfang Technology Journal full-text database, PubMed, EMbase and Web of Science and the studies included is from January 1, 2001 to November 24, 2019. Results There are seven articles compliance with inclusion criteria. Four symptom clusters were most commonly reported: Cluster 1: nausea/vomiting; Cluster 2: pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste; Cluster 3: sadness/distress/nervous; Cluster 4: jaundice/abdominal distension/itching/diarrhea/constipation. Conclusion This systematic review summarized the statistical methods, assessment tools, symptom cluster and composition of 7 included studies. Due to the lack of consensus on the definition of symptom cluster, the differences of statistical methods, assessment tools, sample characteristics and measuring time, the conclusion of the symptom cluster of HCC patients varied considerably in combinations.

Keywords: Symptom Cluster, Symptom Management, Liver Cancer, Systematic Review

1. Introduction

Patients with hepatocellular carcinoma (HCC) have no obvious symptoms and signs at the early stage, so that many patients are diagnosed with HCC at an advanced stage [1]. Only 20%~30% of HCC patients are considered to be treated by surgery, and most of them treated by palliative care [2, 3]. Various side effects, complications and complications of palliative care can usually lead to many symptoms. Studies showed that patients' symptom experiences are closely related to their functional status, quality of life, and disease outcomes [4-7]. Effective symptom management can reduce

patient's painful symptom experience and improve their quality of life [8]. Management of one symptom may cause the aggravation or improvement of another [9], therefore, it should consider all symptoms in the "symptom cluster", not just a single symptom [10]. The concept of "symptom cluster" was first proposed by Dodd. [11]. And in 2005, Kim [12] defined the "symptom cluster" as a group of two or more correlated and concurrent symptoms experienced by patients. Some scholars have proposed that when multiple symptoms exist at the same time, the "crossover" intervention strategy can relieve the burden of symptoms to a greater extent than the targeted symptom intervention and has

a higher efficiency advantage [13]. Researches on symptom cluster can help improving the understanding and developing appropriate strategies for symptom management. As a result, it is necessary to strengthen the awareness of synergistic effects of symptoms, prevent the occurrence of related symptoms.

At present, the researches on symptom management have shifted from single symptom to multiple symptoms occurring simultaneously [14]. However, different studies varied considerably on the symptom clusters and its composition. Some studies claim that it is strongly necessary to investigate whether symptom clusters are consistent across different measures and approaches [15, 16]. Therefore, in this study we systematically reviewed the articles on symptom cluster of liver cancer patients, summarize the core symptom clusters and its composition, exploring the reasons of differences between different studies.

2. Purpose

A comprehensive review of investigative studies of symptom clusters in HCC patients, and systematically describe the symptom clusters and characteristics.

3. Methods

3.1. Aims and Design

The aim of our systematic review was to summarize the compositions, measures, and analytical techniques of symptom clusters in HCC patients.

3.2. Literature Search

We searched both Chinese and English databases including

National Knowledge Infrastructure (CNKI), Chinese Science and Technology Journal Database (VIP), Wanfang Technology Journal full-text database, PubMed, EMBase and Web of Science. The retrieval time is from January 1, 2001 (The concept of symptom clusters was first applied to cancer patients) to November 24, 2019. For the English databases, the following medical subject heading terms and text words were used: (“Symptom Cluster OR Symptom Clusters” AND “Liver Cell Carcinoma OR Liver Cancer OR Hepatocellular Carcinoma OR Hepatoma”).

3.3. Eligibility Criteria

The literature selection in this study was based on the following inclusion criteria: Investigation of symptoms clusters in patients with HCC; Research type is descriptive; Chinese or English literature. Exclusion criteria: The study of liver cancer symptom clusters was performed using a preset method (validation method); Conference papers; Unable to obtain full text and duplicate publications.

3.4. Study Procedure

First, we searched Chinese and English databases, extracted the title and abstract of relevant articles, removed duplicates with Endnote. And then, two researchers remaining or excluded articles according to the title and abstract independently. Read the full text carefully after the primary screening to obtain the final articles.

3.5. Data Extraction

The following data were extracted from the selected articles: authors and year of the study, research design, sample, subject or measurement time, statistical methods, assessment tools, symptom cluster and composition of symptom cluster.

4. Results

4.1. Search Outcome

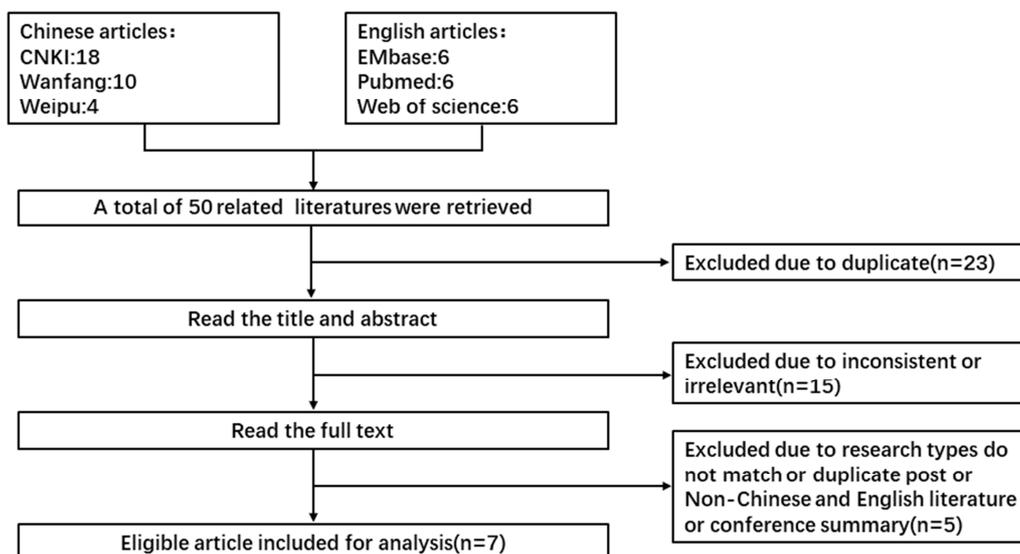


Figure 1. Flowchart of selection process.

A total of 50 potentially relevant articles were obtained through systematic search. After using Endnote to remove duplicates, 23 articles remaining. 15 irrelevant articles were excluded after screening the title and abstract, and after reading the full text of 12 papers, 7 papers met the predefined inclusion criteria. (Figure 1).

4.2. Description of Studies

Table 1 provides further details for each study. There are 5 studies in China, 1 study in the United States, 1 study in Korea. Of all the 7 articles included, 5 were cross-sectional studies and 2 were longitudinal studies. The sample size for cross-section studies is 100-277, and the sample size for longitudinal studies is 155-160. The M. D. Anderson

Symptom Inventory is the most frequently used tool among included studies, with 5 studies used this assessment scale. One study used the memory symptoms assessment scale, and the remaining study used a Symptom Checklist which associated with liver cancer. Among the 7 studies included, factor analysis was the most frequently used method which used 6 times; regression analysis, t test were used twice; principal component analysis, pearson correlation analysis, spearman correlation analysis, cluster analysis, ANOVA and Cronbach's α were used once. The number of symptom clusters extracted from each study ranges from 3 to 6, while the number of symptoms in each symptom cluster ranges from 2 to 7.

Table 1. Characteristics of studies included.

Study	Research design	Sample	Subject or Measurement time	Statistical methods	Assessment tools	Symptom cluster	Composition of symptom cluster
Wenting Cao et al. (2013) [17]	longitudinal study	155	The patients received their first episode of TACE	Principal component analysis and Spearman's correlations	M. D. Anderson Symptom Inventory and the symptom checklist particularly for HCC	Psychological symptom cluster Sickness symptom cluster Upper gastrointestinal symptom cluster Liver function impairment symptom cluster	1) Distress and sadness 2) Pain, fatigue, sleep disturbance, lack of appetite, dry mouth, abdominal distention and weight loss 3) Nausea and vomiting 4) Jaundice and itching
Ryu, E. et al. (2010) [18]	Cross-sectional study	180	Patients who were receiving active treatment for HCC	Factor analysis, t test	Symptom Checklist consisting of 21 symptoms and concerns associated with hepatobiliary cancer	Pain-appetite symptom cluster Fatigue-related symptom cluster Gastrointestinal symptom cluster Itching-constipation symptom cluster	1) Pain, nausea, loss of appetite, fever, and change in taste 2) Fatigue, back pain, lack of energy and sadness 3) Jaundice, stomach pain/discomfort, stomach swelling/cramps and diarrhea 4) Itching and constipation
Chung, M. H et al. (2017) [19]	Cross-sectional study	100	no previous surgery or chemotherapy	Pearson correlation, regression, factor analysis and hierarchical cluster analyses	M. D. Anderson Symptom Inventory	Cluster 1 Cluster 2	1) Sadness, fatigue, lack of appetite, distress, drowsiness, sleep disturbance, pain and dry mouth 2) Nausea, vomiting, numbness, shortness of breath and difficulty remembering
Che Guan hong et al. (2014) [20]	Cross-sectional study	243	3 days after TACE	Factor analysis	Memorial Symptom Assessment Scale	Upper gastrointestinal symptom cluster Sickness symptom cluster Psychological symptom cluster Pain-related symptom cluster Respiratory-digestion symptom cluster Treatment-related symptom cluster	1) Nausea and vomiting 2) Taste change, weight loss, lack of appetite and fatigue 3) Anxious, irritable and nervous 4) Fever, sweat, sleep disturbance 5) Abdominal distension, coughing, dry mouth, drowsiness and dizziness 6) Constipation and pain
Ma Hongqi et al. (2018) [21]	longitudinal study	160	3 days before surgery (T1), 1 to 3 days after surgery (T2), and 1 to 3 days before discharge (T3)	Factor analysis	M. D. Anderson Symptom Inventory and The Symptom Module Specific to Primary Liver	Affective symptom cluster Liver function related symptom cluster Pain-related symptom cluster	1) Nervous, distress, sad and sleepless 2) Bloating, diarrhea, weight loss, lack of appetite and dry mouth 3) Pain and fatigue

Study	Research design	Sample	Subject or Measurement time	Statistical methods	Assessment tools	Symptom cluster	Composition of symptom cluster
Yixin Wang et al. (2012) [22]	Cross-sectional study	277	Receiving active and/or supportive treatment for PLC	Factor analysis, t test, ANOVA, multivariate linear regression	Cancer M. D. Anderson Symptom Inventory and six additional symptom items specific to PLC	Emotional nerve symptom cluster Mental symptom cluster Gastrointestinal symptom cluster Gastrointestinal-sickness symptom cluster The neuropsychological symptom cluster Liver dysfunction symptom cluster	4) Nervous, distress, sad and forgetfulness 5) Fatigue, sleepy and sleepless 6) Nausea, lack of appetite and weight loss 1) Nausea, vomiting, pain, fatigue, dry mouth, fever and poor appetite 2) Sadness, distress, difficulty remembering, shortness of breath, sleep disturbance, drowsiness and numbness 3) Weight loss, jaundice, abdominal distension, pruritus, diarrhea, and poor appetite
Zhang Xuehua et al. (2019) [23]	Cross-sectional study/	120	First time receiving treatment of ultrasound-guided percutaneous microwave ablation	Factor analysis and Cronbach's α /M. D. Anderson Symptom Inventory and The Symptom Module Specific to Primary Liver Cancer		Pain-related symptom cluster Sickness symptom cluster Ablation-related symptoms cluster Gastrointestinal symptom cluster	1) Pain, fatigue and dyspnea 2) Jaundice, numbness, sad, pruritus and amnesia 3) Fever, weight loss, vomiting, poor appetite and abdominal distension 4) Diarrhea, uneasy sleep, upset, nausea, dry mouth and somnolence

4.3. Symptom Clusters

Four most commonly reported symptom clusters were found in this study: Cluster 1: nausea/vomiting; Cluster 2: pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste; Cluster 3: sadness/distress/nervous; Cluster 4: jaundice/abdominal distension/itching/diarrhea/constipation. The further details were listed in Table 2.

The nausea/vomiting cluster has been reported in four studies, three studies found that they exist independently, and one study reported it occurs in conjunction with other additional symptoms, which include numbness, shortness of breath and difficulty remembering.

The pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste cluster was the most commonly

reported symptom cluster, which has been reported in all included studies. Five studies found that they were grouped in the same cluster, and two studies divided symptoms into two or three separate clusters.

The sadness/distress/nervous cluster has been reported in five studies. Two studies found that the symptoms occurred independently, one study divided symptoms into two separate clusters, and two studies reported that difficulty in concentrating, anxious, irritable, difficulty remembering, shortness of breath, sleep disturbance, drowsiness and numbness were grouped in the same clusters.

The jaundice/abdominal distension/itching/diarrhea/constipation cluster co-occurred in one study, while three studies found that the symptoms occurred independently, and one study divided symptoms into two separate clusters.

Table 2. Summary of Symptom Combinations.

Study	Cluster1: nausea/vomiting	Cluster2: pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste	Cluster3: sadness/distress/nervous	Cluster4: jaundice/abdominal distension/itching/diarrhea/constipation	Other clusters
Wenting Cao et al. (2013) [17]	Yes	Yes with abdominal distention and weight loss	Yes but without nervous	Yes but without abdominal distension, diarrhea and constipation	
Ryu, E. et al. (2010) [18]		1) Yes: Pain/loss of appetite/change in taste 2) Yes: fatigue/back pain		3) Yes: jaundice/stomach swelling/diarrhea 4) Yes: Itching/constipation	
Chung, M. H et al.	Yes with numbness,	1) Yes: fatigue/lack of appetite/sleep	1) Yes: sadness/distress		

Study	Cluster1: nausea/vomiting	Cluster2: pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste	Cluster3: sadness/distress/nervous	Cluster4: jaundice/abdominal distension/itching/diarrhea/constipation	Other clusters
(2017) [19]	shortness of breath and difficulty remembering	disturbance/pain/dry mouth			
Che Guanhong et al. (2014) [20]	Yes	2) Yes: taste change/lack of appetite/fatigue	3) Yes: with difficulty in concentrating, anxious, irritable		4) fever/sweat/sleep disturbance 5) abdominal distension/coughing/dry mouth/drowsiness/dizziness 6) constipation/pain
Ma Hongqi et al. (2018) [21]		2) Yes: lack of appetite/dry mouth 3) Yes: pain/fatigue 5) Yes: fatigue/sleepy/sleepless	1) Yes with sleepless 2) Yes with forgetfulness	2) Yes: Bloating/diarrhea	6) nausea/lack of appetite/weight loss
Yixin Wang et al. (2012) 1) Yes [22]		1) Yes: pain/fatigue/dry mouth/poor appetite	2) Yes: with difficulty in concentrating, difficulty remembering, shortness of breath, sleep disturbance, drowsiness and numbness	3) Yes: with difficulty in concentrating, weight loss, poor appetite, itching and constipation	
Zhang Xuehua et al. (2019) [23]		1) Yes : pain/fatigue		2) Yes: jaundice/pruritis	3) fever/weight loss/vomiting/poor appetite/abdominal distension 4) diarrhea/uneasy sleep/upset/nausea, dry mouth/somnolence

4.4. Quality of Articles

We evaluated the quality of articles by a cross-sectional study bias risk assessment which developed by Australian Joanna Evidence-Based Nursing Centre (JBI). The points were assigned according to the degree of compliance of the

entry: 0 means it was not met the requirements; 1 means it was mentioned but not described in detail; 2 means it was described in detail. A general score > 70% of the total score can be considered with a low risk of bias. And all of the included studies presented a low risk of bias. (Table 3).

Table 3. Risk of Bias.

Study	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	Total
Wenting Cao et al. (2013) [17]	2	2	2	1	0	2	1	2	2	1	15
Ryu, E. et al. (2010) [18]	2	1	2	2	1	1	2	2	2	2	17
Chung, M. H et al. (2017) [19]	2	1	2	2	2	1	2	2	2	2	18
Che Guan hong et al. (2014) [20]	2	2	2	2	2	2	2	2	2	2	20
Ma Hongqi et al. (2018) [21]	2	2	2	2	2	1	2	2	2	2	19
Yixin Wang et al. (2012) [22]	2	2	2	2	1	1	2	2	2	2	18
Zhang Xuehua et al. (2019) [23]	2	2	2	2	1	2	1	2	2	1	17

C1: Was the purpose of the research clear and the proposal sufficient? C2: Whether the research object was selected in an appropriate way? C3: Whether the inclusion and exclusion criteria of samples were clearly described? C4: Whether the characteristics of samples were clearly described? C5: Whether the data collection tool has reliability and validity? C6: Whether the measures to verify the authenticity of the data were appropriate? C7: Whether ethical issues were considered? C8: Was the statistical method correct? C9: Was the presentation and analysis of results appropriate and accurate? C10: Whether the value of research was clearly stated?

5. Discussion

5.1. The Significance of Studying Liver Cancer Symptom Clusters

China has the highest incidence and mortality of HCC in the world, with more than half of the cases and 45% of related deaths [24]. With continuously deepen exploring of

cancer symptom management, there is no doubt that people will pay more attention on the symptom management of HCC patients in the future. A proof of this is that the number of publication on HCC patients' symptom management is increasing in recent years. From the view of publication quantity, the number of Chinese publications of liver cancer symptom cluster far more than that of other countries, this is in contrast to the studies of other diseases. There are two

main reasons may explain this phenomenon: 1) Chinese researches on symptom clusters started late [25], consequently China has fewer studies of symptom clusters; 2) China has the largest number of HCC patients in the world [24], so that they would pay more attention on this kind of disease. Though a growing number of people have begun to focus on the researches of HCC symptoms clusters, it is not enough. In the future, we need more researches on the intervention and treatment of HCC symptom clusters.

5.2. Symptom Cluster Analysis

It can be clearly seen from table 2. that nausea/vomiting, pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste, sadness/distress/nervous and jaundice/abdominal distension/itching/diarrhea/constipation are the most commonly reported symptom clusters, that each of them has been reported at least four times.

The results showed that the nausea/vomiting to be the most robust cluster. It probably because they all belong to upper gastrointestinal symptom, and having the same mechanism of symptom occurrence. A number of studies [26, 27] have proved that there is a strong internal correlation between gastrointestinal symptoms, which tend to occur simultaneously. It has been reported that the incidence of nausea and vomiting in patients who receiving chemotherapy is about 60% and 36% respectively [28]. Meanwhile chemotherapy as one of the most important approach treating cancer patients can cause small intestinal pheochromocytoma release 5-hydroxytryptamine (5-HT) which excite vagus afferent nerve, causing nausea, vomiting and other gastrointestinal symptoms [29]. Besides, the active substance, such as Tumor necrosis factor - α , interleukin-1 and interleukin-6, released by the tumor tissue itself or induced by the body can also causing nausea and vomiting [30].

Another robust cluster among included studies were pain/fatigue/sleep disturbance/dry mouth/lack of appetite/change in taste and sadness/distress/nervous. Tang, Lili *et al.* found that sadness (39.4%), lack of appetite (35.4%), fatigue (32.9%) and pain (21.1%) to be the most common symptoms in cancer inpatients in China [31]. Another study also reveals that patients who receiving cancer treatment often experience symptoms such as sleep disturbance, pain, anxiety, depression, and low energy/fatigue [32]. Moreover, chemotherapy drugs cause changes of mucous membrane which lead to the secretion of glands inhibited, so that patients developed a dry mouth [33]. It may explain why these symptoms can be found in all included studies. However, there should be more further researches on their internal connection.

We found that the jaundice/abdominal distension/itching/diarrhea/constipation cluster may have specific relationship with abnormal liver function. Most liver cancer patients (83%) had mildly impaired liver function [34]. Meanwhile the occurrence rate of jaundice/itching in HCC patients is particularly high which is ranged 19%~40% [35], and it seldom occurs in other diseases. Therefore, the

improvement of liver function may be of great significance to the relief this symptom cluster.

5.3. The Influencing Factors of the Results

Symptom cluster is a new concept in the field of cancer symptom management, and there still exist cognitive differences on the definition of symptom cluster. Dodd *et al.* [11] believed that symptom cluster consists of three or more simultaneous and interrelated symptoms, while Kim *et al.* [12] believed that two or more simultaneous and interrelated symptoms can constitute a symptom cluster. Another main factor influencing the results is the differences of measuring tools. Such as the Symptom Checklist used by Ryu, E. *et al.* [18], pain was classified as pain, back pain and stomach pain. On the one hand, subdivision like this can describe patient's symptoms accurately. On the other hand, as a result different studies may varied considerably in combinations. Other factors including statistical methods, sample characteristics, the number of sample, measuring time and so on. In the future, studies should be take into account to unify the minimum number of symptoms which can constitute a symptom cluster, and it is necessary to unify the measurement tools and standardize the investigation methods to obtain more accurate symptom clusters.

6. Conclusion

In this systematic review, we summarized the statistical methods, assessment tools, symptom cluster and composition of 7 included studies. Due to the lack of consensus on the definition of symptom cluster, the differences of statistical methods, assessment tools, sample characteristics and measuring time, the conclusion of the symptom cluster of HCC patients varied considerably in combinations. Though more and more studies are paying attention to the symptom clusters of cancer patients, there is still little researches on the relationship between symptoms cluster and mechanism of symptom occurrence, and few studies have focused on symptom cluster's intervention. In the future, we should standardize and unify the assessment tools and statistical methods, explore the symptom clusters with clinical consensus, provide reference theory for HCC symptom management, and promote the management of cancer symptoms in clinical practice.

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