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Metabolomics studies on cachexia in patients with cancer: a scoping review protocol

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ABSTRACT

Introduction Cancer seriously threatens human health worldwide. Cancer cachexia is one of the life-threatening consequences that occurs commonly in patients with cancer, and severely worsens patient survival, prognosis and quality of life. Previous studies have demonstrated that cancer cachexia is closely related to differential metabolites and metabolic pathways based on metabolomics analysis. This scoping review protocol, therefore, aims to provide the strategy for a formal scoping review that will summarise the differential metabolites and related metabolic pathways of cachexia in patients with cancer.

Methods and analysis The proposed scoping review will follow the Arksey and O'Malley's methodological framework, Levac et al's recommendations for applying this framework, and Peters' enhancements of the framework. The key information from the selected studies will be extracted, including author, year of publication, cachexia definition, country/origin, study design, setting, population and sample size, biological specimens, independent variables, independent variables' measure and statistical analysis. A summary of metabolites will be divided into several sections depending on the biological specimen. Differential metabolites will be compared between paired groups, and the number and names of related metabolic pathways will be counted and described. The reporting of this scoping review will be in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews checklist. This is a scoping review protocol and describes the planned review process and provides data examples extracted from a pilot study to confirm the feasibility of further investigation of the subject.

Ethics and dissemination An ethical approval is not required for this scoping review protocol, nor for the scoping review. The results of this scoping review will be disseminated through publication in a peer-reviewed journal, or presentation at a national or international conference.

Strengths and limitations of this study

► Limited scoping reviews, systematic reviews and research syntheses on metabolomics studies of cancer cachexia exist at present.
► The development of this scoping review will follow the Arksey and O'Malley's methodological framework, Levac et al's recommendations for applying this framework, and Peters' enhancements of the framework.
► This scoping review will explore and illustrate the differential metabolites and related metabolic pathways of cachexia in patients ith cancer using different biological specimens.
► This scoping review will focus on cachexia in patients with cancer, and the results may not be generalisable to other types of cachexia.
► This scoping review will be limited to studies published in English and simplified Chinese.

INTRODUCTION

Cancer is one of the major health problems faced by all countries, and seriously threatens human health and social development. There were an estimated 18.1 million new cancer cases and 9.6 million deaths worldwide.[1] The projected numbers of new cancer cases and deaths were almost 1.81 million and 0.61 million, respectively in the USA, 3.91 million and 1.93 million, respectively, in Europe, and 4.29 million and 2.81 million, respectively, in China.[2–4]

The survival time of patients with cancer is prolonged with the progress of cancer treatment.[2] However, patients with cancer always experience a series of physical, psychological, social and cultural issues due to the disease and related treatment, which seriously damages their quality of life.[5] Cachexia is a common problem in patients with cancer.[6–8] Shibata et al examined 150 patients with colorectal cancer who received first-line systemic chemotherapy, indicating a cachexia incidence of 50.7% at 24 weeks, and 91.3% over the whole study period.[9] Vagnildhaug et al in a study of 386 patients with cancer found cachexia prevalence of 51% and 22% among inpatients and outpatients, respectively, with the highest prevalence in patients with gastrointestinal cancer (62% and 42%) and lung cancer (83% and 36%).[10]

Existing studies have shown that cancer cachexia significantly shortens the survival of patients, increases the risk of mortality, treatment-related toxicity and reduces quality of life. Kays *et al* followed 53 patients with advanced pancreatic ductal adenocarcinoma on 5-fluorouracil, leucovorin, irinotecan and oxaliplatin as first-line therapy, and reported that patients without cachexia had significantly improved overall median survival and decreased risk of mortality.[11] da Rocha *et al* recruited 60 patients with gastrointestinal cancer and followed them for a mean of 55 days, reporting that cachexia was associated with severe toxicity events during chemotherapy.[12] Sun *et al* demonstrated that cachexia was associated with worse depression, anxiety and quality of life in a study of 528 patients with cancer.[13] In addition, several studies have explored the relationship between cancer cachexia and fatigue, which may also impair quality of life.[14–16] Thus, it is crucial to prevent and manage cancer cachexia.

However, the molecular mechanism of cancer cachexia is still controversial, involving genomics, transcriptomics, proteomics and metabolomics.[17–19] Metabolomics is a powerful bioanalytical strategy that studies the chemical processes of all metabolites in biological systems.[20] In recent decades, metabolome analysis has rapidly developed and has been widely used in various fields of healthcare. Miller *et al* carried out liquid chromatography mass spectrometry-based metabolomics using plasma in 18 patients with upper gastrointestinal cancer, which demonstrated that 40 metabolites were associated with cancer cachexia.[21] They found a close correlation between cancer cachexia and a combination profile of lysoPC (18:2), L-proline, hexadecanoic acid, octadecanoic acid phenylalanine and lyso-PC (16:1).[21] Yang *et al* recruited 222 patients with cancer and 74 healthy control participants, and performed ^{1}H nuclear magnetic resonance-based metabolomics with serum and urine, indicating that 45 metabolites and 18 metabolic pathways were related to cachexia.[22] Moreover, they developed a more accurate diagnostic model using carnosine, leucine and phenyl acetate.[22] Animal studies have provided similar findings.[23 24] These studies revealed that cancer cachexia was closely associated with differential metabolites and related metabolic pathways using metabolomics. To our knowledge, scoping reviews, systematic reviews and research syntheses on this topic have been limited.

A scoping review is generally used to explore the breadth or extent of the literature, map and summarise the evidence, and inform future research.[25] This project is planned to examine the research status on distinct metabolic profiling and fingerprinting and related metabolic pathways of cachexia in patients with cancer. The results could provide a reference for the exploration of molecular mechanisms, prevention and management of cancer cachexia. The proposed scoping review will be able to explore the following research questions: (1) What are the differential metabolites of cachexia in patients with cancer? (2) What are the metabolic pathways related to cachexia in patients with cancer? (3) What are the additional concerns regarding differential metabolites and related metabolic pathways of cancer cachexia?

Objectives
The objective of the proposed scoping review will be to explore and illustrate the differential metabolites and related metabolic pathways of cachexia in patients with cancer using different types of biological specimens.

METHODS
The proposed scoping review will follow the Arksey and O'Malley's methodological framework,[26] Levac *et al*'s recommendations for applying this framework,[27] and Peters *et al*'s enhancements of the framework.[28] The reporting of this scoping review will be according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews checklist.[29]

Eligibility criteria of considering studies
Only the participants who fulfilled the following characteristics were included for the proposed scoping review: (1) human, (2) 18 years or older, (3) confirmed to have a pathologic diagnosis of cancer and (4) diagnosed with cachexia with a valid standard.

Cancer cachexia is defined as a multifactorial syndrome characterised by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment.[30] The accepted diagnostic criteria for cachexia is weight loss greater than 5% over past 6 months (in absence of simple starvation), or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (body mass index <20 kg/m) or skeletal muscle mass (sarcopenia).[30] Metabolomics approach consists in identifying and determining the set of metabolites (or specific metabolites) in biological samples (tissues, cells, fluids or organisms) under normal conditions in comparison with altered states promoted by disease, drug treatment, dietary intervention or environmental modulation.[20] A targeted metabolomics approach is defined as a quantitative analysis (concentrations are determined) or semiquantitative analysis (relative intensities are registered) of a few metabolites and/or substrates of metabolic reactions that might be associated to common chemical classes or linked to selected metabolic pathways, and includes metabolic profiling.[20] An untargeted metabolomics approach is based primarily on the qualitative or semiquantitative analysis of the largest possible number of metabolites from a diversity of chemical and biological classes contained in a biological specimen.[20] Both fingerprinting and footprinting metabolomics belong to this definition.

Studies considered in this scoping review will include acute care, primary healthcare, community care and similar anywhere in the world.

Sources will include cross-sectional studies, case–control studies and cohort studies. Randomised controlled trials, non-randomised controlled trials, quasi-experimental studies, before and after studies, qualitative studies, reviews, letters, guidelines and conference abstracts will be excluded.

Search strategy and study selection

The following eight English databases and three Chinese databases will be searched: The Cochrane Library, MEDLINE, Embase, CINAHL, Web of Science, Scopus, ProQuest, Google Scholar, CNKI, WanFangdata and SinoMed.

The search terms will consist of three parts, namely "Cancer", "Cachexia", and "Metabolomics". The search terms for "Cancer" will be "Cancer* OR Tumor* OR Tumour* OR Neoplas* OR Malignan* OR Carcinoma*". "Cachexia" will be searched using the terms "Cachexia OR Cachectic OR Emaciation OR Weight OR Weights OR Muscle OR Muscles OR Malnutrition OR Undernutrition OR Malnourishment OR Nutrition*". "Metabolomics" will be searched using the terms "Metabolomics OR Metabolomic OR Metabonomics OR Metabonomic OR Lipidomics OR Lipidomic OR Lipidome OR Lipidomes".

The search field will be "Abstract". The language will be limited to English and simplified Chinese. The time period will be set as the day that the database was built to 31 December 2021. In addition, the reference lists of the articles that will be included will be reviewed to ensure that the proposed scoping review does not miss relevant studies. Corresponding authors will be contacted, if necessary. Examples of the search strategies in MEDLINE and CNKI were shown in online supplemental tables S1, S2.

Selection of sources of evidence

The references identified by the search strategy will be exported from the databases and imported into EndNote. The duplicates will be deleted via the deduplicating function of EndNote. Manual screening will be applied when duplicates are not detected by EndNote. Then, the references will be exported from EndNote, and imported into Covidence software. The references in Covidence software will be screened by two reviewers independently, according to the inclusion criteria described previously. The screening process will include the screening of titles and abstracts, and full-text screening. Any disagreements will be resolved by the decision of a third reviewer. An example of the study selection process was shown in figure 1.

Data extraction

The data extracted from the references included in the study will be verified by two independent reviewers. Any disagreement will be resolved by the decision of a third reviewer. The key information from the references will be recorded in tables and will include, author, year of publication, cachexia definition, country/origin, study design,
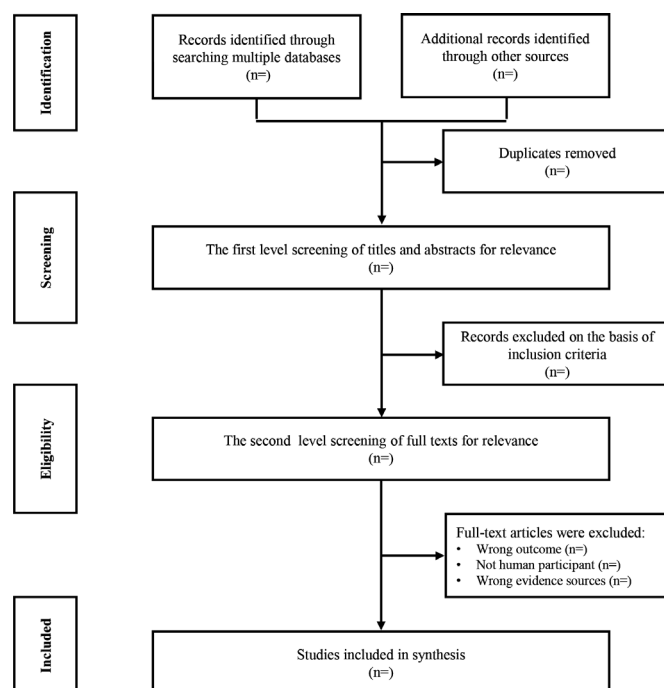

Figure 1 Schematic representation of the process employed for selecting the studies.

setting, population and sample size, biological specimens, independent variables, independent variables' measure and statistical analysis. An example of the key information records was presented in online supplemental table S3.

Data analysis

The synthesis will be performed using narrative summaries, thematic analyses, frequency distributions and descriptive statistics of the extracted data. To metabolites, data analysis will be divided into several sections depending on the biological specimen, such as plasma, serum and urine. Meanwhile, the differential metabolites will be compared between two groups. The groups will include: the cachectic group and non-cachectic group, the cachectic group and precachectic group, the cachectic group and healthy control group, the precachectic group and non-cachectic group, the precachectic group and healthy control group and the non-cachectic group and healthy control group. The number and names of the differential metabolites will be counted and described. For metabolic pathways, the number and names of related metabolic pathways will also be counted and described. In addition, other concerns regarding differential metabolites and related metabolic pathways cachectic in patients with cancer will also be summarised in a separate section. For example, the diagnostic model of cancer cachexia, the relative abundance of the lysolipids and so on.

Presentation of the results

The results of the differential metabolites and the related metabolic pathways will be summarised and presented in tables. The sample tables were listed in online supplemental tables S4–S7.

Patient and public involvement

Patients or the public will not be directly involved in the design, or conduct, or reporting, or dissemination plans of our research.

Ethics and dissemination

An ethical approval is not required for this scoping review protocol, nor for the scoping review. The results of this scoping review will be disseminated through publication in a peer-reviewed journal, or presentation at a national or international conference.

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Table S1 The Search Strategy of MEDLINE

#	Search Strings
1	(cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma*).ab.
2	(Cachexia or Cachectic or Emaciation or Weight or Weights or Muscle or Muscles or Malnutrition or Undernutrition or Malnourishment or Nutrition*).ab.
3	(Metabolomics or Metabolomic or Metabonomics or Metabonomic or Lipidomics or Lipidomic or Lipidome or Lipidomes).ab.
4	#1 and #2 and #3

Table S2 The Search Strategy of CNKI

#	Search Strings
1	(摘要=肿瘤 + 癌)
2	(摘要=恶病质 + 恶液质 + 消瘦 + 体重 + 肌肉 + 营养)
3	(摘要=代谢组学 + 脂质组学)
4	#1 and #2 and #3

Table S3 The key information of included studies

No.	Author	Year of publication	Cachexia definition	Country/ Origin	Study design	Setting	Population and sample size	Biological specimens	Independent variables	Independent variables' measure	Statistical analysis

Table S4 The significantly differential metabolites in plasma of cancer cachexia patients

No.	Name of metabolites (n=)	Cachectic VS Non-Cachectic	Cachectic VS Pre-Cachectic	Cachectic VS Healthy control	Pre-Cachectic VS Non-Cachectic	Pre-Cachectic VS Healthy control	Non-Cachectic VS Healthy control	References

Green: Changed; Red: Increased; Blue: Decreased; Tawny: Not reported.

Table S5 The significantly differential metabolites in serum of cancer cachexia patients

No.	Name of metabolites (n=)	Cachectic VS Non-Cachectic	Cachectic VS Pre-Cachectic	Cachectic VS Healthy control	Pre-Cachectic VS Non-Cachectic	Pre-Cachectic VS Healthy control	Non-Cachectic VS Healthy control	References

Green: Changed; Red: Increased; Blue: Decreased; Tawny: Not reported.

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Table S6 The significantly differential metabolites in urine of cancer cachexia patients

No.	Name of metabolites (n=)	Cachectic VS Non-Cachectic	Cachectic VS Pre-Cachectic	Cachectic VS Healthy control	Pre-Cachectic VS Non-Cachectic	Pre-Cachectic VS Healthy control	Non-Cachectic VS Healthy control	References

Green: Changed; Red: Increased; Blue: Decreased; Tawny: Not reported.

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Table S7 The related metabolic pathways of cancer cachexia patients

No.	Name of related metabolic pathways (n=)	References