

INPLASY2023120065

doi: 10.37766/inplasy2023.12.0065

Received: 15 December 2023

Published: 15 December 2023

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**ADMINISTRATIVE INFORMATION****Support** - No source of financial support.**Review Stage at time of this submission** - Data extraction.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2023120065**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 December 2023 and was last updated on 25 December 2023.**INTRODUCTION**

**Review question / Objective** The aim of this systematic review is to systematically evaluate the incidence, influencing factors and the association with postoperative outcomes of preoperative frailty in patients with head and neck cancer, and to provide scientific basis for its prevention and early intervention. To this end, the proposed systematic review will address the following questions: What is the incidence of preoperative frailty in patients with head and neck cancer? What are the influencing factors of preoperative frailty? What is the association between preoperative frailty and postoperative outcomes in patients with head and neck cancer?

**Rationale** The importance of preoperative frailty in HNC patients should be strengthened. Currently, studies on preoperative frailty in HNC patients have been conducted both at home and abroad; however, different studies have reached different conclusions about the incidence of preoperative

frailty and the factors affecting it. Therefore, this systematic review and Meta-analysis aimed to identify all the studies on the incidence of preoperative frailty in patients with head and neck cancer surgery, to clarify the prevalence of preoperative debility in patients with head and neck cancer surgery, and to review the influencing factors, so as to provide evidence support for caregivers to do a good job in the early screening and intervention of frailty, to improve the prognosis of patients with head and neck cancer surgery, and to improve the quality of life of these patients.

**Condition being studied** Head and neck cancer (HNC) refers to malignant tumors occurring below the base of the skull and above the chest, including oral cavity cancer, nasopharyngeal cancer, hypopharyngeal cancer, and laryngeal cancer, etc. It is currently the seventh most common malignant tumor worldwide. According to statistics, in 2020, there were about 930,000 new cases of HNC and 470,000 new deaths worldwide<sup>1</sup>. Surgical resection is the main

treatment for HNC2. Radical surgery for head and neck cancer is often accompanied by lymph node dissection and free flap reconstruction, which is invasive and time-consuming, with high possibility of postoperative adverse outcomes and slow postoperative recovery<sup>3,4</sup>. Frailty is a dynamically evolving and reversible multidimensional syndrome due to the loss of physiologic functions of the body, which leads to a decrease in the patient's physiologic reserve and an increase in stress susceptibility<sup>5</sup>. Frailty appears to be more prevalent in HNC patients compared to other solid malignancies, and recognition that frail patients have unique vulnerabilities and challenges is increasing in HNC surgery<sup>6</sup>. Preoperative frailty is associated with poorer postoperative outcomes and puts patients at higher risk of morbidity, postoperative complication rates, delayed discharge, and death<sup>7</sup>. Therefore, the importance of preoperative frailty in HNC patients should be strengthened. At present, there have been studies on preoperative frailty in patients with head and neck cancer at home and abroad, but different studies have drawn different conclusions on the incidence of preoperative frailty, its influencing factors, and its association with postoperative outcomes. Therefore, this review and meta-analysis aims to identify all studies on the occurrence of preoperative frailty in patients undergoing head and neck cancer surgery, to clarify the incidence of preoperative frailty in patients undergoing head and neck cancer surgery, to review its influencing factors, and to analyze its relationship with postoperative outcomes, so as to provide evidence support for early screening and intervention of frailty in caregivers, improving postoperative adverse outcomes and promoting postoperative recovery of patients undergoing head and neck cancer surgery.

## METHODS

**Search strategy** PubMed, Embase, CINAHL, Cochrane Library, Web of Science Core Collection, China National Knowledge Infrastructure (CNKI), Chinese biomedical literature service system (SinoMed), Wan fang Data, and China Science and Technology Journal Database (VIP) will be systematically searched from inception to November 30, 2023, regardless of document type and publication language. The search will be conducted using a combination of subject headings and free words. Chinese search terms will include 头颈癌, 头颈部肿瘤, 头颈部癌, 耳鼻咽喉肿瘤, 衰弱, 衰弱综合征等, etc. English search terms will include head and neck neoplasms,

head and neck cancer, head neoplasms, neck neoplasms, head cancers, neck cancers, frailty, asthenia, etc.

The search strategy of the English database PubMed will be as follows:

#3. #1 AND #2 1 010

#2. ("Frailty"[Mesh]) OR "Asthenia"[Mesh] OR (Infirmary OR debility OR Frailty OR Asthenia OR Fraillities OR Frailness OR Debility OR Debilities OR (Frailty Syndrome)) 74 220

#1. (((((((("Head and Neck Neoplasms"[Mesh]) OR "Otorhinolaryngologic Neoplasms"[Mesh]) OR "Laryngeal Neoplasms"[Mesh]) OR "Mouth Neoplasms"[Mesh]) OR "Nasopharyngeal Carcinoma"[Mesh]) OR "Tongue Neoplasms"[Mesh]) OR "Nose Neoplasms"[Mesh]) OR "Hypopharyngeal Neoplasms"[Mesh]) OR "Oropharyngeal Neoplasms"[Mesh]) OR "Pharyngeal Neoplasms"[Mesh]) OR ((Head and Neck Neoplasms) OR (Head and Neck Cancer) OR (Head Neoplasms) OR (Neck Neoplasms) OR (Head Cancers) OR (Neck Cancers) OR (Otorhinolaryngologic Neoplasms) OR (Otorhinolaryngological Neoplasms) OR (Laryngeal Neoplasms) OR (Larynx Neoplasms) OR (Larynx Cancers) OR (Laryngeal Cancers) OR (Mouth Neoplasms) OR (Oral Neoplasms) OR (Mouth Cancers) OR (Oral Cancers) OR (Nasopharyngeal Carcinoma) OR (Tongue Neoplasms) OR (Tongue Cancers) OR (Nose Neoplasms) OR (Nasal Neoplasms) OR (Nose Cancers) OR (Nose Cancers) OR (Hypopharyngeal Neoplasms) OR (Hypopharyngeal Cancers) OR (Oropharyngeal Neoplasms) OR (Oropharynx Neoplasms) OR (Oropharynx Cancers) OR (Oropharyngeal Cancers) OR (Pharyngeal Neoplasms) OR (Pharynx Neoplasms) OR (Pharynx Cancers) OR (Pharyngeal Cancers) OR HNC OR (Head and Neck Tumor) OR (Larynx Tumor) OR (Mouth Tumor) OR (Nasopharynx Carcinoma) OR (Tongue Tumor) OR (Nose Tumor) OR (Hypopharynx Tumor) OR (Oropharynx Tumor)) 524 624

The search strategy of the Chinese database CNKI will be as follows:

(篇文摘: 头颈癌 + 头颈部肿瘤 + 头颈部癌 + 耳鼻咽喉肿瘤 + 喉癌 + 口腔癌 + 鼻咽癌 + 舌癌 + 舌肿瘤 + 鼻腔肿瘤 + 鼻肿瘤 + 鼻癌 + 鼻部癌 + 下咽癌 + 下咽肿瘤 + 口咽癌 + 口咽部癌 + 咽肿瘤 + 咽癌 (精确) ) AND (篇文摘: 衰弱 + 衰弱综合征 (精确) ) 12

**Participant or population** The CoCoPop model will be used to construct the problems of incidence and epidemic trend evaluation, including Condition (Co), Context (Co) and Population (Pop). "Condition" refers to preoperative frailty. When the

frailty state is dichotomized, we will capture the proportion of frail patients. When the debilitation is divided into two levels, we will merge the frailty and moderate frailty into frailty and capture the proportion of frail patients. "Context" refers to the whole world. "Population" refers to patients who will undergo inpatient head and neck cancer surgery. The following studies will be included in this review: participants aged  $\geq 18$  years, who were about to undergo surgery for head and neck cancer in a non-emergency hospital, who had their degree of weakness measured before surgery, and who reported the results. Participants will be excluded if they have non-head and neck cancers (such as thyroid cancer) or have other cancers in combination.

**Intervention** The CoCoPop model will be used to construct the problems of incidence and epidemic trend evaluation, including Condition (Co), Context (Co) and Population (Pop). "Condition" refers to preoperative frailty. When the frailty state is dichotomized, we will capture the proportion of frail patients. When the debilitation is divided into two levels, we will merge the frailty and moderate frailty into frailty and capture the proportion of frail patients. "Context" refers to the whole world. "Population" refers to patients who will undergo inpatient head and neck cancer surgery. The following studies will be included in this review: participants aged  $\geq 18$  years, who were about to undergo surgery for head and neck cancer in a non-emergency hospital, who had their degree of weakness measured before surgery, and who reported the results. Participants will be excluded if they have non-head and neck cancers (such as thyroid cancer) or have other cancers in combination.

**Comparator** The CoCoPop model was used to construct the incidence and epidemic trend evaluation questions, which included Condition, Context and Population. "Condition" refers to preoperative frailty. Where frailty status was dichotomized, we will capture the proportion of patients with frailty. Where frailty was categorized in 2 levels, we will combine frailty and moderate frailty into frailty and capture the proportion of frailty. "Context" refers to the world "Population" refers to patients who are going to undergo non-emergency inpatient head and neck cancer surgery. This review will consider studies that include if the participants are  $\geq 18$  years of age, are going to undergo non-emergency inpatient head and neck cancer surgery, frailty are measured before surgery, and relevant outcomes are reported. Participants will be excluded if they with

non-head and neck cancers (e.g., thyroid cancer) or have a combination of other cancers.

**Study designs to be included** Only prospective and retrospective cohort studies and cross-sectional studies will be considered in this review. Reviews, conferences, reviews, case-controls, experimental studies will be excluded.

**Eligibility criteria** Inclusion Criteria: (1) Number of patients with reported frail or non-frailty; (2) Hospitalized patients; (3) Age  $\geq 18$  years old; Diagnosed with head and neck cancer (excluding thyroid cancer); Undergoing any surgical treatment for therapeutic purposes; (4) cross-sectional studies or cohort studies; (5) Published in Chinese or English; (6) the full text is available; (7) Non-duplicate publication. Exclusion Criteria: (1) Number of frail or non-frail patients not reported; (2) non-hospital settings (e.g., community); (3) The subjects of the study were head and neck cancer (including thyroid cancer) and received non-surgical treatment such as radiotherapy, chemotherapy, combination therapy or palliative care; (4) reviews, conferences, reviews, case-controls, and experimental studies; (5) Not published in Chinese or English; (6) the full text is not available or only the abstract is available; (7) Duplicate publication.

**Information sources** PubMed, Embase, CINAHL, Cochrane Library, Web of Science Core Collection, CNKI, SinoMed, Wanfang Data, and VIP Chinese Journal Database (VIP) will be systematically searched. Reference lists of included articles will be handsearched as supplements.

**Main outcome(s)** All preoperative frailty incidence, influencing factors, and postoperative outcomes for which raw data are available were included.

**Data management** The search results obtained by applying the above search strategies will be imported into EndNote.X9 for literature management. First, the duplicate bibliographies will be manually eliminated, then the abstract and title will be read, and the literature that is obviously inconsistent with the study will be further deleted, and then the full text of the remaining literature will be read to determine the final included literature according to the inclusion criteria. Reference lists of included articles will be handsearched as supplements. The literature extraction will include authors, publication date, country, study type, tumor type, sample size, incidence of preoperative frailty, frailty assessment tools, influencing factors, postoperative outcomes and risk of bias scores. Two researchers will extract the literature that meet

the inclusion and exclusion criteria according to the developed literature information data extraction form, and will decide through intra-group discussion or consultation with the third investigator when they disagree. R 4.3.0 software was used for statistical analysis.

**Quality assessment / Risk of bias analysis** The risk of bias assessment tool developed by Hoy et al.<sup>8</sup> will be used to assess the quality of the literature. The tool consists of 10 entries, each of which is rated with a score of 0 for low risk and 1 point for high risk. The risk of bias was classified as low (0-1 points), moderate (2-3 points), and high (4-10 points). The quality evaluation was carried out independently by two researchers, and then a consensus was reached on the evaluation results of each study through meeting discussions.

**Strategy of data synthesis** Meta-analysis will be performed using R 4.3.0 software, and the incidence of preoperative frailty and 95% CI in patients with head and neck cancer will be calculated. If the influencing factors and postoperative outcomes are dichotomous, the OR value will be used as the effect size. In the case of continuous variables, SMD will be used as the effect size. The heterogeneity test will be analyzed using the chi-square test (test level  $\alpha=0.10$ ), and the heterogeneity will be evaluated in combination with  $I^2$ . If the  $P>0.10$  and  $I^2\leq 50\%$ , it indicates that the studies are homogeneous, and the fixed-effect model will be used for data pooling. If the  $P\leq 0.10$  and  $I^2>50\%$  indicate heterogeneity between studies, random-effects models will be used for data pooling, and subgroup analyses and meta-regression analyses will try to identify sources of heterogeneity. If the number of included studies are 10 or more, the Egger's test<sup>9</sup> will be used to assess the potential for publication bias of each literature, and  $P>0.05$  indicates that there is no publication bias.

**Subgroup analysis** Where possible, subgroup analysis will be conducted based on publish time, regions, cancer types, study types, sample size, and frailty assessment tools.

**Sensitivity analysis** The sensitivity analysis of the included studies will be carried out by the one-by-one elimination method and the model exchange method to evaluate the stability of the results.

**Language restriction** Articles published in Chinese and English will be considered for inclusion.

**Country(ies) involved** China.

**Keywords** head and neck cancer surgery; preoperative frailty; incidence; influencing factors; systematic review; Meta-analysis

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