# RESEARCH



# Definition and assessment of adherence to oral nutritional supplements in patients with neoplasms: a scoping review



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# Abstract

**Introduction** Cancer remains a leading cause of death globally, with patients frequently experiencing malnutrition due to both the disease and its treatment, which negatively affects their quality of life and treatment outcomes. Oral nutritional supplements (ONS) provide a noninvasive solution to improve nutritional status, but poor patient adherence limits their effectiveness. Studies on ONS adherence vary in their definitions and assessment tools, creating inconsistencies. A scoping review is essential to synthesize these studies and establish a foundation for future research and clinical practice.

**Method** We systematically searched six databases, including Web of Science, PubMed, and Scopus, up to August 2024. Our criteria focused on oncology patients, ONS interventions, and outcomes related to adherence definitions, assessment methods, and adherence rates.

**Results** 37 studies from 2005 to 2024 met the inclusion criteria. Definitions of ONS adherence and assessment methods vary widely, with the most common definition being the ratio of actual intake to the recommended amount. The assessment tools included self-reported ONS diaries, and MMAS scores, among others. Adherence rates also vary significantly, with some studies reporting a decline in adherence over time.

**Conclusion** The lack of standardized definitions and assessment methods for ONS adherence across studies hinders comparability. Future research should focus on developing standardized, comprehensive adherence assessment tools that incorporate both quantitative and qualitative data. This would allow for a better understanding of adherence factors and enable more targeted interventions to improve long-term adherence in cancer patients.

Keywords Neoplasm, Oral nutritional supplementation, Adherence, Assessment, Definition

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## Introduction

Globally, cancer remains a leading cause of death, with an anticipated increase in incidence and mortality rates in the coming decades. The International Agency for Research on Cancer (IARC) has projected that in 2022, approximately 20 million individuals would be diagnosed, leading to more than 9.7 million deaths [1]. As the prevalence of cancer has increased, the nutritional problem of cancer patients has emerged as a significant concern in the medical community. Cancer and its associated treatments commonly result in deterioration of a patient's nutritional status. This deterioration is characterized by weight loss, muscle wasting, cachexia, etc [2–6]. These nutritional issues negatively impact quality of life and have implications for tolerance of treatment and overall survival [7, 8].

Oral nutritional supplements (ONS), which provides a noninvasive and straightforward method of nutritional intervention, is commonly utilized in clinical settings to improve nutritional status and provide support treatment [9–11]. ONS are typically rich in protein, energy, vitamins, and minerals, and can provide sufficient nutritional support to patients to compensate for nutritional deficiencies resulting from disease and treatment [12–15]. Concurrently, research has demonstrated that ONS not only enhances patients' weight and nutritional status, but also may diminish treatment-related adverse effects, reinforce immune function, and potentially enhance the efficacy of cancer therapy in cases where it is indicated [9, 16–18].

Nevertheless, despite the theoretically significant potential benefits of ONS for cancer patients, the issue of patient adherence in practical application has constituted a significant barrier to the realization of these benefits [19, 20]. Adherence refers to whether patients consistently take ONS and the amount recommended by the healthcare provider [21]. Adherence to ONS is generally low among cancer patients, and many patients do not take their supplements in time or in the right amounts to benefit from them [22]. Since adherence to ONS is directly related to the nutritional status and therapeutic outcome of cancer patients [23], understanding and improving patient compliance has become an important topic in current oncology nutrition research. Although several studies have focused on adherence to ONS in cancer patients, these studies tend to be methodologically heterogeneous, employing different assessment tools and definitions of adherence [24, 25]. It is difficult to directly compare the results of different studies, which hinders the overall understanding of the topic.

Therefore, it is necessary to conduct a scoping review to sort and integrate existing studies, clarify the definition and assessment tools of ONS adherence, and understand the research gaps. This study provides a scientific basis and guidance for future research and clinical practice.

## Methods

Our review followed the scoping review methods of Arksey and O'Malley [26]. There are five steps in total: (a) determining the research question; (b) identifying the relevant literature; (c) filtering the literature; (d) delineating the data; and (e) organizing, summarizing, and reporting the results. We reported the scoping review via the PRISMA-ScR checklist, and the protocol was therefore not registered. The reference management software Endnote20 was used to manage all the citations.

#### Stage 1: determining the research question

The scoping review aimed at drafting the literature on adherence to oral nutritional supplements in neoplasm patients. Thus, our research questions are as follows: (a) How does current research specifically define good and poor ONS adherence? (b) What are the main tools available for assessing adherence to ONS in cancer patients? (c) What is the current adherence rate for this population? (d) What are the current research gaps in this area?

## Stage 2: identifying relevant literature

Our research systematically retrieved six databases, including Web of Science, PubMed, Scopus, CINAHL, Embase and the Cochrane Library. From the earliest available time up to 9 August 2024. The retrieval form originated from PubMed as shown in Table 1, and was adjusted for other databases. The search strategy was developed as a result of team discussion to ensure a comprehensive search. The search terms included: neoplasms, oral nutritional supplements and adherence. In addition, we searched the references of the reviews to ensure a complete search of the literature.

## Stage 3: filtering literature

First, all the literature was imported into Endnote20 for the screening of duplicate studies. Next, on the basis of the inclusion and exclusion criteria (Table 2), titles, keywords, and abstracts were reviewed by two team members (ZL and QG). Finally, two other team members (BL and YL) performed a full-text literature review. If a disagreement arises during the review process, a third person will decide whether to accept or reject it.

## Stage 4: delineating the data

Data extraction from the final included studies was conducted by two reviewers (BL and ZL) via a standardized EXCEL spreadsheet and included the following data: author, year, country, disease, treatment regimen, sample size, ONS adherence assessment method, adherence definition, and adherence rate.

#### Table 1 Search strategy

Search Strategy	PubMed
#1	(neoplasm*[MeSH Terms]) AND (Tumor*[Title/Abstract] OR Neoplasia*[Title/Abstract] OR Cancer*[Title/Abstract] OR Malignant Neoplasm*[Title/Abstract] OR Malignanc*[Title/Abstract] OR Neoplasm*, Malignant[Title/Abstract])
#2	ONS[Title/Abstract] OR oral nutritional supplement[Title/Abstract] OR oral nutritional supplementation[Title/Abstract] OR oral nutrition[Title/Abstract] OR oral supplement[Title/Abstract] OR nutritional supplement[Title/Abstract]
#3	(Patient Compliance[MeSH Terms]) AND (Client Compliance* OR Compliance, Patient OR Compliance, Client OR Client Adherence OR Adherence, Client OR Patient Cooperation OR Cooperation, Patient OR Patient Adherence OR Adherence, Patient OR Patient Non-Compliance OR Non-Compliance, Patient OR Patient Non Compliance OR Non-Adherent Patient OR Non-Adherent Patient* OR Patient, Non-Adherent OR Patient Non-Adherence OR Non-Adherence, Patient Non Adherence OR Patient Nonadherence OR Nonadherence, Patient OR Patient Noncompliance OR Noncompliance, Pa- tient OR Treatment Compliance* OR Compliance, Treatment OR Therapeutic Compliance* OR Compliance, Therapeutic)
#4	#1 AND #2 AND #3

#### Table 2 Summary of eligibility criteria

	Inclusion criteria	Exclusion criteria
Population	<ul> <li>Adult patients aged ≥ 18 years</li> <li>Neoplasm</li> </ul>	• Children
Intervention	<ul> <li>Oral nutritional supplement</li> </ul>	<ul> <li>Patients with tube feeding or parenteral</li> </ul>
Publication	<ul> <li>Full-text article in English</li> <li>Quantitative study</li> </ul>	Languages other than English

**Stage 5: Organizing, summarizing, and reporting of results** The results are presented in tabular form by category, including information on defining adherence, methods used to assess adherence, and adherence rates.

# Results

# Study characteristics

A total of 1,156 articles were retrieved from all sources. After removing duplicates (n=116; software=89, manual=27), 1,040 records remained for eligibility screening. ZL and QG independently screened these 1,040 titles, keywords, and abstracts. Among these, 98 articles were read in full and assessed for eligibility, resulting in the exclusion of an additional 61 articles. Ultimately, 37 studies met the inclusion criteria. The number of articles screened and retrieved at each stage is shown in Fig. 1.

These studies were published between 2005 and 2024, and about 62% (n=23) of them were published in the last 5 years. Ten of these studies were conducted by researchers from China [25, 27–35], one from Australia [36], one from Brazil [37], one from Canada [24], two from Denmark [38, 39], two from France [40, 41], one from Greece [42], one from Ireland [43], five from Japan [44–48], one from Malaysia [49], two from the Netherlands [50, 51], two from Norway [52, 53], four from Spain [54–57], one from Sweden [58], one from Switzerland [59], one from the UK [60], and one from the USA [61].

In accordance with the scoping review protocol guiding this review, these studies are summarized in Table 3.

# **Definition of ONS adherence**

ONS adherence was defined in 15 articles, and the definition of ONS adherence varied from article to article. Most of these studies defined ONS adherence as the ratio of an individual's total intake to the total recommended amount [36, 39, 42, 45, 47, 52–54, 56, 59, 61].Some articles defined adherence on the basis of adherence scale score [29, 31, 34, 35], with higher scale scores indicating better adherence. Some studies have also defined ONS adherence in terms of container consumption [36, 61].

#### Methods for assessing ONS adherence

Methods of assessing ONS adherence were reported in all 37 papers, with Evelina's team using more than one method to assess adherence [58], with the most widely used method being the self-reported ONS diary (n=22), followed by custom ONS adherence score (n=4), MMAS (n=4, MMAS-m=1, MMAS-C=1) and cans consumption (n=4), and other methods including estimated intake (n=3), laboratory data (n=2),mHealth app (n=1), 24-hour dietary recall (n=2), and MPR (n=1).

## Adherence rate

A total of 35 articles reported adherence rates, and the observed adherence rates varied widely, ranging from a low of 24.7% to a high of 98% [28, 43]. Evelina Liljeberg's study revealed that measuring adherence via different assessment tools led to different results [58]. During the observations, we found that patients' adherence decreased over time [30, 48]. For example, from 55.69% at 5 weeks post-intervention to 25.95% at 12 weeks post-intervention [30]. The intervention group consistently performed better in terms of ONS adherence [30, 31, 56].



Fig. 1 PRISMA diagram

# Discussion

In the included literature, there is a significant variation in reported ONS compliance, ranging from 24.7–98% [28, 43]. This variation in compliance may be related to the heterogeneity of study designs, the diversity of patient population characteristics, differences in the definition of compliance, and the various methods of compliance assessment. The lack of standardized definitions for concepts can lead to confusion and inefficiency in various fields such as scientific research, academic exchanges, policy-making, data management, medical services, and international cooperation [62–64], affecting the accumulation and accurate application of knowledge. Through systematic review, it is evident that there is a significant variance in the concept of ONS, with existing studies often defining ONS adherence based on intake levels. For instance, adherence levels often categorized as 'good adherence' when patients consume 75%-100% of the recommended dosage, and 'poor adherence' when intake falls below 50% [53, 54]. However, this simplistic approach overlooks critical nuances, such as the duration and continuity [28], which are crucial for understanding the true impact of ONS on patient health. Moreover, defining adherence solely based on intake is overly simplistic as it fails to account for the complex behaviors that influence a patient's willingness and ability to adhere, including psychological and socio-economic factors, as well as decision-making processes [65]. Adherence is

# Table 3 Detailed summary of the included articles

First Authors	Year	Country	Disease	Treatment	Sample	Adherence Definition	Assessment Method	Adherence Rate
Judith Bauer	2005	Australia	PC	nc.	200 T=95 C=105	Consump- tion of a minimum of 1.5 cans/ day of either supple- ment over 4 weeks	Cans consumption	47%
Carla Alberici Pastore	2014	Brazil	Cancer	nc.	69 T=35 C=34	nc.	Self-reported ONS diary and cans consumption	T=71.4% C=88.3%
Vanessa Ferreira	2021	Canada	LC	surgery	34 T=24 C=10	NC.	Self-reported ONS diary	93.2%, 95% to the powder 91.3% to the oil
Xiao-han Jiang	2022	China	GC	Preoperative or Chemotherapy	162	nc.	Self-reported ONS diary	24.70%
Guang-ying Wan	2021	China	GC	Postoperative	122	nc.	Self-reported ONS diary	30.59%
Liyuan Qin	2022	China	GC	nc.	111	nc.	Custom ONS Adherence Score	50%
Yilin Chen	2024	China	CRC	NC.	103	nc.	Self-reported ONS diary	57.6%
Yuan Qi	2024	China	Cancer	nc.	123	nc.	mHealth app	85%
Liqing Su	2024	China	GC	Postoperative	300	A higher score indi- cates better adherence. Good: more than 2 Poor: less than 2	MMAS	1.61
Liqing Su	2024	China	GC	Surgery	242	A higher score indi- cates better adherence. Good: more than 2 Poor: less than 2	MMAS	2.4
Jingru Wang	2023	China	GC	Surgery	269	Scores are posi- tively cor- related with medication compliance. Good:8 points me- dium:6~8 points poor:<6 points	MMAS-C	6.43

First Authors	Year	Country	Disease	Treatment	Sample	Adherence Definition	Assessment Method	Adherence Rate
Jia Wang	2023	China	GC	Surgery	108 T=54 C=54	nc.	Self-reported ONS diary	T1(5 weeks after): T = 55.69% C = 32.86% T2(12 weeks after): T = 25.95% C = 21.4%
Jun-fang Pi	2023	China	CRC	Postoperative	84 T=42 C=42	The higher the total score, the better the medication adherence.	MMAS-m	T1(after 7 days): T=25.16 C=19.11; T2(after 14 days): T=25.95 C=20.57
Poula Patursson	2021	Denmark	cancer	Abdominal Radiotherapy	26	A sufficient nutritional intake was defined as a minimum of 75% of nutritional requirements	24-hour Di- etary Recall	45.50%
Nina Schmidt	2019	Denmark	cancer	Chemotherapy	41	nc.	Self-reported ONS diary and labora- tory data	Capsule group:96.4% Drink group:80.8%
Pierre Boisselier	2020	France	HNC	Adjuvant Chemoradiotherapy	172	nc.	Estimated intake	112 patients ( $65.1\%$ ) had $\geq 75\%$ compliance and 60 patients had < 75% compliance.
Olivier L. Mantha	2022	France	BC	nc.	63 T=31 C=32	nc.	Self-reported ONS diary and labora- tory data	ONS compliance declined over time
Irene Lidoriki	2020	Greece	GC	Surgery	78	Compliant: consume at least 3/4(23 doses) of the prescribed quantity; Noncompli- ant: did not achieve the target.	Self-reported ONS diary	35.90%
Laura A. Healy	2017	Ireland	EC	Postoperative	191 T=97 C=94	NC.	Self-reported ONS diary	In hospital:98% In home:96%
Hiroshi Imamura	2016	Japan	GC	Gastrectomy	112	nc.	Self-reported ONS diary	68.70%
Tateaki Naito	2019	Japan	PC and NSCLC	Chemotherapy	30	Good: attending more than 3 out of 6 planned sessions	Self-reported ONS diary	96.70%

First Authors	Year	Country	Disease	Treatment	Sample	Adherence Definition	Assessment Method	Adherence Rate
Daisuke Kobayashi	2016	Japan	GC	Gastrectomy	118	high: daily intake more than 200 ml; low: daily intake less than 200 ml.	Custom ONS Adherence Score	nc.
Hiroshi Imamura	2021	Japan	GC	Chemotherapy	71	nc.	Self-reported ONS diary	T1(4th course of treatment):81.8% T2(8th course of treatment):52.9%
Naoki Hashizume	2019	Japan	Outpatients	nc.	255 P-ONS Group = 107 NP-ONS Group = 148	nc.	Custom ONS Adherence Score	The number and duration of P-ONS was higher than in the NP-ONS (P<0.0001).
Vignesh Balasubaramaniam	2022	Malaysia	GC	Surgery	223	nc.	Self-reported ONS diary	nc.
Anne-Marie Dingemans	2023	Netherlands	CRC and LC	Chemotherapy/ Radiotherapy/ Immunotherapy	42 T=28 C=14	nc.	Self-reported ONS diary	73.40%
Sabien H. van Exter	2023	Netherlands	CRC and EC	NC.	66	nc.	Self-reported ONS diary	92.20%
Tora S. Solheim	2017	Norway	LC and PC	Chemotherapy	46 T=25 C=21	Compliance of $\geq$ 50% of the specific intervention in $\geq$ 50% of patients was considered acceptable	Self-reported ONS diary	48%
Jon Arne Sandmæl	2017	Norway	HNC	Radiotherapy ± Chemo- therapy	50	Adherence rates of 80% or higher for PRT and ONS were consid- ered good compliance.	Self-reported ONS diary	EN-DUR:57% EN-AF:76%
P. B. Pedrianes-Martin	2023	Spain	Malnutrition patients	nc.	548 physicians and 2516 patients	Adhere to 75% or more of your prescribed ONS.	Custom ONS Adherence Score	57.11%
Isabel Cornejo-Pareja	2021	Spain	Patients at risk of malnutrition, 63% of whom were cancer patients	nc.	283	nc.	Estimated intake	more than 65%
Samara Palma-Milla	2016	Spain	HNC	Surgical treatment	33 T=17 C=16	Good: daily consume: at least 400 ml	Self-reported ONS diary and cans consumption	T = 18.47 cans C = 17.93 cans
Samara Palma Milla	2024	Spain	cancer	Chemotherapy/ Immunotherapy/ Radiotherapy	57 T=26 C=31	nc.	Self-reported ONS diary	T=80.08% C=81.94%

First Authors	Year	Country	Disease	Treatment	Sample	Adherence Definition	Assessment Method	Adherence Rate
Evelina Liljeberg	2019	Sweden	Malnutrition patients	nc.	96	nc.	Estimated Intake, 24- hour Dietary Recall, MPR	Frequency question:93% 24-hour recall question:87% MPR:76%
F Grass	2015	Switzerland	GC	Surgery	141	the compli- ant group consumed between 11 and 15 doses, noncompli- ant group, consumed ≤ 10 doses	Self-reported ONS diary	58%
Amy Kerr	2022	UK	LC	Surgery	64 T=33 C=31	nc.	Self-reported ONS diary	before surgery:97% after surgery:89%
Timothy D. Lyon	2017	USA	BLCA	Surgery	144 T=40 C=104	Good compliance was defined as consum- ing all prescribed shakes.	Cans consumption	83.0%

Abbreviations: oral nutritional supplement, ONS; not clear, nc; Pancreatic Cancer, PC; Nasopharyngeal Carcinoma, NPC; Esophageal Cancer, EC; Gastrointestinal Cancer, GC; Colorectal Cancer, CRC; Head and Neck Cancer, HNC; Breast cancer, BC; Non-small Cell Lung Cancer, NSCLC; Lung Cancer, LC; Bladder Cancer, BLCA; Morisky Medication Adherence Scale, MMAS; Morisky Medication Adherence Scale-Chinese version, MMAS-C; Morisky Medication Adherence Scale-modified version, MMAC-m

not a linear phenomenon [66, 67], and these factors are crucial for understanding how adherence patterns evolve over time. Factors such as subjective experiences (e.g., taste and texture [54, 68, 69]), psychological states (e.g., anxiety and depression), and external challenges (e.g., treatment side effects or lack of social support [34, 70]) are critical to understanding adherence patterns. Initially, patients may find it relatively easy to adhere to ONS treatment due to fear of the disease and adequate social support, but as time progresses, the cumulative burden of therapy, the fatigue induced by long-term treatment, and the absence of medical team supervision impose multifaceted challenges on patients, can lead to decrease in adherence. Additionally, the timing and consistency of ONS intake during the treatment process should also be components of a standardized definition of adherence, as some ONS need to be consumed at specific times and in specific amounts to achieve optimal effects; irregular or intermittent intake may reduce their efficacy. Therefore, ONS adherence should be defined as a multidimensional concept, encompassing not only the quantity of intake but also the timing, consistency of intake, and various factors that influence adherence throughout the cancer treatment process.

Another major challenge in ONS adherence research is the heterogeneity of assessment methods. Current studies use a variety of methods, including self-reported diary [28], researcher-custom adherence scores [54], and objective measures such as the number of containers consumed [61] or estimated intake [55]. Each method has its own strengths and weaknesses, and their reliability can vary considerably depending on the context and design of the study. While self-reports like diary are easy to implement, they are prone to recall bias, inaccuracies, and social desirability bias, which can lead to overestimation of adherence [71]. In comparison, objective measurement tools, such as recording the number of containers or estimating intake, provide more reliable quantitative data, but their limitation lies in their inability to capture qualitative factors like patients' subjective experiences, such as emotions and taste preferences when consuming ONS, and their measurement of ONS adherence is too one-sided. Moreover, certain mixed-method tools, which combine self-reporting with objective measurements, have demonstrated higher comprehensive reliability, yet they are costly to implement and still lack standardization. Scales seem to be a good option. Currently, the main scales for assessing ONS adherence include MMAS-4, MMAR-8, and MARS, etc. These scales have shown good reliability and validity in the assessment of medication adherence in chronic diseases [73, 74], but their items are too brief to quantify adherence and have limited ability to reveal the specific reasons for non-adherence. Furthermore, these scales were originally developed to measure medication adherence, and their questions may not fully capture the characteristics of ONS adherence. In comparison, objective measurement tools, such as recording the number of containers or estimating intake, provide more reliable quantitative data [72], but their limitation lies in their inability to capture qualitative factors like patients' subjective experiences, such as emotions and taste preferences when consuming ONS. Moreover, certain mixed-method tools, which combine self-reporting with objective measurements, have demonstrated higher comprehensive reliability, yet they are costly to implement and still lack standardization. Scales seem to be a good option. Currently, the main scales for assessing ONS adherence include MMAS-4, MMAR-8, and MARS, etc. These scales have shown good reliability and validity in the assessment of medication adherence in chronic diseases [73, 74], but their items are too brief to quantify adherence and have limited ability to reveal the specific reasons for non-adherence. Furthermore, these scales were originally developed to measure medication adherence, and their questions may not fully capture the characteristics of ONS adherence. Heterogeneity in assessment methods not only complicates cross-study comparisons but also limits our ability to identify consistency in adherence, further exacerbating the challenge of designing effective interventions. To bridge this gap, it is imperative to standardize adherence tools for both research and clinical practice. Firstly, a validated, unified tool should integrate quantitative measures of intake with qualitative data on patient experiences [75], integrating the status of the patient's objective intake and the patient's subjective experience, a final composite score is generated, with high scores indicating good adherence and low scores triggering intervention prompts. Secondly, the development of an ONS adherence assessment tool requires a systematic approach, including a comprehensive literature review, generation of items through qualitative research, refinement via expert evaluation, reliability and validity testing, and large-scale validation. Finally, standardized scoring and guideline dissemination are essential to ensure the tool's scientific rigor and applicability. The implementation of a standardized assessment instrument will be instrumental in yielding more robust and granular data, which is essential for devising tailored, enduring, and adaptive intervention protocols. Such protocols must incorporate a comprehensive consideration of both the objective determinants and subjective elements influencing adherence to treatment, with the ultimate aim of augmenting the therapeutic efficacy of ONS regimens.

Despite this systematic review synthesizing studies related to cancer patients' use of ONS, there are certain limitations in the methodological design and study inclusion. The inclusion of both cross-sectional and interventional studies in this review, while conducive to a comprehensive understanding of the current state of adherence and the efficacy of interventions, introduces heterogeneity in the results due to differences in design objectives, assessment tools, and subject characteristics between the two types of studies. This heterogeneity may lead to discrepancies in reported adherence rates, thereby affecting the generalizability and comparability of the outcomes to a certain extent. Moreover, this review did not conduct a meta-analysis or an assessment of the quality of the literature, nor did it include grey literature, which may result in the omission of some evidence. Future research should stratify data from different types of studies, standardize assessment tools to reduce heterogeneity, and enhance the scientific rigor and comprehensiveness of reviews by including grey literature, as well as quality assessments.

## Conclusion

Establishing standardized adherence assessment tools is essential for enhancing the reliability of research and improving clinical outcomes. By addressing these gaps in how adherence is defined and measured, future research can provide stronger evidence for effective interventions that support cancer patients' nutritional needs and improve treatment outcomes.

#### Abbreviations

ARC	The International Agency for Research on Cancer
SNC	Oral Nutritional Supplements
PRISMA-ScR	Preferred Reporting Items for Systematic Reviews and Meta-
	Analyses extension for Scoping Reviews
MMAS	Morisky Medication Adherence Scale
MMAS-C	Morisky Medication Adherence Scale-Chinese version
MMAS-m	Morisky Medication Adherence Scale-modified version
MPR	Medication Possession Ratio

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#### Author contributions

Research concept and design by BL, ZL, QG, YL, GH, JL, NW and XT; searching the databases by BL, ZL and NW; screening the literature by BL, ZL, QG, GH and YL; graphing the data by BL, ZL and XT; writing-manuscript by BL, writing-review and editing by ZL, YL, GH and XT, quality control by XT, JL and GH.

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#### Data availability

All the data generated or analyzed in the course of this study will be made available upon reasonable request to the corresponding author.

#### Declarations

**Ethics approval and consent to participate** Not applicable.

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# Competing interests

The authors declare no competing interests.

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