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Review

Supplemental parenteral nutrition in cancer care: why, who, when

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***Abstract*:** Malnutrition is an often-overlooked challenge for patients with cancer. It is associated with muscle mass reduction, poor compliance and response to cancer treatments, decreased quality of life, and reduced survival time. The nutritional assessment and intervention should be a vital part of any comprehensive cancer treatment plan. However, data on artificial nutrition supplied based on caloric needs during cancer care are scarce. In this review, we discuss the recommendations of the European and American societies for clinical nutrition on the use of nutritional interventions in malnourished patients with cancer in the context of current clinical practice. In particular, when enteral nutrition (oral or tube feeding) is not feasible or fails to meet the complete nutritional needs, supplemental parenteral nutrition (SPN) can bridge the gap. We report the available evidence on SPN in cancer patients and identify the perceived barriers to the wider application of this intervention. Finally, we suggest a 'permissive' role of SPN in cancer care but highlight the need for rigorous clinical studies to further evaluate the use of SPN in different populations of cancer patients.

Keywords: cachexia, nutritional status, parenteral nutrition, quality of life, sarcopenia, weight loss

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Introduction

Pathophysiology of malnutrition in cancer

More than half of the cancer patients present with nutritional impairment at their first oncologic visit.[1,2] The proportion varies based on type, site, grade, and stage of cancer, with a high incidence of nutritional impairment (up to 85%) in advanced (inoperable, incurable, or metastatic) stages.[1,2]

The definition of malnutrition has been widely discussed. Actually, two other terms related to the loss of skeletal muscle mass are commonly in use: cachexia and sarcopenia. Weight loss in cancer can progress to cachexia, a severe and specific form of malnutrition, characterized by muscle wasting and loss of fat-free mass and function.[3] Although physical exercise might have a positive impact on muscle mass and strength, cancer cachexia is still a hindrance.[4] Cachexia develops progressively and is classified into precachexia, cachexia, and refractory cachexia.[3,5] Increased energy expenditure, prevalent in patients with cancer, is a potential contributor to cachexia and is linked with a higher risk of treatment-related complications.[6,7]

As cachexia, sarcopenia contemplates changes in body composition as criteria for diagnosis, with the latter adding functionality disorders to its definition. The most recent consensus on sarcopenia defines it as 'progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality'.[8] Notably, patients who were obese before cancer diagnosis may still be malnourished or sarcopenic despite apparently normal or even increased weight.[9–11]

Malnutrition in patients with cancer can be caused by a combination of tumor- and treatment-induced effects, and is considerably impacted by age, sex,

baseline nutritional status, and personal predispositions.[2,12] Tumor-induced malnutrition is caused by systemic or local effects of the tumor, such as mechanical obstruction, hypermetabolism, malabsorption, and dysmotility,[13] with tumor location and alterations in metabolism caused by the tumor being the primary contributors.[13] Local effects are more prominent in patients with head and neck cancer or digestive system cancers. Tumor-induced weight loss is observed more often in patients with pancreatic and gastrointestinal (GI) tract tumors, and to a lesser extent in those with breast and lower GI cancers.[14] A common adverse effect of anticancer treatments such as 5-fluorouracil, irinotecan, or epithelial growth factor receptor monoclonal antibodies (e.g. cetuximab and panitumumab) is GI toxicity, manifesting as nausea, vomiting, mucositis, or diarrhea, which prevents oral intake of sufficient nutrition. Moreover, some oncologic drugs can decrease muscle mass and function, causing sarcopenia.[15] Malnutrition also may have a direct impact on mental health, mood, and social relationships.[16]

Prognostic value of malnutrition in cancer

Weight loss and sarcopenia are associated with morbidity and mortality in patients with cancer[2] including poor quality of life (QoL),[17–20] treatment-related toxicities,[21,22] increased complications,[23] reduced tolerability and adherence to antitumor treatments (such as chemotherapy, targeted therapy, and immunotherapy),[20,22,24,25] poor response to therapy,[26–28] prolonged hospital stays, decreased survival,[2,20,21,29,30] and higher healthcare costs.[31] Even subtle weight loss (>2.4%, or precachexia) is significantly associated with decreased survival.[32]

Nutritional interventions

Early detection of malnutrition is key to early intervention and nutritional optimization. At initial stages of nutritional deficiency, diet management, behavioral strategies, counseling, and oral nutritional supplements (ONS) can be moderately effective.[33] ONS is prescribed if standard food cannot meet nutritional requirements. Enteral nutrition (EN) is usually prescribed as treatment if inadequate oral intake persists following a trial of ONS and the GI tract is functional and accessible. Conversely, in patients with a non-functioning or compromised GI tract parenteral nutrition (PN) may be adopted.[33–35] In a recent randomized controlled trial (RCT) in medical inpatients at nutritional risk, the authors describe an algorithm for escalation of nutrition support where EN is level 2 and PN is level 3 support.[36] This approach is based on the benefits of EN with regard to its trophic effect on the GI tract and immune response.[37] Unlike total PN (TPN), which supplies the entire daily nutritional requirement, supplemental PN (SPN) is the addition of PN when full EN (tube feeding or oral) is not possible or fails to meet caloric targets.[38] SPN is preferred over TPN as it is less time-consuming, and requires fewer infusion days or shorter infusion times (usually 6–8 h for several days instead of 12–18 h every day).[39]

Management of malnutrition in cancer

Current landscape

Real-world data from Italy, France, and Germany suggest that cancer-related malnutrition is severely underdiagnosed. The data show that nutritional interventions are often used in very advanced stages of disease[40] but are not often used in patients who may benefit from 'early' initiation of nutritional supplementation. Indeed, preventive nutrition and metabolic interventions should be recommended at the preliminary stages of anorexia and weight loss.[3,32]

Screening and assessment of nutritional status

Early diagnosis of malnutrition can be achieved through routine screening at diagnosis or hospital admission, and should be repeated at regular intervals during the treatment course.[31] Even in precachexia, a window of anabolic potential exists, creating an opportunity for nutritional intervention to stop or reverse progress to cachexia.[41] Weight loss, body mass index (BMI), and low serum protein are not reliable measures of malnutrition when assessed individually,[42,43] as they do not adequately reflect the metabolic and physiological changes in patients with cancer.[33,42] Thus, several screening tools which also consider the nutritional intake and inflammatory status of patients have been validated for use in cancer patients.[44] Nutrition Risk Screening (NRS-2002) considers weight loss, BMI, dietary intake, and severity of disease.[45] The Malnutrition Universal Screening Tool evaluates BMI, weight loss, and disease severity to assign risk. The Malnutrition Screening Tool consists of two questions and has been validated in both inpatient and outpatient settings.[46]

Although prospective cohort studies suggest some benefit,[47] there is no RCT evidence that general

screening in heterogeneous cancer patient populations results in improved clinical outcomes or reduced morbidity or mortality. In certain cancer types (e.g. head and neck cancer) or treatments (e.g. chemoradiotherapy) where reduced food intake is prevalent and is not accompanied by severe metabolic derangements, screening is expected to identify accurately patients at risk of malnutrition.[48]

However, nutrition screening looks at risk of malnutrition rather than a diagnosis of malnutrition. Therefore, patients at risk of malnutrition should undergo a more comprehensive objective and quantitative nutritional assessment, including the analysis of nutritional intake, nutrition impact symptoms, muscle mass, physical performance, and the degree of systemic inflammation.[33,42] Subjective global assessment (SGA) and patient generated-SGA (PG-SGA) are detailed assessment tools used for comprehensive nutritional assessments.[33,42] They are based on the patient's weight/weight history, food ingestion, symptoms, activities, medical tests, nutrition-focused physical assessment, medical history, and treatment plan.[49]

For the diagnosis of malnutrition, a recent global consensus [Global Leadership Initiative on Malnutrition (GLIM)] proposed a scheme based on three phenotypic criteria (non-intentional weight loss, low BMI, and reduced muscle mass) and two etiologic criteria (reduced food intake or assimilation and inflammation or disease burden). It is recommended that one phenotypic criterion and one etiologic criterion provide the diagnosis of malnutrition, and the severity is supported by variations in any of the phenotypic criteria.[50]

Assessment of muscle mass reduction (MMR) is preferably identified by specific measurements. In particular, this may be performed with dual-energy X-ray absorptiometry, bioelectrical impedance analysis, and computed tomography/magnetic resonance imaging scan at the L3 lumbar vertebra.[35] It is important to include MMR in the GLIM framework. Indeed, body composition measurement improved the performance of GLIM criteria in diagnosing malnutrition compared to PG-SGA in cancer patients.[51]

Current interventions for cancer-related malnutrition

Nutritional interventions in patients undergoing cancer therapy aim at improving nutritional status, reducing therapy-related complications and toxicities, thereby maintaining dose intensity and improving response to therapy. According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines,[33] in a patient undergoing curative anticancer drug treatment, a nutritional intervention is indicated if patients are unable to eat adequately (e.g. no food for >1 week or <60% of requirement for >1–2 weeks). In particular, 'If a decision has been made to feed a patient, the guidelines recommend EN if oral intake remains inadequate despite nutritional interventions (counseling, ONS), and PN if EN is not sufficient or feasible'. Generally, oral nutrition should always be the first choice in these patients. The guidelines recommend the use of enteral tube feeding if oral intake is insufficient. In practice, PN is reserved for use in patients with a non-functioning or compromised GI tract.[33] However, it is common that patients undergoing intensive chemotherapy and/or radiation therapy lose weight caused by nausea, vomiting, diarrhea, and mucositis which prevent adequate nutritional requirements by the use of oral nutrition.[52–55]

The benefits of oral nutrition, EN, and PN are similar, and strong evidence is lacking regarding the clinical outcomes of patients with cancer and nutritional issues to support one *versus* the other. Therefore, the clinical situation, risks, and benefits associated with each type of nutrition support would be considered as well as taking into consideration patient preferences.[56]

In incurable cancer, the goal of nutritional interventions is to improve the QoL and physical performance of the patient.[57] These patients are sometimes treated with the intent of delaying an earlier death due to malnutrition or starvation. When the expected survival is >2 months and the Karnofsky Performance Score (KPS) is >50, PN is considered as supportive treatment for palliative care.[58] A validated nomogram, including Glasgow Prognostic Score (GPS), KPS, tumor site, and spread, can be useful in estimating survival on home PN (HPN).[59]

Timing for PN/SPN

The optimal timing for initiating nutritional interventions during the continuum of care of patients with cancer is not well established. In the recent American Society of Clinical Oncology recommendations endorsed by the National Comprehensive Cancer Network, the expert panel suggests early palliative care involvement within 8 weeks of

diagnosis for newly diagnosed patients with advanced cancer, supporting the benefits of early nutritional intervention.[60] The ESPEN guidelines do not discuss SPN in detail, but they do refer to the potential need to augment enteral or oral intake in certain patients. In particular, 'In a patient undergoing curative anticancer drug treatment, if oral food intake is inadequate despite counseling and ONS, we recommend supplemental enteral or, if this is not sufficient or possible, PN'.[33]

EN is considered first-line therapy in many malnourished patients; however, data suggest that many patients receive amounts far less than prescribed for a variety of reasons.[61] In a 2018 review, Russell and Wischmeyer[38] encouraged clinicians to consider the use of SPN in appropriate hospitalized patients with cancer based on the presence of a diagnosis of malnutrition. Specifically, SPN should be considered from the time of hospital admission in severely malnourished patients who do not receive full nutrition support. Conversely, in well-nourished patients, it should be considered later (days 5–7) in the hospital stay based on clinical course and adequacy of nutrition delivery.[38]

For many years, multimodal prehabilitation programs (including optimization of nutritional status and physical performance) in newly diagnosed cancer patients before initiating acute treatments have been discussed.[62] Similarly, nutritional interventions could also play a role in patients who become unable to tolerate an intensive regimen of oncologic therapy due to severe GI toxicity. Indeed, increasing tolerance to therapy-related toxicity may translate into a better therapy response and improve the outcomes.[63] In particular, an early initiation of SPN could have a 'permissive' role in improving compliance to cancer treatment and maintaining its dose intensity. However, high-quality trials specifically addressing this issue are needed to support this.

Key studies on PN/SPN

Three RCTs have been conducted to date. Patients with incurable cancer and progressive cachexia primarily due to GI tumors received standard dietary and pharmacologic support with or without an intensified nutritional support program (including possibility of HPN).[63] In this advanced palliative setting, energy balance, body fat, exercise capacity, and survival improved among parentally supported patients based on an 'as-treated' analysis.[63] In patients with advanced GI cancer, home SPN not only prevented the loss, but also may have resulted in an increase of fat-free mass. While no difference in survival was recorded, the QoL improved at 12 weeks in the SPN arm.[64]

In patients with incurable cancer randomized to receive optimized nutritional care with or without SPN, PN did not have a significant impact on the health-related QoL or survival.[65] However, the authors acknowledge that the short survival time of study population was the major cause of PN failure (i.e. at 2 months only 23 out of 48 patients in the PN arm were alive).[65]

In a prospective cohort study of 761 cancer patients on HPN (75% receiving SPN), predictors showing significant association with decreased survival were GPS, weight loss (>15%) in the 3 months before HPN start, and IV stage while protective factors of survival were KPS (>50), albumin level (>3.5 g/dL), oral protein intake, BMI (>20.5), and weight at HPN start.[66]

Prospective trials using validated scores showed some beneficial effects of HPN (Table 1).[67–73] In these studies, HPN improved QoL, performance, and nutritional status. An early 7-day SPN regimen demonstrated improvement in body composition, handgrip strength, and serum pre-albumin levels in hospitalized hypophagic cancer patients.[74]

Overall, these studies suggest that PN may improve outcomes in selected cancer patients; however, all of these studies have limitations because they were carried out without a control group.

Patient populations potentially candidates for early SPN

Patients with GI cancers have reduced tolerance to food intake, dysmotility, and malabsorption which could be due to peritoneal carcinomatosis and/or intra-abdominal recurrences.[29,39,75] Furthermore, 31–87% of patients present clinically significant weight loss at diagnosis.[75] Although preoperative prehabilitation is an ideal intervention to improve clinical conditions in patients with cancer, there are many challenges in practice, including the short time interval between diagnosis and surgery, as well as the development of key and effective interventions. RCT and meta-analysis have shown that malnourished patients

Table 1. Prospective studies demonstrating the effects of HPN on QoL, performance, and nutritional status, using validated scores.

Study	No. of patients	Mode of HPN	Scores	Cancer stage	Results	Comments
Finocchiaro *et al.*[69]	70	SPN/TPN Overnight 27 Kcal + 1.1 g AA/kg/d	TIQ at >2 months	Advanced cancer	QoL = 48%, ↑31.5%, ↓20.5%	27 patients evaluated
Culine *et al.*[67]	437	SPN/TPN Overnight 26 Kcal + 1.15 g AA/kg/d	FACT-G days 1–28	Metastatic cancer (65%)	↑Physical, functional, emotional, familial/social status	Responsiveness to therapy might affect QoL; QoL increased 48.35–49.95 (statistically significant)
Seys *et al.*[70]	221	SPN/TPN Overnight	FACT-G days 1–28	Metastatic cancer (69%)	↑Global QoL in 59% patients (and sub-score physical, functional, and emotional)	Regimen ill-defined; no statistical analysis; responsiveness to therapy might affect QoL
Vashi *et al.*[71]	52	SPN/TPN Cyclic 22–30 Kcal + 1.5–2.5 g AA/kg/d	EORTC QLQ-C30 every month for 3 months; SGA, KPS	Stage I–IV	↑Global QoL index at 1–3 months; ↑SGA; ↑KPS	Small sample; Loss of patients; responsiveness to therapy might affect QoL; assessment of requirements was unpractical
Girke *et al.*[72]	36	SPN/TPN	EORTC QLQ-C30 day 1–28	End-stage cancer	↑Emotional/social domains = muscle strength, physical activity; ↓Phase angle	Nutritional regimen not assessed; large number of patients dropped out
Cotogni *et al.*[68]	111	SPN Overnight 20–30 Kcal + 1–1.5 g AA/kg/d	EORTC QLQ-C30 every month for 4 months	Stage III/IV	↑Global QoL; ↑Physical, role, and emotional functioning; ↓Appetite loss and fatigue scores	High attrition rate due to the death of 49/111 patients; completed at 4 months
Cotogni *et al.*[73]	65	SPN/TPN Overnight 20–30 Kcal + 1–1.5 g AA/kg/d	PG-SGA, KPS, mGPS every month for 3 months	Stage III/IV	↑PG-SGA; ↑KPS ↓mGPS	Responsiveness to therapy may affect results

AA, amino acid; EORTC QLQ-C30, The European Organization for Research and Treatment of Cancer Quality of Life 30 Questionnaire; FACT-G, Functional Assessment of Cancer Therapy – General; HPN, home parenteral nutrition; KPS, Karnofsky performance status; mGPS, modified Glasgow prognostic score; PG-SGA, patient-generated subjective global assessment; QoL, quality of life; SPN, supplemental parenteral nutrition; TIQ, Therapy Impact Questionnaire; TPN, total parenteral nutrition; ↑, statistically significant increase or improvement; ↓, decrease.

undergoing GI surgery who received individualized preoperative nutritional interventions (ONS, EN, or PN based on the patient's nutritional status) had a 20% decrease in postoperative complications. For severely malnourished patients, PN should be provided before surgery to reduce postoperative complications.[76]

In patients with GI toxicity due to neoadjuvant therapy (i.e. radiation enteritis or chemotherapy/radiation-induced diarrhea), short-term PN was shown to be better tolerated and more effective than EN in restoring intestinal function and preventing nutritional deterioration.[39]

Patients with ovarian cancer frequently exhibit symptoms of obstruction for a considerable amount of time before the obstructions are detected, which renders them intolerant to oral nutrition.[77] Thus, it is important that clinicians are aware of this and screen for malnutrition early. Treatments for ovarian cancer, such as platinum-based chemotherapy, are highly effective, but also cause severe GI complications. Patients with similar complications stemming from other types of cancers, and those who are malnourished due to aggressive chemotherapy could be potential candidates for early initiation of SPN.[77,78]

Therefore, we hypothesize that cancer patients who are at risk of inadequate oral nutritional intake (<60%) and decreased EN (oral or tube feeding) tolerance could benefit from early initiation of SPN as part of their comprehensive cancer treatment plan. We emphasize that the primary role of SPN is 'permissive', to support aggressive cancer treatment, which also forms the main rationale for including SPN in the cancer care plan.

Research needs surrounding SPN as part of cancer treatment

Designing a conventional RCT demonstrating efficacy of PN is ethically complex, as PN is not a drug but a potentially vital supporting therapy. An RCT would need to include a control cohort who do not receive PN, which poses ethical problems. Despite a prospective study showing that patient characteristics at the beginning of nutritional interventions correlated with survival,[66] no direct inference regarding the benefits of PN can be made, as a control arm was absent. Thus, alternative study designs are needed to generate evidence-based data. Indeed, there are options for further research to compare PN/SPN to ONS and/or EN which would be an ethical option.

Evidence from real-world studies of SPN in cancer patients is also limited. In particular, SPN is not often used in the United States.[38] Existing literature focuses on PN as palliative care in the advanced setting, yet studies that examine the possible benefits of early initiation of PN in patients with cancer still amenable to therapy are lacking.[40] This is a key unmet need in the landscape of nutrition in oncology. Studies in patients with potentially curable disease would allow assessment of the effect of early SPN on patient outcomes, and the optimal duration of PN for different cancer patient groups are needed.

Barriers in the initiation of SPN in patients with cancer

Lack of evidence and awareness

The main barriers preventing the initiation of nutritional therapy in patients with cancer are the lack of clear and reliable evidence, minimal inclusion of nutritional support in oncological guidelines, limited knowledge and training, financial issues, and inefficient referral systems.[79–81] The establishment of multidisciplinary medical teams and effective collaboration between oncologists and nutritionists and the formal introduction of lectures on nutrition within the specialty curriculum of oncology can overcome some of these barriers.[79] In addition, patients and their caregivers should be educated about the potential clinical benefits of PN.[39]

Accessibility and cost-effectiveness

Based on its reimbursement status and costs, the availability, accessibility, and cost-effectiveness of SPN vary among countries. In countries where SPN is widely accessible, like Italy and Germany, it could be provided to all patients who might benefit from it. A literature review showed that SPN has the potential to be more cost-effective when prescribed earlier and in patient groups with less severe disease.[12] However, further research is needed to assess this.

Complications related to administration of PN

A major proportion of complications are catheter-related infections. Because of the reported complication rates in earlier experiences, some oncologists are still concerned about the risks

potentially associated with the use of central venous catheters (CVCs) in patients requiring PN.[82] A meta-analysis comparing complication rates between EN and PN showed that oral nutrition with or without ONS and PN had comparable incidences of all complications except for infections.[83] Notably, the authors did not differentiate TPN from SPN, which is expected to have a lower burden due to shorter infusion times and thus, a lower risk of infection, nor did they specify the severity of infections. The most serious infection-related complication is catheter-related bloodstream infections (CRBSIs). While serious and sometimes fatal, CRBSIs are rare, even in cancer patients receiving active oncological treatments. A recent study in 761 cancer patients on HPN reported 0.29 CRBSIs per 1000 catheter days, with eight patients requiring hospitalization and one CRBSI-related death.[82] Other complications related to catheter are of mechanical nature – related to the placement and maintenance of the CVC.

The safety of PN can be assured if patients are carefully screened for PN eligibility and carefully followed-up, and if patients and caregivers are adequately trained on sterile infusion techniques.[82] Thus, the risks of complications should not be a deterrent for recommending SPN when the benefits outweigh the risks.

Psychosocial burdens

There are few reports of the social and psychological burdens of HPN care impacting QoL in cancer patients. HPN has been shown to have a major impact on the patient's social life, psychological state, and mobility. It can pose major hindrances to the patient's daily life and social engagements.[17,72] Similarly, families of patients receiving HPN report a lack of social activities, disrupted family relationships, lost friendships, withdrawal of external family/social support, and repeated episodes of depression.[84] Therefore, HPN-related burdens need to be weighed against the expected benefits, with the knowledge and consent of the patient.[33] One way to address this would be infusion delivery at night and stopping administration at the right time.[85]

Actually, alleviating nutrition impact symptoms may relieve the burden of the disease.[16,19] Generally, studies about the use of HPN in cancer patients found that they had a favorable perception of the impact of HPN on their QoL.[64,67,68,71] Conversely, a recent RCT reported that PN did not improve QoL in a mixed population (79% cancer patients).[65] However, this study has some limitations, as in the PN arm 46% of patients had an Eastern Cooperative Oncology Group performance status of 3 or 4, and therefore the inclusion criteria did not comply with indications for HPN according to guidelines.[33] In addition, in the PN arm, 59% of patients had gained weight or had weight loss 0–5% in the previous month, and so were unlikely to be malnourished.[86]

In most cases, patients relate their reduced QoL more to the incapacity to eat than to the HPN dependence.[17,72] Orrevall *et al.*[87] reported the sense of relief and security of both patients and families when the nutritional requirements were met through HPN. Patients with ovarian cancer on HPN experienced a burden of treatment that did not mitigate the benefits of HPN; in particular, in the interviews, they stated that the motivation to live outweighed the constraints imposed, and patients and relatives recognized HPN as a lifeline and were grateful for it.[88]

Conclusions

Nutrition-related issues are frequently overlooked during cancer treatment, even though there is evidence to show that nutritional optimization could potentially improve QoL, tolerance to systemic therapy, tumor response, and survival. We recommend that nutritional assessment and intervention should be an essential component of best supportive cancer care. Indeed, it should be a vital part of any comprehensive cancer treatment plan.

Data on artificial nutrition supplied based on caloric needs during standard cytostatic therapies are scarce. Because of this lack of reliable direct evidence supporting the benefits of nutritional support (especially SPN) for these patients, we suggest increasing the invasiveness of the nutritional intervention after carefully assessing the inadequacy of the more physiological oral route (ONS or EN). If EN is not feasible, we propose SPN which potentially has a key 'permissive' role in cancer care, that is, allowing uninterrupted anticancer treatments and optimizing patient compliance.

Finally, we emphasize the need for the development of clinical nutrition trials with special focus on patients with different types and stages of cancer to evaluate the role of SPN for its use as an alternative to EN.

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Author contribution(s)
Paolo Cotogni: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

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