

Prevalence of Metastasis and Involvement of Level IV and V in Oral Squamous Cell Carcinoma: A Systematic Review

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Abstract

The occurrence of occult metastases in oral cavity squamous cell carcinoma (OSCC) to lower levels in the neck (levels IV and V) or development of skip metastases that bypass the upper neck levels (levels I to III) and go directly to level IV or V is common. This challenges the efficacy of conventional neck dissection approaches in the treatment of OSCC. Therefore, the decision to include lower levels cervical nodes during elective neck dissection of OSCC remains controversial.

This systematic review was designed to assess the prevalence of level IV and/or V involvement or skip metastases in patients with the clinically negative neck (cN0) or positive (cN+) oral squamous cell carcinoma (OSCC). We searched for studies published between December 2000 and December 2020. Potentially relevant abstracts and full-text articles were screened, and data from the studies were extracted. Quality was rated using the Newcastle Ottawa Scale (NOS) criteria.

In total, 802 abstracts and 227 full-text articles were screened, and 32 studies were included in this analysis. The prevalence of metastasis ranged from 1.8% to 66.0%. The incidence for skip metastasis to level IV or V was low, reaching 8.5%. Evidence favored elective neck dissection, including levels I to III, in selected patients with OSCC and patients with cN0 or cN+ neck. The literature was non-conclusive on the recommendation for inclusion of lower levels.

Categories: Otolaryngology, Pathology, Oncology

Keywords: supraomohyoid neck dissection, selective neck dissection, skip metastasis, level v, level iv, metastasis, elective neck dissection, oral squamous cell carcinoma

Introduction And Background

Oral squamous cell carcinoma (OSCC), constituted by a broad range of tumors with diverse etiologies, is a life-threatening malignant tumor that ranks as the sixth most common cancer by incidence, with 500,000 new cases reported worldwide annually, accounting for 32%-40% of all head and neck cancers [1,2]. It can metastasize to cervical lymph nodes via lymphatic vessels [2,3], with neck metastasis being the most important prognostic factor which affected survival by a nearly 50% decline [4]. The incidence of clinical cervical metastases from OSCC has been found to occur in as many as 40% of cases [5]. Moreover, occult regional lymph node metastases incidence detected using histopathological and immunohistochemical methods was found to range between 15% and 34% [6] among patients without clinical or radiologic evidence of lymph node metastases preoperatively.

Selective neck dissection (SND), which removes lymph node groups at designated anatomic levels (I-III), is accepted as the standard of care for the management of regional disease in OSCC patients with clinically positive node (cN+) involvement [7,8], as well as the standard elective procedure for clinically node-negative (cN0) patients or those with microscopic disease [9,10], resulting in improved quality of life and a lower likelihood of orofacial complication or shoulder dysfunction compared to other modalities, including comprehensive neck dissection, such as modified radical neck dissection (MRND) or radical neck dissection (RND) [11,12]. However, several studies have concluded that supraomohyoid neck dissection (SOHND, level I-III) is inadequate in patients with OSCC, owing to occult metastasis to neck level IV and that this level should be routinely dissected [13,14].

In view of the controversies surrounding the inclusion of lower levels for dissection, the present study was designed with the objectives of conducting a systematic review of all relevant published literature: (i) to study the prevalence and distribution of metastasis levels and related adverse outcomes in clinically N0 and N+ OSCC; and (ii) to determine the frequency of involvement of levels IV and V, as well as skip metastasis to level IV in patients diagnosed with OSCC without preoperative evidence of neck involvement. We aimed to summarize the recommendations for routine dissection of lower levels of nodes in patients with OSCC.

Review

Methodology

Search Strategy

A comprehensive search for all relevant articles published in English between January 2000 and December 2020 was performed using the electronic databases PubMed, Embase, Ovid, Google Scholar, and Science Direct. We included retrospective, prospective, clinical trials, and cross-sectional studies. The key search terms used either alone or in combination were neck dissection, radical neck dissection, cN0 neck, cN+ neck, oral squamous cell carcinoma, skip metastasis, occult metastasis, lymph node management, neck metastasis, oral cavity cancer, and tongue cancer. The references of articles and citations were also searched

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for additional potentially relevant publications.

Study Eligibility Criteria

All studies that included patients who underwent a neck dissection (ND) of at least levels I through III or I-IV and presented information on clinically node-negative (cN0) and/or clinically node-positive (cN+) necks were eligible for inclusion. The inclusion criteria were as follows: (1) any prospective or retrospective cohort, (2) a study population with the histopathologic diagnosis of OSCC, and (3) full text available in the English language. In addition, studies that reported skip metastasis (metastasis solely at neck level IV or V) were also eligible for inclusion. Exclusion criteria were as follows: (1) studies on patients who underwent treatment other than surgery as primary treatment, such as preoperative radiotherapy and chemotherapy, and (2) studies on recurrent tumors or tumors other than SCC.

Data Extraction

Information regarding patient characteristics, primary tumor site, treatment, sample size, metastasis, authors, publication year, and the country was retrieved from the selected articles. Data were initially extracted and evaluated by two authors (AA, TA). The distributions of the T category, the extent of ND, the subsite of the primary tumor, and nodal metastasis were recorded. A skip metastasis was defined as a positive level IV (or lower) node on final pathology without the involvement of higher levels (i.e., levels I-III). A level IV nodal metastasis coexisting with nodes at other neck levels was assessed separately. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting the included observational studies [15].

Quality Evaluation

The quality of literature was evaluated according to the Newcastle Ottawa Scale (NOS) evaluation criteria [16]. By quality evaluation, 21 references were ranked high, seven references were medium, and only four were ranked low (Table 1).

Author	Year	NOS quality rating
Silverman [17]	2003	8
Anderson [18]	2002	7
Jena [19]	2013	7
Liao [20]	2011	6
Jayasuriya [21]	2020	8
Haranadha [22]	2018	7
Chhedha [23]	2014	7
Kakei [24]	2020	8
Marchiano [25]	2016	4
Givi [26]	2012	5
Pandey [27]	2018	7
Agarwal [28]	2018	3
Mishra [29]	2010	6
Shimura [30]	2019	7
Parikh [31]	2013	6
Jerjes [32]	2010	6
Cariati [33]	2018	7
Patel [34]	2019	5
Lodder [35]	2008	5
Lim [36]	2006	6
Kowalski [37]	2002	7
Feng [38]	2013	8
Sivanandan [39]	2004	7
Crean [40]	2003	4
Khafif [41]	2001	6
Balasubramanian [42]	2012	7
Köhler [43]	2018	8
Deo [44]	2007	7
de Vicente [45]	2015	7
Rani [46]	2015	3
Chatterjee [47]	2019	6
Vishak [48]	2014	7

TABLE 1: The quality rating of included studies using the Newcastle Ottawa Scale (NOS)

Results

The search and selection process of the articles is presented in Figure 1. A total of 1482 articles were identified via the database search based on the selection criteria, and two additional articles were later found through reviewing articles and reference lists of retrieved articles. After removing duplicates, 453 articles were screened by their titles and abstracts, and 61 were retained. After full-text revision, 31 articles were excluded (Figure 1). Thus, 32 studies [17-48], all published in English, were included for further analysis.

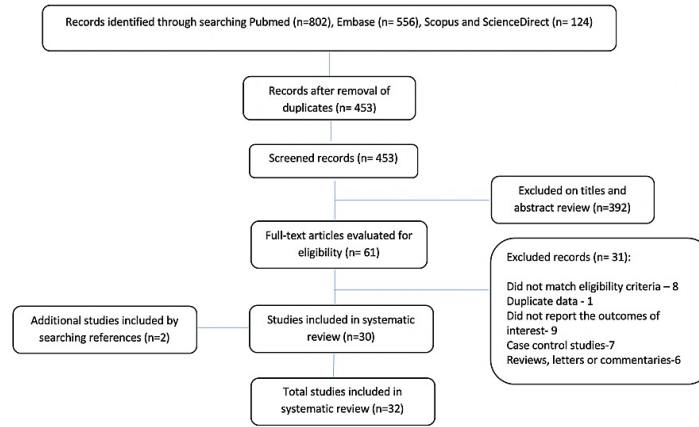


FIGURE 1: PRISMA flowchart: selection of studies for systematic review

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Description of the Studies

Data of 12,309 patients included in the 32 studies were analyzed. In all studies, cases of level IV or V metastasis and cervical IIb metastasis were confirmed by pathologic examination or other technologies. All studies did not, however, have consistent inclusion criteria and exclusion criteria. Five studies [19,23,28,30,40] reported data from only OSCC patients with cN0, while three [18,21,24] had only data on cN+; five studies [17,29,31,33,35] had mixed data of clinical N0 and N+ cases. The details of the studies included are summarized in Table 2.

Author	Year	Region	n	Male %	Primary site	Clinical staging	Metastasis prevalence %	Metastasis level	Treatment given	Recurrence/Survival	Other risk factors	O
Silverman [17]	2003	US	74	55%	HNSCC Oral cavity- 47.3%	TNM	4.40%	N0- 1.6% (in level IIB) N1- 11.1% (in level IIB)	SND Level II	Recurrence- 5.6%	NA	Le re
Anderson [18]	2002	US	106	71.70%	Oral cavity- 39.6%	TNM	all N+ve	N1- 54.7% N2a- 4.7% N2b- 26.4% N2c- 13.2% N3- 0.9%	SOHND I-III SND II-IV SND I-IV	5 year-DSS- 68.8% Local Recurrence- 12.3% Regional recurrence- 4.3%	NA	N
Jena [19]	2013	India	218	15.60%	Oral ca. Buccal mucosa- 53.2% Gingivobuccal sulcus- 33%	cN0- 31.1%	10.4% (occult metastasis) LN metastasis 30.27%	I- 50 Pts II- 32 Pts III-15 Pts IV- 2 Pts V- 2 Pts Skip metastasis- 1.8%	SOHND MRND	NA	Alcohol Betelnut Smoking Tobacco	In de or ris th di sc st of m
Liao [20]	2011	Taiwan	255	94.10%	OSCC Tongue-34% FOM- 6%	T1-T4	33% (Distant)	IV/V-8.2%	Radical or modified neck dissection I-IV	Local recurrence- 16% Neck recurrence- 19% local/neck recurrence - 9% local/distant	Alcohol Betelnut	Le in a

Author	Year	Country	n	%	Site	Stage	LN	Neck	SOHND	Metastasis	Notes			
Jayasuriya [21]	2020	Sri Lanka	187	72%	Lip- 1%				SOHND I-III	metastasis 3%	fo			
					Buccal- 37%					neck/distant metastasis-14%	Tobacco			
					Gum- 15%					locoregional/distant - 7%				
					RMT- 6%									
Jayasuriya [21]	2020	Sri Lanka	187	72%	OSCC						R			
					Anterior 2/3 rd of tongue- (4/68)	cN+	NA		I- 58.3%			nc		
					Buccal mucosa- (4/68)				II- 56%	Neck dissection	NA	NA	re	
									III- 40%				ct	
									IV- 27.3%				Lt	
				V- 6.4%					di					
Haranadh [22]	2018	India	199	45%	Buccal mucosa- 171			Level IIB involvement when IIA involved by 2 or more LN - 40%;	pN0- 125	MRND- 178		Lt		
					Tongue- 15			Level V involvement when level III involved by 2 or more LN 100%	pN1-74	SND I-III- 11		re		
					RMT- 6								w	
					Lower alveolus- 4	TNM			IA-4%		NA	NA	pr	
					Lip- 2				IB-30%				bt	
					FOM- 1			occult metastasis 17%	IIA-14%	SND I-IV- 10				
									IIB-3%					R
									III- 5%					w
									IV-1%					in
									V-3%					>
Chheda [23]	2014	India	210	74.20%	Tongue-71.4%	TNM			IA- 28 Pts	Modified neck dissection- 120 Pts		R		
					Buccal mucosa- 14.2%			LN metastasis 42 Pts (20%)	IIA- 16	Extended SOHND- 40 Pts		nc		
					Lower alveolus- 12.3%	cN0			IIB- 2 (0.95%)		NA	NA	re	
					RMT - 1.9%				III- 2	SOHND- 50 Pts				
									IV/V- 0					
					Tongue-45 Pts	cTN1M0			pN1:					
					Lower gingiva- 24 Pts	IA-2 Pts			IA-2 Pts					
					Buccal mucosa- 15 Pts	IB-61 Pts			IB-20 Pts					
					Oral floor-8 Pts	II-37 Pts			II-14 Pts					
									III-1Pts					
Kakei [24]	2020	Japan	100	58%		III-0	LN metastasis 66%		IV/V-0	SOHND	NA	Lt		
						IV-0							e)	
									pN2b:				IV	
									IA-1 Pts				cc	

Author	Year	Country	n	Survival (%)	Site	TNM	Lymph Node	Upper gingiva-8 Pts		IIB-8 Pts		Recurrence	DSS	Notes	
								V-0	V-0	II-10 Pts	III-8 Pts				IV-2 Pts
Marchiano [25]	2016	USA	8281	62.30%	OSCC	TNM	N+ve (24.1%)	in T1 : level IV (3.1%) level V (1.1%)	Neck dissection	5 year DSS: with Level I, II, or III involvement - 42%	NA				
								buccal (6.2%)							in T2 : level IV (6.5%) level V (3.1%)
								FOM (16.4%)							in T3 : level IV (9.5%) level V (3.7%)
								gum (9.6%)							in T4 : level IV (11.2%) level V (4.9%)
								Hard palate- (2.3%)							distant metastasis (1.6%)
								lip (18%)							
								RMT (5.4%)							
tongue (42.1%)															
Givi [26]	2012	Canada	108	64%	Mucosal SCC of head and neck	TNM	N+ve - 108 (all Pts)	I-III: (11.1%)	SND	recurrence- 5.5%	NA				
								Oral cavity- 71.3%						I-IV: (79.6%)	
								Oropharynx - 22.2%						II-IV: (4.6%)	
								larynx - 4.6%						II-V: (4.6%)	
Pandey [27]	2018	India	32 cN-ve Pts	87.50%	OSCC	TNM 1-4	3 Pts has pN+ level Ib	I-III: 30	IIB preserving super-selective neck dissection (SSND), SOHND	DFS- 83% in (SSND)	NA				
								Buccal mucosa- 18						I-IV: 2	
								Lower alveolus- 6							
Agarwal [28]	2018	India	231	82.75%	OSCC	N0	LN mets 30.73%	IIA- 11.68%	SND	local recurrence 2.59%	NA				
								buccal - 50.2%						IIB- 0.86%,	
Mishra [29]	2010	India	81	NA	OSCC	T1-2N0M0;	26% (occult)	N0 Cases: Levels I, II, III (26%)	SOHND, Extended SOHND, MRND-I	local recurrence 2 Pts	NA				
								Tongue - 34 Pts						Level IV/IV- No metastasis	
								buccal -19 Pts						N+ Cases: Level IV-9%	
								others-28 Pts						Level V- 0	
Shimura [30]	2019	Japan	131	59%	OSCC	TNM 1-4	LN mets 52%	ipsilateral I-VI	SND, MRND/ RND	Primary Recurrence- 28%	NA				
								Tongue- 41%						contralateral I-IV	
								lower gum - 22%							
					Buccal mucosa- 43%		cN0 - 23% (occult metastasis)	Level V- 4.3%							

Kowalski [37]	2002	Brazil	164	86.60%	oral cavity ca	T1-T4 /cN1,cN2a	LN mets 57.9%	level I - 8.5%	RND	regional recurrence- 8.5%	NA	Surgical
					Tongue- 43.9%			level II 35.4%				
					Floor of the mouth- 23.8%			level III - 2.4%				
					retromolar - 16.5%			Level IV- 0.6%				
					buccoalveolar sulci- 3.7%			level V- 0%				
lower gum - 12.2%	multi-levels- 11.6%											
Feng [38]	2013	China	637	55.40%	OSCC	N0, N+ve	occult metastasis 28.4%	II- 38.2%	SOHND, RND/ MRND	neck recurrence- 9.2%	NA	Surgical
					I- 55.1%							
					III- 6.7%							
					Skip metastasis Level IV/V- 0%							
					N2-N3 neck disease- 59 Pts							
Sivanandan [39]	2004	USA	100	74 Pts	oropharynx & oral cavity- 80%	N0-N3	LN 25%	I-IV	RND, MRND	Neck Recurrence- 7% (after radiotherapy 4%)	NA	Neure
					Level IV occult metastasis- 10%							
					ESOHND							
					neck recurrence- 8.2%							
					NA							
Crean [40]	2003	UK	49	24 Pts	oral cavity	N0	LN 26.5%	Level IV occult metastasis- 10%	ESOHND	neck recurrence- 8.2%	NA	Erectile dysfunction
					FOM 16 Pts							
					Tongue 14 Pts							
					NA							
					NA							
Khafif [41]	2001	USA	51	NA	Oral Tongue	T1-T3/ N0	occult metastasis 26%	Level IV mets 4%	Neck dissection I-III, and IV	16% neck recurrence	NA	Surgical
					NA							
					NA							
					NA							
					NA							
Balasubramanian [42]	2012	India	52	43 Pts	Oral Tongue	T1-T4, N0-N2	LN mets 39.5% (17 Pts)	Level III skip mets- 3.8%	Neck dissection	Recurrence- 3 Pts (1 in neck)	NA	Surgical
					Level IV skip mets- 1.9%							
					Combinations present for levels							
					MRND							
					Deaths-61 Pts							
Köhler [43]	2018	Brazil	163	89.57%	tonsillar SCC	T1-T4	6% (levels IV-V)	Level III skip mets- 3.8%	MRND	neck recurrence -12 Pts	Tobacco	Inferior limb vessels
					Level IV skip mets- 1.9%							
					Combinations present for levels							
					MRND							
					Deaths-61 Pts							
Deo [44]	2019	India	945	77.57%	Buccal mucosa- 28.78%	T1-T4	LN mets- 39.7%	Skip metastasis Level III-5%	Modified neck dissection	NA	Tobacco chewing	In the
					Tongue- 21.16%			skip metastasis Level IV-2%				
					Alveolo-buccal-18.73%			SOHND				
					Alveolus- 11.01%			SOHND				
					Central arch and FOM- 9.52%			SOHND				
RMT- 5.71%	SOHND											
de Vicente [45]	2015	Spain	56	75%	Tongue- 35.7%	TNM	LN mets 51.8%	IIb	MRND (I-V)	Survival (without	Tobacco, alcohol	Radiation
					Floor of the mouth-23.2%							
					Gum- 23.2%							
					NA							
					NA							

and concluded that SND I-III was sufficient in most cases. However, these studies also went on to recommend dissection of levels IV and V based on the surgeons' clinical decisions during surgery. Of these, one [19] reported data on cN0 neck, one [18] on N+ neck, and four [34,39,41,47] had mixed nodal status. In addition, twelve studies [20,25-27,32,33,38,40,42-44,46] did not make any clear recommendation on inclusion or non-inclusion of lower levels for neck dissections for lack of such data. A study by Jayasuriya et al. [21] presented ambiguous results wherein the authors did not recommend routine neck dissection for level V; however, they went on to recommend level V dissection when nodal stages >N2b and metastasis to level II and IV were observed in a case.

Discussion

This review revealed that the available literature favored either selective neck dissection, including only the upper levels (I-III), or was inconclusive. Most studies support the view that primary neck dissections should be limited to upper levels only, owing to the low rates of lower level (level IV and beyond) metastasis and the difficulty as well as the damage incurred (thereby introducing complications) due to the inclusion of those levels. Through independent studies, most authors have supported that high efficacy and minor morbidity for selecting pN+ OSCC patients may be achievable using SND (I-III) [38,49,50]. In a meta-analysis that compared SND with MRND/RND in OSCC patients with cN+ disease, authors [51] suggested that cN+ OSCC patients treated with SND (I, I-III, or I-IV) or those treated with MRND/RND had comparable clinical outcomes measured by no significant difference for regional recurrence, overall survival (OS), or disease-specific survival (DSS) between any of the dissection treatment types. The meta-analysis was, however, limited by the inclusion of studies where the extent and selection of the SND levels differed between studies other than levels I-II. The result of this meta-analysis supports our claim that even with variable surgical methods, it is not advisable to routinely include lower-level dissections. Contrary to the findings of the present study, independent studies, such as one by Shah et al. [52], have reported that 15%-16% of tongue/oral cancer with clinically detected lymph node(s) (cLN(s)) had pathological lymph node(s) (pLN(s)) to level IV, thereby recommending extended SOHND, which includes dissecting level IV.

Skip metastasis, described by Byers et al. [14], refers to the condition in which OSCC bypasses levels I, II, or both and goes directly to levels III or IV. The rate of skip metastasis in the original study was reported as 15.8%, thereby recommending routine dissection at neck level IV. Later analysis, however, revealed that among cN0 patients, only 5.5% had skip metastasis to level IV, making the recommendations controversial. Later, Crean et al. [40] similarly demonstrated that 10% of patients had involvement of neck level IV despite having been preoperatively diagnosed with a cN0 neck, with only 2% having a true skip metastasis to level IV. In a recent meta-analysis, the authors found the rate of skip metastasis to be low (overall involvement rate of 2.53% and skip metastasis rate of 0.50%), even with advanced tumor stages, wherein the final recommendation was not to include dissection of lower levels routinely [53]. A meta-analysis was conducted in 2020 to investigate the prevalence of level IV involvement and skip metastases in patients with clinically negative neck (cN0) oral tongue squamous cell carcinoma. It also recommended elective neck dissection that includes levels I to III because of the low rates of level IV involvement and skip metastasis [54]. Our review also supports the view for non-inclusion of lower levels in ND for suspicion of skip metastasis.

Some arguments may be made in terms of benefits archived in ipsilateral, contralateral, or bilateral node infiltration. Although we did not study the laterality of recurrence, the available literature [30] suggested that SND (I-III) could achieve good regional control and had a favorable prognosis for cN+ OSCC. In a study with ipsilateral neck recurrence rates ranging from 11%-14%, similar conclusions were drawn for the pN+ cohort [30].

Some studies reported data on oral tongue SCC, which is the most common primary site for OSCC, with most studies suggesting metastasis to level IIB [55,56], leading scholars to recommend level IIB dissection routinely in tongue SCC. Few studies [57,58] found no statistical significance between site and metastasis, which makes a contrary view due to the difficulty of approach, questionable benefits, and avoidance of postoperative shoulder disability [8]. Even with regards to level IV metastasis, most studies present a reserved view to include lower-level dissection as an exception for tongue carcinoma [14]. Our study found that all included literature for oral tongue carcinoma recommended lower-level dissection, probably owing to the tendency of tongue cancer toward early metastasis, the possible reason being that the tongue possesses an extensive lymphatic network.

Strengths and limitations

The present review included studies that reported varied study groups and regions, thereby introducing heterogeneity. The heterogeneity of study groups is considered an important confounder. In our case, it resulted in the lack of appropriate data stratification by T stage, subsites, and involvement of other neck levels that we could not address. The retrospective nature of the included studies also introduced bias, which could not be addressed. However, we exercised caution in including studies with primary neck dissection data only. We excluded all studies with patients with revision NDs and omitted all groups lacking this information to eliminate bias from combining the results of the primary neck surgery with those of revision surgeries for neck recurrences, which may falsely inflate the rate of level IV or lower-level involvement. While most studies presented mixed data for cN0 and cN+ necks, we segregated data wherever possible to report the differences according to nodal status. Lastly, the decision for SND or MRND techniques is widely debated due to the lack of universally accepted guidelines for the anatomic limits for the variety of SND procedures available. The exact anatomic boundaries for an SND are also thought to vary among institutions and even among surgeons within an institution [59]. The analysis of these differences could not be accounted for in the present review.

Conclusions

OSCC is constituted by a broad range of tumors with diverse etiologies. It can metastasize to cervical lymph nodes via lymphatic vessels. SND is considered a standard of care for most subsites, even in early-stage disease. Based on the evidence reviewed in the present study, the frequency of lower-level metastasis (level IV or V), as well as skip metastasis in OSCC, was low. Hence, routine dissection of these levels in cN0 and cN+ necks may be avoided except for tongue cancer. Since dissection of level IV/V is a burden with extra

time and might expose patients to more complications, dissection might be selected for specific subsites and extension. It is recommended to dissect level IIb and lower levels for tongue cancers without considering the stage of primary lesions or lymph node status. Most studies recommended sparing lower-level neck dissections, while some were inconclusive.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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