Prevalence of acute oral mucosal damage secondary to the use of systemic antineoplastics: A systematic review and meta-analysis

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Objective. The aim of this study was to determine the prevalence of acute oral mucosal toxicities in non-irradiated patients treated with systemic antineoplastics agents. The secondary objective was to find out differences in its prevalence among the different types of systemic antineoplastics.

Study design. A systematic review and meta-analysis was performed. Articles from 2010 to July 2022 were retrieved and included if patients were adults undergoing oral assessment after administration of commercially available systemic antineoplastics. Data was extracted and pooled proportions were estimated using random-effect model method (Der Simonian and Lair).

Results. Eighty-two articles were included in the study. The overall prevalence of acute oral mucosal damage across studies was 38.2% (95% CI: 33.1%-43.3%). The prevalence was 42.9% (95% CI: 32.8%-53%) in patients treated with chemotherapy alone, 38% (95% CI: 29.1%-47%) in patients treated with a combination of chemotherapy and targeted therapies, and 32.1% (95% CI: 26.8%-37.5%) in targeted therapies alone-treated patients. No statistically significant differences were found in the prevalence of oral mucosal toxicities between the different types of systemic antineoplastic treatments.

Conclusions. Oral mucosal toxicity is a major side effect in non-irradiated cancer patients undergoing systemic antineoplastics. (Oral Surg Oral Med Oral Pathol Oral Radiol 2023;135:385−395)

Oral mucosal damage (OMD) is one of the most frequently reported adverse events in cancer therapy. It is described as oral coating injury, characterized by the presence of inflammation, erythema, atrophy, and/or ulceration that may develop acutely or be long-lasting in certain cases.[1-3] The pathophysiology of acute oral mucosal damage in patients with cancer has not been completely unveiled yet, which precludes the development of effective treatments or prophylactic measures and limits the clinical approach to symptomatic or palliative care.[4] Patients who have these side effects often experience symptoms that may include xerostomia or localized acute pain that directly affect their quality of life up until recovery or death.[5,6] Occasionally, it might prompt more significant consequences, such as dehydration and malnutrition.[7,8] Multiple clinical research articles have been published showing controversial results on the best clinical practice in oral mucositis. Antimicrobials, analgesia, anesthesia, or laser are some of the treatments that have been described so far.[8,9]

The prevalence of acute oral mucositis varies according to the oncological treatment. Radiation therapy leads the ranking, causing oral mucositis to nearly every head and neck cancer patient receiving it. The incidence is slightly lower (60%-80%) in patients with hematologic malignancies that undergo hematopoietic cell transplantation, whereas cases in patients treated with chemotherapy account for 20% to 40% of the total.[3]

From a medical oncology perspective, it is interesting to analyze the incidence of oral mucosal lesions caused by prescribed treatments. Over the last years, the management of patients with cancer has changed considerably, and the use of target drugs has increased

Statement of Clinical Relevance

The prevalence of acute oral mucosal damage in non-irradiated patients treated with commercially available systemic antineoplastics is 38.2%. There is no significant difference according to the type of systemic antineoplastic regime administered.

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remarkably, despite the significance of traditional chemotherapeutic agents.[10]

The main objective of this study was to determine the frequency of acute oral mucosal damage development in non-irradiated cancer patients because it is a major side effect in oncology treatment. In addition, we also aimed to elucidate differences in the prevalence of this phenomenon in patients with cancer according to the type of systemic antineoplastic regime.

MATERIAL AND METHODS

Protocol design and registration

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines[11] and registered on PROSPERO (ID: CRD42021276728). The research question adhered to the Patient-Intervention-Comparison-Outcome (PICO) asset[12] and was as follows: ≥18-year-old patients diagnosed with cancer (P = Patient); whose oral mucosa was examined (I = intervention); after receiving systemic antineoplastics (C = Comparison); to assess the prevalence of oral mucositis (O = outcome).

Sources of information and search strategy

The bibliographic search was carried out in: PubMed/MEDLINE, Web of Knowledge, Cochrane, Directory of Open Access Journals, Literatura Latinoamericana y del Caribe en Ciencias de la Salud, and SciELO from 2010 to July 2022. A further electronic search was performed on databases of specific journals related to this topic.

The agreed search strategy was defined by the following algorithm with the aim of being applied in MEDLINE: (stomatitis OR "oral mucositis" OR "oral ulcer" AND cancer) AND ("Antineoplastic agent" OR Chemotherapy OR "targeted therapy" OR "Induction Chemotherapy" OR "Molecular Targeted Therapy"). The syntax was adapted specifically for each database; however, “oral mucositis” and “cancer therapy” were the main keywords. The human species filter was applied when available.

Eligibility criteria

The literature was retrieved from the databases, and the studies were included if they met the following inclusion criteria: original articles, cohort studies, clinical trials using approved drugs and case series, and with no language limitations. Participants in the included studies had to be ≥18 years of age and have undergone oral assessment after administration of systemic antineoplastics. The exclusion criteria included the following: letters, abstracts, literature reviews, systematic reviews, doctoral thesis, case reports, and original in vitro and in vivo articles. Studies that did not use grading scales for oral mucosa damage assessment were also excluded. Moreover, clinical trials using experimental drugs or other interventions that may potentially influence results, studies that included pediatric patients or pregnant women, as well as those involving patients who undergo/underwent radiotherapy alone or in combination with systemic antineoplastics were discarded.

Study selection and data extraction process

Two researchers (M.P.S. and M.E.R.F.) independently performed the selection of the studies in different phases, as follows: (1) reading the titles and abstracts and (2) fully reading the remaining articles and excluding those that did not meet eligibility. A third researcher (X.M.M.) intervened to deliver a verdict when discrepancies occurred about eligibility of specific articles. Later, a database was created including all the relevant available variables on each paper. Finally, the results were compared to ensure they matched.

The information extracted included first author, year of publication, country, sample size, sex, age, type of cancer, type of therapy, metastases, previous exposure to anticancer therapies, and number of patients with different grades of oral mucosal damage based on World Health Organization(WHO) Scores or National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).[1]

Evaluation of risk of bias

The risk of bias was assessed for each study by both researchers, following a similar pattern to study selection, using different tools for each specific paper type. For this research, and given our approach to it, it was agreed that most of the studies would be considered case series reports, although their initial design might have not been. Thus, the Joanna Briggs Institute Critical Appraisal Checklist for Case Series was the chosen tool for risk of bias assessment.[13] Those cases that did not meet ≥3 items were excluded. The Risk of Bias in Non-Randomized Studies − of Interventions tool[13,14] was chosen for risk of bias assessment in non-randomized clinical trials (NRCT). Moreover, in the case of randomized clinical trials, the Cochrane Risk of Bias 2.0 tool for Randomized Clinical Trials[13,15] was applied.

Statistical analysis

A proportion meta-analysis was conducted using STATA version 17 (StataCorp, LLC, College Station, TX, USA). Pooled proportions were estimated using random-effect model method (Der Simonian and Lair) with the following variables: type of tumor, study type, and continent. To analyze the heterogeneity among the

studies, the Q statistical test and the I^2 were used as well as funnel plots for the publication bias. A P value of $< .10$ and I^2 of $>50\%$ indicated that there was heterogeneity between the studies, meaning that a random-effects model would be used.

RESULTS

Study selection

The initial search generated 503 references. We excluded 421 at different stages of the process, as shown in Figure 1, which left us with 82 articles suitable for inclusion.

Risk of bias assessment

Each type of article that met eligibility criteria was thoroughly evaluated (N = 82). Three out of 79 case series obtained an overall appraisal of "excluded,"[16-18] whereas the remaining 76 received an "included" rating[19-94] (Supplemental Table S1; available at [URL/link*]). One NRCT was classified as low risk of bias[95]

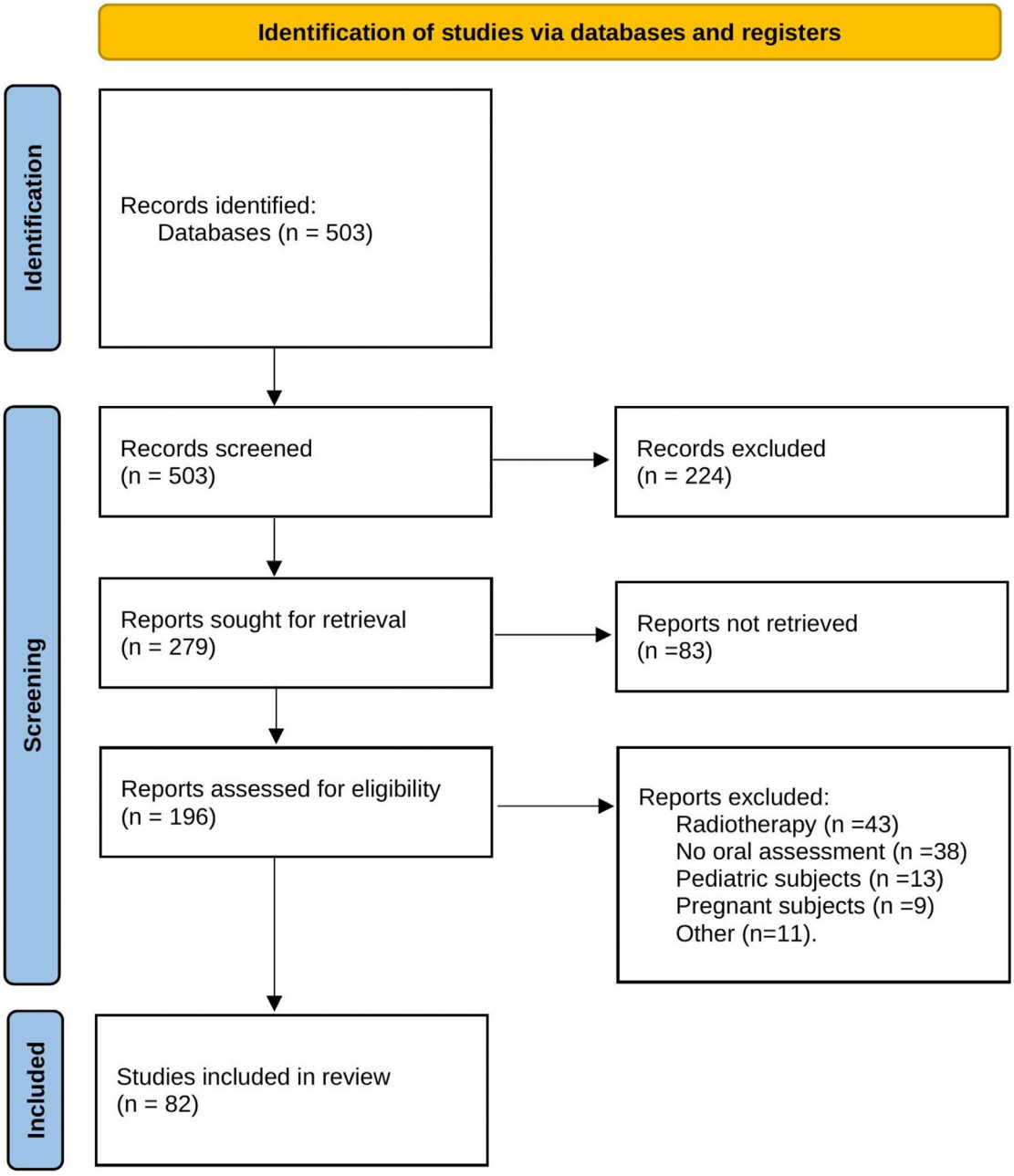

Fig. 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram. From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

Table I. Main characteristics of the included literature

Study-related features (N = 82)			
Type of article		*Total*	*%*
	Case series	79	96.3
	NRCT	2	2.5
	RCT	1	1.2
Oral assessment tool	CTCAE	58	71.6
	WHO scale	14	17.3
	Unknown	9	11.1
Type of cancer	Haematologic	17	20.7
	Kidney	15	18.3
	Digestive system	15	18.3
	Breast	10	12.2
	Lung	10	12.2
	Lymphoma	5	6.1
	Various	5	6.1
	Neuroendocrine	3	3.7
	Ovarian	2	2.4
Geographical location	Asia	39	47.6
	Europe	27	32.9
	North America	10	12.2
	Australia	5	6.1
	South America	1	1.3

Participant-related features				
	Mean	*Range*	*SD*	*Total*
Patients	123	(9-1790)	227	10104*
Male†	53	(0-609)	82	4064†
Female†	82	(0-1790)	208.6	5465†
Mean age	58	(29-75)	8.5	-
CT patients	156	(9-1790)	32.2	5678
TT patients	98	(12-404)	92.7	3184
Combined therapy patients	73	(10-353)	8.5	1165
Oral mucosal damage	46	(1-701)	89.2	3668

CT, chemotherapy; *TT*, targeted therapy; *RCT*, randomized clinical trial; *NRCT*, non-randomized clinical trial; *CTCAE*, common terminology criteria for adverse events; *WHO*, World Health Organization.
*No. of patients differs from meta-analysis due to 3 patients' loss.
†Data was not available for every article.

and 1 as moderate risk of bias[96] (Supplemental Table S2; available at [URL/link*]). One RCT was rated as overall low risk of bias[97] (Supplemental Table S3; available at [URL/link*]).

Main characteristics of the studies and their samples

To maximize the information available and to allow data analysis in those scientific papers that passed the bias assessment, it was agreed that it would be appropriate to split 3 of them in 2[19-21]. Subsequently, they were considered as independent articles, so we can state that a total of 82 have been included in our analysis.

Table I details that case series were the predominant type of article (96.3%), followed by NRCT (2.5%) and RCT (1.2%). Among the oral mucosa assessment tools, the CTCAE was the most frequently used in 71.6% of the articles, on any of its available versions (including the primary and its updates: 2.0, 3.0, 4.0, and 5.0). In 17.3% of the papers, authors chose the World Health Organization Oral Toxic Scale, whereas in 11.1% of the articles it was not specified. The most recurrent type of primary cancer among the studies was hematologic (20.7%), followed by kidney (18.3%), digestive system (18.3%), breast (12.2%), and lung (12.2%). In terms of location, 47.6% of the studies were carried out in Asia, 32.9% in Europe, and 12.2% in North America.

The sample size obtained from the 82 studies was 10104 patients (Table I). The mean number of patients in each one was 123 ± 227, with 9 being the smallest group of participants and 1790 the largest. Of these, ≥4064 were male and ≥5465 female. The included population had a mean age of 58 ± 8.5 years, and across the articles it ranged from 29 to 75. Patients treated with traditional chemotherapy drugs integrated the largest group with 5678 patients, those receiving targeted therapies alone summed 3184, whereas only 1165 patients were prescribed a combination of chemotherapy and targeted therapies. Overall, 3668 cases of oral mucosal toxicities were reported and at least 3447 cases of metastases were reported. Further information about all the included articles is displayed on Supplemental Table S4 (available at [URL/link*]).

Meta-analysis

The prevalence of acute oral mucosal damage was 38.2% (95% CI: 33.1%-43.3%) across all studies. Despite finding relevant heterogeneity (I^2 = 97.7%; P < .001; Figure 2), no publication risk of bias was identified using a funnel plot (P = .215; Figure 3).

Subgroup analysis was accomplished for type of therapy, cancer type, study design, and geographic location of studies (Table II).

Chemotherapy alone had the highest prevalence of oral mucosal damage prevalence at 42.9% (95% CI: 32.8%-53%), followed by the combination of conventional chemotherapy and targeted therapies at 38% (95% CI: 29.1%-47%), and the lowest prevalence showed on the targeted therapies at 32.1% (95% CI: 26.8%-37.5%). However, heterogeneity was very high overall (I^2 = 97.8%; P = .00; Figure 4), no statistically significant differences were found among them (P = .15).

Regarding the type of cancer, articles including patients suffering various types of cancer presented the higher prevalence of oral mucosal toxicities with 62.3% (95% CI: 33.1%-91.4%), followed by hematologic with 47.5% (95% CI: 32.4%-62.6%), lymphoma with 38.3% (95% CI: 8%-68.6%), ovarian with 39.1% (95% CI: 36.8%-41.3%), kidney with 33.6% (95% CI:

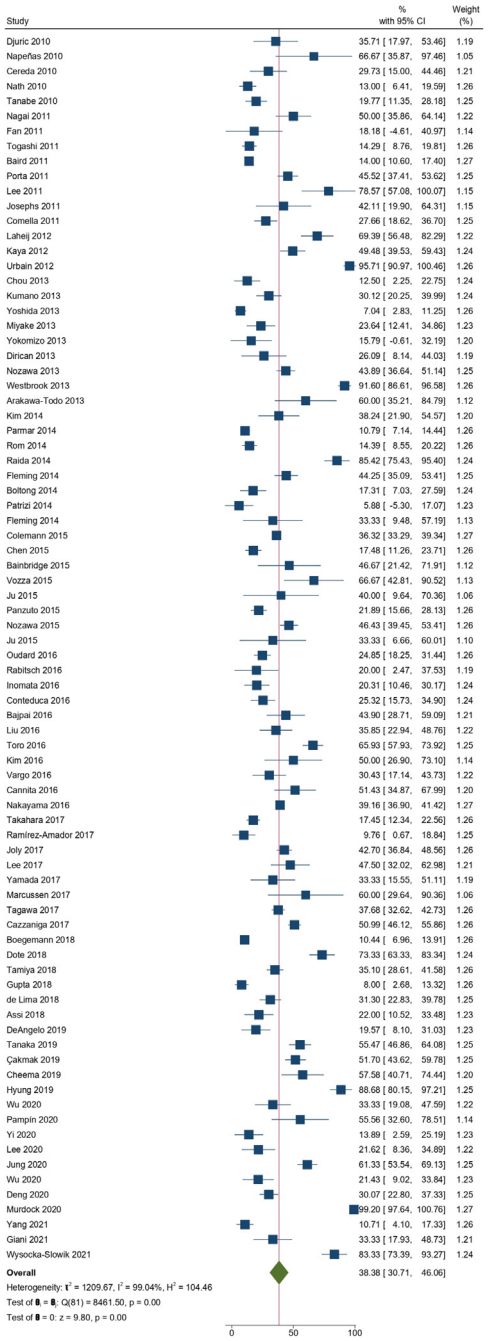

Fig. 2. Forest plot for the prevalence of acute oral mucosal damage.

26.7%-40.5%), and breast with 33.1% (95% CI: 22.8%-43.4%). Among them no significant differences were noted (P = .19). The heterogeneity was $I^2 > 50\%$ to all groups except for ovarian cancer ($I^2 = 0\%$), which was overall significant (P = .00; Figure 5).

According to study design, the prevalence was very similar; 38.2% (95% CI: 33%-43.4%) in observational studies and 39.4% (95% CI: 10.1%-68.8%) in experimental studies without statistically significant differences (P = .93). Both groups showed high heterogeneity (I^2 = 97.7%; P = .00; Figure 6).

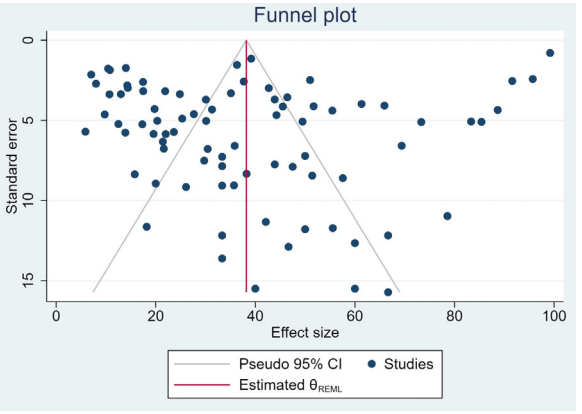

Fig. 3. Funnel plot test for publication bias. The *y*-axis represents the standard error, the *x*-axis displays the effect size (P = .215).

With regards to the locations where the studies had been carried out, the highest prevalence of oral mucosal appeared in studies developed in North America 48.6% (95% CI: 28.1%-69%), the second location was Europe with 42% (95% CI: 32.7%-51.2%), and the third location was Asia with 34.1% (95% CI: 27.8%-40.3%). Oral mucosal prevalence was not statistically different among the locations (P = .24). Similarly to what has been observed for all previous parameters, heterogeneity was significantly elevated (I^2 = 97.7%; P = .00; Supplemental Figure S1; available at [URL/link*]).

Supplemental Figure S2 (available at [URL/link*]) shows how each new study has chronologically contributed to the estimate of the prevalence of oral mucosal damage in patients receiving systemic antineoplastics since year 2010.

Meta-regression

We ran meta-regressions to investigate possible sources of heterogeneity in our covariates. No differences were found in the prevalence of oral mucosal toxicities according to the study design and the type of therapy (P = .663) or cancer type and type of therapy (P = .340). Similar results were found when considering location and year of publication (P = .569; location and type of therapy (P = .523); location and cancer type (P = .424); and study design, location, cancer type, type of therapy, and year of publication (P = .660).

DISCUSSION

Oral mucositis is a side effect of systemic antineoplastics with a noteworthy prevalence in cancer patients.[1] This statement is consistent with our finding that

Table II. Subgroup analysis of the variables

Parameter	*Category*	*Studies, n*	*% CI*	*Heterogeneity I^2*	*Heterogeneity P value*	*Subgroup analysis P value*
Cancer type	**Breast**	10	33.09 (22.78-43.4)	92.32	< .001	.19
	Digestive	16	33.17 (23.82-42.53)	94.11	< .001	
	Hematologic	17	47.5 (32.4-62.61)	98.76	< .001	
	Kidney	15	33.63 (26.73-40.54)	89.8	< .001	
	Lung	10	31.3 (19.07-43.53)	95.2	< .001	
	Lymphoma	5	38.25 (7.95-68.56)	97.02	< .001	
	Neuroendocrine	3	29.96 (17.03-42.9)	59.1	.087	
	Ovarian	2	39.07 (36.83-41.31)	0	.524	
	Various	4	62.27 (33.13-91.41)	98.45	< .001	
Type of study	**Observational**	79	38.15 (32.95-43.35)	97.8	< .001	.93
	Experimental	3	39.4 (10.1-68.8)	95.84	< .001	
Type of therapy	**Chemotherapy**	32	42.92 (32.8-53.01)	99.12	< .001	.15
	Combined	34	38.03 (29.05-47.01)	87.6	< .001	
	Targeted therapy	16	32.14 (26.77-37.52)	91.94	< .001	
Location	**Australia**	5	28.65 (14.91-42.39)	85.49	< .001	.24
	Asia	39	41.98 (32.73-51.24)	97.32	< .001	
	Europe	27	31.3 (22.83-39.78)	-		
	North America	10	48.58 (28.13-69.04)	99.45	< .001	
	South America	1	34.08 (27.79-40.34)	95.82	< .001	

estimates the prevalence of acute oral mucosal damage to be 38.2% in non-irradiated patients treated with systemic antineoplastics. Despite all the scientific discoveries on cancer pathophysiology, as well as in research and development of new therapeutic strategies in recent years, which seem to be more specific for each type of cancer, side effects are common.[98] Therefore, knowing prevalence data could encourage further research focus into the biological basis that triggers oral mucosal damage, which could lead to the discovery of possible therapeutic targets. Hence, our results suggest that differences in oral mucosal damage prevalence in conventional chemotherapy, targeted therapies, or a combination of both are not significant. The clinical implication of this finding supports the need to approach all cancer patients equally, regardless of the therapy of choice, promoting the multidisciplinary team to collaborate on the patient's behalf. This means that medical oncologists should be supported by other professionals such as odontologists, maxillofacial surgeons, dermatologists, palliative care providers, and nurses, aiming for preventive or curative treatments.

Non-randomized clinical trials, large cohort studies, or case-control studies have traditionally been considered optimal to determine the incidence or prevalence of adverse events in pharmacovigilance.[99] The nature of the present study to assess the prevalence of oral mucosal damage considering only commercially available systemic antineoplastics was decisive when designing how to tackle our topic and led us to perform a systematic review of the available data to achieve representative measures, and research has proven its reliability.[100] Moreover, we decided to establish a timeframe for inclusion that starts in 2010, coinciding with the development of new monoclonal antibodies directed toward tumor antigens or T-cell receptors and the growth of other targeted therapies use worldwide.[101]

Throughout our research, we encountered several challenges. For example, the method of assessment of oral mucosa involvement was not homogeneous in all articles because some used the WHO scale, whereas others used the CTCAE in its consecutive versions, and, in some cases, the tool used was not even reported. This discrepancy has been remedied by taking into account only reported cases of oral mucosal injuries in general, which means scoring >0 for the WHO scale or ≥1 for the CTCAE. Conversely, many of the articles only reported those cases in which the involvement was ≥3, or ≥2, thus ignoring mild cases of oral damage. The fact of not precisely reporting the number of patients that developed each certain severity degree of their lesions could influence the results obtained. Likewise, this lack of detail has prevented us from studying and determining possible associations between the type of systemic antineoplastics and the severity of the oral lesions. Note that the wide variety of treatments, doses, routes of administrations, and adjuvant therapies within the included articles may have influenced the results.

Data analysis based on sociodemographic features (e.g., sex and age) was not feasible due to differences in samples of each study. Some articles did not describe certain characteristics of their sample and others included a population that was completely female, given that they had breast or ovarian cancer.

Lastly, although it could be thought that patients with hematologic cancer might show different prevalence data for oral mucosal damage than other solid

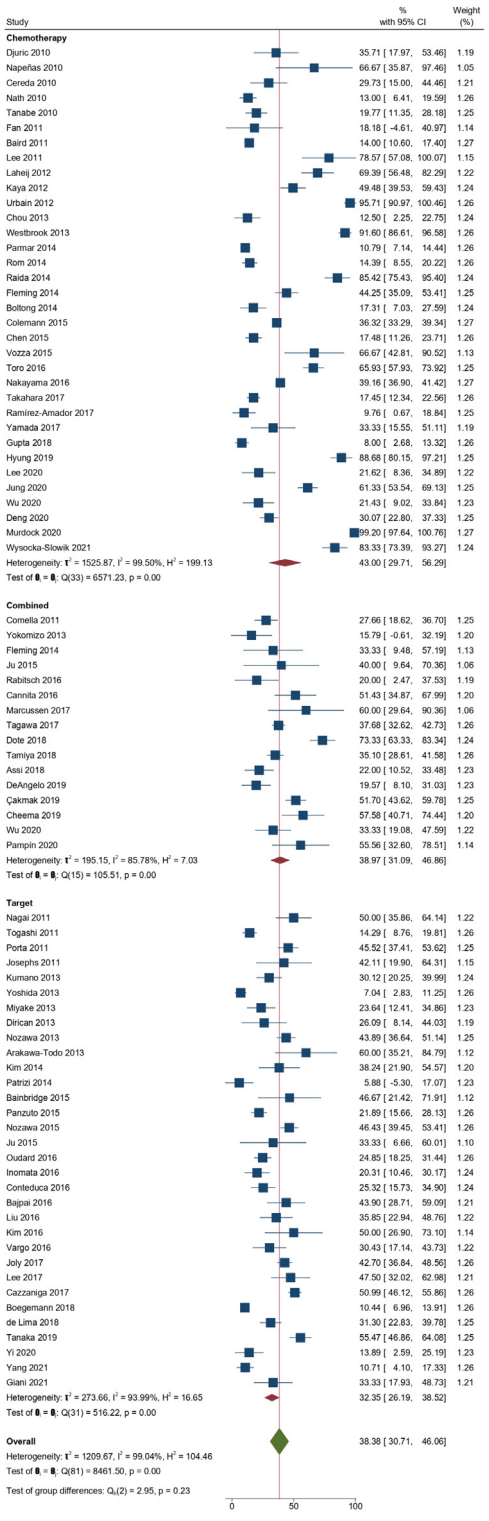

Fig. 4. Forest plot for the prevalence of acute oral mucosal damage by type of systemic antineoplastic.

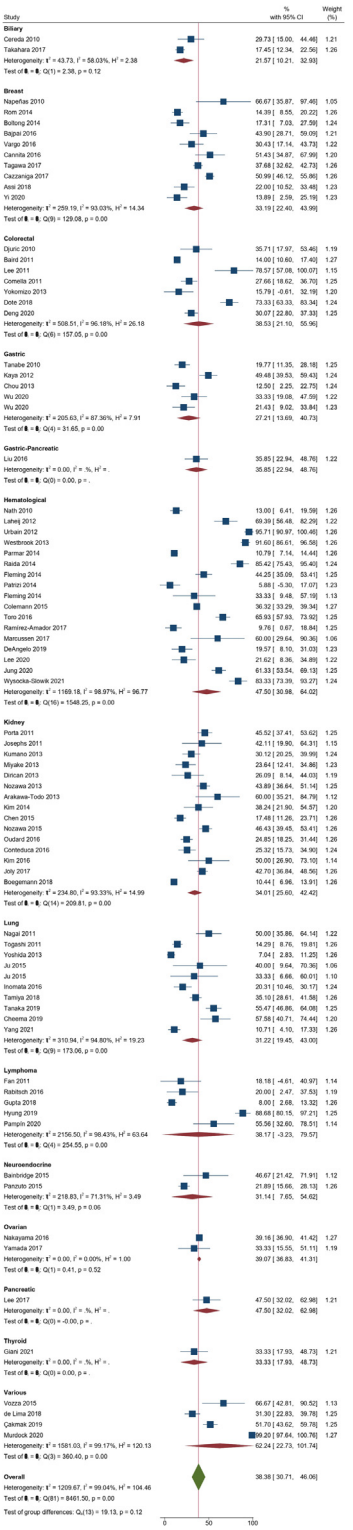

Fig. 5. Forest plot for the prevalence of acute oral mucosal damage according to cancer type.

tumors, due to the peculiarities in the approach to the disease and the therapies used (including transplants), no statistically significant differences have been observed.

The present study may lead researchers to further work on this highly prevalent side effect in patients with cancer treated with systemic antineoplastics, whether it be discovering effective treatments for this condition, preventive

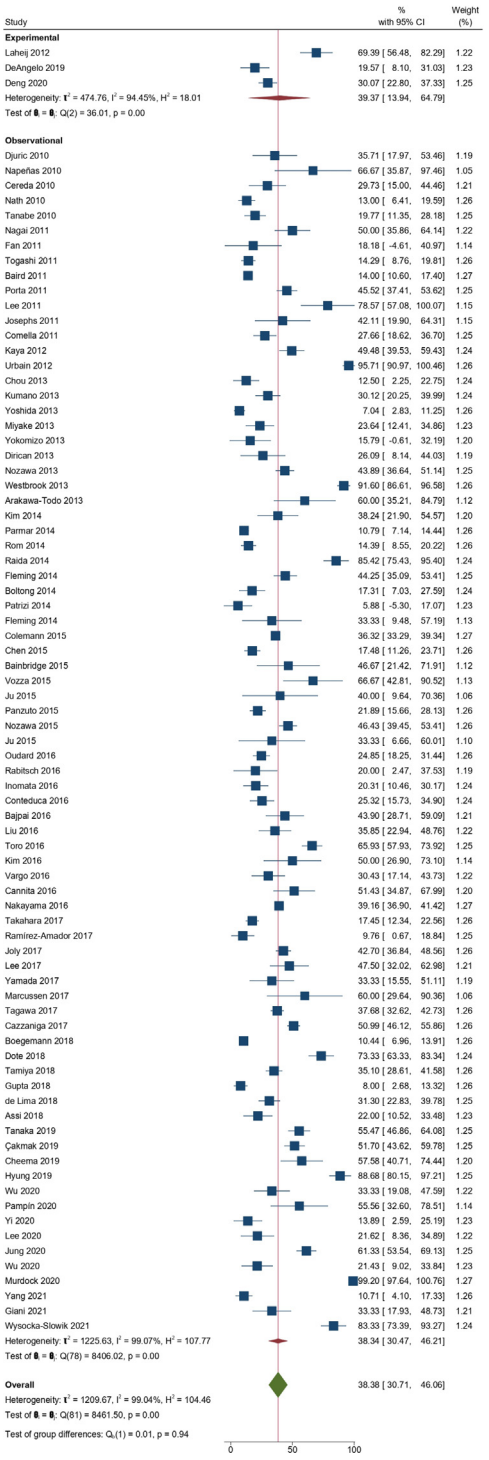

Fig. 6. Forest plot for the prevalence of acute oral mucosal damage categorized by study design.

therapies, or developing innovative cancer therapies that do not produce this side effect.

CONCLUSIONS

Oral mucosal damage has a prevalence of 38.2% in patients receiving systemic antineoplastics. No significant differences were found among traditional chemotherapy alone, targeted therapies, or their combination. This finding supports the need to assess oral mucosa of all patients receiving any type of systemic antineoplastics in the same manner to avoid underdiagnosis because it is a highly prevalent side effect.

DECLARATION OF INTEREST

None.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2022.11.016.

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