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Oral squamous cell carcinomas and oral potentially malignant disorders: A Latin American study

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Abstract

Objective: To determine the frequency of oral squamous cell carcinoma (OSCC) associated or not with oral potentially malignant disorders (OPMD), and the epidemiological profile and traditional risk factors in Latin America.

Methods: A retrospective observational study was conducted in 17 Latin American centres. There were included cases of OSCC, analysing age, gender, OSCC and their association with previous OPMD. Clinicopathological variables were retrieved. The condition of sequential-OSCC versus OSCC-de novo (OSCC-dn) was analysed concerning the aforementioned variables. Quantitative variables were analysed using Student's *t*-test, and qualitative variables with chi-square.

Results: In total, 2705 OSCC were included with a mean age of 62.8 years old. 55.8% were men. 53.75% of the patients were smokers and 38% were common drinkers. The lateral tongue border was the most affected site (24.65%). There were regional variations in OPMD, being leukoplakia the most frequent. Of the overall 2705 OSCC cases, 81.4% corresponded to OSCC-dn, while s-OSCC were 18.6%. Regarding lip vermillion

For affiliations refer to page 16.

SCC, 35.7% corresponded to de novo lip SCC and 64.3% were associated with previous OPMD.

Conclusions: In Latin America, OSCC-dn seems to be more frequent with regional variations of some clinical and histopathological features. Further prospective studies are needed to analyse this phenomenon.

KEYWORDS
Latin America, leukoplakia, oral cancer, oral potentially malignant disorders, oral squamous cell carcinoma

1 | INTRODUCTION

Lip and oral cavity cancer are together the 17th most common cancer worldwide with approximately 377,713 new cases and 177,757 deaths annually (Global Cancer Observatory: Cancer Today, n.d.). Oral squamous cell carcinoma (OSCC), the most frequent oral malignancy, ranks 12th in mortality (Sung et al., 2021). These results are different according to the geographic areas, where some countries of Latin America and the Caribbean are particularly characterized by high incidence rates, such as Brazil, Uruguay and Puerto Rico (Warnakulasuriya & Kerr, 2021).

The prognosis of OSCC is associated with different factors related to diagnosis delay (patients, professionals and health system aspects) (Morelatto et al., 2007). Several studies have shown that diagnostic delays impact OSCC mortality outcomes (Seoane et al., 2012). Despite being a malignancy rather easy to detect, a large proportion of OSCC are diagnosed in advanced stages, which negatively impacts in prognosis (Walsh et al., 2021). One of the preventive strategies that are usually performed to reduce the diagnosis delay of OSCC is the detection of oral potentially malignant disorders (OPMD) (Abati et al., 2020).

OPMD are conditions of the oral mucosa that could be associated with an increased risk of developing cancer (Warnakulasuriya et al., 2020). They constitute morphological alterations of the oral mucosa with a predisposition to malignant transformation. Leukoplakia, erythroplakia, proliferative verrucous leukoplakia (PVL), oral submucous fibrosis (OSMF), oral lichenoid disease and actinic keratosis/cheilitis are considered OPMD, showing variable rates of malignant transformation (Iocca et al., 2020). These OPMD could develop oral malignancies, and they can also coexist at the margins of OSCC, harbouring morphological, molecular and chromosomal changes analogous to those found in OSCC (Warnakulasuriya, 2020). However, a subset of OSCC develops without previous lesions, arising de novo and hence not allowing for prediction in the same way as OSCC developing from OPMD (Saito et al., 2012). Moreover, its prevention and early diagnosis strategy may be different from the approach used for OSCC associated with OPMD. Nevertheless, there is a paucity of original research assessing the proportion of carcinomas arising from OPMD.

Oral leukoplakia is the most frequent OPMD. 11% to 60% of OSCCs are associated with this precursor lesion (Haya-Fernández et al., 2004; Schepman et al., 1999). Differences in this frequency can be partially explained by OPMD geographic variations, conditioned by the prevalence of different risk factors. For instance, areca nut chewing is a frequent condition in Southeast Asia, and consequently, this region shows a high incidence of OSCC arising from OSMF, an OPMD produced by this practice (Gupta & Jawanda, 2021). These differences in demographics and clinical-epidemiological factors of oral cancer in the world are strongly conditioned by the lifestyles and cultural behaviours of each of the geographical areas where the research is developed. In this regard, data from South America is limited and there is null or little information obtained from a multicenter contribution.

The aim of this study was to determine the frequency of OSCC associated and not associated with OPMD, comparing the epidemiological profile and traditional risk factors between both groups of malignancies from different diagnostic centres in Latin America.

2 | MATERIALS AND METHODS

A retrospective observational study was conducted with the contribution of 17 Oral Medicine and Oral Pathology centres from Argentina, Brazil, Chile, Costa Rica, Mexico, Peru, Uruguay and Venezuela. This study was performed in accordance with the Helsinki Declaration and was coordinated by the Oral Medicine Department 'A', Facultad de Odontología, Universidad Nacional de Cordoba (Argentina) approved by the research ethics committee: Comité Académico en Investigación de Ciencias de la Salud y Comité Institucional de Ética de las Investigaciones en Ciencias de la Salud, Facultad de Odontología, Universidad Nacional de Córdoba, Argentina Protocolo Number T08/16 and 31/15, Consejo de Evaluación Ética en Investigaciones en Salud, Córdoba Healthy Ministery Protocol Number 05/J094 (Appendix A).

2.1 | Data collection

Patients from different Latin American centres were included by searching on registry databases or clinical records. Within a period between 1982 and 2022, the participating centres included cases of at least 1 year, corresponding to patients with OSCC who

presented all the available information detailed in the inclusion criteria. All cases were sequentially retrieved. The periods from which the different participating centres extracted the available data for this study are shown in Appendix A. Data collection was performed throughout 2022.

2.2 | Inclusion criteria

Histopathological diagnosis of OSCC, including different OSCC histological subtypes, lip SCC (ICD 10 C00.0, C00 *-excluding C00.0, C00.1 and C00.2-*, C01, C02, C03, C04, C05, C06) and OPMD with definitive clinical diagnosis (arriving at the definitive clinical diagnosis of OPMD by ruling out other benign oral conditions); or histopathological diagnosis considering the last WHO consensus—classification (Warnakulasuriya et al., 2020).

2.3 | Exclusion criteria

Cases recorded for recurrence, patients without a record of excluding variables (histopathological diagnosis of OSCC and definitive clinical or histopathological diagnosis of OPMD). Cases of lip skin cancer were excluded.

The following variables were recorded:

- Age: in years.
- Gender: female and male
- Histopathological diagnosis of OSCC.
- Definitive clinical (arrived at diagnosis having previously ruled out other benign oral conditions) or histopathological diagnosis of OPMD. The presence of OPMD was categorized as Yes–No. OSCC was considered associated with previous OPMD when the patient presented at the initial consultation with OSCC accompanied by OPMD; or when the patient under follow-up for OPMD developed cancer. OPMD could be located in the same area or distant from the OSCC. When OSCC was associated with OPMD, the group was referenced as *sequential-OSCC* (s-OSCC). When OSCC was not associated with OPMD, the group was referenced as *OSCC arising* de novo (OSCC-dn).
- Cell differentiation grade: according to histopathological report, categorized as well-differentiated, moderately differentiated and poor differentiated.
- Tumour epicentre: Unicentric: when OSCC was in a single anatomical location. Multicentric: when OSCC presented clinically with multiple foci synchronously or asynchronously, in the same or different anatomical regions.
- Location: according to ICD classification and anatomical subregions: retromolar area, gingiva, labial mucosa, labial vermillion, tongue lateral border, tongue dorsum, buccal mucosa, soft palate, hard palate, floor of the mouth.
- Tobacco: yes/no. A smoker was someone who has smoked a daily average of one cigarette for at least 1 year.
- Alcohol: yes/no. A drinker was someone who has consumed alcoholic beverages at least once a week for at least 1 year.
- OPMD: considering the WHO 2020 Consensus (Warnakulasuriya et al., 2020).
- OPMD site matching with OSCC: (a) Coincidence was considered when the tumour was surrounded by an area of mucosa clinically consistent with OPMD considered by the WHO 2020 Consensus. (b) It was considered No coincidence with OPMD, when the development of OSCC occurred far from the site of OPMD appearance, with clinically healthy mucosa separating both lesions.

Cases lacking data (low-quality photographic documentation of malignancy and OPMD areas, clinical and medical records, anatomopathological reports or other available information) to be categorized as de novo or sequential were excluded from the study.

2.4 | Control of sources of bias

To reduce the sources of bias, a virtual calibration meeting was held to record the retrieved variables. An explanatory video with the registration of the variables (to reduce arbitrariness in the registration of the association of OSCC with OPMD) was timely sent to each participating centre. A main investigator was appointed from each centre, who was in charge of supervising the data collection. Any queries during the retrospective recording of the variables were consulted with six investigators (BM from Chile, ARSS from Brazil, RP and EP from Argentina, MV from Venezuela and RB from Uruguay), who acted as internal consultants.

2.5 | Statistical analysis

A narrative descriptive synthesis was provided, using mean, range and absolute frequency values, discriminating the data according to participating centres. The condition of s-OSCC versus OSCC-dn was analysed concerning age, sex, histopathological diagnosis, degree of cellular differentiation, unicentricity or multicentricity, specific location, involvement of multiple anatomical areas and tobacco and alcohol consumption. Quantitative variables were analysed using Student's *t*-test, and qualitative variables using chi-square. A *p*-value of ≤0.05 was considered significant. Statistical analysis was performed using Infostat 2020 (Universidad Nacional de Córdoba, Argentina). Cases with missing data were not included in the description of frequencies or statistical analyses referring to the missing variable.

3 | RESULTS

From the multicentre contribution of 17 Latin American Oral Medicine and Oral Pathology diagnostic centres, 2705 cases of proven OSCC with histopathological diagnosis were included.

Figure 1 shows a map of the distribution of OSCCs recruited by each collaborative centre. The mean age of the patients was 62.8 years old (8–103 years) 55.8% ($n=1509$) were men, while 44.2% ($n=1196$) were women; with a ratio of 1.26:1. A total of 300 (11%) patients were under 45 years, of which 175 were women and 125 men.

Regarding OSCC risk factors, 53.75% ($n=895$) of the patients were smokers and 46.24% ($n=770$) were non-smokers, with 1040 cases without data. Concerning alcohol consumption, in 1155 cases, this data could not be obtained. Of the remaining cases, 38% ($n=590$) were common drinkers, while 62% ($n=960$) were non-drinkers. Table 1 presents the general features of the population and Table 2 shows this characterization grouped by different collaborative centres.

The most frequent histopathological diagnosis was conventional OSCC in 89.9% of cases ($n=2428$) (Table 3). In addition, 115 Verrucous Carcinomas (VC) (4.25%) were diagnosed, 98 cases of ISC (3.6%), 47 cases of micro-invasive OSCC (1.75%), 6 cases of Papillary SSC (0.2%), 2 Basaloid SCC (0.08%), 2 Clear Cell Carcinomas (0.08%) and 1 Acantholytic SCC (0.03%).

The degree of cell differentiation was obtained from 1677 cases. From these cases, 63% ($n=1069$) were well-differentiated OSCC, 29% ($n=477$) were moderately differentiated OSCC and 8% ($n=131$) were undifferentiated OSCC.

Concerning the tumour epicentre, data was obtained from 2045 cases. Of these, 90% ($n=1856$) were unicentric and the remaining 10% ($n=189$) were multicentric. The totality of all OSCC subtypes, counting the individual cases (that arose in the same patient with a multicentric pattern) that also presented with multiple foci was 2841.

The anatomical site with the highest frequency of OSCC was the lateral border of the tongue (700; 24.65%), followed by gingiva (629; 22.15%), the floor of the mouth (377; 13.25%), buccal mucosa (288; 10.15%) and tongue non-specified sites (144; 5.06%).

Table 4 shows the characterization of OPMD grouped by each collaborative centre. There were regional variations in OPMD diagnosis. The most frequent OPMD was homogeneous leukoplakia ($n=212$; 42.23%), followed by erythroleukoplakia (non-homogeneous leukoplakia) ($n=65$; 12.94%), oral lichen planus ($n=63$; 12.54%), actinic cheilitis ($n=53$; 10.55%) and multifocal proliferative

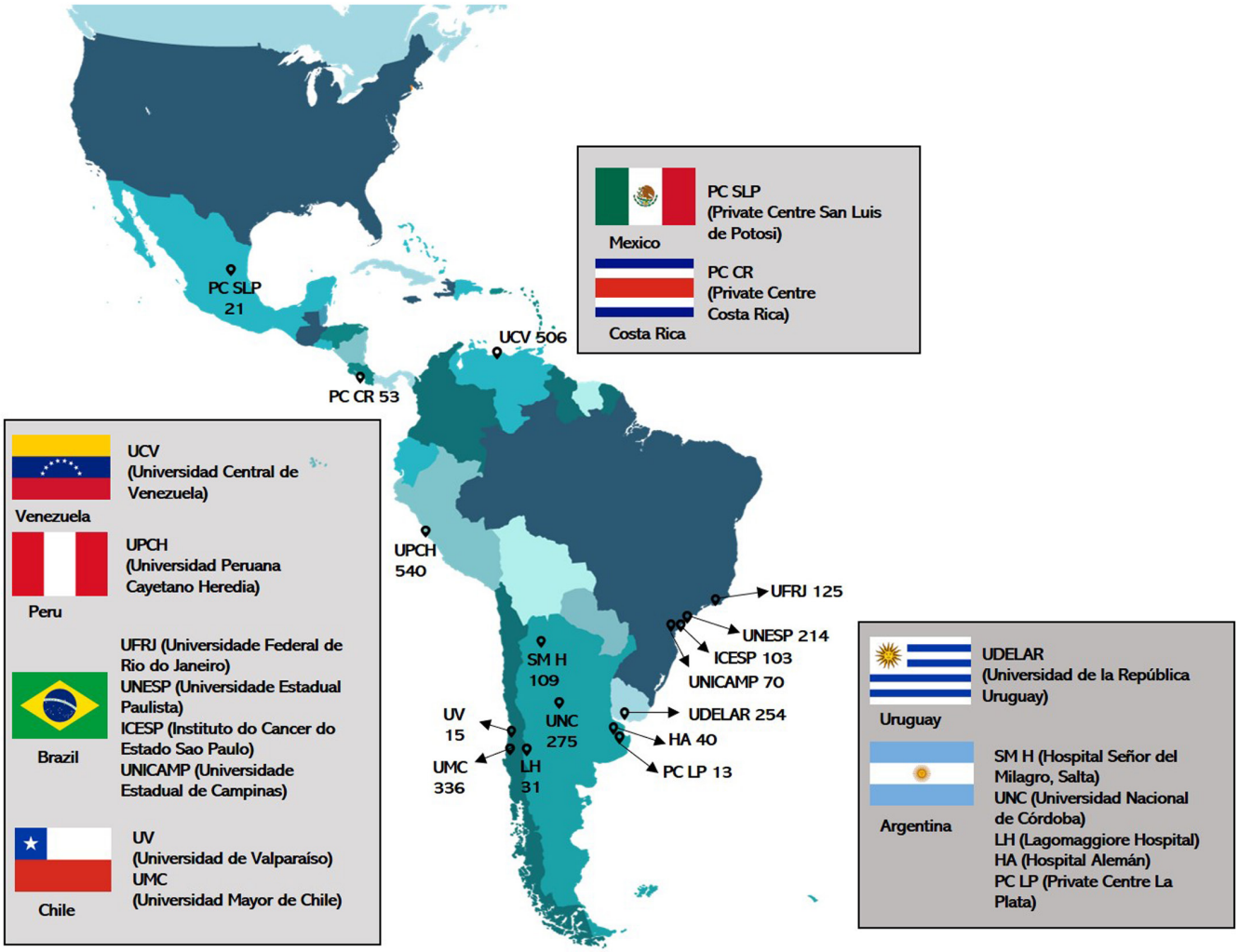

FIGURE 1 Map detailing the participating centres.

TABLE 1 Demographic and clinicopathological characterization.

	n	%
Total	2705	100
Age		
Media	62.77	-
Range	8–103	
Gender		
Males	1509	55.79
Females	1196	44.21
Males:females ratio	1.26:1	
Tobacco		
No	895	53.76
Yes	770	46.24
No data	1040	-
Alcohol		
No	960	61.94
Yes	590	38.06
No data	1155	-
Histopathological diagnosis		
Oral squamous cell carcinoma-conventional	2428	89.76
Verrucous carcinoma	115	4.25
In situ carcinoma	98	3.62
Microinvasive carcinoma	47	1.73
Papillary carcinoma	6	0.22
Spindle cell carcinoma	6	0.22
Basaloid carcinoma	2	0.07
Clear cell carcinoma	2	0.07
Acantholytic carcinoma	1	0.03
Cell differentiation degree		
Well-differentiated	1069	63.7
Moderately differentiated	477	28.4
Undifferentiated	131	7.9
No data	1028	-
Tumoral epicentre		
Unicentric	1856	90.75
Multicentric	189	9.25
No data	660	-
Location		
Retromolar pad	94	3.31
Gingiva	629	22.16
Lip mucosa	26	0.91
Lips non specified	23	0.8
Lip vermillion	98	3.47
Tongue lateral border	700	24.66
Tongue dorsum	41	1.44
Tongue ventral	83	2.92
Tongue, non-specified	144	5
Buccal mucosa	288	10.14
Alveolar sulcus	43	1.5
Non specified	28	0.98
Soft palate	89	3.13
Hard palate	120	4.25
Palate non specified	55	1.93
Floor of the mouth	377	13
Total	2838[a]	100
Oral potentially malignant disorders		
No	2203	81.44
Yes	502	18.56
Oral potentially malignant disorders diagnosis		
Leukoplakia	212	42.23
Erythroleukoplakia	65	12.94
Oral lichen planus	63	12.54
Actinic keratosis or cheilitis	53	10.55
Proliferative verrucous leukoplakia	52	10.35
Erythroplakia	33	6.57
Oral lichenoid lesions	14	2.78
Palatal lesions in reverse smokers	4	0.79
Systemic lupus	2	0.39
No data	4	0.79
Coincidence of OSCC with OPMD		
No	59	12.62
Yes	409	87.38
No data	34	-

Note: Those categories lacking data were not included in the final calculation, except for OPMD.

Abbreviations: OPMD, oral potentially malignant disorders; OSCC, oral squamous cell carcinoma.

[a]OSCC categorized by location totaled 2838 because in 133 cases multifocal OSCC were diagnosed involving more than one anatomical area.

leukoplakia ($n=52$; 10.35%), erythroplakia ($n=33$; 6.57%), lichenoid lesions ($n=14$; 2.78%), palatal lesions in reverse smokers ($n=4$; 0.79%) and erythematous lupus ($n=2$; 0.40%).

Of the overall 2705 OSCC cases, 81.4% ($n=2203$) corresponded to OSCC-dn, while s-OSCC were 18.6% ($n=502$). Considering lip vermillion cancer, 35.7% ($n=35$) corresponded to de novo lip vermillion SCC and 64.3% ($n=63$) were associated with previous conditions, being actinic keratoses/cheilitis the most frequent OPMD associated with lip vermillion cancer. The remaining 2607 OSCC with intraoral locations, corresponded to 2168 cases of OSCC-dn (83.13%) and 439 cases of s-OSCC (16.87%).

In total, 13 of the 17 participating centres showed a higher frequency of OSCC-dn than s-OSCC, with heterogeneous data even in centres of the same city and the same country (e.g. Córdoba,

TABLE 2 Demographic characterization by collaborative centre.

Centre	UNICAMP	ICESP	UNESP	FOUNC-A	FOUNC-B	PC-CR	HABA	FD V	PC-LP	LH-M	PC-MX	UPCH	HSM-S	UCV	UFRJ	UMCH	UDELAR	
Country	BR	BR	BR	AR	AR	CR	AR	CH	AR	AR	MX	PE	AR	VE	BR	CH	UR	Total
n	70	103	214	108	167	53	40	15	13	31	21	540	109	506	125	336	254	2705
Age																		
Mean	64.0	60.4	61.7	64.3	61.9	62.4	66.8	66.8	60.9	59.3	62.5	64.8	57.3	60.2	63.1	65.0	63.5	62.77
Range	39–87	22–87	19–102	27–90	23–97	24–93	43–88	49–83	23–85	38–89	31–94	8–103	28–87	13–98	30–91	22–95	16–99	8–103
Gender																		
Males	46	80	159	55	101	24	25	7	6	22	11	242	80	247	90	164	150	1509
Females	24	23	55	53	66	29	15	8	7	9	10	298	29	259	35	172	104	1196
M:F ratio	1.9:1	3.5:1	2.9:1	1:1	1.5:1	0.8:1	1.7:1	0.9:1	0.8:1	2.4:1	1.1:1	0.8:1	2.7:1	0.9:1	2.6:1	1:1	1.4:1	1.26:1
Tobacco																		
No	20	27	32	59	53	32	20	6	5	13	13	462	87	2	47	17	0	895
Yes	38	76	142	49	113	21	20	9	8	18	8	78	22	5	78	85	0	770
No data	12	0	40	0	1	0	0	0	0	0	0	0	0	499	0	234	254	1040
Alcohol																		
No	31	39	52	66	72	42	28	3	7	2	13	437	95	0	68	5	0	960
Yes	26	64	80	42	95	11	12	10	6	18	8	102	14	0	57	45	0	590
No data	13	0	82	0	0	0	0	2	0	11	0	1	0	506	0	286	254	1155

Abbreviations: AR, Argentina; BR, Brazil; CH, Chile; CR, Costa Rica; FD V, Oral Pathology Diagnostic Center, Faculty of Dentistry, Facultad de Odontología, Universidad de Valparaíso; FOUNC-A, Oral Medicine Department A, Facultad de Odontología Universidad Nacional de Córdoba, Argentina; FOUNC-B, Oral Medicine Department B, Facultad de Odontologia, Universidad Nacional de Córdoba, Argentina; HABA, Oral Medicine Department, Hospital Aleman, Buenos Aires, Argentina; HSM-S, Stomatology Service, Señor del Milagro Hospital, Salta, Argentina; ICESP, Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, Fundação da Faculdade de Medicina da Universidade de SãoPaulo (FMUSP), São Paulo, Brazil; LH-M, Lagomaggiore Hospital, Mendoza, Argentina; MX, Mexico; PC-CR, Private Centre, Costa Rica; PC-LP, Private Centre, La Plata, Argentina; PC México, Private Centre Mexico FD, Mexico; PE, Peru; UCV, Oral Pathology Department, Universidad Central de Venezuela, Caracas, Venezuela; UDELAR, Oral Pathology Department, Facultad de Odontología, Universidad de la República, Montevideo, Uruguay; UFRJ, Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro; UMCH, Oral Pathology Department, Facultad de Odontología, Universidad Mayor de Chile, Santiago de Chile, Chile; UNESP, Department of Bioscience and Oral Diagnosis, Institute of Science and Technology, UNESP-SJC-São Paulo-Brazil; UNICAMP, Oral Diagnosis Department Piracicaba Dental School, State University of Campinas, Brazil; UPCH, Facultad de Estomatología Peruana Cayetano Heredia, Lima Perú; UR, Uruguay; VE, Venezuela.

TABLE 3 Clinical and histopathological characteristics.

Centre	UNICAMP	ICESP	UNESP	FOUNC-A	FOUNC-B	PC-CR	HABA	FD V	PC-LP	LH-M	PC-MX	UPCH	HSM-S	UCV	UFRJ	UMCH	UDELAR	
Country	BR	BR	BR	AR	AR	CR	AR	CH	AR	AR	MX	PE	AR	VE	BR	CH	UR	Total
Diagnosis																		
OSCC	67	100	202	85	165	42	36	13	12	24	11	493	105	428	115	278	252	2428
Mic OSCC	2		7			1	1	1				6		8	9	12		47
In situ Carcin	1			8	1	4	1			2	9	20	4	37	1	10		98
VC		3		14	1	5	1	1	1	5		19		33		30	2	115
Pa-OSCC			4	1												1		6
SC-OSCC						1	1					2				2		6
Ba-OSCC			1								1							2
CC-OSCC																2		2
Ac. OSCC																1		1
Cell differentiation																		
WD	4	29	6	15		31	16	5	8	13		398	45	322		62	115	1069
MD		53	2	48		10	19	4	4	5		44	38	100		44	106	477
U		11	3	23		2	2			2		30	13	6		9	30	131
Tumor epicentre																		
Unicentric	68	101	198	98	0	48	39	10	13	22	20	473	105	57	120	273	211	1856
Multicentric	2	0	13	10	0	5	0	5	0	9	1	67	4	19	5	6	43	189
No data	0	2	3	0	167	0	1	0	0	0	0	0	0	430	0	57	0	660
Location																		
Retromolar pad		5	11	3	11	2	1		2	2		14	1	17	5	6	14	94
Gingiva	8	11	35	13	32	14	11	2	3	1	4	148	34	134	17	92	71	629
Lip mucosa		5	2	1								13				4	1	26
Lip non-specified			10		1							4	1			7		23
Lip vermillion	13		23	3	5	3	1		1	4		1	2	11	18	6	7	98
Lateral tongue border	12		54	61	54	14	20	5	3	11	15	152	21	61	41	127	49	700
Tongue dorsum	4		3	1	8			1	1	2		5	2	10	2	1	1	41

(Continues)

TABLE 3 (Continued)

Centre	UNICAMP	ICESP	UNESP	FOUNC-A	FOUNC-B	PC-CR	HABA	FD V	PC-LP	LH-M	PC-MX	UPCH	HSM-S	UCV	UFRJ	UMCH	UDELAR	
Country	BR	BR	BR	AR	AR	CR	AR	CH	AR	AR	MX	PE	AR	VE	BR	CH	UR	Total
Ventral tongue	4		10	2	7	3	2		1	1		16	5	15	4	10	3	83
Tongue, non-specified		40	8	2	3							1	2	67		5	16	144
Buccal mucosa	5	6	12	10	17	6	6	2		4	2	53	27	56	15	35	32	288
Buccal mucosa and vestibulus	2		4		1	3		3		1		1	3	17	1	7		43
Oral mucosa, non specified			9			1	1			1			4	1		8	3	28
Oral soft palate	2	9	3	2	14	1	2			1		11		20		5	14	89
Hard palate	4	9	4		5	3	1	1		3		25	1	39	2	8	13	120
Palate non specified		7		3	3								1	28	3	6	4	55
Floor of the tongue	18	11	41	11	30	3	2	1	2	3		96	15	65	23	31	26	377

Abbreviations: Ac. OSCC, Acantholytic oral squamous cell carcinoma; AR, Argentina; Ba-OSCC, Basaloid oral squamous cell carcinoma; BR, Brazil; CC-OSCC, Clear Cell oral squamous cell carcinoma; CH, Chile; CR, Costa Rica; FD V, Oral Pathology Diagnostic Center, Faculty of Dentistry, Facultad de Odontología, Universidad de Valparaíso; FOUNC-A, Oral Medicine Department A, Facultad de Odontología Universidad Nacional de Córdoba, Argentina; FOUNC-B, Oral Medicine Department B, Facultad de Odontologia, Universidad Nacional de Córdoba, Argentina; HABA, Oral Medicine Department, Hospital Aleman, Buenos Aires, Argentina; HSM-S, Stomatology Service, Señor del Milagro Hospital, Salta, Argentina; ICESP, Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, Fundação da Faculdade de Medicina da Universidade de SãoPaulo (FMUSP), São Paulo, Brazil; In situ Carcin, In situ Carcinoma; LH-M, Lagomaggiore Hospital, Mendoza, Argentina; MD, moderately differentiated; Mic OSCC, Microinvasive Oral squamous cell carcinoma; MX, Mexico; OSCC, Oral squamous cell carcinoma; Pa-OSCC, Papilar Oral squamous cell carcinoma; PC-CR, Private Centre, Costa Rica; PC-LP, Private Centre, La Plata, Argentina; PC México, Private Centre Mexico FD, Mexico; PE, Peru; UCV, Oral Pathology Department, Universidad Central de Venezuela, Caracas, Venezuela; SC-OSCC, Spindle Cell oral squamous cell carcinoma; U, undifferentiated; UDELAR, Oral Pathology Department, Facultad de Odontología, Universidad de la República, Montevideo, Uruguay; UFRJ, Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro; UMCH, Oral Pathology Department, Facultad de Odontología, Universidad Mayor de Chile, Santiago de Chile, Chile; UNESP, Department of Bioscience and Oral Diagnosis, Institute of Science and Technology, UNESP-SJC-São Paulo-Brazil; UNICAMP, Oral Diagnosis Department Piracicaba Dental School, State University of Campinas, Brazil; UPCH, Facultad de Estomatología Peruana Cayetano Heredia, Lima Perú; UR, Uruguay; VC, Verrucous Carcinoma; VE, Venezuela; WD, well-differentiated.

Argentina and Sao Paulo, Brazil). Two centres reported the frequency of OPMD based on histopathological databases, reporting as s-OSCC those cases where the same patient presented separate reports with diagnoses of OPMD and OSCC. In these two centres, the frequency of OPMD was significantly lower than in the rest of the participating centres. Excluding these two centres, out of 2237 OSCCs, the frequency of OSCC-dn was 78.2% and that of s-OSCC was 21.8%. The most frequent OPMD was homogeneous leukoplakia ($n=212$; 42.23%), followed by erythroleukoplakia (non-homogeneous leukoplakia) ($n=65$; 12.94%), oral lichen planus ($n=63$; 12.54%), actinic cheilitis ($n=53$; 10.55%) and multifocal proliferative leukoplakia ($n=52$;10.35%), erythroplakia ($n=33$; 6.57%), lichenoid lesions ($n=14$; 2.78%), palatal lesions in reverse smokers ($n=4$; 0.79%) and lupus erythematous ($n=2$; 0.40%). OPMD subtype could not be established in four cases (0.79%). In 87% ($n=409$) of cases, OSCC coincided with the OPMD site, whereas in the remaining 19% ($n=59$) of cases, OSCC developed away from the OSCC site. Concerning this variable, data were not obtained from 34 patients.

Table 5 shows the differences according to OSCC-dn and s-OSCC status with demographic, clinical and histopathological features. While age and gender did not have statistically significant differences according to the OSCC subtype (showing a marked similarity in their proportions), histopathological diagnosis, the degree of cell differentiation, tumour epicentre and sites, yielded statistically significant differences. The histopathological diagnosis (subclassified in OSCC, ICS, VC and other OSCC subtypes) and the degree of cell differentiation presented with statistical significance according to the OSCC subtype ($p<0.0001$; $p=0.0101$ respectively).

OSCC-dn had a mostly unicentric tumour epicentre in relation to s-OSCC with statistically significant differences (OR = 2.74 CI 2–3.75; $p<0.0001$). Tumour location revealed statistically significant differences according to OSCC-dn and s-OSCC ($p<0.0001$). For both OSCC-dn and s-OSCC, the most frequent sites were tongue and gingiva, although with different percentages. Then, the floor of the mouth and buccal mucosa for OSCC-dn and buccal mucosa and floor of the mouth for s-OSCC. Lip vermilion SCC was the location most frequently associated with OPMD (s-OSCC) (Table 5).

4 | DISCUSSION

Based on the available evidence, this is the first multicentre collaborative study of OSCC diagnosed in universities, private centres and Hospital diagnostic centres from Latin America, including clinicopathological characterization and linkage with its origin (associated with OPMD or de novo). In the study by Curado et al. (2016), describing the epidemiological characteristics of OSCC in South America, data were obtained from Cancer Incidence in Five Continent Publication, IARC for the period 1998–2007 (Curado et al., 2016). These studies showed that records in Latin America are incomplete with underreporting and missing data. This is not a minor issue since most of the OSCC preventive strategies are based on foreign experiences. Consequently, this could lead to the performing of preventive actions that are not adequately focused on the specific OSCC characteristics of Latin America. Therefore, this study could be useful for adapting and designing novel preventive strategies in this continent.

This study showed that the distribution of OSCC according to the age was homogeneous among the different recruitment centres and similar to what is known in current literature (higher frequency in the sixth decade). However, the distribution by gender was variable, although close to 1:1 in the total group. The data from Venezuela, Peru, Costa Rica and Chile showed a higher frequency of the female gender. Authors from these participating centres argued that these rates could reflect a strong interest in medical attention seeking in their oral health by women in reference to the male gender. Healthcare-seeking behaviour is influenced by different features, such as gender, age, knowledge of illness prevention and others (Thompson et al., 2016). However, healthcare-seeking behaviour was not conditioned by gender in other geographical regions (Rath et al., 2018). Interestingly, the Venezuelan cohort showed a peculiar characteristic of OSCC for this population, due to the development of palatal lesions in reverse smokers, almost exclusive to the female gender (Quigley et al., 1964). Nevertheless, the researchers of these centres do not consider that this condition is the key factor behind the higher frequency of OSCC among females. Some European studies described similar results in terms of regional variation across Europe and the frequency of OSCC in the female gender. This situation occurs in Denmark, probably associated with an increase in tobacco consumption among females (Diz et al., 2017). A recent study showed that since 1990, OSCC has been increasing in elderly subjects in France, particularly in women (72%) but alcohol and tobacco consumption alone does not seem to explain this increase (Renou et al., 2023). Figure 2 shows a case of OSCC-dn in a young woman from Costa Rica without tobacco or alcohol consumption. On the contrast, data obtained by Brazilian centres offered an OSCC frequency strongly linked to the male gender and heavy tobacco consumption, and this scenario was also reported in previous studies from that country (Kuze et al., 2021; Pires et al., 2013). These trends are in agreement with the records obtained in areas where there is a higher frequency of OSCC worldwide, such as Southeast Asia (Choi & Thomson, 2019; Gilyoma et al., 2015; Singh et al., 2015).

Due to the retrospective nature, only OSCC traditional risk factors were included in this study. Although there were centres where tobacco and alcohol consumption were highly reported, less than half of the included population were smokers or drinkers. These results would not equally explain the development of all OSCCs per se. Following recent findings, there would be other less-studied risk factors (Renou et al., 2023). Among them, oral dysbiosis, Candida spp and HPV infection, chronic mechanical irritation, oxidant diets and others (Gall et al., 2013; La Rosa et al., 2020; Piemonte et al., 2022; Sánchez et al., 2003) are accepted as non-canonical risk factors for OSCC. The influence of particular lifestyles of each geography on the risk factors for OSCC is a phenomenon also reported in South

TABLE 4 OPMD associated with s-OSCC grouped by collaborative centre.

Centre	UNICAMP	ICESP	UNESP	FOUNC-A	FOUNC-B	PC-CR	HABA	FD V
Country	BR	BR	BR	AR	AR	CR	AR	CH
OPMD (%)								
No	27 (38)	81 (78)	205 (96)	52 (48)	122 (73)	31 (58)	28 (70)	3 (20)
Yes	43 (62)	22 (22)	9 (4)	56 (52)	45 (27)	22 (42)	12 (30)	12 (80)
OPMD diagnosis								
EL	4	3		6				5
Erythroplakia	3	10		5		5		
Leukoplakia	20	6		22	9	9	1	7
PVL	4	3		18	9	3		
OLP				3	13	2	11	
OLL					10			
AC	12		9	2	4	3		
PLRS								
LE								
No data								
Not applicable	27	81	205	52	122	31	28	3
Coincidence of OSCC with OPMD								
No	8	9	0	13	3	3	0	0
Yes	35	13	9	43	37	19	12	12
Without data	0	0	0	0	5	0	0	0
Not applicable	27	81	205	52	122	31	28	3

Abbreviations: AR, Argentina; BR, Brazil; CH, Chile; CR, Costa Rica; EL, erythroluekoplakia; FD V, Oral Pathology Diagnostic Center, Faculty of Dentistry, Facultad de Odontología, Universidad de Valparaíso; FOUNC-A, Oral Medicine Department A, Facultad de Odontología Universidad Nacional de Córdoba, Argentina; FOUNC-B, Oral Medicine Department B, Facultad de Odontologia, Universidad Nacional de Córdoba, Argentina; HABA, Oral Medicine Department, Hospital Aleman, Buenos Aires, Argentina; HSM-S, Stomatology Service, Señor del Milagro Hospital, Salta, Argentina; ICESP, Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, Fundação da Faculdade de Medicina da Universidade de SãoPaulo (FMUSP), São Paulo, Brazil; LE, lupus erythematosus; LH-M, Lagomaggiore Hospital, Mendoza, Argentina; MX, Mexico; OLL, oral lichenoid lesions; OLP, oral lichen planus; OPMD, oral potentially malignant disorders; PC-CR, Private Centre, Costa Rica; PC-LP, Private Centre, La Plata, Argentina; PC México, Private Centre Mexico FD, Mexico; PE, Peru; PLRS, Palatal lesions in reverse smokers; PVL, proliferative verrucous leukoplakia; UCV, Oral Pathology Department, Universidad Central de Venezuela, Caracas, Venezuela; UDELAR, Oral Pathology Department, Facultad de Odontología, Universidad de la República, Montevideo, Uruguay; UFRJ, Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro; UMCH, Oral Pathology Department, Facultad de Odontología, Universidad Mayor de Chile, Santiago de Chile, Chile; UNESP, Department of Bioscience and Oral Diagnosis, Institute of Science and Technology, UNESP-SJC-São Paulo-Brazil; UNICAMP, Oral Diagnosis Department Piracicaba Dental School, State University of Campinas, Brazil; UPCH, Facultad de Estomatología Peruana Cayetano Heredia, Lima Perú; UR, Uruguay; VE, Venezuela.

America. For instance, there are peculiar habits of inverted smoking in Venezuela and Colombia, which results in a very aggressive condition, the so-called palatal lesions in reverse smokers (Alvarez Gómez et al., 2008), which is considered an OPMD by the last WHO consensus (Warnakulasuriya et al., 2020). Figure 3a shows a case of OSCC of the palate associated with palatal keratosis in a patient with a reverse smoking habit from Venezuela. Other factors could be co-associated with OSCC, such as diets low in fruits and vegetables and high in the consumption of roasted red meat in Argentina (Secchi et al., 2015). The chewing of coca leaves is a particular habit in some regions of northern Argentina (Salta), Peru and Bolivia (Molina Ávila et al., 2020, 2022); with comparable characteristics to the well-known habit of betel chewing and the prevalence of cancer of the gingivobuccal complex in Southeast Asia. Figure 3b shows a case of OSCC located on the buccal mucosa from Salta, Argentina, without classical risk factors, who chewed coca leaves for more than 6 h a day.

Several Latin American areas (Argentina, Chile, Mexico, Brazil and Colombia) present a strongly increased level of arsenic in water due to geological, mining and agricultural contamination (Bundschuh et al., 2021). Some studies have shown that drinking water with a high arsenic content could co-contribute to oral carcinogenesis (Carrica, 2006; Guber et al., 2021). Interestingly, these findings were also validated by other groups, which showed the highest rates of OSCC in geographical regions (such as Antofagasta, Chile) possibly influenced by environmental factors of arsenic water contamination (Candia et al., 2018; Leonardi et al., 2020). Additionally, mate is a hot beverage frequently consumed by American populations (Uruguay,

PC-LP AR	LH-M AR	PC-MX MX	UPCH PE	HSM-S AR	UCV VE	UFRJ BR	UMCH CH	UDELAR UR	Total
10 (77)	5 (16)	11 (52)	481 (89)	81 (74)	466 (92)	78 (62)	273 (81)	249 (98)	2203 (81.4)
3 (23)	26 (84)	10 (48)	59 (11)	28 (26)	40 (8)	47 (38)	63 (19)	5 (2)	502 (18.6)
	1	5	25		1	10	5		65
	1				6		3		33
	12	5	22	14	13	23	45	4	212
			9	4	1		1		52
3	6		3	9	10		2	1	63
							4		14
	3			1	3	14	2		53
					4				4
					2				2
	3						1		4
10	5	11	481	81	466	78	273	249	2205
0	3	6	0	0	8	3	3	0	59
3	18	4	50	28	32	44	50	0	409
0	5	0	9	0	0	0	10	5	34
10	5	11	481	81	466	78	273	249	1737

Argentina, southern Brazil and Paraguay). According to published data, mate consumption increased the risk of occurrence of upper aerodigestive tract cancer, including oral cancer (Mello et al., 2018). Interestingly, these carcinogenic effects could interact with smoking and drinking, increasing the risk of OSCC through the combination of hot temperature and chemical composition (Deneo-Pellegrini et al., 2013). Accordingly, all of these factors distinctive of Latin America, with a scarce presentation in other regions, could also modify the clinicopathological, epidemiological and pathogenic landscapes of OSCC and its precursor lesions. Future studies should also incorporate the analysis of these non-canonical risk factors that are particular from Latin America.

Conventional OSCC was the most frequent diagnosis and this is in accordance with current literature, while the frequency of VC was approximately 5%, data also consistent with other studies (frequency of 2%–12%) (Koch et al., 2001). However, these rates could be different because 20% of VC coexist with invasive foci within OSCC (Medina et al., 1984). Considering the other histological subtypes of OSCC, few studies report them. Therefore, it is difficult to compare it with similar databases, establishing extremely rare histological variables with similar behaviour to conventional OSCC (Takenaka et al., 2023).

In this study, the tongue was the most frequent site of s-OSCC and OSCC-dn, according to what is usually reported in the literature (Dantas et al., 2003). However, the high prevalence of gingival cancer found in this study is noticeable, with this location being the second in order of frequency (close to tongue-OSCC proportions). Gingival OSCC increased in recent years, especially related to non-smoker females (Sundermann et al., 2018).

TABLE 5 Differences between OSCC-dn and s-OSCC.

Variable	OSCC-dn (%)	s-OSCC (%)	OR	95% CI	*p*-value
Total *N*	2203 (81.4%)	502 (18.6%)			
Age					
Media (SD)	62.76 (15.13)	62.86 (14.30)			0.88
Range	8–103	22–99			
Sex					
Female	955 (43%)	241 (48%)	1.21	0.99–1.47	0.0579
Male	1248 (57%)	261 (52%)			
Histopathological diagnosis					
OSCC	2050 (93%)	425 (84.6%)			**<0.0001**
In situ carcinoma	57 (2.5%)	41 (8.2%)			
Verrucous carcinoma	81 (3.6%)	34 (6.8%)			
Other histological variants	15 (0.8%)	2 (0.4%)			
Cell differentiation degree[a]					
Well-differentiated	941 (64.7%)	128 (57.4%)			**0.0101**
Moderately differentiated	395 (27.2%)	82 (36.8%)			
Undifferentiated	118 (8.1%)	13 (5.8%)			
Tumoral epicentre[b]					
Unicentric	1495 (93%)	362 (82.8%)	2.74	2.00–3.75	**<0.0001**
Multicentric	113 (7%)	75 (17.2%)			
Location[c]			dn:s		
Lip, vermillion	35 (1.66%)	63 (12.54%)	0.55:1		**<0.0001**
Lip, mucosa	52 (2.5%)	30 (5.97%)	1.73:1		
Tongue	706 (33.6%)	203 (40.43%)	3.47:1		
Buccal mucosa	238 (11.32%)	57 (11.35%)	4.17:1		
Palate	172 (8.1%)	32 (6.37%)	5.37:1		
Floor of the mouth	283 (13.55%)	47 (9.38%)	6.02:1		
Gingiva and alveolar ridge	591 (28.13%)	70 (13.98%)	8.44:1		
Non-specified	24 (1.14%)	0 (0%)	-		
Total	2101	502	4.18:1		
Multiple anatomical involvements					
No	2099 (95.3%)	470 (93.6%)	1.37	0.92–2.06	0.1260
Yes	104 (4.7%)	32 (6.4%)			
Tobacco consumption[b]					
No	689 (55.3%)	206 (49%)	1.29	1.03–1.61	**0.0253**
Yes	556 (44.7%)	214 (51%)			
Alcohol consumption[b]					
No	736 (63%)	225 (58%)	1.25	0.99–1.58	0.0628
Yes	427 (37%)	163 (42%)			

Abbreviations: CI, confidence interval; OR, odds ratio; OSCC-dn, oral squamous cell carcinoma de novo; s-OSCC, sequential oral squamous cell carcinoma; SD, standard deviation.

[a]In situ carcinoma, microinvasive carcinoma, verrucous carcinoma and others histological variants were not included for the obtention of this data.

[b]There were not included cases without data.

[c]There were included only cases of OSCC affecting one anatomical location.

The diversity of OSCC anatomical involvement is another phenomenon that reflects how particular risk factors are in Latin America. As previously described, patients from Venezuela represent the group with the highest incidence of palate cancer, probably due to inverted tobacco consumption and the presentation of inverted smoking keratosis as OPMD. The patients included

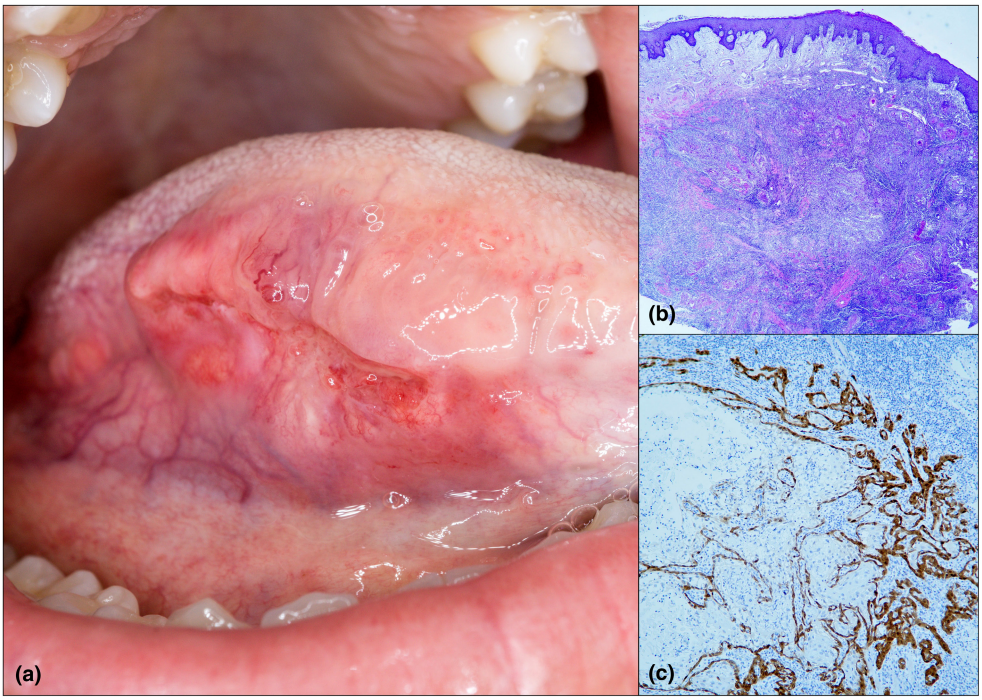

FIGURE 2 (a) A non-smoker, non-drinker female with OSCC on the right lateral border of the tongue, showing extensive central ulceration associated with chronic trauma. (b) Photomicrograph—hematoxylin/eosin staining demonstrating marked invasion by neoplastic cells generating a significant inflammatory response and atrophy of the muscle fibres of the tongue. (c) Photomicrograph—continuous nuclear and cytoplasmic positivity for the p16 marker in invading neoplastic cells. Courtesy of Professor Roberto Gerber Mora (Costa Rica). OSCC, oral squamous cell carcinoma.

in Salta, Argentina had the lowest consumption of tobacco and alcohol (<30%). In this population, which is characterized by a high frequency of coca chewing, the most frequent site was the buccal mucosa (Figure 3b).

One of the novelties of this original study is the OSCC background, considering that of the 2705 cases included, about 80% corresponded to OSCC-dn, while 20% were s-OSCC. There are relatively few works (without original studies from Latin America) that report the proportion of OSCC and its association with OPMD. In the study by Pires et al. (2013), on a cohort from Brazil, the clinical phenotype of the lesions was studied (without considering an accurate OPMD diagnosis). Interestingly, they found that about 30% of OSCCs were associated with precursor leukoerythroplastic areas (Pires et al., 2013). Consistent with the reviewed literature, this study would be the first regional research to include clinical variables that defined s-OSCC and all OPMDs categories recognized by WHO. Most of the studies comparing s-OSCC and OSCC-dn include only one subtype of OPMD such as leukoplakia or erythroplakia (Bouckaert et al., 2016; Haya-Fernández et al., 2004; Scheifele & Reichart, 1998).

The noticeable frequency of OSCC-dn, and consequently, the low proportion of s-OSCC, is consistent with previous studies (Haya-Fernández et al., 2004). However, the high proportion of OSCC-dn and the high heterogeneity in the frequencies according to the diagnosis centres could be explained by several reasons: underreported OPMDs, loss of evidence of an OPMD in advanced-OSCC, decrease in the frequency of s-OSCC due to better control of OPMD and its follow-up, development of OSCC arising from clinically healthy mucosa or the existence of potential underrecognized lesions that are not catalogued by the WHO as OPMD. For instance, two collaborative centres, where the main source of data was histopathological databases, showed the highest frequency of OSCC-dn (98%). A similar scenario was previously identified in other studies where the source of data was also retrieved from two oral pathology diagnostic services and hospital pathology databases. Of 10,987 cancer cases, 378 (3.44%) had a preceding OPMD (McCord et al., 2021). The very low number of s-OSCC would not be reflecting the reality of these patients, since there is a great discrepancy with what is known in the literature where the number of s-OSCC is estimated to be higher. Furthermore, it is possible that the available histopathological samples taken by biopsy procedures revealed proven OSCC without including OPMD areas. The ideal practice to record the frequency of s-OSCC would be the standardized biopsy of the suspected OSCC composed with areas of supposed OPMD, whether they are adjacent to the OSCC or in other anatomical locations.

Moreover, it is possible that due to the increase in size, many s-OSCC can alter their clinical presentation precluding proper visualization of the precursor OPMD, except in cases where OSCC are associated with multicentric OPMD. In these cases, white plaques or reticular patterns are usually seen in other parts of the oral mucosa. Therefore, advanced s-OSCC associated with a unifocal pattern of OPMDs may have been misclassified as OSCC-dn. Interestingly, in

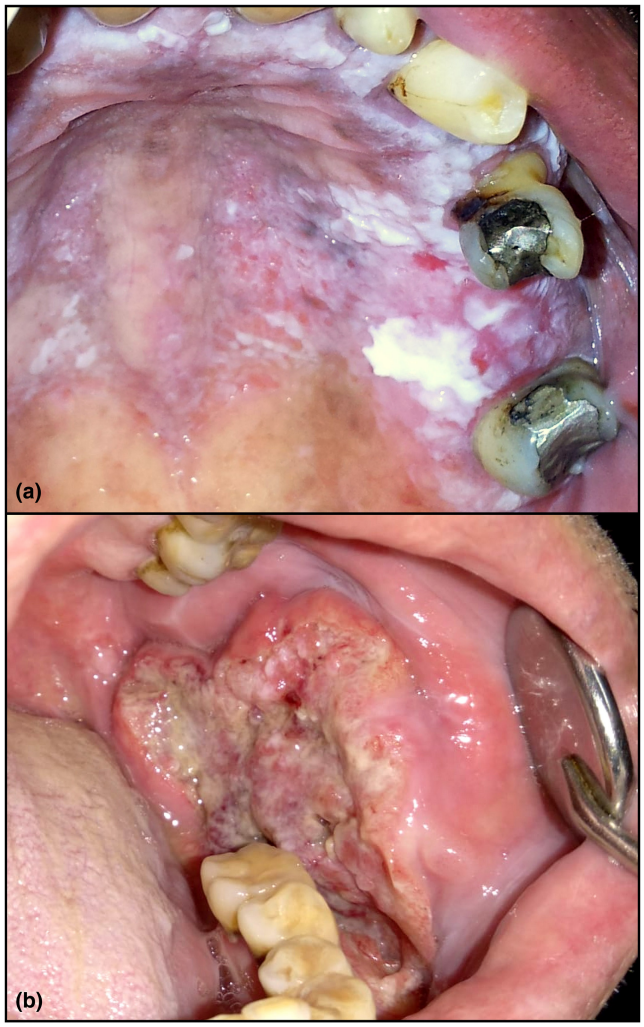

FIGURE 3 (a) OSCC of the palate in a female patient with reversed smoking from Venezuela. OSCC developed in the context of multiple white and red plaques with an erythroplastic appearance (palatal keratosis associated with reverse smoking, considered an OPMD by the 2020 WHO Consensus). Courtesy of Professor Mariana Villarroel-Dorrego (Venezuela). (b) Male patient with OSCC of the buccal mucosa and gingivobuccal complex. The patient from Salta, Argentina was a non-smoker and non-drinker with the habit of '*coqueo*' (chewing coca leaves mixed with bicarbonate and ash particles for more than 6 h a day for more than 20 years). Courtesy of Dr Ignacio Molina Avila and Dr Juan Pimentel Sola (Argentina). OSCC, oral squamous cell carcinoma.

a Brazilian cohort, about 30% of OSCC showed leukoerythroplakic areas, when the tumor sizes were predominantly T1 and T2 (Pires et al., 2013). These data, added to those obtained in the present study, showed that even in the early stages, and considering some biases in the registry, OSCC-dn would be more frequent than s-OSCC.

Several strategies are used to decrease OSCC diagnosis delays, such as screening and control of OPMD (Warnakulasuriya & Kerr, 2021). Similarly, OPMD detection allows the identification of high-risk patients (Bouvard et al., 2022), including them in interventional and monitoring programs that have proven to be effective (Warnakulasuriya & Kerr, 2021). Consequently, OPMD may not develop into OSCC as a consequence of proper management of such precursor lesions (Awadallah et al., 2018). There are many campaigns for early diagnosis of OPMD and OSCC throughout Latin America (e.g. *Saca la lengua al cancer*) (Linares et al., 2023; Morelatto et al., 2022). These actions allow the early detection of OPMD and subsequently reduce the likelihood of s-OSCC. OSCC-dn, lacking previous OPMD, would not be included in these preventive actions, making early diagnosis difficult. This aspect should be fully addressed with future studies that identify the profile of the patient with OSCC-dn and consequently, their identification to achieve early diagnoses.

In the analysis of OSCC-dn versus s-OSCC offered in Table 5, the degree of cell differentiation, histopathological diagnosis, tumour epicentre, location and tobacco use were variables that showed statistically significant differences. Previous studies have established that OSCC-dn histologically presents a lower degree of cell differentiation than s-OSCC and consequently a worse prognosis. This data is different from what was found in this study. This could be because, in most centres, the specimens analysed were obtained from incisional (diagnostic) biopsies and not from the surgical resection specimen, leading to the analysis of only one sector. In addition to being molecularly heterogeneous, OSCC displays heterogeneity concerning cell populations, including transit-amplifying cancer cells, mitotic cancer cells at different stages of maturation and de-differentiated cancer cells. All of these contribute to the phenotypic heterogeneity of OSCC (Feller et al., 2010, 2023).

The location of OSCC according to its categorization in s-OSCC and OSCC-dn had different ratios depending on the anatomical region. Due to the marked frequency of OSCC-dn, these tumours were more frequent in all anatomical sites with large ratios in the tongue, buccal mucosa, palate and floor of the mouth. However, the ratio of 8.44:1 in favour of gingival OSCC-dn is an outstanding finding, possibly explained by chronic inflammation and periodontal disease (Sarkar et al., 2021). Recent literature reported that microorganisms play an important role in oral carcinogenesis through various biological mechanisms leading to a permanent cellular change and progression to cancer (Lafuente Ibáñez de Mendoza et al., 2020). The persistent inflammatory response may result in oncogene alterations increasing the risk of MT (Kavarthapu & Gurumoorthy, 2021). These data advocate for the role of chronic inflammation in the oral carcinogenesis of OSCC-dn. The second most frequent site of s-OSCC was also gingiva, and this phenomenon could be associated with the high frequency of gingival cancer in PVL (Bagan et al., 2003) (Figure 4). In contrast, lip vermilion cancer was the malignancy with the highest frequency of s-OSCC (64.3%), being actinic keratosis or cheilitis the most frequent OPMD. The separate statistical analysis of lip carcinomas from intraoral SCC is significant since it allowed us to establish a different cancer profile with a high association with other precursor conditions and risk factors such as actinic damage that are specific to lips. These results are consistent with a previous Brazilian study. They found histopathological findings of actinic cheilitis and solar elastosis adjacent to lip SCC in 61.3% of the cases (Abreu et al., 2006).

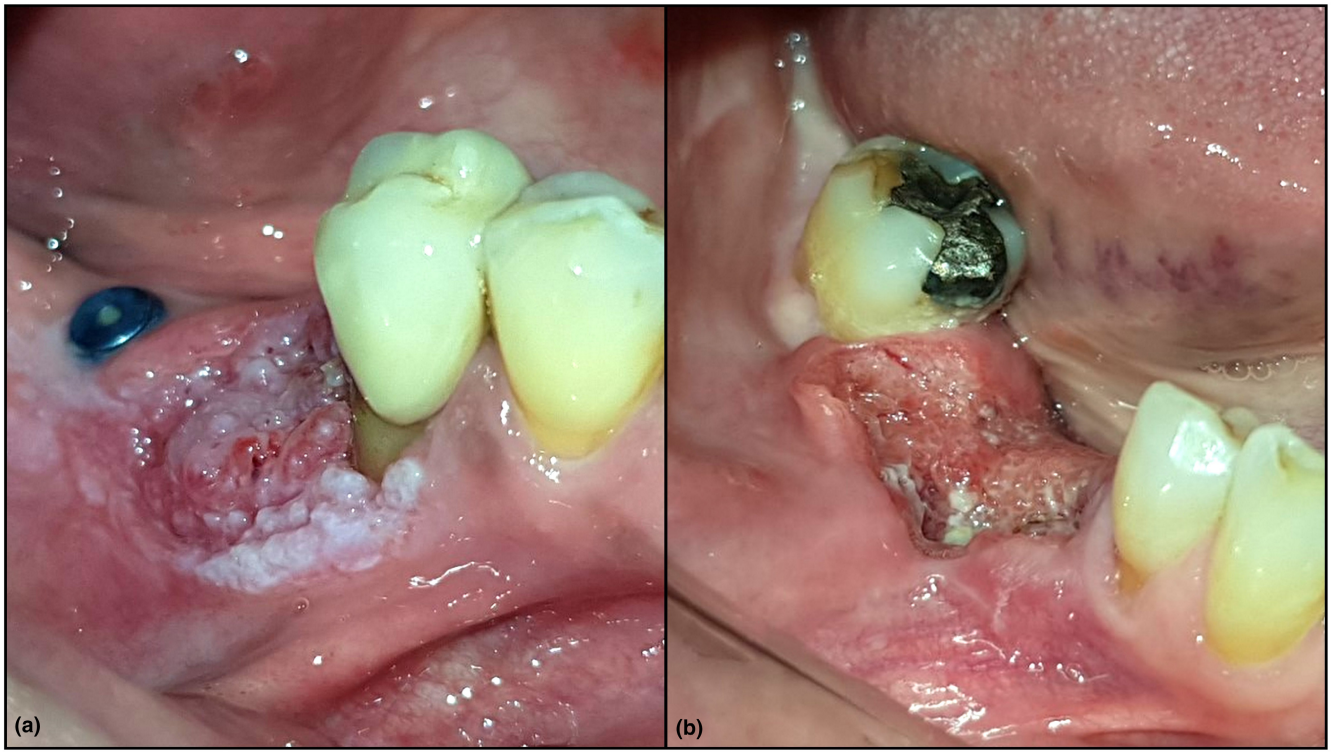

FIGURE 4 (a) Gingival s-OSCC in a heavy smoker male with a previous diagnosis of Proliferative Verrucous Leukoplakia. The patient developed a warty lesion in the context of a large white plaque located on the alveolar ridge and gingiva. An incisional biopsy revealed a moderately differentiated OSCC. The lesion was diagnosed 5 months after the placement of a dental implant in the affected area. Courtesy of Dr Rene Panico. (b) Gingival OSCC-dn in an elderly woman with no risk factors. The lesion was presented clinically as a non-healing chronic ulcer without OPMD. The patient suffered from advanced periodontal disease. Courtesy of Dr Gerardo Gilligan. OSCC, oral squamous cell carcinoma.

Data addressing s-OSCC development in the same anatomical region as its precursor lesion or distant from it is not commonly found in current literature. In this study, 87% of the s-OSCC arose from its adjacent OPMD and 13% of s-OSCC did not coincide with the anatomical region of the OPMD. This data highlights that these malignancies presented with a greater chance of having a multifocal pattern with different tumour epicentres than OSCC-dn, possibly associated with the field cancerization phenomenon (Slaughter et al., 1953). In these cases, some OPMD are specifically involved such as OLP, PVL or PVL with lichenoid features (Gilligan et al., 2020; Lopes et al., 2015; Thomson et al., 2018).

4.1 | Limitations

Our results showed in some cases heterogeneous data highlighting regional differences. These types of limitations associated with geographical differences within the same continent were also observed in European multicentre studies and would be particularities of multicentre studies involving many countries. This limitation is also associated with the inclusion of collaborative centres that extracted their data from databases with purely histopathological information. Thus, many of the included clinical variables were lost.

Although there were developed different resources to reduce the sources of bias, the retrospective design of this collaborative study contributed to the heterogeneity of the data. Since not all countries have been fully addressed, with little participation from Caribbean and Central American countries and only one Mexican recruitment centre, the results of this study would not be completely extrapolated to the entire continent.

Finally, this study focused on revising only traditional risk factors such as tobacco and alcohol consumption, leaving aside many factors that condition the regional variations of the obtained data. Another variable that unfortunately could not be collected, which could have supported or explained the large proportion of OSCC-dn is tumour staging at the time of diagnosis.

5 | CONCLUSION

In Latin America, OSCC-dn seems to be more frequent than s-OSCC (80% vs. 20%). The large frequency of OSCC-dn highlights the need to redefine oral cancer prevention strategies in the Latin American population. This first multicentric collaborative study showed heterogeneity and regional variations of some characteristics of OSCC and its relationship with OPMD. The heterogeneity of these findings

suggests that further prospective studies are needed to analyse specific and non-canonical risk factors for each geographical region.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

All authors have seen and agree with the contents of the manuscript and there is no conflicts of interest to report. We certify that the submission is original work and is not under review at any other publication.

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APPENDIX A

Research ethics committees

This study was performed in accordance with the Helsinki Declaration and was approved by all research ethics committees: Comité Académico en Investigación de Ciencias de la Salud y Comité Institucional de Ética de las Investigaciones en Ciencias de la Salud, Facultad de Odontología, Universidad Nacional de Córdoba, Argentina Protocolo Number T08/16 and 31/15, Consejo de Evaluación Ética en Investigaciones en Salud, Córdoba Healthy Ministery Protocol Number 05/J094, Comité Institucional de Ética de las Investigaciones en Ciencias de la Salud Hospital Luis C. Lagomaggiiore, Mendoza, Argentina, Comité de Ética en Investigación from the Hospital Aleman, Buenos Aires, Argentina Protocol Number 6596, Comité de Ética del Hospital del Señor del Milagro, Salta, Argentina; Comitê de Ética em Pesquisa da Faculdade de Odontologia de Piracicaba,

Brazil Protocol Number 45545121.1.3002.5432; Comitê de Ética em Pesquisa—Universidade Federal do Rio de Janeiro, Brazil 727728 17.5.0000.5257, Protocol Number 2.281.838, Aprovação na Plataforma Brasil CAAE: 54715216.7.0000.0077, Unidad de Gesión Universidad Peruana Cayetano Heredia, Perú SIDISI Protocol Number 205665 and Comité de Ética from Facultad de Odontología, Universidad Central Venezuela Protocol Number CB-062-2018.

A.1. | Periods time of available data

UNICAMP: Oral Diagnosis Department Piracicaba Dental School. State University of Campinas, Brazil: 2021–2022.

ICESP: Dental Oncology Service, Instituto do Câncer do Estado de São Paulo, Fundação da Faculdade de Medicina da Universidade de SãoPaulo (FMUSP), São Paulo, Brazil: 2010–2020.

UNESP: Department of Bioscience and Oral Diagnosis, Institute of Science and Technology, UNESP-SJC-São Paulo-Brazil: 2013-2022.

FOUNC-A: Oral Medicine Department A, Facultad de Odontología Universidad Nacional de Córdoba, Argentina: 2010–2021.

FOUNC-B: Oral Medicine Department B, Facultad de Odontologia, Universidad Nacional de Córdoba, Argentina: 2003–2020.

PC-CR: Private Centre, Costa Rica: 2019–2022.

HABA: Oral Medicine Department, Hospital Aleman, Buenos Aires, Argentina: 2008–2022.

FD V: Oral Pathology Diagnostic Center, Faculty of Dentistry, Facultad de Odontología, Universidad de Valparaíso: 2004–2022.

PC-LP: Private Centre, La Plata, Argentina.

LH-M: Lagomaggiore Hospital, Mendoza, Argentina: 2017–2021.

PC México: Private Centre Mexico FD, Mexico: 2005–2022.

UPCH: Facultad de Estomatología Peruana Cayetano Heredia, Lima Perú: 2012–2022.

HSM-S: Stomatology Service, Señor del Milagro Hospital, Salta, Argentina: 2016–2021.

UCV: Oral Pathology Department, Universidad Central de Venezuela, Caracas, Venezuela: 2005–2018.

UFRJ: Department of Oral Diagnosis and Pathology, School of Dentistry, Federal University of Rio de Janeiro: 2021–2022.

UMCH: Oral Pathology Department, Facultad de Odontología, Universidad Mayor de Chile, Santiago de Chile, Chile: 2006–2021.

UDELAR: Oral Pathology Department, Facultad de Odontología, Universidad de la República, Montevideo, Uruguay: 1982–2022.