Dentistry Section

Evaluation of Salivary Lactate Dehydrogenase Level as a Biomarker for Early Detection in Oral Cancer and Potentially Malignant Disorders: A Systematic Review and Meta-analysis

ARUNIMA SARMA[1], SUNIL S MISHRA[2], SUKANYA DAS[3], HARSHAWARDHAN SAWANE[4], TRUPTI GAIKWAD[5]

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ABSTRACT

Introduction: Saliva diagnostics are emerging tools which are being explored as a non invasive method for early detection of oral premalignant lesions and Oral Cancer (OC). Salivary Lactate Dehydrogenase (LDH) is one such promising biomarker which has shown potential to be utilised in future for detection of premalignant lesions and conditions. The rationale behind this systematic review was to evaluate whether salivary LDH can be considered as biomarker for OC and Oral Potentially Malignant Disorders (OPMDs).

Aim: To review the literature for levels of salivary LDH in patients with OC and OPMD.

Materials and Methods: A comprehensive search was done and this systematic review was conducted in the Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Pimpri, Pune, Maharashtra, India, following (Preferred Reporting Items for Systematic Reviews and Meta-analyses) PRISMA guidelines. Literature search was done for the period of 10 years from 2012-2022, while the study duration was 18 months, from January 2021-July 2022. The International Prospective Register of Systematic Reviews (PROSPERO) registration Identity Document (ID) was (CRD42022366117). Electronic data was searched through the database PubMed, ScienceDirect and Cochrane Library from 2012-2022. Observational and analytical studies, original longitudinal or case-control, randomised clinical trials, prospective controlled clinical trials with the inclusion of cases diagnosed with oral leukoplakia, Oral Lichen Planus (OLP), Oral Submucous Fibrosis (OSMF), OC and having salivary LDH levels were included. The data was collected from the studies that were included based on study design, eligibility criteria, histological differentiation, collection method, LDH level and the data were subjected to meta-analysis.

Results: A total of 16 articles were included. The meta-analysis showed increased salivary LDH levels between cases with OC and Control Group (CG). The pooled estimate was 5.71 (95% CI: 3.89-7.53) with statistical significance of <0.05. In OSMF and controls the levels of salivary LDH was significantly increased. The pooled estimate was 30.38 (95% CI: 15.82-44.94) with statistical significance of <0.05. The level of salivary LDH among cases with premalignant lesions and controls was increased. The pooled estimate was 9.10 (95% CI: 3.45-14.75) with statistical significance of <0.05. In case of OLP and controls, the levels of salivary LDH were seen elevated. The pooled estimate was 6.76 (95% CI: 6.86-20.38) with no statistical significance of p-value <0.05.

Conclusion: To sum up, the results of this systematic review showed that levels of salivary LDH were higher in OC and OPMD patients than in healthy patients. Furthermore, the levels of salivary LDH are more in OC than OPMDs.

Keywords: Premalignant lesion, Saliva, Salivary bionomics, Squamous cell carcinoma

INTRODUCTION

The OC has been accounted as a concerning problem in many parts of the globe with highest incidence seen in Southeast Asia. Globally, 300,000 to 700,000 new cases are reported every year with mortality rate being 145,000 deaths [1]. Oral and pharyngeal cancer together, is considered the sixth most common cancer in the world with highest incidence seen in males than females [1]. Almost all the cases of OC are preceded by some visible changes or alterations to the oral mucosa. These alterations are in the form of either white or red lesions, with a variable risk of malignant transformation. Due to this risk, these lesions and conditions are termed as the potentially malignant disorders [2,3].

In recent times the prevalence of OPMD has increased worldwide including conditions such as OSMF, OLP which are seen most commonly in Asian population [4]. The OPMDs vary in their malignant transformation with OSMF reported to have a malignant transformation of about 4.5% to 7.6% [5]. The potential for malignant transformation is generally credited to fibrosis, hypoxia and a shift to anaerobic glycolysis [6]. The prevalence of OLP and other Oral Lichenoid Reactions (OLRs) in the general population is 1-2% and 2.4%, respectively [7]. However, sufficient data regarding malignant transformation of different types of OLRs is lacking, but it appears that different types of graft versus host disease and oral lichenoid contact lesions have higher malignant transformation risk than drug-induced OLRs [7]. As the percentage seems to be relatively high so a timely recognition of such OPMDs not only favours a decreased rate of OC but also improves the chances of survival in subjects developing OC. It has been found that the prognosis rate varies i.e. up to 80% when diagnosed at Stage-I, 65% in Stage-II and 50% when diagnosed at Stage-III or higher [8,9].

Biopsy is generally considered as a gold standard for cancer diagnosis, but the process of biopsy has few limitations such as the method is invasive, time consuming, technique sensitive, difficult in inaccessible areas, patients with blood disorders and other systemic conditions and most importantly subjective patient compliance. Pertaining to the various challenges and disadvantages of biopsy many alternatives are used for early detection of OC. One such alternative and promising technique is the use of tumour biomarkers. LDH is one of the biomarkers which is being used in the early detection of premalignant lesions and conditions. The mechanism of increase in LDH enzyme in tissues in OPMDs and OC is in glycolytic pathway which manifests as a shift from aerobic

to anaerobic glycolysis [10]. However, the levels of LDH found in the healthy oral epithelium and in whole saliva are similar [4]. Therefore, salivary LDH serves as early promising tool in the diagnosis of OC at its preliminary stage by acting as a diagnostic marker [11].

Saliva as a diagnostic tool can be used in the diagnosis and screening of OPMDs and OC, yet its routine usage is lacking. More studies are required to establish its correlation as biomarkers for early detection of OC. The rationale behind this systematic review was to evaluate whether salivary LDH can be considered as biomarker for OC and OPMDs.

Objectives
To review the literature for levels of salivary LDH in patients with OC and OPMD

PICO
- Patient population: Patients with oral leukoplakia, OLP, OSMF, OC
- Intervention: Salivary LDH level
- Outcome: Potential biomarker for early diagnosis of OC and OPMDs.

MATERIALS AND METHODS
A comprehensive search was done and this systematic review was conducted in the Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Pimpri, Pune, Maharashtra, India, following PRISMA guidelines. The present systematic review was prepared by following PRISMA guidelines [Table/Fig-1]. Literature search was done for the period of 10 years from 2012-2022, while the study duration was 18 months, from January 2021-July 2022. The systematic review was registered before commencing the study with (PROSPERO registration id CRD42022366117).

[Table/Fig-1]: PRISMA flowchart.
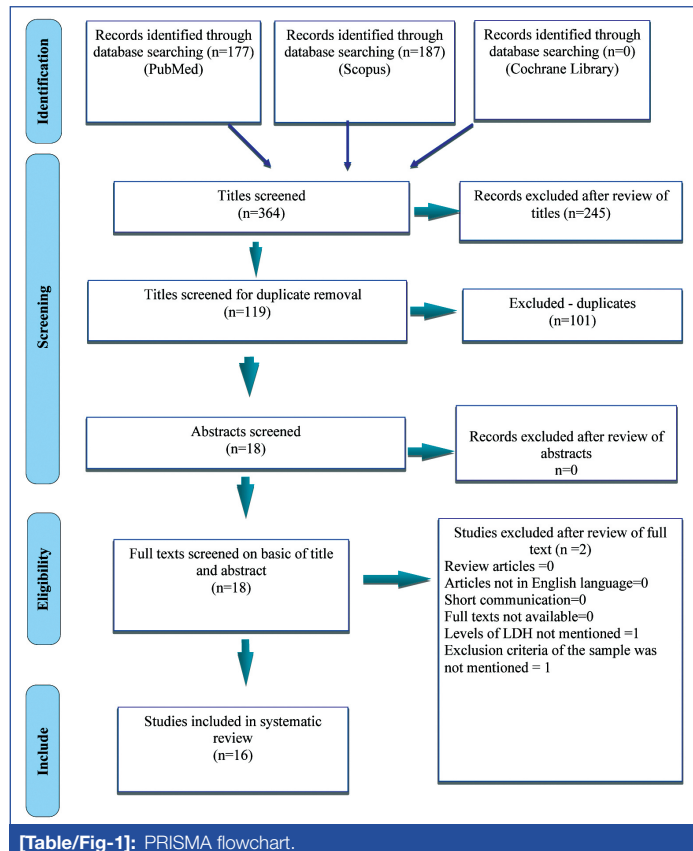
Inclusion criteria: Observational and analytical studies, original longitudinal or case-control studies published in scientific journals between 2012-2022 were included. Studies done to assess the Salivary LDH levels in patients with OC or OPMD when compared to a healthy CG, studies in English or studies in other languages where translation to English was possible and studies using Unstimulated Whole Saliva (UWS) or Stimulated Whole Saliva (SWS), which could be used to detect salivary LDH levels which must be presented in IU/L or μ/L units and could be analysed by spectrophotometers, autoanalysers, semi-autoanalysers, and standardised kits, were included.

Exclusion criteria: Review articles, animal studies, case reports, commentaries, and letters to the editor. Studies that did not have full text, different languages and studies, where in patients have been treated for OC or OPMDs and studies in which salivary LDH values were not reported, were excluded.

Information sources: Electronic data was searched through the database PubMed, ScienceDirect and Cochrane Library from 2012-2022. Manual electronic search was done and articles were handpicked. Language barriers such as English were applied. All electronic strategies had similar title/abstract and MeSH terms and texts. Search terms for PubMed were: "Leukoplakias Oral", "Oral Submucous Fibrosis" and "Mouth Neoplasm".

Data collection: The data was collected from the studies that were included based on the author's name, study design, eligibility criteria, age, histological differentiation, collection method, LDH level. Two independent authors screened the initial titles and abstracts to find all the eligible studies. All differences of opinions were discussed and resolved.

Study selection and data extraction: The data was extracted based on the eligibility criteria by two independent authors after assessing the titles and abstracts of potential studies identified by the search strategy. After obtaining the full texts of the articles they were screened by reading the whole article by the first author. Whenever there was uncertainty regarding any study to be eligible for inclusion, the problem was resolved by discussing it with the second author.

Assessment of bias in included studies: Newcastle-Ottawa scale modified for cross-sectional analytical studies was used to assess appropriateness of research design, recruitment strategy, response rate, representativeness of sample, objectivity/reliability of outcome determination, power calculation provided, and appropriate statistical analysis [12]. This tool consists of three domains namely, selection, comparability and outcome assessment. Maximum score of nine could be assigned to each study. According to this tool, a score of >7 implies good quality, score 5-6 implies moderate quality and score <4 implies poor quality [Table/Fig-2] [4-7,9,11,13-22]. Among the sixteen included studies, six studies showed good quality (score of >7), nine showed moderate quality (score of 5-6) and one study showed poor quality (score <4). In the selection domain, all the studies included population that truly represented the target population. A validated measurement tool (Newcastle-Ottawa scale) was used for ascertainment of exposure in five studies [7,11,12,15,21].

RESULTS
After screening the studies for 364 titles, 245 studies were excluded. The abstract of the remaining 18 articles was included for the full text review. After reading full text articles, two articles were excluded. Total of 16 articles were included for analysis. All the studies were cross-sectional analytical studies published between 2012-2022. Among all the studies, there was no mention of age group in three of the 16 selected studies [11,13,14].

Nine studies evaluated salivary LDH levels between cases with OC and CG [5,7,11,14,15,17,19-21]. The pooled estimate was 5.71 (95% CI 3.89-7.53). The cumulative difference between case and CG was 5.7, implying that salivary LDH levels were more in case group as compared to controls. Random effects model was used because I^2 indicates heterogeneity >50%. These results were

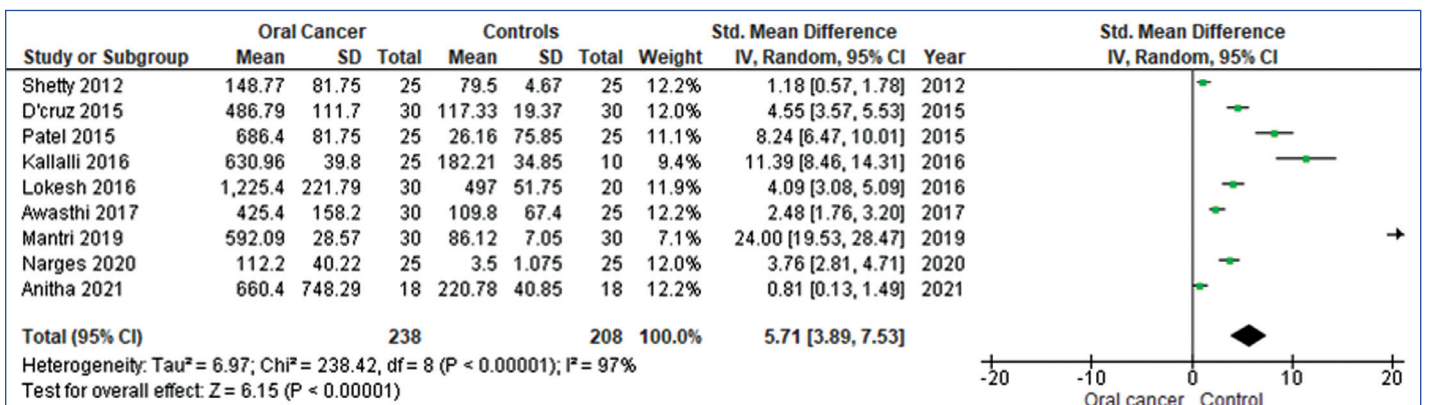| Author and year of the study	Selection				Comparability		Outcome		Total score	Quality
	Representativeness of sample	Sample size	Non responders	Ascertainment of exposure	Main factor	Additional factor	Assessment of outcome	Statistical test		
1. Shetty SR et al., 2012 [19]	*	-	-	*	*	-	**	*	6	Moderate
2.. Joshi PS and Golgire S, 2014 [16]	*	-	*	*	*	-	*	*	6	Moderate
3.. Sivaramakrishnan M et al., 2014 [6]	*	-	*	*	*	-	**	*	7	Good
4. D'Cruz AM and Pathiyil V 2015 [14]	*	-	-	*	*	-	*	*	5	Moderate
5. Patel S and Metgud R, 2015 [11]	*	-	*	**	*	-	*	*	7	Good
6. Lokesh K et al., 2016 [15]	*	-	*	**	*	-	*	*	7	Good
7. Kallalli BN et al., 2016 [5]	*	-	*	*	*	-	*	*	6	Moderate
8. Awasthi N, 2018 [20]	*	-	-	*	-	-	*	*	4	Poor
9. Mishra S et al., 2018 [9]	*	-	*	*	*	-	*	*	5	Moderate
10. Mantri T et al., 2019 [17]	*	-	*	*	*	-	*	*	6	Moderate
11. Bhuvaneswari M et al., 2020 [22]	*	-	*	*	*	-	**	*	7	Good
12. Goyal G, 2020 [13]	*	-	*	-	*	-	*	*	5	Moderate
13. Javaraiah RK et al., 2020 [18]	*	-	*	*	*	-	*	*	6	Moderate
14. Gholizadeh N et al., 2020 [7]	*	-	*	**	*	-	**	*	8	Good
15. Panda A et al., 2020 [4]	*	-	*	*	*	-	*	*	6	Moderate
16. Anitha G et al., 2022 [21]	*	-	*	**	*	-	*	*	7	Good

[Table/Fig-2]: Risk of bias according to New-Castle Ottawa tool for cross-sectional studies [4-7,9,11,13-22].
*A maximum of one star for each numbered item within the selection and exposure categories; **A maximum of two stars can be given for compatibility, a score of >7 implies good quality, score 5-6 implies moderate quality and score <4 implies poor quality

statistically significant (p-value <0.05) [Table/Fig-3]. Four studies evaluated salivary LDH levels among cases with OSMF and controls [4-6,17]. The pooled estimate was 30.38 (95% CI: 15.82-44.94). The cumulative difference between case and CG was 30.38, implying that salivary LDH levels were more in case group as compared to controls. Random effects model was used because I² >50%. These results were statistically significant (p-value <0.05) [Table/Fig-4].
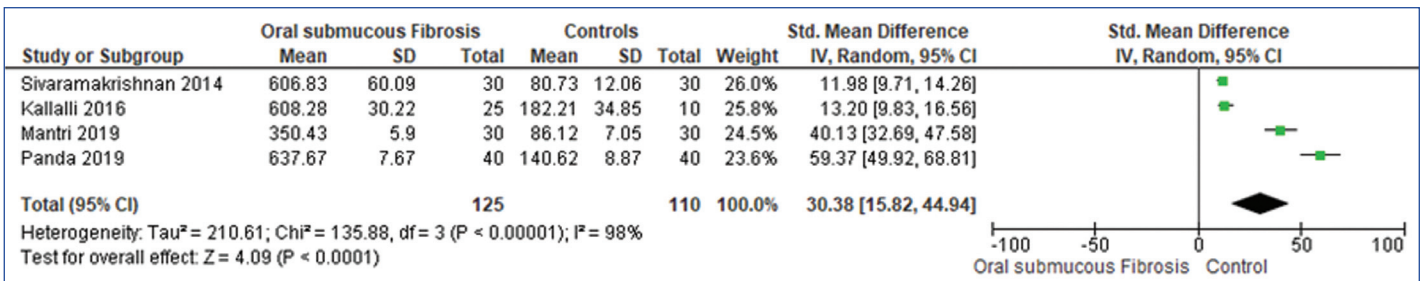
Three studies evaluated salivary LDH levels among cases with premalignant lesions and controls [4,20,22]. The pooled estimate was 9.10 (95% CI: 3.45-14.75). The cumulative difference between case and CG was 9.1, implying that salivary LDH levels were more in case group as compared to controls. Random effects model was

used because I² >50%. These results were statistically significant (p-value <0.05) [Table/Fig-5]. Two studies evaluated salivary LDH levels among cases with OLP and controls. The pooled estimate was 6.76 (95% CI: 6.86-20.38) [7,19]. The cumulative difference between case and CG was 6.76, implying that salivary LDH levels were more in case group as compared to controls. Random effects model was used because I² >50%. These results were not statistically significant (p-value >0.05) [Table/Fig-6].
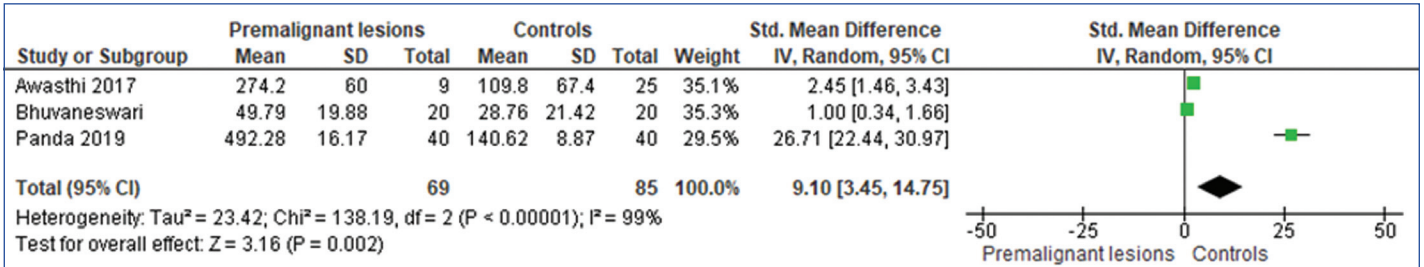
The present systematic review showed that the salivary LDH levels are higher in OC and OPMD patients than in healthy patients. However, the elevated salivary LDH levels were more significant in OC than OPMD [Table/Fig-7] [4-7,9,13-22].

Study or Subgroup	Oral Cancer Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Shetty 2012	148.77	81.75	25	79.5	4.67	25	12.2%	1.18 [0.57, 1.78]	2012
D'cruz 2015	486.79	111.7	30	117.33	19.37	30	12.0%	4.55 [3.57, 5.53]	2015
Patel 2015	686.4	81.75	25	26.16	75.85	25	11.1%	8.24 [6.47, 10.01]	2015
Kallalli 2016	630.96	39.8	25	182.21	34.85	10	9.4%	11.39 [8.46, 14.31]	2016
Lokesh 2016	1,225.4	221.79	30	497	51.76	20	11.9%	4.09 [3.08, 5.09]	2016
Awasthi 2017	425.4	158.2	30	109.8	67.4	25	12.2%	2.48 [1.76, 3.20]	2017
Mantri 2019	592.09	28.57	30	86.12	7.05	30	7.1%	24.00 [19.53, 28.47]	2019
Narges 2020	112.2	40.22	25	3.5	1.075	25	12.0%	3.76 [2.81, 4.71]	2020
Anitha 2021	660.4	748.29	18	220.78	40.85	18	12.2%	0.81 [0.13, 1.49]	2021
Total (95% CI)			238			208	100.0%	5.71 [3.89, 7.53]	

Heterogeneity: Tau² = 6.97; Chi² = 238.42, df = 8 (P < 0.00001); I² = 97%
Test for overall effect: Z = 6.15 (P < 0.00001)

[Table/Fig-3]: Forest plot comparing salivary LDH level between Oral Cancer (OC) and control.

Study or Subgroup	Oral submucous Fibrosis Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Sivaramakrishnan 2014	606.83	60.09	30	80.73	12.06	30	26.0%	11.98 [9.71, 14.26]
Kallalli 2016	608.28	30.22	25	182.21	34.85	10	25.8%	13.20 [9.83, 16.56]
Mantri 2019	350.43	5.9	30	86.12	7.05	30	24.5%	40.13 [32.69, 47.58]
Panda 2019	637.67	7.67	40	140.62	8.87	40	23.6%	59.37 [49.92, 68.81]
Total (95% CI)			125			110	100.0%	30.38 [15.82, 44.94]

Heterogeneity: Tau² = 210.61; Chi² = 135.88, df = 3 (P < 0.00001); I² = 98%
Test for overall effect: Z = 4.09 (P < 0.0001)

[Table/Fig-4]: Forest plot comparing salivary LDH level between oral sub mucous fibrosis and control.

Study or Subgroup	Premalignant lesions Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Awasthi 2017	274.2	60	9	109.8	67.4	25	35.1%	2.45 [1.46, 3.43]
Bhuvaneswari	49.79	19.88	20	28.76	21.42	20	35.3%	1.00 [0.34, 1.66]
Panda 2019	492.28	16.17	40	140.62	8.87	40	29.5%	26.71 [22.44, 30.97]
Total (95% CI)			69			85	100.0%	9.10 [3.45, 14.75]

Heterogeneity: Tau² = 23.42; Chi² = 138.19, df = 2 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.16 (P = 0.002)

[Table/Fig-5]: Forest plot comparing salivary LDH level between oral premalignant lesions and control.

Study or Subgroup	Oral Lichen Planus Mean	SD	Total	Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Narges 2020	3.36	1.31	25	3.5	1.07	25	50.5%	-0.12 [-0.67, 0.44]
Shetty 2012	136.46	3.36	25	79.5	4.67	25	49.5%	13.78 [10.91, 16.65]
Total (95% CI)			50			50	100.0%	6.76 [-6.86, 20.38]

Heterogeneity: Tau² = 95.45; Chi² = 86.92, df = 1 (P < 0.00001); I² = 99%
Test for overall effect: Z = 0.97 (P = 0.33)
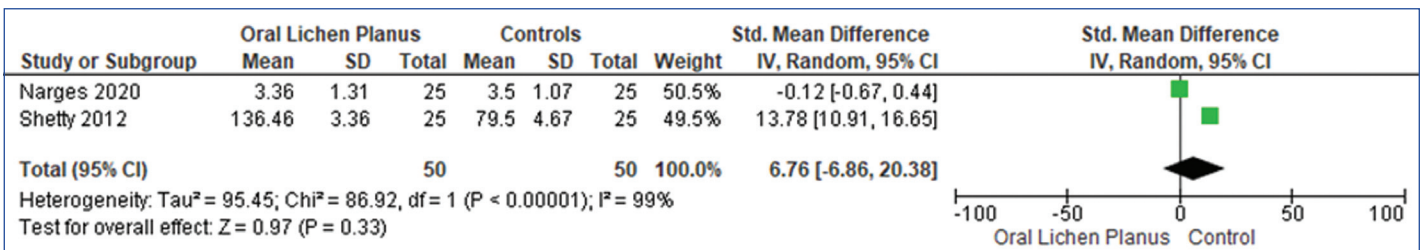
[Table/Fig-6]: Forest plot comparing salivary LDH level between Oral Lichen Planus (OLP) and control.

Author	Place and year of the study	Histological differentiation	LDH level Control and Oral Potentially Malignant Disorders (OPMD)	Oral Cancer (OC)
Patel S and Metgud R [11]	Rajasthan 2015	Grade I: 745.53±98.403 IU/L Grade II: 799.129±89.404 IU/L Grade III: 828.25±79.752 IU/L	Control: 261.16±75.851 IU/L OLP: 497.00±100.404 IU/L	686.40±81.752 IU/L
Shetty SR et al., [19]	Karnataka 2012	Not mentioned	Control: 79.50±4.67 IU/L OLP: 136.46±3.36 IU/L	148.77±4.83 IU/L
Goyal G [13]	Punjab 2020	Well differentiated: LDH=670 U/L Moderately differentiated: LDH=906 U/L Poorly differentiated: LDH=1008 U/L	Control: 115 U/L OL: 412 to 917 U/L OLP: 412 to 917 U/L	599 to 1100 U/L
Mishra S et al., [9]	Chennai 2018	Not mentioned	Control: 668.25±498.45 µg/dL OSMF: 1057.30±640.12 µg/dL	-
Kallalli BN et al., [5]	Saudi Arabia 2016	Not mentioned	Control: 182.21±34.85 OSMF: 608.28±30.22	630.96±39.80
Joshi PS and Golgire S [16]	Warana, Maharashtra 2014	16: No evidence of dysplasia 11: mild dysplasia 2: moderate dysplasia 1: severe dysplasia	Control: 267.2 IU/L OL: 519.3667 IU/L	788.7333
Mantri T et al., [17]	Maharashtra 2019	Not mentioned	Control: 86.12±7.05 IU/L OSMF: 350.43±5.90 IU/L	592.09±28.57 IU/L
Panda A et al., [4]	Odisha 2020	Not mentioned	Control: 140.62±8.87 U/L OL: 492.28±16.17 U/L OSMF: 631.67±7.67U/L	Not mentioned
Sivaramakrishnan M et al., [6]	Pondicherry 2015	Stage-II: Mean 2.774 Stage-III: Mean 2.778	Control: 80.73±12.060 IU/L OSMF: 606.83±60.009 IU/L	Not mentioned
Lokesh K et al., [15]	Bangalore 2016	Well differentiated: LDH=1049.07 U/L. Moderately differentiated: LDH=1309.50 U/L Poorly differentiated: LDH=1586.20 U/L	Control: 497±51.75 IU/L	1.225.40±221.79 IU/L
D'Cruz AM and Pathiyil V [14]	Karnataka 2015	Well differentiated: LDH=355.83 U/L. Moderately differentiated: LDH=484.18 U/L Poorly differentiated: LDH=484.18 U/L	Control: 117.33±19.37 IU/L	486.79±111.7 IU/L
Gholizadeh N et al., [7]	Iran 2020	-	Control: Unstimulated Saliva: 3.833±1.1044 U/L Stimulated Saliva: 3.500±1.0751U/L OLP: Unstimulated Saliva: 4.917±1.3104 U/L Stimulated Saliva: 3.638±0.9776 U/L Lichenoid reaction: Unstimulated Saliva :14.682±3.0041U/L Stimulated Saliva: 20.909±5.5424 U/L	Unstimulated Saliva: 99.833±49.3260 U/L Stimulated Saliva: 112.208±40.2209 U/L

Awasthi N [20]	Uttar Pradesh 2017	-	Control: 109.8±67.4 IU/L OL+OSMF+OLP:274.2±60 IU/L	425.4±158.2 IU/L
Javaraiah RK et al., [18]	Karnataka 2020	-	Control: 267±27.64 U/L OL+OSMF: 706.1±199 U/L	
Anitha G et al., [21]	Karnataka 2021	-	Control: 220.78±40.85 U/L	660.44±748.29 U/L
Bhuvaneswari M et al., [22]	Tamil Nadu 2022	-	Control: 28.76±21.42 IU/L Smokers: 27.21±24.08 IU/L Oral leukoplakia: 49.79±19.88 IU/L)	106.97±32.75 IU/L

[Table/Fig-7]: LDH levels of the included studies [4-7,9,13-22].

DISCUSSION

The LDH is an enzyme present in any tissue and body fluid. It seems that various epithelial changes results in change of levels of salivary LDH levels. The positive correlation of which were shown by all the studies [4-7,11,14,15,17-22]. The levels of LDH was increased proportionally in relation to the differentiation grade of OC, showing higher values when OC was poorly differentiated in comparison with moderately or well-differentiated tumours [11,14,15]. Elevated level of salivary LDH in OSMF has been reported in six studies compared to that of CG [4-6,9,17,18] and two studies showed lower level of LDH compared to that of OC [5,16]. In case of OL, eight studies showed elevated level of LDH [4,11,13,14,16,18,20,21] and seven studies showed lower level of LDH compared to that of OC [4,11,13,16,19-21]. Only one study was conducted on OLP and OLR, and the level of LDH was noticeably higher in the OSCC group followed by the OLR, OLP and CGs [7]. Three studies evaluated levels of LDH in tobacco users without PMD but the results were not significant [13,17,18]. Only one study compared the level of LDH with the stages of OSMF. The result showed a non significant difference in Stage-III than Stage-II [6].

Several LDH measurement methods were used in the included studies, out of which spectrophotometer was most commonly used. Only one study used agarose gel electrophoresis method [16]. Various LDH kits were used for analysis, out of which three studies did not specify the kit [5,14,15]. Salivary LDH is an epithelium-dependent enzyme any tissue alterations which could compromise the results of the test. Only two studies selected patients subjected for ultrasonic scaling two weeks prior to sample collection [15,18]. Hence, in future studies these cofounding factors should be pointed out, so as to avoid the risk of bias.

Both stimulated and unstimulated saliva were used, two studies had used stimulated saliva [6,7]. While, 12 studies used unstimulated saliva. As the enzymes levels in saliva vary at different time periods and on its precollection measures. Most studies showed collection time period in the morning, from 7-12 am. Seven out of 14 studies did not specify the saliva collection time interval [9,13,16-19,22]. Therefore, in future studies some protocolised measures should be followed to ensure the reliability of the results. Results from the present review showed that most of the studies were being carried out in South East Asian countries. Henceforth, more studies are needed to be carried out in other developed and developing countries, so that a precise cut-off value can be established.

Limitation(s)

Only PubMed, web of science, Scopus and Cochrane databases were searched. The articles published in English language were only considered with duration of 10 years. Also, the confounding factors were not considered for the variation analysis.

CONCLUSION(S)

In the present systematic review and meta-analysis, authors found that the salivary LDH levels are higher in OC and OPMD patients than in healthy patients. However, the elevated salivary LDH levels were more significant in OC than OPMD. In future, standardised protocol should be developed in terms of saliva collection method and analysis in perspective longitudinal studies having a large sample size. Studies should be conducted in different demographic regions and variation in terms of confounding conditions should be considered and analysed.

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PARTICULARS OF CONTRIBUTORS:
1. Postgraduate Trainee, Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India.
2. Professor and Head, Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India.
3. Assistant Professor, Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India.
4. Postgraduate Trainee, Department of Public Health Dentistry, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India.
5. Postgraduate Trainee, Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pimpri, Pune, Maharashtra, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sunil S Mishra,
Professor and Head, Department of Oral Medicine and Radiology, Dr. DY Patil Dental College and Hospital, Dr. DY Patil Vidyapeeth, Pimpri, Pune-411018, Maharashtra, India.
E-mail: arunimasarma44@gmail.com; sunil.mishra@dpu.edu.in

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? No
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No