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REVIEW PAPER

Salivary LDH and Salivary Ferritin as a Prognostic Marker in Oral Potentially Malignant Disorders: A Systematic Review and Meta-Analysis

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Abstract

Aim To systematically review the existing scientific literature in providing a comprehensive, quantitative analysis on prognostic ability of salivary lactate dehydrogenase (LDH) and ferritin in oral potentially malignant disorders (OPMD's) through meta-analysis.

Methods Review was adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines 2020 and registered in PROSPERO – CRDXXXXX. Electronic databases were searched for studies having sufficient data on the effect of salivary LDH and ferritin on overall disease prognosis in patients with OPMD's like Oral Submucous Fibrosis (OSMF), Oral Lichen Planus (OLP) and Oral Leucoplakia (OL) compared to healthy controls. Quality assessment of included studies was evaluated through Newcastle Ottawa scale (NOS). The standardized mean difference (SMD) was used as summary statistic measure with random effect model and p value 0.05 as statistically significant through Review manager (RevMan) version 5.3.

Results Seventeen studies (15 comparative studies and 2 case control studies) fulfilled the eligibility criteria and were included in qualitative synthesis and thirteen studies for meta -analysis with data being evaluated from 1210 patients, of 605 cases and controls each. Included studies had moderate to low risk of bias. Meta-analysis showed that mean Salivary Ferritin level was 2.80 (–9.54 – 3.94) decreased in OPMD cases compared to control (p 0.05) while mean salivary LDH level was 12.04 (8.72 – 15.37) times higher in OSMF cases compared to controls while for leucoplakia, the level was 7.79 (4.53 – 11.04) times more in cases compared to controls (p 0.05).

Conclusion It was found that low and high quantity of salivary ferritin and LDH was found in various OPMD cases and is related with overall disease prognosis. Therefore, these salivary biomarkers overall can act as a good prognostic and therapeutic marker in disease progression and advancements and should be assessed early to reduce patient's mortality and morbidity.

Keywords Lactate Dehydrogenase · Salivary Ferritin · Salivary Biomarker · Oral Potentially Malignant Disorder · Prognosis · Systematic Review

Introduction

Oral cancer, along with cancers of the oropharynx, ranks as the sixth most prevalent malignancy globally [1]. Each year, over 400,000 new cases of oral cancer are reported, with the majority occurring in regions such as India, Sri Lanka, Pakistan, Bangladesh, and Indonesia [1, 2]. Overall 5-year survival rate of oral cancer is 40%, but if diagnosed early, survival rates can improve up to 80% [3]. About half of all oral cancer cases are not diagnosed until in their later stages, due to lack of symptoms in early stages and patients seeking medical help only in case of symptoms such as pain,

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on identifying growth in the mouth or surrounding areas, or when lymphatic spread has taken place [4].

Oral cancer can occasionally be preceded by lesions of oral precancer which predominantly includes oral submucous fibrosis and leukoplakia [5]. Prevention and timely recognition of such OPMDs not only favour a decreased rate of oral cancer but also improve chances of survival in subjects developing oral cancer [6]. A recent systematic review has reported a general malignant transformation rate of OPMD to be about 7.9% (99% CI 4.9–11.5%), though with high values in the heterogeneity test [7].

Oral cancer is usually diagnosed when it gets symptomatic, but by this stage around two-third of patients develop advanced disease with regional metastasis [8]. Delayed detection is the primary reason for high morbidity and mortality rates; this strongly supports the need for early detection of oral cancers [9]. The gold standard for diagnosing oral cancer is a biopsy, which is not suitable for screening purposes due to its invasive nature, high cost, and requirement for specially trained medical personnel and equipment. There is a constant search for biomarkers in saliva, a body fluid that can be collected easily and non-invasively [10]. Salivary biomarkers offer a promising diagnostic adjunct due to their simple non-invasive collection method and can be used for screening a large population [11].

Salivary lactate dehydrogenase is one of the biomarkers used in the early detection of premalignant lesions and conditions. A shift from aerobic to anaerobic glycolysis is the mechanism of increased LDH enzyme in tissues in OPMDs and oral cancer. Therefore, salivary LDH serves as promising tool in the diagnosis of OC at its preliminary stage by acting as early diagnostic marker [12–14].

Recent studies have demonstrated that ferritin possesses additional functions beyond its primary role as an iron-storage protein. These functions include the possibility of linking ferritin to various pathways associated with cancer, including suppressor evasion, cell proliferation, growth angiogenesis, cell death inhibition, immune modification, invasion, and metastasis. Ferritin is an iron-storage protein related to acute and chronic inflammation. It appears to be depleted and utilized ferritin in patients with malignant tumours [15, 16]

Till date, very few studies have provided a comprehensive, quantitative analysis of the prognostic test of salivary LDH and salivary ferritin in OPMDs. Therefore, we updated our research for related articles and conducted a systematic review and meta-analysis intending to provide updated evidence on salivary LDH and salivary ferritin as a prognostic marker in oral potentially malignant disorders.

Methodology

Protocol Development

This review followed the 2020 guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and was duly registered in the PROSPERO database and number is CRD42024520334.

Study design

The following focused research was proposed:

1. Is there any difference in level of Salivary Biomarker LDH and Salivary Ferritin in healthy patients and patients with OPMDs?
2. Is Salivary Biomarker able to be used for clinical application for early detection and screening for large population?

The PICO criteria for this review were as follows:
Participants—Patients with OPMDs.
Exposure—Patients with habit history.
Comparison—To compare the salivary level of LDH and ferritin in healthy individuals and patients with OPMDs.
Outcome—To evaluate the screening ability of salivary LDH and Ferritin.

Eligibility Criteria:

a) **Inclusion Criteria:**
b) Studies published in English language
c) Studies published between January 2000 and April 2023 and having relevant sufficient data on the patients histologically and clinically diagnosed with OPMDs for the effect of salivary LDH and ferritin on overall disease prognosis in patients with OPMDs compared to normal healthy controls.
d) Case–control study, cohort study, and comparative and cross-sectional studies were selected
e) Studies from open access journals
f) Articles reporting the study outcomes in terms of odd's ratio (OR) and risk ratio (RR).
g) **Exclusion Criteria:**
h) Any studies conducted before 2000
i) Articles in other than English language
j) Reviews, abstracts, letter to the editor, editorials, animal studies and in vitro studies were excluded

k) Articles not from open access journals
l) Studies reporting effect of salivary LDH and Ferritin on disease prognosis in Oral Cancer patients compared to controls.

Search Strategy

A comprehensive electronic search was performed till December 2023 for the studies published within the last 23 years (from 2000 to 2023) using the following databases: PubMed, Google Scholar and EBSCOhost to retrieve articles in the English language. The searches in the clinical trials database, cross-referencing and grey literature were conducted using Google Scholar, Greylist, and OpenGrey.

Appropriate key words and Medical Subject Heading (MeSH) terms were selected and combined with Boolean operators like AND. The relevant data were searched using the following keywords and their combinations: "Cancer" (MeSH term) AND "malignancy" (MeSH term); "saliva" (MeSH term) AND "salivary biomarkers" (MeSH term); "oral submucous fibrosis" (MeSH term) AND "oral leucoplakia" (MeSH term) AND oral lichen planus (MeSH term); "oral candidiasis" (MeSH term) AND "salivary lactate dehydrogenase" (MeSH term) AND "salivary ferritin" AND "association and risk" AND "disease prognosis" AND "survival rate" (MeSH term); "comparative study" AND "prospective study" (MeSH term).

Screening Process

The search and screening according to previously established protocol were conducted by two authors. A two-phase selection of articles was conducted.

Data Extraction

For all included studies, following descriptive study details were extracted by two independent reviewing authors and using pilot-tested customized data extraction forms in Microsoft Excel Sheet with the following headings included in the final analysis: author(s), country of study, year of study, sample size, study design, outcome assessed and conclusion.

After eliminating duplicates, the reference list of included studies underwent screening, resulting in the exclusion of studies. Following this, full text articles were assessed for eligibility and articles that did not meet the inclusion criteria were excluded. Seventeen studies were included in the review and thirteen studies were included in meta-analysis as illustrated in Fig. 1.

Quality Assessment of Included Studies

Quality of included studies for observational studies was evaluated based on Newcastle Ottawa Scale, and accordingly a numeric score (NOS Score) was assigned [17]. Quality appraisal of the included studies were undertaken by the two authors, and a third author was consulted in the event of any discrepancy.

Statistical Analysis

Risk ratio (RR) and standardized mean difference (SMD) with 95% CI were calculated for dichotomous and continuous outcomes through random effects model using the RevMan 5.3 and keeping the significance level at $p < 0.05$ [18].

Assessment of Heterogeneity

The heterogeneity was assessed by means of Cochran's test and the I^2 statistics [19].

Investigation of publication bias Publication bias was investigated using Begg's funnel plot. Asymmetry of funnel plot indicates publication bias and other biases related to sample size, although asymmetry may also represent a true relationship between trial size and effect size. 20

Results

Study Selection

After eliminating duplicates, the reference list of included studies underwent screening, resulting in the exclusion of studies. Following this, full text articles were assessed for eligibility and articles that did not meet the inclusion criteria were excluded. Seventeen studies were included in the review, and thirteen studies were included in meta-analysis as illustrated in Fig. 1.

Study Characteristics

As shown in Table 1, data were evaluated from seventeen studies [20–37] from an aggregate of total sample size of 1210 patients, of which cases and controls of 605 each, respectively, with 1:1 ratio. Among the included studies, majority were conducted in India, while one study was conducted in Iran [32] and one study in Spain [37]. Majority of included studies were comparative studies, while two studies [32, 37] had case control study design. Among the included studies, sixteen studies [21–34, 36] assessed the salivary LDH level in patients with various OPMDs (Oral Leucoplakia, Oral Lichen Planus and Oral Submucous Fibrosis) and compared with healthy controls, while only two studies [35,

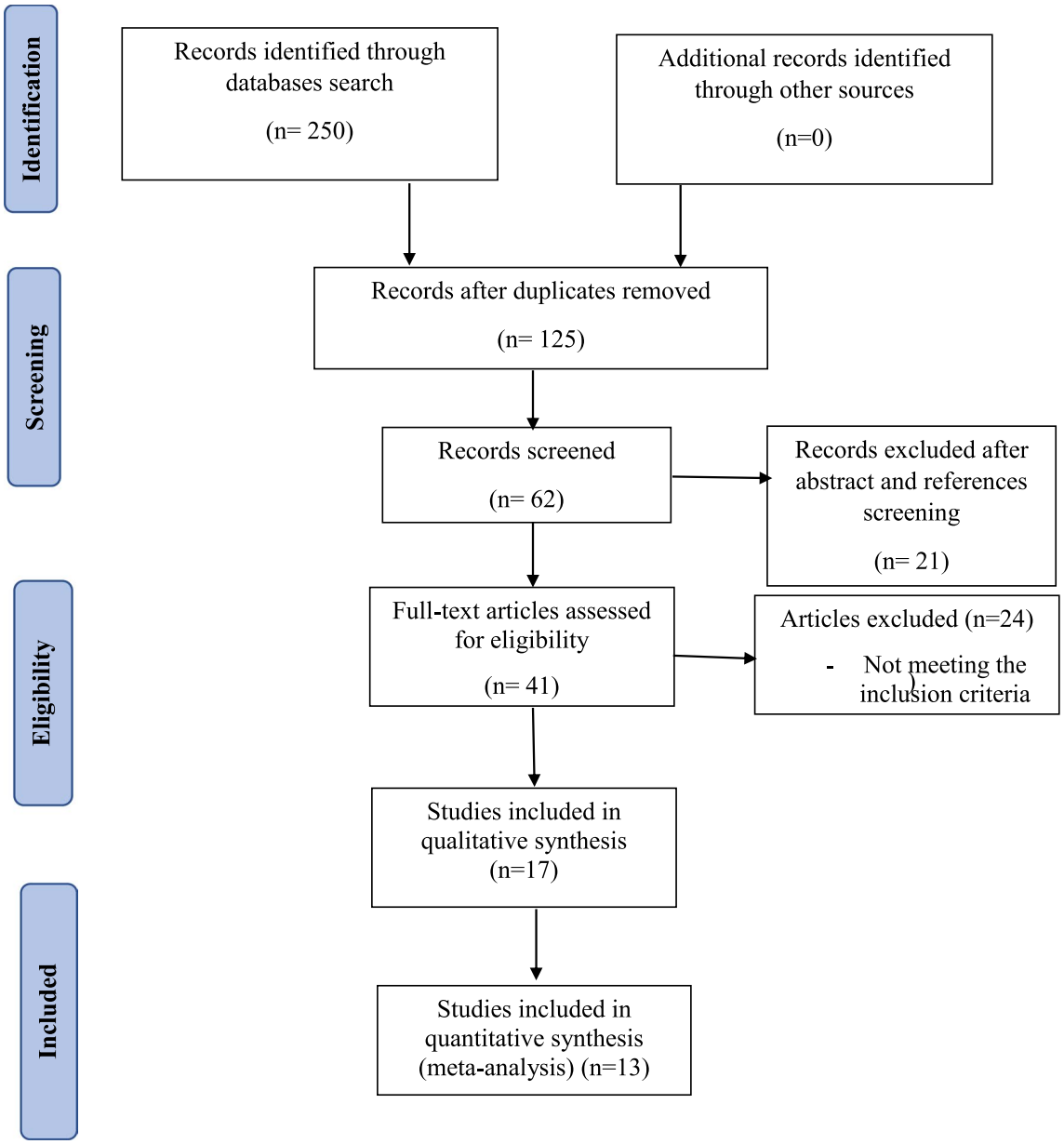

Fig. 1 PRISMA 2020 flow diagram assessment

37] assessed the salivary ferritin level in OPMD's patients and healthy controls.

Assessment of Methodological Quality of Included Studies

Among the included study, only four studies [24, 28, 34, 36] reached the maximum score of the Newcastle Ottawa Scale. For selection bias, four studies [24, 28, 34, 36] reached the maximum score, while for the comparability outcome, five studies [22, 25, 31, 32, 35] did not reach the maximum score, and for exposure outcome, six studies [23, 24, 28, 33, 34, 36] reported maximum score and considered to have the highest level of quality with an estimated low risk of bias. Included studies had moderate to low risk of bias with overall quality of study being good. Risk of bias of included studies through Newcastle Ottawa Scale is depicted in Fig. 2.

Synthesis of Results

The meta-analysis was performed for assessing the levels of salivary ferritin and salivary LDH in patients with OPMD compared to controls on disease prognosis by thirteen

Table 1 Descriptive study details of included studies

Sr. No.	Author, years of study	Country	Study design	Cases/controls	OPMDs assessed	Mean salivary LDH and ferritin level
1	Shetty et al. (2012) [21]	India	Comparative study	25/25	OL and control for LDH	136.46 ± 3.36 and 79.50 ± 4.67
2	Dhivyalakshmi et al. (2014) [22]	India	Comparative study	21/21	OL and control for LDH	%1.%2 and 11.88
3	Patel et al. (2015) [23]	India	Comparative study	25/25	OL and control for LDH	686.40 ± 81.752 and 261.16 ± 75.85
4	Sivaramakrishnan et al. (2015) [24]	India	Comparative study	30/30	OSMF and controls for LDH	606.83 ± 60.09 and 80.73 ± 20.06
5	Bhambhal et al. (2016) [25]	India	Comparative study	80/80	OSMF and controls for LDH	625.47 ± 96.43 and 8.97 ± 0.83
6	Kallalli et al. (2016) [26]	India	Comparative study	20/20	OSMF and controls	608.28 ± 30.22 and 182.21 ± 34.85
7	Shah et al. (2017) [27]	India	Comparative study	25/25	OSMF and controls for LDH	299.86 ± 193.97 and 159.25 ± 57.56
8	Mishra et al. (2018) [28]	India	Comparative study	20/20	OSMF and controls for LDH	1057.30 ± 640.12 and 668.25 ± 498.45
9	Mantri et al. (2019) [29]	India	Comparative study	40/40	OSMF and controls for LDH	350.43 ± 5.90 and e 86.12 ± 7.05
10	Shamlin et al. (2019) [30]	India	Comparative study	20/20	OL, OSMF and controls for LDH	962.8 ± 945.58 and 398.1 ± 523.08
11	Sharma et al. (2019) [31]	India	Comparative study	15/15	OPMD and control for LDH	813 ± 86.92 and 714.53 ± 217.95
12	Gholizadeh et al. (2020) [32]	Iran	Case control	50/50	OLP and controls	4.91 ± 1.13 and 3.83 ± 1.10
13	Javaraiah et al. (2020) [33]	India	Comparative study	26/26	Tobacco users with OPMD and controls	706 ± 1.99 and 267 ± 27.64
14	Panda et al. (2020) [34]	India	Comparative study	40/40/40	OSMF, OL and controls	631.67 ± 7.67, 492.28 ± 16.17 and 140.62 ± 8.87
15	Buch et al. (2022) [35]	India	Comparative study	30/30	OPMD and controls for salivary ferritin	17.49 ± 5.40 and 38.47 ± 8.08
16	Bhuvaneshwari et al. (2022) [36]	India	Comparative study	27/27	OL and controls for LDH	49.78 ± 19.87 and 28.75 ± /-21.41
17	López-Jornet et al. (2023) [37]	Spain	Case control study	91/91	OPMD and controls for salivary ferritin	7.19 ± 4.44 and 12.66 ± 10.50

LDH lactate dehydrogenase; *OL* oral leucoplakia; *OLP* oral lichen planus; *OPMD* oral potentially malignant disorders; *OSMF* oral submucous fibrosis

studies [21, 23–30, 33, 34, 36, 37] as shown in Figs. 3, 4, 5, 6, 7, and 8.

A) Salivary Ferritin levels in OPMD cases and controls

Two studies [33, 37] containing data on 149 patients, of which ($n = 87$) patients were evaluated as OPMD cases group and ($n = 62$) patients by control group. As shown in Fig. 3. the SMD is 2.80 (−9.54 to 3.94) and the pooled estimates favour cases signifying that overall lesser mean level of salivary ferritin on an average of 2.80 times lower in cases group ($p > 0.05$).

The funnel plot did show significant asymmetry, indicating the presence of publication bias as shown in Fig. 4.

B) Salivary LDH levels in OPMD cases and controls

Eight studies [24–30, 34] contained data on 486 patients, of which ($n = 270$) patients were evaluated as OSMF cases group and ($n = 216$) patients by control group. As shown in Fig. 5**,** the SMD is 12.04 (8.72–15.37) and the pooled estimates favour OSMF cases signifying that overall greater mean level of salivary LDH level on an average of 12.04 times greater in cases group ($p < 0.05$).

The funnel plot did not show significant asymmetry, indicating the absence of publication bias as shown in Fig. 6.

Five studies [21, 23, 29, 34, 36] contained data on 260 patients, of which ($n = 130$) patients were evaluated as Oral Leucoplakia cases group and ($n = 130$) patients by control group. As shown in Fig. 7, the SMD is 7.79 (4.53–11.04) and the pooled estimates favour cases signifying that overall greater mean level of Salivary LDH on an average of 7.79 times greater in cases group ($p < 0.05$).

Sr. No	Author, year	Selection (Max = 4)	Comparability (Max = 2)	Exposure (Max = 3)	Overall quality score (Max = 9)
1.	Shetty et al., 2012[21]	**	**	**	6
2.	Dhivyalakshmi et al., 2014[22]	***	*	**	6
3.	Patel et al., 2015[23]	**	**	***	7
4.	Sivaramakrishnan et al., 2015[24]	****	**	***	9
5.	Bhambhal et al., 2016[25]	**	*	**	5
6.	Kallalli et al., 2016[26]	**	**	**	6
7.	Shah et al., 2017[27]	***	**	**	7
8.	Mishra et al.,2018[28]	****	**	***	9
9.	Mantri et al., 2019[29]	**	**	*	5
10.	Shamlin et al., 2019[30]	**	**	**	6
11.	Sharma et al., 2019[31]	**	*	**	5
12.	Gholizadeh et al., 2020[32]	***	*	**	6
13.	Javaraiah et al., 2020[33]	**	**	***	7
14.	Panda et al., 2020[34]	****	**	***	9
15.	Buch et al., 2022[35]	**	*	**	5
16.	Bhuvaneshwari et al., 2022[36]	****	**	***	9
17.	López-Jornet et al., 2023[37]	**	**	*	5

Fig. 2 Risk of bias (ROB) through Newcastle Ottawa Scale (NOS)

The funnel plot did not show significant asymmetry, indicating the absence of publication bias as shown in Fig. 8.

Discussion

In 1973 Rho et al. first used term "Biomarker" for the presence or absence of specific biologic material although this term was previously used by Mundkar in 1949 as "Biochemical Marker" and by Porter in 1957 as "Biological Marker" [38–40]. Biomarkers are compounds that can be found or measured in certain pathologic changes or biological processes. Numerous biomarkers have been identified so far and related to clinicopathological characteristics of several human malignancies. Some of these biomarkers have been used since the past few decades to identify tumours or as a prognostic indicator of treatments because of their unique characteristics [41]. They are classified based on different parameters including their characteristic, clinical application, genetic and molecular biology technique. On the basis of clinical application, they divide into diagnostic, prognostic, and therapeutic biomarker [42].

The ground basis research of Otto Warburg (1930) revealed cancer tissues exhibit increased aerobic glycolysis. This sparked extensive studies on cancer enzymology. Researchers have investigated enzymes in various tissues, serum, and plasma and its variations in systemic diseases [43]. In OSCC there is considerable variation in protein expression, so there is a variety of potential biomarkers of OSCC. These biomarker can be broadly classified into (i) tissue-based biomarkers, (ii) secretomes (plasma, saliva, blood, or other secretions), and (iii) autoantibodies [42]. Various studies show serum and saliva have been used for the assessment of either individual or a group of protein markers together to assist in the early recognition of Oral Cancer and in employing a suitable therapy.

To date, tissue biopsy and histopathological analyses are the gold standard for diagnosis of premalignant lesion and oral cancer, but the premalignant lesion which progresses into Oral Cancers diagnosed in the later stages with consequent poor survival rate due to limited screening programme

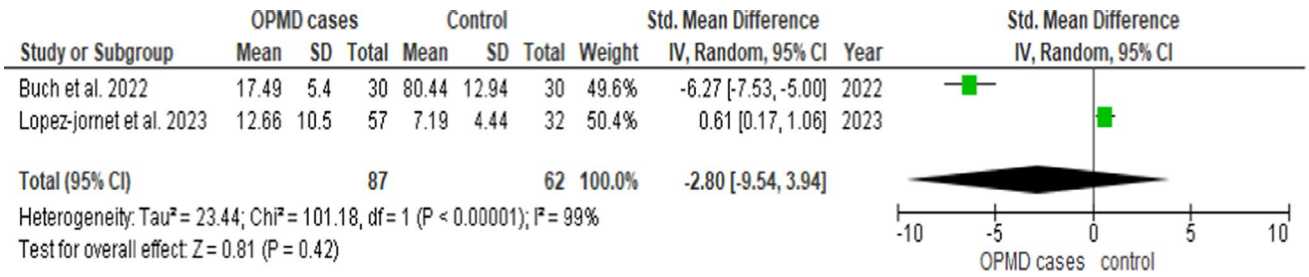

Fig. 3 Salivary ferritin levels in cases and controls

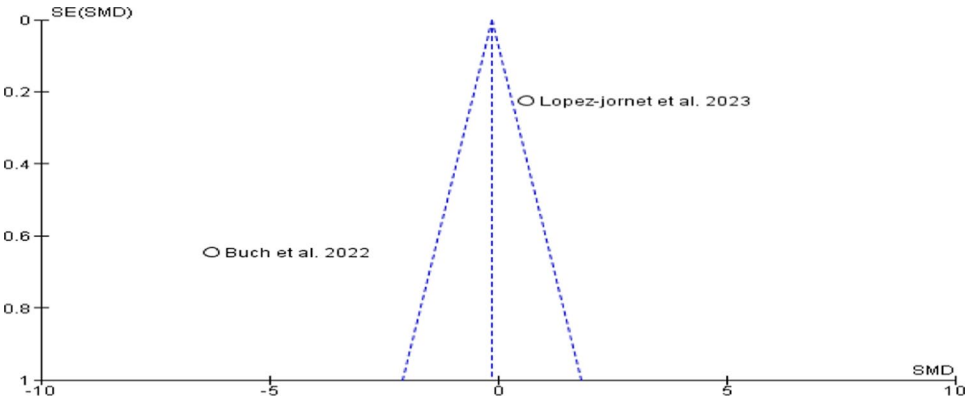

Fig. 4 Salivary LDH levels in OSMF cases and controls

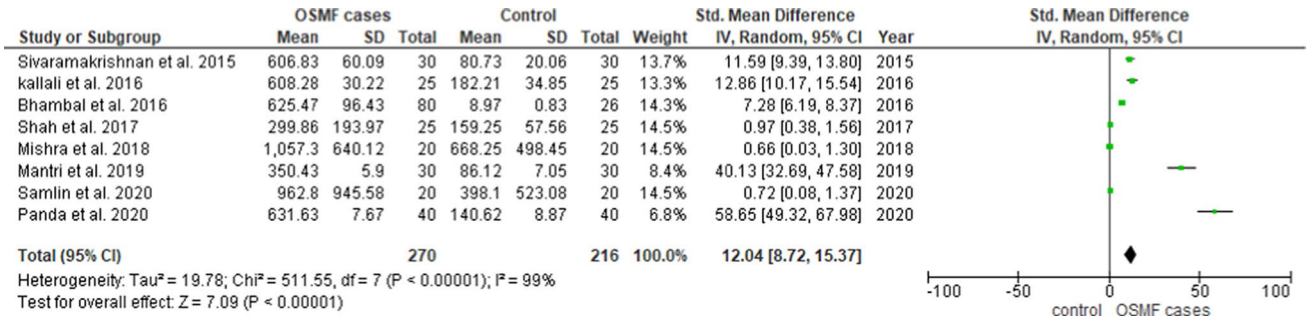

Fig. 5 Salivary LDH levels in Oral Leucoplakia cases and controls

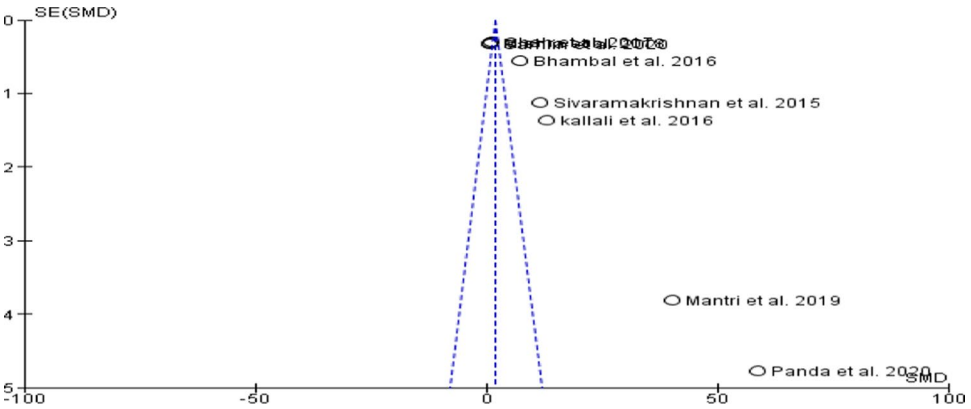

Fig. 6 Begg's funnel plot with 95% confidence intervals showing the absence of publication bias

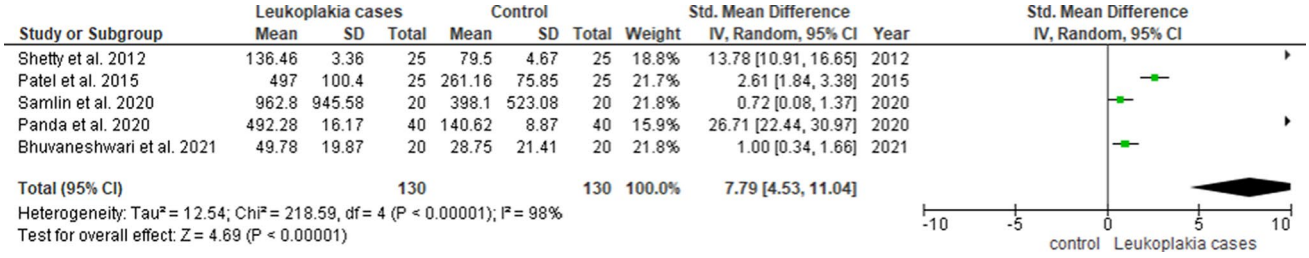

Fig. 7 Salivary LDH levels in oral leucoplakia cases and controls

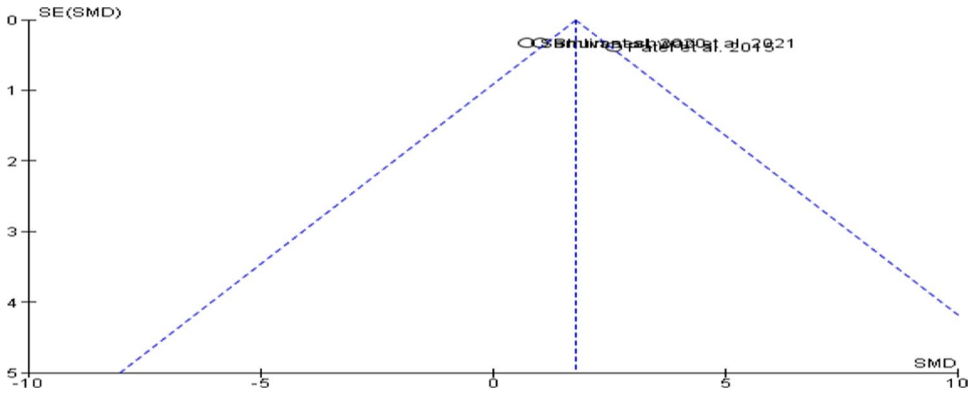

Fig. 8 Begg's funnel plot with 95% confidence intervals showing the absence of publication bias

and inefficient physical examination. Strategies to overcome this limitation liquid biopsy are emerging novel minimally invasive tool for early identification of tumour and evaluation and prognosis of patient. Biomarkers have been developed through existing biological techniques such as cytological features, promoter methylation, polymorphism, mRNAs, microRNA, non-coding RNAs, etc. [44]. These biomarkers were all developed for detection in a solid biopsy specimen. A term which is becoming increasingly popular is "liquid biopsy" which is obtaining bodily fluid samples for the detection of potential biomarkers. These methods have unique advantages as the samples are easy to collect, showed less invasiveness, and high patient acceptance, although more research is needed to establish its utility [45].

This systematic review was undertaken to provide comprehensive, quantitative analysis on salivary LDH and salivary ferritin as prognostic biomarkers in OPMDs. Existing literature for this review was evaluated from an aggregate total sample size of 1210 patients with cases and controls of 605 each respectively. Sixteen of the included studies [21–34, 36] assessed the salivary LDH level, while two studies [35, 37] assessed the salivary ferritin level in OPMD (OSMF, Oral Leukoplakia and Erythroplakia, etc.) patients and healthy controls.

LDH is an enzyme that is commonly found in the cytoplasm of animal cells. Salivary glands produce salivary LDH. Oral epithelial cells are also considered a major source of salivary LDH [46]. It catalyses the oxidation of lactate to pyruvate in the glycolytic pathway. Cell death due to tissue breakdown causes LDH confined within cell cytoplasm to be released extracellularly. The presence of LDH is always related to a pathologic process [47]. Even small amount of damaged tissue can increase the levels of LDH to a significant level justifying its use as a biomarker in tissue damage. In our study, it was found that OSMF cases had an overall greater mean level of salivary LDH in the cases group than in the control group. Meta-analysis showed that Salivary LDH, in OSMF, the level was 12.04 (8.72–15.37) times higher in cases compared to controls, while in leucoplakia, the level was 7.79 (4.53–11.04) times more in cases compared to controls which was statistically significant ($p < 0.05$). These findings clearly justify that salivary LDH is a potential biomarker in the detection of OPMD. The findings of our study are congruent with the meta-analysis conducted by Iglesias-Velazquez et al [48] where it was observed that level of Salivary LDH in leucoplakia and OSMF was 11.67 (1.01–22.33) and 25.83 (− 1.74 to 53.40) times higher in cases compared to controls. Sarma et al. [49] conducted a systematic review and meta-analysis where it was observed that OSMF cases had LDH level 30.38 (15.82–44.84) and OLP cases had LDH level 6.76 (− 6.86 to 20.38) higher than that of control. It is notable that the values of salivary LDH in OSMF are reportedly higher than in Oral Leukoplakia. It has been speculated that the findings of higher values of salivary LDH can be due to the general extensiveness of the involvement of oral tissues in this condition or due to the added components of hypoxia [50] and fibrosis [51] in the tissues increasing the levels higher as compared to other OPMDs. The existing literature comparing patients with frank oral cancer, OPMDs and healthy individuals shows that salivary LDH values are observed to be consistently higher in oral precancer and are paramount in oral cancer patients [52]. Based on the literature, salivary LDH levels could be a valuable prognostic tool as a future trend for patients with OPMDs.

Ferritin is an iron-storage protein related to acute and chronic inflammation. It appears to be over-expressed in patients with malignant tumours [53] and has been implicated in pathways associated with cancer, such as cell evasion and proliferation, angiogenesis, the inhibition of cell death, invasion, and metastasis. In the context of cancer, the ferritin levels are seen to be increased in the serum of many cancer patients, and the highest levels are correlated to more aggressive disease and a poor clinical outcome [37]. Buch et al. [35] reported decreased salivary ferritin levels in OPMDs and concluded that the cause could be due to increased utilization of iron, as comparable results were seen in serum ferritin levels of OPMDs. Buch et al.'s. study group

consisted of 18 cases of OSMF, 8 of oral leukoplakia, and 4 cases of oral lichen planus. Thakur et al. found a significant decline of serum ferritin in OSMF patients as compared to normal healthy controls and further showed a progressive decrease in serum ferritin levels as the histopathological grade increased. The reduced serum ferritin in OSMF may be related to the increased utilization of iron in OSMF for collagen synthesis. Thus, as the iron stores get depleted, serum ferritin level decreases and is downregulated [54].

The adherence to the PRISMA guidelines, the thorough unrestricted literature search, utilization of reliable methodology with regard to the qualitative synthesis of data, and the quality assessment of evidence with the Newcastle Ottawa Scale for included case control and comparative studies strengthens this systematic review. The quality assessment of all the included studies showed low–moderate risk of bias, whereas overall quality was high, specifying lack of potential and inevitable sources of bias with limited variability and reporting deficiencies. In the present systematic review, sufficient studies with a brief observation period and a known risk of bias were included. As a result, the presently available literature is sufficient to make therapeutic recommendations on the use of salivary ferritin and salivary LDH as biomarkers.

Limitation

Further RCTs and Case-Controlled Trials should be carried out with larger sample size to obtain overall good-quality evidence.

Conclusion

Liquid biopsy has shown a great potential as a non-invasive, rapid and convenient approach for the diagnosis and prognosis of OPMD's and Oral Cancer. Future challenges are going to be cost-effective and highly sensitive technologies for the detection of circulating biomarkers which can be predictive for OPMD's, and further clinical studies should be performed to confined diagnostic and prognostic accuracy as salivary biomarker in liquid biopsy.

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