Systematic Review

To evaluate an association between prognostic significance of Moesin with histopathological grading of oral squamous cell carcinoma: A systematic review

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Abstract

Purpose: The aim of the present Aetiology/Risk type and Prognostic type of systematic review is to evaluate the value of Moesin as a biomarker of invasiveness in Oral Squamous Cell Carcinoma patients and to review/assess the available evidence regarding the prospective prognostic association between Moesin and histopathological grading of OSCC to enhance the quality of life and survival rate of oral cancer patients.

Method: A systematic wide-range literature search was performed by authors (BS, KS, and DK) till October 2022 using both, electronic search media and manual search by hand, searching appropriate journals as per the focussed guiding question and inclusion/exclusion criteria. Major databases such as Scopus, EMBASE, Web of Science, Cochrane central register for controlled trials, PubMed & Google Scholar were conducted by two calibrated reviewers independently to gauge the association between the prognostic significance of Moesin with histopathological grading of oral squamous cell carcinoma. As this study is based on tissue samples of oral squamous cell carcinoma patients, all the selected studies were mostly, cross-sectional studies, and retrospective in nature. The studies were integrated with this review to gauge the association between the prognostic significance of Moesin with histopathological grading of oral squamous cell carcinoma (OSCC). The review included a total of 7 studies with tissue samples of 645 cases. The prime outcome was to assess the immunoexpression of Moesin among the different histopathological grades i.e well-differentiated SCC, moderately differentiated SCC, and poorly differentiated SCC and the subordinate outcome was to consider the extent of strong immunoexpression characteristics (cytoplasmic, membranous and mixed type) in different grades of OSCC as well as to correlate with morbidity, mortality, and/or 5 years or 10 years survival rate.

Results: The results were analyzed and presented narratively using the Critical Appraisal Tools developed by the University Of Oxford; Risk of Bias - Cochrane Risk of Bias tool - RoB 2.0, and GRADE-pro (Grading of Recommendations, Assessment, Development, and Evaluations) which rates the features of the evidence as high, moderate, low and very low. The risk of mortality expressed in terms of *Hazard ratio* has been elicited as a 1.37 times higher rate of mortality in the advanced histopathological stages of the OSCC cases. As the sample size of this review was insignificant, therefore, the authors have incorporated hazard ratios

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of some other studies of carcinomas in diverse sites in the body to give a flavor of prognostic outcomes of Moesin. It was observed that Moesin expression in Breast cancer and UADT carcinomas have a higher mortality rate as compared to OSCC and lung carcinoma cases and this decree strengthens our conviction that Moesin expression in the cytoplasm of advanced histopathological stages of cancer can be assumed as a sign of poor prognosis in all carcinomas including OSCC patients.

Conclusion: A sample of seven studies is inadequate as definite evidence for claiming that Moesin is a strong biomarker of invasiveness in OSCC cases and more clinical trials need to be conducted on the prognostic efficacy of Moesin expression in the various histopathological grades of OSCC cases.

Keywords: Histopathological grading, Moesin, oral squamous cell carcinoma (OSCC), prognostic correlation, systematic review

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the 6th most common malignant epithelial neoplasm of the oral cavity with a prevalence of 45% of all cancers found in India. Among the oral, salivary, and pharyngeal cancers, at least 90% are OSCC. It is one of the most underdiagnosed of all cancers despite its straightforward access into the oral cavity and its diagnosis is usually established in the advanced stages, resulting in a lower five-year survival rate.[1] Worldwide, the morbidity and mortality rates attributed to OSCC in females are 3.1/100,000 and males are 6.6/100,000. Globally, OSCC has ascended new magnitudes in terms of afflicting an overwhelming number of people i.e., more than three and a half lakh new cases and 1,77,384 deaths have been recorded since 2018.[2,3]

Histopathological grading is the hallmark of assessing risk and providing tailored treatment to OSCC patients.[3] The contemporary method of detecting OSCC is dependent on a triad of three main factors: host, tumor, and tumor-host interface.[3] The grading system has advanced over the years with the inclusion of extra-nodal and extracapsular spread (ECS) into the 'N' stage and depth of invasion (DOI) in the 'T' stage.[4,5] The DOI is different from the clinical tumor thickness and uses MRI and Ultrasound as tools of estimation for the depth of the lesion.[3] This additional classification complements the World health organization (WHO) classification (2017) which had limited features of differentiating the histopathological grading system and previously divided the tumor into three grades: poorly differentiated, well-differentiated, and moderately differentiated sequence. The former WHO grading classification did not seem to associate well with the prognosis and required more tools like biomarkers in conjunction with the present grading system to enhance its prognostic value.[3] Moreover, it did not have features that showed the growth pattern of the tumor; or stromal reactions like local immune response, desmoplasia, tumor stromal ratio, etc.[3]

Description of Moesin

Due to relapse and poor survival rate among OSCC cases, the detection of biomarkers like Moesin has emerged as essential elements in improving the diagnosis, treatment, metastasis, and prognosis of OSCC patients.[6] It is a portion of the Ezrin, Radixin, and Moesin (ERM) fraction of proteins that control the carcinogenesis progression. Moesin unambiguously controls the progression into metastasis by phosphorylation of the C-terminal part of Moesin that sends signals to the actin filament which results in changing the morphology of the cell, cell-to-cell adhesion, cell migration, and tumor incursion. Its overexpression in cancer cells spells poor prognosis.[6]

Pathogenesis of Moesin

Moesin is a biomarker of invasiveness in the advancement of carcinogenesis, especially in the II, III, and IV stages of OSCC as it stereotypically moves from the plasma membrane of the neoplastic cells to the cytoplasm[6,7] during the malignant alteration of the oral epithelium as it crosslinks between the plasma membrane and actin filament and has a greater incidence of lymph node metastasis.[8] Moesin is usually found in the basal and parabasal layers of the normal oral epithelium and in OSCC patients it is discovered more in the cytoplasm of the malignant cells. The hypothesis inferred behind this enigmatic phenomenon is correlated to the exposure of Phosphorylation of Thr-558[9,10] and proteolytic dispensation of CD44 receptor for hyaluronan[9,11] leading to the shift of moesin moiety from the plasma membrane towards the cytoplasm, thereby increasing the tumor cell migration and annexation into the deeper stratum of another cell causing invasiveness. Moreover, Moesin is not usually found in well-differentiated neoplastic cells which have more keratin pearls.[8,12]

Rationale and significance of the review

Moesin has emerged as an important and valuable new biomarker along with being a prognostic factor in OSCC

as it is a strong factor to predict mortality as its five-year survival rate is 22.7%. Robust expression of Moesin in neoplastic cells predicts an overall survival rate of 6.8% and with a low expression rate the survival rate is pegged at 23.8% in ten years.[7,9,12] Therefore, it is worthwhile to study the role of Moesin and its expression in neoplastic cells. Based on this rationale, we aimed to conduct an Aetiology/Risk type and Prognostic type of systematic review with the:

Focussed Guiding Question: Does Moesin as a prognostic biomarker have an influence and an association with histopathological grades of OSCC?

OBJECTIVES

Primary Objective: To evaluate an association between the prognostic significance of Moesin with histopathological grading of oral squamous cell carcinoma (OSCC) to gauge the severity of the condition in terms of 5 to 10-year survival.

Secondary objective: To estimate the detection of Moesin as a biomarker in the membranous, mixed and cytoplasmic sections of the oral squamous cell carcinomatous lesion.

The authors classified it as an aetiology/risk type of systematic review (as it determines to what degree a relationship exists between the exposure and health outcome) and a prognostic type of systematic review (as it identifies the relationships between the specific prognostic factors and outcomes).

METHODOLOGY

The present systematic review protocol is registered under **PROSPERO with Trial Registration No: CRD42022375824**. The authors (BS, KS, and DK) initiated the systematic review by forming a review team that included the experts in information retrieval and an advisory group i.e reviewers. The timeline set was approximately 8 months from initiation. The authors piloted an exploratory wide-ranging literature search using electronic media (Scopus, EMBASE, Web of Science, Cochrane central register for controlled trials, PubMed and Google Scholar) and manual search from appropriate journals till October 2022. The review was written and conducted as per the PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analyses). Studies relevant to this review were agreed upon using a tentative search in *Pubmed, Scopus, Web of Sciences (*http://scientific.thom*son.com/products/sci/), Cochrane library (www.cochranelibrary.com)& google scholar. Unpublished literature was searched electronically through ClinicalTrials.gov* http://www.clinica*ltrials.gov) and the ISRCTN registry (*http://www.con*trolled-trials.com). The following keyword algorithm in PubMed was applied: "Moesin", "squamous cell carcinoma of head and neck", "OSCC", "Oral Squamous Cell Carcinoma", "Histopathological, Grading", "Prognosis"*. This search was revised and improvised using the Advanced Search algorithm with the following criteria: English Language; abstracts and full texts illustrating the expression of Moesin among the histopathological grades of OSCC patients and 5 to 10-year survival rates among the cancer patients.

Inclusion criteria: Cross-sectional studies and retrospective studies to evaluate the association between the prognostic significance of Moesin with histopathological grading of oral squamous cell carcinoma (OSCC). They were appraised based on the *PICO* format (Population, Intervention, Comparison, and Outcome) listed below:

- **Population:** Studies with Adult Patients (18 years and above) whose definitive OSCC status was established with oral pathological slides were included in this study.
- **Intervention:** Detection of Moesin (biomarker) in the membranous, mixed, and cytoplasmic sections of the carcinoma.
- **Comparison:** Comparison of Moesin among the histopathological grades of oral cancer to assess its prognostic value in OSCC cases.
- **Outcome:** *Primary outcome*- the expression of Moesin among the different histopathological grades to gauge its prognostic value in terms of 5-10 year survival rates and mortality among OSCC patients.
  Secondary outcome- over-expression of Moesin in the membranous, mixed, and cytoplasmic sections of the carcinoma and lymph node metastasis as a sign of invasiveness.

Exclusion criteria: Studies with patients below 18 years of age; Studies with Moesin as a biomarker in other carcinomas other than the oral cavity were mentioned but not included in the main-stay of the research; Inclusion of literature review articles, short communications, case reports, case series, letters to the editor, and conference abstracts was excluded from this review.

Collection of data and its analysis

The pertinent studies were selected by (SB, KS, and DK) independently and the carefully chosen studies were evaluated according to the inclusion criteria mentioned above and disagreements were resolved by debate before including or excluding the study. The summary of the

design of selected and excluded studies is depicted in the PRISMA flow diagram[13] [Figure 1] and then the full-text selected studies were evaluated using GRADE-Pro GDT[14] and Rob (Risk of Bias) 2.0 Tool.[15]

Data extraction and quality management

Two reviewers (SB and KS) extracted and critically analyzed the data and tabulated the findings systematically as study reference; author; country; study design; number and age of the patients; study intervention, comparison, and outcome measures [Tables 1, 2, and 3]. The outcome was appraised and reported quantitatively, and narratively described using: the GRADE-Pro GDT tool[13] (See: Appendix), and the bias of every study was appraised using Cochrane RoB 2.0 tool[15] [Figure 2]

Assessment of data synthesis and heterogeneity

On appraising the data the authors found that the data collected from the seven studies were too heterogeneous for conducting quantitative meta-analysis or subgroup analysis and decided to report the results in a narrative format.

Risk of assessment bias

The Cochrane Risk of Bias tool[15] helped to judge the following: Randomization process (D1); Deviation from intended intervention (D2); Missing outcome data (D3); Measurement of the outcome (D4); Selection of reported result (D5); Overall Risk. The risk of bias based on the appraisal of the studies is then classified into low, high, unclear, and tabulated for convenience [Figure 3].

Addressing missing data

The problem of missing data was handled by emailing or calling the author or co-authors of the study and in case of no response, the data from the study was not discussed at the end of the study in the *Discussion* segment.

Confidence in the evidence (using Grade System for assessment of outcome measures)

The confidence in the evidence of this research was estimated using the Cochrane GRADE-Pro GDT tool.[13] This tool assigned levels such as high, moderate, low, or very low to the studies included in the review based on the estimated effect or outcome (See: Appendix).

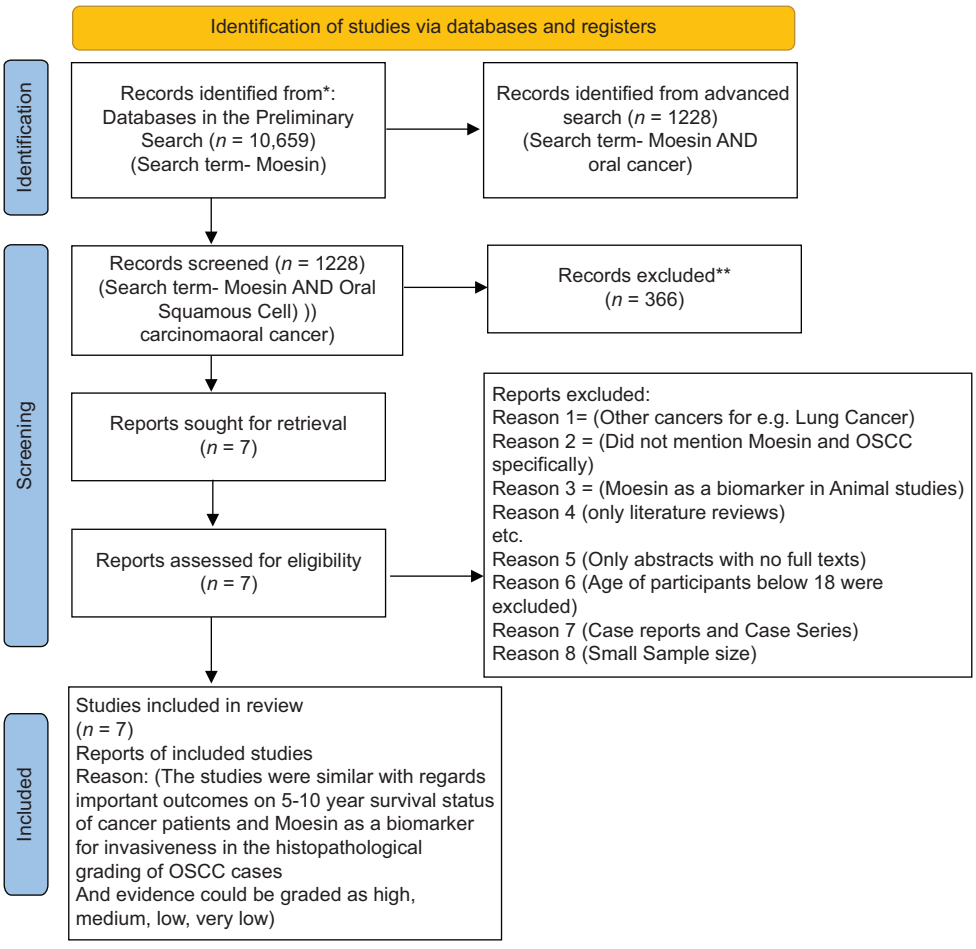

Figure 1: Illustrates prisma flow diagram. (From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.)

Table 1: Depicts study characteristics of the selected studies

Ref. No	Author/ Year	Country	Study Design	Number of cases (Tissue samples)	Age (years)	Gender	Most common Location of Lesion	Study Intervention (Moesin expression in the membranous, mixed, and cytoplasmic sections of the carcinoma)	Comparison (Moesin and histopathological Grading)	Outcome
[6]	Barros *et al*. 2018	Brazil	Cross-sectional	84	33-95 (Mean 58 years)	M=85.7%	Tongue -54.8%	Strong cytoplasmic expression of Moesin=44 tumors Weak expression of Moesin=40 tumors	Well/moderately differentiated=86.7% Poorly differentiated=13%	Strong Moesin expression (NS) In the following variables: Males, White, >58 years, tobacco consumption, alcohol consumers, T2 stage, N+, ipsilateral lymph node involvement, no recurrence, no second tumor, presence of vascular embolization, per neural infiltration, muscular infiltration, no bone infiltration Strong Moesin expression* in cases with no radiotherapy*, Lymph node involvement with 48.8%* Muscular infiltration=86.4%* Overall survival (5 years) with strong Moesin Expression* = 22.7/84 cases and 10 years=6.8/84 cases Strong moesin expression of neoplastic epithelial cells=1.737 - times higher chance of HR of death*(P<0,022)
[8]	Kobayashi *et al*. 2004	Japan	Cross-sectional	103	>65=44 <65=59	M=59 F=44	Tongue	Moesin* expression higher in the cytoplasm was higher in T3; N1/7 N2	Moesin* expression higher in the cytoplasm was higher in -Moderately differentiated	In two third patients' there was enhanced cytoplasmic expression of Moesin in metastatic lymph nodes. Tumour size and lymph node metastasis are signs of tumor aggressiveness and poor survival. Expression patterns not associated with Age or Gender Kaplan survival *for Membranous, mixed and cytoplasmic was different=(X^2=18.84* Overall survival* was dependent on Moesin expression. Moesin expression in pre-treatment cases can help with the strategic planning of OSCC cases
[9]	Kobayashi *et al*. 2003	Japan	Cross-sectional	59	>65=29 <65=30	M=34 F=25	Tongue=34	Moesin expression in OSCC cases Membranous=11 Mixed=20 Cytoplasmic=28 Cytoplasmic expression was strong at 47.5% of cases (28/59 OSCC cases)	Moesin cytoplasmic expression in * Well differentiated=13/38) Moderately differentiated=9/13 Poorly differentiated=6/8	Cytoplasmic expression of Moesin was maximum in stage II (9/25) and IVA (14/23)
[16]	Li *et al*. 2015	China	Cross-sectional	176	>60=53 <60=53	M=61 F=45	Tongue=41	Moesin expression: Membranous=27.4% Mixed=32.1% Cytoplasmic=40.5%	Strong Moesin* cytoplasmic expression Well=3/2 differentiated2 Moderately differentiated=11/30 Poorly differentiated=29/54	Lymph node metastasis with strong Moesin cytoplasmic expression=27/46* and was associated with poor 5- year survival

Contd...

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[17]	Jubair *et al.* 2016	Baghdad	Cross-sectional	30/42 (OSCC tissue samples)	24-99 years (Mean age 59±15.3 years)	M=27 F=15	Tongue	Moesin expression (NS) Cytoplasmic=86.7% Membranous=1% Mixed=3%	Moesin* Well -differentiated 46.7% Moderately differentiated=40% Poorly differentiated=13.3%	No statistical significance between the Moesin score and different grades of oral squamous cell carcinoma
[18]	Assao *et al.* 2018	Brazil	Cross-sectional	91	<45 years=24 >45-70=44 >70=22	M=75 F=16	Lip	Moesin expression was scored as 0=absent to strong 6-8) The results of the clinic-pathological Moesin expression were strong in 73 cases but they were statistically NS Nevertheless, the following factors showed strong Moesin expression: Male Gender; >45 to seventy years; usage of tobacco and alcohol; T1N0 stages; no radiotherapy; no vascular embolization; no peri neural infiltration; no muscular, glandular infiltration	Histopathological Grading Moesin expression was strong in the low=risk cases (50.7%) and the intermediated cases (49.3%) (NS).	There was a significant lymph-node metastasis in the lip carcinoma cases and the overall survival rate reduced from 67% to 34.4% The Moesin expression* was highest in the category of non-dissected nodes with 92% having atleast 5- year survival and 81% with a 10 -year survival. Loco- regional recurrence in: 24/91 patients. Overall disease free- survival 5-10 year survival was mean 247 months (s.d=23.3 months) (NS) Overall survival rates in tumurs having strong Moesin expression had a reduced 5-10 year survival rate -80.8% and 65.8% respectively. (NS). Disease-free 5-10 year survival rates were: 73.9% and 63% in strong Moesin expression (NS)
[19]	Belbin *et al.* (2005)	US	Cross-sectional	102	Not mentioned	Not Mentioned	Tongue	Moesin expression is enhanced in the cytoplasm of OSCC cases as compared to the normal epithelium.	Moesin expression is higher in stages III and IV of OSCC cases	Moesin expression was highest in the primary tumor Mean- (70.9% CI=70.2-81.9%) and lowest in the normal epithelium (7.2% CI=4.3-10%). Moesin expression was highest in lymph node metastasis and OSCC progression.

*Statistical significance - $P<0.05$; NS=Non-Significant

Table 2: Depicts appraisal of selected studies

Ref. No	Author/Year	Setting	Treatment	Follow-up time	Controls
[6]	Barros *et al*. 2018	Cancer Hospital	84 surgical specimens of cases who underwent primary surgical removal of the carcinoma	288 months	Not Mentioned
[8]	Kobayashi *et al*. 2004	University Hospital	31 with no lymph-node metastasis underwent Radiotherapy 72 underwent surgery	32 months	Yes- normal mucosa of the third molar region
[9]	Kobayashi *et al*. 2003	University Hospital	Not mentioned	Not Mentioned	Yes- normal mucosa of the third molar region
[16]	Li *et al*. 2015	University Hospital	146 OSCC cases 50 epithelial dysplasia	60 months	Normal Mucosa (20 cases)
[17]	Jubair *et al*. 2016	Laboratory archives	Not Mentioned	Not Mentioned	Not Mentioned
[18]	Assao *et al*. 2018	Cancer Hospital	436 underwent primary surgical resection of lower lip carcinoma and 91 were considered for the study based on the inclusion criteria	394 month	Not Mentioned
[19]	Belbin *et al*. 2005	Tertiary care facility	Specimens from 9 patients with OSCC	Not mentioned	Normal Mucosa

*Statistical significance - $P<0.05$; NS=Non-Significant

Table 3: Depicts validity of the selected studies

Ref. no	Author/Year	Clearly focused question (Yes/No/Unclear)	Use of valid methods to address the question (Yes/No/Unclear)	Are the results reliable, valid, and important (Internal validity) (Yes/No/Somewhat clear/Unclear)	External Validity
[6]	Barros *et al*. 2018	Yes	Yes	Yes	Yes
[8]	Kobayashi *et al*. 2004	Yes	Yes	Yes	Yes
[9]	Kobayashi *et al*. 2003	Yes	Yes	Unclear	Unclear
[16]	Li *et al*. 2015	Yes	Yes	Somewhat Clear	Unclear
[17]	Jubair *et al*. 2016	Yes	Yes	Unclear	Unclear
[18]	Assao *et al*. 2018	Yes	Yes	Unclear	Unclear
[19]	Belbin *et al*. 2005)	Yes	Yes	Somewhat Clear	Unclear

*Statistical significance - $P<0.05$; NS=Non-Significant

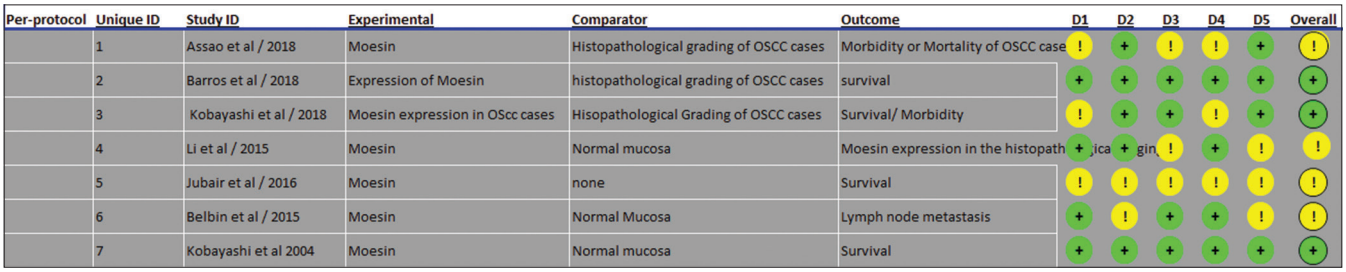

Figure 2: Illustrates the risk of bias analysis of included studies using Cochrane RoB 2.0 tool

RESULTS

Search results

A maiden literature search found 10,659 studies [Figure 1] which included mostly cross-sectional studies on the immunochemistry of tissues of oral squamous cell carcinoma patients. An advanced search narrowed it down to 1228 studies. A detailed search of the specific inclusion criteria reduced the sample of the studies to seven [Figure 1] and the excluded studies are listed [Table 4]

Characteristics of included studies

The seven main studies were tabulated for quantitative, qualitative, and critical analysis [Table 1]. Out of the seven pertinent studies, only two studies[6,8] were of good quality. The studies included in the review ranged from different countries like Japan, Brazil, China, Baghdad, and the United States, giving the review a vast overall outlook. Most of the studies were cross-sectional and were conducted in university hospitals, cancer hospitals, or tertiary care centers.[6,9,16-18,20,27] The tissues samples were stereotypically collected from male patients, more than 55 years of age, and at least 40% of the samples showed marked expression of Moesin in their cytoplasm [Table 1].

Cytoplasmic Moesin expression was higher in the poorly differentiated histopathological stages of OSCC cases as compared to the well-differentiated cases indicative of poor outcome in terms of 5 to 10-year survival rate.[6,8,16,18]

Clinical expediency of Moesin in the OSCC cases

This review has illustrated that Moesin as a biomarker is a representation of tumor aggressiveness, lymph node metastasis, and poor prognosis among OSCC cases[16]

and even other non-oral cancers [Figures 4-6]. Advanced carcinoma stages with enhanced Moesin expression in the cytoplasm have shown higher lymph node involvement in 48.8% of cases and muscular infiltration in 86.4% of patients.[6]

Moreover, the manifestation of Moesin in at least 40% of the OSCC cases is strongly associated with histopathological differentiation of the tumor cell.[9]

Moesin and survival rates in OSCC cases

Moesin expression in the cytoplasm in the later stages of cancer in OSCC cases is a hallmark of lowered survival rate (5 years = 38.5%; and 10-year survival rate is 23.8%) and 1.737 higher risks of mortality.[6] This result is echoed across other studies where the survival rate was decreased from 67% to 34.4% in lip carcinoma cases and overall survival rates were pegged at a mean of 247 months and overall survival rates among cases with strong moesin expression in the cytoplasm was 80.3% (5 years) and 65.8%(10 years) 18 [Table 1; See: Appendix].

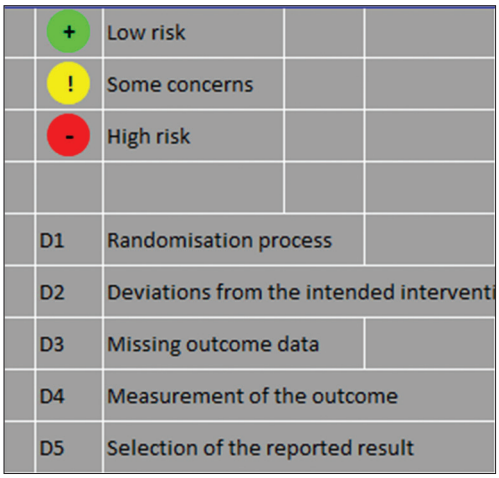

Figure 3: General explanation of risk of Bias Symbols

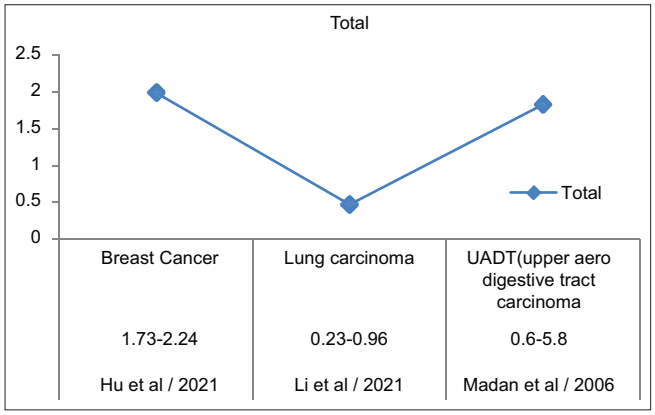

Figure 5: Hazard ratio of different cancers (excluded studies)

Risk of mortality with strong Moesin expression in the cytoplasm

The risk of mortality in terms of Hazard ratio has been elicited in two studies out of the seven Kobayashi *et al.* 2004[8] (0.209; CI (0.080- 0.554) and Barros *et al.*, 2018[6] (HR * = 1.37(CI = 1.08-2.78) [Figure 4].

As the sample size of this review was small the authors have included hazard ratios in some other studies [Figures 5 and 6] of carcinomas in diverse sites in the body [Figure 6] to give a flavor of the prognostic outcomes of Moesin. Figure 6 shows that Moesin expression in Breast cancer and UADT carcinomas have a higher mortality rate as compared to OSCC cases and this strengthens our conviction that Moesin expression in the cytoplasm of advanced histopathological stages of cancer can be assumed as a sign of poor prognosis in all carcinomas including OSCC patients.

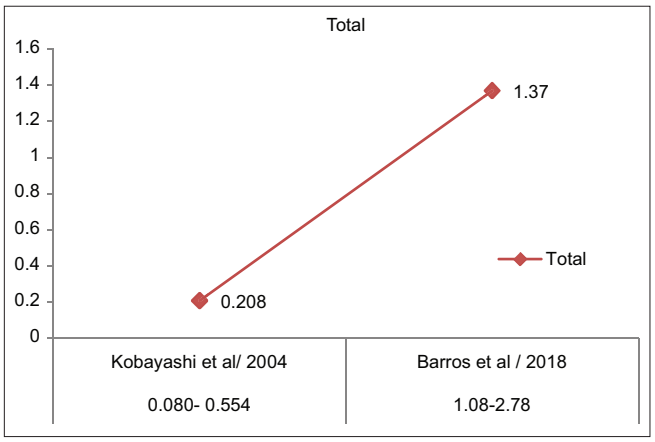

Figure 4: Hazard Ratio of included studies

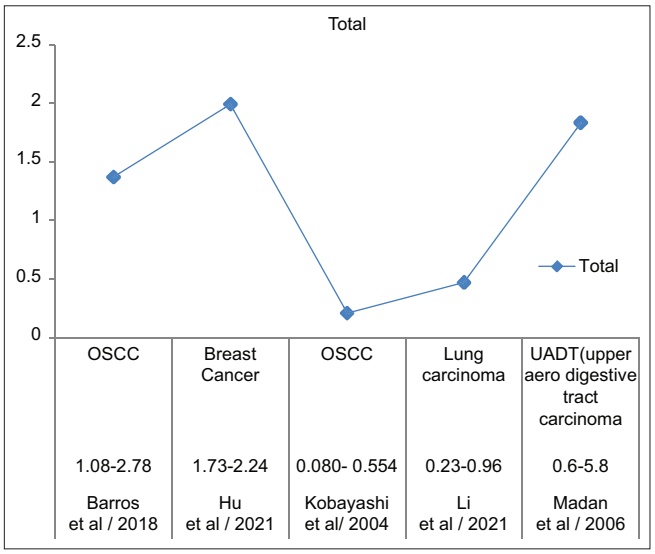

Figure 6: Hazard ratio of different cancers (all studies)

Table 4: Depicts all the excluded studies

Reference No.	Study (Author/ Year)	Reason for exclusion	Observations of excluded studies
[12]	Madan *et al*. 2006	ERM expression of the upper aerodigestive tract (UADT).	Strong cytoplasmic Moesin expression (HR=1.83 CI=0.6-5.8) was associated with Poor survival but NS)
[20]	Li *et al*. 2021	Moesin expression in Lung Carcinoma	Moesin has a lower expression in Lung cancer cases. Its expression was positively associated with the TNM staging* and with the histopathological stages*. Moesin expression HR=0.47* (CI=0.23-0.96) Immune lymphocyte infiltration was a mechanism of Moesin i.e., it has a strong interaction with inflammatory related molecules and therefore it has good prognostic value.
[21]	Liang *et al*. 2019	Moesin expression in Pancreatic Cancer	Moesin expression was * significant in the pathological stage of the cancer; its expression correlated with nerve infiltration (R^2=0.4291*) and pain severity due to cancer R^2=0,2743*).
[22]	Mhawech-Fauceglia *et al*. 2012	Moesin in Endometrial Adenocarcinoma	Strong association of Moesin* and high tumour grade (OR=2.56* CI=1.50-4.38) and tumour subtypes (OR=0.31 CI=O.15-0.60)^ But Moesin was not associated with predicting the outcome of the disease.
[23]	Hu *et al*. 2021	High Moesin expression in Breast Cancer	High Moesin expression is associated with poor outcomes in Breast cancer (HR=1.99 CI=1.73-2.24)
[24]	Bartholow *et al*. 2011	Moesin in prostatic adenocarcinoma	There was a significant decrease in Moesin stain from stage II to stage IV and therefore is not useful as a clinical biomarker in prostatic adenocarcinoma
[25]	Yonglitthipagon *et al*. 2012	Moesin Binding in cholangiocarcinoma	Moesin was correlated with moderately and poorly differentiated tumours* especially in lymphatic and vascular vessels* and reduced survival rate*. Therefore it is considered as an important prognostic biomarker in cholangiocarcinoma
[26]	Wang *et al*. 2014	Moesin expression in Laryngeal Carcinoma	Moesin had a higher intensity of expression in the laryngeal squamous cell carcinoma and the cervical metastatic lymph nodes as compared to the normal epithelium and negative moesin expression had longer survival rates. It was not significantly associated with the clinical staging of the LSCC. Wang *et al*.

*Statistical significance - $P<0.05$; NS=Non-Significant

DISCUSSION

Clinical efficacy of Moesin as a biomarker in OSCC cases

Moesin has emerged as an important biomarker with an enhanced expression in the cytoplasm as compared to the membranous sections during malignant translation of the normal oral epithelium of OSCC cases.[8,9] The presence of Moesin has materialized as a sign of lymph node metastasis and poor prognosis in terms of reduced survival rates in OSCC patients. This verdict is consistent with previous studies.[8,9,16] But Moesin has been corroborated as an unfavorable prognostic biomarker in OSCC cases.[6,9,16,18]

Prognostic value of Moesin in the histopathological grades of OSCC patients

Most studies in this review found that Moesin was strongly associated with the histopathological grading for cancer[6,8,9,16,18,26] but was not elicited in a study[17] done in Baghdad where no statistical significance was elicited between the expression of Moesin and its association with the histopathological grading in OSCC cases. In a study[26] on laryngeal squamous cell carcinoma (LSCC), Moesin expression did not show any association with the advanced clinical staging (III and IV). Moreover, Moesin has not been known to be associated with the demographic and clinical features of the patients.[6,8,9,26]

Survival among OSCC cases

Moesin expression in the cytoplasm of OSCC cases spells poor 5 to 10 survival rates. The overall survival rates dip from 67% to almost 34% among OSCC patients.[18] This finding is consistent with even other findings in different types of cancers[16,18,21-25] where the hazard ratio is depicted in Figure 4 and the risk or mortality ranges from 1.73 to 5.8 [Figure 6].

Limitations of the study

The small sample has been the prime limitation of this review as most studies are cross-sectional with no randomized control trials conducted on this issue according to the author's search for relevant studies. Most studies did not calculate or report the Hazard ratio or Odds ratio of Moesin expression making it difficult to elicit the survival rates as a prognostic outcome among OSCC cases. This element of divergence in the conduct of the heterogeneous studies did not allow the authors to conduct a meta-analysis to estimate the size of the effect among the OSCC patients.

CONCLUSION

Albeit the sample size of this review is inadequate the importance of Moesin as a clinical biomarker among OSCC cases points towards its importance as a prognostic tool to elicit survival and mortality rates among the different histopathological grades of oral carcinoma.

Ethics and dissemination

Acknowledgments

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Contributors

BS, SK, and DK contributed to drafting and revising the protocol of this research by developing the research question, and research design, formulating the research strategy, and extracting & critically appraising the data using the tools mentioned in the protocol. They were responsible for the final draft and publication of the research.

Patient consent for publication

Not needed.

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Conflicts of interest

There are no conflicts of interest.

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APPENDIX

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

(Ref no. 6) Barros *et al*. 2018 Summary of findings:				
Moesin as a biomarker compared to histopathological grading in OSCC cases Patient or population: OSCC cases Setting: Multicenter Intervention: Moesin as a biomarker Comparison: histopathological grading in OSCC cases				
Outcome No of participants (studies) 84	Impact High	High Certainty	Survival and Mortality (Moesin and Histopathological grading) Noof participants: 84 (1 study)	Strong Moesin expression Lymph node involvement with 48.8%* Muscular infiltration=86.4%* Survival rate with strong Moesin expression 5 years=38.5% 10 years=23.8%. Strong moesin expression of neoplastic epithelial cells=1.737 - times higher chance of relative risk of death* (*P*<0,022)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio

Ref. no 8: Kobayashi *et al*., 2004
Summary of findings:

Moesin expression in cytoplasm of advanced stage of carcinoma compared to normal mucosa for cancer prognosis
Patient or population: cancer prognosis
Setting:
Intervention: Moesin expression in cytoplasm of advanced stage of carcinoma
Comparison: normal mucosa

Outcome No of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
				Difference		
5-10 year survival (survival) assessed with: Hazard Ratio follow-up: mean 32 months no of participants: 108 (1 non-randomised study)	HR 0.209 (0.080 to 0.554) [5-10 year survival]	0.0%	Low NaN% (NaN to NaN)	– (– to –)	⊕⊕⊕⊕ High	Moesin* Cytoplasmic -HR (1.000) Mixed HR (0.20)/CI (0.067-0.61) Membranous (0.07)/CI (0.009-0.532) In two third patients there was enhanced cytoplasmic expression of Moesin in metastatic lymph nodes. Tumour size and lymph node metastasis is a sign of tumour aggressiveness and poor survival. Moesin expression in cytoplasm of advanced stage of carcinoma results in a slight increase/reduction in 5-10 year survival.
New outcome no of participants: (studies)					-	
New outcome no of participants: (studies)	not estimable	0.0%	0.0% (0-0)	0.0% fewer (0 fewer to 0 fewer)	-	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; HR: hazard Ratio
GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Ref. no 9: Kobayashi *et al*. 2003
Summary of findings:

Moesin as a biomaker compared to histopathological grading for OSCC cases
Patient or population: OSCC cases
Setting: Multicenter
Intervention: Moesin as a biomaker
Comparison: histopathological grading

Outcome No of participants (studies) = 111	High Impact	Low Certainty	Survival, Morbidity and Mortality (Moesin and Histopathological grading) no of participants: 116 (1 study)	Cytoplasmic expression was strong at 47.5% cases. Cytoplasmic expression of Moesin was maximum in stage II (9/25) and IVA (14/23) Expression of Moesin was statistically significant (P<0.05) with the differentiation of the tumor cells.	-

Ref no 16: Author(s): Li *et al.*/2015

Question: Expression of Moesin as a biomarker compared to histopathological grading in OSCC cases for oral cancer patients

Setting: Multicenter

Certainty assessment							Impact	Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
New outcome (assessed with: Histopathological grading of oral cancer)									
1	Observational	not serious	none	not serious	not serious	strong association dose response gradient	Moesin expression is seen in poorly differentiated OSCC cases and its expression is enhanced in the cytoplasm during malignant transformation of oral epithelium. It is a biomarker for poor prognosis of OSCC cases Moesin may be a potential candidate for targeted gene therapy for OSCC cases in the future	Low	CRITICAL

CI: confidence interval

Ref no. 17: Jubair *et al*. 2016 Summary of findings					
Moesin as a biomarker compared to histopathological grading for OSCC cases Patient or population: OSCC cases Setting: Multicenter Intervention: Moesin as a biomarker Comparison: histopathological grading					
Outcome	No of participants (studies) = 42	Low Impact Due to smaller sample size	Low Certainty	Histopathological cellular differentiation between OSCC cases (Moesin and Histopathological grading) No of participants: 42 (1 study)	Moesin expression (NS) Cytoplasmic=86.7% Membranous=3.3% Mixed=3% No statistical significance between the Moesin score and different grades of oral squamous cell carcinoma	-

Ref: 18: Assao *et al*. 2018
Summary of findings

Moesin as a biomaker compared to histopathological grading for OSCC cases
Patient or population: OSCC cases
Setting: Multicenter
Intervention: Moesin as a biomarker
Comparison: histopathological grading

Outcome No of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI) Difference	Certainty	What happens
Moesin expression in lip carcinoma (Moesin and Histopathological grading) assessed with: Semi-quantitative score method No of participants: 42 (1 study)	No statistical significance between the Moesin score and clinic pathological variables of lip oral squamous cell carcinoma. But Moesin had a strong expression in lip cancer cases and low -10 year survival rates. Moesin * expression was strong in the low risk cases and the intermediated cases alike. Strong cytoplasmic expression at the invasive front of the lip carcinoma relating to a higher potential of invasion and metastasis But Moesin has not proved to be a good prognostic marker in this study		Low	There was a significant lymph-node metastasis in the lip carcinoma cases and the overall survival rate reduced from 67% to 34.4%The Moesin expression* was highest in the category of non-dissected nodes with 92% having atleast 5 year survival and 81% with 10 year survival.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; RR: risk ratio
GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Ref 19: Belbin *et al*., 2005
Summary of findings

Moesin expression in the cytoplasm compared to Normal Mucosa in OSCC progression
Patient or population: OSCC progression
Setting:
Intervention: Moesin expression in the cytoplasm
Comparison: Normal Mucosa

Outcome No of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
New outcome No of participants: (studies)	-	The mean new outcome was 7.2	-	mean 70.9 higher (70.2 higher to 81.9 higher)	Low-	Moesin expression is enhanced in the cytoplasm of OSCC cases as compared to the normal epithelium. Moesin expression is higher in stage III and IV of OSCC cases. Moesin expression was highest in lymph node metastasis and OSCC progression
Mean expression of Moesin in OSCC cases vs. Normal mucosa assessed with: Mean No of participants: 102 (observational studies)	Mean 70.9 (70.2 to 81.9)	0.0%	0.0% (0 to 0)	0.0% fewer (0 fewer to 0 fewer)	-	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval

GRADE Working Group grades of evidence. High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.