REVIEW

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Diagnostic Efficacy of Serum Biomarkers for Oral Cancer: An Updated Systematic Review and Meta-Analysis

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Abstract

Aim: Evaluating Diagnostic Ability Of Various Serum Biomarkers For Oral Cancer (OSCC). **Methods:** Review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – Diagnostic Test Accuracy (PRISMA-DTA) checklist, and the review protocol was registered under PROSPERO (CRD42024625802). Databases were searched from January 2000 to December 2024 to identify the diagnostic potential of various serum biomarkers. Quality assessment was evaluated based on the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) tool, and meta-analysis was performed in Meta-Disc 1.4 software and Review Manager 5.3 for pooled sensitivity, specificity, positive likelihood ratio (+PLR), negative likelihood ratio (–NLR), diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves. **Results:** Twenty-three studies were included in the review, with data evaluated from 3,309 subjects (diseased – 2,069 and 1,240 – controls). The included studies showed a moderate to high risk of bias. Various biomarkers such as CYFRA 21-1, E-cadherin, interleukins (IL-6, IL-8), protein peaks, matrix metalloproteinases (MMP-9), vascular endothelial growth factor (VEGF), galectins (1, 3), and various RNA biomarkers were evaluated, belonging to the protein and microRNA classes of biomarkers. It was found that these biomarkers had sensitivity and specificity ranging from 16% to 94% and 37% to 100%, respectively, with the highest accuracy shown by IL-8, which had a mean sensitivity and specificity of 86.5% and 98%. The highest AUC was observed for CYFRA 21-1 (0.53), suggesting that the overall diagnostic accuracy of these serum biomarkers is moderate to good in diagnosing the desired condition. **Conclusion:** Serum biomarkers are a valid tool and, overall, have good diagnostic potential in identifying the target condition. They can be used as an alternative adjunct to histopathology. Serum biomarkers also have significant potential in predicting and diagnosing disease outcomes, and they can improve the quality and reach of early screening and detection of OSCC. Serum biomarkers can be employed for early diagnosis and prompt treatment under the secondary level of prevention.

Keywords: Biopsy- diagnosis- histopathology- prognosis- serum biomarkers- systematic review

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Introduction

Oral cancer is the sixth most common malignancy worldwide [1]. Approximately, 90% of cancer located in the oral cavity are oral Squamous Cell Carcinoma (OSCC) [1]. Most oral cancers are superficial and easily detected, but deeply located tumours may not be noted until they have grown large and reached an advanced stage [2].

Oral cancer ranks among the top 10 most common cancers globally, with over 500,000 new cases annually [3]. Approximately 90-95% of oral cancers originate from mouth-lining cells [3]. This disease poses significant global health concerns, responsible for over 200,000 deaths in 2012 and projected to rise to 856,000 cases by 2035 [4].

Despite easy accessibility for examination, effective screening mechanisms for early lesions remain elusive [5]. Most lesions go untreated until advanced or metastasized. A technique distinguishing between normal, inflammatory, premalignant, and malignant cases rapidly would enhance detection and treatment efforts [6].

Adjuvant diagnostic techniques have been suggested, but evidence supporting their use is limited [7]. Biopsy, the gold standard for oral cancer diagnosis, is often impractical for screening due to its invasive nature and limited expertise [8]. Disappointingly, survival has not markedly improved in recent decades because patients still frequently develop local and regional recurrences, distant metastases and secondary tumours [9].

At present, several therapeutic approaches are used in the management of OSCC, but they are typically aggressive and associated with numerous side effects that significantly hamper patient quality of life [10].

The main treatments for OSCC are Surgery,

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Radiotherapy, Chemotherapy, or a combination of two or more of these techniques [10]. The search for new OSCC therapies should consider both the ability of patients to tolerate the treatment's side effects and the toxicity associated with that treatment [11]. To reduce the side effects and toxicity caused by these conventional treatments, researchers have invested great efforts to develop effective and less invasive diagnostic methods capable of identifying OSCC at early stages [11].

Biomarkers have emerged as critically important tools to detect diseases in their various clinical stages by increasing the accuracy to precisely characterize the disease in a diagnostic or prognostic level. Serum Biomarkers are defined as substances changing quantitatively in the serum during tumour development [12]. Classically, a marker is synthesized by the tumour and released into circulation or expressed at the cell surface in large quantity by malignant cells [13]. These markers can been used in the prognosis of tumour recurrence or metastasis because the development of the malignant tumour changing their concentrations [14].

The mortality rate in OSCC can be effectively reduced through the prevention, early detection, and treatment, thus leading to better outcomes in OSCC patients [15, 16].

Till date, no studies have provided a comprehensive, quantitative and diagnostic accuracy analysis of various Serum Biomarkers for OSCC diagnosis. Therefore, we updated our research for existing scientific evidences and conducted this review with the aim to assess and evaluate the diagnostic accuracy of Serum Biomarkers compared to histopathological investigation in patients with Oral Squamous Cell Carcinoma (OSCC).

Materials and Methods

Protocol and Registration

The review was adhered in accordance to PRISMA- DTA checklist and registered in PROSPERO (CRD42024625802).

Study Design

The focused research question in the Participants (P), Index test (I), Reference standard (R) and Target Condition (T) format was proposed "Is there a difference in the diagnostic accuracy of Serum Biomarkers (Index Test) compared to biopsy/histopathological investigations (gold standard) for Oral Squamous Cell Carcinoma (OSCC) diagnosis?

P – Patients With Oral Cancer

I – Serum Biomarkers

R – Biopsy followed by histopathological investigation

D – Sensitivity, Specificity, Area Under The Curve (AUC), Likelihood Ratio (LR), Diagnostic Odds Ratio (DOR)

Eligibility Criteria

Inclusion Criteria

(1) Cross-sectional and analytical studies comparing the diagnostic accuracy of Serum Biomarkers compared to biopsy followed by histopathological investigation were included

(2) Studies involving the diagnostic ability of various Serum Biomarkers for OSCC

(3) Outcome measure reported in terms of sensitivity, specificity, accuracy with their estimation method.

(4) Articles written in English language and from open access journals

(5) Articles from January 2000 – December 2024 and available as free available full text articles

Exclusion Criteria

(1) In-vitro studies, animal studies, case reports and case series were excluded

(2) Patients with presence of any systemic complication

(3) Patients with oral potentially malignant disorders (OPMD) or oral epithelial dysplasia (OED) were excluded

(4) Studies not reporting primary outcomes of accuracy, sensitivity, and specificity

Search Protocol

Keywords and Medical Subject Headings terms were selected and combined with Boolean operators such as AND/OR, and we conducted the search strategy according to the PIRD format (population, index test, reference standard, and diseased condition) as shown.

Search Strategy according to PIRD Format

	Strategy
Population	("Oral Cancer Diagnosis"[Mesh Terms] OR "Oral Cancer Prediction" OR "Malignant Transformation" OR ("Oral Squamous Cell Carcinoma"[Mesh Terms] OR "Head And Neck Cancer") OR ("Diagnosis"[Mesh Terms] OR ("Prognosis").
Index Test	("Serum Biomarkers"[Mesh Terms] OR "Diagnosis" AND "Oral Cancer" AND "Oral Squamous Cell Carcinoma" OR "Diagnostic Accuracy" OR "Tissue Fluids" OR "Tissue Biopsy" AND "Treatment/Surgery" OR "Oral Tissue" OR ("Diagnostic Accuracy" AND "Sensitivity" AND "Specificity"
Reference Standard	"Histopathology" OR "Oral Biopsy"[Mesh Terms] OR "Tissue Biopsy" AND "Treatment/Surgery" OR "Oral Tissue" OR ("Diagnostic Accuracy" AND "Sensitivity" AND "Specificity"
Diseased Condition	((("Sensitivity AND Specificity"[Mesh Terms] OR "Head And Neck Cancer" OR ("Oral Cancer"[Mesh Terms] OR ("Diagnostic Accuracy") AND "Oral Potentially Malignant Disorder" OR "Oral Squamous Cell Carcinoma" OR ("Comparative Study" AND "Randomized Controlled Trial" AND "Cross-Sectional Study" OR "Prospective Study".

Screening process

A rigorous two-phase screening process was conducted by two authors to select relevant articles. Initially, titles

and abstracts were reviewed, and non-relevant articles were excluded. In phase two, full-text reviews were performed independently by the same reviewers, with disputes resolved through discussion. A third reviewer was consulted when necessary to ensure consensus.

Data extraction

For included studies, study details were extracted under following headings: authors, study year, sample size (diseased cases/controls), study design, Biomarkers evaluated, class of biomarker and method of estimation. Metrics such as sensitivity and specificity were gathered, and data like true positive (TP), true negative (TN), false positive (FP), and false negative (FN) were computed for the studies using the formulas following formulas: a) False positive = (1-specificity) x (1- diseased cases/ total sample); b) True negative = specificity x (1- diseased cases/ total sample); c) True positive = sensitivity x diseased cases/ total sample; d) False negative = (1- sensitivity) x diseased cases/total sample.

Assessment of methodological quality

To assess methodological quality, we used the quality assessment of diagnostic accuracy studies - 2 (QUADAS-2) tool [17], evaluating several domains like patient selection, index test, reference standard, and timing and flow of patients. Each domain included flagging questions with responses of "Yes," "No," or "Unclear." The overall risk of Bias was assessed as high when answered 'No' to any question, low when responded 'Yes' to all inquiries, and unclear when replied 'Unclear' to all questions or combined with any 'Yes' within the Review Manager (revman) software version 5.3.

Statistical analysis

Sensitivity and specificity were calculated with SROSCC which is interpreted as: >80% as excellent, 70% - 80% as good, 60% - 69% as fair and <60% as poor diagnostic ability [18].

Data synthesis

For calculating heterogeneity, Higgins I^2 test was utilized which could be low (I^2 <50%) or high (I^2 >50%) [19].

Additional analysis

Positive Likelihood Ratio (PLR) And Negative Likelihood Ratio (NLR) with DerSimonian-Laird's method employing random effect model was considered. Positive likelihood ratio (PLR) in range of 2-5, 5-10 and >10 represents small, moderate and large increase in probability of disease when test is positive while negative likelihood ratio (NLR) in range of 0.2-0.5, 0.2-0.1 and <0.1 represents small, moderate and large decrease in probability of disease when test is negative [20].

Results

Study Selection

After copies evaluation, references of all included studies were screened. Of which 30 records were barred. After this full text articles were evaluated for qualification and articles that didn't meet consideration rules were barred. Twenty-three studies fitted into inclusion criteria and were subjected to qualitative analysis and twenty-one studies for meta-analysis as shown in Figure 1.

Study Characteristics

A summary of descriptive characteristics of all included studies is shown in Table 1. Data was evaluated from twenty-three studies21-43 from an aggregate sample size of 3309 patients, of which diseased cases were 2069 and 1240 were controls. All the included studies were cross-sectional in nature. Among the included studies, five studies were from India [33,35,36,39,41], four studies were from USA [23,27,30,34] and China [22,28,38,42] three studies each from Spain [21,26,31], Taiwan [25,32,40] and one study each from France [24], Belgium [29], Germany [37] and Iran [43]. All the included studies, assessed and evaluated the diagnostic accuracy of various Biomarkers like CYFRA 21 -1, E – Cadherin, interleukins, (IL-6, IL-8), protein peaks, Matrix Metalloproteinases (MMP ,9), Vascular Endothelial Growth Factor (VEGF), Galectin (1,3) And Various RNA Biomarkers. All these Biomarkers belong to protein and microRNA class of biomarkers.

As shown in below Table 2, various Serum Biomarkers (index test) were compared with the reference standard. It was found that all these Biomarkers had sensitivity and specificity ranging from 16% to 94% and 37% to 100%. CYFRA 21-1 had mean sensitivity and specificity of 60.5% and 93.5%. E-CADHERIN mean sensitivity and specificity of 56% and 71%. Protein peaks had mean sensitivity and specificity of 80.3% and 77%. MMP-2 had mean sensitivity and specificity of 32.5% and 67% while MMP-9 had mean sensitivity and specificity of 50% and 74.67%. VEGF had mean sensitivity and specificity of 76% and 88.33%. GALECTIN 1 had mean sensitivity and specificity of 56% and 80% while GALECTIN 3 had mean sensitivity and specificity of 63% and 75%. IL -6 had mean sensitivity and specificity of 73% and 99% while IL-8 had mean sensitivity and specificity of 86.5% and 98% and mirna Biomarkers had mean sensitivity and specificity of 77.75% and 81.5%.

Risk of Bias within Studies

For risk of Bias domain, the patient selection and index test criteria were at the highest risk while reference standard and flow and timing were at lowest risk while for applicability concern, the patient selection and index test were at highest risk while reference standard at lowest risk. The flow and timing and reference standard had low risk due to absence of insufficient details reported. Patient selection had high risk, which was mainly due to use of case-control design as depicted in Figure 2 and 3.

Synthesis of Results

Summary statistics measure was calculated in terms of pooled sensitivity, specificity, positive and negative likelihood ratio (PLR & NLR), diagnostic odd's ratio (DOR) and area under the curve (AUC) for determining the overall diagnostic accuracy of various serum

Table 1. Descriptive Study Details of Included Studies

Authors, year of study	Country	Sample size (Diseases/ total)	Study Design	Biomarkers evaluated	Class of biomarker	Estimation method
Ayude et al., 2003 [21]	Spain	40/101	Cross-sectional	CYFRA 21 -1	protein	Colorimetry assay, biuret method
Deng et al., 2003 [22]	China	142/50	Cross-sectional	CYFRA 21 -1	protein	ECLIA
St. John et al., 2004 [23]	USA	19/31	Cross-sectional	IL-6	Protein, mRNA	RNA isolation, RT-PCR, real time PCR
Ceruse et al., 2005 [24]	France	300/71	Cross-sectional	CYFRA 21-1	protein	IRMA
Cheng et al., 2005 [25]	Taiwan	57/29	Cross-sectional	Protein peaks	protein	MALDI-TOFMS
Al Kassam et al., 2007 [26]	Spain	39/10	Cross-sectional	MMP-2, MMP-9	protein	ELISA
Linkov et al., 2007 [27]	USA	116/117	Cross-sectional	MMP- 2	protein	Multiplex immunobead-based serum analysis
Cheng et al., 2008 [28]	China	252/110	Cross-sectional	Protein peaks	protein	SELDI – TOF MS
Saussez et al., 2008 [29]	Belgium	102/38	Cross-sectional	Galectin -1, Galectin -3	protein	ELISA, immunohistochemistry
Gourin et al., 2009 [30]	USA	46/97	Cross-sectional	Protein peaks	protein	SELDI – TOF MS
Marcos et al., 2009 [31]	Spain	39/10	Cross-sectional	E-Cadherin, MMP-2, MMP-9	Protein	ELISA
Liu et al., 2010 [32]	Taiwan	43/21	Cross-sectional	miR -31	microRNA	RT-qPCR
Singh et al., 2011 [33]	India	75/50	Cross-sectional	MMP-2, MMP-9	protein	ELISA
Malhotra et al., 2012 [34]	USA	78/49	Cross-sectional	IL-6, IL-8, VEGF	protein	ELISA, immune-array
Naik et al., 2012 [35]	India	60/20	Cross-sectional	VEGF -A	mRNA	RT-qPCR, ELISA
Aggarwal et al., 2014 [36]	India	70/30	Cross-sectional	VEGF	protein	ELISA
Ries et al., 2014 [37]	Germany	57/33	Cross-sectional	microRNA	microRNA	RT-PCR
Wang et al., 2014 [38]	China	52/49	Cross-sectional	miR-21	microRNA	qRT-PCR
Aggarwal et al., 2015 [39]	India	60/30	Cross-sectional	Galectin 1, Galectin 3	protein	ELISA
Lu et al., 2015 [40]	Taiwan	90/53	Cross-sectional	miR-196a and miR-196b	microRNA	RT-qPCR
Rajkumar et al., 2015 [41]	India	100/100	Cross-sectional	CYFRA 21	Protein	ELISA
Fan et al., 2020 [42]	China	212/121	Cross-sectional	LOC284454	microRNA	RT-qPCR
Karimi et al.,2020 [43]	Iran	20/20	Cross-sectional	miR-21, miR-24, and miR-29a	microRNA	RT-qPCR

CYFRA, cytokeratin fragment; ELISA, enzyme linked immunosorbent assay; IL, interleukin; IRMA, immunoradiometric assay; MALDI – TOF MS, matrix-assisted laser desorption ionization time -of-flight mass spectrometry; MMP, matrix metalloproteinase; RNA, ribonucleic acid; RT-PCR, reverse transcriptase polymerase chain reaction; SELDI – TOF MS, surface enhanced laser desorption/ionization time-of-flight mass spectrometry; VEGF, vascular endothelial growth factor

biomarkers.

A) CYFRA 21 -1

As shown in Figure 4. (a), (b), data was evaluated from four studies [21,22,24,41] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.37 (CI 0.03- 0.87) and pooled specificity was 0.42 (CI 0.03- 0.91) with I^2 being 0%.

Likelihood ratio was estimated which signifies the ability of the index test to predict the test results (positive / negative) when the disease condition in actual is present or absent. As shown in Figure 5 (a), (b), pooled positive likelihood ratio (PLR) 0.65 (0.16 – 2.53) and negative likelihood ratio (NLR) 1.33 (0.41 – 41.26) was estimated. Pooled +PLR suggested that CYFRA 21-1 is 0.65 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that CYFRA 21-1 is 1.33 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 1. The pooled Diagnostic Odds Ratio (DOR) is 0.36 (0.01 – 9.26) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

A) E CADHERIN

As shown in Supplementary Figure 2. (a), (b), data was evaluated from two studies [27,31] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.46 (CI 0.01- 0.98) and pooled specificity was 0.14 (CI 0.01- 0.98) with I^2 being 0%.

As shown in Supplementary Figure 3. (a), (b), pooled positive likelihood ratio (PLR) 0.53 (0.10 – 2.81) and negative likelihood ratio (NLR) 3.93 (0.03 – 441.65) was estimated. Pooled +PLR suggested that E-CADHERIN is 0.53 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that E-CADHERIN is 1.14 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

Table 2. Showing Descriptive Diagnostic Accuracy Values

Authors, year of study	True positive (TP)	True negative (TN)	False positive (FP)	False negative (FN)	Sensitivity (%)	Specificity (%)
		CYFRA 21 -1				
Ayude et al., 2003 [21]	0.14	0.67	0.24	0.86	50	96
Deng et al., 2003 [22]	0.44	0.2	0.68	0.56	60	94
Ceruse et al., 2005 [24]	0.58	0.13	0.75	0.42	72	94
Rajkumar et al.,2015 [41]	0.3	0.4	0.4	0.7	60	90
		E CADHERIN				
Al Kassam et al., 2007 [26]	0.44	0.08	0.5	0.55	56	71
Marcos et al.,2009 [31]	0.44	0.08	0.5	0.55	56	71
PROTEIN PEAK						
Cheng et al.,2005 [25]	0.54	0.29	0.62	0.45	82	96
Cheng et al.,2008 [28]	0.6	0.15	0.55	0.39	87	85
Gourin et al.,2009 [30]	0.23	0.18	0.18	0.77	72	50
		MMP -2				
Marcos et al.,2009 [31]	0.38	0.01	0.57	0.62	49	39
Singh et al., 2011 [33]	0.09	0.35	0.55	0.43	16	95
		MMP -9				
Al Kassam et al., 2007 [26]	0.24	0.16	0.67	0.76	49	37
Marcos et al.,2009 [31]	0.24	0.16	0.67	0.76	32	92
Singh et al., 2011 [33]	0.09	0.35	0.55	0.43	69	95
		VEGF				
Malhotra et al.,2012 [34]	0.54	0.36	0.59	0.39	89	98
Nayak et al.,2012 [35]	0.55	0.25	0.75	0.4	73	100
Aggarwal et al.,2014 [36]	0.46	0.2	0.37	0.54	66	67
		GALECTIN -1				
Saussez et al.,2008 [29]	0.16	0.27	0.73	0.84	22	100
Aggarwal et al.,2015 [40]	0.57	0.17	0.51	0.43	90	60
		GALECTIN -3				
Saussez et al.,2008 [29]	0.26	0.17	0.63	0.74	36	90
Aggarwal et al.,2015 [39]	0.56	0.17	0.51	0.4	90	60
		IL-6				
St. John et al.,2004 [23]	0.21	0.63	0.37	0.78	57	100
Malhotra et al.,2012 [34]	0.55	0.36	0.59	0.45	89	98
		IL-8				
Malhotra et al.,2012 [34]	0.55	0.36	0.59	0.45	89	98
Linkov et al.,2014 [27]	0.42	0.48	0.51	0.58	84	98
		miRNA				
Liu et al.,2010 [32]	0.5	0.14	0.48	0.5	74	81
Ries et al.,2014 [37]	0.27	0.31	0.29	0.73	55	80
Wang et al.,2014 [38]	0.48	0.21	0.24	0.5	94	73
Lu et al.,2015 [40]	0.55	0.58	0.55	0.45	88	92

As shown in Supplementary Figure 4. The pooled Diagnostic Odds Ratio (DOR) is 0.14 (0.00 – 52.20) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

As shown in Supplementary Figure 5. (a), (b), data was evaluated from three studies [25,28,30] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.46 (CI 0.03- 0.95) and pooled specificity was 0.31 (CI 0.00- 0.96) with I^2 being 0%.

As shown in Supplementary Figure 6. (a), (b), pooled positive likelihood ratio (PLR) 0.75 (0.18 – 3.15) and negative likelihood ratio (NLR) 1.55 (0.16 – 14.83) was estimated. Pooled +PLR suggested that protein peak is 0.75 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that protein peak is 1.44 times as likely to have

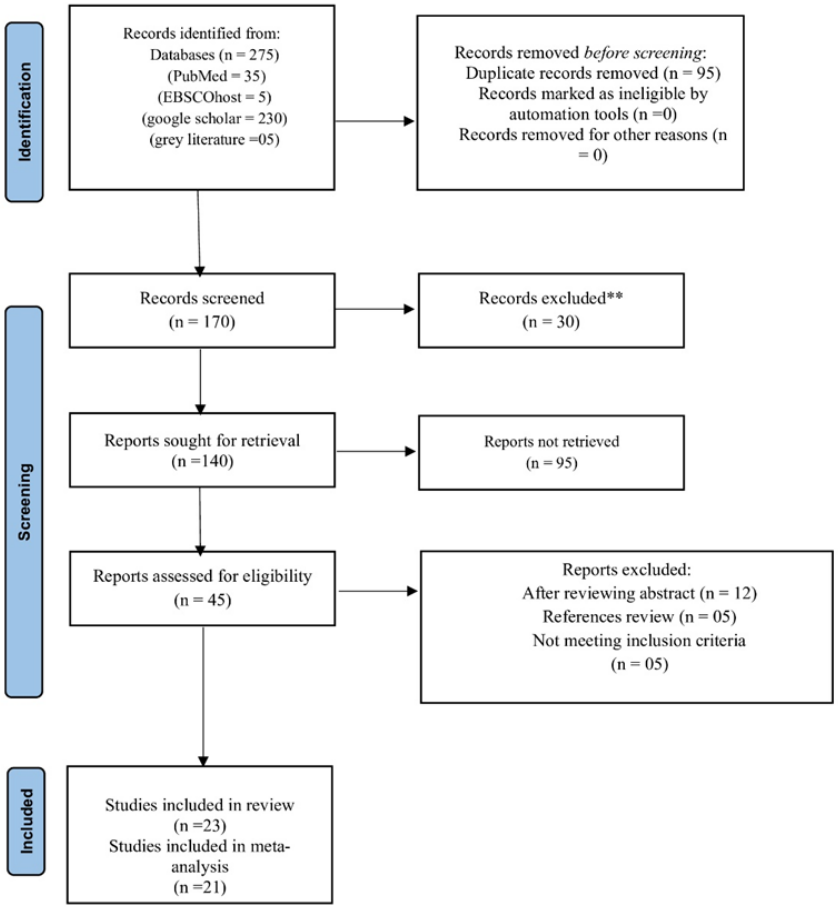

Figure 1. PRISMA 2020 Flow Diagram

a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 7. The pooled Diagnostic Odds Ratio (DOR) is 0.44 (0.01 – 22.55) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

As shown in Supplementary Figure 8 (a), (b), data was evaluated from two studies [31,33] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.31 (CI 0.00- 0.98) and pooled specificity was 0.25 (CI 0.00- 0.97) with I^2 being 0%.

As shown in Supplementary Figure 9. (a), (b), pooled positive likelihood ratio (PLR) 0.37 (0.04 – 3.84) and negative likelihood ratio (NLR) 2.18 (0.14 – 34.28) was estimated. Pooled +PLR suggested that MMP-2 is 0.37 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that MMP-2 is 2.18 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 10. The pooled Diagnostic Odds Ratio (DOR) is 0.10 (0.00 – 210.08) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

As shown in Supplementary Figure 11, 12(a), (b), data was evaluated from three studies [26,31,33] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.30 (CI 0.00- 0.89) and pooled specificity was 0.26 (CI 0.00- 0.90) with I^2 being 0%.

As shown in Supplementary Figure 13. (a), (b), pooled positive likelihood ratio (PLR) 0.43 (0.06 – 2.92) and negative likelihood ratio (NLR) 2.39 (0.26 – 21.98) was estimated. Pooled +PLR suggested that MMP-9 is 0.43 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that MMP-9 is 2.39 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 14. The pooled Diagnostic Odds Ratio (DOR) is 0.63 (0.08 – 5.20) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

As shown in Supplementary Figure 15. (a), (b), data was evaluated from three studies [34-36] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.54 (CI 0.05- 0.97) and pooled specificity was 0.32 (CI 0.00- 0.93) with I^2 being 0%.

As shown in Supplementary Figure 16. (a), (b), pooled positive likelihood ratio (PLR) 0.81 (0.21 – 3.14) and negative likelihood ratio (NLR) 1.38 (0.15 – 12.74) was estimated. Pooled +PLR suggested that VEGF is 0.81 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that VEGF is 1.38 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

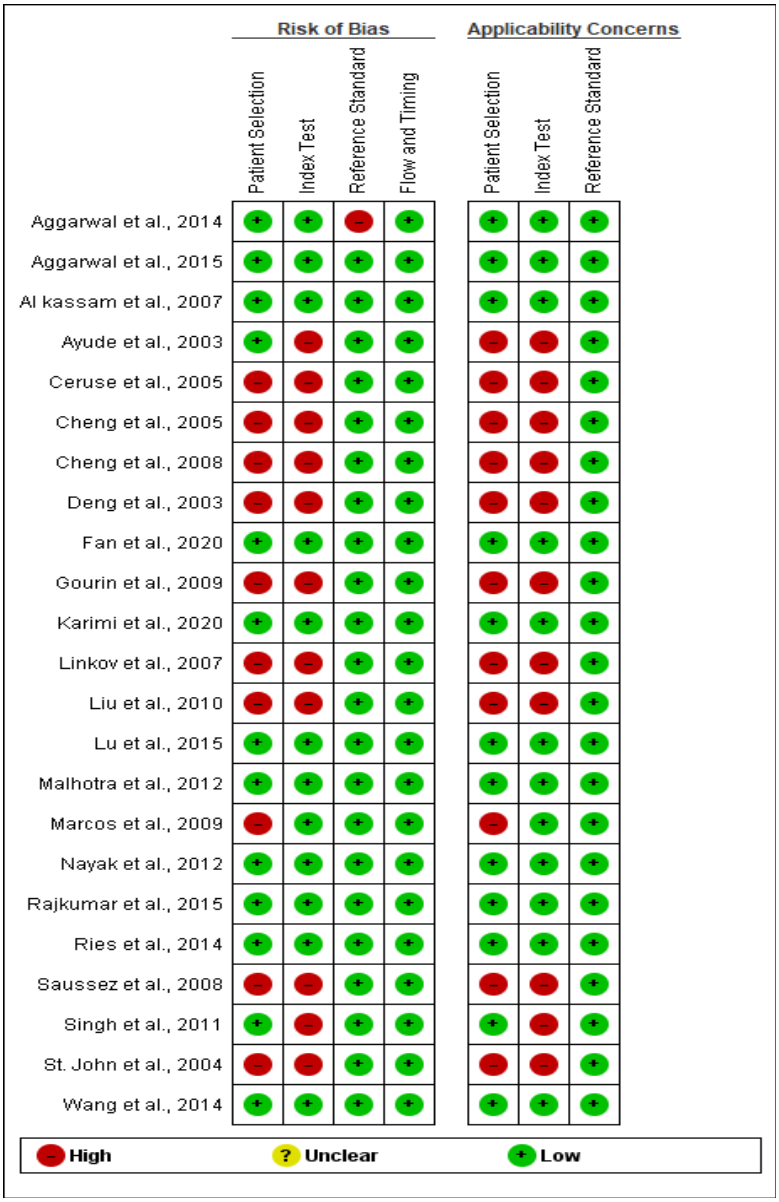

Figure 2. Risk of Bias Graph: presented as percentages across all included studies.

As shown in Supplementary Figure 17. The pooled Diagnostic Odds Ratio (DOR) is 0.58 (0.02 – 20.48) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

G) GALECTIN 1

As shown in Supplementary Figure 18. (a), (b), data was evaluated from two studies [29,36] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.37 (CI 0.00- 0.97) and pooled specificity was 0.26 (CI 0.00- 0.96) with I^2 being 0%.

As shown in Supplementary Figure 19. (a), (b), pooled positive likelihood ratio (PLR) 0.61 (0.08 – 4.39) and negative likelihood ratio (NLR) 2.55 (0.17 – 38.66) was estimated. Pooled +PLR suggested that Galectin -1 is 0.61 times more likely to have a positive detection of

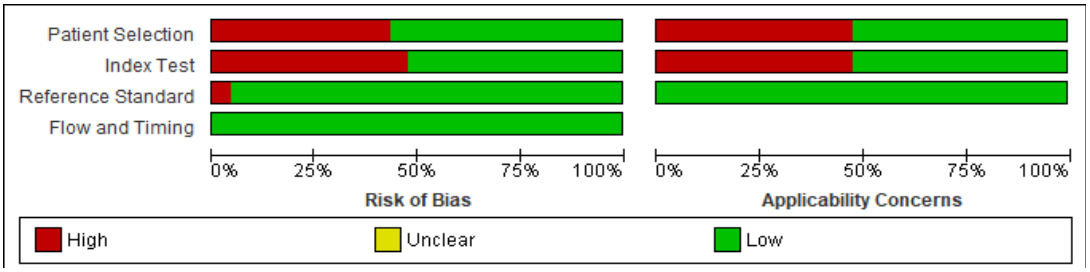

Figure 3. Risk of Bias Summary: for each included study

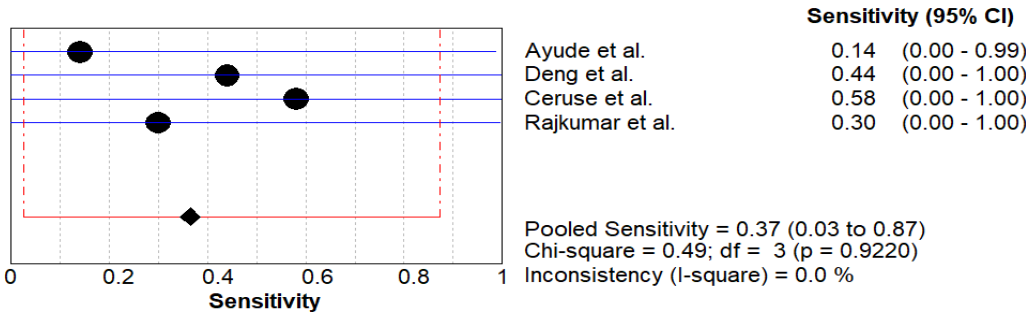

Figure 4 (a). Pooled Sensitivity of CYFRA 21 -1 for OSCC

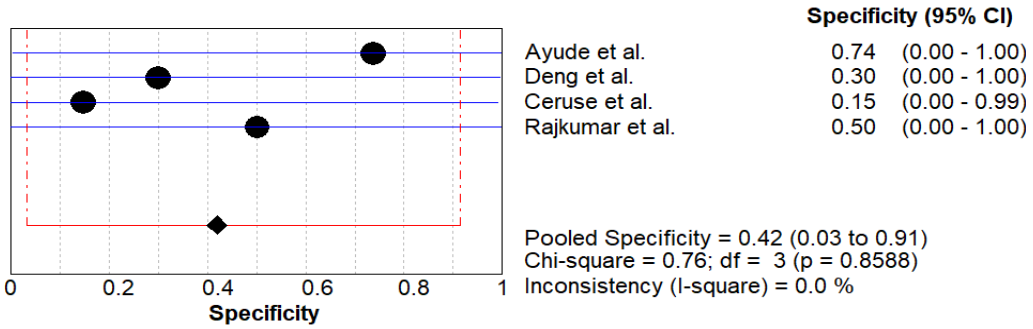

Figure 4 (b). Pooled Sensitivity of CYFRA 21 -1 for OSCC

target condition than someone without while pooled -NLR suggested that Galectin-1 is 2.55 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 20. The pooled Diagnostic Odds Ratio (DOR) is 0.18 (0.00 – 22.8) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

H) GALECTIN 3

As shown in Supplementary Figure 21. (a), (b), data was evaluated from two studies [29,26] investigating the

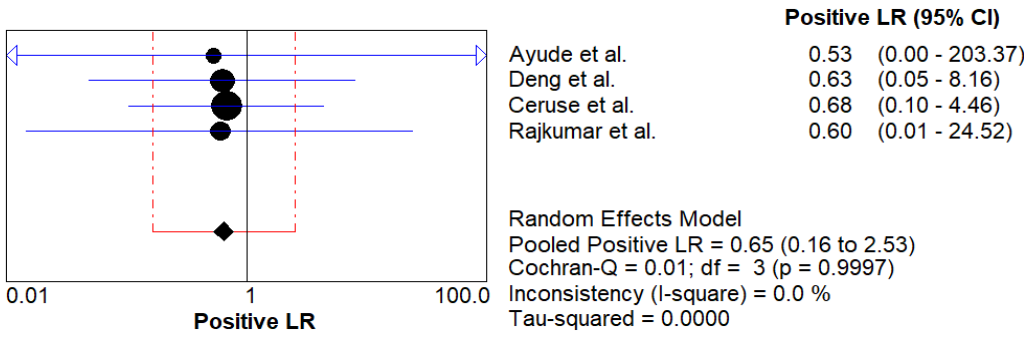

Figure 5 (a). Pooled +LR of CYFRA 21 -1 for OC

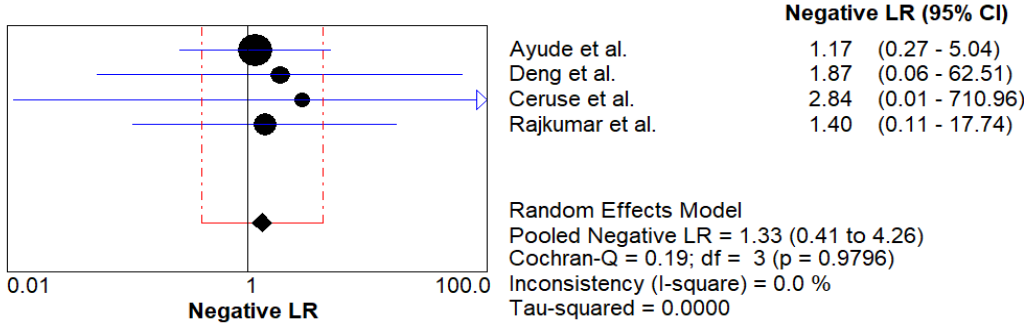

Figure 5 (b). Pooled +LR of CYFRA 21 -1 for OC

overall diagnostic accuracy. The pooled sensitivity was 0.42 (CI 0.01- 0.98) and pooled specificity was 0.23 (CI 0.00- 0.97) with I^2 being 0%.

As shown in Supplementary Figure 22. (a), (b), pooled positive likelihood ratio (PLR) 0.61 (0.10 – 3.89) and negative likelihood ratio (NLR) 2.48 (0.10 – 62.00) was estimated. Pooled +PLR suggested that galectin -3 is 0.61 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that galectin -3 is 2.48 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 23. The pooled Diagnostic Odds Ratio (DOR) is 0.21 (0.00 – 28.1) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

I) IL – 6

As shown in Supplementary Figure 24 (a), (b), data was evaluated from two studies [23.34] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.38 (CI 0.00- 0.97) and pooled specificity was 0.51 (CI 0.01- 0.99) with I^2 being 0%.

As shown in Supplementary Figure 25. (a), (b), pooled positive likelihood ratio (PLR) 0.81 (0.10 – 6.62) and negative likelihood ratio (NLR) 1.24 (0.25 – 6.11) was estimated. Pooled +PLR suggested that IL-6 is 0.81 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that IL-6 is 1.24 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 26. The pooled Diagnostic Odds Ratio (DOR) is 0.60 (0.01 – 41.30) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

As shown in Supplementary Figure 27. (a), (b), data was evaluated from two studies [27,34] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.49 (CI 0.01- 0.99) and pooled specificity was 0.43 (CI 0.01- 0.98) with I^2 being 0%.

As shown in Supplementary Figure 28. (a), (b), pooled positive likelihood ratio (PLR) 0.86 (0.13 – 5.50) and negative likelihood ratio (NLR) 1.19 (0.15 – 9.46) was estimated. Pooled +PLR suggested that IL-8 is 0.86 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that IL-8 is 1.19 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 29. The pooled Diagnostic Odds Ratio (DOR) is 0.71 (0.01 – 38.80) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

K) miRNA

As shown in Supplementary Figure 30. (a), (b), data was evaluated from four studies [32,37,38,40] investigating the overall diagnostic accuracy. The pooled sensitivity was 0.45 (CI 0.05- 0.91) and pooled specificity was 0.44 (CI 0.02- 0.95) with I^2 being 0%.

As shown in Supplementary Figure 31. (a), (b), pooled positive likelihood ratio (PLR) 0.81 (0.19 – 3.48) and negative likelihood ratio (NLR) 1.20 (0.23 – 6.14) was estimated. Pooled +PLR suggested that mirna biomarker is 0.81 times more likely to have a positive detection of target condition than someone without while pooled -NLR suggested that Serum Biomarkers is 1.20 times as likely to have a negative OSCC condition detection as someone without the presence of OSCC.

As shown in Supplementary Figure 32. The pooled Diagnostic Odds Ratio (DOR) is 0.67 (0.03 – 16.74) suggesting that overall ability of index test in correctly diagnosing the target condition is moderate to good.

The area under the curve (AUC) with summary receiver operating characteristics (SROSCC) curve was plotted for all the Biomarkers with their estimation method as shown in Supplementary Figure 33. (a) & (b). The highest and lowest AUC was seen was MMP -9 (0.53) and CYFRA 21 -1 (0.33) respectively.

Discussion

Early disease diagnosis is the hallmark for any planned treatment in order to reduce patient's mortality and morbidity [5]. Presence of OSCC is a major public health concern worldwide. Biopsy is the gold standard for oral lesion diagnosis but its several disadvantages has limited its use [6].

Fernández-Olavarría et al., 2016 [44] conducted a systematic review to assess the role of Serum Biomarkers in diagnosis and prognosis of oral cancer (OSCC). Databases were searched case control, retrospective and prospective studies which yielded 29 studies. It was found that among the various biomarkers, cancerous phenotype was determined by 2 biomarkers, worse prognosis was shown by 11 Biomarkers and overall survival, 4 Biomarkers had shown association between biomarker concentration with clinical stage of disease, 4 studies found that these Biomarkers could be helpful in disease diagnosis while 8 studies did not explain exact diagnostic mechanism of serum biomarkers. It was found and concluded that sufficient scientific evidences should be present to support the role of Serum Biomarkers as a therapeutic agent in oral cancer diagnosis and prognosis.

Guerra et al. [45] carried out systematic review and meta-analysis to evaluate the diagnostic accuracy of Serum Biomarkers for head and neck cancer when used in combination with each other or individually. Databases were searched till April 2015, yielding sixty-five studies which were included in analysis with data evaluated form 9098 subjects. It was found that combined Biomarkers had shown greater overall better accuracy than individual biomarkers. 12.8% of individual Biomarkers and 34.3% of Biomarkers differentiated patients with head and neck cancer (HNC) with controls. It was concluded that Serum Biomarkers has the ability to be used as a potential biomarker for HNC diagnosis.

Rezaei et al. [46] conducted a systematic review and meta-analysis to assess and evaluate the serum concentrations of interleukin Biomarkers (IL-6, IL-8) in patients with Oral Squamous Cell Carcinoma (OSCC).

Databases were searched till 2019 yielding 26 studies included in final analysis. Meta-analysis showed that OSCC patients had high serum concentration of IL-6 (Mean difference (MD) = 19.06, 95% CI 14. 78 – 23.33) and IL-8 (MD = 199.14, 95% CI 47.39 – 350.89) compared to healthy controls. Serum concentration of IL-6 and IL-8 were significantly elevated in OSCC patients. Hence, it was concluded that these Biomarkers could be considered as a potent biomarker in overall OSCC disease diagnosis and prognosis.

Marakala et al.[47] conducted systematic review and meta-analysis to evaluate the diagnostic ability of various Biomarkers present in plasma, serum, tissue and saliva of patients with head and neck cancer (HNC) compared to healthy controls. Databases were searched till October 2022 yielding 17 comparative studies. From the results of the study, it was found that sensitivity and specificity of Biomarkers ranged from 29.5% to 100% and 57.1% to 100%. It was concluded that theses Biomarkers have good therapeutic applications and may help in HNC diagnosis.

There have been few systematic reviews and meta-analysis [44-47] published in past but due to presence of data heterogeneity, none of them actually could provide a comprehensive qualitative and quantitative analysis on overall diagnostic accuracy of Serum Biomarkers compared to histopathology for OSCC diagnosis. According to our knowledge, this is the first systematic review and meta-analysis which assessed and evaluated the overall diagnostic ability between various Serum Biomarkers for early OSCC diagnosis.

Twenty-three studies fulfilled the eligibility criteria's and were included in review, for which the diagnostic accuracy values of various serum biomarkers. Included studies, assessed and evaluated the diagnostic accuracy of various Biomarkers like CYFRA 21 -1, E – Cadherin, interleukins, (IL-6, IL-8), protein peaks, matrix metalloproteinases (MMP ,9), vascular endothelial growth factor (VEGF), galectin (1,3) and various RNA biomarkers. All these Biomarkers belong to protein and microrna class of biomarkers. From the results of the study, it was found that these Biomarkers had sensitivity and specificity ranging from 16% to 94% and 37% to 100% while highest accuracy was shown by IL-8 with mean sensitivity and specificity of 86.5% and 98% suggesting that the overall diagnostic accuracy of these Serum Biomarkers is being moderate to good in diagnosing the desired condition.

Although the findings of the study, confirmed Serum Biomarkers overall has a good diagnostic accuracy in diagnosing the underlying desired target condition as a whole, however the study is limited by the fact that high risk of Bias was reported by many included studies. Therefore, furthermore diagnostic or analytical cross-sectional studies should be conducted with strict and vigorous reporting through "Standards For Reporting Diagnostic Accuracy Studies" (STARD) checklist [48], so as to validate the study findings.

The systematic review adhered to PRISMA guidelines, employing a comprehensive literature search and rigorous methodology, including QUADAS-2 tool ROB assessment. This resulted in high-quality studies with minimal Bias, providing a robust evidence base for therapeutic recommendations on optimizing the usage of Serum Biomarkers for diagnosing the target condition.

Systematic reviews and meta-analyses are considered the highest level of evidence, offering transparency and reproducibility in addressing specific research questions. However, the quality of included studies impacts the strength of evidence. This review included sufficient studies with brief observation periods and known risk of Bias.

In conclusion, from the results of the study, it was concluded that Serum Biomarkers is a valid tool and overall has good diagnostic potentiality in diagnosing the target condition and can be used as an alternative adjunct to histopathology. It has great potential in predicting and diagnosing disease outcome and can improve the quality and reach of OSCC early screening and detection, Serum Biomarkers can be undertaken for early diagnosis and prompt treatment under secondary level of prevention.

Author Contribution Statement

All authors contributed equally in this study.

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