

REVIEW

Is salivary IgA level a potential biomarker for immunosuppression in HIV-positive children? A systematic review and meta-analysis

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Summary

The aim of this systematic review was to determine whether or not assessment of salivary secretory immunoglobulin A (sIgA) levels could be a potential biomarker for immunosuppression in HIV-positive children. The Patient, Exposure, Comparative, Outcome question was "Is sIgA level a potential biomarker for immunosuppression in HIV-positive children?" Electronic and manual literature searches were conducted in indexed databases (MEDLINE, PubMed, EMBASE, ScienceDirect, and SCOPUS databases) up to and including June 2017. The primary outcome was total mean salivary levels of IgA among HIV seropositive and seronegative children (controls). The weighted mean differences (WMD) of outcomes and 95% confidence intervals (CI) for total mean salivary IgA levels were calculated using a random effect model. Six studies were included. Three studies showed significantly lower salivary IgA levels in HIV-infected children compared with controls. Two studies showed comparable IgA levels in HIV infected and controls. One study showed significantly higher levels of salivary IgA in HIV-infected children as compared to controls. Considering the total mean salivary IgA levels among HIV seropositive and seronegative children, a high degree of heterogeneity (Q value = 254.09, $P < .0001$, $I^2 = 98.82\%$) was noticed among both groups. The overall WMD was not significant (WMD = -1.18 , 95% CI, -1.91 to -0.44 , $P = .39$). Whether salivary IgA level is a potential biomarker for immunosuppression in HIV-positive children remains debatable because of limited information available in the current literature. Further, high-quality case-control studies with larger sample size and more solid methodological aspects are required.

KEYWORDS

children, human immunodeficiency virus, immunoglobulin A, saliva, systematic review

1 | INTRODUCTION

Saliva is a complex biological fluid that is essential for physiological functions including mastication, deglutition, and digestion. Studies have shown that under oral and systemic pathological conditions, such

as periodontitis and acquired immune deficiency syndrome, respectively saliva demonstrates altered protein levels (including cytokines and immunoglobulins).¹⁻³ These proteins act as potential biomarkers that could facilitate the screening of oral and systemic inflammatory diseases.⁴ Another advantage of using saliva for screening purposes is that saliva can be collected noninvasively using simple methods such as expectoration.^{5,6} The type of saliva samples required for a particular study depends upon the objectives of the investigation. Saliva can be collected by spitting/drooling (unstimulated whole saliva), paraffin chewing (stimulated saliva), and parotid gland suction (serous saliva) using targeted nuclear magnetic resonance spectroscopy and liquid chromatography coupled to tandem mass spectrometry.⁷

Abbreviations used: ART, antiretroviral therapy; CI, confidence intervals; MeSH, Medical Subject Headings; PECO, Patient, Exposure, Comparative, Outcome; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; SFR, salivary flow rate; sIgA, secretory immunoglobulin A; STROBE, Strengthening the Reporting of Observational studies in Epidemiology; SWS, stimulated whole saliva; UWS, unstimulated whole saliva; WMD, weighted mean differences

Secretory immunoglobulin A (sIgA) is the predominant antibody with biologic activity found in saliva, which serves as a major source of antigenic material in the oral cavity.^{8,9} Low sIgA concentration in HIV-positive patients has been associated with the presence of oral infections and low numbers of CD4+ lymphocytes in peripheral blood.² Subramaniam and Kumar¹⁰ assessed the association between sIgA levels and oral mucosal status in 150 HIV-positive children aged between 6 and 18 years. These patients were divided into 2 groups: Group 1: children prior to antiretroviral therapy and Group 2: children undergoing antiretroviral therapy (for a maximum duration of 3 years). The results¹⁰ showed significantly lower sIgA levels in Group 1 compared with Group 2. The results also showed an inverse relationship between the occurrence of angular cheilitis and sIgA levels in the study population.¹⁰ Similarly, Mandal et al¹¹ assessed the association between salivary IgA levels and dental caries status among 28 HIV-positive children aged between 6 and 14 years and 28 age-matched systemically healthy children (controls). The results showed that the scores of decayed missing filled teeth were significantly higher and salivary IgA levels were significantly lower in HIV-positive children compared with controls.¹¹ In conclusion, the authors suggested that children with salivary IgA deficiency are more susceptible to dental caries compared with controls. Similar results have been reported in other studies.^{12,13} It is therefore anticipated that assessment of sIgA could reflect immunosuppression particularly among unexamined individuals. However, controversial results have also been reported in this regard. In the study by Silva-Boghossian et al,¹⁴ there was no statistically significant difference in the salivary IgA levels among HIV positive and controls. Likewise, Castro et al¹⁵ investigated the concentrations of total IgA and IgA specific to cariogenic bacteria in HIV-positive children and controls. The results showed a statistically significant increased level of total salivary IgA in the HIV-positive children; however, specific IgA levels to cariogenic microbes were comparable among HIV-positive children and controls.¹⁵

With reference to the currently available evidence from the indexed literature, it remains unclear whether or not salivary IgA could be a potential biomarker of immunosuppression in HIV-positive children. Therefore, the aim of the present systematic review and meta-analysis was to determine whether or not assessment of salivary sIgA levels is a potential biomarker of immunosuppression in HIV-positive children.

2 | MATERIALS AND METHODS

2.1 | Protocol and registration

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews (<http://www.crd.york.ac.uk/PROSPERO>, registration number: CRD42017058747).¹⁶ Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines,¹⁷ a specific question was constructed: "Is salivary IgA level a potential biomarker for immunosuppression in HIV-positive children?"

PECO Question (Patient, Exposure, Comparative, Outcome)¹⁸

- (P) Patients in the included studies must be children.
- (E) HIV.
- (C) Systemically healthy children without HIV.
- (O) The outcome of interest was salivary IgA levels.

2.2 | Selection criteria

Screening and assessment of articles was conducted independently by 2 reviewers (FJ and ZA). Any disagreement involving the eligibility was resolved through discussion or by consulting a third reviewer (TA). Studies that did not fulfill the inclusion criteria were excluded.

The following eligibility criteria were used: cross-sectional or case-control studies; children examined with HIV disease having at least 10 participants per group; participants allocated to experimental (HIV seropositive) and control (HIV seronegative) groups; evaluated mean IgA levels in saliva as outcomes; and articles published only in English language. In vitro studies, case series, case reports, animal studies, letters to the editor, opinion articles, abstract, review papers, and unpublished articles were excluded.

2.3 | Search strategy

Electronic and manual literature searches were conducted by 2 independent reviewers (ZA and FV) in the following databases, MEDLINE, PubMed, EMBASE, ScienceDirect, and SCOPUS, up to and including June 2017 for articles addressing the focused question. For the PubMed library, combinations of following MeSH (Medical Subject Headings) and free text words were used: ((saliva [MeSH Terms]) AND ((immunoglobulin A [MeSH Terms]) AND ((HIV [MeSH Terms]) OR ((human immunodeficiency virus [Text Word]) AND ((child [MeSH Terms])).

2.4 | Screening and selection

Two authors (FJ and ZA) independently screened titles and abstracts for eligible papers. If information relevant to the eligibility criteria was not available in the abstract, or if the title was relevant but the abstract was not available, the paper was selected for full reading of the text. Next, full-text papers that fulfilled the eligibility criteria were identified and included in the review. Reference lists of original studies were hand searched to identify articles that could have been missed during the electronic search. Manual searching of the following journals was performed: *International Journal of Pediatric Dentistry*, *Oral Microbiology and Immunology*, *Journal of Oral Pathology and Medicine*, *Journal of Clinical and Diagnostic Research*, *Journal of Indian Society of Pedodontics and Preventive Dentistry*, *AIDS*, and *Journal of Clinical Pediatric Dentistry*. Studies that fulfilled the selection criteria were processed for data extraction. Figure 1 describes the screening process according to PRISMA guidelines.¹⁷

2.5 | Data extraction

Two authors (FJ and ZA) performed the data extraction independently. The information from the accepted studies was tabulated according to the study designs, participant demographics, salivary sample

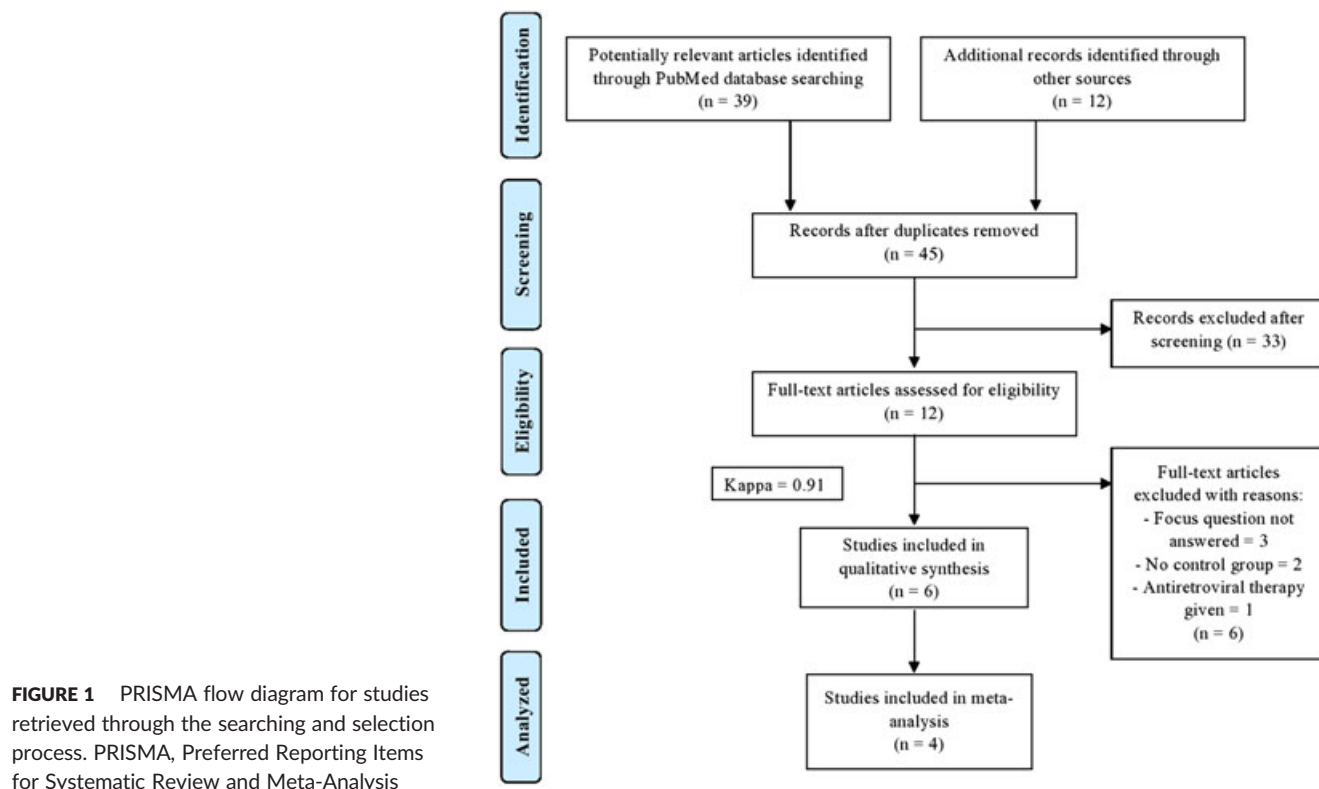


FIGURE 1 PRISMA flow diagram for studies retrieved through the searching and selection process. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis

characteristics, biochemical analysis, mean salivary IgA levels, and main outcomes. Data collected were based on the focused question outlined for the present systematic review. The reviewers cross-checked all extracted data. Any disagreement was resolved by discussion until consensus was reached.

2.6 | Methodological qualitative assessment

A modified Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist was applied to assess the quality of included studies (Table 2).²⁰ Ten items, including inclusion and exclusion criteria, HIV diagnostic criteria, experienced and calibrated examiner, saliva collection and analysis description, statistical analysis, inclusion of paired groups, and blinding of the study, were included in the STROBE checklist. Each item was scored 1 point if sufficiently reported and each relevant paper scored from 0 to 10. The studies that presented at least 7 of the 10 evaluated criteria were considered as “low risk of bias”; those that presented from 4 to 6 of the criteria were considered “moderate risk of bias”; and those studies which presented 3 criteria or less were considered “high risk of bias”. Moreover, considering the risk of bias (low, moderate, and high), the studies were also classified as studies with high, moderate, and low evidence, respectively. The STROBE checklist was assessed in duplicate by FV and ZV independently. Interreader agreement of the STROBE checklist was assessed by κ value (Cohen's κ).

2.7 | Statistical analysis

Meta-analyses were conducted for total means of salivary IgA levels. Heterogeneity among the included studies for each outcome

was assessed using the Q-statistic and I^2 statistics. When heterogeneity was not statistically significant ($P > .05$), the fixed-effects model was used; otherwise, the random-effects model was used.²¹ Forest plots were computed reporting weighted mean differences (WMD) of outcomes and 95% CI. The pooled effect was considered significant if P value was $<.05$. Data unsuitable for quantitative analysis were assessed descriptively. Moreover, funnel plots were generated to evaluate publication bias. Publication bias was suggested if the funnel plot was asymmetrical. All the above statistical analyses were performed using specialized statistical software (MedCalc Software—B-8400 Ostend v 15.11.04, Belgium).

3 | RESULTS

3.1 | Study selection

A total of 51 study titles and abstracts were initially identified. After removal of the duplicates ($N = 45$), initial screening of titles and abstracts was performed, and 33 articles were excluded as irrelevant to the PECO question. A total of 12 papers were selected for full-text reading. Of these 12 studies, 6 studies were further excluded. After the final stage of selection, 6 studies^{6,11,12,14,15,19} for qualitative synthesis and 4 studies^{11,12,14,15} for quantitative synthesis were included (Figure 1). The κ score for interassessor agreement at full-text eligibility was 0.91. All studies^{6,11,12,14,15,19} were performed at either universities or outpatient hospital clinics. Figure 1 shows the study identification flow chart according to PRISMA¹⁷ with the reasons for exclusion of articles.

3.2 | General characteristics of included studies

All studies^{6,11,12,14,15,19} included in the systematic review were observational studies in which 3 studies^{6,11,12} were cross-sectional design and 3 studies^{14,15,19} were case-control. In all studies,^{6,11,12,14,15,19} number of participants ranged between 41 and 80 individuals with mean age ranging between 9 months and 9.53 years. Only 2 studies^{13,19} reported the percentage of female participants with 29.6% only (Table 1).

3.3 | Salivary sample characteristics

Three studies^{6,11,12} collected unstimulated whole saliva, 2 studies^{14,15} collected stimulated whole saliva, while one study¹⁹ did not report the type of saliva collected. Three studies^{11,12,19} collected saliva in falcon tubes, 2 studies^{14,15} used suction bulbs, while one study⁶ used a catheter to collect saliva from the study participants. Commercial ELISA kits were used for IgA levels in saliva in 4 studies^{11,12,14,15}; one study¹⁹ used radioimmunoassay, while one study⁶ used Western blotting for the detection of salivary IgA levels. The storage temperature for the samples were reported by 5 studies^{6,11,12,14,15} of which 4

studies^{11,12,14,15} stored at -20°C while one study⁶ stored at -70°C (Table 2).

3.4 | Main outcome of the studies

Three studies^{6,11,12} showed significantly lower salivary IgA levels in HIV-infected children as compared to healthy children. Two studies^{14,19} showed comparable levels whereas one study¹⁵ showed significantly higher levels of salivary IgA in HIV-infected children as compared to HIV seronegative children.

For quantitative data assessment, a meta-analysis was performed. Considering the total mean salivary IgA levels among HIV seropositive and seronegative children, only 4 studies^{11,12,14,15} presented data to be included in the meta-analysis. Archibald et al⁶ reported per milligram of salivary albumin in median and 25th to 75th percentile; hence, this study was excluded from quantitative synthesis. The authors were contacted to collect missing data, but no response was obtained. As significant heterogeneity was observed for total mean salivary levels of IgA, the random model was used. Considering the total mean salivary IgA levels among HIV seropositive and seronegative children, a high degree of heterogeneity (Q value = 254.09,

TABLE 1 Demographic characteristics of included studies

Author et al	Study Design; Setting; Country	Number of Patients	Gender (Male/Female)	Mean Age/Age Range in Years
Archibald et al ⁶	Cross-sectional; University hospital; United States	41	NA	NA (1 d-46 mo)
Mandal et al ¹¹	Cross-sectional; University clinic; India	56	NA	Group 1: 9.53 (6-14) Group 2: 9.53 (6-14)
Acharya & Mandal ¹²	Cross-sectional; University clinic; India	56	NA	Group 1: 9.53 (6-14) Group 2: 9.53 (6-14)
Silva-Boghossian et al ¹⁴	Case-control; Outpatient clinic; Brazil	78	40/38	Group 1: 4.31 (± 0.17) Group 2: 4.32 (± 0.06)
Castro et al ¹⁵	Case-control; Outpatient clinic; Brazil	80	43/37	Group 1: 4.33 (± 0.16) Group 2: 4.34 (± 0.07)
Mascart et al ¹⁹	Case-control; NA; Belgium	47	NA	Group 1: 9 mo-13 y Group 2: 9 mo-13 y

Abbreviation: NA, not available.

TABLE 2 Salivary sample characteristics and main outcomes of the included studies

Author et al	Salivary Sample Characteristics: [Sample Type; Collection Tool; Storage Temperature]	Biochemical Analysis	Mean Salivary IgA Levels, $\mu\text{g}/\text{mL}$	Main Outcomes
Archibald et al ⁶	UWS; catheter; -70°C	Western blotting	NA	Lower salivary IgA levels were found in infants with proven HIV infection
Mandal et al ¹¹	UWS; falcon tubes; -20°C	ELISA	HIV+: 81.6 ± 6.2 Control: 145.5 ± 17.8	Group 1 had significantly lower levels of salivary IgA than Group 2
Acharya & Mandal ¹²	UWS; falcon tubes; -20°C	ELISA	HIV+: 81.6 ± 6.2 Control: 145.5 ± 17.8	Group 1 had significantly lower levels of salivary IgA than Group 2
Silva-Boghossian et al ¹⁴	SWS; suction bulb; -20°C	ELISA	HIV+: 33.9 ± 4.2 Control: 28.11 ± 3.1	Total salivary IgA levels were comparable among both the groups
Castro et al ¹⁵	SWS; suction bulb; -20°C	ELISA	HIV+: 51.9 ± 3.2 Control: 45.6 ± 2.6	Group 1 had significantly higher levels of salivary IgA than Group 2
Mascart et al ¹⁹	NA; falcon tubes; NA	Radioimmunoassay	HIV+: $3.20 (2.00-3.80)^{\text{a}}$ Control: $3.30 (2.08-5.40)^{\text{a}}$	Total salivary IgA levels were comparable among both the groups

Abbreviations: ELISA, enzyme-linked immunosorbent assay; IgA, immunoglobulin-A; NA, not available; SWS, stimulated whole saliva; UWS, unstimulated whole saliva.

^aExpressed per milligram of salivary albumin in median and 25th to 75th percentile.

$P < .0001$, $I^2 = 98.82\%$ [Figure 2]) was noticed among both the groups. The overall WMD was not significant (WMD = -1.18 , 95% CI, -1.91 to -0.44 , $P = .39$).

3.5 | Quality of the clinical studies

The κ value of interreader agreement of the STROBE checklist was 0.94. All the included clinical studies^{6,11,12,14,15,19} in this systematic review were observational studies. The quality of 3 studies^{11,14,15} was regarded as high, since these studies received a score ≥ 7 with low risk of bias (Tables 2 and 3). The risk of bias was considered moderate in 2 studies^{12,19} and high in one study assessed.⁶

3.6 | Publication bias

Funnel plots appeared asymmetrical as none of the studies were in the confidence area suggesting significant publication bias regarding salivary sIgA levels among HIV seropositive and seronegative children (Figure 3).

4 | DISCUSSION

The present systematic review and meta-analysis was performed to answer the following focused question: "Is salivary IgA level a potential biomarker for immunosuppression in HIV-positive children?" Through the literature search, 6 studies^{6,11,12,14,15,19} were identified of which

nearly 66.6% ($n = 4$) studies^{6,11,12,15} showed that salivary IgA levels were significantly lower among HIV-positive children compared with controls. Results by Archibald et al⁶ also suggested that since saliva can be collected noninvasively from infants and children, it is a useful tool for assessing antibodies associated with immunosuppression (including sIgA) in contrast to more invasive techniques such as venipunctures. These results suggest that assessment of salivary IgA concentration could be a biomarker for the assessment of immunosuppression in children. However, it is imperative to take a number of factors into consideration. It is known that determination of the study sample via power calculation is essential for the detection of statistical significance.^{22,23} Therefore, power calculation is an important methodological protocol in the design of a planned research design. It is noteworthy that only a limited number of studies ($n = 6$) with a relatively small number of participants (up to 80 participants) addressed our focused question.^{6,11,12,14,15,19} Upon a vigilant review of the studies included, it was noted that none of the studies included had estimated the study sample size based on a power calculation. Therefore, the outcomes of the studies^{6,11,12,14,15,19} included in the present systematic review and meta-analysis should be interpreted with caution.

Studies²⁴⁻²⁶ have shown that HIV-positive patients have a reduced salivary flow rate (SFR) compared with healthy individuals. Moreover, alterations in SFR may increase the concentration of its constituents, notwithstanding an overall reduced output. None of the studies^{6,11,12,14,15,19} included in the present systematic review and meta-analysis measured the SFR in their respective study groups.

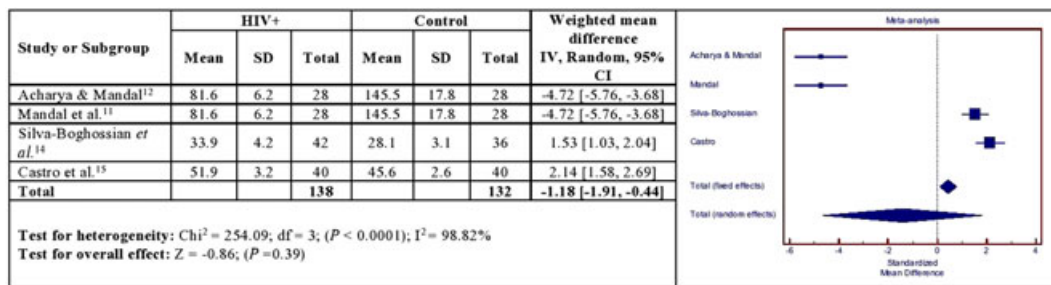


FIGURE 2 Forest plot presenting mean salivary IgA in HIV seropositive and control groups. IgA, immunoglobulin A

TABLE 3 Quality assessment of the included studies using STROBE checklist

Criteria	Authors et al					
	Archibald et al ⁶	Mandal et al ¹¹	Acharya & Mandal ¹²	Silva-Boghossian et al ¹⁴	Castro et al ¹⁵	Mascart et al ¹⁹
Inclusion criteria	NA	X	X	X	X	X
Exclusion criteria	NA	X	X	X	X	X
HIV diagnostic criteria	X	X	NA	NA	X	NA
Experienced examiner	NA	NA	NA	X	X	NA
Calibrated examiner	NA	NA	NA	NA	NA	NA
Salivary collection description	X	X	X	X	X	X
Salivary analysis description	X	X	X	X	X	X
Statistical analysis description	NA	X	X	X	X	X
Paired groups	NA	X	X	X	X	X
Blinding	NA	X	NA	NA	NA	NA
Risk of bias	High	Low	Moderate	Low	Low	Moderate
Level of evidence	Low	High	Moderate	High	High	Moderate

Abbreviation: STROBE, Strengthening the Reporting of Observational studies in Epidemiology; NA, Not available.

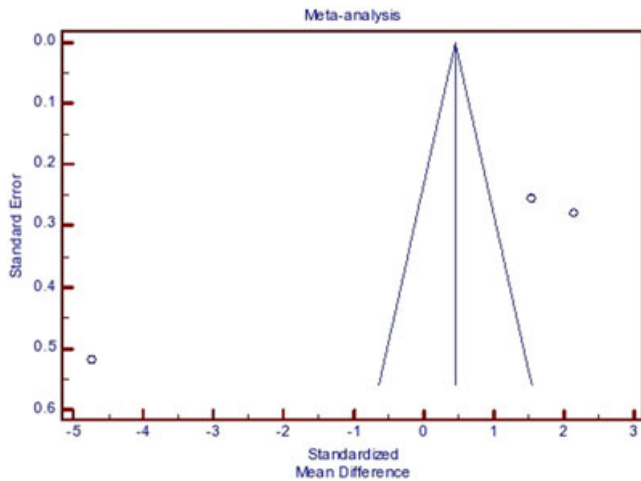


FIGURE 3 Funnel plot for secretory immunoglobulin A levels among both the groups

Although in the study by Castro et al,¹⁵ total salivary IgA levels were statistically significantly higher in 40 HIV-positive children (aged 2-5 years) compared with age-matched 40 controls; differences in SFR among HIV-positive and control children could be responsible for the higher levels of total IgA in the HIV-positive children. However, results by Archibald et al⁶ showed significantly lower salivary IgA levels in HIV-positive children aged 1 day to 46 months. An explanation in this regard could be derived from the fact that in children below 6 years old, the amount of sIgA present in saliva is less due to the immature lymph epithelial system and it does not reach maturity until puberty. In this context, it remains unclear whether or not salivary IgA is a biomarker of immunosuppression or not.

The CD4+ cell count plays an essential role in the maturation of the mucosal immune system, and since these cells are decreased in HIV-positive patients, secretory immunity (including salivary IgA levels), is expected to be compromised with the advancement of HIV infection. These factors have a greater influence on immunity than merely assessing salivary IgA levels. The study by Mandal et al¹¹ was conducted at one time only and CD4+ cell count was excluded. The same discrepancy was observed in the studies by Acharya and Mandal¹² and Archibald et al.⁶ The only study in which CD4+ measured was by Castro et al,¹⁵ which showed that HIV infection does not influence salivary IgA levels. However, since SFR in the study population remained uninvestigated in this study,¹⁵ a clear conclusion related to our focused question could not be extracted.

The meta-analysis of the present study indicated no significant difference in the sIgA levels among test and control group. Moreover, asymmetry funnel plots of mean sIgA levels generated from Figure. 3 suggest substantial heterogeneity of the studies in the meta-analyses, which indicate overestimation of the effects calculated.^{11,12,14,15} The heterogeneity may be influenced by non-standardized diagnostic criteria for HIV, different methodological protocols, and/or varying levels of sIgA levels in HIV participants in some of the studies included in the meta-analyses.^{11,12,14,15} Therefore, these methodological shortcomings should be cautiously considered when interpreting the findings of the study. A robust study design with larger sample size is highly recommended to improve the quality of work in this area.

5 | CONCLUSION

Whether salivary IgA level is a potential biomarker for immunosuppression in HIV-positive children remains debatable because of limited information available in the current literature. We recommend that further well-designed and high-quality case-control studies with larger number of participants enrolled, and more solid methodological aspects should be performed for further investigations.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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