



A narrative review of exploring potential salivary biomarkers in respiratory diseases: still on its way

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Abstract: Saliva is abundant with proteins, metabolites, DNA, and a diverse range of bacterial species. During the past two decades, saliva has emerged as a novel diagnostic and evaluation medium for several diseases. Collection of saliva samples is simple, minimally invasive, and convenient even in infants, children, and patients with anxious. Furthermore, with the development of hypersensitive techniques [e.g., microsensor arrays, enzyme-labeled immunosensors, nanoparticle-labeled immunosensors, capacitive or impedimetric immunosensors, magneto immunosensors, field effect transistor immunosensors, and surface enhanced Raman spectroscopy (SERS)], the sensitivity and accuracy of saliva diagnostic procedures have been improved. Nowadays, saliva has been used as a potential medium for several disease diagnosis and assessment, such as periodontitis, caries, cancers, diabetes mellitus, and cardiovascular diseases. Saliva has been used widely for studying microbiomics, genomics, transcriptomics, proteomics, and metabolomics of respiratory diseases, however, the use of salivary biomarkers for the diagnosis, prognosis, and monitoring of respiratory disease is still in its infancy. Herein, we review the progress of research on salivary biomarkers related to several respiratory diseases, including bronchial asthma, chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), pneumonia, tuberculosis (TB), Langerhans cell histiocytosis (LCH) and cystic fibrosis (CF). Furthermore, several limitations of saliva test such as the lack of standard protocol for saliva collection and reasonable reference values for saliva test are also mentioned in this review.

Keywords: Saliva; biomarker; respiratory disease

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Introduction

Saliva has been used widely for biomarker studies related to several diseases, such as periodontitis, caries, cancers, diabetes mellitus, and cardiovascular diseases because more than 2,000 types of proteins and peptides, 3,000 unique mRNAs, and 700 bacterial species have been detected in it (1-10).

Collection of saliva samples is simple, minimally invasive, and convenient even in infants, children, and anxious patients (11). With the development of hypersensitive techniques, such as microsensor arrays, enzyme-labeled immunosensors, nanoparticle-labeled immunosensors, capacitive or impedimetric immunosensors, magneto immunosensors, field

effect transistor immunosensors (FET), and surface enhanced Raman spectroscopy (SERS) (10,12-15), the sensitivity and accuracy of diagnostic procedures have been improved. Nowadays, saliva has been used as a potential medium for disease diagnosis and assessment. However, exploration of salivary biomarkers for the diagnosis, monitoring, and prognosis of respiratory diseases is still in its infancy, although the first study on this topic was reported in 1977 (16). Thus, we reviewed the studies on potential saliva biomarkers related to respiratory diseases (Table 1 and Figure 1) and analyzed the progress and obstacles concerning this issue.

We present this paper in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/jtd-21-202>).

Methods

In this study, we searched the PubMed database to identify eligible studies on salivary biomarkers of respiratory diseases. The search terms used were “saliva” or “salivary” in combination with “respiratory disease,” “asthma,” “chronic obstructive pulmonary disease,” “COPD,” “obstructive sleep apnea,” “OSA,” “pneumonia,” “tuberculosis,” “TB,” “lung cancer,” or “lung carcinoma.” Two of our investigators independently searched the databases and reviewed each of the retrieved articles. Any discrepancies were discussed and solved by the third investigator together with the two investigators. The last literature search was performed on Jan 20, 2021.

Bronchial asthma

Bronchial asthma is characterized by airway inflammation and hyperresponsiveness (17). Levels of cytokines and inflammatory proteins have been reported to be high in the saliva of patients with asthma (15,18-20,60). Significant differences in the levels of biomarkers, including IL-8 (3,056.9 vs. 1,070.87 pg/mL, $P=0.008$), IL-10 (24.60 vs. 15.82 pg/mL, $P=0.008$), sCD163 (1,852.08 vs. 659.56, $P=0.003$), Eosinophil cationic protein (ECP) (486–845 vs. 246–467 $\mu\text{g/L}$, $P<0.01$), IL-5 ($P=0.003$), IL-6 ($P=0.035$), and VEGF ($P=0.016$), were found between patients with asthma and controls (18,20). In addition, salivary IL-8, IL-10, sCD163, ECP, and IP-10/CXCL10 levels were found to be correlated with the forced expiratory volume in 1 s (FEV1), fraction of exhaled nitric oxide (FeNO) levels, and exacerbation of asthma, which implies that these indicators could be used as potential biomarkers for monitoring airway

obstruction and exacerbation of asthma (15,18,20). Notably, Gaber *et al.* conducted a study on patients with aspirin-intolerant asthma (AIA) and found that these patients showed a higher salivary cysteinyl-leukotriene (CysLT) level than did those with aspirin tolerant asthma (ATA; 144 vs. 69 pg/mL, $P=0.007$); therefore, salivary CysLT level could be a potential biomarker for diagnosing AIA (22).

Recently, a salivary microbiome study has demonstrated that patients with asthma have a higher salivary bacterial diversity than do controls (Shannon index: 2.12 ± 0.23 vs. 2.01 ± 0.24 , $P=0.013$; Pielou index: 0.81 ± 0.04 vs. 0.79 ± 0.05 , $P=0.01$). The relative abundances of the genera *Streptococcus* (13.0% vs. 18.3%, $P=0.003$) and *Veillonella* (11.1% vs. 8.0%, $P=0.002$) were significantly different between the asthma and control groups (17). However, the pathophysiological mechanisms associated with these changes of salivary microbiomes in patients with asthma need to be studied further.

Additionally, saliva samples have been used as a source of DNA for epigenetic studies on asthma (61-63). An increase in DNA methylation in the promoter-regulatory region of PM20D1 in infant saliva was found to be associated with the occurrence of early childhood wheezing (21).

Chronic obstructive pulmonary disease (COPD)

COPD is characterized by progressive airflow obstruction and chronic airway inflammation. Few studies that focused on the inflammatory and oxidant stress-related factors indicated the importance of exploring potential biomarkers. Among the inflammatory factors (Table 1) investigated (23,24,64,65), salivary IL-8 and matrix metalloproteinase (MMP-9) levels showed a negative relationships with lung function ($P=0.009$ and 0.003 , respectively) (24). An increase in salivary C-reactive protein (CRP), PCT, and neutrophil elastase (NE) levels could predict the risk of acute exacerbation of COPD (AECOPD), but these biomarkers were not found to be suitable for evaluating the severity of COPD (23). With regard to the biomarkers of oxidative stress, it was found that salivary uric acid (UA) level in patients with COPD was 2.2 times higher than that in controls ($P=0.05$), while no difference in total antioxidant status (TAS), peroxidase level, and super oxide dismutase (SOD) level was found between groups (25).

During the past two decades, microbiomes have been hot spots of COPD research; however, studies on salivary

Table 1 Summary of saliva studies in respiratory diseases

Author (ref.)	Sample size (patients/ control)	Biomarkers	Technique	Primary outcome(s)
Bronchial asthma (BA)				
Zamora-Mendoza (15)	26/18	37 cytokines	Immunoassay and surface enhanced Raman spectroscopy (SERS)	Salivary IL-8, IL-10, and sCD163 levels were significantly association with bronchial obstruction
Espuela-Ortiz (17)	57 /57	Microbiome	16S ribosomal RNA amplicon profiling	Patients with asthma showed a high bacterial diversity. The relative abundance of <i>Streptococcus</i> spp. and <i>Veillonella</i> spp. was high in patients with asthma
Little (18)	180/0	10 cytokines	Qiagen Luminex apparatus (Luminex) with custom designed 10-plex kits (BioRad)	Patients with asthma had significantly elevated salivary IL-5, IL-6, MCP-1, and VEGF levels. Salivary IP-10/CXCL10 level was associated with exacerbation of asthma
Bowton (19)	14/0	Eosinophil cationic protein (ECP)	Radioimmuno-assay	There was no correlation between ECP levels in sputum and saliva
Schmekel (20)	38/16	ECP	Radioimmuno-assay	Elevated levels of ECP in saliva were found in patients with asthma
Popovic (21)	79 /72	DNA methylome	HumanMethylation450k array	High DNA methylation of PM20D1 was associated with the occurrence of early childhood wheezing
Gaber (22)	21/0	Cysteinyl-leukotrienes (CysLTs)	Enzyme immunoassays	Patients with aspirin-intolerant asthma had significantly elevated levels of salivary CysLTs
Chronic obstructive pulmonary disease (COPD)				
Patel (23)	98 /45	CRP, PCT, Neutrophil elastase (NE)	Enzyme linked immunosorbent assay (ELISA)	Salivary CRP, PCT, and NE levels were suitable for predicting the risk of acute exacerbation of COPD (AECOPD)
Ji (24)	28/61	IL-6, IL-8, MMP-9, TNF- α , TIMP-1	ELISA	Salivary IL-8 and MMP-9 levels showed a significant negative relationship with lung function
Yigla (25)	20/20	TAS, uric acid (UA), peroxidase, SOD	Xanthine oxidase/XTT method/2-nitrobenzoic acid-thiocyanate (NBS) assay	Saliva UA levels were 2.2 times higher in patients with COPD (P=0.05) than in controls
Lin (26)	21/50	Microbiome	16S ribosomal RNA amplicon profiling	<i>Veillonella</i> , <i>Rothia</i> , <i>Actinomyces</i> were observed frequently in patients with COPD
Yoshimatsu (27)	70/0	Repetitive saliva swallowing test (RSST)		RSST could be a strong predictor of AECOPD
Obstructive sleep apnea (OSA)				
Akpinar (28)	32/24	Myeloperoxidase (MPO)	Flow cytometry	Salivary concentration of MPO was positively correlated with AHI, ODI, and sleep efficiency
Tóthová (29)	24/0	TBARS, AGEs, and AOPP	The multimode spectrofluorometer Sapphire II Tecan	Patients with OSA had elevated salivary TBARS, AGE, and AOPP levels in the morning, TBARS and AGE levels were positively correlated with apnea-hypopnea index (AHI)

Table 1 (continued)

Table 1 (continued)

Author (ref.)	Sample size (patients/control)	Biomarkers	Technique	Primary outcome(s)
Yan (30)	46/12	Cortisol and alpha-amylase	Enzyme immunoassay	Salivary cortisol and α -amylase levels were significantly higher in patients with OSA showing hypertension than in those with OSA alone
Ghiciuc (31)	10/7	Cortisol	Immuno-enzymatic kits	Patients with OSA showed low levels of salivary cortisol at awakening
Park (32)	48/32	Cortisol	Enzyme immunoassay	M-sCor, sub-sCor, and r-sCor levels showed significant negative correlations with oxygen desaturation index (ODI)
Bublitz (33)	4/21	Cortisol	Enzyme immunoassay	OSA was associated with blunting of the saliva cortisol awakening response
Patacchioli (34)	27/7	Cortisol	ELISA	Children with OSA showed overall significant and severity-dependent increases in salivary cortisol production
Papaioannou (35)	22/22	Melatonin	ELISA	There were no differences in salivary melatonin levels between patients with OSA and healthy subjects
Zheng (36)	38/0	Proteins/peptides	Mass spectrometry (MS)	Levels of two peptides (3,038.6 and 2,164.3 Da) in saliva were highly predictive of cardiovascular diseases (CVDs) in patients with OSA
Traxdorf (37)	40/20	S100B	ELISA	Salivary S100B was not suitable for use as a biomarker to detect hypoxia-induced cerebrovascular stress in patients with OSA
Roedig (38)	76/0	APOE- ϵ 4 allele	Oragene-DNA Saliva Collection Kits	There was no synergistic association between APOE- ϵ 4 allele in saliva and skeletal class of patients with OSA
Pneumonia (P)				
To (39)	12/0	Nucleic Acid of SARS-CoV-2	Real-time reverse transcription-quantitative polymerase chain reaction (RT-qPCR)	Saliva could be used for the qualitative detection of SARS-CoV-2
Azzi (40)	25/0	Nucleic Acid of SARS-CoV-2	Real-time reverse transcription polymerase chain reaction (rRT-PCR)	Saliva could be used for the qualitative detection of SARS-CoV-2
Tsai (41)	106/60	CRP and chemokine	Milliplex MAP human cytokine immunoassay (Millipore, St Charles, MO, USA) in a Luminex [®] xMAPTM system/ELISA	Salivary CRP level was highly correlated with serum CRP level in pediatric patients with pneumonia Higher salivary CRP levels were reported in pediatric patients with pneumonia than in the healthy children
Omran (42)	35/35	CRP	ELISA	Salivary CRP level was suitable as diagnostic marker for late onset neonatal pneumonia

Table 1 (continued)

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Author (ref.)	Sample size (patients/control)	Biomarkers	Technique	Primary outcome(s)
Klein Kremer (43)	15/16	Flow rate, pH, UA, Phosphate, total protein	Lowry's method/ Phadebas amylase test	Salivary flow rate, pH, and levels of UA, phosphate, and total protein showed significant differences between patients with pneumonia and controls
Tuberculosis (TB)				
Jacobs (44)	18/33	69 host markers	Multiplex cytokine platform	A 5-marker combination of salivary IL-1 β , IL-23, ECM-1, HCC1 and fibrinogen could help diagnose TB with a sensitivity 88.9% and specificity of 89.7%
Namuganga (45)	39/39	10 host markers	Luminex immunoassay	A 3-marker model comprising of salivary G-CSF, TNF- α and VEGF was recommended for TB diagnosis (sensitivity of 63% and specificity of 63%)
Phalane (46)	11/27	33 host markers	Luminex Multiplex Immunoassay	A 5-marker combination of salivary IL-5, IL-6, IL-15, TNF- α , and CRP was recommended for TB diagnosis (accurately predicted 81.8% of the TB cases)
Jacobs (47)	32/72	33 host markers	Multiplex cytokine platform	A 7-marker combination of salivary CRP, ferritin, serum amyloid P, MCP-1, alpha-2-macroglobulin, fibrinogen, and tissue plasminogen activator was recommended for TB diagnosis (sensitivity of 78.1% and specificity of 83.3%)
van den Elsen (48)	6/0	Amikacin	Immunoassay	Salivary sample was not found to be suitable for therapeutic drug monitoring (TDM) of amikacin
Ghimire (49)	23/0	Levofloxacin	Liquid chromatography-tandem mass spectrometry (LC-MS)	Salivary sample was not found to be suitable for TDM of Levofloxacin
Lung cancer (LC)				
Sun (5)	3/3	Exosomes	Western Blot (WB), LC-MS/Mass Spectrometry (MS) analysis	11 high potential salivary protein biomarkers were identified
Ding (6)	68/41	EGFR	Droplet digital PCR	Salivary cfDNA was found to be suitable for detecting EGFR mutations
Wei (50)	66/0	EGFR	Electric field-induced release and measurement (EFIRM)	Salivary cfDNA was found to be suitable for detecting EGFR mutations
Pu (51)	17 /0	EGFR	EFIRM	Salivary cfDNA was found to be suitable for detecting EGFR mutations

Table 1 (continued)

Table 1 (continued)

Author (ref.)	Sample size (patients/control)	Biomarkers	Technique	Primary outcome(s)
Zhang (52)	42/74	Transcriptomic	Gene microarray	5-mRNA combination of CCNI, EGFR, FGF19, FRS2, and GREB1 could help diagnose lung cancer with high sensitivity (93.75%) and specificity (82.81%)
Xiao (53)	36/36	Proteomics	Two-Dimensional Difference Gel Electrophoresis (2D-DIGE) and MS	Salivary haptoglobin hp2(HP), zinc α 2-glycoprotein (AZGP1) and human calprotectin levels could be used as biomarkers for lung cancer diagnosis
Wang (54)	55/15	Microbiome	16S rDNA amplification sequencing	Patients with lung cancer had lower salivary microbial diversity. Salivary Filifactor was a potential bacterial biomarker
Zhang (55)	39/20	Microbiome	16S rDNA amplification sequencing	Salivary Veillonella and Streptococcus abundances were strongly increased in patients with NSCLC
Yan (56)	61/25	Microbiome	16S rDNA amplification sequencing	Salivary Capnocytophaga and Veillonella abundances were significantly increased in patients with lung cancer
Langerhans cell histiocytosis (LCH)				
Preliasco (57)	29/12	IL-1b and prostaglandin E2 (PGE2)	Enzyme Immune Assay System	Salivary IL-1b and PGE2 levels played a critical role as markers of LCH disease progression
Cystic fibrosis (CF)				
Gonçalves (58)	80 /84	Ions	ABL 835 Radiometer	Elevated salivary chloride and sodium concentrations could be used to diagnose CF
Madsen (59)	14/0	Tobramycin	Beckman Synchron CXR Systems	Saliva was not found to be suitable for the TDM of tobramycin

TAS, total antioxidant status; SOD, super oxide dismutase; M-sCor, morning salivary cortisol; n-sCor, night salivary cortisol; sub-sCor, m-sCor minus n-sCor; r-sCor, m-sCor/n-sCor; TBARS, thiobarbituric acid reacting substances; AOPP, advanced oxidation protein products; AGEs, advanced glycation end products.

microbiomes have only been conducted on patients with COPD showing periodontitis. These studies revealed that patients with periodontitis showing COPD had a significantly higher bacterial richness and diversity in saliva than did those with periodontitis alone (26).

Obstructive sleep apnea (OSA)

OSA is a common sleep disorder associated with breathing. The main pathophysiology of this disorder involves chronic intermittent hypoxia and sleep fragmentation, which are related to inflammation, oxidative stress, and sympathetic activation (66).

Several inflammatory and oxidative stress-related markers in saliva have been identified. In a previous study, patients with OSA showed a significantly higher salivary myeloperoxidase (MPO) level than did the controls ($P < 0.0001$). The MPO level was found to be correlated with apnea-hypopnea index (AHI) and oxygen desaturation index (ODI; both $P = 0.0001$) (28). In another study, markers of high oxidative stress such as thiobarbituric acid reacting substances (TBARS), advanced oxidation protein products (AOPP), and advanced glycation end products (AGEs) were found in the saliva of patients with OSA in the morning, and TBARS and AGEs showed a positive correlation with AHI ($r = 0.48$ and 0.49 , respectively;

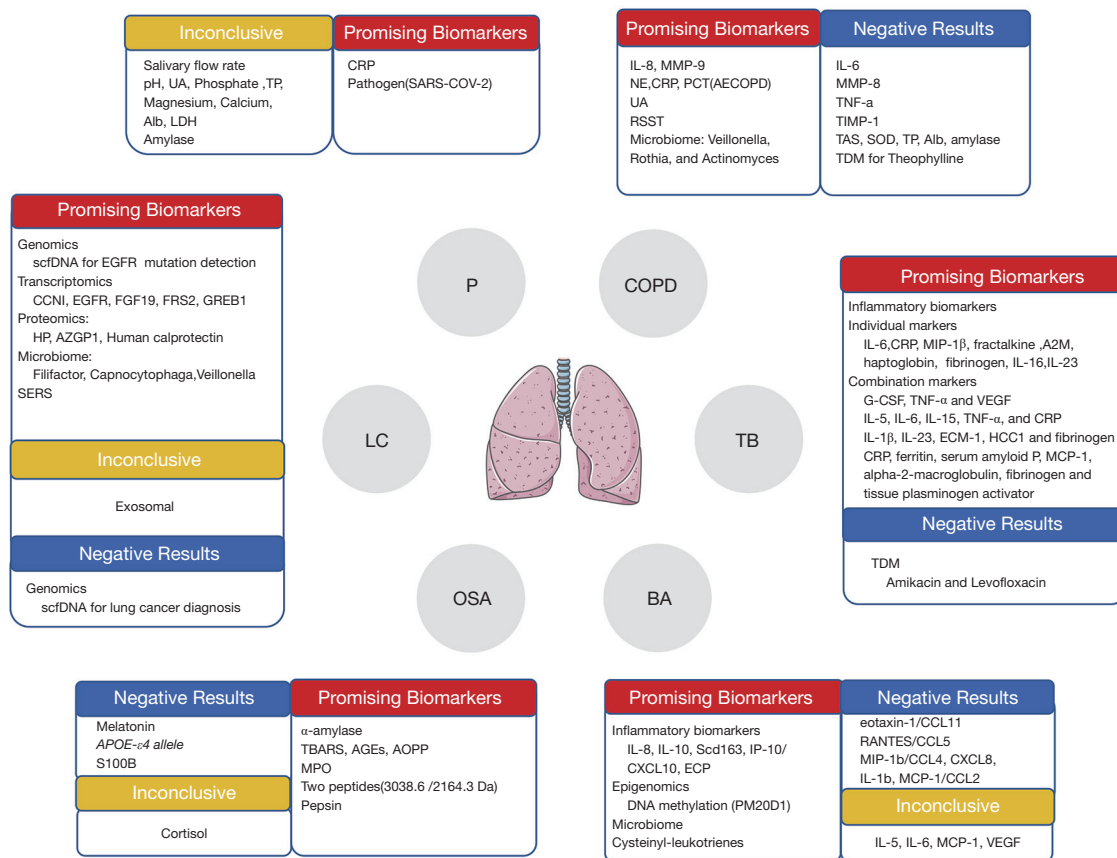


Figure 1 Potential of salivary biomarkers and their current state of validity. This figure includes the most common respiratory diseases: bronchial asthma (BA), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea (OSA), Pneumonia (P), Tuberculosis (TB), and lung cancer (LC). For these diseases, a categorical system classifies the biomarkers as: promising, inconclusive or negative results based upon the findings of our work. Uric acid (UA), Total protein (TP), Albumin (Alb), Lactate dehydrogenase (LDH), C-reactive protein (CRP), neutrophil elastase (NE), Repetitive saliva swallowing test (RSST), Total antioxidant status (TAS), Super oxide dismutase (SOD), Therapeutic drug monitoring (TDM), Eosinophil cationic protein (ECP), Thiobarbituric acid reacting substances (TBARS), Advanced glycation end products (AGEs), Advanced oxidation protein products (AOPP), Myeloperoxidase (MPO), Surface Enhanced Raman Spectroscopy (SERS), Haptoglobin hp2 (HP), Zinc α 2-glycoprotein (AZGP1).

$P < 0.05$). Furthermore, treatment with continuous positive airway pressure (CPAP) could significantly decrease the morning salivary concentrations of TBARS, AOPP, and AGEs ($P < 0.05$) (29).

Alfa-amylase (α -amylase) level is a biomarker of the activation of the sympathetic adrenomedullary (SAM) system. Salivary α -amylase level was found to be higher in patients with moderate-to-severe OSA ($P < 0.01$), and it showed a correlation with OSA severity (AHI, microarousal index, and the lowest pulse oxygen saturation). A cut-off value (17.64 U/mL) of salivary α -amylase level could indicate the presence of moderate-to-severe OSA with the sensitivity of

85% and specificity of 91% (30). In addition, saliva was also used to test cortisol levels in patients with OSA (31,32,67). The blunting of the cortisol awakening response was reported in patients with OSA. The morning cortisol level tended to be lower in patients with OSA than in controls ($P < 0.05$), and it showed a negative correlation with AHI ($P < 0.05$) (32,33). However, in a special group of OSA, inconsistent results were reported. Patacchioli *et al.* reported that children with OSA showed significant and severity-dependent increases in salivary cortisol production (34). Moreover, patients with OSA showing hypertension also showed higher salivary cortisol levels than did those with OSA alone (10.01 ± 2.77 vs.

5.52±1.90 ng/mL, $P < 0.05$) (30).

Pneumonia

Studies on saliva in patients with pneumonia mainly focus on the identification of pathogens. It has been reported that influenza virus A, Ebola virus, Cytomegalovirus, and Herpes simplex virus could be identified in salivary samples (68). During the pandemic of COVID-19, testing of saliva samples for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) attracted a lot of attention because of the ease associated with self-collection and a decrease in the risk of exposure associated with the collection of nasopharyngeal or oropharyngeal samples by healthcare workers (39,40,69–74). The coincidence rate for the detection of SARS-CoV-2 between salivary samples and nasopharyngeal swabs was 91.7–100% (39,40). The US Food and Drug Administration granted an emergency authorization for the use of the first saliva testing kits for the diagnosis of SARS-CoV-2 (75). It was also reported that salivary viral load was significantly correlated with COVID-19 severity and showed a superior ability over nasopharyngeal viral load as a predictor of mortality (AUC =0.90) (69).

Other salivary indicators were also reported in studies on pneumonia. Serum CRP is a sensitive biomarker for pneumonia. It was reported that salivary CRP level was highly correlated with serum CRP level in pediatric patients with pneumonia ($r=0.679$, $P < 0.001$). Higher salivary CRP level was reported in pediatric patients with pneumonia than in the healthy children (48.77±5.52 *vs.* 14.78±3.92 ng/mL, $P < 0.001$) (41). It was reported that an increase in salivary CRP level (cut-off value of 3.8 ng/L) could help diagnose neonatal pneumonia with a sensitivity of 91.4% and a specificity of 80.9% in a study conducted by Omran *et al.* (42). Salivary CRP level could be a surrogate biomarker for serum CRP level in the diagnosis of pneumonia, especially in pediatric patients. However, the value of salivary CRP level in the diagnosis of different types of pneumonia has rarely been mentioned. Salivary flow rate ($P=0.0001$), pH ($P=0.0498$), and UA ($P=0.048$), phosphate ($P=0.0437$), and total protein ($P=0.0128$) levels changed significantly in children with pneumonia than in healthy children (43). It was also reported that the pathogenic bacteria present in the salivary samples collected before operation could be predictive of the risk of postoperative aspiration pneumonia (76). Finally, salivary sIgA level has been used to evaluate the efficacy of influenza vaccine (77).

Tuberculosis (TB)

Inflammatory and immune markers have been used in the diagnosis of TB (44,78). In patients with TB, levels of several inflammatory biomarkers, including IFN- γ , IL-1 α , IL-12 (p70), IL-13, IL-15, IL-17, fractalkine, GM-CSF, and EGF, in saliva samples were found to be significantly higher than those in serum samples (45,46). Salivary IL-6, CRP, MIP-1 β , fractalkine, A2M, haptoglobin, fibrinogen, IL-16, and IL-23 levels are potentially valuable in the diagnosis of TB, with an AUC of ≥ 0.70 (44,46,47). Furthermore, a combination of salivary biomarkers could improve the diagnostic accuracy of TB (44–47). For example, a five-marker combination of IL-1 β , IL-23, ECM-1, HCC1, and fibrinogen could help diagnose TB with a sensitivity of 88.9% and a specificity of 89.7% (44). Furthermore, salivary proteomic analysis showed that there were differences between patients with active TB versus infected and uninfected contacts in terms of the composition of salivary protein and quantities of its components, including haptoglobin, alpha-1-acid glycoprotein 1 and 2, immunoglobulin gamma 4 chain, fibrinogens, dermcidin, glutathione synthetase, lactoylglutathione lyase, protein disulfide isomerase, triosephosphate isomerase, tropomyosin alpha 4, and ras GTPase-activating like protein (9).

Lung cancer (LC)

Some studies on LC have focused on genomics, transcriptomics, proteomics, and microbiomics of saliva. Saliva could act as the source of cell-free DNA (cfDNA) for the detection of EGFR mutations; the coincidence rate for the detection of EGFR mutations between salivary cfDNA and plasma cfDNA reached 83.78% (6), and a new technology named electric field-induced release and measurement (EFIRM) was used to detect EGFR mutations in saliva with an improved accuracy (50,51). Levels of other salivary indicators such as transcriptomic biomarkers (e.g., BRAF, CCNI, EGFR, FGF19, FRS2, GREB1, and LZTS1), proteins (e.g., haptoglobin hp2, zinc α 2-glycoprotein and human calprotectin), and exosomes (e.g., Aquaporin5 and Mucin-5B) were also found to be significantly different between patients with LC and control subjects, and this finding has potential diagnostic value for LC (5,52,53). For example, it was reported that a combination of five mRNA biomarkers (CCNI, EGFR, FGF19, FRS2, and GREB1) could differentiate patients with LC from normal control subjects with 93.75% sensitivity and 82.81%

specificity, yielding an AUC value of 0.925 (52), and that salivary proteins including haptoglobin hp2(HP), zinc α 2-glycoprotein (AZGP1), and human calprotectin could predict LC with a sensitivity of 88.5%, a specificity of 92.3%, and an AUC of >0.90 (53).

The link between cancer and microbes has been well established (79-82). Salivary microbiomics become another subject of growing interest with regard to LC studies. Low microbial diversity in the saliva of patients with LC has been reported (Shannon index, $P=0.002$; Simpson index, $P=0.033$). Relative abundances of the genera *Veillonella*, *Streptococcus*, *Prevotella*, *Bacteroides*, *Faecalibacterium*, *Capnocytophaga*, and *Actinomyces* was found to be significantly different in patients with LC and controls ($P<0.05$). *Filifactor*, *Capnocytophaga*, and *Veillonella* showed diagnosis value for LC with a ROC value >0.7 (54-56). The pathophysiological mechanisms by which LC influences salivary microbiota is currently under investigation. Microbiome dysbiosis may promote LC development and progression through production of toxins and various other pathways, such as affecting long-term immune response.

Others

Studies on saliva in patients with Langerhans cell histiocytosis (LCH) and cystic fibrosis (CF) have also been reported. These studies found that salivary interleukin-1b (IL-1b) and prostaglandin E2 (PGE2) levels could be used as biomarkers for the diagnosis and evaluation of disease severity of LCH in children (57), and salivary ions including chloride and sodium could be used for the diagnosis of CF (58). Moreover, gastroesophageal reflux disease (GERD) is associated with several respiratory diseases, for example COPD, asthma, idiopathic pulmonary fibrosis (IPF), and OSA, and it has been reported that salivary pepsin detection could be used to monitor GERD (83-86). Furthermore, therapeutic drug monitoring (TDM) studies on saliva with regard to respiratory diseases also should be mentioned. However, the negative results associated with the levels of theophylline, amikacin, levofloxacin, or tobramycin in salivary sample imply that salivary samples are not suitable for TDM in patients with COPD, TB, and LC (16,48,49,59).

Discussion

Saliva can be collected in a simple, minimally-invasive, and repeated manner, and is used widely for studying microbiomics, genomics, transcriptomics, proteomics,

and metabolomics of respiratory diseases. It showed potential value in the diagnosis, monitoring, and prognosis of respiratory diseases. However, the pathophysiological mechanisms by which respiratory diseases influence the levels of saliva indicators are rarely mentioned. Furthermore, several limitations of saliva test also should be mentioned. Firstly, oral environment is affected by many factors, and a standard protocol for saliva collection and saliva preservation has not been established (15,44,87). Several methods have been reported, such as spitting into a sterile tube (15), chewing a sterile cotton swab (Salivette) (44), and chewing 1 g of nonsweet paraffin for 15 minutes to stimulate saliva production (87); however, the influence of these methods on the results has not been studied. Establishing a standard protocol for saliva collection and saliva preservation is a challenge for saliva test in the future. Secondly, recent studies have demonstrated that most biomarkers that are collected from serum and other body fluids used for the diagnosis and treatment of respiratory diseases can also be detected in saliva; although the relationship between levels of indicators in saliva and other samples is reported (6,41,45,46), reference values of various salivary biomarkers have not been established. Establishing reasonable reference values need to be considered in the further studies. Thirdly, most of the results came from cross-sectional study with small samples rather than RCT studies.

In conclusion, the use of salivary biomarkers for the diagnosis, monitoring, and prognosis of respiratory disease is still in its infancy. Multicenter, prospective clinical studies are needed in the future.

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Footnote

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