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REVIEW PAPER

Detection of gastrointestinal cancers using salivary biomarkers – a systematic review

Anna Angelaki [1], Datis Kalali [2], Chara Chantzara [1], Lanya Faiq [1], Maram Gad [1], Sabina Kadłubek [3], Jakub Kamiński [3], Zoi Charalampidi [1], Charalampos Charalampidis [2], Doxakis Anestakis [2,4]

[1] School of Medicine and Dentistry, European University of Cyprus, Nicosia, Cyprus
[2] Medical School, University of Cyprus, Nicosia, Cyprus
[3] Faculty of Medical Sciences, Medical University of Silesia, Katowice, Poland
[4] Laboratory of Autopsy Pathology, Forensic Service of Thessaloniki, Ministry of Justice, Thessaloniki, Greece

ABSTRACT

Introduction and aim. Cancers of the gastrointestinal tract are highly prevalent worldwide, with usually symptomless presentations making diagnosis at an early stage challenging. At the same time, salivary biomarkers are a promising method of early diagnosis in different malignancies. To this end, the present systematic review was carried out to investigate if salivary biomarkers can help with the early detection of gastrointestinal cancer and ascertain their diagnostic value.

Material and methods. Major electronic databases were searched using a combination of keywords and Boolean operators to retrieve all existing literature on the topic from April 2024 until inception. Clinical studies with relevant information were included in the quantitative synthesis.

Analysis of the literature. A total of 48 studies exploring the use of potential salivary biomarkers in esophageal, gastric, colorectal, pancreatic, hepatocellular and biomarkers were included in the present review. All studies retrieved statistically significant correlations between the presence of certain markers in the saliva and development of gastrointestinal cancers.

Conclusion. Salivary biomarkers can help detect different gastrointestinal cancers. However, more studies are required to determine their diagnostic value. The use of artificial intelligence might help clinicians in exploiting these biomarkers.

Keywords. cancer diagnosis, gastrointestinal cancers, salivary biomarkers

Introduction

Malignancies of the gastrointestinal tract and the accessory organs of digestion, known as gastrointestinal cancers, account for more than 25% of cancer cases and 30% of cancer-related deaths worldwide.[1] Gastrointestinal cancers are classified into the following major categories: esophageal, gastric, colorectal, hepatobiliary, pancreatic and bile duct cancers.[2] Most of these malignancies are symptomless at their onset and present symptoms at relatively late stages, indicating the need for continuous screening for detection in early stages.[3-5] The gold standard for screening malignancies of the gastrointestinal tract is through gastroscopy and colonoscopy which can be inconvenient for patients and costly, whereas cancers of the accessory organs are even more difficult to screen and require techniques of imaging

Corresponding author: Datis Kalali, e-mail: kalali.datis@ucy.ac.cy

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with high doses of radiation which bear high risks of developing other malignancies throughout time.[6,7]

The use of salivary biomarkers for screening diseases is a relatively novel screening and diagnostic method which is fully non-invasive and bears low-costs, requiring only a sample of a patient's saliva and is reliable in detecting gastrointestinal disease since it contains many different biomolecules like the blood and the histological composition of the gastrointestinal tract is similar to that of the oral cavity.[8,9]

Aim

Since tumors of the gastrointestinal tract and accessory organs of digestion can release different molecules into the gastrointestinal tract and henceforth into saliva, the use of salivary biomarkers for screening them is a very possible rationale, probably revolutionizing the future of cancer diagnostics. Nonetheless, the available evidence on the use of such markers is scattered in different literature records. To this end, the present systematic review was performed to determine whether and which gastrointestinal cancers are detectable using salivary biomarkers, as described in the existing literature. An observed correlation would indicate the need for further research and possible future clinical use of these biomarkers.

Material and methods

The present systematic review was conducted in full compliance with PRISMA 2020 guidelines. The questions guiding the review study were as follows:

1. 'Can salivary biomarkers be used to detect gastrointestinal cancers?',
2. "What gastrointestinal cancers are detectable using salivary biomarkers and what are their diagnostic values?".

Search strategy

The online databases PubMed, Scopus and EMBASE were searched systematically for articles dating from inception until 30 April 2024, using the keywords "saliva", "salivary", "anal", "bile duct", "colon", "colorectal", "rectal", "bowel", "esophageal", "oesophageal", "gallbladder", "liver", "hepatocellular", "pancreas", "pancreatic", "stomach", "gastric", cancer", "carcinoma", "tumor", "cholangiocarcinoma", "marker" and "biomarker" combined with Boolean operators. The search was limited to articles written in the English language.

Using the citation manager EndNote release version 20.6 (Clarivate Plc, Philadelphia, USA), duplicates were removed and subsequently citations were screened based on their titles and abstracts. The inclusion criteria were cohort and case-control studies, including a total of more than 20 participants who evaluated salivary biomarkers for gastric cancer. The final selection was made after the remaining studies were evaluated on their full text. The selection process was performed by two independent reviewers (AA and DK). Any discrepancy that arose was resolved by a third researcher (CC).

Data extraction

The following data was extracted from each study and included in the qualitative analysis:

1. The neoplastic conditions studied,
2. Number of patients enrolled in the study,
3. Baseline characteristics of the included patients,
4. The salivary biomarkers assessed in the study and their respective detection method,
5. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of each biomarker calculated in the study.

Analysis of the literature

The database search on the Internet retrieved a total of 3387 citations (321 from PubMed, 1052 from Scopus and 2014 from EMBASE) and an addition of 3 other citations were retrieved manually through alternative sources. After removal of duplicates a total of 2701 citations remained, amongst which a total of 2597 citations were excluded after screening, since irrelevance to the research question was obvious from their titles or abstracts. Among the remaining 104 studies which were assessed based on their full texts, a total of 47 studies did not contain relevant data for our research, 7 were review studies,, 2 were animal studies and two had cohorts of less than 20 participants, leaving a total of 46 studies included in the qualitative synthesis. The selection process is illustrated in Figure 1.

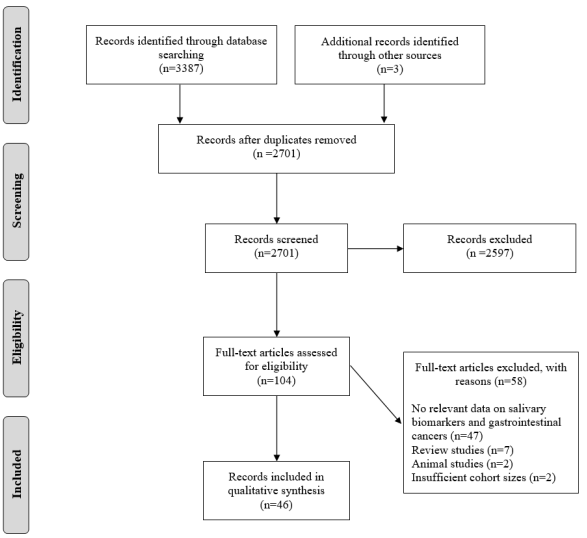

Fig. 1. PRISMA diagram of the inclusion process

The characteristics of all included studies are recorded in Tables 1–6.

Table 1. Characteristics of studies on detecting esophageal cancer

Study (Author, year, country)	Participants (n)	Histological subtype	Age of participants	Biomarker type	Biomarkers assessed	Method of assessment	Association in cancer patients /p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Aznab et. al, 2023, Iran[10]	Cases: 6 Controls: 57 Total: 63	Not mentioned	Cases - 56 Controls - 42	Protein	E-cadherin	ELISA	0.59				
Graham et. al., 2016, United Kingdom[11]	Cases: 20 Controls: 20 Benign: 40 Total: 80	Adenocarcinoma	Unknown	RNA	TP53, CDKN2a, SMAD7, EGFR, AMY2, TLR6, KIT9, KRAS, PTEN and PIK3CA	RNA extraction -QIAzol and chloroform based process RNA expression analysis – RT-qPCR with 18s rRNA	<0.05	93%	73%		
Li et. al., 2022, China[12]	Cases: 340 Controls: 180 Total: 520 ESCC	Squamous cell carcinoma	Cases: 52–70.11 Controls: 51.93 – 70.33	RNA (sesncRNA)	1. tRNA-GlyGCC-5 2. sRESE (small RNA identified in Exosome from Saliva of ESCC patients) 3. Bi-sesncRNA signature (1+2 combined)	RT-qPCR	<0.001 for all	1. 79% 2. 77% 3. 90.50%	1. 91.67% 2. 88.33% 3. 94.20%	1. 94.05% 2. 91.67% 3. 96.28%	1. 72.37% 2. 69.73% 3. 85.61%
Li et. al., 2023, China[13]	Cases: 512 Controls: 254 Total: 766 ESCC	Squamous cell carcinoma	Training cohort: Cases - 61.09+7.77 and Controls -60.98+8.02 Internal validation cohort: Cases - 62.44+6.97 and Controls - 61.64+4.90 External validation cohort: Cases - 63.17+5.36 and Controls - 63.21+5.57	EVP miRNA	Increased in ESCC – EVP miR-1268a, miR-4505 Decreased in ESCC – miR1972, miR-4274, miR-4701-3p and miR-6126	RT-qPCR	<0.001 for all	Training Cohort – 87.39% Internal Validation Cohort – 86.43% External Validation Cohort – 88.05%	Training Cohort – 91.67% Internal Validation Cohort – 91.05% External Validation Cohort – 88.06%	Training Cohort – 95.10% Internal Validation Cohort – 95.28% External Validation Cohort – 94.59%	Training Cohort – 79.71% Internal Validation Cohort – 76.25% External Validation Cohort – 75.64%
Shu et. al, 2021, China[14]	Cases: 16 Controls: 25 Total: 41 ESCC	Squamous cell carcinoma	Cases: ≤ 60 = 43.75% >60 = 56.25 % Controls: ≤60 = 44% >60 = 56%	Glycoprotein	GalNAc, Gal, sialic acid and GlcNAc	MALDI-TOF/TOF-MS					
Stone et. al., 2024, United Kingdom[15]	Cases: 88 Controls: 168 Total: 256 Adenocarcinoma	Adenocarcinoma	Cases (mean) – 70.3 Controls (mean) – 62.2	Ca biomarkers based on DNA methylation (detection of epigenetic changes)	Used probes not specified	Illumina EPIC methylation arrays	NA	88%	31%		
Wu et. al, 2013, China[16]	Cases: - Controls: 50 Benign: - Total: -	Not mentioned		RNA	miRNA-144	RT-PCR	<0.05	Whole saliva - 74.6% Saliva supernatant – 53.7%	Whole saliva - 92% Saliva supernatant – 94%		
Xie et. al., 2013, China[17]	Cases: - 39 Controls: 19 Total: - 58	Not mentioned	Cases (mean ± SD): 59.7±9 Controls (mean ± SD): 55.9±8.8	RNA	Whole saliva markers: 1. miR-10b 2. miR-144 3. miR-451 Supernatant markers: 1. miR-10b 2. miR-144 3. miR-21 4. miR-451	RT-qPCR	Whole saliva markers: 1. 0.001 2. 0.012 3. 0.002 Supernatant markers: 1. 0.013 2. 0.036 3. 0.015 4. 0.006	Whole saliva markers: 1. 89.7% 2. 92.3% 3. 84.6% Supernatant markers: 1. 79.5% 2. 43.6% 3. 89.7% 4. 51.3%	Whole saliva markers: 1. 57.9% 2. 47.4% 3. 57.9% Supernatant markers: 1. 57.9% 2. 89.5% 3. 47.4% 4. 84.2%		
Xie et. al., 2012, China[18]	Cases: - 32 Controls: 16 Total: - 48	Not mentioned	Cases (mean ± SD): 61.6±9.3 Controls (mean ±SD): 57.5±7.1	RNA	Saliva supernatant miR-21	RT-qPCR	0.003	84.4%	62.5%		
Ye et. al., 2014, China[19]	Cases: - 100 (50 in stage I, 50 in stage II) Controls: 50 Total: - 150	Not mentioned	NA	RNA	miR-21	qPCR		Stage I – 90% Stage II – 88% Stage I+II combined – 89%	64% for all		

Table 2. Characteristics of studies on detecting gastric cancer

Study (Author, year, country)	Participants (n)	Histological subtype	Age	Biomarker type	Biomarkers assessed	Method of assessment	Association in cancer patients /p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Aznab et.al., 2023, Iran [10]	Cases: 32 Controls: 57 Benign: 0 Total: 89	Not mentioned	Cases (mean): 56 Controls (mean): 42	Protein	E-cadherin	ELISA	Higher				
Bel'skaya et.al., 2020, Russia [20]	Cases: 11 Controls: 16 Benign: 0 Total: 27	Adenocarcinoma	Cases: 56.8 ± 5.5 Controls: 57.1 ± 6.4	Volatile organic compounds	Acetaldehyde, acetone, propanol-2, and ethanol	Capillary gas chromatography	Higher (p<0.05)	80.0%	100%		
Chen et.al., 2022, China [21]	Cases: 120 Controls: 20 Benign: 31 AG , 35 NAG, 26 GP Total: 232	Adenocarcinoma	Cases: Age<61: 56 Age≥61: 64 Controls: 56.90 ± 16.02 Benign: 62.13 ± 10.56 AG, 60.80 ± 14.54 NAG , 58.17± 15.26 GP	Microbe	Fusobacterium nucleatum	Digital droplet polymerase chain reaction (ddPCR)	Higher (p=0.780)	73.33%	82.14%	81.48%	74.19%
Huang et al., 2021, China [22]	Cases: 99 Controls: Benign: 101 SG, 93 AG (21 without IM and 72 with IM) Total: 293	Adenocarcinoma	Cases: 49.6 ± 8.8 Benign: 48.2 ± 10.2 SG, 49.9 ± 12.5 AG without IM and 48.5 ± 11.7 AG with IM	Microbes	Salivary Microbiota	Sequence analysis of the 16S ribosomal RNA gene	0.3582				
Kaczor-Urbanowicz et.al., 2022, USA[23]	Cases: 51 Controls: 49 Benign: Total: 100	Adenocarcinoma	Cases: 61.0 Controls: 60.0	RNA	Salivary exRNA	qPCR	0.0809				
Koopaie et.al., 2022, Iran [24]	Cases: 31 Controls: 31 Benign: Total: 62	Adenocarcinoma	Unknown	Protein	CSTB and DMBT1	ELISA and Machine Learning	CSTB p-value: 0.001 DMBT1 p-value: 0.002	CSTB sensitivity: 83.87% DMBT1 sensitivity: 80.65 %	CSTB specificity: 70.97 % DMBT1 specificity: 64.52 %		
Li et.al., 2018, Korea [25]	Cases: 163 Controls: 131 Benign: 0 Total: 294	Not mentioned	Cases: 51.9 ± 9.2 Controls: 55.7 ± 8.1	RNA	Extracellular RNA (exRNA)	RT-qPCR	Lower ANXA1: 0.008 CD24: 0.001 CSTB: 0.004 EIF3G: 0.945 ERO1A: 0.002 KRT4: 0.035 KRT6A:0.001 PPL: 0.007 RANBP9: 0.157 S100A10: 0.006 SEMA4B: 0.149 SPINK7:0.001 MIR140-5p: <0.001 MIR37a: <0.001 MIR454: 0.003 MIR15b: <0.001 MIR28-5p: 0.024 MIR301a: 0.01	82%	77%		
Shu et.al., 2018, China [26]	Cases: 51 Controls: 51 Benign: 0 Total: 102	Not mentioned	Cases: 54.1±7.4 Controls: 53.7 ± 5.5	Glycans	N- and O-linked glycans	MALDI-TOF	Six fucosylated N-linked glycans (?				

Shu et.al., 2017, China [27]	Cases: 64 Controls: 30 Benign: 0 Total: 94	Not mentioned	Unknown	Protein	Protein glycosylation patterns (15 lectins)	Lectin microarray	Higher and altered glycosylation patterns in GC	96%	80%
Swarup et.al., 2023, USA [28]	Cases: 10 Controls (gastritis): 10 Benign: 0 Total: 20	Not mentioned	Cases (mean): 59.4 Controls (mean): 40.5	DNA	Cell-free DNA	PCR	Higher (p= 0.0361)		
Xiao et.al., 2016, China [29]	Cases: 20 Controls: 20 Benign: 0 Total: 40	Not mentioned	Cases: 54.45 ± 11.14 Controls: 44.45 ± 12.54	Protein	Cystatin B (CSTB), triosephosphate isomerase (TPI1), and deleted in malignant brain tumors 1 protein (DMBT1)	ELISA	Lower (p<0.04)	85%	80%
Xu et.al.,2020, China [30]	Cases: 60 Controls: 60 Benign: 0 Total: 120	Adenocarcinoma	Cases: 60.17 ± 11.78 Controls: 58.80 ± 14.38	Protein and RNA	Carcinoembryonic antigen (CEA) and mRNAs (SPINK7, PPL, SEMA4B, SMAD4)	Immunoassay system and RT-qPCR	Carcinoembryonic antigen: Higher (p<0.001) SPINK7, PPL, SEMA4B and SMAD4: Lower (p<0.001)	Combined: 92%	Combined: 87%

Table 3. Characteristics of studies on detecting colorectal cancer

Study (Author, year, country)	Participants (n)	Age	Biomarker type	Biomarkers assessed	Method of assessment	Association in cancer patients /p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Aznab et.al., 2022, Iran [10]	Cases:68 Controls:57 Benign:0 Total:125	49.66 ± 15.71 years	Soluble E-cadherin (sE-cadherin)	Levels of soluble E-cadherin in saliva and serum	Enzyme-linked immunosorbent assay (ELISA)	Elevated levels of soluble E-cadherin in cancer patients compared to healthy controls/p=0.031				
Bel'skaya et.al., 2020, Russia [20]	Cases:11(stomach Ca)+18(colorectal ca) Controls:16 Benign:0 Total:45	Age Range:30–70 Stomach Cancer Patients: Average age 56.8 ± 5.5 Colorectal Cancer Patients: Average age 58.2 ± 3.8	Volatile Organic Compounds (VOCs)	Acetaldehyde, Acetone, Propanol-2, Ethanol, Methanol, Lipid Peroxidation Products: triene conjugate and Schiff base	VOCs Analysis: Capillary gas chromatography	Significant differences in the levels of VOCs in saliva between cancer patients and healthy controls.	For Cancer/Control Classification: 95.7% For Stomach Cancer: 80.0% For Colorectal Cancer: 92.3%	For Cancer/Control Classification: 90.9% For Stomach and Colorectal Cancer: 100%		
Holten-Andersen et.al., 2012, Denmark [31]	Cases:56 Controls:105 Benign: Total:161	61 (range 25–87) Cancer individuals:68,2 Non-cancer individuals:56,6	TIMP-1 (Tissue Inhibitor of Metalloproteinases-1)	TIMP-1 concentration in saliva and plasma	ROC curves	Plasma TIMP-1 concentration significantly associated with the diagnosis of CRC (p = 0.0003)				
Kiseleva et.al, 2023, Russia[32]	Cases:100 Controls:66 Benign: Total:166	CRC: >61, LC: ≥54	miRNA-21	CMR-21(miRNA-21 in saliva) and PMR-21(miRNA-21 in blood plasma)	Reverse transcription polymerase chain reaction(RT-PCR)	CMR-21 and PMR-21 levels were statistically significantly different among CRC, LC, GCT, and healthy controls (p < 0.001) Higher CMR-21 in CRC with a small depth of tumor invasion (p = 0.004; p = 0.042)	CRC: SMR-21= 52%, PMR-21=61% LC: SMR-21=100%, PMR-21=78% GCT: CMR-21=88%, PMR-21=57%	CRC: SMR-21=89%, PMR-21=83% LC: SMR-21=86%, PMR-21=64% GCT: CMR-21=77%, PMR-21=71%		
Koopaei et.al., 2024, Iran[33]	Cases:42 Controls:33 Benign: Total:75	CRC patients: 54.12±13.98 years, healthy controls: 42.33±12.50 years	Salivary microRNAs	miR-29a miR-92a	Real-time quantitative reverse transcription PCR (RT-qPCR)	miR-29a and miR-92a expression levels: Significantly higher in CRC patients compared to controls.	miR-29a: 88% miR-92a: 85.3%	miR-29a: 93% miR-92a: 93%	miR-29a PPV:94%	
Kuwabara, et.al.,2019, Japan[34]	Cases:231 Controls:2272 Benign:99 Total:2602		Metabolites	Numerous hydrophilic metabolites in saliva	Capillary electrophoresis-mass spectrometry-based metabolomics	High area under the receiver operating characteristic curve (AUC ¼ 0.876; P < 0.0001) in the training data-set. This combination also showed high AUC values using the validation dataset (AUC ¼ 0.861; P < 0.0001).				
Kuwabara et.al., 2022, Japan [35]	Cases:235 Controls:2317 Benign:50 Total:2602		Salivary metabolites	122 quantified metabolites	Metabolite concentrations were calculated using CE-MS based on the ratio of peak area divided by the area of internal standards. Polyamine LC-MS was used redundantly to detect peaks. Data analysis included partial least squares discriminant analysis (PLS-DA) and machine learning models (ADTree and MLR).	63 metabolites showed a p-value < 0.05 between HC and CRC.				
Lazaro-Sanchez et.al., 2019, Spain [36]	Cases:15 Controls:10 Benign: Total:25		Soluble HLA-G (sHLA-G)	sHLA-G levels in saliva and serum	Measurement of sHLA-G levels in saliva and serum	Higher sHLA-G levels in advanced stages (III-IV) compared to early stages (I-II) in both saliva and serum. Significant association between higher sHLA-G levels and advanced tumor stages. No significant association with tumor location, DNA repair protein instability, or sex of patients. Higher sHLA-G levels in patients over 70 years old compared to those under 70 years. Difference between CRC patients and controls: p = 0.036 (saliva)				

Rapado-Gonzalez et.al., 2019, Spain [37]	Cases:51 Controls:37 Benign:19 Total:107		Salivary microRNAs (miRNAs)	miR-186-5p, miR-29a-3p, miR-29c-3p, miR-766-3p, miR-491-5p.	ROC curve analysis to discriminate CRC patients from controls based on salivary miRNA levels. Screening of 754 miRNAs in saliva samples using RT-qPCR.	No significant association between the five salivary miRNAs and age, lymph node metastasis, distant metastasis, tumor grading, serum CEA levels, TNM staging, tumor location, body mass index, alcohol intake, and smoking status. Levels of miR-186-5p, miR-29a-3p, and miR-29c-3p were significantly increased in males ($p < 0.05$)	miR-186-5p, miR-29a-3p, miR-29c-3p, miR-766-5p and miR-491-5p 72% (Combined with CEA levels: 89.36%)	miR-186-5p, miR-29a-3p, miR-29c-3p, miR-766-5p and miR-491-5p 66.67%
Rapado-Gonzalez et.al., 2018, Spain [38]	Cases:14 Controls:10 Benign:4 Total:28		MicroRNA (miRNA)	754 miRNAs analyzed, with a panel of specifically dysregulated miRNAs identified	Sample collection: Non-stimulated saliva RNA isolation: miRNeasy extraction Micro Kit (QIAGEN) miRNA expression analysis: TaqMan Array Low-Density Human MicroRNA Arrays (TLDA; Applied Biosystems, Thermo Fisher Scientific) Validation: qRT-PCR in an independent cohort			
Sazanov et.al., 2017, Poland [39]	Cases: 31 Controls: 34 Benign: 0 Total: 65	≤60	microRNA (miRNA)	miRNA-21	Real-time quantitative PCR (qPCR)	miRNA-21 expression levels were significantly higher in CRC patients compared to healthy controls/ P=5e-12	97%	91%
Waniczek, et.al.,2022, Poland [40]	Cases:39 Controls:40 Benign: Total:79	>60y.o	Proteins (chemerin, α-defensin 1, TNF-α)	Serum chemerin, Salivary chemerin, Serum α-defensin 1, Salivary α-defensin 1, Serum TNF-α, Salivary TNF-α	ROC Curve Analysis	The salivary and serum concentrations of chemerin, α-defensin 1, and TNF-α were significantly higher in cancer patients compared to the control group/p-values < 0.001 for all biomarkers tested	Salivary chemerin, a-defensin 1, TNF-a 100% Serum chemerin, a-defensin 1, TNF-a 100%	Salivary chemerin, a-defensin 1, TNF-a 100% Serum chemerin, a-defensin 1, TNF-a >90%
Zhang et.al.,2022, China [41]	Cases:207 Controls:117 Benign:76 Total:324	Median age:63y.o	Salivary DNA and Serum Levels of CEA and CA19-9	Fn DNA (Fusobacterium nucleatum DNA), CEA (Carcinoembryonic Antigen), CA19-9 (Carbohydrate Antigen 19-9)	Fn DNA levels were measured using qPCR and calculated as the ratio of the NusG gene level to the geometric mean of GAPDH and TERT levels	Fn DNA: Higher in CRC patients compared to control groups. CEA: Significantly higher in CRC patients compared to controls. CA19-9: Significantly higher in CRC patients compared to controls	Salivary Fn DNA: 71.5% CEA 22.2% and CA19-9 10.1%	Salivary Fn DNA: 82.1%

Table 4. Characteristics of studies on detecting pancreatic cancer

Study (Author, year, country)	Participants (n)	Age	Biomarker type	Biomarkers assessed	Method of assessment	Association in cancer patients /p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Asai et.al., 2018, Japan [42]	Cases: 45 Controls: 10 Benign: 13 Total: 68	Unknown	Metabolomic	300 metabolites	CE-TOMS (capillary electrophoresis mass spectrometer)	Values of AUC (cases vs controls): spermine (0.8978) spermidine (0.7929) N1-Acetylspermidine (0.8526) N1,N8-Acetylspermidine (0.8526) N1,N12-Acetylspermidine (0.8526) Three metabolite-based MLR model's value of AUC (cases vs controls + benign): 0.8725	Unknown	Unknown	Unknown	Unknown
Asai et.al., 2018, Japan [43]	Cases: 39 Controls: 26 Benign: 14 Total: 79	Cases : 66.1 ± 9.8 Controls: 50.8 ± 16.4 Benign: 51.1 ± 12.4	Metabolomic	292 metabolites	CE-TOMS (capillary electrophoresis mass spectrometer)	(1) MLR model included four metabolites (cases vs controls + benign): AUC= 0.887; p = 0.002 Cases vs controls + benign (p<0.05): alanine; N1-acetylspermidine; 2-oxobutyrate; 2-hydroxybutyrat Cases vs controls (p<0,001): spermine; N1-acetylspermine; 2-aminobutanoat	(1) 0.71 (0.55-0.85)	(1) 0.95 (0.83-0.99)	(1) 0.93 (0.78-0.99)	(1) 0.77 (0.63-0.88)
Farrell et.al., 2009, USA [44]	Cases: 30 Controls: 30 Benign: 30 Total: 90	Unknown	Microbiome transcriptomic metabolomic	The combination of four biomarkers (mRNA biomarker MBD3L2, GLTSCR2; microbial biomarker Prevotella nigrescens, Neisseria elongata)	The Affymetrix U133 Plus 2.0 array; RT-PCR; CE-TOMS	AUC value (four biomarkers): (1) cases vs controls 0.940 (p < 0.001) (2) cases vs benign 0,900 6 microbial, 11 mRNA and 8 metabolites p<0.05 (cases vs controls + benign)	(1) 0.89 (0.73-0.98)	(1) 0.89 (0.73-0.98)	(1) 0.90 (0.73-0.98)	(1) 0.90 (0.73-0.98)
Gao et.al, 2014, China [45]	Cases: 30 Controls: 32 Total: 62	Cases: 33-78	Epigenomic	384 miRNAs	miScript miRNA PCR array human miRNome (384-well plate) from Qiagen; SYBR Green-based qPCR; qRT-PCR	Positive association p<0.05 (amount of 19 miRNAs)	Unknown	Unknown	Unknown	Unknown
Liu et al., 2017, China [46]	(1) Cases: 12 Controls: 12 Total: 24 (2) Cases 8 Benign: 4 Total: 12	Unknown	Transcriptomic	516 mRNAs (1,2) set of 29 of them	microarrays and qRT-PCR	Positive association p<0.01 (23 up-regulated and 12 down-regulated transcripts)	(1) 0.92 (0.62-1.00) (2) 1.00 (0.63-1.00)	(1) 1.00 (0.74-1.00) (2) 1.00 (0.40-1.00)	(1) 1.00 (0.72-1.00) (2) 1.00 (0.64-1.00)	(1) 0.92 (0.64-1.00) (2) 1.00 (0.40-1.00)
Machida et al., 2016, Japan [47]	Cases: 12 Controls: 13 Total: 25	Cases: 65 (45-84) Controls: 66 (53-83)	Epigenomic	miR-1246, miR-3976, miR-4306, miR-4644	high-performance liquid chromatography; latex agglutination; bromocresol green albumin; electrochemiluminescence immunoassays; Total Exosome Isolation Reagent RT-qPCR Mx3000P Real-Time QPCR System	(1) miR-1246: AUC 0.814; p = 0.008 (2) miR-4644: AUC= 0.763; p=0.026 (3) combination of miR-1246 and miR-4644: AUC=0.833; p= 0.005	(1) 0.667 (0.35-0.90) (2) 0.75 (0.43-0.95) (3) 0.83 (0.52-0.98)	(1) 1.00 (0.75-1.00) (2) 0.77 (0.46-0.95) (3) 0.92 (0.64-1.00)	(1) 1.00 (0.63-1.00) (2) 0.75 (0.51-0.90) (3) 0.91 (0.59-1.00)	(1) 0.76 (0.59-0.88) (2) 0.77 (0.54-0.90) (3) 0.86 (0.62-0.96)

Xie et al., 2016, China [48]	Cases: 55 Controls: 55 Benign tumors: 20 Total: 130	Cases: median: 61 (13–81) Controls: median: 61 (13–81) Benign: median: 49 (34–79)	Epigenomic	lncRNA: H19, HOTAIR, HOTTIP, MALAT1 PVT1	qPCR	Cases vs controls: (1) HOTAIR: p< 0.001; AUC: 0.880 (2) PVT1 p< 0.001; AUC: 0.870 (3) HOTAIR + PVT: p< 0.001; AUC: 0.909 Cases vs benign: (4) HOTAIR: p< 0.001; AUC: 0.863 (5) PVT1 p< 0.001; AUC: 0.846 (6) HOTAIR + PVT: p< 0.001; AUC: 0.909	(1) 0.78 (0.65-0.88) (2) 0.96 (0.87-1.00) (3) 0.78 (0.65-0.88) (4) 0.80 (0.67-0.90) (5) 0.69 (0.55-0.81) (6) 0.82 (0.70-0.91)	(1) 0.85 (0.73-0.93) (2) 0.64 (0.50-0.76) (3) 0.91 (0.80-0.97) (4) 0.90 (0.68-0.99) (5) 0.95 (0.75-1.00) (6) 0.95 (0.75-1.00)	(1) 0.84 (0.71-0.93) (2) 0.73 (0.61-0.82) (3) 0.90 (0.77-0.97) (4) 0.96 (0.85-0.99) (5) 0.97 (0.87-1.00) (6) 0.98 (0.88-1.00)	(1) 0.80 (0.67-0.89) (2) 0.95 (0.82-0.99) (3) 0.81 (0.69-0.90) (4) 0.62 (0.42-0.79) (5) 0.53 (0.35-0.70) (6) 0.66 (0.46-0.82)
Xie et al., 2015, China [49]	Cases: 40 Controls: 40 Benign: 20 Total: 100	Cases: median: 59,5 (13-81) Controls: median: 60,5 (23-71) Benign: median: 49 (34-79)	Epigenomic	miR-4433-5p miR-4665-3p miR-940 miR-1273g-3p miR-3676-5p miR-3679-5p miR-3940-5p miR-4327 miR-4442 miR-5100	qPCR ABI 7500 Real-Time PCR System (Life Technologies); SYBR Premix ExTaq (TaKaRa)	Cases vs (controls + benign): (1) miR-3679-5: p=0.002; AUC=0,688 (2) miR-940 p=0.001; AUC= 0,696 (3) MLR model (miR-3679-5p + miR-940): p<0.001; AUC= 0.763 Cases vs controls (4) miR-3679-5 p = 0.008; AUC: 0.673 (5) miR-940 p = 0.006; AUC: 0.680 (6) MLR model (miR-3679-5p + miR-940): p < 0,001; AUC: 0,750 Cases vs benign: (7) miR-3679-5 p = 0.007; AUC: 0.716 (8) miR-940 p = 0.004; AUC: 0.729, (9) MLR model (miR-3679-5p + miR-940): p < 0.001; AUC: 0,821	(1) 0.85 (0.70-0.94) (2) 0.90 (0.76-0.97) (3) 0.70 (0.53-0.83) (4) 0.83 (0.67-0.93) (5) 0.90 (0.76-0.97) (6) 0.73 (0.56-0.85) (7) 0.90 (0.76-0.97) (8) 0.63 (0.46-0.77) (9) 0.63 (0.46-0.77)	(1) 0.45 (0.32-0.58) (2) 0.42 (0.29-0.55) (3) 0.70 (0.57-0.81) (4) 0.43 (0.27-0.59) (5) 0.40 (0.25-0.57) (6) 0.70 (0.53-0.83) (7) 0.45 (0.23-0.68) (8) 0.75 (0.51-0.91) (9) 0.80 (0.56-0.94)	(1) 0.51 (0.38-0.63) (2) 0.51 (0.39-0.63) (3) 0.61 (0.45-0.75) (4) 0.59 (0.45-0.72) (5) 0.59 (0.46-0.72) (6) 0.71 (0.54-0.84) (7) 0.77 (0.62-0.88) (8) 0.83 (0.65-0.94) (9) 0.86 (0.68-96)	(1) 0.82 (0.65-0.93) (2) 0.86 (0.68-0.96) (3) 0.78 (0.64-0.88) (4) 0.71 (0.49-0.87) (5) 0.80 (0.56-0.94) (6) 0.72 (0.55-0.85) (7) 0.69 (0.39-0.91) (8) 0.50 (0.31-0.69) (9) 0.52 (0.33-0.70)
Wong et al., 2009, USA [50]	Cases: 30 Controls: 30 Benign: 30 Total: 90	Unknown	Transcriptomic and microbiome	ACRV1 DMXL2 DPM1 Neisseria longate Streptococcus mitis	The Affymetrix Human Genome U133+2.0 array, The Human Oral Microbe Identification Microarray (HOMIM)	MLR models: Cases vs controls: (1) ACRV1, DMXL2, DPM1 AUC: 0.974; p < 0.0001 (2) Neisseria elongata i Streptococcus mitis AUC: 0,895; p < 0,0001 Cases vs (controls + benign): (3) (ACRV1, DMXL2, DPM1, S. mitis) AUC: 0.949; p < 0.0001	(1) 0.93 (0.78-0.99) (2) 0.97 (0.83-1.00) (3) 0.93 (0.78-0.99)	(1) 0.90 (0.73-0.98) (2) 0.83 (0.65-0.94) (3) 0.85 (0.73-0.93)	(1) 0.90 (0.74-0.98) (2) 0.85 (0.69-0.95) (3) 0.76 (0.59-0.88)	(1) 0.93 (0.77-0.99) (2) 0.96 (0.80-1.00) (3) 0.96 (0.87-0.99)

Table 5. Characteristics of studies on detecting hepatocellular cancer

Study (Author, year, country)	Participants (n)	Age	Biomarker type	Biomarkers assessed	Method of assessment	Association in cancer patients /p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Ding et. al., 2019 China [51]	Cases: 14 Controls: 14 Total: 28	Cases (mean): 61.64 +- 9.40 Controls (mean): 53.8 +-11.25	Protein	1. SOD-2 2. HP	iTRAQ, ELISA and LC-MS	1. 1.83×10^{-7} 2. 1.71×10^{-9}				
He et. al., 2022 China [52]	Cases: 90 Controls: 50 Benign: 100 Total: 240	34.6 – 63.96	Protein	1. ORM-1 2. AFP 3. ORM-1 + AFP	iTRAQ and ELISA	1. <0.001	1. 77.5% 2. 78.75% 3. 95%	1. 81.67% 2. 80% 3. 74.17%		
Hershberger et. al., 2021, USA [53]	Cases: 37 Controls: 43 Benign: 30 Total: 110	Cases (mean): 67.3 Controls (mean): 57.6 Benign (mean): 58	Metabolites (lipids, amino acids, peptides and sugars)	1.Acetophenone 2. Octadecanol 3. Lauric acid 4. 3-hydroxy-butyric acid	GC-TOF MS	1.Acetophenone – <0.001 2. Octadecanol – <0.001 3. Lauric acid – <0.001 4. 3-hydroxy-butyric acid – 0.002	87.9%	95.5%	29.3%	65.5%
Mariam et. al., 2022, USA [54]	Cases: 20 Controls: NA Benign: 19 Total: 39	Cases (mean): 67.9 Benign (mean): 57.2	RNA	miRNA: 1. hsa-mir-3198-2 2. hsa-miR-3198 3. hsa-mir-1246 4. hsa-miR-1246 5. hsa-mir-3648-2	qPCR	1. 6.56×10^{-8} 2. 5.96×10^{-9} 3. 1.54×10^{-8} 4. 1.18×10^{-8} 5. 3.59×10^{-8}				
Sun et. al., 2017, China [55]	Cases: 10 Controls: 10 Total: 20	Unknown	RNA	mRNA (5 ?	RT-qPCR	<0.01				

Table 6. Characteristics of studies on detecting bile duct cancer

Study (Author, year, country)	Participants (n)	Age	Biomarker type	Biomarkers assessed	Method of assessment	Association in cancer patients /p	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Machida et.al., 2016, Japan [47]	Cases: 12 (2 with bile duct cancer) Controls: 13 Benign: Total: 25	Range Case: 65 (45-84) Control: 66 (53-83)	RNA	miRNA	RT-qPCR	miR-1246/U6: p= 0.007 miR-4306/U6: p=1.000 miR-4644/U6: p=0.026	miR-1246: 66.7% miR-4644: 75.0 % miR-1246 + miR-4644: 83.3%	miR-1246: 100% miR-4644: 76.9% miR-1246 + miR-4644: 92.3%	miR-1246: 1.000 miR-4644: 0.750 miR-1246 + miR-4644: 0.909	miR-1246: 0.765 miR-4644: 0.769 miR-1246 + miR-4644: 0.857

Esophageal cancer

As Table 1 suggests, the data on salivary E-cadherin indicate that with a p-value of 0.59, further research is required to consider it a potential biomarker for detecting esophageal cancer. Likewise, the use of detecting epigenetic changes based on DNA methylation also require further studies, but provide promising opportunities as illustrated by Stone et al.[15] The glycoproteins GalNAc, Gal, sialic acid and GlcNAc, were significantly higher in patients with esophageal squamous cell carcinoma (ESCC) compared to the control group. According to results obtained by Graham et al. and Li et al., salivary RNA proved to be far higher in case groups than the control. This is particularly true for TP53, CDKN2a, SMAD7, EGFR, AMY2, TLR6, KIT9, KRAS, PTEN, and PIK3CA as well as tRNA-GlyGCC-5, sRESE and Bi-sesnucRNA.[11,12] The same results demonstrate a promising future for RNA as a salivary marker for esophageal cancer. Similarly, and with few exceptions, some miRNA biomarkers have been consistently elevated in the case groups compared to the control ones. These include miR-144, miR-451 and miR-10b at an overall p-value of <0.05.[16,18] Moreover, with a collective sensitivity of >84.4% and specificity of >47.4, miR-21 has also shown optimistic results.[17,19] Li et al. also identify two additional up-regulated miRNA salivary biomarkers in early stage ESCC: miR-1268a and miR-4505 with p-values of <0.001, but miR1972, miR-4274, miR-4701-3p and miR-6126 were also isolated but contrastingly, down-regulated in the case groups compared to the control ones.[12,13] It is also worth mentioning that RNA markers have been more studied in squamous cell cancers whereas protein and other markers more in adenocarcinomas.

Gastric cancer

As shown in the Table 2, there are several saliva biomarkers that can be used to detect gastric cancer. Research found that when assessed with ELISA, E-cadherin, which is a protein has a high association in cancer patients.[10] Acetaldehyde, acetone, propanol-2, and ethanol have also a high predictive value with sensitivity to be 80.0% and specificity 100%.[20] Some microbes can be used as a biomarker. In more details, Fusobacterium nucleatum has high association with gastric cancer (p=0.780) with sensitivity to be 73.33% and specificity 82.14%, but the Salivary microbiota shows lower association (p=0.3582).[21,22] Studies shown that exRNA can be used as a biomarker. Salivary exRNA, when assessed with qPCR has low association (p= 0.0809) and when exRNA is assessed with RT-qPCR has sensitivity 82% and 77% specificity.[23] Additionally, research used CSTB (p=0.001) and DMBT1 (p=0.002). CSTB has 83.87% sensitivity and 70.97% specificity and DMBT1 has 80.65% sensitivity and 64.52% specificity. However, when assessed together CSTB, DMBT1 and TPI1 have lower association in cancer patients and the sensitivity is 85% and specificity 80%.[24] N- and O-linked glucans when assessed by MALDI-TOF may be used as a biomarker with association varying on the number and type of glycans.[26] Furthermore, protein glycosylation patterns when assessed with lectin microarray show higher and altered glycosylation patterns in GC with sensitivity 96% and specificity 80%. The cell-free DNA when evaluated with PCR has higher association (p=0.0361).[28] Finally, CEA and mRNAs (SPINK7, PPL, SEMA4B, SMAD4) after evaluation with the immunoassay system and RT-qPCR have shown 92% sensitivity and 87% specifiicty.[30]

Colorectal cancer

Numerous saliva biomarkers are available for the detection of colorectal cancer, as the Table 3 illustrates. According to research, there is a strong correlation between cancer patients' ELISA results for E-cadherin (substantially higher levels in cancer patients).[10] Also, significant differences were observed in the levels of acetaldehyde, acetone, propanol-2, ethanol, methanol, lipid peroxidation products: triene conjugate, and Schiff base among diseased and healthy patients, with sensitivity reaching 92.3% and specificity 100%.[20] Furthermore, measurements of TIMP-1 in saliva do not indicate the existence of colorectal cancer (CRC), so plasma TIMP-1 testing is still the standard for CRC identification (saliva TIMP-1 levels in cancer patients and non-patients with CRC are comparable).[31] Studies shown that miRNA-21 can be used as a cancer biomarker. Salivary miRNA, when assessed with qPCR has a sensitivity of 97% and specificity of 91%, but when assessed with RT-PCR, CMR-21(miRNA-21 in saliva) has a sensitivity of 52% and specificity 89%.[32,56] On the other hand, miR-186-5p, miR-29a-3p, miR-29c-3p, miR-766-3p, and miR-491-5p presented a sensitivity of 72% (Combined with CEA levels: 89.36%) and specificity of 66.67%. Additionally, research has shown that miR-29a and miR-92a levels are significantly higher in cancer patients, with a sensitivity of 88% and 85.3% and specificity of 93% respectively.[33,39] It is also worth noting that salivary metabolites show high potential as a screening tool for CRC. Additionally, according to a study, there was a significant association between higher sHLA-G levels and advanced tumor stages.[36] Proteins like chemerin, α-defensin 1, TNF-α showed a strong association in cancer patients with a sensitivity 100% in all three proteins and specificity of 100% in salivary chemerin/a-defensin 1 and over 90% in TNF-a.[40] Finally, Fn DNA (Fusobacterium nucleatum DNA), CEA(Carcinoembryonic Antigen), CA19-9 (Carbohydrate Antigen 19-9) have a sensitivity of 71.5%, 22.2%, 10.1% respectively , and the salivary specificity of Fn DNA is 82.1%.[41]

Pancreatic cancer

Biomarkers of pancreatic cancer, including metabolomic, microbiomic, epigenomic transcriptomic markers have been discovered in saliva (Table 4).[44,50] Differences have been found in the levels of various individual metabolites in pancreatic cancer patients ($p<0.05$).[42] Significant differences in the microbiome have been found in the saliva pancreatic cancer patients, including variations in the quantitative and qualitative flora *Neisseria elongata*, *Prevotella nigrescens* and *Streptococcus mitis* as well as the Leptotrichia/Porphyromonas ratio.[44] Statistically significant differences in the expression of some genes have also been observed in patients with pancreatic cancer. These differences have been described using MLRs based on several gene transcripts, reaching in all cases $p<0.01$: models included transcripts such as ACRV1, DMXL2, DPM1, and these three transcripts in combination with *Streptococcus mitis* and transcripts MBD3L2 GLTSCR2 in combination with *Prevotella nigrescens* and *Neisseria elongata*, as well as set of 29 different mRNAs.[44,50] Simultaneously, in pancreatic cancer patients, significant differences ($p<0.05$) in the amount of different salivary miRNAs have been described compared to the control groups, as well as to patients with benign changes.[47,49] In addition, differences in IncRNA (HOTAIR, PVT1 and MLR based on both) have observed between in the saliva of cancer patients and other patients such as controls and those with benign conditions.[48]

Hepatocellular cancer

SOD-2, HP, ORM-1, AFP and ORM-1 + AFP are proteins that have shown remarkable results as salivary biomarkers for hepatocellular cancer, all with p-values <0.001 and were considerably elevated in the case groups compared to the control groups.[51,52] Furthermore, different metabolites were analyzed by Hershberger et al., including acetophenone, octadecanol, lauric acid and 3-hydroxybutyric acid.[53] All four had p-values <0.05 with a sensitivity of 87.9% and specificity of 95.5% - all promising results for potential biomarkers. The 5 miRNA biomarkers distinguished by Mariam et al. have all been shown to be increased in apparently healthy individuals with a p-value of <0.001.[54] Moreover, Sun et al. identified 5 mRNA biomarkers that were isolated and upregulated in the case groups as well as 8 mRNA biomarkers that were down-regulated in the case groups.[55] All 13 had p-values of <0.01, demonstrating the use of the transcriptomic profile in early ECC is a useful asset for detecting hepatocellular cancer (Table 5).

Bile duct cancer

The salivary miRNA markers miR-1246 and miR-4644, also correlated with pancreatic cancer have been shown to detect bile duct cancer as well with adequate sensitivity and specificity (Table 6).

Quality assessment

The quality of the studies included in the meta-analysis was assessed according to the QUADAS-2 scale and the results are recorded in Table 7. No serious concerns were found regarding the applicability of the studies.

Discussion

Gastrointestinal (GI) cancers, which include esophageal, gastric (stomach), colorectal, pancreatic, liver, and biliary tract cancers, contribute significantly to global cancer burden. By examining a range of biomarkers across various gastrointestinal cancer types, this study contributes valuable new insights to the critical field of cancer detection and diagnosis. It is known that early detection and treatment improve prognosis, but many GI cancers are diagnosed late, contributing to poor survival outcomes.[57] So, the introduction of biomarkers that promote early cancer identification is of primary importance. Nevertheless, it is worth mentioning that the salivary profile can be affected by the viscosity of saliva based on patient's hydration status, the intensity of stimulation of salivary flow and time of day saliva is collected. Viscous saliva in dehydrated patients may affect concentration of molecules in saliva leading to inaccurate results in ELISA.[58] Moreover, stimulated saliva may contain higher concentrations of certain biomarkers compared to unstimulated saliva.[59,60] It is also worth noting that salivary biomarkers may show circadian variation and differ after consumption of meals as well as after fasting.[61]

In esophageal cancer, certain glycoproteins, such as GalNAc, Gal, and sialic acid, along with specific RNAs and miRNAs like miR-21 and miR-144, have demonstrated potential for cancer detection and indeed show better diagnostic values compared to plasma biomarkers.[12,14,19] However, additional studies are needed to confirm their reliability. For gastric cancer, protein markers like E-cadherin, volatile organic compounds (e.g., acetaldehyde and acetone), and microbial markers such as *Fusobacterium nucleatum* have shown high sensitivity and specificity in identifying the disease.[21,25,27] These findings suggest that salivary biomarkers could serve as effective diagnostic tools in gastric cancer cases. In colorectal cancer, salivary miRNAs such as miRNA-21 and miR-29a have exhibited significant diagnostic potential, with higher accuracy compared to plasma miRNAs.[39] Nevertheless, some limitations were noted in certain biomarkers like TIMP-1 in saliva, which did not correlate well with cancer detection.[31] Pancreatic cancer research has identified promising biomarkers based on metabolomic, microbiome, and gene transcript analyses. Variations in metabolites, bacterial profiles, and specific gene transcripts have shown strong predictive power for distinguishing between cancer and non-cancer patients.[42,44,49] For hepatocellular can-

Table 7. Quality assessment of studies in the meta-analysis

Study (Author, year)	Risk of bias				Applicability concerns		
	Patient selection	*Index test*	*Reference standard*	*Flow and timing*	*Patient selection*	*Index test*	*Reference standard*
Asai et.al., 2018 [42]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Asai et.al., 2018 [43]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Aznab et. al, 2023 [10]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Bel'skaya et.al., 2020 [20]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chen et.al., 2022 [21]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Ding et. al., 2019 [51]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Farrell et.al., 2009 [44]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Gao et.al, 2014 [45]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Graham et. al.,2016 [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
He et. al., 2022 [52]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Hershberger et. al., 2021 [53]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Holten-Andersen et.al., 2012 [31]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Huang et al., 2021 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kaczor-Urbanowicz et.al., 2022 [23]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Kiseleva et.al, 2023 [56]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Koopaie et.al., 2022 [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Koopaei et.al., 2024 [33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kuwabara, et.al.,2019 [34]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kuwabara et.al., 2022 [35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Lazaro-Sanchez et.al., 2019 [36]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Li et.al., 2022 [12]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Li et.al., 2023 [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Liu et.al., 2017 [46]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Machida et.al., 2016 [47]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Mariam et.al., 2022 [54]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Rapado-Gonzalez et.al., 2019 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Rapado-Gonzalez et.al., 2018 [38]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Sazanov et.al., 2017 [39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shu et. al., 2021 [14]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shu et.al., 2018 [26]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Shu et.al., 2017 [27]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Stone et. al.,2024 [15]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Sun et. al., 2017 [55]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Swarup et.al., 2023 [28]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Waniczek, et.al.,2022 [40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wong et al., 2009 [50]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear
Wu et. al, 2013 [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xiao et.al., 2016 [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xie et. al., 2013 [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xie et. al., 2012 [18]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xie et al., 2016 [48]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xie et al., 2015 [49]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Xu et.al.,2020 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ye et.al., 2014 [19]	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk
Zhang et.al.,2022 [41]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

cer, salivary proteins like AFP and certain metabolites, including acetophenone and lauric acid, have demonstrated strong sensitivity and specificity.[54,55] Additionally, miRNA and mRNA profiles have been highlighted as valuable tools for early detection.

The future of salivary biomarkers in cancer detection is highly promising, with exciting potential for non-invasive, accessible, and accurate screening across various cancer types. While significant progress has been made in understanding the role of these biomarkers, further advancements are needed to ensure they become reliable tools for routine cancer diagnosis.

In esophageal cancer, future research will likely focus on improving the specificity and reliability of the markers, which could lead to non-invasive screening options for early detection. Given the poor prognosis of advanced esophageal cancer, early diagnostic tools could drastically improve patient outcomes.

For gastric cancer, protein markers and microbial markers have already demonstrated high sensitivity and specificity. Future prospects include the development of personalized medicine approaches, specially involving RNA markers that tailor treatments based on a patient's unique biomarker profile.[62] Additionally, advances in microbiome research could provide a more comprehensive understanding of gastric cancer development. As technology evolves, rapid, at-home testing devices may allow patients to monitor these biomarkers in real-time, making diagnosis more convenient and accessible, a method used today for detecting respiratory infections.[63,64]

In colorectal cancer, the future could see the creation of combined biomarker panels that improve diagnostic accuracy by integrating miRNAs, proteins, and volatile compounds. Early and routine screening for colorectal cancer using saliva could reduce mortality rates by identifying the disease at more treatable stages.[65]

For pancreatic cancer, salivary biomarkers identified through metabolomic, microbiome, and gene transcript analyses have shown strong predictive power. Given that pancreatic cancer is often diagnosed in late stages, the future holds great potential for developing saliva-based tools for early detection, which could significantly increase survival rates.[66] With ongoing research, new biomarkers are likely to be discovered, leading to more comprehensive diagnostic panels. Non-invasive saliva tests could replace more invasive methods and provide a simpler way to monitor high-risk individuals.

In hepatocellular cancer, salivary proteins have already demonstrated strong sensitivity and specificity, and miRNA and mRNA profiling have shown value in early detection. The future may see further advancements in metabolomic profiling, offering more precise diagnostic tools that differentiate between various liver diseases. Additionally, combining biomarker data with genetic and lifestyle factors could help identify high-risk patients earlier, allowing for preventive interventions before cancer develops.[67] Saliva-based tests could also provide affordable and scalable screening tools in regions with high liver cancer incidence, such as Asia and Africa, where access to traditional diagnostic resources, such as imaging, is limited.[68]

Looking more broadly, salivary biomarkers hold the potential to revolutionize cancer screening across the board. As research progresses, these tests could be widely adopted as part of routine medical care, replacing invasive procedures like biopsies and endoscopies. Future diagnostic tools may integrate salivary biomarkers with other "omics" technologies (e.g., genomics, proteomics, metabolomics) to create more accurate, personalized cancer diagnostics.[69,70] With the development of portable, cost-effective devices, cancer detection could become more accessible to underserved populations, potentially transforming global cancer care. Artificial intelligence and data analytics will likely play a key role in the future of salivary biomarker research.[71] AI could enhance the interpretation of complex biomarker data, leading to more accurate predictions and personalized treatment plans. As a result, the integration of salivary biomarkers into cancer diagnosis could not only improve early detection but also provide tailored therapeutic approaches based on individual risk profiles.[72]

In spite of the fact that the present study was performed according to PRISMA guidelines, three different electronic data bases were searched and quality assessment showed no serious risk of bias, it had some notable limitations. Firstly, different laboratory methods used in each study may cause biased results. At the same time, some studies had very small cohorts making the results unreliable, and such studies must by investigated further by researchers in the future. Moreover, most studies were performed in Caucasian and Asian populations, possibly leading to a small degree of bias. It is also worth mentioning that the literature was limited to articles written in the English language and some notable articles in other languages may have been missed.

Conclusion

In summary, the future of salivary biomarkers in cancer detection is bright, with potential applications in early diagnosis, personalized treatment, and global accessibility. Ongoing advancements in technology, bioinformatics, and large-scale clinical studies will be crucial in ensuring these biomarkers become reliable tools in the fight against cancer.

Declarations

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Author contributions

Conceptualization, D.K.; Methodology, A.A., D.K. and Chara. C.; Software, D.K.; Validation, A.A., D.K. and Chara. C.; Formal Analysis, A.A. and D.K.; Investigation, A.A., D.K., Chara. C, M.G., L.F., S.K., J.K. and Z.C.; Resources, D.K.; Data Curation, A.A., D.K., Chara. C, M.G., L.F., S.K. and J.K.; Writing – Original Draft Preparation, A.A., D.K., Chara. C, M.G., L.F., S.K. and J.K.; Writing – Review & Editing, A.A., D.K., Chara. C, M.G., L.F., S.K. and J.K..; Visualization, D.K..; Supervision, Charal. C. and D.A.; Project Administration, D.K.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

Not applicable.

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