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Gastric cancer detection by non-blood-based liquid biopsies: A systematic review looking into the last decade of research

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Abstract

Gastric cancer (GC) screening is arguable in most Western countries. Liquid biopsies are a great promise to answer the unmet need for less invasive diagnostic biomarkers in GC. Thus, we aimed at systematically reviewing the current knowledge on liquid biopsy-based biomarkers in GC screening. A systematic search on PubMed/MEDLINE and Scopus databases was performed on published articles reporting the use of non-blood specimen (saliva, gastric juice [GJ], urine and stool) on GC diagnosis. 3208 records were retrieved by June 2022. After removal of duplicate records, 2379 abstracts were screened, and 84 full texts included in this systematic review. More than 90% of studies were reported on Asian populations. Overall, 9 studies explored stool-, 12 saliva-, and 29 urine-derived biomarkers for GC detection. Additionally, 37 studies, representing the majority, analyzed GJ, focusing on nucleic acid molecules. Several miRNAs and lncRNA molecules have been associated with GC risk, particularly *miR-21* (area under the curve [AUC] = 0.97, 95% CI: 0.94–1.00). Considering salivary biomarkers, the best described model in validation sets included the soybean agglutinin and Vicia villosa agglutinin lectins (AUC = 0.89, 95% CI: 0.80–0.99). Most studies in urine carried out metabolomic approaches, with two discriminatory models presenting AUC values superior to 0.97. This systematic review emphasizes the potential role of non-blood-based biomarkers, although further validation, particularly in Western countries, is mandatory, namely for non-invasive screening and/or monitoring, as well as the use of GJ as a tool to enhance upper gastrointestinal endoscopy accuracy.

KEYWORDS

feces, gastric juice, saliva, stomach neoplasms, urine

INTRODUCTION

According to the International Agency for Research on Cancer (IARC), gastric cancer (GC) ranks fifth for incidence and fourth for mortality worldwide in 2020, being responsible for one in every 13 cancer-related deaths globally.[1] The number of new GC cases is estimated to increase from 945,000 in 2020 to 1.48 million in 2040 in countries with high and very high human development index (HDI), emphasizing that this is not a resolved issue.[2]

There is a particularly high incidence of GC in Asian countries, such as Japan and Korea, where population-wide mass screening is implemented.[3] Upper gastrointestinal (GI) endoscopy remains the gold standard for GC diagnosis. However, in medium to low-incidence countries, such as in Europe, this strategy as a stand-alone is unwarranted.[4]

Liquid biopsies represent a great promise in precision medicine, as they are less invasive, improving patients' adherence to screening, and allow the monitoring of the real-time tumor dynamics, critical for early diagnosis, prediction of disease prognosis and recurrence, and even assessment of therapy efficacy.[5,6] While most studies have been focusing on the sampling of blood as the standard concept of liquid biopsy, common bodily fluids, such as saliva, urine, and stool have demonstrated potential as a source of cancer biomarkers, having the potential to improve the cost-effectiveness of GC screening in low to intermediate risk regions and empower citizens in their own personal risk, enabling a better management of (by default) limited resources.[6]

Several blood-based GC biomarkers used in clinical practice have been reported, with carcinoembryonic antigen (CEA) and cancer antigen (CA)19-9 still being the most frequently used.[7] Other examples include CA72-4, CA12-5, alpha-fetoprotein, BCA-225, and pepsinogen I/II.[7] Nevertheless, in spite of being widely used for cancer screening in several countries, the former biomarkers have low sensitivity and have been shown to be inappropriate as a screening modality for GI cancer.[8] In 2020, GASTROClear, the world's first molecular blood test for early detection of GC, was made available in Singapore to assess the risk for this type of cancer in asymptomatic healthy people. With an accuracy of 87% higher than any other blood biomarkers previously assessed for detection of GC, namely *Helicobacter pylori* serology, serum pepsinogen, CEA and CA19-9 tumor markers, this cancer test uses a clinically-validated algorithm to detect a unique signature of 12 microRNA in the blood.[9] Recently, non-invasive biomarkers for GC detection, including blood-based, have been non-systematically reviewed from a molecular perspective and using distinct methodology.[5,10]

A non-despicable rate of missed lesions (up to 10%) can still be expected during endoscopy.[11] This could be overcome by improved endoscopists training, appropriate surveillance programs, and maybe the development of functional endoscopy for the detection and diagnosis of GC.[12] Gastric juice (GJ), despite requiring access to the stomach through endoscopic examinations, is a renewable reservoir of potential biomarkers and could easily be obtained during those procedures without additional discomfort to the patient.[13] This biofluid is usually thrown away during upper GI endoscopy, while it could provide valuable information concerning patients' gastric conditions, potentially contributing to improving the accuracy of the endoscopic screening, through detection of missed lesions, monitoring, and surveillance.[13]

Herein, using a systematic approach, we report the currently available evidence published in the last decade on the role of non-blood-based circulating biomarkers in GC detection, particularly targeting saliva, urine, and stool as non-invasive liquid biopsies, aiming to summarize potential targets for early cancer detection. Furthermore, we also explore GJ as a potential source of valuable biomarkers that can enhance the accuracy of endoscopic procedures by reducing the rate of missing lesions.

METHODS

Search strategy and selection criteria

A systematic search was conducted following the PRISMA guidelines (Figure 1).[14] The MEDLINE (Pubmed) and Scopus databases were searched for studies reporting the role of saliva, GJ, urine, and stool-derived biomarkers for GC screening or diagnosis, from January 2010 to June 2022. The search for records available online was performed using the following query: *((“liquid biops*” OR “body fluid” OR “bodily fluid” OR “Liquid biopsy” [Mesh]) OR (saliva OR salivary) OR (urine [Mesh] OR urinary) OR (fecal OR feces OR stool OR “fecal material” OR “faecal material”) OR (“gastric juice” OR “stomach juice” OR “gastric fluid” OR “stomach fluid” OR “gastric juice” [Mesh])) AND ((gastroesophag* OR stomach OR gastric OR gastrointestin*) AND (cancer OR neoplasm OR neoplasia OR carcinoma OR tumor)) AND biomarker*. This query was adjusted for Scopus and no filters besides publication date were applied. A complementary search was carried out in the reference lists of the included papers, as well as of two relevant reviews.[5,10]

Eligibility criteria

After duplicate records removal, the abstracts were screened for eligibility by two independent researchers (Catarina Lopes and Jéssica Chaves). Case-control or cohort studies identifying non-invasive liquid biopsy-derived biomarkers for GC detection were included. Studies with no English or Portuguese version, not enrolling human patients, not performed on saliva, GJ, urine or stool, with no independent controls, reporting on precancerous gastric lesions were excluded. Retracted records, reviews, letters, case-reports, or book chapters were also excluded. Disagreements were analyzed and resolved by a third element (RO).

The full texts meeting the primary criteria were then reviewed by the same authors for final inclusion of all potential studies.

Data extraction

Data was extracted independently by two researchers (Catarina Lopes and Jéssica Chaves), including (i) study characteristics (i.e., first author, year, and reference); (ii) country; (iii) study design; (iv) sample size and percentage of females; (v) groups included in the analysis that are significant for this review; (vi) type of liquid biopsy analyzed; (vii) biomarker under study; (viii) method of detection; (ix) main results.

Quality assessment

Two review authors (Catarina Lopes and Jéssica Chaves) assessed the risk of bias of each included study independently, following a modified version of the Newcastle-Ottawa quality assessment scale for case control studies.[15] Three domains were included: selection, comparability, and outcome. Selection was composed by five items, comparability by one item and outcomes by three items.[15] The article

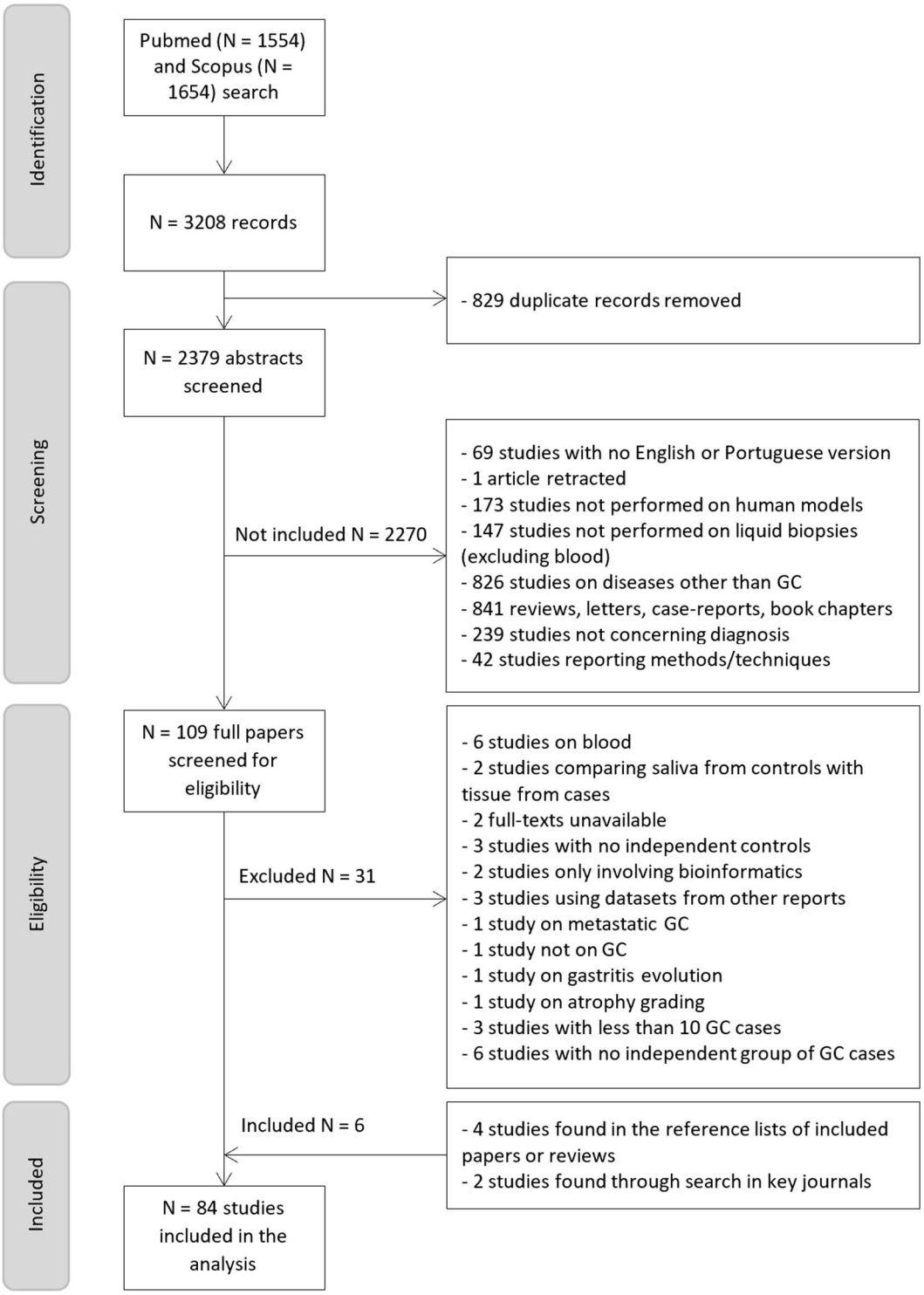

FIGURE 1 Flow chart of selection process. Of the 2379 records retrieved, 84 studies were included in the systematic review.

could receive one point in each item, getting a maximum to five points in selection, one or two in comparability, and a maximum of four in outcome. Thus, each article could receive a maximum of 11 points. Detailed information can be found in Online Resource.

If the information was missing or not described in the study, the corresponding authors were contacted by email. A third author was consulted to resolve disagreements when they could not be resolved by consensus.

RESULTS

Studies characteristics

Out of 2379 abstracts screened after duplicate records removal, 84 full papers were analyzed and considered eligible after applying the inclusion and exclusion criteria (Figure 1).

Most studies explored GJ ($n = 36$) and urine ($n = 28$), with only 10 and seven studies reporting on saliva or tongue coating and stool, respectively. Additionally, one study reported on tongue coating and gastric fluid, one study used oral swab and stool samples and one study used stool and urine. Despite the interest in early GC detection, few studies committed to earlier stages of the disease. In fact, only two studies assessed salivary biomarkers in patients with atrophic gastritis, and one and three studies focused on early-stage patients to address urinary and GJ biomarkers, respectively.

All the included studies were written in English and their baseline characteristics and study design variables are summarized in Table S1 of Online Resource. Studies were conducted in 12 countries: seven in Asia (China, Iran, Japan, Singapore, South Korea, Taiwan, Turkey), three in Europe (Germany, Italy, Russia), two in America (Canada and United States of America), and one in Africa (Zambia). Sample sizes ranged from 22 to 1506 participants (median: 135 participants). Regarding quality control assessment, over 85% of the included studies scored under 5.5/11 points, which means most studies have some degree of risk of bias. Worth highlighting, the risk of selection bias associated with the representativeness of controls, which failed to be reported in over 95% of the studies. Another potential weakness of most studies is the lack of statistical power or its adequate report.

Non-blood non-invasive liquid biopsies in GC screening

Saliva

We included 12 eligible studies performed in saliva, tongue coating or oral swab samples in this review, exclusively performed in Asian populations: nine from China,[16–24] two from South Korea,[25,26] and one from Iran.[27] Specifically, studies by Xu et al.[28] and Cui et al.[24] used tongue coating samples and focused on oral microbiota analysis by polymerase chain reaction (PCR) and sequencing. In saliva, microbiota was assessed in three studies.[18,23,29] Serine peptidase inhibitor kazal type 7 (*SPINK7*), periplakin (*PPL*), semaphoring 4B (*SEMA4B*), and SMAD family member 4 (*SMAD4*) messenger RNAs (mRNAs) were assessed in two studies,[21,25] as well as salivary glycans,[19,20] and proteins, namely CSTB and DMTB1.[26,27] Amino acids were characterized only once.[16] Table 1 summarizes the identified salivary biomarkers with reported C-statistic values for GC and atrophic gastritis detection. The biomarkers with best discriminatory power are Aleuria aurantia lectin (AAL, area under the curve [AUC] = 0.98) and Vicia villosa agglutinin (VVA, AUC = 0.96), although not validated in independent cohorts.[20] Considering only studies with a validation set, two models reached AUC values equal or superior to 0.87: one including two lectins, soybean agglutinin (SBA) and VVA (AUC = 0.89, 95% CI: 0.80–0.99),[20] and another including three mRNA molecules (*SPINK7*, *PPL*, and *SEMA4B*), two microRNAs (*miR-140-5p* and *miR-301a*), and demographic factors (AUC = 0.87, 95% CI: 0.80–0.93).[25] Focusing on precancerous conditions, the biomarkers with the best performance for the detection of atrophic gastritis were lectins Datura stramonium agglutinin (DSA, AUC = 0.97, 95% CI: 0.95–1.00) and Lycopersicon esculentum lectin (LEL, AUC = 0.96, 95% CI: 0.93–1.00), but similarly to GC they were not validated.[20] On the other hand, a model including the lectins DSA and VVA was independently validated and reached an AUC of 0.83.[20]

Stool

All the included reports in stool samples were performed in Asian populations, seven in China[23,30–35] and one in Iran,[36] and were case-control studies. Overall, four biomarkers were explored: (a) fecal calprotectin in two studies[33,36]; (b) B-cell activating factor (BAFF) protein in one study[33]; (c) telomerase reverse transcriptase (*TERT*) gene promoter methylation in one population[30] and (d) the fecal microbiota was explored in five Chinese populations,[23,31,32,34,35] either targeting bacterial 16S ribosomal RNA (rRNA) and fungal 18S rRNA or bacterial DNA. Stool-based biomarkers with reported expression in GC, as well as AUC values, are summarized in Table 2. The bacterial genera *Desulfovibrio*, *Escherichia*, *Faecalbacterium*, and *Oscillospira* exhibit the best diagnostic performance, achieving AUC values ≥ 0.90.[31] Those results involved a five-fold cross-validation for data preparation of a random forest mode in a single study gathering 73 participants with 76% of patients diagnosed at more advanced stages of the disease. Additionally, two models including fecal microbiota achieved AUC values of 0.97 and 0.94, the latter involving cross-validation for data preparation.[23,34] None of the remaining biomarkers included in Table 2 were validated.

Urine

Urine was the second most explored liquid biopsy in GC detection over the last decade, with 29 eligible studies included in this

TABLE 1 Salivary and tongue coating biomarkers for gastric cancer and atrophic gastritis detection with available expression and AUC data

Gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
Saliva							
Lectins	AAL[20]	↓	**0.98 (0.97–1.00)**	**<0.001**	**92.0**	**95.0**	No
	ECA[20]	↑	0.86 (0.80–0.93)	<0.001	72.0	88.0	No
	VVA [20]	↑	**0.96 (0.93–0.99)**	**<0.001**	**85.0**	**94.0**	**No**
RNA	mRNA *PPL*[21]	↓	0.72	NA	63.0	64.0	Validation set
	miR-140-5p[25]	↓	0.70 (0.64–0.78)	NA	NA	NA	Validation set
Proteins	CSTB[27]	↓	0.73 (0.60–0.83)	0.002	83.9	71.0	No
	DMBT1[27]	↑	0.74 (0.61–0.84)	<0.001	80.7	64.5	No
Models[Ref.]							
10 amino acids SERS spectra bands[16]			NA	NA	94.8	90.2	No
Bacterial genera [18]			**0.91 (0.78–0.99)**	**NA**	**NA**	**NA**	**CV**
2 lectins (SBA and VVA)[20]			0.89 (0.80–0.99)	<0.001	96.0	80.0	Validation set
3 mRNAs and 2 miRNAs[a] [25]			0.81 (0.72–0.89)	NA	75.0	83.0	Validation set
3 mRNAs, 2 miRNAs[a] and demographic factors[25]			0.87 (0.80–0.93)	NA	82.0	77.0	Validation set
3 proteins (CSTB, TPI1, DMBT1) [26]			**0.93**	NA	**85.0**	**80.0**	**Pre-validation**
Oral swab							
Oral microbiota (13 OTUs)[23]			0.82 (0.73–0.92)	NA	NA	NA	Pre-validation
Tongue coating							
6 bacterial genera[b] [28]			0.88 (0.80–0.95)	NA	NA	NA	Pre-validation
Atrophic gastritis detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
Saliva							
Lectins	**DSA[20]**	↓	**0.97 (0.95–1.00)**	**< 0.001**	**87.0**	**96.0**	**No**
	LEL[20]	↑	**0.96 (0.93–1.00)**	**< 0.001**	**93.0**	**92.0**	**No**
	VVA[20]	↑	0.81 (0.71–0.91)	<0.001	70.0	91.0	Validation set
Models[Ref.]							
Bacterial genera[18]			0.76	NA	NA	NA	CV
2 lectins (DSA and VVA)[20]			0.83 (0.71–0.94)	<0.001	70.0	91.0	Validation set

Note: Only molecules with reported relative abundance and reaching AUC >0.70 were included (suggested by[38] as moderate accuracy). In bold are AUC values > 0.90. Pre-validation means the biomarkers have been validated using the same population, whereas CV is a resampling validation technique that tests and trains a model using different portions of the data.

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval; CV, cross-validation; GC, gastric cancer; OTU, operational taxonomic units.

[a]*SPINK7*, *PPL*, *SEMA4B*, *miR-140-5p*, and *miR-301a*.

[b]*Fusobacterium*, *Peptococcus*, *Peptostreptococcus*, *Porphyromonas*, *Megamonas*, and *Rothia*.

systematic review. Similarly to that observed with saliva and stool, most studies were performed in Asian populations: 12 from China,[39–50] five from Japan,[51–55] four from Taiwan,[56–59] three from South Korea,[37,60,61] and one from Iran.[62] The remaining four studies were carried-out in Canada,[63] European portion of Russia[64,65] and Zambia.[66] Most urine-based reports focused on metabolites, mainly using metabolomic approaches.[39,41,44–47,50,56,59–63,66] Six studies focused on protein analysis[42,43,48,54,55,65] and three on RNA molecules, particularly miRNAs, quantified in urine samples by reverse transcription-real time PCR (RT-qPCR).[52,57,58] Other biomarkers include nitrate, nitrite, and N-nitroso compounds,[49] nematode-NOSE (N-NOSE),[53] analyzed by the olfactory behavior of *C. elegans* according to chemotaxis value, oxidative modifications, such as 8-hydroxydeoxyguanosine (8-OHdG) and 8-hydroxyguanosine

TABLE 2 Stool-based biomarkers for gastric cancer detection with available expression and AUC data

Stool					
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p* Value**	**With validation**
Protein	Fecal calprotectin[36]	↑	0.71[b]	NA	No
DNA (*TERT* promoter methylation)	CpG site 1[30]	↑	0.77 (0.66–0.88)	NA	No
	CpG site 2[30]	↑	0.79 (0.69–0.88)	NA	No
	Mean of sites 1 and 2[30]	↑	0.80 (0.70–0.90)	NA	No
Microbiota genera[a]	***Desulfovibrio***[31,32]	↑	**0.90**	**NA**	**CV**
		↑	0.71 (0.60–0.82)	0.001	No
	Escherichia[31]	↑	**0.90**	**NA**	**CV**
	Faecalbacterium[31]	↓	**0.92**	**NA**	**CV**
	Megasphaera[32]	↑	0.75 (0.64–0.85)	<0.001	No
	Oscillospira[31]	↑	**0.90**	**NA**	**CV**
	Prevotella 7[32]	↑	0.74 (0.64–0.84)	<0.001	No
	Veillonela[32]	↑	0.86 (0.77–0.94)	<0.001	No
	Streptococcus 1[35]	↑	0.77	<0.001	No
	Streptococcus 2[35]	↑	0.84	<0.001	No
Microbiota species[a]	*Bifidobacterium dentium*[32]	↑	0.74 (0.64–0.85)	<0.001	No
	Lactobacillus salivarius[32]	↑	0.71 (0.59–0.82)	0.001	No
	Streptococcus mitis[32]	↓	0.72 (0.61–0.83)	<0.001	No
	Streptococcus salivarius subsp. *Salivarius*[32]	↑	0.74 (0.63–0.84)	<0.001	No
Models[Ref.]					
Fecal microbiota (9 OTUs)[34]			**0.97 (0.94–1.00)**	**NA**	**No**
Fecal microbiota (13 OTUs)[23]			**0.94 (0.88–1.00)**	**NA**	**CV**
Stool pellet-based model[c] [37]			0.76	NA	No

Note: In bold are AUC values > 0.90. CV is a resampling validation technique that tests and trains a model using different portions of the data.

Abbreviations: AUC, area under the curve; CI, confidence interval; CV, cross validation; GC, gastric cancer; OTU, operational taxonomic units; *TERT*, telomerase reverse transcriptase.

[a]Only microbiota genera and species with reported relative abundance and reaching AUC >0.70 were included (suggested by[38] as moderate accuracy).

[b]$P < 0.001$.

[c]*Klebsiella*, *Subdoligranulum*, *Prevotella 9*, *Streptococcus*, *Ruminiclostridium 9*.

(8-OHG),[40] glycans,[51] and volatile organic compounds (VOCs),[64] all reported once. Table 3 includes the urinary biomarkers able to distinguish between GC patients, including early GC, and controls. Most studies included training and validation sets although from the same sample of recruited participants. Considering all biomarkers independently, endothelial lipase presented the highest AUC value of 0.97.[42] On the other hand, several models, mostly including metabolites, reached C-statistics superior to 0.95, particularly a model including age, β-(pyrazol-1-yl)-L-alanine (L-PA), D-isoleucine, and D-serine (AUC = 0.98, 95% CI: 0.95–1.00).[44] Furthermore, only one study reporting a model of 17 metabolites included a validation set (AUC = 0.97).[60] Focusing on early GC detection, two miRNAs, *miR-6807-5p* and *miR-6856-5p*, were assessed and a model including both molecules and *H. pylori* infection reached an AUC value of 0.75.[52]

Gastric juice as a tool to enhance upper gastrointestinal endoscopy accuracy

In the last decade, 45% of published studies that explored the role of non-blood-based circulating biomarkers in GC detection characterized GJ samples following a case-control study design and mostly including Han Chinese participants (23 of 36 reports).[67–89] A high level of heterogeneity regarding the class of analyzed biomarkers was observed: (a) 17 studies focused on distinct nucleic acids, including mRNA, miRNA, long non-coding RNA (lncRNA), long intergenic non-coding RNA (lincRNA), piwi-interacting RNA (piRNA), circular RNA, and DNA[67,68,71,74–79,81–86,88,90]; (b) nine studies on proteins or amino acids[69,70,72,80,91–94]; (c) four studies primarily on metabolites[95–98]; (d) two studies focused on glycoproteins, including CEA, CA19-9, CA72-4, and

TABLE 3 Urinary biomarkers for gastric cancer and early gastric cancer detection with available expression and AUC data

Gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
Urine							
Metabolites	3-Hydroxybutyrate[61]	↓	0.71 (0.63–0.79)	NA	NA	NA	Pre-validation
	Ala[41,61]	↑	0.80	NA	78.3	67.8	Pre-validation
		↑	0.75 (0.65–0.83)	NA	70.0	80.0	Pre-validation
	Benzylmalonic acid[41]	↑	0.67	NA	47.2	83.9	Pre-validation
	Citrate[61]	↑	0.63 (0.53–0.72)	NA	50.0	70.0	Pre-validation
	Creatine[61]	↑	0.86 (0.79–0.92)	NA	80.0	90.0	Pre-validation
	Creatinine[61]	↓	0.72 (0.63–0.80)	NA	60.0	80.0	Pre-validation
	Glycerol[61]	↓	**0.94 (0.89–0.98)**	**NA**	**90.0**	**90.0**	Pre-validation
	Gly[41]	↑	0.74	NA	91.5	41.4	Pre-validation
	Hippurate[61]	↑	0.74 (0.65–0.82)	NA	70.0	70.0	Pre-validation
	D-Ile[44]	↑	0.76 (0.65–0.87)	NA	58.1	95.0	Pre-validation[a]
	Ethyl 2-methylacetoacetate[41]	↑	0.72	NA	53.8	80.4	Pre-validation
	Ile[41]	↑	0.77	NA	67.0	72.4	Pre-validation
	Met[41]	↑	0.78	NA	67.9	78.2	Pre-validation
	Levulinic acid[41]	↑	0.67	NA	65.1	64.4	Pre-validation
	L-PA[44]	↓	0.89 (0.82–0.96)	NA	83.7	77.5	Pre-validation[a]
	p-cresol[41]	↑	0.70	NA	72.6	62.1	Pre-validation
	Phe[61]	↑	0.80 (0.74–0.88)	NA	80.0	70.0	Pre-validation
	Pro[41]	↑	0.79	NA	84.0	63.2	Pre-validation
	D-Ser[44]	↑	0.78 (0.68–0.88)	NA	58.1	87.5	Pre-validation[a]
	Ser[41]	↑	0.81	NA	72.6	75.9	Pre-validation
	Taurine[61]	↑	0.76 (0.66–0.84)	NA	80.0	70.0	Pre-validation
	Thr[41]	↑	0.82	NA	81.1	67.8	Pre-validation
	Trp[41]	↑	0.70	NA	82.1	51.7	Pre-validation
	Tyr[41]	↑	0.69	NA	85.8	47.2	Pre-validation
	Val[41]	↑	0.73	NA	62.3	73.5	Pre-validation
Modified nucleosides spectra[46]		↑	**0.95**	**NA**	**84.0**	**95.8**	No
N-NOSE[53]		↑	0.87 (0.82–0.93)	<0.001	NA	NA	No
Oxidative modification	DNA (8-OHdG)[40]	↑	0.78 (0.70–0.86)	NA	NA	NA	No
	RNA (8-OHG)[40]	↑	0.84 (0.77–0.91)	NA	NA	NA	No
Proteins	ADAM12[54,55]	↑	0.76 (0.64–0.88)	<0.001	NA	NA	No
		↑	0.70 (0.59–0.81)	0.001	NA	NA	Pre-validation
	Endothelial lipase[42,43]	↓	**0.97 (0.94–0.99)**	**NA**	**79.0**	**100.0**	No
		↓	**> 0.90**	**NA**	**NA**	**NA**	No
	MMP-9/NGAL[55]	↑	0.66 (0.53–0.79)	0.02	NA	NA	No
	TFF1[54]	↑	0.85 (0.77–0.93)	<0.001	NA	NA	Pre-validation
	TFF3[48]	↑	0.87	<0.001	80.4	80.1	No

TABLE 3 (Continued)

Gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
RNA	*miR-376c*[57]	↑	0.70	NA	60.0	64.0	No
	miR-6807-5p[52]	↑	0.87 (0.80–0.99)	NA	NA	NA	Pre-validation
	miR-6856-5p[52]	↑	0.71 (0.60–0.81)	NA	NA	NA	Pre-validation
Models[Ref.]							
Age and amino acids (L-PA, D-Ile, D-Ser)[44]			**0.98 (0.95–1.00)**	**NA**	**90.7**	**95.0**	Pre-validation
Metabolites (2-HIB, 3-IS, Ala)[63]			**0.95 (0.86–0.99)**	**NA**	**95.0**	**80.0**	No
2 metabolites[39]			**1.00**	**NA**	**NA**	**NA**	No
5 metabolites[b 47]			**0.96 (0.92–1.00)**	**NA**	**85.7**	**90.3**	Pre-validation
14 metabolites[41]			0.89	NA	77.4	85.1	Pre-validation
17 metabolites[60]			**0.97**	**<0.001**	**NA**	**NA**	Validation set
Microbiota[c 37]			0.82	NA	67.7	84.9	No
Urine							
miRNAs (*miR-6807-5p* and *miR-6856-5p*)[52]	0.87 (0.81–0.94)	NA	NA	NA	Pre-validation		
miRNAs (*miR-6807-5p* and *miR-6856-5p*) and *H. pylori*[52]	0.89 (0.82–0.95)	NA	NA	NA	Pre-validation		
Proteins (ADAM12 and TFF1)[54]	0.81 (0.72–0.90)	<0.001	NA	NA	Pre-validation		
Proteins (ADAM12 and TFF1) and *H. pylori*[54]	0.87 (0.79–0.95)	<0.001	NA	NA	Pre-validation		
Proteins (MMP-9/NGAL and ADAM12)[55]	0.83 (0.72–0.93)	<0.001	NA	NA	No		

Early gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
Urine							
RNA	*miR-6807-5p*[52]	↑	0.68 (0.62–0.75)	NA	NA	NA	Pre-validation
	miR-6856-5p[52]	↑	0.64 (0.57–0.71)	NA	NA	NA	Pre-validation
Models[Ref.]							
2 miRNAs (*miR-6807-5p* and *miR-6856-5p*)[52]			0.68 (0.62–0.75)	NA	NA	NA	Pre-validation
2 miRNAs (*miR-6807-5p* and *miR-6856-5p*) and *H. pylori*[52]			0.75 (0.68–0.81)	NA	NA	NA	Pre-validation

Note: In bold are AUC values > 0.90. Pre-validation means the biomarkers have been validated using the same population.

Abbreviations: 2-HIB, 2-hydroxyisobutyrate; 3-IS, 3-indoxylsulfate; AUC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval; GC, gastric cancer.

[a]Values relative to training set.

[b]Myo-inositol, lactic acid, 3-indoxylsulfate, glutamine, and 1-methylnicotinamide.

[c]*Peptoniphilus*, *Diaphorobacter*, *Neisseria*, *Staphylococcus*, *Bifidobacterium*, *Corynebacterium 1*, *Actinomyces*, *Acinetobacter*, *Sphingomonas*.

CA50[99,100]; (e) two studies on microbiota[89,101]; (f) one study on intrinsic fluorescence spectra[87]; (g) one study on blood.[102] GC-associated biomarkers found in GJ with reported expression, AUC, or sensitivity and specificity values, are summarized in Table 4. Overall, proteins pepsin A, α1-antitrypsin, and gastricsin had the best discriminatory power, with AUC values of 0.96, 0.96, and 0.94, along with miRNA molecules miR-21 and miR-133a, reaching 0.97 and 0.91, respectively.[68,75,91,93] Moreover, three models of amino acids reached AUC values equal or superior to 0.90, one including 14 GJ free amino acids (AUC = 0.90, 95% CI:

TABLE 4 Gastric juice-based biomarkers for gastric cancer and early gastric cancer detection with available expression and AUC data

Gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
Gastric juice							
Amino acids	Leu[73]	↑	0.87 (0.79–0.95)	NA	NA	NA	Pre-validation
	Phe[70,72,73]	↑	0.86 (0.76–0.96)	<0.001	87.9	79.4	No
		↑	0.83 (0.73–0.93)	NA	NA	NA	Pre-validation
		↑	0.76 (0.65–0.88)	NA	NA	NA	Pre-validation
	Ser[73]	↑	0.87 (0.79–0.96)	NA	NA	NA	Pre-validation
	Thr[73]	**↑**	**0.90 (0.83–0.97)**	**NA**	**NA**	**NA**	**Pre-validation**
	Trp[70,72,73]	↑	0.85 (0.76–0.94)	NA	NA	NA	Pre-validation
		↑	0.82 (0.72–0.91)	<0.001	60.6	94.1	No
		↑	0.77 (0.65–0.89)	NA	NA	NA	Pre-validation
	Tyr[70,72,73]	↑	0.84 (0.74–0.94)	<0.001	63.6	94.1	No
		↑	0.84 (0.75–0.93)	NA	NA	NA	Pre-validation
		↑	0.78 (0.67–0–89)	NA	NA	NA	Pre-validation
Fluorescence intensity[70]		↑	0.73 (0.62–0.85)	<0.001	69.7	72.1	No
Glycoproteins	CA19-9[99]		NA	<0.002	51.4	93.3	No
	CA50[99]		NA	<0.01	48.4	96.7	No
	CA72-4[86,99]		0.67 (0.58–0.77)	0.05	65.4	62.1	No
			NA	0.07	30.6	96.7	No
	CEA[86,99]		0.64 (0.54–0.74)	0.005	81.8	57–6	No
			NA	0.36	88.5	34.3	No
Intrinsic fluorescence spectra[87]		↑	0.87	NA	83.2	80.7	Pre-validation
pH[72]		↑	0.79 (0.69–0.90)	NA	NA	NA	Pre-validation
Proteins	α1-antitrypsin[93]	↑	0.84 (0.72–0.95)	<0.001	74.0	88.0	Validation set
	Cystatin D[91]	↓	0.79	NA	91.4	64.7	Pre-validation
	Elastase 3A[91]	↑	0.85	NA	72.9	88.2	Pre-validation
	Gastric lipase[91]	↓	0.89	NA	78.6	94.1	Pre-validation
	Gastricsin[91]	**↓**	**0.93**	**NA**	**88.6**	**94.1**	**Pre-validation**
	GIF[94]	↓	0.75	0.003	NA	NA	Validation set
	Pepsin A[91]	**↓**	**0.96**	**NA**	**90.0**	**100.0**	**Pre-validation**

TABLE 4 (Continued)

Gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
	S100A9[94]	↑	0.77	0.001	NA	NA	Validation set
	Total protein[70]	↑	0.71 (0.60–0.82)	0.001	81.8	55.9	No
RNA	*lncRNA-AA174084*[76]	↑	0.85 (0.78–0.92)	<0.001	46.0	93.0	No
	lncRNA-ABHD11-AS1[81]	↑	0.65 (0.54–0.77)	<0.01	41.0	93.4	No
	lncRNA-RMRP[79]	↑	0.70 (0.59–0.81)	<0.001	56.4	75.4	No
	miR-106a[68]	↓	0.87 (0.80–0.95)	<0.001	73.8	89.3	No
	miR-106a + miR21[68]	↓	0.98	NA	NA	NA	No
	miR-129-1-3p[82]	↓	0.64 (0.54–0.74)	0.009	45.2	83.8	No
	miR-129-2-3p[82]	↓	0.65 (0.55–0.75)	0.005	42.9	85.9	No
	miR-129-1-3p + miR-129-2-3p[82]	↓	0.66 (0.56–0.76)	0.003	68.7	71.9	No
	miR-133a[75]	↓	**0.91 (0.86–0.96)**	**< 0.001**	**85.9**	**84.8**	**No**
	miR-21[68]	↓	**0.97 (0.94–1.00)**	**< 0.001**	**85.7**	**97.8**	**No**
	miR-421[84]	↓	0.77 (0.68–0.85)	<0.001	71.4	72.7	No
	piR-1245[86]	↑	0.89 (0.83–0.94)	<0.0001	90.9	74.2	No
Models[Ref.]							
Gender, pH, Tyr, Phe, Trp[72]			0.81 (0.70–0.91)	NA	NA	NA	Pre-validation
3 aromatic amino acids (Phe, Trp, Tyr)[73]			0.85 (0.76–0.94)	NA	NA	NA	Pre-validation
3 non-aromatic amino acids (Leu, Ser, Thr) [73]			**0.90 (0.83–0.97)**	**NA**	**NA**	**NA**	**Pre-validation**
6 amino acids[a] [73]			**0.91 (0.85–0.98)**	**NA**	**71.9**	**97.4**	**Pre-validation**
14 amino acids[b] [73]			**0.90 (0.85–0.96)**	**NA**	**85.1**	**89.2**	**No**

(Continues)

TABLE 4 (Continued)

Early gastric cancer detection							
Type of biomarker	**Biomarker[Ref.]**	**Expression in GC**	**AUC (95% CI)**	***p*-value**	**Sensitivity (%)**	**Specificity (%)**	**With validation**
Amino acids	**Leu**[73]	↑	**0.90 (0.78–1.00)**	**NA**	**NA**	**NA**	**Pre-validation**
	Phe[69,73]	↑	0.84 (0.69–0.99)	NA	NA	NA	Pre-validation
		↑	0.83 (0.75–0.91)	<0.001	NA	NA	No
	Ser[73]	↑	0.87 (0.71–1.00)	NA	NA	NA	Pre-validation
	Thr[73]	↑	**0.90 (0.77–1.00)**	**NA**	**NA**	**NA**	**Pre-validation**
	Trp[69,73]	↑	0.87 (0.72–1.00)	NA	NA	NA	Pre-validation
		↑	0.82 (0.74–0.90)	<0.001	NA	NA	No
	Tyr[69,73]	↑	0.87 (0.73–1.00)	NA	NA	NA	Pre-validation
		↑	0.79 (0.70–0.88)	<0.001	NA	NA	No
Proteins	AAT[94]	↑	0.71	0.03	NA	NA	Validation set
	S100A9[94]	↑	0.75	0.01	NA	NA	Validation set
	AAT + S100A9[94]	↑	0.81	0.001	NA	NA	Validation set
	Total protein[69]	↑	0.72 (0.62–0.81)	<0.001	59.2	81.4	No
Models[Ref.]							
3 aromatic amino acids (Phe, Trp, Tyr)[73]			0.87 (0.72–1.00)	NA	NA	NA	Pre-validation
3 non-aromatic amino acids (Leu, Ser, Thr) [73]			**0.90 (0.79–1.00)**	**NA**	**NA**	**NA**	**Pre-validation**
6 amino acids[a] [73]			**0.91 (0.81–1.00)**	**NA**	**72.7**	**97.4**	Pre-validation
14 amino acids[b] [73]			0.88 (0.79–0.97)	NA	NA	**NA**	No

Note: In bold are AUC values ≥ 0.90. Pre-validation means the biomarkers have been validated using the same population, whereas CV is a resampling validation technique that tests and trains a model using different portions of the data.

Abbreviations: AUC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval; GC, gastric cancer.

[a]Including leucine, threonine, serine, tyrosine, phenylalanine, and tryptophan.

[b]Including threonine, serine, alanine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, lysine, arginine, phosphoserine, ethanolamine phosphate, and urea. To note that the AUC of these differential GJ free amino acids ranged from 0.65 to 0.86.

0.85–0.96), another including six (AUC = 0.91, 95% CI: 0.85–0.98), and a third including three non-aromatic amino acids (AUC = 0.90, 95% CI: 0.83–0.97).[73] A few studies reported the capability of GJ biomarkers distinguishing between early GC cases and controls and that data is also displayed in Table 4. The better model includes the same six amino acids as previously mentioned, leucine, threonine, serine, tyrosine, phenylalanine, and tryptophan, with an AUC superior to 0.90.[73] Most of reported biomarkers were either not validated in an independent population or were pre-validated, that is, validated using a subset from the same pool of participants.

DISCUSSION

By 2040, an increase of at least 30% is expected in GC incidence and mortality in Western countries, if no new strategies are implemented.[2] The early screening and diagnosis of GC is of paramount importance to improve the poor overall survival currently reported, of no more than 31% at 5 years, associated with diagnosis at advanced stages of the disease.[103]

The concept of liquid biopsy has been widely associated with the study of blood samples. In fact, the National Cancer Institute definition of "liquid biopsy" states: "A test done on a sample of blood to look for cancer cells from a tumor that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood".[104] Although some authors considered it a noninvasive source of biomarkers,[105] that definition is not consensual, as blood is primarily drawn by venipuncture, leading to a poorly empowered citizen since it must be performed by a health care provider and normally in a laboratory or clinical setting.[106,107] Therefore, the focus of this systematic review was to explore the role of circulating biomarkers derived from non-invasive liquid biopsies, namely saliva, urine, and stool, in GC detection over the last decade.

While these samples can be non-invasively collected by the patients themselves, without the need of medical assistance, potentially reducing inequalities in access to health care, GJ requires access to the stomach in a hospital setting. As a liquid biopsy, GJ represents a renewable reservoir of potential biomarkers, reflecting the functional state of the stomach through its direct contact with the gastric epithelium.[13] It avoids the lack of specificity and dilution of other circulating biomarkers, as it represents a fluid exclusively found in the stomach.[108] This liquid biopsy is not meant to substitute endoscopy as the gold standard for GC detection, but rather complement and enhance its accuracy, as it can be easily obtained during endoscopy without enduring additional discomfort to the patient, improving this one-stop-shop approach.[13]

Whereas tissue biopsies fail to capture tumor clonal heterogeneity, liquid biopsies allow the analysis of a variety of circulating biological factors shed by the tumor and across distinct tumor-cell subpopulations.[6] Moreover, they allow the serial sampling of proteomic, transcriptomic, genomic, and epigenetic cancer-associated alterations.[6]

The identification of minimally invasive or noninvasive biomarkers for the early detection of GC has been an emerging field in the last few years. Eighty-four studies were included in this systematic review, published over the last decade on non-invasive liquid biopsies-derived biomarkers for GC detection, approximately a 10th of the blood-based studies found in the literature, and most were reported on GJ and urine samples. Saliva has only been characterized in 12 studies; however, it is important to note that this liquid biopsy started being explored more recently, with the first report included in this systematic review published in 2016.

Over 10 classes of molecules were analyzed, including more than 60 circulating biomarkers. However, it is important to note the lack of representativeness of early lesions in the included studies. Overall, promising results have been published identifying biomarkers with high sensitivity and specificity for GC detection, irrespectively of sample type and biomarker class (Figure 2), although mostly deriving from single studies with no independent validation. Several molecules reached AUC values equal or superior to 0.90, the best ones being AAL lectin in saliva (AUC = 0.98, 95% CI: 0.97–1.00)[20] and a model including age and three amino acids in urine (L-PA, D-isoleucine, and D-serine, AUC = 0.98, 95% CI: 0.95–1.00).[44] The most promising model with independent a validation set in the same study includes 17 metabolites and exhibited a discrimination capacity of 0.97 for GC.[60]

When applying a modified version of the Newcastle-Ottawa quality assessment scale to each study, several quality concerns were highlighted, mostly associated with undetailed information on (1) sample size or statistical power estimations; (2) comparativeness of groups; (3) representativeness of cases; (4) definition and selection of controls, with most articles not providing information on the screening method used to define the outcome. If in fact biases in study design exist, particularly associated with representativeness of the population, an overestimation of the true association can be assumed, overrating the diagnostic value of the assessed biomarkers, and impairing the results of this systematic review. As highlighted in a review by Herrera-Pariente et al.,[10] there is a need to standardize the methodology for liquid biopsy sample collection and processing, as there is a high heterogeneity, as well as the statistical methods performed in similar studies, in order to increase comparability and implementation in a clinical setting. For example, for detection of salivary biomarkers, in most reports, participants were asked to refrain from eating or drinking for at least 30 min before sampling and whole saliva was collected in the morning. Centrifugation varied between 2600 x*g* and 13,000 x*g* during 10–30 min at 4°C. Concerning stool, samples were either preserved at 4°C, −20°C or −80°C until use. Most studies using urine involved collection in the morning before any treatment and storage at −80°C. GJ samples were collected after fasting and centrifuged in most studies, varying between 1000 x*g* and 10,000 x*g* from 10 to 30 min before storage. Regarding techniques, most heterogeneity was noticed across different classes of biomarkers: microbiota has been analyzed by sequencing, a high-throughput technique; RNA molecules by RT-qPCR, a more targeted approach; glycans and proteins mostly by

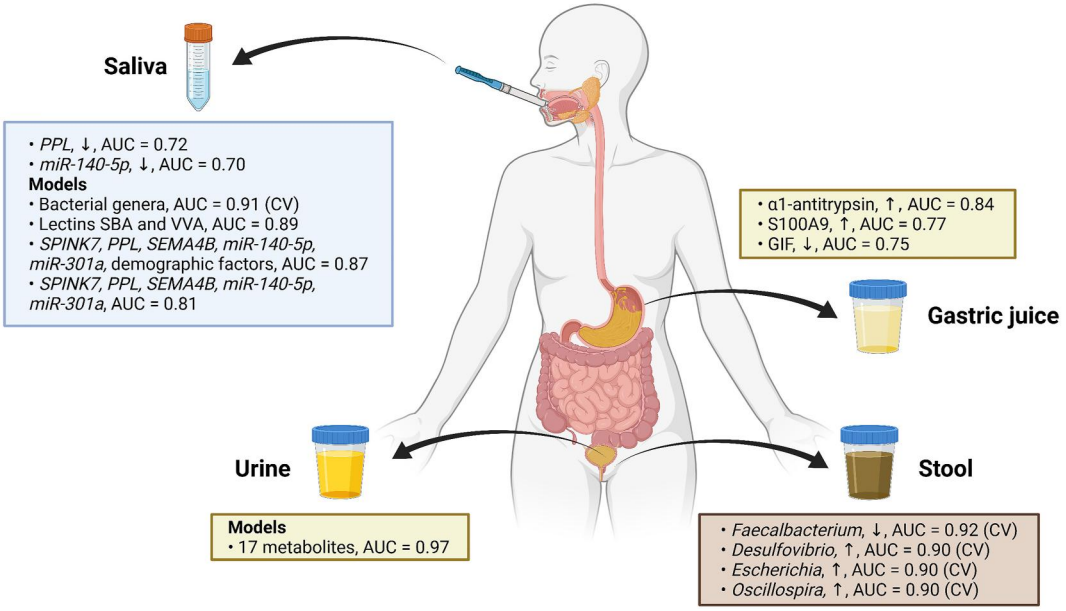

FIGURE 2 Validated biomarkers with high sensitivity and specificity for gastric cancer detection across all the analyzed liquid biopsy samples, including saliva, gastric juice, urine, and stool, including their expression in cancer (upregulated, ↑, or downregulated, ↓), and area under the curve (AUC) values (created with Biorender.com).

mass spectrometry, microarrays, ELISA, and western blot; and metabolites by mass spectrometry, from gas chromatography-mass spectrometry to high performance liquid chromatography-tandem mass spectrometry, as well as proton nuclear magnetic resonance, which allow the possibility of large-scale analysis.[109] Overall, a difference in the techniques used was not clearly noticed over time.[27,93] However, radioimmunoassay for protein or metabolite detection has only been performed in studies from 2011.[80,97]

In this systematic review, most included studies were performed in high-risk Eastern countries, namely China, Japan and South Korea. Translation of those findings in Western populations, without previous validation studies, should be taken with caution due to reported differences in biology, such as the lower proportions of signet ring histology and proximal stomach involvement in Eastern GC patients.[110] A few studies have reported the validation of Eastern survival nonograms or overall survival prediction models in Western populations, particularly American,[111,112] and Turkish, who constitute a bridge between East and West.[113] In fact, the Western nonogram was found to be more effective in the Turkish population to estimate the 5-year overall probability of survival compared to the Eastern nonogram.[113] More recently, Pereira et al.[114] compared Eastern and Western cohorts and disparities reported in survival outcomes appeared not to be molecularly driven, although this study only targeted the E-cadherin and CD44v6 protein expression. An anticipation in the diagnosis (8 years on average) and more extensive surgical procedures were reported in Eastern populations.[114] Interestingly, a study by Lin et al.[115] compared gene expression profiles from Asian and non-Asian GC cohorts and found differentially expressed gene signatures related to inflammation and immune function. Genomic and clinical similarities between esophageal and gastric adenocarcinomas located in the cardia have been reported in the literature.[116] Non-cardia GC is more prevalent globally and shows higher incidence in Asian countries,[117] which represent over 90% of the study population included in this systematic review. In fact, and although only 21 out of 84 studies offered data on tumor location, between 52% and 95% of tumors were ascribed to the non-cardia site. Future studies should not only report on tumor location but also provide stratified data on unique molecular signatures.

The promise of precision oncology to improve diagnosis and treatment of cancer relies on the molecular profiling of tumors, that mostly depend on invasive sampling procedures that are not always feasible or prone to serial monitoring. An increasingly shift towards liquid biopsies has been observed in the last decade, with several promising non-blood-based circulating biomarkers here highlighted. Future research should consider the standardization of preanalytical variables and statistical methods together with adequate reporting, the design of multicenter studies with large enough and independent study populations, to facilitate the comparability of results and demonstration of both the clinical validity and clinical utility, the first step in the clinical adoption of a liquid biopsy test.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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