Circulating long noncoding RNAs as potential biomarkers for stomach cancer: A systematic review and meta-analysis

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Research

Keywords: stomach cancer, circulating IncRNAs, diagnosis, meta-analysis.

Posted Date: February 8th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-81358/v2

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Version of Record: A version of this preprint was published on March 26th, 2021. See the published version at https://doi.org/10.1186/s12957-021-02194-6.
Abstract

**Background:** Recent researches have suggested that long noncoding RNA (lncRNA) is involved in the tumorigenesis and development of stomach cancer (SC). This meta-analysis aimed to identify the diagnostic performance of circulating lncRNAs in SC.

**Methods:** All relevant studies were systematically searched through PubMed, Web of Science, Cochrane Library and EMBASE databases. The diagnostic values of lncRNAs were mainly assessed by pooled sensitivity, specificity, and summary receiver operating characteristic area under the curve (SROC AUC). Meta-DiSc 1.4, Review Manager 5.3 and STATA 12.0 were used for statistical analysis.

**Results:** A total of 42 eligible studies were included in this meta-analysis. The pooled sensitivity, specificity, and SROC AUC were 0.78 (95% CI: 0.75-0.81), 0.75 (95% CI: 0.71-0.78), and 0.83 (95% CI: 0.80-0.86) respectively, suggesting that the lncRNAs test had a high accuracy for the diagnosis of SC. Obvious heterogeneity might come from the type of lncRNA through subgroup and meta-regression analysis. Fagan diagram shows the clinical value of lncRNAs test in SC.

**Conclusions:** Abnormal expression of circulating lncRNAs exhibits a high efficacy for diagnosing SC, which is promising in clinical application.

**Background**

Based on 2018 global cancer data, stomach cancer (SC) is the 5th most common neoplasm and the 3rd most deadly cancer, causing an estimated 783,000 deaths in 2018.[1]. Studies have shown that SC patients are often diagnosed at later stages due to the absence of typical early signs[2]. As a result, the overall survival in patients with advanced SC is poor; the 5-year survival rate ranges from approximately 10% to 30%[3]. The prognosis of SC is highly dependent on the timing of the diagnosis[4]. Blood-based cancer biomarkers are ideal for screening and early detection due to their convenience and low invasiveness. However, the low sensitivity and specificity of conventional blood biomarkers limit their application, such as carcinoembryonic antigen and carbohydrate antigen 19-9[5]. Although considerable effort has been devoted to identifying the underlying mechanism of SC, the identification of new diagnostic markers for SC is still a considerable challenge.

In recent years, the regulation of gene expression by noncoding RNAs has been studied thoroughly. Long noncoding RNA (lncRNAs) are RNA molecules greater than 200 nucleotides that modulate gene expression at the levels of transcription, posttranscription and translation, but are not able to encode proteins[6]. An increasing body of evidence has suggested that lncRNAs play a major role during the processes of tumorigenesis and development, which may offer new ideas for the early diagnosis of SC. For instance, for distinguishing SC patients from normal subjects, the lncRNAs PCGEM1 and LOC80054 have higher area under the curve (AUC) values than other conventional tumor markers (AFP, CEA, CA12-5, CA19-9 and CA72-4)[7, 8]. Similarly, lncRNAs can also be detected in blood, and circulating noncoding RNAs have become a new source of noninvasive cancer biomarkers[9], which can serve as new diagnostic biomarkers for SC.

However, considering the small sample size and limitations of the research design, there is insufficient evidence to confirm the diagnostic accuracy of circulating lncRNAs in SC patients. To address this shortcoming, a comprehensive systematic review and meta-analysis was conducted to explore the diagnostic roles of circulating lncRNAs in SC.
Methods

Search strategy

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[10]. The PubMed, Web of Science, Cochrane Library, and Embase databases were systematically searched for potentially relevant articles, which were independently screened by two authors (Cao F and Xu J). The references lists of relevant meta-analyses and reviews were also searched to identify articles that were not included in the initial search. In addition, relevant articles in scientific congresses and conferences were reviewed. The search strategy and Participant, Index test, Comparison, Outcome, and Study (PICOS) design strategy are shown in Table 1. The publication search was updated regularly until July 9, 2020.

Table 1. Systematic search strategy (PICOS strategy).

| Search strategy |
|-----------------|
| **Participant** | #1 (Stomach Neoplasms[MeSH Terms] OR "Neoplasm, Stomach" OR "Stomach Neoplasms" OR "Gastric Neoplasms" OR "Gastric Neoplasm" OR "Cancer of Stomach" OR "Stomach Cancers" OR "Gastric Cancer" OR "Cancer, Gastric" OR "Gastric Cancers" OR "Stomach Cancer" OR "Cancer, Stomach" OR "Cancers, Stomach" OR "Cancer of the Stomach" OR "Gastric Cancer, Familial Diffuse") |
| **Index test**  | #2 (RNA, Long Noncoding[MeSH Terms] OR "RNA, Long Noncoding" OR "Noncoding RNA, Long" OR "RNA, Long Non-Translated" OR "Long Non-Translated RNA" OR "Non-Translated RNA, Long" OR "RNA, Long Non Translated" OR "Long Non-Coding RNA" OR "Long Non Coding RNA" OR "Non-Coding RNA, Long" OR "RNA, Long Non-Coding" OR "Long Non-Protein-Coding RNA" OR "Non-Protein-Coding RNA, Long" OR "RNA, Long Non-Protein-Coding" OR "Long Noncoding RNA" OR "RNA, Long Untranslated" OR "Long Untranslated RNA" OR "Untranslated RNA, Long" OR "Long LncRNAs" OR "ncRNAs, Long" OR "Long Intergenic Non-Protein Coding RNA" OR "Long Intergenic Non-Protein Coding RNA, Long") |
| **Comparison**  | None |
| **Outcome**     | #3 (Biomarkers[MeSH Terms] OR "Biomarkers" OR "Biomarker" OR "Markers, Biological" OR "Biologic Markers" OR "Markers, Biologic" OR "Biologic Marker" OR "Marker, Biologic" OR "Biologic" OR "Marker, Biologic") |
| **Study design**| None |
| **Search**      | #1 AND #2 AND (#3 OR #4) |
| **Database search** |
| **Language**    | No restriction |
| **Electronic databases** | PubMed, Web of Science, Cochrane Library, and Embase databases |
Selection criteria

The following inclusion criteria were used:

(i) The expression of lncRNAs was determined in plasma or serum by quantitative reverse transcription-polymerase chain reaction or other molecular techniques;

(ii) Study on the relationship between lncRNA expression levels and cancer diagnosis;

(iii) Sufficient data to determine false negatives, true negatives, false positives and true positives.

The exclusion criteria were as follows:

(i) Duplicate publications;

(ii) Meta-analysis, correspondence, single case reports, review articles and animal model studies.

Data extraction

The two authors (Cao F and Xu J) reviewed the full texts and independently extracted data from all included studies. The following data were extracted: first author, year of publication, race of participants, pathological type of experimental group/control group, sample size, specimen type, lncRNA type, dysregulated state of lncRNAs, sensitivity and specificity.

Quality assessment

Two authors (Xu J and Cao F) independently evaluated the quality of each diagnostic study. The methodological quality and applicability of the included studies were examined using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)\(^ {[11]} \) tool in using Review Manager software version 5.3. The QUADAS-2 tool is used to assess the quality of diagnostic accuracy studies\(^ {[11]} \). The QUADAS-2 tool contains 4 main areas: process and timing, index testing, reference standards, and patient selection. The risk of prejudice and apprehension were classified as "low", "high" or "unclear". The differences were resolved through discussions among all the researchers.

Statistical analysis

Meta-analyses were performed using Meta-DiSc 1.4 (Romany Cajal Hospital, Madrid, Spain)\(^ {[12]} \), Review Manager 5.3 (Cochrane Collaboration, Oxford, England), and STATA 12.0 (Stata Corp LP, TX, USA).

For a meta-analysis of diagnosis, the sensitivity, specificity, negative likelihood ratio, positive likelihood ratio, diagnostic odds ratio and the corresponding 95% CIs were used to determine the diagnostic value of lncRNAs. To quantitatively assess the accuracy of diagnosis, the area under the curves (AUCs) of summary receiver operating characteristic curves (SROCs) were determined. A hierarchical summary receiver operator characteristic (HSROC) model was adopted to extend the fixed-effects SROC model and evaluate the accuracy of multiple diagnostic tests.

The heterogeneity tests were carried out by the Q-test and \( I^2 \) statistics. \( P \) values of < 0.05 were regarded as statistically significant. An \( I^2 \) value > 50% and a \( P \) value < 0.05 indicated significant heterogeneity between the included studies, and a random effects model was applied. Otherwise, if there was no obvious heterogeneity, the fixed effects model was applied to evaluate the aggregated results. The heterogeneity induced by the threshold
effect was evaluated by the ROC plane. Galbraith Star charts and bivariate boxplots were employed to estimate the degree of heterogeneity. Subgroup analysis and meta-regression were used to assess the source of heterogeneity. Subgroup results were examined one at a time.

Sensitivity analysis was used to determine the stability of the results. Potential publication bias was examined by Deeks’ funnel plot. A P-value of > 0.1 indicates that there is no publication bias. Fagan's nomogram was applied to judge the clinical value of lncRNAs as a diagnostic method.

Results

Literature searching and study screening

In total, 1867 articles were obtained from the four databases. After eliminating 639 duplicate articles, 1228 studies were further screened. After screening the titles, abstracts, and full texts, 42 eligible studies \[2, 7, 13-52\] were finally included based on the selection criteria (Fig 1).

Quality evaluation and main characteristics of the eligible studies

The diagnostic meta-analysis analyzed 42 eligible studies \[2, 7, 13-52\] published between 2013 and 2020. Thirty-seven studies detected lncRNA expression in Asian population, while 5 studies detected lncRNA expression in Caucasian populations. Sample types included plasma, serum, and plasma/serum exosomes. All SC patients were pathologically confirmed, and the control groups consisted of healthy donor individuals and benign stomach disease patients. A total of 49 different lncRNAs were examined across all included studies; most of the lncRNAs were upregulated in SC (Table 2). The quality assessment is shown in Fig 2.

Table 2. Main characteristics of eligible studies for diagnosis.
| First author, year | Race       | Pathologic type (E/C) | Sample size (E/C) | Specimen | InC RNA | State | Sensitivity | Specificity | TP | FP | FN | TN | QUADAS-2 (Refs) |
|-------------------|------------|----------------------|------------------|----------|---------|-------|-------------|-------------|----|----|----|----|-----------------|
| Liu W, 2019       | Asian      | GC/HD                | 89/73            | Serum    | FEZF1-AS1 | Up    | 75.3%       | 65.8%       | 67 | 25 | 22 | 48 | 5               |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
|                     |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
| oruke E, Caucasian 2018 | GC/non-GC | 40/42                | Plasma           | H19      | Up       | 87.2% | 38.1%       | 35           | 26 | 5  | 16 | 6  | 14              |
| Liu Y, 2019       | Asian      | GC/HD                | 100/100          | Serum    | MALAT1   | Up    | 85.8%       | 74.5%       | 86 | 26 | 14 | 75 | 4               |
| Hashad D, 2016    | Caucasian  | GC/HD                | 32/30            | Plasma   | H19      | Up    | 68.8%       | 56.7%       | 22 | 13 | 10 | 17 | 5               |
| Li Q, 2014        | Asian      | GC/HD                | 79/81            | Plasma exosome | LINC00152 | Down  | 48.1%       | 85.2%       | 38 | 12 | 41 | 69 | 6               |
| Liu Z, 2014       | Asian      | GC/HD                | 83/80            | Plasma   | FER1L4   | Up    | 67.2%       | 80.3%       | 56 | 16 | 27 | 64 | 7               |
| Liu J, 2018       | Asian      | GC/HD                | 50/50            | Plasma   | CTC-501O10.1 | Up    | 90.0%       | 51.0%       | 45 | 25 | 5  | 26 | 19              |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
| Mohamed, Caucasian W, 2019 | GC/HD | 35/25                | Serum            | H19      | Up       | 90.9%| 100.0%      | 32           | 0  | 3  | 25 | 5  | 21              |
| Piao H, 2020      | Asian      | GC/HD                | 281/80           | Plasma exosome | CEBPA-AS1 | Up    | 74.0%       | 88.0%       | 208| 10 | 73 | 70 | 6               |
| Zhou H, 2016      | Asian      | GC/HD                | 77/60            | Plasma   | ZFAS1    | Up    | 76.6%       | 63.9%       | 59 | 22 | 18 | 38 | 5               |
| Cai C, 2019       | Asian      | GC/HD                | 63/29            | Serum exosome | PCSK2-2:1 | Up    | 84.0%       | 86.5%       | 53 | 4  | 10 | 25 | 6               |
| Zhou X, 2015      | Asian      | GC/HD                | 90/90            | Plasma   | H19      | Up    | 82.9%       | 72.9%       | 75 | 24 | 15 | 66 | 7               |
| Elsayed E, 2018   | Caucasian  | GC/HD                | 50/50            | Plasma   | HOTAIR   | Up    | 86.0%       | 94.0%       | 43 | 3  | 7  | 47 | 4               |
| Xian H, 2018      | Asian      | GC/HD                | 50/50            | Plasma   | HULC     | Up    | 58.0%       | 80.0%       | 29 | 10 | 21 | 40 | 5               |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
| Feng W, 2019      | Asian      | GC/HD                | 107/87           | Serum    | B3GALT5-AS1 | Up    | 64.5%       | 87.4%       | 69 | 11 | 38 | 76 | 5               |
| Fu M, 2017        | Asian      | GC/HD                | 72/72            | Serum    | LINC00978 | Up    | 80.0%       | 70.0%       | 58 | 22 | 14 | 50 | 5               |
| Gao J, 2015       | Asian      | GC/HD                | 20/20            | Plasma   | UCA1     | Up    | 85.0%       | 96.3%       | 17 | 1  | 3  | 19 | 6               |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
|                   |            |                      |                  |          |          |       |             |             |    |    |    |    |                  |
| Shaedi H, 2018    | Asian      | GC/HD                | 62/40            | Plasma   | H19      | Up    | 74.2%       | 90.0%       | 46 | 4  | 16 | 36 | 6               |

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| Name            | Area          | Cell Type                  | Exosome Type | Gene     | Expression | Sample Size | Detection Method | Up/Down | Percentages | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 | Value 6 | Value 7 | Value 8 | Value 9 | Value 10 | Value 11 |
|-----------------|---------------|----------------------------|--------------|----------|------------|-------------|-----------------|----------|--------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| Guo X, 2020    | Asian         | EGC/HD                     | Plasma exosome | MEG3    | Down       | 217/219     | GC1             | Up       | 97.0%       | 83.0%   | 210    | 37      | 7       | 182     | 5       | 32      |
| Arita T, 2013  | Asian         | GC/HD                      | Plasma        | co-CHR1  | Up         | 43/34       | H19             | Up       | 74.0%       | 58.0%   | 32      | 14      | 11      | 20      | 6       | 33      |
| Jin B, 2019    | Asian         | GC/HD                      | Plasma        | LINC00086| Down       | 168/74      | PCGEM1          | Up       | 72.9%       | 88.9%   | 231    | 11      | 86      | 89      | 7       | 7       |
| Jiang H, 2019  | Asian         | GC/HD                      | Plasma        | GC1     | Up         | 317/100     | UEGC1           | Up       | 88.0%       | 82.0%   | 45      | 11      | 6       | 49      | 5       | 35      |
| Lin L, 2018    | Asian         | GC/HD                      | Plasma exosome | UE GC1  | Up         | 51/60       | UEGC2           | Up       | 89.0%       | 58.0%   | 45      | 25      | 6       | 35      |
| Pan L, 2017    | Asian         | GC/HD                      | Serum exosome  | ZFAS1   | Up         | 60/37       | HULC            | Up       | 71.7%       | 75.7%   | 142    | 18      | 31      | 92      | 6       | 37      |
| Jin C, 2016    | Asian         | GC/HD                      | Serum         | INHBAAS1| Down       | 173/110     | MACC1           | Up       | 68.0%       | 89.0%   | 52      | 6       | 24      | 48      | 5       | 39      |
| Zhang X, 2018  | Asian         | GC/HD                      | Serum exosome  | UFC1    | Up         | 57/29       | INHBAAS1        | Down     | 92.7%       | 74.5%   | 47      | 14      | 4       | 39      | 6       | 40      |
| Zhao R, 2018   | Asian         | GC/HD                      | Serum exosome  | HOTTIP  | Up         | 126/120     | MIR4435-2HG     | Down     | 65.4%       | 87.2%   | 31      | 7       | 16      | 45      | 3       | 36      |
| Žurock S, Caucasian, 2015 | Asian   | GC/non-GC                  | Plasma       | INHBAAS1| Down       | 76/54       | CEBPA-AS1       | Down     | 96.2%       | 57.4%   | 52      | 6       | 24      | 48      | 5       | 39      |
| Ke D, 2017     | Asian         | GC/HD                      | Plasma        | MIR4435-2HG | Down   | 51/53       | HOXA11-AS       | Up       | 78.7%       | 97.8%   | 74      | 1       | 20      | 39      | 7       | 41      |
| Liu Y, 2019    | Asian         | GC/HD                      | Serum         | CEBPA-AS1| Down       | 94/40       | UCA1            | Down     | 73.2%       | 82.3%   | 37      | 14      | 44      |
| Shan L, 2019   | Asian         | GC/HD                      | Serum         | AK001058| Down       | 117/100     | AK001058        | Down     | 95.1%       | 72.3%   | 49      | 15      | 2       | 38      |
| Shao Y, 2016   | Asian         | GC/HD                      | Plasma        | INHBAAS1| Down       | 83/90       | MIR4435-2HG     | Down     | 65.4%       | 87.2%   | 31      | 7       | 16      | 45      |
| Yang Z, 2019   | Asian         | GC/HD                      | Plasma        | CEBPA-AS1| Down       | 109/106     | AK001058        | Down     | 96.9%       | 92.3%   | 36      | 4       | 11      | 48      |
| Xu H, 2020     | Asian         | GC/HD                      | Serum         | PANDAR  | Up         | 109/50      | MIAT            | Up       | 81.5%       | 87.5%   | 89      | 6       | 20      | 44      | 5       | 45      |
| Xu Y, 2018     | Asian         | GC/HD                      | Plasma        | SMARCC2 | Up         | 34/34       | SMARCC2         | Up       | 85.0%       | 63.0%   | 93      | 39      | 16      | 67      |
| Xu Y, 2019     | Asian         | GC/HD                      | Plasma        | SMARCC2 | Up         | 45/45       | LINC01225       | Up       | 50.0%       | 90.0%   | 23      | 5       | 23      | 41      | 4       | 47      |
Diagnostic accuracy of lncRNA

A total of 42 eligible diagnostic studies were meta-analyzed. As illustrated in Fig 3, the pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio were 0.78 (95% CI: 0.75-0.81), 0.75 (95% CI: 0.71-0.78), 3.09 (95% CI: 2.66-3.58), 0.29 (95% CI: 0.25-0.33), and 10.67 (95% CI: 8.34-13.65), respectively. As demonstrated in Fig 4A, the AUC value of the SROC was 0.83 (95% CI: 0.80-0.86). The SROC results were further evaluated through the HSROC model. As shown in Fig 4B, the $\beta$ estimate was 0.11 (95% CI: -0.19-0.40) and the corresponding P value was 0.485. The lambda estimate was 2.38 (95% CI: 2.13-2.63).

Heterogeneity analysis

As illustrated in Fig 3, obvious heterogeneity was found in the pooled sensitivity ($I^2 = 88.93\%, P < 0.01$), specificity ($I^2 = 88.14\%, P < 0.01$), positive likelihood ratio ($I^2 = 88.49\%, P < 0.01$), negative likelihood ratio ($I^2 = 88.71\%, P < 0.01$), and diagnostic odds ratio ($I^2 = 100.00\%, P < 0.01$).

A nontypical shoulder arm appearance was observed in the ROC plane (Fig 5A). Twenty out of the 63 studies of the Galbraith star chart and 10 out of 42 studies of the bivariate box plot fell outside the 95% CI (Fig 5B and 5C). Fig 5D shows the meta-regression forest map. All studies were grouped according to race, pathological types of experimental groups, pathological types of control groups, sample size, specimen type, dysregulated state of lncRNAs, and lncRNA types. Table 3 shows the changes in sensitivity, specificity, and $I^2$ values after meta-regression and subgroup analysis.

Table 3. Subgroup analysis of the diagnostic efficacy of lncRNA in stomach cancer.
| Group                  | Subgroup    | No. of studies | No. of patients | Sensitivity | Specificity | Heterogeneity Specificity (I²; P value) | Heterogeneity AUC (I²; P value) | Meta-regression (P value) |
|-----------------------|-------------|----------------|-----------------|-------------|------------|----------------------------------------|-------------------------------|---------------------------|
| Overall               |             | 42             | 7524            | 0.78 [0.75, 0.81] | 88.93%; <0.001 | 0.75 [0.71, 88.14%; 0.78] ; <0.001 | 0.83 [0.80 - 0.86] | 0.48                      |
| Race                  | Asian       | 60             | 7090            | 0.78 [0.75, 0.81] | 89.38%; <0.001 | 0.74 [0.70, 87.51%; 0.77] ; <0.001 | 0.83 [0.79 - 0.86] | 0.48                      |
|                       | Caucasian   | 5              | 434             | 0.81 [0.70, 0.89] | 75.16%; <0.001 | 0.86 [0.52, 94.22%; 0.97] ; <0.001 | 0.87 [0.84 - 0.90] | 0.48                      |
| Pathologic types (E)  | GC          | 60             | 6936            | 0.78 [0.74, 0.81] | 88.19%; <0.001 | 0.75 [0.71, 88.35%; 0.79] ; <0.001 | 0.83 [0.80 - 0.86] | 0.38                      |
|                       | EGC         | 5              | 588             | 0.85 [0.72, 0.93] | 91.39%; <0.001 | 0.71 [0.58, 90.27%; 0.81] ; <0.001 | 0.84 [0.80 - 0.87] | 0.38                      |
| Pathologic types (C)  | health      | 61             | 6549            | 0.79 [0.75, 0.82] | 89.32%; <0.001 | 0.75 [0.71, 86.53%; 0.79] ; <0.001 | 0.84 [0.80 - 0.87] | 0.15                      |
|                       | non-GC      | 2              | 212             | -            | -          | -                                      | -                             | 0.86                      |
|                       | GS          | 2              | 763             | -            | -          | -                                      | -                             | 0.10                      |
| Sample size           | N≤100       | 21             | 1153            | 0.79 [0.74, 0.84] | 74.67%; <0.001 | 0.77 [0.69, 84.82%; 0.84] ; <0.001 | 0.85 [0.82 - 0.88] | 0.62                      |
|                       | 100<N≤200   | 28             | 2722            | 0.79 [0.74, 0.82] | 79.14%; <0.001 | 0.74 [0.68, 85.75%; 0.79] ; <0.001 | 0.83 [0.80 - 0.86] | 0.95                      |
|                       | N>200       | 16             | 3649            | 0.77 [0.68, 0.84] | 95.41%; <0.001 | 0.73 [0.65, 92.57%; 0.79] ; <0.001 | 0.81 [0.77 - 0.84] | 0.58                      |
| Specimen              | Plasma      | 23             | 3467            | 0.78 [0.74, 0.82] | 87.25%; <0.001 | 0.72 [0.67, 86.87%; 0.77] ; <0.001 | 0.82 [0.79 - 0.85] | 0.34                      |
|                       | Serum       | 12             | 2468            | 0.78 [0.72, 0.83] | 90.56%; <0.001 | 0.75 [0.67, 90.37%; 0.82] ; <0.001 | 0.84 [0.80 - 0.87] | 0.99                      |
|                       | Exosome     | 8              | 1589            | 0.81 [0.70, 0.89] | 92.18%; <0.001 | 0.81 [0.76, 69.40%; 0.86] ; <0.001 | 0.87 [0.84 - 0.90] | 0.17                      |
| Dysregulated state    | Upregulated | 46             | 6003            | 0.78 [0.74, 0.82] | 90.19%; <0.001 | 0.75 [0.71, 87.40%; 0.80] ; <0.001 | 0.84 [0.80 - 0.87] | 0.78                      |
|                       | Downregulated | 19           | 1521            | 0.79 [0.72, 0.84] | 84.54%; <0.001 | 0.72 [0.64, 89.12%; 0.79] ; <0.001 | 0.82 [0.79 - 0.86] | 0.78                      |
| IncRNA                | H19         | 7              | 848             | 0.78 [0.70, 0.84] | 75.98%; <0.001 | 0.72 [0.49, 89.62%; 0.88] ; <0.001 | 0.82 [0.78 - 0.85] | 0.69                      |
|                       | UCA1        | 3              | 361             | 0.87 [0.81, 0.91] | 83.60%; 0.02  | 0.82 [0.76, 45.20%; 0.88] ; 0.161 | 0.92 [0.84 - 0.99] | 0.13                      |
|                       | CEBPA-AS1   | 3              | 564             | 0.77 [0.73, 0.81] | 86.00%; 0.001 | 0.76 [0.69, 86.80%; 0.82] ; 0.001 | 0.88 [0.84 - 0.92] | 0.63                      |
Note: E/C: experimental group/control group; GC: gastric cancer; EGC: early gastric cancer; HD: healthy donor individuals; GS: superficial gastritis; AUC, area under the curve.

Sensitivity analysis and publication bias

First, sensitivity analysis was carried out to determine the stability of our results. The removal of individual studies exhibited no noticeable changes in pooled results (Additional file 1: Supplementary Figure 1, Fig. S1A). The P value of Deeks’ funnel plot asymmetry test was 0.12 (Additional file 1: Supplementary Figure 1, Fig. S1B).

Clinical values of IncRNAs for SC diagnosis

As shown in Fig 6, Fagan’s nomogram revealed that if the patient had a positive IncRNA test result, the actual probability of suffering from SC was 76%, while the probability was 22% if a negative test result was obtained.

Discussion

In recent years, IncRNAs have been recognized as potential diagnostic biomarkers for different cancers\cite{53}. As a diagnostic biomarker for cancer, IncRNAs have the following special advantages. First, the abundance of IncRNAs is relatively high. In the human genome, the number of IncRNAs is four times greater than that of coding RNAs\cite{54}. Second, IncRNAs are highly expressed in the plasma, tissue and exosomes of cancer cases\cite{55}. Third, IncRNAs have complex biological functions and are closely related to tumorigenesis and development. Therefore, IncRNAs may be promising biomarkers for the early detection and prognosis of various cancers\cite{56}.

In the present meta-analysis, a total of 42 eligible studies were screened. The aggregated results of sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio, and SROC AUC indicated that the abnormal expression of circulating IncRNAs exhibits a high accuracy for the diagnosis of SC. The $\beta$ estimate in the HSROC model indicated that the SROC is symmetrical. Meanwhile, the estimate of lambda reflected the diagnostic accuracy of IncRNAs. Sensitivity analysis verified the stability of the results, and the Deeks funnel chart asymmetry test showed that there was no obvious publication bias. The Fagan diagram also shows its advantages in clinical application, which was mainly due to its moderately high positive and negative predictive value.

For the obvious heterogeneity in the pooled estimates, many analyses have been applied to explore the source of heterogeneity. The ROC plane suggests the absence of a threshold effect, while the Galbraith star charts and bivariate boxplots suggest heterogeneity between studies. Meta-regression and subgroup analysis showed that the heterogeneity might come from the type of IncRNA: when IncRNA UCA1 was used as the grouping condition, the $I^2$ of sensitivity was reduced to 83.60%, and the $I^2$ of specificity was reduced to 45.20% ($P = 0.161$). In addition, the diagnostic value of IncRNA UCA1 was above average (AUC: 0.92 (95% CI: 0.84-0.99) versus 0.83 (95% CI: 0.80-0.86)). There was no evidence that race, pathological types of experimental groups, pathological types of control groups, sample size, specimen type, and dysregulated state of IncRNAs significantly affected the pooled results.

Although meta-analysis of IncRNAs in the diagnosis of SC has been reported before\cite{57,58}, most of them focus on IncRNAs in SC tissues. Although IncRNAs in tissue also have high diagnostic accuracy (AUC= 0.755\cite{57}; 0.80\cite{58}), their
clinical application value is limited for the following reasons: first, the diagnosis of SC after surgery depends on the pathological morphology and immunohistochemical analysis, and the auxiliary role of lncRNAs is optional; second, in regard to endoscopic biopsy specimens, the diagnosis of SC still depends on the pathological morphology, and no extra tumor tissue can be used to extract lncRNAs. In contrast, circulating lncRNAs are ideal biomarkers due to their convenience and low invasiveness. Therefore, the present study on the application of circulating lncRNAs in the diagnosis of SC has greater clinical significance.

Nevertheless, this meta-analysis possessed some limitations. First, this systematic review and meta-analysis lacks eligible non-Asian studies. Second, almost every study focuses on different lncRNAs, and it was difficult to perform subgroup analysis based on lncRNA types to explain the possible sources of heterogeneity. Third, obvious heterogeneity was found in the included studies. Although diagnostic meta-analysis suggested that the type of lncRNA was a source of heterogeneity through meta-regression and subgroup analysis, the heterogeneity of sensitivity and specificity were still high in each subgroup.

**Conclusions**

In conclusion, the findings of the diagnostic meta-analysis provide evidence that circulating IncRNA tests exhibit a high accuracy for diagnosing SC, which is promising in clinical application due to their high positive and negative predictive value. This study provides an important reference value for the application of circulating IncRNAs as biomarkers for the early diagnosis of SC. Due to potential limitations, further investigations are warranted to verify the diagnostic role of circulating IncRNAs in SC.

**List Of Abbreviations**

| LncRNA | Long noncoding RNA |
|--------|--------------------|
| SC | Stomach cancer |
| SROC | Summary receiver operating characteristic |
| AUC | Area under the curve |
| CI | Confidence interval |
| CA-153 | Cancer antigen 153 |
| CEA | Carcinoembryonic antigen |
| QUADAS-2 | Quality Assessment of Diagnostic Accuracy Studies 2 |
| HSROC | Hierarchical summary receiver operator characteristic |

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.
Availability of data and material
All relevant data are within the paper and its additional files.

Competing interests
The authors declare that they have no competing interests.

Funding
The current study was supported by grants from 2019 Kunshan Key R&D Plan (Ecological Agriculture and Social Development)-Social Development Science and Technology Project (KS1941), and Medical clinical science and technology development fund project of Jiangsu University (JLY20160040).

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Acknowledgements
The current study was supported by grants from 2019 Kunshan Key R&D Plan (Ecological Agriculture and Social Development)-Social Development Science and Technology Project (KS1941), and Medical clinical science and technology development fund project of Jiangsu University (JLY20160040).

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Figures

Figure 1

Flow chart of the study selection process.
Figure 2

Quality assessment of eligible studies for diagnostic meta-analysis.

| Study ID | Diagnosis | Sensitivity | Specificity | DLR Positive | DLR Negative | Odds Ratio |
|----------|-----------|-------------|-------------|--------------|--------------|------------|
| Study 1  | SC        | 0.78 [0.75-0.81] | 0.76 [0.71-0.78] | 3.09 [2.66-3.58] | 0.29 [0.25-0.33] | 10.67 [8.34-13.68] |
| Study 2  | SC        | 0.80 [0.78-0.82] | 0.77 [0.74-0.78] | 3.10 [2.67-3.59] | 0.28 [0.25-0.32] | 10.71 [8.36-14.05] |
| Study 3  | SC        | 0.79 [0.77-0.81] | 0.75 [0.72-0.78] | 2.98 [2.59-3.46] | 0.27 [0.24-0.30] | 10.54 [8.17-13.43] |
| Study 4  | SC        | 0.81 [0.79-0.83] | 0.78 [0.75-0.80] | 3.12 [2.70-3.62] | 0.29 [0.26-0.32] | 10.89 [8.47-13.48] |
| Study 5  | SC        | 0.80 [0.78-0.82] | 0.76 [0.73-0.78] | 3.07 [2.64-3.49] | 0.28 [0.25-0.31] | 10.63 [8.30-13.26] |

Figure 3

Forest plots of the diagnostic value for lncRNAs test in detecting SC. (A) Sensitivity, (B) Specificity, (C) Positive likelihood ratio, (D) Negative likelihood ratio, (E) Diagnostic odds ratio.
Figure 4

SROC curve of lncRNAs test in detecting SC. (A) SROC curve, (B) HSROC model.

Figure 5

Heterogeneity analysis of diagnostic tests. (A) ROC Plane of the pooled studies. (B) Galbraith star charts of the pooled studies. (C) Bivariate boxplots of the pooled studies. (D) Subgroup and meta-regression analysis for heterogeneity of the pooled studies.
Figure 6

Fagan's nomogram of lncRNAs test in detecting SC.

**Supplementary Files**

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