

Long Non-Coding RNA as a Potential Diagnostic Tool in Coronary Artery Diseases - A Systematic Review

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Received:
05-Apr-2024;
Revision:
10-Nov-2024;
Accepted:
15-Dec-2024;
Published:
17-Mar-2025

ABSTRACT

Coronary Artery Disease (CAD) remains a leading global health challenge. Long non-coding RNAs (lncRNAs) have emerged as promising biomarkers for CAD. A systematic review following PRISMA guidelines evaluated 22 studies to assess long non-coding RNAs (lncRNAs) as biomarkers for Coronary Artery Disease (CAD). Among 27 identified lncRNAs in 5,301 participants, KCNQ1OT1, HIF1A-AS2, and APOA1-AS showed notable diagnostic accuracy, with 100% sensitivity and 80% specificity. One lncRNA, OTTHUMT00000387022, exhibited the highest specificity at 98%. Despite methodological differences, consistent diagnostic relevance was observed across studies, with sensitivity and specificity reaching 100% and 98%, respectively. This review underscores the potential of lncRNAs as CAD biomarkers, with 23 upregulated and 4 downregulated lncRNAs identified. Their stable presence in human biofluids and strong association with CAD suggest their utility as diagnostic markers and potential therapeutic targets.

KEYWORDS: Biomarkers, coronary artery disease, diagnostic accuracy, long non-coding RNA, systematic review

INTRODUCTION


Cardiovascular disease (CVD) carries significant mortality and morbidity throughout the globe, with coronary artery disease (CAD) representing one of the most catastrophic forms of the disease. Despite

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How to cite this article: Arthi Sri AS, Veeraraghavan VP, Patil S, Raj AT. Long non-coding RNA as a potential diagnostic tool in coronary artery diseases - A systematic review. Niger J Clin Pract 2025;28:1-7.

Access this article online	
Quick Response Code: 	Website: www.njconline.com
	DOI: 10.4103/njcp.njcp_256_24

innovation in preventive, diagnostic, and therapeutic modalities, the prognosis of patients with CAD remains dismal.

The etiology of CAD is complex, involving both ecological and genetic factors that contribute to the illness independently and in combination. Numerous risk variables, including, physical activity, smoking, dyslipidemia, sex, genetic diversity and, diabetes mellitus have been linked to CAD.^[1-3] Although risk factors for CAD are well known, its genetic basis remains unclear. Cardiologists currently use several biomarkers, primarily creatine kinase-MB, cardiac troponin I, T, and heart fatty acid binding protein, for the differential diagnosis of CAD. Because the clinical symptoms vary widely, the utility of these biomarkers in clinically assessing CAD risk and making treatment decisions is not sufficient.^[1,3] Therefore, it is crucial to identify novel diagnostic markers and therapeutic targets with a higher sensitivity and specificity.^[4,5]

Recent studies have elicited the growing popularity of non-coding RNAs,^[6,7] including the Long non-coding RNAs (lncRNAs).^[7] In a wide range of human diseases and disorders, the lncRNAs were found to be dysregulated. Their active roles in epigenetic modification, cell signaling, transcriptional, or post-transcriptional regulation indicate their potential role in disease pathogenesis.^[6,8] Human biofluid contains lncRNAs at detectable, very stable concentrations that can precisely reflect the environment *in vivo*, suggesting their potential application as biomarkers.^[9] The various diagnostic lncRNA associated with CAD studied extensively in the literature include HOTAIR, H19, LIPCAR, MALAT, etc.,^[5,9-11] The present systematic review explores to evaluates the diagnostic accuracy of long non-coding RNAs in CAD.

MATERIALS AND METHODS

Registration protocol

The review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO-CRD42023466700). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed [Figure 1].

Databases

A literature search was performed in the Pubmed, Scopus, and Web of Science databases using the keywords “coronary artery diseases” OR “CAD” OR “coronary heart disease” AND “Long non-coding RNA”

OR “lncRNA OR long intergenic non-coding RNA” AND “Biomarkers” OR “Marker”.

Eligibility criteria

Inclusion criteria

Original studies published in the English language involving human participants analyzing the diagnostic accuracy of long non-coding RNAs (lncRNAs) for coronary artery disease.

Exclusion criteria

Animal or *in vitro* studies, studies that do not report diagnostic accuracy data for lncRNAs, expert opinions, letters to the editor, and reviews were excluded from the study.

Strategy for data synthesis

From the identified articles, duplicates were removed and assessed for relevance based on the title and abstract. Later the full text of the remaining article was read and selected based on the eligibility criteria. Finally, the quality of the included studies was assessed according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) checklist [Figure 2].

QUADAS -2 assesment

The QUADAS-2 assessment graphs for 22 studies reveal that most studies showed a low risk of bias in patient selection and reference standards, indicating good practices in these areas. However, there were concerns regarding the index test and flow timings, with many studies having unclear risks, pointing to possible issues or insufficient reporting. In terms of applicability, most studies were relevant to the research question, though there were some concerns, particularly with a few studies' reference standards. Overall, the findings suggest that while the studies are generally applicable, there are areas, especially regarding the index tests and study follow-up, where improvement or clearer reporting could enhance the quality of the research.

Following this data extraction and analysis of data were done. Data including the author's name, year of publication, study design, lncRNA type and expression, sample size, sample type, and methodology employed were extracted.

RESULTS

Study selection

A total of 293 articles (PubMed-154, Scopus-65, Web of Science- 74) were identified. 81 duplicates were excluded. 212 articles were screened and 74 full-length articles were selected for full text evaluation. Based on the inclusion and exclusion criteria 22 original research

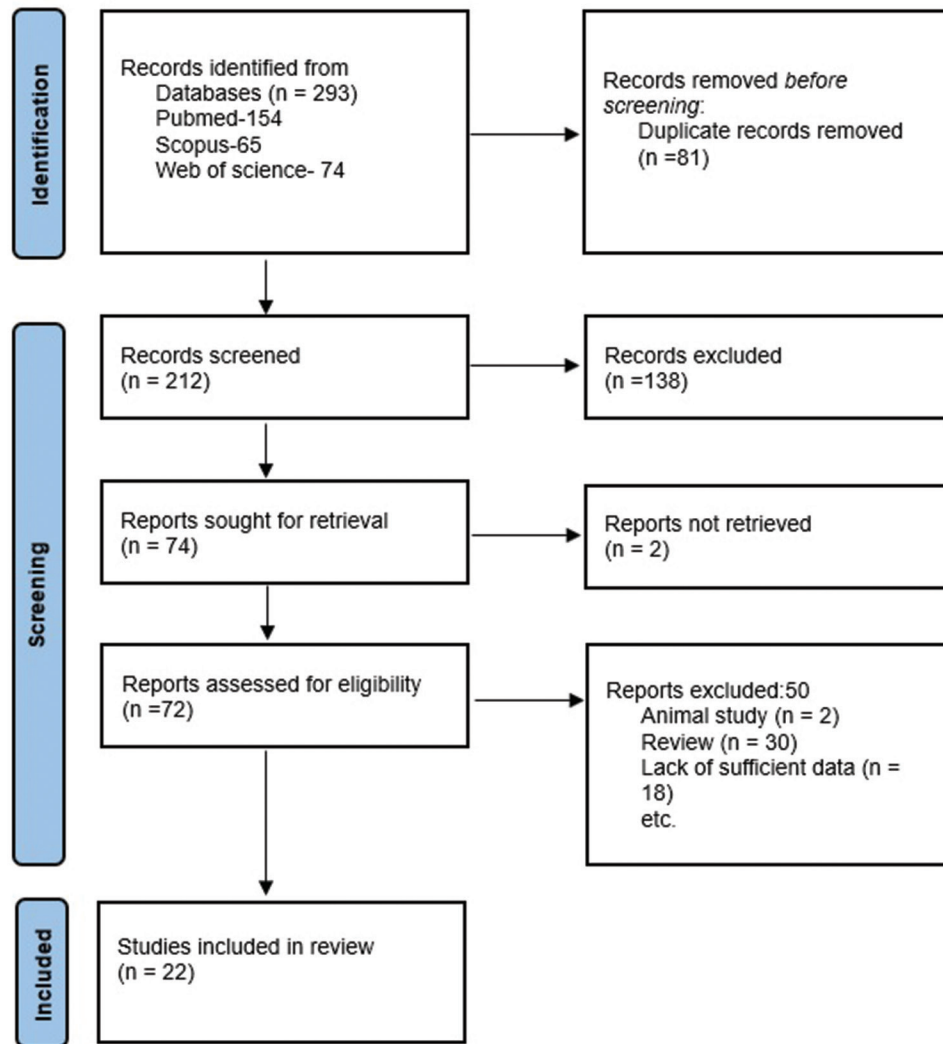


Figure 1: Prisma flow chart search strategy

articles were included in the study. Figure 1 illustrates the PRISMA flowchart summarizing the search strategy of the study.

Data collected

The systematic review encompasses 22 studies, collectively analyzing a total of 5301 patients. These studies extensively investigated the role of nearly 27 long non-coding RNAs (lncRNAs) in various biological conditions, using a methodology primarily focusing on PCR to analyze lncRNA expression in sample types such as plasma, serum, and PMBCs [Table 1].

Publication Year: Publications are spread across the years 2015 to 2023, with the distribution as follows: 2015 (1 publication, 4.55%), 2016 (3 publications, 13.64%), 2017 (4 publications, 18.18%), 2018 (2 publications, 9.09%), 2019 (4 publications, 18.18%), 2020 (2 publications, 9.09%), 2021 (3 publications, 13.64%), and 2023 (3 publications, 13.64%). This

highlights a relatively even spread over the years, with peaks in 2017 and 2019 [Figure 3].

Study Types: Study types are categorized into case-control studies (13 studies, 59.09%), cohort studies (5 studies, 22.73%), and observational cross-sectional studies (4 studies, 18.18%), and the majority are case-control studies, indicating a preference for this research design [Figure 4].

Specimen: Specimens used in the studies include plasma (6 instances, 27.27%), blood (6 instances, 27.27%), PMBC (4 instances, 18.18%), serum (2 instances, 9.09%), plasma extracellular vesicles, plasma PMBC, plasma and heart tissue, and blood and PMBC (each 1 instance, 4.55%). Plasma and blood are the most commonly used specimens, reflecting their significance in medical research.

Methods: The methods employed are predominantly q RT-PCR (18 instances, 81.82%), with qPCR

Table 1: Data extracted from the included studies

Author	Year	Sample size	Specimen	Method	Study design	Lnrna	State	Sensitivity specificity
Yujia Yang ^[28]	2015	221 (187)	Plasma, extracellular vesicles	qPCR	Case-control study	COROMARKER, AC100865.1	Up	60.98 83.78
Yue Cai ^[21]	2016	50 (50)	Plasma, PMBC	q RT-PCR	Case-control study	OTTHUMT00000387022	Up	80 98
Yue Cai ^[26]	2016	211 (171)	PBMC	q RT-PCR	Cohort study	LncPPARδ ⁷	Up	55 80
Mingjiao Zhang ^[29]	2016	30 (102)	Serum	q RT-PCR	Case-control study	uc022bqs. 1	Up	89 76.7
Qiong Yin ^[24]	2017	30 (30)	Plasma	q RT-PCR	Case-control study	GAS 5	Down	95 95
Xuejie Li ^[25]	2017	137 (115)	Blood	Qpcr	Cohort study	ENST00000512246.1 (referred to as Upperhand)	Up	73.7 65.2
Jialong Zhu ^[23]	2017	28 (28)	Plasma & heart tissue	q RT-PCR	Case-control study	NOVLNC6	Down	90 90
Zhen Zhang ^[20]	2017	300 (180)	Plasma	q RT-PCR	Observational cross-sectional	H19 & LIPCAR	Up	53.6 73 72.2 62.3
Niloofer Avazpour ^[10]	2018	20 (20)	PBMC	q RT-PCR	Case-control study	HOTAIR	Up	95 85
Lin Li ^[10]	2018	412 (295)	PMBC	q RT-PCR	Observational cross-sectional	ENST00000444488.1 and uc010yfd. 1	Up	70 80
Sara Bitarafan ^[13]	2019	50 (50)	Blood	qPCR	Case-control study	H19	Up	56 44
Jiao Huang ^[11]	2019	550 (550)	Blood	q RT-PCR	Case-control study	H19	Up	86.7 91.8
Xiong ^[12]	2019	30 (30)	Serum	q RT-PCR	Case-control study	H19	Up	93.67 93.67
Yuan Zhang ^[19]	2019	30 (24)	Blood	q RT-PCR	Case-control study	KCNQ1OT1, HIF1A-AS2 and APOA1-AS	Up	100 60 55 100 100 80
Ping Li ^[30]	2020	187 (150)	Blood	q RT-PCR	Observational cross-sectional	ENST00000416361.	Up	79.02
Caihong Liang ^[22]	2020	111 (68)	Plasma	q RT-PCR	Cohort study	Exosomal SOCS2-AS1	Down	71.4 63.4
Fanqin Lv ^[18]	2021	149 (90)	Plasma	q RT-PCR	Cohort study	MALAT	Up	80 90
Chao Liu ^[31]	2021	30 (30)	Blood and pmbc	q RT-PCR	Cohort study	AC010082.1 and AC011443.1	Up	63.3 60
Hamide Saygili ^[16]	2021	45 (45)	Blood	q RT-PCR	Case-control study	MEG3 MIAT	Up Down	62.2 62.2 68.9 68.9
Teodora Barbalata ^[5]	2023	23 (33)	Plasma	TAQMAN PCR	Observational cross sectional	LIPCAR and MALAT1	Up	80 90

Contd...

Table 1: Contd...

Author	Year	Sample size	Specimen	Method	Study design	Lncrna	State	Sensitivity specificity
Meili Zheng ^[17]	2023	100 (48)	Plasma	q RT-PCR	Case control study	Exosomal lncRNA ENST00000424615.2 and ENST00000560769.1	Up	65 64.58 72 72.92
Shu He ^[27]	2023	270 (47)	PBMC	q RT-PCR	Case control study	PDXDC1-AS1 and SFI1-AS1	Up	67.78 68.09

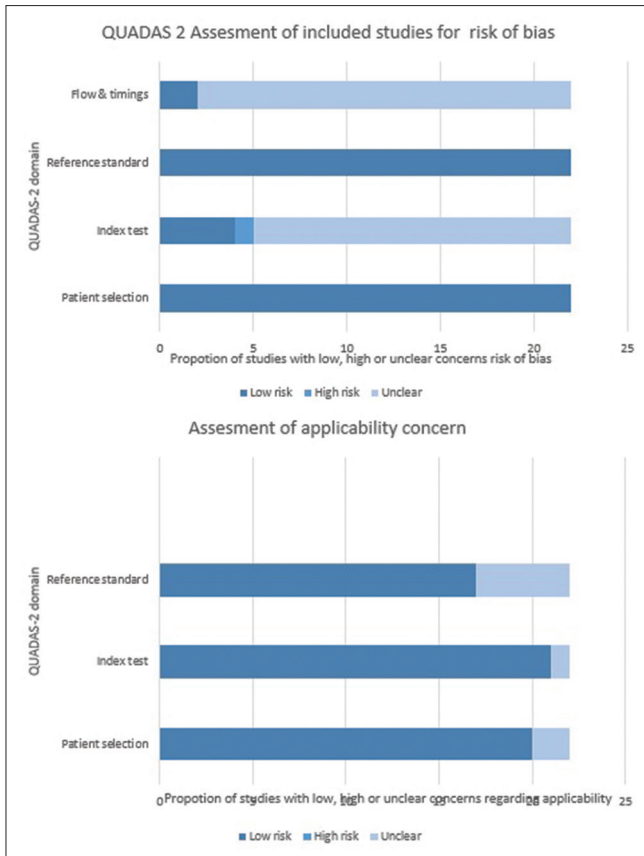


Figure 2: QUDAS 2 assessment graph

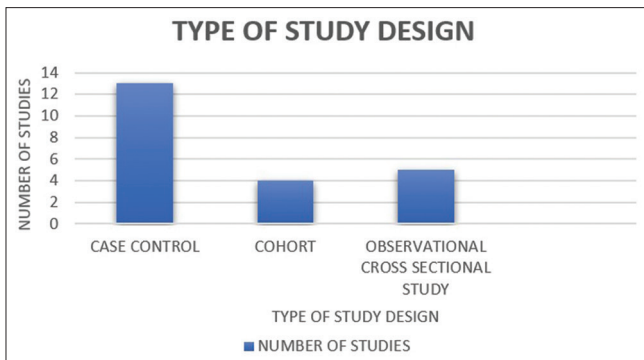


Figure 4: Study types

(3 instances, 13.64%) and TAQMAN PCR (1 instance, 4.55%) also utilized. The dominance of q RT-PCR

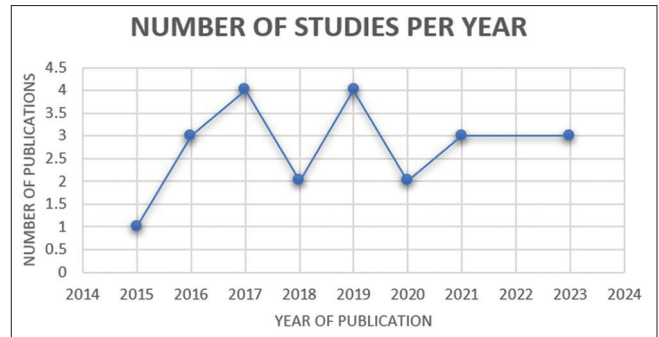


Figure 3: Number of publications per year

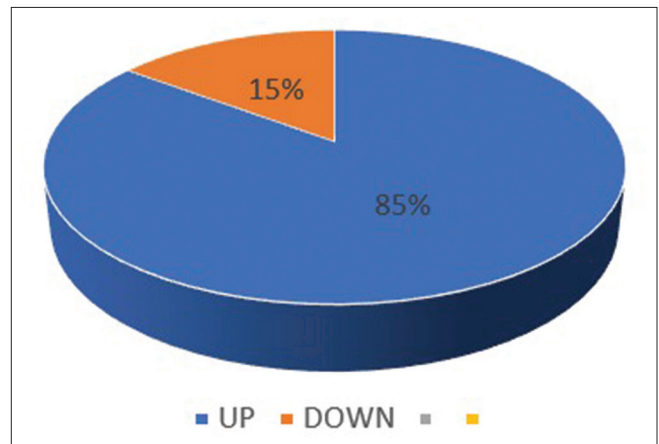


Figure 5: State of lncRNA

underscores its importance in contemporary research methodologies.

State of lncRNAs: Regarding the state of the lncRNAs, the majority reported an ‘Up’ state (23 instances, 85.18%), with a smaller number reporting a ‘Down’ state (4 instances, 14.81%). This suggests a focus that most of the lncRNAs are increased in the CAD patients [Figure 5].

Sensitivity and Specificity: The average sensitivity across all listed long non-coding RNAs (lncRNAs) is 74.89%. The average specificity across the lncRNAs is 78.29%. Among the lncRNAs analyzed, the one with the highest sensitivity is “KCNQ1OT1, HIF1A-AS2, and APOA1-AS,” achieving a remarkable 100% sensitivity

and 80% specificity. The lncRNA with the highest specificity is OTTHUMT00000387022, showcasing a specificity of 98% and a sensitivity of 80%. The lncRNA with the highest sensitivity and specificity is GAS 5, showing both sensitivity and specificity at 95%. This suggests an exceptional potential for these lncRNAs in clinical diagnostics.

On the other hand, the lncRNA with the lowest sensitivity is LncPPAR δ , with a sensitivity of 55% and a specificity of 80%. While H19 shows the lowest specificity at 44%, its sensitivity is 56%, indicating a different lncRNA from the one with the lowest sensitivity. For H19, sensitivity and specificity varied across studies, with one study showing 56% sensitivity and 44% specificity, while another reported 86.7% sensitivity and 91.8% specificity.

DISCUSSION

The systematic review meticulously explores the diagnostic accuracy of long non-coding RNAs (lncRNAs) in coronary artery disease (CAD), with a total of 23 lncRNAs upregulated and 4 lncRNAs downregulated. The variability in the diagnostic performance of lncRNAs can be attributed to differences in study designs, sample sizes, and analytical methods, necessitating further investigations to standardize lncRNA analysis for clinical applications.

The findings, which highlight a diverse array of lncRNAs like HOTAIR, H19, LIPCAR, and MALAT, among others, underscore the complexity and multifaceted roles of lncRNAs in CAD.^[5,10,12,13] These results resonate with the literature, which has increasingly reported the involvement of lncRNAs in various biological and pathological processes, including epigenetic regulation, cell signaling, and transcriptional or post-transcriptional regulation, thereby affirming their diagnostic and therapeutic potential in CAD.^[5,14-18]

The present systematic review identified lncRNAs with high sensitivity and specificity, such as KCNQ1OT1, HIF1A-AS2, and APOA1-AS, corroborating the precision of lncRNAs in reflecting the *in vivo* environment and their stability in human biofluids.^[19] The sensitivity and specificity of these lncRNAs are particularly compelling, with some achieving up to 100% sensitivity and 98% specificity. Such diagnostic precision is crucial for the early identification of CAD, enabling timely intervention and potentially improving patient outcomes. However, the sensitivity and specificity of H19 lncRNA varied across studies, with one study showing 56% sensitivity and 44% specificity, while another reported 86.7% sensitivity and 91.8% specificity, indicating the need for cautious interpretation of individual lncRNA performance.^[12,13,20]

Attributes including high sensitivity advocate their use as reliable biomarkers for CAD. However, the variance in sensitivity and specificity among different lncRNAs, as noted in the review, suggests a nuanced understanding of their roles and the necessity for further validation in larger, diverse cohorts to find their utility in clinical practice.

The predominance of studies employing qRT-PCR for lncRNA analysis, as revealed in the review, highlights the technical reliability this method has in lncRNA detection in genetic research.^[11,21-23] However, this uniform approach also indicates a potential shortcoming in the range of methods available for detection, underscoring the importance of delving into emerging technologies like next-generation sequencing (NGS) and microarrays. The evolution of novel, more sophisticated emerging technologies may offer opportunities to uncover additional lncRNAs and elucidate their mechanisms of action, thereby enhancing the diagnoses of CAD.

The systematic review also sheds light on the significant variability in the expression levels of lncRNAs among CAD patients, with a majority showing an 'Up' state.^[5,10,11,14,19,21,22,24-27] This is indicative of the potential regulatory roles these lncRNAs may play in the disease's pathogenesis, possibly through mechanisms like modulation of gene expression, influencing inflammatory pathways, or affecting lipid metabolism.^[10,11,16,17,21,25,28-31] Understanding these mechanisms in detail could pave the way for not only diagnostic markers but also therapeutic targets.

While the review presents a promising outlook on the use of lncRNAs as diagnostic biomarkers for CAD, it also highlights the necessity for further research. The variability in sensitivity and specificity among the studied lncRNAs indicates the complexity of CAD's molecular underpinnings and the need for a nuanced approach to biomarker selection and application. Additionally, the review points to the importance of standardizing study designs and methodologies to enhance the comparability and reproducibility of future research.

CONCLUSION

The identification of 23 upregulated and 4 downregulated lncRNAs in over 5,000 patients offers valuable insights for early diagnosis and potential therapeutic intervention. This elucidates the significant potential of lncRNAs as diagnostic tools in CAD, with specific lncRNAs exhibiting high diagnostic accuracy. These findings pave the way for further investigations into the utility of lncRNAs in clinical practice, suggesting a promising future for their role in the early detection and personalized management of CAD. To conclude,

the integration of lncRNA-based diagnostics could significantly impact the prognosis of CAD, offering a new horizon in cardiovascular medicine.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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