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# Role of long non-coding RNAs and circular RNAs in kawasaki disease: a systematic review

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## Abstract

**Objective** Previous research has identified the significant roles of non-coding RNAs (ncRNAs) in Kawasaki disease (KD). This systematic review aims to elucidate the involvement and significance of long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in the pathogenesis and progression of KD.

**Study design** A systematic search was conducted across four databases (PubMed, Embase, Scopus, and Web of Science) up to June 19, 2023, without year restrictions. The risk of bias was assessed using the Newcastle-Ottawa Scale.

**Results** This review included 9 studies encompassing a total of 1894 individuals diagnosed with KD. Seven lncRNAs—Slco4a1, SOCS2-AS1, SRA, HCG22, MHRT, XLOC_006277, and HSD11B1-AS1—were found to be associated with KD, including polymorphisms such as lncRNA rs1814343 C>T and AC008392.1 rs7248320. Additionally, four circRNAs—circRNA-3302, circ7632, circANRIL, and hsa_circ_0123996—were associated with KD.

**Conclusions** Both linear lncRNAs and circRNAs play critical roles in unraveling the mechanisms underlying KD, contributing to biomarker identification and potential therapeutic advances.

**Keywords** Non-coding RNA, Long non-coding RNA, Circular RNA, Kawasaki disease, Systematic review

## Introduction

Kawasaki Disease (KD) is a systemic vasculitis predominantly affecting children under five years of age, although it can also present in older children and adolescents [1]. KD has a notable predilection for the coronary arteries, with coronary artery lesions (CAL) representing its most serious complication. KD is, therefore, the leading cause of acquired heart disease among children in developed countries. Standard treatment with intravenous immunoglobulin (IVIG) significantly decreases the incidence of CAL from 25 to 30% to less than 3–5%. However, approximately 20% of patients exhibit resistance to IVIG, which elevates their risk of CAL development [1, 2]. The incidence of KD varies substantially by ethnicity, with East Asia—particularly Japan and Korea—demonstrating the highest rates, at nearly 265 cases per 100,000

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children under five years of age annually, compared to approximately 20 cases per 100,000 in the United States and European countries [1].

Despite extensive research indicating that systemic inflammation and immune activation are central to KD pathogenesis, its precise etiology remains largely unclear [3]. While KD is not generally classified as a genetic disorder, emerging evidence suggests that specific genetic factors may contribute to susceptibility [3].

Recent advancements in high-throughput sequencing technologies have shown regulatory noncoding RNAs (ncRNAs), such as long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs) are implicated in KD [4]. Nevertheless, the specific functions of ncRNAs in KD remain poorly understood. Consequently, investigating the regulatory roles of ncRNAs in KD is of great importance, as it may reveal novel and effective therapeutic targets for managing the disease. lncRNAs, which are defined by their length of over 200 nucleotides, play crucial roles in numerous biological processes, including transcription, splicing, translation, protein localization, cellular structure integrity, imprinting, cell cycle regulation, and apoptosis, among others [5–7]. Their tissue- and cell-type-specific expression patterns indicate significant roles in developmental processes [8, 9]. Although research on the association between lncRNAs and KD is limited, evidence has emerged linking KD with alterations in lncRNA expression [4].

Circular RNAs (circRNAs) represent another class of ncRNAs that, unlike linear RNAs, possess a closed-loop structure lacking 5′–3′ polarities. Key functions of circRNAs include the inhibition of microRNA(miRNA) activity by acting as miRNA sponges, regulation of selective splicing or transcription, interaction with RNA-binding proteins, and serving as protein decoys [10, 11]. Their high stability makes circRNAs potential biomarkers for various diseases. While preliminary studies have begun to investigate the roles of circRNAs in KD, significant gaps remain in understanding their associations with KD pathogenesis. Recent findings suggest that altered serum levels of certain circRNAs are associated with the acute phase of KD and tend to normalize following a response to IVIG therapy [12].

This systematic review aims to provide a comprehensive review of the roles of lncRNAs and circRNAs in KD. By examining their potential functions and associated signaling pathways, we seek to enhance the understanding of KD pathogenesis and foster future research in this area.

## Methods

### Search strategy and study selection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13]. Four databases (PubMed, Embase, Web of Science, and Scopus) were searched systematically up to June 19, 2023, without any time restriction. The main search terms utilized were "long non-coding RNA*", "circular RNA*", and "Kawasaki disease*". Detailed search queries are provided in Supplementary Table 1. The protocol for this systematic review was registered in PROSPERO in September 2024 (registration code: CRD42024529490).

The inclusion criterion for this systematic review was the exploration of the expression or role of lncRNAs or circRNAs in patients with KD. Conference abstracts, protocols, review articles, animal model studies, and studies that didn't conduct experimental investigations but relied solely on bioinformatics analyses were excluded. Additionally, reference lists from eligible studies and relevant review articles were carefully examined to identify additional studies not retrieved in the initial database search. All records identified through the search were imported into an EndNote library, and duplicates were removed. Two independent reviewers (ZA and SHA) initially screened studies by title and abstract and conducted a thorough review of the full texts. In cases of disagreement, a third reviewer (MM) provided expertise to resolve discrepancies and finalize the study selection. Figure 1 provides an overview of the study identification and selection process.

### Quality assessment and data extraction

Two independent reviewers (ZA and SHA) extracted pre-specified data from the included studies, which encompassed: (1) article title, first author's name, publication year, country of publication, and study design; (2) study population and baseline demographic characteristics; (3) identified lncRNAs/circRNAs; (4) levels of lncRNA/circRNA expression; (5) target genes and effects of lncRNAs/circRNAs on their target genes; and (6) other principal findings. Any discrepancies were resolved through discussions between ZA and SHA, with a third author (MM) consulted when necessary.

A thorough quality evaluation of each included study was conducted by two independent reviewers (ZA and FSH), utilizing the Newcastle-Ottawa Scale (NOS), a validated method for assessing the quality of observational studies [14]. Disagreements were resolved by consulting a third reviewer (MM). The NOS assigns scores from 0 to 9, with studies scoring 6 or higher classified as high quality.

## Results

### Characteristics of the included studies

The initial search yielded 159 results across four databases: 82 from PubMed, 29 from Embase, 23 from Web of Science, and 25 from Scopus. Following the removal

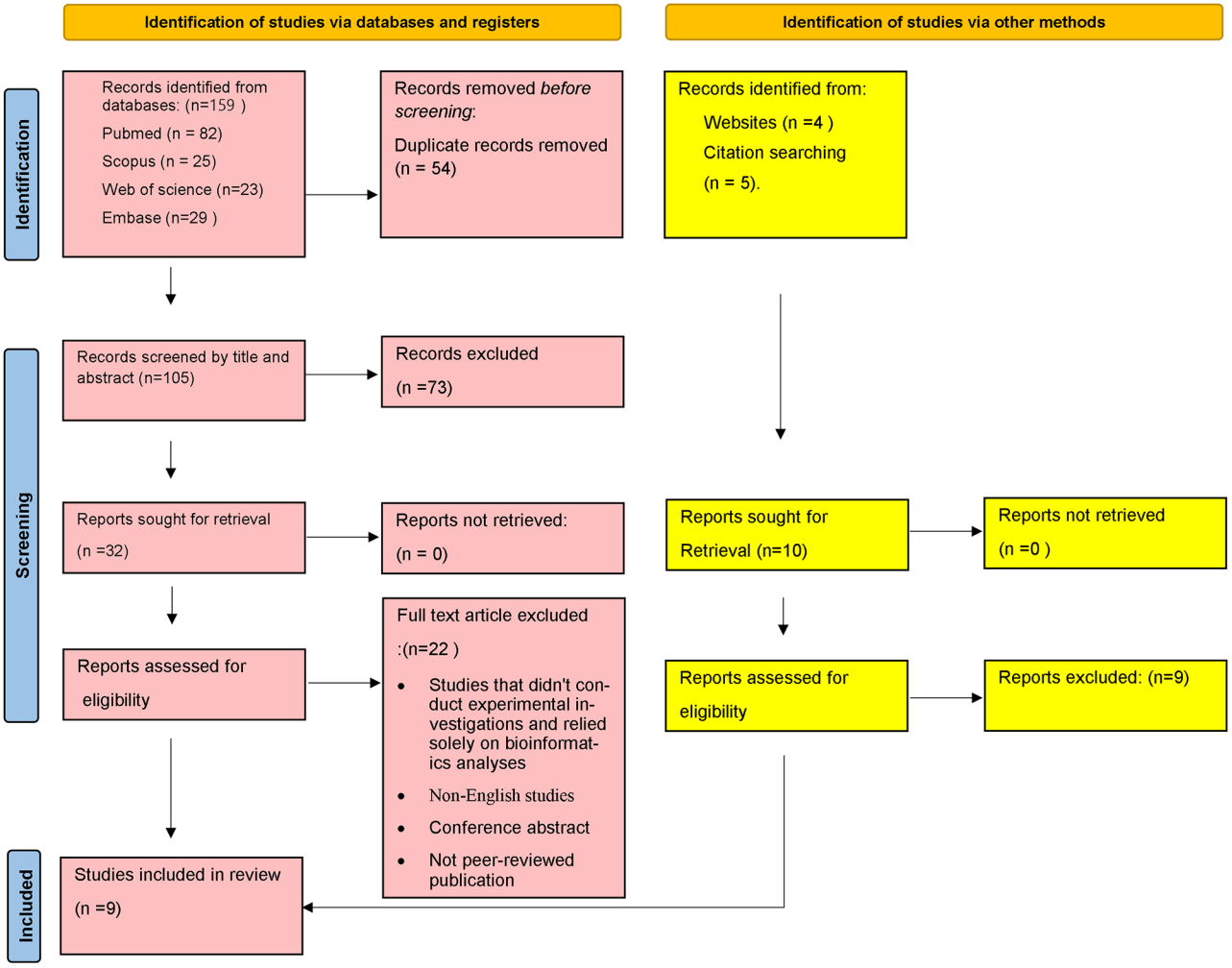


**Fig. 1** PRISMA flowchart

of duplicates ($n = 54$), 105 unique studies remained and were screened based on their titles and abstracts. This screening process led to the selection of 31 studies for comprehensive full-text evaluation. From these, 9 studies were ultimately selected for inclusion in this review. An additional search of websites and citations identified 10 further studies; however, none met the eligibility criteria. Consequently, a total of 9 studies were included in this review. Figure 1 illustrates the selection process and reasons for exclusion, while Table 1 provides an overview of the included studies, published from 2019 to 2023.

Analysis of the study distribution indicated that China had the highest representation with 8 studies, followed by Taiwan and Japan, each contributing one study. The combined study population consisted of 1894 individuals diagnosed with KD. Among the 10 studies included, 7 investigated the expression of lncRNAs, while the remaining 3 focused on circRNAs. Quality assessment using the NOS indicated that 7 of the 10 studies were of high quality (NOS > 6), with an average score of 6. Detailed NOS scoring is presented in Supplementary Table 2.

## LncRNAs

LncRNAs are RNA molecules over 200 nucleotides in length that lack protein-coding function. In this section, we focus exclusively on linear lncRNAs. To date, six lncRNAs have been associated with KD [15–20].

### *LncRNA Slco4a1*

LncRNA Slco4a1 was found to be significantly elevated in the serum of KD patients compared to healthy individuals and was also upregulated in human umbilical vein endothelial cells (HUVECs) treated with KD serum. Overexpression of lncRNA Slco4a1 enhanced the expression of inflammatory factors and increased apoptosis in HUVECs [15]. Additionally, lncRNA Slco4a1 functions as a molecular sponge for miR-335-5p, thereby negatively regulating its expression [15, 21]. POU5F1 was identified as a downstream target of miR-335-5p,

**Table 1** Characteristics of studies evaluating Non-coding RNAs(LncRNAs / circRNAs) in Kawasaki disease. (NOS: Newcastle-Ottawa scale. N/A: Not applicable)

| Type of non-coding RNA | Study | year | Country | Samples | Patients(*n*) | Phase of KD patients | Controls (*n*) | Non-coding RNAs | Level of expression | Target genes | Other finding | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Ko | 2019 | Taiwan | Whole blood | Total KD: 37 IVIG-sensitive: 30 IVIG-resistance: 7 CAA: 11 Without CAA:26 | - | - | XLOC-006277 | Upregulated | - | XLOC-006277 suppresses expresion of inflammatory markers MMP8 and MMP9. XLOC-006277 is increased in coronary artery aneurysm patients | 4 |
| | Zhao | 2020 | China | Serum | KD:48 | Samples collected in acute phase | HC:30 | SOCS2-AS1 | Upregulated | | SOCS2-AS1 promotes the proliferation of HUVECs in KD, while simultaneously facilitating apoptosis in HUVECs by upregulating CUEDC2 through the sponging of miR-324-5p | 5 |
| LncRNAs | Zhou | 2021 | China | Serum | KD: 40 | Samples collected in both acute and subacute stage of all patients | HC: 40 | • Steroid receptor RNA activator(SRA) • Human leukocyte antigen complex group 22 (HCG22) • Human leukocyte antigen complex group 22 (HCG22 | A ll upregulated | - | MHRT was upregulated following IVIG therapy compared to before receiving IVIG | 6 |
| | Hao | 2022 | China | Serum | KD: 32 | 21 patients were in the acute KD stage and 11 were in the recovery stage | HC:25 | lncRNA Slco4a1 | Upregulated | | lncRNA Slco4a1 by sponging miR-335-5p downregulaing its expression | 5 |
| | Okabe | 2022 | Japan | Monocytes of the peripheral blood | KD: 50 | Samples collected in both acute and subacute stage of all patients | Total control:50 Febrile patients without KD: 25 HC: 25 | HSD11B1-AS1 | Upregulated | G0S2 | G0S2 increases in response to inflammation in THP monocytes | 7 |
| | Chen | 2023 | China | Whole blood | Total KD: 1625 CAL: 583 NCAL: 1042 | - | 1000 | Rs 1,814,343 C > T polymorphism | Upregulated in male patients | - | Higher risk of KD in the TT genotype compared to the CC/CT genotype | 7 |

**Table 1** (continued)

| Type of non-coding RNA | Study | year | Country | Samples | Patients(*n*) | Phase of KD patients | Controls (*n*) | Non-coding RNAs | Level of expression | Target genes | Other finding | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CircRNAs | Wu | 2019 | China | Serum | KD: 56 | Samples collected in both acute and subacute stage of all patients | HC: 56 | • has-circ-0123996<br>• CircANRIL | • Upregulated<br>• Downregulated | - | | 6 |
| | Ni | 2022 | China | Serum | KD: 6 | Samples collected in both acute and subacute stage of all patients | HC: 6 | circRNA-3302 | Upregulated | KIT | circRNA-3302 can lead to induction of endothelial-to-mesenchymal transition (Endo-MT) by sponging miR-135b-5p | 7 |
| | Qiu | 2023 | China | Serum | KD: 6 | Samples collected in acute phase | HC: 6 | circ7632 | Upregulated | - | circ7632 increases the expression of vimentin, alpha-SMA, and IL-33 which correlates with Endo-MT along with decreasing ZO-1 and cell proliferation | 6 |

with overexpression of miR-335-5p enhancing POU5F1 expression. Furthermore, miR-335-5p overexpression was observed to suppress inflammatory factor expression and apoptosis in HUVECs. Additional investigation indicated that lncRNA Slco4a1 may activate the mitogen-activated protein kinase (MAPK) signaling pathway [15].

#### *LncRNA rs1814343 C > T polymorphism*

Genotype analysis of 1,625 KD patients found no significant association between the rs1814343 C > T polymorphism and overall susceptibility to KD. However, male patients carrying the rs1814343 C > T polymorphism exhibited an increased risk of developing coronary artery lesions (CAL). Specifically, the TT genotype was associated with a higher incidence of CAL in male KD patients compared to those with the CC or CT genotypes [16].

#### *LncRNA HSD11B1-AS1*

Transcriptome and gene ontology analyses revealed that the G0/G1 switch gene 2 (G0S2) and its antisense lncRNA, HSD11B1-AS1, were upregulated during the acute phase of KD, with expression levels significantly higher than those observed in the subacute phase. These elevated expression levels decreased rapidly following IVIG therapy. To further investigate the roles of HSD11B1-AS1 and G0S2 in KD-related inflammation, THP-1 monocytes were stimulated with Toll-like receptor (TLR) ligands, which led to increased expression of both tumor necrosis factor- α (TNF-α) and HSD11B1-AS1. This finding suggests that HSD11B1-AS1 and G0S2 may contribute to the regulation of innate immune responses in KD [17].

#### *LncRNA AC008392.1 rs7248320 polymorphism*

A case-control study involving 559 KD patients and 1,055 non-KD controls from a Han Chinese population identified the rs7248320 variant of lncRNA AC008392.1, located upstream of the Caspase-associated recruitment domain 8 (CARD8) gene on chromosome 9, as a significant factor influencing KD susceptibility. Specifically, the study found that the rs7248320 G allele was associated with a reduced risk of KD, particularly in male children, compared to the A allele. The protective effect of AC008392.1/rs7248320 may be attributed to its impact on CARD8 expression. CARD8 plays an immunosuppressive role by inhibiting the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, which, when activated, can contribute to coronary endothelial damage in KD and is a key factor in the immunopathogenesis of KD vasculitis. However, this polymorphism was not found to be associated with the development of coronary artery lesions in KD patients [18].

#### *XLOC_006277*

XLOC_006277, a long non-coding RNA transcript, was found to be highly expressed during the acute phase of KD, with expression levels decreasing during the convalescent phase. The expression of XLOC_006277 was significantly higher in KD patients with coronary artery aneurysms compared to those without. Although expression levels were slightly elevated in IVIG-resistant patients compared to IVIG-sensitive patients, this difference did not reach statistical significance. Inhibition of XLOC_006277 expression led to a reduction in the mRNA levels of inflammatory markers Matrix metalloproteinase-8 (MMP-8) and MMP-9, suggesting that this lncRNA may play a role in the inflammatory pathogenesis of KD and contribute to the development of coronary complications [19].

#### *SRA, HCG22, and MHRT*

In the acute phase of KD, serum levels of the lncRNAs steroid receptor RNA activator (SRA) and human leukocyte antigen complex group 22 (HCG22) were elevated compared to healthy controls. SRA acts as a coactivator for nuclear receptors, including glucocorticoid, androgen, estrogen, and progesterone receptors, playing a crucial role in steroidogenesis and myogenesis. This lncRNA has been implicated in pathological conditions such as insulin resistance, obesity, cardiomyopathy, and various malignancies. Additionally, the myosin heavy chain-associated RNA transcript (MHRT) was upregulated following IVIG therapy. Notably, the levels of MHRT in KD patients after IVIG therapy were even higher than those observed in healthy controls [22].

#### *LncRNA SOCS2-AS1*

lncRNA SOCS2 antisense RNA 1 (SOCS2-AS1) is significantly elevated in the serum of KD patients compared to healthy controls. Furthermore, SOCS2-AS1 expression was higher in KD patients with coronary aneurysms than in those without. SOCS2-AS1 promotes the proliferation of HUVECs in KD, while simultaneously facilitating apoptosis in HUVECs by upregulating CUEDC2 through the sponging of miR-324-5p [20].

### Circular RNAs

Numerous studies indicate that circRNAs primarily function as miRNA sponges, sequestering miRNAs and thereby enhancing the regulation of downstream targets. As a type of competing endogenous RNA (ceRNA), circRNAs competitively bind to miRNA target genes, influencing miRNA-mediated gene regulation [23, 24]. Four circRNAs—circRNA-3302, circ7632, circANRIL, and hsa_circ_0123996—have been identified as relevant in KD [12, 25, 26].

#### *circRNA-3302*

In KD, the expression level of circRNA-3302 is significantly increased. Overexpression of circRNA-3302, through sponging miR-135b-5p, enhances KIT expression at the mRNA level. This upregulation of KIT expression subsequently promotes the endothelial-to-mesenchymal transition (EndMT), a process critical for vascular endothelial damage in KD. Additionally, silencing circRNA-3302 reduces KIT expression at both the mRNA and protein levels, thereby alleviating EndMT. These findings confirm the regulatory role of circRNA-3302 in KIT expression [25].

#### circ7632

CircRNA sequencing analysis has shown upregulation of circ7632 in an in vitro KD model. Qiu et al. reported that circ7632 expression is elevated in HUVECs treated with KD serum. Further investigation revealed that circ7632 overexpression is positively associated with EndMT through regulation of interleukin-33 (IL-33) expression. Conversely, downregulation of circ7632 leads to decreased IL-33 levels, mitigating EndMT [26].

#### *CircANRIL*

CircANRIL, a circular antisense non-coding RNA located near the INK4/ARF locus on chromosome 9p21.5, has been implicated in susceptibility to atherosclerotic cardiovascular disease. Studies indicate that serum circANRIL levels are lower in KD patients during the acute phase compared to healthy controls; however, these levels increase following IVIG therapy, marking the convalescent phase of the disease. Additionally, circANRIL expression in KD patients is negatively correlated with albumin, creatine kinase, and pre-albumin levels, and positively correlated with C-reactive protein levels [12].

#### *hsa_circ_0123996*

The expression of hsa_circ_0123996 is significantly elevated in KD patients during the acute phase compared to healthy individuals. After IVIG therapy, its expression remains stable. hsa_circ_0123996 levels exhibit positive correlations with total protein, albumin, sodium, uric acid, total cholesterol, high-density lipoprotein (HDL), CK-MB, and pre-albumin, while showing negative correlations with alanine aminotransferase (ALT) and CRP levels [12].

## Discussion

Recent advancements in high-throughput sequencing technologies have shown regulatory noncoding RNAs (ncRNAs) such as long noncoding RNA (lncRNA) and circular RNA (circRNA) are implicated in biomarker discovery and therapeutic advancements in KD [4]. Since the functions of ncRNAs in KD is not yet well

understood, investigating the regulatory roles of ncRNAs in KD is of great importance, as it may reveal novel and effective therapeutic targets for managing the disease. The review highlights four key lncRNAs and four circRNAs associated with KD, demonstrating significant involvement in various aspects of KD's inflammatory processes and coronary artery lesion (CAL) formation.

Epidemiological studies have shown a male predominance in KD incidence and CAL development [27–29]. Additionally, emerging evidence suggests that genetic factors may contribute to gender-specific differences in KD and its associated CAL susceptibility. In a genome-wide association study (GWAS) and subsequent replication study conducted in Korean and Japanese population, the was found that the single nucleotide polymorphism (SNP) p.His167Arg (rs1801274) in the FCGR2A gene was associated with KD susceptibility in males, but not in females, highlighting distinct genetic contributions to KD risk based on gender [30]. Another recent GWAS in the Korean population identified six male-specific loci (CPNE8, DLG2, FUNDC1, GABRQ NOS3, and PDE1C) and two female-specific loci (IL1RAPL1 and SMAD3) associated with susceptibility to coronary artery aneurysms in KD patients [31]. Similarly, the lncRNA rs1814343 C > T polymorphism was found to be significantly associated with increased CAL risk in male KD patients, emphasizing a sex-specific genetic influence on KD complications [16]. Another variant that influences KD susceptibility differentially by gender is the rs7248320 A > G polymorphism in lncRNA AC008392.1, located upstream of CARD8, where the G allele is associated with a reduced KD risk, especially in males [18].These findings aligns with previous research suggesting sex-based differences in KD susceptibility and associated complications.

lncRNA HSD11B1-AS1 and G0S2 levels increased during the acute phase of KD, but decreased after IVIG treatment, indicating their role in inflammation and their potential as disease activity markers [17]. The lncRNA HSD11B1-AS1 has also been implicated in cutaneous melanoma, where its overexpression inhibits tumor growth and dissemination, while low levels correlate with poor clinical outcomes and reduced survival [32].

Although studies on the roles of circRNAs in KD, alongside investigations of linear lncRNAs, have been initiated, the field of circRNA research in KD remains in its early stages, and the current body of knowledge is limited. Nevertheless, circRNAs have shown promise as potential biomarkers and therapeutic targets in KD. A circular isoform of antisense non-coding RNA in the INK4A locus (CircANRIL) which is located on chromosome 9p21is associated with the development of atherosclerotic cardiovascular disease [12]. CircANRIL exerts atheroprotective effects by promoting apoptosis and inhibiting cell proliferation in atherosclerotic plaques via impaired ribosome biogenesis and p53 activation [33]. CircANRIL also acts as a miR-622 sponge, where its silencing has anti-apoptotic and anti-inflammatory effects by positively regulating miR-622 and inhibiting the nuclear factor (NF)-κB pathway-622 and subsequently inhibiting nuclear factor (NF)-κB pathway [34]. In contrast to the atheroprotective effects of circANRIL, linear ANRIL has been found to exert proatherogenic effects [35]. Razeghian-Jahromi et al. [36] reported that hypertensive patients with coronary artery disease (CAD) have lower levels of circANRIL and a decreased circular/linear ANRIL ratio, alongside elevated levels of linear ANRIL, compared to hypertensive patients without CAD. These findings support a potential atheroprotective role for circANRIL. However, contrary to other studies suggesting an atheroprotective role for crcANRIL, song et al. [37] demonstrated elevated circANRIL expression could promote coronary atherosclerosis by exacerbating vascular endothelial inflammation and increasing serum levels of lipids. In KD patients, serum circANRIL levels are lower during the acute phase compared to controls, but increase following IVIG treatment [12]. Given the multifaceted functions of circANRIL, its role in coronary disease is not yet fully understood, warranting further research. Collectively, circular RNAs like circANRIL show potential as candidates for developing targeted treatments for coronary artery lesions in KD.

In this systematic review, we identified several lncRNAs and circRNAs associated with KD, highlighting their potential roles in disease pathogenesis Clinically, the upregulation of these ncRNAs highlights their potential as biomarkers for predicting disease severity, treatment response, and the risk of coronary artery complications in KD, which should be considered for the prompt therapeutic measurement to prevent consequent adverse outcomes. The modulation of inflammatory pathways by these molecules suggests that they not only reflect underlying pathophysiological changes but may also serve as therapeutic targets.

#### Strengths and limitations

This systematic review provides a comprehensive assessment of lncRNAs and circRNAs investigated in KD, with no time restrictions applied to the literature search. However, certain limitations exist. The study of lncRNAs and circRNAs in KD is an emerging field, resulting in limited data availability. Additionally, due to the small number of studies and study heterogeneity, we were unable to conduct a meta-analysis. Moreover, six out of nine included studies originated from China, raising concerns regarding the generalizability of findings across different ethnic groups. This limitation underscore the need for further research in more diverse studies to validate and expand

upon the clinical potential of ncRNAs in Kawasaki disease.

## Conclusion

By examining their potential functions and associated signaling pathways, this review aims to enhance understanding of KD pathogenesis and support future research directions. The systematic review underscores the intricate roles of lncRNAs and circRNAs in the pathogenesis and progression of KD, potentially paving the way for novel therapeutic strategies.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-025-01087-2.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

### Author contributions

Conceptualization: Zahra Amirsardari. Design, Literature Search, Study Selection, Screening, and Data Extraction: Zahra Amirsardari Alireza Shalviri, Mohammadmahdi Abbasi, Shana Ahadi, Aida Rezaee,. Writing-Original Draft Preparation: Zahra Amirsardari, Alireza Shalviri, Farnaz Shavandi, Reihaneh Alidousti, and Shana Ahadi. Writing-Review and Editing: Zahra Amirsardari and Mohammadmahdi Abbasi. Supervision: Malakootian and Mahdavi.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

All the authors agree with the publication of this systematic review.

### Competing interests

The authors declare no competing interests.

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