

lncRNA deregulation in childhood acute lymphoblastic leukemia: A systematic review

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Abstract. Childhood acute lymphoblastic leukemia (ALL), the most common pediatric cancer, is a heterogeneous disease comprised of multiple molecular subtypes with distinct somatic genetic alterations, which results in different outcomes for the patients. Accurate patient risk stratification through genetic markers could increase survival rates, but the identification of reliable biomarkers is needed, as 20-30% of B-ALL patients cannot be classified in the clinic with routine techniques and some patients classified as low-risk and good-responders to treatment will eventually relapse. Long non-coding RNAs (lncRNAs) can represent novel candidates with diagnostic, classification, prognosis, and treatment response potential. However, regarding childhood ALL, there is inconsistency in the data reported due to the lack of a consensus nomenclature for lncRNA naming and the methodology and designing applied for their study. Therefore, the aim of the article is to clarify the potential of lncRNAs as biomarkers in childhood ALL through a systematic review. From a revision of 23 manuscripts, it was found that *AWPPH* overexpression could represent a novel marker for ALL diagnosis, including both B and T immunophenotypes,

and 18 lncRNAs were specifically associated with B-cell ALL (B-ALL) patients. We identified subtype-specific signatures for *ETV6-RUNX1*, hyperdiploidy and *KMT2A* subtypes. These signatures hold promise as novel diagnostic markers and could refine the classification of patients.

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1. Introduction

Childhood acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and the leading cause of death among cancer patients under 20 years of age (1). Although ALL has been defined as a single disease, it is highly heterogeneous comprising multiple molecular subtypes with distinct somatic genetic alterations. At the immunophenotypic level, ALL is subclassified in two main groups: B-cell ALL (B-ALL), affecting 85% of patients, and T-cell ALL (T-ALL) (1). Among B-ALL, another 9 subtypes have been defined depending on the distinctive cytogenetic features associated with different clinical outcomes, according to the World Health Organization's 2016 classification (2). For instance, hyperdiploidy ALL, representing 25% of cases, is associated with favorable outcome (3). Chromosomal translocations are also common, with t(12;21) (*ETV6-RUNX1*) related with good prognosis, while t(9;22) (*BCR-ABL1*), or *KMT2A*-rearrangements are associated with poor outcomes (1). Cases of B-ALL lacking these abnormalities are considered as B-ALL Not Otherwise Specified (B-ALL-NOS) (2) and are classified in an intermediate risk group. We are still limited in our ability to stratify ALL subtypes, as 20-30% of childhood ALL cases currently cannot be subclassified clinically using standard cytology or

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molecular diagnostic techniques based on chromosomal aberrations (4) T-ALL subclassification is more ambiguous. The World Health Organization's classification only considers the early T-cell precursor ALL (ETP-ALL) subtype (2), which is characterized by worse prognosis and chemoresistance in comparison to non-ETP-ALL (5).

Gene expression analysis studies have shown that expression profiles can classify molecularly defined ALL subtypes (6,7). These studies have primarily focused on the analysis of protein-coding transcripts. Nevertheless, non-coding RNAs (ncRNAs), such as miRNAs, also display subtype-specific expression (8) and association with prognosis markers (9). Recently, attention has focused on long non-coding RNAs (lncRNAs), transcripts with a length >200 nucleotides that do not encode proteins (10). Large-scale profiling has identified thousands of lncRNAs expressed in different cell types and stages of development (11). The number of known human lncRNA transcripts is still evolving with more than 120,000 annotated lncRNAs in the LNCipedia repository (<http://lncipedia.org/>). They are implicated in many cellular processes, including the regulation of chromatin/DNA conformation and modification, transcriptional gene regulation, splicing, translation and degradation (11-13), by several mechanism of action, as shown in Fig. 1 [adapted from Morlando *et al* and Sweta *et al* (11,14)]. Their deregulation promotes tumor formation, progression and metastasis in many types of cancer (15), including hematologic malignancies (16,17). Regarding childhood ALL, several studies have analyzed the differential expression of lncRNAs as markers for diagnosis, subtype classification, prognosis, and treatment response. For instance, Garitano-Trojaola *et al* analyzed the expression of 7,419 lncRNAs in B/T-ALL patients and discovered 43 especially deregulated lncRNAs (18). Regarding prognosis, another group identified 57 and 124 lncRNAs related with early relapse and early death, respectively (19). Finally, lncRNA zinc finger antisense (ZFAS) was shown to be upregulated in drug-resistant patients, suggesting a possible role as a therapeutic target (20). Additionally, other studies have investigated how differential expression of lncRNAs affects leukemia progression. For instance, cancer susceptibility 15 (*CASC15*) was found to promote cellular survival and proliferation in *ETV6-RUNX1* ALL through the regulation of its adjacent gene SRY-Box transcription factor 4 (*SOX4*) (21). In T-ALL patients, *AWPPH* was observed to be upregulated and related with cell proliferation and apoptosis inhibition (22). Thus, lncRNAs have huge potential as biomarkers for patient diagnosis and stratification, as well as an involvement in disease pathogenesis, but reliable signatures are still lacking. Therefore, this article consists of a systematic review to clarify the existing information and propose lncRNA signatures for childhood ALL with clinical value.

2. Research methods

An exhaustive search to identify studies that examined lncRNA expression in childhood ALL in relation to diagnosis, subtype classification, prognosis and treatment response was performed on PubMed (<https://www.ncbi.nlm.nih.gov/>) and Scopus (<https://www.scopus.com/search/form.uri?display=basic#basic>) bibliographic databases (23). We used the key words 'Long non-coding RNA*' AND 'Acute

lymphoblastic leukemia' without data restrictions. The search was last updated in November 2020.

The inclusion criteria were as follows: the study was original, performed in pediatric patients with ALL and analyzed lncRNA expression in relation to diagnosis, classification, prognosis and treatment response. Articles were excluded if they analyzed a disease different from ALL, other non-coding RNAs different from lncRNAs, polymorphisms, genetic variants, and mutations. Moreover, articles analyzing cell lines, organisms other than humans or not published in English were excluded. The specificity of these strict criteria, which were based on previously published studies (24,25), allowed the identification of reliable signatures in childhood ALL. Two reviewers independently screened the abstracts and articles for eligible studies and extracted the information (JT and AGC). Discrepancies concerning eligibility were discussed for final decision. The references of the selected papers were then screened to search for additional matches. Duplicated articles were deleted using Jabref software Version 5.1. (<https://www.jabref.org>) (MIT License Copyright © 2003-2021).

For each included article, information concerning the year of publication, number of patients and controls, type of material (bone marrow, blood), classification by subtype, ethnicity, quantification method and analyzed parameters were collected. Then, the patient age was analyzed. Studies which did not provide enough information about age or if they studied an adult population were excluded. Articles were evaluated according to the following ratings (modified from the Oxford Centre for Evidence-based Medicine for ratings of individual studies): i) properly powered and conducted randomized clinical trial, systematic review with meta-analysis: 1; well-designed controlled trial without randomization, prospective comparative cohort trial: 2; case-control studies, retrospective cohort study: 3; case series with or without intervention, cross-sectional study: 4; opinion of respected authorities and case reports: 5.

Articles were classified in four categories depending on the parameter analyzed: Diagnosis (cases vs. controls), subtype classification (specific subtype vs. other subtypes), prognosis (patients with good prognostic markers vs. patients with poor prognostic markers), and treatment response (good drug responders vs. bad drug responders). We included in our review all lncRNAs studied by quantitative reverse transcription polymerase chain reaction (RT-qPCR) which were differentially expressed. When sequencing or array expression was performed, all lncRNA information provided in the article or supplemental material was recorded. In order to unify lncRNA nomenclature, Ensembl codes from Ensembl GRCh38.p13 (<https://www.ensembl.org/index.html>) and LNCipedia version 5.2 (<https://lncipedia.org/>) were used when the annotation was available. The systematic review was performed following the PRISMA guidelines (26).

3. Results

A total of 38 and 65 articles were found in PubMed and Scopus databases, respectively. After removing duplicates (n=36) using Jabref software, 67 articles were included for screening (Fig. 2). First, all abstracts were reviewed to identify potentially eligible articles and 36 articles were excluded for not complying with the inclusion criteria, while 31 remained. After checking the

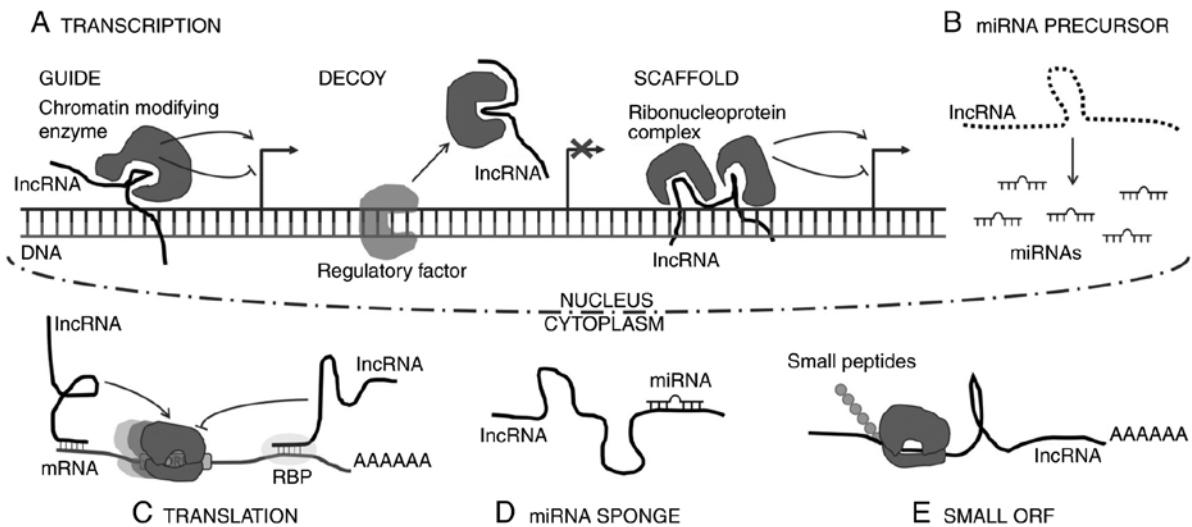


Figure 1. Functions and mechanisms of action of lncRNAs (A) Transcription regulation: guiding chromatin modifying enzymes and changing the conformation of DNA (guide lncRNAs); removing regulatory factors bounded to the DNA (decoy lncRNAs); promoting formation of ribonucleoprotein complexes (scaffold lncRNAs). (B) Serve as primary miRNA precursors, which are later processed to mature miRNAs. (C) mRNA translation regulation. (D) Endogenous competitor acting as miRNA sponges. (E) A small number of lncRNAs can be translated into active small peptides. lncRNA, long non-coding RNA; miRNA, microRNA; RBP, RNA binding protein; ORF, open reading frame.

references, one additional article was included. Full lecture of these 32 articles was performed and 23 articles with lncRNA expression data in pediatric patients were included in the review. Among these 23 articles, 9 were incorporated in the diagnosis study group, 12 in the classification category, 3 were considered for prognosis and 5 for treatment response. In some articles, more than one parameter was analyzed and therefore it was counted in each of them, being the total sum of the items of all parameters greater than 23. The search and study selection process are shown in Fig. 2 and a detailed description of the 23 articles (18-22,27-44) is included in Table I.

In global, the expression levels of 1,159 lncRNAs were studied in 9 articles analyzing diagnosis (patient samples vs. controls); 3,377 lncRNAs in 12 articles related with classification (subtype specific vs. other subtype); 1,123 lncRNAs in three articles studying prognosis (patients with good prognosis vs. patients with bad prognosis); and 6 lncRNAs in 5 articles related with treatment response (responders vs. no responders) (Fig. 2). We found that many lncRNAs were the same among studies but presented different expression patterns depending on the analyzed population. Nevertheless, there were some lncRNAs for which the expression patterns were consistent among different populations, quantification methods or subgroups. Due to the low number of articles available for each parameter, we established a signature with those lncRNAs with the same expression pattern among populations and supported by at least two different studies.

lncRNAs as biomarkers for diagnosis in childhood ALL. A total of 19 deregulated lncRNAs were selected for the diagnosis signature. Among these, *AWPPH* (also termed microRNA-4435-2HG) was upregulated in both B-ALL and T-ALL. Focusing on B-ALL, a signature of three upregulated and 15 downregulated lncRNAs was identified (22,27,33,37) (Table II). A complete list of all deregulated lncRNAs (18,22,27,29,33,37,39,43,44) is displayed in Table SI.

lncRNAs as biomarkers for classification among subtypes in childhood ALL. Regarding classification, 12 lncRNAs were selected for specific subtype signatures. For instance, the *ETV6-RUNX1* subtype was characterized with 9 upregulated and 1 downregulated lncRNA. The hyperdiploidy subtype showed *LINC00870* upregulation and *KMT2A* displayed *BALR-2* upregulation (30,32,33,35,37) (Table III).

Due to the limited articles analyzing the subtypes including *TCF3-PBX1*, *BCR-ABL1*, hypodiploidy, *DUX4*, *BRC-ABL1* like, *NOTCH1*⁺, *TALR*, *TLX1/TLX3* and *HOXA*, it was not possible to define a signature for each subtype. A complete list of all deregulated lncRNAs (21,28,30-33,35-37,38,41,42) is displayed in Table SII.

lncRNAs as biomarkers for prognosis in childhood ALL. We identified three articles investigating the expression levels of 1,123 lncRNAs in relation to different markers of prognosis. However, no study showed differential expression in more than one article (Table SIII) (19,33,36). The lncRNA *AWPPH*, upregulated in both B-ALL and T-ALL, was also found upregulated in early relapse patients and was associated with death in B-ALL patients (19).

lncRNAs as biomarkers for treatment response in pediatric ALL. We identified 6 lncRNAs associated with treatment response in 5 studies, but no one showed differential expression in more than one article (29,33,34,40,45) (Table SIV). Only *BALR-2* which was upregulated in *KMT2A*-rearranged subtype was related with poor prognosis and prednisolone treatment response (33).

4. Discussion

In this systematic review, we performed a deep analysis of the current literature in relation to the potential role of long non-coding RNAs (lncRNAs) as biomarkers for diagnosis,

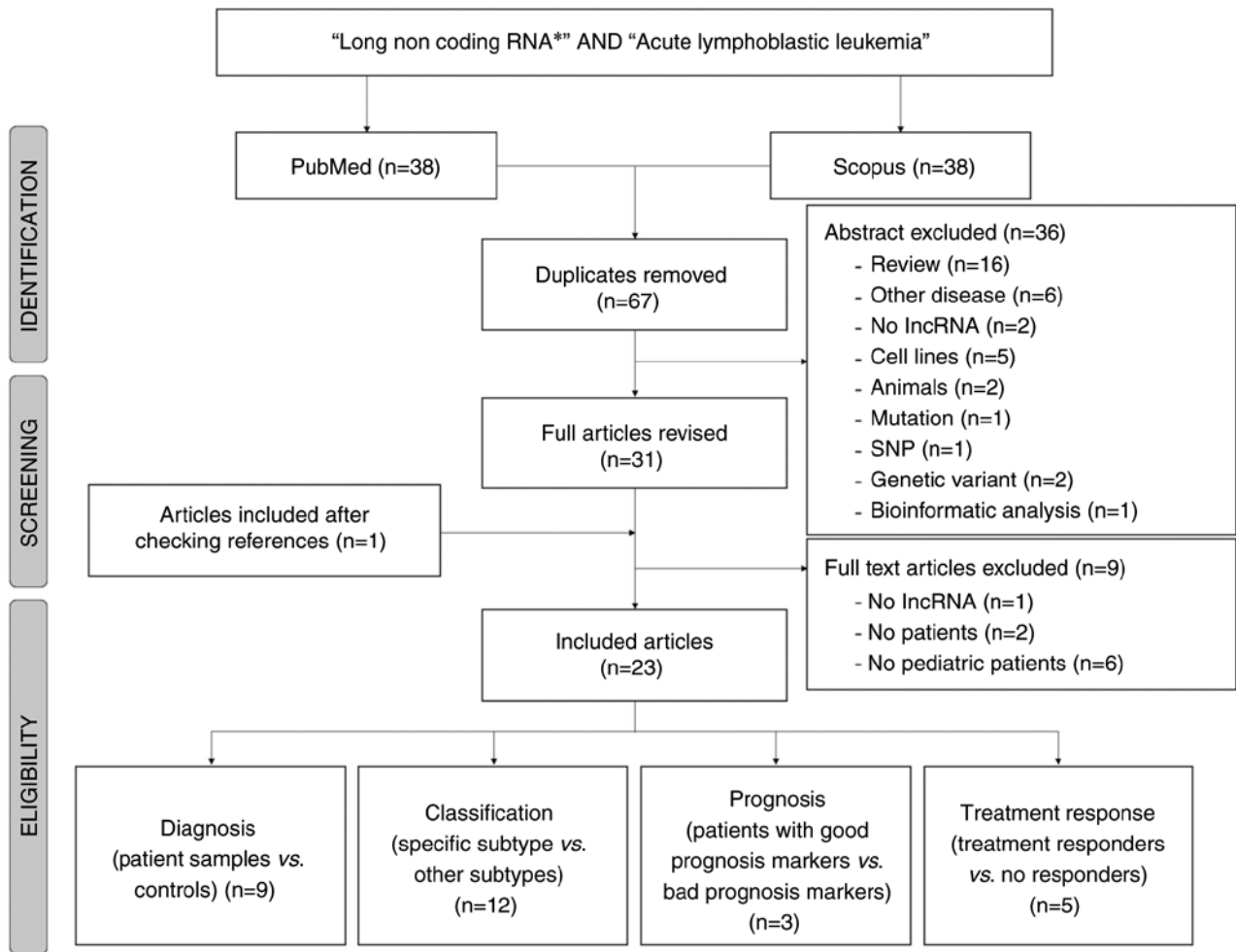


Figure 2. Study selection flow diagram. lncRNA, long non-coding RNA.

subtype classification, prognosis, and treatment response in patients with childhood acute lymphoblastic leukemia (ALL). We found several signatures for these categories defined by a total of 31 lncRNAs extracted from the 23 articles included in the review. The detection methods for the lncRNAs were addressed carefully in order to obtain comparable results (Table I). However, it must be considered that many of these lncRNAs are novel transcripts, thus the information about their function in cancer progression, especially in ALL, is still very scarce.

The signature for ALL diagnosis was formed by the lncRNA *AWPPH* (*MIR4435-1HG*) which was upregulated in both B-cell ALL (B-ALL) (37) and T-cell ALL (T-ALL) patients (22). In the latter, *AWPPH* was involved in the development of the disease through the interaction with the *ROCK2* oncogene. The authors showed that *AWPPH* overexpression increased the expression of *ROCK2* at the mRNA and protein level and vice versa. They also observed that the overexpression of either *AWPPH* or *ROCK2* promoted proliferation and inhibited apoptosis in T-ALL cell lines (22). In addition, *AWPPH* upregulation was found to be a prognostic marker for early relapse and early death in B-ALL, as well (19). Interestingly, *AWPPH* was also found deregulated in other cancers, such as hepatocellular carcinoma or colorectal adenocarcinoma (45,46). All the above suggest that *AWPPH* could act as an oncogene in childhood ALL.

Specifically, in the B-ALL subtype, the diagnostic signature included 3 upregulated and 15 downregulated lncRNAs. Notably, among the upregulated ones we found *TPTEPI*, which was reported downregulated in acute myeloid leukemia (AML) (47). The fact that *TPTEPI* shows different expression pattern in ALL and AML makes it an interesting marker for differential diagnosis, especially for those acute leukemias of ambiguous lineage difficult to identify as lymphoid or myeloid, since a proper classification is critical to determine the correct treatment. Another lncRNA upregulated in B-ALL was *TEX4I*, which was also found highly expressed in the lymph nodes of oral mucosal, and hepatocellular carcinoma (48,49). Finally, *LINC00958* was also observed upregulated in various types of cancer, such as hepatocellular carcinoma, bladder cancer and cervical cancer. In these tumors, *LINC00958* could act sponging certain miRNAs and thus, positively regulate the expression of their target genes at the protein levels, accelerating cancer progression, proliferation and metastasis (50-52). In breast cancer, the overexpression of *LINC00958* was associated with METTL3-mediated N6-methyladenosine (m6A) modification, which promoted RNA transcript stability (53). Since *LINC00958* was confirmed to sponge miRNAs in many types of cancer, it would be interesting to identify what miRNAs control in ALL and thus specify its function in leukemogenesis.

Table I. Characteristics of the studies included in this review.

Study	Sample	Method	Analysis	Quality rating	(Refs.)
Affinito <i>et al</i>	3 B-ALL/3 controls	Sequencing	Diagnosis	3	(27)
Bárcenas-López <i>et al</i>	62 B-ALL: 23 early relapse and 39 non-relapse	Array/qPCR	Prognosis	3	(19)
das Chagas <i>et al</i>	32 T-ALL, 30 B-ALL/4 controls	qPCR	Classification	3	(28)
Chen <i>et al</i>	42 T-ALL/20 controls	qPCR	Diagnosis, treatment	3	(29)
Cuadros <i>et al</i>	24 <i>ETV6-RUNX1</i> ⁺ , 18 <i>ETV6-RUNX1</i> ⁻ /4 controls	Array	Classification	3	(30)
Durinck <i>et al</i>	7 <i>NOTCH1</i> ⁺ , 8 <i>NOTCH1</i> ⁻	Sequencing/Array	Classification	3	(31)
Fang <i>et al</i>	18 <i>KMT2A</i> ⁺ , 29 <i>KMT2A</i> ⁻ /3 controls	Array/qPCR	Classification	3	(32)
Fernando <i>et al</i>	118 B-ALL: 38 <i>ETV6-RUNX1</i> , 8 <i>TCF3-PBX1</i> , 16 <i>KMT2A</i> , 3 <i>BCR-ABL1</i> , 53 normal karyotype	qPCR	Diagnosis, classification, prognosis, treatment	3	(33)
Fernando <i>et al</i>	125 B-ALL: 39 <i>ETV6-RUNX1</i> , 8 <i>TCF3-PBX1</i> , 16 <i>KMT2A</i> , 3 <i>BCR-ABL1</i> , 59 normal karyotype	qPCR	Classification	3	(21)
Garitano-Trojaola <i>et al</i>	28 B-ALL, 9 T-ALL/3 controls	Array/qPCR	Diagnosis	3	(18)
Gasic <i>et al</i>	26 B-ALL, 3 T-ALL	qPCR	Treatment	2	(34)
Ghazavi <i>et al</i>	62 B-ALL: 25 <i>ETV6-RUNX1</i> , 7 <i>TCF3-PBX1</i> , 15 HH, 17 normal karyotype	Array	Classification	3	(35)
James <i>et al</i>	45 B-ALL: 12 <i>DUX4</i> , 11 <i>BCR-ABL1</i> like, 9 HH, 3 LH, 10 unassigned	Sequencing/Array	Classification, prognosis	3	(36)
Lajoie <i>et al</i>	56 B-ALL/CD19 ⁺ CD10 ⁺ controls	Sequencing/qPCR	Diagnosis, classification	3	(37)
Li <i>et al</i>	32 T-ALL/32 controls	qPCR	Diagnosis	3	(22)
Liu <i>et al</i>	46 T-ALL: 23 MDR ⁺ , 23 MDR ⁻	qPCR	Treatment	3	(20)
Ngoc <i>et al</i>	27 T-ALL	Sequencing	Classification	3	(38)
Ouimet <i>et al</i>	56 B-ALL/CD19 ⁺ CD10 ⁺ controls	Sequencing/qPCR	Diagnosis	3	(39)
Pouyanrad <i>et al</i>	46 new diagnosis (10 MRD ⁺ , 36 MRD ⁻) and 18 relapse/30 controls	qPCR	Treatment	3	(40)
Verboom <i>et al</i>	85 T-ALL: 18 immature, 28 <i>TALR</i> , 27 <i>TLX1/TLX3</i> and 12 <i>HOXA</i>	Sequencing	Classification	3	(41)
Wang <i>et al</i>	20 T-ALL/10 controls	qPCR	Classification	3	(42)
Yang <i>et al</i>	37 T-ALL/43 controls	qPCR	Diagnosis	3	(43)
Zhang <i>et al</i>	21 T-ALL/unspecified controls	qPCR	Diagnosis	3	(44)

ALL, acute lymphoblastic leukemia; T-ALL, T-cell ALL; B-ALL, B-cell ALL; qPCR, quantitative polymerase chain reaction; HH, high hyperdiploidy; LH, low hypodiploidy; MDR, multidrug resistance; MRD, minimal residual disease.

Among the downregulated lncRNAs in B-ALL, we found several lncRNAs described as tumor suppressors in leukemia and other malignancies, as well as in association with prognostic markers. For instance, *RP11-624C23.1* was described as a tumor suppressor gene in ALL, since its overexpression promoted tumor suppressor-like phenotypes including apoptosis and DNA damage response in B-ALL cell lines (54). This *RP11-624C23.1* downregulation was recently confirmed in another population of ALL patients (55). *LINC00926* was shown to act as a tumor-suppressor lncRNA reducing proliferation, invasion, and migration in breast cancer (56). Moreover, it was identified as a prognostic marker in AML (57) and Hodgkin lymphoma (58), where high expression was associated with

poor overall prognosis. Due to its role as a prognostic marker in other tumors, further studies analyzing how *LINC00926* expression affects the prognosis of ALL patients could provide insights into its role in childhood B-ALL. Additionally, the downregulation of *AC009495.3* and *CECR7* was related with metastasis in hepatocellular carcinoma (59), and pancreatic and colorectal cancers (60,61), respectively. *AC083949.1* was also found to be downregulated in lung cancer (62). Regarding *AF131215.5*, many articles found an association with both good and bad prognosis, depending on the disease. For instance, low expression of *AF131215.5* was identified as a favorable prognosis factor in bladder (63) and endometrial cancer (64), while in lung adenocarcinoma, higher expression

Table II. lncRNAs deregulated in patients with ALL and B-ALL in comparison with normal controls.

Subtype	Expression	lncRNAs	(Refs.)
ALL	Upregulated	<i>AWPPH (MIR4435-2HG/LINC00978)</i>	(22,37)
B-ALL	Upregulated	<i>TPTEP1, TEX41</i>	(27,37)
		<i>LINC00958</i>	(33,37)
	Downregulated	<i>AP001055.6/LINC01678, (CTD-2516F10.2)/AC107884.1, RP11-693J15.5/LINC02397, AC009495.2/AC009495.3, CERC7, LINC00926, RP11-624C23.1/AC120193.1, RP11-219E7.1/AL133371.2, AF131215.6, SNX29P2/AC025279.1, AC083949.1/EML4-AS1, RP5-1071N3.1/ECE1-AS1, AF131215.2/AF131215.5, RP11-325K4.2/AC012181.1, RP11-79H23.3</i>	(27,37)

ALL, acute lymphoblastic leukemia; B-ALL, B-cell ALL.

Table III. Signature of lncRNAs for the different acute lymphoblastic leukemia subtypes.

Subtype	Expression	lncRNAs	(Refs.)
<i>ETV6-RUNX1</i>	Upregulated	<i>CRNDE, IFNG-AS1, RP11-69I8.3, RP1-159A19.4, HOTAIRM1</i>	(30,35)
		<i>LINC00670, RP1-35C21.2, RP11-359E19.2, RP11-214L13.1</i>	(35,37)
	Downregulated	<i>CCDC26</i>	(30,35)
Hyperdiploidy	Upregulated	<i>LINC00870</i>	(35,37)
<i>KMT2A</i> ⁺	Upregulated	<i>BALR-2 (CDK6-AS1)</i>	(32,33)

of *AF131215.5* was associated with better survival prognosis (65). Finally, *RP11-79H23.3* was also downregulated in bladder cancer patients, and its restoration suppressed cell proliferation, migration and induced apoptosis *in vivo* through the binding of miR-107 and the consequently upregulation of its target gene, *PTEN* (66). The upregulation of *PTEN* led to the inactivation of PI3K/Akt signaling pathway (66), a pathway commonly activated in childhood ALL (67). Another 8 lncRNAs were found downregulated in B-ALL patients, but no information was found on its involvement in other diseases.

In relation to subtype classification, we identified three different signatures for *ETV6-RUNX1*, hyperdiploidy and *KMT2A*-rearranged subtypes. *ETV6-RUNX1* signature included the upregulation of 9 lncRNAs and the downregulation of *CCDC26*. In other diseases, such as AML or gastrointestinal stromal tumors, *CCDC26* was overexpressed (68,69). In AML, *CCDC26* overexpression was related with cell proliferation and invasion and reduction of apoptosis via controlling *PRR11* expression by sponging miR-195a-5p, and thus altering PI3K/AKT and NF- κ B pathways (70). In gastrointestinal stromal tumor patients, the *CCDC26* overexpression was associated with sensitivity to imatinib treatment (69). Imatinib is a first-generation Abl-tyrosine kinase inhibitor (TKI) that has become a first-line treatment in *BCR-ABL1* subtype ALL (71). Thus, it would be interesting to analyze *CCDC26* levels in *BCR-ABL1* patients. Among the upregulated lncRNAs, one of the most interesting results was the upregulation of *CRNDE*. This was shown to significantly reduce the miR-345-5p levels and increase the expression of the transcription factor *CREB*, which was found to promote cell proliferation and inhibited apoptosis in ALL cell lines (72). This expression pattern was

also observed in other blood malignancies, such as acute promyelocytic leukemia (APL) (73) or AML (74,75), suggesting that it may have an important role in hematopoiesis. Furthermore, *CRNDE* was also upregulated in other type of cancers, such as colorectal cancer, glioma, multiple myeloma and hepatocellular carcinoma. In all cases, *CRNDE* was related with promotion of cell proliferation, migration invasion and inhibition of apoptosis, suggesting that it may have a crucial role in cancer progression (76). Moreover, some studies identified *CRNDE* as a poor prognosis marker (74-76), but there is still no information concerning its prognostic role in ALL. Another upregulated lncRNA was *AL133346.1*, which was strongly correlated with *CCN2* mRNA in B-ALL pediatric patients, a protein involved in intercellular signaling and that plays an important role in the differentiation of hematopoietic stem cells (77). Low expression level of *AL133346.1* was associated with lower overall survival (77) and with early relapse and mortality in another study concerning B-ALL patients (19). Thus, the high expression of *AL133346.1* in *ETV6-RUNX1* may be related to the good prognosis in this subtype. Finally, *HOTAIRM1*, upregulated in *ETV6-RUNX1*, is also overexpressed in solid tumors (78,79) and in AML patients, where it was found to negatively target and sponge miR-148b, thus inducing cell proliferation and reducing apoptosis (80). The remaining lncRNAs specific to the *ETV6-RUNX1* subgroup (*RP11-359E19.2, IFNG-AS1, LINC00670, RP1.159A19.4* and *RP11-214L13.1*) were less studied and further research is warranted to understand their mechanism of action in this subtype.

The signature of *KMT2A* was defined by the upregulation of *BALR-2 (CDK6-AS1)*. The overexpression of *BALR-2* was found to be related to worse survival, bad prognosis and

resistance to prednisone treatment (33) in childhood ALL. The authors suggested that *BALR-2* may act in promoting B-ALL cell survival via inhibition of genes of the glucocorticoid receptor signaling pathway, such as *FOS*, *JUN* and *BIM* (33). Due to the use of glucocorticoids in childhood ALL therapy (81), it may be important to perform *in vitro* studies to determine whether this lncRNA could represent a new target for ALL therapy. In the case of hyperdiploidy, its signature consisted in the overexpression of *LINC00870*. Nevertheless, no information was found regarding its mechanism of action.

Finally, it must be noted that this review presents several limitations that should not be overlooked. First, many of the studies included in the systematic search analyzed a limited number of lncRNAs, underestimating the effect of other lncRNAs that might be involved in ALL. Moreover, usually only significant results are published, which may lead to the underrepresentation of non-significant results. It also has to be noted that pre-existing knowledge on lncRNAs is limited, and even more regarding the subtypes of a very heterogeneous disease such as ALL. Therefore, generating a reliable and consistent signature with a reduced number of lncRNAs is still difficult, and even more for each of the subtypes. In addition, many of the lncRNAs obtained for these signatures were novel transcripts, thus the information about them is still scarce and, in most cases, their biological functions have not yet been studied either in childhood ALL or in other cancer types. Finally, since lncRNA nomenclature is still in progress, it was sometimes difficult to contrast the results extracted from the different articles. Following the nomenclature proposed by LNCipedia, a database collecting human lncRNA sequences and annotation which merges redundant transcripts across the different data sources, will result in highly consistent and comparable data (82).

In summary, this systematic review has allowed the identification of deregulated lncRNA signatures for diagnosis and patient stratification, showing the great potential of these molecules as biomarkers. Nevertheless, increasing knowledge concerning these non-coding molecules will be essential for a better understanding of their role in the leukemogenesis of childhood ALL.

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Availability of data and materials

All information and data provided in this review is documented by relevant references.

Authors' contributions

Conceptualization of the review article was achieved by IMG, ELL and AGC. Systematic search was conducted by IT and AGC. Data curation was conducted by UI. Writing-original draft preparation was conducted by IMG, ELL, AGC, JT and UI. Writing-review and editing, was performed by all authors. Supervision of the project was the responsibility of IMG, ELL, AGC, NBA and JB. Funding acquisition was undertaken by IMG and ELL. All authors confirm the accuracy of the data provided in the review and have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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