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REVIEW

MicroRNAs: Potential prognostic and theranostic biomarkers in chronic lymphocytic leukemia

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Abstract

Small noncoding ribonucleic acids called microRNAs coordinate numerous critical physiological and biological processes such as cell division, proliferation, and death. These regulatory molecules interfere with the function of many genes by binding the 3'-UTR region of target mRNAs to inhibit their translation or even degrade them. Given that a large proportion of miRNAs behave as either tumor suppressors or oncogenes, any genetic or epigenetic aberration changeing their structure and/or function could initiate tumor formation and development. An example of such cancers is chronic lymphocytic leukemia (CLL), the most prevalent adult leukemia in Western nations, which is caused by unregulated growth and buildup of defective cells in the peripheral blood and lymphoid organs. Genetic alterations at cellular and molecular levels play an important role in the occurrence and development of CLL. In this vein, it was noted that the development of this disease is noticeably affected by changes in the expression and function of miRNAs. Many studies on miRNAs have shown that these molecules are pivotal in the prognosis of different cancers, including CLL, and their epigenetic alterations (e.g., methylation) can predict disease progression and response to treatment. Furthermore, miRNAs are involved in the development of drug resistance in

Abbreviations: SNP, single nucleotide polymorphisms; CLL, chronic lymphocytic leukemia; miRNA, micro RNA; RISC, RNA-induced silencing complex; HSC, hematopoietic stem cell; CMP, common myeloid progenitor; GMP, granulocyte/monocyte precursor; MEP, megakaryocyte-erythrocyte precursor; CLP, common lymphoid progenitor; Bcl-2, B cell lymphoma 2; BCR, B cell receptor; ITAM, immunoreceptor tyrosine-based activation motif; OS, overall survival; HIF-1, hypoxia-inducible factor 1; SOCS1, suppressor of cytokine signaling 1; EV, extracellular vesicle; tRNAs, transfer RNA; ssDNA, single-stranded DNA; dsDNA, double-stranded DNA.

CLL, and targeting these molecules can be considered a new therapeutic approach for the treatment of this disease. MiRNA screening can offer important information on the etiology and development of CLL. Considering the importance of miRNAs in gene expression regulation, their application in the diagnosis, prognosis, and treatment of CLL is reviewed in this paper.

KEYWORDS
chronic lymphocytic leukemia, epigenetics, hematopoiesis, microRNA, prognosis, therapeutic biomarker

1 | BACKGROUND

Chronic lymphocytic leukemia (CLL) is the most prevalent type of leukemia in adults, characterized by the abnormal accumulation of CD5+/CD19+ B cells in the bone marrow, peripheral blood, lymph nodes, and the spleen [1, 2]. Disease course and manifestation of CLL vary greatly, ranging from asymptomatic cases that do not require treatment to aggressive forms that show resistance to therapy and have a short overall survival (OS) [3, 4]. There are several molecular mechanisms pathways deregulated in CLL, including B cell receptor (BCR) signaling, mitogen-activated protein kinase (MAPK/ERK), phosphatidylinositol 3-kinase (PI3K)/serine/threonine kinase (AKT), ataxia telangiectasia mutated (ATM), TP53 tumor suppressor pathway, and nuclear factor kappa B (NF-κB) [5-7]. New studies have discovered certain targeted therapies, including Venetoclax, Ibrutinib, Fostamatinib, and, Idelalisib, that have shown effectiveness in treating hematologic malignancies by targeting these deregulated molecular pathways [1, 3, 811]. Moreover, the roles of microRNAs (miRNAs) have also attracted scientific attention in understanding the development of CLL [12]. These small noncoding RNAs (known as miRNAs) are made of 19–25 nucleotides and interact with their target mRNA's 3′-UTR region to degrade them or prevent their translation, consequently affecting their expression [13]. About 30% of human genes are regulated by miRNAs, half of which are tumor-related genes [14]. Depending on the tissue in which they are expressed, some miRNAs can function as tumor suppressors or oncogenes (OGs), and it is fascinating to note that some of them can even serve both functions [15-17]. It can also be deduced that numerous physiological processes, including proliferation, differentiation, apoptosis, hormone secretion, hematopoiesis, and immunological responses are governed by miRNAs due to their significance in controlling gene expression [16]. Structural and functional alterations of miRNAs due to different factors such as gene mutations in pri-miRNAs, single nucleotide polymorphisms (SNPs), copy number variation, and abnormal transcription can lead to various diseases such as muscular dystrophy, diabetes, or cancer [18, 19]. Therefore, understanding miRNAs profiles and molecular mechanisms involved in CLL can provide valuable insights for improving clinical management of the disease, predicting therapy outcomes, and developing targeted therapies [20, 21]. The significance of these bioregulatory molecules and their functions in the pathogenesis, prognosis, and treatment of CLL will be reviewed in this study.

1.1 | Overview of miRNAs biogenesis

miRNA biosynthesis is a multistep procedure. A lengthy transcript of the associated gene, known as pri-miRNA, is first produced by the RNA polymerase II enzyme. An enzyme complex situated in the nucleus then cleaves and processes the structure of this initial transcript. This complex transforms pri-miRNA into pre-miRNA, a stem-loop structure with a length of about 85 nucleotides, using an RNase III (Drosha) and RNA-binding proteins (DGCR8). Pre-miRNA is then transported from the nucleus to the cytoplasm by the Ran/GTP/Exportin 5 membrane complex, where it is transformed into a mature miRNA with 20–22 nucleotides by the action of another RNase III endonuclease named Dicer. Finally, mature miRNA can regulate gene expression by acting via the RNA-induced silencing complex (RISC) [22]. Figure 1 shows the biogenesis of miRNAs.

1.2 | miRNAs and lymphoid lineage development

B lymphocyte development is a controlled process. It starts in the bone marrow, transforming hematopoietic stem cells (HSCs) into common lymphoid progenitors, pro-B cells, pre-B cells, and immature B cells. B cells then migrate to the spleen in the peripheral blood, where they can bind an antigen and differentiate into follicular or marginal zone B cells. The increase in the apoptosis rate of primary B cells due to the lack of DGCR8, which iscrucial for miRNA biogenesis, suggests the importance of miRNA in B cell development [23]. There are different miRNAs involved in this process. For example, miR-181 is highly expressed in primary lymphoid organs, especially the thymus, while miR-223 is more specific to the bone marrow. It is also expressed in the primary hematopoietic organ, which contains HSCs as well as myeloid, erythroid, and lymphoid cells at various stages of development. Expression of miR-142 has also been observed in all hematopoietic tissue [24, 25]. Studies have shown that high expression of miR-181 increases the proportion of B lymphocytes in blood and this upregulation is associated with a decrease in $CD8^+$ T lymphocytes [26]. On the other hand, high expression levels of miR-142 and miR-223 promote cell differentiation toward T lymphocytes and myeloid cells [27, 28]. In accordance with findings from previous research, more recent studies

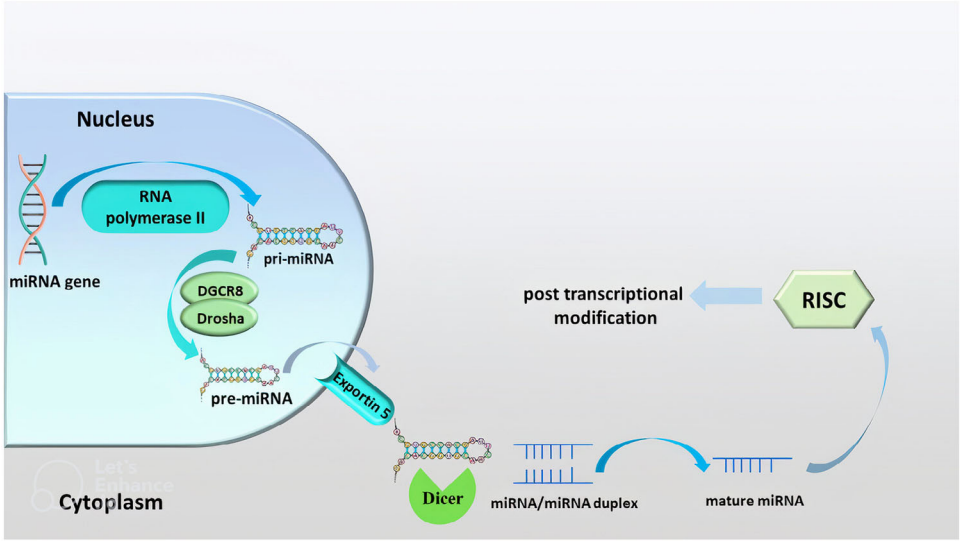

FIGURE 1 Biogenesis of microRNAs (miRNAs). First, the miRNA gene is transcribed by RNA polymerase II enzyme to form a primary transcript called pri-miRNA. After processing this initial transcript by DGCR8 and RNase III (Drosha), pri-miRNA is transformed into a hairpin loop structure with 85 nucleotides (pre-miRNA). The pre-miRNA is transported from the nucleus to the cytoplasm via the Ran/GTP/Exportin 5 membrane complex and converted to the miRNA/miRNA duplex structure by the Dicer enzyme and finally, mature miRNA is formed. Mature miRNA can regulate the expression of the target gene by being located in the RISC protein complex.

have also evidenced that the expression levels of miR-181a-5p, miR-150-5p, miR-132-3p, and miR-126-3p varied according to the stage of B cell development in the bone marrow [29, 30]. The overall number of B cells was reduced as a result of the overexpression of miR-23a-5p, a member of the miR-23a cluster, in HSCs [31].

1.3 | MiRNAs in hematologic malignancies

There is abundant evidence that hematological malignancies, as well as cancer in general, stem from defective expression of miRNAs, at least partly. Recently, a study that screened deregulated miRNAs in acute lymphoblastic leukemia (ALL) and CLL provided a list of miRNAs involved in leukemogenesis and of candidates for additional research aimed at figuring out their potential implications as OGs, tumor-suppressor genes (TSGs), or both [32, 33]. As an example, miR-155 overexpression has been linked to ALL, CLL, cutaneous T cell lymphoma (CTCL), diffuse large B cell lymphoma (DLBCL), and other hematopoietic diseases [34-37]. MiR-204 was also suggested to be downregulated in T cell acute lymphoblastic leukemia (T-ALL) via DNA methylation in the CpG promoter region and therefore, the overexpression of miR-204 in vitro can inhibit the proliferation of T-ALL and enhance apoptosis [38]. It has been demonstrated that miR-143 and miR-145 exhibited underexpression in numerous B cell malignancies such as B cell lymphomas, CLL cell lines, and Epstein–Barr virus-transformed B cell lines [39] The findings of Long et al. also demonstrated that miR-140-3p acted as a suppressor of tumor growth by reducing the rate of proliferation and stimulating apoptosis in multiple myeloma [40].

1.4 | The correlation between miRNAs and CLL pathogenesis

CLL is the most common type of adult leukemia and it is caused by clonal proliferation and accumulation of dysfunctional mature lymphocytes (mostly $CD5^+$, $CD23^+$, and $CD19^+$ B cells) in the peripheral blood, lymph nodes, and bone marrow [41]. This leukemia is increasing rapidly in the Western world, with more than 15,000 new cases and about 4500 deaths per year. The age of diagnosis is about 72 years and men are at a higher risk than women [42]. Genome-wide studies suggest that CLL may be caused by deletions or insertions in either specific genes or the chromosomes. The genomes of B-CLL patients have been found to contain a large number of mutated genes, the majority of which are found in the *NOTCH1*, *MYD88*, *TP53*, *ATM*, *SF3B1*, and *BIRC3* genes. Furthermore, deletions of 11q, 13q, 17p, 8p, and trisomy 12 are the most common chromosomal abnormalities in CLL [43, 44]. For example, cytogenetic studies have shown that 13q deletion is observed in 50% of patients with aggressive and indolent CLL [43, 45]. Interestingly, the first attention to the role of miRNAs in cancers began with a study of the 13q14 region in CLL patients. In this study, Croce et al. evidenced that the 13q14 locus, which is eliminated in many patients with CLL, is actually the site of miR-15a and miR-16-1 [45, 46]. After that, other studies also identified miR-15a and miR-16-1 as tumor suppressors that were deleted or downregulated due to 13q deletion. Therefore, these miRNAs have high clinical significance in the pathogenesis of CLL [47]. In fact, they target genes involved in cell proliferation and apoptosis such as *BCL-2* (B cell lymphoma 2), CCND1, CCND3, and CDK6, and act as tumor suppressors [48]. According to in vitro research, the primary mechanisms by which miR-15a/16-1 exert

their pathogenic roles in B cells are through controlling cell cycle and apoptosis, specifically by modulating the expression of genes involved in the G0/G1-S transition; for instance, by inducing the activation of G1-S-specific cyclin D2 (CCND2 and CCND3) and the antiapoptotic *BCL2* gene [49, 50]. The Bcl-2 family is a group of anti-apoptotic proteins that are overexpressed in many human cancers [51]. Research in New Zealand black (NZB) mice, a de novo model of CLL, validated the role of miR-15a/16-1; a point mutation in the miR-15a/16-1 precursor (located at the mouse genomic region homologous to 13q14) caused a reduction in miR-16-1 production in NZB lymphoid tissues and an increase in Bcl-2 levels [52]. An increasing number of studies have introduced different dysregulated miRNAs in CLL that require further research to clarify the pathogenesis and progression of this disease. For example, a study by Balatti et al. focused on the effects of miR-34b/c, miR-29, miR-155, miR-150, miR-17/92, and miR-181b [53]. miRNAs can also play a role in the pathogenesis of other lymphocytic malignancies. Patients with 11q23/MLL, TEL-AML1, BCR-ABL, and E2A-PBX1 translocations, as well as hyperdiploid individuals, were shown to have different miRNA profiles [54]. In samples of ALL, miR-204, miR-148, miR-210, miR-218, miR-296, and miR-381 had high expression levels, whereas miR-216 had low expression, according to studies by Silva-Jr et al. Additionally, miR-96, miR-188b, miR-130, miR128, and miR-181c had relatively low levels of expression in CLL but significant levels in ALL [33]. Gerenda et al. also studied numerous miRNAs in 35 patients with CLL, including hsa-miR-15a, 161, 29a, 29c, 34a, 34b, 155, 181a, 181b, 221, 222, and 223. Their results showed that expression levels of miR181a, 221, and 223 were significantly higher in the group with a low risk of disease progression (stage 0) compared to the group at high risk of CLL development. This study found that the expression levels of miRNA-181b and miRNA-223 were considerably greater in individuals who did not have the D13S319 deletion [55]. Numerous investigations have also shown that miR-192 plays a significant role in the pathogenesis of CLL by increasing the levels of CDKN1A/p21, suppressing Bcl2, and enhancing wild-type P53 and cell cycle arrest. MiR-192 expression has been evaluated in peripheral blood mononuclear cells from CLL patients by Fathullahzadeh et al. They showed that miR-192 expression is significantly downregulated (~ 2.5 folds) in CLL patients compared to healthy individuals using real-time PCR and in silico molecular signaling pathway enrichment analysis [56].

1.5 | MiRNAs control signaling pathways in CLL

Recent scientific techniques have found thousands of miRNAs in the human genome that regulate the expression of various genes and can degrade their target mRNAs by posttranscriptional alterations. Today, a huge number of genes, miRNAs, and cellular pathways connected to the development of CLL have been discovered, including those in charge of ensuring that B cells function correctly. B cells' proliferation and differentiation are noticeably dependent on the maturation and function of BCRs. BCR, a transmembrane protein found on the surface of B lymphocytes, regulates B cells' survival, maturation, and even antibody production [57, 58]. When an antigen binds the "immunoglobulin region" of this receptorITAM motifs are phosphorylated by tyrosine kinase enzymes such as Lyn and Fyn. Then, the Syk enzyme is activated through binding to phosphorylated ITAMs and subsequently phosphorylates the BLNK protein [59]. This process triggers the downstream signaling cascade and ultimately activates pathways associated with cell proliferation and differentiation such as NF-κB [60]. Signal transductions by BCR as well as the regulatory role of miRNAs in the downstream signaling pathways are shown in Figure 2.

Given that CLL is affected by miRNAs, the role of these molecules in regulating signaling pathways associated with the proliferation and differentiation of lymphoid cells, such as BCR, is undeniable. One of the regulators of the BCR signaling pathway is miR-150. Several studies have shown that this miRNA adjusts the level of the FOXP1 transcription factor in CLL cells [61-63]. FOXP1 is an essential factor in the BCR, NF-κB, and Wnt signaling [64, 65] and its overexpression is associated with several B lymphocyte malignancies and adverse outcomes in the corresponding patients [64, 66]. MiR-155 is another vital regulator of gene expression in B lymphocytes which is upregulated in many lymphoid malignancies such as CLL [67]. In a study, Bing Cui and colleagues revealed that high expression of miR-155 could affect the BCR signaling pathway and develop an aggressive form of CLL with poor clinical outcome [68]. Also, the results of another research by Costinean demonstrated that the overexpression of miR-155 in mice caused polyclonal expansion of B cells [69]. Sharma et al. also studied changes in miRNA expression levels and numerous miRNAs previously shown to influence BCR signaling and microenvironmental interactions (e.g., miR-155, miR-150, and miR-22) were among the dozens of miRNAs identified. Lower miR-29 (a/b/c) levels were also substantially associated with shorter OS in CLL patients and an increase in the relative susceptibility of CLL cells to BCR ligation. They also revealed that elevated levels of tumor necrosis factor receptor–associated factor 4 (TRAF4) could enhance CLL responsiveness to CD40 activation and alter nuclear factor-kB (NF-kB) signaling. In CLL, miR-29 expression is repressed by MYC through BCR, which in turn allows for concurrent upregulation of TRAF4 and stronger CD40–NF-κB signaling. [70]. Carabia and colleagues demonstrated that the activation of BCR signaling by the microenvironment can exert a regulatory effect over the expression of miR-21 and its target repressor genes, including programmed cell death 4, protein inhibitor of activated *STAT3* (PIAS3), and phosphatase and tensin homolog (*PTEN*), through a signaling pathway that is stimulated or progressed by MAPK and STAT3. The outcomes of this analysis revealed that miR-21 was highly expressed in patients exhibiting higher levels of ZAP70 expression [71]. In addition to the BCR activating pathways, other pathways may be affected by miRNAs as well. For example, Chen and colleagues stated that miR-155 reduced apoptosis in a CLL cell line. In this study, after induction of IL-4 in the MEC-1 cell line, it was observed that this interleukin could stimulate the expression of miR-155 that subsequently enhanced STAT6 phosphorylation and finally prolonged the survival of leukemic cells [72]. NOTCH1 activating mutations were found in 8.3% of CLL patients at diagnosis, 31% of CLL patients with Richter's syndrome, and 20% of CLL patients with chemorefraction [73]. When diagnosed, CLL patients with a NOTCH1 mutation had more advanced clinical stages and had

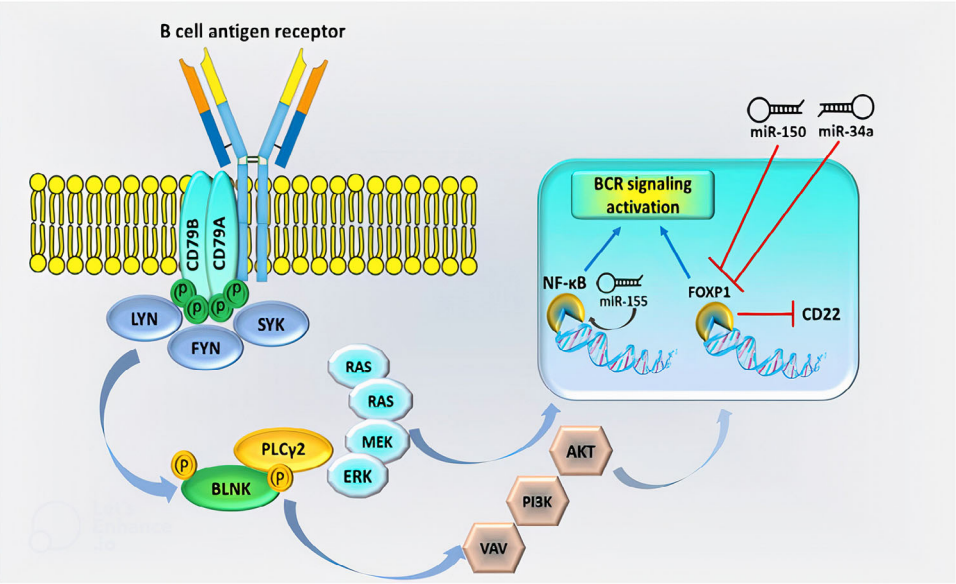

FIGURE 2 Signaling pathways of B cell receptor (BCR). BCR contains a membrane-bound immunoglobulin molecule (that attaches the antigen) and a heterodimer subunit consisted of Ig-α and Ig-β (signal transduction moiety) that has tyrosine kinase properties due to its ITAM motifs. After the activation of BCR, ITAM motifs are phosphorylated by tyrosine-protein kinase Lyn, proto-oncogene tyrosine-protein kinase Fyn and tyrosine-protein kinase SYK. Phosphorylation of CD79A and CD79B activates a set of kinases and adaptor proteins that ultimately triggers signaling pathways related to cell proliferation and differentiation, including NF-κB. The miR-150 and miR-34a disrupt signal transduction from BCR and inhibit cell proliferation in CLL by negative regulation of FOXP1.

a worse 10-year OS rate (21%) than those without NOTCH1 mutations (56%) [74]. Mutations in the NOTCH1 gene in CLL result in an early stop codon, leading to the formation of a constitutively active and more stable NOTCH1 protein. This mutated protein lacks the C-terminal domain that contains the PEST sequence. These mutations serve as an independent prognostic marker for CLL and are often mutually exclusive with *TP53* mutations, portending a poor prognosis [75]. Finally, the findings of research represent that miRNAs implicated in NOTCH1 mutation are significant in several diseases, there is not enough research on the correlation between miRNAs and NOTCH1 mutations in CLL at present. As a result, additional research into the mechanisms of miRNAs and NOTCH1 in CLL may lead to a more accurate prognosis for CLL patients [76]. Therefore, it can be concluded that the study of different miRNAs can be considered a useful approach for better recognition of tumors.

1.6 | MiRNAs and Wnt signaling pathway in CLL

Another noticeable pathway in CLL etiology is the Wnt signaling pathway. The Wnt protein family is made up of 19 secreted glycoproteins that are involved in a variety of cellular activities including self-renewal properties of stem cells, migration, survival, and proliferation [77]. The Wnt/β-catenin signaling pathway has been known to be unusually activated by mutations in a variety of human malignancies, including CLL, pediatric kidney cancer, colorectal cancer, and colon cancer. Consequently, it may be considered that a highly conserved Wnt signaling pathway is crucial to the pathogenesis of CLL [78]. According to previous studies, miRNAs control signal transduction by binding to the corresponding 3′-UTR sequences of the target mRNA to regulate protein expression at diverse levels in CLL [79, 80]. Numerous studies have shown that a number of miRNAs play very important roles in the Wnt signaling cascade. Among the miRNAs that have received the most attention are miR-34a, miR-26a, miR-126, miR-135a, miR-135b, miR-155, miR-21, and miR-29 [81-86]. It is known that miRNAs increase the expression of target OGs by decreasing the level of the TSG's expression. In contrast, increased expression of miRNAs regulating oncogenic proteins decreases the expression level of TSGs [87]. The *GSK-3β* gene (glycogen synthase kinase) in humans encodes the GSK-3β protein, a residue of the proline-rich serine-threonine kinase [88], which is primarily associated with neuronal cell growth, metabolism, and embryonic body patterning and is a key member of the Wnt pathway [89, 90]. Interestingly, one of the several families of miRNAs conserved in mammals and variably expressed in various malignancies is the miR-135 family [91, 92]. Both miR135-a and miR135-b can activate the Wnt signaling pathway by blocking GSK-3β and causing stabilized β-catenin to translocate into the nucleus [93, 94] and subsequently, its interaction with the TCF/LEF family stimulates CLL cells' prolifreation and promotes blood cancer. The Wnt signaling pathway in CLL cells is also negaticontrolled negatively by miR-21 and positively by miR-29 [95, 96]. MiR-21 can decrease Wnt protein transcription, according to mRNA and protein level investigations. In this regard, adding exogenous Wnt protein or transfection with miR-21 antagonists suppressed the segregation of monocyte-derived dendritic

cells [97]. However, intriguingly, miR-29 transcription induced the Wnt signaling cascade by blocking all Wnt signaling pathway inhibitors [98].

1.7 | miRNAs as potential diagnostic and prognostic biomarkers for CLL

The significance of genetic and molecular information is unquestionable in the diagnosis and prognosis of CLL, but many of their mechanisms are still unknown. miRNAs can be thought of as useful biomarkers in the clinical diagnosis and prognosis of malignancies because they are involved in the regulation of numerous crucial cellular processes [99, 100]. It should be noted that miRNAs can have significant implications for patient care due to their ability to predict tumor aggressiveness, metastasis, and disease prognosis [101]. The most significant genetic biomarkers related to CLL prognosis and diagnosis are reviewed in the following sections.

1.8 | Mutation in the immunoglobulin heavy-chain variable-region (IGHV) gene

About 50%–70% of patients with CLL show hypermutation in the *IGHV* gene, suggesting this gene as a prognostic factor in CLL [102, 103]. Interestingly, patients who have no mutation in this region experience a more invasive form of the disease. Conversely, patients with such mutations are associated with favorable treatment outcomes and longer OS. Therefore, surveying the *IGHV* gene might provide an indicator for predicting the clinical outcomes of CLL [104, 105].

1.9 | Chromosomal abnormalities

Chromosomal aberrations such as deletion of 13q, 17p, 11q, and trisomy 12 are common examples of genetic abnormalities that are momentous in the early detection of CLL [106]. For instance, del (11q) is seen in 10%–17% of CLL patients. The 11q22.3-q23.1 region is the location for the *ATM* gene which is a tumor suppressor and controls the cell cycle by activating the p53 protein (a crucial cell cycle regulator) [107, 108]. This deletion is associated with poor clinical outcomes in one-third of CLL patients [109-111]. Del (13q) is the most common genetic variation at the diagnostic level of CLL and occurs in about 35%–45% of patients. Compared to del (11q), del (17p), and trisomy 12, del (13q) leads to a good prognosis [45, 112]. Moreover, del (17p), mainly in the 17p13.1 region, is observed in 3%–7% of CLL cases [113, 114] and causes the loss of the *TP53* gene. The occurrence of this abnormality is mainly associated with unmutated *IGHV* gene, high expression of CD38 and ZAP70, and consequently poor prognosis in CLL [115, 116]. Deletion or mutation in this gene causes an unfavorable response to treatment and an aggressive form of the disease [117, 118]. Trisomy 12 is also a genetic abnormality with a moderate prognostic value which is detected in the karyotype of 11%–16% of CLL cases. The corresponding patients have an appropriate response to treatment [119, 120].

1.10 | MicroRNAs

A thorough analysis of the genetic makeup of CLL has revealed that because of the tight relationship between various cytogenetic abnormalities of particular subtypes and miRNA levels, these molecules may serve as novel diagnostic, prognostic, and therapeutic markers for CLL in the foreseeable future. The importance of miRNAs in CLL prognosis has been investigated in various research. as well as other research groups, have examined miRNAs in CLL patients with overexpression of ZAP70 and unmutated *IGHV* gene; they reported a significant association between the overexpression of miR-15a, miR-16-1, miR-16-2, miR-23b, miR-24-1, miR-146, miR-155, miR-195, miR-221, and down-expression of miR-223, miR-29a-2, miR-29b-2, and miR-29c with unmutated *IGHV* gene, high expression of ZAP70, and unfavorable prognostic in CLL cases [121-123]. Another study conducted by Due et al. showed that oncomiR-155, which contributes to the progression of large B cell lymphoma and CLL, is overexpressed in malignant cells and associated with poor prognosis [124]. In another study performed by Braga et al. it was found that in the indolent form of CLL, deletion in the 13q14 region led to the deletion of miR-15-a and miR-16-1; low expression of these molecules induced the expression of anti-apoptotic Bcl-2 protein and inhibited the apoptotic process and eventually, survival and accumulation of leukemic cells was increased in the patients' bodies [103]. Papageorgiou et al. suggested that high expression of miR-20b-5p may result in better OS in CLL patients and it can be generally recognized as a favorable prognostic factor [125]. MiR-150, miR-29a, miR-135a, and miR-195 are extracellular circulating miRNAs that, in addition to cellular expression, may be detected in the plasma of CLL patients. The results of a study conducted by Stamatopoulos et al. showed that the decrease in cellular expression and the increase in serum expression of miR-150 led to adverse prognosis in CLL patients [126]. Furthermore, Nateghi et al. introduced miR-95 as a biomarker in the early diagnosis of CLL [127]. According to the findings of Marton et al., a global decrease in miRNA expression levels in CLL cells was associated with consistent underexpression of miR-181a, let-7a, and miR-30d [32]. Using quantitative PCR (qPCR), Andrade et al. evaluated miR-197, miR-26a, and miR-27a in 82 CLL patients and 62 controls in which CLL patients were shown to have significantly lower miRNA levels than the controls; this trait was negatively correlated with patients' clinical stages [128]. Rahimi et al. also conducted a study on blood samples of 32 CLL patients who were recruited from Kermanshah province, Iran, and were matched for age and sex with 34 healthy individuals. The results of the study indicated a significant decrease in the expression of miR-32, miR-98, and miR-374 in CLL patients compared to controls; data analysis suggested that the studied miRNAs have the potential to act as biomarkers for the early diagnosis of CLL [129]. In another study, real-time PCR was used by Hadi et al. on 30 patients and 30 healthy controls and showed that patient samples contained significantly higher levels of miR-574 and miR-499, while miR-125b, miR-106a, while miR-9 expression levels were lower [130]. Similarly, using a Taqman-based evaluation, Casabonne et al. examined the serum of 224 CLL patients (diagnosed between 3 months and 18 years following enrolment) and 224 matched controls.

According to the results of this study, hsa-miR-29a, hsa-miR-150-5p, and hsa-miR-155-5p were moderately predictive biomarkers for CLL risk, while no correlation between hsa-miR-16-5p and hsa-miR-223-3p levels and the risk of CLL was detected [131]. Recently, it was discovered that CLL patients have decreased levels of miR-223 and miR-125a, as well as greater levels of their targets *BCL-2* and *STAT3* [132]. Additionally, Salah et al. discovered that the levels of miR-29a expression in CLL patients were considerably higher than in healthy controls in a study of 158 patients with CLL and 21 healthy controls. Furthermore, there was a significant link between high miR-29a expression and poor prognostic indicators (high CD38 and ZAP70 expression, Stage III Rai stage, high LDH levels, unfavorable cytogenetic finding, and longer time to first treatment, suggesting that determining miR-29a expression levels upon diagnosis could be used as a predictive biomarker in CLL patients [133]. Another study by Samia et al. suggested miRNA 223/125a and Cordon-bleu Protein Like 1 (COBLL1) as other prognosis predictive markers, since high levels of COBLL1 expression were shown to be significantly correlated with high levels of ROR-1 (receptor tyrosine kinase-like orphan receptor-1) expression in a novel flowcytometry-based CLL monitoring. However, low ROR-1 percentage expression was statistically substantially correlated with high levels of miRNA 223/125a expression [134]. Furthermore, using a bioinformatics prediction approach, Bagheri et al. suggested that miR-15b and miR-195 target the DLEU7, a gene typically inactivated in CLL patients. When compared to healthy individuals, the plasma of B-CLL patients contained considerably higher levels of miR-15b and miR-195 and considerably lower levels of DLEU7 gene expression. [135]

1.11 | miRNAs and epigenetics in CLL

In addition to genetic abnormalities, epigenetic factors can also play a crucial role in tumor formation. The difference between epigenetic and genetic factors is that the former alters gene expression without changing DNA sequences and can be reversibly inherited [136, 137]. Several important biological processes, including embryonic growth and cellular differentiation, are controlled by epigenetic factors [138]. The alteration of chromatin structure, DNA methylation, and histone modifications are among the most important epigenetic events [139]. If the epigenetic mechanisms are disrupted, they can create OGs or even inhibit TSGs, leading to out-of-control cell growth and eventually, cancer incidence [140, 141]. Considering the vital roles of miRNAs in important cellular processes such as growth and differentiation, epigenetic changes affecting these molecules can increase the risk of cancer. A recent study found that hsa-miR-203a-3p and hsa-miR-29a-3p analyses revealed a negligibly reduced expression in melanoma cell line compared to control. Another study found that the expression of the TNFAIP3 gene, miR-203a-pa-p, and miR-29b reduced while the expression of the DNMT3B gene increased [142]. The 3′UTR of the DNMT3B gene is expected to be the target of miR-339 and miR-766. The reduction in luciferase activity observed in the HEK293T cell upon individual and co-transfection of miR-766 and miR-339 was confirmed by the luciferase reporter assay. Moreover, DNMT3B expression was downregulated upon transduction of viruses expressing miR-339 and miR-766 into colon cancer cell lines (SW480 and HCT116) [143]. The first global study on the methylation pattern of miRNAs in CLL by Baer et al. introduced 128 recurrent targets for abnormal DNA methylation in promoter regions [144]. According to research by Wong et al. in CLL, the promoter sequence of miR-129-2 is hypermethylated, which silences the gene. This miRNA is a tumor suppressor and therefore, the subsequent lower expression causes negative treatment results in patients [145]. Similarly, Deneberg and colleagues found that the promoter of the miR-34b/c gene was hypermethylated in half of CLL patients and the corresponding hypermethylation was associated with decreased expression and gene silencing. In this experiment, by inducing the miR-34 a/b/c TSG related to the TP53 signaling network in the HG3 cell line, the rate of apoptosis significantly increased [146]. Also, Wang et al. reported that miR-3151 is hypermethylated in the promoter region. This miRNA is a tumor suppressor and normally increases apoptosis by inhibiting the MEK/ERK and PI3K/AKT signaling pathways. Interestingly, treatment of CLL patients by demethylating miR-3151 can restore its normal expression and activity as a tumor suppressor [147]. Another study identified miR-26A1 as a tumor suppressor and suggested that its inhibition due to promoter hypermethylation was associated with poor prognosis in CLL patients [148]. Figure 3 depicts several miRNAs that act as tumor suppressors in CLL and their epigenetic changes.

1.12 | miRNA contents of CLL cell-derived extracellular vesicles

Extracellular vesicles (EVs; exosomes and microvesicles) are cellular components with different sizes and molecular contents that can originate from distinct parts of cells [149, 150]. Depending on the originating cell, EVs contain components such as RNA, DNA, and proteins and play an important role in intercellular communications [151]. After releasing from the source cell, these vesicles are absorbed by the target cells (through direct membrane attachment, endocytosis, phagocytosis, and ligand-receptor interaction), transfer their contents, and induce the desired biological activity [152].EVs are known as carriers for many small regulatory molecules such as small non-coding RNAs (such as miRNAs), transfer RNAs (tRNAs), mitochondrial DNA, single-stranded DNA (ssDNA), and genomic double-stranded DNA (dsDNA) [153], [154]. In addition to the function of these vesicles in normal biological processes, EVs play roles as biomarkers in various pathological conditions such as cancer development and progression. In a study, Jones et al. found that approximately 400 miRNAs, including miR-127-3p, miR-24-3p, miR-21-5p, miR-155, and miR-21, were present in the serum-derived EVs of Hodgkin's lymphoma patients [155]. Another study also showed that the presence of miR-125b-5p and miR-99a-5p in serum-derived EVs of diffuse large B-cell lymphoma patients was associated with drug resistance and short progression-free survival time [156]. There is not much information about the role of EVs in CLL, however, it has been suggested that these vesicles may affect the physiology of cancer cells in CLL through certain miRNAs. In

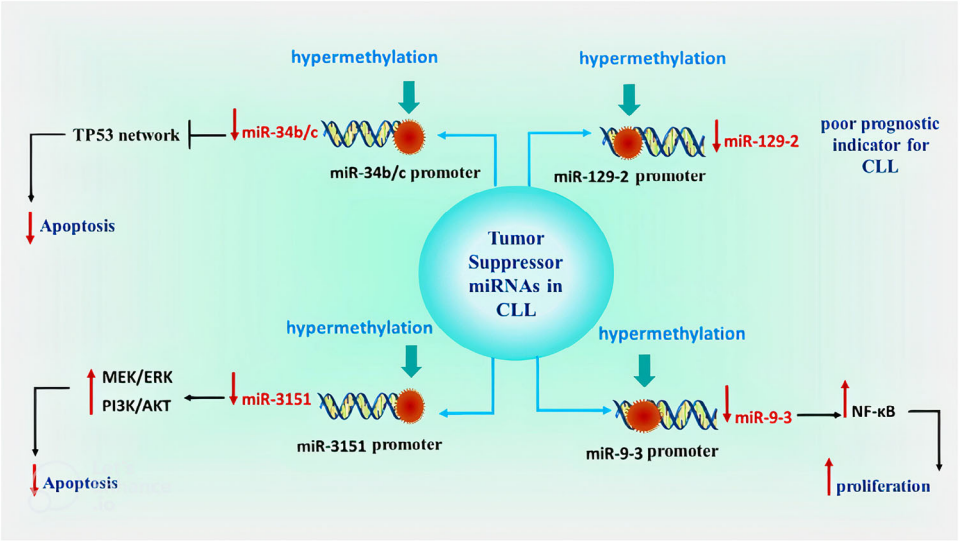

FIGURE 3 Epigenetic changes in miRNAs and their role in CLL prognosis. MiR-129-2, miR-34b/c, miR-3151, and miR-9-3 are tumor suppressors and hypermethylation of their promoter regions decreases their expression. Low expression of miR-34b/c inhibits the activation of the Tp53 signaling pathway and reduces apoptosis. On the other hand, decreased expression of miR-3151 and miR-9-3 initiate the MEK/ERK, PI3K/AKT, and NF-κB pathways, leading to reduced apoptosis, increased cell proliferation, and unfavorable prognosis of CLL.

addition, cellular membrane-derived EVs are used as indicators for the prognosis of CLL [157, 158].

1.13 | miRNAs as important targets in CLL treatment

The first-line treatment for CLL is the use of drugs such as chlorambucil which are widely used due to their cost-effectiveness and low toxicity. However, their long-term use will lead to side effects including myelodysplasia, cytopenia, and secondary acute leukemia. Fludarabine, pentostatin, and cladribine are also effective drugs used in CLL chemotherapy. Monotherapy with fludarabine shows a better overall response and 7%–40% complete remission. Furthermore, the application of monoclonal antibodies (such as anti-CD20), agents that target signaling pathways in CLL cells (such as ibrutinib), Bcl-2 inhibitors (such as Venetoclax), and CAR T cell therapy are other therapeutic approaches for CLL patients [42]. Despite the existence of effective and diverse treatment approaches, a high number of patients experience an aggressive form of disease and chemotherapy resistance. Among all factors that may lead to resistance in patients, dysregulation of miRNAs is of particular importance. For instance, in CLL patients, DNA damage activates p53, which in turn increases the expression of tumor suppressor miR-34a and causes cell cycle arrest and apoptosis; notably, the p53 pathway is closely related to chemotherapy resistance as well. On the other hand, mutations in *TP53*, del (17p), or del (11q) can reduce the expression of this miRNA and as a result, disruption of the p53/miR-34a network leads to change in the apoptotic pathway, response to DNA damage, and resistance to treatment [159, 160]. In normal cells, through the activation of ATM, DNA damage causes the induction of p53. P53 directly targets p21, Puma, Rax, and miR-34a to induce cell death and cell cycle arrest. Furthermore, elevated miR-34a affects cell death by targeting Sirtuin 1, CDK4, CDK6, CCND1, MYCN, and BCL2. However, in malignant cells with *TP53* mutation/17p deletion, ATM mutation/11q deletion, or miR-34a downregulation, chemoresistance happens due to diminished cell apoptosis and cell cycle arrest, as well as DNA damage response pathway reduction [161, 162]. Salerno et al. described an increased drug sensitivity in mice with a genetically determined, age-associated increase in malignant B-1 clones and decreased expression of miR-15a-5p and miR-16-5p in B-1 cells, after the correction of the miR-15a-5p and miR-16-5p defect. Cell cycle arrest in the G1 phase was observed after the exogenous addition of miR-16-5p mimics [163]. Other miRNAs involved in chemoresistance are miR-181a and miR-181b. Studies have evidenced that in aggressive CLL cases, the expression of miR-181b was decreased while conversely, the expression of this miRNA was constant in stable conditions of the disease [164, 165]. In fact, miR-181b increased susceptibility to chemotherapy by targeting the 3'UTR region of the anti-apoptotic *BCL-2* gene [166]. In addition, miR-181a and miR-221 were overexpressed in fludarabine-resistant patients, whereas miR-29a expression was decreased in these patients ([167], [168]. Ferracin et al. reported that high expression of miR-221 and miR-21 can make patients resistant to fludarabine since targeting these miRNAs activate caspases and increased tumor cells' apoptosis [169]. Notably, miR-155 is another oncogenic miRNA effective in resistance to chemotherapy in different cancers. Increased expression of miR-155-3p has been shown to increase the expression of Toll-like receptor 9, which protects CLL cells against fludarabine-induced apoptosis [170]. Remarkably, if a decreased expression of a miRNA leads to drug resistance, the induction of an appropriate miRNA mimic can resensitize tumor cells.

This new promising approach is currently being investigated in several phase I clinical studies and MRX34 (miR-34 mimic) is the first applied miRNA mimic in clinical trials [171, 172]. MiRNAs appear to be promising therapeutic molecules and therapeutic targets for CLL given their multifaceted roles in B-CLL regulation, the fact that they are naturally produced molecules by organisms and their levels can be easily regulated with miRNA-mimics or miRNA-antagomiRs. For example, Dereani et al. recommended downregulation of miR-17-5p expression levels as an effective treatment method for B-CLL. In MEC-1 cells, in vitro treatment of antagomiR-17-5p, a miRNA inhibitory oligonucleotide molecule, drastically lowered miR-17-5p expression levels and cell growth [173]. Other miRNAs have also been identified as regulators of B-CLL therapy, among which miR-181a-5p and miR-181b-5p have shown promising results. When *TP53*^{wt} patients' leukemic B cells were transfected with miR-181a-5p and miR-181b-5p mimics, a significant increase in apoptosis was observed compared to controls. However, no effect was observed in B-CLL patients with decreased expression of *TP53* [174-176]. Additionally, it was observed that miR-181b-5p had an impact on the levels of TCL1A, AKT, and the phosphorylation of both ERK1 and ERK2. This resulted in a decrease in the proliferation of leukemic cells and an improvement in the survival rate of a transgenic mouse model that underwent treatment [177]. In 2019, Chiang and colleagues developed an immuno-nanoparticle-based miR-29b delivery formulation with selectivity to CLL cells but not normal B cells due to specific targeting of *ROR1*, which is expressed in 95% of CLL cells but not in normal B cells. [178]. Treatment with this drug resulted in a 600-fold increase in intracellular miR-29b levels, downregulation of the DNA methyltransferases 1 (DNMT1), 3 alpha (DNMT3A), and SP1 transcription factor (SP1) in cancer cells, and decreased selective hypermethylation of CLL while restoring apoptotic mechanisms [179]. MRX34 was used in the first Phase I study of miRNA-based cancer therapy in 2013. The clinical study (ClinicalTrials.gov identifier NCT01829971) focused on a variety of solid tumors and hematologic malignancies, showing a dose-dependent modulation of related target genes in solid tumors. However, the trial was abruptly stopped when four people died and significant adverse effects were reported [180, 181]. A similar approach was designed for miR-155, which is overexpressed in the majority of tumors including CLL. Patients with CTCL, CLL, DLBCL, and adult T cell leukemia/lymphoma (ATLL) were treated in the first phase I clinical trial with Cobomarsen (MRG-106), a synthetic locked nucleic acid (LNA anti-miR) of miR-155 inhibitor, in February 2016 (ClinicalTrials.gov; Identifier: NTC02580552). Six CTCL patients were evaluated, and the initial preliminary findings indicated that cobomarsen was well-tolerated and improved therapy outcomes [182]. The results of studies on a patient with aggressive ABC-DLBCL and corresponding xenograft mouse models revealed that Cobomarsen led to a decline in cell proliferation in vitro and tumor volume in vivo. Furthermore, this compound was observed to decrease tumor growth in the patient without any adverse effects [183]. The study by Ashofteh et al. revealed that miRNA-15a significantly and time-dependently decreased the mRNA levels of BCL-2 and Mcl-1, which then inhibited CLL-II cell growth and increased apoptosis. The IC_{50} value of fludarabine lowered and the cell survival rate decreased as a result of miRNA-15a transfection. High expression levels of other miRNAs, for example, miR-17~92, miR-155-3p, miR-21, miR-221, and miR-222, have also been detected to be closely associated with treatment resistance in ALL and CLL, making these miRNAs attractive therapeutic targets for these malignancies. The role of various miRNAs in CLL and their clinical significance are summarized in Table 1.

TABLE 1 The function, clinical importance, and expression changes of some microRNAs (miRNAs) in chronic lymphocytic leukemia (CLL).

Name	Genetic status	Function	Expression pattern in CLL	Importance in CLL	Reference
miR-15a miR-16-1	13q14	Inhibition of Bcl-2 family proteins and induction of apoptosis	Decreased	Play a role in pathogenesis	[47]
miR-150 miR-34a	19q13 1p36	Inhibition of FOXP1 and prevention of cell proliferation	Decreased	Play a role in pathogenesis and reduce overall survival	[184]
miR-155	21q21	Increasing the activity of BCR and polyclonal development of tumor cells	Increased	Creates an aggressive form of CLL, adverse clinical outcomes, and poor prognosis	[69, 68]
miR-34b/c	11q	Regulating the Tp53 signaling pathway	Decreased	Creates an aggressive clinical course	[146]
miR-3151	8q22	Inhibiting the MEK/ERK and PI3K/AKT pathways and apoptosis induction	Decreased	unfavorable prognosis of CLL	[147]
miR-9-3	15q26	Inhibiting the NF-κB pathway and apoptosis induction	Decreased	unfavorable prognosis of CLL	[185]
miR-181b	9q33	Targeting 3'UTR of *Bcl-2* gene	Decreased	Favorable response to treatment	[166]
miR-155-3p	21q21	Increasing the Toll-like receptor 9 and inhibition of apoptosis	Increased	Fludarabine resistance	[170]

2 | PERSPECTIVES

Adults with CLL are at risk of developing CLL as a fatal hematologic cancer. Examining the disease's overall profile reveals that CLL is a heterogeneous disorder and different causes, including mutations, chromosomal and molecular abnormalities, and epigenetic factors, are involved in the initiation and development of this cancer.MiRNAs have become interesting subjects of n research among the genetic changes linked to the pathophysiology of CLL. These noncoding molecules are essential for controlling gene expression because they have the power to influence the activity of a variety of crucial genes, including tumor suppressors and OGs. Evidently, critical cellular functions such as proliferation, differentiation, and cell death are hampered if the normal function of miRNAs is disrupted. Therefore, miRNA screening can offer important information on the etiology and development of CLL. Additionally, miRNAs can be employed as biomarkers to predict prognosis and therapy response. MiRNA mimics and alteration are among the interesting therapeutic approaches in the fight against this hematologic malignancy. It is important to remember that each miRNA has the potential to regulate several genes and that multiple miRNAs may act in concert to regulate a single gene. Therefore, thorough studies on potential miRNAs and their target genes should be carried out before miRNAs can be widely used as diagnostic, prognostic, and therapeutic tools.

AUTHOR CONTRIBUTIONS

MSB and RV supervised all aspects of the work and proposed the original concept and designed the study. MSB, AA and SP participated in the data acquisition. MSB, AH and AA contributed to writing the manuscript. MJMP, SHF, HM and BK contributed to the text revising. ABM, EH and RL contributed to the text editing

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The authors declare that they have no competing interests.

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