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Review Article

Small Nucleolar RNAs as Novel Biomarkers and Therapeutic Targets in Hematologic Malignancies: A Systematic Review

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Abstract

Background: Carcinogenesis is associated with the dysregulated expression of small nucleolar RNAs (snoRNAs). However, their specific expression profiles and clinical implications in hematologic malignancies remain limited. This systematic review aims to evaluate the role of snoRNAs as potential diagnostic and prognostic biomarkers and to assess their utility in monitoring treatment responses in hematologic cancers.

Materials and Methods: A systematic review was conducted following PRISMA guidelines. The protocol was registered in PROSPERO (CRD42024574222). Relevant data regarding study characteristics, cancer subtypes, specimen types, sample sizes, methodologies, and clinical outcomes were extracted. The quality of the studies and risk of bias were independently assessed using the Newcastle-Ottawa Scale (NOS), with discrepancies resolved through consensus.

Results: From an initial pool of 783 records, 12 studies met the inclusion criteria, highlighting the novelty of this research field. Despite the limited number of studies, the analysis identified 133 distinct snoRNAs with complex roles in the pathogenesis of hematologic malignancies. Dysregulated snoRNA expression was found to significantly influence critical cellular functions, including proliferation, invasion, and apoptosis. Furthermore, aberrant snoRNA levels showed a strong association with prognostic outcomes, particularly overall survival in multiple myeloma (MM) and chronic lymphocytic leukemia (CLL).

Conclusion: This review emphasizes the emerging significance of snoRNAs as promising biomarkers for diagnosis, prognosis, and therapeutic monitoring. The limited available data, compared with miRNAs and lncRNAs, highlight a significant knowledge gap. Nonetheless, current evidence suggests that snoRNAs offer distinct advantages, including greater molecular stability and higher specificity. While challenges such as incomplete functional characterization and limited clinical validation persist, this first systematic examination emphasizes the potential of snoRNAs to complement existing RNA-based biomarkers. Current findings highlight the need for more extensive research to fully utilize their diagnostic and therapeutic value in precision oncology.

Keywords: Biomarker, Gene Expression, Hematologic Neoplasm, Multiple Myeloma, Small Nucleolar RNA

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Introduction

Hematologic malignancies can arise during the process of hematopoiesis, significantly affecting the production and function of blood cells. The bone marrow houses hematopoietic stem cells, which serve as precursors for both lymphoid and myeloid lineages. Disruptions in the normal differentiation of these blood cells may result in the development of three major types of blood cancers: leukemia, lymphoma, and myeloma (1). In 2022, the global age-standardized incidence rates (ASIR) for lymphoma, leukemia, and multiple myeloma were 5.3, 6.55, and 1.8 per 100,000 individuals, respectively (2). Over the past 30 years, hematologic malignancies have constituted a major contributor to the global tumor burden (3). Projections suggest that by 2030, both the ASIR and the age-standardized death rate (ASDR) for leukemia and lymphoma will continue to rise (4, 5). While the prevalence of hematopoietic malignancies varies across regions according to the Socio-demographic Index (SDI), they remain a significant cause of morbidity worldwide (2). Recent research has highlighted the critical roles of genetic, epigenetic, and molecular alterations in the development of hematopoietic malignancies. Chromosomal aberrations are widely recognized as key drivers of disease progression in these malignancies. Despite advancements in chemotherapy-based treatments, the prognosis for aggressive hematopoietic malignancies remains poor. The diverse subtypes of hematopoietic malignancies, characterized by distinct clinical presentations, prognoses, and responses to treatment, emphasize the urgent need for more accurate diagnostic, prognostic, and therapeutic biomarkers (6-11).

Small nucleolar RNAs (snoRNAs) are a class of non-coding RNAs predominantly located in the nucleus of eukaryotic cells. Ranging in length from 60 to 300 nucleotides, snoRNAs play a critical role in the modification and processing of other RNA molecules within the cell (12, 13). The snoRNAs possess conserved structural elements and are integral to various RNA maturation processes. They are classified into two main families: C/D snoRNAs and H/ACA snoRNAs, each distinguished by unique structural features and mechanisms of replication regulation. Beyond their established roles in essential biological processes such as development and carcinogenesis (14-18), snoRNAs are pivotal in post-transcriptional regulation, including rRNA acetylation, RNA splicing, and modulation of translation efficiency (16). The involvement of snoRNAs in directing chemical modifications of rRNAs and tRNAs is critical for maintaining hematopoietic stem cell (HSC) homeostasis and mediating stress responses (17, 19-21). Figure 1 provides a schematic representation of the diverse roles of snoRNAs in the regulation of hematological malignancies.

Understanding the functional mechanisms of snoRNAs not only sheds light on the molecular underpinnings of blood cancer development (22-25) but also offers potential for enhancing therapeutic results. Recent research on leukemia, multiple myeloma (MM), and lymphoma has increasingly focused on analyzing the expression profiles of snoRNAs. For example, ACA11 is overexpressed in multiple myeloma patients with the t(4;14) karyotype (26). Similarly, the overexpression of SNORD116-18 and SNORA74A has been linked to reduced progression-free survival (PFS) in patients diagnosed with chronic lymphocytic leukemia (CLL) (27). In diffuse large B-cell lymphoma (DLBCL), SNORD125, a specific small nucleolar RNA (snoRNA), functions as a guide RNA (gRNA) for 2′-O-methylation during ribosome biogenesis. It is associated with the LSU-G4593 region of ribosomes and shows potential as a prognostic marker for DLBCL (28). Emerging evidence underscores the value of snoRNAs as promising candidates for diagnostic and prognostic biomarkers in a variety of diseases. Furthermore, their therapeutic potential is actively being explored (15, 19). This systematic review examines the roles of snoRNAs in hematologic malignancies, evaluating their utility as prognostic, diagnostic, and therapeutic biomarkers in these diseases.

Material and Methods

This systematic review was conducted in

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accordance with the Preferred Reporting Items for Systematic Reviews and Meta‑Analyses (PRISMA) guidelines (29) and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024574222). This study was conducted strictly according to the registered PROSPERO protocol, and no methodological deviations occurred. The protocol did not include a planned meta‑analysis; therefore, the absence of quantitative pooling does not represent a deviation. The review followed all predefined procedural steps, including eligibility criteria, comprehensive search strategy, study selection, data extraction, and quality assessment using the Newcastle–Ottawa Scale (NOS). The NOS is widely used for observational biomarker studies due to its structured evaluation of selection, comparability, and outcome domains; it was therefore appropriate for the included study designs. The review was designed to address the following research question: Which small nucleolar RNAs (snoRNAs) exhibit consistent differential expression in individuals with leukemia, myeloma, and lymphoma, and could potentially serve as prognostic, diagnostic, or subtype‑specific markers.

Search Strategy and Literature Inquiry

Comprehensive database searches were performed across PMC, PubMed, Embase, SCOPUS, and Web of Science between June 26, 2024, and August 27, 2024. Initially, each database was assessed to confirm the inclusion of terms such as "long non-coding RNAs" and "acute lymphoblastic leukemia." The search strategy was first developed in PubMed using Medical Subject Headings (MeSH) terms and keywords, and subsequently adapted for other databases. The PubMed search strategy was as follows: ((snoRNA [Text Word]) OR (RNA, Small Nucleolar [MeSH Terms])) AND ((Leukemia [MeSH Terms]) OR (Lymphoma [MeSH Terms]) OR (Multiple Myeloma [MeSH Terms]) OR (Cancer [Title])). For Embase, the search strategy included: ((snoRNA) OR ('small nucleolar RNA'/exp)) AND (('Leukemia'/exp) OR ('Lymphoma'/exp) OR ('multiple myeloma'/exp) OR (cancer)). The search strategy for PMC was: (snoRNA [Text Word] OR "RNA, small nucleolar"[MeSH Terms]) AND ("leukemia"[MeSH Terms] OR "lymphoma"[MeSH Terms] OR "multiple myeloma"[MeSH Terms]). In Scopus, the following query was used: (TITLE-ABS-KEY("snoRNA") OR TITLE-ABS-KEY("small nucleolar RNA")) AND (TITLE-ABS-KEY("leukemia") OR TITLE-ABS-KEY("lymphoma") OR TITLE-ABS-KEY("multiple myeloma")). For Web of Science (WoS), the search strategy was: ALL=(snoRNA) AND (AB=(Leukemia) OR TI=(Leukemia) OR AK=(Leukemia) OR AB=(Lymphoma) OR TI=(Lymphoma) OR AK=(Lymphoma) OR AB=(Multiple Myeloma) OR TI=(Multiple Myeloma) OR AK=(Multiple Myeloma)). All retrieved records were exported to EndNote (version 21) for further management and analysis.

Study Selection

In the first screening step, studies were exclusively selected that met the following criteria: 1) Articles written in English; 2) Studies that measured snoRNA levels; 3) Studies that provided data on patients with leukemia, myeloma, or lymphoma subtypes; 4) Original research studies; 5) Studies with full-text availability. Conference abstracts, studies involving animal models, dataset samples, cell lines, retracted papers, and book chapters were excluded. Two authors (FT and MKH) independently performed the initial review of titles and abstracts from all identified studies using the predetermined inclusion and exclusion criteria. After compiling the qualified studies, both authors conducted an in-depth assessment of the full texts. Any disagreements during the review process were resolved through a consensus-based approach involving FT, MKH, and MMH. In the final screening step, studies that lacked relevant data, did not include a control group comparison, or were letters to the editor were excluded.

Data Extraction and Quality Evaluation

FT extracted the following information from each publication: author name, publication year, type and subtype of blood cancer, main findings, patient specimen type, sample sizes for both

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patients and controls, study methodology, and conclusions. All supplementary materials, including supplementary tables and figures, were thoroughly reviewed to ensure comprehensive data extraction. The included studies were evaluated for quality and assessed for risk of bias by three authors using the Newcastle-Ottawa Quality Assessment Scale (NOS). Discrepancies in the evaluations were resolved through discussion among the authors. The NOS assesses three main types of bias: selection bias, comparability bias, and outcome bias. Based on the NOS scores, studies were categorized into three quality groups: scores of 7–9 were classified as 'good,' scores of 4–6 as 'fair,' and scores of 0–3 as 'poor.'

Results

A total of 783 articles were identified through database searches, including 192 from PubMed, 188 from Embase, 132 from PMC, 230 from Scopus, and 41 from Web of Science (WoS). After eliminating 232 duplicate records using EndNote, 551 articles remained for title and abstract screening according to the predefined inclusion and exclusion criteria. During this step, 528 studies were excluded for the following reasons: animal models (n = 1), dataset and cell-line samples (n = 11), non-English articles (n = 1), studies not measuring snoRNA (n = 4), conference abstracts (n = 13), review articles (n = 64), studies unrelated to hematologic malignancies (n = 142), and studies not related to snoRNAs (n = 292). Following the initial screening, 23 studies were selected for full-text reading and data extraction. Of these, 11 studies were excluded for the following reasons: lack of relevant data (n = 5), letters to the editor (n = 3), and absence of control group comparison (n = 2). In total, 12 studies met the eligibility criteria and were included in the final analysis. The study selection process is outlined in the flowchart shown in Figure 2.

Collectively, these studies encompassed 1,240 cases of hematologic malignancies. The distribution of cases is as follows: 461 cases of Multiple Myeloma (MM), 25 cases of B-Cell Acute Lymphoblastic Leukemia (B-ALL); 2 cases of T-Cell Acute Lymphoblastic Leukemia (T-ALL); 112 cases of Acute Myeloid Leukemia (AML); 143 cases of B-Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL); 211 cases of Chronic Lymphocytic Leukemia (CLL); 122 cases of Peripheral T-Cell Lymphomas (PTCL) including Angioimmunoblastic T-cell Lymphoma (AITL), PTCL-Not Otherwise Specified (PTCL-NOS), and Anaplastic Large Cell Lymphoma (ALCL); 8 cases of Secondary Plasma Cell Leukemia (sPCL); and 156 cases of high-risk smoldering multiple myeloma (HR-SMM). RNA sequencing (RNA-seq) was utilized in 2 studies, reverse transcription polymerase chain reaction (RT-PCR) in 8 studies, and microarray analysis in 7 studies. A total of 133 unique snoRNAs showed differential expression across various hematologic malignancies. Table I provides a detailed summary of studies examining the role of small nucleolar RNAs (snoRNAs) in hematologic oncology, including key study characteristics such as research design, sample size, methodology, and major findings (the complete list is available in Supplementary File 1).

According to the Newcastle-Ottawa Scale (NOS), the quality scores of the included studies ranged from 5 to 9, with an average score of 6.4. Six studies (50%) were classified as high quality (score ≥7), while the remaining six showed moderate quality. In terms of exposure ascertainment, all studies received maximum points, indicating reliable methodology in measuring snoRNA levels and consistent ascertainment methods between cases and controls. However, the selection domain revealed some limitations; specifically, several studies lacked clarity regarding the representativeness of cases or the selection process of controls. Regarding comparability, most studies controlled for the most important factor (e.g., age or gender), with only one study (30) adjusting for additional confounding factors, achieving the maximum score of 9 (Table II).

Multiple Myeloma (MM)

The most extensively studied hematologic malignancy in this systematic review was multiple myeloma, which was the focus of 50% of the included studies. RNA-seq analysis was performed

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in one study (31), while microarray analysis and RT–PCR were utilized in five studies (32-36). According to microarray expression profiling, SNORA71A, SNORD55, SCARNA22, and ACA11 were overexpressed in multiple myeloma patients (32, 33, 35, 36). Additionally, SNORD25, SNORD27, SNORD30, and SNORD31 were found to be overexpressed in patients with high-risk smoldering multiple myeloma (HR-SMM) (34).

Transcriptome analysis of the transition from MGUS to high-risk smoldering myeloma (HR-SMM) and active MM revealed that, despite globally similar expression profiles, a specific cluster of eight snoRNAs (including SNORD55) exhibited progressive upregulation throughout the disease evolution, contrasting with the progressive downregulation of the pro-apoptotic gene APAF1 (33). Within the HR-SMM cohort specifically, the overexpression of SNORD25, SNORD27, SNORD30, and SNORD31 proved to be a robust predictor of rapid progression to symptomatic MM. Unlike chromosomal abnormalities, which failed to predict outcomes, high levels of these snoRNAs were significantly associated with a shorter time to progression ($P<0.03$) (34). SNORA71A was identified as a candidate diagnostic biomarker through transcriptomic network analysis. Validation in patient samples confirmed significant upregulation of SNORA71A, which correlated positively with serum creatinine levels ($P=0.0002$), linking its expression to renal impairment (36).

Elucidating the snoRNA landscape in MM demonstrated that snoRNA expression profiles are intrinsically determined by specific cytogenetic alterations. Through comprehensive RNA-sequencing of CD138+ myeloma cells, SNORD78 was identified as a critical oncogenic snoRNA; its upregulation was directly driven by the high-risk chromosomal aberration Gain(1q) (where the gene is located at 1q21.2) and was significantly associated with poor overall survival (OS) and progression-free survival (PFS). Furthermore, hierarchical clustering revealed distinct molecular subgroups, notably the specific overexpression of the SNORD115 family in patients with hyperdiploid karyotypes (31).

Comprehensive transcriptional profiling in plasma cell dyscrasias has revealed that snoRNA expression patterns can stratify Multiple Myeloma patients into distinct molecular subgroups. Both Ronchetti et al. and Chu et al. identified the orphan H/ACA box snoRNA, ACA11 (SCARNA22), as a critical marker specifically overexpressed in patients harboring the high-risk t(4;14)(p16.3;q32.3) translocation. This upregulation is driven by a gene-dosage effect, as ACA11 is encoded within the introns of the WHSC1 (also known as MMSET or NSD2) gene, which is constitutively activated by the IgH enhancer in this translocation (32, 35).

Functionally, Chu et al. demonstrated that ACA11 acts as a downstream effector of the t(4;14) abnormality. It localizes to nucleoli, associates with specific snRNP complexes, and downregulates ribosomal protein genes. This modulation of ribosome biogenesis leads to a significant suppression of oxidative stress (ROS) levels, creating a cellular environment that promotes tumor growth and chemotherapy resistance. ACA11 in MM does not exhibit a significant impact on either PFS ($P = 0.561$) or OS ($P = 0.729$). However, its expression is elevated in patients with the t(4;14) translocation, and this overexpression was associated with decreased survival (32). In contrast to the specific upregulation of ACA11 in MM, Ronchetti et al. highlighted a distinct pattern during the transition to Secondary Plasma Cell Leukemia (sPCL). This aggressive, extramedullary phase is characterized by a global downregulation of snoRNAs. Specifically, reduced levels of SNORD32A and SNORA42 were identified as a signature distinguishing sPCL from intramedullary MM, marking the progression to a terminal leukemic stage (35).

Table III summarizes the snoRNAs with prognostic significance reported across the studies included in this systematic review.

Acute Lymphoblastic Leukemia (ALL)

Two studies investigated snoRNA expression in patients with different subtypes of acute lymphoblastic leukemia (ALL). One study focused on patients with B-cell acute lymphoblastic

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leukemia (B-ALL) and T-cell acute lymphoblastic leukemia (T-ALL) (37), while the other examined patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL) (27).

While global expression profiling often indicates a widespread downregulation of snoRNAs in ALL compared to healthy lymphoid progenitors, distinct molecular subtypes exhibit specific upregulation patterns that hold prognostic significance. In the context of B-cell precursor ALL (BCP-ALL), particularly within the heterogeneous "B-other" group (patients lacking common chromosomal aberrations), Vendramini et al. identified a unique non-coding RNA signature associated with the ERG-related leukemia subtype. Analysis of 143 pediatric BCP-ALL samples revealed that this subtype is characterized by the coordinate overexpression of orphan C/D box snoRNAs mapping to the Prader-Willi Syndrome (PWS) locus on chromosome 15q11.2. Microarray expression profiling of snoRNAs in the PWS locus revealed upregulation of SNORD109A, SNORD64, SNORD107, SNORD55, and twelve snoRNAs from the orphan SNORD116 cluster (SNORD116-11, SNORD116-14, SNORD116-15, SNORD116-16, SNORD116-17, SNORD116-18, SNORD116-20, SNORD116-21, SNORD116-22, SNORD116-23, SNORD116-24, and SNORD116-27) in ERG-related patients with BCP-ALL. The specific signature included the upregulation of the SNORD116 cluster (specifically SNORD116-1, -18, -23, and -24), alongside SNORD109A, SNORD64, and SNORD107. Clinically, this snoRNA expression profile is of high value for patient stratification.The high expression of the SNORD116 cluster successfully delineates a subgroup of patients with favorable event-free survival (EFS). Notably, this favorable prognostic impact was observed even in the presence of IKZF1 deletions, a genetic marker typically associated with poor outcomes in BCP-ALL (27).

In terms of global expression patterns, Valleron et al. reported a widespread suppression of the snoRNA transcriptome in ALL. Their high-throughput analysis revealed that approximately 61% of screened snoRNAs were significantly downregulated in ALL blasts compared to healthy lymphoid controls (CD3+/CD19+ cells). This global downregulation suggests that, beyond specific oncogenic drivers, a broad disruption of the translational machinery or widespread epigenetic silencing of snoRNA host genes may characterize the lymphoblastoid leukemic state (38).

Acute Myeloid Leukemia (AML)

Three studies examined the differential expression of snoRNAs in patients with AML (38-40). Utilizing next-generation sequencing (RNA-seq), Warner et al. provided a comprehensive map of the snoRNA transcriptome in normal hematopoiesis and AML. The study revealed that snoRNA expression is highly lineage- and developmental-stage specific. In normal physiology, snoRNAs located within the imprinted DLK1-DIO3 (14q32) and SNURF-SNRPN (15q11) loci are highly expressed in hematopoietic stem/progenitor cells (CD34+) and significantly downregulated during myeloid differentiation. In AML blasts, while the high expression of these "stemness-associated" imprinted snoRNAs is retained, a distinct subset of 102 snoRNAs—including SNORA21, SNORA36C, and SCARNA15—was consistently downregulated compared to normal CD34+ controls (Supplementary Table I) (39).

Further functional analysis revealed that this downregulation is not random but selectively affects snoRNAs involved in specific rRNA modifications (pseudouridylation and 2′-O-methylation). Notably, there was a reduced expression of snoRNAs that specifically target the peptidyl transferase center (PTC) and the internal spacer boundary (ISB) regions of the 60S ribosomal subunit (39).

In addition, several snoRNAs involved in the pseudouridylation of small nuclear RNAs (snRNAs) at splicing-critical regions were identified. For example, scaRNA15, which guides modification of the branch site recognition region in U2 snRNA, showed a 2.81-fold reduction in AML. Pseudouridylation at this site is crucial for the proper formation of enhancer RNAs (eRNAs) (41-44).

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A distinct dichotomy in snoRNA expression was identified by Valleron et al. in myeloid leukemias. While the majority of AML subtypes exhibited a global downregulation of snoRNAs compared to CD33+ myeloid progenitors, Acute Promyelocytic Leukemia (APL) presented a unique signature characterized by the specific upregulation of the SNORD112–114 cluster located at the imprinted DLK1-DIO3 locus (14q32). This upregulation was found to be driven by the PML-RARα fusion protein. Mechanistically, the study demonstrated that SNORD114-1 functions as an oncogene in this context, promoting cell growth by modulating the G0/G1 to S phase transition via the Rb/p16 cell cycle pathway (38).

Beyond the classical nucleolar roles, Han et al. identified a novel functional class of chromatin-associated snoRNAs (casnoRNAs) involved in AML pathogenesis. They focused on the orphan snoRNA SNORA73 (specifically SNORA73A and SNORA73B), which was found to be significantly downregulated in AML patients compared to healthy donors. Clinically, reduced expression of SNORA73 correlated with adverse cytogenetic risk and poor overall survival. Mechanistically, SNORA73 functions through a non-canonical pathway by interacting directly with PARP1 within the chromatin compartment. It inhibits PARP1 auto-PARylation, thereby regulating the DNA damage response (DDR). The downregulation of SNORA73 in leukemic cells disrupts this regulatory axis, leading to genomic instability and maintaining the differentiation block characteristic of AML blasts (40).

Chronic Lymphocytic Leukemia (CLL)

In a comprehensive study by Ronchetti et al., the snoRNA transcriptome of 211 early-stage (Binet A) CLL patients was profiled relative to distinct normal B-cell subsets. The analysis revealed that the global snoRNA expression profile of CLL cells closely mirrors that of normal memory and marginal-zone B-cells, implying a specific cellular origin. Despite this global similarity, a distinct subset of snoRNAs, including SNORA70F, SNORA71C, SNORA62, SNORA6, and SNORA31, was significantly downregulated in leukemic cells compared to controls. A key finding of this study was the tight correlation between snoRNA expression and its host gene, reinforcing the concept of host-gene dependence in CLL. SNORA70F downregulation was associated with the reduced expression of its host gene, COBLL1. SNORA31 showed significant co-downregulation with its host gene, TPT1. SNORA6 and SNORA62 were downregulated alongside their shared host gene, RPSA. Clinically, SNORA70F emerged as a critical biomarker; its reduced expression was strongly associated with established poor prognostic indicators, including unmutated IGHV status, CD38 positivity, and high ZAP-70 expression. Conversely, SNORA74A and SNORD116-18 were found to be upregulated. Based on these expression patterns, a prognostic model was developed that successfully stratified patients into distinct risk groups regarding progression-free survival (PFS), independent of conventional clinical markers (30).

Lymphoma

Valleron et al. conducted a comprehensive expression profiling of 80 snoRNAs in a cohort of 122 patients with Peripheral T-Cell Lymphoma (PTCL). This cohort included cases of Angioimmunoblastic T-cell Lymphoma (AITL)—a rare subtype of non-Hodgkin T-cell lymphoid malignancy—and PTCL-Not Otherwise Specified (PTCL-NOS), which represents the most prevalent and heterogeneous form of T-cell lymphoma. The study revealed a widespread global downregulation of snoRNAs in tumor samples compared to normal T-cells and reactive lymph nodes. Despite this general suppression, specific signatures emerged; notably, distinct snoRNA profiles successfully discriminated Anaplastic Large Cell Lymphoma (ALCL) from other PTCL subtypes. Most significantly, microarray analysis identified that the orphan C/D box snoRNA HBII-239 (SNORD71) was overexpressed in both AITL and PTCL-NOS subtypes, serving as the strongest statistically significant biomarker associated with longer OS and PFS (37).

Conflicts and Accord of Studies

This systematic review highlights lineage-

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specific divergences in snoRNA expression between lymphoid and myeloid malignancies. Vendramini et al. reported that ten members of the imprinted SNORD116 family (including SNORD116-11, -14, -15, -16, -20, -21, -22, -23, -24, and -27) were specifically upregulated in the ERG-related subtype of BCP-AL (27). In contrast, Warner et al. observed that these exact same members were downregulated in AML patients compared to controls (39). Secondly, the study by Valleron et al. (37) reported overexpression of SNORD114-1 in APL patients, while Warner et al. (39) observed its downregulation in AML patients.

Also, there were consistent findings across different studies. For instance, Ronchetti et al. (30) and Vendramini et al. (27) both found upregulation of SNORD116-18 in CLL and BCP-ALL patients, respectively. Similarly, Ronchetti et al. (30) and Warner et al. (39) observed downregulation of SNORA31 in CLL and AML patients, respectively.

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Table I: Key snoRNA alterations and clinical associations in hematologic

Subtypes	study ID	Specimen (n)	Control (n)	D.E. Method	snoRNA type	snoRNA level	Key Findings	Prognostic value	Ref.
MM & Plasma Cell Dyscrasias									
	1	MM /Bone marrow/75	CD19+ B cells from healthy donor peripheral blood (3)	RNA-seq	SNORD78 SNORD115 family	Upregulation	Gain(1q)-driven SNORD78 overexpression associates with poor prognosis, while SNORD115 is selectively upregulated in hyperdiploid MM	+ (Adverse)	**Zhao et al., 2023 (31)**
	2	MM/ Bone marrow (32) & peripheral blood (19)	Bone marrow (13) and peripheral blood (37)	RT–PCR	SNORA71A	Upregulation	SNORA71A, a WGCNA hub gene, serves as a diagnostic biomarker and correlates with serum creatinine, linking it to renal impairment	+ (Adverse/ Diagnostic)	**Xu et al., 2022 (36)**
	6	MM(41), HR-SMM (33) / Bone marrow	Bone marrow (5)	Microarray (GEP) & RT–PCR	8 snoRNAs (Including SNORD55)	Upregulation	Eight snoRNAs show progressive upregulation from MGUS to SMM and MM, implicating them in multistep plasma -cell transformation	-	**López-Corral et al., 2014 (33)**
	12	MM (239)/ bone marrow	Normal plasma cells (7)	Northern Blot, qRT-PCR, Microarray (GEP)	ACA11 (SCARNA22)	Overexpression	t(4;14)-driven ACA11 overexpression suppresses ROS, downregulates ribosomal proteins, and promotes proliferation and chemoresistance	-	**Chu et al., 2012 (32)**
	10	MM-t(4;14) subgroup (55) / Bone marrow	Tonsil (4)	Microarray & qRT-PCR	ACA11 (SCARNA22)	Upregulation	ACA11 overexpression in t(4;14) MM is driven by gene dosage and promotes proliferation via oxidative stress regulation	-	**Ronchetti et al., 2012 (35)**
	10	sPCL (8)/ Bone marrow	Tonsil (4)	Microarray	SNORD32A SNORA42	Downregulation	Global snoRNA downregulation distinguishes sPCL from MM, marking transition to an aggressive leukemic phase	-	**Ronchetti et al., 2012 (35)**
	11	HR-SMM (123)/ Bone marrow	Comparison between patients who progressed rapidly vs. those who didn't (HR-SMM group)	Microarray (GEP) FISH, SNP-arrays	SNORD25, SNORD27, SNORD30, SNORD31	Overexpression	Overexpression of SNORD25/27/30/31 is significantly associated with shorter time to progression to symptomatic MM	-	**López-Corral et al., 2012 (34)**

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Table I:Continued

8	PTCL (122 total, 46 AITL, 26 PTCL-NOS)	blood or lymph node (35)	High-throughput RT-qPCR	Overexpression HBII-239 (SNORD71)		HBII‑239 (SNORD71) overexpression is the strongest predictor of favorable OS and PFS in AITL and PTCL‑NOS	+ (Favorable)	**Valleron et al., 2012, Blood (37)**
5	BCP-ALL/ Bone marrow or PBMC (143; 35 identified as ERG-related)	non-ERG related BCP-ALL (108)	Microarray & RT-qPCR	SNORD109A SNORD64 SNORD107 12 snoRNAs in SNORD116 cluster (15 in total)	Upregulation	High SNORD116/PWS‑locus expression defines ERG‑related ALL with favorable EFS despite IKZF1 deletions	+ (favorable)	**Vendramini et a;., 2017 (27)**
9	B-ALL(25)/ bone marrow	Healthy Donors (CD33+ Myeloid cells, n=7)	Microarray & High-throughput qPCR	SNORD112, SNORD113, SNORD114 (Cluster)	Downregulation	Global snoRNA downregulation in AML/ALL, except DLK1‑DIO3 (SNORD112–114) upregulated in APL (PML‑RARα+); SNORD114‑1 promotes growth via the Rb/p16 pathway	-	**Valleron et al., 2012, Leukemia (38)**
9	T-ALL(2)/ bone marrow	Healthy Donors (CD33+ Myeloid cells, n=7)	Microarray & High-throughput qPCR	SNORD112, SNORD113, SNORD114 (Cluster)	Downregulation	Global snoRNA downregulation in AML/ALL, except DLK1‑DIO3 (SNORD112–114) upregulated in APL (PML‑RARα+); SNORD114‑1 promotes growth via the Rb/p16 pathway	-	**Valleron et al., 2012, Leukemia (38).**

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7	CLL/ PBMC (211)	PBMC (6) and Tonsils (12)	Microarray (Affymetrix GeneChip Human Gene 1.0 ST)	Downregulation: SNORA70F, SNORA31, SNORA62, SNORA6 Upregulation: SNORD116-18, SNORA74A		CLL snoRNA expression largely mirrors normal memory/marginal‑zone B cells SNORA70F downregulation correlates with poor prognosis and COBLL1 expression A 2‑snoRNA signature (SNORA74A, SNORD116‑18) independently predicts PFS	+ ((SNORA70F , SNORA74A, SNORD116-18))	Ronchetti et al., 2013 (30)	**Lymphoma** ALL
3	AML/ Bone marrow (53)	Bone marrow (5)	RNA-seq & qRT-PCR	SNORA73A/B (Orphan casnoRNA)	Downregulation	SNORA73A/B downregulation distinguishes AML from controls, associates with adverse risk and poor outcomes, and mechanistically limits DNA damage and differentiation	+ (Positive correlation between downregulation and poor outcome)	Han et al., 2022 (40)	
4	AML/ Bone marrow (33)	Bone marrow (32)	RNA-Seq	102 snoRNAs Including SNORA21 and SNORA36C and SCARNA15	Downregulation	A set of 102 snoRNAs is downregulated in AML independent of host gene expression, distinguishing leukemic blasts from normal CD34+ progenitors	+ (Diagnostic/ Distinction value)	Warner et al., 2018 (39)	
9	AML (26)/ bone Marrow (including 8 APL and 18 non-APL cases)	Healthy Donors (CD33+ Myeloid cells, n=7)	Microarray & High-throughput qPCR	SNORD112, SNORD113, SNORD114 (Cluster) Specifically: SNORD114-1	Upregulation	Global snoRNA downregulation in AML/ALL, except DLK1‑DIO3 (SNORD112–114) upregulated in APL (PML‑RARα+); SNORD114‑1 drives growth via the Rb/p16 pathway	-	Valleron et al., 2012, Leukemia (38)	

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CLL	AML

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Table II: Quality assessment of included studies using the Newcastle–Ottawa Scale (NOS)

Study ID	Ref.	selection				Comparability	Exposure			Overall Score
		case definition	Representativeness of the cases	Selection of Controls	Definition of Controls		Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
1	Zhao et al., 2023 (31)	*	*		*	*	*	*	*	7
2	Xu et al., 2022 (36)	*	*		*	*	*	*	*	7
3	Han et al., 2022 (40)	*	*		*	*	*	*	*	7
4	Warner et al., 2018 (39)	*			*	*	*	*	*	6
5	Vendramini et a;.,2017 (27)	*				*	*	*	*	5
6	López-Corral et al., 2014 (33)	*			*	*	*	*	*	6
7	Ronchetti et al., 2013 (30)	*	*	*	*	**	*	*	*	9
8	Valleron et al., 2012, Blood (37)	*	*		*	*	*	*	*	7
9	Valleron et al., 2012 (38)	*				*	*	*	*	5
10	Ronchetti et al., 2012 (35)	*	*		*	*	*	*	*	7
11	López-Corral et al., 2012 (34)	*				*	*	*	*	5
12	Chu et al., 2012 (32)	*			*	*	*	*	*	6

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Table III: Association of snoRNA overexpression with reduced survival in hematologic malignancies

SnoRNA	Disease	OS			PFS				Ref.
		HR	HR, 95% CI	P value	HR	HR, 95% CI	P value	Follow-up median (months)	
SNORD78	MM	14.4	1.17-179	0.038	3.73	1.19-11.7	0.024	31.74 months	(31)
SCARNA22	MM	2.12	0.17-26.4	0.561	0.828	0.28-2.41	0.729	31.06 months	(31)
SNORD116-18	CLL	na	na	na	2.72	2-4.93	0.001	30 months	(30)
SNORA74A	CLL	na	na	na	2.93	1.6-5.34	0.0004	30 months	(30)
SNORD56	CLL	na	na	na	2.99	1.62-5.52	0.0005	30 months	(30)
SNORD1A	CLL	na	na	na	2.71	1.5-4.89	0.0009	30 months	(30)
SNORA70F	CLL	na	na	na	2.78	1.53-5.06	0.0008	30 months	(30)

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, Overall survival; PFS, Progression-free Survival

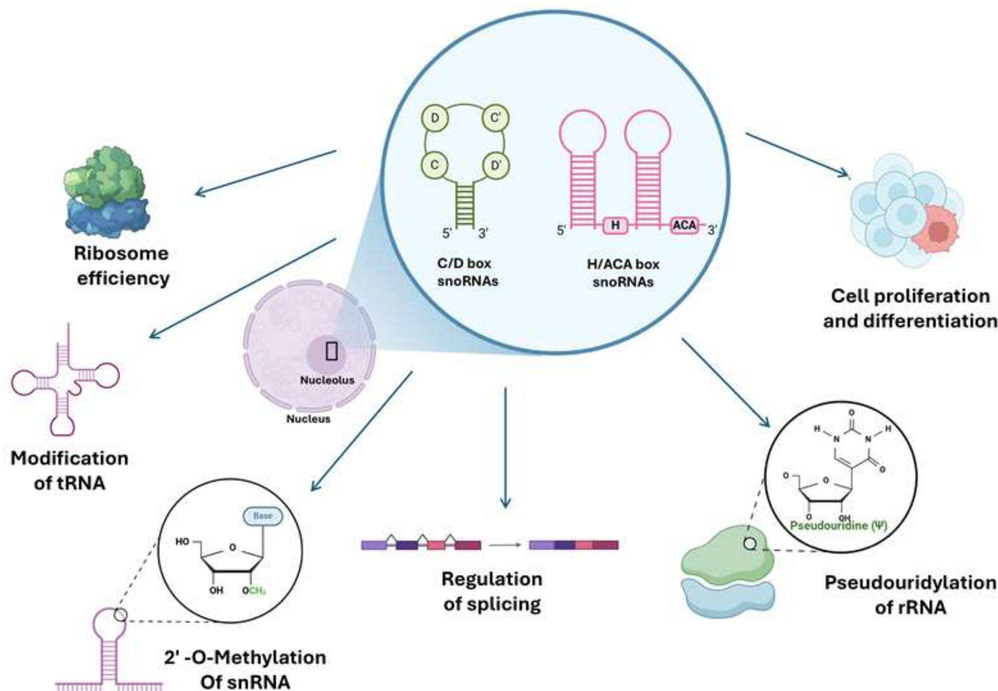

Figure 1. A schematic representation illustrating the diverse functions of snoRNA in the regulation of hematological malignancies.

Alterations in snoRNA expression lead to fluctuations in their levels, which in turn influence cellular processes such as RNA modification, alternative splicing, ribosomal function, and mRNA expression. These molecular alterations can impact pathological mechanisms, as evidenced by their involvement in the regulation of proliferation and self-renewal capabilities in blood disorders (created with BioRender).

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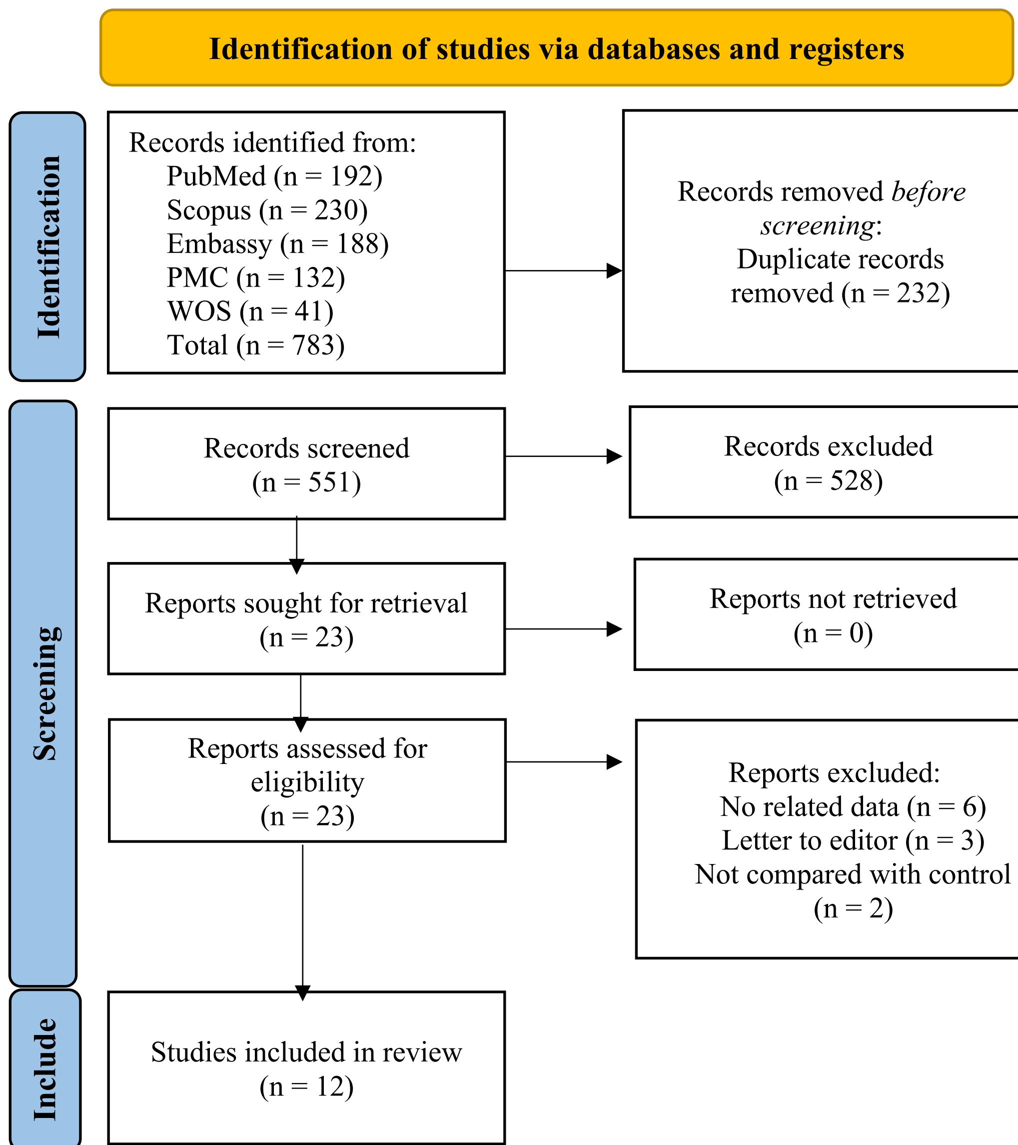

Figure 2. The flowchart of complete search strategy.

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Discussion

This systematic review investigated alterations in snoRNA expression profiles in patients diagnosed with hematologic cancers, aiming to explore their potential roles in diagnosis, real-time treatment monitoring, and prognostication. Among the studies, Multiple Myeloma (MM) represents the most mature area of snoRNA research, offering compelling evidence for their utility in risk stratification and diagnosis. By synthesizing data from 12 studies involving conditions such as MM, AML, ALL, and lymphoma, these findings reveal that snoRNAs are not merely housekeeping genes but are actively dysregulated in blood cancers. This dysregulation exhibits lineage-specific patterns and holds significant prognostic value. Given the limitations of current therapeutic modalities and the molecular heterogeneity of hematologic neoplasms, the identification of

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snoRNAs as stable, detectable biomarkers offers a promising avenue for improving early diagnosis, risk stratification, and potentially, therapeutic targeting (4, 45).

Hematologic malignancies are highly heterogeneous at the molecular level and often remain incurable. Recent studies have identified recurrent mutations, abnormal DNA methylation patterns, and dysregulation of histone deacetylases, particularly in leukemia and lymphoma. Understanding the role of these factors in hematologic oncogenesis is critical for developing innovative, targeted treatments that enhance prognosis and therapeutic response (46). Extensive genomic and epigenomic analyses have demonstrated that dysregulation of epigenetic mechanisms plays a significant role in hematologic malignancies (47).

Although miRNAs and lncRNAs are critical in the pathogenesis of blood cancers (48, 49), their clinical utility faces limitations, such as the structural complexity of lncRNAs (49) and the reduced specificity of miRNAs seen across various tumor types (50). In contrast, snoRNAs emerge as superior biomarker candidates due to their high conservation and remarkable stability in biofluids (51, 52). Their smaller size and stability make them more practical for clinical assays compared to lncRNAs (53-55). The snoRNAs, together with miRNAs and lncRNAs, map a more comprehensive epigenetic landscape of hematologic oncogenesis.

SnoRNAs, a class of small non-coding RNAs, play diverse roles in cellular processes, including ribosomal biogenesis, precursor ribosomal RNA (pre-rRNA) splicing and modification, small nuclear RNA (snRNA) modification, translation regulation, and mRNA processing (56-59). Their improper regulation can affect cellular functions such as proliferation (57), apoptosis (60), differentiation (61), cell cycle progression (37), and oxidative stress response (60). Emerging research highlights their involvement in the differentiation, proliferation, and apoptosis of hematopoietic cells, suggesting their potential utility as prognostic biomarkers and therapeutic targets in hematologic malignancies (30, 36, 39, 62-66).

Recent studies have shown that snoRNAs regulate gene expression and signaling pathways (67), serving as biomarkers in various cancers (68), including liver (69) and colorectal cancers (70). However, the mechanisms underlying their roles in hematologic malignancies remain insufficiently understood. Given their prevalence in tumors and circulation, snoRNAs hold promise as biomarkers and therapeutic targets for cancer diagnosis and treatment.

Our review focused on human studies, but it aligns with findings from cell line and dataset-based research. For example, Li et al. identified 12 prognostic snoRNAs in a DLBCL dataset (SNORA66, SNORA60, SNORD1A, SNORD44, SNORA71A, SNORA4, SNORA17, SCARNA16, SNORD88C, SNORD19B, SNORA73A) and constructed a three-snoRNA signature (SNORD1A, SNORA60, and SNORA66) linked to ribosomal and mitochondrial functions (71). Liu et al. demonstrated that SNORD116-4, SNORD20, and SNORD28 interact with the RNA-binding protein MLLT3, influencing post-transcriptional gene regulation in high-risk AML (72). In a study using cultured AML cell lines, Datta et al. demonstrated that FXR1 regulates snoRNAs, which modify specific sites on ribosomal RNA (rRNA) essential for translation. Elevated levels of snoRD58A and snoRA22 were associated with increased modifications on 28S rRNA. Additionally, FXR1 was found to influence U3 and U8 snoRNAs, which are involved in processing the 47S Pol I precursor rRNA, thereby altering the mature forms of 28S, 18S, and 5.8S rRNAs (73). Similarly, Pauli et al. identified that elevated expression of SNORD42A, together with U116-mediated 2'-O-methylation of 18S rRNA, is essential for the proliferation and survival of leukemia cells in AML patient-derived cell cultures (64). In another study, Oliveira et al. explored multiple MM cell lines and revealed that ACA11 snoRNA promotes ribosome production and impacts chemotherapy response. Their findings suggest that ACA11 could serve as a pivotal

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target for personalized treatment strategies, particularly in myeloma patients harboring the t(4;14) translocation (26). These parallel pieces of evidence reinforce the conclusion that snoRNA dysregulation is a pervasive feature of hematologic malignancies. Also, several reviews have explored the roles of snoRNAs in hematopoiesis and hematologic neoplasms, aligning with findings of this study (21, 24, 25, 74).

Molecular Mechanisms

Mechanistically, this systematic review reveals that snoRNA dysregulation is not uniform but exhibits lineage-specific expression dynamics driven by distinct oncogenic stresses. Crucially, recent data provide a mechanistic explanation for the heterogeneity observed in MM snoRNA profiles, establishing a direct causal link between chromosomal instability (CIN) and snoRNA dosage. While previous studies focused on expression levels, Zhao et al. demonstrated that snoRNA upregulation in MM is often a "gene dosage effect" driven by copy number variations (CNVs). Specifically, the overexpression of SNORD78 was identified not merely as a random transcriptomic event but as a direct consequence of the Gain(1q21) chromosomal aberration, a well-established high-risk marker in myeloma. This finding suggests that snoRNAs residing in amplified chromosomal regions act as oncogenic drivers that confer a proliferative advantage, potentially through the modification of rRNA methylation patterns (revealed by RiboMethSeq) to support the high translational demand of malignant plasma cells (31). This contrasts with SCARNA22, which, despite being elevated in t(4;14) carriers, does not independently predict survival (26, 31), suggesting that while some snoRNAs act as drivers (SNORD78), others may function as passenger markers of underlying translocations. However, the findings by Ronchetti et al. provide critical evidence supporting the "host-gene dependence" hypothesis in plasma cell dyscrasias, presenting a regulation model distinct from the "uncoupled" expression patterns observed in AML (Warner et al.). In MM, the overexpression of ACA11 (SCARNA22) is a direct consequence of the t(4;14) chromosomal translocation, demonstrating how cytogenetic aberrations can drive the expression of intronic snoRNAs alongside their host genes (in this case, WHSC1/MMSET) via a gene-dosage effect. Yet, ACA11 is not merely a passive surrogate marker; Chu et al. identified it as a critical downstream effector that actively drives the aggressive phenotype. Functionally, ACA11 acts as a potent "onco-RNA" by downregulating ribosomal proteins and, consequently, suppressing cellular oxidative stress (ROS). Since high levels of ROS are typically toxic to cancer cells and are required for the efficacy of many chemotherapeutic agents, ACA11-mediated ROS suppression confers a significant survival advantage. This mechanism directly contributes to resistance against proteasome inhibitors and alkylating agents, explaining the poor prognosis associated with t(4;14) patients (32).

Unlike snoRNAs driven strictly by chromosomal copy number variations, SNORA71A was identified as a 'hub gene,' suggesting it occupies a central position in the transcriptional regulatory network of myeloma cells. This implies that SNORA71A may be functionally coupled with key metabolic or proliferative pathways essential for plasma cell survival, distinguishing it as a potential therapeutic target independent of specific cytogenetic subgroups (36). Furthermore, the progressive deregulation of specific snoRNA subsets suggests they play a direct functional role in the multistep transformation process of monoclonal gammopathies. The steady increase of SNORD55 and the SNORD25–31 cluster indicates that these molecules are intrinsic to the clonal expansion required to bridge the gap from an indolent precursor to an aggressive malignancy. The authors propose that this upregulation is not merely a bystander effect but likely contributes to the enhanced ribosome biogenesis and metabolic adaptation necessary for the malignant clone to thrive and evolve into symptomatic disease, highlighting these

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snoRNAs as potential biomarkers for monitoring the risk of transformation (33). Specifically, in a cohort of HR-SMM patients classified as 'high-risk' by clinical criteria, conventional genetic markers (such as FISH) failed to distinguish subgroups with faster progression. In contrast, snoRNA overexpression served as a more precise and independent molecular indicator. Mechanistically, all four of the identified snoRNAs (SNORD25, SNORD27, SNORD30, SNORD31) are located within the introns of the RPL13A gene (encoding ribosomal protein L13a). This co-localization and co-expression suggest that their upregulation likely reflects heightened ribosome biogenesis machinery activity. This increased protein translation capacity provides the necessary fuel for rapid cell proliferation, driving smoldering cells toward an active, aggressive malignancy. Therefore, these snoRNAs are not merely prognostic markers but may also play a functional role in the pathophysiology of the transition from the smoldering phase to active disease (34).

Beyond the specific upregulation in MM, the study by Ronchetti et al. highlights a complex biological paradox during the transition to Secondary Plasma Cell Leukemia (sPCL). While early tumorigenesis in high-risk MM is driven by specific snoRNA overexpression (like ACA11), the progression to the terminal, leukemic phenotype is characterized by a global downregulation of the snoRNA transcriptome, including SNORD32A and SNORA42. Crucially, this downregulation exhibits significant co-expression with their respective host genes, suggesting that the snoRNA dysregulation in sPCL is not an isolated event but rather a downstream consequence of the extensive genetic imbalances and chromosomal instability inherent to this advanced disease state. This "switch" implies that the molecular requirements for tumor survival change drastically during evolution. The progression to an aggressive extramedullary state may involve a broad suppression of the ribosome biogenesis machinery or widespread transcriptional repression, underscoring the dynamic nature of non-coding RNA regulation in cancer evolution (35).

Emerging evidence suggests that snoRNAs function well beyond the nucleolus, acting as direct regulators of genome integrity. Han et al. (2022) introduced the concept of "chromatin-associated snoRNAs" (casnoRNAs), fundamentally expanding the topological landscape of snoRNA activity. They demonstrated that the orphan SNORA73 is not merely a bystander but actively translocates to the chromatin to form a non-canonical complex with PARP1. Under normal conditions, SNORA73 inhibits PARP1 auto-PARylation, thereby preventing excessive DNA damage response signaling. In AML, the specific downregulation of SNORA73 disrupts this "brake," leading to hyper-activated PARP1, genomic instability, and a blockade in myeloid differentiation. This discovery establishes a direct mechanistic link between snoRNA loss and the DNA damage response (DDR) machinery, suggesting that restoring these casnoRNAs could sensitize leukemic cells to differentiation therapies (40). While most snoRNAs are involved in guiding the chemical modifications of other RNAs, orphan snoRNAs are thought to perform distinct functions. For example, they may play a role in regulating DNA damage-induced differentiation and inhibiting PARP1 auto-PARylation, processes that are crucial for maintaining cancer genome stability (62).

Conversely, APL defies the global suppression pattern observed in other acute leukemias, exemplifying the functional versatility of snoRNAs. While general AML signatures suggest a collapse of the translational machinery, APL is characterized by a "gain of proliferative function" driven by the specific upregulation of the SNORD112–114 cluster (at the DLK1-DIO3 locus). Valleron et al. demonstrated that this cluster is directly regulated by the chimeric PML-RARα transcription factor. Mechanistically, SNORD114-1 bypasses canonical ribosomal functions to act as a downstream oncogenic effector, modulating the G0/G1 cell cycle

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transition via the Rb/p16 pathway. This distinction highlights that snoRNA dysregulation is not merely a passive byproduct of leukemia but can be a targeted, subtype-specific driver of disease maintenance (38).

In contrast to the broad suppression observed in myeloid lineages, B-cell precursor acute lymphoblastic leukemia (BCP-ALL) displays a highly specific upregulation of the Prader-Willi syndrome (PWS) locus, particularly within ERG-related subtypes. This distinct signature is dominated by the overexpression of the orphan SNORD116 cluster (alongside SNORD109A, SNORD64, and SNORD107), marking a functional pivot away from canonical translation control (27). As orphan snoRNAs lack complementary rRNA targets, their accumulation in ERG-driven BCP-ALL likely serves a non-canonical role in preserving leukemic survival during replicative stress. Specifically, the SNORD116 cluster has been implicated in regulating DNA damage-induced differentiation and inhibiting PARP1 auto-PARylation (62). By interfering with PARP1—a critical sensor of DNA strand breaks—these snoRNAs may modulate the DNA Damage Response to prevent catastrophic genomic instability while blocking the differentiation pathways that would otherwise halt leukemic proliferation. This suggests that in lymphoid malignancies, specific snoRNA subsets function as “genome guardians” rather than metabolic accelerators.

In Acute Myeloid Leukemia (AML), the functional landscape of snoRNAs reveals a striking mechanistic dichotomy between general myeloid malignancy and the APL subtype. The findings by Warner et al. fundamentally challenge the prevalent “host-gene passenger” model observed in other hematologic malignancies, such as Multiple Myeloma, where snoRNA expression (e.g., ACA11) typically mirrors host gene activation due to gene dosage effects. In stark contrast, AML displays a significant “uncoupling” of snoRNA expression from transcriptional controls. The specific downregulation of the 102 identified snoRNAs (e.g., SNORA21 and SCARNA15) occurs independently of their host gene repression or alternative splicing, pointing towards a distinct, likely post-transcriptional, regulatory mechanism specific to the leukemic state. Furthermore, the selective suppression of snoRNAs targeting the ribosomal peptidyl transferase center (PTC) suggests that AML cells may modulate ribosomal function and translational fidelity to support leukemogenesis. This highlights a complex layer of regulation—potentially linking “ribosomopathy” to leukemia maintenance—where snoRNAs are not merely transcriptional byproducts but are subject to independent pressures to maintain an undifferentiated state or promote survival (39). While individual modification losses might be tolerated, the cumulative absence of 2′-O-methylation and pseudouridylation at these critical sites likely produces synergistic defects, driving oncogenesis through increased stop codon read-through and altered tRNA selection. This “ribosomopathy-like” state is further compounded by splicing defects; the 2.81-fold reduction of scaRNA15 implies impaired U2 snRNA maturation, potentially destabilizing the spliceosome’s branch site recognition (41-44).

The investigation into Chronic Lymphocytic Leukemia (CLL) by Ronchetti et al. provides a crucial pivot in understanding snoRNA dysregulation, substantiating the “host-gene dependence” hypothesis observed in Multiple Myeloma while contrasting sharply with the “uncoupled” phenotype described in AML. In CLL, the snoRNA landscape largely preserves the cell-of-origin architecture (memory B-cells), implying that dysregulations are not random but stem from a mechanism of “coordinated silencing” where the transcriptional status of snoRNAs is tightly synchronized with their host genes. This biological synchronization is most evident in the specific downregulation of SNORA70F, which parallels the reduction of its host, COBLL1 (30). Since COBLL1 is integral to cytoskeletal morphogenesis and cell migration, its concurrent suppression in poor-prognosis subgroups suggests a functional shift in leukemic cell motility and structural plasticity (75). A similar pattern drives the co-downregulation of SNORA31 and TPT1; given

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that TPT1 is a direct target of TP53 and a regulator of the mTORC1/autophagy axis (76), this likely reflects the broader p53 dysfunction characteristic of aggressive CLL. Furthermore, the reduction of SNORA6 and SNORA62 alongside their host RPSA (a laminin receptor involved in invasion) reinforces the concept that snoRNA profiles in CLL act as surrogates for the loss of critical adhesive and metabolic machinery.

Interpreting Discrepant Findings

Our analysis reveals that snoRNA dysregulation is not uniform across hematologic malignancies but rather exhibits distinct, lineage-dependent expression dynamics. These apparent contradictions in expression profiles, such as those seen in the SNORD116 family and SNORD114-1, can be reconciled by examining the epigenetic context. The DLK1–DIO3 imprinted region, which hosts SNORD114 and SNORD113 clusters, demonstrates differential methylation in APL versus other AML subtypes, creating distinct transcriptional contexts among myeloid subtypes. Another striking divergence is observed in the imprinted SNORD116 cluster; while Vendramini et al. reported significant upregulation of cluster members (including -11, -14, and -24) specifically in the ERG-related subtype of B-cell precursor ALL (BCP-ALL) (27), Warner et al. observed a comprehensive downregulation of these exact targets in AML (39). This suggests that SNORD116 activity may be oncogenic in specific lymphoid lineages while acting as a tumor suppressor in myeloid progenitors. While increased snoRNA expression is often associated with high proliferation rates in solid tumors, Valleron et al. presented a contrasting landscape in acute leukemias. They observed a global downregulation of snoRNAs in both AML (non-APL) and ALL compared to their normal counterparts. This phenomenon mirrors the global downregulation of miRNAs frequently observed in cancer, suggesting that widespread suppression of small non-coding RNAs might be a hallmark of the undifferentiated leukemic state. This challenges the simplistic view that snoRNA levels solely reflect ribosomal biogenesis demand, indicating that their regulation is tightly coupled to differentiation blocks characteristic of acute leukemias (38).

Despite this heterogeneity, certain signatures appear conserved. SNORA31 shows consistent downregulation across both CLL and AML, hinting at a common tumor-suppressive role. Conversely, SNORD116-18 is consistently upregulated in both CLL and BCP-ALL, identifying it as a potential pan-B-cell malignancy marker.

Collectively, these mechanisms underscore that snoRNA alterations are not random epiphenomena but a consequence of oncogenic stress, ribosome reprogramming, and genomic-epigenetic remodeling unique to each hematologic lineage.

Clinical and Prognostic Significance

The functional roles of snoRNAs translate directly into clinical utility. This review identifies specific snoRNAs as potent prognostic markers. Quantitative survival analysis further solidifies the utility of snoRNAs as independent prognostic factors (Table III).

In Multiple Myeloma (MM), the prognostic utility of snoRNAs is deeply intertwined with the disease's cytogenetic architecture. SNORD78 emerges as a particularly potent risk factor; its upregulation is not merely a passenger event but a direct downstream consequence of the high-risk Gain (1q21) aberration. Clinically, this overexpression is associated with a dramatic hazard ratio for Overall Survival (HR=14.4, P=0.038) and significantly shorter Progression-Free Survival (P=0.024), suggesting that SNORD78 could refine high-risk stratification panels beyond standard karyotyping (30, 31). Additionally, SNORA71A serves as a molecular marker for end-organ damage, with elevated levels correlating positively with serum creatinine (P=0.0002), thus providing a potential diagnostic adjunct for monitoring renal insufficiency in symptomatic patients (36). Furthermore, the identification of ACA11 (SCARNA22) as a key driver of the t(4;14)

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phenotype offers a novel therapeutic perspective. Since ACA11 mediates resistance to proteasome inhibitors by suppressing oxidative stress, it represents a high-value target for re-sensitizing high-risk patients to chemotherapy (32).

In Chronic Lymphocytic Leukemia (CLL), snoRNA signatures provide critical insight into the heterogeneity of early-stage disease. Ronchetti et al. identified a specific transcriptomic signature comprising SNORD56, SNORA74A, and SNORD116-18 that consistently predicts rapid disease progression (HR ~2.7–2.9, P<0.001). This signature is particularly valuable for stratifying patients with Binet A stage disease, allowing clinicians to distinguish between truly indolent cases and those destined for aggressive evolution who may require earlier therapeutic intervention (30).

For Acute Myeloid Leukemia (AML), clinical applications focus on both targeted therapy and disease monitoring. The functional link between snoRNAs and the DNA damage response—specifically the SNORA73-PARP1 axis—unveils a tangible therapeutic opportunity. Since SNORA73 downregulation results in PARP1 hyperactivation, leukemic cells harboring this deficiency may possess a unique vulnerability to pharmacological PARP inhibitors, suggesting SNORA73 could serve as a predictive biomarker for patient selection in future clinical trials (40). Moreover, distinct snoRNA expression patterns offer a new avenue for monitoring Minimal Residual Disease. Warner et al. demonstrated that while AML blasts share high expression of imprinted snoRNAs with normal hematopoietic stem cells, they can be discriminated by the specific loss of SNORA21 and SCARNA15, potentially improving the sensitivity of post-treatment monitoring (39).

In B-cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL), the snoRNA signature identified by Vendramini et al.—comprising the SNORD116 cluster, SNORD109A, SNORD64, and SNORD107—delineates a biological entity associated with favorable clinical outcomes. The overexpression of these transcripts enables the stratification of patients who, despite harboring high-risk genetic markers such as IKZF1 deletions, exhibit a superior prognosis relative to other 'B-other' ALL cohorts (27).

Finally, the diagnostic potential of snoRNAs extends to rare lymphoid malignancies. In T-cell non-Hodgkin lymphomas, specifically PTCL-NOS and Angioimmunoblastic T-cell lymphoma (AITL), SNORD71 has been identified as a paramount biomarker. Microarray analyses reveal that SNORD71 is significantly overexpressed in both conditions, effectively distinguishing these pathologies from reactive lymphadenopathies despite their clinical heterogeneity (37). Collectively, these findings underscore the potential of snoRNA-based panels to enhance current risk stratification strategies and move hematologic oncology toward precision RNA-based medicine.

Limitations and Future Directions

This review has limitations. First, despite adhering to PRISMA guidelines and a registered PROSPERO protocol, the final number of included studies (n=12) is small, reflecting the nascent nature of this field. Second, the heterogeneity in study designs, patient populations, and normalization methods precluded a quantitative meta-analysis. Third, many snoRNAs' biological functions remain poorly characterized, and their potential overlap with other non-coding RNAs poses challenges for specificity.

Future research should focus on multi-center validation studies with larger, diverse patient cohorts to confirm these prognostic associations. Mechanistic studies using RNA-seq and functional assays (e.g., knockdown/overexpression) are essential to establish causality. Additionally, integrating machine learning approaches to identify robust snoRNA panels could pave the way for their clinical implementation. As the field matures from this early scoping landscape, future systematic updates will likely provide more definitive evidence for the routine use of snoRNAs in hematologic oncology.

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Conclusion

This systematic review highlights the pivotal yet distinct roles of small nucleolar RNAs (snoRNAs) across the spectrum of hematologic malignancies. Beyond their canonical functions in ribosomal biogenesis and RNA modification, this study underscores that snoRNAs exhibit lineage-specific dysregulation patterns—ranging from the loss of translational fidelity in myeloid leukemias to the activation of orphan snoRNAs as genome guardians in lymphoid malignancies. Their superior stability compared to other non-coding RNAs positions them as robust candidates for non-invasive diagnosis and risk stratification, particularly in identifying high-risk subgroups in Multiple Myeloma and Acute Leukemias. However, challenges regarding normalization standards, tissue-specific variability, and the need for large-scale validation persist. Future research must prioritize multi-center studies to decipher the complex mechanistic duality of snoRNAs (as both drivers and passengers) and to translate these molecular insights into targeted therapies, such as antisense oligonucleotides, ultimately advancing precision medicine in hematologic oncology.

Availability of Data

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Considerations

None

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The authors confirm that no artificial intelligence (AI) tools were employed in data analysis or manuscript preparation.Conflict of Interest

The authors declare no conflict of interests regarding this study.

Authors' Contributions

FT: Conceptualization, Methodology, Software, Investigation (screening and data extraction), Data Curation, Writing - Original Draft, Visualization

MKH: Conceptualization, Methodology, Validation, Writing - Review & Editing, Supervision

MMH: Validation, Writing - Review & Editing

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All authors declare that they have no conflicts of interest.

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