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The Role of HSP70 in Leukemia: A Systematic Review and Meta-Analysis Investigating Its Potential as a Biomarker Through Expression Differences and Hematological Associations

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ABSTRACT

Background: Leukemia is a major cause of cancer-related morbidity and mortality, representing the most common childhood malignancy and remaining associated with poor outcomes and relapse in adult acute subtypes. Despite therapeutic progress in leukemia management, survival outcomes remain poor, highlighting the urgent need for reliable biomarkers and novel therapeutic targets. Heat shock protein 70 (HSP70), a molecular chaperone central to protein folding, apoptosis regulation, and oncogenic signalling, has been increasingly implicated in leukemogenesis and therapy resistance. However, the clinical utility of HSP70 remains uncertain due to small cohorts and methodological heterogeneity across studies. This systematic review and meta-analysis provides a quantitative evaluation of HSP70 expression in leukemia and explores its potential as a diagnostic, prognostic, and therapeutic biomarker.

Methods: A systematic review was conducted in accordance with PRISMA guidelines. EBSCO, PubMed, ProQuest, ScienceDirect, and Scopus were searched for studies reporting quantitative HSP70 expression in leukemia and healthy controls. Eligible studies met predefined inclusion and exclusion criteria. Data were pooled using a random-effects model, with effect sizes calculated as standardised mean differences (Cohen's d), and statistical analyses performed in IBM SPSS Statistics (v28.0).

Results: After applying eligibility criteria, data from 261 leukemia patients and 214 healthy controls across three studies (four datasets) were included. Pooled analysis demonstrated significantly elevated HSP70 expression in leukemia patients compared with controls (Cohen's d = 1.498, 95% CI: 1.279 - 1.717, $p < 0.001$), representing a large effect size. No heterogeneity was observed ($I^2 = 0\%$). The study was prospectively registered with PROSPERO (CRD420251019261).

Conclusion: This meta-analysis demonstrates consistent overexpression of HSP70 in leukemia, supporting its potential as a diagnostic, prognostic, and therapeutic biomarker, while highlighting the need for further clinical validation.

Introduction

Globally, leukemia remains one of the most prevalent and life-threatening haematological malignancies [1], ranking 15th in cancer incidence and 11th in cancer-related mortality, with over 461,000 new cases and 320,000 deaths reported in 2021 [2]. Projections indicate a further increase by 2031, highlighting leukemia's growing public health burden [3]. Despite advances in chemotherapy, immunotherapy, targeted therapies, and stem cell transplantation, relapse and drug resistance remain major clinical challenges, contributing to nearly 90% of cancer-related deaths [4]. Leukemia originates from cells at different stages of hematopoietic maturation, contributing to its marked biological heterogeneity. Advances in the identification of oncogenic drivers and survival pathways have enabled the development of targeted therapies, including kinase and antiapoptotic protein inhibitors [5]. Nonetheless, recent molecular profiling has

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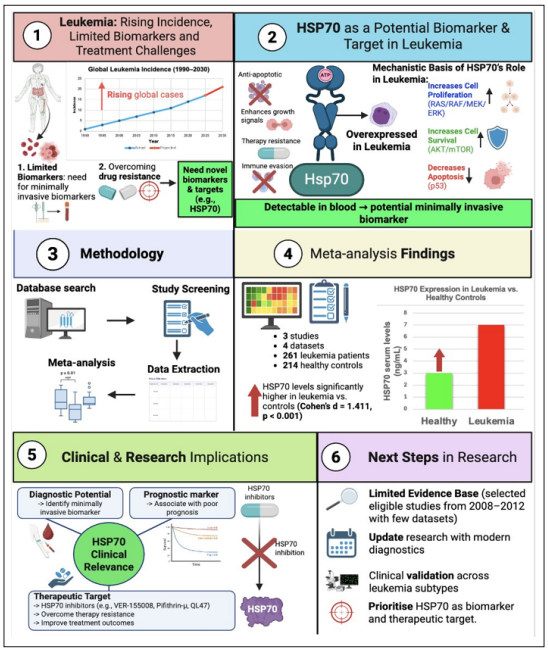
uncovered extensive clonal complexity, providing an explanation for the variable therapeutic responses observed among patients [7]. Resistance mechanisms, whether present at diagnosis or acquired during treatment, further compromise durable clinical benefit [7]. Collectively, these challenges underscore the urgent need for novel biomarkers and therapeutic targets to improve diagnosis, refine risk stratification, and enable personalised treatment approaches. Among potential candidates, heat shock proteins (HSPs) have emerged as promising biomarkers with established roles in cancer diagnosis, prognosis, and therapeutic targeting [8,9].

Graphical Abstract



HSPs are a highly conserved family of stress proteins first discovered in 1962 by Ritossa, who observed their upregulation in cells exposed to heat shock [10]. Subsequent studies revealed that HSPs respond not only to heat but also to oxidative stress, hypoxia, DNA damage, and inflammation [11]. Among them, the HSP70 family is the most widely studied, owing to its potent cytoprotective activity [12] Intracellular HSPs (iHSPs) act as molecular chaperones, maintaining proteostasis by folding nascent proteins, refolding damaged ones, and targeting irreparably misfolded proteins for degradation, thereby preventing toxic aggregate formation and reducing cellular stress [13,14]. Although traditionally characterised as intracellular, HSPs can also be actively released into the extracellular environment, primarily via extracellular vesicles (EVs), or passively through necrotic and apoptotic cell death [15,16]. Extracellular HSPs (eHSPs) function as danger-associated molecular patterns (DAMPs), binding pattern recognition receptors such as TLRs and CD91 on antigen-presenting cells [17], thereby stimulating cytokine release, enhancing antigen presentation, and promoting tumour immunosurveillance [18,19]. Their detectable presence in circulation underscores their potential as diagnostic biomarkers and therapeutic targets [20,21].

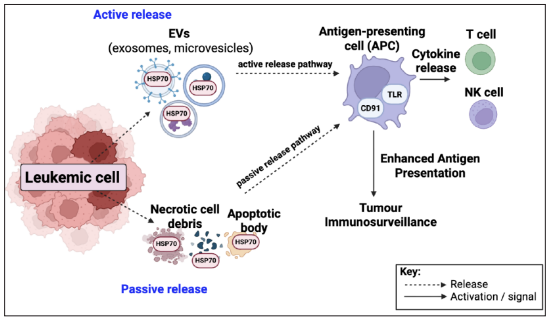


Figure 1: Mechanisms of HSP70 Release and Immunomodulatory Functions in Leukemia

HSP70 is secreted via extracellular vesicles (exosomes, microvesicles) or passively released from necrotic/apoptotic leukemic cells. Once in the extracellular environment, HSP70 interacts with TLR and CD91 on antigen-presenting cells (APCs), promoting cytokine release, enhanced antigen presentation, and activation of T and NK cells, thereby contributing to tumour immunosurveillance [19]. Figure created using biorender.com.

HSP70 Functions and Roles in Leukemia

The HSP70 family comprises several members distributed across different cellular compartments, encoded by distinct genes, and contributing to proteostasis in diverse contexts (Table 1) [22,23]. Under physiological conditions, HSP70 is essential for hematopoietic progenitor cell maintenance, sustaining erythropoiesis, myelopoiesis, and thrombopoiesis [24].

Table 1: Key HSP70 Family Members

Summary of key HSP70 family members, their encoding genes, cellular localisation, and main functions [22,23].

HSP70 Member	Gene	Primary Location	Main Functions
HSP70 / HSP72 (major inducible form)	HSPA1A	Cytoplasm and nucleus	Supports in folding nascent polypeptides, and prevents aggregation of misfolded proteins
HSC70 / HSP73 (constitutive form)	HSPA8	Cytoplasm and nucleus	Maintains protein quality control through constitutive chaperone activity
mtHSP70 / Grp75	HSPA9	Mitochondrial matrix	Facilitates import and folding of proteins encoded by nuclear and mitochondrial DNA
GRP78 / BiP	HSPA5	Endoplasmic reticulum	Regulates unfolded protein response (UPR), and Supports in ER protein folding

In cancer, however, HSP70's cytoprotective role is subverted to promote malignant survival. HSP70 overexpression has been shown to drive leukemogenesis, therapy resistance, and disease progression [25,26]. For instance, AML patients with elevated HSP70 exhibit lower remission rates and shorter survival [27]. In erythroleukemia (M6-AML), dysregulated HSP70 disrupts GATA-1 stability, impairing differentiation and promoting immature progenitor accumulation [28,29]. In CML, HSP70 stabilises the BCR-ABL fusion protein, thereby sustaining oncogenic signalling and conferring resistance to apoptosis, even under tyrosine kinase inhibitor therapy [30]. Collectively, these findings illustrate HSP70's dual nature: while indispensable for normal hematopoietic homeostasis, its dysregulation fosters leukemic progression and therapeutic resistance. This functional versatility underscores HSP70's importance as both a mechanistic driver of leukemogenesis and a promising biomarker and therapeutic target.

Clinical Overview of Leukemia Subtypes

Leukemia is classified into four main subtypes based on lineage (myeloid or lymphoid) and disease progression rate (acute or chronic): acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML) [31]. ALL is the most common childhood malignancy, whereas AML predominates in older adults and is associated with poor outcomes [32]. CLL is often indolent but can progress aggressively, while CML is driven by the BCR-ABL1 fusion gene and advances from chronic to blast crisis phases [33]. Despite therapeutic advances, prognosis remains poor for many subtypes. The five-year survival rate is approximately 32% for AML and ~40% for adult ALL [34,35]. Resistance and relapse also remain major clinical challenges in both CML and CLL [36,37]. These limitations underscore the urgent need for novel biomarkers with diagnostic and prognostic relevance (Figure 2).

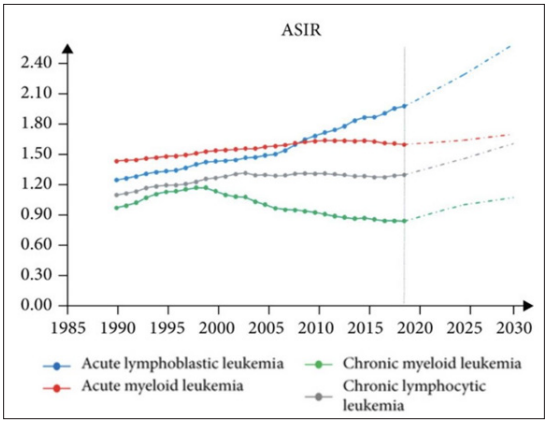


Figure 2: Historical and Projected Trends in Age-Standardised Incidence Rates (ASIR) of the Four Main Leukemia Subtypes (1985 to 2030).

Global ASIR trends for ALL, AML, CLL, and CML. Projections indicate a continued increase in ASIR for all subtypes, with the most significant rise (31.1%) expected in ALL, highlighting the growing epidemiological impact of leukemia in the coming decades [38].

HSP70-Mediated Mechanisms of Leukemic Survival

Mechanistically, HSP70 promotes leukemic survival by blocking apoptosis and stabilising oncogenic signalling. In the intrinsic pathway, it prevents Bax translocation and cytochrome c release, disrupting apoptosome assembly and inhibiting caspase-9 activation. In the extrinsic pathway, HSP70 interferes with death receptor signalling, reducing caspase-8 activity. Together, these effects elevate the apoptotic threshold and decrease chemosensitivity [39,40] (Figure 3).

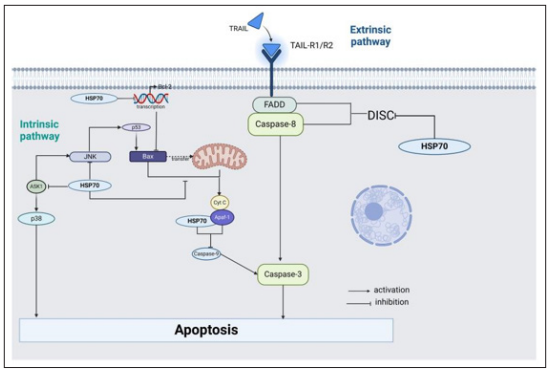


Figure 3: HSP70 Inhibition of Intrinsic and Extrinsic Apoptotic Pathways in Leukemia

HSP70 blocks Bax translocation in the intrinsic pathway, preventing cytochrome c release and caspase-9 activation. In the extrinsic pathway, it disrupts DISC formation downstream of death receptor signalling, limiting caspase-8 activation. By converging on caspase-3, these mechanisms collectively raise the apoptotic threshold and promote leukemic cell survival [41].

Beyond apoptosis, HSP70 sustains proliferative signalling by stabilising oncogenic drivers such as BCR-ABL in CML and FLT3-ITD in AML. This, in turn, activates major pathways including RTKs-RAS-RAF-MEK-ERK and PI3K/AKT/mTOR [42,43]. It also impairs the tumour suppressor p53 by blocking nuclear translocation and promoting degradation, which further drives leukemic progression [44]. Collectively, these mechanisms support resistance, survival, and immune evasion (Figure 4).

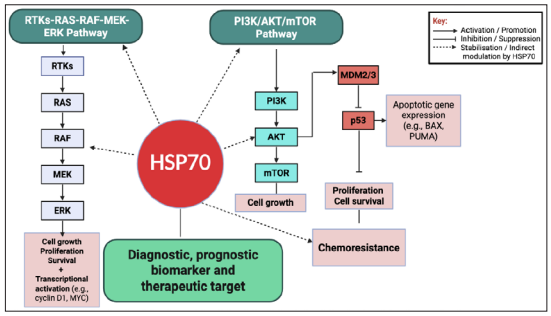


Figure 4: HSP70 as a Regulator of Survival Pathways and Chemoresistance in Leukemia

Schematic illustrating how HSP70 sustains leukemic survival by modulating RTKs-RAS-RAFMEK-ERK and PI3K/AKT/mTOR pathways. It stabilises upstream effectors, enhances downstream signalling, and suppresses p53-dependent apoptosis, thereby promoting proliferation, survival, and drug resistance. These interactions underscore HSP70's relevance as a diagnostic, prognostic, and therapeutic target in leukemia [45]. Figure created using Biorender.com.

HSP70's multifaceted roles position it as a promising therapeutic target. Preclinical studies have shown that selective inhibition of HSP70, using agents such as Pifithrin-μ and QL47, can restore apoptosis and disrupt oncogenic signalling in leukemia models [46,43]. Despite this promise, the available evidence remains fragmented, with most studies focusing on single subtypes, involving small patient cohorts, or employing variable methodologies [47,48]. Importantly, to date, no systematic review or meta-analysis has yet synthesised HSP70 expression patterns across all major leukemia subtypes, leaving its diagnostic and prognostic relevance unresolved.

Meanwhile, the rising global burden of leukemia, coupled with high relapse rates, and persistent drug resistance [3,4], underscores the urgent need for reliable, non-invasive biomarkers to support early detection, patient stratification, and therapeutic development. HSP70 is a compelling candidate due its established roles in leukemogenesis, apoptosis regulation, oncogenic signalling, and therapy resistance [45].

Therefore, this study aims to address this gap by conducting the first systematic review and meta-analysis to quantitatively assess HSP70 expression patterns across the four major leukemia subtypes. Specifically, it compares expression levels between leukemia patients and healthy individuals to evaluate the diagnostic, prognostic, and therapeutic potential of HSP70 as a clinically relevant biomarker. By identifying consistent expression patterns and critically examining their clinical implications, this study endeavors to advance precision oncology approaches in leukemia. Based on prior evidence, the proposed hypothesis is that HSP70 expression is significantly upregulated in leukemia patients compared to healthy individuals [49,50].

Methods

Study Design

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [51]. These guidelines, including the PRISMA Checklist, were strictly followed to ensure methodological transparency and reproducibility [51]. A detailed study protocol was developed prior to the data collection and was followed throughout the entire stages of screening, extraction, and analysis to minimise bias and enhance consistency. This project was prospectively registered in the International Prospective Register for Systematic Reviews (PROSPERO) under registration number CRD420251019261.

Eligibility Criteria

Eligibility criteria were predefined in accordance with PRISMA guidelines to ensure methodological transparency and reproducibility [51].

Inclusion Criteria

Studies were eligible if they: (a) involved human participants diagnosed with any leukemia subtype (AML, ALL, CML, or CLL); (b) quantitatively measured HSP70 expression in leukemia patients and healthy controls; (c) used validated protein-based assays (e.g., ELISA, Western blot) in biological fluids such as peripheral blood; (d) reported results as mean ± standard deviation (SD) or median with range/interquartile range (IQR) for meta-analysis, only data in mean ± SD format or convertible to it were included; (e) expressed HSP70 concentrations in ng/mL to ensure unit consistency; and (f) were original, peer-reviewed articles published in English.

Exclusion Criteria

Studies were excluded if they: (a) lacked a comparative control group; (b) involved only in vitro or animal models; (c) had no extractable quantitative data or insufficient information to compute hazard ratios and 95% confidence intervals; (d) were reviews, editorials, or conference abstracts; (e) focused on other HSPs rather than HSP70; or (f) investigated malignancies other than leukemia.

Literature Search Strategy

A comprehensive search was conducted across the following electronic databases: EBSCO, PubMed, ProQuest, ScienceDirect, and Scopus. The search strategy was carried out using the PICO framework: population (human participants with leukemia), intervention (expression levels of HSP70), comparison (healthy human controls), outcomes (HSP70 concentration data in ng/mL and its potential role as a biomarker). In PubMed, Medical Subject Headings (MeSH) were applied, and CINAHL Headings were applied when searching the CINAHL database, following recommendations in the Cochrane Handbook for Systematic Reviews [52]. Keyword combinations with Boolean operators (AND/OR) were used to refine results.

An example of a search string includes: ("HSP70" OR "HSP72" OR "Heat Shock Protein 70" OR "HSC70" OR "HSPA1A protein" OR "heat-shock response") AND ("leukemia" OR "leukaemia" OR "ALL" OR "AML" OR "CML" OR "CLL") AND ("expression" OR "concentration" OR "biomarker") AND ("healthy controls" OR "normal controls"). Additionally, reference lists from included papers and relevant reviews were manually screened for other studies meeting the inclusion criteria [52].

Study Selection

All gathered studies were imported into EndNote 20 (Clarivate Analytics) for initial screening and duplicate removal, then exported into Rayyan (Qatar Computing Research Institute), for systematic screening [53]. Titles and abstracts were screened against the predefined eligibility criteria, and non-eligible studies were excluded.

As stated in section 2.2.1, only studies reporting HSP70 expression in ng/mL, either as mean ± standard deviation (SD) or as median values that could be reliably converted, were included in the final analysis and proceeded to meta-analysis. Due to the very limited number of studies available on this topic, it was necessary to include those reporting medians. In such cases, when data were presented as median and interquartile range (IQR), or median and range, conversions to mean and SD were performed using the formulas described by Wan et al. (2014) [54]. Furthermore, as stated by Higgins and Li (2022) when multiple leukemia subtypes shared a single control group, the control sample size was divided approximately equally among intervention groups to prevent double counting and to preserve statistical independence between comparisons [52]. The entire study selection process was documented in a PRISMA 2009 flow diagram (Figure 5), detailing the number of records identified, screened, excluded, and included in the final analysis [51].

Data Extraction

Extracted variables included: study ID (author name and publication year), country, leukemia subtype, sample sizes for patient and control groups, HSP70 expression levels in both groups, detection method (e.g., ELISA, Western blot), units of measurement (ng/mL), and statistical metrics (mean ± SD or converted values). Reported p-values or other indicators of statistical significance were also recorded.

Risk of Bias and Quality Assessment

A formal risk of bias assessment was not conducted due to the limited number of studies included in this meta-analysis. As outlined in the Cochrane Handbook for Systematic Reviews of Interventions, Higgins and Li (2022) recommend that methods such as Egger's test and funnel plots are not recommended when fewer than ten studies are available, as they are underpowered and potentially misleading [52]. However, thorough steps were taken to minimise potential reporting bias, a comprehensive search was conducted across multiple databases, supplemented by manual screening of reference lists. Studies were included regardless of whether they reported statistically significant findings, and only those meeting the predefined methodological quality standards were retained.

Statistical Analysis

The meta-analysis was performed using IBM SPSS Statistics (version 28.0). Continuous outcome data were analysed using Cohen's d to estimate the standardised mean differences (SMD) in HSP70 expression between leukemia patients and healthy controls, following the guidelines for interpretation proposed by Cohen (1988) [55]. Calculations were performed under a random-effects model, using the Restricted Maximum Likelihood (REML) method to estimate between study variance. The following input variables were used: sample sizes for both leukemia and control groups, mean and SD values for each group, and study ID for labelling.

Forest plots were generated to visually represent individual study effect sizes, their 95% confidence intervals, and the pooled effect estimate. Heterogeneity across studies was evaluated using Cochran's Q (test for homogeneity), Tau-squared (τ^2), H-squared (H^2), and I^2 statistics. As outlined by Deeks et al. (2019), I^2 values between 0% and 40% indicate no/low heterogeneity, 30% to 60% suggest moderate heterogeneity, 50% to 90% reflect substantial heterogeneity, and values between 75% and 100% are considered indicative of considerable heterogeneity [56]. As recommended by Kulinskaya et al. (2011), the homogeneity test was also applied to verify the consistency of effect sizes across studies. Statistical significance was determined using a two-sided p-value threshold of $\alpha = 0.05$, whereby $p < 0.05$ was considered statistically significant [57].

Results

Study Selection and Characteristics

Following full text screening and data extraction, several studies were initially considered for inclusion in the meta-analysis. However, many were excluded due to incompatible data formats, inability to convert reported medians to mean ± standard deviation (SD) using Wan et al. (2014), use of inconsistent units, lack of a healthy control group, or incomplete statistical data [54].

Although the initial objective was to include all four major leukemia subtypes (AML, ALL, CML, and CLL), no eligible CLL studies met the inclusion criteria due to insufficient or incompatible reporting formats. Following screening, six studies were included in the qualitative synthesis. However, three could not be quantitatively pooled due to incomplete or non-comparable data, leaving three studies (four datasets) for the final meta-analysis. The selection process is summarised in the PRISMA flow chart (Figure 5).

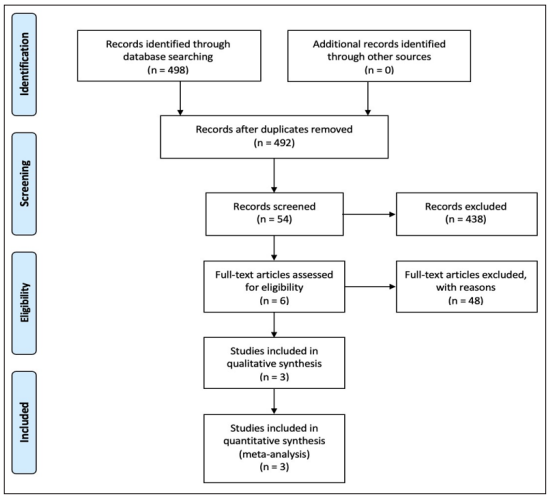


Figure 5: PRISMA Flow Chart Summarising the Study Selection Process.

Out of 498 records identified, only three studies (four datasets) met all inclusion criteria for the meta-analysis. These final datasets investigated AML, ALL, and CML, and all reported HSP70 expression in ng/mL with matched healthy control groups.

In total, the included datasets encompassed 261 leukemia patients and 214 healthy controls. All studies quantified HSP70 protein levels using validated techniques (ELISA, electrochemiluminescence immunoassay, or whole-cell lysate kits) in peripheral blood samples, with results reported in ng/mL. Two datasets came from Yeh et al. (2008), investigating CML in the chronic phase (n = 93) and blast phase (n = 46), each with matched controls. Yeh et al. (2009) analysed ALL patients (n = 40) versus controls (n = 99), while Fredly et al. (2012) studied AML patients (n = 82) versus controls (n = 20) [49,58,59]. Table 2 presents the main characteristics of these studies, including year, country, leukemia subtype, sample sizes, HSP70 levels (mean ± SD), p-values, detection methods, and sample type.

Table 2: Main Characteristics of the Studies Included in the Meta-Analysis.

All included datasets showed significantly elevated HSP70 expression in leukemia patients compared with matched healthy controls ($p < 0.001$) all cases). The fable summarises study details, including country, leukemia subtype, sample sizes, mean ± SD HSP70 concentrations (ng/mL), detection methods, and sample types.

Study	Year	Country	Leukemia Subtype	Sample Size (Leukemia)	Sample Size (Control)	HSP70 Level (Leukemia) mean ± SD	HSP70 Level (Control) mean ± SD	p value	Measurement Method	Sample Type
Yeh et al.	2008	United States	CML (chronic phase)	93	47	38.34 ± 31.08 ng/mL	4.93 ± 5.74 ng/mL	p< 0.001	Whole cell lysate kits	Peripheral blood
Yeh et al.	2008	United States	CML (blast phase)	46	48	33.52 ± 27.55 ng/mL	4.93 ± 5.74 ng/mL	p< 0.001	Whole cell lysate kits	Peripheral blood
Yeh et al.	2009	United States	ALL	40	99	47.47 ± 46.11 ng/mL	5.9 ± 4.39 ng/mL	p< 0.0001	Electrochemiluminescence immunoassay	Peripheral blood
Fredly et al.	2012	Norway	AML	82	20	2 ± 1 ng/mL	0.5 ± 0.25 ng/mL	p< 0.0001	EIA/ ELISA kits	Peripheral blood

Meta-Analysis Findings

The meta-analysis was conducted using IBM SPSS (version 28). Figure 6 shows the forest plot, illustrating the individual and pooled effect sizes of HSP70 expression in leukemia patients compared to healthy control groups. As summarised in Table 3, the standardised mean differences (SMDs) were calculated for each included study. The overall pooled effect size was Cohen's $d = 1.498$ (95% CI: 1.279 - 1.717, $p < 0.001$), indicating a statistically significant and large increase in HSP70 levels. According to Cohen's guidelines, an effect size above 0.8 is considered large, indicating a substantial biological difference between patient and control groups [55].

All individual studies reported elevated HSP70 expression in leukemia compared with controls, with standardised mean differences (SMDs) consistently indicating large and statistically significant effects (Table 3). A confidence interval that lies entirely above zero indicates a statistically significant and consistently positive effect across studies [60]. In this analysis, the 95% CI (1.279 - 1.717) meets this criterion, confirming both the statistical significance and the positive direction of the effect. The narrow CI further indicates high precision in estimating the true effect size (Figure 7). Furthermore, the p-value of < 0.001 underscores the reliability of this finding, indicating a probability of less than 0.1% that the observed difference occurred by chance. Collectively, these results strongly support the hypothesis that HSP70 overexpression is a consistent and biologically relevant feature of leukemia.

Table 3: Meta-Analysis Effect Size Estimates for HSP70 Expression in Leukemia Compared with Controls

Effect Size Estimates						
	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval	
					Lower	Upper
Overall	1.	0.	13.	.000	1.	2.

All individual studies demonstrated large and statistically significant effect sizes ($p < 0.001$), with the pooled analysis indicating a robust and consistent upregulation of HSP70 in leukemia patients. The table presents Cohen's d, 95% confidence intervals, p-values, and weights assigned to each study.

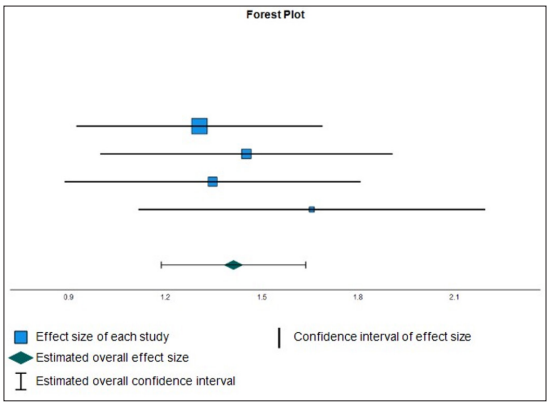


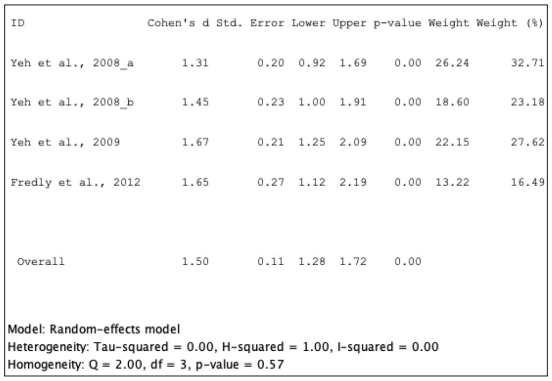
Figure 6: Meta-Analysis Forest Plot of HSP70 Expression in Leukemia Patients Compared with Controls

Each square represents an individual study's effect size (Cohen's d), with the horizontal line showing the 95% confidence interval. The size of the square indicates the study's weight. The diamond at the bottom represents the overall pooled effect size and its confidence interval from the meta-analysis. All included studies showed statistically significant ($p < 0.001$)) results with moderate to large effect sizes.

Heterogeneity and Homogeneity Assessment

Heterogeneity was evaluated using Tau-squared (τ^2), H-squared (H^2), and I-squared (I^2) statistics, and Cochran's Q-test. The meta-analysis showed $\tau^2 = 0.00$, $H^2 = 1.00$, and $I^2 = 0.0\%$, indicating no between-study variance and complete consistency across the included datasets (Figure 7). Cochran's Q-test for homogeneity ($Q = 2.00$, $df = 3$, $p = 0.57$) further confirmed the absence of significant heterogeneity, supporting the assumption

of homogeneity [46,60]. Collectively, these findings validate the use of a random-effects model and demonstrate robust agreement among studies.



ID	Cohen's d	Std. Error	Lower	Upper	p-value	Weight	Weight (%)
Yeh et al., 2008_a	1.31	0.20	0.92	1.69	0.00	26.24	32.71
Yeh et al., 2008_b	1.45	0.23	1.00	1.91	0.00	18.60	23.18
Yeh et al., 2009	1.67	0.21	1.25	2.09	0.00	22.15	27.62
Fredly et al., 2012	1.65	0.27	1.12	2.19	0.00	13.22	16.49
Overall	1.50	0.11	1.28	1.72	0.00		

Model: Random-effects model
Heterogeneity: Tau-squared = 0.00, H-squared = 1.00, I-squared = 0.00
Homogeneity: Q = 2.00, df = 3, p-value = 0.57

Figure 7: Effect Size Summary with Heterogeneity and Homogeneity Testing Results.

This table displays the individual effect sizes (Cohen's d), standard errors, 95% confidence intervals, p-values, and weights assigned to each study included in the meta-analysis. The overall pooled effect size was 1.498 with a standard error of 0.11, indicating a statistically significant increase in HSP70 levels in leukemia patients ($p < 0.001$). Heterogeneity was moderate, with $Tau^2 = 0.00$, $H^2 = 1.00$, and $I^2 = 0\%$, supporting the use of a random-effects model.

Discussion

The aim of this systematic review and meta-analysis was to evaluate HSP70 expression in individuals with leukemia compared to healthy controls, with the primary goal of assessing its potential as a diagnostic, prognostic, and therapeutic biomarker. It was hypothesised that HSP70 expression would be significantly elevated in leukemia patients. This hypothesis was strongly supported by the meta-analysis findings. The pooled analysis revealed a large effect size (Cohen's d = 1.498, 95% CI: 1.279 - 1.717, $p < 0.001$), confirming significantly higher HSP70 expression in leukemia patients compared to healthy controls. The forest plot (Figure 6) visually reinforced these results, with all datasets showing elevated HSP70 levels. Additionally, in line with Cameron et al. (2021), the fact that the 95% confidence intervals for each dataset lie entirely above zero indicates that the observed effects are both statistically significant and consistently positive across studies, thereby reinforcing the reliability of the findings [60]. As shown in Figure 7, no heterogeneity was observed ($I^2 = 0.0\%$), indicating complete consistency across studies. Furthermore, the homogeneity test produced a non-significant result ($Q = 2.00$, $p = 0.57$), providing additional confirmation of the reliability and stability of the pooled findings [56]. Together, these outcomes offer quantitative confirmation that HSP70 is consistently dysregulated in leukemia, providing a foundation for considering it as a clinically relevant biomarker.

The findings of the present meta-analysis align strongly with individual results from the included studies. Yeh et al. (2008) and Yeh et al. (2009) each reported significant HSP70 upregulation in both ALL and CML, including in both the chronic and blast phases of CML [49,58]. Both studies proposed that HSP70 plays a cytoprotective role by stabilising oncoproteins and inhibiting caspase-mediated apoptosis, thereby enabling leukemia cells to resist oxidative and chemotherapeutic stress. Similarly, Fredly et al. (2012) observed significantly higher plasma concentrations of HSP70 in AML patients [59]. Additionally, as Steiner et al. (2006) reported, such consistent overexpression across subtypes may reflect a conserved adaptive mechanism: the high cellular turnover and metabolic demands of leukemia create a proteotoxic environment that necessitates increased chaperone activity to maintain protein homeostasis [61]. HSP70 mitigates protein aggregation and facilitates refolding of misfolded proteins, functions that leukemic cells may exploit to sustain survival, drive proliferation, and evade apoptosis [62].

In addition to the studies included in the meta-analysis, these findings also align with and extend a number of previous studies. For example, a study by Kondratiuk et al. (2020) evaluated serum HSP70 levels in children with ALL and reported a substantial difference between patients and healthy controls (median 5.51 ng/mL vs. 0.45 ng/mL, $p = 0.000$), highlighting the diagnostic potential of circulating HSP70 [63]. This was further supported by Guo et al. (2019), who demonstrated significantly elevated HSP70 expression in blood samples from ALL patients [50]. This study also showed that HSP70 inhibition in leukemic cell lines suppressed cell proliferation and promoted apoptosis, indicating both diagnostic and therapeutic relevance. Additionally, the present study's hypothesis is further supported by findings from Li and Ge (2021), who reported significant upregulation of HSPA8 (HSP70) in AML patients compared to healthy controls, in fact, Li and Ge (2021) also found that higher HSPA8 expression was associated with reduced overall survival, reinforcing its potential prognostic value [64].

Although CLL was excluded from the meta-analysis due to incompatible reporting formats, Frezzato et al. (2016) also reported HSP70 overexpression in CLL, reinforcing the understanding that HSP70 dysregulation is a common molecular feature across leukemias [48]. Collectively, these findings provide compelling evidence that HSP70 is consistently overexpressed in leukemia, supporting its potential use as a biomarker for detection, prognosis, and therapeutic targeting.

Diagnostic Biomarker Potential of HSP70 in Leukemia

Leukemia diagnosis typically relies on bone marrow biopsy and cytogenetic or molecular testing. While effective, these procedures are invasive and can pose challenges for routine follow-up and long-term monitoring [65]. Consequently, as highlighted by Chanteloup et al. (2020) and Werner et al. (2021), there is growing interest in minimally invasive, blood-based biomarkers [66,67]. The present meta-analysis strengthens the case for HSP70 in this role, demonstrating its consistent overexpression in patient samples across leukemia subtypes. Extracellular HSP70, either in soluble form or packaged within extracellular vesicles (EVs), is detectable in circulation and reflects tumour biology [68,69].

Several studies support this utility. Madden et al. (2012) showed that HSP72 expression in PBMCs from CLL and chronic myelomonocytic leukemia (CMML) patients was 4-6 fold higher than in healthy individuals, with a substantial proportion localised to the cell surface (65% in CLL lymphocytes, 80%

in CLL monocytes) [70]. Similar findings were reported by Raimondo et al. (2015) and Szczepanski et al. (2020), who demonstrated that circulating HSP70 reliably distinguishes leukemia patients from controls. Importantly, Bayer et al. (2014) provided preclinical evidence that soluble HSP70 levels correlate with tumour burden and treatment response in vivo [72]. In mouse models, sHSP70 levels rose in proportion to tumour volume and declined after radiation therapy, returning to baseline upon remission. Although not leukemia-specific, these findings suggest that soluble HSP70 may function as both a diagnostic marker and a non-invasive indicator of treatment response, supporting the broader concept that extracellular HSP70 reflects disease burden.

Exosomal HSP70 further strengthens this potential. Gobbo et al. (2015) demonstrated that tumour-derived exosomes are enriched with membrane-bound HSP70, with cancer patients showing markedly higher plasma levels of HSP70-positive exosomes compared to healthy donors (mean ± SD: 3.5 ± 1.7 ng/mL vs. 0.17 ± 0.11 ng/mL, $p = 0.004$) [72]. Although this study focused on solid tumours, it underscores the tumour-specific enrichment and stability of exosomal HSP70 in circulation. Consistent with this, Georgievski et al. (2022) reported that ~40% of EVs from leukemic cells carried HSP70, whereas none were detected in controls, and these HSP70-positive EVs impaired hematopoietic stem cell function, highlighting both their biological relevance and diagnostic potential [73]. Collectively, these findings indicate that circulating HSP70, especially in its exosomal form, holds strong promise as a clinically relevant, minimally invasive biomarker for leukemia diagnosis and ongoing disease surveillance. Its detectability in blood, association with disease burden, and stability within EVs further underscore its potential for integration into future biomarker panels and validation through prospective clinical studies [21].

Prognostic Biomarker Potential of HSP70 in Leukemia

Considering the consistent overexpression of HSP70 observed in this study, and in line with numerous previous investigations, its potential prognostic significance in leukemia has been extensively examined, with reported associations between elevated HSP70 expression and key clinical outcomes including treatment response, complete remission (CR) rates, and overall survival [74-76,27]. Emerging evidence indicates that elevated HSP70 expression is associated with poorer prognosis, potentially by enabling leukemic cells to evade apoptosis, sustain uncontrolled proliferation, and resist chemotherapeutic stress. For example, in a cohort of patients with AML, Steiner et al. (2006) reported that high membrane expression of HSP70 on leukemic cells was significantly correlated with inferior prognosis [76]. The authors highlighted that HSP70 overexpression on the cell surface may facilitate immune evasion and enhance cellular survival mechanisms, thereby contributing to adverse clinical outcomes. This provides direct clinical evidence of the prognostic impact of HSP70 and reinforces its potential role as a negative biomarker in AML.

Similarly, Piszcz et al. (2014) evaluated serum anti-HSP70 antibodies and HSP70 antigen levels in 80 AML patients, reporting significantly higher antibody concentrations in patients compared to controls (354.62 ± 21.3 pg/mL vs. 247.59 ± 16.04 pg/mL, $p = 0.007$) [75]. In fact, this study also determined that patients with higher HSP70 antigen levels and lower antibody titres had significantly shorter overall survival. In contrast, patients with elevated anti-HSP70 antibody concentrations experienced longer survival outcomes, suggesting that a protective antibody response against HSP70 may offer some extent of clinical benefit. These findings indicate that both intracellular overexpression and immune response to HSP70 may contribute to disease progression and prognostic variability. Further supporting these observations, Frezzato et al. (2016) examined HSP70 and its transcriptional regulator HSF1 in CLL and found that both were significantly overexpressed in leukemic cells compared to controls [48]. Importantly, this overexpression was associated with markers of poor prognosis, implying that the HSP70/HSF1 axis plays a functional role in supporting neoplastic cell viability. These findings reinforce the relevance of HSP70 dysregulation in leukemia not only at a molecular level but also in terms of its clinical implications, including resistance to apoptosis and treatment failure [77,78]. In addition, Chalmin et al. (2010) found that HSP70 within tumourderived exosomes activates STAT3 signalling in myeloid-derived suppressor cells (MDSCs), promoting their expansion and impairing immune surveillance [79]. Although the study focused on solid tumours, MDSC-mediated immunosuppression is also recognised in leukemia, as demonstrated by Giallongo et al. (2015), suggesting that exosomal HSP70-driven immune evasion may contribute to poorer prognosis in haematologic malignancies [80].

Comparable findings were reported by Thomas et al. (2005), who investigated the prognostic value of HSP70 in AML patients and observed that individuals with low HSP70 expression had significantly higher CR rates and longer median overall survival compared to those with high expression [27]. This inverse relationship between HSP70 levels and patient outcomes supports its value as a prognostic marker.

Nevertheless, the collective evidence strongly supports the prognostic significance of HSP70 across multiple leukemia subtypes. Consistent overexpression appears mechanistically linked to poorer clinical outcomes through anti-apoptotic, pro-survival, and immune-modulatory functions. This reinforces HSP70's potential as a negative prognostic biomarker and underscores the need for further studies to evaluate its predictive value for treatment response and disease progression [76-78].

Therapeutic Potential of HSP70 Inhibition

The strong overexpression of HSP70 demonstrated in this meta-analysis, together with its wellestablished cytoprotective functions, positions it as a compelling therapeutic target. Preclinical studies consistently show that HSP70 inhibition disrupts leukemic survival by restoring apoptosis and destabilising oncogenic proteins [46,62]. These findings align with the present meta-analysis, which confirmed significantly elevated HSP70 expression in leukemia patients compared to controls. Accordingly, substantial efforts have focused on developing HSP70-targeted strategies, including small-molecule inhibitors and siRNA-based approaches, many of which show promising antileukemic activity in preclinical models [80,46].

A central justification for HSP70 inhibition is its role in drug resistance [82,30,83]. For example, Pocaly et al. (2006)

demonstrated that imatinib-resistant CML cell lines exhibited threefold higher HSP70 expression than sensitive counterparts, while siRNA knockdown restored drug sensitivity and reduced cell viability [28]. Similarly, blast cells from resistant patients displayed elevated HSP70, underscoring its clinical relevance. Complementary studies have shown that inhibitors such as MKT-077 and S1g-6 display greater potency in CML cells than in normal controls, suggesting that direct HSP70 targeting can impair leukemic cell survival and overcome resistance [84-86].

Additionally, similar findings have been reported in AML, where HSP70 inhibition has shown therapeutic promise. Reikvam et al. (2013) demonstrated that the HSP70 inhibitor VER-155008 reduced proliferation and induced apoptosis in primary AML cells, while Sharma et al. (2012) also highlighted its antileukemic activity [87]. Additionally, combining HSP70 and HSP90 inhibition produced additive effects, reinforcing the therapeutic relevance of dual chaperone targeting across both myeloid and lymphoid leukemias [88,80,46]. These consistent synergy findings strengthen the rationale for combination strategies, further supported by studies of chaperone-based chemotherapy approaches [89,90].

Pifithrin-μ (PFT-μ), a selective HSP70 inhibitor, has been extensively studied and exhibits potent antileukemic activity. Kaiser et al. (2010;2011) demonstrated that PFT-μ reduced viability in AML and ALL cells while sparing normal hematopoietic cells [88, 46]. Mechanistically, it induced cell cycle arrest, activated caspase-3, and reduced AKT and ERK1/2 signalling. Importantly, PFT-μ enhanced the activity of standard chemotherapeutics such as cytarabine and sorafenib, as well as HSP90 inhibitors like 17-AAG, with dual blockade producing synergistic reductions in viability. These findings are supported by subsequent work showing enhanced cytotoxicity when PFT-μ is combined with additional agents [91].

Another promising HSP70 inhibitor is QL47, a novel small molecule that covalently binds to the nucleotide binding domain of inducible HSP70. Hu et al. (2021) demonstrated that QL47 degraded FLT3-ITD protein via proteasome-mediated pathways and disrupted STAT5-MYC signalling in FLT3-ITD-positive AML [43]. QL47 also overcame midostaurin resistance and reduced leukemic burden in murine models, highlighting its ability to target genetically defined leukemia subsets. Additionally, Methylene blue (MB), which inhibits HSP70 ATPase activity also showed activity in preclinical models, for example, Soans et al. (2014) reported that MB suppressed proliferation and induced apoptosis in B-ALL while inhibiting the E2A transcription factor, an important regulator of B-cell development, suggesting a dual-targeted therapeutic approach [92].

Beyond pharmacological inhibition, gene-silencing approaches provide further support. Guo et al. (2019) demonstrated that siRNA-mediated knockdown of HSP70 in ALL cell lines significantly increased apoptosis and reduced proliferation through downregulation of the TAK1/Egr-1 pathway [50]. This finding reinforces the link between HSP70 and prosurvival signalling, validating its therapeutic relevance. Similarly, immunotherapeutic strategies have also been explored, for example Jimbo et al. (2008) showed that immunisation with leukemia-derived HSP70 induced strong antibody responses with complement-dependent cytotoxicity, while Sato et al. (2001) reported that HSP-peptide complex vaccination induced antileukemic immunity in murine models [93].

Mechanistic studies further clarify HSP70's role in leukemic persistence. By stabilising RAF and AKT, it sustains RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signalling, while impairing p53mediated apoptosis through MDM2 interactions [95,96]. In CLL, HSP70 stabilises Tcl1, thereby enhancing AKT activation, while inhibition with myricetin degrades Tcl1 and impairs leukemic survival [97]. These mechanisms explain both the overexpression patterns observed in this meta-analysis and their association with poor prognosis and therapeutic resistance.

Despite this compelling body of preclinical evidence, no HSP70-targeted therapy has yet reached clinical approval, reflecting challenges such as isoform selectivity, toxicity, poor pharmacokinetics, and compensatory induction of other heat shock proteins [98,99]. Nonetheless, the consistent overexpression demonstrated in this meta-analysis, together with the broad preclinical evidence base, underscores HSP70's translational potential. Rational combination strategies, particularly with tyrosine kinase inhibitors, chemotherapeutics, or immunotherapies, may prove more effective than monotherapy [100,45]. Biomarker-guided clinical trials will be critical to determine whether HSP70 inhibition can be translated into a viable therapeutic approach in leukemia.

Limitations and Future Direction

This meta-analysis provides strong evidence for consistent HSP70 overexpression in leukemia, but several limitations must be acknowledged. The number of eligible studies was small, with most published between 2008 and 2012, highlighting a lack of recent data and limiting the ability to perform subgroup analyses. Conversion of some datasets from median to mean may also introduce minor uncertainty [54]. In addition, CLL data were excluded due to incompatible reporting formats, restricting generalisability across all subtypes. Most therapeutic evidence remains confined to preclinical models, with clinical validation of HSP70 inhibitors still lacking [101]. Future research should therefore focus on large, well-designed studies across all leukemia subtypes using standardised reporting. Prospective clinical trials are needed to evaluate the safety and efficacy of HSP70-targeted therapies, particularly in rational combinations with existing treatments. Moreover, circulating and exosome-associated HSP70 require further investigation as non-invasive biomarkers for diagnosis and disease monitoring [66,102].

Conclusion

This study demonstrates that HSP70 expression is significantly upregulated in leukemia patients compared with healthy individuals. Overexpression is consistently associated with poorer survival and adverse prognosis across subtypes, supported by mechanistic and preclinical evidence highlighting HSP70's role in leukemogenesis, disease progression, and therapeutic resistance. These findings position HSP70 as a promising diagnostic, prognostic, and therapeutic biomarker in leukemia. However, the lack of recent clinical data and the small number of eligible studies underscore the need for future large-scale investigations, especially those using standardised

methodologies, alongside mechanistic studies and clinical trials to validate HSP70's clinical use. Understanding the precise biological functions of HSP70 in leukemia may also contribute to the development of novel, targeted treatment strategies. Overall, this study provides a foundation for prioritising HSP70 as a clinically relevant biomarker and therapeutic target in future leukemia research.

Authorship contribution statement

PP and EO conceived of the study and designed the experiments. EO supervised the study. PP carried out the research and data analysis. PP, EO, and HM interpreted the data and planned the publication. PP wrote the first draft of the manuscript, and all authors edited and approved of the manuscript.

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