Clin. Lab. 2025;71:XXX-XXX

ORIGINAL ARTICLE

The Correlation between Serum Heat Shock Protein 90α and the Diagnosis and Classification of Acute Myeloid Leukemia in Children

Wan Y. Qin [1], Miao M. Ma [1], Bin F. Wang [2], Jing Deng [1]

[1] *Department of Pediatrics, People's Hospital of Tongchuan, Tongchuan City, Shaanxi Province, China*
[2] *Department of General Surgery, People's Hospital of Tongchuan, Tongchuan City, Shaanxi Province, China*

SUMMARY

Background: **The purpose of this study was to investigate the correlation between serum heat shock protein 90α (HSP90α) level and disease diagnosis and classification in children with acute myeloid leukemia (AML).**
Methods: **Sixty-six children with treatment-naive AML and 35 healthy controls were enrolled. Serum HSP90α levels were measured by ELISA. Serum HSP90 levels were analyzed in relation to AML diagnosis, classification, and prognosis prediction among children.**
Results: **Serum HSP90α in children with AML was significantly higher than that in healthy controls. The ROC curve showed that serum HSP90α had excellent diagnostic efficacy for AML, with an AUC of 0.820 (95% CI: 0.737 - 0.902). Serum HSP90α was differentially expressed in different FAB subtypes of AML, which was significantly increased in M1 and M2 subtypes. Compared with the low HSP90α level group, the proportion of BM blast (%) in the high HSP90α level group was significantly increased, and the cytogenetic risk was higher. Serum HSP90α was positively correlated with BM blast (%), but no correlation was observed with the proportion of BM monocytes, lymphocytes, and red blood cells. Children with high HSP90α levels tended to have shorter overall survival than those with low HSP90α levels.**
Conclusions: **HSP90 level in serum may serve as a reliable biomarker for the diagnosis of childhood AML and its subtypes, and abnormal expression may contribute to disease occurrence and progression.**
(Clin. Lab. 2025;71:xx-xx. DOI: 10.7754/Clin.Lab.2024.241043)

Correspondence:
Jing Deng
Department of Pediatrics
People's Hospital of Tongchuan
No. 12 Jiankang Road, Wangyi District
Tongchuan City, 727000
Shaanxi Province
China
Email: dengjing73245@163.com

Manuscript accepted November 4, 2024

KEYWORDS

diagnosis, classification, HSP90α, AML

INTRODUCTION

Acute myeloid leukemia (AML) accounts for about 15 - 20% of all acute leukemia in children [1,2]. It is a highly heterogeneous group of hematopoietic malignancies arising from the cloning of hematopoietic stem cells, progenitor cells, and myeloid precursors that carry gene mutations affecting cell proliferation and damaging differentiation [3-6]. It is equally prevalent among boys and girls of all races under the age of 15 and affects children with a median age of about 6 years [5]. In recent decades, with the continuous adjustment of the risk stratification of leukemia, the improvement of MICM

detection technology, especially gene detection, and the development of targeted drugs, the long-term prognosis of children with AML has been improved to a certain extent, but more than one-third of them continue to relapse and experience an unsatisfactory long-term prognosis [5,7].

Heat shock proteins (HSPs) are widely present in organisms from prokaryotes to eukaryotes. They are a group of highly conserved proteins that initiate a series of special genes to encode and synthesize under stress and are called molecular chaperones [8,9]. HSP can be divided into HSP110, HSP90, HSP70, medium molecular weight HSP, and small molecular weight HSP. HSP90α is encoded by the HSP90AA1 gene and is a stress-inducible subtype of HSP90 [10]. HSP90α is highly expressed in multiple tumor tissues, and its level is closely related to the occurrence, progression, and drug resistance of malignant tumors [10-13]. Plasma HSP90α is regarded as a novel diagnostic biomarker for tumors but may be affected by ADAM10 expression [14]. HSP90α has also been reported as a biomarker in the diagnosis and prognosis of liver cancer and lung cancer [15-20].

Therefore, this study intended to collect data on serum HSP90α levels in 66 treatment-naive AML children and 35 healthy controls and to explore the relationship between serum HSP90α levels and clinical data such as age, gender, laboratory indicators, and risk stratification in children with AML.

MATERIALS AND METHODS

Patients

From 2018 to 2022, 66 newly diagnosed children with AML admitted to People's Hospital of Tongchuan were recruited. In addition, 35 healthy children in the outpatient physical examination at the same time period with age and gender matching were selected as the healthy control group. AML was classified using a standardized MICM classification system, including cell morphology, immunology, cytogenetics, and molecular biology. Inclusion criteria: All children with AML were diagnosed as AML by MICM classification system, and there were no other abnormalities in the healthy control group. All participants were < 15 years of age and had written informed consent from their legal guardians. All participants did not undergo anti-cancer treatment such as radiotherapy, chemotherapy, or surgery, and complete clinical data were obtained.

Exclusion criteria: Those with juvenile myelomonocytic leukemia (JMML), secondary AML, mixed phenotype acute leukemia, Down's syndrome, comorbidity with other malignant tumors, connective tissue disease, infectious diseases and heart, lung, liver, and kidney dysfunction, congenital immunodeficiency, long-term use of immunosuppressive agents, and mental disorders were excluded.

The study protocol was based on the Declaration of Helsinki. The study was approved by the ethics committee of People's Hospital of Tongchuan. The legal guardians of all participants agreed to provide blood samples for research.

Sample collection and serum HSP90α detection

Fasting elbow vein blood samples were obtained from all participants in the early morning, centrifuged at 3,000 r/minute for 10 minutes, and stored at -70°C. HSP90α level was determined using the human HSP90α ELISA kit (Yantai Protgen Biotechnology Development Co., Ltd., Shandong, China).

Diagnostic criteria

The diagnosis was made according to the 2023 NCCN Clinical Practice Guidelines in Oncology [21] and the 5th edition of the World Health Organization Classification of Hematolymphoid Tumors [22].

French-American-British (FAB) classification

M0 (minimally differentiated AML): bone marrow (BM) blasts accounted for ≥ 30%, without azurophil granule and Auer bodies, myeloperoxidase- and Sudan black B-positive cells accounted for < 3%.

M1 (undifferentiated AML): myeloblasts (type I [no granules in the cytoplasm] + type II [few granules in the cytoplasm]) account for more than 90% of non-erythroid cells (NEC; karyocytes that do not include plasma cells, lymphocytes, basophilic cells, macrophages, and all erythroid cells).

M2 (partially differentiated AML): myeloblasts (type I + II) accounted for 30 - 89% of NEC, with other granulocytes > 10% and monocytes < 20%.

M3 (acute promyelocytic leukemia): The bone marrow was mainly composed of promyelocyte with increased granules, and these cells were more than 30% in NEC.

M4 (acute myelomonocytic leukemia): BM blasts accounted for more than 30% of NEC, granulocytes accounted for 30 - 80%, and monocytes accounted for more than 20%.

M5 (acute monocytic leukemia): monoblasts, promonocytes, and monocytes in NEC accounted for ≥ 80%. M5a was classified with protomonocytes ≥ 80%, and M5b was classified with protomonocytes < 80%.

M6 (erythroleukemia): red blood cells accounted for ≥ 50%, and myeloblasts (type I + II) in NEC accounted for ≥ 30%.

M7 (acute megakaryocytic leukemia): megacaryoblast in BM accounted for ≥ 30%. Platelet antigen and platelet peroxidase were tested for positivity.

Risk stratification

AML is stratified according to the 2017 European Leukemia Network AML risk stratification [23]. Good prognosis: t (8; 21) (q22; q22.1)/RUNX1-RUNX1T1, inv (16) (p13; q22) or t (16; 16) (p13; q22)/CBFB-MYH11, NPM1 mutation and FLT3-1TD negative or mutation low load, CEBPA biallelic mutation. Moderate prognosis: nPM1 mutation and FLT3-1TD mutation

high load, NPM1 wild type and FLT3-1TD negative or mutation low load (no other adverse prognostic genetic abnormalities), (t 9; 11) (p21,3; q23,3)/MLLT3-KMT-1A and other cytogenetic abnormalities with good or poor prognosis. Poor prognosis: (t 6; 9) (p23; q34, 1)/DEK-NUP214, (t v; 11q23,3)/KMT2A rearrangement, (t 9; 22) (q34, 1; q11,2)/BCR-ABL1, TP53/RUNX1/ASXL1 mutation, complex karyotype/monomer karyotype, etc. Children with good prognosis were classified into the low-risk group, those with moderate prognosis into the middle-risk group, and those with poor prognosis into the high-risk group.

Observation indicators and follow-up

The gender, age, blood routine, FAB classification, peripheral blood (PB) and BM blast ratio, monocyte, lymphocyte and red blood cell ratio, risk stratification, and overall survival were collected at initial diagnosis. At the same time, hospitalization and outpatient medical records or telephone follow-up were reviewed, and the follow-up was conducted every 3 - 6 months until December 2023. Overall survival (OS) refers to the period from the diagnosis to death or last follow-up due to any cause.

Statistical analysis

SPSS 22.0 (IBM, NY, USA) and GraphPad Prism 9.0 (GraphPad Software, CA, USA) were used to analyze and plot the data, respectively. In this study, measurement data were expressed as mean + standard deviation (Mean + SD), and normality was tested using the Shapiro-Wilk test. The *t*-test or one-way analysis of variance was used to compare the groups that met the normality. The comparison of the measurement data between groups that did not meet the normality was performed using the independent sample Mann-Whitney U test (Independent sample Mann-Whitney U test). Enumeration data were expressed as n (%), and the chi-squared test or Fisher 's exact test was used for comparison. ROC curve and area under the ROC curve (AUC) were used to evaluate the diagnostic value of serum HSP90α level in children with AML. Bivariate correlation analysis was performed using Pearson correlation analysis. Kaplan-Meier method was used to draw the survival curve and calculate the cumulative survival rate. Log-Rank test was used to compare the survival curves between groups. $p < 0.05$ was corrected by Benjamini-Hochberg false discovery rate with adjusted $p < 0.05$ representing statistical significance.

RESULTS

HSP90α in serum of children with AML is upregulated and has diagnostic value

A total of 66 children with AML were enrolled in this study, including 36 males (54.5%) and 30 females (45.6%), with a male to female ratio of 1.2:1. The average age was (8.5 ± 3.4) years. In addition, 35 healthy children, including 20 males (57.1%) and 15 females (42.9%), met the inclusion criteria, with an average age of (7.9 ± 3.2) years. There was no difference in the general data between the two groups ($p > 0.05$) (Figure 1A, B).

ELISA showed that HSP90α in AML children was 166.38 ± 99.95 (ng/mL), while it was 71.56 ± 24.14 (ng/mL) in healthy children, and the difference was statistically significant ($p < 0.05$) (Figure 1C). The ROC curve showed that serum HSP90α had excellent diagnostic efficacy as a diagnostic marker for childhood AML (Figure 1D), and the AUC was 0.820 (95% CI: 0.737 - 0.902). The cutoff value of HSP90α was 110.5 ng/mL, and the maximum Youden index was 0.685. The sensitivity and specificity of HSP90α in the diagnosis of AML were 74.2% and 94.3%, respectively.

The relationship between HSP90α level and clinical characteristics of children with AML

The relationship between serum HSP90α and various clinical characteristics of children with AML was further evaluated. According to the cutoff value, 66 children with AML were divided into high HSP90α level group (n = 18) and low HSP90α level group (n = 48). BM blasts (%) in the high HSP90α level group were significantly higher than those in the low HSP90α level group ($p < 0.05$) and had higher cytogenetic risk ($p < 0.05$). However, there were no significant differences in gender, age, white blood cell count (WBC), hemoglobin, platelet count, and the proportion of blasts in PB between children with high and low HSP90α levels ($p > 0.05$).

Serum HSP90α is differentially expressed in different subtypes of childhood AML

Among the AML children included in this study, there were 1 case (1.5%) of M0 type, 12 cases (18.2%) of M1 type, 25 cases (37.9%) of M2 type, 3 cases (4.5%) of M3 type, 5 cases (7.6%) of M4 type, 4 cases (6.1%) of M5 type, 3 cases (4.5%) of M6 type, 6 cases (9.1%) of M7 type, and 7 cases (10.6%) of unknown type. Fisher 's exact test analysis showed that FAB classification was correlated with HSP90α level ($p < 0.05$) (Table 1, Supplementary Figure 1).

Serum HSP90α was differentially expressed in different FAB types of AML in children, and there was a statistical difference between M1 and M2 types and healthy control group ($p < 0.05$), among which HSP90α expression in M2 type was elevated most obviously. The comparison between FAB subtypes showed that there was a difference in serum HSP90α levels between M2 and M3 and unknown types ($p < 0.05$), and there was a difference in serum HSP90α levels between M1 and M3 types ($p < 0.05$) (Figure 2).

Since FAB classification is mainly based on the observation of cell morphology and histochemical staining of BM smears, further analysis of the correlation between serum HSP90α and the proportion of BM cells in children with AML showed that serum HSP90α was posi-

Table 1. Relationship between clinical data and serum HSP90α level in children with AML.

Characteristics		Number (%)/Mean ± SD			p
		All (n = 66)	HSP90α-low (n = 17)	HSP90α-high (n = 49)	
Gender	male	36 (54.5)	8 (12.1)	28 (42.4)	0.575
	female	30 (45.6)	9 (13.6)	21 (31.8)	
Cytogenetic risk	low risk	20 (30.3)	10 (15.2)	10 (15.2)	0.016
	intermediate risk	34 (51.5)	5 (7.6)	29 (43.9)	
	high risk	12 (18.2)	2 (3.0)	10 (15.2)	
Age		8.5 ± 3.4	7.8 ± 3.3	8.6 ± 3.5	0.245
White blood cell count (x 10^9/L)		51.6 ± 54.1	49.0 ± 37.0	52.6 ± 59.2	0.541
Hemoglobin (x g/L)		81.3 ± 22.7	79.7 ± 22.6	81.9 ± 23.0	0.747
Platelets (x 10^9/L)		51.2 ± 40.5	45.6 ± 39.7	53.1 ± 41.0	0.561
Bone marrow blast (%)		51.2 ± 19.6	42.2 ± 17.1	55.2 ± 19.4	0.019
Peripheral blood blast (%)		53.8 ± 22.1	60.2 ± 20.6	51.6 ± 22.3	0.121
French-American-British classification	M0	1 (1.5)	1 (1.5)	0	0.003
	M1	12 (18.2)	0	12 (18.2)	
	M2	25 (37.9)	4 (6.1)	21 (31.8)	
	M3	3 (4.5)	3 (4.5)	0	
	M4	5 (7.6)	2 (3.0)	3 (4.5)	
	M5	4 (6.1)	2 (3.0)	2 (3.0)	
	M6	3 (4.5)	0	3 (4.5)	
	M7	6 (9.1)	2 (3.0)	4 (6.1)	
	Unknown	7 (10.6)	3 (4.5)	4 (6.1)	

Data were expressed as the number of patients, n (%) or mean ± standard deviation (Mean ± SD). Statistically significant differences were defined as adjusted $p < 0.05$.

tively correlated with BM blast (%) ($r = 0.445$, $p < 0.001$). There was no correlation between serum and the proportion of monocytes, lymphocytes, and red blood cells ($p > 0.05$).

High expression of HSP90α in serum predicts poor OS in children with AML

Sixty-six children with AML were followed up for 6 - 36 months, with a median follow-up period of 24 months. There was no loss of follow-up, and 20 patients died. The OS rate at 36 months was 69.7% (46/66). Kaplan-Meier survival curve analysis showed that OS in children with high serum HSP90α levels was shorter than that in children with low serum HSP90α levels ($p = 0.038$) (Figure 3).

DISCUSSION

HSP90 can promote cancer by maintaining a variety of cancer characteristics, including cell death resistance, tumor immunity, angiogenesis, invasion, and metastasis [9]. Therefore, HSP90 is considered to be necessary for malignant progression. In AML, HSP90 plays a central role in regulating apoptosis and cell proliferation through client proteins, including growth factor receptors and cyclin-dependent kinases [24]. It has been noted that [25] HSPs, including HSP90, can be detected in all AML cases, and the positive expression rate (56%) of HSP90 in AML (M5 subtype) is higher. However, in children with AML, there is no study to elucidate the abnormal expression or effect of HSP90α.

Our study showed that serum HSP90α in children with AML was significantly higher than that in healthy control group. According to the ROC curve, serum HSP90α level had a satisfactory diagnostic effect on children with AML, suggesting that serum HSP90α level may be a sensitive tumor biomarker for the diagnosis or monitoring of AML in children. Further analysis of the relationship between serum HSP90α levels and various clinical features of children with AML showed that BM blast (%) in children with high HSP90α levels was significantly higher than that in children with low HSP90α levels and had higher cytogenetic risk, suggesting that high serum HSP90α levels were associated with malignant clinical features in children with AML. The proportion of BM blasts is crucial for the diagnosis of AML [26,27]. We confirmed that serum HSP90α levels

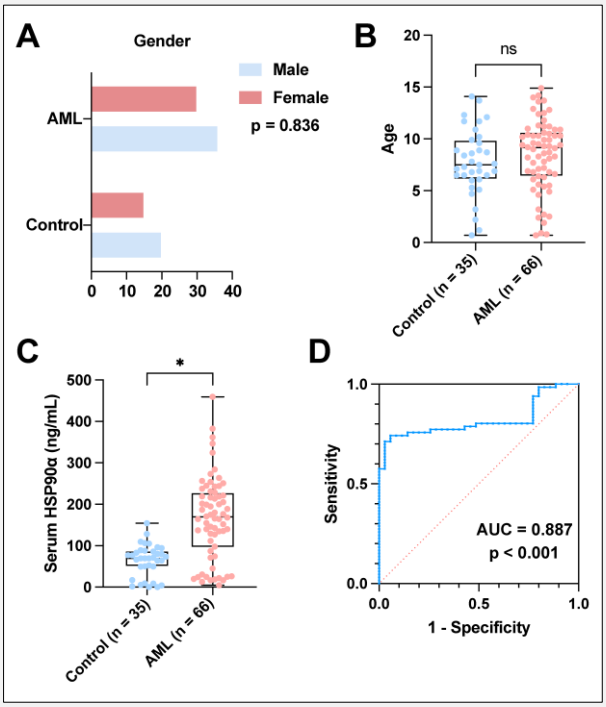

Figure 1. HSP90α is upregulated in the serum of children with AML and has diagnostic value.

A - B: Comparison of gender and age between AML children and healthy control group; C: comparison of serum HSP90α levels in children with AML and healthy controls; D: the diagnostic value of serum HSP90α level in children with AML. * p < 0.05.

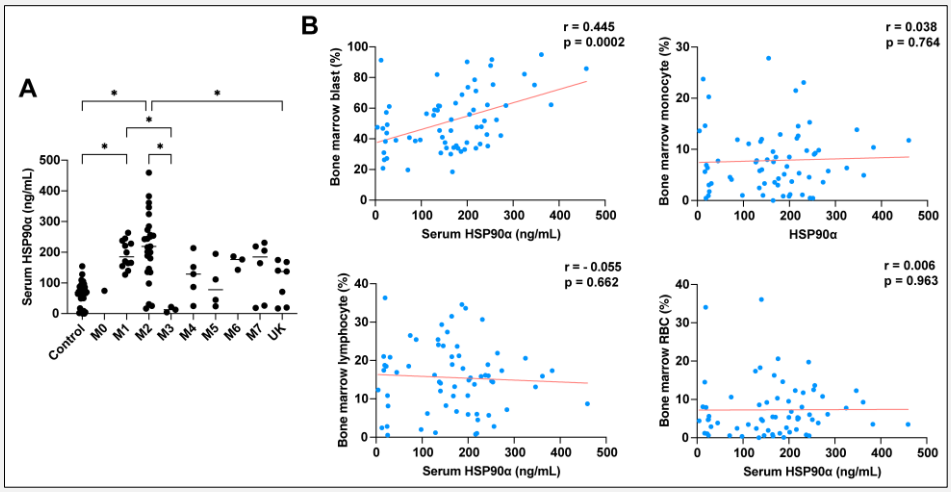

Figure 2. Serum HSP90α shows differential expression in different subtypes of AML in children.

A: Comparison of serum HSP90α levels in children with AML of different FAB types; B: correlation between serum HSP90α level and the proportion of BM blasts, monocytes, lymphocytes, and red blood cells. * p < 0.05.

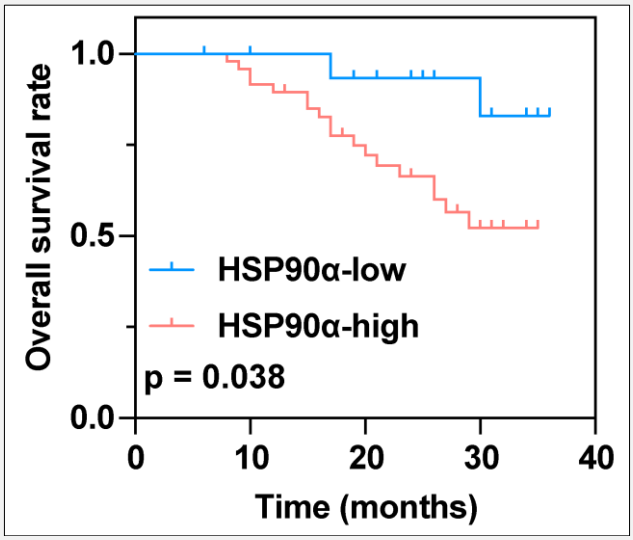

Figure 3. Kaplan-Meier survival curve analyzes the effect of serum HSP90α level on OS in children with AML (p = 0.038).

were positively correlated with BM blasts in children with AML by Pearson correlation analysis ($r = 0.445$, $p < 0.001$), and this further verified the diagnostic value of serum HSP90α levels in children with AML.

At present, there are two main classification methods for AML, namely FAB classification and WHO classification [28]. FAB classification is the earliest established classification standard. The FAB classification system divides AML into 8 subtypes of M0 - M7. This study found that serum HSP90α was differentially expressed in different FAB types of AML in children, especially in M1 and M2 types compared with the healthy control group, and HSP90α was elevated in M2 type most obviously. Statistical analysis showed that FAB classification was significantly correlated with HSP90α level, but further analysis did not observe the correlation between serum HSP90α and the proportion of monocytes, lymphocytes, and red blood cells. This may be related to the small number of samples and the wide difference between the included FAB subtype patients. Increased HSP90α levels can be observed in leukemia and are associated with disease prognosis [29,30]. However, the expression level of HSP90α in serum of children with AML and its correlation with the prognosis of children with AML have not been studied. In this study, OS in children with high serum HSP90α level was shorter than that in children with low serum HSP90α level, and high HSP90α level indicated poor prognosis in children with AML. However, whether serum HSP90α is an independent factor for the prognosis of children with AML remains to be uncertain.

This study is single-centered with small sample size. It is therefore imperative that more centers are involved and larger samples are collected in the future to confirm serum HSP90's value in diagnosing, classifying, and prognosticating AML in children in the future.

CONCLUSION

In summary, serum HSP90α levels are significantly upregulated in children with AML, which can be used as a reliable biomarker for the diagnosis of AML and its subtypes in children. Serum HSP90α level is an influencing factor but not an independent factor affecting prognosis in children with AML.

Data Availability Statement:
Data is available from the corresponding author on request.

Ethical Approval Statement:
All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All subjects were approved by People's Hospital of Tongchuan (no. 201706TC-5).

Declaration of Interest:
The authors have no conflicts of interest to declare.

References:

1. Tosic N, Marjanovic I, Lazic J. Pediatric acute myeloid leukemia: Insight into genetic landscape and novel targeted approaches. Biochem Pharmacol 2023;215:115705. (PMID: 37532055)

2. Quessada J, Cuccuini W, Saultier P, Loosveld M, Harrison CJ, Lafage-Pochitaloff M. Cytogenetics of Pediatric Acute Myeloid Leukemia: A Review of the Current Knowledge. Genes (Basel) 2021;12(6):924. (PMID: 34204358)

3. Elgarten CW, Aplenc R. Pediatric acute myeloid leukemia: updates on biology, risk stratification, and therapy. Curr Opin Pediatr 2020;32(1):57-66. (PMID: 31815781)

4. Shiba N. Comprehensive molecular understanding of pediatric acute myeloid leukemia. Int J Hematol 2023;117(2):173-81. (PMID: 36653696)

5. Obszanski P, Kozłowska A, Wancowiat J, Twardowska J, Lejman M, Zawitkowska J. Molecular-Targeted Therapy of Pediatric Acute Myeloid Leukemia. Molecules 2022;27(12):3911. (PMID: 35745032)

6. Wachter F, Pikman Y. Pathophysiology of Acute Myeloid Leukemia. Acta Haematol 2024;147(2):229-46. (PMID: 38228114)

7. Egan G, Tasian SK. Relapsed pediatric acute myeloid leukaemia: state-of-the-art in 2023. Haematologica 2023;108(9):2275-88. (PMID: 36861399)

8. Birbo B, Madu EE, Madu CO, Jain A, Lu Y. Role of HSP90 in Cancer. Int J Mol Sci 2021;22(19):10317. (PMID: 34638658)

9. Albakova Z. HSP90 multi-functionality in cancer. Front Immunol 2024;15:1436973. (PMID: 39148727)

10. Zuehlke AD, Beebe K, Neckers L, Prince T. Regulation and function of the human HSP90AA1 gene. Gene 2015;570(1):8-16. (PMID: 26071189)

11. Zhang Y, Zhao G, Yu L, et al. Heat-shock protein 90α protects NME1 against degradation and suppresses metastasis of breast cancer. Br J Cancer 2023;129(10):1679-91. (PMID: 37731021)

12. Zhang S, Wang C, Ma B, et al. Mutant p53 Drives Cancer Metastasis via RCP-Mediated Hsp90α Secretion. Cell Rep 2020;32(1): 107879. (PMID: 32640214)

13. Arkhypov I, Ozbay Kurt FG, Bitsch R, et al. HSP90α induces immunosuppressive myeloid cells in melanoma via TLR4 signaling. J Immunother Cancer 2022;10(9):e005551. (PMID: 36113897)

14. Liu W, Li J, Zhang P, et al. A novel pan-cancer biomarker plasma heat shock protein 90alpha and its diagnosis determinants in clinic. Cancer Sci 2019;110(9):2941-59. (PMID: 31343810)

15. Sourbier C. Plasma HSP90α and liver cancer: a potential biomarker? EBioMedicine 2017;25:7-8. (PMID: 29037606)

16. Mohamed E, García Martínez DJ, Hosseini M-S, et al. Identification of biomarkers for the early detection of non-small cell lung cancer: a systematic review and meta-analysis. Carcinogenesis 2024;45(1-2):1-22. (PMID: 38066655)

17. Fu Y, Xu X, Huang D, et al. Plasma Heat Shock Protein 90alpha as a Biomarker for the Diagnosis of Liver Cancer: An Official, Large-scale, and Multicenter Clinical Trial. EBioMedicine 2017; 24:56-63. (PMID: 28939487)

18. Wang Y, Seyed Barghi SM, Yang Y, Akhavan-Sigari R. Value of HSP90α in Lung Cancer Diagnosis and Recurrence Prediction: A Cohort Study. Oncol Res Treat 2021;44(11):583-9. (PMID: 34547748)

19. Wang M, Jıang Z, Lıu R. The diagnostic value of Hsp90α in monitoring treatment responses in lung cancer. Turk J Med Sci 2022;52(3):747-53. (PMID: 36326305)

20. Shi Y, Liu X, Lou J, et al. Plasma levels of heat shock protein 90 alpha associated with lung cancer development and treatment responses. Clin Cancer Res 2014;20(23):6016-22. (PMID: 25316816)

21. Pollyea DA, Altman JK, Assi R, et al. Acute Myeloid Leukemia, Version 3.2023, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2023;21(5):503-13. (PMID: 37156478)

22. Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Myeloid and Histiocytic/Dendritic Neoplasms. Leukemia 2022;36(7):1703-19. (PMID: 35732831)

23. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424-47. (PMID: 27895058)

24. Abdalla AN, Abdallah ME, Aslam A, et al. Synergistic Anti Leukemia Effect of a Novel Hsp90 and a Pan Cyclin Dependent Kinase Inhibitors. Molecules 2020;25(9):2220. (PMID: 32397330)

25. Thomas X, Campos L, Mounier C, et al. Expression of heat-shock proteins is associated with major adverse prognostic factors in acute myeloid leukemia. Leuk Res 2005;29(9):1049-58. (PMID: 16038731)

26. Yang C-F, Gau J-P, Hsiao L-T, Hsu C-Y. Clinical significance of blast percentage assessed by bone marrow trephine biopsy and aspirate smear of myeloid malignancies. Pathology 2021;53(6): 740-5. (PMID: 33745704)

27. Percival M-E, Lai C, Estey E, Hourigan CS. Bone marrow evaluation for diagnosis and monitoring of acute myeloid leukemia. Blood Rev 2017;31(4):185-92. (PMID: 28190619)

28. Carter JL, Hege K, Yang J, et al. Targeting multiple signaling pathways: the new approach to acute myeloid leukemia therapy. Signal Transduct Target Ther 2020;5(1):288. (PMID: 33335095)

29. Tian W-L, He F, Fu X, et al. High expression of heat shock protein 90 alpha and its significance in human acute leukemia cells. Gene 2014;542(2):122-8. (PMID: 24680776)

30. Yufu Y, Nishimura J, Nawata H. High constitutive expression of heat shock protein 90 alpha in human acute leukemia cells. Leuk Res 1992;16(6-7):597-605. (PMID: 1635378)

Additional material can be found online at:
http://supplementary.clin-lab-publications.com/241043/