RESEARCH ARTICLE

Evaluation of the Level of Human P-glycoprotein in Acute Myeloid Leukemia and Its Association with Treatment Response

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ABSTRACT

Background: Accurate diagnosis and classification of acute myeloid leukemia (AML) are essential for treatment decisions and assessment of prognosis. P-glycoprotein (P-gp) plays a key role in multidrug resistance and has been associated with adverse outcomes in AML.

Objective: is to evaluate the prognostic significance of serum P-gp levels in newly diagnosed AML patients, specifically regarding their association with initial treatment response. The study also explored correlations between P-gp levels and baseline laboratory parameters to identify potential biomarkers of multidrug resistance.

Methods: In this case-control observational study, P-gp levels were measured in 40 newly diagnosed AML patients admitted to Ibn-Sina and Al-Hadbaa hospitals before and after induction of chemotherapy in the period between January 2025 and June 2025. A total of 15 healthy individuals were included in this study as a control group.

Results: A significant statistical correlation was observed between P-gp level (pre-induction) and hemoglobin level, hematocrit and blood urea. Receiver operating characteristic analysis demonstrated a sensitivity of 75% and specificity of 64.3% at a cut-off value of 10.75 ng/mL indicating that a pre-induction P-gp level may serves as a predictor of poor treatment response and adverse patient prognosis. Furthermore, post-induction P-gp levels were significantly higher in patients with incomplete remission compared to those who achieved complete remission supporting the role of elevated P-gp as a biomarker of chemoresistance and adverse treatment outcome.

Conclusion: This study demonstrated that P-glycoprotein levels are higher in acute myeloid leukemia patients at the time of diagnosis than in the control group. Furthermore, higher levels of human P-glycoprotein may serve as a potential biomarker for poor treatment response. While these findings highlight the role of P-gp in chemoresistance, further evidence is needed to establish a definitive link between P-gp level and increased mortality.

Keywords: Acute myeloid leukemia, Human P-glycoprotein, Multi-drug resistance

INTRODUCTION

Acute myeloid leukemia (AML) is a rapidly progressing myeloid neoplasm characterized by the clonal proliferation of immature myeloid-derived cells (myeloblasts) in the peripheral blood and/or bone marrow. This expansion results in bone marrow infiltration that manifests as a relatively rapid bone marrow failure [1]. In general, AML incidence rises with age, and it constitutes a very small percentage of leukemia cases in children [2,3]. AML has a complex etiology, with both genetic and environmental factors contributing to the development of the disease [4]. The prognosis of AML is influenced by both patient-specific and disease-specific factors. Age is the most important prognostic factor among patient-specific variables, while genetic abnormalities are the main disease-specific prognostic determinants. Moreover, despite advanced treatment modalities, drug resistance and disease relapse remain significant challenges in AML patients with P-gp being the most extensively studied protein responsible for drug resistance [5].

Blast cells exhibit decreased sensitivity to the therapeutic effects of various agents, a phenomenon known as multidrug resistance (MDR), which poses a significant challenge to the treatment of cancer [6]. Transmembrane proteins that belong to the ATP-binding cassette (ABC) transporters superfamily [7] mediate much of MDR activity. ABC transporters are a specialized and extensive sub-family of transport proteins that use energy from ATP hydrolysis to transport various substances across the cell membrane [8]. P-gp was the first protein discovered related to drug resistance in cancer. In 1976, it was identified in drug-resistant Chinese hamster ovary cells as a membrane glycoprotein with a molecular weight of about 170 kDa [9]. P-gp is encoded by the ABCB1 gene and is the most studied transmembrane

transporter in the ABC transporter family [10]. Structurally, it consists of two transmembrane domains (TMDs), each containing six transmembrane α-helices (TMHs), and a nucleotide-binding domain (NBD). The hydrolysis of ATP provides the energy required for the TMDs to alternate between inward-facing and outward-facing conformations, facilitating the efflux of chemotherapeutic drugs [11]. In AML, P-gp expression is linked to a reduced rate of complete remission, disease-free survival, and overall survival [12].

The study aims to evaluate P-gp level in patients with acute myeloid leukemia and to determine its association with clinical and laboratory parameters; and also to assess the clinical outcome in acute myeloid leukemia patients with high P-glycoprotein level who are treated with standard chemotherapy.

PATIENTS AND METHODS

This case-control observational study was conducted in Nineveh Province at AL-Hadbaa Specialized Hospital for Hematology and Bone Marrow Transplantation and Ibn-Sina Teaching Hospital between January and June 2025.

The study included Fifteen healthy individuals and 40 patients with a confirmed diagnosis of AML based on clinical assessment and laboratory findings including complete blood count (CBC), blood film, bone marrow study and flow cytometry. All recruited patients were newly diagnosed cases who had not yet initiated induction therapy. The inclusion criteria encompassed both pediatric and adult patients across all age groups and both sexes.

Patients were included regardless of their baseline performance status or the presence of associated chronic comorbidities. Patients were excluded from the study if they had relapsed AML or were currently receiving maintenance therapy. Further exclusion criteria included cases of secondary AML arising from a preceding myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (MPN). Additionally, patients were excluded if they had received a blood transfusion within the previous 72 hours or were taking medications known to function as P-gp inhibitors, such as amiodarone, colchicine, omeprazole, or verapamil, to avoid interference with biomarker levels.

Follow up for the patients was done for one-month duration to assess response to induction therapy through the examination of bone marrow aspirate. The following characteristics were used to define complete remission (CR) in AML, neutrophil count greater than 1×10^9/L, platelet count greater than 100×10^9/L, bone marrow blasts less than 5% as determined by microscopic examination with no evidence of extramedullary AML [2]. AML patients were classified according to the French-American-British (FAB) classification system [13] based on the diagnostic records available at the Hematology Center. The FAB subtype assigned to each patient was obtained from the medical records at the time of diagnosis. Classification was performed by the treating hematopathologists using standard morphological and cytochemical criteria according to the FAB system.

Diagnosis and post-induction remission status were established through the examination of peripheral blood films and bone marrow aspirate smears prepared via standard procedures published by Bain BJ and Lewis SM [14].

Investigations

Laboratory investigations included a CBC performed on all patients and controls using an automated hematological analyzer (Sysmex XN-350, Japan) with EDTA-anticoagulated blood samples. Biochemical analyses, including lactate dehydrogenase (LDH), liver function tests, and renal function tests, were conducted using the Abbott C4000 (USA) and Indiko 836 (Finland) clinical chemistry analyzers according to the manufacturers' protocols.

Human P-glycoprotein levels were quantified in serum using a sandwich enzyme-linked immunosorbent assay (ELISA). The assay utilized an immunoassay analyzer from Shanghai YL Biont / China, Catalog NO: YLA1848HU. The test followed kit instructions and was conducted using a semi-automated device Chromate, USA

The expression of CD markers on the blast cells was obtained from the patients' clinical records. These data were generated through flow cytometry analysis (BD FACSCanto II- eight color) performed as part of the routine diagnostic workup.

Statistical Analysis

IBM-SPSS 26 was used to conduct statistical analysis. The continuous data were expressed as mean±standard deviation (SD). For all primary comparisons, effect sizes were calculated, and results were presented with their corresponding 95% confidence intervals (CI) to provide a more robust estimate of the findings. The normality of these data was evaluated by Shapiro-Wilk analysis, and the parametric tests were decided to be chosen. The numerical data were compared by the t-test performed for independent two means and by one-way ANOVA for the mean differences among the multiple groups (more than 2 groups). The Spearman correlation was done, and the correlation coefficients were estimated. The ROC test was also conducted to find the area under the curve and the sensitivity, specificity, positive and negative predictive values, in addition to the accuracy for the marker. P-value ≤ 0.05 is considered significant.

RESULTS

The study included 40 newly diagnosed cases of AML and 15 healthy controls. Among the AML group, ages ranged from 9 months to 80 years, with a mean age at diagnosis of 33.99 ±23.18 years. This cohort included 23 males and 17 females, yielding a male-to-female (M:F) ratio of 1.3:1. The control group consisted of 15

individuals with a mean age of 28.53±18.27 years, including 9 males and 6 female (Table 1).

The distribution of the samples studied based on AML subtype according to (FAB) classification, indicates that AML/M2 is the most frequent subtype at 27.5%, followed by AML/M4 at 22.5% (Fig. 1).

A comparison of the mean levels of P-gp between the cases and the controls revealed that the mean level in the cases was significantly higher compared to controls. This difference was statistically significant, with p-value = 0.018 (Fig. 2). However, no significant statistical difference was observed when comparing the mean level of P-gp in patients (pre-induction) across age groups (p=0.93), (Table 2).

The relationship between pre-induction P-gp levels and hematological parameters was evaluated using Spearman's rank correlation. A significant negative correlation was observed between P-gp levels and both hemoglobin (p = -0.38, P = 0.016) and hematocrit (p = -0.40, P = 0.010). Conversely, no statistically significant correlations were found between P-gp levels and other parameters, including platelet count, total white blood cell (WBC) count, or absolute counts for neutrophils, lymphocytes, and monocytes (P > 0.05 for all). Similarly, blast percentages in both peripheral blood and bone marrow showed no significant association with P-gp levels (Fig. 3). Spearman's rank Correlation between P-glycoprotein levels (pre) and prognostic indices indicates no significant statistical correlations (Fig. 4).

Table 1
Demographic characteristics of AML patients and healthy controls

Parameter	AML Patients (n = 40)	Healthy Controls (n = 15)
	Gender, n (%)	
Male	23 (57.5%)	9 (60%)
Female	17 (42.5%)	6 (40%)
Overall Age (years)		
Mean±SD	33.99±23.18	28.53±18.27
Age range	9 months- 80 years	1.5-55 years
Age categories, n (Mean ±SD)		
Pediatric (<18 years)	12 (10.54 ± 5.92)	5 (10.10 ± 5.72)
Adults (>18 years)	28 (44.03 ±18.96)	10 (37.75 ± 12.01)

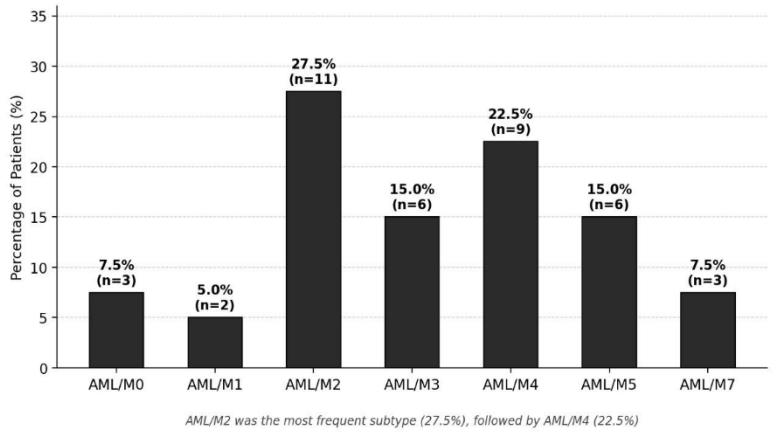

Fig. 1. The Distribution of the sample studied according to AML subtype (FAB) classification

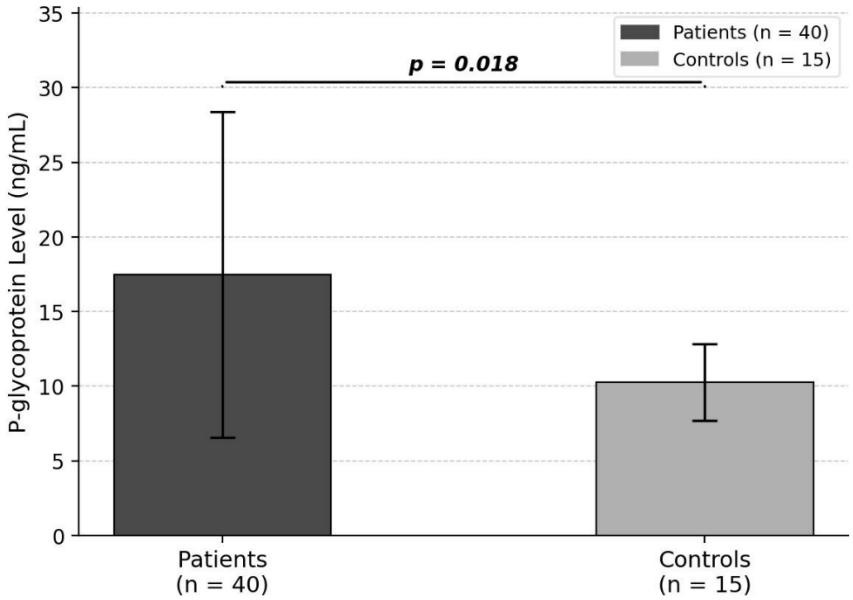

Fig. 2. Comparison of P-glycoprotein levels among the patients and controls

Table 2
Comparison of pre-induction serum P-glycoprotein levels (ng/mL) across age groups

Age groups	n	Mean±SD	95% Confidence interval (CI)	p-value
0-20 years	16	17.14±12.26	10.36 - 23.92	
21-60 years	17	17.10±10.54	11.26 – 22.94	0.93
≥60 years	7	18.86±9.98	12.67 – 25.05	

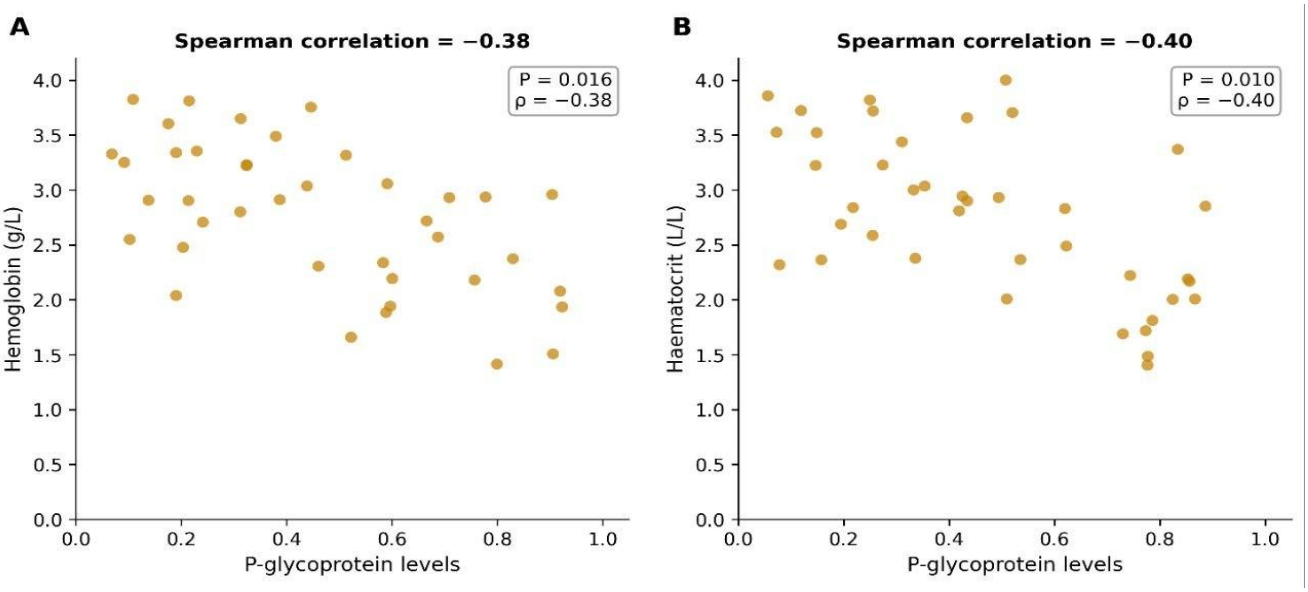

Fig. 3. Spearman's rank Correlation between pre-induction P-glycoprotein levels (X-axis) and hematological parameters (Y-axis). A: correlation with Hb (g/L), B: Correlation with Hct (L/L). Hb: Haemoglobin, Hct: Haematocrits

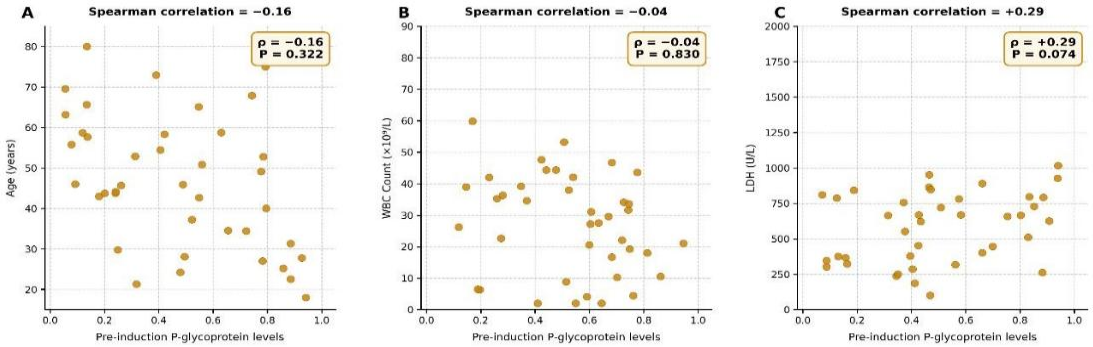

Fig. 4. Spearman's rank Correlation between pre-induction P-glycoprotein levels (X-axis) and prognostic indices (Y-axis): A: correlation with age, B: correlation with WBC count ($\times 10^9$/L), C: correlation with LDH level (IU/L). WBC: White Blood Cell Count, LDH: Lactate Dehydrogenase

Table 3
Comparison of P-glycoprotein level in relation to aberrant antigen expression

Aberrant Ag. expression	Status (n)	P-glycoprotein level ng/mL Mean±SD	P-value
CD2	Positive (n =1)	52.18 (single case)	N/A
	Negative (n =39)	16.58±9.46	
CD7	Positive (n =13)	17.26±12.33	0.929
	Negative (n =27)	17.58±10.31	
CD19	Positive (n =5)	18.55±17.16	0.816
	Negative (n =35)	17.31±10.08	
CD56	Positive (n =5)	16.32±9.13	0.805
	Negative (n =35)	17.63±11.24	

Comparison of P-glycoprotein level in patients (pre-induction) in relation to CD34 expression

The association between pre-induction P-glycoprotein levels and CD34 expression was also evaluated; the mean P-gp level in CD34-positive samples (n=24) was 16.54 ±10.47 ng/mL, compared to 18.86 ±11.72 ng/mL in CD34-negative samples (n=16). This difference was not statistically significant (P = 0.516), suggesting that P-gp levels in this cohort were not primarily driven by CD34 positivity (data not shown).

Comparison of P-glycoprotein level in patients (pre-induction) and aberrant antigen expression

The relationship between aberrant antigen expression and pre-induction P-glycoprotein levels was also examined (Table 3). A notably high P-gp level of 52.18 ng/mL was observed in a single patient expressing CD2. However, due to the limited sample size for this marker (n=1), no statistical inference could be drawn. For all other aberrant antigens, including CD7, CD19, and CD56, no significant differences in P-gp levels were found between positive and negative cases (P > 0.05).

Correlation of P-glycoprotein level in patients (pre-induction) with liver and renal function

The correlation between pre-induction P-glycoprotein levels and markers of liver and renal function is presented in Fig. 5. Analysis using Spearman's rank correlation revealed a significant, direct relationship between P-gp levels and blood urea (p = 0.34, P = 0.032). In contrast, no statistically significant correlations were observed with serum creatinine, serum alkaline phosphatase, or GPT (ALT) levels (P > 0.05).

The distribution of patients according to the response to treatment

Fig. 6 indicates that 21 patients, representing 52.5% of the study population, achieved complete remission. In contrast, approximately 14 patients (about 35%) revealed induction failure. A total of 5 patients (about 12.5%) showed early mortality. The overall survival rate (OSR) in this study was 87.5%

By comparing the mean levels of P-glycoprotein before and after induction therapy in relation to patients' outcomes, we found that the pre-treatment mean level did not show a statistically significant difference. However, the post-treatment level revealed a statistically significant difference (p=0.030). Specifically, the mean level of P-glycoprotein post-treatment was higher among patients with incomplete remission (21.52 ± 18.576 ng/mL) compared to those with complete remission (11.53 ± 6.726 ng/mL) as shown in Table 4.

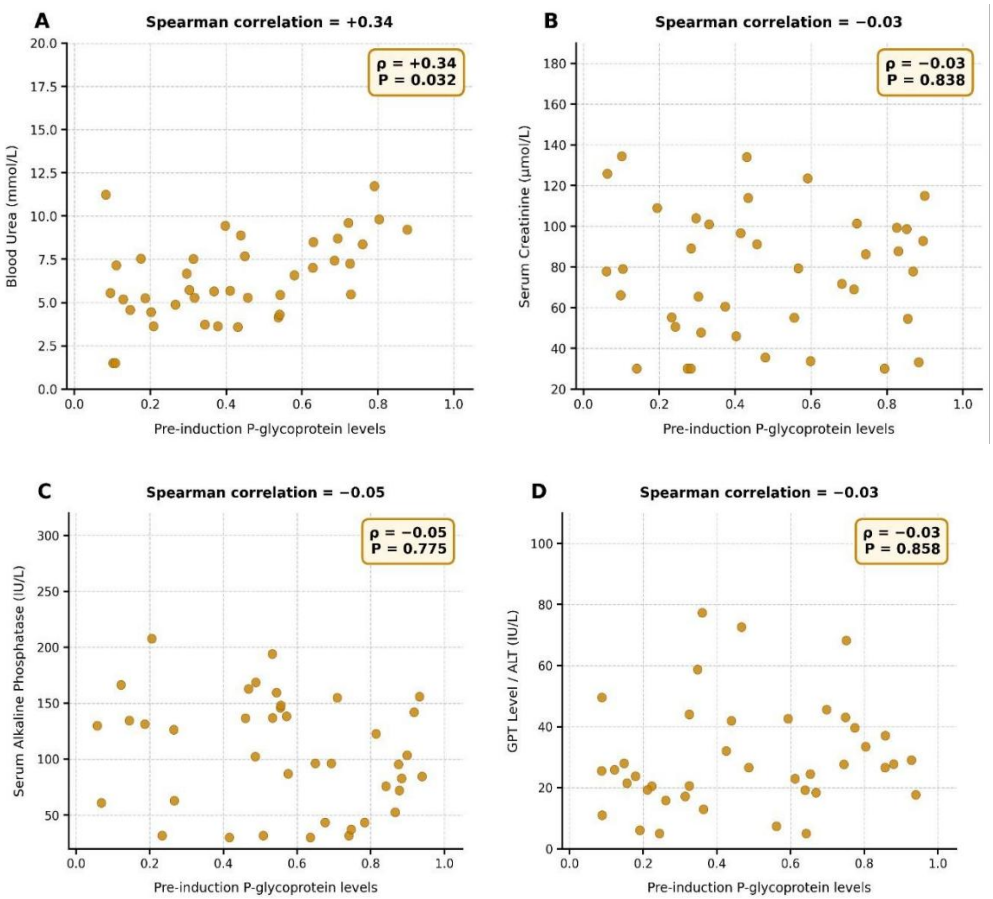

Fig. 5. Spearman's rank correlation between pre-induction P-glycoprotein levels and renal function tests; blood urea (A), serum creatinine (B) and liver function tests serum Alkaline phosphatase (C), GPT (D).

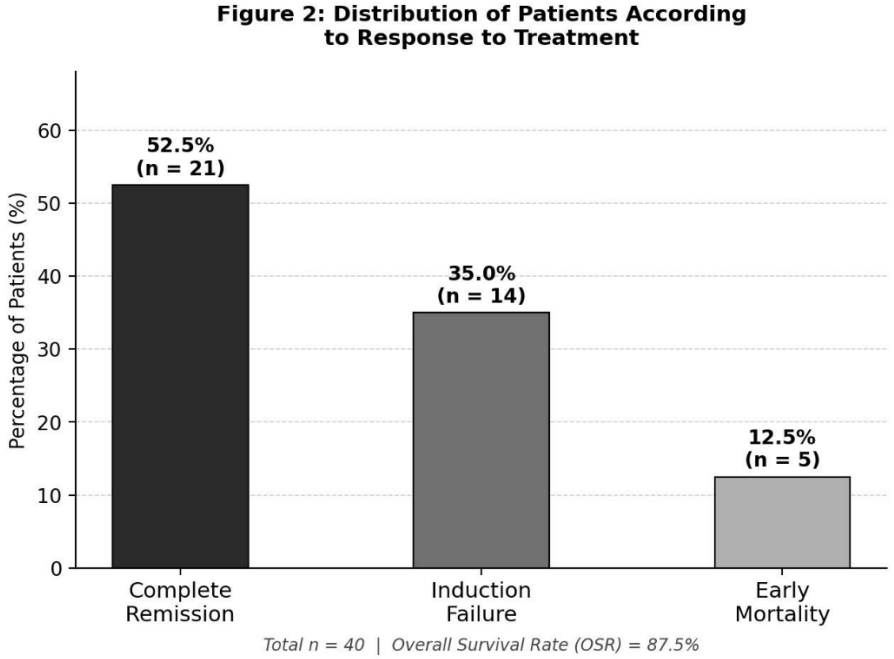

Fig. 6. The distribution of patient outcomes

Table 4

Comparison of P-glycoprotein level (pre & post) with patients' outcomes

Patients' outcomes	P-glycoprotein level ng/mL		p-value
	Pre	Post	
	Mean±SD	Mean±SD	
Complete remission (n=21)	15.89±11.546	11.53±6.726	0.286
Incomplete remission (n=14)	18.01±10.524	21.52±18.576	0.351
Death (n=5)	22.59±9.244	-------	------
p-value	0.465*	0.030**	

*One-Way ANOVA; ** Independent t-test for two means

Table 5
Sensitivity and specificity of pre-induction P-gp levels at various cut-off points.

Cut-off (ng/mL)	SN%	SP%	PPV%	NPV%	AC%
0.31	100.0	0.0	62.50	0.0	50.00
8.75	87.5	14.3	80.9	14.1	50.9
10.75*	75.0	64.3	73.8	63.4	69.65
12.87	57.5	92.9	56.9	91.3	75.2
14.43	47.5	100	47.0	97.8	73.75

Area under the Curve for P-gp in predicting response to treatment

The ROC test was performed, estimating the area under the curve for P-glycoprotein levels in patients (pre-induction) at 75.3%, demonstrating a significant statistical association (p=0.005), as shown in Fig. 7.

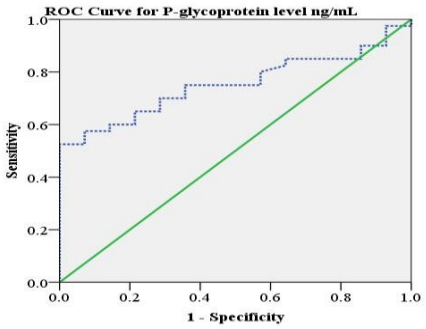

Fig. 7. ROC curve for P-glycoprotein level in patients (pre-induction)

Cut-off points for P-glycoprotein level in patients (pre-induction)

The prognostic performance of various P-glycoprotein cut-off points was analyzed to identify the threshold with the highest clinical utility. As demonstrated in Table 5, the cut-off of 10.75 ng/mL was determined to be the most effective threshold for predicting induction failure. At this level, the assay achieved the optimal balance between sensitivity and specificity using the Youden Index (Sensitivity = 75.0%, Specificity = 64.3%, Accuracy = 69.65%).

DISCUSSION

Despite significant advances in chemotherapy, a considerable proportion of AML cases remain refractory to treatment, a phenomenon largely attributed to multidrug resistance. In the last few years, the most investigated MDR mechanism in patients with leukemia has been the extrusion of chemotherapeutic agents by drug efflux pumps, specifically P-glycoprotein (P-gp) [15-17]. However, not all MDR cases can be explained by the presence of an increased cellular concentration of P-gp, because these proteins are also detected in normal tissues [15,16] and the outcome is highly affected by the characteristics of the disease and the clinical state at time of diagnosis [18]. This case-control observational study included 40 newly diagnosed AML patients, with male to female ratio of 1.3:1, these results are consistent with other Iraqi reports [19, 20]. In this study, among the forty patients, the M2 subtype was the most common AML subtype (27.5%), which is comparable to other Iraqi studies [21, 22] but differs from other study [23] in which M3 was the most common subtype. This variation could be due to different sample sizes and different study populations. The complete remission (CR) rate in this study is (52.5%) which is higher than that reported by another study, in which the CR rates were 40% [24]. The discrepancies in these findings may be attributed to the difference in sample size, disease-related factors (genetic factors) and patient specific factors (comorbidities, performance status), and other treatment-related factors [25]. In this study, we evaluated serum human P-glycoprotein levels in AML patients using the ELISA method. The difference between P-gp level between patients and healthy controls was statistically significant;

a finding that is similar to other study [26], which suggests that high levels of human p-gp in AML patients is a leukemia associated change. The mean level of P-glycoprotein (pre-induction) showed no significant statistical difference across age groups (p=0.925), which is similar to the findings observed in another study suggesting that age is not a major determinant of P-gp level in AML and other factors like disease biology and genetic abnormalities are more likely to contribute to variation in P-gp levels [27].

Regarding the hematological parameters, P-gp level was indirectly related to hemoglobin level (Hb) and hematocrit (Hct.), with both relationships being statistically significant. This negative correlation could suggest that patients with high p-gp levels may have more aggressive disease with more bone marrow infiltration and more severe anemia. Furthermore, studies have shown that P-gp level influences cytokine secretion and cytotoxic function within the hematologic microenvironment, which may predispose to our finding [28]. Direct and non-significant correlation was found between P-gp level and bone marrow blast percentage, which is comparable to that observed in another study [29]. This finding suggests that p-gp level is independent of BM blast percentage and the multidrug resistance mediated by P-gp reflects distinct biological mechanisms within leukemic cells [30]. The correlation between P-glycoprotein levels and CD34 expression was not statistically significant which is similar to the findings of other study suggesting that P-gp expression is heterogeneous and it is not confined to CD34-positive progenitor cells [31]. In the current study, a notably high P-glycoprotein level was observed in a single patient exhibiting aberrant CD2 expression (52.18 ng/mL). While statistical significance could not be determined due to the single-case nature of this finding, it may reflect a more chemo-resistant phenotype, as CD2-positive AML blasts have previously been reported to show an adverse prognosis [32] The study also revealed a direct correlation of P-gp level (pre-induction) and blood urea, which is statistically significant; however, no well-established correlation has been reported between P-gp level and renal function (blood urea and serum creatinine) in AML patients in the published literature, and this could be due to the focus on its main role in MDR [33]. In this study, no significant statistical correlation (p=0.465) between P-glycoprotein level (pre-induction) and patients' early outcomes (CR, IR, early death) is noted, a finding that is similar to another study [34], this finding indicates that P-gp alone may be insufficient as a prognostic marker and may need to be considered in the context of cytogenetic abnormalities and other resistance mechanisms [35]. While our ROC analysis demonstrated a promising AUC of 0.75, we acknowledge that these findings are exploratory given the small cohort size. These results should be interpreted as a pilot evaluation of P-gp's predictive potential rather than a validated clinical tool at this stage, this finding is closely aligned with the findings in another study [36]

The cut-off value was 10.75 ng/mL; in the context of a confirmed AML diagnosis, patients with levels above this threshold were significantly more likely to exhibit chemoresistance. This cut-off yielded a sensitivity of 75% and a specificity of 64.3%, suggesting that while P-gp is reasonably effective in identifying positive cases, there remains a moderate rate of false positives. This indicates that P-gp alone may not be sufficient as a stand-alone predictor but could be valuable as part of a biomarker panel [37]. It could be important to note that the discrepancy in results among different studies may be explained by variation in sample size and population characteristics, in addition to the method used to measure P-gp level (flow cytometry, ELISA, Western Blotting, Reverse Transcription Quantitative PCR (RT-PCR), or measuring the P-gp functional activity).

CONCLUSIONS

This study demonstrated that P-glycoprotein levels are higher in acute myeloid leukemia patients at the time of diagnosis than in the control group. Furthermore, higher levels of human P-glycoprotein may serve as a potential biomarker for poor treatment response. While these findings highlight the role of P-gp in chemoresistance, further evidence is needed to establish a definitive link between P-gp level and increased mortality.

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Conflict of Interest

No conflict of interest is declared.

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Ethical consideration

This study was approved by the Ministry of Health / Nineveh Health Department (order NO.1535). The Institutional Review Board – Research Project (IRB-RP) (Issue NO., also approved the study Path78, Date 31/10/2024). The study was explained to all enrollers (also for the parents of pediatric patients), and verbal consents were obtained from all patients and controls.

Author Contribution

Khudhur AM: Conceptualization, Data curation, Resources, Investigation, Writing - original draft

Al-Shabkhoon SO: Visualization, Methodology, Validation, reviewing, and editing, Supervision.

All authors have read and approved the final version of the manuscript and take full responsibility for its content.

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