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Age-related dynamics in acute myeloid leukemia: Implications for prognosis, risk stratification, and treatment response

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Abstract:

BACKGROUND: Acute myeloid leukemia (AML) is a complex, heterogeneous disease driven by acquired somatic mutations. The presence of specific mutations advances stratification, treatment, and prognosis. Linear accumulation of mutations over time is a crucial factor in cancer development, particularly among elderly patients. Our recent study on gene rearrangement in AML revealed a significant association between age and adverse risk cases.

AIM: The aim of this study was to examine the distribution of age, molecular characteristics, risk stratification, and treatment response based on age among patients with *de novo* AML in Iraq.

PATIENTS AND METHODS: A prospective cohort study enrolled 115 Iraqi adult patients diagnosed with *de novo* AML using morphology and flow cytometry from December 2020 to May 2022. The Leukemia Q-Fusion Screening Kit, employing multiplex reverse transcription–real-time quantitative polymerase chain reaction with 30 gene rearrangements, was employed for the identification of gene rearrangement. The patients received care and follow-up at the Hematology Unit of Baghdad Teaching Hospital in Medical City. Ethical approval from the College of Medicine's Ethical Committee at the University of Baghdad was secured before commencing the research, ensuring adherence to ethical standards throughout the study.

RESULTS: The age distribution exhibited a bimodal pattern, with a mean of 45.1 ± 17.5 years, ranging from 18 to 84 years, and a median of 46 years. A total of 39.1% of patients were diagnosed with AML before the age of 35 years, while 43% were diagnosed after the age of 51 years. AML patients with RARA mutations, RUNX1::RUNX1T1 alterations, and NPM1 mutations were predominantly observed in younger individuals, as well as those diagnosed with AML defined by differentiation. Conversely, KMT2A rearrangements were more prevalent among older age groups, with a statistically significant difference in the distribution of AML classifications according to the World Health Organization (WHO) by age categories ($P = 0.001$). The risk stratification based on age and response assessment showed a notable higher risk profile observed among elderly patients that was associated with adverse risk and poorer response and mortality ($P < 0.05$). The prediction of treatment response accuracy rate was improved by adding age to the WHO classification and ELN 2022 risk stratification (73.5%–87.9%).

CONCLUSION: Age significantly influences AML prognosis and treatment response. Incorporating age into risk stratification improves accuracy. Tailored approaches considering age are vital for optimizing AML management and outcomes.

Keywords:

Acute myeloid leukemia age stratification, acute myeloid leukemia risk stratification, gene rearrangement

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Introduction

Acute myeloid leukemia (AML) is a complex and heterogeneous disease

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which developed after acquired of somatic mutation in most of cases.[1] The presence of mutation also has advanced the stratification, treatment, and prognosis for AML patients.[2] However, the presence of such specific mutation required further support to develop the required changes to affect the cell clones.[3] For that, linear accumulation of such mutations over time is a specific factor for cancer development, not only AML, among elderly patients.[4] In our recently published study of gene rearrangement among AML patients, we found that age was significantly associated with a higher proportion of adverse risk cases, and we emphasized the importance of considering age when classifying risk, as the impact of certain genetic abnormalities may differ between younger and older patients.[5] Therefore, the objective of this study is to examine the distribution of age, molecular characteristics, risk stratification, and treatment response based on age among patients with *de novo* AML in Iraq.

Patients and Methods

A prospective cohort study recruited 115 Iraqi adult patients who were diagnosed with *de novo* AML (by morphology and flow cytometry) and multiplex reverse transcription–real-time quantitative polymerase chain reaction system with 30 gene rearrangement (Leukemia Q-Fusion Screening Kit, Zeesan Biotech Co., Ltd.) used to identify gene rearrangements among included patients.[5] The collection period was from December 2020 to May 2022, and the result was analyzed in a private laboratory. The patients were seen and followed up in the Hematology Unit of Baghdad Teaching Hospital in Medical City. The treatment protocol was followed as per the hospital treatment protocol. The ELN 2022 risk classification has been used to stratify patients at initial diagnosis [Table 1].

The assessment of response was conducted following the initial cycle of induction. Complete response (CR) was defined as bone marrow (BM) blasts less than 5%, the absence of circulating blasts and blasts with Auer rods, no presence of extramedullary disease, and absolute neutrophil count greater than or equal to 1.0×10^9 /L and platelet count greater than or equal to 100×10^9 /L. Alternatively, CR with incomplete hematological recovery met all CR criteria except for either residual neutropenia (<1.0 × 10^9 /L) or thrombocytopenia (<100 × 10^9 /L). Blast persistence (BP) after the first induction was defined as BM blasts equal to or greater than 5% assessed at any time after day 13 of the first induction but before the next chemotherapy cycle.[2]

Before commencing the research, the study protocol received ethical approval from the esteemed Ethical Committee of the College of Medicine at the University of Baghdad, ensuring that all ethical standards were adhered to throughout the study.

Results

The age distribution exhibited a bimodal pattern, with a mean of 45.1 ± 17.5 years, ranging from 18 to 84 years, and a median of 46 years [Figure 1]. A total of 39.1% of patients were diagnosed with AML before the age of 35 years, while 43% were diagnosed after the age of 51 years [Table 1]. There was no significant difference observed in the distribution of sex and the presence of splenomegaly across age categories [Table 2].

There were no observed differences in hematological parameters between age categories before and after 1 month of treatment [Table 3].

Table 1: 2022 ELN risk classification by genetics at initial diagnosis*

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*
	Mutated *NPM1* without *FLT3*-ITD
	bZIP in-frame mutated *CEBPA*
Intermediate	Mutated *NPM1* with *FLT3*-ITD
	Wild-type *NPM1* with *FLT3*-ITD
	t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/*DEK*::*NUP214*
	t(v; 11q23.3)/*KMT2A*-rearranged
	t(9;22)(q34.1;q11.2)/*BCR*::*ABL1*
	t(8;16)(p11;p13)/*KAT6A*::*CREBBP*
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)*
	t(3q26.2;v)/*MECOM(EVI1)*-rearranged
	−5 or del(5q); −7; −17/abn(17p)
	Complex karyotype, monosomal karyotype
	Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2*
	Mutated *TP53*

*Adapted from Döhner *et al*.[2]

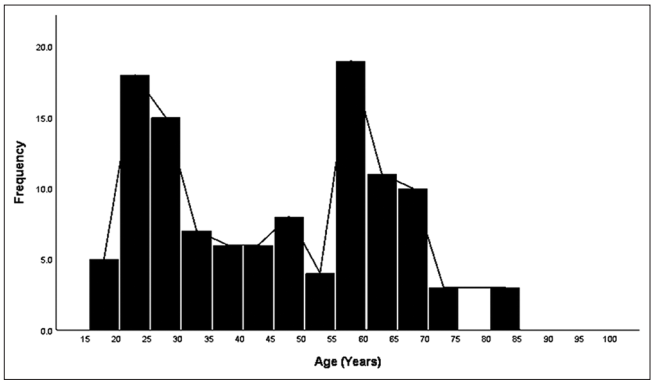

Figure 1: Histogram of age distribution

The analysis of gene rearrangement patterns based on age revealed distinct associations within specific subtypes of AML. AML patients with RARA mutations, RUNX1::RUNX1T1 alterations, and NPM1 mutations were predominantly observed in younger individuals, as well as those diagnosed with AML defined by differentiation. Conversely, KMT2A rearrangements were more prevalent among older age groups. Furthermore, a statistically significant difference was observed in the distribution of AML classifications according to the World Health Organization (WHO) criteria when stratified by age categories (P = 0.001) [Table 4].

Upon applying the ELN 2022 risk stratification based on age, a notable disparity in risk levels was identified, with a higher risk profile observed among elderly patients (P = 0.0001) [Table 5], in which an increased percentage of adverse group patients with an increase in age [Figure 2].

After the first cycle of treatment, the response assessment have been done and we found that the frequency of BP and death increased with advanced age (P = 0.013) [Table 6 and Figure 3].

Table 2: Demographics of acute myeloid leukemia by age

	Age (years)			
	<35	35–50	51–65	≥66
Number, *n* (%)	45 (39.1)	20 (17.4)	34 (29.6)	16 (13.9)
Sex, *n* (%)				
Female	24 (20.9)	11 (9.6)	21 (18.3)	12 (10.4)
Splenomegaly, *n* (%)	11 (9.6)	1 (0.9)	15 (13)	5 (4.3)

Table 3: Hematological parameters at baseline and 1 month after treatment by age

	Mean±SD				*P*
	<35 years	35–50 years	51–65 years	≥66 years	
Baseline					
RBC	2.59±1.66	3.02±0.86	2.89±1.18	3.20±2.00	0.45
Hb	7.73±2.93	8.98±1.89	7.60±1.77	6.87±2.03	0.054
WBC	6.39±4.29	6.46±3.16	5.29±2.95	3.78±3.45	0.065
PLT	79±64	105±116	78±45	63±49	0.32
1 month					
RBC	3.41±1.08	3.77±1.27	3.55±1.07	4.29±1.54	0.15
Hb	10.5±2.2	11.0±1.9	10.3±2.2	10.2±2.6	0.7
WBC	6.61±3.28	6.83±2.26	5.87±2.31	5.10±2.11	0.25
PLT	142±53	162±59	158±56	137±68	0.39

RBC=Red blood cell, WBC=White blood cell, Hb=Hemoglobin, PLT=Platelet, SD=Standard deviation

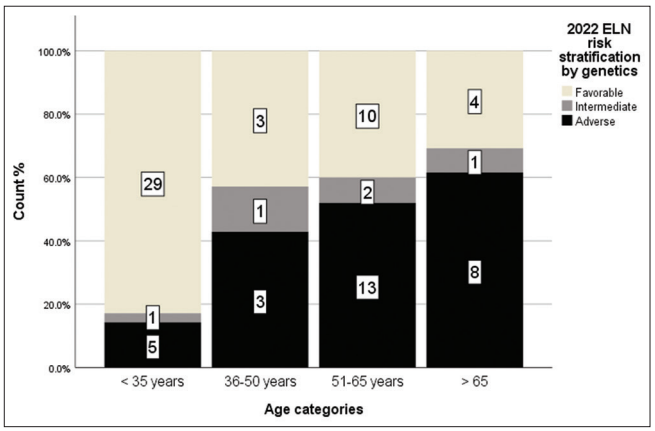

Figure 2: Risk stratification by age category

Table 4: Cases classification based on the World Health Organization (2022) by age

WHO classification	<35 years	35–50 years	51–65 years	≥66 years	Total
AML with defining genetic abnormalities, *n* (%)					
Acute promyelocytic leukemia					
PML::*RARA* t(15;17)(q24;q21)	4 (66.7)	0	2 (33.3)	0	6 (100)
PLFZ::*RARA* t(11;17)(q23;q21)	3 (100)	0	0	0	3 (100)
NPM::*RARA* fusion t(5;17)(q32;q21)	7 (100)	0	0	0	7 (100)
AML					
RUNX1::*RUNX1T1* t(8;21)(q22;q22)	10 (52.6)	2 (10.5)	3 (15.8)	4 (21.1)	19 (100)
CBFB::*MYH11* t(16;16)(p13;q22)	1 (16.7)	1 (16.7)	4 (66.7)	0	6 (100)
DEK::*NUP214* t(6;9)(p23;q34)	1 (14.3)	2 (28.6)	3 (42.9)	1 (14.3)	7 (100)
AML with *KMT2A* rearrangement					
t(10;11)(p12;q23)	2 (13.3)	0	8 (53.3)	5 (33.3)	15 (100)
t(11;17)(q23;p13)	0	0	1 (33.3)	2 (66.6)	3 (100)
t(9;11)(p22;q23)	1 (20)	1 (20)	2 (40)	1 (20)	5 (100)
AML with NPM1 mutation	4 (80)	0	1 (20)	0	5 (100)
AML, defined by differentiation, *n* (%)					
Minimal differentiation	3 (42.9)	2 (28.6)	2 (28.6)	0	7 (100)
Without maturation	4 (44.4)	1 (11.1)	3 (33.3)	1 (11.1)	9 (100)
With maturation	2 (40)	2 (40)	1 (20)	0	5 (100)
Acute myelomonocytic leukemia	0	6 (60)	2 (20)	2 (20)	10 (100)
Acute monocytic leukemia	3 (37.5)	3 (37.5)	2 (25)	0	8 (100)

AML=Acute myeloid leukemia, WHO=World Health Organization

Using neural networks to predict response as the dependent variable, we conducted two models. In the first model, we predicted the response for 115 patients in the study based on ELN 2022 risk stratification and WHO 2022 classification. This model achieved a 73.5% accuracy rate, with area under the curve (AUC) values of 0.88, 0.8, and 0.9 for CR, progression (BP), and death, respectively [Figure 4]. Notably, the independent importance was 100% (0.76) for WHO 2022 classification and 30.4% (0.23) for ELN 2022 risk stratification [Figure 5].

In the second model, we added the age category with ELN 2022 risk stratification and WHO 2022 classification. This model enhanced the correct prediction rate to 87.9%, with AUC values of 0.91, 0.81, and 0.92 for CR,

Table 5: ELN 2022 risk stratification of acute myeloid leukemia by age

	Age (years)				Total
	<35	35–50	51–65	≥66	
Favorable, *n* (%)	29 (63)	3 (6.5)	10 (21.7)	4 (8.7)	46 (100)
Intermediate, *n* (%)	1 (20)	1 (20)	2 (40)	1 (20)	5 (100)
Adverse, *n* (%)	5 (17.2)	3 (10.3)	13 (44.8)	8 (27.6)	29 (100)
Unclassified, *n* (%)	10 (28.6)	13 (37.1)	9 (25.7)	3 (8.6)	35 (100)

ELN= European leukemia net

Table 6: Response assessment by age

	Age (years)				Total
	<35	35–50	51–65	≥66	
CR, *n* (%)	32 (45.1)	16 (22.5)	18 (25.4)	5 (7)	71 (100)
BP, *n* (%)	10 (31.3)	4 (12.5)	12 (37.5)	6 (18.8)	32 (100)
Death, *n* (%)	3 (25)	0	4 (33.3)	5 (41.7)	12 (100)
Total, *n* (%)	45 (39.1)	20 (17.4)	34 (29.6)	16 (13.9)	115 (100)

CR=Complete response, BP=Blast persistence

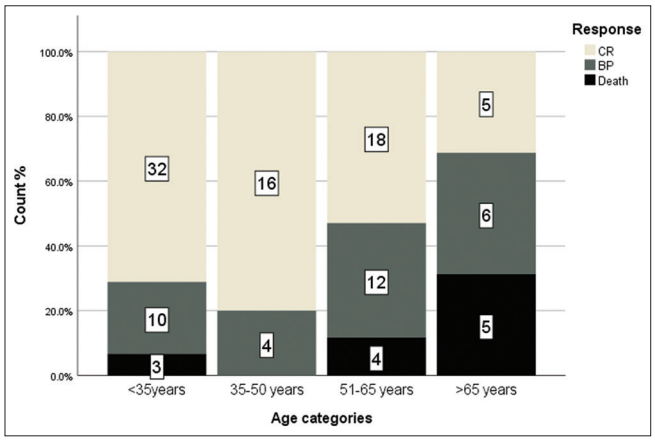

Figure 3: Response assessment by age category. CR = Complete response, BP = Blast persistence

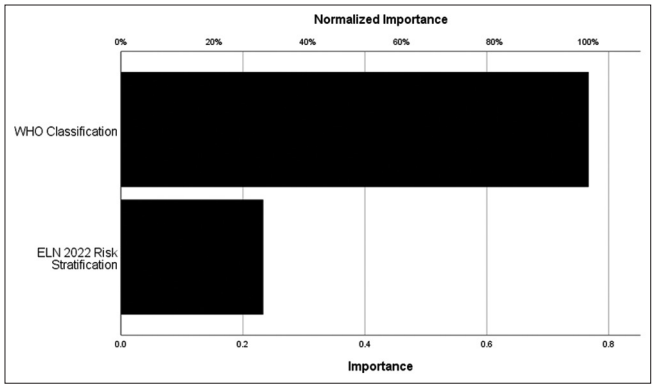

Figure 5: Normalized importance for response prediction by age category, ELN 2022 risk stratification, and World Health Organization 2022 classification (*n* = 115). WHO = World Health Organization

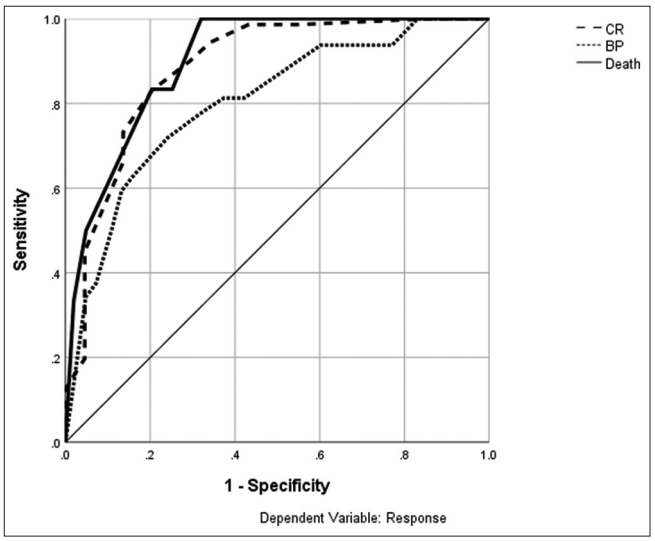

Figure 4: Receiver operating characteristic for response prediction by neural networks analysis by age category, ELN 2022 risk stratification, and World Health Organization 2022 classification. Area under the curve: 0.88 for complete response, 0.8 for blast persistence, and 0.9 for death (*n* = 115). CR = Complete response, BP = Blast persistence

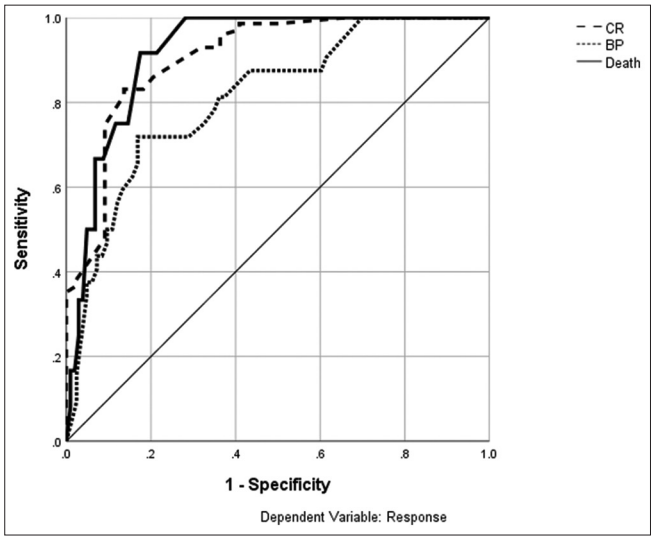

Figure 6: Receiver operating characteristic for response prediction by neural networks analysis by age category, ELN 2022 risk stratification, and World Health Organization 2022 classification. Area under the curve: 0.91 for complete response, 0.81 for blast persistence, and 0.92 for death (*n* = 80). CR = Complete response, BP = Blast persistence

BP, and death, respectively [Figure 6]. The independent importance in this model was 100% (0.5) for WHO 2022 classification, 80.3% (0.4) for ELN 2022 risk stratification, and 18.5% (0.093) for age category [Figure 7].

Discussion

Age emerges as a pivotal factor influencing not only the prognosis of AML but also that of various cancers across diverse patient populations.[6,7] Its significant impact on prognosis underscores its crucial role, particularly in shaping treatment decisions.[2] The inclusion of age as a key variable in the assessment of prognostic factors and risk classification for AML has the potential to enhance and refine the existing risk stratification strategies.

In this investigation, the average and middle age of patients diagnosed with AML was situated in the mid-forties. This aligns with findings from another study in Iraq, which similarly indicated that the mean age of AML patients tends to be in the fourth decade of life.[8] Conversely, a separate study conducted in Iraq reported a younger mean age of 28 years among a group of 50 AML patients.[9] From a global perspective, the American Cancer Society documented that, on average, individuals are diagnosed with AML around the age of 68 years.[10]

Notably, a study by Yi *et al*., focusing on the trends in AML incidence rates from 1990 to 2017, revealed that developed countries exhibited a higher age-standardized incidence rate compared to developing countries.[11] This observation suggests variations in AML epidemiology between regions with differing levels of socioeconomic development. Additionally, the higher age-standardized incidence rate in developed countries, as highlighted by Yi *et al*.,[11] could be influenced by factors such as an aging population in developed countries, and potential differences in risk factors. These findings emphasize the dynamic nature of AML demographics and the necessity of a nuanced approach in epidemiological studies and health-care planning on a global scale to involve the diagnostic trend among developing countries in the global guidelines.

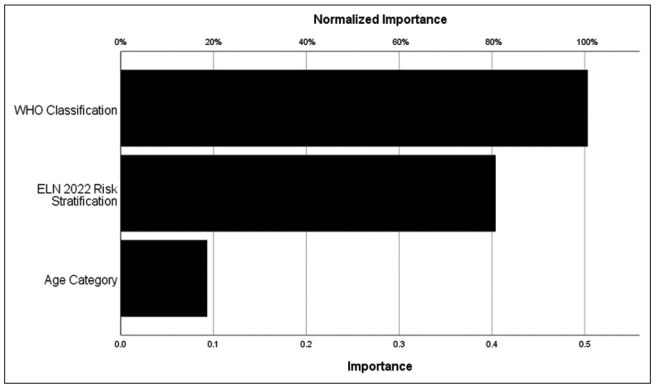

Figure 7: Histogram of normalized importance for response prediction by age category, ELN 2022 risk stratification, and World Health Organization 2022 classification (n = 80). WHO = World Health Organization

Additionally, our study revealed a bimodal age distribution, with elevated incidences observed among individuals aged 20–30 years and those aged 55–70 years. Intriguingly, this pattern exhibited variations across different types of AML based on the WHO classification. Specifically, acute promyelocytic leukemia (APL) and core-binding factor (CBF) AML were more prevalent among younger age groups, whereas AML with KMT2A rearrangement was more frequently observed in older age groups. The association between specific genetic abnormalities, such as KMT2A rearrangement, and older age groups may reflect the cumulative effects of genetic alterations over time. On the other hand, the higher incidence of APL and CBF-AML among younger individuals may be indicative of distinct underlying mechanisms or predispositions in this age cohort. This trend aligns with the findings of Sasaki *et al*.,[12] who reported that patients with APL and CBF-AML 62% and 58% were aged 20–59 years, respectively, despite an overall median patient age of 65 years and 60% of patients were aged 60 years or older. Moreover, Gopishetty *et al*.[13] reported that approximately 71% of patients with AML enrolled in clinical phase III trials were under the age of 65 years. The alignment of our findings with those of Sasaki *et al*.[12] reinforces the consistency of age patterns across different populations and supports the notion that certain genetic subtypes of AML may exhibit age-specific predilections.

Additionally, our investigation revealed a positive correlation between age and risk stratification, indicating that as age increases, there is a concurrent rise in adverse risk classifications. Moreover, among patients without gene rearrangements, only three were aged over 65 years, underscoring the notion that elderly patients exhibit a higher frequency of acquired genetic mutations in comparison to young age AML patients.[14] The observed relationship between age and adverse risk, coupled with the higher prevalence of acquired genetic mutations in the elderly, suggests the importance of age as a key determinant in AML prognosis.

Furthermore, our findings demonstrated a direct impact of age on treatment response, with an increase in age corresponding to an elevated mortality rate. This pattern aligns consistently with numerous other studies that have identified advanced age as a significant factor associated with higher mortality rates.[2,12,14] Consistent with the research conducted by Silva *et al*., our findings corroborate that elderly patients face an increased risk of higher relapse rates and poorer outcomes compared to their younger counterparts.[15] The diminished tolerability of chemotherapy in the elderly emerges as an additional factor contributing

to adverse risk in this age group.[16] A comprehensive analysis conducted by Appelbaum *et al*. on a large scale further emphasized that elderly patients exhibit adverse risk profiles across various dimensions when compared to younger patients. Furthermore, the combination of a compromised performance status and advanced age identifies a subgroup of patients with a heightened likelihood of mortality within the initial 30 days of initiating induction therapy.[17]

Significantly, the inclusion of age categories alongside WHO classification and ELN risk stratification in predicting treatment response resulted in a substantial improvement in accuracy rates. The accuracy rate, which initially stood at 73.5%, notably increased to 87.9% with age. This enhancement in predictive accuracy was particularly pronounced in the refinement of ELN risk stratification. The incorporation of age categories into predictive models evidently contributes to a more robust and precise assessment of treatment response. This improvement is crucial in the context of AML management, as it suggests that considering age as a distinct factor alongside established classifications can enhance the overall predictive power of the model. The observed boost in accuracy rates implies that age-related considerations play a significant role in determining treatment response in AML patients. This highlights the importance of a comprehensive and age-inclusive approach in risk stratification and treatment decision-making. The refined ELN risk stratification further underscores the potential benefits of incorporating age-related factors in predicting and optimizing treatment outcomes for individuals with AML.

Incorporating age into the prognostic considerations is essential for a more comprehensive understanding of the disease outcomes. As individuals age, factors such as physiological resilience, comorbidities, and treatment tolerability can significantly influence the prognosis of cancer, including AML. Therefore, accounting for age in risk stratification models can provide a more nuanced and accurate prediction of disease progression and response to treatment.

The study encountered limitations, notably a small patient sample, impeding the generalization of results. Additionally, a longer follow-up period is essential to comprehensively assess outcomes and draw more robust conclusions.

Conclusion

Recognizing and incorporating age-related considerations into prognostic models and treatment strategies is paramount for a nuanced understanding of AML dynamics.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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