The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 4106- 4112

Prognostic value of Elevated Serum Inflammatory Markers in Adult Patients receiving Induction Chemotherapy for Acute Leukemia

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ABSTRACT

Background: Leukemias are a diverse collection of neoplastic illnesses with distinct morphological, immunophenotypic, cytogenetic, and molecular characteristics of malignant cells. C-reactive protein (CRP) testing is traditionally used to assess the degree of infection, diagnosis of sepsis as well as the response to antimicrobial treatment. In the absence of iron overload, cancer patients have a higher level of serum ferritin. CRP and serum ferritin (SF) are inflammatory indicators that can predict the presence of systemic illness**.**

Objective: Our study aimed to estimate the role of serum ferritin and CRP in the early detection of systemic infection and the prognostic value of these markers in denovo adult patients receiving chemotherapy for acute leukemia.

Methods: This cross-sectional study was performed in the period from February 2016 to February 2017 in the Clinical Hematology Unit, Internal Medicine Department, and included 30 denovo adult patients who were diagnosed with acute leukemia; 14 of them were females and 16 were males.

Results: After a median follow-up period of 1 year with a range (1.1- 11.2) months; there was a statistically significant cumulative overall survival in younger, non-hyperferritinemia, non-septic patients, and in whom responded to therapy (p=0.02, 0.02 and 0.03 respectively). Furthermore, there was no statistically significant correlation of OS with CRP or erythrocyte sedimentation rate (ESR). Hyperferritinemia (>150) and elevated CRP (>33) were independable risk factors predicting sepsis (P=0.007 and 0.016 respectively) by using a Multivariate logistic regression model.

Conclusion: Modest elevation of the blood level of CRP and ferritin above the normal range showed an association with the probability of systemic infection in patients who underwent dose-intensive induction chemotherapy even in absence of clinical evidence of sepsis.

Keywords: Prognostic, Inflammatory markers, Acute leukemia**.**

INTRODUCTION

Acute leukemias are malignancies arising in the bone marrow as a result of neoplastic change in the hematopoietic stem cells followed by clonal proliferation. Classically, the phenotypic and immunophenotypic features have helped distinguish acute myeloid leukemia (AML) from acute lymphoid leukemia (ALL) [1], although a subset of patients with acute leukemia is considered as having ambiguous lineage (commonly referred to as mixed phenotype acute leukemia) with clinical and therapeutic implications[2].

Chemotherapy induction is a dynamic and occasionally risky operation. There are several risk factors linked to substantial morbidity and even fatality, including acute systemic infection during induction chemotherapy, which can lead to a decrease in the patient's PS and poor survival [3].

Inflammatory indicators in the blood, such as C-reactive protein (CRP) and serum ferritin, can indicate the likelihood of systemic infection[4]. The acute phase reaction is characterized by increased levels (i.e., at least 25% increase in serum levels) of several proteins in response to inflammation, infection, or tissue injury, but the name is misleading because the reaction can also be seen in chronic diseases with fluctuating conditions (e.g., cancers), or be a chronic or long-lasting response that is maintained during the chronic disease[5].CRP is a plasma protein, is the main mediator of inflammation synthesized in the liver in response to Interleukin-6 (IL-6), and is used as an early marker of opportunistic infection[6].

Ferritin is a 450 kDa protein made up of 24 H-ferritin and L-ferritin subunits. H-ferritin overexpression promotes lymphomagenesis and has been linked to resistance to chemotherapy drugs such as doxorubicin, which causes oxidative stress [7]. It was reported that there is an association between serum ferritin levels and a poorer response to induction chemotherapy as well as a higher incidence of relapse would suggest that ferritin may play a role in chemoresistance [8].

So we aimed to estimate the role of serum ferritin and CRP in the early detection of systemic infection and the prognostic value of these markers in denovo adult patients receiving chemotherapy for acute leukemia.

MATERIALS AND METHODS

Patients:

The Cross-sectional study was performed in the period from February 2016 to February 2017 in the Clinical Hematology Unit, Internal Medicine Department at Zagazig University Hospitals, and included 30 denovo adult patients who were diagnosed with acute leukemia; 14 of them were females and 16 were males.

Received: 21/4/2022
Accepted: 20/6/2022

Ethical consent:

Written Informed consent was taken from the patient to participate in the study. Approval for performing the study was obtained from Internal Medicine and Clinical Pathology Departments, Zagazig University Hospitals after taking Institutional Review Board (IRB) approval. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Data collection:

All patients of this study were subjected to detailed history taking; with special considerations for age, sex, smoking, Co-morbidities, and medications, Full physical examination was done. Laboratory investigations were done according to the methods applied in the Clinical Pathology and laboratories of Zagazig University Hospitals and included: complete blood count, liver function tests, kidney function tests, uric acid, electrolytes, lactate dehydrogenase (LDH), ESR, Cultures (blood, stool, urine &sputum), human immunodeficiency virus (HIV) ab, hepatitis C (HCV) ab, HBc ab, and HBs Ag. Furthermore, specific investigations including CRP, Ferritin, bone marrow aspiration, flow cytometry, cytogenetic analysis, pelvi-abdominal sonography, chest X-ray (CXR), and echocardiography were done.

Methods:

Ferritin: Test was performed by Electrochemiluminescence on Roche(r) Cobas 8000 platform-602e module, using a dedicated reagent from the system vendor.

CRP: It was performed by Immune-turbidimetry on Roche(r) Cobas 8000 platform-702c module, using a dedicated reagent from the system vendor.

Bone Marrow aspiration: Bone marrow samples were aspirated from patients by Islam needle under complete aseptic conditions with local anesthesia. Bone marrow smears were prepared and bone marrow samples were delivered into Ethylenediamine tetraacetic acid (EDTA) vacutainer tube for immune phenotyping by flow cytometry. Flow Cytometry: Immunophenotyping by flow cytometry using Bectron Dickenson FacsCalibar device to detect the following markers (MPO, CD13, CD33, HLA-DR, TdT, CD14, CD64, CD34, CD 3, CD20, and CD22).

Treatment:

AML patients received induction chemotherapy with 3+7 protocol followed by consolidation with high dose Ara- C for favorable-risk patients or referral to allogenic BMT in unfavorable risk and eligible patients [9]. The main treatment for acute lymphoblastic leukemia (ALL) in adults involves the long-term use of chemotherapy Hyper-CVAD alternating with high dose methotrexate and cytarabine protocol in the form of dose-intensive phase and maintenance phase [10].

Treatment Outcome:

Response to induction therapy was assessed after one or two courses of chemotherapy. CR was defined according to standard criteria as less than 5% blasts in bone marrow aspirates with evidence of the maturation of cell lines and restoration of peripheral blood counts. Hematological relapse was considered when more than 5% blasts were seen in bone marrow aspirates. Disease-free survival (DFS) was measured from the time of CR to the time of relapse or death, and OS from the time of initial diagnosis to the time of death.

Follow Up:

The median follow-up period of 1 year with a range of (1.1- 11.2) months for studied cases. AML patients who ended consolidation therapy and ALL patients that were on maintenance therapy were monitored with clinical examination and laboratory investigations including; complete blood count (CBC), with a blood smear every 1–3 months then every 3–6 months till the study end. If pathological cytopenias developed, BM aspiration and biopsy were recommended to rule-out relapse, as recommended by the National Comprehensive Cancer Network (NCCN) guideline [11].

Statistical analysis

The collected data were computerized and statistically analyzed using the SPSS program (Statistical Package for Social Science) version **20**. Data were tested for normal distribution using the Kolmogorov–Smirnov test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) and Fisher exact were used to calculate the difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). The Independent T-test was used to calculate the difference between quantitative variables in two groups in normally distributed data. Pearson correlation coefficient was used to calculate the correlation between two quantitative variables. (ROC) curve was built to allow for the setting of test result threshold values as well as the comparison of different testing procedures. Any predictor with $p < 0.2$ in univariate was used in a backward multivariate logistic regression analysis model. Kaplan and Meier's method was used to estimate overall and event-free survival and log-rank test compared survival curves.

RESULTS

Our study included 30 patients, 16 of them were males and 14 were females, the number of patients more than 60 years was 7 while the number of patients less than 60 was 23. There was a statistically significant difference between the septic and non-septic patients regarding bleeding, **Table (1).**

Table (1): patient characteristics and clinic-demographic data regarding the presence of clinical sepsis

		Clinical Sepsis			P
		Yes N=17		No N=13	
Sex		Female	10(58.8%)	4(30.8%)	0.159
		Male	7(41.2%)	9(69.2%)	
Age		Less than 60	11(64.7%)	12(92.3%)	0.104
		60 or more	6(35.3%)	1(7.7%)	
		Presentation			
Anemic Symptoms		10(58.8%)		9(69.2%)	0.556
Bleeding		7(53.8%)		2(11.8%)	0.011*
Gum Swelling		5(29.4%)		7(53.8%)	0.328
LN		6(35.3%)		6(46.2%)	0.548
Type of Leukemia	ALL	5(29.4%)		5(38.5%)	0.896
	AML	12(70.6%)		8(61.5%)	0.896
		PAU/S			
Splenomegaly		4(23.5%)		6(46.2%)	0.193
Hepatomegaly		6(35.3%)		5(38.5%)	0.859
Abd LN		5(29.4%)		8(61.5%)	0.077
		TTT outcome			
Relapse		No	10(58.8%)	8(61.5%)	0.88
		Yes	7(41.2%)	5(38.5%)	
Response		No. CR	8(47.1%)	3(23.1%)	0.171
		CR	9(52.9)	10(76.9%)	

There is a statistically significant difference between the septic and non-septic patients regarding platelet count, CRP, and ferritin. In septic patients, there was less platelet count, higher CRP level, and higher ferritin, **Table (2).**

Table (2): Comparison of laboratory data regarding the presence of sepsis

		Clinical Sepsis		P
		Yes	No	
WBCs x109 (L)		26.3±4.3	51 ±11.6	0.78
Hb (gm/dl)		7.9 ± 1.5	7.9 ± 1.3	0.905
PLT x109 (L)		24.8 ± 5.4	44.0 ± 8.5	0.008*
CRP (mg/l)		25.7 ± 4.6	40.7 ± 8.6	0.041*
ESR (mm/h)		66.0 ± 13.7	48.5 ± 11.4	0.075
Ferritin (ng/ml)		674±161.4	132±28.9	0.018*
HCV	No	14 (82.4%)	10 (76.9%)	0.713
	Yes	3 (17.6%)	3 (23.1%)	
PB Blast %		39.2 ± 30.3	42.2 ± 30.0	0.791
BMA Blast%		67.5 ± 19.3	74.2 ± 16.9	0.325
BM Cellularity	Hypercellular	9 (52.9%)	10 (76.9%)	0.171
	Normocellular	8 (47.1%)	3 (23.1%)	
Cytogenetics	Favorable	3 (17.6%)	3 (23.1%)	0.926
	Inter	8 (47.1%)	6 (46.2%)	
	Unfavorable	6 (35.3%)	4 (30.8%)	
Organism	G –Ve	8 (47.1%)	4 (30.8%)	0.421
	G +Ve	5 (29.4%)	3 (23.1%)	
	No	4 (23.5%)	6 (46.2%)	
Karyotyping	Normal	13 (76.5%)	10 (76.9%)	0.239
	Inversion16	0 (0.0%)	1 (7.7%)	
	t (4;11)	0 (0.0%)	1 (7.7%)	
	t (8;21)	3 (17.6%)	0 (0.0%)	
	t (9;22)	1 (5.9%)	1 (7.7%)	

At serum ferritin level >150 ng/ml, ESR level > 47 mm/hr and CRP level > 33 mg/L, the sensitivity was (72.7%, 70.6% and 82.5% respectively), specificity was (87.5%,38.4% and 69.3% respectively), positive predictive value was (94.1%,60% and 77.8% respectively)and negative predictive value was (53.8%50% and 75% respectively) in predicting sepsis. In comparing serum ferritin level at >150 ng/ml and CRP level at >33 mg/L, the sensitivity was 76.47% and specificity was 30.77% and positive predictive value was 59.09% and negative predictive value was 50.00% in predicting sepsis. In comparing serum ferritin level at >150 ng/ml and ESR level at >47 mm/hr, the sensitivity was 94.12% and specificity was 30.77% and positive predictive value was 64.00% and negative predictive value was 80.00% in predicting sepsis, **Table (3).**

Table (3): Cut off levels of serum Ferritin, ESR, and CRP in predicting clinical sepsis

	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
SF, ng/ml	>150	72.70% (49.8 - 89.3%)	87.50% (47.3 - 99.7%)	94.10% (71.3 - 99.9%)	53.80% (25.1 - 80.8%)
ESR	> 47	70.59% (44.0 - 89.7%)	38.46% (13.9 - 68.4%)	60% (36.1 - 80.9%)	50% (18.7 - 81.3%)
Hs CRP	> 33	82.35% (56.6 - 96.2%)	69.23% (38.6 - 90.9%)	77.80% (52.4 - 93.6%)	75% (42.8 - 94.5%)
ESR.SF	>150 &> 47	94.12% (71.31% to 99.85%)	30.77% (9.09% to 61.43%)	64.00% (42.52% to 82.03%)	80.00% (28.36% to 99.49%)
CRP.SF	>150 &> 33	76.47% (50.10% to 93.19%)	30.77% (9.09% to 61.43%)	59.09% (36.35% to 79.29%)	50.00% (15.70% to 84.30%)

There was a statistically significant difference between the hyperferritinemic and non- hyperferritinemic patients regarding the presence of enlarged LN and peripheral blood blast cells, which are increased in hyperferritinemic patients. Moreover, it was noticed a statistically significant difference in the presence of sepsis which is more in hyperferritinemic patients but highly statistically significant regarding organisms.
Regarding response, complete remission was statistically significantly better in non- hyperferritinemic patients. Besides, there was no statistically significant difference in disease-free survival (Relapse), **Table (4).**

Table (4): Comparison of clinico-demographic and laboratory data between groups regarding ferritin level

		Hyperferritinemia		P
		Yes	No	
		(N=16)	(N=14)	
Age (years)		36.7 ± 14	40.9 ± 13.6	0.41
Sex	Female	7 (43.8%)	7 (50.0%)	0.73
	Male	9 (56.3%)	7 (50.0%)	
Anemic Symptom		8 (50.0%)	11 (78.6%)	0.11
Bleeding		4 (25.0%)	5 (35.7%)	0.52
Gum Swelling		4 (25.0%)	8 (57.1%)	0.07
LN		9 (64.3%)	3 (18.8%)	**0.01***
Splenomegaly		3 (18.8%)	7 (50.0%)	0.07
Hepatomegaly		5 (31.3%)	6 (42.9%)	0.51
WBCs x109 (L)		23.4 ± 5.1	50.5 ± 11.6	0.856
Hb (g/dl)		7.9 ± 1.3	7.9 ± 1.6	0.867
PLT x109 (L)		27.5 ± 6.7	42.8 ± 9.8	**0.039***
CRP (mg/L)		32.9 ± 7.6	31.4 ± 6.3	0.849
ESR (mm/hr)		61.4 ± 13.7	55 ± 12.4	0.525
PB Blast %		52.6 ± 12.4	29.9±6.6	**0.034***
AL	ALL	7 (43.8%)	3 (21.4%)	0.196
	AML	9 (56.3%)	11 (78.6%)	
Sepsis	Yes	13 (81.3%)	4 (28.6%)	**0.01***
	No	3 (18.8%)	10 (71.4%)	
Organism	G –Ve	9 (56.3%)	3 (21.4%)	**<0.001***
	G +Ve	6 (37.5%)	2 (14.3%)	
	No	1(6.3%)	9 (64.3%)	
Response	C.R	9 (43.8%)	13 (92.9%)	**0.039***
	No C.R	7 (43.8%)	1 (7.1%)	
Relapse	Yes	6 (37.5%)	6 (42.9%)	0.53
	No	10 (62.5%)	8 (57.1%)	

The cumulative 1-year overall survival rate was 67.3% with a mean of 9.6 ± 0.6 months (95% CI; 8.5 – 10.7 months) after a median follow-up period of 1 year with a range of (1.1- 11.2) months. There was a statistically significant cumulative overall survival in younger, non-hyperferritinemic, non-septic patients who responded to therapy (p=0.02, 0.02, and 0.03 respectively). Furthermore, there was no statistically significant correlation between OS with CRP or ESR, **Table (5).**

Table (5): The overall survival concerning some studied parameters

Variable		Cumulative 1-year OS Rate (%)	p-value (Sig)
Sex	Male	56.10%	0.25 (NS)
	Female	30.50%	
Age	≤ 60 yrs.	52.30%	**0.02* (S)**
	> 60 yrs.	17.90%	
Type of Leukemia	ALL	52.50%	0.69
	AML	40%	(NS)
Hyperferritinemia	Yes	12.10%	**0.02* (S)**
	No	77.40%	
Elevated CRP	Yes	92.90%	0.119
	No	42.80%	
Elevated ESR	Yes	73%	0.976
	No	85.70%	
Sepsis	Yes	15.70%	**0.049* (S)**
	NO	75.50%	
Organism	G –Ve	37.50%	**0.03* (S)**
	G +Ve	25%	
	No	77.10%	
Response	C.R	73.70%	**<0.001* (HS)**
	No C.R	0.00%	

Hyperferritinemia (>150) can be an undependable risk factor predicting sepsis (P=0.007) as well elevated CRP (>33) can be an undependable risk factor predicting sepsis (P=0.016). However, we did not find that hyperferritinemia, age, sepsis, and organism are undependable risk factors predicting mortality, **Table (6A, B).**

Table (6A): Multivariate logistic regression of some potential predictors of clinical sepsis in studied patients

	B	SE	OR	95% CI	p-value
Hyperferritinemia (>150)	3.665	0.368	39.06	(2.677 - 569.831)	**0.007***
Elevated ESR(>44)	3.121	0.575	22.68	(1.036 - 496.499)	0.062
Elevated CRP (>33)	3.959	0.636	2.02	(1.041 - 12.71)	**0.016***
Elevated. TLC (>11)	0.187	0.091	1.21	(0.117 - 12.45)	0.875
Constant					-1.89
	Overall predicted correct percentage of the model is 86.7%				

β: regression coefficient; SE: standard error; OR: odds ratio; 95%CI: 95% confidence interval, p< 0.05 is significant.

Table (6B): Multivariate logistic regression of some potential predictors of Mortality in studied patients

	B	S.E.	OR	95% C.I.	P
Hyperferritinemia	0.629	1.86	1.876	0.049-71.824	0.735
Response	-2.73	1.598	0.065	0.003- 1.493	0.087
Age	-0.167	1.379	0.846	0.057-12.614	0.903
Sepsis	1.551	1.622	4.717	0.196-113.243	0.339
No Growth		1ref			
Gram –ve	-1.981	2.127	0.138	0.002-8.911	0.352
Gram +ve	-0.045	1.873	0.956	0.024-37.600	0.981
Constant					-1.96
	Overall predicted correct percentage of the model is 90.3%				

β: regression coefficient; SE: standard error; OR: odds ratio; 95%CI: 95% confidence interval.

DISCUSSION

Acute leukemia is the most common malignancy whose treatment, in developed countries, is highly specialized [12]. Immunocompromised patients, such as those diagnosed with malignancies and receiving chemotherapy, are at even higher risk of neutropenia and resultant infections [13]. Despite significant advances in supportive care, infectious complications continue to be a significant cause of morbidity and mortality in leukemia patients [14].

Early diagnosis and timely therapy in these critically ill patients may be delayed while waiting for specialized labs such as IL-2Rα[15]. In recent years, ferritin is synthesized and secreted by several malignant tumors, early literature suggests that the serum ferritin level in patients with leukemia, Hodgkin's disease, breast cancer, ovarian cancer, and colon carcinoma markedly increases, and is correlated with the degree of the disease [16]**.** Moreover, serial measurement of serum ferritin in cancer patients receiving chemotherapy indicated that a return to the normal level is associated with therapy response[17].

C-reactive protein (CRP) is one such marker whose elevated serum levels are seen in acute Gram-positive, Gram-negative, and fungal infections. Thus, a single CRP measurement is reasonably useful in the diagnosis of sepsis, which suggests that infection should always be suspected if there is a steady increase in CRP levels for two to three days, and in the absence of any intervention [12]. So our present study evaluates the role of Ferritin in the early detection of systemic infection in acute leukemia patients receiving induction chemotherapy.

In our study, the incidence of leukemia is higher in males than in females, which coincided with **Jemal and coworkers**[18] **and Hamad *et al.***[19] who reported the incidence of leukemia is higher in males, while **Schlenk *et al.***[20] reported that the incidence of leukemia is higher in females. **Hong and his colleagues** [21] reported that serum ferritin was ≥ 290ng/dl in 63% of patients. Our study reported similar results but we are different in the median range of ferritin level which was 150ng/dl. Lymph node enlargement is not related to serum ferritin in leukemic patients at initial presentation [22], on the other hand, we reported that there was a positive correlation between lymph node enlargement and hyperferritenemia. Ferritin is higher in septic leukemic patients and a higher level is associated with the incidence of sepsis in patients receiving induction chemotherapy for acute leukemia [21,22], we evaluated and observed similar results. CRP was one of the important infection markers because it is readily accessible and well-known as a sepsis reference marker[12, 21, 23].

These results are supporting our study as we found that CRP level was a sensitive and specific predictor marker for sepsis. increased the number of peripheral blasts is always associated with increased serum ferritin[16], this is in line with our findings while **Chesonand and coworkers**[24] reported that peripheral blasts at initial presentation are not related to any inflammatory markers. The younger the age of the leukemic patient the more overall survival and overall survival was better in patients responding to chemotherapy [16] which is in line with our study. Normoferritinemic patients have more overall survival than hyperferritinemic patients and concluded that the occurrence of sepsis decreases the overall survival [21], we also found a significant negative correlation between overall survival concerning hyperferritinemia and sepsis. CRP concentration increases even more with the presence of an infection and can be a dependable risk factor for sepsis prediction [21, 23, 25], this is in concordance with our study. Elevated blood levels of ESR and TLC (>11) were not found to be independable risk factors for the prediction of sepsis however, hyperferritinemia can be a dependable risk factor for sepsis prediction [21], these findings agreed with our results.

The usefulness of the serum levels of CRP and ferritin in the early diagnosis and in the monitoring of the course of bacterial infections in acute leukemia patients should be investigated in future broader studies for more confirmation as technical mistakes in laboratory studies are not unusual.

Study Limitations: Statistical correlation of elevated inflammatory biomarkers with patients' comorbidities should be taken into consideration seeing that this statistical analysis can help in determining other risk factors affecting prognosis therefore further studies will be needed in the future to verify this correlation.

CONCLUSION

Modest elevation of the blood level of CRP and ferritin above the normal range showed an association with the probability of systemic infection in patients with acute leukemia who underwent dose-intensive induction chemotherapy even in absence of clinical evidence of sepsis, assessment of the serum inflammatory markers levels can help in the early diagnosis and the monitoring of the course of bacterial infections. Increased inflammatory markers can affect the response but are not independable factors predicting mortality.

Conflict of interest: The authors declare no conflict of interest.
Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Author contribution: Authors contributed equally to the study.

REFERENCES

1. **Arber DA, Orazi A, Hasserjian R (2016):** The 2016 revision to the World Health Organization classification

of myeloid neoplasms and acute leukemia. Blood, 127(20):2391–2405.

2. **Matutes E, Pickl W, Van't Veer M (2011):** Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Blood, 117(11):3163–3171.
3. **Hong J, Woo H, Ahn H (2016):** Pre-treatment blood inflammatory markers as predictors of systemic infection during induction chemotherapy: results of an exploratory study in patients with acute myeloid leukemia. Support Care Cancer, 24:187–194.
4. **Hong J, Moon S, Ahn H (2013):** Comparison of characteristics of bacterial bloodstream infection between adult patients with allogeneic and autologous hematopoietic stem cell transplantation. Biol Blood Marrow Transplant., 19(6):994–999.
5. **Markanday A (2015):** Acute phase reactants in infections: Evidence-Based review and a guide for clinicians. Open Forum Infect Dis., 2: 98-102.
6. **Salazar J, Martínez M, Chávez-Castillo M *et al.* (2014):** C-reactive protein: An in-depth look intostructure, function, and regulation. doi: 10.1155/2014/653045
7. **Buranrat B, Connor J (2015):** Cytoprotective effects of ferritin on doxorubicin-induced breast cancer cell death. Oncol Rep., 34(5):2790–96.
8. **Récher C (2021):** Clinical Implications of Inflammation in Acute Myeloid Leukemia. doi: 10.3389/fonc.2021.623952.
9. **Fernandez H (2009):** Anthracyclin dose intensification in acute myeloid leukemia. N Engl J Med., 361:1249-1259.
10. **Kantarjian H (2004):** Long-term follow–up results of hyperfractionated cyclophosphomide, vincristine, doxorubicin, and dexamethasone(Hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer, 101: 2788-2801.
11. **Tallman S, Wang S, Altman K *et al.* (2019):** Acute Myeloid Leukemia, Version 3.2019, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Cancer Netw., 17(6)721-749.
12. **Biswal S, Godnaik C (2013):** Incidence and management of infections in patients with acute leukemia following chemotherapy in general wards. doi: 10.3332/ecancer.2013.310
13. **Kumar A, Roberts D, Wood K (2006):** Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med., 34(6): 1589–96.
14. **Chandran R, Hakki M, Spurgeon S (2012):** Infections in Leukemia. Critical Care and Emergency Medicine, "Sepsis - An Ongoing and Significant Challenge". http://dx.doi.org/10.5772/50193
15. **Jain P, Casteel K, Allen C *et al.* (2016):** Elevated Ferritin Predicts for Inferior Survival in Patients with Acute Leukemia and May be an Early Marker of an Underlying Systemic Pathologic Inflammation. Blood, 128: 2791-96.
16. **Li X, Lu J, Ren H *et al.* (2013):** Combining multiple serum biomarkers in tumor diagnosis: A clinical assessment. Molecular and Clinical Oncology, 1: 153-160.
17. **Ahmed A, James R (2013):** The significance of ferritin in cancer: Anti-oxidation, inflammation, and tumorigenesis. Biochimica et Biophysica Acta., 1836 (2): 245–254.
18. **Jemal A, Siegel R, Brawly O *et al.* (2011):** Cancer statistics. CA Cancer J Clin., 61:212–236.
19. **Hamad M, Kamal M, Saeed M *et al.* (2019):** Assessment of Serum Ferritin Levels in Sudanese Patients with Acute Lymphoblastic Leukemia. International Journal of Medical Research &Health Sciences, 8(7): 92-96.
20. **Schlenk R, Benner A, Krauter J *et al.* (2004):** Individual patient data-based meta Analysis of patients aged 16 to 60 years with core binding factor acute myeloid leukemia: a survey of the German Acute Myeloid Leukemia Intergroup. J Clin Oncol., 22:3741.
21. **Hong J, Woo H, Kyung H *et al.* (2015):** Pre-treatment blood inflammatory markers as predictors of systemic infection during induction chemotherapy: results of an exploratory study in patients with acute myeloid leukemia. Support Care Cancer, 24(1):187-194.
22. **Armand P, Kim H, Rhodes J (2011):** Iron overload in patients with acute leukemia or MDS undergoing myeloablative stem cell transplantation. Biology of Blood and Marrow Transplantation, 17: 852–860.
23. **Sidharta B, Suparyatmo J, Astuti A (2021):** C-Reactive Protein as A Fungal Infection Marker in Acute Leukemia Patients. Indonesian Journal of Clinical Pathology and Medical Laboratory, 27(2): 212-216.
24. **Cheson B, Bennett J, Kopecky K *et al.* (2003):** Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in AML. J Clin Oncol., 21: 4642-4649.
25. **Vladimirova S, Tarassova L, Mustafina G *et al.* (2009):** C-reactive protein (CRP) concentration in patients with acute myeloblastic leukemia (AML) manifestation. doi: 10.3205/ctt-2009-No5-abstract65.