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Serum hepcidin levels related to interlukin-6 in patients with acute myeloid leukemia before and after treatment

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Abstract:

BACKGROUND: Acute myeloid leukemia (AML) is a heterogeneous malignant disease of hematopoietic tissue. It is characterized by accumulation of abnormal blast cells mainly in bone marrow. Hepcidin is a small bioactive peptide hormone produced in many tissues mainly by the liver, macrophage, and adipocyte and it has been proposed as a marker of inflammation. The aims of study were to assess the changes in serum levels of hepcidin, interleukin-6, and ferritin in addition to iron-binding capacity levels in patients with AML before and after chemotherapy treatment and to compare their levels to healthy controls.

MATERIALS AND METHODS: This study includes 43 AML patients (24 males and 19 females). They were divided into two groups: Group 1: Patients with AML before starting chemotherapy and Group 2: after chemotherapy. The protocol used was (3 + 7) where doxorubicin was given from day 1 to day 3 and Cytarabine (Ara-C) was given from day 1 to day 7 then evaluation is done on 28th day to evaluate response of patients. The control group (Group 3) included 43 healthy controls (24 males and 19 females) who were matched with patients group in gender and age.

RESULTS: Serum samples were investigated before and after treatment and compared with its corresponding data of healthy control group and then statistically analyzed. Results revealed that: the prevalence of AML was higher in males than in females. Hepcidin levels were significantly higher in serum of (AML) patients (Group 2) compared to newly diagnosed (Group 1) and to healthy controls ($P < 0.0001$). Serum (interleukin-6) levels were higher but not statistically significant in (Group 1) when compared to (Group 2) while it was statistically significantly when compared to healthy controls ($P < 0.214$ and $P < 0.0001$, respectively). Regarding serum levels of ferritin and total iron capacity (TIBC) predicted highly significant increase for all patients when compared to controls.

CONCLUSION: Hepcidin and interleukin-6 may be used as diagnostic criteria for treatment response of AML and also can utilized as biomarkers for the progression of the AML.

Keywords:

Acute myeloid leukemia, hepcidin, interleukin-6

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Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematopoietic disease with increasing incidence of a specific genetic alteration and epigenetic changes; this leads to increase number of granulocytes with the presence of immature cells in peripheral blood cells and bone marrow.[1] Changes in white blood cells lead to impaired ability to fight infection and decrease the ability of the bone marrow to form red blood cells and platelets.[2] The rate of AML incidence raises in males than in females and with

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progressive of age.[3] The development is associated with myelodysplastic syndromes, genetic disorders, acquired diseases, and exposures to ionizing radiation, alkylating agents, and anti-cancer chemotherapy.[4] Patients suffering from AML are treated with anti-cancer drugs chemotherapy to damage and disrupting leukemia cells. The main induction therapy consists of cytarabine (Ara-C) and anthracycline-based regimen "3 + 7" (daunorubicin 45 to 60 mg/m^2 per day intravenously for 3 days and cytarabine 100 mg/m^2 per day) for 7 days. It has been found that the complete remission rate is approximately 60% to 80% in newly diagnosed younger adult patients with AML treated with 3 + 7"[5] Post remission therapy "consolidation therapy" is needed to damage remaining AML cells and prevent relapse.[6] Research study decreasing of rest leukemic cells accomplished by cytotoxic chemotherapy, leading to significant myelosuppression.[7]

Hepcidin is a small bioactive peptide hormone produced in many tissues mainly by the liver, macrophage, and adipocyte.[8] In the biologic fluids, two forms of hepcidin were detected by previous research studies, hepcidin-25 amino acid (hepcidin-25) and 2 smaller forms (hepcidin-22 and hepcidin-20), but only hepcidin-25 has been found involving in the controlling of iron metabolism.[9] A typical feature of research study hepcidin is the presence of a cysteine disulfide bridge between two adjacent molecules of cysteines amino acids near the turn of the hairpin that acting as a vital domain in the great chemical reactivity of the molecule.[10,11] In addition, the activity of hepcidin molecule is based on its binding with ferroportin. Ferroportin is found on the surface of reticuloendothelial macrophages, liver, duodenal enterocytes, and placenta cells.[12,13] Hepcidin is considered as a sensitive hormone to inflammatory stimuli and an essential role in anemia of inflammation. Both acute and chronic inflammatory process stimulates hepcidin synthesis. It was found that macrophages are significantly elevated through the inflammatory process. The induction of hepcidin synthesis based on the severity of inflammation. Activated macrophages released a group of cytokines. One of these cytokines is interleukin-6, which consider one of the stimulations of hepcidin synthesis, and hypoferremia.[14] This was explained by a previous studies which stated that the inflammation process induces the expression of interleukin-6 (IL-6) and activin B in the liver, which activates the transcription of hepcidin through the STAT3/JAK2 pathway and the BMP signaling pathway.[15,16] The aims of study were to assess the changes in serum levels of hepcidin, interleukin-6, and ferritin in addition to iron-binding capacity levels in patients with AML before and after chemotherapy treatment and to compare their levels to healthy controls.

Materials and Methods

This prospective cohort research study enrolled 58 subjects, 30 males and 28 females, aged from 15 to 65 years who were recruited from those attending the National Center of Hematology and Baghdad Teaching Hospital in the Medical City. It was approved by institutional committee of Mustansiriyah Medical College. Before starting the study, all patients were given their written informed consent. The Inclusion criteria included patients with newly diagnosis of AML, age from 15 to 65 years and no history of other illness, while the exclusion criteria including patients of AML with subtype M_3, age under 15 years and above 65 years, patients with relapse and refectory of AML and frail patients not suitable for chemotherapy.

Fifteen patients out of 58 were excluded from this study because they refused to take chemotherapy, or went to another center outside Baghdad, or loss of follow-up, or early death during the period of study. Forty-three patients continued the study, 24 males and 19 females were divided into two groups: Group (1) comprised patients with AML before starting chemotherapy and Group (2) represented the same AML patients after four weeks of chemotherapy. All AML patients were subjected to complete their medical history and physical examination. On the other hand, the diagnosis of disease was established by complete blood count test and blood film, in addition to bone morrow aspirated and biopsy, liver functions test, and renal functions test.

The treatment of patients was done according to international protocol (3 + 7) where doxorubicin 30 mg/m^2 was given in the 1st day to 3rd day and Cytarabine (Ara-C) 100 mg/m^2 was given from the 1st day to 7th day then the evaluation is done on 28th day to evaluate response of patients. Group 3 represented the 43 healthy controls consisting of (24 males and 19 females) were mainly selected from medical staff and their families with age- and sex-matched to patients group. From all studied subjects (patients and controls), 8 ml of venous blood were taken. Blood samples were divided into two parts: 6ml of each blood sample were collected in plain polyethylene tubes and allowed to clot at room temperature for thirty minutes, then samples were centrifuged at (3000 rpm) for 10 min. The obtained serum was frozen at –80°C to be analyzed later. The remaining 2 ml of each blood sample were put into ethylenediaminetetraacetic acid tube, mixed gently, and put on shaker for complete blood count measurement. In addition to Hepcidin and IL-6 (CUSABIO, CHINA), serum ferritin (Monobind, USA) and TIBC (Human Germany) were estimated.

Data analysis has been performed by using SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM

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Corp. Data have been provided in simple measures of percentage, frequency, standard deviation (SD), mean, and range (min.-max. values). The importance of the difference of various means (i.e., the quantitative data) has been tested with the use of the Student's *t*-test for the differences between 2 independent means or ANOVA testing for the differences amongst more than 2 independent ways. The importance of the difference of different mean (i.e., qualitative data) has been tested with the use of the Pearson Chi-square test (χ^2-test). Statistical significance has been taken under consideration whenever the *P* value has been ≤ 0.05.

Results

The demographic characterization for the present study was summarized in Table 1. This table shows the age and gender distribution of patients groups included in this study as well as the healthy control group. Forty-three newly diagnosis AML patients before chemotherapy course (24 males, 55.8%) and (19 females, 44.2%) compared with the same patients after treatments for 4 weeks of starting the chemotherapy, on the other hand, compared to (43) control subjects group (24 males, 55.8%) and (19 females, 44.2%). In AML patients, there were 7 (16.3%) patients with age group <20 years, 10 (23.3%) patients with age group of 20–39 years, 13 (30.2%) patients with the age group of 40–59 years, and 13 (30.2%) patients with the age group ≥60 years. The age mean ± SD was 43.0 ± 18.6 years and 44.0 ± 17.8 in AML and control groups respectively. Regarding gender, 24 (55.8%) patients were male, while 19 (44.2%) were females.

Regarding hepcidin, study results showed that there is a significant increase in mean serum hepcidin levels in AML patients during remission compared to newly diagnosis. Values were statistically significant (423.7 ± 26.12; 364.39 ± 39.00 ng/ml), respectively ($P < 0.0001$), the mean is significantly increase in the newly diagnosis and controls (364.39 ± 39.00; 86.40 ± 22.01 ng/ml, respectively [$P < 0.0001$] and significantly increase in the patients during remission and controls (423.7 ± 26.12; 86.40 ± 22.01 ng/ml, respectively [$P < 0.0001$]) as shown in Table 2 and Figure 1.

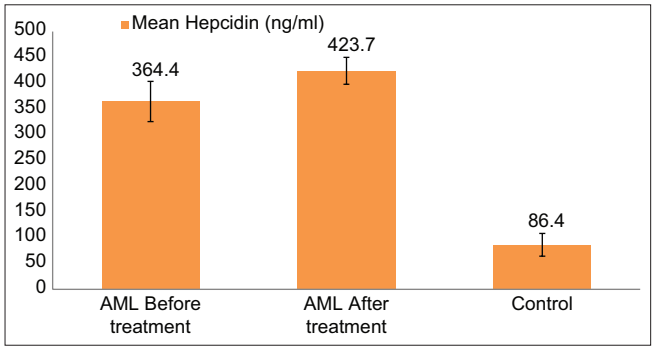

Figure 1: Comparison of the mean of serum hepcidin levels (ng/ml) in acute myeloid leukemia patients before treatment, after treatment, and controls. AML = Acute myeloid leukemia

As shown in Table 3 and Figure 2, results were predicted that there was no significant decrease in (IL-6) levels for AML patients during remission compared to newly diagnosis patients (20.47 ± 18.17; 24.44 ± 13.956 ng/ml), respectively [$P < 0.214$]), but Table 3 shows a significant increase in levels of IL-6 in the newly diagnosed patients and in patients during remission when compared to controls (24.44 ± 13.956; 20.47 ± 18.17; 9.383 ± 3.965 ng/ml), respectively ($P < 0.0001$).

Table 1: Demographic characterization of all study subjects

Characterization	AML, *n* (%)	Controls, *n* (%)
Age (years)		
<20	7 (16.3)	8 (18.6)
20-39	10 (23.3)	10 (23.3)
40-59	13 (30.2)	12 (27.9)
≥65	13 (30.2)	13 (30.2)
Mean±SD (range)	43.0±18.6 (15-65)	44.0±17.8 (15-65)
Gender		
Male	24 (55.8)	24 (55.8)
Female	19 (44.2)	19 (44.2)

SD=Standard deviation, AML=Acute myeloid leukemia

Table 2: Serum hepcidin levels (ng/ml) for the studied groups

Hepcidin (ng/ml)	Prechemotherapy	Postchemotherapy	Controls
n	43	43	43
Mean±SE	364.39±5.947	423.7±3.984	86.40±3.357
P value compared to control	0.0001*	0.0001*	-
P value compared to AML after	0.0001*	-	-

*Significant difference between two independent means using Student's *t*-test ≤0.05 level. AML=Acute myeloid leukemia, SE=Standard error

Table 3: Serum interlukin-6 levels in (ng/ml) for studied groups

IL-6 (ng/ml)	Prechemotherapy	Postchemotherapy	Controls
n	43	43	43
Mean±SE	24.44±2.127	20.47±2.771	9.383±0.605
Range	5.094-44.14	2.547-62.97	2.743-15.90
P value compared to control	0.0001*	0.0001*	-
P value compared to AML after	0.214	-	-

*Significant difference between two independent means using Student's *t*-test ≤0.05 level. IL-6=Interlukin-6, AML=Acute myeloid leukemia, SE=standard error

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Regarding biochemical and hematological findings, serum ferritin levels showed a significant increase in mean values in AML patients during remission compared to newly diagnosis, values were (849.1 ± 777.6; 624.0 ± 197.68 ng/ml, respectively [$P < 0.002$]) and the mean levels of ferritin is significantly increase in the newly diagnosis and in patients during remission when comparing to controls (624.0 ± 197.68; 849.1 ± 777.6; 132.4 ± 138.7 ng/ml), respectively [$P < 0.015$]) and [$P < 0.0001$]) as shown in Table 4.

In addition, results in this study showed a significant decrease in mean serum TIBC levels (mmol/l) in patients with AML during remission when compared to newly diagnosed, values were statistically significant (37.63 ± 7.63; 51.32 ± 4.78 mmol/L, respectively [$P < 0.0001$]) and results, on the other hand, showed a significantly lower in levels of TIBC in newly diagnosis patients when compared to control levels (healthy controls) (51.32 ± 4.78; 58.24 ± 5.27M mmol/L, respectively [$P < 0.0001$]), and significant decrease in the patients during remission compared to controls represented a significant decrease in TIBC levels (37.63 ± 7.63; 58.24 ± 5.27 mmol/L, respectively [$P < 0.0001$]), these results are shown in Table 5.

To assesses the utility of a measured biomarker studied in this research work was based on used the rough guide of its AUC as follows: 0.9 ≥1.0 = excellent; 0.8 >0.9 = good; 0.7 >0.8 = fair; 0.6 >0.7 = poor; 0.5 >0.6 = fair. Results in Tables 6 and 7 in addition to Figures 3 and 4 were explained using the area under the curve for AML patients, which an excellent guide to help researchers to represent the validation and clinical implementation of newer or better diagnostic different biomarkers for different diseases that may have a long-lasting impact on human health and quality of life.

Discussion

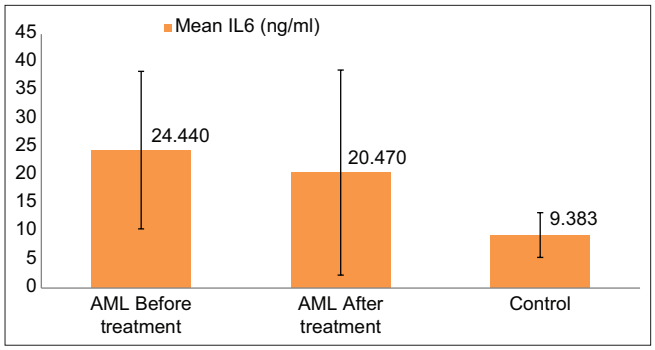

Figure 2: Comparison of the mean of serum IL-6 levels (ng/ml) in acute myeloid leukemia patients before treatment, after treatment, and controls. IL-6 = Interlukin-6 AML = Acute myeloid leukemia

In males, the rate of incidence is more than in females and high in industrialized countries.[17] The results of the present study showed that AML was diagnosed in 24 males (55.8%) and in 19 females (44.2%) which may be due to the higher prevalence of AML observed in men, this result is agreed with the previous study

Table 4: Serum ferritin (ng/ml) levels in studied groups

Serum ferritin (ng/ml)	Prechemotherapy	Postchemotherapy	Controls
n	43	43	43
Mean±SE	624.0±30.146	849.1±118.588	132.4±21.157
Range	300-1200	410-5704	40.9-982
P value compared to control	0.015*	0.0001*	-
P value compared to AML after	0.002*	-	-

*Significant difference between two independent means using Student's *t*-test ≤0.05 level. AML=Acute myeloid leukemia, SE=Standard error

Table 5: Serum total iron-binding capacity (mmol/L) levels in studied groups

TIBC (mmol/L)	Prechemotherapy	Postchemotherapy	Controls
n	43	43	43
Mean±SE	51.32±0.729	37.63±1.163	58.24±0.804
Range	42.00-69.00	15.00-60.20	49.00-69.00
P value compared to control	0.0001*	0.0001*	-
P value compared to AML after	0.0001*	-	-

*Significant difference between two independent means using Student's *t*-test ≤0.05 level. TIBC=Total iron-binding capacity, AML=Acute myeloid leukemia, SE=Standard error

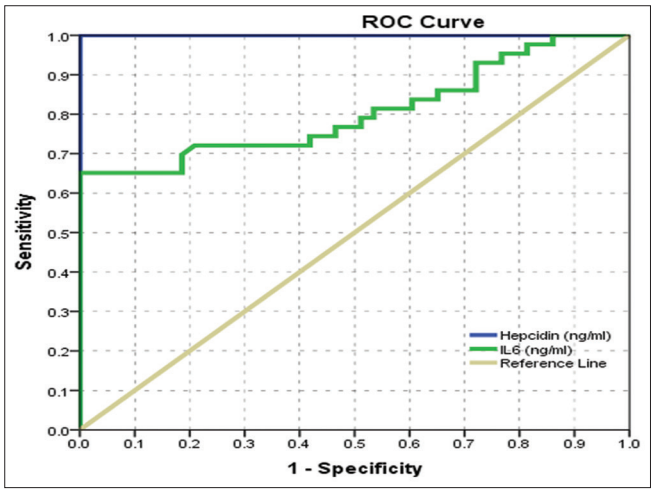

Figure 3: Sensitivity and specificity of AML patient before treatment and controlfor hepcidin and IL-6. AML = Acute myeloid leukemia, IL-6 = Interlukin-6, ROC = Receiver operating characteristic

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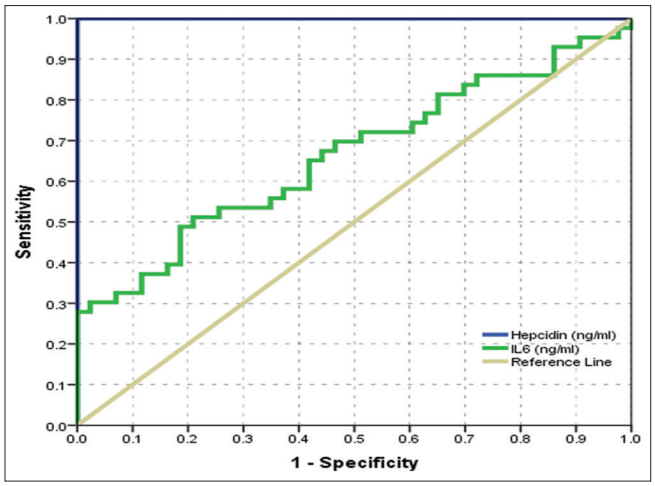

Figure 4: Sensitivity and specificity of AML patient after treatment and control for hepcidin and IL-6. AML = Acute myeloid leukemia, IL-6 = Interlukin-6

Table 6: Area under the curve for the patient's prechemotherapy

Test result variable	Area under the curve	SE	*P*	95% CI	
				Lower bound	Upper bound
Hepcidin (ng/ml)	1.000	0.001	0.0001*	1.000	1.000
IL-6 (ng/ml)	0.806	0.049	0.0001*	0.709	0.902

*Significant $P \leq 0.05$ level. SE=Standard error, CI=Confidence interval, IL-6=Interlukin-6

Table 7: Area under the curve for the patients postchemotherapy

Test result variable	Area under the curve	SE	*P*	95% CI	
				Lower bound	Upper bound
Hepcidin (ng/ml)	1.000	0.001	0.0001*	1.000	1.000
IL-6 (ng/ml)	0.663	0.059	0.009*	0.547	0.778

*Significant $P \leq 0.05$ level. SE=Standard error, CI=Confidence interval, IL-6=Interlukin-6

predicted by Kinga *et al*.[18] Regarding the assessment of age, the prevalence of AML was higher in patients group with age between 40 and 59 years and ≥65 years, than in other age groups. These results were agreed with previous study results which showed that AML is more common in elderly and old age.[19] Hepcidin levels of all patients involved in this study were elevated significantly before and after chemotherapy treatment when compare to healthy controls as shown in Table 2 and Figure 1. These present findings were showed an agreement with a previous research results reported by Osman *et al*.[20] and Sachelly *et al*.,[21] they observed that there were a significantly higher hepcidin concentrations in AML patients comparing to healthy controls because of the high hepcidin production in AML patient. Other studies showed that serum hepcidin levels significantly increased during inflammation and infection in cancer diseases including leukemia which cause iron dysfunction with hypoferremia and anemia of chronic diseases.[14,22] The same results were explained by additional studies which found significant higher levels of hepcidin in AML patients before and after chemotherapy treatment course when compared to healthy group and reported that the elevation in hepcidin levels might keep the body from excessive iron parenchymal and the organs from the damage in the presence of iron loading.[23-25] Another explanation for the results of this study was available in a previous study report.[14] In addition, this study predicted that the binding of hepcidin to the receptor (ferroportin) lead to the retention of iron in macrophages and decreasing iron bound to transferrin.

The elevation in hepcidin levels may regulate iron release from hepatocytes, enterocytes, and macrophages resulting in iron restriction.[26] Mean levels of serum interlukin-6 in patients with AML in this study before chemotherapy treatment showed highly significant levels compared to the same patients after chemotherapy treatment and both results showed significantly higher levels when compared to healthy controls. These results were in agreement with the previous result predicted by Clara *et al*.[27] In addition, Alexandra *et al*.,[28] predicted that the elevation in IL-6 levels in newly diagnosed patients was due to the role of interleukins in inflammation, which is promoting the growth of malignant cells and therefore believed to participate to the aggressiveness. A previous study was done by Satyendra *et al*.[22] who found that during the inflammatory process, macrophages are appeared to be depending on the severity of inflammation. Activated macrophages release cytokines, including IL-6, which are considered as primary inducers of hepcidin production. There was a close association between IL-6 and fever indicating that IL-6 is a multiple functions cytokine involved in the many inflammatory response, the presence of high levels of IL-6 during inflammatory states can induce hepcidin synthesis, iron deficiency, and lower of Hb levels.[15,29] In addition, a study by Yacoub *et al*.[30] concluded that IL-6 plays an important role in the pathogenesis of AML disease, and it could be used as follow-up parameters in AML disease for early detection of relapse. Total iron-binding capacity levels were lower.

Results of the present study revealed that the levels of serum ferritin in AML patients before and during chemotherapy were significantly higher than its levels in the controls. These results were agreed with Osman *et al*.[20] who suggested that the production of iron-binding proteins has become weak before, during, and after chemotherapy and decrease the ability of the liver to absorb nontransferrin bound iron from the circulation. TIBC presents the availability of iron-binding sites, which is influenced by the following factors included: iron status, malnutrition, inflammation, chronic infection, and cancer.[18] In

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malabsorption syndromes and in chronic diseases, TIBC level is reduced because patients with hematologic disorder including AML cannot mobilize and utilize iron, which is stored in excess in the reticuloendothelial system leading to decrease in serum TIBC.[31]

Serum ferritin concentrations were estimated in this study in patients with AML and found that there was an increase in values of ferritin in newly diagnosed patients and during remission when compared to healthy controls. These results were agreed with Kumar *et al*.'s study,[32] who found that the significant increased level in serum ferritin among patients newly diagnosed, or on remission stage may indicate that leukemia cell could affect iron metabolism leading to iron overload, also Fang *et al*.[33] suggested that the highest levels of ferritin were found in AML patients under chemotherapy course treatment. The previous study by Alexandra *et al*.[28] showed that factors contribute to increase in serum ferritin levels in AML including anemia, acute phase response, and chemotherapy treatment.[34,35] The receiver operating characteristic (ROC) curves analysis for serum hepcidin and serum IL-6 when used as a test to diagnosis AML among cases before treatment showed the AUC of serum hepcidin was 1.000 (95% CI, 1.000–1.000) and the AUC of serum IL-6 was 0.806 (95% CI, 0.709–0.902) as shown in Figure 3 and Table 6.

The ROC curves analysis for serum hepcidin and serum IL-6 when used as a test to diagnosis AML among cases after treatment showed AUC of serum hepcidin was 1.000 (95% CI, 1.000–1.000). The AUC of serum IL-6 was 0.663 (95% CI, 0.547–0.778) as shown in Figure 4 and Table 7.

This study conluded that Hepcidin and interleukin-6 may be used as diagnostic criteria for treatment response of AML and also can utilized as biomarkers for the progression of the AML.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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