



# Prognostic and diagnostic roles of serum ferritin level in cancer

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## Abstract

The ferritin level, a protein responsible for iron metabolism and storage, is a sensitive indicator of iron overload in various pathological conditions. In leukemia, ferritin levels increase with disease stages and can predict survival after transplantation. Leukemia-induced dysregulation of the ferroportin-hepcidin regulatory axis results in intracellular iron accumulation, activation of the reactive oxygen species (ROS)-related signaling pathway, and inhibition of hematopoiesis, leading to anemia and increased dependence on red blood cell transfusions, thereby disrupting the physiological cycle. Additionally, ferritin levels rise in other types of cancer, indicating its potential as a target for both diagnosis and treatment. Therefore, understanding the role of ferritin and iron metabolism in leukemia and other diseases is crucial in developing effective treatment strategies to enhance patient outcomes.

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## Introduction

Although serum ferritin was first introduced by the French scientist, Laufferger, in the 1930s (1), it was not clinically introduced until the 1970s (2). Ferritin is present as a cytosolic protein in most tissues. However, the mitochondrial form of ferritin has been recently described. This form has an important role in intracellular iron storage (3-5). Ferritin is a protein composed of 24 subunits, which are of two types; H and L subunits. The H and L subunits are isolated from the human heart and liver. The H-to-L subunit ratio varies based on the tissue type and developmental stage. Furthermore, ferritin is secreted from hepatocytes, macrophages, and Kupffer cells (5). Although ferritin has quantitative properties, it is commonly used as a sensitive parameter to detect iron overload. It increases during inflammatory responses as well as in sickle cell anemia, human leukocyte antigen, and myelodysplastic syndromes (MDS) (6, 7). When there is a decrease in serum iron and an increase in macrophage iron due to inflammatory anemia, the expression of hepcidin is upregulated by inflammatory

cytokines, leading to a reduction in dietary iron uptake. However, with increased iron load, decreased macrophage iron, and accelerated dietary iron uptake mediated by hereditary hemochromatosis, the increase in hepcidin levels is caused by its dysregulated expression (5). Iron plays a crucial role in various physiological activities and is an essential element for living organisms. It promotes cell growth and proliferation, among other important functions. On the other hand, it may cause oxidative damage. Therefore, the body has a precise mechanism for regulating iron metabolism (7). Iron is involved in the activation of vital enzymes that participate in several physiological processes, such as adenosine triphosphate (ATP) production, DNA (deoxyribonucleic acid) synthesis, and oxygen transport. Iron can gain and lose oxygen which enables it to be involved in free radical reactions. However, the accumulation of excessive iron and reactive oxygen species (ROS) can result in oxidative stress, leading to damage to DNA, proteins, lipids, and other biomolecules, ultimately resulting in cell death. Leukemia includes a group of heterogeneous



**Key point**

The dysregulation of the regulatory axis between ferroportin and hepcidin in leukemia results in the accumulation of iron in cells, activation of the reactive oxygen species-related signaling pathway, and inhibition of hematopoiesis. These effects lead to the development of anemia and increased dependence on red blood cell transfusions, disrupting the physiological cycle. Ferritin levels also rise in other types of cancer, indicating its potential as a target for both diagnosis and treatment. Therefore, understanding the role of ferritin and iron metabolism in leukemia and other diseases is crucial in developing effective treatment strategies to enhance patient outcomes.

hematological malignancies characterized by the abnormal accumulation of undifferentiated blasts in the bone marrow, leading to interference with the generation of normal blood cells. Several genetic alterations are involved in leukemia. Some of these genes include the transferrin receptor-related gene, hemochromatosis-related gene, and some of the genes implicated in iron metabolism (7). On the other hand, leukemic patients require blood transfusions during the treatment period. Each red blood cell (RBC) unit contains about 200-250 grams of iron and around 10 to 20 transfusions may lead to systematic iron overload (6). The metabolism of iron changes in leukemia. It involves the uptake, storage, efflux of cellular iron, and dysregulation of the ferroportin-hepcidin regulatory axis. ROS acts as signal messengers in normal hematopoiesis and is involved in the control of hematopoietic stem cells (HSCs). However, ROS-induced redox dysregulation promotes malignancies of the HSCs by increasing the double-strand breaks and repair errors in DNAs. The iron-dependent enzyme ribonucleotide reductase is required for DNA synthesis during the rapid growth of leukemic cells. Therefore, iron is essential for the progression of leukemia. In addition, iron overload stimulates NK cell apoptosis adjacent to CD4 and CD8 cells by increasing the percentage of regulatory T-cells. This allows the leukemic cells to escape from the immune system (7). Excessive iron alters the distribution of T-lymphocyte subsets and suppresses the function of CD4 cells. This mechanism disrupts the change in CD4 to CD8 ratio and monitoring of cancer cells (5). The serum ferritin level is positively correlated with leukemia stages. Increased ferritin levels indicate high disease activity and a high number of circulatory blasts (8). Ferritin level is, as well, a strong predictor of survival after allogeneic transplantation. Increases in ferritin levels in patients with MDS increase the likelihood of progression to leukemia (5). Furthermore, the ferroportin-hepcidin regulatory axis is impaired in leukemic patients. The serum hepcidin levels increase significantly at the early diagnosis in leukemic patients and decrease after recovery, but are still higher than in healthy individuals. Elevated levels of hepcidin in leukemia result in the accumulation of iron in leukemia cells, which can contribute to leukemogenesis by activating the Wnt and nuclear factor kappa-B signaling pathways. Furthermore,

the release of iron from enterocytes and macrophages into the circulation is inhibited, thereby suppressing red blood cell production and iron accumulation in cells. Iron overload initially accumulates in the macrophage, then in the liver, and spreads to the endocrine glands and the heart (5, 7). Iron overload can destroy bone marrow stem cells which suppress hematopoiesis through the ROS-related signaling pathway. Therefore, anemia results from the inhibition of hematopoiesis leading to further dependence on RBC transfusion and a defective cycle (7). An increase in ferritin is observed in other malignancies as well. For example, neuroblastoma is directly associated with the ferritin secreted by tumor cells. Patients with newly diagnosed breast cancer (locally recurrent and metastatic disease) have been reported to have elevated ferritin levels. In some cases, increased circulating ferritin is associated with a change in the type of ferritin. For instance, type H is increased in histiocytic malignancies. In solid tumors, ferritin has been mostly detected in the stroma and the histiocytes that surround the neoplastic cells indicating a stromal reaction (5). In leukemia, ferritin levels of more than 1000 ng/mL are associated with poor prognosis and death (6). In addition, it has been reported that in patients with acute lymphocytic leukemia and acute myelogenous leukemia (AML), ferritin levels of more than 5000 ng/mL are indicative of the possibility of progression to hemophagocytic lymphohistiocytosis (9). Currently, there are no specific guidelines to screen for iron overload in cancer patients (6). Iron chelators arrest cell growth and induce apoptosis in leukemic cells (dose-dependently and time-dependently) (6,7). Leukemic cells are more vulnerable to the effects of iron chelators than normal cells due to their dependency on iron for proliferation. Moreover, iron supplementation can hinder the anti-leukemia effect of iron chelators, indicating that iron deprivation is a potential anti-leukemic strategy. Iron deprivation prevents the production of deoxyribonucleotides, leading to the inhibition of leukemic cell proliferation. This is achieved by arresting the G1/S cell cycle through the inhibition of DNA synthesis. Iron chelators can also decrease ROS levels by reducing the substrates for the Fenton reaction. Importantly, iron deprivation can differentiate leukemia blasts and normal bone marrow precursors into monocytes and macrophages through increased ROS levels (10). Iron chelators not only have anti-leukemia effects, but a synergistic effect along with chemotherapy drugs. This combination results in more effective anti-cancer effects. Deferoxamine increases the sensitivity of leukemia and myeloid cells to doxorubicin (11). Deferoxamine, together with all-trans-retinoic acid, has synergistic effects on anti-proliferation and induction of apoptosis in AML M3, specifically, with L-asparaginase or dexamethasone to reduce blood cell survival or is associated with DNA-damage inducing agents to increase apoptosis in T-cells (7). Treatment with iron chelators seems to be useful in this regard (5).

## Conclusion

Ferritin plays a crucial role in iron metabolism and storage, and its level is a sensitive indicator of iron overload in various pathological conditions. In leukemia, ferritin levels are positively correlated with disease stages and predict survival after transplantation. The dysregulation of the ferroportin-hepcidin regulatory axis in leukemia results in cellular iron accumulation, ROS-related signaling pathway activation, and inhibition of hematopoiesis. Therefore, anemia results from the inhibition of hematopoiesis, leading to further dependence on RBC transmission and a defective cycle. In addition to hematological malignancies, elevated levels of Ferritin have been observed in other types of malignancies, suggesting its potential as a promising target for cancer diagnosis and therapy. Understanding the role of ferritin and iron metabolism in leukemia and other diseases is essential for developing effective treatment strategies to improve patient outcomes.

## Authors' contribution

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## Ethical issues

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