REVIEW ARTICLE

Hematologic disorders in liver failure: pathophysiology and therapeutic considerations

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ABSTRACT

Alterations in blood cell counts are the most prominent and recurrent clinical findings among patients suffering from both acute and chronic liver disease. These changes are an important marker of liver failure and often play a key role in the evaluation and management of these patients. Together with the prolongation of coagulation tests, thrombocytopenia is the most common disorder among these individuals. This condition, as well as leukopenia, is largely attributable to hypersplenism, a disorder in which the spleen retains and destroys blood cells, including platelets. However, when the platelet count drops below 10 x 10^3/µl, it is essential to consider other causes, such as autoimmune factors that may be contributing to the development of thrombocytopenia. Anemia, defined as a decrease in red blood cell count or hemoglobin levels, is another common characteristic of liver disease. Although in most cases macrocytic anemia occurs, in some situations it can be secondary to hemolytic events, as observed in Zieve's syndrome. This wide range of manifestations of anemia among liver patients highlights the complex interaction between liver and blood components. Despite advances in understanding the underlying causes of these cytopenias, treatment options remain limited. Therapeutic options generally focus on the transfusion of blood products to compensate for deficiencies in cell counts or on the use of thrombopoietin (TPO) analogues to temporarily stimulate platelet production in the bone marrow. However, these treatments tend to address the symptoms rather than the root causes of hematologic disorders in liver disease. The persistence and worsening of these disorders may serve as early indicators of the progression of liver failure. The complicated relationship between liver and hematologic homeostasis remains the subject of research. A deeper understanding of these mechanisms could potentially open the door toward more targeted and effective therapeutic approaches to address cytopenias in the context of liver disease.

Keywords: Liver Cirrhosis; Thrombocytopenia; Leukopenia; Anemia; Bone Marrow; Hypersplenism (Source: MeSH NLM).

INTRODUCTION

Although hemostatic disorders are the most common blood disorders in patients with liver disease, they are not the only ones. Depending on the severity of the condition, various abnormalities can occur in the structure and function of red blood cells, leading to alterations in white blood cell count due to hypersplenism, as well as abnormalities in platelet count and function. Changes in red blood cell size are the most frequent alteration; however, in rare cases, the mean corpuscular volume (MCV) can exceed 120 fL, while thrombocytopenia is considered multifactorial.

Currently, only thrombocytopenia has a specific but transient treatment, while the use of stimulants for leukopenia and anemia remains controversial. This review presents the main blood disorders identified in adults with chronic liver disease associated with alcohol consumption or hepatitis viruses.

Figure 1 summarizes the main blood changes associated with chronic liver disease.

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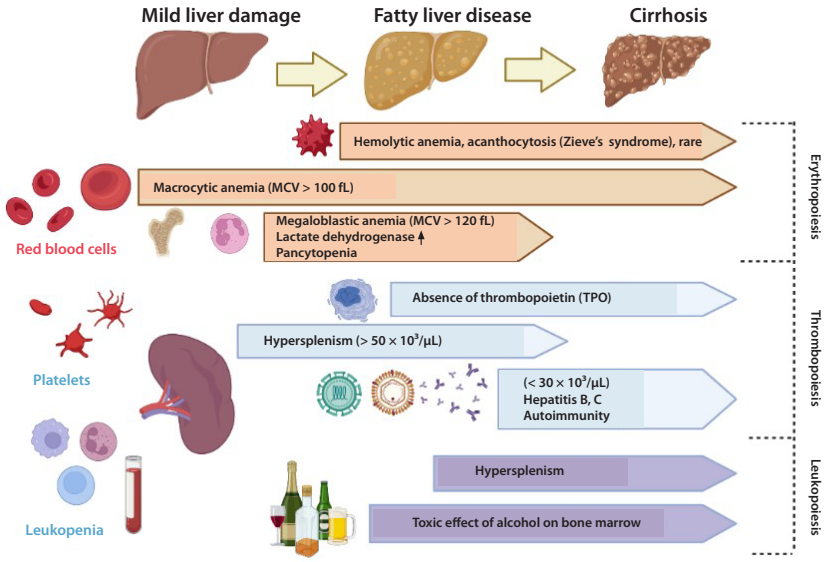

Figure 1. Blood changes associated with liver disease

SEARCH STRATEGY

A systematic literature search of retrospective and prospective studies was conducted using the PubMed database, including representative articles and those published in the last five years. Hematologic disorders in liver disease were researched with the following search terms: "anemia AND liver disease," "anemia AND cirrhosis," "thrombocytopenia AND liver disease," "thrombocytopenia AND cirrhosis," "leukopenia AND liver disease," "leukopenia AND cirrhosis," and "portal hypertension AND thrombocytopenia." A total of 66 studies were analyzed, covering hematologic disorders associated with liver disease—with or without portal hypertension—and including normal reference values for comparison with patients with liver disease.

Eligibility criteria

The inclusion criteria for this study were as follows: (1) results from clinical trials, prospective or retrospective cohort studies, case series and observational studies; (2) studies published in either English or Spanish; and (3) studies focusing on nonimmune chronic alcoholic and nonalcoholic fatty liver disease, as well as portal hypertension secondary to chronic liver disease.

The exclusion criteria included (1) studies involving patients with autoimmune liver disease, acute liver failure, sepsis, infections and coagulation disorders in the context of chronic liver disease; and (2) studies of chronic liver disease without reported hematologic disorders or with preexisting hematologic diseases. Two authors of the present study screened all abstracts and full texts to assess eligibility. Figure 2 illustrates the search and selection process of articles for inclusion in this review.

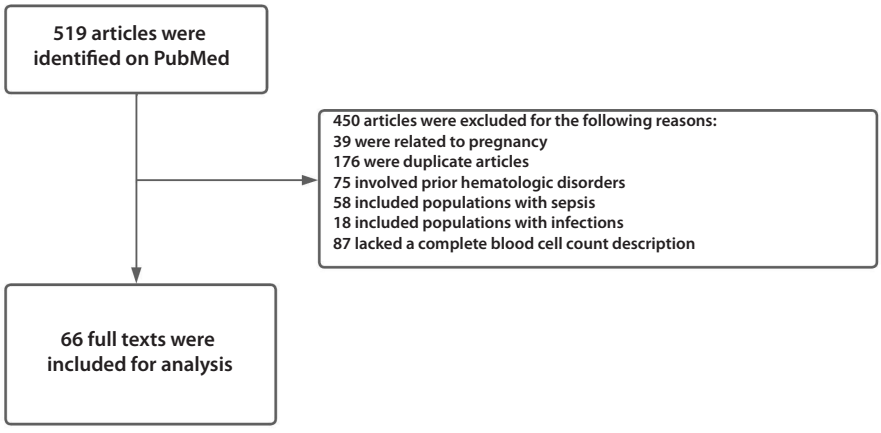

Figure 2. Flowchart of the literature search and selection process of studies for inclusion in the review

MAIN BLOOD CHANGES ASSOCIATED WITH LIVER DISEASE

Alterations in the erythroid series

Most liver disorders, especially those involving alcohol intake (100-110 fL), often present with high MCV. An MCV greater than 120 fL suggests the possibility of cobalamin or folate deficiency, while a high reticulocyte count (> 100,000/µL) may indicate a hemolytic event [1]. According to Unnikrishnan et al., the main etiology of macrocytosis is megaloblastic anemia (38.4 %), followed by liver disorders (15 %) and hemolytic events (8.3 %) [2]. The MCV in alcoholic patients is 114 fL, a value similar to that observed in individuals with bone marrow failure syndromes [3]. Gupta et al. suggest that red cell distribution width (RDW) may be used to distinguish bone marrow failure syndromes from megaloblastic anemia, since it is increased in cases of nutritional deficiencies [4,5]. Together with the MCV, RDW serves as another useful index; it is slightly elevated in pathologies associated with alcoholism, although it does not effectively distinguish the type of damage or its severity [6,7]. The primary reason for these changes are alterations in the absorption of folic acid. However, if these alterations persist, other etiologies—such as bone marrow failure syndromes or the use of medications—should be suspected [8,9].

Hemolytic disorders

Hemolysis in individuals with liver damage is uncommon and may be associated with alterations in red blood cell membrane lipoproteins [10,11]. The combination of these rare manifestations, with a prevalence 0.17 %, is referred to as Zieve's syndrome [12]. This syndrome, first described by Leslie Zieve in 1958, is characterized by jaundice, hyperlipidemia and hemolytic anemia associated with alcohol-induced liver disease. Although it is infrequent, the main treatment involves stopping alcohol consumption [13,14]. Other changes indicative of this syndrome include vitamin E deficiency and decreased levels of polyunsaturated fatty acids, which lead to the oxidation of glutathione in erythrocytes, resulting in the hemolytic event [15]. Additionally, a peripheral blood smear may reveal microspherocytes, macroovalocytes or polychromatic cells, suggestive of reticulocytosis. These findings can be observed in both intravascular and extravascular hemolytic states, which may occur in deposit diseases, infections or inherited disorders [16-18].

Normal or low MCV

In cases of low MCV, blood loss leading to iron deficiency anemia (IDA) should be suspected [19]. The prevalence of anemia is variable (80 %) and is primarily due to gastrointestinal bleeding (variceal rupture, gastropathy, stomach ulcer, peptic ulcer, bleeding hemorrhoids) [20]. However, since the liver is the main iron storage organ, diagnosing iron deficiency may be challenging in some cases. Changes in iron metabolism in hepatopathies include increased ferritin levels, which serves as an inflammatory reactant. This necessitates the use of additional kinetic parameters to make a diagnosis [21]. For treatment, caution should be exercised with oral iron formulations due to the risk of constipation, while intravenous formulations may accumulate in the liver [22,23]. It is essential to carefully calculate iron deficiency, as an excess of free iron molecules can slightly increase the risk of infections (*RR* 1.17; 95 % CI) [24].

Other changes include decreased hepcidin expression, especially in nonalcoholic fatty liver disease, leading to a condition known as dysmetabolic iron overload syndrome (DIOS) [25,26].

CYTOPENIAS ASSOCIATED WITH LIVER DISEASE

Thrombocytopenia: Together with anemia, thrombocytopenia is one of the most common changes observed in liver disease, especially in patients with cirrhosis (78 %). It is classified as mild when platelet counts are 100-150 x 10^3/µL, moderate with 50-100 x 10^3/µL and severe when counts fall below 50 x 10^3/µL [27,28].

The most frequent cause of thrombocytopenia is hypersplenism, a condition established by Aster in 1966, which primarily accounts for cases of mild or moderate thrombocytopenia. However, in severe cases (< 50 x 10^3/µL), the possibility of immune thrombocytopenia mediated by anti-Gp IIb-IIIa autoantibodies, often related to infections such as hepatitis C, should be considered [29].

Hypersplenism causes blood sequestration through the splenic circulation, which occurs independently of spleen size [30]. According to the Baveno VII consensus, in cases of thrombocytopenia, endoscopy should be performed to rule out portal hypertension [31]. For management, some authors suggest partial embolization, particularly in cases with mild liver disease (Child-Pugh A), as it reduces portal flow and hypertensive gastropathy [32,33].

Following splenic sequestration, the reduced production of TPO—one of the primary causes of thrombocytopenia—has been targeted as the main therapeutic strategy for increasing platelet count [34,35].

The first licensed TPO analog was eltrombopag. Kamaguchi et al. reported the effect of two dosages (25 mg and 37.5 mg), noting a rise in platelet counts from the first week, which persisted for up to two weeks after treatment [36-38]. In the ELEVATE study, a higher dose (75 mg) was used, which—consistent with other observations—reduced transfusion requirements but increased the risk of portal vein thrombosis (six out of 145 patients) [39]. Other analogs, such as avatrombopag, improved pre-procedure counts at both 40 mg and 60 mg (ADAPT-1 and ADAPT-2) without showing an increase in adverse events [40]. Recently,

Eguchi et al. reported the effects of avatrombopag at 20 mg, 40 mg and 60 mg for five days, defining responses as increases were observed 10-13 days after treatment. Both 40 mg (63.6 %) and 60 mg (40 %) showed favorable responses with no significant adverse events [41]. Lusutrombopag is another TPO analog that has recently been used in patients with chronic liver failure. Like the previous two analogs, lusutrombopag has been tested in an Asian population and has been shown to reduce bleeding (3.7 % vs. 8.2 % for placebo) and transfusion requirements [42]. In the L-PLUS-2 study, the average duration of platelet increase with lusutrombopag was 19.2 days, with no significant adverse events reported [43].

The use of these analogs should be considered when the platelet count is very low (< 10 x 10^3/µL), especially if an association with immune thrombocytopenia is suspected [44]. Due to its liver metabolism, the initial dose of eltrombopag is 25 mg, necessitating strict liver monitoring. In contrast, other analogs, such as avatrombopag, can be used safely regardless of liver failure [45,46].

Finally, in the evaluation of severe thrombocytopenia, it is essential to rule out associations with infections such as hepatitis B or C, as well as drug toxicity [47,48].

Leukopenia: Leukopenia generally presents late and is associated with both hypersplenism and viral infections [49]. The role of cytokines, as well as granulocyte-colony growth factor (G-CSF), remains unclear; however, their use has been beneficial for transiently increasing white blood cell count [50]. Lv et al. reported that, in a group of patients with liver cirrhosis who underwent splenectomy, white blood cell counts improved in 79.2 % (309 out of 390 individuals) [51]. Similar to thrombocytopenia, leukopenia associated with hypersplenism can improve with strategies such as embolization, portosystemic shunts or eventually splenectomy [52].

Other notable abnormalities observed in the granulocytes of individuals with liver impairment include blue-green neutrophilic inclusion bodies in the cytoplasm. These bodies may be accompanied by vacuoles and are mainly found in individuals with fulminant liver failure [53]. A summary of the different therapeutic options for various blood disorders is shown in Table 1.

Table 1. Recommendations for the treatment of hematologic disorders and their adjustments in liver disease

Blood disorder	Recommendation	Changes in liver disease
Macrocytic anemia MCV 100-120 fL	Oral folate supplementation. Parenteral folate supplementation with cobalamin.	Most common blood disorder; avoid proton pump inhibitors and stop alcohol consumption. High suspicion of megaloblastic anemia; useful tests include homocysteine, methylmalonic acid (MMA), serum folate and cobalamin levels.
MCV > 120 fL	Oral or parenteral iron supplementation. Deficiency calculation using the Ganzoni formula.	
Microcytic anemia MCV < 80 fL		In cases of active bleeding, begin parenteral supplementation according to iron deficit.
	Pre-procedural prophylactic strategies. Transfusion of one unit of platelets per 10 kg.	Transfuse prior to invasive surgical procedure or in cases of active bleeding. Monitor liver function tests.
Thrombocytopenia < 50 x 10^3/µL	Eltrombopag: 25 mg orally every 24 hours before the procedure.	Monitor for adverse events (headache, nausea, fatigue).
TPO receptor agonists Use with counts below 50 x 10^3/µL	Avatrombopag: 40 mg or 60 mg for five days. Lusutrombopag: 3 mg for seven days.	Monitor for adverse events (headache).
Leukopenia Granulocytopenia	Administration of granulocyte colony-stimulating factor (filgrastim).	Recommendation based only on case reports; further information is needed for guidance.

Bone marrow and liver disease

Most blood disorders observed in patients with liver disease affect the peripheral blood. Findings in the bone marrow, documented over 60 years ago, include increased cellularity (associated with hypersplenism) and elevated levels of erythroblasts and megakaryocytes [54]. One of the largest series (608 cases) identified that 13.5 % of the patients showed dyspoietic changes, mostly in erythroid series (75.6 %) and megakaryocytes (15.8 %). Erythroid hyperplasia is a consistent finding in patients with refractory anemia [55].

One proposed treatment strategy for liver disease involves hematopoietic stem cell transplantation, based on the stem cell's potential to differentiate into various tissue types [56]. Similarly, another hypothesis suggests mesenchymal cells as a possible mechanism for liver tissue regeneration [57]. In a randomized trial, Mohamadnejad et al. evaluated the efficacy of mesenchymal stem cell infusions (120-295 million cells) in 15 patients with liver disease, but no benefit was observed [58]. In a related study, Zekri et al. used autologous infusion of hematopoietic stem cells in nine patients with liver failure, noting improvements in the degree of ascites, as well as in albumin (0.8 g/dL increase), international normalized ratio (INR) (0.4) and bilirubin levels [59]. Additionally, bone marrow may contribute to liver fibrosis through stellate cells and myofibroblasts by increasing the production of collagen type I and II [60].

Use of blood cell counts in prognostic scales

Blood cells are used in various prognostic scales, not only in liver disease. One widely used index is the neutrophil-to-lymphocyte ratio (NLR), especially valuable in assessing infectious or inflammatory conditions. Magalhães et al. evaluated the usefulness of the NLR in patients with liver cirrhosis and found that cases with an NLR exceeding 14 (typical range: 3.6 to 14) were associated with a higher risk of infection [61]. This index is easy to obtain, with normal values ranging from 0.78 to 3.53, and serves as a prognostic marker in cardiovascular diseases, infectious and inflammatory conditions, and even cancers [62]. In cirrhosis, similarly to NLR, other inflammatory biomarkers such as C-reactive protein (CRP) can help predict infections, particularly in advanced liver disease [63,64]. The aspartate aminotransferase (AST)/platelet ratio index (APRI), which combines AST and platelet counts, assists in evaluating liver damage severity. In its initial validation, an APRI score above two had a 65 % positive predictive value for cirrhosis [65]. Other indices that consider platelet use are FIB-4 (calculated as age [years] × AST [IU/L])/(number of platelets [10^3/mm^3] × alanine aminotransferase [ALT] [IU/L]) and FIB-5 (calculated as albumin [g/L] × 0.3 + platelet count [10^9/L] × 0.05 − alkaline phosphatase [IU/L] × 0.014 + AST/ALT ratio × 6 + 14), which includes albumin to the predictive model.

CONCLUSION

Alterations in the quantity and quality of blood cells are common in liver diseases, both in early stages and in patients already affected by cirrhosis. Macrocytic anemia and thrombocytopenia are the primary observed abnormalities, with both thrombocytopenia and leukopenia largely stemming from splenic sequestration. New strategies, such as the use of TPO analogues, offer effective alternatives for transient platelet elevation, particularly when considering the risks associated with splenic embolization or portosystemic shunts.

Abnormalities in blood cell counts not only help identify severe stages of liver disease but also facilitate prognostic modeling and even raise suspicion for concurrent infections. In summary, blood disorders are present in more than half of individuals with liver failure, and their presence correlates with further impaired liver function.

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