



## Review Article

# Secondary Iron Overload and the Liver: A Comprehensive Review

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## Abstract

Iron overload is a condition involving excessive iron deposit in various organs, the liver being the main target organ for iron deposition and overload which are associated with significant liver morbidity and mortality. Iron overload can be categorized into primary and secondary causes. Primary iron overload, so-called hereditary hemochromatosis, is a well-recognized disease with available standard treatment recommendations. However, secondary iron overload is a more diverse disease with many unclear areas to be explored. Secondary iron overload is more prevalent than primary iron overload and occurs as a consequence of various causes which differ significantly across geographic regions. The main causes of secondary iron overload are iron-loading anemias, and chronic liver disease. The liver-related outcomes, patient outcomes, and treatment recommendations in these patients differ depending on the cause of iron overload. This review summarizes the causes, pathophysiology, liver-related outcomes, disease outcomes, and treatments of secondary iron overload.

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**Keywords:** Iron overload; Hemochromatosis; Cirrhosis; Hepatocellular carcinoma; Thalassemia.

**Abbreviations:** ALD, alcoholic liver disease; DIOS, dysmetabolic iron overload syndrome; DMT1, divalent metal transporter 1; ESLD, end-stage liver disease; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HH, hereditary hemochromatosis; HIC, hepatic iron concentration; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MRE, magnetic resonance elastography; MRI, magnetic resonance imaging; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; NTDT, nontransfusion-dependent thalassemia; RBC, red blood cell; SCD, sickle cell anemia; SI, serum iron; SQUID-BLS, superconducting quantum interference device biomagnetic liver susceptometry; TDT, transfusion-dependent thalassemia; TE, transient elastography; TI, thalassemia intermedia; TM, thalassemia major, TSAT, transferrin saturation.

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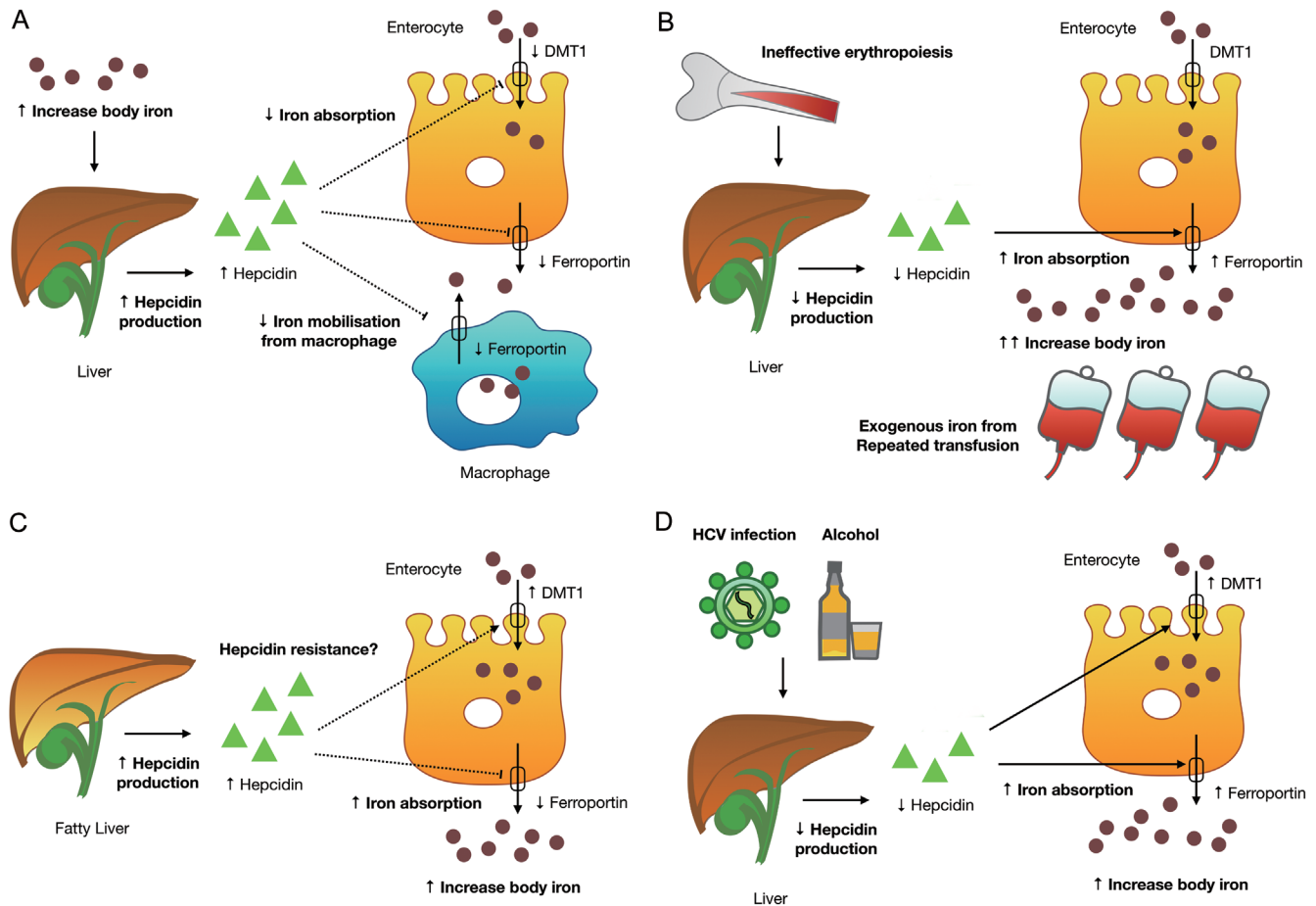
## Introduction

Iron overload is an important condition which may cause significant liver morbidity and mortality. Primary iron overload (hereditary hemochromatosis, HH) is caused by inheritance of mutated hemochromatosis-related genes. Secondary iron overload is a consequence of a wide-spectrum of causes, including hematologic disorders causing ineffective erythropoiesis, anemic conditions requiring repeated transfusion of red blood cells (RBCs), and chronic liver diseases. The cause of iron overload significantly differs across geographic regions which is largely attributed to ethnic differences due to the mutation of the homeostatic iron regulator (HFE) gene<sup>1,2</sup> and the worldwide distribution of thalassemia.<sup>3</sup>

In this review, we summarize and discuss the cause, pathophysiology, clinical outcomes and treatment recommendations for various causes of secondary iron overload. Relevant publications in the PubMed database were selected for this review using the inclusion of the search terms 'hemochromatosis' or 'iron overload' and 'liver'. Only the articles published in the English language were reviewed.

## Physiology of iron metabolism

The normal adult human body contains 3–5 g of iron with over 70% being utilized for erythropoiesis, being present in the form of heme.<sup>4</sup> The major locations used for storage of iron are the liver (20%), and tissue macrophages (5%). Muscle myoglobin contains approximately 2.5% of body iron and small iron amounts are present in the plasma. Ferritin is a cytosolic protein which plays a significant role in intracellular iron storage of excess body iron. In the physiologic condition, iron loss is minimal at 1–2 mg per day<sup>5</sup> and the human body lacks mechanisms to excrete excess iron from the body. Only 1–2 mg of iron per day from the diet is required to maintain body iron balance. Rate of iron absorption is negatively correlated with body iron and the regulation of iron absorption from enterocytes plays an important role in inhibiting excess iron absorption, thereby preventing iron overload. Hepcidin, a liver-derived peptide, has the ability to control iron absorption from the intestine and iron recycling from macrophages. If the level of iron in the body is high, hepcidin binds to ferroportin, a transmembrane protein expressed on enterocytes and macrophages that acts as a cellular iron exporter.<sup>4,6</sup> This



**Fig. 1. Hepcidin-mediated regulation of iron homeostasis and pathophysiology of iron overload in various diseases.** (A) Hepcidin-mediated regulation of iron homeostasis (adapted from Brissot P, *et al*.<sup>6</sup>). (B) Pathophysiology of iron overload in iron-loading anemias. (C) Pathophysiology of iron overload in non-alcoholic fatty liver disease. (D) Pathophysiology of iron overload in hepatitis C virus infection, and alcoholic liver disease. DMT1, divalent metal transporter 1.

leads to a reduction in iron absorption and limiting iron released into the bloodstream. Hepcidin-mediated regulation of iron homeostasis is shown in Figure 1A.<sup>6</sup>

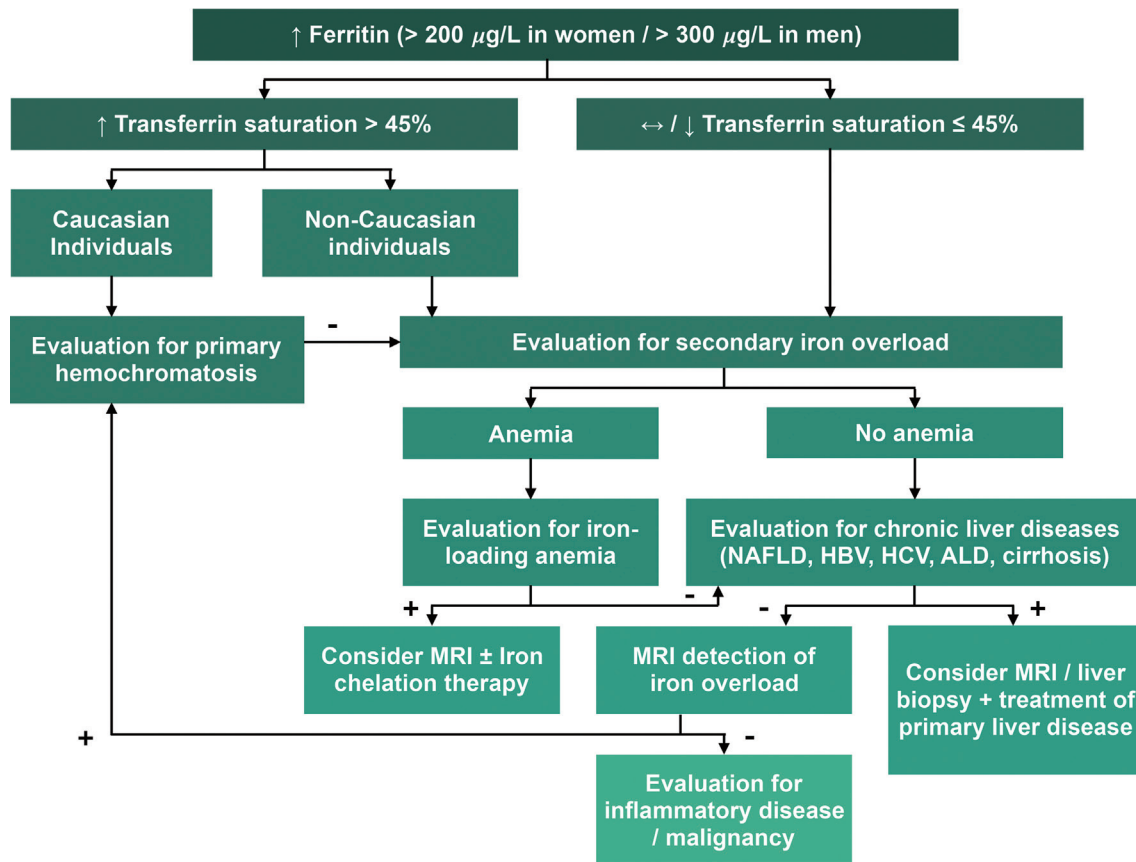
**Evaluation of iron overload and hyperferritinemia**

Iron overload is a condition in which excessive iron is deposited in various organs, such as the liver, heart, pancreas, endocrine gland, joints, and skin. Evidence of iron overload is essential for the diagnosis of this condition. The iron study is the initial test to determine increased body iron contents, including serum iron (SI), total iron-binding capacity, and ferritin. Serum ferritin measurement has proved to be a valuable tool which has a good diagnostic accuracy for iron overload in the liver,<sup>7</sup> however hyperferritinemia is not always equivalent to iron overload as it can result from systemic inflammation or malignancy. Elevated serum ferritin with or without elevation of transferrin saturation (TSAT) indicates the need for further evaluation for an increased in iron stores. TSAT is another important marker for the evaluation of iron overload. It reflects the body's iron stores as well as the balance between reticuloendothelial iron release and bone marrow iron uptake. TSAT is approximately 30% under normal physiologic conditions,<sup>8</sup> and it is usually elevated in cases where there is increased body iron. Expert consensus considers the upper limit of normal TSAT to be 45% and the elevation above

this level is suggestive of iron overload.<sup>9</sup> Ferritin is an acute-phase reactant and TSAT is typically low in inflammatory conditions.<sup>10</sup> However, TSAT could also be normal to mildly elevated in certain causes of iron overload, e.g., nonalcoholic fatty liver disease, hepatitis C infection,<sup>8,11</sup> and chronic kidney disease.<sup>9</sup>

The prevalence of HH, and secondary iron overload ranged from 0–41%, and 4.8–35% respectively, in various populations with hyperferritinemia.<sup>12</sup> The exclusion of acquired secondary iron overload is the recommended next step in management of this condition. In Caucasian populations, the high prevalence of HFE mutation<sup>13</sup> supports the need for further genetic testing, while in non-white populations in which there is a low prevalence of this mutation,<sup>13</sup> confirmation of iron overload by liver biopsy or other non-invasive method is proposed as the next step management. In Asia-Pacific populations, HH is uncommon and most of the HH patients are non-HFE hemochromatosis.<sup>14</sup> A proposed algorithm of approach to patients with hyperferritinemia is shown in Figure 2.

Liver biopsy is a standard procedure for the direct quantitative evaluation of hepatic iron content, measuring hepatic iron concentration (HIC) and the hepatic iron index. Iron overload is defined as HIC that exceeds the upper reference limit of 1.8 mg/g of dry weight liver tissue.<sup>15</sup> HIC has been shown to be representative of total body iron.<sup>16</sup> Although it is the gold standard for assessment of HIC and evaluation



**Fig. 2. Proposed algorithm of approach to patients with hyperferritinemia.** ALD, alcoholic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease.

of liver fibrosis, liver biopsy is an invasive procedure with possible intra-liver iron concentration variability, especially in smaller samples<sup>17,18</sup> or in the presence of cirrhosis.<sup>5</sup> As an alternative to this invasive procedure, non-invasive methods to assess hepatic iron content have been developed. Currently, two non-invasive liver iron quantification methods are used, magnetic resonance imaging (MRI) and superconducting quantum interference device biomagnetic liver susceptometry (SQUID-BLS). SQUID-BLS is not widely available, which limits its use. MRI is a validated technique for determining HIC. The correlation between the results of MRI and liver biopsy for the detection of moderate to high iron overload from various causes is excellent.<sup>19,20</sup> Therefore, MRI is currently considered an alternative standard non-invasive method for assessment of HIC.

Liver fibrosis assessment in patients with hemochromatosis is essential for prognostic evaluation and liver biopsy remains the gold standard. Liver stiffness measurement either by magnetic resonance elastography (MRE) or by transient elastography (TE) is widely conducted in various liver diseases. In a study of HH patients with elevated ferritin (>1,000 ng/mL) and/or raised transaminases, all patients with liver stiffness  $\geq 13.9$  kPa had severe fibrosis as determined by histological examination.<sup>21</sup> With the use of TE, liver biopsy could be restricted to the 39% of patients who had intermediate or invalid TE results.<sup>21</sup> Liver stiffness assessed by TE has also been shown to have a positive correlation with fibrosis stage in thalassemia patients.<sup>22</sup> However, specific cut-off values for stratification of fibrosis stages has yet to be defined. MRE is

generally an accurate method for detecting patients with advanced fibrosis.<sup>23</sup> Despite that, the presence of high liver iron causing a very low hepatic signal is associated with failure of the standard gradient recall echo-based MRE techniques.<sup>24</sup> To our knowledge, there have been no reports specifically comparing the MRE technique to liver biopsy results in patients with hemochromatosis. Additionally, no proposed cut-off level for each fibrosis stage is available due to limited data. Whether non-invasive techniques could substitute liver biopsy is currently inconclusive and more data is required. At present, liver biopsy should be considered only in cases in which a liver sample is required to evaluate concomitant liver diseases, in cases where the biochemical and radiologic results are discordant, for liver fibrosis assessment, or in the rare cases where MRI is unavailable.

**Etiologies of secondary iron overload and their pathophysiology, and liver-related outcomes**

Etiologies of secondary iron overload can be categorized into two main types of disorders, specifically iron-loading anemias, and chronic liver diseases (Table 1). Summary of the causes of secondary iron overload and their pathophysiology are shown in Figure 1.

**Iron-loading anemias**

Hematologic disorders requiring RBCs transfusion causes iron overload by acquiring iron from transfused blood. Conditions with ineffective erythropoiesis, characterized by the destruc-

**Table 1. Major causes of secondary iron overload**

<b>Iron-loading anemias</b>
With ineffective erythropoiesis
Thalassemia major or transfusion dependent thalassemia
Thalassemia intermedia or non-transfusion dependent thalassemia
Myelodysplastic syndrome
Sideroblastic anemia
Without ineffective erythropoiesis
Post hematopoietic stem cell transplantation
Sickle cell disease
Aplastic anemia
Chronic hemolytic anemia requiring red blood cells transfusion
Chronic kidney disease
<b>Chronic liver diseases</b>
Non-alcoholic fatty liver disease
Chronic viral hepatitis B and hepatitis C infection
Alcoholic liver disease
Cirrhosis and advanced liver disease

tion of erythroblasts within the marrow, directly increase body iron. Additionally ineffective erythropoiesis suppresses hepcidin.<sup>25</sup> Therefore, despite increased body iron, intestinal iron absorption is increased in these patients.

### **Thalassemia**

Thalassemia is an inherited hemolytic syndrome caused by a reduction in or no production of the globin chains of hemoglobin. It is the most widely-recognized cause of iron-loading anemia causing iron overload. There are two most important types of thalassemia, alpha and beta, named after the affected globin chains. Thalassemia can be classified into three types based on disease severity and the need for transfusion. (1) Thalassemia minor with rare blood transfusion requirement, includes patients with the thalassemia alpha or beta trait, and homozygous HbE. (2) Thalassemia intermedia (TI) or non-transfusion-dependent thalassemia (NTDT) includes patients with beta thalassemia intermedia, HbE/ $\beta$ -thalassemia, and deletional HbH disease who occasionally require blood transfusion. (3) Thalassemia major (TM) or transfusion dependent thalassemia (TDT), includes patients with  $\beta$ -thalassemia major, severe HbE/ $\beta$ -thalassemia, and non-deletional HbH disease who regularly require blood transfusion.

Each RBC unit contains 200–250 mg of iron. Inevitable iron loading from repeated transfusion is the main mechanism of iron overload in patients with TDT. However, in NTDT patients, iron overload is more likely to be related to increased iron absorption secondary to hepcidin suppression from ineffective erythropoiesis.<sup>25</sup> There are different patterns of organ complication of iron overload in patients with TDT, and NTDT. Selective involvement of liver rather than the myocardium is observed in NTDT patients.<sup>26,27</sup> Complications of iron overload in TDT patients present early in life after 10–20 transfusions, while NTDT patients develop complications at 10–15 years of age. Liver fibrosis is found in 20–45%, and cirrhosis is found in 8–9% of thalassemia patients.<sup>28–30</sup> Liver-related causes account for 5% of the deaths of TM patients.<sup>31</sup> Advances in thalassemia treatment extends patients' lives.<sup>32</sup>

The incidence of hepatocellular carcinoma (HCC) in thalassemia patients is increasing in parallel to the aging population of thalassemia.<sup>32</sup> The annual incidence of HCC is estimated to be 1–2% and the risk in TI is twice greater than in TM patients.<sup>33,34</sup> It is worth noting that high concomitant infection with viral hepatitis C has been observed.<sup>35</sup> This condition is significantly related to the course of liver complications, especially the development of HCC in TDT patients.<sup>33,35,36</sup> HCC may also develop in patients who are not infected with viral hepatitis, mainly in patients with TI.<sup>36</sup> Despite cirrhosis being the strongest risk factor for HCC development, HCC occurrence in thalassemia patients with noncirrhotic liver were reported.<sup>37,38</sup> HCC is now a well-recognized complication in the thalassemia population and regular HCC surveillance in liver cirrhosis patients is advocated.

### **Hematopoietic stem cell transplant patients**

Hematopoietic stem cell transplantation (HSCT) is a cure of beta thalassemia major. The significant effect of pre-transplantation iron toxicity status on transplant outcomes in thalassemia patients has been recognized since the 1980s.<sup>39</sup> The concept of regular and adequate chelation therapy being a key to successful transplantation is well accepted.<sup>39</sup> Despite the curative nature of this treatment, patients may still have acquired iron overload prior to the transplantation as a consequence of the process of ineffective erythropoiesis and transfusions before and during transplantation. Liver damage caused by iron overload in these patients does not revert follow transplantation, and majority of the patients have progression of fibrosis after transplantation.<sup>40</sup> Furthermore, bone marrow and liver iron released from the toxicity of pre-transplantation conditioning regimen may potentiate this condition.<sup>41</sup> High iron loading with hepatic iron contents over 16 mg/g dry weight is associated with fibrosis progression following transplantation.<sup>42</sup> When post-HSCT iron depletion is regular and efficient, hepatic fibrosis and even cirrhosis can be reversed.<sup>41</sup> This highlights the need for both long-term monitoring of hepatic and iron status and adequate



iron depletion treatment. Phlebotomy until complete removal of excess iron is an effective treatment<sup>43</sup> and is a preferred method in this setting. Alternatively, deferasirox is a relatively safe and effective treatment with higher rates of patient satisfaction compared to phlebotomy.<sup>44</sup>

In transplant patients with other malignant and nonmalignant disorders besides thalassemia, serum ferritin has been identified as a surrogate marker associated with post-transplantation adverse outcomes.<sup>19</sup> However, the impact of pretransplant iron overload on transplant outcomes, including mortality and complications, is inconclusive as there are multiple studies with conflicting results.<sup>45–48</sup> The heterogeneity of underlying diseases with varying prognoses differ from homogenous thalassemia populations, and the varying duration of iron overload may in part explained these results. The pre-transplantation packed red cell transfusion burden of 20 or more correlated well with increased hepatic iron, and is a better predictor than ferritin level.<sup>47</sup> Iron overload in a post-HSCT population is prevalent at 32% in adult allogeneic HSCT patients,<sup>49</sup> and 26% in childhood cancer survivors who had HSCT.<sup>50</sup> Excess iron is associated with cardiac, liver, and endocrine organ dysfunction.<sup>50</sup> Iron overload is also a significant cause of liver dysfunction after allogeneic HSCT in these patients with the dysfunction being caused solely by iron overload in 10% of cases.<sup>51</sup> Normalization of alanine aminotransferase in these patients was shown to be achievable by iron depletion therapy.<sup>51</sup>

#### **Other hematologic disorders**

Myelodysplastic syndrome (MDS) causes iron overload as a result of transfusion and ineffective erythropoiesis. Selective deposition of iron in the liver in MDS patients is observed. There is a relatively low rate of myocardial siderosis despite a higher degree of hepatic siderosis.<sup>26</sup> Hepatic iron overload is very common in MDS with a prevalence of 68% and is associated with a significant decrease in patient survival.<sup>52</sup> Any cases of anemia that required transfusion could cause hepatic iron overload and its consequences such as liver fibrosis.<sup>53</sup> In a cohort of combining patients with anemia from other causes besides MDS and thalassemia, hepatic siderosis was found in 57% of patients.<sup>26</sup> In patients with sickle cell disease (SCD), the autopsy findings revealed 23% with liver iron deposition, and 13% with liver cirrhosis.<sup>54</sup> Transfusion volume was correlated with HIC and liver fibrosis in SCD patients requiring transfusion.<sup>55</sup> Iron chelation is necessary in SCD patients with iron overload to prevent hepatic complications.

Anemia of chronic inflammation is characterized by active inflammatory illnesses leading to anemia. Iron dysregulation resulting in reduction of iron uptake at various sites is considered one of the pathogeneses of this condition. Hepcidin overproduction is induced by inflammatory cytokines, predominantly by interleukin-6,<sup>10,56</sup> which leads to the degradation of ferroportin, thereby reducing iron released to plasma and inducing iron sequestration in macrophages. Hypoferremia, which is associated with high plasma ferritin and hepcidin levels, is a characteristic of this type of anemia. Ferritin is an acute-phase protein that is elevated during inflammation.<sup>57</sup> For that reason, the condition is generally described as hyperferritinemia and iron sequestration rather than iron overload. However, iron overload may occur in that setting if the patient has received recurrent transfusions. To our knowledge, there is no study evaluating the prevalence and outcomes of liver iron overload in anemia of inflammation. It is expected that patient outcomes would be influenced by the quantity of blood transfused, as well as by the underlying causes of the inflammation.

#### **Chronic kidney disease**

Liver iron deposition is common in hemodialysis patients with a prevalence of 57%, which is negatively correlated with the degree of anemia.<sup>7</sup> Changes in iron metabolism in chronic kidney disease patients is recognized but with unclear mechanisms. Shifting of the iron pool to the liver,<sup>33</sup> and a blockade of iron utilization from reticuloendothelial cells have been proposed.<sup>4</sup> Before the use of erythropoiesis stimulating agents, regular RBCs transfusion and parenteral iron administration have been important treatments to correct anemia in hemodialysis patients which lead to iron overload. After an introduction of erythropoiesis stimulating agents, which improve anemia and reduce iron overload, the concern regarding transfusion-related iron overload is reduced. However, parenteral iron is now regularly administered to replenish iron stores in hemodialysis patients and cause the cumulative iron dose to correlate with HIC.<sup>58</sup> Despite high rates of liver iron overload, the presence of excess iron in the liver was not found to be associated with liver fibrosis,<sup>7,59</sup> which suggests the limited clinical significance of this condition. Current international guideline does not recommend routine iron supplementation in patients with TSAT index >30% or serum ferritin >500 ng/mL due to limited data regarding risks and benefits.<sup>60</sup>

#### **Chronic liver disease**

More than a quarter of patients with chronic liver diseases have excessive iron deposition evidenced by liver biopsy specimens.<sup>61</sup> Iron overload is found in patients with non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), viral hepatitis, and advanced liver disease.

#### **Non-alcoholic fatty liver disease**

The association between iron overload and liver steatosis in patients with insulin-resistant syndrome was first documented in the late 1990s.<sup>62</sup> Hyperferritinemia is detected in about one-third of NAFLD patients,<sup>63</sup> which is associated with hepatic iron deposition, a presence of non-alcoholic steatohepatitis (NASH), and worsened histologic activity, and is a predictor of advanced fibrosis.<sup>64</sup> Increasingly higher mortality was also observed in NAFLD patients with high ferritin compared to those with normal ferritin value.<sup>65</sup> The term, dysmetabolic iron overload syndrome (DIOS) is an iron overload condition characterized by hyperferritinemia or hepatic iron overload with normal or moderately increased TSAT associated with various components of metabolic syndrome.<sup>66</sup> DIOS is detected in about one-third to half of patients with NAFLD.<sup>67,68</sup>

Stainable iron is found in the liver in 48% of patients with biopsy-proven NAFLD and is associated with higher hepatic events.<sup>68</sup> In general, the pattern of iron deposition can present in three ways; parenchymal (hepatocellular) deposition, mesenchymal (reticuloendothelial system) deposition, or a mixed pattern. The patterns correlate with the mechanisms of iron deposition, iron stores in the reticuloendothelial system reflecting inflammatory causes, and iron deposition in hepatocytes is related to transfusion-related or primary iron overload. Iron overload in patients with NAFLD can present as any of these patterns and the pattern may be associated with the severity of disease and outcomes. The presence of mesenchymal iron is associated with increased liver-related events,<sup>68</sup> and the mixed pattern is found to be associated with the diagnosis of NASH.<sup>69</sup> However, another study reported more severe liver disease in patients with predominant hepatocellular iron deposition.<sup>70</sup>

Currently, the mechanisms underlying iron overload in

patients with NAFLD is uncertain. Increased duodenal iron absorption through the upregulation of divalent metal transporter 1 (DMT1) in patients with NASH was demonstrated despite high serum hepcidin.<sup>71</sup> Hepcidin increase in patients with NAFLD, and its role in DIOS remain elusive. Preserved hepcidin upregulation in response to increased iron stores is observed in patients with DIOS.<sup>72,73</sup> However, a subtle hepcidin resistance state was demonstrated by impaired ability to limit iron absorption following iron challenge.<sup>74</sup> This mechanism might partially explains increased DMT1 upregulation despite high hepcidin level. A genetic predisposition to iron accumulation may also contribute to the pathogenesis. In an Italian cohort of patients with NAFLD, the variants of genes related to iron metabolism, specifically ceruloplasmin, are associated with NAFLD-associated liver iron deposition, high ferritin levels, higher iron stores and more severe liver fibrosis.<sup>75</sup> There is no association between HFE genotype and NAFLD.<sup>76</sup> The homozygous H63D, and the combined heterozygous C282Y/H63D genotypes are found more frequently in patients with DIOS than in general population.<sup>77</sup> However, the role of heterozygous mutation, and the effect of HFE mutation specifically in DIOS with NAFLD remained unknown. The elevation of SI or TSAT were associated with a 2- to 3-fold increased risk of HCC in patients with NAFLD.<sup>78</sup> Evidence from case-control study shows that liver iron deposition was more frequent in patients with NASH cirrhosis and HCC than those without HCC.<sup>79</sup> The risk of HCC in NAFLD patients with iron overload has not yet been evaluate in longitudinal study and the causal relationship cannot be concluded by current evidences.

### **Viral hepatitis**

HIC is higher in patients with hepatitis C virus (HCV) and hepatitis B virus (HBV) infection than in other causes of chronic hepatitis.<sup>80</sup> Approximately one-third of HCV patients had hyperferritinemia, but only half of the cases were associated with hepatic iron overload.<sup>81</sup> In a cohort of HCV patients, serum ferritin was not found to be related to fibrosis and it only increases when alcoholism co-exists with HCV infection.<sup>82</sup> The hepatitis C virus suppresses hepcidin expression<sup>83,84</sup> resulting in upregulation of ferroportin, and increased duodenal iron absorption.<sup>85</sup> Iron overload is well-recognized in patients with hepatitis C and is identified as an important factor associated with advanced disease.<sup>86</sup> It is unclear whether hepatic iron is a surrogate marker for disease severity or the stimulating factor for increased hepatic inflammation and fibrosis. Current literatures leans toward the former as several studies show no correlation between baseline liver iron and liver fibrosis<sup>81</sup> and progression of liver fibrosis.<sup>87</sup> Prior to the direct-acting antivirals treatment era, there were efforts to evaluate the effect of phlebotomy on liver biochemical and histology,<sup>88</sup> the increasing effectiveness of antiviral therapy,<sup>89</sup> or for the treatment in those who fail to achieve sustained virological response.<sup>90</sup> Currently, as direct-acting antivirals treatment cures more than 95% of treated patients, the role of phlebotomy might need to be re-evaluated.

Data on liver iron overload in patients infected with HBV is limited and the pathophysiology of this condition is rarely reported. Hepatic iron deposit is detected in 35.1% of patients and is more common in patients with hepatitis D virus-coinfection, in which there are more severe iron deposits and more advanced fibrosis than in monoinfected patients.<sup>91</sup> The degree of iron deposition is less in HBV patients than in those with HCV.<sup>86</sup> Serum hepcidin, and prohepcidin, a prohormone of hepcidin appears to be lower in patients with HBV,<sup>92,93</sup> and the lower prohepcidin concentrations are related to the more

advanced liver disease.<sup>93</sup> Currently, there are no reports regarding the liver outcomes in patients with HBV and iron overload. The data regarding the treatment of this condition is also limited. Treatment with a combination of phlebotomy and deferoxamine was only described in a case report on a patient on long-term adefovir showing improvement of HIC.<sup>94</sup> Another case report demonstrated complete resolution of iron overload symptoms and almost normalization of ferritin level with nucleoside analogue treatment.<sup>95</sup>

### **Alcoholic liver diseases**

Iron deposition is common in patients with ALD with a prevalence of 57%.<sup>96</sup> Iron overload plays a significant role in a pathogenesis of ALD by inducing oxidative stress. Alcohol down-regulates hepcidin leading to upregulation of iron transporters expression in the duodenum and increases iron absorption.<sup>97</sup> Active alcohol drinking is a major factor associated with iron overload.<sup>98</sup> Most of the studies found that HFE mutation carriers are not related to severity of liver disease<sup>99-101</sup> and that the iron overload in this setting is not relevant to HFE status. Presence of hepatic iron increases the risk of death in patients with alcohol-associated cirrhosis with a relative risk of 2.27 (95% CI: 1.23-4.19).<sup>102</sup> Increased liver iron overload is associated with a higher risk of HCC in alcohol-associated cirrhosis.<sup>103</sup> A study to evaluate the treatment with phlebotomy in patients with compensated alcohol-associated liver cirrhosis was started in 2011, and terminated in 2015 due to delayed recruitment.<sup>104</sup> Therefore, despite the apparent risk of iron overload in the progression of ALD, the treatment with phlebotomy has not yet been evaluated.

### **Cirrhosis, end-stage liver disease, hepatocellular carcinoma, and liver transplantation**

Iron overload is detected in patients with other causes of end-stage liver disease (ESLD) besides the causes that are well-known as being related to iron overload.<sup>105</sup> The pathogenesis of iron overload in patients with cirrhosis excepting those with HH is poorly understood. Multifactorial causes, such as extravascular hemolysis caused by hypersplenism, RBCs transfusion, exogenous oral iron in the state of reduced hepcidin level, and portosystemic shunting may have contributed to this phenomena.<sup>106</sup> Stainable hepatic iron was detected in 32-37% of explanted liver<sup>105,107</sup> with a more common prevalence in patients with nonbiliary cirrhosis.<sup>105</sup> The presence of hepatic hemosiderosis in cirrhotic patients is associated with more advanced liver disease, accelerates hepatic decompensation, and decreases survival.<sup>108</sup>

It has been postulated from preclinical studies that chronic iron overload causes direct hepatocarcinogenesis by generation of reactive oxygen species, resulting in oxidative damage, and subsequent mutagenesis.<sup>109</sup> Iron overload is associated with the presence of HCC in patients with ESLD of diverse etiologies.<sup>110</sup> A large case-control study in Japan demonstrated that lower plasma hepcidin and higher plasma ferritin levels were associated with an increased risk of liver cancer (HR: 4.49, 95% CI: 2.71-7.43).<sup>111</sup> Increased HIC is not a determinant of hepatic outcome after liver transplantation.<sup>107</sup> However, iron loading in non-HFE related ESLD may be associated with concurrent pancreatic<sup>112</sup> and cardiac iron overload.<sup>112,113</sup> These patients are at increased risk of cardiovascular complication after liver transplantation for ESLD.<sup>114</sup> Thorough cardiovascular evaluation prior to transplantation to investigate potential subclinical myocardial dysfunction in candidates with elevated ferritin or evidence of iron overload in other organs is recommended.

**Table 2. Summary of laboratory findings, disease outcomes, liver-related outcomes, and recommendations for the treatment of iron overload in secondary iron overload**

Cause	Laboratory findings	Disease outcomes and liver-related outcomes	Treatment recommendations
Thalassemia major	↑Ferritin; ↑TSAT; ↓Hepcidin	↑Liver fibrosis/cirrhosis; ↑HCC; ↓HSCT outcome	Deferasirox/deferiprone/ deferoxamine
Thalassemia intermedia	↑Ferritin; ↑TSAT; ↓Hepcidin	↑Liver fibrosis/cirrhosis; ↑HCC	Deferasirox/deferiprone/ deferoxamine
Ex-thalassemia (Post HSCT)	↑Ferritin; ↑TSAT;	↑Liver fibrosis/cirrhosis	Phlebotomy/deferiasirox until excess iron is completely removed
Post HSCT (other diseases besides thalassemia)	↑Ferritin; ↑TSAT	↑Liver dysfunction	Phlebotomy or deferoxamine in patients with unstable erythroid engraftment
Myelodysplastic syndrome	↑Ferritin; ↑TSAT; ↔Hepcidin	↓Patient survival	Deferasirox
Sickle cell disease	↑Ferritin; ↑TSAT; ↔/↓Hepcidin	↑Liver fibrosis/cirrhosis	Deferasirox/deferiprone/ deferoxamine
Chronic kidney disease	↑Ferritin; ↔/↑TSAT; ↑Hepcidin	↔Liver fibrosis	Judicious parenteral iron administration when TSAT index >30% or serum ferritin levels >500 ng/mL
Nonalcoholic fatty liver disease	↑Ferritin; ↔/↑TSAT; ↑Hepcidin	↑NASH; ↑Histologic activity; ↑Advanced fibrosis; ↑Hepatic events	No recommendation (Phlebotomy is not recommended)
Chronic viral hepatitis B infection	↑Ferritin; ↑TSAT;	↑Liver fibrosis (in patients with HDV coinfection)	No recommendation (antiviral treatment may improve iron overload)
Chronic viral hepatitis C infection	↑Ferritin; ↔/↑TSAT; ↓Hepcidin	↔Liver fibrosis	No recommendation
Alcoholic liver disease	↑Ferritin; ↑TSAT; ↓Hepcidin	↑Death/HCC (in patients with cirrhosis)	No recommendation
Advance liver disease	↑Ferritin; ↑TSAT	↑HCC; ↔LT outcomes (concurrent cardiac iron overload may increase risk of LT cardiovascular complications)	No recommendation

HCC, hepatocellular carcinoma; HDV, hepatitis D virus; HSCT, hematopoietic stem cell transplantation; LT, liver transplantation; NASH, non-alcoholic steatohepatitis; TSAT, transferrin saturation.

### Treatment of secondary iron overload

The aim of treatment is to prevent and restore organ damage by reduction of body iron. Currently, phlebotomy and iron chelation are the two main treatments in this setting. A summary of the outcomes of secondary iron overload and the treatments recommended for each disease is shown in Table 2.

#### Phlebotomy

Phlebotomy is the cornerstone treatment of HH and HSCT patients. Its role has been evaluated in diverse causes of iron overload without anemia. In patients with NAFLD, venesection significantly reduces serum ferritin and HIC.<sup>115</sup> However, its effect on NAFLD outcomes shows conflicting results. A randomized-controlled trial by Valenti *et al.*<sup>116</sup> showed significant histologic improvement following phlebotomy in an iron-depleted group compared to control.<sup>117</sup> However, subsequent studies demonstrated null effects.<sup>117,118</sup> It does not improve liver biochemistry in patients with DIOS and is associated with high rates of poor adherence to treatment, and treatment-related fatigue in a quarter of patients.<sup>118</sup> Therefore, phlebotomy in NAFLD patients lacks supporting beneficial evidence and is not recommended. Venesection

treatment in other chronic liver diseases was discussed earlier. Data supporting its use is lacking and is not routinely recommended. Phlebotomy is not considered the treatment of choice of iron overload in ineffective erythropoiesis-related anemia diseases because phlebotomy-induced anemia will further cause hepcidin dysregulation and increases intestinal iron absorption.

#### Iron chelating agents

Iron chelation is the mainstay treatment for patients with secondary iron overload with anemia, especially thalassemia patients. The association between iron overload and morbidity in thalassemia patients has been strongly substantiated and the need for chelation therapy is well established. Currently, there are three types of iron chelators. The use of these chelators in TM showed significant decreases of HIC.<sup>119-121</sup> The first chelator that was approved is deferoxamine. It has a short half-life and is administered intravenously or subcutaneously, which has a significant impact on patient compliance and quality of life. The second is deferiprone, which is an oral chelator. Long-term use of deferiprone is associated with progression cessation of hepatic fibrosis in the majority of TM patients.<sup>122</sup> Its most serious side effect is agranulocytosis

and the neutrophil count should be monitored. The third is deferiasirox. Its use is associated with significant improvement in HIC and liver stiffness in TDT patients.<sup>123</sup> It is also effective in reducing liver iron in TDT patients,<sup>124</sup> and MDS or AA patients with transfusional iron overload.<sup>125</sup>

## Conclusions

Secondary iron overload is an important condition which significantly influence the liver outcomes in affected patients. Iron overload is a well-recognized complication of chronic transfusion in patients with iron-loading anemias. It is associated with increased liver fibrosis and cirrhosis in these patients. Iron chelation therapy is required to prevent iron overload and for the treatment of liver-related complications in patients with iron-loading anemias. In addition to liver-related complications, this condition may also have significant impact on primary hematologic disorders. The data relevant to patients with chronic liver disease is limited and currently, there is no treatment recommended. Future studies in patients with chronic liver disease should aim to explore the mechanisms associated with iron overload, the population at risk of liver-related complications, and the effect of treatments for iron overload on patient outcomes.

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## Conflict of interest

The authors have no conflict of interests related to this publication.

## Author contributions

Designed, conducted the literature search, data collection, manuscript drafting (KP), interpreted the data, made critical revisions and approved the manuscript (KP, AT, AL, AS, ST).

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