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REVIEW ARTICLE

Anemia

Hepatic and cardiac iron overload quantified by magnetic resonance imaging in patients on hemodialysis: A systematic review and meta-analysis

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Abstract

Introduction: Few studies have reported hepatic and cardiac iron overload in patients with end-stage renal disease (ESRD), and the current evidence regarding the prevalence is still scarce.

Aim: This review aims to estimate the prevalence of hepatic and/or cardiac iron overload quantified by magnetic resonance imaging (MRI) in patients with ESRD who receive hemodialysis (HD), peritoneal dialysis (PD), or have undergone a kidney transplant.

Methods: A systematic review with meta-analysis was conducted and reported in line with PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines. MEDLINE and Embase bibliographic databases were searched using a comprehensive list of controlled vocabulary and keywords to identify relevant studies. All studies reporting the prevalence of hepatic and/or cardiac iron overload quantified by MRI in ESRD patients were considered. The Newcastle-Ottawa scale was used to assess the methodological quality of included studies. To investigate the heterogeneity between studies, random-effect meta-analyses for proportions were used.

Results: The review comprised seven studies that included 339 patients. Using meta-analysis, the pooled prevalence of severe and mild to moderate hepatic iron overload quantified by MRI was 0.23 [95% CI: 0.08–0.43] and 0.52 [95% CI: 0.47–0.57], respectively. Only three studies included cardiac iron quantification, and none reported iron overload.

Conclusions: This review has revealed a high prevalence of severe hepatic iron overload in patients with ESRD treated by HD. Further studies with a larger sample size are needed to determine the impact of iron overload on vital organs in patients with ESRD and guide future research in this understudied field. Proper use of iron chelation and continuous monitoring will help in the early detection of unsolicited complications; however, the low renal clearance

of most iron chelators limits the options for treating iron excess in patients with ESRD.

KEYWORDS
end-stage renal disease, heart, hemodialysis, iron overload, liver, meta-analysis, systematic review, T2*MRI

INTRODUCTION

Chronic kidney disease (CKD) is a challenging health issue across the world. Globally, the prevalence estimates for CKD range between 11.7% and 15.1%.[1] Moreover, the progression of CKD to cardiovascular diseases and end-stage renal disease (ESRD) directly influences morbidity and death rates.[2] About 1 in 7 adults in the United States (around 37 million people) are affected by CKD, which is more often caused by chronic conditions such as hypertension and diabetes.[3] While anemia represents the feature complication in patients with ESRD,[4] the possibility of iron overload toxicity associated with continuous intravenous (IV) iron replacement is currently one of the most contentious issues in the management of anemia in patients with ESRD.[5]

Classically, iron excess may have a negative impact on the heart (e.g., heart failure, arrhythmias, and sudden cardiac death) and the liver (hepatocellular carcinoma), and it causes other complications, such as diabetes mellitus, hypogonadism, and musculoskeletal and skin-related conditions.[6,7] In addition, higher iron stores may negatively affect the immune-regulatory balance, weakening the immune system and hindering effective treatment of underlying illnesses.[8] In dialysis patients, liver iron accumulation increases dramatically hepcidin production which has been associated with a risk of cardiovascular events and mortality.[9,10] Moreover, liver iron accumulation in dialysis patients has recently been shown to increase liver fat fraction, with the ability to induce or worsen fatty liver disease.[11]

Unfortunately, the low renal clearance of most iron chelators limits the options for treating iron excess in patients with ESRD who undergo hemodialysis (HD), peritoneal dialysis (PD), or kidney transplant.[12] This creates a clinical problem in balancing the need to correct hemoglobin while avoiding iron excess.[13]

Remarkably, some researchers are emphasizing more on the importance of iron overload prevention by establishing a routine screening of dialysis patients for iron overload especially in patients who have received a high cumulative dose of IV iron, or have long cumulative dialysis vintage.[13] other researchers are suggesting more pragmatic approach by a novel treatment (known as HIF stabilizers) method for anemia in patients with CKD (now in Phase-III trials). These stabilizers block the proteasomal degradation of HIF-α, causing the erythropoietin gene to be upregulated. The possible benefits of this medication include the fact that it is orally active (avoiding injections) and exposes patients to lower circulating levels of erythropoietin. However, the long-term safety of this method must be verified in more and larger clinical trials.[14]

A systematic review and meta-analysis of aggressive IV iron use (>200 mg/month) in dialysis patients published in 2018 found no association between an increased incidence of infection and IV iron; however, the review should be viewed with caution due to numerous limitations, including the inclusion of only four RCTs, all of which were small and of short duration.[15] On the other hand, the cumulative dose of IV iron injected into HD patients has increased in recent years as clinical practice is moving towards more liberal iron use and less erythropoietin-stimulating agents. However, there is a scarcity of evidence demonstrating that accumulated dosages per person surpass predicted losses.[16–18]

As the liver is the main iron storage site in healthy humans and in iron overload disorders and the liver iron concentration (LIC) gives an accurate picture of total body iron stores in patients with secondary hemosiderosis such as thalassemia major, sickle-cell disease and in patients suffering from genetic hemochromatosis and a virgula and hepatic with a minuscule. Hepatic magnetic resonance imaging (MRI) has become the gold standard method for estimating and monitoring iron stores, providing "iterative radiological biopsy" in the setting of iron overload diseases.[19] Quantitative MRI is based on the paramagnetic properties of iron and there are three validated qMRI modalities for liver iron quantification: the signal-intensity ratio (SIR), R2 relaxometry and R2* relaxometry validated in cohorts of patients with genetic hemochromatosis, hepatic disorders and secondary hemosiderosis related to thalassemia and sickle cell disease requiring liver biopsy for biochemical iron assay. Measurement of cardiac iron is based on R2* relaxometry.[20] SIR and R2* relaxometry MRI have recently been shown to accurately measure iron load in HD patients when compared with quantitative liver histology

(Deugnier and Turlin Scoring) with Perls staining on trans-jugular liver biopsy.[21,22]

Previous studies have reported a wide range of prevalence estimates of hepatic and/or cardiac iron overload in patients with ESRD ranging between 50% and 100%.[23,24] However, to our knowledge, no systematic reviews have been conducted to synthesize the epidemiologic evidence on the prevalence of hepatic and cardiac iron overload in patients with ESRD. Thus, this systematic review and meta-analysis aims at estimating the prevalence and severity of iron overload (cardiac and/or hepatic) in patients who receive HD, PD, or have undergone kidney transplantation.

METHODS

The protocol for this systematic review and meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P).[25] The protocol was registered with the International Prospective Register of Systematic Reviews PROSPERO under registration number CRD42022306803 (available from https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=306803) and has been recently published elsewhere.[26] The reporting of this systematic review and meta-analysis was guided by the PRISMA statement (Table S1).[27]

Search strategy

An extensive search was conducted for published studies with no time restrictions. MEDLINE and Embase bibliographic databases were searched from inception to March 1, 2022 using a comprehensive set of controlled vocabularies, including medical subject headings (MeSH) and Emtree keywords as well as free-text terms pertaining to iron overload/toxicity and ESRD/CKD (Table S2). For example, MEDLINE was searched using the following terms: ("chronic kidney disease" OR "chronic renal disease" OR "chronic kidney insufficiency" OR "chronic renal insufficiency" OR "end-stage renal disease" OR "hemodialysis" OR "peritoneal dialysis" OR "kidney transplant*" OR "renal transplant*") AND ("iron imbalance" OR "iron overload" OR "iron deposition" OR "iron toxicity" OR "haemochromatosis" OR "hemochromatosis") AND ("heart" OR "cardiac" OR "Liver" OR "hepatic"). A backward and forward reference check was performed to identify any eligible studies. In addition, the citations of included studies were traced using the Web of Science and Scopus citation indices to identify any relevant studies.

Study selection criteria

All epidemiologic studies reporting on the prevalence of hepatic and/or cardiac iron overload quantified by MRI the gold standard method[16] among adults aged 18 years and above with ESRD receiving PD, HD, or underwent kidney transplant were included. Studies about patients aged <18 years or having other co-existing hematologic or hepatic disorders were excluded.

All literature, including cross-sectional, retrospective, prospective cohort studies, and randomized controlled trials reported were included, with no date restrictions. Reviews, commentaries, protocols, conference abstracts, case reports, and posters were excluded.

Screening and data extraction

Studies retrieved from all databases were exported to EndNote™ and duplicate records were eliminated. Then, the titles, abstracts, and keywords of the remaining records were screened for eligibility. The full texts of relevant papers, or when a decision could not be made based on titles and abstracts, were reviewed for eligibility. The following items were retrieved from included studies: author, publication year, country, study design, setting, sample size, gender, mean age, and prevalence and severity of hepatic and/or cardiac iron overload (quantified by MRI). Records' screening, full-text review, study selection, and data extraction were performed by two reviewers independently (Abdulqadir J. Nashwan & Mujahed Shraim). Any discrepancies were settled by consensus or arbitration by a third reviewer.

Quality assessment and risk of bias

The Newcastle-Ottawa Scale (NOS)[28] was utilized to evaluate the methodologic aspects of observational studies (cross-sectional and cohort studies), which consists of eight items evaluating selection, comparability, and exposure (Table S3). Two reviewers (Abdulqadir J. Nashwan and Alaa Abd-Alrazaq) appraised the methodological quality of the included studies independently, and any disagreements were resolved by consensus. Each study got up to one star for each aspect of the sample selection procedure and outcomes, and up to two stars for the comparability section. The sample selection phase assessed: (a) the representativeness of the exposed cohort (representative of ESRD patients with iron overload), (b) the selection of the nonexposed group, (c) exposure determination, and (d) proof that the outcome was not present at the

beginning of the study. The comparability section assessed: (a) if a research purposefully adjusted for the most relevant risk variables and (b) whether a study adjusted for other key risk factors. The result section assessed: (a) the technique used to measure the outcome, (b) if the follow-up time was long enough for outcomes to occur, and (c) the rate of loss to follow-up. The methodological quality scores were variable as 3 studies scored 8 which revealed high quality and the rest scored 6–7.

Outcome measures

The outcome of interest was the prevalence and severity of hepatic and/or cardiac iron overload. For those studies provided; multicategory prevalence analysis[29] was utilized and the estimates were pooled to arrive at MRI severity-related prevalence estimates. These proportions were synthesized based on predefined multigroups to improve homogeneity by categorizing into MRI hepatic and cardiac quantification: (1) cardiac: normal (T2* > 20 ms), mild to moderate (T2* =10–20 ms), and severe (T2* < 10 ms). (2) hepatic: severe (T2* < 1.8 ms), mild to moderate (T2* = 1.8–11.4 ms), and normal (T2* > 11.4 ms) or (T2* > 15 ms).[20,30]

Iron overload severity in studies has been classified using SIR except one study with R2 relaxometry (Ferriscan®),[24] the scale of classification for these studies using for SIR and R2 relaxometry (Ferriscan®) as follows: Normal LIC values are usually set at <40 or 50 μmol/g dry weight; LIC values of 41/51–100 μmol/g represent mild iron overload, 101–200 μmol/g moderate iron overload, and > 200 μmol/g severe iron overload.[31]

Statistical analysis

Proportional meta-analysis to estimate overall proportion was performed on the transformed scale using Arcsine-based transformations, which is a common procedure for stabilizing the variance of proportion in meta-analysis methods.[32] Then, the back transformation was applied to the transformed effect size in order to retrieve the original effect size (prevalence). The Cochran's Q, based on the χ^2 statistic, was utilized to test the statistical heterogeneity of the included studies, and I^2 was computed to describe the proportion of total variation due to heterogeneity.[29] R 4.1.3 package was used to perform the random effect meta-analysis. The risk of bias publication was investigated using the Rosenthal's fail-safe N test, if the p-value was less than 0.05 then the chance of bias is very low. Visual inspection of a funnel plot was not done due to the small number of studies included (<10).[33,34] In addition, high heterogeneity (like what have in this study) will make funnel plot unlikely to be informative about publication bias.[35] Also, a rule of thumb, tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry.[36]

RESULTS

The search of databases yielded 138 studies. Of them, 14 duplicates were eliminated. After screening the titles and abstracts, 124 articles were identified as potentially eligible for inclusion. After full-text review, 7 studies published from 2012 to 2019 and including 339 patients with ESRD were included in the final analysis (see Figure 1).[11,21,23,24,37–39]

The sample size ranged between 10 and 212 patients with a mean age of 59.7 (51.0–66.5 years), and around 61% of them were males (see Table 1). All the patients were receiving hemodialysis, and only three studies[23,24,37] included cardiac iron quantification and none of them reported abnormal iron overload. One study had three patients on PD,[11] and none of them had kidney transplant patients.

For the normal category, the overall prevalence was 0.17 [95% CI: 0.03–0.39] which was statistically significant (p-value < 0.001; Figure 2). The model heterogeneity (I^2) reached 95.4%, which was significant (Q = 133.71, df = 6, p-value < 0.001). The Rosenthal's method resulted in a very significant test (p-value < 0.001) indicating that the likelihood of publication bias in our meta-analysis was minimal.

In respect of the mild to moderate category, the overall prevalence was 0.52 [95% CI: 0.47–0.57] which was statistically significant (p-value < 0.001; Figure 3). The model heterogeneity (I^2) reached 1.5%, which was not significant (Q = 11.24, df = 6, p = 0.08). The Rosenthal's method resulted in a very significant test (p-value < 0.001) indicating that the likelihood of publication bias in our meta-analysis was minimal.

Regarding severe category of hepatic iron overload, the overall prevalence was retrieved using inverse of the arcsine transformation, and hence the overall prevalence was 0.23 [95% CI: 0.08–0.43] (Figure 4). The model heterogeneity (I^2) reached 94.1%, which is was significant (Q = 37.82, df = 6, p-value < 0.001). The Rosenthal's method resulted in a very significant test (p-value < 0.001) indicating that the likelihood of publication bias in our meta-analysis was minimal.

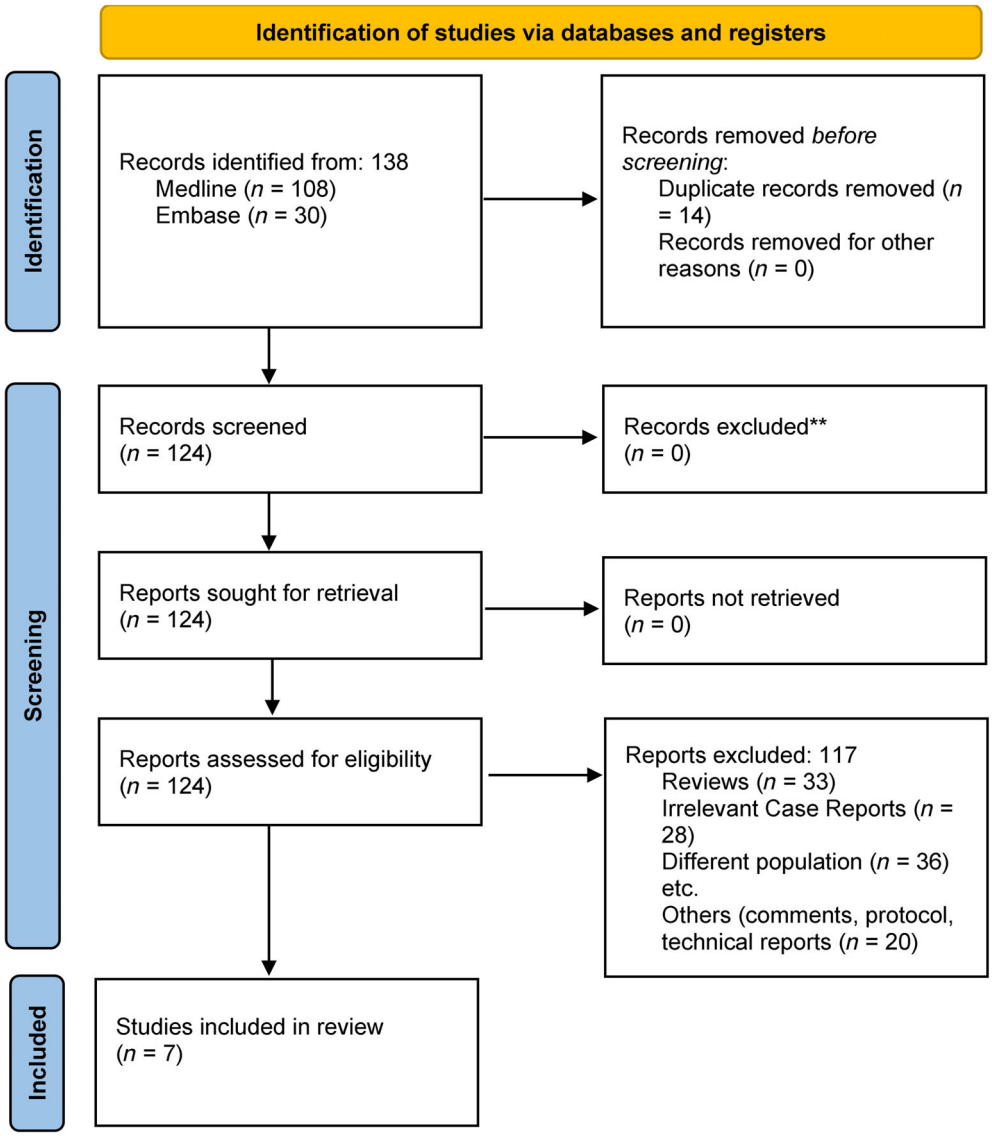

FIGURE 1 PRISMA (preferred reporting items for systematic reviews and meta-analyses) flowchart of the systematic literature search. [Color figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

This systematic review and meta-analysis aimed at estimating the prevalence of hepatic and cardiac iron overload in patients with ESRD found that the prevalence of mild to moderate and severe hepatic iron overload was 23% and 52%, respectively. The findings of this review may help nephrologists and hematologists optimize the management of iron overload in patients with ESRD through screening, early detection, and continuous monitoring. Furthermore, it will serve as the foundation for future observational studies assessing prevalence and prognostic factors in patients with ESRD.

Patients with ESRD, especially those on hemodialysis, have major changes in their iron balance and tissue distribution because they absorb less iron, lose more iron, and cannot get iron out of storage as well.[40] Several studies have reported hepatic iron overload in patients on HD which ranged from 60% to more than 90%.[23,24,37–39,41,42] However, the findings of our review have revealed a high prevalence of hepatic iron overload in patients with ESRD and the prevalence estimates were heterogeneous where the reasons for this heterogeneity are not clear, but could be explained by several factors such as the severity of CKD, years on dialysis, IV iron intake, other treatment modalities such as PD, kidney transplant, and other risk factors, such as age, co-morbidities, and concomitant medications.

Issad et al.[43] measured LIC by MRI in a cohort of 32 adult patients receiving PD and their study revealed that iron overload on MRI is rare and mostly mild in patients receiving PD compared with those receiving HD (6 patients out 32 studied, of whom 5 had mild iron overload and only 1 with severe iron overload due to iron sucrose infusions). These "striking" differences between PD and HD have been further explored by the

TABLE 1 Characteristics of included studies.

Authors	Publication year	Design	Country	*N*	Mean age	Sex (F) %	Inclusion criteria	Overall liver iron overload (*N*)	Overall liver iron overload (%)	Severe[a]	Mild to moderate[b]	Normal[c]
Tolouian et al.[23]	2016	Prospective	USA	17	55	47	CKD Stage 5, on IV iron, ferritin >100 ng/ml, serum transferrin saturation (TSAT) > 20%	8	50	3	5	9
Holman et al.[24]	2017	Prospective	Australia	10	61	70	Ferritin > 100 μg/l and/or TSAT > 20%	10	100	8	2	0
Rostoker et al.[39]	2015[d]	Prospective	France	93	69	35	Ferritin > 200 ng/ml and/or TSAT > 20%	60	75	10	50	33
Rostoker et al.[38]	2012	Prospective	France	119	51	42	Ferritin > 200 ng/ml and/or TSAT > 20%	100	84	36	64	0
Ghoti et al.[37]	2012	Prospective	Israel	21	63	38	Ferritin >1000 ng/ml	19	90	6	13	2
Rostoker et al.[21]	2017	Prospective	France	11	58	36	Ferritin > 200 ng/ml and/or TSAT > 20%	7	64	0	7	4
Rostoker et al.[11]	2019	Prospective	France	68	57	37	Ferritin > 200 ng/ml and/or TSAT > 20%	39	57	7	32	29

Abbreviation: CKD, chronic kidney disease.

[a]T2* < 1.8 ms.

[b]T2* = 1.8–11.4 ms.

[c]T2* > 11.4 ms or T2* > 15 ms, or normal LIC values are usually set at <40 or 50 μmol/g dry weight; LIC values of 41/51–100 μmol/g represent mild iron overload, 101–200 μmol/g moderate iron overload, and > 200 μmol/g severe iron overload.

[d]This study has included comparison of 2 cohorts: one is the same 119 patients published in the previous 2012 study[38] and the other 93 patients are a new cohort treated with different serum iron markers target.

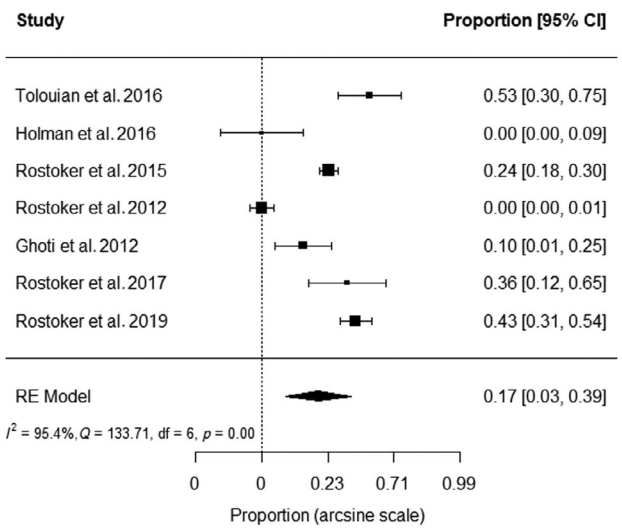

FIGURE 2 Forest plot for effect size using arcsine transformed prevalence of normal iron overload category

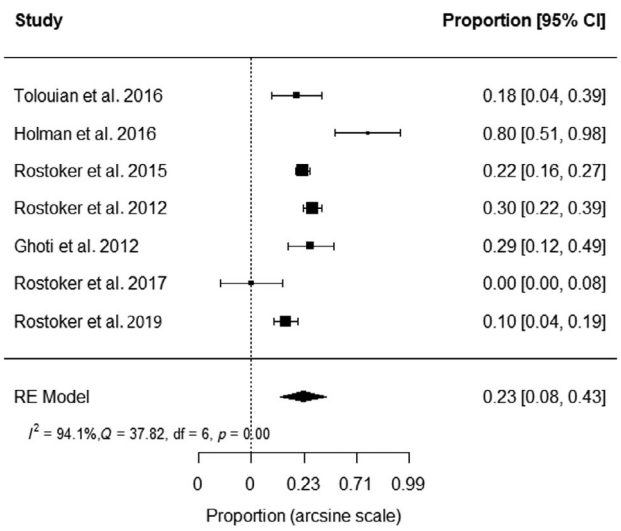

FIGURE 4 Forest plot for effect size using arcsine transformed prevalence of severe iron overload category.

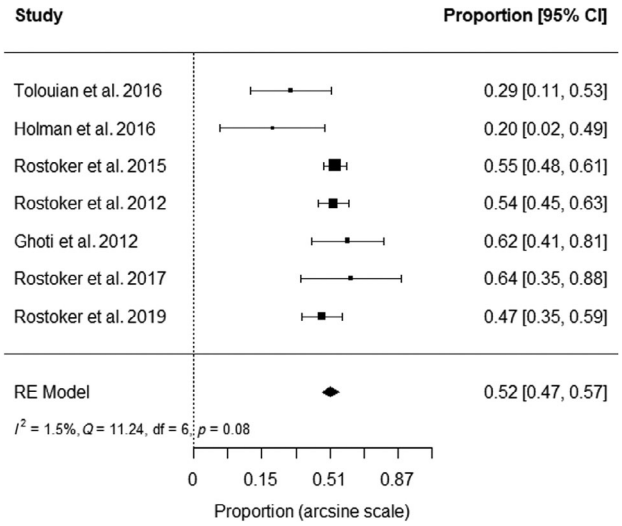

FIGURE 3 Forest plot for effect size using arcsine transformed prevalence of mild to moderate iron overload category.

retrospective comparison between French HD and PD cohorts highlighting that ESRD "per se" is not the culprit of iron overload but rather the therapeutics and management of anemia, which strongly differ between these two modalities of dialysis.[44]

Furthermore, several recent observational studies have revealed that high IV iron levels may increase cardiovascular events and overall mortality in patients with ESRD on hemodialysis.[45–48] Despite the recent progress in understanding the iron overload (cardiac and hepatic) in patients with hemoglobinopathies, many aspects still are unanswered concerning patients with CKD. Furthermore, the duration, magnitude, and speed of iron overload in ESRD patients may not match those seen in hematological disorders considering that IV iron usage in HD patients has expanded significantly in recent years.[40,49] A systematic review and meta-analysis published in 2019 revealed that the overall prevalence of cardiac iron overload—for example—in thalassemia major patients was 25% [95% CI: 22–28%].[50] Although, the findings of this review have revealed no cardiac iron overload. Still, no definite conclusions can be reached about the risk of cardiac iron overload in patients with CKD due to the scarcity and limitations of published studies.

LIMITATIONS

This review has some limitations, such as the inclusion of a limited number of studies with a small sample size and the likely possibility of publication bias due to the limited number of studies on iron overload in patients with ESRD, and our results might not be generalizable to other populations, such as ESRD with PD or kidney transplant. More work is required to validate the use of MRI in patients with ESRD.

IMPLICATIONS FOR PRACTICE AND FUTURE RESEARCH

Iron overload was once uncommon in patients receiving hemodialysis, but it is becoming a more common clinical condition. Clinical guidelines must be improved by paying more attention to the consequences of iron overload and implementing better diagnostic options in order to optimize the care of this growing complicated condition. In addition, recent quantitative MRI studies obviously imply a relationship between IV iron dosage and the risk

of iron overload, calling into question both current iron biomarker cutoffs and clinical guidelines, particularly regarding recommended iron doses and the frequency of iron monitoring.[51] On the other hand, patients need to be aware of the signs and symptoms of iron overload and the importance of early detection and continuous monitoring.

CONCLUSIONS

In conclusion, our review of pooled iron overload prevalence in patients with ESRD revealed a high prevalence of hepatic iron overload. Proper use of iron chelation and continuous monitoring will help in early detection of unwanted complications; however, the low renal clearance of most iron chelators limits the options for treating iron excess in patients with ESRD. Still, more research with a bigger group of people and standardized methods is needed to find out how iron overload affects vital organs in people with ESRD.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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