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MANAGEMENT OF PATIENTS WITH ANAEMIA IN CHRONIC CARDIORENAL SYNDROME

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Abstract. Anaemia is a common and clinically significant complication in patients with chronic cardiorenal syndrome, negatively affecting functional capacity, quality of life, and overall prognosis. This study aimed to evaluate the effectiveness of oral versus intravenous iron therapy, each in combination with erythropoiesis-stimulating agents (ESAs), in the outpatient management of anaemia in patients with coexisting chronic kidney disease and chronic heart failure. A total of 80 patients were enrolled and divided into two equal groups: one received oral iron with ESAs, while the other was treated with intravenous iron and ESAs. Over a 16-week follow-up period, the group receiving intravenous iron demonstrated significantly greater improvements in haemoglobin levels, functional status (NYHA class), iron indices (ferritin, TSAT), and treatment satisfaction. They also required fewer ESA dose adjustments and had a lower incidence of anaemia-related hospitalisations. These findings support the superiority of intravenous iron supplementation in anaemia correction among patients with chronic cardiorenal syndrome, particularly in the presence of inflammation or poor gastrointestinal absorption.

Keywords: Anaemia, chronic kidney disease, chronic heart failure, cardiorenal syndrome, intravenous iron, oral iron, erythropoiesis-stimulating agents, haemoglobin, outpatient management.

Introduction

Anaemia is a frequent and clinically significant complication in patients with chronic kidney disease (CKD), particularly when it coexists with chronic heart failure (CHF), a condition known as chronic cardiorenal syndrome. The interdependence between the kidneys and heart in this syndrome creates a complex pathophysiological environment in which the dysfunction of one organ exacerbates the other. Anaemia in such patients not only contributes to fatigue and reduced quality of life but also worsens the prognosis by accelerating the progression of both renal and cardiac dysfunction.

The prevalence of anaemia in patients with chronic cardiorenal syndrome is reported to be as high as 60–70%, and its presence is independently associated with increased hospitalisation rates and mortality. The pathogenesis of anaemia in this setting is multifactorial. It includes reduced erythropoietin production due to renal impairment, chronic inflammation leading to functional iron deficiency, hemodilution, nutritional deficiencies, and the suppressive effects of uremic toxins on erythropoiesis. Additionally, the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, though essential for cardiorenal protection, may further impair erythropoietin levels and contribute to anaemia.

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Given this complex interplay of factors, anaemia management in cardiorenal patients poses a significant clinical challenge. A one-size-fits-all strategy is often inadequate, and individualised treatment approaches are necessary. Current international guidelines recommend a combination of therapies, including iron supplementation (preferably intravenous), erythropoiesis-stimulating agents (ESAs), and correction of underlying nutritional and inflammatory states. However, the timing, dosage, and combination of these interventions must be carefully balanced to avoid complications such as hypertension, thrombosis, or excessive erythropoiesis.

Recent studies also highlight the importance of novel agents such as hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), which stimulate endogenous erythropoietin production and improve iron metabolism. These agents offer promise, especially for patients who are hyporesponsive to conventional ESA therapy. Nevertheless, they are not yet widely accessible in many regions, including Uzbekistan, and their long-term safety remains under evaluation.

In Uzbekistan, the burden of cardiorenal syndrome is steadily increasing, paralleling global trends in diabetes, hypertension, and aging populations. However, anaemia in these patients often remains underdiagnosed and undertreated, particularly in outpatient settings. There is a need for more structured protocols and awareness among general practitioners and cardiologists regarding early screening, risk stratification, and comprehensive anaemia correction strategies.

This study aims to investigate current clinical approaches and treatment outcomes for anaemia in patients with chronic cardiorenal syndrome, with a particular focus on outpatient care. The objective is to evaluate the effectiveness of combined iron and ESA therapy in real-world conditions, assess factors influencing treatment response, and propose recommendations for optimising anaemia management protocols in regional healthcare settings.

The results of this study are expected to provide valuable insights into improving the quality of care, reducing rehospitalisation, and enhancing the life expectancy of patients suffering from this dual-organ failure syndrome. By aligning local practice with international standards and adapting evidence-based strategies to regional realities, healthcare providers can significantly mitigate the burden of anaemia in chronic cardiorenal patients.

Methodology

This prospective observational study was conducted between 2022 and 2024 at the outpatient department of the Samarkand Regional Multidisciplinary Medical Centre in collaboration with the Department of Hematology, Samarkand State Medical University. The study aimed to assess the effectiveness of current anaemia management strategies in patients with chronic cardiorenal syndrome and to identify key factors affecting treatment response in real-world outpatient conditions.

A total of 80 patients were enrolled in the study based on the following inclusion criteria: a confirmed diagnosis of chronic heart failure (NYHA Class II–IV), chronic kidney disease (Stage 3–5, eGFR < 60 ml/min/1.73m²), and anaemia as defined by WHO criteria (haemoglobin levels < 130 g/L in men and < 120 g/L in women). Exclusion criteria included active bleeding, recent blood transfusion (within the past 3 months), malignancy, acute infection, uncontrolled hypertension, or hypersensitivity to iron or erythropoiesis-stimulating agents (ESAs).

All patients underwent a comprehensive baseline evaluation, including clinical examination, NYHA functional classification, echocardiography, serum creatinine, estimated glomerular

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filtration rate (eGFR), haemoglobin level, ferritin, transferrin saturation (TSAT), C-reactive protein (CRP), serum iron, total iron-binding capacity (TIBC), vitamin B12, and folate levels. Based on their iron status and inflammatory profile, patients were stratified into two therapeutic subgroups.

Group A (n=40) received oral iron supplementation (ferrous sulfate or fumarate) and standard ESA therapy (epoetin alfa or beta) with dose titration according to the patient's response. Group B (n=40) was treated with intravenous iron (ferric carboxymaltose or iron sucrose) combined with subcutaneous ESAs. The decision to use oral versus IV iron was guided by ferritin levels (<100 ng/mL or TSAT <20%) and the presence of elevated inflammatory markers (CRP > 5 mg/L), in which case IV iron was preferred due to poor absorption of oral preparations.

The duration of follow-up was 16 weeks. Haemoglobin levels were monitored every 4 weeks, while iron parameters, renal function, and cardiovascular status were reassessed at 8 and 16 weeks. The primary endpoint was the increase in haemoglobin by ≥10 g/L from baseline without the need for blood transfusion. Secondary endpoints included improvement in functional capacity (NYHA class), reduction in ESA dosage, correction of iron deficiency, and incidence of adverse events such as hypertension, thromboembolic events, or intolerance to therapy.

Treatment response was evaluated using both absolute haemoglobin gain and composite clinical improvement (including symptom reduction and hospital admission rates). Data were analysed using SPSS software version 26.0. Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test. Categorical data were analysed using the chi-square test. A p-value <0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Institutional Review Board of Samarkand State Medical University, and informed consent was obtained from all participants. Patients were educated about their anaemia condition, treatment options, potential side effects, and the importance of adherence to therapy during regular outpatient visits.

This methodology ensured a structured and comparative evaluation of real-world anaemia management practices and aimed to generate evidence for improving protocol-based care for patients suffering from anaemia in the context of chronic cardiorenal syndrome in Uzbekistan.

Results

The 16-week follow-up period revealed distinct differences in treatment response between the two patient groups. Among the total 80 patients enrolled, 76 (95%) completed the study, while 4 were lost to follow-up due to relocation or unrelated health complications. Both groups were comparable at baseline in terms of age, sex distribution, severity of anaemia, eGFR, and NYHA class.

In Group A, which received oral iron therapy combined with subcutaneous erythropoiesis-stimulating agents (ESAs), the mean baseline haemoglobin level was 96.4 ± 8.2 g/L. By the end of the follow-up period, a mean haemoglobin increase of 7.8 ± 4.6 g/L was recorded. However, only 47.5% of patients (19 out of 40) achieved the target haemoglobin increase of ≥10 g/L without the need for transfusion. Furthermore, 30% of patients required ESA dose escalation, and 4 patients (10%) experienced gastrointestinal side effects such as nausea or constipation, which impacted adherence to oral iron therapy.

In contrast, Group B, which received intravenous iron (ferric carboxymaltose or iron sucrose) in addition to ESA therapy, demonstrated significantly better outcomes. The mean baseline haemoglobin level in this group was 95.7 ± 7.9 g/L, and the mean increase by week 16 was

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13.1 ± 5.2 g/L ($p < 0.01$ compared to Group A). A total of 77.5% of patients (31 out of 40) in this group achieved the target haemoglobin response. Inflammatory markers (CRP) also declined modestly in this group, suggesting improved systemic iron availability and reduced anaemia of chronic disease.

Additionally, functional improvement was more evident in Group B, with 65% of patients moving up at least one NYHA class compared to 40% in Group A. Fewer ESA dose adjustments were needed in Group B, indicating better erythropoietic responsiveness. No serious adverse events were reported in either group, though mild infusion-related reactions (such as transient flushing and dizziness) occurred in 3 patients in Group B, resolving spontaneously without intervention.

Iron parameters also differed significantly between the two groups by week 16. In Group A, only 55% of patients normalised ferritin and transferrin saturation, whereas in Group B, 85% of patients reached target iron indices (ferritin > 100 ng/mL and TSAT > 20%). This confirmed superior bioavailability and utilisation of intravenous iron in the presence of inflammation.

The overall treatment satisfaction reported by patients, based on standardised questionnaires, was higher in Group B, primarily due to faster symptom relief, fewer side effects, and reduced fatigue. Hospital admission rates related to anaemia or CHF decompensation during the follow-up were lower in the IV iron group (2 cases) compared to the oral iron group (6 cases), although this difference was not statistically significant ($p = 0.08$).

In summary, the results indicate that intravenous iron therapy, when combined with ESAs, is more effective than oral iron in correcting anaemia, improving functional capacity, and enhancing quality of life in patients with chronic cardiorenal syndrome. These findings support the early use of IV iron in outpatient management protocols, particularly in patients with inflammation, low iron stores, or poor tolerance to oral supplementation.

Discussion

The findings of this study demonstrate that anaemia in patients with chronic cardiorenal syndrome requires a strategic, individualised management approach that goes beyond standard oral iron supplementation. The superiority of intravenous (IV) iron therapy, observed in Group B, aligns with a growing body of international evidence suggesting that in the presence of inflammation and reduced gastrointestinal absorption—common in patients with chronic kidney disease and heart failure—IV iron is not only more effective but also better tolerated than oral preparations.

The enhanced haemoglobin response in Group B patients is largely attributable to the increased bioavailability of parenteral iron, which bypasses the regulatory blockades caused by hepcidin overexpression, a peptide hormone that inhibits intestinal iron absorption in states of chronic inflammation. This mechanism is particularly relevant in the context of chronic kidney disease and heart failure, where inflammation-induced functional iron deficiency is a key contributor to treatment-resistant anaemia. Our study's data supports previous findings that IV iron, particularly ferric carboxymaltose or iron sucrose, achieves faster replenishment of iron stores, increases transferrin saturation more efficiently, and improves erythropoietin responsiveness [Macdougall et al., 2020, p. 118].

The improved NYHA functional class observed in Group B further highlights the systemic benefits of effective anaemia correction. As anaemia impairs oxygen delivery to tissues and increases cardiac workload, its correction can relieve cardiac stress, enhance exercise tolerance, and improve overall quality of life. Patients in Group B not only achieved better haemoglobin targets but also required fewer ESA dose adjustments, which is clinically

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important given the risks associated with high ESA dosages, including thrombosis and hypertension.

Interestingly, despite a statistically non-significant difference, Group B also experienced fewer hospitalisations for anaemia-related complications or heart failure decompensation. This suggests that better anaemia control may contribute to improved clinical stability, although longer follow-up is needed to confirm this association. Moreover, treatment satisfaction was higher among patients receiving IV iron, underlining the practical importance of symptom relief and reduced side effects, such as gastrointestinal intolerance, which often limits the use of oral iron.

These findings are highly relevant for outpatient settings in Uzbekistan and other similar healthcare environments, where anaemia is frequently underdiagnosed or treated conservatively due to cost or resource limitations. This study highlights the need for greater awareness among outpatient clinicians about the limitations of oral iron and the benefits of early transition to IV iron in appropriate patients. At the same time, the data call for the development of local clinical protocols and treatment pathways to standardise anaemia screening and ensure timely correction based on evidence-based criteria.

However, the study has certain limitations. The follow-up period was limited to 16 weeks, and the long-term sustainability of haemoglobin response and cardiovascular outcomes could not be assessed. Additionally, although the study was conducted under real-world outpatient conditions, it was restricted to a single centre and a moderate sample size. Future multicentre studies with extended follow-up and the inclusion of newer therapeutic agents, such as hypoxia-inducible factor stabilisers, would provide more comprehensive insights.

In conclusion, this study confirms that intravenous iron therapy, in combination with erythropoiesis-stimulating agents, is a more effective strategy for managing anaemia in patients with chronic cardiorenal syndrome than oral iron supplementation. This approach leads to faster haemoglobin recovery, better iron repletion, improved functional status, and higher patient satisfaction. Integration of these findings into routine outpatient practice can significantly improve outcomes for a growing population of patients with dual kidney and heart failure complications.

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