International Journal of Nephrology and Renovascular Disease

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ORIGINAL RESEARCH

Treatment Inertia and Symptom Burden in Anemia of CKD: Insights from the SATISFY Survey in the Middle East, South Africa, and Türkiye

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Introduction: Limited data exist regarding treatment patterns and symptom burden of patients with anemia of chronic kidney disease (CKD) in the Middle East, South Africa, and Türkiye.

Methods: This real-world study explored clinical characteristics, symptom burden, and treatment patterns of patients with anemia of CKD living in the Middle East, South Africa, and Türkiye. Physician and patient perceptions of treatment were captured via cross-sectional surveys; patients' clinical characteristics were recorded by retrospective review of medical records.

Results: Data were collected from 1788 patients and 217 physicians. A high proportion of patients had never received treatment for their anemia (n = 701, 39.2%); the most common treatment was erythropoietin-stimulating agents (ESAs) + intravenous iron (n = 457, 50.3%). High symptom burden was reported, with lack of energy being the most common symptom (n = 394, 75.6% treated and n = 133, 59.9% non-treated patients). Patients' self-reported symptom burden was higher than physician-reported burden; less agreement was seen for non-dialysis-dependent (NDD) patients (kappa = 0.193, standard deviation [SD]: 0.081) than dialysis-dependent (DD) patients (kappa = 0.442, SD: 0.103). Median hemoglobin thresholds that physicians reported using for initiating treatment (NDD: <10.5 [interquartile range, 9.5–12.0] g/dL; DD: <9.3 [9.0–10.0] g/dL) were higher than actual test levels at treatment initiation (NDD: 9.2 [8.7–10.0] g/dL; DD: 9.0 [8.1–10.0] g/dL).

Conclusion: Treatment inertia is apparent despite high symptom burden in the Middle East, South Africa, and Türkiye, and disagreement was seen in physician and patient perspectives on symptomology. Improved awareness of this disagreement may help facilitate physician–patient dialogue to improve patient experience.

Plain Language Summary: A survey to understand the experiences of people living with anemia and kidney disease in the Middle East, South Africa, and Türkiye

Background

- People living with kidney disease can have a low number of red blood cells (anemia).
  - This can cause heart problems, make kidney disease worse, and lead to death.
- Not much is known about the experiences of people living with kidney disease and anemia in the Middle East, South Africa, and Türkiye.
  - For example, what symptoms do they experience, and which treatments do they receive for their anemia?

What we did

- We carried out surveys in the Middle East, South Africa, and Türkiye between June and September 2022.
  - We surveyed 1788 people living with kidney disease and anemia, and 217 of their doctors.
  - We asked about symptoms experienced by people living with kidney disease and anemia, and which treatments they received for their anemia.

Received: 21 June 2024
Accepted: 13 December 2024
Published: 22 January 2025

What we found

- People living with kidney disease and anemia experienced many different symptoms.
  - Lack of energy was the most common.
  - People living with kidney disease and anemia mentioned symptoms more frequently than their doctors.
- Almost 40% of people living with kidney disease did not receive any treatment for their anemia.
  - The most common treatment was iron combined with drugs that increase production of red blood cells (erythropoietin-stimulating agents).

What does this mean?

- To improve communication and care, doctors should be made aware of how much the symptoms of anemia affect the lives of people living with kidney disease.

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Keywords: anemia, chronic kidney disease, treatment patterns, treatment satisfaction, symptom burden, real-world evidence

Introduction

Chronic kidney disease (CKD) is estimated to affect around 697 million people worldwide as of 2019,[1] and around 2.8–4.6% of people in the Middle East, Africa, and Türkiye are living with stage 3–5 CKD.[2–4] Anemia is a known complication of CKD[5] and is associated with an increased risk of major adverse cardiovascular (CV) events, CKD progression, and mortality,[6] as well as a high symptom burden, particularly tiredness, shortness of breath, and feeling weak.[7] It also has a substantial impact on quality of life (QoL).[8,9] Despite the high burden of anemia of CKD, many patients remain untreated, with data from the CKDOPPS study showing that around 60% of patients with hemoglobin (Hb) levels <10 g/dL did not receive anemia medication.[10,11]

The pathophysiology of anemia of CKD includes reduced oxygen sensing, chronic inflammation with increased pro-inflammatory cytokines (interleukin [IL]-1, IL-6, tumor necrosis factor, interferon)[12,13] and increased hepcidin levels. Hepcidin, the master regulator of iron metabolism,[14,15] downregulates ferroportin, a critical iron exporter, thereby reducing dietary absorption of iron and increasing sequestration to macrophages, resulting in functional iron deficiency and reducing iron available for erythropoiesis.[16] Inflammation is a key factor in Hb variability and iron homeostasis, leading to upregulation of hepcidin and suppression of bone marrow erythropoiesis. Uremic toxins, shortened erythrocyte lifespan and blood loss are among other factors contributing to anemia of CKD.[12,17]

Current treatments focus on relieving iron depletion through iron supplementation and stimulating erythropoiesis,[18] rather than directly addressing the underlying complex pathophysiology of the disease.[19] Currently, the Kidney Disease Improving Global Outcomes Clinical Practice Guidelines for Anemia of CKD recommend iron and erythropoietin-stimulating agents (ESAs) for the treatment of anemia of CKD.[20] However, available treatments each have their own limitations.[20]

Oral iron often leads to gastrointestinal side effects[21,22] and elevated hepcidin levels,[23] resulting in reduced tolerability, poor adherence, and deficient absorption.[21–23] More recent oral iron preparations have shown improved tolerability compared with conventional oral iron agents.[24] Intravenous (IV) iron avoids issues surrounding absorption,[23] but it can cause hypersensitivity reactions[25] and requires administration by healthcare professionals.[26] More recently, ferric carboxymaltose has been used as an alternative IV option, but it has a higher drug acquisition cost compared with other IV iron formulations.[27,28]

ESAs can help to compensate for the erythropoietin deficit;[18,20] however, they may be associated with increased risk of myocardial infarction, heart failure, stroke, and death if used in high dosages.[29–31] Due to the risk of CV-related side effects with ESAs, guidelines typically recommend using the dose of ESAs sufficient to control anemia while maintaining a Hb level of <12 g/dL, and that patients must be monitored regularly during treatment.[18,20,32] However, ESAs and iron supplementation do not address the underlying impact of inflammation and hypoxia on anemia; consequently, iron may be stored rather than utilized leading to functional iron deficiency, and increasing doses of ESA treatments may be required to treat patients with anemia of CKD.[19]

Correctly balancing Hb targets, erythropoietin use, and iron therapy, therefore, remains challenging. Understanding management practices and clinical characteristics of patients with anemia of CKD, along with factors that influence treatment inertia, is vital to improve the lives of patients with this condition. Real-world data on patient characteristics, disease burden, and treatment for people with anemia of CKD in the Middle East, South Africa, and Türkiye are limited; this study aimed to address this lack of data to better inform treatment decisions in these regions. New data on disease burden and local treatment patterns may influence new regional treatment guidelines.

Materials and Methods

Study Design

SATISFY (A Survey on treatment patterns in Anemia of CKD, patient Treatment satISFaction and perspectives as reported by patients and phYsicians) was a non-interventional, real-world study conducted in Egypt, Saudi Arabia, South Africa, and Türkiye. Data were collected between June 01 and September 01, 2022 (Supplementary Figure 1).

A cross-sectional physician survey was conducted to explore physicians' perceptions of the management of anemia of CKD. Physicians were recruited by local fieldwork agencies. Additionally, each physician abstracted patient-level retrospective data from medical charts into an electronic case report form (eCRF) concerning demographics, clinical characteristics, treatment patterns, and clinical outcomes for their next 7–10 consulting patients with a diagnosis of anemia of CKD that met the eligibility criteria. The online survey and eCRF were developed and delivered using the Confirmit platform. The survey materials underwent a user acceptance testing process, in which physicians from the relevant countries completed the draft surveys and provided feedback to improve their suitability. Fieldwork agencies in each country were trained in data collection procedures. These agencies were responsible for training physicians and answering any of their questions related to study materials while ensuring physician anonymity.

An opportunistic sampling approach was used to recruit patients for a paper-based self-completion survey (PSC). Each eligible consulting patient was invited to complete the PSC; however, PSC completion was not mandatory, and a physician may have completed an eCRF for patients that did not complete a PSC. All patients that did complete a PSC had a corresponding eCRF. The PSC collected data on demographics, patients' experiences of living with anemia of CKD, and treatment management and preferences.

Participants

Eligible physicians were practicing nephrologists with ≥1 year of experience, who were actively involved in the drug management of patients with anemia of CKD and were managing ≥12 patients per month. As physicians were asked to abstract data for 7–10 patients, a 12-patient-per-month minimum threshold was set to facilitate patient recruitment.

Eligible patients were, at the time of diagnosis, ≥18 years of age with a physician-confirmed diagnosis of anemia of CKD stage 3b, 4, or 5; Hb <13 g/dL in males and <12 g/dL in females; ferritin levels of ≤500 ng/mL; and ≥2 years of follow-up data from the date of their diagnosis. Patients who were both dialysis-dependent (DD) and non-dialysis-dependent (NDD) were included in the study. Patients with conditions that may have confounded kidney function or Hb levels, such as functioning kidney transplant, acute kidney injury, a known history of myelodysplastic syndrome, multiple myeloma, hereditary hematologic disease (eg, sickle cell disease, pure red cell aplasia, or other known causes of anemia other than CKD), and patients enrolled in a clinical trial were excluded.

Objectives

The objectives of this study were to describe the clinical and demographic characteristics of patients with anemia of CKD living in the Middle East, South Africa, and Türkiye, and to monitor test results at diagnosis and data extraction, treatment patterns, reasons for choices of therapy, treatment changes and reasons for not initiating treatment, and patient and physician satisfaction with anemia treatment.

Statistical Analyses

All pre-specified analyses were descriptive, and no formal hypotheses were tested. Sample size justification was based on the precision of estimates. A post hoc elastic net regression analysis was conducted to explore which covariates were most strongly correlated with Hb, ferritin, and transferrin saturation (TSAT) test levels. The investigated covariates included the presence of specific symptoms, time on dialysis, current treatment, Charlson Comorbidity Index (CCI), CKD stage, and demographic information, including sex, age, and body mass index at the time of data extraction. A 10-fold cross-validation was used to determine the mixing parameter alpha and the penalty parameter lambda for each outcome. Separate analyses were performed for DD and NDD patients. A further post hoc analysis explored inter-rater reliability between patient self-reports and medical chart data for patients by deriving weighted kappa statistics, with a value of 1 indicating perfect agreement and 0 indicating a level of agreement equivalent to chance. Analyses were performed using Stata v17.0 (StataCorp, College Station, Texas, USA) and Unicom Intelligent Responder v7.5 (UNICOM Global, Inc., Los Angeles, California, USA). No imputation was made for missing data, except for dates, where the first day of the month was used in cases of missing data for day of the month.

Ethics

An ethical approval exemption for this study was granted by Pearl IRB in accordance with US Food and Drug Administration 21 Code of Federal Regulations 56.104 and US Department of Health and Human Services 45 Code of Federal Regulations 46.104. The study was conducted following the ethical principles outlined in the Declaration of Helsinki, as well as applicable local and international guidelines. All physicians and patients recruited provided written informed consent. Patients who did not provide consent did not complete the PSC, but their data may still have been included in the anonymized eCRF. Patient and physician data were non-identifiable, and results were aggregated and anonymized to ensure privacy and confidentiality.

Results

Physician and Patient Disposition

In total, 217 physicians were included in the study, and eCRF data were collected from 1788 patients. Of these patients, 1749 (97.8%) had data available on dialysis status at the time of data extraction; 1138 (63.6%) were NDD, and 611 (34.2%) were DD. Patient populations according to country, dialysis status, and PSC completion status are presented in Supplementary Table 1.

Patient Demographics and Clinical Characteristics

Patient demographics and clinical characteristics at data extraction are shown in Table 1. DD patients were slightly older than NDD patients (mean age, 53.2 years vs 41.5 years, respectively). The ethnicity of the majority of patients was either White (35.2%) or Middle Eastern (31.8%), and 16.7% of patients were Black African.

All DD patients were stage 5 CKD, while the majority of NDD patients were either stage 3b (54.8%) or 4 (43.4%). Mean time since diagnosis was longer for DD (3.0 years, standard deviation:[33] 1.4) than NDD (2.7 years, SD: 0.5) patients. The most common comorbidity was hypertension, with over 40% of NDD patients and over 50% of DD patients having this comorbidity. The majority of patients had a CCI of 0 (n = 1325, 74.1%), indicating a high probability of 10-year survival and demonstrating a need for treatment.

The most recent Hb results available in records at the time of data extraction showed that overall, 0.8% (n = 15) of patients had a Hb level of <8 g/dL, 12.0% (n = 214) of patients had a Hb level of ≥8–<10 g/dL, 72.1% (n = 1289) of patients had a level of ≥10–<13 g/dL and 14.5% (n = 259) of patients had a Hb level >13 g/dL. Data were missing for 11 patients.

Treatment

At the time of data extraction, a large proportion of patients had never been prescribed treatment for anemia (overall: n = 701, 39.2%; NDD: n = 558, 49.0%; DD: n = 126, 20.6%) (Figure 1A). More than half of patients were not actively receiving

Table 1 Patient Demographics and Clinical Characteristics at Data Extraction

	Overall (n=1788)	NDD (n=1138)	DD (n=611)
Age, years	45.6 (13.8)	41.5 (12.7)	53.2 (12.8)
Sex, male, n (%)	1004 (56.2)	620 (54.5)	361 (59.1)
BMI, kg/m^2	24.1 (3.1)	23.8 (2.8)	24.5 (3.5)
Ethnicity, n (%)			
Asian-Indian subcontinent	68 (3.8)	48 (4.2)	20 (3.3)
Southeastern Asian	124 (6.9)	81 (7.1)	42 (6.9)
Black African	299 (16.7)	176 (15.5)	109 (17.8)
Middle Eastern	569 (31.8)	326 (28.7)	228 (37.3)
White	629 (35.2)	450 (39.5)	172 (28.2)
CKD stage, n (%)			
Stage 3b	593 (33.2)	583 (51.2)	0 (0)
Stage 4	553 (30.9)	524 (46.1)	0 (0)
Stage 5	642 (35.9)	31 (2.7)	611 (100.0)
Time since diagnosis, years, median (IQR)	2.6 (2.5–3.2)	2.6 (2.4–3.0)	2.8 (2.5–3.4)
Test levels, median (IQR)			
Hb, g/dL	11.6 (10.7–12.5)	12.0 (11.1–12.7)	10.8 (10.0–11.4)
Ferritin, ng/mL	192.0 (132.0–260.0)	165.0 (125.0–220.0)	231.0 (178.0–340.0)
TSAT, %	27.0 (22.0–34.0)	30.0 (25.0–35.0)	25.0 (20.0–27.0)
Charlson Comorbidity Index, n (%)			
0	1325 (74.1)	874 (76.8)	423 (69.2)
1	86 (4.8)	42 (3.7)	39 (6.4)
2+	377 (21.1)	222 (19.5)	149 (24.4)
Comorbidities, n (%)			
Hypertension	858 (48.0)	497 (43.7)	340 (55.7)
Proteinuria	204 (11.4)	98 (8.6)	101 (16.5)
Dyslipidemia	156 (8.7)	91 (8.0)	60 (9.8)
Diabetes	324 (18.1)	156 (13.7)	153 (25.0)
AIDS/HIV	12 (0.7)	5 (0.4)	7 (1.2)

Notes: Data shown are mean (SD) unless otherwise stated. Data are shown at time of data extraction. At time of data extraction, dialysis status was unknown in 39 patients.

Abbreviations: AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CKD, chronic kidney disease; DD, dialysis-dependent; Hb, hemoglobin; HIV, human immunodeficiency virus; IQR, interquartile range; NDD, non-dialysis-dependent; TSAT, transferrin saturation.

treatment and were not on a prescriber-driven holiday. Physicians' reasons for not treating their patients and patients' reasons for not being treated are presented in Supplementary Figure 2. Physicians rated patient refusal and the risk of adverse reactions as the two most important reasons for not prescribing treatment (rated as "very important" by n = 172, 79.3% and n = 168, 77.4% of physicians, respectively), while data from the PSC showed that non-severe symptoms (98/232, 42.2%) and physicians' concerns about treatment adherence (64/232, 27.6%) were the most common reasons patients listed for not receiving treatment.

The median time between patients' initial diagnosis of anemia of CKD and initiating their first treatment was 61 days (min–max: 0–1151 days), with the same median length of time seen regardless of dialysis status at diagnosis. Of the patients who were receiving treatment at the time of data extraction (n = 909, 50.8%), the most common treatment option, regardless of dialysis status, was ESA + IV iron, used by 457 (50.3%) patients overall (Figure 1B).

Factors shown to affect Hb, TSAT, and ferritin test levels according to elastic net regression analyses are shown in Figure 2. Results from the elastic net regression analysis showed that, of the investigated treatments, ESA + oral iron had the largest

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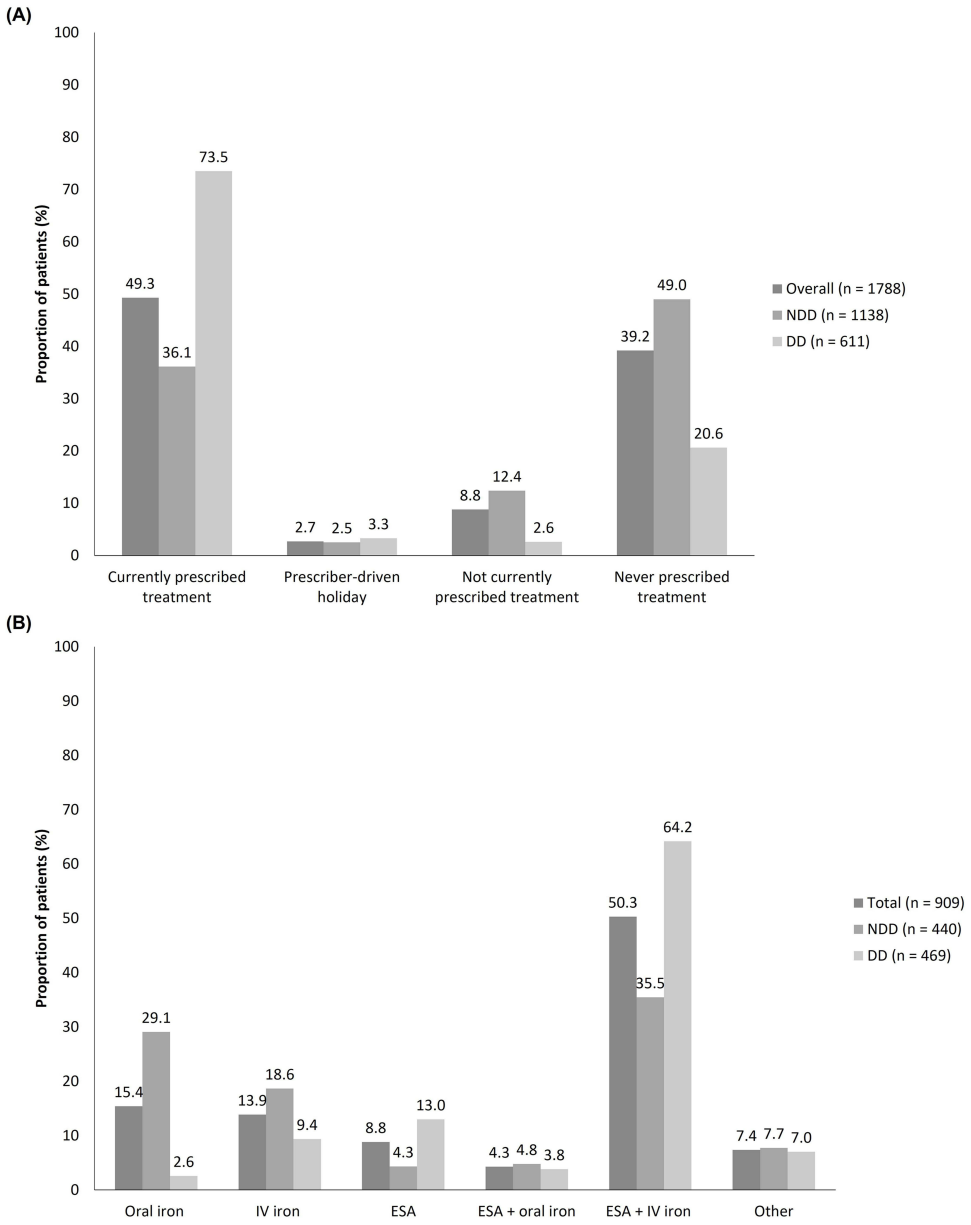

Figure 1 (**A**) Patient treatment status and **(B)** prescribed treatments* at data extraction.
Notes: *Includes patients on a prescriber-driven holiday. Patients are grouped by dialysis status at data extraction. "Currently" refers to treatment status at data extraction.
Abbreviations: DD, dialysis-dependent; ESA, erythropoietin-stimulating agent; IV, intravenous; NDD, non-dialysis-dependent.

positive association with Hb, ferritin, and TSAT test levels (Figure 2A). ESA + IV iron was also found to have a positive association with Hb and ferritin levels but was not an important predictor of TSAT levels. ESA monotherapy was found to have a negative association with Hb and TSAT levels but to have a large positive association with ferritin levels.

Hb, Ferritin, and TSAT Test Levels for Diagnosis and Treatment Initiation

Median patient Hb levels at data extraction are shown in Figure 3. Overall, median Hb levels were largely consistent within each of the populations, with a median of 11–12 g/dL in NDD and 10–11 g/dL in DD patients, except for a small number of patients treated with an ESA + oral iron, who had median Hb levels slightly above 12 g/dL. Most patients had Hb levels between 10 and 13 g/dL (Figure 4).

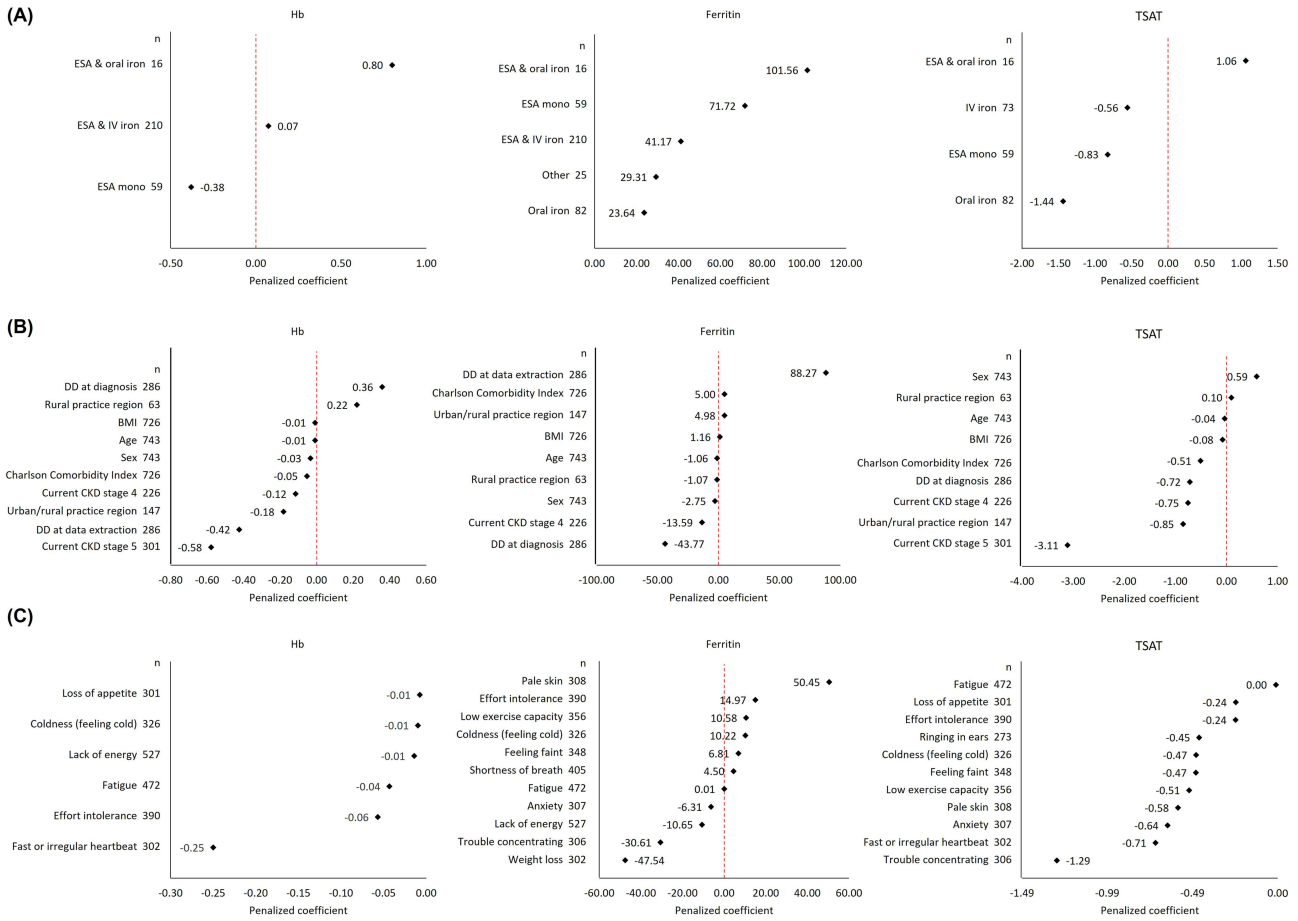

Figure 2 Elastic net regression analysis of patients with a completed PSC showing the impact of (**A**) treatments, (**B**) clinical characteristics, and (**C**) symptoms on Hb, ferritin, and TSAT test levels.
Notes: Data shown are for patients who completed the PSC and were receiving treatment or on a treatment holiday (n = 743). Covariates on the Y-axis were chosen by the elastic net model as important predictors of the most recent Hb/ferritin/TSAT level. Data were based on outcomes at the time of data extraction.
Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; IV, intravenous; PSC, patient self-completion survey; TSAT, transferrin saturation.

There was a disagreement between the thresholds that physicians stated should be used to diagnose anemia or to initiate treatment and the actual reported test levels from medical records (Figure 5). The median Hb thresholds physicians reported using for diagnosing anemia of CKD and initiating treatment were <11.0 g/dL and <10.5 g/dL, respectively, for NDD patients and <10.0 g/dL and <9.3 g/dL, respectively, for DD patients. However, the actual observed test levels at diagnosis and treatment initiation were below these levels for both NDD and DD patients

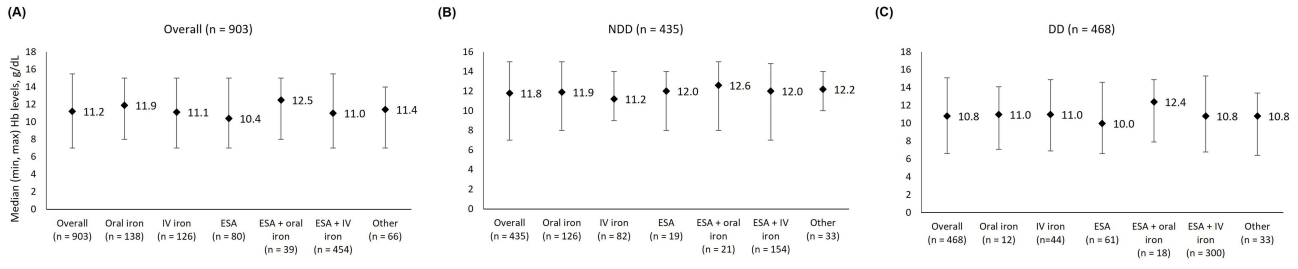

Figure 3 Patient Hb test levels at data extraction by treatment type in (**A**) overall, (**B**) NDD, and (**C**) DD patient populations.
Notes: Error bars show minimum/maximum scores.
Abbreviations: DD, dialysis-dependent; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; IV, intravenous; NDD, non-dialysis-dependent.

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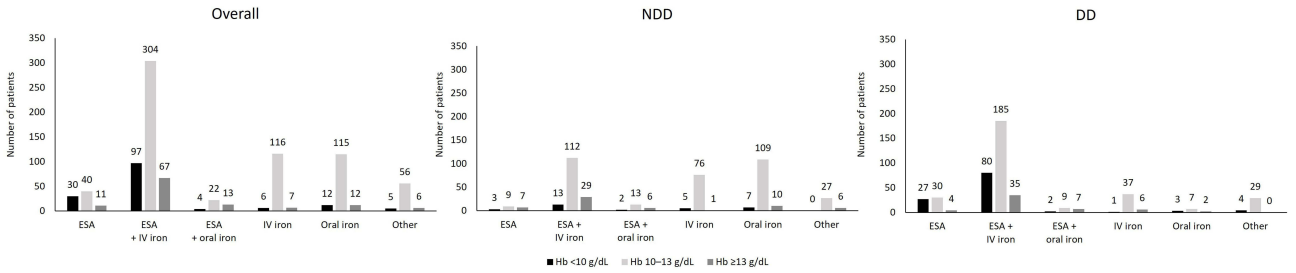

Figure 4 Proportion of patients in Hb level categories at data extraction.
Notes: Dialysis status shown at the time of data extraction. Dialysis status at data extraction is missing for n = 7, n = 10, and n = 3 patients in the Hb <10 g/dL, Hb 10–13 g/dL, and Hb ≥13 g/dL groups, respectively.
Abbreviations: DD, dialysis-dependent; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; IV, intravenous; NDD, non-dialysis-dependent.

(Figure 5A). A similar pattern was observed for TSAT levels: physicians reported a median threshold of <20% saturation for both diagnosis and initiation of treatment for both NDD and DD patients, but the actual observed levels at treatment initiation and diagnosis were below this in DD patients. Conversely, ferritin test levels used for diagnosis and treatment initiation were higher than actual values (Figure 5B and C).

Being on dialysis at diagnosis had a moderate positive association with Hb and a negative association with ferritin levels (Figure 2B). Conversely, patients being DD at data extraction had a strong positive association with ferritin levels. CKD stage 5 was also found to have a negative association with Hb and TSAT levels (Figure 2B).

Symptoms

At diagnosis, the most commonly reported symptom was a lack of energy, with 394/521 (75.6%) treated patients and 133/222 (59.9%) non-treated patients reporting they had this symptom (compared with physicians reporting this symptom in 257/521 [49.3%] and 108/222 [48.6%] of their treated and non-treated patients, respectively; Figure 6A).

There were noticeable differences in the patient and physician perspectives on the prevalence of symptoms, with patients being much more likely to report most symptoms. Treated patients typically reported a much greater prevalence of symptoms compared with non-treated patients. Conversely, the differences in the proportion of treated vs non-treated patients presenting with symptoms were smaller among physician-reported data. Physicians reported a higher prevalence of some symptoms, such as trouble concentrating and loss of appetite, in non-treated patients than treated patients. Overall, the symptom for which patients and physicians had the highest level of agreement was a sense of coldness (kappa = 0.390, SD: 0.606, $p < 0.001$), and the symptom for which they had the lowest level of agreement was weight loss (kappa = 0.140, SD: 0.530, $p < 0.001$) (Table 2).

There were also differences in the proportion of patients reporting symptoms when comparing patients of different dialysis status, with NDD patients (Figure 6B) being more likely to report symptoms than DD patients (Figure 6C). Treated DD patients were more likely to be reported by physicians as having symptoms than treated NDD patients.

Greater agreement was seen in physician and patient symptom reporting with DD patients than for NDD patients, with the mean kappa scores for each individual symptom being higher for DD than NDD patients. In particular, there was very low agreement between physician and NDD patient reporting for the presence of tinnitus (kappa = 0.080, SD: 0.431, $p < 0.001$) and weight loss (kappa = 0.082, SD: 0.360, $p < 0.001$).

Results from the elastic net regression showed that symptoms of loss of appetite, sense of coldness, lack of energy, fatigue, effort intolerance, and heart palpitations were all negatively associated with Hb levels (Figure 2C). Ferritin levels had a negative association with weight loss, trouble concentrating, lack of energy, and anxiety, while all symptoms except fatigue had a negative association with TSAT levels (Figure 2C).

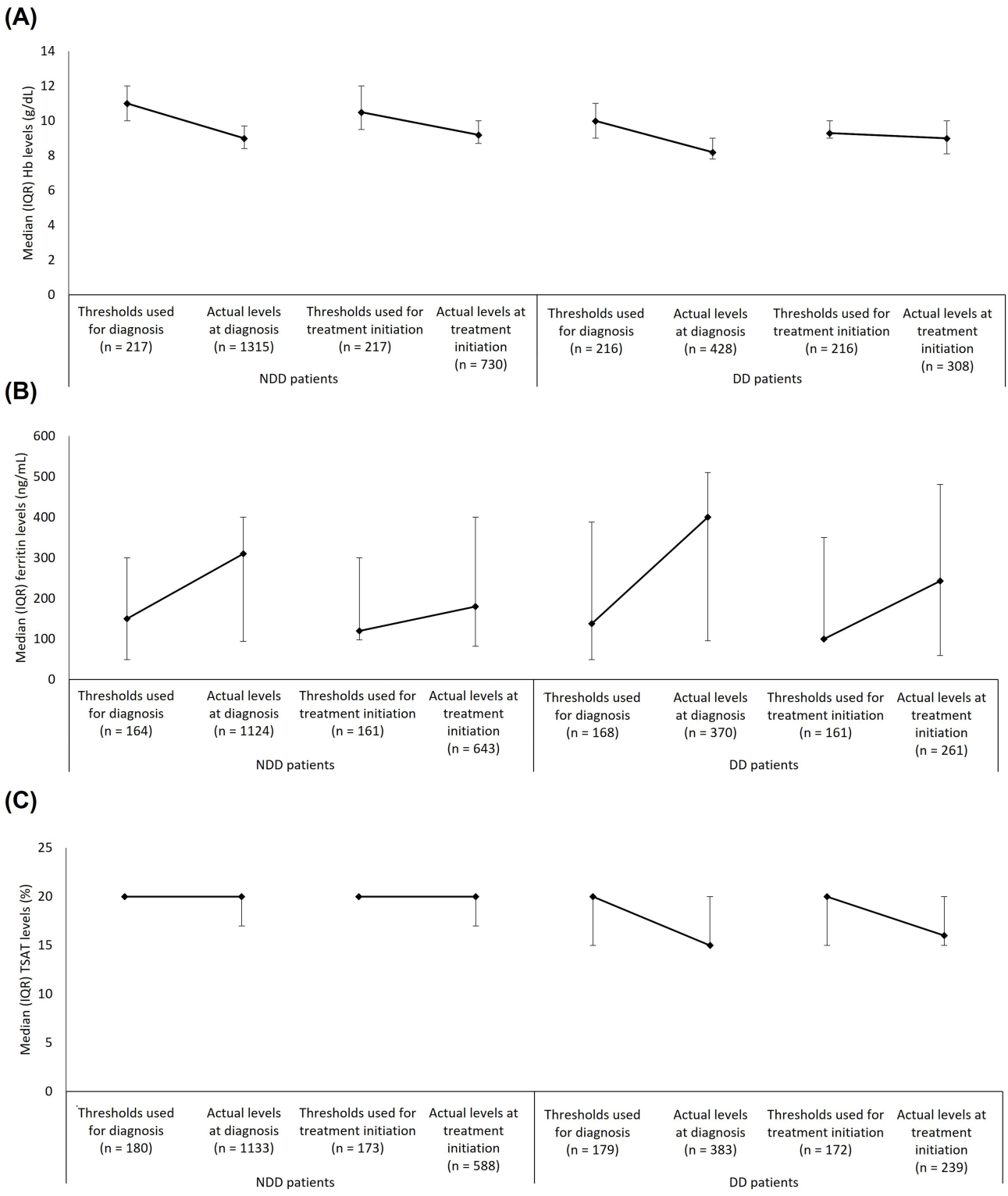

Figure 5 (**A**) Hb, (**B**) ferritin, and (**C**) TSAT test levels physicians reported using for anemia of CKD diagnosis and treatment initiation, and actual patient test levels upon anemia of CKD diagnosis and treatment initiation.

Notes: Error bars show interquartile range.

Abbreviations: CKD, chronic kidney disease; DD, dialysis-dependent; Hb, hemoglobin; IQR, interquartile range; NDD, non-dialysis-dependent; TSAT, transferrin saturation.

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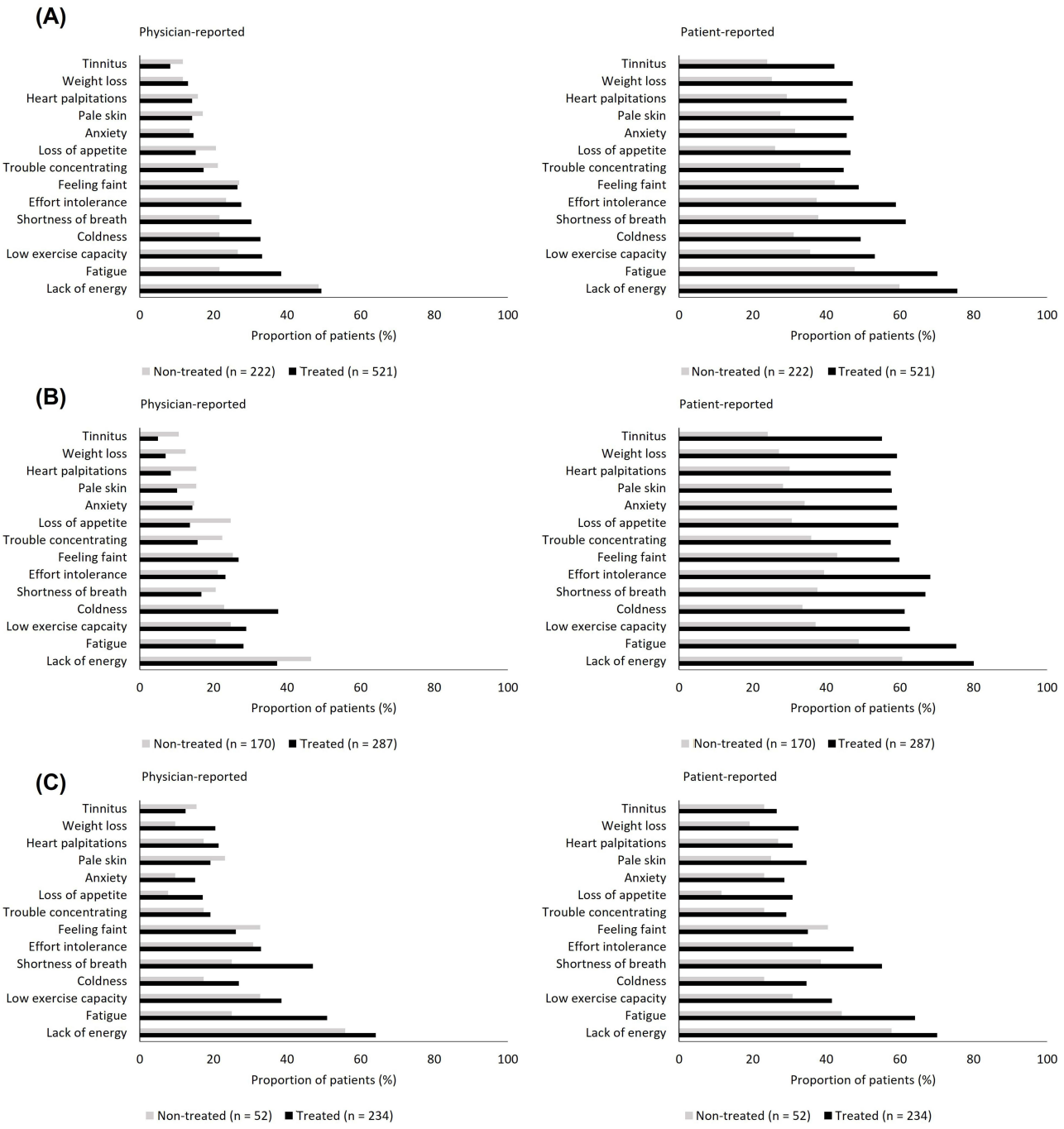

Figure 6 Proportion of patients affected by different symptoms as reported by physicians, or as self-reported by patients, by treatment status (**A**) overall, (**B**) for NDD patients, and (**C**) for DD patients.
Notes: Data collected from n = 217 physicians and n = 743 patients who completed PSC with dialysis status at data extraction.
Abbreviations: DD, dialysis-dependent; NDD, non-dialysis-dependent; PSC, patient self-completed survey.

Discussion

Results of the SATISFY survey revealed substantial treatment inertia in the Middle East, South Africa, and Türkiye, with almost 40% of patients not receiving treatment for their anemia of CKD, despite high reported symptom burden. These findings align with previous reports from other regions, which also demonstrated substantial treatment inertia in patients with anemia.[10,11]

Table 2 Kappa Statistics Showing Symptom Burden Agreement Between Physicians and Patients by Dialysis Status

	Overall			NDD			DD		
	N	Kappa	SD	N	Kappa	SD	N	Kappa	SD
Sense of coldness	732	0.390	0.606	450	0.312	0.554	282	0.562	0.697
Low exercise capacity	735	0.386	0.721	454	0.325	0.665	281	0.506	0.763
Trouble concentrating	739	0.358	0.712	454	0.274	0.646	285	0.536	0.800
Feeling faint	739	0.341	0.612	455	0.254	0.523	284	0.534	0.735
Lack of energy	730	0.326	0.597	455	0.224	0.514	275	0.525	0.673
Effort intolerance	738	0.303	0.652	455	0.230	0.582	283	0.438	0.728
Fatigue	729	0.298	0.613	451	0.190	0.525	278	0.471	0.692
Shortness of breath	724	0.295	0.608	450	0.189	0.496	274	0.475	0.700
Pale skin	738	0.244	0.611	452	0.165	0.523	286	0.438	0.742
Heart palpitations	739	0.211	0.598	456	0.120	0.476	283	0.409	0.739
Anxiety	730	0.192	0.527	451	0.151	0.444	279	0.299	0.683
Loss of appetite	735	0.165	0.529	456	0.143	0.453	279	0.220	0.673
Tinnitus	742	0.163	0.542	456	0.080	0.431	286	0.389	0.715
Weight loss	738	0.140	0.530	455	0.082	0.360	283	0.329	0.749

Notes: All p values <0.001. Higher kappa scores indicate greater levels of agreement between patient self-reported symptoms and medical chart abstracted symptoms, eg kappa scores of 0.8–1.0 indicate almost perfect agreement, while kappa scores of 0.0–0.2 indicate very little agreement.
Abbreviations: DD, dialysis-dependent; NDD, non-dialysis-dependent; SD, standard deviation.

Results also revealed that, while physician-reported thresholds for anemia treatment initiation were consistent with guidelines,[18] patients' actual Hb levels at the time of treatment initiation were generally lower than guideline-recommended targets,[18] further suggesting inertia in initiating anemia of CKD treatment. This effect was less pronounced in the DD population, suggesting that this may, in part, be a consequence of how frequently patients interact with their physicians, with more frequent visits allowing physicians to make interventions more quickly. As such, approaches to reducing treatment inertia may focus on increasing and improving patient–physician interactions.

Treatment Regimens and Treatment Impact

The most commonly prescribed treatment was a combination of IV iron and ESA therapy, regardless of dialysis status, and elastic net regression analysis highlighted the positive association of this ESA + IV iron treatment with Hb and ferritin levels. Particularly for DD patients, guidelines typically suggest IV iron over oral iron, although they note that this choice should be individualized based on factors such as the severity of iron deficiency and availability of venous access,[18,20] as IV has been shown to have greater efficacy than oral iron.[34] Of note, in the present study, elastic net regression analysis also showed a high positive association between ESA in combination with oral iron and Hb, ferritin, and TSAT test levels, although few patients (4.3%) were receiving this treatment regimen, and they represented a small proportion of those included in the study.

Notably, of patients receiving treatment, 8.8% received ESA monotherapy, which had a large negative association with Hb levels, likely the result of erythropoiesis further depleting existing iron stores. Indeed, guidelines typically recommend concomitant iron treatment to ensure adequate iron stores and optimize ESA response.[20] However, a careful balance is required to ensure optimal iron and ESA dose. High ESA dose is associated with increased risk of myocardial infarction, heart failure, stroke, and death.[29–31] However, while high IV iron doses have been shown to reduce required

doses of ESA in patients with anemia of CKD undergoing hemodialysis,[35] high dose IV iron therapy can potentially cause increased risk of atherothrombosis, vascular calcification, oxidative stress, and infection.[36] Consequently, high iron doses are not a suitable way of maintaining lower doses of ESA, with guidelines recommending that serum ferritin levels not exceed 800 ng/mL and ESAs sufficient to control anemia while maintaining a Hb level of <12 g/dL.[18,20] It is, therefore, interesting to note that the 97 patients within this study who had received ESA + IV iron therapy had Hb levels of <10 g/dL, which could suggest either suboptimal iron supplementation or ESA hyporesponsiveness.

Symptom Burden

As noted previously, patients generally reported a high symptom burden, with the most commonly reported symptom being lack of energy, and other highly reported symptoms being closely related (ie fatigue, shortness of breath, effort intolerance, and low exercise capacity). These findings are similar to the symptoms observed in a study of North American patients and highlight the substantial symptom burden for patients with anemia of CKD.[8,9] The symptoms with greatest agreement between patients and physicians were a sense of coldness, low exercise capacity, trouble concentrating, feeling faint, lack of energy, effort intolerance, fatigue, and shortness of breath. However, the highest level of agreement was only 56% in DD patients and 32% in NDD patients, highlighting a disparity between physician and patient perceptions of symptom burden, particularly for NDD patients.

Based on the elastic net regression analysis, the symptom most negatively associated with Hb levels was "a fast or irregular heartbeat", while "loss of appetite", "coldness", and "lack of energy" showed weaker associations. The symptom with the most negative association with ferritin and TSAT test levels was "trouble concentrating". This is consistent with previous research showing an association between serum ferritin and TSAT with cognitive functioning in children[37,38] and patients with Alzheimer's disease.[39] Given the real-world design of this study, any links between symptoms and anemia should be interpreted with caution. However, these findings offer valuable insights for future research.

Interestingly, the symptom with the highest level of disagreement between patients and physicians was weight loss, a symptom that can be objectively measured, highlighting that there may be a psychological or psychosomatic component in a patient's perspective of their own symptoms or a potential for question priming, as patients were also asked to report "loss of appetite", which was another prevalent symptom. A patient experiencing this symptom may assume that they are losing weight as they are eating less, without considering that they may also have reduced physical activity. A large degree of symptom overlap may also make it challenging to differentiate symptoms, particularly for patients with more severe CKD, and may also help to explain the disagreement between physicians and patients.

The observed disagreement between physician and patient perspectives was larger in NDD patients than DD patients. This may be explained by DD patients having more frequent consultations with their physician, providing a greater opportunity for symptoms to be discussed.[40] Similarly, we observed that a greater proportion of treated patients self-reported symptoms than non-treated patients. One explanation for this could be that the most heavily impacted patients, or those who were more likely to discuss their symptoms with their physicians, were more likely to be offered treatments. Physicians also tended to report a higher frequency of symptoms in treated patients, yet there were notable exceptions, such as trouble concentrating, loss of appetite, and tinnitus, where physicians reported a higher prevalence of symptoms in non-treated patients.

As many of the most prominent symptoms for patients with anemia of CKD are subjective, strong communication between physicians and patients is essential for physicians to be able to comprehend a patient's symptom burden, which highlights the importance of a holistic approach in the treatment of anemia of CKD. A recent survey study conducted in Japan found that the preference for management of anemia of CKD varied between patients and physicians, and patient involvement may help optimize outcomes.[41] Over 50% of physicians rated "anemia diagnosis not affecting a patient's QoL" and "anemia diagnosis not affecting the patient's health" as very important reasons for not initiating anemia treatment, while the reason most commonly provided by patients for not receiving treatment was less severe symptoms. When considered in combination with the finding that there was a large patient-reported symptom burden and often poor agreement between patients' and physicians' perceptions of symptoms, these results highlight that the observed disagreement in patient and physician perspectives can impact optimal care. Improved patient-reported outcome instruments[7] designed to better capture symptoms may help to reduce this disagreement between physician and patient perspectives. Exploring avenues to enhance the patient's

voice in their treatment decisions in general should be a target for improving the quality of care patients receive. A large proportion of patients reported being uninformed about available treatments for their anemia of CKD,[42] suggesting improvements in facilitating such patient–physician discussions are needed.

Strengths and Limitations

SATISFY collected real-world data from a population of physicians and patients in countries where there is a paucity of data on patient characteristics and treatment patterns for anemia of CKD.

There are a number of limitations of the present study. Participating patients may not reflect the general anemia of the CKD population since the studied population only includes patients who are consulting with their physicians. To minimize selection bias, physicians were asked to provide data for a consecutive series of eligible patients. This means that patients who consult more frequently may have a higher likelihood of being included. The population is based on a pseudo-random sample of physicians or patients. While minimal inclusion criteria governed the selection of participating physicians, participation was influenced by their willingness to complete the survey.

Patient eligibility was based on the judgment of the respondent physician and not on a formalized diagnostic checklist; however, it is representative of the physician's real-world classification of their patients. Recall bias and missing data might also have affected responses; however, physicians were able to refer to patient records while completing the physician survey, thus minimizing the possibility of recall bias. Furthermore, data were collected at the time of each patient's appointment to reduce the likelihood of recall bias where the opinion of the physician was required. Also, the point-in-time design of this survey prevented any conclusions about causal relationships.

Data on outcomes of interest, such as patient adherence to prescribed medication, were not available, limiting the interpretation of these findings. Data on a patient's income status was not collected so the impact of a patient's socioeconomic status on different endpoints was not able to be evaluated.

No formal sample size calculations or hypothesis testing was used. As such, any differences may not be statistically or clinically meaningful. Data derived from small sample sizes should be interpreted with caution. Variations in both population sample sizes and population heterogeneity may have impacted results. A recent meta-analysis has shown that statistical heterogeneity can be noted in observational studies of patients with anemia of CKD.[43] Additionally, in a recent review paper, the treatment of anemia in CKD is shown to be complicated by challenging patient phenotypes, particularly among those who are hyporesponsive to ESAs or have common comorbidities, which pose unique challenges to the current standard of care.[44] Future work is necessary to explore how different patient subgroups may have different clinical characteristics and treatment responses.

Despite such limitations, real-world studies play an important part in highlighting areas of concern that are not addressed in clinical trials, which only include patients representing a specific proportion of the consulting patient population as a result of age restrictions and the requirement to meet stringent eligibility criteria. Data from real-world studies can complement clinical trials and provide insight into the effectiveness of interventions in patients commonly cared for in routine clinical practice.

Conclusions

This study provides a comprehensive exploration of the real-world management of patients with anemia of CKD living in the Middle East, South Africa, and Türkiye. The symptom burden in anemia of CKD patients is high, and there is disagreement between physician and patient perspectives on symptomology. Furthermore, treatment inertia is apparent, with a large proportion of anemia of CKD patients remaining untreated or having their treatment delayed for long periods after anemia of CKD diagnosis, despite the high symptom burden. Improved awareness of the discrepancy between patient and physician perceptions of disease burden is needed to facilitate physician–patient dialogue to help improve physicians' understanding of patients' symptom burden.

Data Sharing Statement

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

Acknowledgments

Medical writing support was provided by Patrick Callaghan, MSc, and Hannah Brown, PhD, of Lumanity.

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This study was sponsored by Astellas Pharma Singapore Pte. Ltd. Medical writing support was provided by Patrick Callaghan, MSc, and Hannah Brown, PhD, of Lumanity, funded by Astellas Pharma, Inc.

Disclosure

MA has received payment or honoraria for lectures, presentations, or speaker's bureaus from Amgen, Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Menarini, MSD, Novo Nordisk, Recordati, and Sanofi, and travel support from AstraZeneca and Astellas Pharma. SMGA-G has received speaker's honoraria from AbbVie, AstraZeneca, and Vifor Pharma. AGA has received honoraria from Astellas Pharma as a speaker and advisor. AFE-K has received payment or honoraria for lectures, presentations, or speaker's bureaus from Astellas Pharma and Roche, and travel support from Roche. AM and LJC are employees of Adelphi Group, contracted by Astellas Pharma to conduct the study. BS and EPL are former employees of Astellas Pharma Singapore Pte. Ltd. MB is an employee of Astellas Pharma Europe Ltd. DBN is an employee of Astellas Pharma Singapore Pte. Ltd. This study was sponsored by Astellas Pharma Singapore Pte. Ltd.

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