

Early Intravenous Iron Sucrose Supplementation for Absolute Iron Deficiency in Acute Heart Failure in the Emergency Department: A Single-Center Randomized Pilot Study

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Abstract

Introduction: Iron deficiency is common in heart failure and is associated with impaired functional capacity and adverse outcomes independently of anemia. Evidence remains limited for intravenous iron initiated directly from the emergency department (ED), particularly iron sucrose. This pilot study evaluated the feasibility, safety, and short-term outcomes of a single early dose of intravenous iron sucrose added to oral iron in stabilized ED patients with acute heart failure and absolute iron deficiency.

Methods: We conducted a prospective, randomized, open-label, pilot study in the Tunisia ED from August 2017 to June 2018. After stabilization, adults with acute heart failure and absolute iron deficiency (ferritin <100 µg/L) were randomized to intravenous iron sucrose plus three months of oral iron or oral iron alone. Primary outcomes were three-month changes in 6MWT distance and iron-deficiency correction; secondary outcomes included functional status, fatigue, healthcare use, length of stay, and exploratory mortality.

Results: Among 510 screened patients, 114 were included (60 IV-plus-oral; 54 oral-only). Mean age was 66 ± 7 years and sex ratio was 1.33. No in-hospital death, shock, cardiac arrest, invasive mechanical ventilation, infusion-related allergic reaction, or anaphylaxis was documented. At three months, mean 6MWT distance increased more in the IV-plus-oral group than in the oral-only group (+43 m vs +11 m; p=0.010). Any increase from baseline occurred in 46/57 (80.7%) versus 17/45 (37.8%), respectively (OR 6.89, 95% CI 2.82–16.81; p<0.001). Correction of absolute iron deficiency occurred in 37/57 (64.9%) versus 23/45 (51.1%; p=0.160). NYHA class, ED revisits, and rehospitalization did not differ significantly. Three-month mortality was 3/60 (5.0%) versus 9/54 (16.7%); this exploratory difference was not statistically significant (OR 0.26, 95% CI 0.07–1.03; p=0.065).

Conclusion: This pilot study suggests that administering a single 200 mg dose of intravenous iron sucrose after clinical stabilization and before ED discharge is feasible, with no documented serious infusion-related hypersensitivity reactions. The observed difference in 6MWT improvement should be interpreted cautiously given the small sample, open-label design, and absence of significant differences in iron-deficiency correction or clinical outcomes. These findings are hypothesis-generating and warrant confirmation in larger, methodologically robust trials

Keywords: Acute Heart Failure; Iron Deficiency; Intravenous Iron; Emergency Department; Six-Minute Walk Test.

INTRODUCTION

Heart failure is a clinical syndrome caused by a structural or functional cardiac abnormality and remains a major cause of ED visits, hospitalization, impaired quality of life, and mortality (1). Iron deficiency is frequent in heart failure and is associated with reduced exercise capacity and poorer outcomes independently of anemia (2).

Randomized evidence has focused mainly on ferric carboxymaltose or ferric derisomaltose. FAIR-HF demonstrated symptomatic and functional improvement with ferric carboxymaltose (3), whereas FERRIC-HF is directly relevant because it evaluated iron sucrose (4). AFFIRM-AHF subsequently assessed ferric carboxymaltose after acute heart failure hospitalization (5). Current ESC guidance supports ferric carboxymaltose or ferric derisomaltose in selected symptomatic patients with HFrEF or HFmrEF and iron deficiency (6).

Evidence remains limited for iron-deficiency screening and intravenous treatment initiated directly within an ED pathway, which requires rapid eligibility assessment, confirmation of stability, monitored infusion, and an actionable transition plan. Conducted in 2017–2018, before contemporary guidance, this study the feasibility, safety, and short-term outcomes of administering a single intravenous dose after stabilization in ED patients with acute heart failure and absolute iron deficiency.

METHODS

Study design and setting

This prospective, randomized, open-label, single-center pilot study was conducted in a university-affiliated ED from August 2017 to June 2018. The manuscript was prepared several years later from the original thesis and archived dataset, limiting the recovery of some methodological details.

Study population and eligibility criteria

Eligible participants had to meet all of the following criteria: age >18 years; de novo left-sided or global acute heart failure or acute decompensation of chronic heart failure; clinical stabilization after initial ED treatment; absolute iron deficiency defined as ferritin <100 µg/L measured before discharge; ability to complete a baseline 6MWT; and written informed consent. Eligibility was irrespective of anemia or left ventricular ejection fraction (LVEF). Acute heart failure diagnosis followed the 2016 ESC guidance applicable during enrollment and required acute or worsening compatible symptoms or signs supported by radiographic and/or echocardiographic evidence of pulmonary or systemic congestion. BNP and NT-proBNP were not systematically measured. Patients were excluded if they had gastrointestinal bleeding, known malabsorption, iron supplementation or blood transfusion within the preceding four weeks, active infection, hepatic or hematological disease, acute COPD exacerbation, acute coronary syndrome, shock, known iron sucrose allergy, persistent clinical instability, or inability to complete the baseline 6MWT.

Sample size and allocation

No formal sample-size calculation was performed because this was a pilot study, and the sample size was determined by recruitment feasibility during the study period. According to the archived study materials, treatment allocation was performed after clinical stabilization and written consent using a die-based procedure described as block allocation, with each die face corresponding to a prespecified allocation block. However, the block structure, sequence implementation, and allocation-concealment procedures could not be fully reconstructed.

Analysis population and missing data

Follow-up analyses were based on participants with available outcome data. The archived

records did not allow the timing of all exclusions relative to allocation or their treatment-group distribution to be reconstructed; therefore, a strict intention-to-treat analysis could not be performed. All follow-up analyses were consequently considered complete-case and exploratory, with potential selection and attrition bias.

Eligibility sequence, interventions, and blinding

Operational screening proceeded sequentially from confirmation and initial treatment of acute heart failure to clinical stabilization, ferritin measurement before discharge, baseline 6MWT, written consent, and randomization. Ferritin was measured by chemiluminescent microparticle immunoassay using an ARCHITECT ci8200 Abbott analyzer. Transferrin saturation was unavailable. Anemia was defined as hemoglobin <13 g/dL in men and <12 g/dL in non-pregnant women (7).

The IV-plus-oral group received a single 200 mg dose of intravenous iron sucrose (two Venofer ampoules diluted in 250 mL of 5% glucose and infused over 20 minutes through a peripheral line), followed by oral elemental iron 100 mg/day for three months. The oral-only group received oral elemental iron 100 mg/day for three months without intravenous loading.

The fixed dose was a pragmatic early-loading strategy based on the locally available formulation and ED workflow; it was not intended to replace individualized correction of the total iron deficit. Both groups received oral iron because it represented the locally used maintenance strategy at the time, so the comparison estimates the incremental effect of early intravenous loading. No placebo infusion was used; participants and treating staff were not blinded, although staff administering the infusion did not assess outcomes.

Follow-up and outcomes

The baseline 6MWT was performed after clinical stabilization and before discharge. At three months, it was repeated by the same

physician under the same local protocol. Corridor length, encouragement wording, stopping criteria, and test–retest reproducibility were not retained. Oral-iron adherence was assessed by interview without a validated scale or pill count. Infusion allergy and anaphylaxis were recorded clinically, but a standardized adverse-event grading system, observation duration, and complete capture of minor events could not be recovered.

The co-primary outcomes at three months were change in 6MWT distance and ferritin-defined correction of absolute iron deficiency (ferritin ≥ 100 $\mu\text{g/L}$). A post hoc sensitivity analysis defined a 6MWT responder as a participant with an improvement ≥ 30 m.

Secondary outcomes included changes in Self-Assigned NYHA class and fatigue category, ED revisits for acute heart failure, rehospitalization, and length of stay. Improvement, stability, and worsening denoted a lower, unchanged, or higher follow-up category, respectively. The original fatigue instrument and its category anchors were not recoverable. Ferritin and hemoglobin changes were summarized continuously. Mortality and the post hoc composite of all-cause death or heart failure rehospitalization were exploratory.

Statistical analysis

Between-group comparisons used Welch's t test for continuous variables and Pearson's chi-square or two-sided Fisher's exact test for categorical variables, as appropriate. Odds ratios with 95% confidence intervals were calculated using the log-Wald method. Results are presented as mean $\pm$ SD, median, or n (%). Analyses were based on available cases, all tests were two-sided, and $p < 0.05$ was considered significant.

The ≥ 30 m responder and death-or-rehospitalization analyses were post hoc and unadjusted for multiplicity. No multivariable analysis was performed because of the small pilot sample and limited event counts; residual

confounding from baseline imbalances therefore cannot be excluded.

Ethical considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants and documented using a consent form. Participant data were anonymized, and medical confidentiality was maintained.

RESULTS

Study population

Of 510 patients screened, 194 initially met the eligibility criteria. Of these, 80 were not retained in the final analytic cohort: 14 did not attend the three-month follow-up, 18 did not adhere to the prescribed treatment, and 48 had protocol violations. The final analytic cohort therefore comprised 114 participants: 60 in the IV-plus-oral group and 54 in the oral-only group (Figure 1).

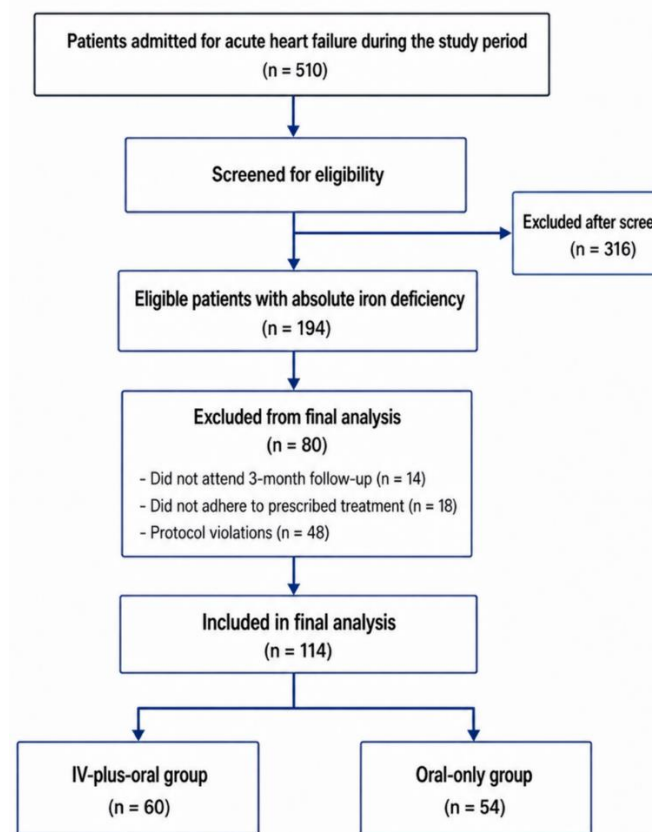


Figure 1. Study flow diagram

At three months, paired functional and biological measurements were available for 102 participants (57 IV-plus-oral and 45 oral-only). Mortality, ED revisits, heart failure rehospitalization, and the death-or-rehospitalization composite were analyzed using the full analytic-cohort denominators of 60 and 54 participants. Functional, biological, NYHA, and fatigue outcomes were analyzed as complete cases using the 57 and 45 participants with available follow-up measurements.

Baseline characteristics and clinical course

Mean age was 66 ± 7 years, and sex ratio was 1.33. Hypertension and coronary artery disease were more frequent in the IV-plus-oral group, whereas atrial fibrillation and COPD were more frequent in the oral-only group (Table 1).

During the index episode, orthopnea was more frequent in the IV-plus-oral group (42/60 (70.0%) vs 27/54 (50.0%); $p=0.029$). Respiratory distress occurred in 12/60 (20.0%) versus 6/54 (11.1%; $p=0.194$), room-air oxygen saturation $<90\%$ in 15/60 (25.0%) versus 5/54 (9.3%; $p=0.027$), and non-invasive ventilation in 23/60 (38.3%) versus 14/54 (25.9%; $p=0.158$). No participant had systolic blood pressure <90 mmHg or required invasive mechanical ventilation; vasopressor exposure was not recorded separately.

Mean ED/hospital stay was 42.1 ± 16 versus 41 ± 22 hours. No in-hospital death, shock, cardiac arrest, documented infusion-related allergic reaction, or anaphylaxis occurred; minor adverse events were not systematically captured. Selected discharge treatments were broadly similar: beta-blocker 53/60 (88.3%) versus 41/54 (75.9%), loop diuretic 60/60 (100%) versus 52/54 (96.3%), angiotensin-converting enzyme inhibitor 52/60 (86.7%) versus 47/54 (87.0%), spironolactone 14/60 (23.3%) versus 12/54 (22.2%), and statin 57/60 (95.0%) versus 52/54 (96.3%). Doses and subsequent treatment changes were unavailable.

Table 1. Baseline characteristics by treatment group

Characteristic	IV-plus-oral group (n=60)	Oral-only group (n=54)	p value
Age, years	65 ± 7	67 ± 8	0.208
Male sex	34 (56.7)	31 (57.4)	0.936
Previously known heart failure	31 (51.7)	28 (51.9)	0.984
Hypertension	47 (78.3)	31 (57.4)	0.016
Diabetes mellitus	29 (48.3)	20 (37.0)	0.224
Coronary artery disease	21 (35.0)	10 (18.5)	0.048
Atrial fibrillation	8 (13.3)	20 (37.0)	0.003
COPD	3 (5.0)	15 (27.8)	0.001
Anemia	40 (66.7)	39 (72.2)	0.521
Hemoglobin, g/dL	11.4 ± 1.8	11.6 ± 1.8	0.569
Serum ferritin, µg/L	52.0 ± 25.0	51.5 ± 23.7	0.914
Creatinine clearance <60 mL/min	18 (30.0)	15 (27.8)	0.794
LVEF, %*	50.2 ± 11.5	47.6 ± 12.0	0.460

Values are mean ± SD or n (%), as appropriate. *LVEF was available for 47 participants: 25 in the IV-plus-oral group and 22 in the oral-only group.

Abbreviations: COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; SD, standard deviation.

Co-primary outcomes

Among participants with paired measurements, mean 6MWT distance increased from 298.6 to 342.4 m in the IV-plus-oral group and from 320.2 to 332.0 m in the oral-only group (Figure 2). Mean change was +43.8 versus +11.8 m, giving an unadjusted between-group mean difference of 32.0 m (95% CI 8.2–55.8; $p=0.009$). Any increase occurred in 46/57 (80.7%) versus 17/45 (37.8%; OR 6.89, 95% CI 2.82–16.81; $p<0.001$).

Ferritin-defined correction occurred in 37/57 (64.9%) versus 23/45 (51.1%; OR 1.77, 95% CI 0.80–3.93; $p=0.160$). Mean ferritin and hemoglobin changes are reported in Table 2, where the biological co-primary outcome is repeated for completeness.

In the post hoc sensitivity analysis, a ≥ 30 m improvement occurred in 35/57 (61.4%) versus

13/45 (28.9%; OR 3.92, 95% CI 1.70–9.04; $p=0.001$).

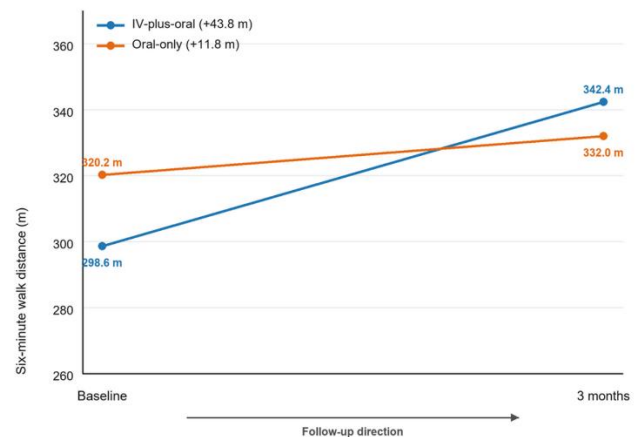


Figure 2. Progression of mean six-minute walk test distance from baseline to three months.

Mean distance increased from 298.6 to 342.4 m and from 320.2 to 332.0 m, respectively; mean changes were +43.8 and +11.8 m (Welch $p=0.009$). Lines show group means, not individual trajectories.

Secondary and exploratory outcomes

NYHA class, fatigue improvement, ED revisits, and rehospitalization did not differ significantly. Fatigue worsening was less frequent in the IV-plus-oral group (14.0% vs 33.3%; $p=0.021$), but this isolated secondary comparison was not adjusted for multiplicity. Three-month mortality was 3/60 (5.0%) versus 9/54 (16.7%; OR 0.26, 95% CI 0.07–1.03; $p=0.065$). The post hoc death-or-heart-failure-rehospitalization composite occurred in 13/60 (21.7%) versus 19/54 (35.2%; OR 0.51, 95% CI 0.22–1.17; $p=0.109$). Remaining outcomes are summarized in Table 2.

DISCUSSION

The strengths of this study include its prospective randomized design, pragmatic ED-based pathway, and assessment of functional, biological, and clinical outcomes. The main finding was a greater improvement in 6MWT distance with IV-plus-oral therapy (+43.8 m vs

+11.8 m), consistent with the functional signal previously reported with iron sucrose in FERRIC-HF (4). Similar functional benefits have been reported with ferric carboxymaltose in FAIR-HF (3) and CONFIRM-HF (8). However, these trials predominantly included stable patients with reduced LVEF and used substantially higher cumulative iron doses, limiting direct comparison with our acute heart failure population and single 200 mg iron sucrose dose.

The post hoc ≥ 30 m responder analysis supported the continuous 6MWT result but remains exploratory. Clinically important thresholds range from approximately 14–15 m in iron-deficient HFrEF to approximately 36 m in stable chronic heart failure (9,10). Recovery from acute decompensation, the open-label design, participant motivation, baseline imbalances, and absence of adjusted analysis may also have influenced this effort-dependent outcome.

Iron-deficiency correction was not significantly different between groups, and ferritin and hemoglobin increased in both groups without a clear incremental effect. Oral iron in both groups may have attenuated the treatment contrast, although IRONOUT-HF found limited repletion and no improvement in exercise capacity with oral iron in HFrEF (11). The fixed intravenous dose may also have been insufficient for complete repletion. Furthermore, ferritin is influenced by inflammation, and the absence of transferrin saturation limits interpretation (12).

No significant overall difference was observed in NYHA class, fatigue evolution, ED revisits, rehospitalization, or the post hoc death-or-rehospitalization composite. Although fatigue worsening was less frequent with IV-plus-oral therapy, this was one of several secondary comparisons, the fatigue instrument was incompletely documented, and no multiplicity adjustment was applied. AFFIRM-AHF

reported fewer heart failure hospitalizations after ferric carboxymaltose following acute heart failure (5), while IRONMAN showed a favorable numerical effect with ferric derisomaltose, although its primary analysis did not reach statistical significance (13). HEART-FID did not demonstrate a significant benefit for its hierarchical primary outcome (14), and FAIR-HF2 did not meet its multiplicity-adjusted criteria for its primary outcomes (15).

A 2025 meta-analysis nevertheless suggested that intravenous iron reduces recurrent heart failure hospitalizations, while its independent effect on mortality remains uncertain (16).

Accordingly, the numerically lower mortality observed in our IV-plus-oral group cannot be interpreted as evidence of efficacy.

evidence. EFFECT-HF suggested preservation of exercise capacity with ferric carboxymaltose,

although its open-label design and handling of deaths complicate interpretation (17). FAIR-HFpEF subsequently reported improvement in 6MWT distance, but recruitment stopped after only 39 participants, making this finding hypothesis-generating (18). These results cannot be directly extrapolated to a fixed 200 mg iron sucrose regimen.

The timing of iron assessment may also be relevant during acute heart failure. Iron indices can change between admission, clinical stabilization, and follow-up, with functional iron deficiency sometimes resolving spontaneously whereas absolute deficiency is more likely to persist (19).

Additional studies provide supportive functional Measuring ferritin after stabilization therefore supports the biological rationale of our eligibility pathway, although the absence of transferrin saturation prevented more precise characterization of iron status. Consistently, an individual-patient-data meta-analysis associated ferric carboxymaltose with fewer recurrent cardiovascular and heart failure hospitalizations

Table 2. Three-month co-primary biological, secondary, and exploratory outcomes excluding the six-minute walk test

Outcome	IV-plus-oral group	Oral-only group	p value	Effect estimate [95% CI]
Co-primary biological outcome				
Correction of absolute iron deficiency	37/57 (64.9%)	23/45 (51.1%)	0.160	OR 1.77 [0.80–3.93]
Continuous biological changes				
Change in serum ferritin, µg/L	+73.8 ± 49.3	+61.9 ± 50.5	0.234	MD +11.9 [–7.8 to +31.7]
Change in hemoglobin, g/dL	+0.57 ± 0.49	+0.41 ± 0.62	0.156	MD +0.16 [–0.06 to +0.39]
Self-Assigned NYHA class				
Improvement	8/57 (14.0%)	8/45 (17.8%)	0.606	OR 0.76 [0.26–2.20]
Stability	43/57 (75.4%)	32/45 (71.1%)	0.623	OR 1.25 [0.52–3.02]
Worsening	6/57 (10.5%)	5/45 (11.1%)	1.000	OR 0.94 [0.27–3.31]
Fatigue score				
Improvement	32/57 (56.1%)	21/45 (46.7%)	0.342	OR 1.46 [0.67–3.21]
Stability	17/57 (29.8%)	9/45 (20.0%)	0.258	OR 1.70 [0.67–4.29]
Worsening	8/57 (14.0%)	15/45 (33.3%)	0.021	OR 0.33 [0.12–0.86]
Clinical events				
ED revisit for acute heart failure*	38/60 (63.3%)	34/54 (63.0%)	0.967	OR 1.02 [0.47–2.18]
Rehospitalization for acute heart failure*	12/60 (20.0%)	14/54 (25.9%)	0.451	OR 0.71 [0.30–1.72]
Three-month mortality*	3/60 (5.0%)	9/54 (16.7%)	0.065	OR 0.26 [0.07–1.03]
Death or heart failure rehospitalization*,†	13/60 (21.7%)	19/54 (35.2%)	0.109	OR 0.51 [0.22–1.17]

Values are n/N (%) or mean change ± SD. Continuous comparisons use Welch's t test. Categorical comparisons use Pearson's chi-square test, except sparse tables, for which two-sided Fisher's exact p-values are reported. Effect estimates are unadjusted ORs for categorical outcomes and unadjusted MDs (IV-plus-oral minus oral-only) for continuous outcomes; 95% CIs for ORs use the log-Wald method. For NYHA and fatigue, each OR compares the displayed category with the other categories combined. *Analyzed using the 60 and 54 analytic-cohort denominators; other outcomes use available cases. †Post hoc composite. **Abbreviations:** CI, confidence interval; ED, emergency department; MD, mean difference; NYHA, New York Heart Association; OR, odds ratio; SD, standard deviation.

but no apparent mortality benefit, with greater benefit suggested at lower baseline transferrin saturation (20).

No serious infusion-related hypersensitivity event was documented, supporting the operational feasibility of ED-based screening and infusion. However, the small sample and incomplete adverse-event grading preclude definitive safety conclusions. As this study was

conducted in 2017–2018, its fixed iron sucrose strategy predates current ESC guidance supporting individualized ferric carboxymaltose or ferric derisomaltose in selected patients with HFrEF or HFmrEF (6) and should be considered a pragmatic historical strategy rather than current standard care.

Principal limitations include the single-center pilot design, small sample, three-month follow-

up, open-label treatment, lack of prospective registration, incompletely documented allocation concealment, baseline imbalances, fixed low intravenous dose, and oral iron in both groups. Overall, the study supports the feasibility of an ED-initiated strategy and generates a functional hypothesis but does not establish efficacy, safety, or survival benefit.

CONCLUSION

This randomized pilot study shows that a single 200 mg iron sucrose infusion can be integrated into the ED pathway after stabilization, with no serious infusion-related reaction documented. The greater three-month 6MWT improvement with IV-plus-oral therapy is an encouraging functional signal, although biological and clinical outcomes were not significantly different. These findings support further evaluation of ED-initiated intravenous iron strategies in adequately powered, prospectively registered multicenter trials using contemporary diagnostic criteria, individualized dosing, concealed allocation, and blinded outcome assessment.

DECLARATIONS

Use of generative artificial intelligence

Generative artificial intelligence was used solely for English-language editing and stylistic improvement of the manuscript. The authors reviewed and approved all revisions and remain fully responsible for the accuracy, integrity, and scientific content.

Competing interests

The authors declare no competing interests.

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Authors' contributions

All authors contributed to study conception, data collection, analysis, interpretation of results, and

manuscript preparation. All authors read and approved the final manuscript.

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