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Gender-Based Differences in Heart Failure Hospitalizations among Patients with Heart Failure Treated with Spironolactone

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ABSTRACT

Background: Gender-based variations in heart failure (HF) management and outcomes have been noted, especially in patients with reduced ejection fraction (HFrEF) treated with mineralocorticoid receptor antagonists (MRAs) like spironolactone. This study aimed to investigate gender-specific differences in HF-related hospitalizations among patients treated with spironolactone.

Methods: In a prospective cohort, 509 ambulatory HFrEF patients (NYHA class II-IV) were enrolled and assessed over six months. Patients received spironolactone and were monitored for HF-related hospitalizations, all adverse events, and mortality.

Results: After adjustment for potential covariates, the multivariate-adjusted regression analysis reveals that male gender was an independent predictor for HF hospitalization (hazard ratio (HR) = 1.972, 95% CI: 1.128–3.447, p = 0.017), a composite endpoint of mortality and morbidity (HR = 1.903, 95% CI: 1.127–3.214, p = 0.016), and all-cause hospitalization (HR = 4.955, 95% CI: 2.985–8.227, p < 0.001) but not all-cause mortality (HR = 0.672, 95% CI: 0.284–1.590, p = 0.366).

Conclusions: Gender differences in spironolactone outcomes were observed; females might achieve more benefits than males in terms of HF and all-cause hospitalizations. These findings underscore the need for gender-sensitive management strategies in HFrEF treatment, particularly to address higher hospitalization risks in males.

KEYWORDS: Heart Failure, Gender, Diuretics, Aldosterone Antagonist, Spironolactone.

1. Introduction

Heart failure (HF) is a significant medical condition with noted gender-related differences in symptoms, risk factors, clinical presentations, and outcomes (1). Treatment for HF with reduced ejection fraction (HFrEF) typically includes beta-blockers (BBs), angiotensin-converting enzymes (ACEIs), angiotensin receptor blockers (ARBs), and mineralocorticoid receptor antagonists (MRAs) (2). Aldosterone antagonists like eplerenone and spironolactone reduce hospitalization and mortality rates in HFrEF patients, enhancing ejection fraction (EF) in those with myocardial infarction (MI) and symptomatic HF or diabetes (1). Eplerenone is more selective for mineralocorticoid receptors, minimizing side effects compared to spironolactone (3). The renin-angiotensin-aldosterone system (RAAS), crucial for HF pathophysiology, exhibits gender-related variations (4). Gender may also influence the use of ACEIs, ARBs, and MRAs. Females generally experience more adverse reactions to cardiovascular medications (6), with a risk estimated 1.5 times higher than males (7, 8). While androgens may increase RAAS activity, less is known about their impact on MRA usage, prompting speculation that males might benefit more from spironolactone due to its androgen receptor-blocking properties (9). Clinical trials like EPHESUS showed a trend where females may gain more benefit from eplerenone than males at 30 days, though this was not confirmed at 16 months (3). The RALES study found no gender differences in spironolactone efficacy, although only 30% of participants were female (10). Recent research indicates spironolactone significantly decreases all-cause mortality in females with HFrEF, but not in males, with no notable gender differences in other clinical outcomes (11). The PARAGON-HF trial introduced a debate on HF pharmacotherapy, suggesting ARNIs may be more beneficial for females (12). Many prior studies were not designed to assess gender differences, leading to inconsistent findings. Additionally, females often underutilize guideline-directed medical therapy (GDMT) due to a higher risk of adverse effects (2). This study aims to explore how gender influences treatment outcomes with spironolactone in NYHA class II-IV patients with HFrEF (LVEF ≤ 40%).48

2. Methods

After approval from the Jazan Health Cluster Ethics Committee, SA (NCBE-KACST, KSA: H-10-Z-141) and informed written consent from patients or their next of kin (legal guardian) to be enrolled in this study, and the enrollment process was initiated. The sample size was calculated using a two-sample Z-test for proportions sample size formula. According to three major trials, the reported HF hospitalization rate is 25% for both genders. Assuming alpha error of 0.05 (5% significance level, two-tailed) and power (1-β) of 80%. If the anticipated difference in hospitalization rates between genders is 10% (detectable difference), the minimum required sample size is 494 patients. Patients were assessed for enrollment according to the following inclusion criteria: all adult (≥ 18 years) ambulatory patients of both genders with a diagnosis of HFrEF (LVEF≤ 40%) and NYHA class II-IV under optimized medical therapy who were presented to the outpatient clinic and started spironolactone at the time of enrollment, were enrolled. The exclusion criteria were pregnancy or breastfeeding, serum creatinine > 2.5 mg/dL in males and > 2 mg/dL in women (or

estimated glomerular filtration rate (eGFR) ≤ 30 mL/minute/1.73 m2), hyperkalemia (serum potassium level > 5 mEq/L), renal transplantation, concomitant administration of strong CYP3A inhibitors, concomitant administration of potassium supplements or other potassium-sparing diuretics, and disorders of the adrenal glands (Addison disease). Additionally, patients who used any MRA in the last 2 weeks before enrollment were excluded.

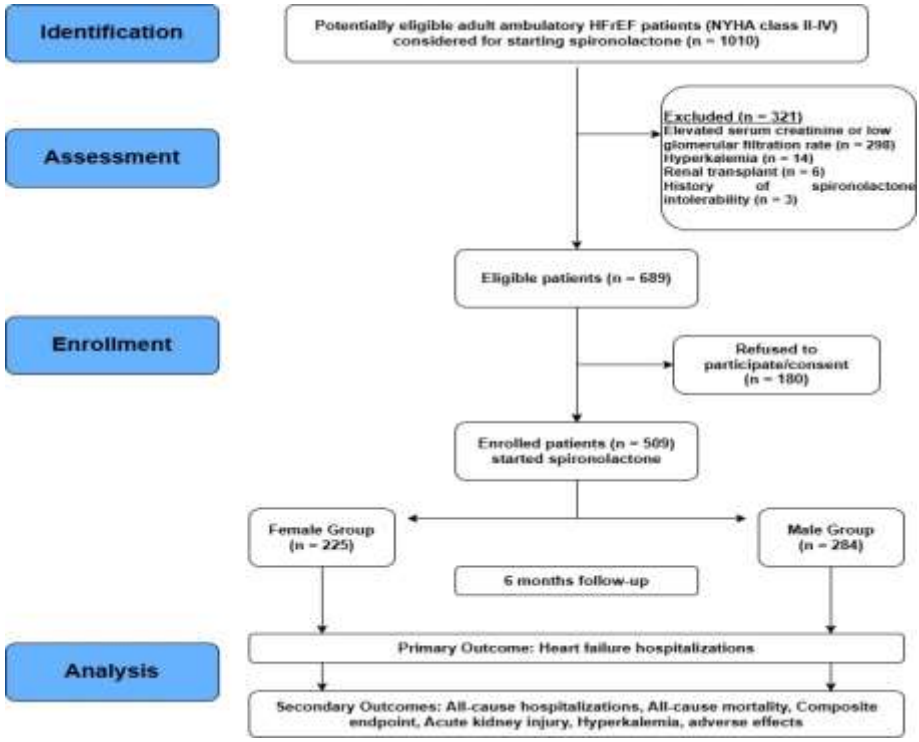

Figure (1): Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flow chart of the study.

In this single-center prospective cohort, 509 consecutive patients (n=509) were enrolled and assessed directly for the following characteristics: medical history (age, gender, body mass index, illness status, medications), physical examination, and routine laboratory investigations (complete blood test results, urea, serum creatinine, serum sodium, serum potassium, serum gamma-glutamyl transferase (GGT), and high-sensitive troponin levels). Formal transthoracic echocardiography was used as a baseline assessment for EF by modified Simpson's method (13) by independent cardiologists were blinded to this study protocol, and cardiac findings were recorded. The echocardiographic assessment was repeated by another experienced independent blinded reviewerto limit variability.

This was a nonintervention study, and the decision to start spironolactone treatment was initiated by the treating cardiologist, who was blinded to the study design, not the principal investigators to minimize selection bias. The spironolactone dose was 25 mg, with the option to titrate up to 50 mg at 8 weeks. Serum creatinine and

potassium levels were repeated 3 days, 1 weeks, and 1 month after the initial dosing. Then, both parameters were measured on the same. schedule after the initiation of maintenance dosing (after 4 weeks). (1) At months 3 and 6, both parameters and serum GGT levels were measured and recorded.

All possible spironolactone adverse effects (diarrhea, headache, cough, fatigue, influenza-like illness, angina, disorder of menstruation, erectile dysfunction, or gynecomastia) were recorded.

Hospital admissions for HF or other causes, acute MI, acute kidney injury (AKI), hyperkalemia (k > 5 mEq/L), electrolyte disturbances, hypochloremic alkalosis, and dehydration were monitored and recorded for 6 months. AKI was defined using the Kidney Disease Improving Global

Outcomes (KDIGO) classification. (14) Another echocardiographic assessment was performed at the end of the study (6 months) for each patient.

Patients were categorized according to their apparent sexual gender into two groups: the male group and the female group. The primary outcome was HF hospitalization. The secondary outcomes were all-cause hospitalization, All-cause mortality, composite endpoint of HF hospitalization and all-cause mortality, acute MI, discontinuation of spironolactone, switching from spironolactone to another MRA, AKI, hyperkalemia, and spironolactone adverse effects. All the reported adverse events were evaluated by two independent reviewers to limit variability. All enrolled patients were included in the final analysis even if spironolactone was discontinued or changed during the 6-month follow-up (intention-to-treat analysis). This study was reported using STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guide. (Figure 1)

Statistical analysis

The data were entered into a computer and analyzed using the IBM SPSS (IBM Corp., Armonk, NY, USA) version 26.0. Qualitative variables are described using numbers and percent." Quantitative variables are described using means or medians. Normally distributed variables are described as the mean ± standard deviation (SD). Nonnormally distributed variables are presented as the median ± interquartile range (IQR). The significance of the obtained results was judged at the 5% level. The chi-square test, Fisher exact test, Monte Carlo correction, the Mann–Whitney test, and Student's t-test were used. The Hosmer–Lemeshow goodness-of-fit test was used in gender-specific multivariate adjusted regression analysis.

3. Results

A total of 509 ambulatory patients with heart failure with reduced ejection fraction (HFrEF) were enrolled at the start of spironolactone treatment, with a mean age of 63.6 years. Most patients (75.8%) were classified as NYHA class II. Hypertension (77.8%) and prior myocardial infarction (MI) (47.9%) were the most common medical histories. The mean initial left ventricular ejection fraction (LVEF) for the cohort was around 31%. Males comprised a larger portion of the group (55.8%) compared to females (44.2%).

Baseline characteristics were generally similar between genders, but differences were noted in smoking history, hypertension, and prior MI—females had lower smoking and MI rates but higher hypertension. Beta-blockers were the most frequently used HF medication (83.9%), with most medication classes used similarly across genders, except for ARB-neprilysin inhibitors, which were more common in males (26.3%) than in females (15.6%) ($p = 0.026$). Statin and anticoagulant use was also higher in males (85.6% and 71.1%, respectively) compared to females (75.6% and 57.8%) with p-values of 0.004 and 0.002, respectively. Males had slightly higher baseline diastolic blood pressure (DBP) and mean arterial pressure (MAP) ($p < 0.05$ for both). Females had a lower estimated glomerular filtration rate (eGFR) (59.2 mL/min/1.73m²) compared to males (63.5 mL/min/1.73m²) ($p = 0.003$). Additionally, gamma-glutamyl transferase (GGT) levels were higher in males (41.7 U/L) than in females (31.8 U/L) ($p < 0.05$). The primary outcome of HF hospitalization was observed in 18.9% of the cohort, with a higher occurrence in males (21.8%) compared to females (15.1%), though this difference was not statistically significant ($p = 0.068$). Among secondary outcomes, all-cause hospitalization was significantly higher in males (44.4%) than in females (23.1%) ($p < 0.05$). The overall mortality rate was 8.3%, nearly comparable across genders. The composite endpoint of HF hospitalization and all-cause mortality was significantly higher in males (27.1%) compared to females (17.8%) ($p = 0.015$). Females showed a statistically significant follow-up LVEF compared to males (33% vs. 32%, $p = 0.007$). Other secondary outcomes, including rates of acute MI, elevated GGT, MRA discontinuation, MRA switching, acute kidney injury (AKI), and hyperkalemia, showed no significant differences between genders. Erectile dysfunction and gynecomastia were noted exclusively in males, affecting 21.5% and 18.3% of them, respectively, reflecting known gender-specific side effects of spironolactone. After adjustment for potential covariates, the multivariate-adjusted regression analysis reveals that males had a significantly higher likelihood of HF hospitalization than females, with a 10 hazard ratio (HR) of 1.972 (95% CI: 1.128–3.447, $p = 0.017$). Male gender was also a significant Predictor for the composite endpoint of mortality and morbidity (HR = 1.903, 95% CI: 1.127–3.214, $p = 0.016$) and all-cause hospitalization (HR = 4.955, 95% CI: 2.985–8.227, $p < 0.001$). Being a male was not a statistically significant predictor for all-cause mortality (HR = 0.672, 95% CI: 0.284–1.590, $p = 0.366$). (Table 3).

Table (1): Baseline characteristics of the overall cohort

Baseline Characteristics	**Overall cohort (n = 509)**	**Male group (n = 284)**	**Female group (n = 225)**	***p-value***
Age (years)	63.6 ± 9.9	63.1 ± 10.5	64.3 ± 9.3	0.207
BMI (kg/m^2)	29.5 (6.7)	29.6 (7.8)	29.5 (5.8)	0.956
Smoker	184 (36.1)	164 (57.7)	20 (8.9)	<0.05*
HTN	396 (77.8)	206 (72.5)	190 (84.4)	0.01*
DM	234 (46.0)	124 (43.7)	110 (48.9)	0.246
Stroke	96 (18.9)	51 (17.9)	45 (20.0)	0.570
MI	244 (47.9)	174 (61.3)	70 (31.1)	<0.05*
AFF	204 (40.1)	124 (43.7)	80 (35.6)	0.069
Loop diuretic	323 (63.5)	189 (66.5)	134 (59.6)	0.115
Non loop diuretic [#]	235 (46.2)	121 (42.6)	114 (50.7)	0.074
ACEIs	177 (34.8)	98 (34.5)	79 (35.1)	0.925
ARBs	229 (45.0)	119 (41.9)	110 (48.9)	0.128

ARB-neprilysin inhibitor	102 (20.0)	67 (23.6)	35 (15.6)	0.026*
Beta-blockers	427 (83.9)	237 (83.5)	190 (84.4)	0.809
Digoxin	91 (17.9)	51 (18.0)	40 (17.8)	1.000
SGLT2i	375 (73.7)	210 (73.9)	165 (73.3)	0.919
Statin	413 (81.1)	243 (85.6)	170 (75.6)	0.004*
Anti-platelets	337 (66.2)	197 (69.4)	140 (62.2)	0.109
Anticoagulants	332 (65.2)	202 (71.1)	130 (57.8)	0.002*
Initial LVEF %	31.3 ± 4.1	31 ± 4.0	31.6 ± 4.2	0.207
NT-proBNP (ng/L)	1640 ± 475.5	1612 ± 483.8	1676 ± 463.4	0.133
NYHA II **NYHA III/IV**	386 (75.8) 123 (24.2)	216 (76.1) 68 (23.9)	170 (75.6) 55 (24.4)	0.917
SBP (mmHg)	119 (21)	121 (22)	117 (16)	0.873
DBP (mmHg)	71 (14)	68 (12)	73 (12)	<0.05*
MAP (mmHg)	88 (11)	87 (11)	90 (11)	<0.05*
HR (beats/min)	76.4 ± 10.3	76.4 ± 10.2	76.4 ± 10.5	0.961
HsTnT (pg/ml)	31.6 (14)	31.9 (16.2)	30.8 (12.1)	0.05
Na (mmol/L)	134.8 ± 4.2	134.9 ± 4.4	134.7 ± 3.9	0.469
K (mEq/L)	3.2 ± 0.44	3.2 ± 0.43	3.2 ± 0.45	0.509
Urea (mg/dL)	36 (13)	36 (14)	36 (10)	0.291
SCR (mg/dL)	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2	0.514
eGFR (ml/min/1.73m^2)	61 (28)	63.5 (32)	60 (22)	0.003*
HbA1c %	6.7 ± 1.3	6.7 ± 1.4	6.7 ± 1.3	0.445
GGT (u/L)	36 (11)	41.7 (9)	31 (8)	<0.05*

"ACEIs: angiotensin-converting enzyme inhibitors, ARBs: angiotensin receptor blockers, ARB-neprilysin inhibitor: angiotensin receptor-neprilysin inhibitor, SGLT2i: sodium-glucose transport protein 2 inhibitors, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure calculated as (MAP=DBP+1/3(SBP-DBP), HR: heart rate, HsTnT: high-sensitive troponin T, Na: sodium, K: potassium, Scr: serum creatinine, eGFR: estimated glomerular filtration rate, HbA1c: glycated hemoglobin, GGT: gamma glutamyl-transferase.

Non-loop diuretics excluding MRA.

Normally distributed variables are expressed as the mean ± standard deviation. Nonnormally distributed variables are expressed as the median (interquartile range).

*: Statistically significant at $p \leq 0.05$

Table (2): Gender-specific multivariate adjusted regression analysis

Outcomes	**Overall cohort (n = 509)**	**Male group (n = 284)**	**Female group (n = 225)**	***p***
HF hospitalization	96 (18.9)	62 (21.8)	34 (15.1)	0.068
All-cause hospitalization	179 (35.2)	126 (44.4)	52 (23.1)	<0.05*
All-cause mortality	42 (8.3)	26 (9.2)	16 (7.1)	0.423
Composite endpoint [#]	117 (23.0)	77 (27.1)	40 (17.8)	0.015*
Follow-up LVEF	32 (6)	32 (8)	33 (5)	0.007*
Acute MI	48 (9.4)	21 (7.4)	27 (12)	0.093
Elevated GGT	60 (11.8)	35 (12.3)	25 (11.1)	1.000
Spironolactone Discontinuation	143 (28.1)	83 (29.2)	60 (26.7)	0.552
Spironolactone switching	76 (14.9)	41 (14.4)	35 (15.6)	0.802
AKI	81 (15.9)	41 (14.4)	40 (17.8)	0.330
Hyperkalemia	91 (17.9)	51 (18)	40 (17.8)	1.000
Erectile dysfunction	-	61 (21.5)	-	-

Gynecomastia	-	52 (18.3)	-	-

HF: heart failure; MI: myocardial infarction; GGT: gamma-glutamyl transferase; AKI: acute kidney injury; LVEF: left ventricular ejection fraction.

□2, p: □2 and p values for the chi-square test for comparisons between two groups. Normally distributed variables are expressed as the mean ± standard deviation.

t, p: t, and p values for Student's t-test for comparisons between two groups.

#Composite endpoint of HF hospitalization and all-cause mortality

*: Statistically significant at $p \leq 0.05$

Table (3): Gender-specific multivariate adjusted regression analysis

Variable	**HF hospitalization**		**Composite endpoint of mortality and morbidity**	
	HR (95%CI)	***p-value***	**HR (95%CI)**	***p-value***
Male	1.972 (1.128–3.447)	0.017*	1.903 (1.127–3.214)	0.016*
Hypertension	1.360 (0.798–2.319)	0.259	1.537 (0.940–2.514)	0.086
Prior MI	1.055 (0.645–1.726)	0.831	0.842 (0.531–1.330)	0.462
Smoker	1.870 (1.083–3.230)	0.025*	1.782 (1.071–2.964)	0.026*
ARB-neprilysin inhibitor	1.615 (0.869–3.005)	0.130	1.004 (0.590–1.707)	0.989
Statin	0.760 (0.410–1.411)	0.385	0.699 (0.384–1.272)	0.241
Anticoagulants	0.707 (0.421–1.189)	0.191	0.744 (0.462–1.200)	0.226
	All-cause hospitalization		**All-cause mortality**	
	HR (95%CI)	***p-value***	**HR (95%CI)**	***p-value***
Male	4.955 (2.985–8.227)	<0.001*	0.672 (0.284–1.590)	0.366
Hypertension	0.990 (.606–1.620)	0.969	0.633 (0.263–1.521)	0.306
Prior MI	0.939 (0.611–1.443)	0.773	0.564 (0.271–1.173)	0.125
Smoker	4.449 (2.706–7.315)	<0.001*	0.691 (0.312–1.529)	0.362
ARB-neprilysin inhibitor	1.743 (1.026–2.960)	0.054	0.235 (0.117–0.471)	<0.001*
Statin	0.510 (0.293–0.888)	0.017*	0.292 (0.067–1.271)	0.101
Anticoagulants	0.475 (0.302–0.747)	<0.001*	0.776 (0.376–1.601)	0.492

MI: myocardial infarction, ARB: Angiotensin receptor blocker Hosmer–Lemeshow goodness-of-fit model.

HR: hazard ratio, 95% CI: 95% confidence interval, LL: lower limit, UL: upper limit.

*: Statistically significant at $p \leq 0.05$

4. Discussion

After treatment with spironolactone in patients with heart failure with reduced ejection fraction (HFrEF), women showed a lower risk than men for HF hospitalization, a composite endpoint of mortality and morbidity, and all-cause hospitalization. A meta-analysis of three principal MRA trials indicated consistent

hazard ratios across genders: males had a hazard ratio of 0.65 (95% CI: 0.58–0.74) and females 0.67 (95% CI: 0.54–0.83). Overall, MRA therapy decreased the risk of HF hospitalization or cardiovascular death by 27% in females (hazard ratio = 0.73; 95% CI: 0.62–0.86) and by 31% in males (hazard ratio = 0.69; 95% CI: 0.62–0.77) (15). In the EPHESUS trial, the mortality rate for the eplerenone group was lower (RR = 0.85, 95% CI 0.75–0.96; p = 0.008), with cardiovascular mortality declining (p = 0.005, relative risk = 0.83, 95% CI: 0.72–0.94). Eplerenone reduced the composite endpoint rate (relative risk = 0.87; 95% CI: 0.79–0.95, p = 0.002) and all-cause mortality (p = 0.02, relative risk = 0.92, 95% CI: 0.86–0.98) (3). The RALES trial linked spironolactone to a 35% decrease in hospitalization and a 30% lower risk of death (relative risk = 0.70, 95% CI: 0.60–0.82, p < 0.001), with similar results for both genders (16). Regarding safety, 28.1% of the cohort discontinued spironolactone due to adverse effects, with 14.9% switching to an alternative MRA. Hyperkalemia developed in 17.9% of participants, and AKI occurred in 15.9%, with no significant gender differences in safety outcomes. In Lopes et al. (2008), 25% of 134 HFrEF patients discontinued spironolactone, with hyperkalemia (17.1%) and AKI (14.5%) being common reasons. The RALES study reported an 8% discontinuation rate, primarily due to gynecomastia and breast discomfort. Although the overall incidence of AKI was higher in females (33.7% vs. 28.9% in males, p = 0.04), hyperkalemia prevalence was similar (p = 0.617) (16). In the EPHESUS study, 3.4% of the eplerenone group experienced hyperkalemia, with 5.5% having severe hyperkalemia. Male rates of gynecomastia and erectile dysfunction were 0.5% and 0.9%, respectively (17). A meta-analysis found similar hyperkalemia rates, but renal function decline was significantly greater in females (40.8% vs. 31.2%, p < 0.001) (15). The study included multicentric, community-based, and investigator-blinded designs, highlighting the need for extended follow-up research to explore potential gender-based effects of eplerenone and sodium-glucose co-transporter-2 inhibitors (SGLT2is). Limitations included a monocentric design, limited sample size, short duration, and potential biases affecting validity. Notably, the decision to initiate spironolactone was made by an independent cardiologist rather than the principal investigator.

5. Conclusions

After 6 months of follow-up of using spironolactone in ambulatory HFrEF patients (NYHA II-IV), gender differences in spironolactone outcomes were observed; females might achieve more benefits than males in terms of HF and all-cause hospitalizations. These findings underscore the need for gender-sensitive management strategies in HFrEF treatment, particularly to address higher hospitalization risks in males.

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Conflicts of interest/Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this research.

Availability of data and material

The data and material are available on reasonable request from the corresponding author, [M. A. Alshrahili].

Code availability

N/A

Authors' contributions

The corresponding author M. A. A. formulated the study question in the initial protocol, and he was responsible for the consenting process. All other authors were involved in the recruitment process and data collection. M. A. A., A. S., and S. A. A. conducted the statistical analyses. All authors contributed to writing the manuscript before submission.

Ethics approval

This study was approved by the Jazan Health Cluster Ethics Committee, Saudi Arabia, National

Registration Number with NCBE-KACST, KSA: H-10-Z-141.

Consent to participate

Informed written consent from patients or their next of kin (legal guardian) to be enrolled in this study.

Consent for publication

Informed written consent from patients or their next of kin (legal guardian) to publish their data in this manuscript.

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