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Sodium-Glucose Co-transporter-2 inhibitors versus Mineralocorticoid Receptor Antagonists in Heart Failure with Preserved Systolic Function: A Retrospective National Study

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Abstract

Background: Heart failure with preserved ejection fraction (HFpEF) accounts for ~50% of heart failure and lacks uniformly effective disease-modifying therapy. Comparative real-world data for sodium–glucose cotransporter-2 inhibitors (SGLT2i) versus mineralocorticoid receptor antagonists (MRAs) at the time of HFpEF diagnosis are limited.

Methods: We conducted a retrospective cohort study on the TriNetX Research network (108 U.S. healthcare organizations). Adults with HFpEF (ICD-10-CM I50.3) who initiated either an SGLT2i (ATC A10BK) or an MRA (VA class CV704) within 30 days of first HFpEF record between January 1, 2019, and January 1, 2024, were identified. Mutually exclusive, new-user cohorts were 1:1 propensity-score matched on demographics, comorbidities, and concomitant therapies, yielding 7,574 patients per arm. Outcomes were assessed from day 1 to day 365 post-index. The primary outcome was time to first composite of all-cause death or all-cause hospitalization; secondary endpoints included the components, MACE, acute heart failure, and laboratory-defined hyperkalemia thresholds; allergic rhinitis served as a negative control. Cox models estimated hazard ratios (HRs).

Results: Compared with MRAs, SGLT2 inhibitors were associated with a lower 1-year all-cause mortality (8.7% vs 15.5%; HR= 0.50, 95% CI 0.45–0.55; p< 0.001). Secondary outcomes also favored SGLT2 inhibitors: all-cause hospitalization (12.6% vs 17.4%; HR= 0.65, 95% CI 0.58–0.74; p< 0.001); MACE (12.1% vs 18.9%; HR= 0.58, 95% CI 0.52–0.63; p< 0.001); and acute heart failure (7.5% vs 9.9%; HR= 0.68, 95% CI 0.59–0.79; p< 0.001). Hyperkalemia was consistently lower across thresholds (>5.0 mmol/L: HR= 0.54; >5.5 mmol/L: HR= 0.50; >6.0 mmol/L: HR= 0.53; all p< 0.001).

Conclusion: In a large, contemporary U.S. real-world cohort of newly diagnosed HFpEF, initiating SGLT2i within 30 days of diagnosis was associated with substantially better 1-year outcomes compared to MRAs. Given the nature of the study, a randomized trial comparing both agents is warranted.

1. Introduction

Heart failure with preserved ejection fraction (HFpEF), defined as heart failure symptoms and signs with left ventricular ejection fraction (LVEF) ≥ 50%, accounts for nearly half of all heart failure cases and carries morbidity and mortality comparable to heart failure with reduced ejection fraction (HFrEF) (1, 2). Its prevalence is rising due to aging populations and a high burden of comorbidities such as hypertension, obesity, diabetes, and atrial fibrillation (3)

HFpEF pathophysiology involves impaired ventricular relaxation, myocardial fibrosis, and concentric remodeling, often driven by systemic inflammation, endothelial dysfunction, and microvascular rarefaction (4, 5). Despite its complex mechanisms, therapeutic options with proven mortality benefits remain scarce.

Sodium–glucose cotransporter-2 inhibitors (SGLT2i) have recently demonstrated consistent reductions in heart failure hospitalizations in patients with HFpEF, leading to guideline endorsements for their use regardless of diabetic status (6, 7). In contrast, the benefits of mineralocorticoid receptor antagonists (MRAs) in HFpEF are less consistent; while some trials suggest improved diastolic function and reduced heart failure events, the mortality benefit remains unproven (8, 9).

Real-world comparative data between these two classes in newly diagnosed HFpEF are limited. This study addresses this evidence gap by evaluating 1-year outcomes of SGLT2i versus MRA initiation within one month of HFpEF diagnosis.

2. Methods

2.1 Data source and oversight

We conducted a retrospective cohort study on the TriNetX LLC® platform, accessed on September 14, 2025, using HIPAA-compliant de-identified EHR data from 108 U.S. healthcare organizations (HCOs) in the TriNetX Research network. The work met criteria for non-human-subjects research and did not require IRB review or informed consent. Reporting follows STROBE and TriNetX publication guidance.

2.2 Study design and coding strategy

We used the Compare Outcomes workflow in TriNetX. Cohorts were defined with structured terminologies, including HFpEF (defined by ICD-10-CM I50.3), HFrEF (defined by ICD-10-CM I50.2), SGLT2 inhibitors (defined by ATC A10BK including canagliflozin, dapagliflozin, empagliflozin, ertugliflozin), and MRAs (defined by Veterans Affairs class CV704 including spironolactone, eplerenone, finerenone). No NLP terms were used. Analytic modules included Measures of Association, Kaplan–Meier survival, and Number of Instances, per platform specifications.

2.3 Cohort definition

Two mutually exclusive new-user of SGLT2 and MRA cohorts were built using data from Jan 1, 2019–Jan 1, 2024.

We included adults (≥ 18 y) with HFpEF (I50.3) diagnosis who received their first prescription of SGLT2 (Cohort A) or MRA (Cohort B) within one month thereafter. The index date was defined as the first prescription date of SGLT2 or MRA for these two cohorts, respectively.

We excluded patients who were diagnosed with HFrEF (I50.2) before the index date. Due to the variation of pathophysiological mechanisms and symptoms between male and female patients with HFpEF, we excluded patients who did not have sex recorded. We enforced the drug-exposure to be mutually exclusive (i.e., using “can-not-have” clauses.. For any outcome, we excluded patients who had that endpoint recorded before follow-up began (In order to identify new-onset of outcomes (either primary or secondary outcomes), we excluded patients who experienced related outcomes at baseline. Thus,

several risk sets were defined for each outcome, respectively.Exclusion was outcome-specific, and a patient excluded for one outcome could remain eligible for others.

2.4 Baseline covariates and propensity-score matching

We extracted demographics (current age, age at index, sex, race), major comorbidities (type 2 diabetes, CKD, chronic ischemic heart disease, atrial fibrillation, hypertension, anemia), concurrent cardiovascular medications (β-blockers, ACE inhibitors, ARBs, loop and thiazide diuretics) within 1 year prior to the index date and extracted body mass index, and estimated GFR at index date.

Using this information, we performed 1:1 propensity-score matching between treatment groups and evaluated the performance of matching by scrutinizing standardized mean differences of this information (less than 0.10 indicates good performance).

2.5 Outcomes and follow-up

The primary outcome was 1-year mortality, which was ascertained using the TriNetX “Deceased” indicator (i.e.,ICD-10-CM R99:ill-defined cause of death).

Secondary outcomes included all-cause hospitalization, MACE, acute heart failure, and hyperkalemia, respectively. All-cause hospitalization was defined byany inpatient or observation encounter mapped to the TriNetX outcome term “Hospital Inpatient and Observation Care Services” (UMLS: CPT:1013659). As a composite outcome, we adopted 3-endpoint MACE, which includes any encounter with a diagnosis of acute myocardial infarction (I21–I22), ischemic stroke (I63), or all-cause mortality Acute heart failure included acute or acute-on-chronic systolic/diastolic/combined HF (defined by encounter with one of the following OCD 10 diagnosis codes I50.21, I50.23, I50.31, I50.33, I50.41, I50.43). Hyperkalemia was defined using laboratory data. Based on three cutoffs (i.e., serum potassium > 5.0 mmol/L, > 5.5 mmol/L, or > 6.0 mmol/L), three separate binary outcomes were defined, and the earliest exceedance defined the event time. We also captured the time to allergic rhinitis (defined by ICD 10 code: J30.9) as a negative control outcome to detect residual confounding, given the exposure to SGLT2i or MRA is not associated with a differentiating risk of allergic rhinitis.

Patients were followed until the first occurrence of outcomes (including death), or being censored at the earliest of the last recorded encounter, end of data capture, or day 365. If outcome and any reasons for censoring occurred on the same calendar day, such as mortality and last recorded encounter, we assumed the outcome was the key driver, and only it was counted. A similar approach was applied for the composite outcome, if a patient experienced ischemic stroke and death on the same date, we assumed the death was the driver and captured death as the only outcome on that date for MACE.

2.6 Statistical analysis

We estimated absolute risks, risk differences, risk ratios, and odds ratios using TriNetX’s Measure of Association report, each with 95% confidence intervals (CIs). Time-to-event endpoints were analyzed with Kaplan–Meier curves (log-rank tests) and Cox proportional-hazards models to estimate hazard

ratios (HRs) with 95% CIs. Before outcome modeling, cohorts were balanced using 1:1 propensity-score matching (greedy nearest neighbor with a caliper on the propensity score), and covariate balance was verified by standardized mean differences (SMD < 0.10). Recurrent-event burden was summarized with the Number-of-Instances report (mean events per patient), with group comparisons as implemented within TriNetX. We conducted several secondary analyses based on the varied secondary outcomes defined above. Two sensitivity analyses were conducted to evaluate the stability of our findings: 1) we modeled death as a competing risk for hospitalization using Fine–Gray subdistribution hazards; 2) we estimated the risk of allergic rhinitis given it is a negative control outcome sharing the same confounder structure and should not be associated with the exposure to either SGLT2i or MRA.

The proportional-hazards assumption could not be formally tested in the portal (Schoenfeld residuals are not available); HRs should be interpreted as average effects over follow-up. All tests were two-sided with $\alpha = 0.05$. Analyses were conducted entirely in the TriNetX portal (September 2025 build); no external software was used.

3. Results

3.1. Study population

During the study window (January 1, 2019–January 1, 2024), 33,422 patients with HFpEF met all eligibility criteria: 7,762 initiated an SGLT2 inhibitor, and 25,660 received an MRA. Propensity-score matching (1:1, nearest neighbor with 0.25 caliper) yielded 7,574 matched pairs (15,148 patients) that comprised the analytic cohort.

3.2. Baseline characteristics

Before matching, notable imbalances were present between treatment groups (Table 1). The SGLT2 group included a higher proportion of male patients (51.7% vs 42.9%; SMD 0.177) and a substantially greater prevalence of type 2 diabetes mellitus (54.0% vs 31.2%; SMD 0.475). Primary hypertension (59.8% vs 53.3%; SMD 0.130), chronic ischemic heart disease (38.6% vs 30.9%; SMD 0.162), and related medication use including ACE inhibitors (21.6% vs 16.9%; SMD 0.120), ARBs (24.4% vs 18.1%; SMD 0.155), and β-blockers (54.2% vs 49.6%; SMD 0.092) were more common in the SGLT2 group. By contrast, patients in the MRA group were modestly older at baseline (mean±standard deviation: 74.6 ± 12.9 vs 73.0 ± 11.8 years; SMD 0.129). Continuous labs showed small pre-match differences; BMI was higher with SGLT2 (33.9 ± 9.1 vs 32.8 ± 9.5 kg/m²; SMD 0.109), while eGFR differed minimally (64.5 ± 28.1 vs 65.9 ± 30.6 mL/min/1.73 m²; SMD 0.049). Race distributions also varied slightly (e.g., Asian 4.0% vs 2.3%; SMD 0.096).

After propensity matching, baseline covariates were well balanced (all SMDs < 0.10; Table 1). The largest pre-match imbalances—diabetes burden, male sex, hypertension/ischemic heart disease, and ACEi/ARB use—were eliminated. Small residual differences in continuous labs remained within accepted thresholds for BMI (33.9 ± 9.1 vs 33.0 ± 9.5 kg/m²; SMD 0.093) and eGFR (64.4 ± 28.0 vs 66.1 ± 31.3

mL/min/1.73 m²; SMD 0.057). Availability of baseline measures was similar across groups (BMI available: 61.7% vs 59.8%; eGFR available: 75.9% vs 74.2%).

Table 1
Baseline characteristics of the study cohort before and after PSM

Variables	Before matching				After matching			
	SGLT2 (N = 7,762)	MRA (N = 25,660)	*P*-Value	SMD	SGLT2 (N = 7,574)	MRA (N = 7,574)	*P*-Value	Std diff.
Demographics								
Age at Index (mean ± SD)	70.2 ± 12.1	70.7 ± 13.4	0.001	0.044	70.3 ± 12	70.2 ± 14.7	0.561	0.009
Current age (mean ± SD)	73 ± 11.8	74.6 ± 12.9	< 0.001	0.129	73.1 ± 11.8	73 ± 13.9	0.423	0.013
Male (n% %)	4,015 (51.7%)	11,014 (42.9%)	< 0.001	0.177	4,117 (51.2%)	4,139 (51.5%)	0.729	0.005
White (n% %)	5,395 (69.5%)	18,866 (73.5%)	< 0.001	0.089	5,285 (69.8%)	5,318 (70.2%)	0.558	0.010
American Indian or Alaska Native (n %)	36 (0.5%)	122 (0.5%)	0.896	0.002	34 (0.4%)	42 (0.6%)	0.358	0.015
Black or African American (n%)	1,215 (15.7%)	3,963 (15.4%)	0.656	0.006	1,183 (15.6%)	1,145 (15.1%)	0.392	0.014
Asian (n %)	311 (4%)	696 (2.3%)	< 0.001	0.096	293 (3.9%)	294 (3.9%)	0.966	0.001
Past medical history								
Type 2 DM (n %)	4,192 (54.0%)	7,998 (31.2%)	< 0.001	0.475	4,009 (52.9%)	4,204 (52.3%)	0.029	0.035
Chronic ischemic heart disease (n %)	2,995 (38.6%)	7,930 (30.9%)	< 0.001	0.162	2,891 (38.2%)	2,793 (36.9%)	0.100	0.027
Chronic kidney disease (CKD) (n %)	2,224 (28.7%)	6,286 (24.5%)	< 0.001	0.094	2,164 (28.6%)	2,078 (27.4%)	0.120	0.025
Primary hypertension (n %)	4,638 (59.8%)	13,680 (53.3%)	< 0.001	0.130	4,491 (59.3%)	4,302 (56.8%)	0.002	0.051
Atrial fibrillation and flutter (n %)	2,386 (30.7%)	8,882 (34.6%)	< 0.001	0.083	2,349 (31.0%)	2,308 (30.5%)	0.740	0.012

Variables	Before matching				After matching			
	SGLT2 (N = 7,762)	MRA (N = 25,660)	*P*-Value	SMD	SGLT2 (N = 7,574)	MRA (N = 7,574)	*P*-Value	Std diff.
Iron deficiency anemia (n %)	793 (10.2%)	2,948 (11.5%)	0.002	0.041	780 (10.3%)	733 (9.7%)	0.203	0.021
Current medication								
Beta blockers (n %)	4,206 (54.2%)	12,723 (49.6%)	< 0.001	0.092	4,081 (53.9%)	4,000 (52.8%)	0.187	0.021
ACE inhibitors (n %)	1,676 (21.6%)	4,329 (16.9%)	< 0.001	0.120	1,604 (21.2%)	1,536 (20.3%)	0.173	0.022
ARBs (n %)	1,892 (24.4%)	4,636 (18.1%)	< 0.001	0.155	1,827 (24.1%)	1,761 (23.3%)	0.207	0.020
Loop diuretics (n %)	4,357 (56.1%)	14,469 (56.4%)	0.692	0.005	4,251 (56.1%)	4,219 (55.7%)	0.601	0.009
Thiazide diuretics (n %)	1,351 (17.4%)	4,464 (17.4%)	0.986	< 0.001	1,327 (17.5%)	1,296 (17.1%)	0.506	0.011
Laboratory								
BMI (mean ± SD) (n%)*	33.9 ± 9.1 (61.9%)	32.8 ± 9.5 (55.8%)	< 0.001	0.109	33.9 ± 9.1 (61.7%)	33.0 ± 9.5 (59.8%)	< 0.001	0.093
GFR (mean ± SD) (n%)*	64.5 ± 28.1 (76.0%)	65.9 ± 30.6 (73.3%)	0.001	0.049	64.4 ± 28.0 (75.9%)	66.1 ± 31.3 (74.2%)	0.003	0.057

Footnotes: *Continuous data are mean ± SD; categorical data are n (%). p-values from the Wilcoxon rank-sum (continuous) or χ^2 test (categorical). PSM = propensity score match, ARBs: angiotensin II receptor blockers, BMI = body mass index, and GFR = glomerular filtration rate. * n (%) in brackets = data availability for this variable (n with a non-missing value out of group total N). The % is availability only, not an event rate or outcome proportion.*

3.3. Clinical outcomes

All-cause mortality within 365 days occurred less frequently with SGLT2 inhibitors than with MRAs (8.7% vs 15.5%; HR = 0.50, 95% CI: 0.45–0.55; p < 0.001) (Table 2).

All-cause hospitalization within 365 days was also lower with SGLT2 inhibitors (12.6% vs 17.4%; HR = 0.65, 95% CI: 0.58–0.74; p < 0.001). SGLT2 was associated with a lower risk of MACE (12.1% vs 18.9%; HR = 0.58, 95% CI: 0.52–0.63; p < 0.001) and acute heart failure (7.5% vs 9.9%; HR = 0.68, 95% CI: 0.59–0.79; p < 0.001). Hyperkalemia was less frequent with SGLT2 across all thresholds: greater than 5.0

mmol/L (12.9% vs 21.3%; HR = 0.54, 95% CI: 0.49–0.59; p < 0.001), greater than 5.5 mmol/L (5.9% vs 10.7%; HR = 0.50, 95% CI: 0.44–0.56; p < 0.001), and greater than 6.0 mmol/L (3.1% vs 5.4%; HR = 0.53, 95% CI: 0.45–0.62; p < 0.001) (Table 2).

Allergic rhinitis did not differ between groups (0.9% vs 0.8%; HR = 1.00, 95% CI: 0.71–1.43; p = 0.972) (Table 2).

Table 2
Primary, secondary, and negative control outcomes—adjusted hazard ratios (%) comparing SGLT2 inhibitors with MRAs

Outcome	SGLT2 (N = 7,574)	MRA (N = 7,574)	Hazard Ratio (HR)	95% CI	*P*-Value
All-cause mortality	640 (8.7%)	1,148 (15.5%)	0.50	(0.45, 0.55)	< 0.001
All-Cause Hospitalizations	459 (12.6%)	554 (17.4%)	0.65	(0.58, 0.74)	< 0.001
MACE	677 (12.1%)	1,059 (18.9%)	0.58	(0.52, 0.63)	< 0.001
Acute Heart Failure	309 (7.5%)	353 (9.9%)	0.68	(0.59, 0.79)	< 0.001
Potassium > 5	667 (12.9%)	1,150 (21.3%)	0.54	(0.49, 0.59)	< 0.001
Potassium > 5.5	392 (5.9%)	717 (10.7%)	0.50	(0.44, 0.56)	< 0.001
Potassium > 6	221 (3.1%)	384 (5.4%)	0.53	(0.45, 0.62)	< 0.001
Allergic rhinitis	66 (0.9%)	60 (0.8%)	1.00	(0.71, 1.43)	0.972

Footnotes: Abbreviations. *MACE: Major adverse cardiovascular events; HF: Heart failure.* **Denominator for absolute risks** *= outcome-specific at-risk population in each arm (matched N minus patients with that outcome before day 1).*

Discussion

In this real-world, U.S.-based cohort of patients with HFpEF, over 365 days, the primary outcome was all-cause mortality was significantly lower with SGLT2i compared to MRAs. Key secondary outcomes including all-cause hospitalization,major adverse cardiovascular events,acute heart failure,and hyperkalemia were also lower with SGLT2i. These data suggest that SGLT2 inhibitors may be superior to MRA in patients with HFpEF.

Prior studies did not show significant benefit with MRAs in patients with HFpEF, particularly the TOPCAT trial, which did not show a statistically significant reduction in the composite outcome of cardiovascular death, aborted cardiac arrest, or heart failure hospitalization in HFpEF patients treated with spironolactone compared to placebo. (10) Additionally, spironolactone appeared to be more effective when compared to placebo in individuals with LVEF at the lower end of the preserved range, defined as 40% or higher, implying that neurohormonal blockade may offer diminishing returns when systolic function is well preserved. (11)

By comparison, SGLT2i have demonstrated benefits in patients with HFpEF, supported by both clinical trials and real-world studies. In the EMPEROR-Preserved trial, empagliflozin compared to placebo significantly reduced the composite outcome of cardiovascular mortality or heart failure hospitalization, primarily driven by a reduction in heart failure hospitalizations. (12) In a similar fashion, DELIVER showed that dapagliflozin depressed the risk of cardiovascular death or worsening heart failure, compared to placebo, exhibiting benefit along the ejection fraction continuum, including patients with LVEF ≥ 60%. (13) Importantly, SGLT2i benefits were consistent regardless of diabetes, coupled with favourable renal effects and reduced symptom burden. Beyond heart failure-specific endpoints, SGLT2i are also effective at slowing renal disease progression, along with, in selected populations, a decrease in atherosclerotic events, reflecting their broad cardiometabolic reach. (14, 15) However, no previous studies compared SGLT2i and MRA head-to-head in this population. The large difference in mortality seen in our study was unexpected and may be a result of residual confounding.

Obesity and diabetes have a prevalence of 55% and 37% in HfpEF patients, respectively, (17) also have significant inflammatory and metabolic effects which influence HfpEF pathophysiology. Here, SGLT2i have two theoretical advantages by their anti-diabetic and weight-reducing effects; SGLT2i have been shown to induce weight loss through glucosuria, which results in a 200–320 calorie loss per day (18), an effect absent in MRAs.

Another key known difference between SGLT2i and MRA is their renal effects; SGLT2i, in theory, exhibit a sustained reno-protective effect independent of their antidiabetic effect by lowering intraglomerular pressure, enhancing the tubuloglomerular feedback loop, and reducing albuminuria(19). Also, while SGLT2i are reported to initially lower GFR, they are shown to have a sustained slowing of GFR deterioration among all CKD stages(20). Furthermore, their reno-protective effects are not limited to just GFR progression; SGLT2i have been shown to lower the risk of AKI and serious hyperkalemia in HFpEF patients with CKD(20). This aligns with this study’s results, showing lower mortality in CKD patients receiving SGLT2i as well as a lower risk of hyperkalemia.

Conversely, HFpEF patients with CKD treated with MRAs showed a higher incidence of worsening renal function and hyperkalemia(9). With CKD being another common comorbidity of HFpEF, with a prevalence of about 50%(21), this could explain SGLT2i's apparent superiority over MRAs

Our study has many strengths, including a large sample size and using clinically meaningful outcomes.However, the principal limitation is the confounding inherent in an observational,

nonrandomized design. Despite matching and adjustment, residual confounding likely persists. Unmeasured or incompletely captured factors include echocardiographic ejection fraction and diastolic parameters, symptom burden and functional class, blood pressure trajectories, medication dose and adherence, and the frequency of laboratory monitoring. HFpEF classification relied on ICD-10 coding rather than universal availability of measured EF, so effect modification by EF could not be assessed. Outcome ascertainment used administrative codes and routine EHR data, which may introduce misclassification. Laboratory-based hyperkalemia outcomes may also be influenced by differential testing frequency. We report 365-day risks using a time-to-first-event framework that does not capture recurrent events or longer-term outcomes.

Conclusion

In this national real-world cohort of newly diagnosed HFpEF, initiation of SGLT2 inhibitors within one month of diagnosis was associated with substantially lower 1-year risk of all-cause death and hospitalization compared with MRAs. Given the limitations of the study, the results should be viewed as hypothesis generating.

Declarations

Author Contributions

Conceptualization/Study design: Mohammad Bdair; Anwar Zahran; Fathi Milhem

Data curation/Analysis/Interpretation: Mohammad Bdair; Anwar Zahran; Fathi Milhem

Methodology/Statistical analysis: Mohammad Bdair; Fathi Milhem; Anwar Zahran

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Writing—review & editing: Anwar Zahran; Hammam Jallad; Mohammad Bdair; Fathi Milhem, Tianze Jiao, Mohammed Ruzieh

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Ethics Statement

All data were fully de-identified in accordance with 45 CFR §164.514 (HIPAA Privacy Rule). Consequently, the study was deemed non-human-subjects research and did not require Institutional Review Board approval or informed consent. The study adhered to TriNetX “Publication Guidelines.”

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Ethics Statement

All data were fully de-identified in accordance with 45 CFR §164.514 (HIPAA Privacy Rule). Consequently, the study was deemed **non-human-subjects research** and did not require Institutional Review Board approval or informed consent. The study adhered to TriNetX “Publication Guidelines.”

Consent for Publication

Not applicable; the analysis used only de-identified aggregate data.

Conflicts of Interest

The authors declare **no conflicts of interest**

Data Availability

The data underlying this article are proprietary to the TriNetX platform. Researchers may request access at https://trinetx.com; use is subject to licensing agreements with TriNetX, LLC.

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Informed consent: Not applicable; only de-identified data were analyzed.

Trial registration: Not applicable.

Guarantor: Hammam Jallad.

Human Ethics and Consent to Participate declarations: Not applicable. This retrospective study used de-identified data from the TriNetX research network. It involved no interaction or intervention with human participants and used data de-identified according to HIPAA standards; therefore, institutional review board (IRB) approval and informed consent were not required.

Consent to participate: Not applicable. Informed consent was exempt because the dataset is de-identified.

Ethics approval: Not applicable. IRB approval was not required because this was a secondary analysis of de-identified data.

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