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Hyponatremia Predicts Adverse Outcomes after Transcatheter Mitral Valve Repair

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Abstract

Background: Transcatheter mitral valve repairs have been utilized significantly more over the last decade to treat mitral valve regurgitation. Hyponatremia, the most common electrolyte abnormality in hospitalized patients, adversely impacts patient outcomes. However, the impact of hyponatremia on cardiovascular outcomes among TMVR patients remains to be explored.

Methods: A retrospective cohort study utilizing the TrinetX US network was conducted. Patients aged 18-90 years who underwent TMVR were identified and categorized into two groups: those with and without hyponatremia. Propensity score matching was employed to mitigate potential confounding factors. The primary outcome was 30-day mortality. Secondary outcomes included acute heart failure hospitalization, acute myocardial infarction, cardiogenic shock, acute kidney injury, and cardiac arrest.

Results: Following PSM, the patient population was predominantly white and male, with a mean age of 77.2 in the hyponatremia cohort and 77.1 in the no-hyponatremia cohort. Covariates were well balanced between both groups. Patients with hyponatremia exhibited a significantly increased risk of 30-day mortality compared to those without (Hazard Ratio [HR] 2.646, 95% Confidence Interval [CI] 1.973-3.548, p<0.001). Additionally, patients with hyponatremia demonstrated a significantly increased risk of acute heart failure hospitalization (HR 1.116, 95% CI 1.032-1.208, p=0.014), acute myocardial infarction (HR 1.54, 95% CI 1.114-2.128, p=0.008), cardiogenic shock (HR 2.1, 95% CI 1.55-2.845, p<0.001), acute kidney injury (HR 2.141, 95% CI 1.781-2.574, p<0.001), and cardiac arrest (HR 1.823, 95% CI 1.1055-3.149, p=0.021). No significant difference was observed in the risk of stroke or hypertensive emergencies between the groups.

Conclusions: Hyponatremia is linked to heightened adverse cardiovascular outcomes in patients undergoing TMVR, including increased 30-day mortality. These findings emphasize the critical importance of vigilant electrolyte monitoring and proactive management of hyponatremia in this patient population to improve post-procedural outcomes.

Keywords: Arrhythmia, Cardiac surgery, Cardiovascular risk reduction, Congestive heart failure, Hyponatremia, Interventional cardiology, Transcatheter, Transcatheter mitral valve repair

Introduction

Transcatheter mitral valve repair (TMVR) is increasingly adopted for symptomatic mitral valve regurgitation in high-risk patients, driven by aging populations and complex comorbidity burden [1]. Hyponatremia is a common electrolyte disorder in hospitalized patients, including those with cardiovascular diseases [2].

It has been shown to worsen the prognosis in these patients, thereby contributing to increased length of stay, reduced functional capacity, and increased mortality rate [3]. Prior

studies have demonstrated a link between hyponatremia and increased risk of 30-day mortality in patients with heart failure [4].

Patients with sodium derangement could possibly have severe neurohormonal dysregulation, which can complicate periprocedural management [5]. It is, therefore, imperative to identify and correct perioperative hyponatremia, as it might help reduce risks associated with the procedure, as well as improve recovery [6].

In a study conducted by Kagase *et al.* on the impact of pre-procedural hyponatremia on clinical outcomes after transcatheter aortic valve repair: A propensity-matched analysis, it was shown that, during a mean follow-up of 330 days, the all-cause and cardiovascular mid-term mortality were higher in the hyponatremia group than in the non-hyponatremia group [7]. Understanding the influence of hyponatremia on TMVR outcomes remains underexplored and sparse, while the impact of hyponatremia on transcatheter aortic valve repair (TAVR) or coronary revascularization have been described in prior studies [8]. Lazzeri *et al.* examined 1,231 patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention. Their findings demonstrated that hyponatremia was associated with significantly higher mortality rates both during intensive cardiac care unit stays and at follow-up, reinforcing its role as a marker of severity in acute cardiac events [8].

The impact of hyponatremia on the outcomes of patients undergoing transcatheter mitral valve replacement is not well understood. To investigate this, we performed a retrospective cohort study using a large database. We used propensity score matching to analyze the impact of hyponatremia on TMVR outcomes in order to minimize the effect of confounding variables.

Methodology

Study design, setting, and participants

This was a retrospective cohort study that included adult patients aged 18-90 who underwent Transcatheter Mitral Valve Repair (TMVR) percutaneous approach, including transseptal puncture or via the coronary sinus or transcatheter mitral valve annulus reconstruction with implantation of annulus reconstruction device within the last 20 years. Exclusion criteria were (1) age <18 years old, (2) age >90 years old, and (3) valve procedure more than 20 years ago. These patients were divided into two cohorts; Cohort 1 had hyponatremia, while 2 did not have hyponatremia. Hyponatremia was queried using ICD codes, and transcatheter mitral valve replacement was queried using the relevant CPT codes.

The index event was defined as the time patients had their procedure done in the patient's EMR, and the follow-up window was from 1 day after the index event occurred till 30 days after the occurrence of the index event.

Data source and de-identification

The data source for this retrospective cohort study was done using the TriNetX global collaborative network database. TriNetX is a global federated research network that provides a database of electronic data (such as diagnosis, medications, procedures, imaging and treatments) from various healthcare organizations using an i2b2 data model. TriNetX complies with the Health Insurance Portability and Accountability Act (HIPAA) which is a federal law of the US that protects the privacy and security of healthcare data. All data on the TriNet platform contains de-identified data only per the de-identification standard in section 164.514(a) of the HIPAA Privacy Rule.

Healthcare organizations contributing de-identified electronic medical records (EMR) include academic university hospitals and specialty physician services from inpatient and outpatient services. Data from electronic medical records (EMR) of about 67 Healthcare organizations all over the US formed part of the global collaborative network analysis. To meet the security requirement of HIPAA, TriNetX maintains an Information Security Management Systems (ISMS) that is certified to the ISO 27001:2013 standard to protect the healthcare data it is privileged to. Data shared via TriNetX undergoes modification so that the information it contains is not sufficient for re-identification or identification of patients whose information has been contributed by the healthcare organizations [9].

This retrospective study is exempt from informed consent and institutional review. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is de-identified per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. The process by which the data is de-identified is attested to through a formal determination by a qualified expert as defined in Section §164.514(b)(1) of the HIPAA Privacy Rule. This formal determination by a qualified expert refreshed on December 2020.

Primary and secondary outcomes

The primary outcome was 30-day mortality. Secondary outcomes included acute heart failure hospitalization, acute kidney injury, stroke, acute myocardial infarction, cardiogenic shock, and cardiac arrest.

Statistical analysis

Demographic and clinical characteristics of both cohorts were summarized using descriptive statistics. Categorical variables were reported as counts and percentages, while continuous variables were reported with mean, standardized mean difference, and 95% confidence interval. Propensity score matching was done using TriNetX, which has been validated and described in prior research studies using TriNetX.

Analysis was performed on TriNetX for each cohort (patients with hyponatremia vs without hyponatremia). We utilized sociodemographic data such as (age, race, and sex), comorbidities (ischemic heart disease, diabetes, and chronic kidney disease) medications (beta blockers, aspirin) for propensity score matching. Cox model analysis on the TriNetX platform was used to calculate hazard ratios and Kaplan-Meier survival curves after PSM with significance set at P values of <0.05. Sample sizes after PSM were closer to the smaller of each cohort pair. Patients with a prior history of the endpoint of interest were excluded for each outcome **(Figure 1)**.

Result

Baseline characteristics

Prior to PSM, we identified 1,978 patients in the hyponatremia cohort (cohort 1) and 5,946 patients in no-hyponatremia cohort (cohort-2) who met the inclusion criteria. The current age of the Cohort 1 and cohort 2 were 76.8 ± 11.7 and 79.2 ± 10.8 respectively prior to propensity score matching. 51.1% of patients in cohort 1 were male as compared to 52.2% in cohort 2. The baseline characteristics of the two cohorts (N = 1,800 each) were well-balanced following propensity score matching. Both cohorts had similar mean ages at index (Cohort 1 (hyponatremia): 74.1 ± 11.9 years vs. Cohort 2 (No hyponatremia): 74.0 ± 11.7 years) and current ages (Cohort 1: 77.2 ± 11.7 years vs. Cohort 2: 77.1 ± 11.6 years). Gender distribution was comparable, with males comprising 51.3% of Cohort 1 and 50.9% of Cohort 2 and females accounting for 42.8% and 43.2%, respectively.

Racial composition was also similar across cohorts, with the majority being White (Cohort 1: 68.4%, Cohort 2: 67.2%). The prevalence of key comorbidities such as ischemic heart disease (Cohort 1: 86.2%, Cohort 2: 86.2%), diabetes mellitus (Cohort 1: 44.6%, Cohort 2: 43.2%), and chronic kidney disease (Cohort 1: 62.4%, Cohort 2: 62.5%) showed no significant differences. Medication use was also well-matched, with a high proportion of patients in both cohorts receiving beta-blockers (Cohort 1: 93%, Cohort 2: 92.6%) and aspirin (Cohort 1: 90.8%, Cohort 2: 90.1%) **(Table 1)**.

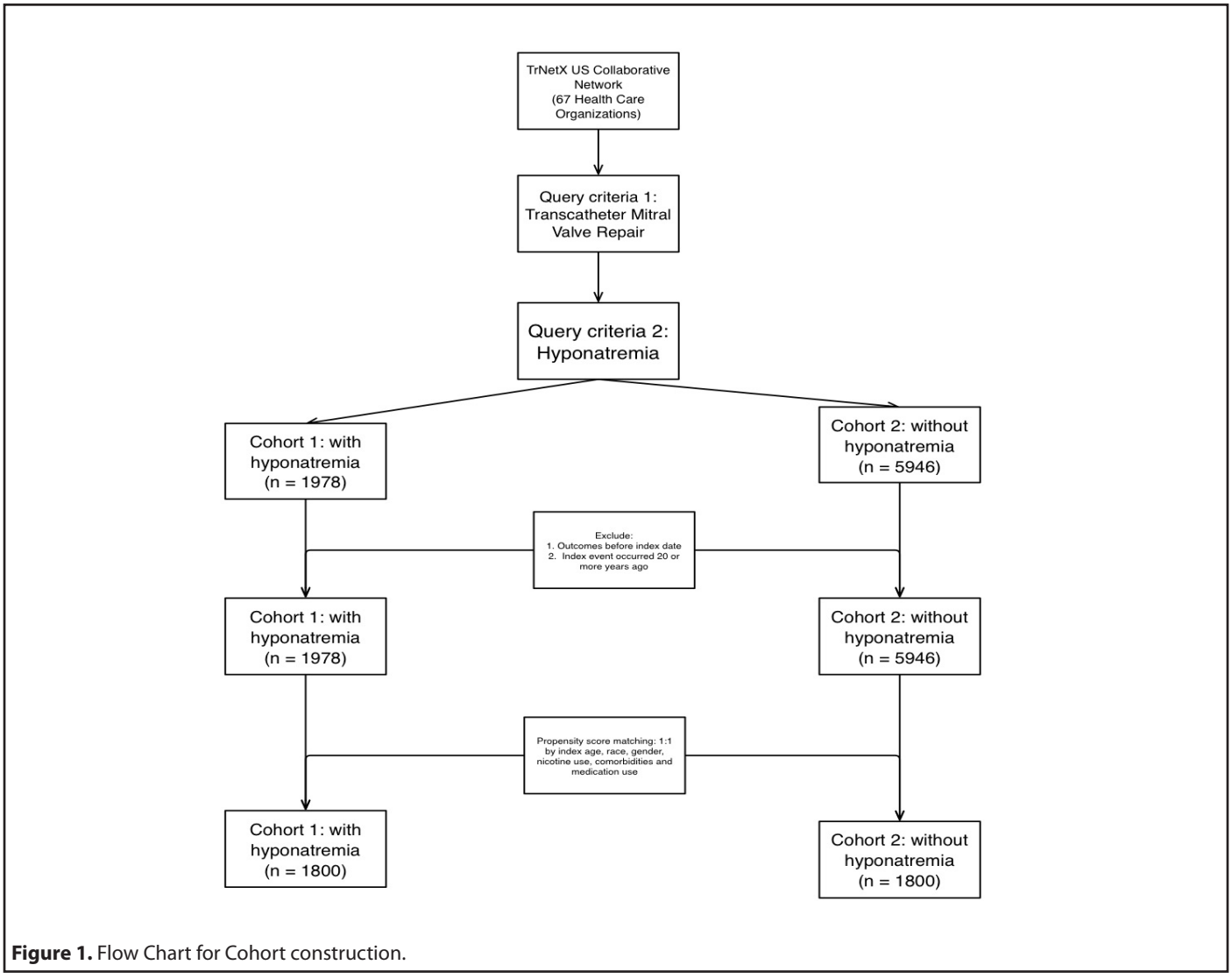

Figure 1. Flow Chart for Cohort construction.

Table 1. Baseline characteristics of study subjects (before and after Propensity score matching).

	BEFORE PROPENSITY MATCHING			AFTER PROPENSITY MATCHING		
Variable	**Hyponatremia group (n=1978)**	**Controls N=5946)**	**Std Diff**	**Hyponatremia group**	**Controls**	**Std Diff**
Age at Index (Mean ± SD)	73.7 ± 11.9	75.9 ± 11	0.215	74.1 ± 11.9	74.0 ± 11.7	0.013
GENDER						
Female	853 (1,978)	2,513 (5,946)	0.017	770 (1,800)	778 (1,800)	0.009
Male	1,011 (1,978)	3,102 (5,946)	0.021	924 (1,800)	916 (1,800)	0.009
RACE						
White	1,365 (1,978)	4,103 (5,946)	<0.001	1,232 (1,800)	1,210 (1,800)	0.026
Black/African American	204 (1,978)	481 (5,946)	0.077	182 (1,800)	194 (1,800)	0.022
Asian	81 (1,978)	219 (5,946)	0.021	74 (1,800)	74 (1,800)	<0.001
Other race	52 (1,978)	140 (5,946)	0.018	48 (1,800)	47 (1,800)	0.003
Unknown race	254 (1,978)	939 (5,946)	0.084	244 (1,800)	252 (1,800)	0.013
COMORBIDITIES (%)						
Ischemic Heart Diseases	1,727 (1,978)	4,400 (5,946)	0.342	1,552 (1,800)	1551 (1,800)	0.002
Diabetes Mellitus	936 (1,978)	1,805 (5,946)	0.353	803 (1,800)	777 (1,800)	0.029
Chronic Kidney Disease (CKD)	1,290 (1,978)	2,525 (5,946)	0.469	1,123 (1,800)	1125 (1,800)	0.002
Peripheral Vascular Disease	497 (1,978)	811 (5,946)	0.294	407 (1,800)	400 (1,800)	0.009
Paroxysmal Atrial Fibrillation	1,060 (1,978)	2,213 (5,946)	0.333	922 (1,800)	923 (1,800)	0.001
Unspecified Atrial Fibrillation	1,376 (1,978)	3,293 (5,946)	0.296	1,220 (1,800)	1,210 (1,800)	0.012
Persistent Atrial Fibrillation	688 (1,978)	1271 (5,946)	0.302	578 (1,800)	552 (1,800)	0.031
Chronic Atrial Fibrillation	716 (1,978)	1532 (5,946)	0.227	619 (1,800)	600 (1,800)	0.022
Chronic Obstructive Pulmonary Disease	704 (1,978)	1516 (5,946)	0.220	617 (1,800)	613 (1,800)	0.005
Cerebral Infarction	294 (1,978)	544 (5,946)	0.176	252 (1,800)	251 (1,800)	0.002
Depressive episode	555 (1,978)	887 (5,946)	0.324	459 (1,800)	463 (1,800)	0.005
Nicotine Dependence	415 (1,978)	697 (5,946)	0.252	351 (1,800)	343 (1,800)	0.011
Nonrheumatic aortic (valve) stenosis	630 (1,978)	1,503 (5,946)	0.146	559 (1,800)	552 (1,800)	0.008
Anemias	1,239 (1,978)	1,796 (5,946)	0.688	1,064 (1,800)	1,099 (1,800)	0.040
Secondary Pulmonary Hypertension	1,396 (1,978)	3,036 (5,946)	0.408	1,231 (1,800)	1,243 (1,800)	0.014
Nonrheumatic aortic (valve) Insufficiency	630 (1,978)	1,331 (5,946)	0.214	539 (1,800)	545 (1,800)	0.007
End stage renal disease	238 (1,978)	234 (5,946)	0.302	159 (1,800)	171 (1,800)	0.023

MEDICATIONS (%)						
Beta Blockers	1,850 (1,978)	4,871 (5,946)	0.359	1,674 (1,800)	1,666 (1,800)	0.017
Angiotensin II inhibitor	988 (1,978)	2,279 (5,946)	0.236	886 (1,800)	871 (1,800)	0.017
Aspirin	1,809 (1,978)	4,782 (5,946)	0.321	1,635 (1,800)	1,622 (1,800)	0.025
Sodium-Glucose co-transporter	407 (1,978)	719 (5,946)	0.231	350 (1,800)	329 (1,800)	0.030
Glucagon-like peptide-1 (GLP-1) analogues	83 (1,978)	120 (5,946)	0.126	67 (1,800)	62 (1,800)	0.015
Spironolactone	914 (1,978)	1,510 (5,946)	0.445	780 (1,800)	749 (1,800)	0.035

Primary outcome

Mortality outcomes: Patients with hyponatremia exhibited a significantly higher 30-day mortality risk (8.8%) compared to those without hyponatremia (3.4%), with a risk difference of 5.4% (95% CI: 3.8%, 6.9%), a risk ratio of 2.57 (95% CI: 1.93, 3.41), and all with p-values<0.001.

Kaplan-Meier survival analysis confirmed a lower survival probability in the hyponatremia cohort (90.86%) compared to the non-hyponatremia cohort (96.46%), with a log-rank test χ^2 value of 45.723 (p<0.001) and a hazard ratio of 2.65 (95% CI: 1.97, 3.55) **(Table 2)**.

Secondary outcomes

Hyponatremia was associated with significantly higher risks of several adverse clinical outcomes:

- **30-day Acute heart failure hospitalization**: 71.6% in the hyponatremia cohort vs. 66.5% in the non-hyponatremia cohort (risk difference: 5.1%, 95% CI: 2.0%, 8.1%; risk ratio: 1.08, 95% CI: 1.03, 1.12; p<0.05).
- **Acute myocardial infarction (MI)**: 5.1% vs. 3.4% (risk difference: 1.7%, 95% CI: 0.4%, 3.0%; risk ratio: 1.51, 95% CI: 1.10, 2.07; p<0.05).
- **Cardiogenic shock**: 7.1% vs. 3.4% (risk difference: 3.6%, 95% CI: 2.2%, 5.1%; risk ratio: 2.05, 95% CI: 1.52, 2.76; p<0.001).
- **Acute kidney injury (AKI)**: 18.9% vs. 9.4% (risk difference: 9.4%, 95% CI: 7.2%, 11.7%; risk ratio: 2.00, 95% CI: 1.68, 2.38; p<0.001).
- **Cardiac arrest**: 2.0% vs. 1.1% (risk difference: 0.9%, 95% CI: 0.1%, 1.7%; risk ratio: 1.80, 95% CI: 1.05, 3.10; p<0.05) **(Table 2)**.

Kaplan-Meier survival analysis for cardiac arrest showed a survival probability of 97.92% in the hyponatremia cohort versus 98.86% in the non-hyponatremia cohort, with a log-rank test χ^2 value of 4.777 (p=0.029) and a hazard ratio of 1.82 (95% CI: 1.06, 3.15).

No significant difference was observed for the risk of hypertensive emergency (risk ratio: 1.00, 95% CI: 0.42, 2.40;) and Stroke (risk ratio: 1.36, 95% CI: 0.98, 1.88) **(Figures 2-5)**.

Table 2. Outcome table.

OUTCOMES	**RR (95% CI)**	**RISK DIFFERENCE**	**NUMBER OF PATIENTS WITH OUTCOME**	
			COHORT 1	**COHORT 2**
Mortality	2.565 (1.926 - 3.414)	0.054	159	62
Acute heart failure	1.076 (1.030 - 1.124)	0.051	1288	1197
Stroke	1.361 (0.984 - 1.881)	0.012	83	61
Acute MI	1.508 (1.099 - 2.071)	0.017	92	61
Hypertensive emergency	1 (0.417 - 2.397)	0	10	10
Cardiogenic shock	2.048 (1.523 - 2.756)	0.036	127	62
AKI	2 (1.684 - 2.376)	0.094	340	170
Cardiac arrest	1.800 (1.46 - 3.097)	0.009	36	20

	χ^2	df	p
Log-Rank Test	45.723	1	0.000

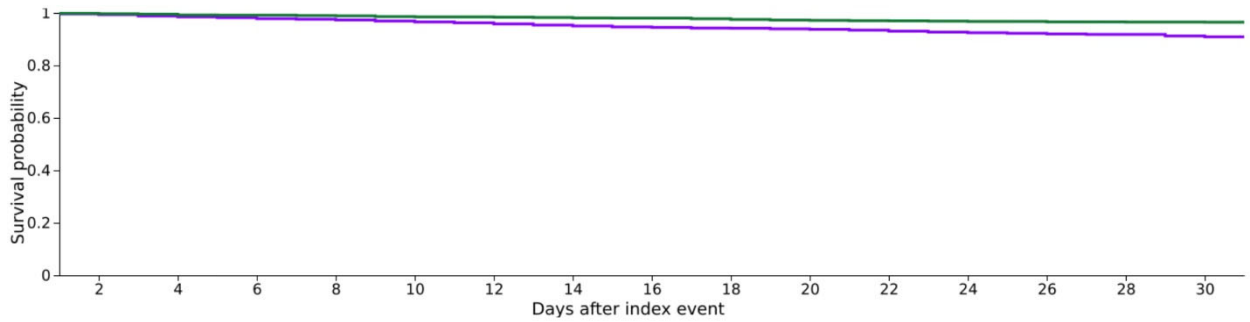

Figure 2. Survival analysis of mortality Hyponatremia cohort VS. controls.

	χ^2	df	p
Log-Rank Test	45.723	1	0.000

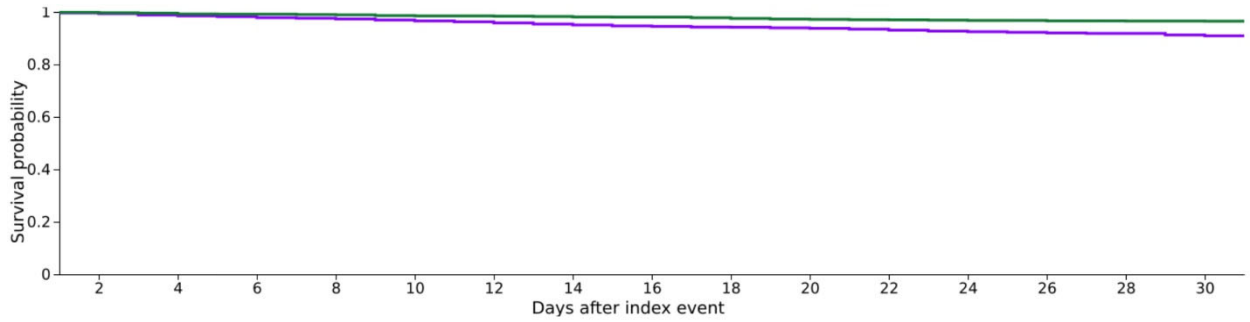

Figure 3. Survival analysis of acute heart failure hospitalization: Hyponatremia cohort vs. controls.

	χ^2	df	p
Log-Rank Test	45.723	1	0.000

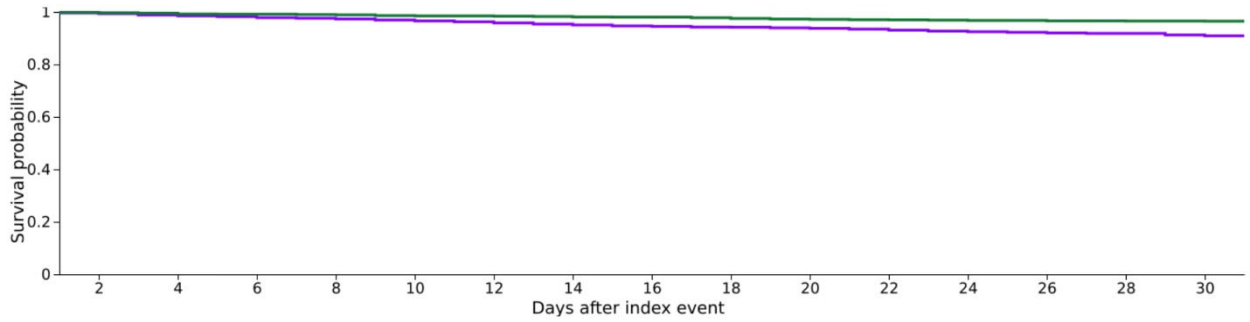

Figure 4. Kaplan-Meier analysis of AKI: Hyponatremia cohort VS. controls.

	χ^2	df	p
Log-Rank Test	4.777	1	0.029

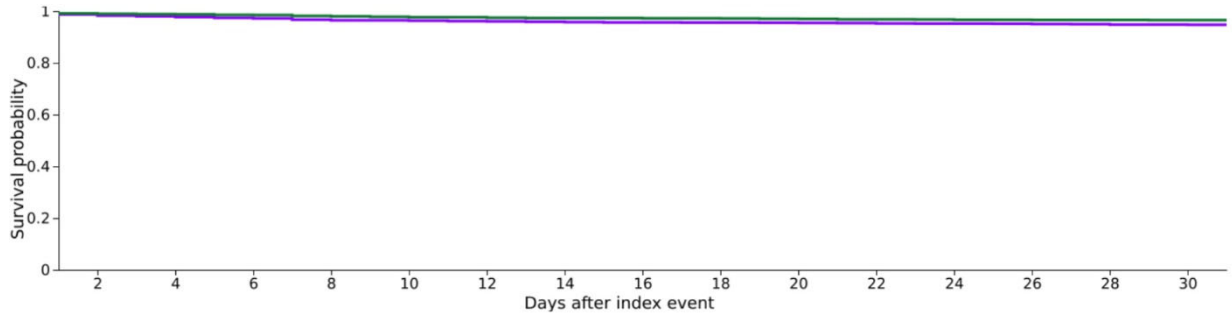

Figure 5. Survival analysis of cardiac arrest: Hyponatremia cohort VS. controls.

Discussion

This retrospective cohort study investigated the effect of hyponatremia on clinical outcomes of patients who underwent Transcatheter Mitral Valve Repair. While numerous studies have examined the association between hyponatremia and outcomes in transcatheter aortic valve replacement (TAVR) and other cardiac procedures [10,11].

To the best of our knowledge, this is the first study that investigated the effect of hyponatremia on clinical outcomes of patients in this group.

Our analysis revealed that preprocedural hyponatremia is associated with significantly worse outcomes following TMVR. Specifically, the hyponatremia cohort (159/1800) exhibited an approximately 2.5-fold increased risk of 30-day mortality compared to the normonatremic (62/1800) cohort (95% CI: 1.926–3.414). We also found a heightened risk of adverse events, including acute heart failure hospitalization, acute myocardial infarction, cardiogenic shock, acute kidney injury, and cardiac arrest.

These findings align with prior studies in other valvular interventions, such as the 2018 retrospective cohort study by Kagase *et al.*, which reported higher 30-day mortality in hyponatremic patients undergoing TAVR [7]. Similarly, Khan *et al.* identified hyponatremia as an independent predictor of adverse outcomes in cardiac surgery, with the magnitude of risk increasing with the severity of hyponatremia [12]. Likewise, Ramberg *et al.* reported that both prevalent and incident hyponatremia are associated with an increased risk of all-cause mortality in patients with Aortic Stenosis [13]. These results underscore the broad impact of hyponatremia on perioperative morbidity and mortality in TMVR patients.

Our study also found a significant association between preoperative hyponatremia and the development of Acute Kidney Injury. These findings correlate with findings in previous studies [14]. Park *et al.* reported an association between postoperative hyponatremia and worse renal prognosis in patients undergoing major urologic surgeries. A previous study established an association between hyponatremia and multi-organ dysfunction syndrome [15].

In our study, while we did include MODS as an independent outcome, our finding of increased risk of AKI, acute heart failure and cardiogenic shock correlates with this finding.

There were no differences in outcomes, such as hypertensive emergencies and stroke in the two cohorts. A similar non-association between preprocedural hyponatremia and stroke was found by Khan *et al.* [12].

The adverse outcomes observed in hyponatremic patients may be attributed to several underlying mechanisms. Hyponatremia is often a marker of advanced heart failure and neurohumoral activation, both of which are associated with poor clinical outcomes [12,16]. For instance, a significant proportion of patients in the study by Kagase *et al.* (56%) were in NYHA class III/IV, highlighting the interplay between hyponatremia and heart failure severity [7]. Additionally, hyponatremia can exacerbate hemodynamic instability and impair renal function, further increasing the risk of complications such as acute kidney injury and cardiogenic shock [17]. The specific etiology of hyponatremia—whether due to volume overload, diuretic use, or other factors—may also play a role in shaping outcomes, warranting further investigation [18]. Additionally, hyponatremia can impair myocardial function and increase the risk of arrhythmias, further complicating the perioperative course [19].

Clinicians should be aware that hyponatremic patients are at increased risk of adverse outcomes following TMVR, as such, the significance of increased vigilance cannot be overemphasized. Early identification of hyponatremia, its potential etiology and treating them is crucial to preoperative optimization of patients undergoing Transcatheter mitral valve repair.

This study benefits from the use of the TriNetX database, which provides a large, diverse sample population and valuable real-world evidence [20]. By employing propensity score matching, we minimized the influence of confounding variables, enhancing the comparability of the hyponatremia and control groups. However, as with all retrospective observational studies, there remains the potential for residual confounding due to unmeasured variables, such as differences in disease severity, medication adherence, or socioeconomic factors. Additionally, the reliance on administrative data introduces the possibility of inaccuracies or incompleteness in coding, which may affect the precision of our results.

Another limitation is the predominantly Caucasian demographic of our study population, which may limit the generalizability of our findings to other ethnic groups. Future studies should aim to include more diverse cohorts to ensure the applicability of these results across different populations. Furthermore, the observational nature of this study precludes the establishment of a definitive causal relationship between hyponatremia and adverse outcomes. Prospective randomized controlled trials are needed to confirm these findings and to evaluate the impact of interventions aimed at correcting hyponatremia prior to Transcatheter mitral valve repair.

Given the anticipated increase in Transcatheter mitral valve repair utilization, there is an urgent need for further research to identify and mitigate modifiable risk factors for adverse outcomes. Prospective studies should explore the mechanisms linking hyponatremia to poor outcomes, as well as the potential benefits of preoperative sodium correction. Additionally, the development of risk stratification tools incorporating hyponatremia and other biomarkers could help optimize patient selection and perioperative management.

Conclusion

In conclusion, this study provides compelling evidence that preprocedural hyponatremia is a significant predictor of adverse outcomes in patients undergoing Transcatheter mitral valve repair. By identifying this modifiable risk factor, our findings have important implications for preoperative risk assessment and patient management. As the field of structural heart disease continues to evolve, further research will be essential to refine our understanding of the factors influencing Transcatheter mitral valve repair outcomes and to develop strategies that enhance the quality of care for this growing patient population.

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