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Impact of hypotonic hyponatremia on outcomes in patients undergoing transcatheter aortic valve replacement: a national inpatient sample

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Abstract

Background Transcatheter aortic valve replacement (TAVR) has emerged as a major therapeutic option for treating aortic stenosis. Hyponatremia is a common electrolyte disorder closely associated with adverse cardiovascular outcomes. However, large-scale studies investigating the impact of hypotonic hyponatremia on outcomes among TAVR patients are lacking.

Methods We queried patients who underwent TAVR with concomitant hypo-osmolar hyponatremia (defined as a serum sodium concentration < 135 mEq/L with a serum osmolality < 280 mOsm/kg) using the National Inpatient Sample (2016–2021). Multivariate regression analysis and 1:1 propensity score matching (PSM) were performed to assess the associations between hypo-osmolar hyponatremia and in-hospital mortality and major adverse events (including acute kidney injury [AKI], acute myocardial infarction [AMI], and cardiogenic shock [CS]). Furthermore, sensitivity analysis was performed to assess the robustness of the findings.

Results Among the total weighted national estimate of 370,680 patients who underwent TAVR, 13,865 (3.7%) had concomitant hypo-osmolar hyponatremia. These patients had a significantly increased risk of in-hospital mortality (aOR: 1.37; 95% CI: 1.08–1.74) and a greater likelihood of developing AKI (aOR: 3.39; 95% CI: 3.07–3.74), AMI (aOR: 3.20; 95% CI: 2.77–3.70), and CS (aOR: 2.96; 95% CI: 2.52–3.47). After PSM and sensitivity analysis, these associations remained significant.

Conclusion In TAVR patients, hypo-osmolar hyponatremia is associated with increased in-hospital mortality and adverse events, including AKI, AMI, and CS.

Keywords Transcatheter aortic valve replacement, Hyponatremia, Cardiovascular outcomes, Acute kidney injury, National inpatient sample

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Introduction

Aortic stenosis is a progressive valvular heart disease that significantly impacts patient quality of life, presenting with various clinical manifestations ranging from asymptomatic valve narrowing to acute heart failure [1]. The classic triad of symptoms includes angina, syncope, and heart failure, while acute presentations may involve cardiogenic shock and pulmonary edema [2]. Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of severe aortic stenosis, particularly for high-risk surgical patients [3, 4]. According to the 2021 ESC/EACTS Guidelines, TAVR is now recommended not only for elderly patients at high surgical risk but also for selected patients at intermediate risk [5].

Since its introduction, TAVR has experienced exponential growth, with over 350,000 procedures performed across more than 70 countries [6]. As TAVR adoption continues to expand globally, understanding the factors influencing patient outcomes becomes crucial for optimizing care. One such factor is hypotonic hyponatremia, which is characterized by low serum sodium and low serum osmolality. This common electrolyte disorder affects 15–30% of hospitalized patients and has been associated with adverse outcomes in various cardiovascular conditions [7–9]. A meta-analysis indicated a significant association between hyponatremia and increased mortality in heart failure patients, underscoring the potential impact of hyponatremia in cardiovascular care, including TAVR [10].

However, the specific impact of hypotonic hyponatremia on TAVR patients remains incompletely understood. Previous studies have been limited by small sample sizes, single-center designs, or a narrow focus on mortality alone. For example, a study of 1,215 TAVR patients revealed that hyponatremia was associated with increased 30-day and 1-year mortality [11]. However, a comprehensive exploration of the effects of hypotonic hyponatremia on a broader range of outcomes, including in-hospital mortality, cardiovascular complications, and renal dysfunction, in TAVR patients has not been conducted in a large, diverse population.

To address these knowledge gaps, we conducted a retrospective analysis using the National Inpatient Sample (NIS), the largest all-payer inpatient healthcare database in the United States. This study aimed to assess the impact of hypotonic hyponatremia on in-hospital outcomes in TAVR patients. Our objective is to provide clinical insights to inform risk stratification and management strategies for TAVR patients with hypotonic hyponatremia, potentially improving their perioperative care and outcomes.

Methods

Study database

The National Inpatient Sample (NIS) is a representative database compiled by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. It encompasses data from Medicaid, Medicare, and both private and uninsured patients. The NIS includes discharge data obtained from a 20% stratified sample of community hospitals [12]. This database is designed to represent all nonfederal acute care hospitals in the United States. Each patient's record includes up to 30 discharge diagnoses and 15 procedures, documented using the International Classification of Diseases-10th Edition-Clinical Modification (ICD-10-CM) after October 2015. Institutional review board approval and informed consent were not required for this study because the NIS data were deidentified and publicly available. The data underlying this article were provided by HCUP under license. Data will be shared on request to the corresponding author with the permission of HCUP.

This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Reporting Guidelines [13]. The data underlying this article were provided by HCUP under license.

Patient population

We utilized data from the NIS database spanning from January 2016 to December 2021. Using ICD-10-CM diagnostic codes, we identified patients who underwent transcatheter aortic valve replacement (TAVR) (02RF3*). Patients with concomitant hypotonic hyponatremia (E87.1) were identified via appropriate ICD-10-CM diagnostic codes. We excluded patients aged < 18 years, those with missing baseline data, and those with other forms of hyponatremia. Demographic characteristics (age, sex, and race), socioeconomic features, and hospital details (teaching status, location, and bed count) along with the primary payer linked to each discharge were retrieved from the HCUP-NIS database. The burden of comorbidities was assessed via the Elixhauser Comorbidity Index. Subgroup analyses were stratified by sex, renal disease, liver disease, and other electrolyte disorders. The appendix contains the ICD retrieval codes employed in this study (Table S1).

Exposure

Hypotonic hyponatremia was defined as a serum sodium concentration < 135 mEq/L with a serum osmolality < 280 mOsm/kg [14].

Outcome measures

The primary study endpoint was in-hospital mortality. The secondary endpoints were major adverse events, including cardiogenic shock (CS), atrial fibrillation (AF),

acute myocardial infarction (AMI), acute kidney injury (AKI), permanent pacemaker implantation (PPI), and cardiac arrest (CA).

Statistical analysis

NIS sampling weights were applied to obtain nationwide estimates of hospital and patient numbers. For baseline characteristics, continuous variables are reported as survey-weighted means with 95% confidence intervals (CIs), and categorical variables are presented as survey-weighted percentages with 95% CIs. Statistical comparisons between groups were conducted using survey-weighted linear regression for continuous variables and survey-weighted Chi-square tests for categorical variables, accounting for the complex survey design of the NIS database [15, 16]. All analyses incorporated the survey weights, strata, and cluster variables following established methodological guidelines [17]. To evaluate the effects of hypotonic hyponatremia on study endpoints among patients who underwent TAVR, we performed multivariable logistic regression analyses. The regression models were adjusted for baseline characteristics and for covariates that showed significant differences between groups in the univariate analysis, including age; sex; race; payment type; median household income for the patient's ZIP Code; hospital teaching status; hospital bed size; smoking; dyslipidemia; obesity; prior stroke/TIA; prior myocardial infarction; potassium metabolism disorders; acid–base imbalance; volume overload or volume depletion; and diabetes. The results are presented as unadjusted and adjusted odds ratios (aORs) with their corresponding 95% confidence intervals (CIs).

Furthermore, we conducted 1:1 propensity score matching (PSM) to validate the stability of our results by minimizing confounding factors between patients with hypotonic hyponatremia and those without hypotonic hyponatremia who underwent TAVR. The propensity score was calculated via a logistic regression model that included demographic characteristics, socioeconomic factors, hospital features, and relevant comorbidities. A nearest-neighbor matching algorithm was employed with a caliper width of 0.01 standard deviations of the logit of the propensity score. The balance between matched groups was assessed via the standardized mean difference (SMD), with SMD < 0.1 indicating good balance. For continuous variables, the SMD was calculated as the absolute difference in means divided by the square root of the average of the squared standard deviations; for categorical variables, the SMD was calculated as the absolute difference in proportions divided by the square root of the average of the variances.

We also performed subgroup analyses to investigate the associations between hypotonic hyponatremia and in-hospital outcomes across different patient subgroups. The stratification factors included sex, renal disease, liver disease, and other electrolyte disorders. For each subgroup analysis, we conducted formal interaction testing using likelihood ratio tests comparing models with and without interaction terms between hyponatremia and stratification variables, to evaluate whether the associations differed significantly between subgroups. Statistical significance for interaction was set at $P < 0.05$. To assess the robustness of our findings, we conducted a sensitivity analysis excluding patients with other electrolyte disorders.

Statistical analyses were conducted via R (http://www.R-project.org, The R Foundation) and Empower Stats (http://www.empowerstats.com, X&Y Solution, Inc., Boston, MA). Statistical significance was determined by a two-tailed P value < 0.05.

Results

Patient characteristics and comorbidities

A total of 370,680 weighted national estimate hospitalizations of patients who underwent TAVR were identified from the National Inpatient Sample (NIS) database between 2016 and 2021, of which 3.7% ($n = 13,865$) had hypotonic hyponatremia (Fig. 1). The baseline characteristics of patients who underwent TAVR with concomitant hypoosmolar hyponatremia are shown in Table 1. Patients with hypotonic hyponatremia were slightly younger (78.20 vs. 78.69 years, $P = 0.01$) and were more likely to be female (46.95% vs. 44.35%, $P = 0.05$). In terms of comorbidities, patients with hypotonic hyponatremia had lower rates of smoking (32.92% vs. 40.53%, $P < 0.01$) and dyslipidemia (65.24% vs. 74.42%, $P < 0.01$) but slightly higher rates of hypertension (90.59% vs. 88.69%, $P < 0.01$). The differences in diabetes mellitus and prior myocardial infarction were not significant. Notably, patients with hypotonic hyponatremia had a significantly greater proportion of patients with Elixhauser comorbidity index scores ≥ 3 (99.68% vs. 92.71%, $P < 0.01$).

Multivariate regression analysis

After adjusting for potential confounders, hypotonic hyponatremia was a significant predictor of acute kidney injury (AKI) (aOR: 3.39; 95% CI: 3.07–3.74, $p < 0.01$), acute myocardial infarction (AMI) (aOR: 3.20; 95% CI: 2.77–3.70, $p < 0.01$), cardiogenic shock (CS) (aOR: 2.96; 95% CI: 2.52–3.47, $p < 0.01$), atrial fibrillation (AF) (aOR: 1.26; 95% CI: 1.16–1.37, $p < 0.01$), and permanent pacemaker implantation (PPI) (aOR: 1.26; 95% CI: 1.11–1.42, $p = 0.02$). Additionally, hypotonic hyponatremia was associated with increased risks of in-hospital mortality (aOR: 1.37; 95% CI: 1.08–1.74, $p = 0.01$). However, the association between hypotonic hyponatremia and cardiac arrest (CA) was not statistically significant in the

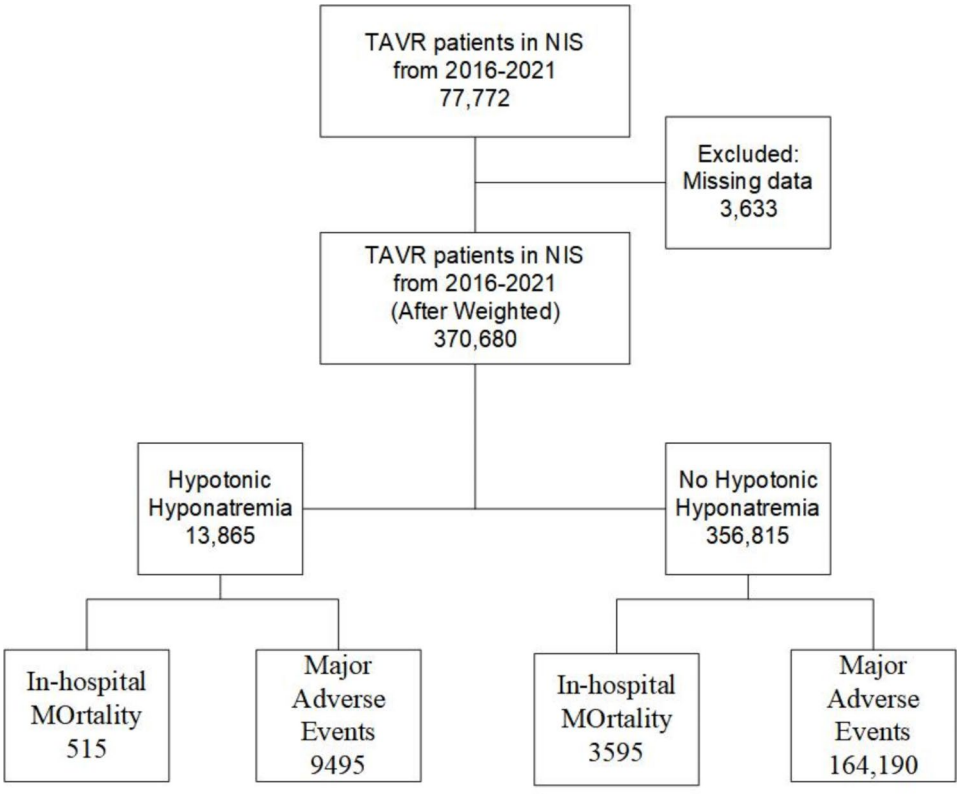

Fig. 1 Flowchart for selecting analyzed participants

adjusted model (aOR: 1.24; 95% CI: 0.93–1.66, $p=0.14$) (see Table 2 for detailed results).

Subgroup analysis

In sex-stratified analyses, hypotonic hyponatremia showed consistent associations with most clinical outcomes in both males and females, except for CS, AMI, and AKI where significant sex-based differences were observed (all interaction $P<0.01$). The association with CS was more pronounced in males (aOR: 3.63, 95% CI: 2.98–4.43) than in females (aOR: 1.93, 95% CI: 1.45–2.56). Similar patterns were observed for AMI (males: aOR 3.67, 95% CI: 3.05–4.42; females: aOR 2.48, 95% CI: 1.94–3.15) and AKI (males: aOR 3.86, 95% CI: 3.38–4.40; females: aOR 2.90, 95% CI: 2.49–3.38).

The presence of liver disease significantly modified the associations between hypotonic hyponatremia and several outcomes. Patients with liver disease demonstrated stronger associations for CS (aOR: 5.73, 95% CI: 4.00-8.20) and AMI (aOR: 8.19, 95% CI: 5.45–12.31) compared to those without liver disease (cardiogenic shock: aOR 2.19, 95% CI: 1.81–2.65; acute myocardial infarction: aOR 2.49, 95% CI: 2.10–2.94; all interaction $P<0.01$).

Among patients with kidney disease, the association between hypotonic hyponatremia and AKI was significantly stronger (interaction $P=0.01$) compared to those without kidney disease (aOR: 3.71, 95% CI:3.27–4.21 vs. aOR: 2.86, 95% CI:2.42–3.37). Other clinical outcomes showed similar associations regardless of kidney disease status.

The impact of hypotonic hyponatremia was generally more pronounced in patients without other electrolyte disorders, particularly for in-hospital mortality (aOR: 3.05, 95% CI: 2.31–4.02 vs. aOR: 0.87, 95% CI: 0.61–1.25; interaction $P<0.01$) and CS (aOR: 5.67, 95% CI: 4.75–6.75 vs. aOR: 1.72, 95% CI: 1.32–2.24; interaction $P<0.01$) (Table 3).

Sensitivity analysis

The results remained robust when patients with other electrolyte disorders were excluded (see Table 4). Among patients who underwent TAVR, hypotonic hyponatremia was significantly associated with CS (aOR: 5.67; 95% CI: 4.75–6.75, $p<0.01$), AKI (aOR: 4.74; 95% CI: 4.26–5.26, $p<0.01$), AMI (aOR: 4.71; 95% CI: 4.03–5.50, $p<0.01$), and CA (aOR: 2.16; 95% CI: 1.54–3.04, $p<0.01$). There was a significant association between hypotonic hyponatremia and in-hospital mortality (aOR: 3.05; 95% CI: 2.31–4.02, $p<0.01$) (Table 4).

Propensity score matching

After 1:1 PSM, the baseline characteristics were well balanced between the matched groups (Table S2). Among patients who underwent TAVR, after adjustment for

Table 1 Characteristics of patients with hypotonic hyponatremia undergoing TAVR after weighted

Characteristic, % (95% CI)	Normal Sodium (*N* = 365,815)	Hyponatremia (*N* = 13,865)	*P*-value
AGE, mean (95% CI)	78.69 (78.56, 78.81)	78.20 (77.84, 78.57)	0.0146
FEMALE, % (95% CI)	44.35 (43.62, 45.09)	46.95 (44.48, 49.44)	0.0484
RACE, % (95% CI)			0.0162
White	87.79 (87.33, 88.24)	86.26 (84.83, 87.57)	
Black	4.03 (3.80, 4.28)	3.79 (3.13, 4.58)	
Hispanic	4.64 (4.31, 4.98)	5.45 (4.64, 6.38)	
Other	3.54 (3.32, 3.78)	4.51 (3.78, 5.36)	
Median Household Income Quartile			0.9453
1st (lowest)	20.71 (20.25, 21.17)	20.63 (19.01, 22.35)	
2nd	24.84 (24.33, 25.36)	24.49 (22.71, 26.35)	
3rd	26.19 (25.57, 26.82)	25.93 (24.10, 27.84)	
4th (highest)	28.26 (27.47, 29.06)	28.96 (26.05, 32.05)	
Primary Payer			0.0054
Medicare	88.03 (87.55, 88.49)	86.48 (85.06, 87.78)	
Medicaid	1.59 (1.33, 1.90)	2.49 (1.96, 3.15)	
Private insurance	8.15 (7.78, 8.54)	8.47 (7.45, 9.62)	
Self-pay/Other	2.23 (2.12, 2.35)	2.56 (2.03, 3.23)	
High teaching			0.6885
Non-teaching	1.29 (1.27, 1.31)	1.19 (0.85, 1.66)	
Low teaching	10.83 (10.26, 11.44)	9.70 (6.84, 13.59)	
High teaching	87.87 (87.28, 88.45)	89.11 (85.32, 92.01)	
Hospital Bed Size			< 0.0001
Small	6.92 (6.72, 7.12)	7.28 (6.39, 8.29)	
Medium	24.08 (23.35, 24.83)	17.56 (16.09, 19.14)	
Large	69.00 (68.30, 69.70)	75.15 (73.32, 76.90)	
Comorbidities, % (95% CI)			
SMOKING	40.53 (39.81, 41.26)	32.92 (30.86, 35.06)	< 0.0001
DYSLIPIDEMIA	74.42 (73.75, 75.08)	65.24 (63.05, 67.36)	< 0.0001
Hypertension	88.69 (88.21, 89.16)	90.59 (89.39, 91.66)	0.0046
Diabetes Mellitus	37.57 (36.87, 38.27)	39.42 (37.15, 41.73)	0.1282
Prior Myocardial Infarction	11.94 (11.50, 12.41)	10.85 (9.69, 12.14)	0.1140
PRIOR_STROKE_TIA	11.62 (11.17, 12.08)	8.51 (7.48, 9.66)	< 0.0001
SIADH, % (95% CI)	0.12 (0.10, 0.15)	0.07 (0.02, 0.29)	0.4477
ELIXHAUSER_INDEX.S, % (95% CI)			< 0.0001
0	0.03 (0.02, 0.04)	0.00 (0.00, 0.00)	
1	1.14 (1.07, 1.23)	0.00 (0.00, 0.00)	
2	6.11 (5.83, 6.41)	0.32 (0.17, 0.62)	
≥ 3	92.71 (92.41, 93.01)	99.68 (99.38, 99.83)	
In-hospital outcomes, %			
In-hospital Mortality	1.01 (0.94, 1.08)	3.71 (3.06, 4.50)	< 0.0001
Cardiogenic Shock	1.60 (1.37, 1.87)	10.24 (7.35, 14.09)	< 0.0001
Permanent Pacemaker Implantation	8.90 (8.56, 9.24)	12.30 (11.06, 13.66)	< 0.0001
Atrial Fibrillation	35.48 (34.80, 36.17)	42.70 (40.34, 45.09)	< 0.0001
Cardiac Arrest	0.84 (0.71, 1.01)	2.16 (1.68, 2.78)	< 0.0001
Acute Myocardial Infarction	2.12 (2.01, 2.23)	10.10 (7.21, 13.96)	< 0.0001
Acute Kidney Injury	8.26 (7.91, 8.63)	34.04 (31.20, 37.01)	< 0.0001

Table 2 Associations between hypotonic hyponatremia and clinical outcomes in patients undergoing TAVR

Outcome	Non-adjusted	Adjust I	Adjust II
In-hospital Mortality	3.79 (3.07, 4.68) < 0.0001	3.66 (2.96, 4.52) < 0.0001	1.37 (1.08, 1.74) 0.0100
Cardiogenic Shock	7.00 (6.11, 8.02) < 0.0001	6.91 (6.01, 7.93) < 0.0001	2.96 (2.52, 3.47) < 0.0001
Permanent Pacemaker Implantation	1.44 (1.28, 1.61) < 0.0001	1.44 (1.28, 1.61) < 0.0001	1.26 (1.11, 1.42) 0.0002
Atrial Fibrillation	1.35 (1.25, 1.46) < 0.0001	1.40 (1.29, 1.51) < 0.0001	1.26 (1.16, 1.37) < 0.0001
Cardiac Arrest	2.60 (1.99, 3.40) < 0.0001	2.64 (2.01, 3.45) < 0.0001	1.24 (0.93, 1.66) 0.1430
Acute Myocardial Infarction	5.19 (4.54, 5.93) < 0.0001	5.10 (4.46, 5.83) < 0.0001	3.20 (2.77, 3.70) < 0.0001
Acute Kidney Injury	5.73 (5.27, 6.22) < 0.0001	5.74 (5.28, 6.24) < 0.0001	3.39 (3.07, 3.74) < 0.0001

Note: Values are presented as Odds Ratio (95% Confidence Interval) *P*-value. All outcomes are compared to the reference group (normal sodium levels)

Models:

• Non-adjusted model: No adjustments

• Adjust I model: Adjusted for Age, Sex, Race, Payment type, Median household income for patient's ZIP Code, Hospital teaching status, Hospital bed size

• Adjust II model: Adjusted for all variables in Adjust I, plus Smoking, Dyslipidemia, Obesity, Prior stroke/TIA, Prior myocardial infarction, Potassium Metabolism Disorder, Acid-Base Imbalance, Volume Overload or Volume Depletion, Diabetes

Table 3 Subgroup analysis of clinical outcomes associated with hypotonic hyponatremia in patients undergoing TAVR

Stratification	*N*	In-hospital Mortality	Cardiogenic Shock	Permanent Pacemaker Implantation	Atrial Fibrillation	Cardiac Arrest	Acute Myocardial Infarction	Acute Kidney Injury
Sex								
Male	41,181	1.37 (0.96, 1.95) 0.0815	3.63 (2.98, 4.43) < 0.0001	1.37 (1.16, 1.61) 0.0002	1.25 (1.12, 1.39) < 0.0001	1.53 (1.05, 2.21) 0.0252	3.67 (3.05, 4.42) < 0.0001	3.86 (3.38, 4.40) < 0.0001
Female	32,958	1.37 (0.98, 1.90) 0.0632	1.93 (1.45, 2.56) < 0.0001	1.14 (0.95, 1.37) 0.1510	1.27 (1.13, 1.43) < 0.0001	0.94 (0.58, 1.51) 0.7951	2.48 (1.94, 3.15) < 0.0001	2.90 (2.49, 3.38) < 0.0001
Interaction *P*-value*		0.98663	< 0.0001	0.3306	0.8741	0.2000	0.0073	0.0035
Kidney Disease								
No	49,338	1.09 (0.76, 1.57) 0.6367	2.41 (1.86, 3.13) < 0.0001	1.26 (1.07, 1.49) 0.0068	1.32 (1.18, 1.47) < 0.0001	1.16 (0.76, 1.76) 0.4944	2.95 (2.36, 3.68) < 0.0001	2.86 (2.42, 3.37) < 0.0001
Yes	24,801	1.72 (1.25, 2.37) 0.0009	3.26 (2.65, 4.01) < 0.0001	1.24 (1.04, 1.47) 0.0166	1.19 (1.05, 1.34) 0.0045	1.33 (0.89, 2.00) 0.1678	3.27 (2.69, 3.97) < 0.0001	3.71 (3.27, 4.21) < 0.0001
Interaction *P*-value*		0.0658	0.0760	0.8972	0.2022	0.6416	0.4929	0.0125
Liver Disease								
No	71,437	1.68 (1.30, 2.16) < 0.0001	2.19 (1.81, 2.65) < 0.0001	1.32 (1.16, 1.49) < 0.0001	1.29 (1.18, 1.40) < 0.0001	1.36 (1.00, 1.86) 0.0507	2.49 (2.10, 2.94) < 0.0001	3.17 (2.86, 3.52) < 0.0001
Yes	2702	0.56 (0.29, 1.06) 0.0726	5.73 (4.00, 8.20) < 0.0001	0.72 (0.43, 1.20) 0.2129	1.20 (0.89, 1.62) 0.2264	0.94 (0.43, 2.08) 0.8794	8.19 (5.45, 12.31) < 0.0001	5.38 (3.91, 7.41) < 0.0001
Interaction *P*-value*		0.0013	< 0.0001	0.0185	0.2600	0.2370	< 0.0001	< 0.0001
Other Electrolyte Disorders								
No	70,403	3.05 (2.31, 4.02) < 0.0001	5.67 (4.75, 6.75) < 0.0001	1.37 (1.19, 1.56) < 0.0001	1.31 (1.20, 1.43) < 0.0001	2.16 (1.54, 3.04) < 0.0001	4.71 (4.03, 5.50) < 0.0001	4.74 (4.26, 5.26) < 0.0001
Yes	3736	0.87 (0.61, 1.25) 0.4539	1.72 (1.32, 2.24) < 0.0001	1.09 (0.85, 1.41) 0.4906	1.28 (1.06, 1.54) 0.0106	1.01 (0.63, 1.62) 0.9504	1.85 (1.38, 2.48) < 0.0001	2.35 (1.94, 2.85) < 0.0001
Interaction *P*-value*		< 0.0001	< 0.0001	0.2047	0.9114	0.0307	< 0.0001	< 0.0001

Note: Values are presented as Odds Ratio (95% Confidence Interval) *P*-value. All outcomes are compared to the reference group (normal sodium levels) within each stratum

Adjusted variables:

• Sex stratification: Age, Race, Payment type, Median household income for patient's ZIP Code, Hospital teaching status, Hospital bed size, Smoking, Dyslipidemia, Prior stroke/TIA, Prior myocardial infarction, Potassium Metabolism Disorder, Acid-Base Imbalance, Volume Overload or Volume Depletion, SIADH, Diabetes

• Kidney disease stratification: Same as sex stratification, plus Sex

• Liver disease stratification: Same as kidney disease stratification, plus Kidney disease

• Other electrolyte disorders stratification: Same as liver disease stratification, except Potassium Metabolism Disorder and Acid-Base Imbalance,

demographics and comorbidities, hypotonic hyponatremia was significantly associated with AKI (aOR: 2.82; 95% CI: 2.49–3.20, $p < 0.01$), CS (aOR: 2.67; 95% CI: 2.11–3.38, $p < 0.01$), AMI (aOR: 2.37; 95% CI: 1.87–3.01, $p < 0.01$), and AF (aOR: 1.26; 95% CI: 1.13–1.41, $p < 0.01$). The association between hypotonic hyponatremia and in-hospital mortality remained significant (aOR: 1.41; 95% CI: 1.05–1.90, $p = 0.02$) (Table 5).

Table 4 Clinical outcomes associated with hypotonic hyponatremia in patients undergoing TAVR: A Sensitivity Analysis

Outcome	Non-adjusted Model	Adjust I Model	Adjust II Model
In-hospital Mortality			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	3.87 (2.95, 5.08) < 0.0001	3.68 (2.80, 4.83) < 0.0001	3.05 (2.31, 4.02) < 0.0001
Cardiogenic Shock			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	7.40 (6.26, 8.75) < 0.0001	7.42 (6.27, 8.79) < 0.0001	5.67 (4.75, 6.75) < 0.0001
Permanent Pacemaker Implantation			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	1.38 (1.21, 1.57) < 0.0001	1.37 (1.20, 1.57) < 0.0001	1.37 (1.19, 1.56) < 0.0001
Atrial Fibrillation			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	1.32 (1.21, 1.44) < 0.0001	1.33 (1.22, 1.46) < 0.0001	1.31 (1.20, 1.43) < 0.0001
Cardiac Arrest			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	2.38 (1.70, 3.33) < 0.0001	2.44 (1.74, 3.42) < 0.0001	2.16 (1.54, 3.04) < 0.0001
Acute Myocardial Infarction			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	5.48 (4.71, 6.38) < 0.0001	5.42 (4.65, 6.31) < 0.0001	4.71 (4.03, 5.50) < 0.0001
Acute Kidney Injury			
Normal Sodium	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
Low Sodium	5.22 (4.74, 5.76) < 0.0001	5.25 (4.76, 5.79) < 0.0001	4.74 (4.26, 5.26) < 0.0001

Note: Values are presented as Odds Ratio (95% Confidence Interval) *P*-value

Model adjustments:

• Non-adjusted model: No adjustments

• Adjust I model: Age, Sex, Race, Primary payer, Median household income quartile, Hospital teaching status, Hospital bed size

• Adjust II model: Age, Sex, Race, Primary payer, Median household income quartile, Hospital teaching status, Hospital bed size, Smoking, Dyslipidemia, Prior stroke/TIA, Prior myocardial infarction, SIADH, Diabetes

Table 5 Clinical outcomes associated with hypotonic hyponatremia in patients undergoing TAVR after PSM

Clinical Outcome	Odds Ratio (95% CI)	*P*-value
In-hospital Mortality	1.41 (1.05, 1.90)	0.0228
Cardiogenic Shock	2.67 (2.11, 3.38)	< 0.0001
Permanent Pacemaker Implantation	1.16 (0.98, 1.38)	0.0813
Atrial Fibrillation	1.26 (1.13, 1.41)	< 0.0001
Cardiac Arrest	1.14 (0.78, 1.66)	0.5028
Acute Myocardial Infarction	2.37 (1.87, 3.01)	< 0.0001
Acute Kidney Injury	2.82 (2.49, 3.20)	< 0.0001

Odds ratios are presented for the low sodium group compared to the normal sodium group (reference)

CI: Confidence Interval

Discussion

Our study, which analyzed 370,680 weighted TAVR hospitalizations, revealed several key findings regarding the impact of hypotonic hyponatremia on patients undergoing TAVR. First, hyponatremia with low osmolality poses a greater risk of mortality and severe complications such as acute kidney injury, acute myocardial infarction, and cardiogenic shock during hospitalization for patients undergoing TAVR. These trends persist even after propensity score matching, indicating an independent association between hypotonic hyponatremia and adverse outcomes. Second, male patients with hypotonic hyponatremia are at greater risk for acute myocardial infarction and cardiogenic shock than female patients. Third, patients with preexisting conditions such as liver disease and kidney disease demonstrated stronger associations between hypotonic hyponatremia and adverse outcomes, particularly for cardiogenic shock and acute kidney injury, respectively.

Our findings are largely consistent with those of previous studies on the impact of hyponatremia on cardiovascular disease patients and provide new insights specific to the TAVR population. A large-scale multicenter study revealed that hyponatremia is associated with a 25% increase in mortality during hospitalization for patients with acute heart failure, and these patients also experience an increased rate of readmission, which is consistent with our findings [18]. However, our study extends these findings to the TAVR patient population. Similarly, a retrospective cohort study by Khan et al. indicated that hyponatremia is associated with adverse outcomes following coronary artery bypass graft surgery, including an 80% increase in the risk of death as well as a heightened incidence of various complications [19]. While their study population differed, the trend of results parallels ours, underscoring the universal importance of hyponatremia in cardiovascular patients. Notably, our

larger sample size and nationwide coverage increase the representativeness and generalizability of our findings. Furthermore, a multicenter study based on the Japanese population indicated that among the 1,215 TAVR patients they investigated, 106 patients with concomitant hyponatremia faced a higher risk of mortality within 30 days postdischarge [11]. However, their research was based on a Japanese population, with a total sample size of only 1,200 individuals, which is insufficient to adequately represent the overall TAVR population. In contrast to their study, our research included a sample from across the United States, and a larger sample size reduces the likelihood of selection bias, making our findings more universally representative. This finding is consistent with the results of Konigstein et al., who identified hyponatremia as an independent predictor of acute kidney injury in heart failure patients [20]. These findings not only complement the literature but also provide new perspectives on perioperative management for TAVR patients, highlighting the importance of monitoring and correcting electrolyte imbalances in this unique population.

Mechanistically, hypotonic hyponatremia may affect the prognosis of TAVR patients through multiple complex pathways. Filippatos and M.S. Elisaf noted that hyponatremia may reflect neurohumoral dysregulation and hemodynamic instability, potentially increasing the risk of cardiovascular events [21]. Specifically, hyponatremia may activate the renin–angiotensin–aldosterone system (RAAS) and the sympathetic nervous system, leading to myocardial remodeling and deterioration of cardiac function [22–24]. This activation may result in vasoconstriction, water and sodium retention, and myocardial fibrosis, further increasing the cardiac burden [25–30]. Interestingly, while RAAS activation contributes to adverse outcomes, recent evidence from the Effect TAVI registry suggests that RAAS inhibitors can significantly reduce cardiovascular mortality in hypertensive patients with severe aortic stenosis undergoing TAVR [31]. However, the management of RAAS activation in TAVR patients with hyponatremia requires careful consideration of the balance between potential cardiovascular benefits and risks of electrolyte disturbances [32]. Future studies are needed to evaluate optimal pharmacological strategies that can effectively address both RAAS activation and electrolyte homeostasis in this unique patient population.

Lim et al.'s review emphasized the complex relationship between hyponatremia and renal dysfunction [33], which may explain the strong association we observed between hyponatremia and acute kidney injury. Hyponatremia may increase the risk of acute kidney injury by affecting renal tubular function and renal hemodynamics. Specifically, hyponatremia may cause renal tubular cell swelling, affecting the tubuloglomerular feedback mechanism and thus altering renal hemodynamics [34–36]. These pathophysiological changes through cardiovascular and renal mechanisms may explain the increased risk of various complications we observed in TAVR patients with hyponatremia.

Our research also revealed that hyponatremia is significantly associated with other major complications, with the risk of patients experiencing cardiogenic shock and acute myocardial infarction increasing by 1.96-fold and 2.20-fold, respectively. These findings are consistent with the results of Breen, T., et al., who reported in a large retrospective study that hyponatremia was significantly associated with multiple organ dysfunction syndrome after cardiovascular surgery [19, 37, 38].

Notably, hyponatremia may affect the prognosis of TAVR patients through other mechanisms. For example, a study from the ACS-NSQIP database indicated that hyponatremia may be associated with an enhanced inflammatory response, which could exacerbate postoperative inflammation and increase the risk of complications [39]. Furthermore, a single-center study based on data from DMC Detroit Receiving Hospital revealed that hyponatremia may affect platelet function and the coagulation system, thereby increasing the risk of bleeding and thrombus formation, which is particularly significant for patients undergoing TAVR who are receiving anticoagulation therapy [40].

Finally, hyponatremia may be related to drug interactions. Falhammar et al. noted that many drugs commonly used to treat cardiovascular diseases, such as diuretics and RAAS inhibitors, may exacerbate or cause hyponatremia. This drug-related hyponatremia may further complicate the management of TAVR patients [32].

This study is the first to systematically evaluate the association between hyponatremia and multiple post-TAVR complications via a large-scale national database, providing a more comprehensive risk assessment basis for clinical decision-making. On the basis of these findings, we recommend incorporating sodium level monitoring into routine preoperative evaluation and postoperative surveillance for TAVR patients and considering individualized electrolyte management strategies for high-risk patients. Furthermore, the strong associations revealed between hyponatremia and specific complications, such as cardiogenic shock and acute kidney injury, suggest potential underlying pathophysiological mechanisms that merit further investigation. Future research directions may include prospective evaluation of the impact of active hyponatremia correction on TAVR patient outcomes, as well as exploration of the causal relationships between hyponatremia and TAVR-related complications.

Strengths

This study has several notable strengths. First, it utilizes the NIS database, which encompasses a large cohort of TAVR patients. This large sample enhances the representativeness of the findings and allows for better generalizability to the broader patient population. Second, the retrospective design employs robust statistical methodologies, such as multivariable regression analysis and PSM. These methods effectively control for potential confounders, thereby increasing the reliability of our results. Additionally, the detailed subgroup analyses demonstrated variations in the impact of hypotonic hyponatremia across different patient populations, highlighting that the effects may differ on the basis of patient characteristics. Overall, these rigorous methods not only strengthen the scientific foundation of the study but also provide critical insights for clinical practice. These findings underscore the importance of vigilant monitoring and management of electrolyte imbalances in TAVR patients.

Limitations

This study has several significant limitations that warrant consideration. First, due to the inherent constraints of the NIS database, we were unable to accurately determine the timing of hypotonic hyponatremia in relation to TAVR procedures (pre-, peri-, or post-procedural onset). This limitation prevents us from establishing a temporal relationship between hyponatremia and TAVR outcomes. Second, the database lacks detailed laboratory values, particularly sodium concentrations, which restricted our ability to investigate the impact of varying degrees of hyponatremia severity on hospital outcomes and evaluate specific treatment approaches. Third, the absence of long-term follow-up data limits our understanding of the extended impact of hyponatremia on patient outcomes beyond the hospital stay. These limitations emphasize the need for future research through prospective, multicenter studies with detailed laboratory data collection and long-term follow-up to better understand the role and effects of hypotonic hyponatremia in TAVR patients.

Conclusion

This study highlights the significant impact of hypotonic hyponatremia on the in-hospital outcomes of patients undergoing TAVR. Our analysis revealed that hypotonic hyponatremia is independently associated with increased risks of in-hospital mortality, acute kidney injury, acute myocardial infarction, and cardiogenic shock, especially in patients with preexisting renal conditions. Given these findings, further research is essential to explore targeted interventions that address the mechanisms behind hypotonic hyponatremia. This underscores the urgent need for heightened awareness and enhanced perioperative care strategies among clinicians to better manage this electrolyte imbalance in TAVR patients.

Abbreviations

AF	Atrial fibrillation
AHRQ	Agency for Healthcare Research and Quality
AKI	Acute kidney injury
AMI	Acute myocardial infarction
AOR	Adjusted odds ratio
CA	Cardiac arrest
CI	Confidence interval
CS	Cardiogenic shock
ICD-10-CM/PCS	International Classification of Diseases, TEN Revision, Clinical Modification/Procedure Coding System
NIS	National Inpatient Sample
OR	Odds ratio
PPI	Permanent pacemaker implantation
PSM	Propensity score matching
SD	Standard deviation
TAVR	Transcatheter aortic valve replacement

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not applicable.

Author contributions

Shizhe Fu and Guangzhi Cong performed the formal analysis and wrote the original draft. Guangzhi Cong, Xueping Ma and Shaobin Jia acquired funding, provided resources, and supervised the project. Kairu Wang, Congyan Ye, Rui Yan, Bo Shi and Ru Yan conducted the formal analysis and developed the software. Israel Gitangaza and Abdul Rehman managed the project administration and carried out the investigation. All the authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analysed during the current study are available on the HCUP website. https://hcup-us.ahrq.gov/. All data supporting this research also can be obtained upon request from Dr. Shizhe Fu and Dr. Guangzhi Gong.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

This study was performed using deidentified dataset and individual consent not required.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

Data collection methods statement
The study focused solely on inpatient data during the hospital stay, without any post-discharge follow-up investigation. The research was conducted entirely using the data from the National Inpatient Sample (NIS) database, which contains standardized hospital discharge records. No questionnaires or interviews were utilized in this study.

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