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Dynamic Changes in Serum Sodium During Acute Hospitalisation for Heart Failure and Their Short-Term Prognostic Significance: A Systematic Review

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Abstract

Hyponatraemia is present in 20–30% of patients hospitalised for acute heart failure (AHF) and independently predicts adverse outcomes. However, most evidence concerns sodium at a single timepoint; whether the trajectory of serum sodium during hospitalisation carries independent prognostic significance beyond admission sodium alone remains incompletely defined. We conducted a systematic review (PROSPERO: CRD420261299525) in accordance with PRISMA 2020 guidelines, searching four electronic databases from inception to March 2026. Studies were eligible if they enrolled adults hospitalised for AHF, characterised dynamic sodium change as the primary exposure, and reported at least one qualifying short-term outcome. Risk of bias was assessed using the Newcastle-Ottawa Scale. Six studies were included, comprising 18,923 participants across 10 countries (2016–2023); all were rated low risk of bias (NOS 8–9/9). Meta-analysis was precluded by methodological heterogeneity. Across three studies reporting in-hospital mortality, persistent hyponatraemia was consistently associated with the highest risk: adjusted OR 3.01 (95% CI 2.17–4.18), HR 2.51 (1.81–3.48), and OR 0.42 (0.20–0.88) for normonatraemia versus persistent hyponatraemia. De novo hyponatraemia was associated with elevated in-hospital mortality (OR 1.99, 95% CI 1.34–2.96) and worsening renal function (OR 14.58, 95% CI 3.44–61.73). Correction of hyponatraemia improved outcomes relative to persistence but did not fully normalise prognosis compared with never-hyponatraemic patients. Dynamic sodium trajectory carries independent short-term prognostic significance in AHF, supporting serial sodium monitoring and trajectory classification in risk stratification. Prospective studies with standardised definitions and contemporary therapies are needed.

Introduction

Acute heart failure (AHF) is responsible for over one million annual hospitalisations in Europe and the United States, with substantial in-hospital mortality and a 30-day readmission rate of 20–25%.[1,2] Identifying risk factors that are clinically actionable and independently prognostic remains a central priority.

Hyponatraemia — serum sodium below 135 mmol/L — is present in approximately 20–30% of patients hospitalised for AHF.[3,4] A robust evidence base has established that **admission hyponatraemia** independently predicts in-hospital mortality, length of stay, and 30-day rehospitalisation in AHF, with a dose-response relationship extending to sodium levels below 130 mmol/L.[5,6]

However, sodium is not static during hospitalisation. Patients may present with hyponatraemia that subsequently corrects; normonatraemic patients may develop hyponatraemia during treatment; and some remain persistently hyponatraemic despite therapy. Each trajectory may reflect distinct pathophysiological states — neurohormonal activation, diuretic response, volume status, and renal reserve — and may confer different prognostic implications that a single timepoint cannot capture.

Despite this biological plausibility, the prognostic significance of sodium trajectory has received systematically limited attention. Prior systematic reviews have largely focused on admission sodium.[7] The evidence on dynamic changes is dispersed across heterogeneous registries using varying definitions, timepoints, and outcomes, with no prior systematic synthesis. This review addresses that gap by evaluating the short-term prognostic significance of in-hospital serum sodium dynamics.

Methods

Protocol and Registration

This systematic review was conducted in accordance with PRISMA 2020 guidelines and prospectively registered with PROSPERO (registration number: CRD420261299525; available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420261299525). No deviations from the registered protocol occurred.

Eligibility Criteria

Population

Adults (≥ 18 years) hospitalised with acute heart failure (AHF) or acute decompensated heart failure (ADHF), all ejection fraction phenotypes (HFrEF, HFmrEF, HFpEF). Studies where > 20% of participants had advanced liver cirrhosis or end-stage renal disease on chronic haemodialysis were excluded, as were patients with cardiogenic shock or mechanical circulatory support at baseline. Stable outpatient or ambulatory heart failure populations were excluded.

Exposure: Assessment of dynamic changes in serum sodium during the index hospitalisation, including at least one of: absolute numerical change (Δ sodium); correction of hyponatraemia (admission < 135 mmol/L → ≥135 mmol/L); persistent hyponatraemia (< 135 at both admission and discharge); acquired (de novo) hyponatraemia (admission ≥ 135 → <135 during hospitalisation); or longitudinal trajectory modelling. Studies reporting sodium at a single timepoint only were excluded.

Comparator

Comparison between distinct sodium trajectory groups (e.g., corrected vs persistent hyponatraemia), or patients with sodium change versus stable normonatraemia during hospitalisation. Studies without a comparator were excluded.

Outcomes: At least one short-term outcome: in-hospital mortality (O1), 30-day all-cause mortality (O2), 30-day unplanned readmission (O3), length of hospital stay (O4), or worsening renal function (O5) as defined by the study. Studies reporting outcomes exclusively beyond 30 days were excluded.

Study designs

Observational cohort studies (prospective or retrospective) or post-hoc analyses of randomised controlled trials reporting observational associations between sodium changes and outcomes. Reviews, editorials, letters, case reports, and conference abstracts without full-text data were excluded.

Search Strategy

We searched the following databases from inception to March 2026: Embase, PubMed, Scopus, and Dimensions. The search strategy combined terms for acute heart failure, serum sodium abnormalities, and dynamic changes. No language restrictions were applied. The complete Boolean search strings for all databases are provided in Supplementary Appendix 1. In addition, backward snowballing (reference list review) and forward citation searching (using Google Scholar and PubMed) were performed for all included studies.

Study Selection

Records were imported into Rayyan for duplicate removal and two-stage screening (title/abstract, then full-text). Both stages were conducted by the lead author (M.M.O.A.) with independent cross-checking by the coauthors. Reasons for full-text exclusion were documented.

Data Extraction

Data were extracted using a standardised pre-piloted form capturing: study identification, design, country, sample size, population characteristics, exposure definition and trajectory groups, outcome definitions and crude rates, adjusted effect estimates (OR, HR, RR with 95% CI), statistical methods, covariate adjustment, and missing data handling. For missing data items, complete case analysis was used as reported in each study; no imputation was performed at the review level.

Risk of Bias Assessment

Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies, adapted for post-hoc RCT analyses where appropriate. Assessment was performed by M.M.O.A. and cross-checked independently by the coauthors; disagreements were resolved by discussion. Studies scoring 7–9 stars were classified as low risk of bias.

Data Synthesis

A narrative synthesis approach was adopted in accordance with the Synthesis Without Meta-Analysis (SWiM) guidelines. Meta-analysis was considered but deemed inappropriate due to: (i) **heterogeneous outcome definitions** across studies; (ii) **systematically different reference comparator groups** — including one study (Yoshioka 2016) with an inverted reference (persistent hyponatraemia); (iii) **sodium measurement timepoint variation** — Day 3 in Yoshioka 2016 versus discharge in all others; (iv) **differing hyponatraemia thresholds** — <136 mmol/L in Liang 2020 versus < 135 mmol/L elsewhere; and (v) **non-equivalent effect measures** — odds ratios from logistic regression and hazard ratios from Cox regression. Findings are reported narratively.

Where studies reported median (IQR) rather than mean (SD), data were tabulated as reported without conversion. No data conversions or imputations were performed at the review level.

No formal investigation of sources of heterogeneity (e.g., subgroup analysis, meta-regression) was conducted, as meta-analysis was not performed. No review-level sensitivity analyses were conducted.

Reporting bias was not formally assessed using funnel plots or statistical tests, as the number of studies contributing to each outcome was fewer than ten — the threshold required for funnel plot asymmetry to be interpretable. Selective reporting was assessed informally by comparing the pre-registered outcomes in PROSPERO (CRD420261299525) with the outcomes reported in each included study; no systematic selective reporting was identified. No meta-analysis was performed, precluding the use of Egger's test or trim-and-fill methods.

Results

Study Selection

The database search yielded 1,384 records. Following removal of 579 duplicates, 805 records were screened at title and abstract; 798 were excluded. Seven full-text articles were assessed; two were excluded (Kitai 2017 *Circ Heart Fail*, PMID 28130379: outcomes beyond 30 days; Militaru 2017 *Rom J Morphol Embryol*, PMID 29556627: no adjusted outcome model). Five studies met eligibility criteria from the database search.

Citation searching identified 323 records; 317 were excluded at title/abstract. Six full-text articles were assessed; five were excluded (outcomes beyond 30 days: Verbrugge FH et al. 2016; Yamazoe M et al. 2018; Matsue Y et al. 2017;

Vicent L et al. 2021; Sato Y et al. 2019). De Vecchis 2016 was identified through citation searching and included. The final review comprised **six studies** (Fig. 1).

Characteristics of Included Studies

The six included studies were published between 2016 and 2023 and comprised a total of **18,923 patients** (range 160 to 8,298). Study designs included retrospective analyses of prospective registries (Kapłon-Cieślicka 2023, Park 2017), single-centre retrospective cohorts (Donzé 2016, De Vecchis 2016), a three-centre Japanese retrospective cohort (Yoshioka 2016), and a post-hoc analysis of the CARRESS-HF RCT (Liang 2020). Geographically, studies originated from Europe (multinational, Italy), North America (USA), and Asia (Japan, Korea). All six studies included both HFrEF and HFpEF patients, except Liang 2020 which focused on type 1 cardiorenal syndrome (all patients had worsening renal function at entry). Table 1 summarises the main study characteristics.

Table 1

Characteristics of included studies. †Qualifying outcomes for this review only (within 30 days of admission or discharge). Post-discharge outcomes beyond 30 days are not qualifying outcomes for this review.

Study (year)	Design	Country	N	Sodium timepoints	Trajectory groups	Reference group	Qualifying outcomes†
Kapłon-Cieślicka 2023	Registry (ESC-HFA EORP)	33 ESC countries	8,298	Admission, discharge	No/No, Yes/No, No/Yes, Yes/Yes	No/No (normo-normo)	In-hospital mortality (O1)
Donzé 2016	Retrospective cohort	USA (single centre)	4,295	Admission, discharge	Persistent (hypo-hypo), corrected (hypo-normo)	Corrected	30-day mortality (O2); 30-day readmission (O3)
Yoshioka 2016	Retrospective cohort	Japan (3 centres)	882	Day 1, Day 3	Hypo-hypo, hypo-normo, normo	Hypo-hypo (persistent)	In-hospital mortality (O1)
Park 2017	Registry (KorAHF)	Korea (10 centres)	5,103	Admission, discharge	Persistent normo, de novo hypo, corrected hypo, persistent hypo	Persistent normo	In-hospital mortality/transplant composite (O1)
Liang 2020	Post-hoc of CARRESS-HF	USA (22 sites)	185	Baseline, Day 4, Day 7, discharge	Recovery, no hypo, persistent, new-onset	Recovery (corrected)	WRF at discharge (O5)
De Vecchis 2016	Retrospective cohort	Italy (2 centres)	160	Admission, discharge	Persistent, normalised	Normalised	30-day mortality (O2); 30-day readmission (O3)

Patient Populations and Hyponatraemia Prevalence

The prevalence of hyponatraemia at admission varied from 14.3% (Yoshioka 2016) to 21% (Park 2017). Two studies (Donzé 2016, De Vecchis 2016) enrolled only patients with hyponatraemia at admission (100%). Liang 2020 included only patients with type 1 cardiorenal syndrome (all had worsening renal function at entry); 30.8% had hyponatraemia at baseline. Baseline characteristics across studies reflected typical AHF populations: mean age 67–78 years, male

predominance (50–75%), and high prevalence of ischaemic aetiology (29–61%), diabetes (28–66%), and chronic kidney disease (19–63%).

Table 2

*Key baseline characteristics by trajectory group. *Calculated from subgroup data; †Overall cohort; ‡Percentage female (calculated). NR = not reported; CKD = chronic kidney disease; LVEF = left ventricular ejection fraction.*

Study	Group (n)	Age (years)	Male (%)	Admission Na (mmol/L)	LVEF (%)	Diabetes (%)	CKD (%)
Kapłon-Cieślicka 2023	No/No (6,002)	72 [62–79]	61*	140 [138–142]	40 [30–52]	38.7*	26.7*
	Yes/No (876)	72 [62–80]	—	133 [130–134]	39 [28–51]	—	—
	No/Yes (666)	69 [59–78]	—	137 [136–140]	35 [25–47]	—	—
	Yes/Yes (754)	68 [59–78]	—	131 [128–133]	35 [25–45]	—	—
Donzé 2016	Corrected (2,496)	66.9 ± 15.4	52.3	131.9 ± 2.7	NR	34.5	19.4
	Persistent (1,799)	67.1 ± 15.9	50.8	130.2 ± 3.8	NR	29.5	17.7
Yoshioka 2016	Normo (756)	78.0†	50.2†	139.6 ± 4.5†	52.0 ± 15.3	51.5	50.0
	Hypo-Normo (62)	77.3 ± 13.4	43.5‡	133 ± 2.9‡	48.3 ± 16.6	43.5	50.0
	Hypo-Hypo (64)	79 ± 14.8	42.2‡	130 ± 4.4‡	48.3 ± 17.4	35.9	62.5
Park 2017	HFrEF normo (2,424)	66.1 ± 14.9	60.8	139.3 ± 2.7	27.2 ± 7.6	34.7	42.8
	HFrEF hypo (662)	66.7 ± 14.2	58.8	130.5 ± 3.9	26.0 ± 7.7	45.0	55.1
	HFpEF normo (1,019)	71.7 ± 13.8	38.0	139.5 ± 2.8	59.4 ± 6.5	27.7	61.1
	HFpEF hypo (265)	73.1 ± 12.2	39.2	129.9 ± 4.2	60.0 ± 6.8	38.9	50.2
Liang 2020	Recovery (21)	67 ± 11	62	132 ± 2	37 ± 17	67	43
	No hypo (94)	69 ± 13	70	139 ± 2	38 ± 16	68	40
	Persistent (36)	69 ± 14	72	130 ± 3	36 ± 18	67	47
	New-onset (34)	67 ± 13	74	138 ± 2	36 ± 15	62	41
De Vecchis 2016	Normalised (104)	77 ± 10.8	51.9	130.7 ± 5.5	40 ± 7.5	33.7	39.4
	Persistent (56)	76 ± 10.4	50.0	130.5 ± 4.4	40 ± 6.6	28.6	41.1

Risk of Bias

All six studies were rated **low risk of bias** (NOS 8–9/9; Fig. 2). Four achieved 9/9 (Yoshioka 2016, Park 2017, Kapłon-Cieślicka 2023, De Vecchis 2016). Donzé 2016 and Liang 2020 each scored 8/9, losing one star on representativeness: Donzé due to single-centre design, Liang due to the highly selected CARRESS-HF population (all patients had worsening renal function at entry). All studies received two stars for comparability, reflecting multivariable adjustment for HF severity markers.

Key study-level limitations: (i) retrospective design in three studies; (ii) Yoshioka 2016 excluded two patients who died before Day 3 (minor survivorship bias); (iii) NT-proBNP missing in 75% of Kapłon-Cieślicka 2023; (iv) all recruitment periods predate SGLT2i use (2003–2018).

Outcome Findings

In-Hospital Mortality (O1)

Three studies reported in-hospital mortality (Kapłon-Cieślicka 2023, Yoshioka 2016, Park 2017; total n = 14,283). All found consistent associations between adverse sodium trajectory and increased mortality, though reference groups differ.

Crude rates were highest in patients with persistent hyponatraemia (Kapłon-Cieślicka: 6.9%; Yoshioka: 23.7%; Park: 13.1% in HFrEF, 6.0% in HFpEF) and lowest in those with no hyponatraemia (Kapłon-Cieślicka: 2.4%; Yoshioka: 6.9%; Park: 4.9% in HFrEF, 1.9% in HFpEF). After adjustment, persistent hyponatraemia remained a strong independent predictor:

- **Kapłon-Cieślicka 2023**: adjusted OR vs No/No: Yes/Yes 3.01 (95% CI 2.17–4.18); Yes/No 2.10 (95% CI 1.48–2.97); No/Yes 1.99 (95% CI 1.34–2.96).
- **Yoshioka 2016**: adjusted OR vs Hypo-Hypo: Hypo-Normo 0.28 (95% CI 0.08–0.93); Normo 0.42 (95% CI 0.20–0.88).
- **Park 2017** (in-hospital mortality/transplant composite): adjusted HR for hyponatraemia vs normonatraemia: overall 2.51 (95% CI 1.81–3.48); HFrEF 2.53 (95% CI 1.71–3.76); HFpEF 2.78 (95% CI 1.10–6.99).

30-Day Post-Discharge Outcomes (O2 and O3)

Two studies reported 30-day outcomes: Donzé 2016 and De Vecchis 2016. Both found that persistent hyponatraemia (vs corrected) was associated with significantly higher risk of the composite endpoint (30-day readmission or death):

- **Donzé 2016 — composite (O2 + O3)**: adjusted OR 1.45 (95% CI 1.27–1.67). 30-day mortality alone: adjusted OR 1.99 (95% CI 1.56–2.55). 30-day readmission alone: adjusted OR 1.28 (95% CI 1.11–1.48).
- **De Vecchis 2016 — composite (O2 + O3)**: adjusted HR 3.07 (95% CI 1.40–6.76) — small sample (n = 160), wide confidence interval. 30-day mortality alone: crude OR 1.26 (95% CI 0.33–4.65), not significant, likely due to insufficient power. 30-day readmission alone: crude OR 29.4 (95% CI 10.93–79.05), exaggerated by very low event rate in the normalised group.

Length of Stay (O4)

LOS was reported as a formal outcome only in Kapłon-Cieślicka 2023, where admission hyponatraemia was associated with increased likelihood of ICCU stay > 2 days (adjusted OR 1.50, 95% CI 1.32–1.71, $p < 0.001$). De Vecchis 2016 reported LOS as a baseline characteristic only (persistent group: median 7.0 days, IQR 4.75–8.0; normalised group: 5.0 days, IQR 4.0–5.0; $p = 0.0186$); it was not modelled as an outcome. Other studies did not report LOS.

Worsening Renal Function (O5)

Liang 2020 (n = 185, CARRESS-HF) was the only study evaluating WRF (creatinine ≥ 0.3 mg/dL above nadir at discharge). Using recovery from hyponatraemia as reference, all three remaining trajectory groups showed significantly higher adjusted odds of persistent WRF at Day 7: no hyponatraemia OR 7.41 (95% CI 2.08–26.47); persistent hyponatraemia OR 15.47 (95% CI 3.44–69.58); new-onset hyponatraemia OR 14.58 (95% CI 3.44–61.73). Restricted cubic spline analysis confirmed a nonlinear relationship. In hyponatraemic-at-baseline patients, continuous delta sodium independently predicted WRF (Day 7 OR 0.677 per mmol/L increase, p = 0.002).

Reporting Bias

Formal assessment of reporting bias was not possible given the small number of studies contributing to each outcome (maximum three studies per outcome domain), which is insufficient for funnel plot construction or statistical tests for asymmetry. Pre-registered outcomes (PROSPERO CRD420261299525) were compared with outcomes reported in each included study; no systematic discrepancy between registered and reported outcomes was identified in any of the six included studies.

Certainty of Evidence

Formal GRADE certainty of evidence assessment was not conducted for this review, consistent with the narrative synthesis design. Given that all six included studies are observational in design, and given the clinical and methodological heterogeneity across outcome domains, the overall certainty of evidence is considered **low** for all outcomes, consistent with GRADE criteria for observational studies with unexplained heterogeneity and absence of randomised evidence. This is acknowledged as a limitation of the current evidence base.

Discussion

Principal Findings

Despite heterogeneity across studies, consistent patterns emerged:

1. **Persistent hyponatraemia** (sodium low at both admission and discharge) is consistently associated with the worst short-term outcomes across all outcome domains: in-hospital mortality, 30-day readmission and death, and worsening renal function.
2. **Correction of hyponatraemia** during hospitalisation is associated with significantly better outcomes compared with persistent hyponatraemia, and in some studies outcomes approach those of patients who were never hyponatraemic.
3. **De novo hyponatraemia** (normal admission sodium that falls during treatment) was associated with elevated in-hospital mortality risk (OR 1.99, Kapłon-Cieślicka 2023) and worsening renal function risk (OR 14.58 at Day 7, Liang 2020). The authors of Kapłon-Cieślicka 2023 describe their de novo findings as 'inconsistent and difficult to interpret', attributing the pattern tentatively to depletional hyponatraemia from intensive diuresis.
4. **The prognostic value of sodium change may differ by HF phenotype**: Park 2017 found hyponatraemia was a significant independent predictor of in-hospital outcomes in both HFrEF and HFpEF.
5. **WRF is associated with sodium trajectories**: correction of hyponatraemia was associated with lower WRF risk (Liang 2020), and improvement in eGFR was observed in patients who corrected hyponatraemia (Kapłon-Cieślicka 2023).
6. **Discharge sodium status** carries greater prognostic weight than admission sodium status (Park 2017): patients normonatraemic at discharge — whether persistently normonatraemic or corrected — had better outcomes than

those with hyponatraemia at discharge.

Possible Mechanisms

Persistent hyponatraemia is an established marker of neurohormonal activation (increased vasopressin, renin-angiotensin-aldosterone system activation) and poor effective circulating volume in AHF.[8,9] Regarding acquired hyponatraemia, Kapłon-Cieślicka 2023 found that patients who developed de novo hyponatraemia during hospitalisation had greater weight loss and the lowest frequency of residual congestion at discharge, and the authors note that the prognostic impact of this pattern 'may not necessarily be as harmful as anticipated.' The authors attribute this tentatively to depletional rather than dilutional hyponatraemia as a consequence of intensive diuretic therapy.

The observation that patients normonatraemic at discharge had better outcomes regardless of admission status (Park 2017) is consistent with the hypothesis that discharge sodium reflects treatment response; however, this interpretation is inferential and is not directly tested in any included study. These mechanisms remain incompletely characterised within the evidence base of this review, and the distinction between dilutional and depletional hyponatraemia warrants dedicated prospective investigation.

Comparison with Prior Literature

Prior meta-analyses have established admission hyponatraemia as an independent predictor of mortality in HF.[7] This review extends that evidence to the dynamic dimension, demonstrating that trajectory carries prognostic information beyond the admission value. The finding from Park 2017 that discharge sodium was a stronger prognostic marker than admission sodium is particularly illustrative — the authors state directly that 'the discharge sodium level better predicts outcomes.' The evidence from Liang 2020 demonstrates that early sodium recovery (by Day 7) is associated with significantly lower WRF risk than all other trajectory groups in a cardiorenal syndrome population.

Limitations

Clinical and methodological heterogeneity precluded meta-analysis. All six studies were conducted in the pre-SGLT2i era (2003–2018); contemporary therapy may modify sodium trajectories and attenuate observed associations. Four studies were retrospective, with inherent risk of unmeasured confounding. Two studies (Donzé 2016, De Vecchis 2016) excluded normonatraemic patients, restricting comparisons to persistent versus corrected hyponatraemia without a normonatraemic reference. The only WRF study (Liang 2020) used a highly selected cardiorenal syndrome population; findings may not generalise to unselected AHF. NT-proBNP was missing in 75% of Kapłon-Cieślicka 2023, limiting HF severity adjustment. **Review-process limitations** include: primary screening was performed by a single reviewer (mitigated by independent cross-checking by coauthors); formal GRADE certainty assessment was not conducted; and the full search strategy, while documented in the protocol, is not reproduced in full within this manuscript (see Supplementary Appendix 1).

Future Research

1. **Standardisation of sodium trajectory definitions**: studies should report sodium at admission and discharge (at minimum) and define trajectory groups consistently. Persistent normonatraemia should be the reference group.
2. **Measurement of short-term outcomes**: core outcome sets for AHF should include in-hospital mortality, 30-day mortality, and 30-day readmission to allow comparability across studies.

3. **Mechanistic studies**: future research should distinguish dilutional from depletional hyponatraemia using biomarkers (e.g., plasma renin activity, aldosterone, BUN/creatinine ratio) to clarify the mechanism-outcome relationship.
4. **Intervention trials**: while observational studies consistently show correction is associated with better outcomes, it remains unknown whether actively correcting hyponatraemia improves prognosis. The EVEREST trial showed tolvaptan corrects hyponatraemia but did not reduce mortality.[11] Pragmatic trials targeting sodium trajectories in hyponatraemic AHF patients are needed.
5. **HF phenotype-specific analyses**: future studies should report results stratified by EF category, given the signal from Park 2017 regarding differential hyponatraemia impact by phenotype.

Conclusion

Dynamic changes in serum sodium during hospitalisation for acute heart failure provide important short-term prognostic information beyond a single admission measurement. Persistent hyponatraemia is associated with the highest risk of in-hospital mortality, 30-day readmission and death, and worsening renal function. Correction of hyponatraemia is consistently associated with better outcomes, while acquired hyponatraemia carries intermediate risk, though its prognostic basis remains incompletely characterised in the current evidence base. Substantial heterogeneity in exposure definitions, outcome timing, and reference groups prevents meta-analysis and limits direct comparison of effect estimates.

Declarations

Conflicts of interest:

None declared.

Funding:

None.

Data availability:

All data extraction forms are available from the corresponding author on reasonable request.

References

1. Ponikowski P, Voors AA, Anker SD et al (2016) 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 37(27):2129–2200
2. Heidenreich PA, Bozkurt B, Aguilar D et al (2022) 2022 AHA/ACC/HFSA Guideline for the management of heart failure. J Am Coll Cardiol 79(17):e263–e421
3. Gheorghiade M, Abraham WT, Albert NM et al (2007) Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry. Eur Heart J 28(8):980–988
4. Sato N, Gheorghiade M, Kajimoto K et al (2013) Hyponatremia and in-hospital mortality in patients admitted for heart failure (from the ATTEND registry). Am J Cardiol 111(7):1019–1025

5. Balling L, Schou M, Videbaek L et al (2011) Prevalence and prognostic significance of hyponatraemia in patients with chronic heart failure. Eur J Heart Fail 13(9):968–973
6. Gheorghiade M, Rossi JS, Cotts W et al (2007) Characterization and prognostic value of persistent hyponatremia in patients with severe heart failure in the ESCAPE Trial. Arch Intern Med 167(18):1998–2005
7. Zhao W, Zhang X, Feng R et al (2023) Association between hyponatremia and adverse clinical outcomes of heart failure: a systematic review and meta-analysis. Front Cardiovasc Med 10:1339203
8. Verbrugge FH, Steels P, Grieten L et al (2015) Hyponatremia in acute decompensated heart failure: depletion versus dilution. J Am Coll Cardiol 65(5):480–492
9. Bettari L, Fiuzat M, Felker GM, O'Connor CM (2012) Significance of hyponatremia in heart failure. Heart Fail Rev 17(1):17–26
10. Verbrugge FH, Grodin JL, Mullens W et al (2016) Transient hyponatremia during hospitalization for acute heart failure. Am J Med 129(6):620–627
11. Konstam MA, Gheorghiade M, Burnett JC Jr et al (2007) Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 297(12):1319–1331
12. Kapłon-Cieślicka A, Benson L, Chioncel O et al (2023) Hyponatraemia and changes in natraemia during hospitalization for acute heart failure and associations with in-hospital and long-term outcomes — from the ESC-HFA EORP Heart Failure Long-Term Registry. Eur J Heart Fail 25(9):1571–1584
13. Park JJ, Cho YJ, Oh IY et al (2017) Short and long-term prognostic value of hyponatremia in heart failure with preserved ejection fraction versus reduced ejection fraction: an analysis of the Korean Acute Heart Failure registry. Int J Cardiol 248:239–245
14. Yoshioka K, Matsue Y, Kagiyama N et al (2016) Recovery from hyponatremia in acute phase is associated with better in-hospital mortality rate in acute heart failure syndrome. J Cardiol 67(5):406–411
15. Liang W, He X, Xue R et al (2020) Association of hyponatraemia and renal function in type 1 cardiorenal syndrome. Eur J Clin Invest 50(9):e13269
16. De Vecchis R, Di Maio M, Di Biase G, Ariano C (2016) Effects of hyponatremia normalization on the short-term mortality and rehospitalizations in patients with recent acute decompensated heart failure: a retrospective study. J Clin Med 5(10):92
17. Donzé JD, Beeler PE, Bates DW (2016) Impact of hyponatremia correction on the risk for 30-day readmission and death in patients with congestive heart failure. Am J Med 129(8):836–842

Figures

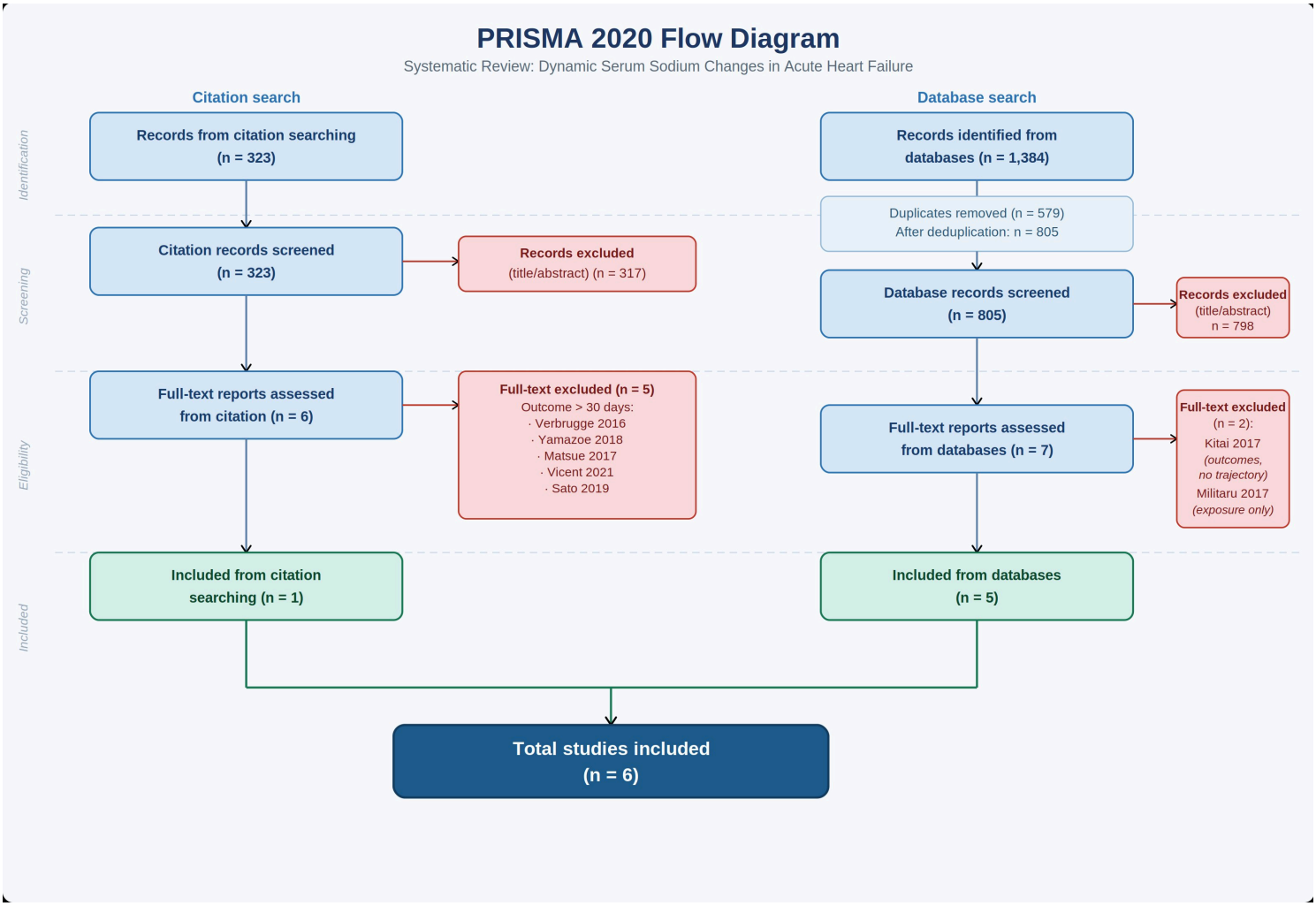


Figure 1

PRISMA 2020 flow diagram. Database search identified 1,384 records; citation searching identified 323 additional records. Total studies included: n = 6.

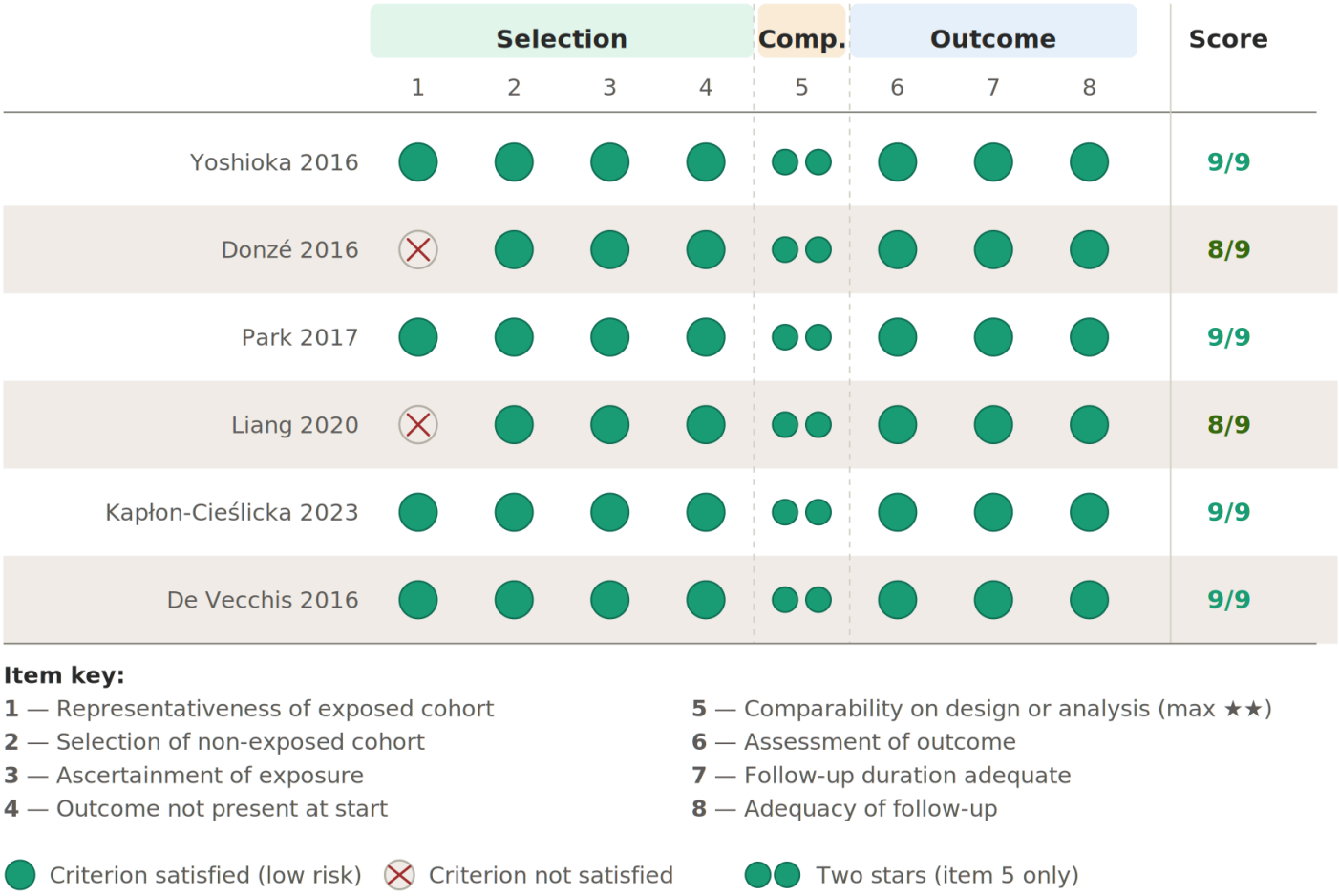


Figure 2

Newcastle-Ottawa Scale risk of bias assessment across six included studies. Filled circles = criterion satisfied (✓). All studies rated low risk of bias (NOS 8–9/9).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryAppendix1SearchStrings.docx
- graphicalabstract.png