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# Improvement of hyponatremia is associated with lower mortality risk in patients with acute decompensated heart failure: a meta-analysis of cohort studies

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**Abstract**
Hyponatremia at admission is predictive of poor prognosis in patients with acute decompensated heart failure (ADHF). We performed a meta-analysis of cohort studies to evaluate whether improvement of hyponatremia is associated with improved survival in patients with ADHF and hyponatremia. Relevant studies were identified through systematic search of PubMed and Embase. A random-effect model was used to pool the results. Predefined subgroup analyses were performed to explore the source of heterogeneity. Five thousand seven hundred fourteen patients with ADHF and hyponatremia from eight cohort studies were included. Results showed that improvement of hyponatremia during hospitalization was associated with lower risk of all-cause mortality (RR = 0.65, 95% CI 0.53 to 0.80, $p < 0.001$) as compared with those without improvement of hyponatremia. Results of subgroup analyses indicated that improvement of hyponatremia was associated with more remarkable changes of short-term (within 3 months after discharge) mortality (RR = 0.54) as compared with long-term mortality (RR = 0.74). Other factors such as study design, sample size, and heart failure subtypes did not affect the association. This was further confirmed by the meta-analysis of studies with multivariate analysis, which also suggested an association between improved hyponatremia and lower risk of all-cause mortality in ADHF patients (adjusted RR = 0.63, 95% CI 0.43 to 0.92, $p = 0.02$; $I^2 = 63\%$). These results suggested that improvement of hyponatremia in ADHF patients is associated with lower mortality risk during follow-up, particularly for the short-term mortality.

**Keywords** Hyponatremia · Heart failure · Mortality · Cohort studies · Meta-analysis

## Introduction

Despite of significant improvement of diagnostic and therapeutic strategies in recent years, heart failure (HF) remains one of the most important causes of morbidity and mortality of people worldwide [1, 2]. Acute events like infections or arrhythmias can cause acute decompensated HF (ADHF) through changes of hemodynamic status [3]. Patients with ADHF need intensive treatment during hospitalization and the prognoses of these patients are generally poor, with an in-hospital mortality rate of 3–4%, and a combined rate of mortality and hospitalization of up to 50% within 3 months after discharge [4–7].

Accumulating evidence from observational studies indicated that hyponatremia is one of the most common electrolyte disorders in patients with ADHF, with a prevalence of about 25% [8–10]. Clinically, ADHF patients with hyponatremia are usually associated with resistance to conventional diuretics and exacerbated symptoms of volume overload, such as breathlessness and edema [11]. More importantly, hyponatremia has been proved to be an independent predictor of mortality in patients with ADHF [12]. Indeed, the results of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) Study showed that per 3-mmol/l decrease of serum sodium at admission was independently associated with 18% increased 60-day mortality in patients hospitalized for ADHF [13]. However, using tolvaptan, a vasopressin V2 receptor blocker targeting hyponatremia, the results of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study

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with Tolvaptan (EVEREST) trial failed to show a favorable influence of tolvaptan on mortality or HF-related morbidity in ADHF patients during a 9.9-months follow-up [14]. Interestingly, a post hoc analysis of the EVEREST trial showed that tolvaptan may reduce cardiovascular morbidity and mortality after discharge in ADHF patients with pronounced hyponatremia (< 130 mmol/L) at admission [15]. Even though the results were not always consistent, a few small-scale cohort studies have evaluated the potential association between hyponatremia improvement and the changes of mortality risk in patients with ADHF [13, 16–22]. Therefore, in this study, we aimed to perform a meta-analysis to evaluate the association between the improvement of hyponatremia and changes of mortality risk in patients with ADHF.

## Methods

We performed the meta-analysis in accordance with the MOOSE (Meta-analysis of Observational Studies in Epidemiology) [23] and Cochrane's Handbook guidelines [24].

### Literature search

Databases of PubMed and Embase were searched for relevant records, using the combination of the following terms: (1) "hyponatremia," "hyponatraemia," or "sodium"; (2) "heart failure," "cardiac failure," or "cardiac dysfunction"; (3) "prognosis," "survival," or "mortality"; and (4) "cohort," "cohorts," "followed," "follow-up," "prospectively," "retrospectively," "prospective," "retrospective," "trial," or "registry." The search was limited to studies in humans and published in English language. The reference lists of original and review articles were also analyzed using a manual approach. The final literature search was performed on Nov 20, 2017.

### Study selection

Articles were included in the meta-analysis if they met all of the following criteria: (1) published as full-length article in English; (2) reported as cohort studies (prospective or retrospective, regardless of sample size); (3) included adult population (≥ 18 years of age) with ADHF and hyponatremia at baseline; (4) improvement of hyponatremia at discharge was identified as exposure of interest at baseline; (5) participants without the improvement of hyponatremia at baseline was used as controls; and (6) documented the numbers of cases with all-cause mortality during follow-up for patients with and without the improvement of hyponatremia. Reviews, letters, editorials, and studies with designs other than cohort study were excluded.

### Data extracting and quality evaluation

Two authors independently performed literature search, data extraction, and quality assessment according to the predefined inclusion criteria. Discrepancies were resolved by consensus. Data that were extracted include: (1) name of first author, year of publication, and country where the study was performed; (2) design characteristics (prospective or retrospective); (3) characteristics and numbers of the participants (age, proportions of male participants, subtypes of HF, and baseline cardiac function as evaluated by the New York Heart Association [NYHA] Classification and left ventricular ejection fraction [LVEF]); (4) criteria for the diagnosis of hyponatremia and definition of improvement of hyponatremia; (5) follow-up period; and (6) variables adjusted when presenting the results. The quality of each study was evaluated using the Newcastle-Ottawa Scale [25], which ranges from 1 to 9 stars and judges each study regarding three aspects: selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.

### Statistical analyses

We used risk ratios (RRs) to present the association between the improvement of hyponatremia during hospitalization and the incidence of all-cause mortality during follow-up for patients with ADHF and hyponatremia. The unadjusted RRs and their corresponding 95% confidence intervals (CIs) were based on the total numbers of patients and numbers of cases with mortality during follow-up in patients with and without improvement of hyponatremia during hospitalization. For studies in which the adjusted RRs were reported, the corresponding stand errors (SEs) were calculated from 95% CIs or $p$ values and were logarithmically transformed to stabilize variance and normalized the distribution [24]. The Cochrane's $Q$ test and $I^2$ test were used to evaluate the heterogeneity among the included cohort studies [24]. A significant heterogeneity was considered if $I^2 > 50\%$ [26]. We used a random effect model to synthesize the HR data because this model is considered as a more generalized method which incorporates of the potential heterogeneity [24]. Sensitivity analyses, by removing individual study one at a time, were performed to test the robustness of the results [27]. Predefined subgroup analyses were performed to evaluate whether the association between improvement of hyponatremia during hospitalization and change of mortality was affected by the design of the study, sample size, HF subtypes, and follow-up durations. For continuous variables, medians of the variables were used as the cutoff values. Moreover, since the improvement of hyponatremia was defined differently in the included studies, subgroup analyses were also performed to evaluate whether improvement or correction of hyponatremia affected the incidence of mortality differently. Potential publication

bias was assessed by funnel plots with the Egger's regression asymmetry test [28]. We used the RevMan (Version 5.1; Cochrane Collaboration, Oxford, UK) and STATA software for the meta-analysis and statistics.

## Results

### Literature search

The processes of database search were presented in Fig. 1. Briefly, 898 articles were found via initial literature search of the PubMed and Embase databases, and 872 were excluded through screening of the titles and abstracts mainly because they were not relevant to the purpose of the meta-analysis. Subsequently, 26 potential relevant records underwent full-text review. Of these, 18 were further excluded because two of them were not cohort studies, five were not in patients with ADHF, two did not include patients with hyponatremia, eight did not report the improvement of hyponatremia during hospitalization, and the other one did not report the outcome of mortality during follow-up. Finally, eight cohort studies [13, 16–22] were included.

### Study characteristics and quality evaluation

The characteristics of the included cohort studies were presented in Table 1. Briefly, our meta-analysis included 5714 patients with ADHF and hyponatremia from eight cohort studies. Five of the studies were performed in the USA [13, 16, 17, 19, 21], while the other three were in France [18], Korea [20], and Japan [22] separately. The mean ages of the patients in the included studies varied from 54 to 78 years, with the percentiles of male patients ranging between 46 and 68%. Three of the studies included patients with HF with reduced ejection fraction (HFrEF) only [13, 16, 17], one study included patients with HF with preserved ejection fraction (HFrEF) only [18], while the other four [19–22] included patients with either the HF subtypes. The baseline LVEF varied between 17 to 61% accordingly. The diagnosis of hyponatremia of the included studies was serum sodium < 134~136 mmol/L. In two of the included studies [17, 19], improvement of hyponatremia was defined as increment of serum sodium ≥ 2 mmol/L, while in the other six studies, improvement of hyponatremia was defined as correction of serum sodium to a normalized level [13, 16, 18, 20–22]. The follow-up duration varied significantly, from duration of hospitalization to 20 months after discharge. Multivariate adjusted RRs for the association between improvement of hyponatremia and changes of mortality were reported in five studies [16, 19–22], and variables that may affect the prognosis of patients with ADHF, such as age, gender, NYHA classification, comorbidities, and HF medications, were adjusted. The Newcastle-Ottawa scale varied from 7 to 9 for the included cohort studies (Table 1).

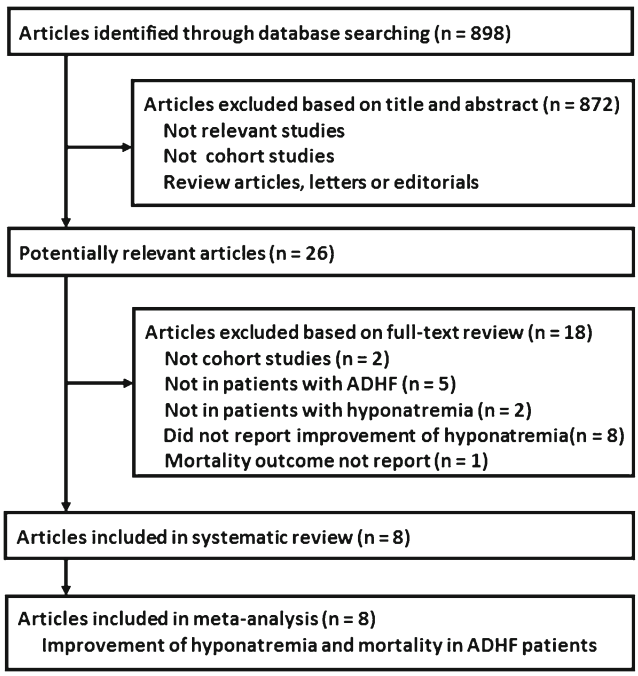


**Fig. 1** Flowchart of literature search and study selection

### Improvement of hyponatremia and mortality risk in ADHF: unadjusted results

All of the eight included cohorts [13, 16–22] reported data on the incidences of all-cause mortality in patients with ADHF and hyponatremia grouped according to whether hyponatremia was improved during hospitalization. Pooled results with a random effect model showed that ADHF patients with improved hyponatremia during hospitalization was associated with significantly lower risk of all-cause mortality as compared with those without improvement of hyponatremia (RR = 0.65, 95% CI 0.53 to 0.80, $p < 0.001$; Fig. 2) with moderate heterogeneity ($p$ for Cochrane's $Q$ test = 0.04, $I^2 = 52\%$). Results of subsequent sensitivity analyses by omitting one study at a time did not significantly change the results (Table 2). Results of subgroup analyses suggested that although both significant, correction of hyponatremia (RR = 0.78) seemed to be associated with a more remarkably lower mortality in ADHF patients as compared with partial improvement of hyponatremia (RR = 0.61, $p$ for subgroup difference = 0.10; Table 3). Moreover, improvement of hyponatremia seemed to be associated with a more remarkably lower short-term (within 3 months after discharge) mortality (RR = 0.54) as compared with long-term mortality (RR = 0.74) in patients with ADHF and hyponatremia ($p$ for subgroup difference = 0.04; Table 3). Other factors such as the study design, sample size, and HF subtypes may not affect the

**Table 1** Characteristics of included studies

| Study | Country | Design | Number of patients | Mean age **Years** | Male % | HF Type % | Ischemic etiology % | NYHA IV % | LVEF % | Cut-off for HN **mmol/L** | Definition of HN improvement | Follow-up duration **Months** | Variables adjusted | NOS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Klein [13] | USA | Retrospective | 244 | 68 | 68 | HFrEF | 55 | 49 | 21 | ≤ 135 | Correction | 2 | NA | 7 |
| Rossi [17] | USA | Retrospective | 69 | 65 | 46 | HFrEF | NR | 52 | 25 | ≤ 135 | Improvement ≥ 2 mmol/L | 2 | NA | 7 |
| Gheorghiade [12] | USA | Retrospective | 103 | 54 | NR | HFrEF | 50 | 100 | 17 | ≤ 134 | Correction | 6 | Age, gender, BP, BUN, NYHA classification, baseline serum sodium, and HF medications | 9 |
| Rusinaru [18] | France | Prospective | 91 | 77 | 46 | HFpEF | 26 | NR | 61 | < 136 | Correction | 12 | NA | 7 |
| Madan [19] | USA | Retrospective | 322 | 66 | 55 | Mixed | 48 | NR | 33 | < 135 | Improvement ≥ 2 mmol/L | 20 | Age, gender, race, baseline serum sodium, comorbidities, and HF medications | 9 |
| Lee [20] | Korea | Prospective | 464 | 71 | 54 | Mixed | 39 | NR | 39 | < 135 | Correction | 20 | Age, gender, previous HF history, BP, HR,BMI, HGB, LVEF, BUN, SCr, NT-ProBNP, ischemic etiology, HF medications, and blood transfusion | 9 |
| Donzé [21] | USA | Retrospective | 4295 | 67 | 52 | Mixed | 44 | NR | NR | < 135 | Correction | 1 | Age, gender, race, number of admissions within the last 6 months, unplanned index admission versus elective, length of stay, AF, IHD, cancer, COPD, DM, and CKD | 9 |
| Yoshioka [22] | Japan | Retrospective | 126 | 78 | 57 | Mixed | 30 | NR | 48 | ≤ 135 | Correction | In-hospital | Age, gender, BP, HR, comorbidities of HTN, DM, AF, IHD, CKD, LVEF, BNP, CRP, baseline serum sodium, and HF medications | 9 |

HF, heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; HN, hyponatremia; NOS, Newcastle-Ottawa Scale; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; NR, not reported; LVEF, left ventricular ejection fraction; NA, not applicable; BP, blood pressure; BUN, blood urea nitrogen; HR, heart rate; BMI, body mass index; HGB, hemoglobin; SCr, serum creatinine; NT-ProBNP, N-terminal pro B-type natriuretic peptide; AF, atrial fibrillation; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CKD chronic kidney disease; BNP, B-type natriuretic peptide; CRP, C-reactive protein

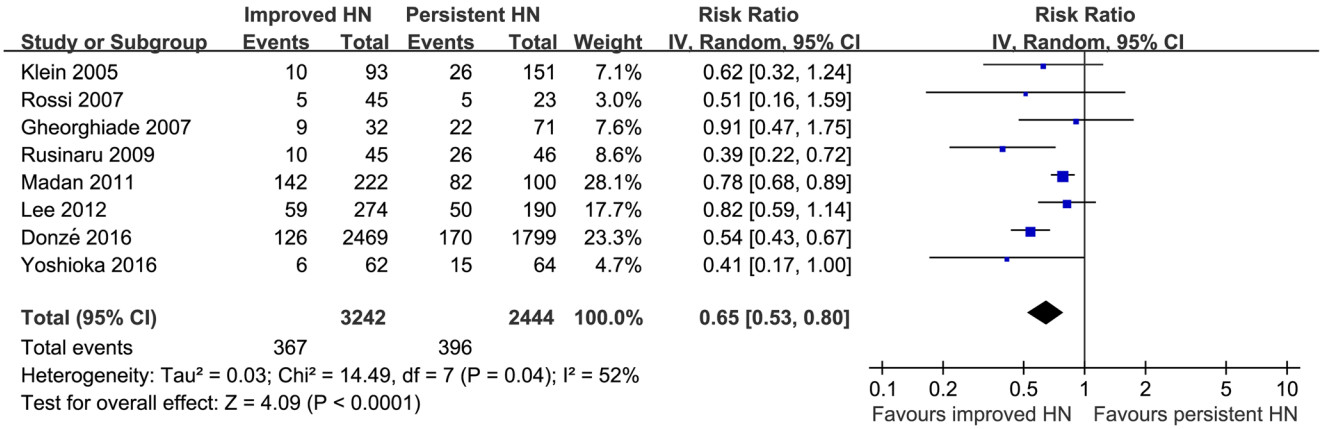


**Fig. 2** Forest plot for the meta-analysis regarding the effect of hyponatremia improvement on mortality risk in patients with ADHF and hyponatremia: unadjusted result

association between improvement of hyponatremia and changes of all-cause mortality in these patients ($p$ for subgroup difference all > 0.05, Table 3).

### Improvement of hyponatremia and mortality risk in ADHF: adjusted results

Five of the included cohorts [16, 19–22] reported multivariate adjusted association between improvement of hyponatremia and changes of mortality risk in ADHF patients. Pooled results with a random effect model indicated that improvement of hyponatremia during hospitalization in ADHF patients was independently associated with a lower risk of all-cause mortality during follow-up (adjusted RR = 0.63, 95% CI 0.43 to 0.92, $p = 0.02$; Fig. 3) with considerable heterogeneity ($p$ for Cochrane's $Q$ test = 0.03, $I^2 = 63\%$).

### Publication bias

Funnel plot for the meta-analysis of the unadjusted association between improvement of hyponatremia and the risk of all-cause mortality in patients with ADHF and hyponatremia was shown in Fig. 4. The plot was symmetry on visual inspection, indicating insignificance of potential publication bias. This was further confirmed by the results of Egger regression test ($p = 0.44$). The publication bias for the meta-analysis of adjusted association between improvement of hyponatremia and the risk of all-cause mortality in patients with ADHF and hyponatremia was difficult to estimate because limited cohorts were included.

**Table 2** Results of sensitivity analysis

| Studies omitted | RR | 95% CI | $I^2$ | $p$ for effect |
|---|---|---|---|---|
| Klein [13] | 0.65 | 0.52 to 0.81 | 58% | < 0.001 |
| Rossi [17] | 0.65 | 0.53 to 0.81 | 58% | < 0.001 |
| Gheorghiade [16] | 0.63 | 0.50 to 0.79 | 57% | < 0.001 |
| Rusinaru [18] | 0.68 | 0.56 to 0.83 | 45% | < 0.001 |
| Madan [19] | 0.61 | 0.48 to 0.76 | 29% | < 0.001 |
| Lee [20] | 0.61 | 0.48 to 0.78 | 56% | < 0.001 |
| Donzé [21] | 0.71 | 0.59 to 0.86 | 23% | < 0.001 |
| Yoshioka [22] | 0.66 | 0.54 to 0.82 | 54% | < 0.001 |

RR, risk ratio; CI, confidence interval

## Discussion

In this meta-analysis, by combing the results of all available cohort studies, we found that improvement of hyponatremia during hospitalization is associated with a significantly lower mortality rate during follow-up in patients with ADHF and hyponatremia. Subsequent analyses with data of multivariate analyses showed that improvement of hyponatremia during hospitalization is independently associated with a lower mortality risk in these patients. Moreover, results of subgroup analyses showed that the improvement of hyponatremia was associated with more remarkable change of short-term mortality (within 3 months after discharge) as compared with long-term mortality. Taken together, these results suggest that ADHF patients with improved hyponatremia during hospitalization may be associated with lower mortality risk as compared with those without the improvement of hyponatremia.

The prognostic efficacy of hyponatremia for patients with HF has been confirmed in previous studies. In a previously meta-analysis of observational studies of diverse population, HF patients with hyponatremia was associated with a more than twofolds increased risk of all-cause mortality as compared those without HF [29]. For patients with ADHF, hyponatremia on admission has also been proved to be predictive of poor outcomes during follow-up by many previously published studies [12, 13, 16]. Randomized controlled trials (RCTs) may be helpful to determine whether hyponatremia is a treatment target for HF patients, thereby indicating that hyponatremia may induce

**Table 3** Results of subgroup analysis

| Variables | Study (patients) number | RR (95% CI) | *p* for subgroup effect | $I^2$ | *p* for subgroup difference |
|---|---|---|---|---|---|
| Design | | | | | |
| Prospective | 2 (555) | 0.59 [0.29, 1.21] | 0.15 | 77% | |
| Retrospective | 6 (5131) | 0.65 [0.51, 0.83] | < 0.001 | 51% | 0.81 |
| Sample size | | | | | |
| < 200 | 4 (388) | 0.54 [0.35, 0.83] | 0.005 | 22% | |
| ≥ 200 | 4 (5298) | 0.69 [0.55, 0.87] | 0.001 | 65% | 0.31 |
| HF subtype | | | | | |
| HFrEF | 3 (415) | 0.72 [0.46, 1.11] | 0.13 | 0% | |
| HFpEF | 1 (91) | 0.39 [0.22, 0.72] | 0.002 | NA | |
| Mixed | 4 (5180) | 0.67 [0.52, 0.87] | 0.002 | 70% | 0.23 |
| Definitions of HN improvement | | | | | |
| Serum sodium increment ≥ 2 mmol/L | 2 (390) | 0.78 [0.68, 0.89] | < 0.001 | 0% | |
| Correction of HN | 6 (5296) | 0.61 [0.47, 0.78] | < 0.001 | 41% | 0.10 |
| Follow up duration | | | | | |
| < 3 months | 4 (4706) | 0.54 [0.44, 0.66] | < 0.001 | 0% | |
| ≥ 3 months | 4 (980) | 0.74 [0.59, 0.93] | 0.01 | 42% | 0.04 |

RR, risk ratio; CI, confidence interval; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction

or worsen HF. However, previous results of studies using tolvaptan, the vasopressin V2 receptor blocker for improving hyponatremia, failed to show that tolvaptan improve clinical outcome in patients with ADHF [14, 30, 31]. To be noticed, the previous clinical trials of tolvaptan was not limited to ADHF patients with hyponatremia, and the small sample sizes of the included patients and relative short follow-up duration may be inadequate to detect a benefit of tolvaptan in ADHF patients. Accordingly, a post hoc study of the EVEREST trial limited in patients with pronounced hyponatremia (< 130 mmol/L; $n = 92$) suggested that tolvaptan may improve the outcomes of cardiovascular morbidity and mortality after discharge in these patients [15]. Our meta-analysis by including the previous cohort studies including only patients with ADHF and hyponatremia ($n = 5714$) showed that improvement of hyponatremia in these patients is associated with a lower mortality risk as compared with patients without the improvement of hyponatremia. Since to the best of our knowledge, no RCT is available regarding the role of hyponatremia improvement for clinical outcomes in patients with ADHF and hyponatremia, results of our study may provide rationale to perform such trials in these patients. Besides, results of our study also have other clinical significance. Firstly, about a quarter of patients with ADHF were with hyponatremia according to previous studies [9, 10], and only about a half of the patients achieved improvement of hyponatremia according to the data of the included cohorts of our meta-analysis. A recently published study of 46 US sites on patients hospitalized with ADHF and hyponatremia showed that correction of hyponatremia only occurred in 19% patients at discharge [8]. These findings indicated that hyponatremia is common in ADHF patients and the potential association between improvement of hyponatremia and changes of mortality risk deserves investigation. Moreover, results of subgroup analyses of our study indicated

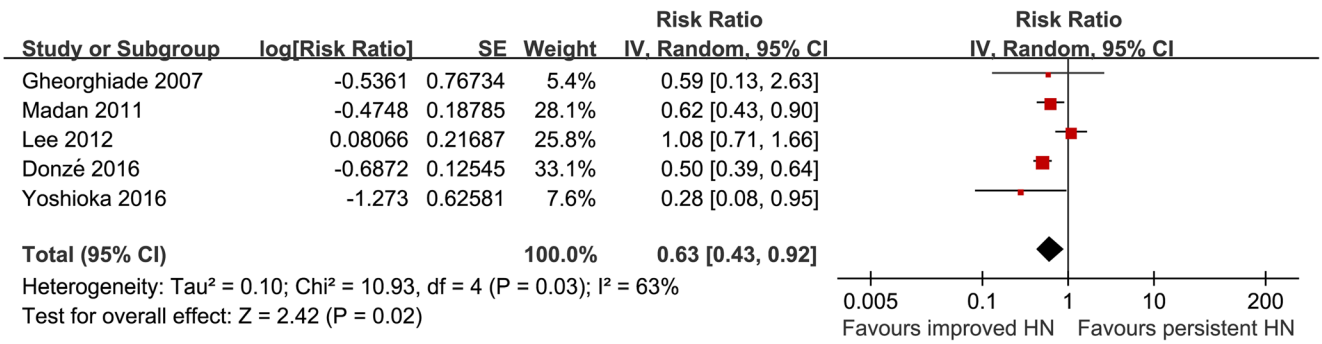


**Fig. 3** Forest plot for the meta-analysis regarding association between hyponatremia improvement and mortality risk in patients with ADHF and hyponatremia: multivariate-adjusted result

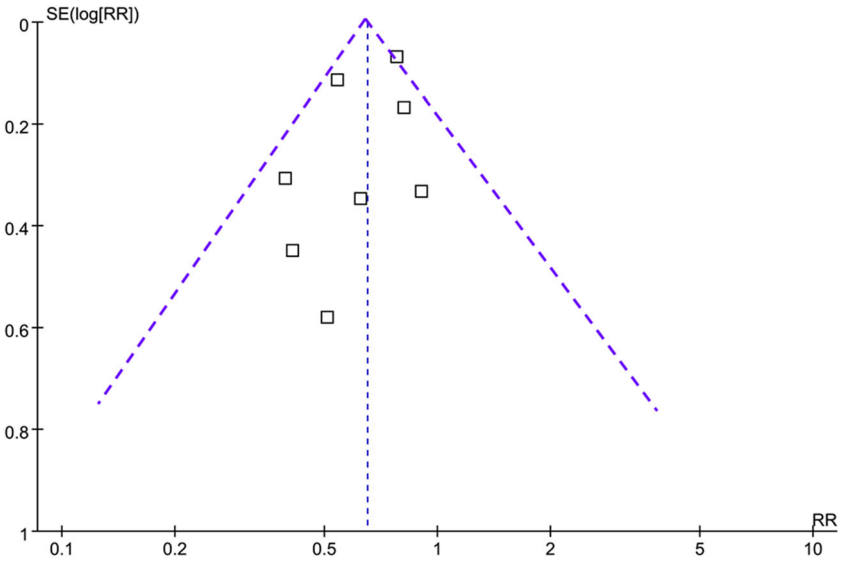


**Fig. 4** Funnel plot for the meta-analysis regarding the effect of hyponatremia improvement on mortality risk in patients with ADHF and hyponatremia

that hyponatremia improvement may be associated with more remarkably improved short-term (within 3 months after discharge) survival in ADHF patients as compared with the changes of long-term survival. In view of the fact that patients with ADHF were associated with substantial mortality within hospitalization or within 3 months after discharge (up to 50%) [4–7], these results are particularly important.

However, it remains undetermined whether hyponatremia could induce myocardial dysfunction or it is simply a pathophysiological change occurred during the pathogenesis of HF. Our results showed that improvement of hyponatremia in ADHF patients is associated with lower mortality risk during follow-up, which supports that treatment targeting hyponatremia may improve prognosis in ADHF patients. A previous study showed that HF patients with hyponatremia had higher serum levels of catecholamine, renin, angiotensin II and aldosterone than those without hyponatremia [32, 33]. These findings implied that hyponatremia may lead to HF by overactivating above neurohormonal factors. Accordingly, improvement hyponatremia may improve the clinical outcome of these patients by attenuating the activation of the neurohormonal factors. Moreover, hyponatremia may cause excessive ventricular ectopy, which may further lead to chronic deterioration of ventricular function [34]. Accordingly, correction of hyponatremia may ameliorate the worsening of ventricular function via reducing the incidence of ventricular ectopy. Future studies are needed to determine the exact mechanisms underlying the potential mechanisms underlying the benefit of improvement of hyponatremia in ADHF patients.

Results of our study have limitations which should be considered when interpreting the results. Firstly, only eight cohorts were included, and we do not have access to data of individual patient. Therefore, results of subgroup analyses should be interpreted with caution, and the potential influences of characteristics of the study and patients on the results should be evaluated in future studies. Secondly, considerable heterogeneity existed among the included cohorts. Differences regarding the cut-off value for the diagnosis of hyponatremia, definitions for the improvement of hyponatremia and variance of follow-up durations may affect the results. Thirdly, as a meta-analysis of cohort studies, although multivariable adjusted data retrieved similar results, we could not exclude the chances that residual confounding factors may affect the potential association between hyponatremia improvement and reduced mortality risk in patients with ADHF and hyponatremia. Fourthly, we did not include the analyses for the potential strategies that were applied to improve hyponatremia (use of tolvaptan, water restriction or intensified supplement of sodium) and whether improvement of hyponatremia via these different strategies confers similar benefits on survival deserve further investigation. At last, results of our study could not prove a causative relationship between improved hyponatremia and reduced mortality risk in patients with ADHF and hyponatremia. As stated above, RCTs are needed to confirm our results.

## Conclusion

In conclusion, improvement of hyponatremia in ADHF patients is associated with lower mortality risk during follow-up, particularly for the short-term mortality. Potential mechanisms underlying the association between hyponatremia improvement and lower mortality in patients with hyponatremia and ADHF should be determined in the future.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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