Association of Hyponatremia and Risk of Short- and Long-Term Mortality in Patients with Stroke: A Systematic Review and Meta-Analysis

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Background: Hyponatremia is the most common electrolyte disorder in the clinic practice and it is closely related to the prognosis of various diseases. Studies reported that hyponatremia increased the risk of stroke mortality while yielded inconsistent findings during the follow-up period. Thus, a systematic review and meta-analysis to assess the relationship between hyponatremia and the short-term (within 90 days) and long-term (more than 1 year) prognosis of stroke patients was conducted. *Methods:* A computerized systematic literature search was performed before November of 2018 for relevant articles evaluating the relationship between hyponatremia and all-cause mortality risk in stroke patients. Pooled relative risk (RR) and hazard risk (HR) with 95% confidence interval (CI) were calculated using DerSimonian-Laird random-effects model. Subgroup analyses were performed according to the follow-up period, types of stroke, different controls, sample size, and sampling time. *Results:* A total of 12 studies with 21,973 patients were identified. Compared to the nonhyponatremia patients, hyponatremia was associated with a higher risk of all-cause mortality in short-term (RR 1.61, 95% CI 1.33-1.96; HR 1.78 95% CI 1.19-2.75) and long-term follow-up (RR 1.77, 95% CI 1.27-2.47; HR 2.23,95% CI 1.30-3.82). Subgroups analysis showed the similar results in most subgroups. *Conclusions:* This meta-analysis concludes that hyponatremia has a significant prognostic value for short- and long-term prognosis to stroke patients.
Key Words: Hyponatremia—stroke—prognosis—meta-analysis

Introduction

Hyponatremia, defined as serum sodium concentration (Na^+) less than 135 mmol/L, is the most common electrolyte disorder in the clinical practice.[1] The prevalence of hyponatremia was 1.72% in general population, 5.5% in hospitalized patients and up to 50% in neurosurgery patients.[2-4] A number of studies have reported that hyponatremia is closely associated with the prognosis of various diseases, including acute coronary syndrome,[5] heart failure,[6] chronic kidney disease,[7] and liver cirrhosis.[8]

Meanwhile, stroke is the third leading cause of mortality and morbidity after coronary artery disease and cancer, with huge social and economic impact.[9] Hyponatremia has been depicted as a risk factor for stroke and has also been a complication of stroke.[10] Several studies reported that hyponatremia of stroke is a predictor of poor prognosis.[11] The exact pathophysiological mechanisms that hyponatremia is related to poor prognosis in stroke remains unclear, promoting cerebral edema and then affecting cerebral perfusion is postulated.[12] However, some studies have yielded inconsistent findings during the follow-up period.[13,14] Thus, we performed this systematic review and meta-analysis to shed light on the relationship between hyponatremia and short- and long-term prognosis of stroke patients.

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Methods

Data Sources

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15] The proponents searched PubMed, Embase, the Cochrane Library, and Web of Science for relevant articles published at the beginning of October 2018 by using Medical Subject Heading (MeSH) terms and key words, such as: "Hyponatremia" combined with “cerebrovascular disorders,” “stroke,” “cerebral infarction,” and “intracranial hemorrhage.” The full electronic search strategy for PubMed was ((((cerebrovascular disorders [Mesh]) OR stroke [Mesh]) OR cerebral infarction [Mesh]) OR intracranial hemorrhages [Mesh]) OR ((((((stroke [Title/Abstract]) OR cerebral infarction [Title/Abstract]) OR cerebral ischemia [Title/Abstract]) OR cerebrovascular disease [Title/Abstract]) OR intracranial hemorrhage [Title/Abstract]) OR hemorrhagic stroke [Title/Abstract]) AND ((((“hyponatraemia” [All Fields] OR “hyponatremia” [MeSH Terms] OR “hyponatremia” [All Fields]))).

The search was delimitedto human studies written in English. The 2 independent investigators (Z.Y.C. and X.Q.J.) scanned several titles and abstracts to find relevant articles and excluded the irrelevant ones. The full text of the relevant articles were downloaded and then were assessed for eligibility according to the inclusion criteria. Any discrepancies of this process were resolved by consensus or consultation with the third author (C.Y.L.).

Study Selection

We included studies in this analysis if they met the following criteria: (1) prospective or retrospective observational studies; (2) hyponatremia was a major exposure in patients with stroke; (3) the outcome measure was all-cause mortality; and (4) Relative risk (RR) or hazard ratio (HR) with 95% confidence interval (CI) or reported sufficient data to calculate these parameters compared hyponatremia with nonhyponatremia.

On the other hand, we excluded studies due to the following criteria: (1) Patients with known subarachnoid hemorrhage; (2) Case reports, case series, review articles, conference abstracts, letters, comments, and meta-analyses; (3) duplicate publications of the same dataset; and (4) insufficient information concerning evaluation rates.

Data Extraction and Quality Assessment

We extracted the following data from the selected article: The first author's name, year of publication, country of origin, study design, sample size, duration of follow-up, and main outcomes included in-hospital mortality, 30-day mortality, 90-day mortality, and all-cause mortality during follow-up. Mortality within 90 days of admission was classified as short-term mortality, and if in-hospital mortality, 30-day mortality, 90-day mortality were all given, the latter was chosen. Studies that reported the long-term outcome at various time intervals, the longer duration of time was chosen.

Data Extraction was done independently by the 2 authors. Any discrepancies in opinion in this process were resolved through discussion.

In addition, we used the Newcastle-Ottawa Quality Assessment Scale (NOS) to evaluate the quality of each study. The NOS contains 3 major parameters, including selection (0-4 points), comparability (0-2 points), and outcome assessment (0−3 points). The NOS ranges from 0 to 9 scores, and higher scores indicate better quality in methodology.

Statistical Analysis

Statistical analyses were performed usingStata 12.0 (Stata Corp, College Station, TX). We used the RRs or HRs with 95% CIs to evaluate the prognostic value of hyponatremia in stroke. We used The Engauge Digitizer V4.1 to obtain the survival data and then used Tierney's method to calculate the HRs and 95% CIs when the prognosis was presented only as the Kaplan-Meier curves.[16] Heterogeneity across the studies was evaluated with Q and I^2 statistics.[17] The heterogeneity was considered statistically significant if P is less than .1 or I^2 is greater than 50%, the method of DerSimonian and Laird by a random-effects model was used; otherwise, the method of Mantel-Haenszel by a fixed-effects model was applied instead. Subgroups were analysed according to follow-up period and stroke type. Sensitivity analysis was performed by removing one study at a time to assess the effect on pooled RRs. The severity of publication bias was evaluated using Egger's test and the Begg's test. A 2-tailed P less than .05 was considered statistically significant.

Results

Included Studies

Our initial search identified a total of 2903 relevant articles. After removing 462 duplicate studies and excluding 2388 articles based on titles and abstracts for various reasons (e.g. conference abstract, case reports, commentary, and irrelevant studies), the remaining 53 full-text articles were systematically reviewed. Ultimately, only 12 articles[11,13,14,18-26] were selected and included in this systematic review and meta-analysis. A detailed flow chart of the search and selection process is depicted in Figure 1.

Characteristics of Included Studies

The characteristics of the 12 studies included in the meta-analysis are listed in Table 1. A total number of 21,973 patients were included in the review. Two studies[11,18] originated from the same database and 1 study[18]

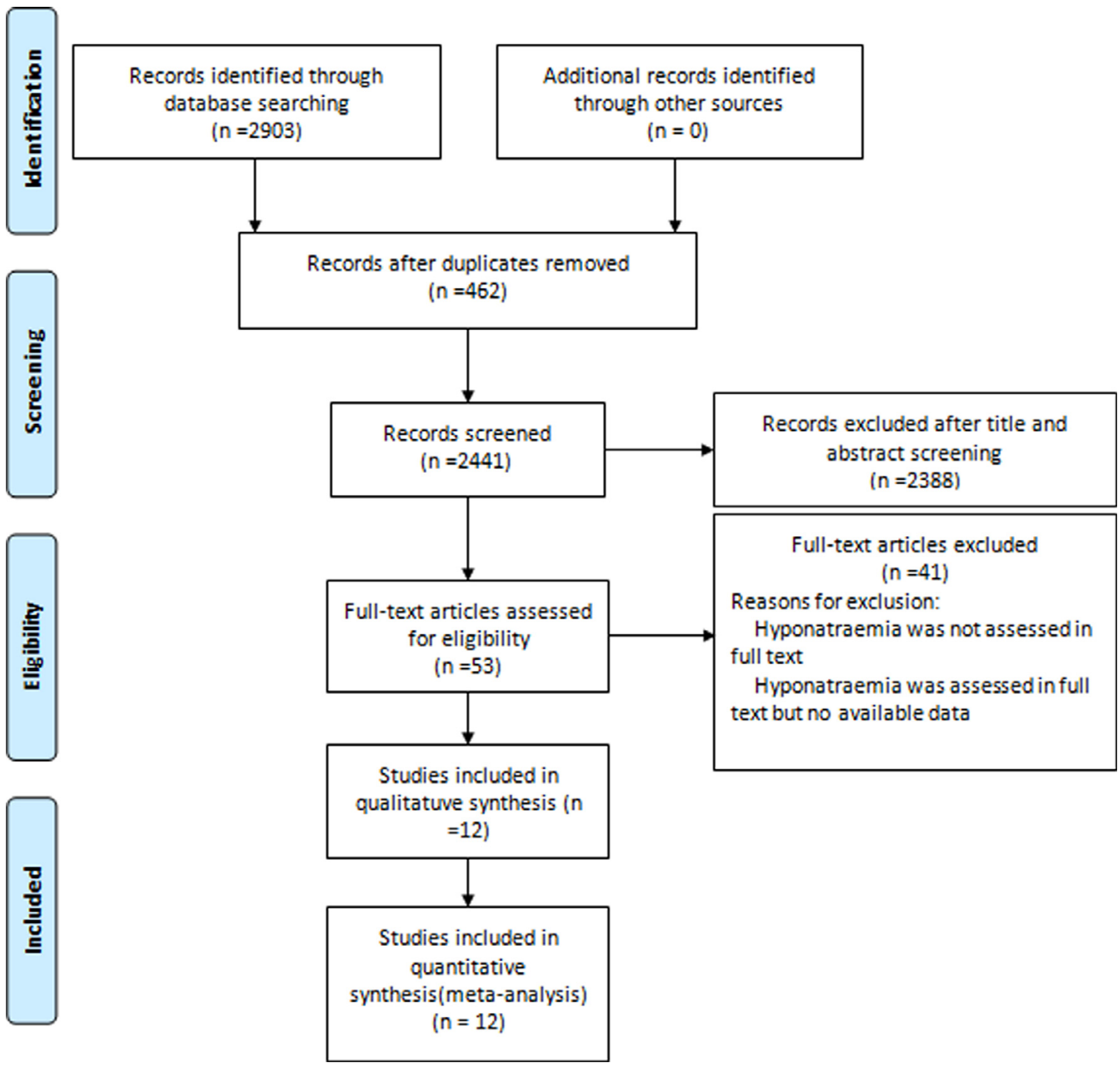

Figure 1. *Flow chart of the search and selection process.*

was included only in subgroup analysis due to different follow-up period. Two studies were performed in China,[13,21] 2 in the United States,[24,25] 2 in India,[22,26] 2 in England (from same database),[11,18] 1 in Australia,[19] 1 in Germany,[23] 1 in Italy,[20] and 1 in Taiwan.[14] Three studies[21,24,25] had retrospective study design and 9 studies[11,13,14,18,20,22,23,26] had prospective study design. Most of the studies defined hyponatremia as below 135 mmol/L. As for study quality assessment, all the included studies have relatively high methodological quality with NOS scores ranging from 5 to 8.

Main Meta-Analysis

The rates of hyponatremia during hospitalization vary widely with a range of 3.9% to 47.8% in stroke patients. In this analysis, we found that the incidence of hyponatremia in stroke was 13.4% (2951/21,973) and incidence of hyponatremia on admission in stroke was 12.2% (2531/20,784). The incidence of hyponatremia on admission in ischemic stroke and hemorrhage stroke were 11.9% (1924/16,228) and 13.3% (607/4556), respectively.

Ten studies using RRs and 5 studies using HRs evaluated the short-term prognostic value of hyponatremia in stroke. Significant heterogeneities across studies were found ($I^2 = 72.9\%$; $P < .000$;$I^2 = 60.0\%$; $P < .058$), thus the random-effects model was used to calculate the pooled RRs or HRs. Overall, patients with hyponatremia associated with significantly increased risk of mortality in short-term (RR 1.61, 95% CI 1.33-1.96; HR 1.78 95% CI 1.19-2.75; Fig 2). Five studies using RRs and 1 study using HR evaluated the long-term prognostic value of hyponatremia in stroke. Random-effects model was used because of significant heterogeneities ($I^2 = 95.5\%$; $P < .000$). Hyponatremia increased the risk of all-cause mortality in long-term follow-up (RR 1.77, 95% CI 1.27-2.47; HR 2.23,95% CI 1.30-3.82; Fig 3).

Table 1. *Characteristics of included studies on association between hyponatremia and clinical outcomes*

study	Country	Patients	Study design	Sample size	Definition of hyponatremia	Different collecting time	Follow-up	Outcomes	Study quality
Fofi 2012	Italy	Ischemic stroke	Prospective study	471	≤135 mmol/L	On admission	NG	In-hospital mortality	6
Huang 2012	Taiwan	Ischemic stroke	Prospective study	925	<135 mmol/L	On admission	3 years	In-hospital, 30-day, 90-day, 3-year mortality	8
Rodrigues 2013	USA	Ischemic stroke	Retrospective study	3541	<135 mmol/L	On admission	1 year	In-hospital, 90 day and 1 year mortality	8
Saleem 2014	India	Ischemic and hemorrhage stroke	Prospective study	1000	<130 mmol/L	During hospitalization	NG	All-cause mortality during follow-ups	5
Gray 2014	USA	Hemorrhage stroke	Retrospective study	99	<135 mmol/L	During hospitalization	NG	In-Hospital mortality	6
Kuramatsu 2014	Germany	Hemorrhage stroke	Prospective study	422	<135 mmol/L	On admission	1 year	In-hospital, 90-day and 1 year mortality	8
Soiza 2015	UK	Ischemic and hemorrhage stroke	Prospective study	9835	<135 mmol/L	On admission	Over full follow-up	90-day, 1 year mortality, all-cause mortality during follow-ups	8
Adekunle-Olarinde 2016	UK	Ischemic and hemorrhage stroke	Prospective study	8493	<135 mmol/L	On admission	NG	In-hospital mortality	8
Kalita 2016	India	Ischemic and hemorrhage stroke	Prospective study	90	<135 mmol/L	During hospitalization	NG	In-hospital mortality	5
Carcel 2016	Australia	Hemorrhage stroke	RCT	3002	<135 mmol/L	On admission	90-day	90-day mortality	-
Bei 2017	China	Ischemic stroke	Prospective study	3314	<135 mmol/L	On admission	NG	In-hospital mortality	7
Gao 2018	China	Ischemic stroke	Retrospective study	718	<135 mmol/L	On admission	30-day	30-day mortality	7

Abbreviation: NG, not given.

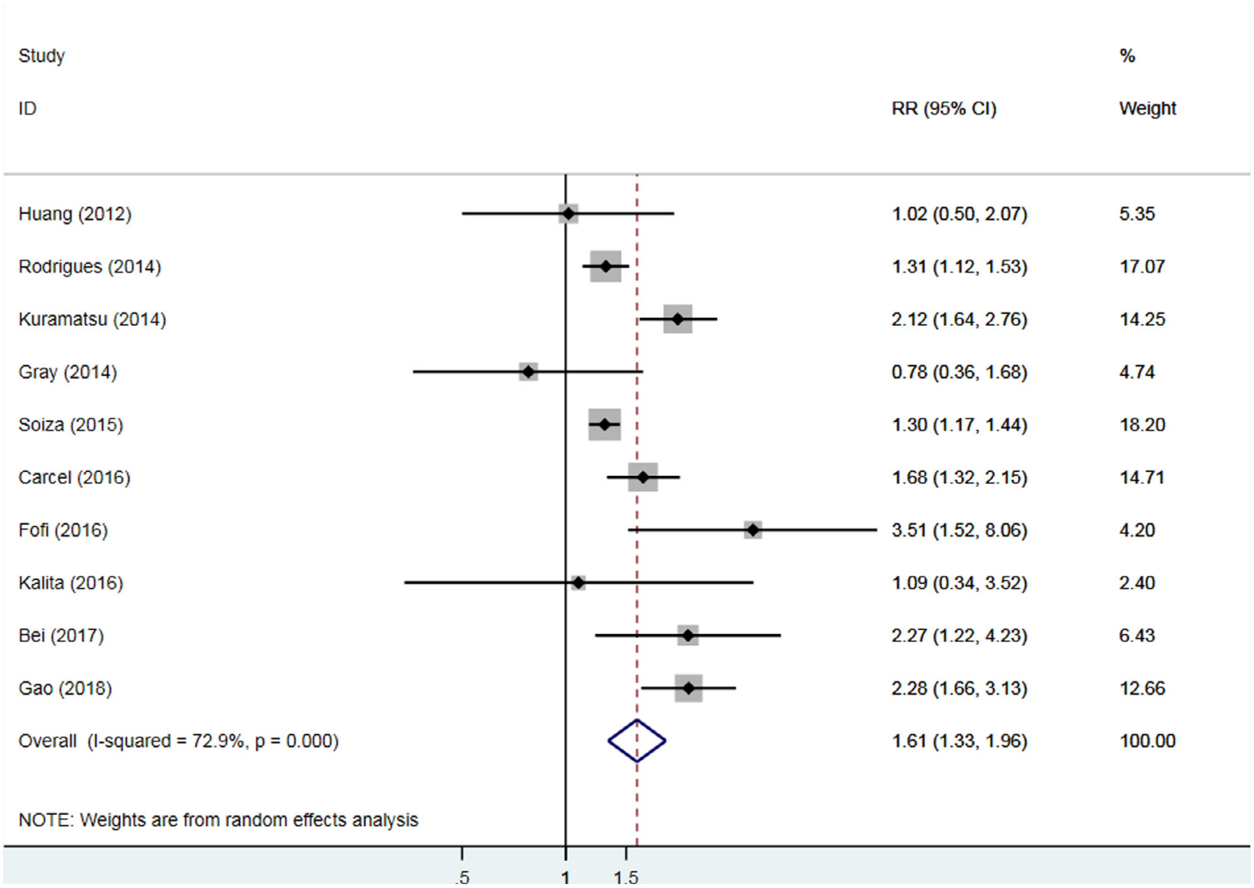

Figure 2. *Meta-analysis of hyponatremia and short-term mortality in patients with stroke.*

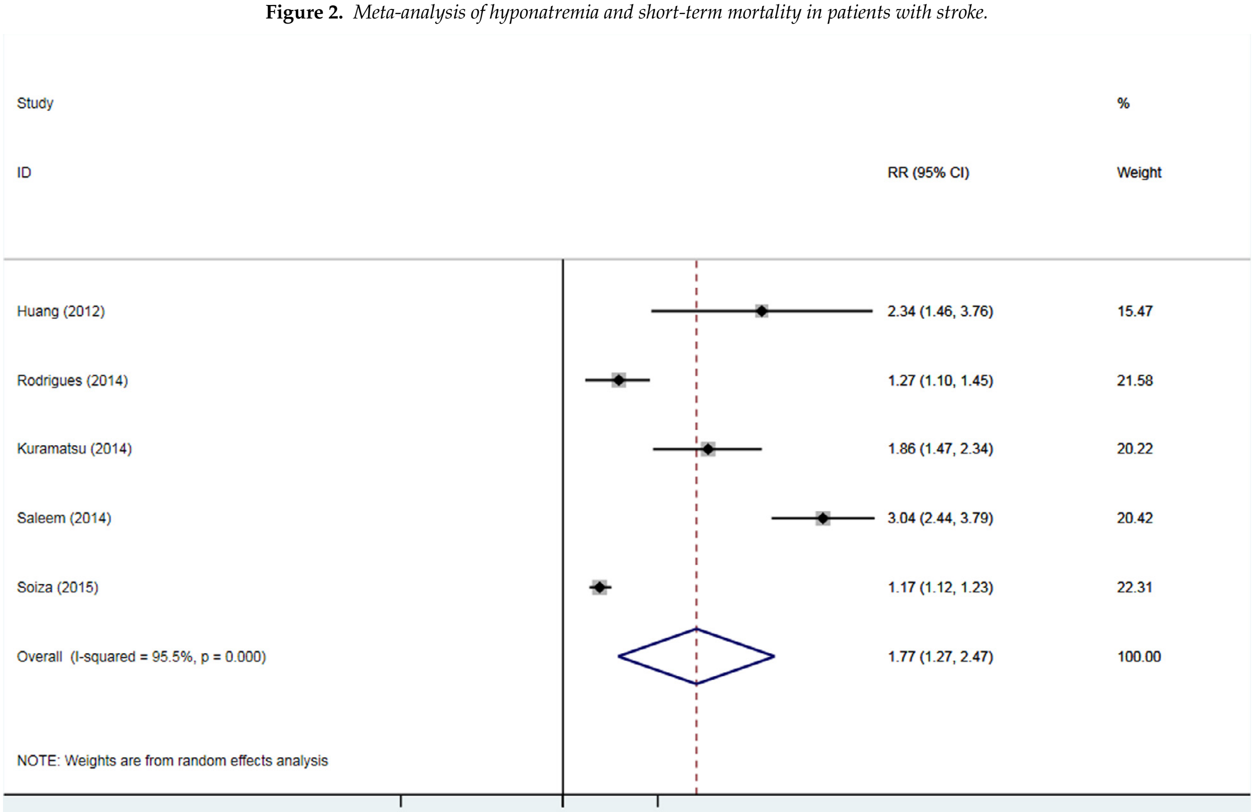

Figure 3. *Meta-analysis of hyponatremia and long-term mortality in patients with stroke.*

Subgroup Analysis

A subgroup analysis was performed according to the follow-up period, types of stroke, different controls, sample size, and sampling time (see Table 2). Subgroups analysis showed the similar results in most subgroups, which suggested a consistent correlation between hyponatremia and all-cause mortality in stroke.

Eight studies reported in-hospital mortality, 3 studies reported all-cause mortality within 30 days, and 4 studies reported all-cause mortality within 90 days. Patients with hyponatremia associated with significantly increased risk of mortality in hospital mortality (RR 1.48, 95% CI 1.20-1.83) and 90-day mortality (RR 1.57, 95% CI 1.20-2.05), while has no relationship with 30-day mortality (RR 1.56, 95% CI .99-2.48).

Five studies were conducted in a population with ischemic stroke, and 3 were conducted in patients with hemorrhage stroke, and 4 studies were conducted in patients with ischemic and hemorrhage stroke. Hyponatremia was associated with the increased the risk of ischemic stroke (RR 1.81, 95% CI 1.23-2.67) and hemorrhage stoke mortality(RR 1.65, 95% CI 1.15-2.35) in short-term follow-up. Hyponatremia increased the risk of mortality in hemorrhage stoke (RR 1.86, 95% CI 1.47-2.35) but not in ischemic stroke (RR 1.65, 95% CI 0.91-2.99) in long-term follow-up.

Five studies and 2 studies reported stroke mortality between hyponatremia and normonatremia in short- and long-term follow-up respectively. Compared to normonatremia, hyponatremia increased the risk of all-cause mortality in short-term (RR 1.44, 95% CI 1.23-1.70) and long-term follow-up (RR 1.20, 95% CI 1.14-1.26).

Sensitivity Analysis

For sensitivity analysis, we removed each single study at a time and then compared the pooled estimate from the remaining studies. The sensitivity analysis showed that there was no significant change in the direction and magnitude of pooled estimates, which suggested that the results of the meta-analysis were relatively robust (Fig. 4 and 5).

Publication Bias

We performed Begg and Egger tests to evaluate the publication bias of the included studies. No significant publication bias was found between hyponatremia and short-term mortality in stroke (Begg's test: $Z = .36$, $P = .721$; Egger's test: $t = 1.19$, $P = .268$, hyponatremia and long-term mortality in stroke (Begg's test: $Z = .73$, $P = .462$; Egger's test: $t = 2.55$, $P = .084$).

Discussion

Hyponatremia is closely associated with the prognosis of various diseases. A previous meta-analysis of 81 studies revealed that moderate hyponatremia was associated with an increased risk of overall mortality (RR: 2.60, 95%CI: 2.31-2.93) in patients with myocardial infarction, heart failure, cirrhosis, pulmonary infection, or mixed diseases.[27] Sun et al[28] also found that hyponatremia (HR 1.34; 95% CI: 1.15-1.57) was independently associated with increased risk of all-cause mortality in CKD patients. A recently published meta-analysis reported that hyponatremia increased not only risks of all-cause mortality but also heart failure in short-term (RR: 2.18, 95% CI: 1.96-2.42; RR: 1.72, 95% CI: 1.38-2.14) and long-term (HR: 1.74, 95%CI: 1.56-1.94; RR:1.69, 95%CI: 1.12-2.55) follow-up in patients after acute coronary syndrome.[5] In this study, we specially focused on stroke patients. This is the first meta-analysis that investigated the association of hyponatremia with all-cause mortality risk in stroke. Our results suggested that hyponatremia is significantly correlated with the increased risk of all-cause mortality in short- and long-term follow-up.

Previous studies have yielded consistent results regarding hyponatremia effect on long-term mortality after stroke, while there is a conflicting evidence that related the effect of hyponatremia on short-term mortality. Rodrigues et al[25] found that hyponatremia was associated with higher mortality in-hospital and at 90-day in ischemic stroke patients. While another study by Huang et al[14] found that hyponatremia was not associated with short-term mortality (either in-hospital, 30-day or 90-day mortality) after ischemic stroke. A Chinese study[13] found that patients with hyponatremia had higher risk of in-hospital mortality in crude analysis, while no association was seen after adjusting for potential confounders. Many factors probably explain part of the variation among those studies, such as inclusion criteria, ethnicity, and sample size. In this study, we confirmed that hyponatremia was both related to increased mortality in short- and long-term follow-up. The mechanism for hyponatremia associated with poor prognosis in short-term and long-term following stroke remains unclear and it has not yet been proven. A postulated mechanism of low serum levels of sodium influencing short-term outcome in stroke would be hyponatremia may promote cerebral edema and then affect cerebral perfusion, which led to a of the vascular injury after stroke.[12] Besides, Hyponatremia is also related to variety of symptoms, including seizures,[29] encephalopathy,[30] pneumonia,[31,32] and urinary tract infection,[25] which would not only prolong hospital stays and financial burden, but also increased mortality risk in short-term. Studies also reported that hyponatremia was related to larger intracerebral hemorrhage volume[19] and worse NIHSS scores,[25] which would also increase the inpatient mortality of stroke. As most of the included studies only utilized admission serum sodium measurements, it is difficult to rule out chronic hyponatremia which is common among general population and has a higher rate in elderly and also as a risk for stroke.[10] Chronic hyponatremia can result in attention deficit and impaired balance or memory

Table 2. *Hyponatremia and risk of mortality in different subgroups*

	Hyponatremia and short-term mortality				Hyponatremia and long-term mortality			
	Studies	RR (95% CI)	I^2 (%)	*P* value*	Studies	RR (95% CI)	I^2 (%)	*P* value*
Follow-up duration								
In-patient mortality	8	1.48 (1.20-1.83)	50.6	.048	NA	NA	NA	NA
30-day mortality	3	1.56 (.99-2.48)	82.0	.004	NA	NA	NA	NA
90-day mortality	4	1.57 (1.20-2.05)	74.2	.009	NA	NA	NA	NA
Types of stroke								
Ischemic stroke	5	1.81 (1.23-2.67)	75.6	.003	2	1.65 (.91-2.99)	83.1	.015
Hemorrhage stroke	3	1.65 (1.15-2.35)	68.5	.042	1	1.85(1.47-2.35)	NA	NA
Dfferent controls								
Hyponatremia versus Nonhyponatremia	10	1.61 (1.33-1.96)	72.9	.000	5	1.77 (1.27-1.47)	95.5	.000
Hyponatremia versus Normonatremia	5	1.44 (1.23-1.70)	54.1	.068	2	1.20 (1.14-1.26)	0	.368
Sample size								
<1000	6	1.67 (1.28-2.18)	59.6	.041	2	1.94 (1.58-2.40)	0	.393
≥ 1000	4	1.45 (1.18-1.78)	63.7	.041	3	1.63 (1.07-2.49)	97.1	.000
Sampling time								
On admission	8	1.69 (1.38-2.07)	77.1	.000	4	1.47 (1.18-1.84)	87.0	.000
During hospitalization	2	.86 (.45-1.64)	0	.639	1	3.04 (2.44-3.79)	NA	NA

Abbreviation: NA, not available.

**P* value for heterogeneity in each group.

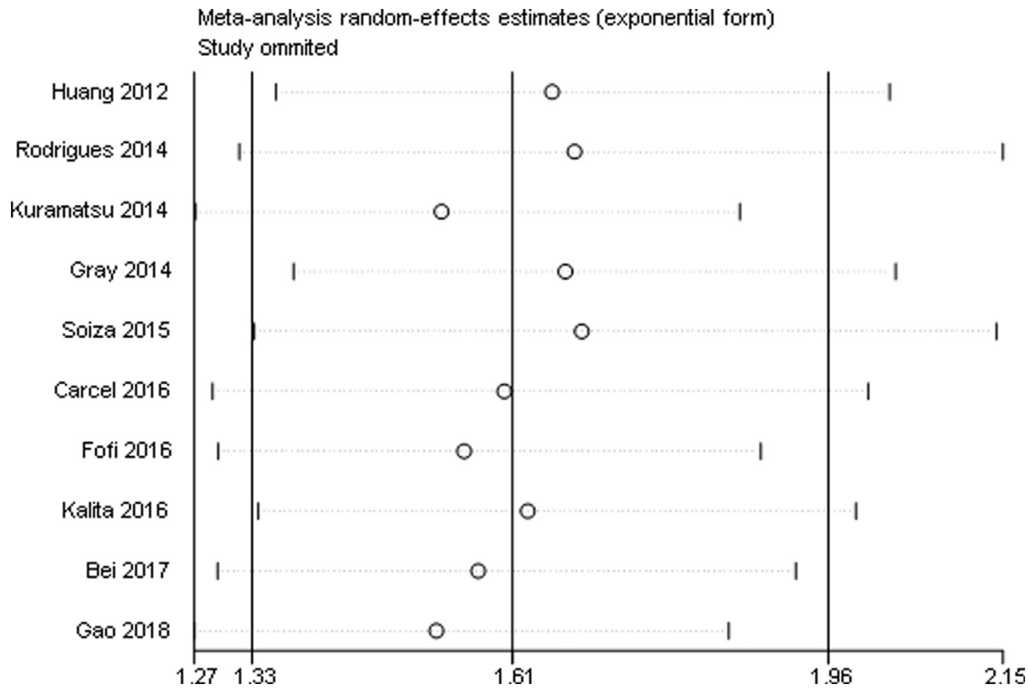

Figure 4. *Sensitivity analysis of hyponatremia and short-term mortality in patients with stroke.*

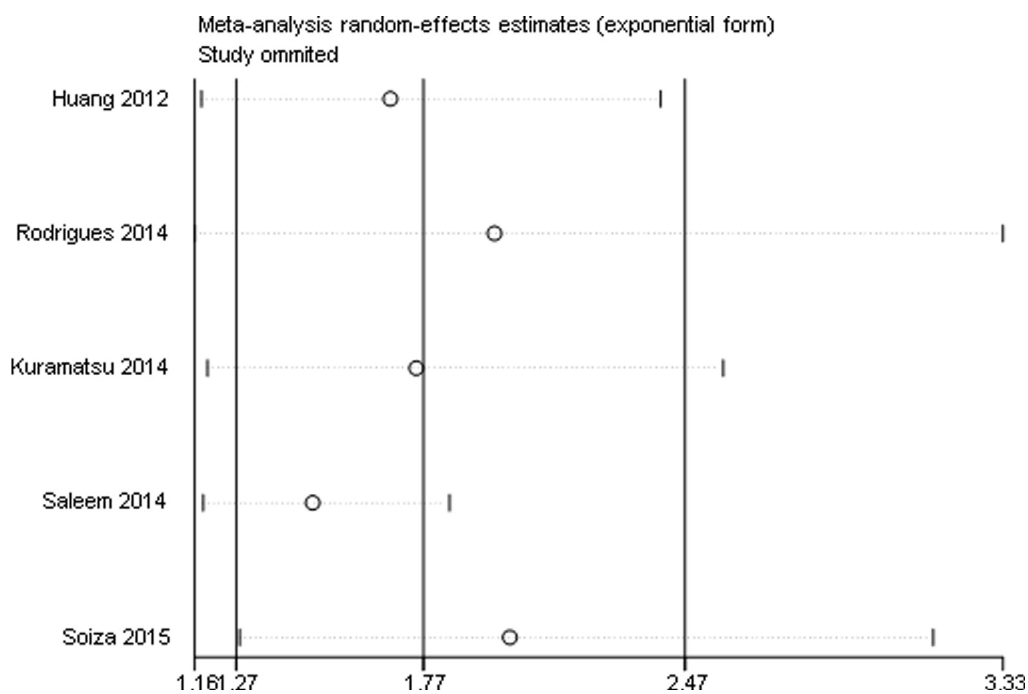

Figure 5. *Sensitivity analysis of hyponatremia and long-term mortality in patients with stroke.*

which are often overlooked, and then lead to significant morbidity, including higher rates of falls/fractures.[33-35] Hyponatremia can also activate the reninangiotensin-aldosterone system and affect left ventricular remodeling, leads to higher risk of suffering heart failure[6,36] and myocardial infarction[5,37] in cardiovascular diseases, which will increase the risk of death in long-term.

Studies reported that serum levels of sodium and stroke mortality have a "U"-typed relation.[10] Hypernatremia has also been associated with early neurological worsening following stroke.[20] As a result, subgroup analysis was performed between hyponatremia and normonatremia groups. The result showed that compared to normonatremia, hyponatremia increased the risk of all-cause mortality in short-term and long-term follow-up. Only 1 study investigated the association between severity of hyponatremia and mortality, hyponatremia was associated with increased mortality at all selected time-points in crude analysis.[11] However, only severe hyponatremia did reach statistical significance to the normonatremic group after adjustments. Furthermore prospective studies with large sample are required to confirm this conclusion.

We recognize that this meta-analysis study has some limitations and it should be considered. First, studies related to the long-term prognostic value of hyponatremia in stroke are limited, which reduced the power of our study. Second, there was notable heterogeneity among the included researches, which can be ascribed to different follow-up period, types of stroke, sample size, and sampling time. Although random-effects and subgroup analyses were conducted to find the source of heterogeneity, these parameters cannot fully explain the heterogeneity. Third, some of the data were extracted from survival curves rather than obtained from original articles, which would be less reliable. Finally, much data used in this analysis was not adjusted or adjusted for different confounding factors, which would have overestimated the risk estimated.

In conclusion, we found that hyponatremia is independently associated with increased short- and long-term all-cause mortality risk in patients after stroke. It is important to monitor the serum sodium levels value dynamically, which could help doctors to identify patients at high risk and guide subsequent in-hospital management.

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