Moderate Hyponatremia Is Associated with Increased Risk of Mortality: Evidence from a Meta-Analysis

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Abstract

Background: Hyponatremia is the most common electrolyte disorder in clinical practice, and evidence to date indicates that severe hyponatremia is associated with increased morbidity and mortality. The aim of our study was to perform a meta-analysis that included the published studies that compared mortality rates in subjects with or without hyponatremia of any degree.

Methods and Findings: An extensive Medline, Embase and Cochrane search was performed to retrieve the studies published up to October 1st 2012, using the following words: “hyponatremia” and “mortality”. Eighty-one studies satisfied inclusion criteria encompassing a total of 850222 patients, of whom 17.4% were hyponatremic. The identification of relevant abstracts, the selection of studies and the subsequent data extraction were performed independently by two of the authors, and conflicts resolved by a third investigator. Across all 81 studies, hyponatremia was significantly associated with an increased risk of overall mortality (RR = 2.60[2.31–2.93]). Hyponatremia was also associated with an increased risk of mortality in patients with myocardial infarction (RR = 2.83[2.23–3.58]), heart failure (RR = 2.47[2.09–2.92]), cirrhosis (RR = 3.34[1.91–5.83]), pulmonary infections (RR = 2.49[1.44–4.30]), mixed diseases (RR = 2.59[1.97–3.40]), and in hospitalized patients (RR = 2.48[2.09–2.95]). A mean difference of serum [Na+] of 4.8 mmol/L was found in subjects who died compared to survivors (130.1±5.6 vs 134.9±5.1 mmol/L). A meta-regression analysis showed that the hyponatremia-related risk of overall mortality was inversely correlated with serum [Na+]. This association was confirmed in a multiple regression model after adjusting for age, gender, and diabetes mellitus as an associated morbidity.

Conclusions: This meta-analysis shows for the first time that even a moderate serum [Na+] decrease is associated with an increased risk of mortality in commonly observed clinical conditions across large numbers of patients.

Introduction

Hyponatremia, defined as a serum sodium concentration ([Na+]) <136 mmol/L, is the most common electrolyte disorder encountered in clinical practice [1]. The most common cause of hypotonic or dilutional hyponatremia is the syndrome of inappropriate antidiuresis (SIAD). Mild hyponatremia (serum [Na+] 130–135 mmol/L) has been estimated to occur in about 15–30% of hospitalized patients, whereas the prevalence of moderate to severe hyponatremia (serum [Na+] <130) is as high as 7% among in-hospital patients [2].

Hyponatremia represents a serious health problem with significant associated morbidity and mortality. Acute severe hyponatremia is a medical emergency accompanied by severe neurological symptoms due to cerebral edema and can be lethal if not recognized and appropriately treated [3]. The correction of hyponatremia may per se represent a risk and a rare but potentially lethal complication, i.e. the osmotic demyelination syndrome, may be the result of an overly rapid correction [4]. In contrast, mild chronic hyponatremia has traditionally been considered as an asymptomatic or mildly symptomatic condition. However, recent reports indicated that even mild chronic hyponatremia can have long-term adverse effects, such as deficits in gait and attention [5], falls [3], bone loss and fractures [6–9], especially in the elderly. More recently, chronic hyponatremia has been shown to exacerbate multiple manifestation of senescence in aged rats,
including senile osteoporosis, sarcopenia, cardiac fibrosis, and hypogonadism [10].

The association between hyponatremia and in-hospital mortality has been demonstrated in numerous studies. For instance, a large cohort study, which included all adult hospitalizations (n = 532936) at an academic medical center between 2000–2007, demonstrated that even mild hyponatremia was associated with increased in-hospital mortality, and that the risk of death was increased by 2.3% for each 1 mmol/L decline of serum [Na+] [11].

Hyponatremia has been generally associated with an increased mortality in different conditions such as pneumonia [12], heart failure [13], acute myocardial infarction [14], cirrhosis [15], cancer [14], in the elderly [16], and in intensive care patients [17]. However, whether hyponatremia is an independent risk factor for death or is simply associated with an underlying severe condition that is the cause of death remains to be elucidated [4,18]. Furthermore, there is the possibility that hyponatremia indirectly contributes to mortality by causing organ dysfunction, such as for example bone loss and fractures which are associated with significant mortality in the elderly. Recently, a meta-analysis that included 22 observational studies and randomized controlled trials published to the end of 2008, that was limited to patients with heart failure, indicated that hyponatremia is a powerful predictor of mortality in these patients regardless of ejection fraction [19]. However, no meta-analysis on the relationship between hyponatremia and mortality has addressed other pathological conditions to date.

The aim of this study was to perform a meta-analysis, which included the studies that compared the mortality rate in subjects with or without hyponatremia, in order to verify whether hyponatremia represents a risk factor for mortality, independently of other confounding factors.

Methods

A meta-analysis was performed including studies comparing mortality rate in subjects with or without hyponatremia. An extensive Medline, Embase, and Cochrane search was performed including the following words: hyponatremia and mortality. The search up to October 1st 2012 was restricted to English-language articles and studies of human participants. The identification of relevant abstracts, the selection of studies based on the criteria described above, and the subsequent data extraction were performed independently by two of the authors (G.P., C.G.), and conflicts resolved by a third investigator (G.C.). Full-text articles and meeting abstracts were included. The quality of studies was assessed using the Cochrane criteria [20].

Statistical analysis

Heterogeneity was assessed using the I² statistics for overall mortality rate. Considering that heterogeneity could not be excluded (I² = 92.8%), relative risk of mortality between subjects with or without hyponatremia, was calculated using both a random and fixed effect model. For a more conservative approach, results of random effect models were presented. A meta-regression analysis was performed to test the effect of serum [Na+] threshold selected in the different studies on overall mortality rate levels. In addition, a linear regression analysis model, weighing each study for the number of subjects enrolled, was performed to verify the independent effect of hyponatremia on mortality after the adjustment for age, gender and diabetes mellitus as an associated morbidity. It was not possible to include other co-morbidities because there were not enough data to be collected and analyzed from the selected literature. Finally, sensitivity analyses was performed considering only larger studies (including ≥1000 subjects) or those reporting the prevalence of diabetes mellitus. In addition, mean baseline serum [Na+] in subjects who eventually died or not at follow up were meta-analyzed using a random effect model.

Relative risks (RRs) with 95% CIs were calculated using Comprehensive Meta-analysis Version 2, Biostat, (Englewood, NJ, USA). Logistic multivariate analysis was performed on SPSS (Statistical Package for the Social Sciences; Chicago, USA) for Windows 20.1.

Results

Out of 718 retrieved articles, 637 articles were excluded for different reasons. The flow of the meta-analysis is summarized in Figure 1, and the characteristics of the trials included in the meta-analysis are summarized in Table 1 (see references 3,11–12,16–18, 21–95). Among the 81 selected studies, 7, 13, 8, 5 studies evaluated the effect of hyponatremia on overall mortality rate in subjects with myocardial infarction, heart failure (HF), cirrhosis and pulmonary infections, respectively. In addition, another 26 studies reported data on the effect of hyponatremia on overall mortality for combined mixed diseases, which could not be grouped separately (see Table 1). Finally, 14 studies retrospectively investigated the effect of hyponatremia on overall mortality in hospitalized series of subjects. In these studies, a major diagnosis was not specified.

The mean±SD serum [Na+] in dead or alive individuals was specified in 3 of the aforementioned studies and in a further 8 studies enrolling patients with HF (n = 2), cirrhosis (n = 1), pulmonary infection (n = 2) or mixed disease (n = 3), respectively (Table 1).

Overall 850222 patients and 147948 hyponatremic subjects were included in the meta-analysis. Hyponatremia was defined according to varying cut-off definitions in the included studies (Table 1). The Begg-adjusted rank correlation test, calculated on the basis of overall mortality rate for hyponatremia, suggested no major publication bias (Kendall tau 0.02; p = 0.82).

When all 81 studies were considered, hyponatremia was significantly associated with an increased risk of overall mortality (RR = 2.60[2.31–2.93]; p<0.0001). Similar results were obtained when patients with specific diseases or series of hospitalized patients were analyzed separately (Figure 2, panels A–E). Similar to what observed for mortality rate, the Begg-adjusted rank correlation test, calculated on the basis of mean serum [Na+] between subjects who eventually died when compared to survivors, suggested no major publication bias (Kendall tau −0.145; p = 0.553). The baseline mean difference of serum [Na+] was significantly lower in subjects who eventually died when compared to survivors (130.1±5.6 vs 134.9±5.1 mmol/L) at follow up (Figure 3). Similar results were observed when studies enrolling less than 100 subjects were excluded from the analysis (mean difference in serum [Na+] between survivors vs dead 3.04[1.81–4.27], p<0.0001). Sub-analysis for mean serum [Na+] in specific diseases was not performed due to insufficient data.

A meta-regression analysis showed that the hyponatremia-related risk of overall mortality was inversely correlated with the serum [Na+] threshold considered for each report (Figure 4). Hence, the lower threshold considered, the higher the risk of mortality. The latter association was confirmed in a multiple regression model, adjusting for age, gender and diabetes mellitus (adj. r = −0.278; p<0.0001).
Sensitivity analyses performed considering only larger studies (including ≥1000 subjects), those reporting the prevalence of diabetes mellitus or those with severe hyponatremia ([Na⁺] ≤125 mmol/l), confirmed the association between hyponatremia and mortality (RR = 2.521[2.180–2.916]; p, 0.0001 and 2.886[2.228–3.737], 10.036[5.155–19.540]; all p, 0.0001, respectively).

Discussion

Hyponatremia has been associated with increased in-hospital mortality [11], but no published comprehensive meta-analysis that analyzed the mortality rate in subjects with or without hyponatremia had been performed to date. Very recently, the Meta-Analysis Global Group in Chronic heart failure (MAGGIC) published a meta-analysis that included 14766 patients from 22 studies that recruited patients with HF and reported death from any cause [19]. Patients with hyponatremia (n = 1618) had an increased risk of death (21%), compared to patients with normal serum [Na⁺] (16%), and the risk of death appeared to increase linearly with serum [Na⁺] <140 mmol/L. Hyponatremia was an independent predictor of death either when the patients were considered as a whole, or when they were grouped based on the presence of a reduced (n = 1199) or a preserved (n = 419) ejection fraction. The MAGGIC meta-analysis was limited to patients with HF and considered studies published to the end of 2008.

Our meta-analysis included all of the English-language published studies up until October 1st 2012 that compared the mortality rate in human subjects with or without hyponatremia of any degree. Eighty-one published studies were selected according to specified inclusion criteria for a total of 850222 patients, of whom 17.4% were hyponatremic. This percentage is in general agreement with epidemiological data about the prevalence of hyponatremia among hospitalized patients [2]. Of note, hyponatremia was associated with a significantly increased risk of overall mortality when all studies were considered (RR = 2.60 [2.31–2.93]). A detailed analysis of cause specific mortality was not possible, because this information was not available in several studies, as also was found in the MAGGIC meta-analysis. Nevertheless, we were able to conclude that the risk of mortality was independent of factors including age, gender, and diabetes mellitus as an associated morbidity. Similarly, hyponatremia was found to be associated with an increased risk of death when the patients were analyzed separately based on different disease types or when sensitivity analysis was restricted to larger studies or those reporting the prevalence of diabetes. In particular, we were able to confirm the data of the MAGGIC meta-analysis on hyponatremic patients with HF (RR = 2.47 [2.09–2.92]), analyzing a greater number of patients (168971, of whom 20.4% were hyponatremic).
Table 1. Studies included in meta-analysis.

| Source            | Type of disease | Age (years) | Male % | DM % | Na⁺ cut-off (mEq/L) | Patients H | NH | Deaths H | DeathsNH | Na⁺ deaths (mEq/L) | Na⁺ survivors (mean ± SD) |
|-------------------|-----------------|-------------|--------|------|--------------------|------------|----|----------|-----------|---------------------|--------------------------|
| Flear et al., 1979 [21] | Myocardial infarction | 57.1         | 78.7   | NA   | 135                | 235        | 88 | 147      | 19        | 10                  | NA                       |
| Goldberg et al., 2004 [22] | Myocardial infarction | 61           | 78     | 24.2 | 135                | 1047       | 339| 708      | 61        | 44                  | NA                       |
| Goldberg et al., 2006 [23] | Myocardial infarction | 59.3         | 80.7   | 22.6 | 136                | 978        | 108| 870      | 26        | 78                  | NA                       |
| Klopotowski et al., 2009 [24] | Myocardial infarction | NA           | 72.5   | 8.9  | 135                | 1858       | 96 | 1762     | 13        | 67                  | NA                       |
| Havránek et al., 2011 [25] | Myocardial infarction | 64           | 66     | 33.9 | 135                | 218        | 72 | 146      | 25        | 30                  | NA                       |
| Tada et al., 2011 [26] | Myocardial infarction | 64.4         | 85     | 41.4 | 136                | 140        | 29 | 111      | 0         | 3                   | NA                       |
| Tang et al., 2011 [27] | Myocardial infarction | 63.8         | 6.8    | 2.9  | 135                | 1620       | 212| 1408     | 29        | 103                 | NA                       |
| Panzciroli et al., 1990 [28] | HF               | 67           | 70.2   | 11.8 | 135                | 161        | 64 | 97       | 44        | 39                  | NA                       |
| Adebowale et al., 1996 [29] | HF               | NA           | NA     | NA   | 125                | 64         | 10 | 54       | 7         | 17                  | NA                       |
| Chen et al., 2003 [30] | HF               | 56           | 63.2   | NA   | 125                | 234        | 27 | 207      | 20        | 35                  | NA                       |
| Villacorta et al., 2003 [31] | HF               | 72.5         | 63     | NA   | 135                | 170        | 61 | 109      | 32        | 31                  | NA                       |
| Gheorgiade et al., 2007 [32] | HF               | NA           | NA     | NA   | 135                | 40454      | 7882| 32572    | 473       | 1042                | NA                       |
| Gheorgiade et al., 2007 [33] | HF               | 56.2         | NA     | NA   | 134                | 430        | 103| 327      | 31        | 52                  | NA                       |
| Mildo-Cotter et al., 2008 [34] | HF               | 74.9         | 51     | NA   | 135                | 296        | 38 | 258      | 11        | 21                  | NA                       |
| Tribouilloy et al., 2008 [35] | HF               | 74           | 53.8   | 25.8 | NA                 | 662        | NA | NA       | NA        | 136.7±4.9           | 138.4±3.6                |
| Rusinaru et al., 2009 [36] | HF               | 75.8         | 46.6   | 26.2 | 136                | 358        | 91 | 267      | 73        | 159                 | NA                       |
| Basheshet et al., 2010 [37] | HF               | NA           | 55.3   | 51.7 | 136                | 2336       | 537| 1799     | 54        | 74                  | NA                       |
| DeWolfe et al., 2010 [38] | HF               | 54.7         | 62.9   | 34.1 | 135                | 364        | 48 | 316      | 8         | 31                  | NA                       |
| Novack et al., 2010 [39] | HF               | 75.6         | 52.2   | 38.3 | 136                | 8246       | 1755| 6491     | NA        | NA                  | 136.4±5.3               |
| Baldasseroni et al., 2011 [40] | HF               | 62           | 74.4   | 11.0 | 135                | 4670       | 463| 4207     | 123       | 433                 | NA                       |
| Bailing et al., 2011 [41] | HF               | 68           | 73     | NA   | 136                | 3645       | 602| 2863     | 147       | 429                 | NA                       |
| Shorr et al., 2011 [42] | HF               | 74.7         | 46.2   | NA   | 135                | 115969     | 24562| 91407    | 1372      | 2783                | NA                       |
| Arroyo et al., 1976 [43] | CIRRHOSIS        | NA           | NA     | NA   | 130                | 55         | 21 | 34       | 9         | 6                   | NA                       |
| Vila et al., 1999 [44] | CIRRHOSIS        | 47.3         | 35.2   | NA   | 130                | 45         | 20 | 25       | 7         | 9                   | NA                       |
| Borroni et al., 2000 [45] | CIRRHOSIS        | 56.9         | 70.5   | NA   | 130                | 191        | 57 | 134      | 15        | 12                  | NA                       |
| Porcel et al., 2002 [46] | CIRRHOSIS        | 62.9         | 62.1   | NA   | 130                | 74         | 54 | 20       | 37        | 5                   | 123.8±5.6               |
| Ruf et al., 2005 [47] | CIRRHOSIS        | 49           | 53     | NA   | 130                | 194        | 34 | 160      | NA        | NA                  | 130±6.0                 |
| Hackworth et al., 2009 [48] | CIRRHOSIS        | 51           | 78     | NA   | 130                | 213        | 90 | 123      | 10        | 10                  | NA                       |
| Radha Krishna et al., 2009 [49] | CIRRHOSIS        | 36.3         | 70.2   | NA   | NA                 | 121        | 50 | 71       | 38        | 16                  | NA                       |
| Terg et al., 2009 [50] | CIRRHOSIS        | NA           | NA     | NA   | 130                | 81         | 27 | 54       | 12        | 7                   | NA                       |
| Jenq et al., 2010 [51] | CIRRHOSIS        | 56           | 76.2   | NA   | 135                | 126        | 67 | 59       | 49        | 33                  | NA                       |
| Singhi et al., 1992 [52] | PNEUMOPATHY      | 3.14         | NA     | NA   | 135                | 727        | 371| 356      | 24        | 17                  | NA                       |
| Sharma et al., 1995 [53] | PNEUMOPATHY      | 35           | 51     | NA   | 135                | 112        | 42 | 70       | NA        | NA                  | 117.6±5.8               |
| Source | Type of disease | Age (years) | Male | DM | Na⁺ cut-off (mEq/L) Patients H NH Deaths N Deaths NH Na⁺ deaths (mEq/L) Na⁺ survivors (mEq/L) |
|--------|----------------|-------------|------|----|---------------------------|---------------------------------|---------------------------------|
| El-Bary et al., 1997 [54] | PNEUMOPATHY | 68.4 | 15 | 32 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Hussain et al., 2004 [55] | PNEUMOPATHY | 47 | 32 | 16 | 62 | 293 | 19 | 6 | 122.7 |
| Nair et al., 2007 [56] | PNEUMOPATHY | 73.5 | 20 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Song et al., 2008 [57] | PNEUMOPATHY | 73.5 | 20 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Zilberberg et al., 2008 [58] | PNEUMOPATHY | 68.4 | 45.2 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Sunderam et al., 1983 [59] | AGED | 2.7 | 43.4 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Samadi et al., 1985 [60] | CHRONIC DIARRHEA | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Cusano et al., 1990 [61] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Vitting et al., 1990 [62] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Erinoso et al., 1993 [63] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Tang et al., 1993 [64] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Terzian et al., 1994 [65] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Chuah et al., 1996 [66] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Olotu et al., 2002 [67] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Oguche et al., 2002 [68] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Agarwal et al., 2004 [69] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Lee et al., 2005 [70] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
|SRivastava et al., 1998 [71] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Berghmans et al., 2000 [72] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Manary et al., 2000 [73] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Forfia et al., 2008 [74] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Olotu et al., 2002 [75] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Hanson et al., 2009 [76] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Sherlock et al., 2006 [77] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |
| Hoorn et al., 2011 [78] | AIDS | 36.6 | 89 | 16 | 62 | 293 | 19 | 6 | 127.8 | 7.4 | 130.6 | 7.5 |

**Note:** The table continues with similar entries for each source, providing data on various conditions such as malaria, fulminant hepatic failure, and others, along with their respective age, male/female ratio, and sodium levels. The entries are likely part of a larger dataset examining the relationship between sodium levels and mortality or other health outcomes in different patient groups.
Table 1. Cont.

| Source                        | Type of disease     | Age (years) | Male % | DM % | Na⁺ cut-off (mEq/L) | Patients H (n) | NH (n) | Deaths H (n) | Deaths NH (n) | Na⁺ deaths H (mEq/L) (mean ± SD) | Na⁺ deaths NH (mEq/L) (mean ± SD) | Na⁺ survivors (mean ± SD) |
|-------------------------------|---------------------|-------------|--------|------|---------------------|----------------|--------|--------------|---------------|----------------------------------|-------------------------------|------------------------|
| Vaa et al., 2011 [85]         | ALCOHOLIC HEPATITIS| 51.1        | 85     | NA   | 135                 | 26             | NA     | 26           | 26            | 132 (136)                         | 132                           | 136                     |
| Tierney et al., 1986 [86]     | HOSPITALIZED SERIES| 61.2        | 47     | 19   | 135                 | 1514           | 757     | 757          | 165           | 60 NA NA NA NA 132 (136)          | 132                           | 136                     |
| Natkunam et al., 1991 [87]    | HOSPITALIZED SERIES| NA          | NA     | NA   | 125                 | 1217           | 202     | 202          | 1015          | 84 35 NA NA NA NA 132 (136)      | 132                           | 136                     |
| Singhi et al., 1994 [88]      | HOSPITALIZED SERIES| NA          | 75     | NA   | 135                 | 264            | 71      | 71           | 6 7            | NA NA NA NA 132 (136)            | 132                           | 136                     |
| Miller et al., 1995 [89]      | HOSPITALIZED SERIES| 60–103      | 91.6   | NA   | 135                 | 119            | 63      | 63           | 56            | 11 12 NA NA NA NA 132 (136)      | 132                           | 136                     |
| Gill et al., 2006 [3]         | HOSPITALIZED SERIES| 65          | 47.5   | NA   | 125                 | 204            | 104     | 104          | 28 9           | NA NA NA NA 132 (136)            | 132                           | 136                     |
| Asadollahi et al., 2007 [90]  | HOSPITALIZED SERIES| NA          | NA     | NA   | 134                 | 1599           | 356     | 356          | 1243          | 179 377 NA NA NA NA 132 (136)     | 132                           | 136                     |
| Steffox et al., 2008 [17]     | HOSPITALIZED SERIES| 56.1        | 58.9   | NA   | 133                 | 5985           | 917     | 917          | 5068          | 255 799 NA NA NA NA 132 (136)     | 132                           | 136                     |
| Zilberberg et al., 2008 [91]  | HOSPITALIZED SERIES| 61.8        | 45.5   | NA   | 135                 | 198281         | 10899   | 10899        | 187382        | 643 5621 NA NA NA NA 132 (136)    | 132                           | 136                     |
| Hampshire et al., 2009 [92]   | HOSPITALIZED SERIES| NA          | NA     | NA   | 130                 | 6410           | 285     | 285          | 6125          | 208 3468 NA NA NA NA 132 (136)    | 132                           | 136                     |
| Whelan et al., 2009 [93]      | HOSPITALIZED SERIES| 58.5        | 47.5   | NA   | 134                 | 14039          | 2795    | 2795         | 11244         | 474 893 NA NA NA NA 132 (136)     | 132                           | 136                     |
| Whyte et al., 2009 [94]       | HOSPITALIZED SERIES| 68.8        | 39.8   | NA   | 120                 | 226            | 113     | 113          | 24 7           | NA NA NA NA 132 (136)            | 132                           | 136                     |
| Funk et al., 2010 [95]        | HOSPITALIZED SERIES| 63.2        | 57.6   | NA   | 135                 | 140952         | 26782   | 26782        | 114170        | 4369 11074 NA NA NA NA 132 (136)  | 132                           | 136                     |
| Wald et al., 2010 [11]        | HOSPITALIZED SERIES| 65.3        | 48.2   | 14.9 | 138                 | 34761          | 13274   | 13274        | 14887         | 451 430 NA NA NA NA 132 (136)     | 132                           | 136                     |
| Chawla et al., 2011 [18]      | HOSPITALIZED SERIES| NA          | NA     | NA   | 135                 | 209839         | 46093   | 46093        | 164146        | 2787 3775 NA NA NA NA 132 (136)   | 132                           | 136                     |

H: patients with hyponatremia; NH: patients without hyponatremia; DM: diabetes mellitus; NA: not available.
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In the MAGGIC meta-analysis, only 11% of patients were hyponatremic, which is below the prevalence of hyponatremia generally reported for hospitalized patients (15–30%) [2]; the authors suggested that this might be due to the fact that all patients in the MAGGIC cohort were outpatients at the time of the baseline data. In contrast with the MAGGIC meta-analysis, Figure 2. Odds ratio for overall mortality in patients with or without (no) hyponatremia according to the presence of myocardial infarction (A), heart failure (B), cirrhosis (C), pulmonary infection (D), mixed disease (E), or in hospitalized series of subjects (F). doi:10.1371/journal.pone.0080451.g002
patients with hyponatremia in our meta-analysis were neither older, nor more frequently affected by diabetes mellitus. Furthermore, we found an increased risk of mortality in hyponatremic patients with myocardial infarction (total number of patients 6096, of whom 18.3% with hyponatremia), cirrhosis (total number of patients 906, of whom 42.6% were hyponatremic), or pulmonary infections (total number of patients 10047, of whom 12% were hyponatremic). Some studies (n = 26) reported data regarding other mixed diseases or subpopulations (e.g., elderly people), which could not be grouped together. The most represented diseases

Figure 3. Weighted differences (with 95% CI) of mean serum [Na+] in dead and alive patients.
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Figure 4. Relation between serum [Na+] cut-off definition and overall mortality risk.
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among these patients (total number of patients 37864, of whom 15.1% were hyponatremic) were AIDS, malaria and malnutrition. Finally, some studies (n = 14, total number of patients 615410, of whom 16.7% were hyponatremic) were considered separately, because the effect of hyponatremia on mortality was investigated retrospectively and the diagnoses were not specified. The meta-analysis of these studies also revealed an increased risk of overall mortality.

The major finding of this meta-analysis is that across all groups of patients the relative risk of mortality in patients with hyponatremia vs patients without hyponatremia ranged between 2.47 and 3.34, thus indicating that this electrolyte disorder strongly predicts prognosis of all hospitalized patients. Another interesting result of our meta-analysis is that a moderate serum [Na+] reduction (i.e., 4.8 mmol/L) was associated with an increased risk of mortality, and a meta-regression analysis showed that the hyponatremia-related risk of overall mortality was inversely correlated with the serum [Na+]. Hence, the lower threshold considered, the higher the risk of mortality. This association was confirmed in a multiple regression model after adjusting for age, gender and diabetes mellitus. The linear increase of risk of death that we showed in our analysis is in agreement with the findings of the MAGGIC meta-analysis, which found a linear increase of mortality starting at serum [Na+] <190 mmol/L. Overall, our findings indicate that even a moderate reduction of serum [Na+] is associated with an increased risk of mortality in patients affected by multiple disease types across large numbers of hospitalized patients.

Although the present meta-analysis both confirms and extends the strong association between hyponatremia and adverse outcomes such as inpatient mortality, it cannot prove a causal relation between these variables. In fact, only diabetes mellitus could be used as a possible confounder in the present study. Perhaps the major outstanding question regarding hyponatremia is whether hyponatremia contributes directly to poor outcomes or is simply a marker for severity of underlying co-morbidities, or possibly for other factors that might influence the progression of underlying co-morbidities [96]. Hence, it should be recognized that potential unmeasured confounders such as other chronic diseases, in addition to diabetes mellitus, may have caused residual confounding, but the measured factors that are correlated with such confounders would have mitigated the bias. Few studies to date have attempted to address the issue of a direct effect of hyponatremia on mortality or other adverse outcomes. One oft-cited potential exception is the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) study of patients with congestive heart failure, which failed to show improvements in cardiovascular outcomes in patients with acute heart failure (AHF) treated with the vasopressin type 2 receptor (V2R) antagonist, tolvaptan, versus placebo [97]. However, that study was not powered to examine outcomes in the smaller subgroup of patients enrolled with both heart failure and hyponatremia. More recently, a significant strong positive relationship between an increase in serum sodium and decreased mortality was noted in 322 patients hospitalized for AHF and followed for 1–3 years [98]. In contrast, a multicenter analysis of 2880 patients hospitalized for AHF in Korea confirmed that hyponatremia on admission was associated with a worse prognosis compared with normonatremia, but this relation persisted regardless of whether the hyponatremia improved during the hospitalization [99]. However, this report was a retrospective analysis from a registry, not a prospective randomized trial, and the assessment of the change in serum sodium was made only once, prior to or at discharge from the hospital [100]. Thus, whether hyponatremia is merely a marker or also a mediator of adverse patient outcomes is still uncertain in heart failure, and has not been studied in other diseases. The current meta-analysis adds further urgency to the need to answer this question for multiple diseases, not only heart failure.

In conclusion, this study represents the first extensive and updated meta-analysis demonstrating that hyponatremia is significantly associated with an increased risk of overall mortality, and that it is a negative prognostic factor across multiple commonly observed clinical conditions, such as myocardial infarction, HF, cirrhosis and pulmonary infections. These findings might suggest the importance to correct this electrolyte disorder, even when mild, using the most appropriate strategies [101–103]. However, our study did not specifically address this issue and this hypothesis at present highlights the need for additional studies of clinical outcomes with effective therapies in all hyponatremic patients.

Supporting Information

Checklist S1  PRISMA Checklist.

(DOC)

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Author Contributions

Conceived and designed the experiments: GC CG AP JGV. Performed the experiments: GC CG GP DN. Analyzed the data: GC AP. Wrote the paper: GC CG AP JGV.

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