Prevalence and Prognostic Significance of Hyponatremia in Lung Cancer Patients: Systematic Review and Meta-Analysis

Eszter Bartalis
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Marin Gergics
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Benedek Tinusz
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Mária Földi
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Szabolcs Kiss
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Dávid Németh
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Margit Solymár
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Zsolt Szakács
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Péter Hegyi
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Emese Mezősi
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
Laszlo Bajnok (bajnok.laszlo@pte.hu)
University of Pecs Medical School: Pecsi Tudomanyegyetem Altalanos Orvostudomanyi Kar
https://orcid.org/0000-0001-7194-5747

Research article

Keywords: Lung Cancer, SCLC, NSCLC, Hyponatremia, SIADH

Posted Date: November 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-104861/v1

Version of Record: A version of this preprint was published at Frontiers in Medicine on December 7th, 2021. See the published version at https://doi.org/10.3389/fmed.2021.671951.

Prevalence and prognostic significance of hyponatremia in lung cancer patients: Systematic Review and Meta-Analysis

Eszter Bartalis[1,2], Marin Gergics[3], Benedek Tinusz[2,4], Mária Földi[2,4,5], Szabolcs Kiss[2,4,5], Dávid Németh[2,4], Margit Solymár[2,4], Zsolt Szakács[2,4], Péter Hegyi[2,4], Emese Mezősi[3], László Bajnok[3*]

[1]- University of Medicine, Pharmacy, Science and Technology of Târgu Mureș, Târgu Mureș, Romania

[2]- Institute for Translational Medicine, Medical School, University of Pécs, Pécs, Hungary

[3]- First Department of Medicine, Medical School, University of Pécs, Pécs, Hungary

[4]- Szentágothai Research Centre, University of Pécs, Pécs, Hungary

[5]- Doctoral School of Clinical Medicine, University of Szeged, Szeged, Hungary

*Corresponding author:

E-mail: bajnok.laszlo@pte.hu

Abstract

Background

The prevalence of hyponatremia is highly variable among lung cancer patients. It is also an important predictive factor, according to numerous studies. However, its prevalence and prognostic significance in subgroups of lung cancer patients, e.g. in small cell and non-small cell lung cancers (SCLC and NSCLC, respectively), have not yet been evaluated in a meta-analysis.

Methods

We report this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) Statement. We have registered our meta-analysis and review's protocol to the PROSPERO International Prospective Register of Systematic Reviews, with the following registration number: CRD42020167013. A systematic search was done in the following sources: MEDLINE, Embase, CENTRAL, Web of Science, ClinicalTrials.gov, a WHO Global Health Library. We extracted the effect measure for each outcome as the relative risk (RR) with the related 95% confidence interval (CI).

Results

We identified a total of 8127 potentially eligible studies and we included 25 studies in our evaluation. The prevalence of hyponatremia in lung cancer patients varied between 3% and 56.1% with an average of 23% without any significant differences between the following subgroups: cancer type (p=0.780), gender (p=0.223), age (p=0.773), ECOG state (p=0.317) and the extent of disease (p=0.999). Hyponatremia was more consistently an independent prognostic factor in NSCLC than in SCLC. The overall survival (OS) was significantly lower in hyponatremic compared to normonatremic patients at 10 months (RR: 0.59, 95% CI, 0.47 to 0.74, p<0.001) and at 20 months (RR: 0.44, 95% CI, 0.33 to 0.59, p<0.001), with worse survival rates in NSCLC than in SCLC (27% vs 42%) (p<0.001). If hyponatremia was corrected, OS at 10 months was 1.83 times higher than in the uncorrected hyponatremia group (95% CI, 1.37 to 2.44, p<0.001), but at 20 months no statistically significant difference could be found between these subgroups (p=0.067).

Conclusions

Low serum sodium levels have a negative impact on mortality at 10 and 20 months, which is more pronounced among NSCLC patients. The correction of hyponatremia has a positive effect on OS rates at 10 months, but this advantage disappears by 20 months.

Key words: Lung Cancer, SCLC, NSCLC, Hyponatremia, SIADH

Background

Lung cancer is one of the most frequent malignancies worldwide in both sexes, and 75% of patients are diagnosed at an advanced stage. According to the reports of the WHO in 2018, it is the leading cause of mortality among cancers [1]. Moreover, based on the WHO's Global Cancer Observatory's report, the incidence of lung cancer is predicted to grow by 72.5% until 2040 [2].

The reported prevalence values of hyponatremia (<135 mmol/L) among lung cancer patients are highly discordant in the literature, varying between 3.7% and 75% [3-8]. Although inappropriate antidiuretic hormone secretion (SIADH) is the most common underlying cause [4-5], the prevalence of SIADH seems to be lower among lung cancer patients compared to hyponatremia, varying from 9.1 to 39% in SCLC [6, 9-11] and 0.7-4% in NSCLC [6, 12]. SIADH was diagnosed even less frequently in the general cancer population [4, 13-14]. This discrepancy may be partially explained by insufficient diagnostic work-up and the presence of other comorbidities that also affect the sodium level [15-17].

Based on literature reports, hyponatremia and SIADH appear to be important negative predictive factors of mortality in numerous medical conditions, including lung cancer [4, 9, 12, 18-22], but not in every paper reached this conclusion [6, 10]. However, a recent meta-analysis of fifteen studies confirmed the prognostic significance of serum sodium levels by demonstrating that the correction of hyponatremia is associated with reduced risk of mortality in hospitalized oncology patients [23].

Following a preliminary search of the literature, we found discordant results regarding the prevalence and prognostic significance of hyponatremia in lung cancer patients, and the findings considerable differ from the studies and reviews cited above. Our study aims to make a reappraisal of the occurrence and prognostic impact of pre- and posttreatment hyponatremia, specifically in patients with lung cancer.

Methods

Protocol and Registration

We report this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2009) Statement [24] described in the Additional File 1. We have registered our meta-analysis and review's protocol to the PROSPERO International Prospective Register of Systematic Reviews, with the following registration number: CRD42020167013. There were no deviations from the study protocol.

Search strategy

The first step was to create a PECO (Patient-Exposure/Prognostic factor-Comparison-Outcome): “P” patients with lung cancer, “E” hyponatremia at the time of the diagnosis/before treatment, “C” normonatremia at the time of the diagnosis/before treatment, “O” overall survival time and rate at 10 and 20 months. Then we created a search key based on our PECO, which included search terms related to the patients group and the prognostic factor: (*lung cancer OR SCLC OR NSCLC OR carcinoid) AND (SIADH OR sodium level OR Na level OR hyponatraemia OR hyponatremia OR syndrome of inappropriate ADH OR antidiuretic hormone OR hypotonicity*).

We searched the following sources: MEDLINE (via PubMed), Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, ClinicalTrials.gov, a WHO Global Health Library. The "human" filter was applied in the case of MEDLINE, Embase, and the WHO Global Health Library. The "trials" and "completed" filters were utilized when searching in the Cochrane Library or ClinicalTrials.gov, respectively. We did not apply any language or date restriction to our search. We also performed a search on the bibliography of the eligible articles. The date of search was 12.03.2019.

Eligibility and exclusion criteria

Studies qualified our systematic review after fulfilling the following requirements: 1.) observational or interventional cohort studies, case-control studies, randomized-controlled trials, case series, and conference abstracts too, if there were sufficient data provided; 2.) trials enrolling adult (18 years or above) lung cancer patients with available information of lung cancer patients’ characteristics (number of patients, age, sex, histological type of cancer, extent of disease, performance status) and pretreatment serum sodium levels; 3.) trials reporting data regarding overall survival (OS) time and rate at 10 and 20 months, or with available information about multivariate analysis of the prognostic significance of hyponatremia.

The exclusion criteria were the following: 1.) case studies, case reports, reviews, comments, letters; 2.) studies investigating other lung pathologies or solid cancers; 3.) lack of data regarding serum sodium levels before treatment; 4.) papers not reporting outcomes mentioned before.

Study selection and data extraction

After the initial search, all records from each database were imported into a reference management program (EndNote X7, Clarivate Analytics, Philadelphia, PA, USA). This software was used to remove duplicates. After the removal of duplicates, the authors screened the remaining articles against the pre-defined eligibility criteria first by title, abstract, and then full text. Two researchers conducted each step independently, and any disagreements were resolved by consensus.

Numerical data were extracted by two independent investigators, any disagreements were resolved by consensus and data were manually entered on an Excel 2018 sheet (Office 365, Microsoft, Redmond, WA, USA). These were collected on first author, year of publication, study design, geographical location, number of patients and basic demographics (age and sex ratio), in each group. Additional information on the tumor's histological type, disease extent, Eastern Cooperative Oncology Group (ECOG) Performance status, the grade of hyponatremia, and the length of follow-up was also obtained. We also collected information about hyponatremia improvement that was achieved by oncologic, symptomatic, and/or supportive treatment, including at least 2 cycles of chemotherapy, sodium supplementation, or fluid restriction. Finally, data were collected on the primary and secondary outcomes of interest such as OS time, rate and results of multivariate analyses.

Risk of Bias Assessment

We used the Quality in Prognostic Studies (QUIPS) tool [25] for assessing the risk of bias, which is described in the Additional File 2. Any disagreements between the two independent researchers were solved by consensus.

Statistical Analysis

The effect measure of dichotomous variables was reported for each outcome as the relative risk (RR) with the related 95% confidence interval (CI). All tests were 2-sided, and a p-value of <0.05 was considered statistically significant (except for heterogeneity, for which a p-value of <0.10 was considered significant). The random-effects model was used because of the minor differences between individual studies.

Heterogeneity was tested by performing both the Cochran's Q test and calculating Higgins' I^2 indicator. A p-value of less than 0.10 was considered suggestive of significant heterogeneity. The I2 index corresponds to the percentage of the total variability across studies that is due to heterogeneity. Based on Cochrane Handbook for Systematic Reviews of Interventions [26], a rough classification of its value is the following: low (0-40%), moderate (30-60%), substantial (50-90%) and considerable (75-100%). All the statistical analyses were performed using Stata IC (version 15.1).

Results

The selection process is summarized in Figure 1. We identified a total of 8127 potentially eligible studies in the literature, 1659 articles in MEDLINE, 5143 articles in Embase, 231 records in CENTRAL, 946 articles in Web of Science, 33 in ClinicalTrials.gov and 115 in WHO Global Health Library. After screening by title, abstract, and full text, we chose 25 studies for our evaluation based on our eligibility criteria. Since not all studies reported on every parameter, we could include only a limited number of studies in each subanalysis.

Figure 1: PRISMA flow diagram representing the process of study search and selection

Systematic review

The characteristics of the studies are summarized in a table included in Additional File 3 (Additional File 3, Table 1). All selected reports were published in peer-reviewed journals, including three prospective and 22 retrospective cohort or case-control studies. The number of participants in the trials varied from 50 to 1083 patients. Every selected article reported demographic information of the investigated population and data regarding the serum sodium levels at admission or before starting oncological treatment. Only 15 studies reported on median OS times and the OS rates at 10 and 20 months were available in even less studies (n=8).

The main clinical characteristics of patients in individual articles are shown in Table 1 from Additional File 3. Out of the 10638 patients included, 65.8% (N=6988) were diagnosed with SCLC, 34.2% (N=3633) with NSCLC, 70.7% (7225) were male and 29.3% were female. The reported median age ranged from 55 to 68 years. With a cut-off value of 60 years (7 studies) 53.1% of the studied population was older than 60 years, while with a cut-off value of 65 years (7 studies) 68.4% was younger. In total, 2182 patients had hyponatremia at admission or before starting oncological treatment. The applied cut-off values varied between 132 mmol/L and 139 mmol/L across studies. Hyponatremia was diagnosed in 1,005 of 5,501 patients (18.3%) using a 135 mmol/L cut-off value in most of the included articles (15 studies), while in 5 studies where the cut-off value was 136 mmol/L, the number of hyponatremic patients was 694 out of 2776 patients (25%).

The results of various outcomes among the selected studies are shown in another additional file (Additional File 4, Table 2). The prognostic significance of hyponatremia was evaluated in 19 studies and was found to be an independent prognostic factor in 12 studies, whereas in 7 studies it was not.

After evaluating the risk of bias in each study using the QUIPS tool, the included reports had high and medium risk of bias (Additional File 5).

Meta-analysis

The summary of the results of the statistical analysis are presented in Table 3.

Table 3. Results of the statistical analyses

Prevalence of hyponatremia					
Subgroups	**RR**	**95% CI**	**P value**	**Heterogeneity (I^2)**	**P value of heterogeneity**
SCLC	0.23	[0.17; 0.29]	NS p=0.780	96.80%	<0.001
NSCLC	0.22	[0.14; 0.30]		96.25%	<0.001
male vs female	1.22	[0.89; 1.68]	NS p=0.223	74.20%	<0.001
<60 years vs ≥60 years	0.97	[0.80; 1.19]	NS p=0.773	0.00%	0.657
ECOG≤1 vs ECOG>1	0.85	[0.62; 1.17]	NS p=0.317	64.40%	0.006
LD vs ED stage	1.00	[0.47; 2.13]	NS p=0.999	89.2%	<0.001

Overall survival rates **Hyponatremic vs Normonatremic patients*:***					
Subgroups	**RR**	**95% CI**	**P value**	**Heterogeneity (I^2)**	**P value of heterogeneity**
10 months	0.59	[0.47; 0.74]	<0.001	81.1%	<0.001
20 months	0.44	[0.33; 0.59]	<0.001	40.5%	0.109
Hyponatremic SCLC vs NSCLC patients at 10 months:					
SCLC	0.42	[0.27; 0.57]	<0.001	92.72%	<0.001
NSCLC	0.27	[0.12; 0.44]	<0.001	-	-
Difference			<0.001		
Corrected vs Uncorrected hyponatremic patients:					
10 months	1.83	[1.37; 2.44]	<0.001	0.0%	0.775
20 months	2.65	[0.94; 7.50]	0.067	23.3%	0.271

Abbreviations: ES- Effect size; RR- Risk ratio; CI- Confidence Interval; SCLC- Small cell lung cancer; NSCLC- Non-small cell lung cancer; ECOG- Eastern Cooperative Oncology Group performance status; LD- Limited disease; ED- Extensive disease

The prevalence of hyponatremia in lung cancer patients varied between 3% and 56.1% (3-46.6% in SCLC and 5.3-46.7% in NSCLC) with an average of 23% (23% SCLC and 22% NSCLC) in the evaluated reports without significant differences between SCLC vs. NSCLC patients (Figure 2), or in the subgroups created by the following criteria: gender, age, ECOG state, the extent of disease (Figure 3-6).

Figure 2.: The prevalence of hyponatremia in SCLC and NSCLC patients

Legends: Black diamonds represent the individual studies effect and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect on the weight of a particular study. The blue diamond the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviations: SCLC- Small Cell Lung Cancer; NSCLC- Non-Small Cell Lung Cancer; ES- effect size

Figure 3.: The prevalence of hyponatremia in male and female lung cancer patients

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviation: RR- Risk ratio

Figure 4.: The prevalence of hyponatremia in young (<60 years) and older (>60 years) lung cancer patients

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviation: RR- Risk Ratio

Figure 5.: The prevalence of hyponatremia in lung cancer patients with ECOG≤1 and ECOG>1 performance state

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviations: ECOG- Eastern Cooperative Oncology Group performance status, RR- Risk Ratio

Figure 6.: The prevalence of hyponatremia in SCLC patients with Limited and Extensive Disease stage

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviations: SCLC- Small Cell Lung Cancer, RR- risk ratio

The meta-analysis of the overall survival rates of lung cancer patients with hyponatremia was performed on 8 selected studies, and a subgroup analysis was also carried out comparing SCLC and NSCLC patients.

The hyponatremic patients, in comparison to patients with normonatremia had 0.59 (95% CI: 0.47-0.74) and 0.44 (95% CI: 0.33-0.59) times lower OS at 10 and 20 months, respectively, as shown in Figure 7 and 8.

Figure 7.: The overall survival rates at 10 months comparing hyponatremic and normonatremic lung cancer patients

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviations: RR- Risk ratio

Figure 8.: The overall survival rates at 20 months comparing hyponatremic and normonatremic lung cancer patients

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviation: Risk ratio

You can see in Figure 9, that the overall survival rates at 10 months were significantly lower in hyponatremic NSCLC patients (27%, with 95% CI: 12-44%) than in hyponatremic SCLC patients (42%, with 95% CI: 27-57%) ($p<0.001$).

Figure 9.: The overall survival rates at 10 months in hyponatremic patients comparing Small Cell and Non-Small Cell Lung Cancer patients

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of

a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviations: SCLC- Small cell lung cancer, NSCLC- Non-small cell lung cancer, RR- risk ratio

Information regarding the improvement of overall survival rates following the correction of hyponatremia was available in only 4 studies. In the selected articles, the changes of serum sodium levels were the result of oncologic, symptomatic, or supportive treatment, including at least two cycles of chemotherapy, sodium supplementation, or fluid restriction. After the correction of hyponatremia, the overall survival rates at 10 months were 1.83 (95% CI: 1.37-2.44) times higher when compared with the uncorrected hyponatremia group (Figure 10).

Figure 10.: The overall survival rates after correction of hyponatremia at 10 months (corrected and uncorrected hyponatremic patient groups)

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviation: RR- Risk ratio

However, at 20 months, no significant differences were identified between these groups (p=0.067), as shown in Figure 11.

Figure 11.: The overall survival rates after correction of hyponatremia at 20 months (corrected and uncorrected hyponatremic patient groups)

Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs.
Abbreviation: RR- Risk ratio

Discussion

Regarding the prevalence of hyponatremia in lung cancer patients, discordant results have been published. In one review, the incidence of hyponatremia was suggested to be in the range of 15-75% among lung cancer patients [3]. At the same time, in another one, the prevalence varied in a lower range, from 5 to 36% with an average of 15% in SCLC, and 0.4-

2% in NSCLC [6]. In other reviews, the prevalence of hyponatremia and/or SIADH was even less: Grohe et al. found hyponatremia in 14% of SCLC patients and 2.7% of NSCLC [7], while Christoforos Efthymiou et al showed that SIADH was present in 7-16% of SCLC patients, and was rare among NSCLC patients (1%) [8].

To the best of our knowledge, ours is the first article which is not only a systematic review but also a meta-analysis evaluating the prevalence of hyponatremia in lung cancer patients. According to our systematic search for the available studies in the literature, the prevalence of hyponatremia varies between 3.0 and 56.1%, with a pooled prevalence of 23% in lung cancer patients. However, contrary to the general concept, our comprehensive evaluation and statistical analyses showed no significant difference in the prevalence of hyponatremia between SCLC and NSCLC (23% vs. 22% pooled mean frequency). The prevalence of hyponatremia has not significantly differed in the other subgroups either. So, in contrast to reviews [52-53] and studies about the general hospitalized populations [54-55], in lung cancer patients, the presence of hyponatremia is not associated with age or gender. In respect of ECOG performance status or disease extent, ours is the first meta-analysis to describe that the prevalence of hyponatremia is independent of these parameters in lung cancer.

The differences in the reported frequency values of low serum sodium levels in the cited reviews may be caused by the lack of appropriate studies; different eligibility criteria (hyponatremia at admission or during hospitalization); various patient groups (general hospitalized, general cancer, or only SCLC/NSCLC patients and other subgroups); and different cut-off values (130-136 mmol/l) may cause the differences in the reported frequency values of low serum sodium levels in the cited reviews.

Hyponatremia has an overall negative impact on mortality [5, 56-58]. In a meta-analysis carried out in various hyponatremic patient groups, a significant association was revealed between hyponatremia and overall mortality [20]. However, among the 147948 hyponatremic patients included (from 81 studies) were not only subjects with different solid tumors, but also patients with other medical conditions, such as myocardial infarction, heart failure, liver cirrhosis, pulmonary infections. In a prospective study of cancer patients, the mortality was higher among the hyponatremic cancer patients compared to the whole cancer population (19.5 vs 6.3%) [5]. In a systematic review analyzing the prognostic role of hyponatremia in malignancies, including lung cancer, it was found to be a negative prognostic factor [19]. In lung cancer, many authors also identified hyponatremia as an independent negative risk factor [30, 32, 34-35]. At the same time, Umemura and colleagues found that vasopressin (AVP) is a better prognostic factor than sodium levels [51]. We could confirm that hyponatremia is significantly associated with worse overall survival rates in lung cancer patients.

To the best of our knowledge, this is the first meta-analysis comparing the prognostic significance of pre-treatment hyponatremia in NSCLC and SCLC patients.

According to our analysis, hyponatremia has a more significant negative impact on the overall mortality of NSCLC patients compared to SCLC patients, since the overall survival rates at 10 months were significantly lower in hyponatremic NSCLC patients than in hyponatremic SCLC ones (p<0.001).

We found only one systematic review in the literature analyzing the independent prognostic role of hyponatremia in lung cancer [19]. The authors identified hyponatremia as an independent risk factor for poor outcome in 6 out of 13 and in 1 out of 3 studies in SCLC and NSCLC, respectively. However, this review has some limitations. In the included studies, hyponatremia was detected both before and during treatment, the overall survival times and rates were only partially available and the multivariate analysis of hyponatremia was reported only in a few studies [19]. In our systematic review, we came to similar conclusions regarding SCLC patients: overall, out of the 11 studies, 5 identified hyponatremia as an independent prognostic factor. However, in NSCLC we found low serum sodium to be a significant independent negative predictor more consistently (N=7 vs. only one paper where it was not).

The improvement of hyponatremia correlated with the mortality in retrospective studies in various medical conditions including lung cancer [59-61]. However, in some reviews, it was suggested that the impact of hyponatremia correction on mortality should be further investigated because it still seems to be unclear [62-64]. In a meta-analysis including 15 studies with 13,816 hyponatremic patients, serum sodium improvement was achieved in 53.2% of cases, and it was associated with a significant reduction of overall mortality [23]. Similarly, we found significantly higher OS rates at 10 months among lung cancer patients if the hyponatremia was ameliorated compared to the uncorrected hyponatremia group. However, when assessed later, at 20 months this benefit of the treatment was no longer statistically significant, which is in contrast to the observation of the previous meta-analysis carried out in various medical conditions where reduced mortality could be detected even at 36 months. This discrepancy between the 10- and 20-months prognostic data may be related to the higher progression rate of lung cancer and therefore, a shorter beneficial effect of the improvement of sodium level compared to other (malignant) diseases. However, statistical uncertainties (e.g. discrepant ratios of data available and/or patients lost to follow up at the two time-interval) may also influence this observation.

These results show the importance of the correction of hyponatremia and raises awareness about further therapeutic options in treatment-resistant cases. Numerous papers highlighted the beneficial effect of V2R antagonists (mostly Tolvaptan), with close monitoring of sodium levels in the treatment of hyponatremic lung cancer patients [65-71]. These studies reported effective correction of hyponatremia and improvement of performance status, without any serious adverse events. However, according to our systematic search, in lung cancer patients, the effect of V2R antagonist treatment on mortality has only been evaluated in one study, which also demonstrated the cost-effectiveness of tolvaptan treatment in Swedish patients with SIADH in pneumonia or SCLC [72].

Limitations

The most significant limitations of our meta-analysis are the following: the lack of randomized controlled trials, the low number of prospective and higher number of retrospective studies, the limited number of studies available in respect of certain relevant questions, the considerable heterogeneity of the included studies and the variable cut-off values for serum sodium levels, which all can lead to biased results. The severity of hyponatremia at the time of diagnosis could potentially have been influenced by some interfering factors, which were not fully evaluated, such as comorbidities and treatments.

From the available data, no certain answer can be given to the question of whether the negative prognostic significance of resistant hyponatremia was due to oncological unresponsiveness or inappropriate sodium correction. Furthermore, incomplete data reporting of follow-up time and the patients lost to follow-up, as well as the demographic characteristics of hyponatremic patients have also been important limitations. E.g. lack of information about hyponatremic patient's demographic characteristics may distort the results. More data for a better understanding would be desirable.

Conclusions

In the literature, the prevalence of hyponatremia in lung cancer patients varies between 3% and 56.1% with a pooled mean frequency of 23%. In our meta-analysis no significant differences could be observed in the prevalence of hyponatremia among various subgroups including SCLC vs. NSCLC.

Hyponatremia significantly and negatively influences the overall survival rates of these patients, especially in NSCLC where data are more consistent. Moreover, the improvement of serum sodium levels by specific or symptomatic treatment may improve the survival rates, at least on the short term.

Overall, the contradictions in the literature suggest that better designed studies are necessary to assess the prevalence and prognostic significance of hyponatremia.

Declarations

Conflicts of interests

The authors declare that they have no competing interests.

Funding

This study was funded by „GINOP-2.3.2-15-2016-00048 - STAY ALIVE” co-financed by the European Union (European Regional Development Fund) within the framework of Programme Széchenyi 2020 and by the Human Resources Development Operational Programme Grant, Grant Number: EFOP 3.6.2-16-2017-00006 – LIVE LONGER which is co-financed by the European Union (European Regional Development Fund) within the framework of Programme Széchenyi 2020.

Author contributions

Conception and design, M.G., E.B., B.T., S.K., M.F., P.H., Z.S., E.M., and L.B.; Administrative support, E.B., M.S.; Provision of study materials or patients P.H., E.M., and L.B.; Collection and assembly of data, E.B., M.G; Data analysis and interpretation, E.B., M.G., D.N.; Manuscript writing: all authors; Final approval of manuscript: all authors; funding acquisition, M.S. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

Not applicable.

Consent for publication

Not applicable.

Acknowledgements

Not applicable.

References

1. World Health Organization [Internet]. Cancer; c2020 [cited 2020 Apr 7]. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer

2. World Health Organization [Internet]. WHO GLOBOCAN; c2018 [cited 2020 Apr 7]. Cancer Tomorrow. Available from: https://gco.iarc.fr/tomorrow/graphic-line?type=0&type_sex=0&mode=population&sex=0&populations=900&cancers=15&age_group=value&apc_male=0&apc_female=0&single_unit=500000&print=0

3. Bowman BT. Electrolyte disorders associated with cancer. J Onco-Nephrol. 2017;1(1):30-35. doi: 10.5301/jo-n.5000004

4. Berardi R, Antonuzzo A, Blasi L, et al. Practical issues for the management of hyponatremia in oncology. Endocrine. 2018;61(1):158-164. doi:10.1007/s12020-018-1547-y

5. Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer. 2000;8(3):192-197. doi:10.1007/s005200050284

6. Sørensen JB, Andersen MK, Hansen HH. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med. 1995;238(2):97-110. doi:10.1111/j.1365-2796.1995.tb00907.x

7. Grohé C, Berardi R, Burst V. Hyponatraemia--SIADH in lung cancer diagnostic and treatment algorithms. Crit Rev Oncol Hematol. 2015;96(1):1-8. doi:10.1016/j.critrevonc.2015.04.005

8. Efthymiou C, Spyratos D, Kontakiotis T. Endocrine paraneoplastic syndromes in lung cancer. Hormones (Athens). 2018;17(3):351-358. doi:10.1007/s42000-018-0046-0

9. Wang X, Liu M, Zhang L, Ma K. Syndrome of Inappropriate Antidiuretic Hormone Secretion: A Poor Prognosis in Small-cell Lung Cancer. Arch Med Res. 2016;47(1):19-24. doi:10.1016/j.arcmed.2015.12.006

10. List AF, Hainsworth JD, Davis BW, Hande KR, Greco FA, Johnson DH. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. J Clin Oncol. 1986;4(8):1191-1198. doi:10.1200/JCO.1986.4.8.1191

11. Lokich JJ. The frequency and clinical biology of the ectopic hormone syndromes of small cell carcinoma. Cancer. 1982;50(10):2111-2114. doi:10.1002/1097-0142(19821115)50:10<2111::aid-cncr2820501023>3.0.co;2-o

12. Fiordoliva I, Meletani T, Baleani MG, et al. Managing hyponatremia in lung cancer: latest evidence and clinical implications. Ther Adv Med Oncol. 2017;9(11):711-719. doi:10.1177/1758834017736210

13. Dimitriadis GK, Angelousi A, Weickert MO, Randeva HS, Kaltsas G, Grossman A. Paraneoplastic endocrine syndromes. Endocr Relat Cancer. 2017;24(6):R173-R190. doi:10.1530/ERC-17-0036

14. Raftopoulos H. Diagnosis and management of hyponatremia in cancer patients. Support Care Cancer. 2007;15(12):1341-1347. doi:10.1007/s00520-007-0309-9

15. Liamis G, Megapanou E, Elisaf M, Milionis H. Hyponatremia-Inducing Drugs. Front Horm Res. 2019;52:167-177. doi:10.1159/000493246

16. Oren RM. Hyponatremia in congestive heart failure. Am J Cardiol. 2005;95(9A):2B-7B. doi:10.1016/j.amjcard.2005.03.002

17. Ginès P, Guevara M. Hyponatremia in cirrhosis: pathogenesis, clinical significance, and management. Hepatology. 2008;48(3):1002-1010. doi:10.1002/hep.22418

18. Peri A. Prognostic and predictive role of hyponatremia in cancer patients. J Cancer Metastasis Treat. 2019;5:40. doi:10.20517/2394-4722.2019.14

19. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist. 2012;17(6):756-765. doi:10.1634/theoncologist.2011-0400

20. Corona G, Giuliani C, Parenti G, Norello D, Verbalis JG, Forti G, et al. Moderate Hyponatremia Is Associated with Increased Risk of Mortality: Evidence from a Meta-Analysis. PLoS ONE. 2013;8(12): e80451. doi: 10.1371/journal.pone.0080451

21. Verbalis JG. Managing hyponatremia in patients with syndrome of inappropriate antidiuretic hormone secretion. J Hosp Med. 2010;5 Suppl 3:S18-S26. doi:10.1002/jhm.783

22. Harper PG, Souhami RL, Spiro SG, et al. Tumor size, response rate, and prognosis in small cell carcinoma of the bronchus treated by combination chemotherapy. Cancer Treat Rep. 1982;66(3):463-470.

23. Corona G, Giuliani C, Verbalis JG, Forti G, Maggi M, Peri A. Hyponatremia Improvement Is Associated with a Reduced Risk of Mortality: Evidence from a Meta-Analysis. PLoS ONE. 2015;10(4):e0124105. doi:10.1371/journal.pone.0124105

24. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7): e1000097. doi:10.1371/journal.pmed.1000097

25. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med. 2006;144(6):427-437. doi:10.7326/0003-4819-144-6-200603210-00010

26. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions. 2nd Edition. Chichester (UK): John Wiley & Sons, 2019.

27. Yang Y, Sun N, Sun P, Zhang L. Clinical Characteristics and Prognosis of Elderly Small Cell Lung Cancer Patients Complicated with Hyponatremia: A Retrospective Analysis. Anticancer Res. 2017;37(8):4681-4686. doi:10.21873/anticanres.11872

28. Osterlind K, Hansen HH, Dombernowsky P, Hansen M, Andersen PK. Determinants of complete remission induction and maintenance in chemotherapy with or without irradiation of small cell lung cancer. Cancer Res. 1987;47(10):2733-2736.

29. Zarzecka M, Kubicki P, Kozielski J. Hyponatraemia - evaluation of prevalence in patients hospitalized in the Pulmonary Department and prognostic significance in lung cancer patients. Pneumonol Alergol Pol. 2014;82(1):18-24. doi:10.5603/PiAP.2014.0004

30. Hermes A, Waschki B, Reck M. Hyponatremia as prognostic factor in small cell lung cancer--a retrospective single institution analysis. Respir Med. 2012;106(6):900-904. doi:10.1016/j.rmed.2012.02.010

31. Wang W, Song Z, Zhang Y. Hyponatremia in small cell lung cancer is associated with a poorer prognosis. Transl Cancer Res. 2016;5(1):36-43. doi:10.3978/j.issn.2218-676X.2016.01.04

32. Berardi R, Santoni M, Newsom-Davis T, et al. Hyponatremia normalization as an independent prognostic factor in patients with advanced non-small cell lung cancer treated with first-line therapy. Oncotarget. 2017;8(14):23871-23879. doi:10.18632/oncotarget.13372

33. Sengupta A, Banerjee SN, Biswas NM, et al. The Incidence of Hyponatraemia and Its Effect on the ECOG Performance Status among Lung Cancer Patients. J Clin Diagn Res. 2013;7(8):1678-1682. doi:10.7860/JCDR/2013/5900.3225

34. Kobayashi N, Usui S, Yamaoka M, et al. The influence of serum sodium concentration on prognosis in resected non-small cell lung cancer. Thorac Cardiovasc Surg. 2014;62(4):338-343. doi:10.1055/s-0033-1359713

35. Fucà G, Galli G, Poggi M, et al. Low Baseline Serum Sodium Concentration Is Associated with Poor Clinical Outcomes in Metastatic Non-Small Cell Lung Cancer Patients Treated with Immunotherapy. Target Oncol. 2018;13(6):795-800. doi:10.1007/s11523-018-0599-5

36. Alamoudi OS. Lung cancer at a University Hospital in Saudi Arabia: A four-year prospective study of clinical, pathological, radiological, bronchoscopic, and

biochemical parameters. Ann Thorac Med. 2010;5(1):30-36. doi:10.4103/1817-1737.58957

37. Hansen O, Sørensen P, Hansen KH. The occurrence of hyponatremia in SCLC and the influence on prognosis: a retrospective study of 453 patients treated in a single institution in a 10-year period. Lung Cancer. 2010;68(1):111-114. doi:10.1016/j.lungcan.2009.05.015

38. Svaton M, Fiala O, Pesek M, et al. Predictive and prognostic significance of sodium levels in patients with NSCLC treated by erlotinib. Anticancer Res. 2014;34(12):7461-7465.

39. Allan SG, Stewart ME, Love S, Cornbleet MA, Smyth JF, Leonard RC. Prognosis at presentation of small cell carcinoma of the lung. Eur J Cancer. 1990;26(6):703-705. doi:10.1016/0277-5379(90)90121-9

40. Li W, Chen X, Wang L, et al. The prognostic effects of hyponatremia and hyperchloremia on postoperative NSCLC patients. Curr Probl Cancer. 2019;43(5):402-410. doi:10.1016/j.currproblcancer.2018.12.006

41. Osterlind K, Andersen PK. Prognostic factors in small cell lung cancer: multivariate model based on 778 patients treated with chemotherapy with or without irradiation. Cancer Res. 1986;46(8):4189-4194.

42. Doshi KH, Shriyan B, Nookala MK, et al. Prognostic significance of pretreatment sodium levels in patients of nonsmall cell lung cancer treated with pemetrexed-platinum doublet chemotherapy. J Cancer Res Ther. 2018;14(5):1049-1053. doi:10.4103/0973-1482.187296

43. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. Am J Respir Crit Care Med. 1997;156(5):1669-1678. doi:10.1164/ajrccm.156.5.96-10075

44. Sagman U, Maki E, Evans WK, et al. Small-cell carcinoma of the lung: derivation of a prognostic staging system. J Clin Oncol. 1991;9(9):1639-1649. doi:10.1200/JCO.1991.9.9.1639

45. Jacot W, Colinet B, Bertrand D, et al. Quality of life and comorbidity score as prognostic determinants in non-small-cell lung cancer patients. Ann Oncol. 2008;19(8):1458-1464. doi:10.1093/annonc/mdn064

46. Hong X, Xu Q, Yang Z, et al. The value of prognostic factors in Chinese patients with small cell lung cancer: A retrospective study of 999 patients. Clin Respir J. 2018;12(2):433-447. doi:10.1111/crj.12534

47. Maestu I, Pastor M, Gómez-Codina J, et al. Pretreatment prognostic factors for survival in small-cell lung cancer: a new prognostic index and validation of three known prognostic indices on 341 patients. Ann Oncol. 1997;8(6):547-553. doi:10.1023/a:1008212826956

48. Kawahara M, Fukuoka M, Saijo N, et al. Prognostic factors and prognostic staging system for small cell lung cancer. Jpn J Clin Oncol. 1997;27(3):158-165. doi:10.1093/jjco/27.3.158

49. Cerny T, Blair V, Anderson H, Bramwell V, Thatcher N. Pretreatment prognostic factors and scoring system in 407 small-cell lung cancer patients. Int J Cancer. 1987;39(2):146-149. doi:10.1002/ijc.2910390204

50. Ma F, Liu X, Hu C, Huang M. [Clinical features and prognosis analysis of small-cell lung cancer complicated with hyponatremia]. Zhong Nan Da Xue Xue Bao Yi Xue Ban. 2011;36(1):64-67. doi:10.3969/j.issn.1672-7347.2011.01.010

51. Umemura S, Segawa Y, Ueoka H, et al. Serum level of arginine-vasopressin influences the prognosis of extensive-disease small-cell lung cancer. J Cancer Res Clin Oncol. 2007;133(8):519-524. doi:10.1007/s00432-007-0196-y

52. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. Am J Med. 2006;119(7 Suppl 1):S30-S35. doi:10.1016/j.amjmed.2006.05.005

53. Peri A. Management of hyponatremia: causes, clinical aspects, differential diagnosis and treatment. Expert Rev Endocrinol Metab. 2019;14(1):13-21. doi:10.1080/17446651.2019.1556095

54. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. Clin Chim Acta. 2003;337(1-2):169-172. doi:10.1016/j.cccn.2003.08.001

55. Mohan S, Gu S, Parikh A, Radhakrishnan J. Prevalence of hyponatremia and association with mortality: results from NHANES. Am J Med. 2013;126(12):1127-37.e1. doi:10.1016/j.amjmed.2013.07.021

56. Sterns RH, Silver SM. Complications and management of hyponatremia. Curr Opin Nephrol Hypertens. 2016;25(2):114-119. doi:10.1097/MNH.0000000000000200

57. Verbalis JG, Goldsmith SR, Greenberg A, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013;126(10 Suppl 1):S1-S42. doi:10.1016/j.amjmed.2013.07.006

58. Kraft MD, Btaiche IF, Sacks GS, Kudsk KA. Treatment of electrolyte disorders in adult patients in the intensive care unit. Am J Health Syst Pharm. 2005;62(16):1663-1682. doi:10.2146/ajhp040300

59. Petereit C, Zaba O, Teber I, Grohé C. Ist die Hyponatriämie (HN) ein Prognosefaktor für das Gesamtüberleben der Patienten mit Lungenkarzinom? [Is hyponatremia a prognostic marker of survival for lung cancer?]. Pneumologie. 2011;65(9):565-571. doi:10.1055/s-0030-1256668

60. Balachandran K, Okines A, Gunapala R, Morganstein D, Popat S. Resolution of severe hyponatraemia is associated with improved survival in patients with cancer. BMC Cancer. 2015;15:163. doi:10.1186/s12885-015-1156-6

61. Berardi R, Santoni M, Newsom-Davis T, et al. Hyponatremia normalization as an independent prognostic factor in patients with advanced non-small cell lung cancer treated with first-line therapy. Oncotarget. 2017;8(14):23871-23879. doi:10.18632/oncotarget.13372

62. Sun L, Hou Y, Xiao Q, Du Y. Association of serum sodium and risk of all-cause mortality in patients with chronic kidney disease: A meta-analysis and sysematic review. Sci Rep. 2017;7(1):15949. doi:10.1038/s41598-017-16242-3

63. Hoorn EJ, Zietse R. Diagnosis and Treatment of Hyponatremia: Compilation of the Guidelines. J Am Soc Nephrol. 2017;28(5):1340-1349. doi:10.1681/ASN.2016101139

64. Rusinaru D, Tribouilloy C, Berry C, et al. Relationship of serum sodium concentration to mortality in a wide spectrum of heart failure patients with preserved and with reduced ejection fraction: an individual patient data meta-analysis(†): Meta-Analysis Global Group in Chronic heart failure (MAGGIC). *E*ur J Heart Fail. 2012;14(10):1139-1146. doi:10.1093/eurjhf/hfs099

65. Dixon MB, Lien YH. Tolvaptan and its potential in the treatment of hyponatremia. Ther Clin Risk Manag. 2008;4(6):1149-1155. doi:10.2147/tcrm.s3115

66. Thajudeen B, Salahudeen AK. Role of tolvaptan in the management of hyponatremia in patients with lung and other cancers: current data and future perspectives. Cancer Manag Res. 2016;8:105-114. doi:10.2147/CMAR.S90169

67. Fraser IM, Brooke AM, Dorey NE, Toy EW. Use of tolvaptan, a new V2 receptor antagonist, in the treatment of syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to small cell lung cancer (SCLC) – a case series. Lung Cancer. 2014;83(Suppl 1):S69. doi: 10.1016/s0169-5002(14)70187-4

68. Petereit C, Zaba O, Teber I, Lüders H, Grohé C. A rapid and efficient way to manage hyponatremia in patients with SIADH and small cell lung cancer: treatment with tolvaptan. BMC Pulm Med. 2013;13:55. doi:10.1186/1471-2466-13-55

69. Li-Ng M, Verbalis JG. Conivaptan: Evidence supporting its therapeutic use in hyponatremia. Core Evid. 2010;4:83-92. doi:10.2147/ce.s5997

70. Zeltser D, Rosansky S, van Rensburg H, Verbalis JG, Smith N; Conivaptan Study Group. Assessment of the efficacy and safety of intravenous conivaptan in euvolemic and hypervolemic hyponatremia. Am J Nephrol. 2007;27(5):447-457. doi:10.1159/000106456

71. Annane D, Decaux G, Smith N; Conivaptan Study Group. Efficacy and safety of oral conivaptan, a vasopressin-receptor antagonist, evaluated in a randomized, controlled trial in patients with euvolemic or hypervolemic hyponatremia. Am J Med Sci. 2009;337(1):28-36. doi:10.1097/MAJ.0b013e31817b8148

72. Jamookeeah C, Robinson P, O'Reilly K, et al. Cost-effectiveness of tolvaptan for the treatment of hyponatraemia secondary to syndrome of inappropriate antidiuretic hormone secretion in Sweden. BMC Endocr Disord. 2016;16(1):22. doi:10.1186/s12902-016-0104-z

Additional files

Additional File 1. PRISMA Checklist

Additional File 2. QUIPS tool for Risk of Bias Assessment

Additional File 3. Table 1 showing the characteristics of the included studies in the systematic review

Additional File 4. Table 2 showing the outcomes in lung cancer patients among the included studies

Additional File 5. Risk of Bias Assessment

Figures

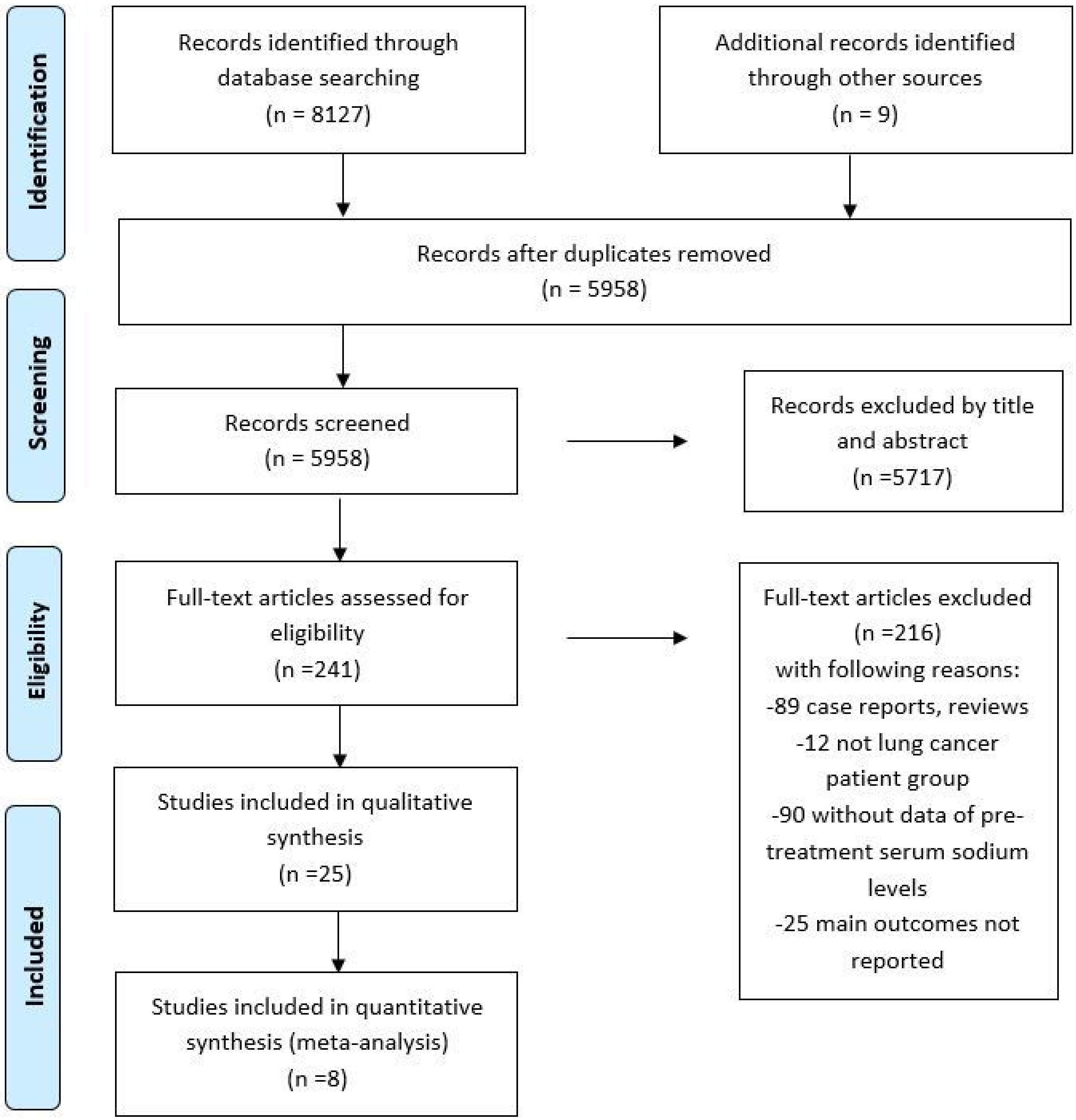

Figure 1

PRISMA flow diagram representing the process of study search and selection

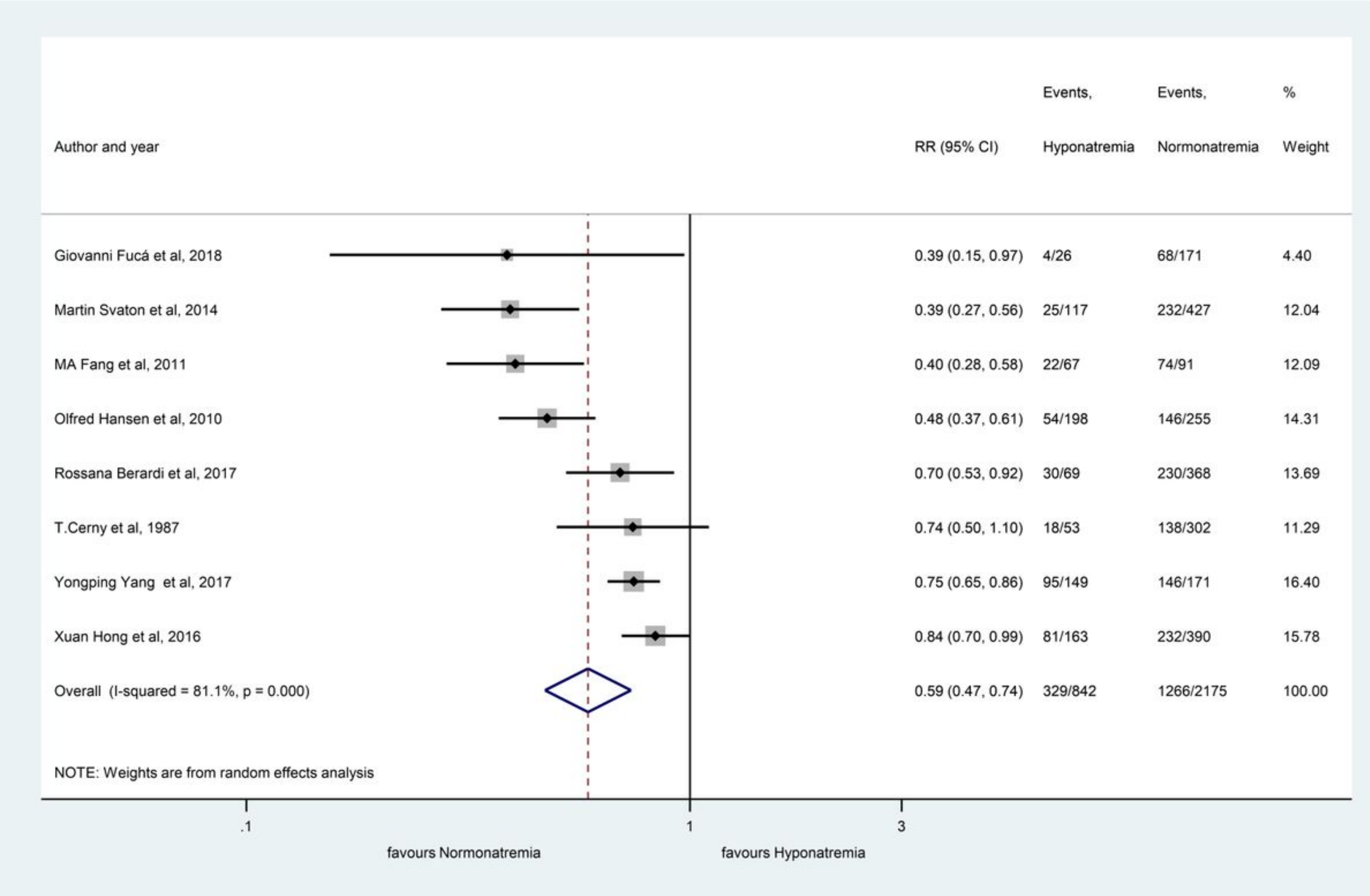

Figure 2

The prevalence of hyponatremia in SCLC and NSCLC patients. Legends: Black diamonds represent the individual studies effect and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflect on the weight of a particular study. The blue diamond the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviations: SCLC- Small Cell Lung Cancer; NSCLC- Non-Small Cell Lung Cancer; ES- effect size

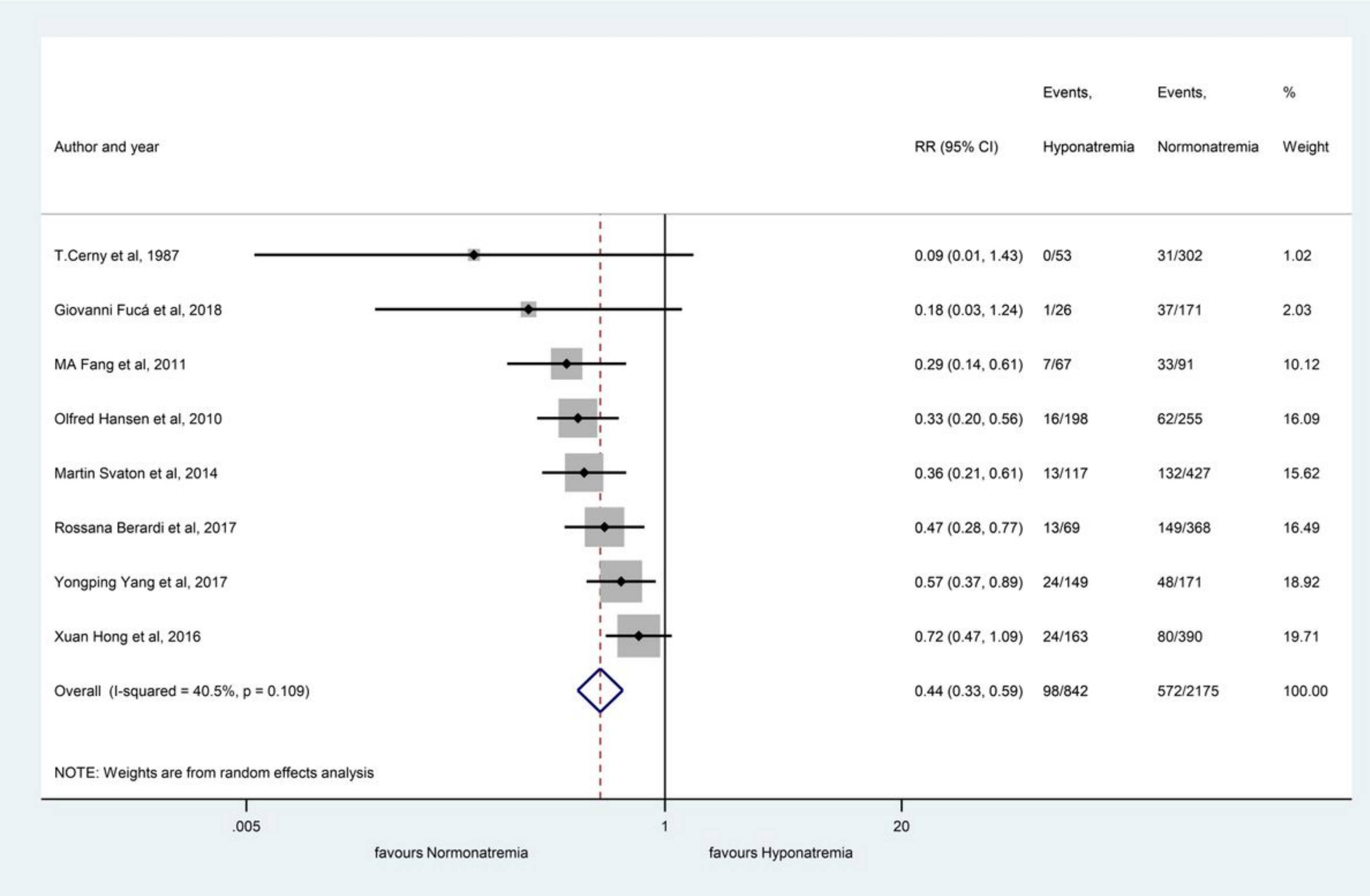

Figure 3

The prevalence of hyponatremia in male and female lung cancer patients. Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviation: RR- Risk ratio

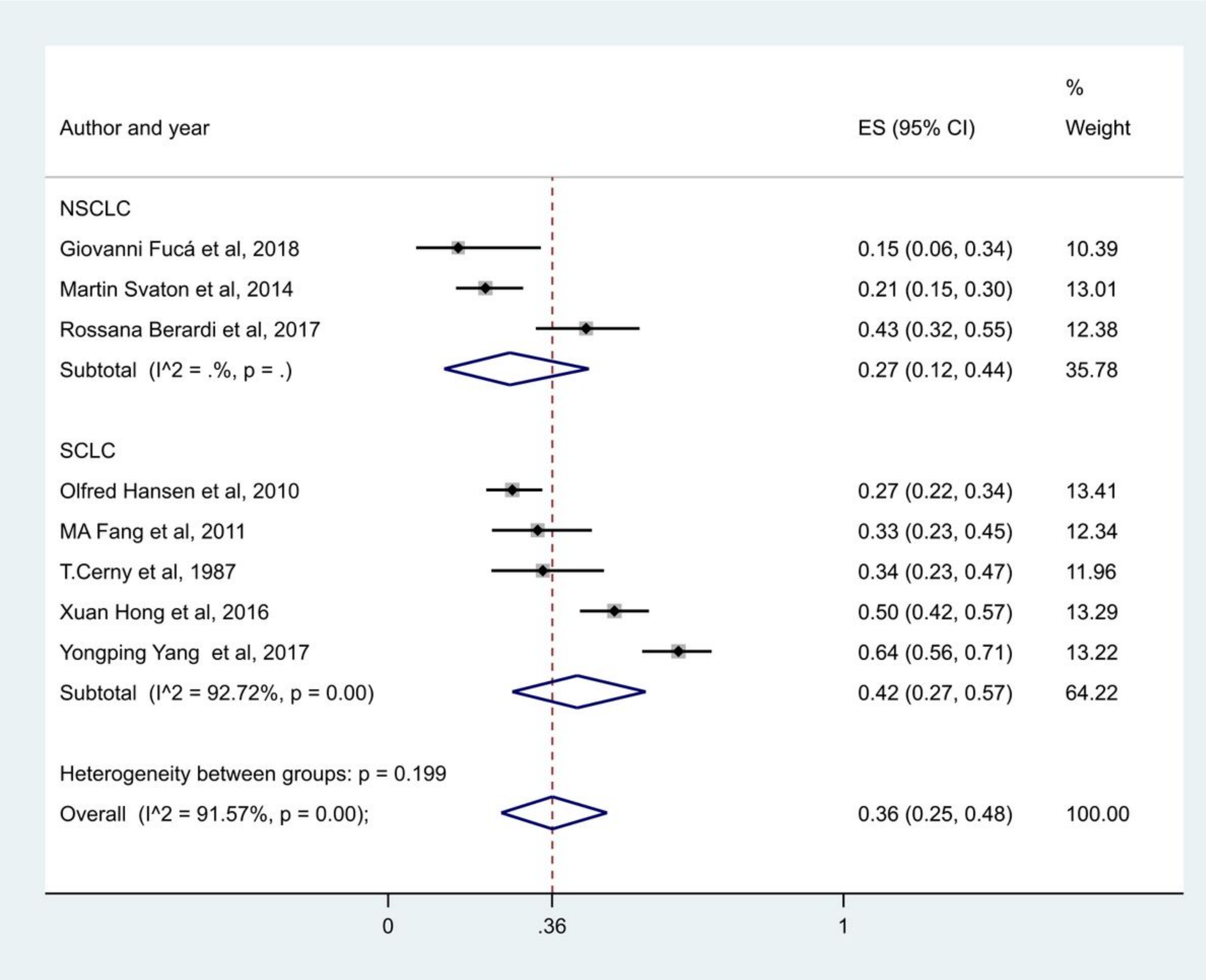

Figure 4

The prevalence of hyponatremia in young (<60 years) and older (>60 years) lung cancer patients Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviation: RR- Risk Ratio

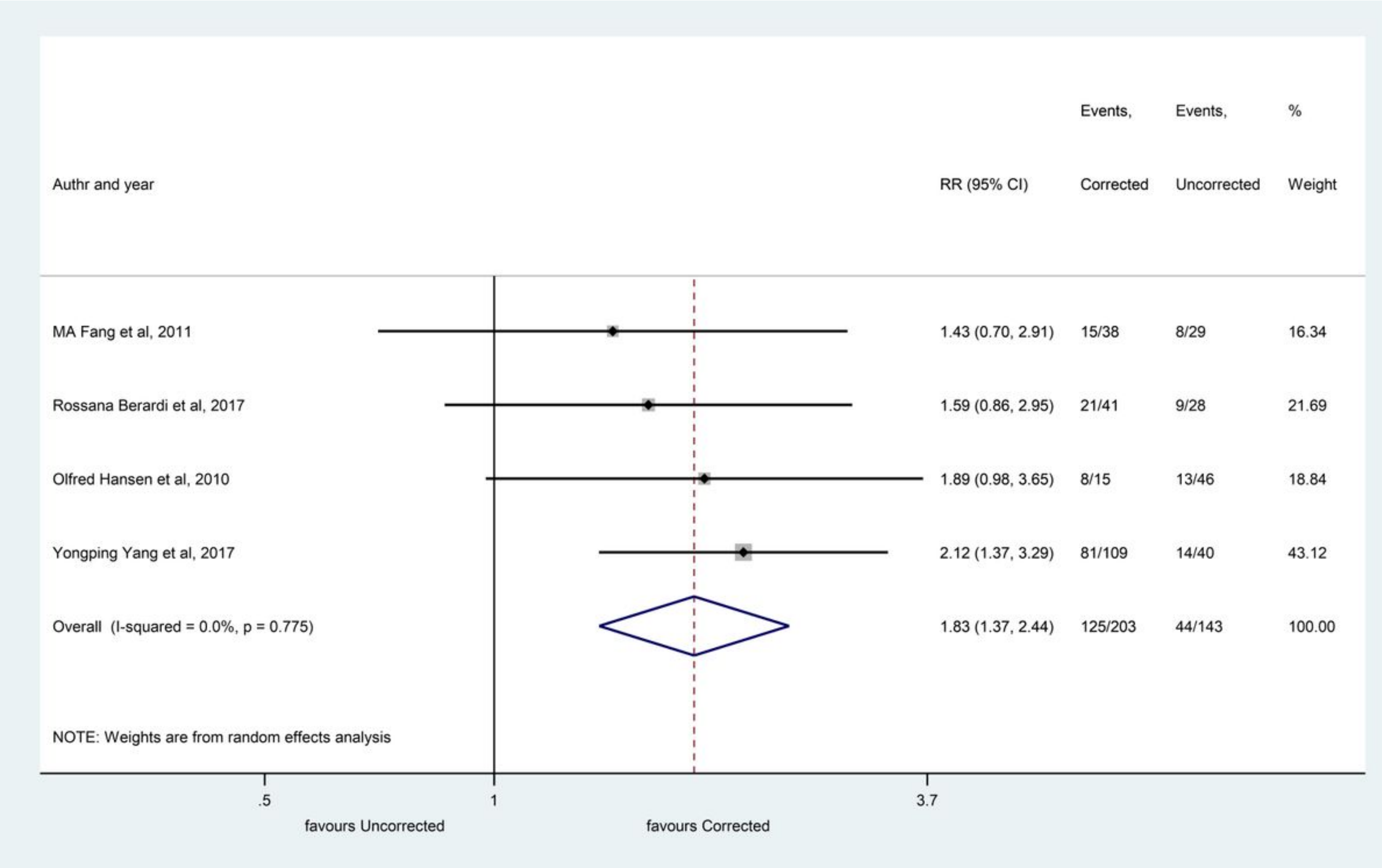

Figure 5

The prevalence of hyponatremia in lung cancer patients with ECOG≤1 and ECOG>1 performance state Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviations: ECOG- Eastern Cooperative Oncology Group performance status, RR- Risk Ratio

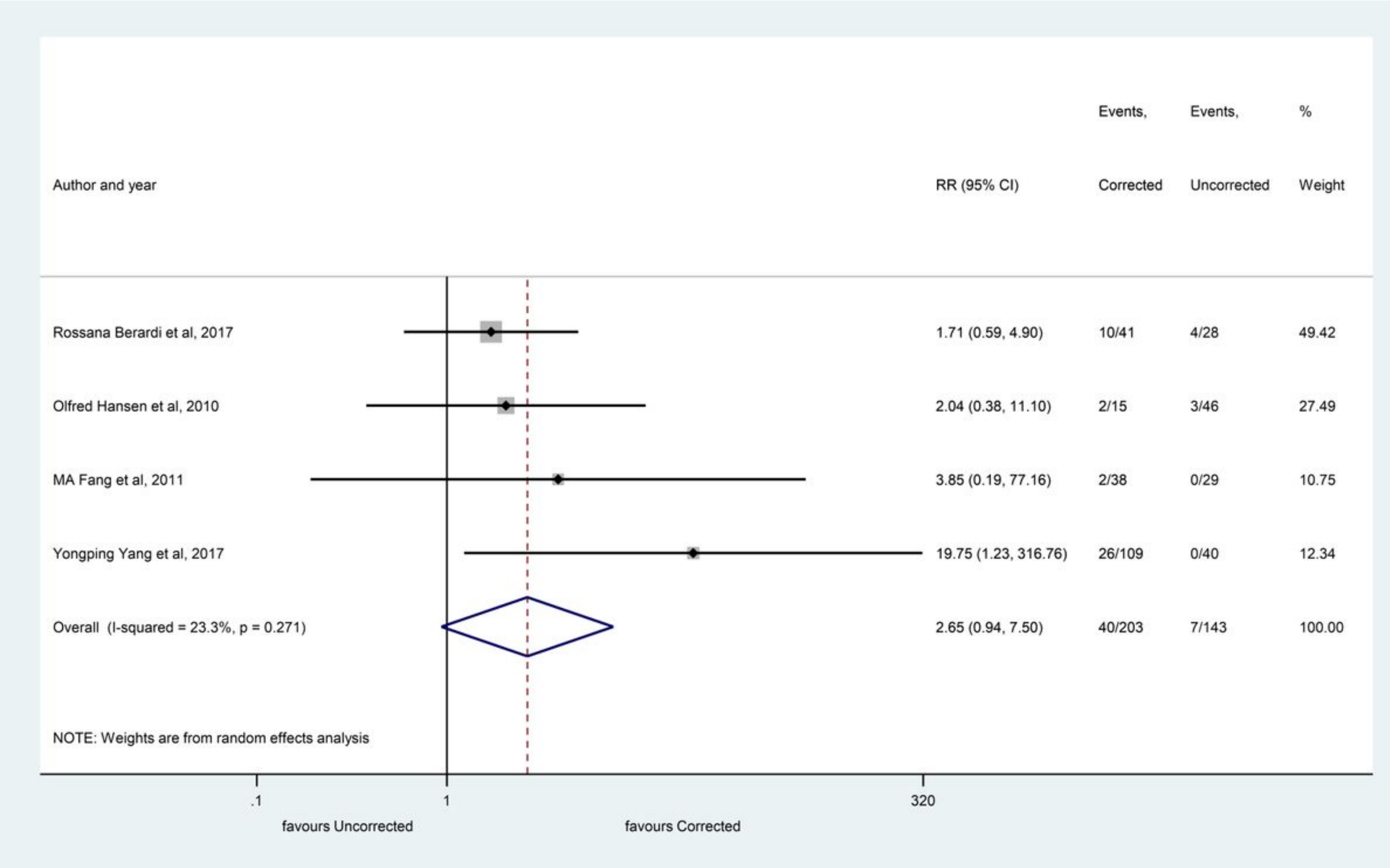

Figure 6

The prevalence of hyponatremia in SCLC patients with Limited and Extensive Disease stage Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviations: SCLC- Small Cell Lung Cancer, RR- risk ratio

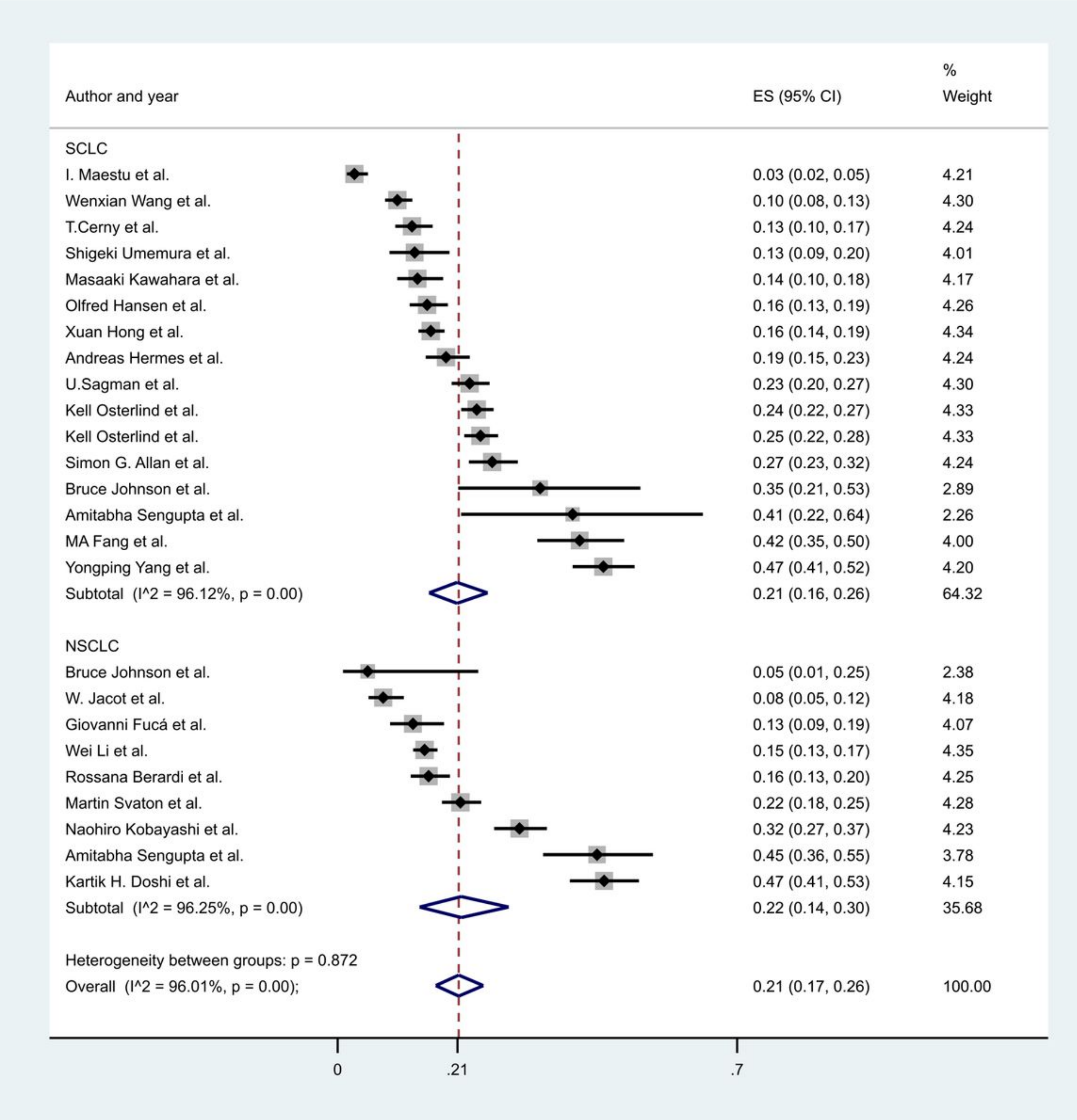

Figure 7

The overall survival rates at 10 months comparing hyponatremic and normonatremic lung cancer patients Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviations: RR- Risk ratio

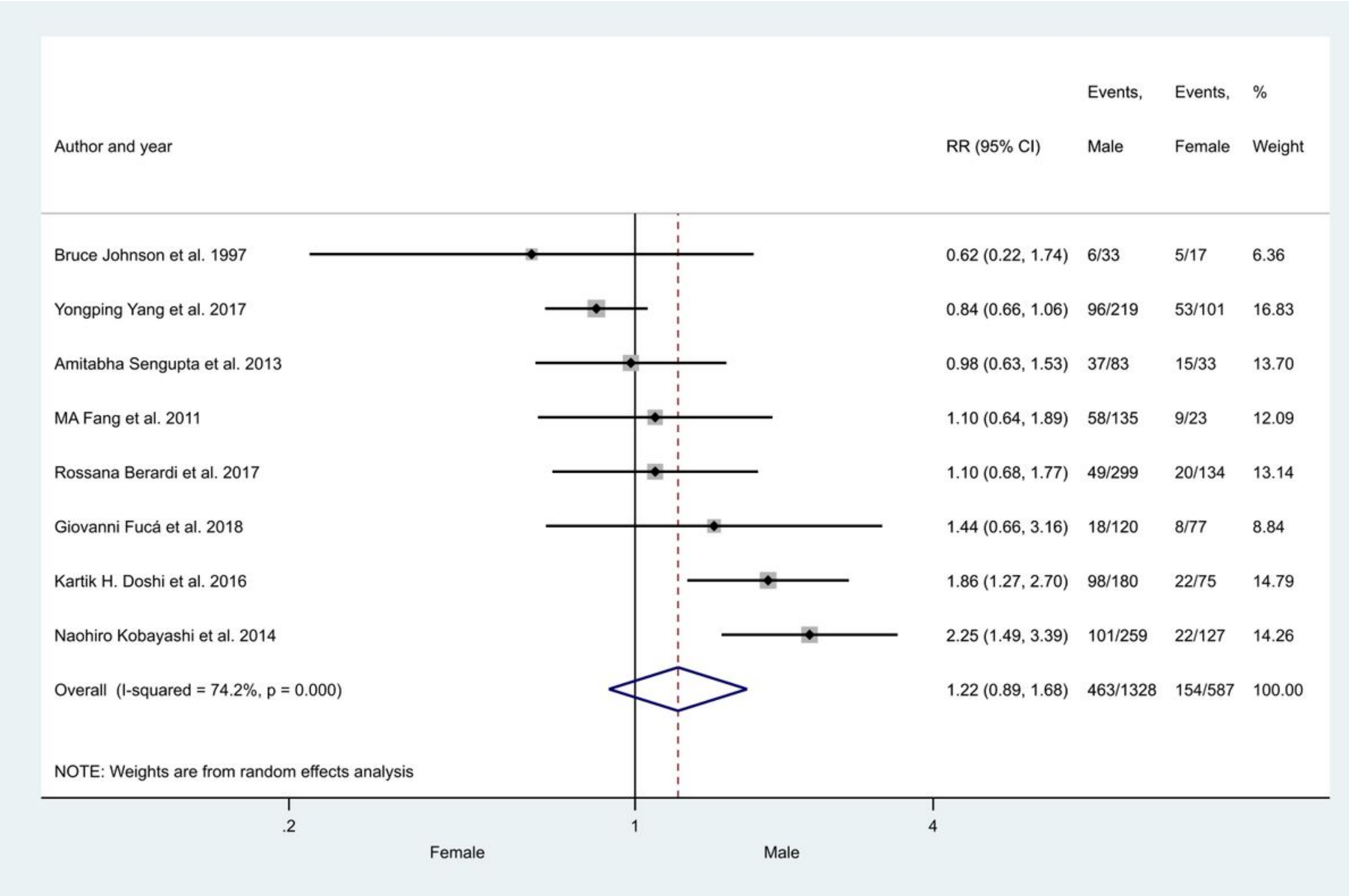

Figure 8

The overall survival rates at 20 months comparing hyponatremic and normonatremic lung cancer patients Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviation: Risk ratio

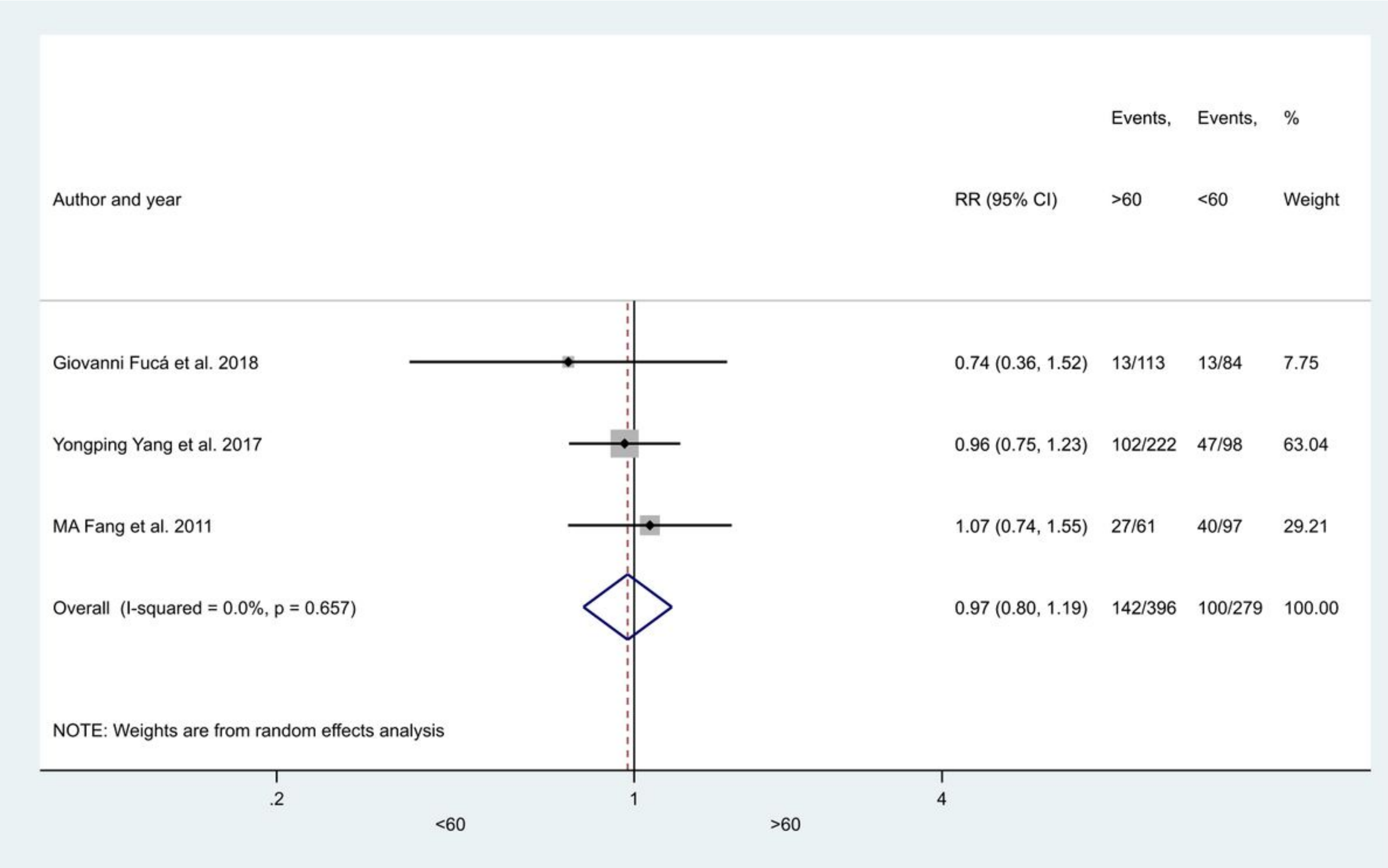

Figure 9

The overall survival rates at 10 months in hyponatremic patients comparing Small Cell and Non-Small Cell Lung Cancer patients Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviations: SCLC- Small cell lung cancer, NSCLC- Non-small cell lung cancer, RR- risk ratio

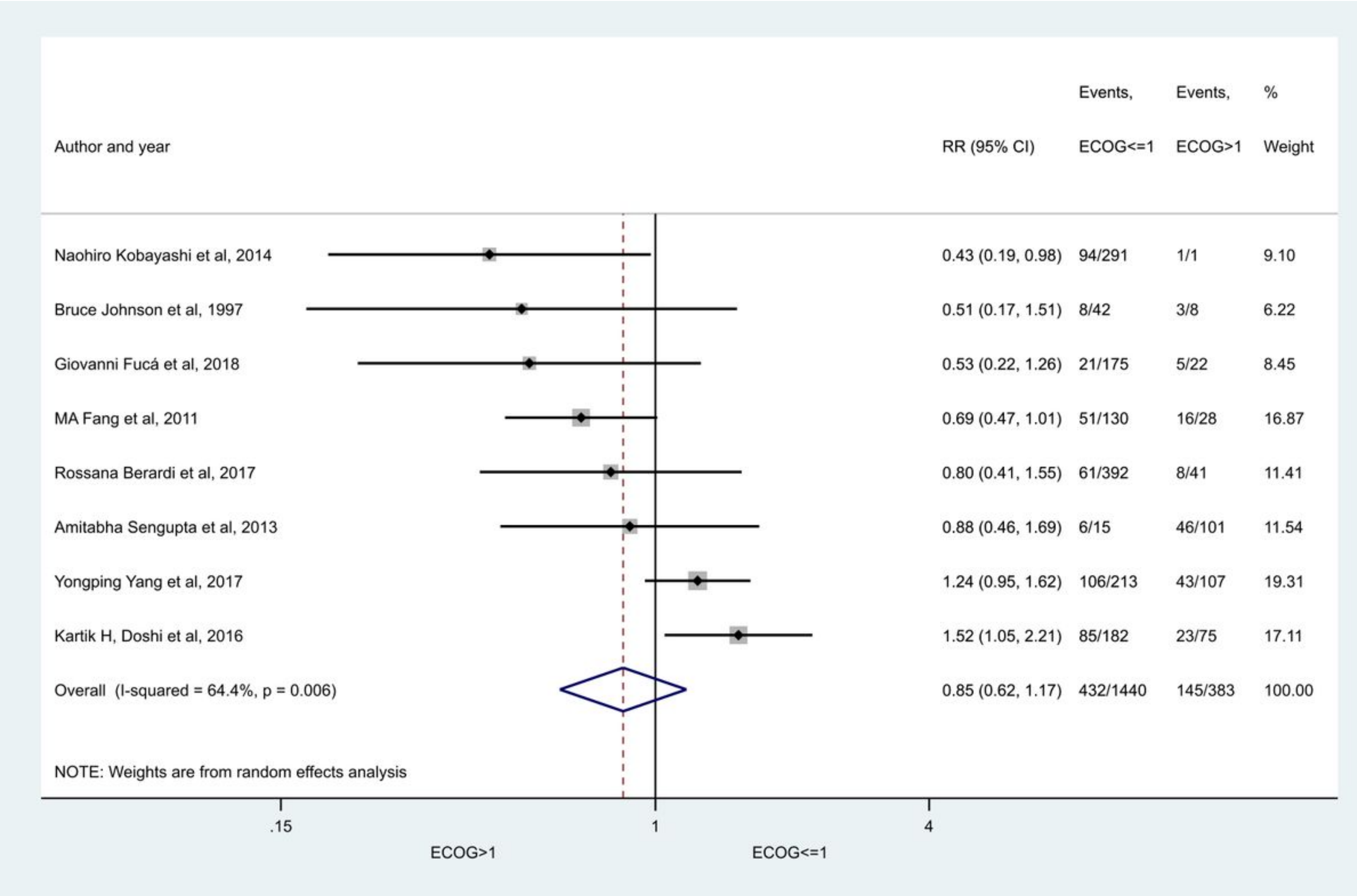

Figure 10

The overall survival rates after correction of hyponatremia at 10 months (corrected and uncorrected hyponatremic patient groups) Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviation: RR- Risk ratio

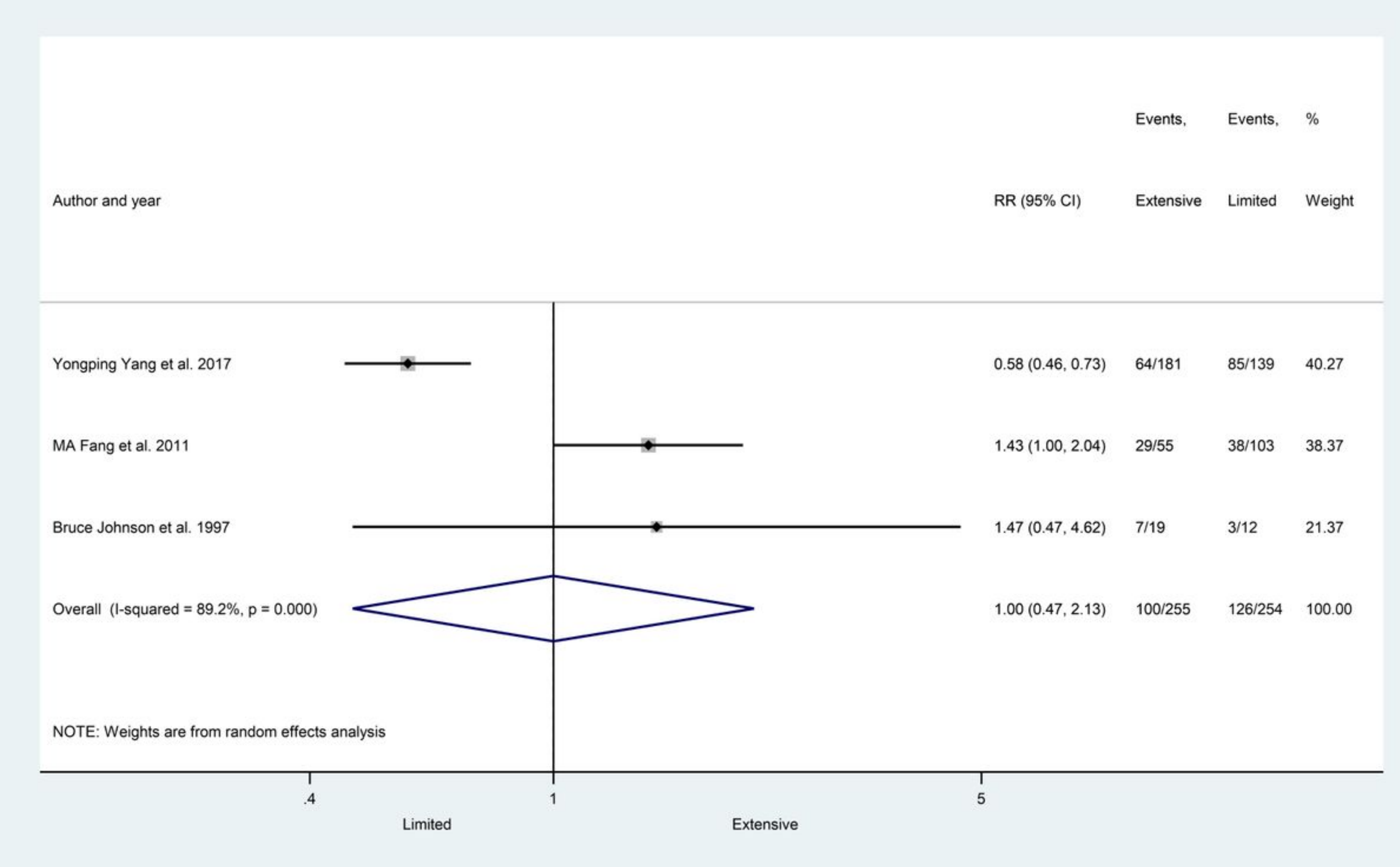

Figure 11

The overall survival rates after correction of hyponatremia at 20 months (corrected and uncorrected hyponatremic patient groups) Legends: Black diamonds represent the individual effects of studies and vertical lines show the corresponding 95% confidence intervals (CI). Size of the grey squares reflects the individual weight of a particular study. The blue diamond shows the overall or summary effect. The outer edges of the diamonds represent the CIs. Abbreviation: RR- Risk ratio

Supplementary Files

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

- AdditionalFile1.pdf
- AdditionalFile2.pdf
- AdditionalFile3.docx
- AdditionalFile4.docx
- AdditionalFile5.pdf