



# Hyponatremia as a prognostic factor in non-small cell lung cancer: a systematic review and meta-analysis

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**Background:** Hyponatremia is a common electrolyte disorder in cancer patients and has been evaluated as a negative prognostic factor in several cancer types, especially in small cell lung cancer (SCLC). However, the prognostic value of hyponatremia is less studied in non-small cell lung cancer (NSCLC) patients. Therefore, we conducted a systematic review and meta-analysis to investigate the prognostic value of pretreatment hyponatremia in NSCLC patients.

**Methods:** The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist. The databases PubMed, Embase, Scopus, and Web of Science were searched on March 26th 2020 without time restrictions. The protocol was submitted to the PROSPERO database (ID 184612). Studies were included if they evaluated sodium level as a prognostic factor in NSCLC patients and contained original data published in English. Hazard ratios (HRs) for overall survival (OS) were pooled in a random-effects model.

**Results:** Of 10,888 identified titles, 14 articles were included in the review including a total of 4,364 NSCLC patients. In 13 of the 14 articles, hyponatremia was found to be significantly correlated to a shorter OS. Ten articles were included in the meta-analysis. Here, patients with hyponatremia had a significantly shorter OS compared with patients with normal sodium level {pooled HR =2.02 [95% confidence interval (CI): 1.65–2.47]}. Two out of four studies found hyponatremia to be associated with a reduced progression free survival (PFS). Normalization of the sodium level during treatment was found to be associated with a prolonged PFS and OS in one study.

**Conclusions:** This meta-analysis indicates that hyponatremia is a relative common condition in NSCLC patients associated with an increased mortality. Hence, sodium level could be a useful biomarker for stratifying NSCLC patients and thereby for preparing individual treatment plans.

**Keywords:** Non-small cell lung cancer (NSCLC); sodium; hyponatremia; biomarkers; survival

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## Introduction

Lung cancer is one of the most common cancers and the most common cause of cancer death worldwide (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer while small cell lung cancer (SCLC) comprises the remaining 15%. In spite of great achievements in anticancer treatment of NSCLC patients in the last decades, the clinical outcome of the disease remains unsatisfactory with a 5-year survival rate less than 20% (2).

To improve the management and survival of NSCLC patients, estimation of a patient's prognosis is fundamental as it can guide clinicians to decide if anticancer therapy is likely to be beneficial for the patient. Moreover, it helps both the clinician and the patient to predict the natural history of the disease leading to more optimal treatment courses and planning of the end-of-life care. Therefore, identification of prognostic factors is essential. To date, disease stage is the most important identified prognostic factor in NSCLC patients together with performance status (PS), age, histology and sex (3). However, additional factors are wanted to guide the clinicians to perform more accurate estimations.

Hyponatremia is a common electrolyte disorder in cancer patients and has been evaluated as a negative prognostic factor of survival in several cancer types (4–6). It is defined as a sodium level below 135 mmol/L and further classified into three severities; mild hyponatremia (130–134 mmol/L), moderate hyponatremia (125–129 mmol/L) and severe hyponatremia (<125 mmol/L). Patients with hyponatremia are often asymptomatic or showing only a few unspecific symptoms like headache, fatigue, confusion, vomiting and hallucinations (6). The incidence is depended on the kind of malignancy as very different frequencies have been described in different cancer types (5,7,8). In lung cancer, the incidence of hyponatremia is high in SCLC patients (9), and the influence of hyponatremia on survival has been intensively evaluated in these patients (10,11). However, the prognostic value of hyponatremia is less studied in NSCLC patients, and studies have shown inconsistent results (12,13). Therefore, we conducted a systematic review and a meta-analysis to investigate the prognostic value of pretreatment hyponatremia in NSCLC patients.

We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting checklist (14) (available at <http://dx.doi.org/10.21037/tlcr-20-877>).

## Methods

### *Data sources and search strings*

A comprehensive search was performed in PubMed, Embase, Scopus and Web of Science on the 26<sup>th</sup> of March, 2020 with no time restriction. PubMed and Embase were filtered for English, Danish, Swedish and Norwegian only while Scopus and Web of Science was filtered for English only. In addition, PubMed and Embase were filtered for “not animals”. The following search strings were used: PubMed: (“Lung Neoplasms”[Mesh] OR lung cancer OR lung carcinoma\* OR lung neoplasm\*) AND (“Hyponatremia”[Mesh] OR Hyponatremia\* OR “Sodium”[Mesh] OR Sodium). Embase: (‘lung tumor’/exp OR (lung AND cancer) OR (lung AND carcinoma\*) OR (lung AND neoplasm\*) AND (‘hyponatremia’/exp OR ‘sodium’/exp OR sodium OR hyponatremia\*). Scopus: (“lung carcinomas” OR “lung carcinoma” OR “lung cancer” OR “lung neoplasm”) AND (“Hyponatremia” OR “sodium”). Web of Science: (“lung cancer” OR “lung tumor” OR “lung tumors” OR “lung carcinoma” OR “lung carcinomas” OR “lung neoplasm” OR “lung neoplasms”) AND (“Hyponatremia” OR “sodium”).

### *Study selection*

The inclusion criteria were as follows: (I) original data, (II) human studies, (III) patients with a pathological proven histology of NSCLC (IV) studies evaluating sodium level as a prognostic factor. Exclusion criteria were as follows: (I) language other than English, Danish, Swedish and Norwegian, (II) reviews, meta-analyses, guidelines, editorials, comments, case reports including fewer than five cases, letters to the editor or other communications without original data, (III) conference abstracts, (IV) animal or *in vitro* studies. When multiple publications using the same study population were identified or when the study populations overlapped, only the study including the largest number of NSCLC patients was included.

To be included in the meta-analysis on survival, articles had to provide a hazard ratio (HR) and a 95% confidence interval (CI) or a beta coefficient and a standard error (SE) for the comparison of mortality risk between patients with and without hyponatremia. Only studies reporting a multivariate HR were included in order to reduce heterogeneity. As insignificant multivariate HRs were not reported in two studies (15,16), the authors were contacted to obtain the data; however, neither of them responded.

Consequently, the two studies were excluded from the meta-analysis.

### **Data extraction and quality assessment**

Titles and abstracts were screened to identify eligible articles. The first 400 abstracts were randomly selected and screened by two authors (AWL and BSP) to validate inclusion and exclusion criteria. Any disagreement was resolved by consensus. The remaining titles and abstracts were screened by one author (AWL), and in any case of doubt, the abstract under consideration was assessed by both authors. After identification of likely eligible full-text articles, 20 randomly selected articles were read and included/excluded by both authors. The remaining articles were included or excluded through full-text reading by one author (AWL), and in case of doubt, the article in question was discussed by the two authors until consensus was reached. Covidence (covidence.org) and Endnote (Clarivate Analytics) were used for reference management during the inclusion and exclusion procedure including duplicate screening. Data extraction was divided between the two authors (AWL and BSP) and subsequently checked by the other author. Following data was extracted from the studies: name of first author, publication year, country, rating, study design, sample size, study design, clinical characteristics of the study population, sodium level cut-off, follow-up time and risk estimate for overall survival (OS). Articles included in the study were quality scored by both authors using a modified version of the Quality of Prognosis Studies Tool (QUIPS) (17) and rated as high quality (+++), acceptable quality (++) and low quality (+). The protocol was submitted to the PROSPERO database (ID 184612).

### **Statistical analyses**

The primary outcome was OS and results from articles reporting adjusted risk estimates with CIs or SEs for mortality was combined in a meta-analysis. Heterogeneity between studies was assessed by using two statistical methods, Cochran Q and  $I^2$  (18). If data indicated the presence of heterogeneity ( $P < 0.1$  and/or  $I^2 > 50\%$ ), the DerSimonian-Laird method for a random-effects model was used to calculate the pooled HRs. Otherwise was the fixed-effects model used. No subgroup analysis was performed owed to the limited number of studies. The possibility of publication bias was evaluated by a funnel plot, Begg's test and Egger's test. We did not pool results for other

outcomes than OS because of the small number of studies. The robustness of the pooled result was evaluated by a sensitivity analysis omitting low quality studies. A P value  $< 0.05$  was considered significant. All statistical analyses were performed with Stata software version 15.1 (Stata Corporation, College Station, TX, USA), and all P values were two-sided.

## **Results**

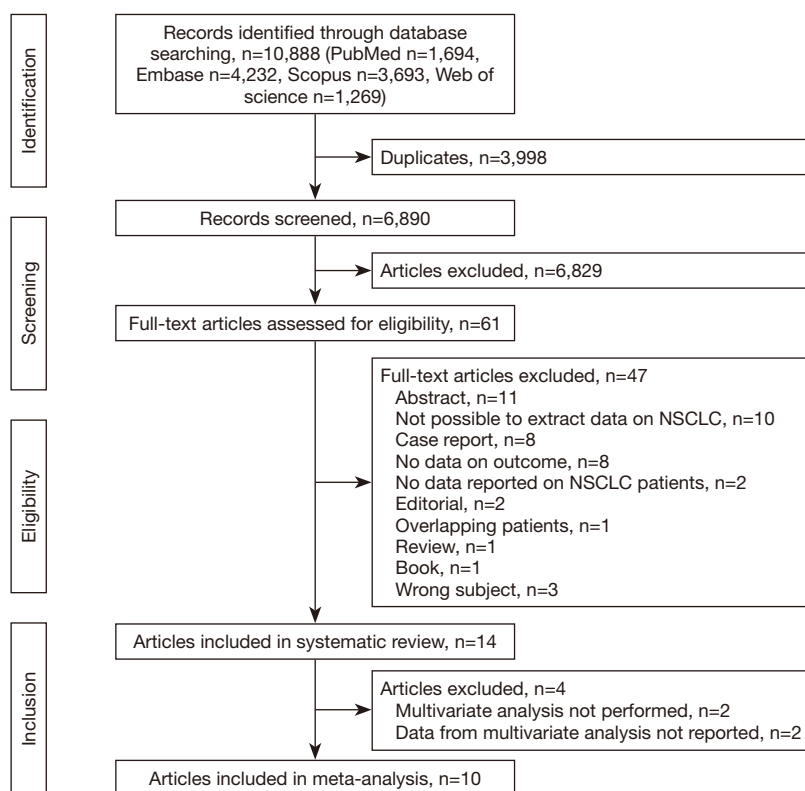
### **Study selection**

The electronic database search identified 10,888 articles. After removal of duplicates, 6,890 articles were identified. Titles and abstracts were screened, and subsequent, 61 full-text articles were examined for eligibility. Of these, 15 articles meet the inclusion and exclusion criteria for the review. However, two studies (12,19) included overlapping study populations, and one of these articles was thus excluded (19). Therefore, a total of 14 articles were included in the systematic review. Only ten of these articles reported a useful risk estimate and were included in the meta-analysis. The inclusion and exclusion procedures are illustrated in *Figure 1*.

### **Study description and quality assessment**

Descriptive data for the studies included in the systematic review are summarized in *Table 1*. All studies were retrospective cohort studies except for a single prospective study (20). The articles were published between 1998 and 2019. The studies included a total of 4,364 NSCLC patients with sample sizes in each paper ranging from 35 to 671 patients. Half of the articles (seven articles) (13,15,16,22,23,26,27) originated from Asia, primarily India. The remaining seven articles originated from Europe (six articles) (12,20,21,24,25,28) and United States (one article) (5). The median/mean age of included patients varied from 49 to 72 years. The majority of studies included only stage IIIb and IV patients (12,13,15,20,22,24,26,28), but three studies included stage I and stage II patients as well as more advanced stage patients (16,20,23). The patients' disease stage was not reported in two studies (5,21). Staging procedure was only reported in two studies (15,22). Smoking history was reported in eight studies (4,12,15,16,24,25,27,28) and the frequency of current and former smokers ranged from 60% to 84%.

The cut-off values used for defining hyponatremia varied



**Figure 1** Flow diagram of the inclusion and exclusion procedures. NSCLC, non-small cell lung cancer.

significantly ranging from 132 to 141.9 mmol/L, but the majority of studies used 135 mmol/L as a predefined cut-off (six studies) (5,12,22,25,27,28). Three studies defined the optimal cut-off for the association by use of either receiver operating curve (13,16) or the maximum log-rank statistical value (23). These studies all used high sodium levels as cut-offs (139, 140 and 141.9 mmol/L). The cut-off was not reported in one study (15). None of the studies reported any data on the underlying causes of the hyponatremia in the patients.

All studies included a mixed cohort of hyponatremic and eunatremic patients, and, using the defined cut-offs, a total of 1,534 patients were classified with hyponatremia in the studies. The frequency of hyponatremic patients was reported in 12 of the 14 studies (5,12,16,20-28) and varied significantly ranging from 13% to 96% with an average of 39%. Follow-up time was reported in five studies (5,12,15,16,23) and the average follow-up time in these studies ranged from 12.6 months to 3.1 years. The overall quality of the studies was rated from low to high quality with six studies rating low quality (5,16,22,23,26,28), seven rating acceptable (13,15,20,21,24,25,27) and one study

rating high quality (12).

### *Hyponatremia and OS*

Of the 14 articles included in the systematic review, 10 articles reported an adjusted risk estimate of mortality risk between patients with and without hyponatremia and were thus included in the meta-analysis. Study characteristics, rating and adjustment variables for each of these studies are listed in *Table 1*. The studies were rated from low to high quality. Adjustment for stage and PS was performed in seven of the studies (12,20,21,24,25,27,28) while six studies adjusted for sex (20,21,24-26,28) and five studies adjusted for age and histology (21,24-26,28). In one study (5), no information was reported on adjustment factors.

Because of substantial between-study heterogeneity ( $Q=32.14$  on 9 df;  $P<0.001$ ;  $I^2=72\%$ ;  $P=0.0631$ ), we calculated a pooled HR using a random-effects model. The pooled result showed that hyponatremia was associated with a 102% increased risk of death in patients with NSCLC [HR =2.02 (95% CI: 1.65–2.47), *Figure 2*].

We observed indications of publication bias as the funnel

**Table 1** Studies investigating hyponatremia as a prognostic factor in NSCLC patients (n=14)

Author, year, country, rating	Design, study population, n, age (years)	Clinical stage	Tumor histology, material for diagnosis	Smoking history	Evaluation time	Treatment	Na <sup>+</sup> cut-off, mmol/L	Patients with hypona <sup>a</sup> , no./total no.	Follow-up time/number of events	Outcome, OS U/M, HR (95% CI) or log-rank P value	Adjustment variables
Rechnitzer, 1998, Germany (20), acceptable quality	Prospective cohort, n=229, median age: 57.4	I: 1 (0.4%); II: 6 (2.6%); IIIA: 20 (8.7%); IIIB: 64 (28.0%); IV: 132 (57.7%); unknown: 6 (2.6%)	Adeno: 125 (54.6%); SCC: 72 (31.4%); large cell: 16 (7.0%); mixed cell <sup>†</sup> : 16 (7.0%); histologically or cytologically	NR	At start of first-line treatment	Chemotherapy, RT to primary tumor in few cases	137.5	59/229 (26%)	220 events (96%) during follow-up. Minimum follow-up time of 3.5 years	M: beta coefficient =0.7736, SE =0.1611	Stage and sex
Jacot, 2001, France (21), acceptable quality	Retrospective cohort, n=231, median age: 59 [32–85]	IV	Adeno: 86 (37%); SCC: 95 (41%); large cell: 50 (22%); histologically	NR	At start of first-line treatment	NA	132	219/229 (96%)	207 death (90%) during follow-up	M: 2.99 (1.17–7.62)	Sex, age, PS, histology, serum NSE level, serum CYFRA 21-1 level, serum albumin, alkaline phosphatases, LDH, blood leucocyte count, presence of bone metastases, presence of liver metastases, neurological symptoms
Bose, 2011, India (22), low quality	Retrospective cohort, n=40, mean age: 49	IIIB: 25 (62%); IV: 15 (38%)	Adeno: 16 (40%); SCC: 11 (28%); large cell: 3 (7%); non-specified: 10 (25%); FNAC or biopsy	NR	At start of first-line treatment	Platinum-based regimens	135	7/35 (20%)	27 events (68%) during 6 months follow-up	U: log-rank P<0.03 (further data NR)	–
Kobayashi, 2014, Japan (23), low quality	Retrospective cohort, n=386, mean age: 67.4, SD 10.1	I: 240 (62%); II: 90 (23%); III: 56 (15%)	Adeno: 241 (62%); SCC: 96 (25%); large: 23 (6%); other: 26 (7%); material NR	NR	Pre operation	NR	139 <sup>‡</sup>	123/386 (32%)	Mean 41.2 months [1–118]	M: 1.527 (1.005–2.322)	Tumor size, pleural invasion, nodal status
Svaton, 2014, Czech Republic (24), acceptable quality	Retrospective cohort, n=544, median age: 64 [28–84]	IIIB: 114 (21.0%); IV: 430 (79.0%)	Adeno: 255 (46.9%); SCC: 260 (47.8%); NOS: 29 (5.3%); histologically or cytologically	Current: 254 (47%); former: 189 (35%); never: 110 (18%)	At start of erlotinib as 2nd, 3rd, 4th or 5th line of treatment	Erlotinib	136	117/544 (22%)	NR	M: 1.87 (1.47–2.39)	Sex, age, smoking, histology, stage, PS, treatment line, EGFR status
Castillo, 2016, USA (5), low quality	Retrospective cohort, n=1,758 (NSCLC n=405), mean age: 60.2, SD 13	NA	NR	NR	At cancer diagnosis and during follow-up until study end or death	NR	135	307/405 (76%)	Total cohort: mean 3.1 years (SD 2.7)	M: 2.8 (2.0–3.9)	NR
Minami, 2016, Japan (13), acceptable quality	Retrospective cohort, n=154 (n=103 evaluated), median age: 70 [42–86]	IIIB: 41 (40%); IV: 62 (60%)	SCC; Histologically or cytologically	NR	At start of first-line treatment	Chemotherapy	140 <sup>§</sup>	NR	NR	U: 0.96 (0.91–1.02)	–
Kogo, 2017, Japan (15), acceptable quality	Retrospective cohort, n=100, median age: 62 [32.5–80.7]	IIIB: 33 (33%); IV: 67 (67%)	Adeno: 73 (73%); SCC: 23 (23%); other: 4 (4%); FNAC or brush cytology	Current/former: 76 (76%)	At start of first-line treatment	Platinum and third-generation chemotherapy	NR	NR	Median 12.6 months (0.2–67.0)	U: 0.909 (0.829–0.996); M: not significant (data NR)	NR
Berardi, 2017, Italy (25), acceptable quality	Retrospective cohort, n=433, median age: 66 [25–86]	III: 112 (26%); IV: 321 (74%)	Adeno: 278 (64%); SCC: 101 (23%); other: 54 (13%); histologically or cytologically	Former/current: 364 (84%); never: 69 (16%)	At start of first-line treatment	Platinum chemotherapy: 348 (80%) Non-platinum based: 57 (13%); EGFR TKI: 28 (7%)	135	69/433 (16%)	281 events (65%) during follow-up	U: 1.71 (1.25–2.34); M: 1.59 (1.14–2.21)	Sex, histology, stage, PS, EGFR status
Doshi, 2018, India (26), low quality	Retrospective cohort, n=257, median age: 55 [21–78]	IIIB/IV	Histology NR; histologically or cytologically	Current: 116 (45%); never: 82 (31%)	At start of first-line treatment	Pemetrexed-platinum doublet	136	137/257 (53%)	NR	M: 2.07 (1.11–3.84) (n=83)	Sex, age, smoking, PS, EGFR status

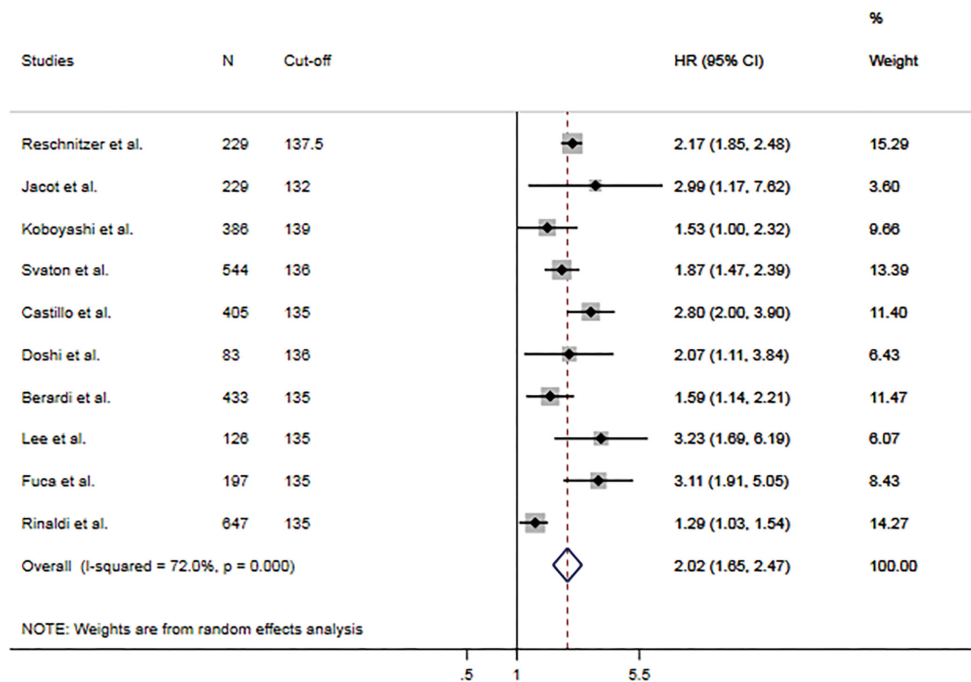
Table 1 (continued)



Table 1 (continued)

Author, year, country, rating	Design, study population, n, age (years)	Clinical stage	Tumor histology, material for diagnosis	Smoking history	Evaluation time	Treatment	Na <sup>+</sup> cut-off, mmol/L	Patients with hypona <sup>†</sup> , no./total no.	Follow-up time/number of events	Outcome, OS U/M, HR (95% CI) or log-rank P value	Adjustment variables
Lee, 2018, Korea (27), acceptable quality	Retrospective cohort, n=126, age: <75 years: 80 (63.5%), ≥75 years: 46 (36.5%)	IV	Non-SCC: 63 (50%); SCC: 63 (50%); material NR	Former/current: 99 (79%); never: 27 (21%)	At start of second-line treatment	EGFR TKI: 52 (41%); chemotherapy: 74 (59%)	135	68/126 (54%)	NR	M: 3.228 (1.685–6.186)	PS, brain metastasis, PFS of first-line treatment, serum albumin, SCS, histology, stage, subsequent treatment, BSA change, plasma Hb
Fucà, 2018, Italy (12), high quality	Retrospective cohort, n=197, age: <65: 84 (43%), ≥65: 113 (57%)	IV	Non-SCC: 152 (77%); SCC: 45 (23%); material NR	Current: 53 (29%); never/former: 127 (71%)	At start of IO as any line of treatment	PD-1/PD-L1 therapy as single therapy (191, 97%) or combined with CTLA-4 blockade (6, 3%)	135	26/197 (13%)	Median 25.7 months	U: 3.00 (1.80–4.80); M: 3.11 (1.91–5.05)	PS, liver metastases, bone metastases
Li, 2019, China (16), low quality	Retrospective cohort, n=1,304 (n=671 evaluated), age: ≤65: 478, >65: 193	I: 323 (48%); II: 156 (23%); III + IV: 192 (29%)	Adeno: 366 (54%); SCC: 239 (36%); others: 66 (10%); material NR	Former/current: 400 (60%); never: 271 (40%)	Before surgery	NR	141.9 <sup>§</sup>	165/671 (25%)	Mean 40.84 [1–92]	U: 0.606 (0.430–0.854); M: not significant (data NR)	NR
Rinaldi, 2019, Italy/UK (28), low quality	Retrospective cohort, n=647, median age: 72 [32–93]	IIIB, IV, and IIIA not suitable for surgery	Adeno: 414 (64%); SCC: 155 (24%); other: 78 (12%); histologically or cytologically	Former/current: 537 (83%); never: 110 (17%)	At start of first-line treatment	Chemotherapy or targeted therapy	135	237/647 (37%)	407 events (63%) during follow-up	U: 1.36 (1.12–1.71); M: 1.29 (1.03–1.54)	Sex, age, PS, smoking, stage, histology, EGFR status, bone metastasis

<sup>†</sup>, Mixed-cell histology consisting of two or all three cell types named above. <sup>‡</sup>, Cut-off defined by the maximum log-rank statistical value. <sup>§</sup>, Cut-off defined by use of receiver operating curve. NSCLC, non-small cell lung cancer; adeno, adenocarcinoma; BSA, body surface area; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CYFRA 21-1, a fragment of cytokeratin subunit 19; EGFR, epidermal growth factor receptor; FNAC, fine needle aspiration cytology; Hb, hemoglobin; IO, immunotherapy; LDH, lactate dehydrogenase; M, multivariate; NA, not available; NOS, not otherwise specified; NR, not reported; NSE, serum neuron-specific enolase; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PFS, progression free survival; PS, performance status; RT, radiotherapy; SCC, squamous cell carcinoma; SCS, simplified comorbidity score; TKI, tyrosine kinase inhibitor; U, univariate.



**Figure 2** Forrest plot showing the HRs for the association of hyponatremia with OS in patients with NSCLC. HR, hazard ratio; OS, overall survival; NSCLC, non-small cell lung cancer; N, number of included patients; cut-off, the sodium cut-off level used in the study to define hyponatremia; CI, confidence interval.

plot visually showed asymmetry (Figure S1). Yet, there was no evidence of publication bias according to either Begg’s test (P=0.531) nor Egger’s test (P=0.442). In spite of this, a Trim and Fill analysis for OS was performed to impute missing studies in the funnel plot, and an adjusted pooled random-effect HR was calculated. The analysis showed a reduced pooled HR [1.84 (95% CI: 1.51–2.23)], which however remained significant.

To assess the impact of the study quality, a sensitivity analyses were performed omitting the four low quality studies. Evaluating only the six studies of acceptable and high quality using a random-effects model, we found a pooled HR of 2.13 (95% CI: 1.76–2.45).

**Hyponatremia and progression free survival (PFS)**

The correlation between hyponatremia and PFS was evaluated in four studies (12,24–26) and showed mixed results. Svaton *et al.* (24) found in a cohort of 544 patients treated with erlotinib as second, third, fourth or fifth line of treatment a significant increased risk of progression in patients with hyponatremia after adjusting for sex,

age, smoking, histology, stage, PS, line of treatment and epidermal growth factor receptor status [adjusted HR =1.25 (95% CI: 1.01–1.55)]. Fucà *et al.* (12) evaluated 197 patients treated with immunotherapy as any line of treatment and did not find a significant correlation between hyponatremia and PFS when adjusting for PD-L1 status, liver and bone metastases. Lastly, two studies evaluated patients treated with chemotherapy as first-line of treatment (25,26). One study (26) found a significant shorter median PFS in hyponatremia patients but did not perform any multivariate analysis adjusting for potential confounders. No correlation was found in the other study (25).

**Sodium level normalization and outcome**

One study evaluated the association between sodium level normalization and PFS as well as OS in 69 stage III and IV patients with hyponatremia at start of first-line chemotherapy or targeted treatment (25). The sodium level was assessed after each treatment cycle. A significant association between normalization of sodium level and longer PFS and OS was reported.

## Discussion

This systematic review and meta-analysis indicates that hyponatremia is a relative common condition in NSCLC patients. Moreover, it was found to be associated with an increased mortality as a more than 100% increase in mortality risk was observed in hyponatremic patients compared with eunatremic patients. This finding was consistent after accounting for a possible publication bias; even though, the pooled HR was reduced. The majority of studies were retrospective studies and the overall quality of the available studies was low. Yet, the association was unchanged after omitting low quality studies from the analysis. Despite these concerns, for the first time this review collects the available literature and evaluates the association in NSCLC patients.

Hyponatremia is a common electrolyte abnormality (29) which has been associated with an increased mortality in several conditions as myocardial infarction (30), hepatic cirrhosis (31) and pulmonary embolism (32). In cancer patients, hyponatremia is mainly caused by the syndrome of inappropriate antidiuretic hormone secretion (SIADH) which may arise due to ectopic secretion of arginine vasopressin (33). Yet, hyponatremia can also develop owing to several other conditions leading to loss of sodium or excess of water in relation to sodium as vomiting, diarrhea, chronic kidney disease, treatment with anticancer therapy and drugs used for palliation (34); all conditions regularly seen in cancer patients. In lung cancer, attention on hyponatremia has been focused on SCLC patients as SIADH is often observed in these patients (34). However, increasingly data has indicated that hyponatremia is additionally a frequent condition in NSCLC patients (5). The frequency of hyponatremia varied significantly in the studies included in this review with frequencies ranging from 13% to 96%. The discrepancy could potentially be explained by different ways of reporting the incidence or different cut-offs. However, only one study evaluated hyponatremia at any time during follow-up, and thus found a high incidence of 76% (5), while the majority of studies (13,15,16,20-23,25,26,28) estimated the frequency at time of diagnosis or before second or later lines of treatment (12,24,27). Likewise, no clear correlation between high cut-offs for defining hyponatremia and incidence could be found as the three studies with highest cut-offs of 137.5 mmol/L (20), 139 mmol/L (23) and 141.5 mmol/L (16) found relatively low incidences of 26%, 32% and 25%, respectively. Nevertheless, despite

these substantial differences, data clearly indicates that hyponatremia is a common condition in NSCLC patients and needs attention in the daily clinic. As none of the included studies reported any data on the underlying causes of the hyponatremia in the patients, no evaluation of the causes of hyponatremia in NSCLC could be performed.

A meta-analysis is a useful tool to integrate results from individual studies in order to detect effects that may be missed by individual studies. In this meta-analysis, ten studies were found eligible including a total of 3,279 NSCLC patients. The combined result demonstrates that hyponatremia is associated with a significantly increased mortality in NSCLC patients with a pooled HR of 2.02 (95% CI: 1.65–2.47), which remained significant in a sensitivity analysis omitting low quality studies. Yet, in planning our meta-analysis, we chose only to include studies reporting an estimate of the adjusted HR to reduce the heterogeneity of the included studies. This caused omission of two studies with insignificant multivariate HRs as these estimates were not reported in the articles. This has undoubtedly led to an overestimation of our estimate. Moreover, we found indications of publication bias in the Funnel plot which can have influenced our estimate. However, our estimate remained significant after using the Trim and Fill analysis. Thus, we believe that the found association is reliable; even though, it may be of a reduced magnitude. Our meta-analysis is the first performed in NSCLC patients, but our finding is in line with a large number of previous studies conducted in cancer patients with other cancer types (4,7,8,10,33,35,36) as well as several meta-analyses performed in other patients groups including patients with stroke (37), acute coronary syndrome (30) and chronic kidney disease (38), which all reports higher risk of mortality in hyponatremic patients. Our result thereby adds data to the existing literature highlighting that an increased focus on this electrolyte abnormality is highly important in NSCLC patients as well.

One study evaluated the value of normalization of sodium level during treatment. They found a significant association between normalized levels and prolonged PFS as well as OS in 69 patients with advanced stage disease. This finding is in line with data from a previous meta-analysis (39) addressing the effect of hyponatremia improvement on mortality in patients with diverse clinical conditions where any improvement of hyponatremia was associated with a reduced risk of overall mortality. One of the included studies comprised 61 patients with SCLC and supported this conclusion (10). However, data is sparse



in lung cancer patients and more data is needed before drawing any firm conclusion.

The strengths of this study are the comprehensive systematic review of the available literature on hyponatremia as a prognostic factor in NSCLC patients and that each article was reviewed by two team members. We used four databases, applied broad search terms and used broad in- and exclusion criteria in order not to miss relevant studies. Nonetheless, the study has some limitations to consider. Firstly, all studies, except for one study, were retrospective cohort studies, and the quality of the studies was overall low. Moreover, there was found substantial heterogeneity between the included studies and despite our attempt to manage this heterogeneity with appropriate meta-analytic techniques (e.g., random-effects model), studies varied in the cut-offs used for defining hyponatremia, the disease stages of the included patients, length of follow-up, and adjustment for confounding variables. Lastly, we excluded studies in language other than English, Danish, Swedish and Norwegian, and thus a language bias cannot be excluded.

## Conclusions

This first systematic review and meta-analysis performed to evaluate hyponatremia as a prognostic factor in NSCLC patients indicates that hyponatremia is a relative common condition in NSCLC patients associated with an increased mortality. Hence, sodium level could be useful for stratifying NSCLC patients and, thereby, for preparing individual treatment plans and is thus a promising biomarker for use in the clinical management of this patient group.

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## Footnote

*Reporting Checklist:* The authors have completed the PRISMA reporting checklist. Available at <http://dx.doi.org/10.21037/tlcr-20-877>

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interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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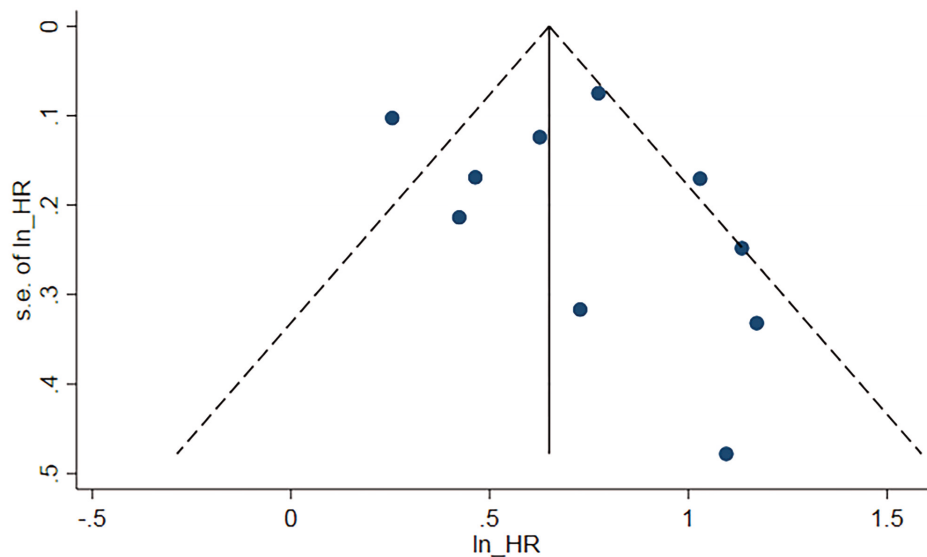
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The funnel plot of the meta-analysis evaluating the impact of hyponatremia on overall survival in patients with non-small cell lung cancer. HR, hazard ratio



**Figure S1** The funnel plot of the meta-analysis of the impact of hyponatremia on OS in patients with NSCLC. OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio.