

Peer Review File

Article Information: Available at <http://dx.doi.org/10.21037/tlcr-20-877>

Reviewer A

Comment 1:

Thank you for the well written paper, giving an overview about prognostic value of pretreatment hyponatremia in NSCLC patients. The topic posed by the Authors can be considered of interest since the paucity of data available in the Literature.

Reply 1:

Thank you for the kind comment.

Reviewer B

Important concept work which requires further refinement.

Comment 1:

Please specify form of histology taken, histology subtypes, staging and correlation to survival and confounding medications taken by the patient cohort studied

Reply 1:

We have added which material there was used to determine the histology in Table 1. Regarding detailed data on staging procedure, this was only reported in two articles and this information has been added to the manuscript in the result section. However, we cannot extract additional data on the histology subtypes than was already given in the table.

Data on the correlation between the form of histology taken, histology subtypes, staging, and survival are interesting aspects; however, these data are not reported in the included articles. Therefore, we cannot add this to the manuscript. Lastly, in this article, we have a focus on the prognostic role of hyponatremia in the overall group of NSCLC. The treatment given to the patients is not a confounder of the results. It might affect the overall survival, however, it does not affect the level of serum sodium.

Changes in the text:

Table 1: "Material for diagnosis" has been added to the "*Tumor histology*" column.

Result section: "*Staging procedure was only reported in two studies (15,21)*" has been added to the manuscript on page 10, line 174.

Reviewer C

It is an interesting study based on meta-analysis of selected articles.

Comment 1:

Please add, if possible, information about smoking habit (pack-year) of patients included in the analysis since smoking seems to affect the clinical outcome.

Reply 1:

We agree with the reviewer that this is important information. We have added smoking history in Table 1 and in the result section. None of the included articles reports the patients' pack-year, and it is thus not possible for us to add these data.

Changes in the text:

Result section: "*Smoking history was reported in eight studies (4, 12, 15, 16, 24, 26–28) and the frequency of current and former smokers ranged from 60% to 84%.*" has been added on page 10, line 174-176.

Table 1: A column with "*Smoking history*" has been added to the table.

Comment 2:

Please clarify which endpoint was considered as the main endpoint in the methods section.

Reply 1:

The main endpoint has been added to the method section

Changes in the text:

Method section: "*The primary outcome was overall survival (OS)*" has been added on page 8, line 140. As a consequence, the abbreviation of overall survival has been changed in line 147, page 9.

Comment 3:

Please may you explain what were the prevailing symptoms associated with hyponatremia and lung cancer.

Reply 1:

Often patients with hyponatremia are asymptomatic and the condition is only recognized biochemically. When symptoms do occur, they are mainly neurological and include symptoms as headache, fatigue, confusion, vomiting, hallucinations, and even coma. Mild chronic hyponatremia can lead to gait instability with an increased risk of falls and fractures. Owing to these symptoms, hyponatremia is a serious condition important to diagnosis. Data from our work enhances the importance of focusing on hyponatremia in all patients, even though, they are asymptomatic.

We agree with the reviewer that this information is missing in the manuscript and we have thus added it in the introduction section.

Changes in the text:

Introduction section: "*Patients with hyponatremia are often asymptomatic or showing only a few unspecific symptoms like headache, fatigue, confusion, vomiting, and hallucinations [6].*" has been added on page 5, line 75-76.

Comment 4:

May you explain in the discussion whether other causes of hyponatremia such as vomiting and diarrhea had been considered. Were anti-emetics used?

Reply 1:

We agree with the reviewer that this is an important issue. Unfortunately, none of the included articles reported any data about the underlying causes of hyponatremia in patients, and we are therefore unable to extract any data concerning this issue. We have added this information to the result section and commented on this in the discussion section.

Changes in the text:

Result section: "*None of the studies reported any data on the underlying causes of the hyponatremia in the patients.*" has been added on page 10, lines 182-182.

Discussion section: *“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.”* has been added on page 14, line 265-267.