PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What is the etiology of dysnatremia in COVID-19 and how is this related to outcomes in patients admitted during earlier and later COVID-19 waves? A multicentre, retrospective observational study in eleven Dutch hospitals
AUTHORS	de Haan, Lianne; ten Wolde, Marije; Beudel, Martijn; Olde Engberink, Rik H G; Appelman, Brent; Haspels-Hogervorst, Esther; Rusch, Daisy; Gritters van den Oever, Niels; Simsek, Suat; Paternotte, Nienke; van den Bergh, Joop; Wyers, Caroline; de Kruif, Martijn; Dormans, Tom; Moeniralam, Hazra; Bokhizzou, Neyma; Brinkman, Kees; Douma, Renee; Collaborator, COVIDPredict Study Group

VERSION 1 – REVIEW

REVIEWER	Chow Kai Ming The Chinese University of Hong Kong, Prince of Wales Hospital
REVIEW RETURNED	26-May-2023

GENERAL COMMENTS	There has been increasing recognition of hyponatraemia and hypernatraemia for COVID-19 disease. This study attempted to assess the prevalence and prognostic significance of dysnatraemia, based on a database known as multicenter COVIDPredict Clinical Course Cohort, covering over 6500 patients with COVID-19 (between February 2020 and August 2022) in nine Dutch hospitals. The most important finding from this study is the proposed mechanism of hyponatraemia in COVID-19 patients requiring hospitalisation. Urinary sodium and osmolality results were available in less than 10% of patients with hyponatraemia. The major comments are: 1) On page 9, it was highlighted that “This study is the largest study on dysnatremia in COVID-19.” The sample size of 7,811 (with available serum sodium concentration) should be considered reasonable, but this does not make the study “the largest.” For instance, Chan GCK et al published in Front Med (Lausanne) a study of hyponatraemia in 53,415 patients with 14,545 hyponatraemic cases (27.2%). This also speaks for the importance of more thorough literature search. 2) As shown in many studies, such as the analysis of dysnatraemia from New York by Liu D et al (published in Kidney360), hypernatraemia was associated with the prevalence of acute kidney injury, which is a strong predictor of mortality in COVID-19 patients. Was this observed?

	3) The prognostic significance of hypernatraemia (and less so for hyponatraemia) has been well described in meta-analysis. An example was published by Shrestha AB et al in Medicine (Baltimore). Again, this is not cited in the manuscript. The reason that hyponatraemia patients have higher odds of intensive care unit admission could have been the reversible nature of this electrolyte disorder (and hence low threshold for intensive care unit to admit such patients despite the relatively low qSOFA score, as shown in this study) and the dogmatic teaching that patients with severe hyponatraemia should be admitted to intensive care unit for close monitoring. In general, such patients have short stay for correction of sodium disorder. This appears to be the case according to the brief description on page 16. Do you have the length of their stay in intensive care unit (as compared to those with hypernatraemia)? Preferably, the median (and mean, if appropriate) length of stay in intensive care unit could be described in Table 3. 4) One of the potential causes of hyponatraemia is low-solute hyponatraemia. The so-called tea and toast syndrome might not be easy to identify without a detailed dietary history or daily urine urea excretion estimation. Are there data on the socioeconomic status? 5) The proposed mechanism of interleukin-6 for hyponatraemia is relevant in COVID-19. Were tocilizumab or monoclonal antibody to IL-6 more often used in hyponatraemia subjects? I realized that there was a brief sentence on tocilizumab on page 17. 6) Complications along the course of disease in patients with hyponatraemia were reported in page 16. Were there information on the trend of sodium level with time, and if so, were there correlation with disease outcomes? 7) According to the study design, diagnosis of hyponatraemia group is defined by the serum sodium level at admission at the participating hospital (as stated on page 11). What is the duration of symptom before presentation to the hospital for the hyponatraemia group? It is not uncommon for COVID-19 patients to present first with fever and respiratory symptoms, and then developed hyponatraemia more than one week after symptom onset. If such patients were not admitted to hospital until, say 10 to 14 days after symptom onset (or sometimes after recovery), with abnormal sodium concentration, were they included in the study cohort? 8) Were there many patients declined ICU admission? For instance, asthmatic patients with severe exacerbation are more often accepted for ICU because of the reversibility of the condition whereas severe chronic obstructive airway disease patients would be less readily admitted (even if they had more severe respiratory failure). This is similar to the condition of hyponatraemia (more “comfortably” admitted to ICU) and hypernatraemia (worse prognosis, and less likely to be admitted even if there were high mortality). 9) The correlation of hyponatraemia with pulmonary aspergillosis was mentioned on page 17. This complication appeared to be more common in Europe than in North America. Causal relationship is considered less likely for hyponatraemia (to drive the higher incidence of aspergillosis). Could this be related to the high ICU admission rate for the hyponatraemia patients? If there is environment factors (proposed reasons including negative pressure environment in ICU and contaminated respiratory equipment), we should reported if the aspergillosis patients occurred more often after ICU admission in the cohort. What about the percentage of dexamethasone and tocilizumab use in the asperigillosis cases? Minor comments include:

	1) The English is not very standard. The sentence “Especially elevated LDH concentration and lymphocytopenia are common…” is an example; we seldom start a sentence like this. We usually use word “lymphopenia” and not “lymphocytopenia.” Words like “readmittance” (page 14) should have been changed to more conventional English (re-admission). 2) There was another typo on page 16. “Conformed” should have been spelt as “confirmed.” 3) The legend of Table 2 has a typo: “sSOFA” should have been “qSOFA”. 4) Detailed description of the clinical features including capillary refill was available (although we are not certain how systemically the findings were documented in a retrospective study). 5) Complication and outcome measures were described on page 13. New entity known as “physical decline” appeared in Table 3. How is this defined? Was that a pre-defined outcome in the database? 6) There was discussion on different waves of COVID-19 with time on page 22. Please state if the current cohort was derived from the period when Omicron variant predominated.

REVIEWER	Ploutarchos Tzoulis Whittington Hospital- UCL, Experimental & Translational Medicine
REVIEW RETURNED	11-Jun-2023

GENERAL COMMENTS	In general, this is a well-designed and well-conducted study with solid methodology. It evaluates the prognostic impact of dynatremias on patients with COVID-19 which has been already thoroughly studied. However, it is interesting and intriguing that the current study addresses this issue on COVID-19 after the initial phase; this is essential since the natural history and burden of COVID-19 has drastically altered as the time progresses. Regarding to hyponatremia, my comments are: 1. There is no information about the recent sodium levels prior to admission. This is potentially important since a proportion of individuals have pre-existing chronic hyponatremia. 2. The study does not look into sodium levels during hospitalization. If there are data, this would be a valuable addition. 3. With respect to the etiology of hyponatremia, the authors need to clarify the relationship between different types of hyponatremia and patients’s prognosis. 4. Similarly, the link of serum sodium and CRP (and the severity of infection / inflammatory reaction) should be examined as per type of hyponatremia, such as hypo- / eu- / hyper-volemic hyponatremia. Hyponatremia is an umbrella term and SIADH may have different impact compared to hypovolemic hyponatremia. There are similar questions / additional data needed with respect to hypernatremia. Finally, questions about the surprising lack of relationship between hyponatremia and mortality in contrast to the general literature for hyponatremia should be addressed more completely. In addition, the authors should highlight the potentially different impact of various types of hyponatremia on prognosis. Finally, any data correction / or not of dysnatremia and its effect on clinical outcomes would be more than welcome. I would also urge the authors to incorporate in their discussion the findings from the initial COVID-19 period and the impact of dysnatremia (summarised in a review in Eur Journal of Endocrinology by Tzoulis et al in 2021). In total, this is a very interesting topic and the authors have access

	to a large database. I would urge them to supplement their data with more information about type of hyponatremia and progress of dysnatremia during the course of illness. Provided the results and discussion sections will be modified appropriately, this manuscript would be a valuable addition to the literature in this field.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Chow Kai Ming, The Chinese University of Hong Kong Comments to the Author: There has been increasing recognition of hyponatraemia and hypernatraemia for COVID-19 disease.

This study attempted to assess the prevalence and prognostic significance of dysnatraemia, based on a database known as multicenter COVIDPredict Clinical Course Cohort, covering over 6500 patients with COVID-19 (between February 2020 and August 2022) in nine Dutch hospitals.
The most important finding from this study is the proposed mechanism of hyponatraemia in COVID-19 patients requiring hospitalisation. Urinary sodium and osmolality results were available in less than 10% of patients with hyponatraemia.

> Thank you for your valuable and thorough revision of our manuscript. Your feedback is highly appreciated. Please find below our reply to each of your comments.

The major comments are:

1) On page 9, it was highlighted that “This study is the largest study on dysnatremia in COVID-19.” The sample size of 7,811 (with available serum sodium concentration) should be considered reasonable, but this does not make the study “the largest.” For instance, Chan GCK et al published in Front Med (Lausanne) a study of hyponatraemia in 53,415 patients with 14,545 hyponatraemic cases (27.2%). This also speaks for the importance of more thorough literature search.
> Thank you for bringing these articles to the attention. A thorough literature search was performed, however, in the meantime a large number of articles on this subject have been published, including the study of Chan et al which included indeed a very large cohort of patients. This once again empathizes the relevance and importance of the topic. We do think our study adds to the currently available data on the subject since we related the different causes of hyponatremia to etiology, included patients from later COVID-19 waves (that were associated with newer treatment modalities and more favorable outcomes), and demonstrated that hyponatremia corrected for glucose is a predictor for worse outcomes to a much lesser extent than the outcomes in studies using uncorrected hyponatremia suggest.

A new literature search on pubmed has been performed using the search ((hyponatremia[MESH] OR hyponatremias[MESH] OR hypernatremias [MESH] OR hypernatremia[MESH] OR (hyponatremia[Title]) OR (hypernatremia[Title]) OR (dysnatremia[Title]) OR (dysnatraemia[Title]) OR (electrolyte[Title])) AND ((coronavirus[Title]) OR (COVID-19[Title]) OR (SARS-CoV-2[Title]) OR (COVID-19[MESH]) OR (SARS-CoV-2[MESH]))). This search provided 133 citations, several of which were found to be relevant to our manuscript. The following references were added:
- Shrestha, et al. 1 reviewed outcomes in COVID-19 patients (2020 and 2021) with hypernatremia, as they found similar results to our study, we cited their study in our discussion.
- Ayus, et al. 2 (2023) emphasized the relationship between CRP levels and hyponatremia in COVID-19 patients. As we also found this relationship, we referred to Ayus et al. in the discussion.
- As you mentioned, Chen, et al. 3 performed a similar study with an even larger patient population then ours. As our results differed from the results in their study, we included them in the discussion.

- Królicka, et al. 4, Machiraju, et al. 5, and Liu, et al. 6 performed similar investigations, albeit in a single center, with smaller populations, and during an earlier COVID-19 period. We compared our study to these previous studies when possible and added them to the reference list.
- Gustafson, et al. 7 compared the incidence of hyponatremia in patients with and without COVID-19 and found that COVID-19 patients significantly more frequently present with hyponatremia than non-COVID-19 patients. This study was cited in the introduction as this emphasizes the relevance of the study.
- Taci Hoca and Berktaş 8, and Sjöström, et al. 9 reported an even higher incidence of hyponatremia in COVID-19 patients than in our study, so the range of reported incidences in the introduction was adjusted.
- Nogueira, et al. 10 reviewed the pathophysiology of acute kidney injury and several electrolyte disorders including hyponatremia in COVID-19 patients. As these findings support our study outcomes, this study was added to the reference list.
- Atlani, et al. 11 studied acute kidney injury in COVID-19 patients confirmed the association between hypernatremia and mortality in COVID-19 patients and was therefore added in the reference list.
- Genovesi, et al. 12, and Sabaghian, et al. 13 studied various electrolyte disorders in COVID-19 and confirmed the association between hypo- and hypernatremia and mortality in COVID-19 patients and was therefore added in the reference list.
- de La Flor, et al. 14 demonstrated that persisted hyponatremia was associated with higher mortality rates. We acknowledge that we did not provide information about sodium levels during admission and therefore could not draw conclusions on the duration of hyponatremia and outcomes. Therefore, we cited this study in our limitations section.
- Malieckal, et al. 15 confirmed that hyponatremia is the most common electrolyte disorder in COVID-19 and was therefore added to the reference list.
- Honore, et al. 16 emphasized the fact that critical illness-related corticoid insufficiency should also be included in the differential diagnosis of hyponatremia in COVID-19. Therefore, we briefly mentioned this disease and referred to Honore et al.

2) As shown in many studies, such as the analysis of dysnatraemia from New York by Liu D et al (published in Kidney360), hypernatraemia was associated with the prevalence of acute kidney injury, which is a strong predictor of mortality in COVID-19 patients. Was this observed?
> As was shown in Table 2, hypernatremia was associated with lower eGFR than normonatremia. Whether these data represent acute kidney injury cannot be concluded as history on kidney function and follow-up data are missing. The association between eGFR and mortality was added to Section 3.3. We found that eGFR in general was associated with slightly higher mortality rates. These results were similar for all groups (normo-, hypo-, and hypernatremia) and when patients with a history of chronic kidney disease were excluded, hazard ratios for mortality and lower eGFR remained similar.

3) The prognostic significance of hypernatraemia (and less so for hyponatraemia) has been well described in meta-analysis. An example was published by Shrestha AB et al in Medicine (Baltimore). Again, this is not cited in the manuscript. The reason that hyponatraemia patients have higher odds of intensive care unit admission could have been the reversible nature of this electrolyte disorder (and hence low threshold for intensive care unit to admit such patients despite the relatively low qSOFA score, as shown in this study) and the dogmatic teaching that patients with severe hyponatraemia should be admitted to intensive care unit for close monitoring. In general, such patients have short stay for correction of sodium disorder. This appears to be the case according to the brief description on page 16. Do you have the length of their stay in intensive care unit (as compared to those with hypernatraemia)? Preferably, the median (and mean, if appropriate) length of stay in intensive care unit could be described in Table 3.
> Thank you for suggesting this valuable addition. Length of ICU admission, which turned out to be similar for all groups regardless of the inclusion of patients with the order ‘do not intubate’, was added to Table 3 and described in Section 3.4. The study by Shrestha, et al. 1 was cited in the manuscript.

4) One of the potential causes of hyponatraemia is low-solute hyponatraemia. The so-called tea and toast syndrome might not be easy to identify without a detailed dietary history or daily urine urea excretion estimation. Are there data on the socioeconomic status?
> Although we think that such information would help to identify the cause of hyponatremia, socioeconomic status, dietary history, and daily urine urea excretion were, unfortunately, not included in our database.

5) The proposed mechanism of interleukin-6 for hyponatraemia is relevant in COVID-19. Were tocilizumab or monoclonal antibody to IL-6 more often used in hyponatraemia subjects? I realized that there was a brief sentence on tocilizumab on page 17.
> Thank you for suggesting this interesting addition. We added the use of tocilizumab and sarilumab (IL6R agonists) and anakinra (IL1R agonist) in Table 3 and to Section 3.4. We found similar administration rates of these agents.

6) Complications along the course of disease in patients with hyponatraemia were reported in page 16. Were there information on the trend of sodium level with time, and if so, were there correlation with disease outcomes?
> We acknowledge the limitation in our study regarding the lack of daily registration of sodium levels during the admission period. Sodium levels during admission were only recorded in the database for the first patients registered (first wave). As the pandemic progressed, we realized that we did not have the capacity to register all daily lab tests in the database for all patients and we limited the input to lab tests at admission. Additionally, the registration of lab tests during admission varies among the participating centers, introducing the risk of selection bias. Therefore, we made the decision not to include this analysis in order to avoid this potential bias.

7) According to the study design, diagnosis of hyponatraemia group is defined by the serum sodium level at admission at the participating hospital (as stated on page 11). What is the duration of symptom before presentation to the hospital for the hyponatraemia group? It is not uncommon for COVID-19 patients to present first with fever and respiratory symptoms, and then developed hyponatraemia more than one week after symptom onset. If such patients were not admitted to hospital until, say 10 to 14 days after symptom onset (or sometimes after recovery), with abnormal sodium concentration, were they included in the study cohort?
> As stated in Section 3.3, a longer duration of complaints (more than 14 days) was associated with a slightly lower sodium level. To provide more insight in the duration of complaints, we did a similar analysis and rewrote the sentence to “Furthermore, patients with hyponatremia had a slightly longer duration of complaints compared to those with normonatremia (8.8 days for hyponatremia vs. 8.6 days for; p = 0.010; assessed using a Kruskal-Wallis test), although this difference was not clinically relevant.” Patient inclusion in the study was irrespective of the reason for admission, so patients who presented with hyponatremia as sole presenting symptom and SARS-CoV-2 PCR positive were included.

8) Were there many patients declined ICU admission? For instance, asthmatic patients with severe exacerbation are more often accepted for ICU because of the reversibility of the condition whereas severe chronic obstructive airway disease patients would be less readily admitted (even if they had more severe respiratory failure). This is similar to the condition of hyponatraemia (more “comfortably” admitted to ICU) and hypernatraemia (worse prognosis, and less likely to be admitted even if there were high mortality).
> Thank you for bringing to our attention the lack of sufficient detail in describing the characteristics of patients with the order ‘do not intubate’. We included a table to the supplemental information (Supplemental Table 2) that provides clarification on the comorbidities of patients that got the ‘do not

intubate' order. Based on these characteristics, we suggest that patients were declined ICU admission based on frailty or limited life expectancy.

9) The correlation of hyponatraemia with pulmonary aspergillosis was mentioned on page 17. This complication appeared to be more common in Europe than in North America. Causal relationship is considered less likely for hyponatraemia (to drive the higher incidence of aspergillosis). Could this be related to the high ICU admission rate for the hyponatraemia patients?
If there is environment factors (proposed reasons including negative pressure environment in ICU and contaminated respiratory equipment), we should reported if the aspergillosis patients occurred more often after ICU admission in the cohort. What about the percentage of dexamethasone and tocilizumab use in the aspergillosis cases?
> Indeed, the occurrence of aspergillosis pneumonia was found to be associated with the use of dexamethasone, tocilizumab/sarilumab/anakinra, and the administration of antibiotics. The following text was added to Section 3.5: After adjusting for sex assigned at birth, age, and a history of chronic kidney disease and hypertension, the course of disease of patients with hyponatremia was more often complicated by an aspergillosis pneumonia (almost exclusively in patients that needed invasive ventilation and more frequently in patients treated with dexamethasone, antibiotics, tocilizumab, sarilumab, or anakinra)

Minor comments include:

1) The English is not very standard. The sentence "Especially elevated LDH concentration and lymphocytopenia are common…" is an example; we seldom start a sentence like this. We usually use word "lymphopenia" and not "lymphocytopenia." Words like "readmittance" (page 14) should have been changed to more conventional English (re-admission).
> Thank you for bringing this to our attention. We have carefully reviewed the manuscript and made revisions to enhance readability by adjusting the sentence structure and word choice.

2) There was another typo on page 16. "Conformed" should have been spelt as "confirmed."
> Thank you, the mistake was corrected.

3) The legend of Table 2 has a typo: "sSOFA" should have been "qSOFA".
> Thank you, the mistake was corrected.

4) Detailed description of the clinical features including capillary refill was available (although we are not certain how systemically the findings were documented in a retrospective study).
> The definition of prolonged / disturbed capillary refill was modified to capillary refill □3 according to the instructions provided to the data administrators.

5) Complication and outcome measures were described on page 13. New entity known as "physical decline" appeared in Table 3. How is this defined? Was that a pre-defined outcome in the database?
> Details on physical decline were provided in Section 3.5 according to the instructions data administrators received. However, we realize that the definition of physical decline may differ between clinicians.

6) There was discussion on different waves of COVID-19 with time on page 22. Please state if the current cohort was derived from the period when Omicron variant predominated.

> Thank you for pointing out that we did not mention the prevalence of SARS-CoV-2 variants among our patient population. Therefore, we added the following text to section 3.1: A total of 6183 patients (79.2%) started having symptoms prior to the seventh week of 2021, when the initial SARS-CoV-2

variants were most prevalent. 747 patients (9.6%) developed symptoms from the seventh to twenty-fifth week of 2021, when alpha-variants dominated in the Netherlands. 686 patients (8.8%) started having symptoms when delta variants dominated (twenty-sixth to fifty-first week of 2021), and 118 patients (1.5%) when the omicron variants dominated (after the fifty-second week of 2021)17. On page 23 of the discussion, we added the following text:
We observed significant variations in mortality, ICU-admission, and intubation rates in the normo- and hyponatremia groups differed significantly between patients that were included during the initial wave in the spring of 2020 (when original SARS-CoV-2 variants dominated) and those included in subsequent COVID-19 waves (with alpha, delta, and omicron variants dominating in the last quartile of patients included).

Reviewer: 2
Dr. Ploutarchos Tzoulis, Whittington Hospital- UCL

Comments to the Author:

In general, this is a well-designed and well-conducted study with solid methodology. It evaluates the prognostic impact of dynatremias on patients with COVID-19 which has been already thoroughly studied. However, it is interesting and intriguing that the current study addresses this issue on COVID-19 after the initial phase; this is essential since the natural history and burden of COVID-19 has drastically altered as the time progresses.
Thank you for your careful review of our manuscript and useful feedback. Please find below our reply to each of them.

Regarding to hyponatremia, my comments are:

1. There is no information about the recent sodium levels prior to admission. This is potentially important since a proportion of individuals have pre-existing chronic hyponatremia.
> Indeed, it would be possible that a proportion of individuals may have had pre-existing chronic hyponatremia. Unfortunately, we did not have this information available in our database. Also, our study aimed to predict the clinical outcomes of COVID-19 patients presenting with dysnatremia, by means of allowing clinicians to make a better estimation of the disease severity of the patients. Although one would expect that these outcomes differ between patients with pre-existing chronic hyponatremia and patients with acute hyponatremia, sodium levels might in practice also not be available to the clinician. Thus, although sodium levels prior to admission would be of interest, this would be beyond the scope of or study.

2. The study does not look into sodium levels during hospitalization. If there are data, this would be a valuable addition.
> We agree that it would be very interesting to include the trend of sodium level with time. However, and as stated above in our answer to the first reviewer of our manuscript, sodium levels during admission were only recorded in the database for the first patients registered (first wave). As the pandemic progressed, we realized that we did not have the capacity to register all daily lab tests in the database for all patients and we limited the input to lab tests at admission. Additionally, the registration of lab tests during admission varies among the participating centers, introducing the risk of selection bias. Therefore, we made the decision not to include this analysis in order to avoid this potential bias.

3. With respect to the etiology of hyponatremia, the authors need to clarify the relationship between different types of hyponatremia and patients's prognosis.

> Thank you for your valuable suggestion. We have included Figure 1D, which displays a cox proportional hazard curve with separate lines for each proposed etiology. Additionally, in Section 3.4, we have provided a description of the relationship between the various causes of hyponatremia and other outcome measures including ICU admission, intubation, duration of ICU admission, and duration of hospital admission.

4. Similarly, the link of serum sodium and CRP (and the severity of infection / inflammatory reaction) should be examined as per type of hyponatremia, such as hypo- / eu- / hyper-volemic hyponatremia. Hyponatremia is an umbrella term and SIADH may have different impact compared to hypovolemic hyponatremia.
> In addition to your former comment, we discussed LDH and CRP levels in relation to the cause of hyponatremia in Section 3.7. Additionally, we incorporated a paragraph in the discussion that elucidates the relationship between CRP and LDH levels, outcomes, and etiology: “The association between ICU admission and hyponatremia was most pronounced in patients with a hyponatremia of unknown etiology. However, it is important to consider that this group may include cases of mild presentations of SIADH due to the limited number of urinary samples available. These findings align with the higher CRP and LDH levels observed in this group. Patients that had a history of gastro-intestinal symptoms had a lower risk of ICU admission, despite having higher levels of CRP and LDH levels. The higher CRP and LDH levels in this group could not be related to the SARS-CoV-2 variants, as the highest CRP levels were observed in patients that developed symptoms during a period in which the delta variant dominated. Notably, this group also had the lowest prevalence of gastro-intestinal symptoms (data not shown). “

There are similar questions / additional data needed with respect to hypernatremia.
> Although we agree that it would be very important to investigate the etiology of hypernatremia, the group of patients that presented with hypernatremia was too small to draw any conclusions on underlying causes and potential relationship to outcomes.

Finally, questions about the surprising lack of relationship between hyponatremia and mortality in contrast to the general literature for hyponatremia should be addressed more completely. In addition, the authors should highlight the potentially different impact of various types of hyponatremia on prognosis.
> Although we realize that our results are in contrast with previous literature, we feel that we addressed the differences between our study and previous studies in sufficient detail. We suggest that there are two main reasons for the differences in outcomes. First, we suggest that our outcomes differ from previous studies because earlier studies only included patients from the first covid waves. As we demonstrated in Figure 2, outcomes improved during later covid waves, and our study reported lower absolute mortality rates than large previous studies (Hirsch et al. reported absolute mortality rates of 23.6-28.9% for hyponatremia and 22.6% for normonatremia, Liu et al. reported an overall mortality of 23%). As overall mortality in our study was 16.7%, we suggest that the lower overall incidence of adverse outcomes led to a lower association between hyponatremia and COVID-19. Second, we hypothesize that our results differ from previous studies because we investigated the relationship between sodium levels corrected for glucose. Hirsch et al. demonstrated that the association between mortality and hyponatremia was only evident prior to correction for glucose, and this association disappeared after correction for glucose. These factors combined could have led to the outcomes of our study that suggest that corrected hyponatremia is associated with a higher risk for ICU admission and uncorrected hyponatremia is associated with a higher risk for ICU admission and intubation, but (un)corrected hyponatremia is not associated with mortality.
We noted that the study by Chan et al (including patients from January 2020 to March 2022) reported a 30-day mortality rate as low as 8.1%, but in line with a different COVID policy in Hong Kong, hospital admission criteria could have differed suggesting that also non-critically ill patients were admitted to the hospital that in other countries might have been left in outpatient care18.

As addressed under comment 3, we incorporated your much appreciated suggestion of outcomes in relationships to the different types of hyponatremia in Section 3.4.

Finally, any data correction / or not of dysnatremia and its effect on clinical outcomes would be more than welcome.
> We acknowledge the limitation in our study regarding the lack of daily registration of sodium levels during the admission period. Unfortunately, we lack data on the specific treatment modalities employed for dysnatremia or the rate at which dysnatremia was corrected. Nonetheless, all participating hospitals followed national protocols for the correction of dysnatremia. The typical approach for hypernatremia involved oral administration of water or intravenous administration of 5% glucose. As for hyponatremia, the treatment varied depending on the presumed underlying cause. Patients with hypovolemic hyponatremia received slow infusion of 0.9% (isotonic) sodium (mostly at a rate of 1-2L/24 hours) depending on the severity of dehydration. Those with supposed syndrome of inappropriate antiduretic hormone secretion (SIADH) were advised to restrict fluid intake. Only individuals with severe symptomatic hyponatremia were administered 3% (hypertonic) saline. However, due to the lack of individual treatment documentation in the database, we were unable to establish a relationship between dysnatremia correction and outcomes.

I would also urge the authors to incorporate in their discussion the findings from the initial COVID-19 period and the impact of dysnatremia (summarised in a review in Eur Journal of Endocrinology by Tzoulis et al in 2021).
> Thank you for your feedback on our discussion. We incorporated several newer studies on hyponatremia including those cited by Tzoulis, et al. 19.

In total, this is a very interesting topic and the authors have access to a large database. I would urge them to supplement their data with more information about type of hyponatremia and progress of dysnatremia during the course of illness. Provided the results and discussion sections will be modified appropriately, this manuscript would be a valuable addition to the literature in this field.

VERSION 2 – REVIEW

REVIEWER	Chow Kai Ming The Chinese University of Hong Kong, Prince of Wales Hospital
REVIEW RETURNED	20-Jul-2023

GENERAL COMMENTS	This is a resubmission of an article on the prevalence and prognostic significance of dysnatraemia, based on a database known as multicenter COVIDPredict Clinical Course Cohort, covering over 6500 patients with COVID-19 (between February 2020 and August 2022) in nine Dutch hospitals. As mentioned in the previous review, this is not the largest study on dysnatremia as claimed in the first version. New literature search was performed by the authors. There were lack of information on the trajectory of sodium level with time. Urinary sodium and osmolality results were available in less than 10% of patients with hyponatraemia. The major comments are: 1) Despite a similar length of stay among different groups, we still cannot exclude the distinct possibility that hyponatraemia patients have higher odds of intensive care unit admission simply because of the reversible nature of this electrolyte disorder (and hence low threshold for intensive care unit to admit such patients despite the

	relatively low qSOFA score). As mentioned, there is dogmatic teaching that patients with severe hyponatraemia should be admitted to intensive care unit for close monitoring. 2) According to the study design, diagnosis of hyponatraemia group is defined by the serum sodium level at admission at the participating hospital (as stated on page 11). What is the duration of symptom before presentation to the hospital for the hyponatraemia group? It is not uncommon for COVID-19 patients to present first with fever and respiratory symptoms, and then developed hyponatraemia more than one week after symptom onset. If such patients were not admitted to hospital until, say 10 to 14 days after symptom onset (or sometimes after recovery), with abnormal sodium concentration, were they included in the study cohort? 3) I asked about patients being declined ICU admission. You gave the information of patients who were ordered “do not intubate.” The two categories are, strictly speaking, not interchangeable. Supplementary information was provided in Supplemental Table 5 (and not 2). Were there result of sodium level (or hyponatremia and hypernatremia) in the two groups of patients? If so, please state in that Supplemental Table 5. Minor comments include: 1) The sentence “8.8 days for hyponatremia vs. 8.6 days for; p = 0.010” on page 11 was incomplete.

REVIEWER	Ploutarchos Tzoulis Whittington Hospital- UCL, Experimental & Translational Medicine
REVIEW RETURNED	09-Aug-2023

GENERAL COMMENTS	In total, a very well designed, undertaken, written paper. This is a very topical subject. The methods as well as the discussion are clear and I complement the authors. The main comments are: 1. I think that an attempt to divide this 2.5 year time period to different periods according to the dominant variants in the community would be extremely useful. This would allow us to compare prevalence and aetiology of hyponatraemia for different variants. 2. A weakness is the small percentage of patients with full biochemical work-up. I do think that the authors should explain in more depth the percentage of SIADH and possible explanation for the low prevalence of SIADH. 3. finally, mortality and ICU and their link to hyponatraemia are worht being explored and compared for different variants too.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Dr. Chow Kai Ming, The Chinese University of Hong Kong Comments to the Author:

This is a resubmission of an article on the prevalence and prognostic significance of dysnatraemia, based on a database known as multicenter COVIDPredict Clinical Course Cohort, covering over 6500 patients with COVID-19 (between February 2020 and August 2022) in nine Dutch hospitals.

As mentioned in the previous review, this is not the largest study on dysnatremia as claimed in the first version. New literature search was performed by the authors.

There were lack of information on the trajectory of sodium level with time. Urinary sodium and osmolality results were available in less than 10% of patients with hyponatraemia.

Thank you again for your thorough revision of our revised manuscript and your useful feedback. Please find below a reply to each of your comments.

The major comments are:

1) Despite a similar length of stay among different groups, we still cannot exclude the distinct possibility that hyponatraemia patients have higher odds of intensive care unit admission simply because of the reversible nature of this electrolyte disorder (and hence low threshold for intensive care unit to admit such patients despite the relatively low qSOFA score). As mentioned, there is dogmatic teaching that patients with severe hyponatraemia should be admitted to intensive care unit for close monitoring.

Thank you for bringing up this consideration. In the Netherlands, ICU admission criteria during the covid pandemic were very strict due to limited capacity. Hyponatremia in the absence of other parameters of disease severity, and in the serum levels as described in this study, was not a reason for ICU admission. If necessary, these patients were admitted to an MCU. Still, a small percentage of patients was admitted to the ICU without needing ventilatory support (high flow nasal therapy or (non)-invasive ventilation), but these percentages were similar among patients with and without hyponatremia. The following sentences were therefore added to the manuscript.

Section 3.4:

Of all hyponatremic patients who were admitted to the ICU (N = 486), 62 (12.8%) did not receive any form of ventilatory support ((non-)invasive ventilation or high flow nasal therapy). This percentage was similar (10.5 %; p = 0.403) among patients with normonatremia admitted to the ICU.

Discussion:

Moreover, 13% of all patients admitted to the ICU did not receive any form of ventilatory support, suggesting that there were reasons other than respiratory failure for ICU admission. In Dutch protocols, hyponatremia is rarely a reason for ICU admittance, and the fact that the percentage of patients without ventilator support was similar among patients with and without normonatremia suggests that hyponatremia was not a frequent reason for ICU admission.

To get more insight in the sodium levels of the patients included, mean and IQR sodium levels for each group were included in Table 1 and Supplemental Table 1.

2) According to the study design, diagnosis of hyponatraemia group is defined by the serum sodium level at admission at the participating hospital (as stated on page 11). What is the duration of symptom before presentation to the hospital for the hyponatraemia group? It is not uncommon for COVID-19 patients to present first with fever and respiratory symptoms, and then developed hyponatraemia more than one week after symptom onset. If such patients were not admitted to hospital until, say 10 to 14 days after symptom onset (or sometimes after recovery), with abnormal sodium concentration, were they included in the study cohort?

Thank you again for bringing this to our attention. As was stated in our previous response, patients that presented with hyponatremia as sole presenting symptom and positive SARS-CoV-2 PCR were still included, irrespective of the duration of symptoms. The duration of complaints at presentation is mentioned in section 3.3: Furthermore, patients with hyponatremia had a slightly longer duration of complaints compared to those with normonatremia (8.8 days for hyponatremia vs. 8.6 days for; p = 0.010; assessed using a Kruskal-Wallis test), although this difference was not clinically relevant."

3) I asked about patients being declined ICU admission. You gave the information of patients who were ordered "do not intubate." The two categories are, strictly speaking, not interchangeable. Supplementary information was provided in Supplemental Table 5 (and not 2). Were there result of sodium level (or hyponatremia and hypernatremia) in the two groups of patients? If so, please state in that Supplemental Table 5.

We agree that the order 'do not intubate' and patients being declined ICU admission are not fully interchangeable. Unfortunately, data on patients that were declined ICU admission irrespective of the order do not intubate were not available in our cohort.

However, most patients with the order 'do not intubate' had an extended treatment limitation ('no resuscitation, no intubation, no IC-admittance') and were therefore not admitted to the ICU. Also, ICU capacity was very limited and practically only patients with the need for ventilation were admitted to the ICU in this period. Almost all patients on the ICU were therefore also intubated patients (as added to Supplemental Table 5). Sodium levels did differ significantly between patients with and without the order do not intubate, but this difference was not clinically relevant.

Minor comments include:

1) The sentence "8.8 days for hyponatremia vs. 8.6 days for; p = 0.010" on page 11 was incomplete.

Thank you for pointing this out, the mistake was corrected.

Reviewer: 2

Dr. Ploutarchos Tzoulis, Whittington Hospital- UCL

Comments to the Author:

In total, a very well designed, undertaken, written paper.

This is a very topical subject. The methods as well as the discussion are clear and I complement the authors.

Thank you for your compliments and careful revision of our revised manuscript. Please find below our response.

The main comments are:1. I think that an attempt to divide this 2.5 year time period to different periods according to the dominant variants in the community would be extremely useful. This would allow us to compare prevalence and aetiology of hyponatraemia for different variants.

Thank you for this useful suggestion. We classified the patients based on the SARS-CoV-2 variant that dominated when the patient started having complaints. We added Supplemental Table 7 that shows the patient characteristics of for each SARS-CoV-2 variant.

2. A weakness is the small percentage of patients with full biochemical work-up. I do think that the authors should explain in more depth the percentage of SIADH and possible explanation for the low prevalence of SIADH.

We agree that due to the limited availability of urinary samples limits our study in that we could not draw definite conclusions on the etiology of hyponatremia. We added three sentences to the discussion to further explain the low prevalence of SIADH.

We suggest that the prevalence of SIADH in our study group was very low for two reasons. Firstly, we included patients during later COVID-19 waves (when alpha, delta, and omicron variants dominated), whereas patients with hyponatremia due to SIADH that was severe enough to perform urinary analysis presented mostly during the period where initial variants dominated. This could have resulted in a lower prevalence that studies that only included patients during the first COVID-19 wave. Secondly, SIADH can only be diagnosed based on urinary sodium excretion and urinary osmolarity, but only a limited number of urinary samples was available, so we were not able to provide a precise estimate.

3. finally, mortality and ICU and their link to hyponatraemia are worth being explored and compared for different variants too.

Thank you for this valuable suggestion. We reclassified the patients in Figure 2 based on the SARS-CoV-2 variant that dominated at the time when the patient started having complaints. Unexpectedly, ICU admission was higher for patients with hypo- or normonatremia that presented during the delta-wave. As our overall mortality was still lower than in other studies, we still suggest that the lower overall mortality could have resulted in better outcomes for hyponatremic patients as compared to earlier studies.

VERSION 3 – REVIEW

REVIEWER	Chow Kai Ming The Chinese University of Hong Kong, Prince of Wales Hospital
REVIEW RETURNED	10-Sep-2023

GENERAL COMMENTS	Thank you for the efforts to revise and improve the manuscript.

REVIEWER	Ploutarchos Tzoulis Whittington Hospital- UCL, Experimental & Translational Medicine
REVIEW RETURNED	15-Sep-2023

GENERAL COMMENTS	Thank you for replying to all the comments in an appropriate manner, clarifying any questions.