PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Aspiration risk in relation to Glasgow Coma Scale score and clinical parameters in patients with severe acute alcohol intoxication: a single-centre, retrospective study
AUTHORS	Conzelmann, Michael; Hoidis, Anne; Bruckner, Thomas; Popp, Erik; Koschny, Ronald

VERSION 1 – REVIEW

REVIEWER	Sinclair, Julia University of Southampton
REVIEW RETURNED	06-Jul-2021

GENERAL COMMENTS	Glasgow Coma Scale predicts aspiration risk in acute alcohol intoxication. Summary This is a retrospective clinical note survey over a 14 year period of patients admitted to ITU in a single centre with alcohol intoxication. Patients were excluded if they there was evidence or a positive urine test for other psychotropic drug use which might lower GCS, but this test was 'not performed on a regular basis' Abstract: States that the GCS has not been validated for non-traumatic intoxicated patients. But that the aim of the study is to analyse the aspiration risk in relation to GCS. It needs to be clearly stated if this was an a -priori hypothesis or whether it was the focus of the paper as the positive finding having found no correlation between alcohol level and GCS. Primary and Secondary outcome measures: - This is not stated only the variables measured Aspiration rate was much higher in patients without preserved reflexes but only with a PPV of 15% for a GCS of 3 (this is based on very incomplete data that could not be included in the multi-variate analysis, and should be highlighted as such). There are several fundamental flaws with this paper: 1. It is uncertain if the title and main positive finding 'GCS predicts aspiration risk in acute alcohol intoxication' is an a-priori research question or not. This needs to be clearly stated, and the analysis plan build around it. 2. Primary and secondary outcome measures are similarly not stated. 3. The results are presented (see table 1) based on the number of admissions (N=411) rather than the number of patients (N=327),

	some of whom were admitted on 2-5 occasions and so are not independent of each other. Results based on 327 individuals would be more robust (the person requiring admission to ITU on 5 occasions for alcohol poisoning is contributing x5 to this data set). 4. The authors have put a lot of thought into the fluctuations of the GCS (which were measured twice) but have not been able to link this with changing levels of alcohol in the blood, which were only measured once. In some patients blood alcohol will have continued to rise on admission, in others it will be falling. This information was not available but the impact needs to be discussed. 5. There is no information on diagnosis of alcohol dependence which will have a significant impact on the association (or otherwise) between blood alcohol level and GCS. Tolerance to alcohol is part of the diagnostic criteria for alcohol dependence, and has a significant impact on all of the results discussed, but is not mentioned- or acknowledged that this is a significant limitation of the study. Other concerns 1. The figures add little to the text results and the authors need to think through the value or otherwise of each of them 2. The main finding about protective reflexes (referred to in the abstract as a main conclusion) seems to be based on only 74/152 patients with a GCS >8 who had this data available 3. The discussion talks beyond the data e.g at the end of the 1st paragraph in the discussion the authors state “Figures 2a and C impressively illustrate the clinical relevance of acute alcohol intoxication as an important differential diagnosis in unconscious elderly patients” As the data on which those figures are based are taken from patients diagnosed with alcohol intoxication this is untrue. In its present state, sadly I do not believe this is a significant addition to the literature. With the data that has been collected it would be more useful to focus on what cannot be used as valid indicators in this vulnerable patient group

REVIEWER	Minville, Vincent Département d'Anesthésie et de Réanimation, Centre Hospitalier et Universitaire de Toulouse
REVIEW RETURNED	13-Jul-2021

GENERAL COMMENTS	In this manuscript, “Glasgow Coma Scale predicts aspiration risk in acute alcohol intoxication” the authors assessed to analyze the aspiration risk in relation to the GCS and clinical parameters in patients with severe acute alcohol monointoxication. They concluded Although the aspiration rate in alcohol monointoxicated patients correlates with GCS and protective reflexes, the decision for endotracheal intubation should be based on the presence of different risk factors for aspiration. This is an exciting paper. This article is well written and clear. However, I have several comments about this manuscript. MAJOR COMMENTS/CONCERNS: 1. “…to the intensive and intermediate care unit of the Department of Gastroenterology at the…” What kind of structure is it? 2. Table 1 the “)” percent “crochet… 3. Too many tables and figures.

	4. Too many results. Results should be ordered. What was the aim of the study? 5. Comparison between males and females? 6. Comparison of first and second GCS is unclear. What was the purpose of this result? 7. Multivariate analysis: 5 items for 21 patients? This is too much. What is the goodness of fit of the model? Results should be checked by a statistician.

REVIEWER	Tadros, Allison West Virginia University
REVIEW RETURNED	21-Jul-2021

GENERAL COMMENTS	One concern is that aspiration pneumonia could have developed after the patient was released from the hospital, as patients admitted for the sole purpose of intoxication usually have short hospital stays. This could be addressed in the limitations. It was unclear to the reviewer what the black line represents in Figure 2B. Figure 2C does not add much to the study. Figure 6 is confusing.

REVIEWER	Patton, R University of Surrey, School of Psychology
REVIEW RETURNED	22-Jul-2021

GENERAL COMMENTS	Thank you for submitting this interesting ppaer. Introduction - can you include additional detail on rates of intubation for non-alcohol intoxicated patients. It would also be helpful (for non medics) to understand the risks associated with the intubation process. It is unfortunate that the authors were unable to include any patient / public involvement in their study - perhaps tghis could be reflected upon in the discussion. Some further detail on rates of aspiration in the general patient population would help add context to the data presented.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Julia Sinclair, University of Southampton
Abstract: States that the GCS has not been validated for non-traumatic intoxicated patients. But that the aim of the study is to analyse the aspiration risk in relation to GCS. It needs to be clearly stated if this was an a -priori hypothesis or whether it was the focus of the paper as the positive finding having found no correlation between alcohol level and GCS. Primary and Secondary outcome measures: - This is not stated only the variables measured

We were searching for parameters which are associated with a higher risk for aspiration. Many studies on this issue investigated a very heterogeneous cohort of mixed intoxication (where respiratory depression might be the leading cause for endotracheal intubation) or in alcoholised trauma patients (where the risk of aspiration might be more influenced by the brain injury). Our study primarily aimed at identifying risk factors for aspiration in alcohol monointoxicated, non-traumatic

patients. We could identify a correlation between the impaired GCS score and the risk of aspiration. The correlation between the blood alcohol level and the GCS score in intoxicated patients is also highly debated. Therefore, as a secondary aim, we evaluated a possible association between the blood alcohol level and the GCS score.
According to the reviewer's suggestion, we more clearly pointed out the primary aim (search for risk factors for aspiration) and secondary aim (association between blood alcohol level and GCS score) of our study.

Aspiration rate was much higher in patients without preserved reflexes but only with a PPV of 15% for a GCS of 3 (this is based on very incomplete data that could not be included in the multi-variate analysis, and should be highlighted as such).

As correctly stated by the reviewer, the influence of protective airway reflexes on the aspiration risk was not included in the multivariate analysis. As discussed in the manuscript, this is because information on protective airway reflexes were available in only 50% of patients and due to the limited number of patients – which is, nevertheless, the so far biggest cohort of alcohol monointoxicated patients published so far on this issue. Data on the protective airway reflexes were nearly exclusively reported by the emergency team in case of a significantly reduced GCS score and no information were provided for patients with a GCS score of >8. This makes sense from a clinical point of view, as no emergency doctor investigated the gag reflex in a drowsy patient with an only slightly reduced GCS score.
However, this should not be mixed up with the calculation of the PPV for aspiration at a reduced GCS score. Even in case of a complete unconscious patient (GCS score=3), the PPV for aspiration was only 15%. Thus, although we detected a significant correlation between a reduced GCS score and the aspiration risk in a multivariate regression model, the clinical prediction for aspiration is rather weak. Since information on protective airway reflexes were limited (see above), the PPV was calculated for as GSC score of 3, irrespective of the presence or absence of protective airway reflexes. In order to more clearly distinguish these two parameters (namely the GCS score and protective airway reflexes) we added a more detailed explanation in the respective Result section. In the Discussion, the value of the GCS score as a single parameter for intubation was already critically discussed.

1. It is uncertain if the title and main positive finding 'GCS predicts aspiration risk in acute alcohol intoxication' is an a-priori research question or not. This needs to be clearly stated, and the analysis plan build around it.

As we changed the title of the manuscript according to the editor´s suggestion, it becomes now clear that this is the primary finding of our study. As stated above, the secondary aim of the study was better demarcated from the primary aim according to the reviewer´s suggestion.

2. Primary and secondary outcome measures are similarly not stated.

This has been addressed in the revised manuscript as stated above.

3. The results are presented (see table 1) based on the number of admissions (N=411) rather than the number of patients (N=327), some of whom were admitted on 2-5 occasions and so are not independent of each other. Results based on 327 individuals would be more robust (the person requiring admission to ITU on 5 occasions for alcohol poisoning is contributing x5 to this data set).

According to the criticism by the reviewer, we discussed this point as another limitation in the section “Strengths and limitations of this study”. However, since most of the repeated admission of identical patients occurred years after the first admission, one might consider them as independent events. Furthermore, only 51 of 411 admissions were due to repeated intoxications (We corrected the number of different patients in table 1, which is n=360. n=327 was the number of patients with only a single admission). We had rethought this issue before submitting the manuscript but could not imagine any relevant bias due to a repeated admission of a minority of identical patients. Each event of intoxication has a new risk of aspiration. It is true, that patients with chronic alcohol abuse might get used to the effects of alcohol. However, we could not find any hint in the literature that there is a habituation to the aspiration risk. Furthermore, we did not find any hint that there is a low or high aspiration risk phenotype of patients, which could influence the frequency of aspiration events in our study population.

However, to rule out any bias of our results by repeated admissions of the same patients, we recalculated our statistics for the first admission only of unique patients (Table 1-3).

We found nearly identical epidemiological data for this subset of n=360 patients (see modified Table 1 in attached file).

Recalculating the univariate analysis of continuous risk factors for aspiration for first admissions only (Table 2), we found identical correlations for the aspiration risk, which were significant for age, blood alcohol level, initial GCS score, SpO2, systolic blood pressure, respiratory rate, and blood glucose level, although the absolute values did slightly differ (see modified Table 2 in attached file).
When recalculating the univariate analysis of binary risk factors for aspiration for first admissions only (Table 3), we also found identical correlations for the aspiration risk, except for gender and the event of vomiting which lost their significance due to the reduced number of events in this subpopulation (see modified Table 3 in attached file).
However, the odds ratio estimates in multivariate analysis of risk factors for aspiration (Table 4) in the subpopulation of first admissions showed identical results compared to the general cohort with a significant correlation for age and GCS score (see modified Table 4 in attached file).

4. The authors have put a lot of thought into the fluctuations of the GCS (which were measured twice) but have not been able to link this with changing levels of alcohol in the blood, which were only measured once. In some patients blood alcohol will have continued to rise on admission, in others it will be falling. This information was not available but the impact needs to be discussed.

To our knowledge, there is no precise and fast preclinical blood alcohol test available for paramedics and emergency doctors. Breath tests for alcohol depend on the patient´s cooperation, require 30min of alcohol abstinence and are, therefore, not applicable in comatose patients. Therefore, the only available blood alcohol level in the clinical routine is the one measured with validated analytic methods in the clinic.
Alcohol is rapidly absorbed by the stomach and small intestine and peak blood alcohol levels were measured as early as 30 minutes after oral ingestion which could be prolongated by delayed gastric emptying to 60 min (Oneta, Simanowski, et al. 1998). Thus, in case of an alcohol-related emergency, the expected peak blood alcohol level would roughly coincide with the arrival of the emergency team some 30 minutes later. Therefore, we hypothesise that only in a few patients the blood alcohol level would increase after medical treatment has started. This was reflected by our observation, that in very few cases (39 out of 336, 11,6%) the GCS score decreased from the first to the second evaluation, whereas in 297 of 336 cases (88,4%) the GCS score did not change or even improved. Furthermore, we do not expect a relevant metabolism of alcohol during the 30-60 minutes duration of prehospital treatment, which can be estimated as 0.15-0.20 g/l (Winek and Esposito 1985). From our point of

view, this has no significant impact on our results showing a mean alcohol level of 2.7 g/l.
According to the reviewer´s suggestion we discussed the fact that we cannot provide data on the blood alcohol level kinetics in the prehospital setting.

5. There is no information on diagnosis of alcohol dependence which will have a significant impact on the association (or otherwise) between blood alcohol level and GCS. Tolerance to alcohol is part of the diagnostic criteria for alcohol dependence, and has a significant impact on all of the results discussed, but is not mentioned- or acknowledged that this is a significant limitation of the study.

We agree with the reviewer, that chronic alcohol abuse might confer some kind of tolerance to the side effects of alcohol. In these patients, the blood alcohol level might not correlate with the level of consciousness. However, as we stated in the Discussion, there was even no correlation between the blood alcohol level and the GCS in the youngest subgroup of our cohort, which might not have undergone habituation to alcohol so far.
Furthermore, we do not have reliable data on the drinking habits of the patients in our study, since this information is not routinely available to the emergency team. Thus, their decisions for or against invasive measures, e.g. endotracheal intubation, is solely based on their clinical assessment, e.g. on GCS score.
We could not find any hint in the literature that there is a lower or higher aspiration risk in patients with alcohol dependence. As correctly stated by the reviewer, tolerance has an impact on individual alcohol levels (which might be reflected by our finding of higher alcohol levels in older patients). We did, however, not find any data suggesting that alcohol tolerance lowers the risk for aspiration. We disagree with the reviewer, that the lack of data on alcohol tolerance of patients in our study mitigates the clinical relevance of our findings.

Other concerns
1. The figures add little to the text results and the authors need to think through the value or otherwise of each of them

According to the reviewer´s suggestion and in agreement with reviewer 2, we tremendously reduced the number of figures by removing Figure 2A, Figure 2B, Figure 5A, Figure 5B, and Figure 6.

2. The main finding about protective reflexes (referred to in the abstract as a main conclusion) seems to be based on only 74/152 patients with a GCS >8 who had this data available

Data on the protective reflexes were only available in patients with a GCS score ≤8. As discussed above, protective reflexes will not be analysed and documented in patients with only marginally impaired level of consciousness. We agree that our data on protective reflexes are very limited and discussed this in the section „Strengths and limitations of this study". Nevertheless, we provide the so far biggest set of data on this matter.

3. The discussion talks beyond the data e.g at the end of the 1st paragraph in the discussion the authors state "Figures 2a and C impressively illustrate the clinical relevance of acute alcohol intoxication as an important differential diagnosis in unconscious elderly patients" As the data on which those figures are based are taken from patients diagnosed with alcohol intoxication this is untrue.

We agree with the reviewer that due to missing data on competing reasons for impaired consciousness in elderly patients, we cannot state that alcohol intoxication is a frequent differential diagnosis. We only wanted to point out that alcohol intoxication might be a differential diagnosis in these patients, too. According to the suggestion of several reviewers we reduced the number of

figures, including Figure 1A, thereby eliminating the criticised statement.

Reviewer: 2
Prof. Vincent Minville, Département d'Anesthésie et de Réanimation, Centre Hospitalier et Universitaire de Toulouse:
This is an exciting paper. This article is well written and clear. However, I have several comments about this manuscript.

1. "…to the intensive and intermediate care unit of the Department of Gastroenterology at the…" What kind of structure is it?

In our hospital critically intoxicated patients requiring „only" constant monitoring and circulatory support are admitted to the intermediate care unit. Patients requiring endotracheal intubation and ventilation are admitted to the intensive care unit. Both units enable permanent monitoring and intensive care for critically ill patients, which cannot be provided at the emergency department. After the initial medical treatment, the doctor at the emergency department of our hospital decides if the patient can be further handled there or needs to be transferred to the intensive care unit.

Since this subtle graduation of intensive care might not be familiar to every reader and might thus be confusing, we – for the sake of convenience - summarised both units as „the intensive care unit of the Department of Gastroenterology".

2. Table 1 the ")" percent "crochet…

We removed the superfluous „]" from Table 1.

3. Too many tables and figures.

We agree that the baseline characteristics in Table 1 could also be summarised in the text. At the editor's discretion we could convert Table 1 to text (although this might take more space).
According to the reviewer´s suggestion we considerably reduced the number of figures by removing Figure 2A, Figure 2B, Figure 5A, Figure 5B and Figure 6.

4. Too many results. Results should be ordered. What was the aim of the study?

According to the reviewer´s suggestion we shortened the figures and presented data. In accordance to the suggestions of reviewer 1 and 2, we more clearly defined the primary and secondary aims of the study.

5. Comparison between males and females?

We performed comparisons between male and female patients regarding data on epidemiology, blood alcohol level and GCS score. The aspiration rate was too low to allow a separate analysis for male and female patients.

6. Comparison of first and second GCS is unclear. What was the purpose of this result?

The GCS score describes a snapshot of the patient´s vigilance which is subject to rapid changes in alcoholised patients. Therefore, we analysed if the GCS score at arrival of the emergency team and at

admission of the patient to the hospital approximately 30 min later is representative for a „mean“ aspiration risk. We, therefore, compared the first and second GCS score. As shown in Figure 3, most GCS scores are identical at both time points. However, some patients show a significant and impressive improvement of their GCS score during the pre-hospital treatment. Therefore, we consider it of paramount importance to standardise the timepoint of GCS score registration in order not to impair the quality of data acquisition regarding aspiration risk and GCS score.

7. Multivariate analysis: 5 items for 21 patients? This is too much. What is the goodness of fit of the model? Results should be checked by a statistician.

As a statistician, TB performed the statistical analysis, provided the statistical results and double-checked the manuscript for statistical correctness. The reviewer is completely right, that the aspiration events were rather rare. Therefore, we restricted the multivariate logistic regression analysis to only 5 parameters which seem to be most prone to interdependence (Table 5). And as only gender is categorical, the risk for convergence problems (complete separation of the data) seems to be low.

Reviewer: 3
Dr. Allison Tadros, West Virginia University:
One concern is that aspiration pneumonia could have developed after the patient was released from the hospital, as patients admitted for the sole purpose of intoxication usually have short hospital stays. This could be addressed in the limitations.

We absolutely agree with Dr. Tadros that in some cases the aspiration pneumonia might have developed after the patient´s discharge from the hospital. We added a corresponding statement to the section “Strengths and limitations of this study”.

It was unclear to the reviewer what the black line represents in Figure 2B. Figure 2C does not add much to the study. Figure 6 is confusing.

The black line in Figure 2B represented the cumulative frequency of alcohol intoxication. In order to shorten the manuscript we removed Figure 2B. According to the reviewer´s suggestion we removed Figure 2C and Figure 6 as well.

Reviewer: 4
Dr. R Patton, University of Surrey
Thank you for submitting this interesting paper.

*Introduction - can you include additional detail on rates of intubation for non-alcohol intoxicated patients? It would also be helpful (for non medics) to understand the risks associated with the intubation process.

Since we focused on alcohol monointoxicated patients, we cannot provide data on the aspiration risk of mixed intoxication. However, mixed intoxication encompasses a broad and very heterogenous spectrum of substances with a highly variable risk for respiratory impairments. For instance, in contrast to intoxications with non-opioid pain killers which nearly never necessitate airway protection, organophosphate or cyanide poisoning routinely require intubation and often cardiopulmonary resuscitation with a high rate of aspiration.
We, therefore, do not think that a comparison between alcohol monointoxicated and non-alcohol intoxicated patients would be helpful in the conclusion of our study.
However, in order to provide the reviewer and non-medical reader with an idea of the frequency and

risks of a pre-hospital intubation, we added a few data from the literature in the Introduction. According to the literature, the general intubation rate for prehospital emergencies is approx. 3-5% (Bernhard, Bein, et al. 2015, Luckscheiter, Lohs, et al. 2019) and approx. 8% of prehospitally intubated patients developed a potentially intubation-related aspiration pneumonia (Driver, Klein, et al. 2018). Furthermore, additional intubation-related adverse events like hypotension and cardiac arrest implies the need for a careful risk-benefit analysis of the invasive emergency procedures.

*It is unfortunate that the authors were unable to include any patient / public involvement in their study - perhaps this could be reflected upon in the discussion.

Patients with alcohol intoxication represent a rather difficult subgroup of ICU admissions. They are often admitted under police escort, stay only for some hours, leave the clinic against explicit doctor's advice etc. Therefore, we were unable to involve patients when designing this retrospective study.

*Some further detail on rates of aspiration in the general patient population would help add context to the data presented.

For several reasons, it is very difficult to answer this question. There are numerous emergency scenarios that put patients under a higher risk for aspiration than the „normal" (healthy) population. Trauma, intoxication, resuscitation, seizures, drowned or pregnant patients have a higher risk of aspiration, regradless of attempts of prehospital endotracheal intubation. Failure of prehospital intubation further increases the risk for aspiration. Intubating patients with no empty stomach considerably increases the risk for aspiration, too. In all these different settings the risk of aspiration varies widely, depending on the conincidence of different risk factors. Compared to patients with a mild heart attack, harbouring a neglectable risk for aspiration, unconscious drowned patients vomit in up to 86% which implies a substancial aspiration risk. Thus, from a clincial point of view, it makes only sense to compare the aspiration risk between very narrowly definded patient populations. Comparing alcohol-intoxicated patients with a „general" population would neither add any insight into the aspiration risk of intoxicated patients nor provide any help for the prehospital management in these patients.

References

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VERSION 2 – REVIEW

REVIEWER	Minville, Vincent Département d'Anesthésie et de Réanimation, Centre Hospitalier et Universitaire de Toulouse
REVIEW RETURNED	15-Sep-2021

GENERAL COMMENTS	Thank you for having taken into account the concerns of the reviewers. However, I still have several comments about this manuscript. MAJOR COMMENTS/CONCERNS: 1. As a secondary aim, we analyzed the association between the blood alcohol level and the GSC score. Is it pertinent? Blood level depends on BMI, height weight ethic origin, habituation to regular alcohol consumption… What is the interest of an isolated association? 2. “Patients with missing data regarding blood alcohol level or GCS score were excluded, as well as patients with severe comorbidities or medical conditions interfering with consciousness, airway situation, aspiration risk or breathing rate.” The last features could have been interesting for the assessment of aspiration risk 3. “The difference of age and GCS score between aspirated and non-aspirated patients is visualized in as box plots in Figure 5A & B. these results are already in table 2.” Please delete. 4. “The empirical distribution of continuous data was described with mean, standard deviation and range, in case of categorical data with absolute and relative frequencies. “ Unclear. 5. “Fig 2 The blood alcohol level strongly correlated with patient´s age (r=0.43, p<0.0001) in the total population, as well as in male (r=0.46, p<0.0001) and female patients (r=0.33, p=0.003).” I still don’t see any interest in this fig. 6. Results should be rounded ex:” (mean age 47 vs. 35 years)” instead of “(mean age 47.4 vs. 34.6 years)” 7. Figure 3 visualizes the strong correlation between the first and second GCS score (r=0.77, p<0.0001). Interest of this result? 8. Correlation between delta GCS and risk of inhalation? 9. Table 2, SpO2 [%] when? 10. w/o please explain this abbreviation. 11. Table 3. presentation of the results is unclear. % of the row? N/case is missing. % of the column is better. 12. The discussion section is too long and should focus on your results. 13. The conclusion is too long and should focus on your results. 14. Multivariate analysis: 5 items for 21 patients? This is too much. What is the goodness of fit of the model? Results should be checked by a statistician

REVIEWER	Tadros, Allison West Virginia University
REVIEW RETURNED	11-Sep-2021

GENERAL COMMENTS	Concern raised with the original review have been addressed adequately.

VERSION 2 – AUTHOR RESPONSE

Prof. Vincent Minville, Département d'Anesthésie et de Réanimation, Centre Hospitalier et Universitaire de Toulouse Comments to the Author:
Thank you for having taken into account the concerns of the reviewers. However, I still have several comments about this manuscript.

MAJOR COMMENTS/CONCERNS:

1. As a secondary aim, we analyzed the association between the blood alcohol level and the GSC score. Is it pertinent? Blood level depends on BMI, height weight ethic origin, habituation to regular alcohol consumption… What is the interest of an isolated association?

As discussed in the manuscript, data on the correlation between blood alcohol level and GCS score are contradictory: „Some studies showed a correlation between blood alcohol level and GCS [22], while others did not [23-25].” Additionally, there are less data in adolescents, which claim a correlation between blood alcohol level and GCS score: “In contrast, in adolescent patients (13-17 years of age) with rather mild alcohol intoxication (mean 1.6g/l) Mick et al. found a significant correlation between the blood alcohol level and the GCS (mean GCS 12.2) [17].“ Thus, the scientific background of this issue is not clear at all. If there was a correlation between blood alcohol level and GCS score, especially as published for adolescents, a discrepancy between blood alcohol level and the predicted GCS score would imply a further clinical workup for differential causes of an impaired GCS score. Our data show, that even in adolescents, there is no such correlation. Thus, even a high GCS score does not exclude a severe alcohol intoxication, which might interfere with other clinical conditions. On the other hand, a low GCS score would not automatically imply severe alcohol consumption, which, in the emergency department, might prompt further diagnostic workup.
Since this issue is only the secondary aim of our study - according to the reviewer´s suggestion - we shortened the section “Discussion” regarding this issue.

2. “Patients with missing data regarding blood alcohol level or GCS score were excluded, as well as patients with severe comorbidities or medical conditions interfering with consciousness, airway situation, aspiration risk or breathing rate.” The last features could have been interesting for the assessment of aspiration risk

In a population with combined risk factors for aspiration, the specific impact of a single factor cannot be analysed. Since we were interested in alcohol-related risk factors for aspiration, we had to exclude interfering and overlapping cofactors for aspiration. In a cohort of mixed intoxication or concomittant trauma, the specific impact of alcohol on the GCS score cannot be determined.

3. “The difference of age and GCS score between aspirated and non-aspirated patients is visualized in as box plots in Figure 5A & B. these results are already in table 2.” Please delete.

Table 2 shows only the results of univariate analysis of continuous risk factors for aspiration. Figure 5A & B represent the visualisation of Table 4, which shows the results of multivariate analysis of risk factors for aspiration. Since this is the main result of the manuscript, a pictorial representation of this data is – from our point of view - of major importance. However, we could delete Figures 5A & B on the Editor´s discretion.

4. “The empirical distribution of continuous data was described with mean, standard deviation and range, in case of categorical data with absolute and relative frequencies. “ Unclear.

This sentence describes the statistical representation of continuous and categorical data, as provided by our statistician. Please specify your query and the assessment as „unclear“.

5. “Fig 2 The blood alcohol level strongly correlated with patient´s age ($r=0.43$, $p<0.0001$) in the total population, as well as in male ($r=0.46$, $p<0.0001$) and female patients ($r=0.33$, $p=0.003$).” I still don’t see any interest in this fig.

According to the reviewer´s suggestion in the first review, we already deleted the former figures 2A & B as a characerisation of our study population. Figure 2 is the visualisation of the correlation between age and blood alcohol level. As already discussed by other reviewers, age – and thus habituation to alcohol consumption – might influence the blood alcohol level. Therefore, this distribution – from our point of view - is of major importance. However, we could delete Figure 2 on the Editor´s discretion.

6. Results should be rounded ex:” (mean age 47 vs. 35 years)” instead of “(mean age 47.4 vs. 34.6 years)”
We rounded the given ages and other results as appropirate according to the reviewer´s suggestion.

7. Figure 3 visualizes the strong correlation between the first and second GCS score ($r=0.77$, $p<0.0001$). Interest of this result?
As already discussed in our answer to reviewer 1 (Dr. Julia Sinclair, University of Southampton), alcoholised patients often demonstrate a fluctuating level of consciousness. Therefore, a clear definition of the collected data is essential for a valid scientific analysis.
We answered to Dr. Sinclair: “Alcohol is rapidly absorbed by the stomach and small intestine and peak blood alcohol levels were measured as early as 30 minutes after oral ingestion which could be prolongated by delayed gastric emptying to 60 min (Oneta, Simanowski, et al. 1998). Thus, in case of an alcohol-related emergency, the expected peak blood alcohol level would roughly coincide with the arrival of the emergency team some 30 minutes later. Therefore, we hypothesise that only in a few patients the blood alcohol level would increase after medical treatment has started. This was reflected by our observation, that in very few cases (39 out of 336, 11,6%) the GCS score decreased from the first to the second evaluation, whereas in 297 of 336 cases (88,4%) the GCS score did not change or even improved. Furthermore, we do not expect a relevant metabolism of alcohol during the 30-60 minutes duration of prehospital treatment, which can be estimated as 0.15-0.20 g/l (Winek and Esposito 1985). From our point of view, this has no significant impact on our results showing a mean alcohol level of 2.7 g/l.“
Please, see also our statement in the „Discussion“ section of our manuscript: „This implies that the measurement time point of the GCS score during the prehospital care should be exactly defined and pooling of GCS data from different phases of care should be avoided.”

8. Correlation between delta GCS and risk of inhalation?
Does Prof. Vincent Minville refer to the correlation between delta GCS and risk of aspiration? Since only 3% of our patients showed a relevant deterioration of the GCS score ($\Delta GCS \geq 3$), this subpopulation is too small for further statistical analysis.

9. Table 2, SpO2 [%] when?
All vital signs were collected from the medical records of the paramedics/prehospital emergency team. To more clearly state this, we added „prehospital“ to the section „Material and Methods”.

10. w/o please explain this abbreviation.

„w/o“ is the standard abbreviation for „without“. We substituted the abbreviation in Tables 2 & 3.

11. Table 3. presentation of the results is unclear. % of the row? N/case is missing. % of the column is better.

In Table 3 „%“ refers to each line according to the standard fourfold table. Since we were interested in the aspiration rate, the sum of patients with and without aspiration is 100% for each parameter. Since the total number of patients is listed for each line („Evaluable patients“), the absolute numbers are indirectly listed for each box. To facilitate this calculation for the reader, we included the absolute numbers in brackets, as proposed by the reviewer.

12. The discussion section is too long and should focus on your results.

We, again, shortened the „Discussion“ section, as proposed by the reviewer.

13. The conclusion is too long and should focus on your results.

We shortened the „Conclusion“ section, as proposed by the reviewer.

14. Multivariate analysis: 5 items for 21 patients? This is too much. What is the goodness of fit of the model?

This question was already raised and answered in the first review and revision:

“7. Multivariate analysis: 5 items for 21 patients? This is too much. What is the goodness of fit of the model? Results should be checked by a statistician. As a statistician, TB performed the statistical analysis, provided the statistical results and double-checked the manuscript for statistical correctness. The reviewer is completely right, that the aspiration events were rather rare. Therefore, we restricted the multivariate logistic regression analysis to only 5 parameters which seem to be most prone to interdependence (Table 5). And as only gender is categorical, the risk for convergence problems (complete separation of the data) seems to be low.”

Results should be checked by a statistician

This question was already raised and answered in the first review and revision: „As a statistician, TB performed the statistical analysis, provided the statistical results and double-checked the manuscript for statistical correctness.”