PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Respiratory function and respiratory complications in spinal cord injury: protocol for a prospective, multi-center cohort study in high income countries.
AUTHORS	Raab, Anja M.; Brinkhof, Martin W G; Berlowitz, David J.; Postma, Karin; Gobets, David; Hirschfeld, Sven; Hopman, Maria TE; Huber, Burkhart; Hund-Georgiadis, Margret; Jordan, Xavier; Schubert, Martin; Wildburger, Renate; Mueller, Gabi

VERSION 1 - REVIEW

REVIEWER	John Yue, MD Department of Neurosurgery, University of California, San Francisco
REVIEW RETURNED	19-Mar-2020

GENERAL COMMENTS	Sufficient study design for an important subject of study. Recommend the authors incorporate plans and/or control processes regarding: - Patients with polytrauma - How long after initial injury are they admitted to rehab - How long after admission to rehab are they approached for enrollment - How to manage concomitant medications and/or rehab interventions - How to control for baseline cardiopulmonary comorbidites - Incorporation of objective imaging findings for study enrollment - How did the authors determine pneumonia to be the surrogate for respiratory function rather than objective measures eg. FEV/FVC - Duration of follow-up - Type of rehab e.g. physical, occupations, speech, respiratory, cognitive - how will the authors differentiate and control?

REVIEWER	Marcel Kopp Charité-Universitätsmedizin Berlin, Germany
REVIEW RETURNED	17-May-2020

GENERAL COMMENTS	The authors submit the study protocol of a prospective observational study to predict pneumonia after cervical and thoracic spinal cord injury (SCI) using parameters of respiratory function. The authors have a very good expertise in the assessment of respiratory function, respiratory therapy and intensive care treatment of

	individuals with SCI. The study is novel because only retrospective studies on the prediction of pneumonia have been published so far and it is important since the indication for respiratory therapy as a non-pharmacological prophylaxis of pneumonia should be supported by prospective evidence. The study protocol is clearly presented in most of its features. However, more details and further information are required at some minor and major points: Abstract and Article Summary: 1) Line 62 and 90: It should be explained that the inclusion of patients with less than 24h mechanical ventilation refers to the entire first 3 months (line 147) after SCI. Introduction: 2) Line 107: There are also recent individual studies that report not only non-modifiable baseline parameters but also modifiable risk factors for pneumonia, e.g. steroid administration (Jaja et al. 2019; doi: 10.1089/neu.2018.6245). Methods and Analyses: 3) Line 150: The sample size calculation is based on a retrospective observational study. The authors refer to "good discriminatory power for key dimensions of respiratory function" demonstrated in this study. However, it remains unclear which key dimensions are involved in the sample size estimation. Was there any primary predictive parameter selected? Which effect can be shown with n=100 cases of pneumonia in the study sample and with which statistical power? 4) Line 189: Primary outcome. Study inclusion occurs at 28+-12 days after injury at the earliest. In general, pneumonia frequency peaks within the first two weeks after SCI. Therefore, many episodes of pneumonia will already have occurred by the time when respiratory function parameters are first assessed. The pneumonia data will be collected from medical records (line 191). However, it will not be possible to include these events as primary outcome in a prediction model with respiratory function as exposure variable, on the one hand of course due to the time relation and on the other hand because the preceding episode of pneumonia probably influences the functional outcome (Kopp et al. 2017, doi: 10.1212/WNL.0000000000003652) involving respiratory independence (Jaja et al. 2019). This relationship has implications for the analysis strategy with "respiratory function" as the main exposure of interest (Figure 2) in terms of casual inference. How is this statistically handled? Can methods like "flexible parametric survival modeling" solve this problem? Should events of pneumonia that occurred prior to inclusion used as covariate in the prediction model? Strength and Limitations: 5) Another question that arises from the fact that a significant proportion of the primary outcome will have most likely occurred before the start of the exposure assessment is whether the expected pneumonia rate of 20% is actually achievable after inclusion up to 3 months (line 147) after SCI. The study is important because pneumonia is an outcome modifying factor associated with functional long-term outcome and survival after SCI and strategies to predict and prevent pneumonia will improve medical care of individuals with SCI. Even though the study

	has the limitation that it can not assess respiratory function in the very acute phase when a relevant proportion of respiratory infections already occur, the prediction of pneumonia during rehabilitation is highly relevant was well. The investigators might consider administrative interim analyses to determine whether the pneumonia rate after inclusion is within the estimated range of 20%.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: John Yue, MD
Institution and Country: Department of Neurosurgery, University of California, San Francisco
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Sufficient study design for an important subject of study. Recommend the authors incorporate plans and/or control processes regarding:

- Patients with polytrauma

Polytrauma is indeed common among patients with traumatic SCI and affects our study in two ways. First, severe additional injuries may disqualify patients for study participation, thus limiting the representativeness of the study and the generalizability of findings. Timely recruitment is for instance unfeasible, if length of ICU stay extends beyond the end of recruitment period of the first three months post injury. In patients who started rehabilitation, the polytrauma may preclude study participation. We acknowledge that these exclusions limit the representativeness of the study to cases of polytrauma of at most mild to moderate severity (Discussion, page 13/14, lines 373-380). Second, among those included in the study, polytrauma may directly affect the risk of pneumonia. For instance, rib fractures may reduce cough capacity and thereby infection risk. Relevant types of trauma and associated complications are therefore assessed at each measurement time-point, as well as ICD-10 coded co-morbidities at discharge. These time-updated data facilitate stratified or adjusted analysis of pneumonia risk that account for the added risk due to dynamic variation in polytrauma. The statistical model involves a time-to-event analysis (event being pneumonia) using time-updated covariates as exposures for accordingly divisions of follow-up time (splitting at each measurement time point). Time at risk will start at injury. This model also accounts for effects of polytrauma on length of rehabilitation stay. This is described on page 12, lines 322-329 in the manuscript.

- How long after initial injury are they admitted to rehab

Time of admission to rehab after injury varies between the participating centers and is dependent on the severity of the injury. We will not recruit patients earlier than one month post injury, and for those with extended ICU or acute hospital stays, a recruitment until 98 days post injury is possible (T2) (see Figure 1). Time of admission to rehab after injury is recorded and will be incorporated into the study analysis.
Pneumonia events as well as relevant complications (e.g. from polytrauma) that occur during the first weeks after injury and before enrollment into our study will be extracted from the patient's medical record. This is described in the manuscript on page 8, lines 194-198. We additionally changed the first sentence of this part to emphasize that pneumonia will be assessed continuously from the time point of injury until the end of inpatient rehabilitation.

- How long after admission to rehab are they approached for enrollment

Admission to rehab is an important determinant of when patients are enrolled into the study, it will be recorded, but time post injury is our most important parameter for recruitment and measurement time-points. See also Figure 1 and answers above. All participating centers typically receive their patients for rehab within 1 to 2 weeks post injury. As noted above, additionally patients with more severe injury who are admitted to rehab later but within the first three months post injury will be eligible for recruitment. In data analysis, time at risk for pneumonia will start at date of injury, while the method of splitting of individual follow-up time will be applied to account for within-person variation in risk that is potentially related to whether clinical data was collected retrospectively (between date of injury and enrollment) or prospectively (from enrollment until discharge from rehab).

- How to manage concomitant medications and/or rehab interventions

Concomitant medications are assessed at each measurement time-point and will be used as potential confounders for analysis. This is described on page 8 lines 206-208 and on page 12 Lines 329-332 in the manuscript. The amount/duration of individual interventions during inpatient rehabilitation which may influence pneumonia and especially respiratory function, is assessed at each measurement time-point. This is described in the paper on page 10, lines 260-266.
To account for potential confounding by medication and rehab interventions in evaluating pneumonia risk, this time-updated information will be included in the analysis risk (using splitting of follow-up time, thus creating temporal risk sets within-persons).

- How to control for baseline cardiopulmonary comorbidities

Baseline cardiopulmonary comorbidities (including pulmonary complications/comorbidities before the accident such as asthma, COPD etc.) may be an important confounder and are assessed as part of the baseline characteristics at inclusion into the study. This is part of the ISCOS pulmonary function dataset (see manuscript page 10, lines 253-255).

- Incorporation of objective imaging findings for study enrollment

Incorporation of imaging findings for study enrollment is not part of this study because we do not believe that it will modify enrollment nor relate directly to our proposed analyses.

- How did the authors determine pneumonia to be the surrogate for respiratory function rather than objective measures e.g. FEV/FVC

We will measure all lung function parameters (FVC, FEV1 and PEF) as well as peak cough flow and in- as well as expiratory muscle strength parameters. Our aim is to create, in a first step (Figure 2), a latent construct "respiratory function" that broadly captures the variation in all different parameters (FEVC, FEV1, etc.) for use as predictor in the analysis of pneumonia risk (SEM). In a second step, the most contributory individual parameters for variation in pneumonia risk will be evaluated.

- Duration of follow-up

As shown in Figure 1, each patient is measured at up to four time points including discharge from inpatient rehabilitation. In most of the participating centers, inpatient rehabilitation will last up to 9 or even 12 months in those patients at highest risk, e.g. those with motor complete tetraplegia. Therefore, these patients will have follow-up measurements at 3 and 6 months as well as at

discharge. In statistical analysis, time at risk starts at data of injury and ends at discharge from rehab or due to another censoring event (e.g., death).

- Type of rehab e.g. physical, occupations, speech, respiratory, cognitive - how will the authors differentiate and control?

Type and duration/amount of physical and respiratory therapy is assessed in detail at each measurement time-point using a questionnaire and individual therapy schedules of each patient (see manuscript page 10, lines 258-266). Therefore, we will be able to differentiate between those interventions which may probably influence our outcome parameters as e.g. respiratory muscle strength training or intensive/high volume physical exercise training, speech therapy etc. Further, the 'BODS' dysphagia score is also assessed at each time-point in order to evaluate any swallowing problems and increased risk for aspiration pneumonia (see manuscript page 10, lines 268-275). As described above, we will include time-updated assessments to account for potential confounding by these factors in evaluating respiratory parameters as predictors for pneumonia risk.

Reviewer: 2
Reviewer Name: Marcel Kopp
Institution and Country: Charité-Universitätsmedizin Berlin, Germany
Please state any competing interests or state ‘None declared’: None declared.

Please leave your comments for the authors below

The authors submit the study protocol of a prospective observational study to predict pneumonia after cervical and thoracic spinal cord injury (SCI) using parameters of respiratory function. The authors have a very good expertise in the assessment of respiratory function, respiratory therapy and intensive care treatment of individuals with SCI. The study is novel because only retrospective studies on the prediction of pneumonia have been published so far and it is important since the indication for respiratory therapy as a non-pharmacological prophylaxis of pneumonia should be supported by prospective evidence. The study protocol is clearly presented in most of its features. However, more details and further information are required at some minor and major points:

Abstract and Article Summary:

1) Line 62 and 90: It should be explained that the inclusion of patients with less than 24h mechanical ventilation refers to the entire first 3 months (line 147) after SCI.

We included this additional information in the abstract at line 62-63 and summary at line 91 in the revised version of the manuscript in order to clarify that patients must be able to breathe at least part-time spontaneously within the first three months post injury to participate in this study.

Introduction:

2) Line 107: There are also recent individual studies that report not only non-modifiable baseline parameters but also modifiable risk factors for pneumonia, e.g. steroid administration (Jaja et al. 2019; doi: 10.1089/neu.2018.6245).

Thank you for this note. We included the mentioned reference in the introduction. See page 5 lines 113-115.

Methods and Analyses:

3) Line 150: The sample size calculation is based on a retrospective observational study. The authors refer to "good discriminatory power for key dimensions of respiratory function" demonstrated in this study. However, it remains unclear which key dimensions are involved in the sample size estimation. Was there any primary predictive parameter selected? Which effect can be shown with n=100 cases of pneumonia in the study sample and with which statistical power?

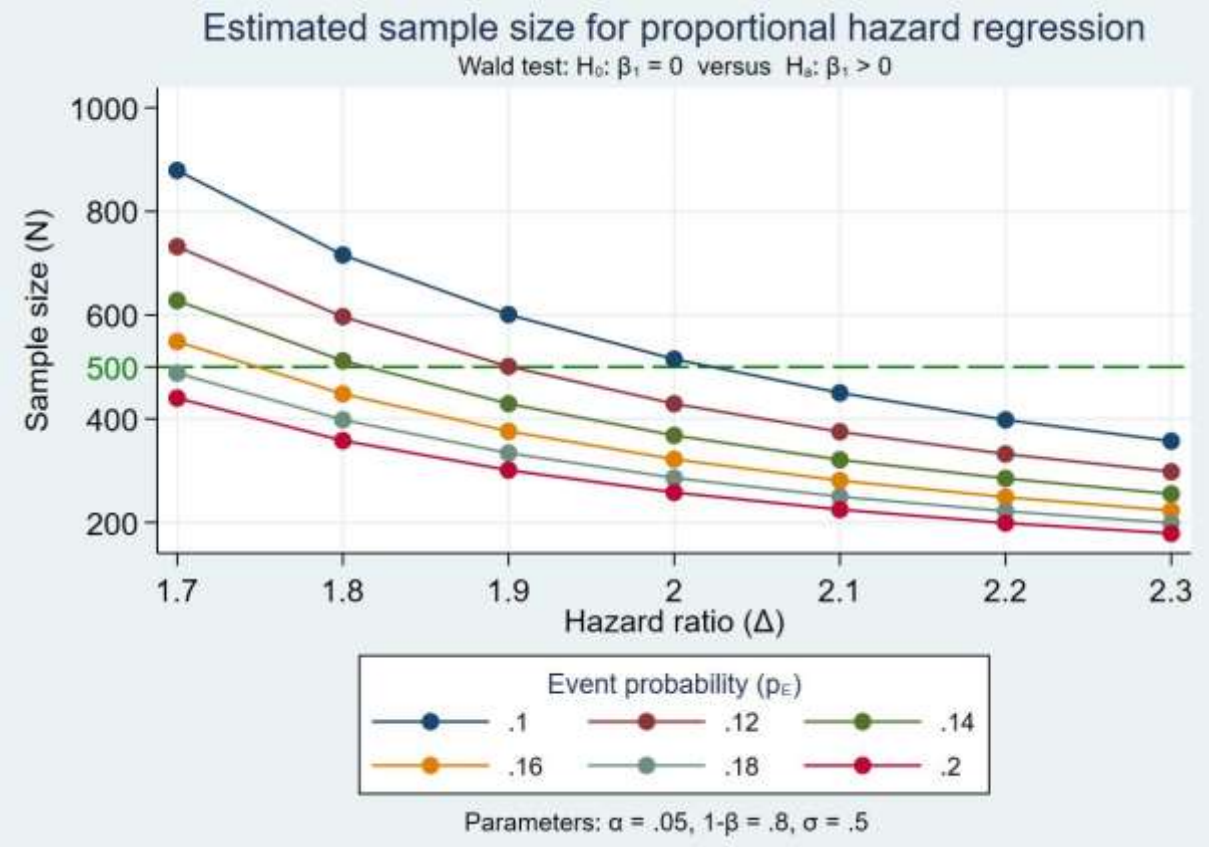
Thank you for this comment. You rightfully point out that the sample size calculation needs more detail in light of anticipated effect sizes and statistical power.

Since our retrospective study (Raab AM, Krebs J, Perret C, et al. Maximum inspiratory pressure is a discriminator of pneumonia in individuals with spinal-cord injury. Respir Care 2016;61(12):1636-43) showed, that inspiratory muscle strength may be highly predictive for pneumonia after SCI, our so called 'key dimensions'/primary predictive parameter involved for sample size estimation of this study was inspiratory muscle strength (i.e. Pimax).

Since this is not an interventional study, but an observational cohort study with the main aim to build predictive models for pneumonia risk, we cannot perform a 'classical' power analysis as known from interventional studies. Instead we calculated the minimal sample size needed to detect a hazard ratio (i.e., the effect size of interest) of 1.7 or more for the risk of pneumonia and for pneumonia event probabilities that ranged from 0.1 to 0.2. This choice of minimal hazard ratio is supported by previous studies on the relative risk of pneumonia in relation to inspiratory muscle strength e.g. Raab et al. 2016. For instance, a HR of 2.0 results when comparing a group with 20% risk to a reference group with 10% risk of pneumonia. Such risks are well within the range reported in the literature (with individual reports of 25% or more), thus our minimal sample size calculation was conservative. Conventially presuming a power of 0.8 and significance evel of 0.05, this analysis indicated that a sample size of 500 as targetted by the present study is adequate to detect a hazard ratio of at least 2.0 over most of the range in pneumonia incidence rates (See figure below). For instance, for a commonly observed pneumonia event probability of 0.2, hazard ratios of at least 1.7 are indicated as statistically detectable (lower red line in figure), while hazard ratios of 2.0 or larger are still detectable for an unlikely low pneumonia probability of 0.1 (upper blue line in figure). This minimal sample size estimation has been done together with our statistician/methodologist, who used the sample size calculation application in Stata (version 16.1).

We are therefore confident that the targetted sample size is adequate for an effective analysis of the models presented in Figure 2. We have rephrased the section as follows (page 6/7 lines 157-162):

" For the analysis of pneumonia risk we estimated, over a conservative range of pneumonia event probabilities from 0.1 to 0.2, the minimal sample size needed to detect a plausible hazard ratio (effect size of interest) of 1.7 or more for inspiratory muscle strength (principal predictor variable).[20] Using a conventional power of 0.8 and significance level of 0.05, this analysis indicated a sample size of 500 as adequate for the purpose of the present study."



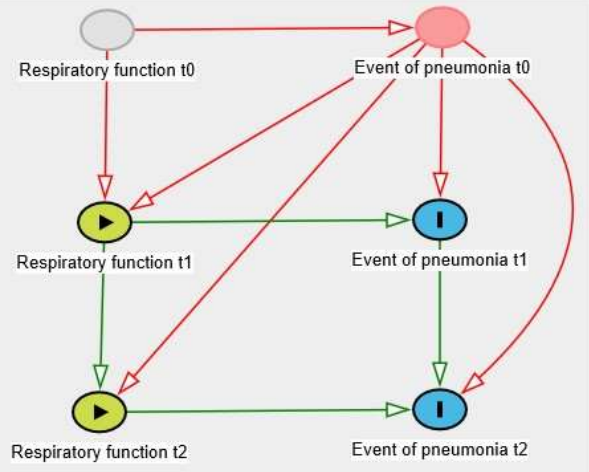
4) Line 189: Primary outcome. Study inclusion occurs at 28+-12 days after injury at the earliest. In general, pneumonia frequency peaks within the first two weeks after SCI. Therefore, many episodes of pneumonia will already have occurred by the time when respiratory function parameters are first assessed. The pneumonia data will be collected from medical records (line 191). However, it will not be possible to include these events as primary outcome in a prediction model with respiratory function as exposure variable, on the one hand of course due to the time relation and on the other hand because the preceding episode of pneumonia probably influences the functional outcome (Kopp et al. 2017, doi: 10.1212/WNL.0000000000003652) involving respiratory independence (Jaja et al. 2019). This relationship has implications for the analysis strategy with "respiratory function" as the main exposure of interest (Figure 2) in terms of casual inference. How is this statistically handled? Can methods like "flexible parametric survival modeling" solve this problem? Should events of pneumonia that occurred prior to inclusion used as covariate in the prediction model?

Thank you for this insightful comment. We agree that the 28 (+/- 12) day delay in study inclusion will make it impossible to evaluate the association between respiratory function and the event of pneumonia for the early period following injury directly. We also recognize that the impact of pneumonia on subsequent respiratory function as evidenced in your previous study (Kopp et al 2017), will make it challenging to obtain unbiased inference for that early period. Such inference could for instance involve the use of longitudinal multiple imputation procedures that include later assessments of respiratory function and pneumonia events as to derive estimates (with uncertainty) of respiratory function for the earliest period. Such analysis may help to deduce whether the measurement-based association of respiratory function with pneumonia risk of the main analysis is potentially generalizable to an early period. We aim to perform such an analysis as part of sensitivity analysis.

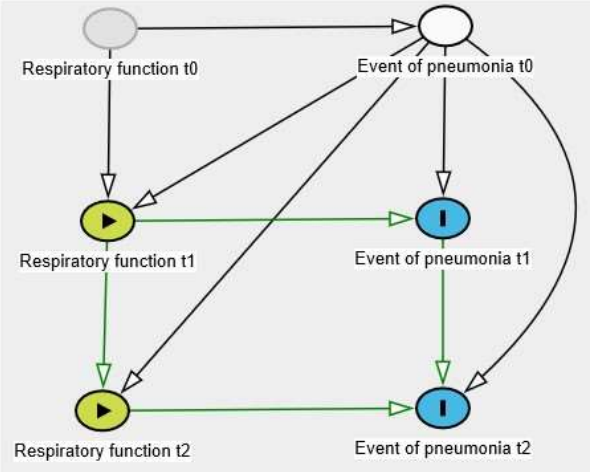
In the main analysis (using measured data only) the unmeasured (latent) respiratory function in the earliest period (here referred to as t0) is unlikely to bias inference regarding the association between

respiratory function and pneumonia risk at later measurement time points of the study (t1, t2, t3, t4). Yet, as indicated in the Directed Acyclic Graphs below (evaluated using the online Dagitty app) the adjustment for the event of pneumonia at t0, which we measure retrospectively in the present study, is needed to facilitate unbiased inference. Thus, we positively confirm the query regarding the need for covariate adjustment by the reviewer.

Basic DAG: The event of pneumonia at t0 may bias the association between respiratory function and the event of pneumonia (pneumonia risk) at later time points (here t1 & t2), as indicated by the reviewer Marcel Kopp



DAG following adjustment for pneumonia at t0: inference regarding the association between respiratory function and the event of pneumonia (pneumonia risk) for later time points (here t1 & t2) is unbiased



Strength and Limitations:

5) Another question that arises from the fact that a significant proportion of the primary outcome will have most likely occurred before the start of the exposure assessment is whether the expected pneumonia rate of 20% is actually achievable after inclusion up to 3 months (line 147) after SCI.

Every pneumonia event before inclusion – also in those patients admitted later and included at t2 (around 3 months post injury) will be assessed in this study. This will often be the case in individuals with high complete lesions, the group with the potentially highest pneumonia incidence rate. The 'good' thing is, that these patients normally have a much longer duration of inpatient rehabilitation and will therefore also have data from t3 and t4.

The study is important because pneumonia is an outcome modifying factor associated with functional long-term outcome and survival after SCI and strategies to predict and prevent pneumonia will improve medical care of individuals with SCI. Even though the study has the limitation that it cannot assess respiratory function in the very acute phase when a relevant proportion of respiratory infections already occur, the prediction of pneumonia during rehabilitation is highly relevant was well. The investigators might consider administrative interim analyses to determine whether the pneumonia rate after inclusion is within the estimated range of 20%.

We did an interim analysis about one year ago, in order to report progression of the study for our funding source Wings for Life. For the 330 eligible patients included we there found a pneumonia incidence rate of 15% over the study period. In case this 15% probability substantiates in the final dataset, we will still have sufficient power to detect hazard ratios for pneumonia risk of at least 1.8 for parameters of respiratory function (our reply to your query 3). Based on previous studies, we are likely to see larger effect sizes for potentially critical parameters (e.g., Pimax), which would here translate into a hazard ratio of substantially more than 1.8.

Further, we just completed a systematic review and meta-analysis (not yet published) on incidence of pneumonia after SCI. The results of this meta-analysis showed a mean pneumonia incidence rate of 32% (27 studies included). The sub-group analysis of individuals in the acute phase after SCI without mechanical ventilation or tracheostomy showed an incidence of pneumonia of 22%. Therefore, our intermediate estimate of 15% may well increase until study completion.

VERSION 2 – REVIEW

REVIEWER	Marcel Kopp Charté - Universitätsmedizin Berlin, Germany
REVIEW RETURNED	20-Aug-2020

GENERAL COMMENTS	The authors have carefully addressed all questions and comments of the reviewers in the manuscript or the accompanying response letter. The sample size calculation is fully adequate for an observational study. The planning of the statistical analysis with adjustment for further confounders and a sensitivity analysis is transparently described in the manuscript. I am looking forward to the results of the study.