Author's response to reviews

Title: Serum cortisol predicts death and critical disease independently of CRB-65 score in community-acquired pneumonia: a prospective observational cohort study

Authors:

Martin Kolditz (martin.kolditz@uniklinikum-dresden.de)
Gert Höffken (gert.hoeffken@uniklinikum-dresden.de)
Peter Martus (peter.martus@charite.de)
Gernot Rohde (gernot.rohde@ruhr-uni-bochum.de)
Hartwig Schütte (hartwig.schuette@charite.de)
Robert Bals (robert.bals@uniklinikum-saarland.de)
Norbert Suttrop (norbert.suttrop@charite.de)
Mathias W Pletz (mathias.pletz@med.uni-jena.de)

Version: 3 Date: 13 February 2012

Author's response to reviews: see over
Reviewer 1, Jorge Salluh

Thank you very much for your valuable comments on our manuscript.

The answers to your comments are as follows:

1: Thank you for the indication to another validated prediction score for critical pneumonia, the SMART-COP. As requested, in the limitations section of the discussion we now included the phrase: “Third, a comparison with other non-inflammatory biomarkers of CAP prognosis or new risk scores recently evaluated to predict ICU admission in CAP like the SMART-COP score [40] is not available from our data” and included the suggested reference.

2: A comparison with the SMART-COP would be interesting, however the included variables “multilobar infiltrates” and “albumin” are not available from our database, and pH only would be available for a minority of patients (N=481; showing no association with critical CAP in our cohort: AUC 0.52). Therefore a meaningful calculation of this score is not possible from our data. However, all other variables of the SMART-COP except tachycardia (low systolic blood pressure, high respiratory rate, confusion, poor oxygenation) are also included in the ATS minor criteria, and cortisol showed significant improvement of their predictive values.

3: The requested phrase now was included in the methods section.

4: As we stated in our limitations section, we are not able to control for concomitant steroid treatment, which includes steroids as adjunctive therapy for CAP, although we feel that this therapy (which is not recommended for CAP treatment) only rarely would be given in CAP patients in Germany. Furthermore, analysis after exclusion of all patients with chronic respiratory disease with the highest probability of receiving steroid treatment revealed no relevant change of the diagnostic properties of cortisol. However, this limitation of our study is clearly stated in the limitations section: “First, we were not able to correct for concomitant steroid medication, as this data were not documented.” and now was further accentuated by inclusion of another phrase: “Thus, deviation of our study results by concomitant steroid medication … cannot be ruled out.”

5: Multivariate analysis was performed including all variables given in table 1 (N=17). This is clearly stated in the results section: “In multivariate analysis including all variables given in table 1, only cortisol level…”

We are sure that our multivariate models are not affected by overfitting and we have three arguments supporting this point: First, it is the absolute number of events and not the percentage which counts and this number was 63 and 85 respectively which is not that few. Second, we carefully selected the multivariate models. In Table 3 all variables included as “candidates” in the variable selection are documented. After forward variable selection, seven predictors for 30 days mortality and five predictors for Critical CAP remained in the analysis. We are fully aware of the fact that tests of significance in the framework of multiple regression are not confirmatory, but most of the p-values were clearly beyond 0.05. Third and most important, a clear indication for overfitting are excessive values of parameters and related standard errors. However, in our multivariate analysis we observed stable coefficients for each variable in the model building process. Except for CRB65 in the 30d mortality model parameters did not change more than 10% of their original value. The coefficient of CRB65 was shrunked from 3.15 to 1.84 after inclusion of age as prognostic variable. This is to be expected because age is part of the CRB65. In the following we document the odds ratios of all covariates from their inclusion to the final model.
30 day mortality: crb65 3.152-->1.62, age 1.07-->1.06, cortisol 1.56-->1.51, tumor 2.76-->2.97, heart 2.28-->2.20, sex 2.2-->2.13, kidney 2.05
Critical CAP: crb65 3.86-->3.05, cortisol 1.74-->1.56, crp 1.42-->1.45, heart 1.94-->1.96, sex 1.73

6: We fully agree with your statement. From the CAPNETZ database we can only report the attending physicians judged mortality causes differentiated in “pneumonia” or “other”, therefore any specific explanation of physician judged alternative causes of death cannot be provided. We fully acknowledge the limitations of such judgement and therefore included this result not within the results section but only as cautious statement within the discussion section: “The CAPNETZ study also records the cause of death as judged by the treating physician. This subjective statement certainly has a lower value than measured parameters. But, of the 22 patients who died within 30 days…”
Reviewer 2, Yoon Kong Loke

Thank you very much for your valuable comments on our manuscript.

The answers to your comments are as follows:

Major points:

Table 2 (now 3) includes results of the multivariate analysis to predict both endpoints. From the p-values for mortality prediction it could be concluded that cortisol is outperformed only by age and malignancy, which is expected for the (not CAP-specific) mortality endpoint. The lower OR for cortisol given in the table results from the encoding by cortisol quartiles, whereas the other variables are dichotomous. If the cortisol cut-off of 795 nmol/l was included in the analysis, the resulting OR would be higher at 3.41.

As it is stated in our manuscript and shown by our data, cortisol was evaluated as adjunct to improve existing clinical risk scores and not as substitute to them, and predictive superiority of such combinations is demonstrated by our data.

Regarding your question about the predictive value of the co-morbidities: If cortisol is evaluated as adjunct to another hypothetic risk score consisting of one point each for congestive heart failure, chronic renal disease and malignancy, significant improvement still would result (AUC for this score: 0.76; AUC for this score plus cortisol 0.81, p=0.002), if CRB65 was added, corresponding AUC without cortisol is 0.83, with cortisol 0.86, p=0.001. Due to manuscript clarity and length we did not include these analyses, but if you would suggest inclusion of these data, we were ready to do so.

We fully agree with your important point, that clinical relevance of biomarker studies is crucial. Our observational study by its design cannot claim to prove clinical superiority of a cortisol-based risk stratification approach in CAP, thus your clinical question is understandable. What can be concluded from our large study cohort is that cortisol is an independent candidate biomarker to be evaluated for supplementation and improvement of clinical high risk prediction. We think that it is not statistically sound to provide PPVs and NPVs because prevalence of endpoints cannot be generalized from study data like those of the CAPNETZ cohort to the German patient population with hospitalised CAP, which differs in terms of demographics and outcome (Ewig Thorax 2009). For your information, PPV and NPV of cortisol alone for mortality are 14/97% and for critical CAP are 18/95% from our cohort, thus resembling these of the much more complicated PSI-score from the data of your extensive meta-analysis.

For clinical implementation, description of diagnostic and / or predictive properties like provided by our study is only the first step. In a second step superiority (and possibly cost-effectiveness) of a biomarker driven strategy has to be proven within an interventional trial, prospectively guiding management decisions like intensive monitoring or early goal directed therapy guided by clinical scores with or without a biomarker. That this approach is feasible has been shown with antibiotic stewardship for procalcitonin and already is planned for risk stratification with proADM. From our data can be concluded, that cortisol would be another candidate marker.

To further clarify this important point, we now included another phrase in our discussion section: “However, before cortisol measurement can be recommended for clinical routine use as biomarker in CAP, a prospective interventional trial is necessary to prove its accuracy and cost-effectiveness in comparison to evaluated clinical scores and competitive biomarkers for predicting patients benefiting from intensified treatment and monitoring strategies.”
Minor points:

Comment 1: We fully agree with your comment and thank you for your valuable advice. The study was prospectively planned as comparison of cortisol with the CRB-65 score, which is the only recommended score by the German guideline (Höffken et al., Pneumologie 2009) for hospitalised and ambulatory CAP patients. However, in other settings the CURB-65 score frequently is used. Thus we now included another post-hoc subgroup analysis of the 889 patients (90%) in whom urea measurement was evaluable in the results section and commented on the results in the discussion section. In short, substitution of age by urea (CURB-score) did not improve prediction; addition of urea to CRB65 did improve prediction. Addition of cortisol again significantly improved the diagnostic properties of both resulting scores (CURB and CURB65), which confirms its independent predictive value.

Comment 2: We agree with your comment on diurnal variation of cortisol levels in healthy persons. As stated clearly in the limitations section of our manuscript, from our study design we cannot control for blood sampling time: “Second, as blood samples were taken at time of first contact, controlling for the time point of blood sampling could not be done.” To even better clarify this important limitation, another phrase now has been added: “Thus, deviation of our study results by concomitant steroid medication or different blood sampling time points cannot be ruled out.” However, during infectious diseases the circadian pattern of cortisol often is lost, therefore we do not believe, that this would have major impact on our results. A controlled sampling time of cortisol would most probably result in a higher prognostic accuracy and thus our data can be taken for the robustness and practicability of the association between serum cortisol and CAP. Moreover this approach also has been used by other cortisol biomarker studies (Christ Crain AJRCCM 2007).

Comment 3: Again we fully agree with your comment. Steroid co-medication cannot be controlled for from our database. However, this already is very clearly stated within the limitations section: “First, we were not able to correct for concomitant steroid medication, as this data were not documented.” Again, to further clarify this limitation after your comment we additionally included the phrase: “Thus, deviation of our study results by concomitant steroid medication or different blood sampling time points cannot be ruled out.” However, the former suggestion here also applies: control for steroid medication most probably would result in higher prognostic accuracy of cortisol. At least for chronic respiratory diseases not interaction could be found. Therefore we do not believe that this limits the conclusion of our results. Of course, in a prospective interventional trial with a cortisol based risk stratification strategy, patients with steroid co-medication had to be excluded.

Comment 4: As requested another phrase now was included in the discussion section: “Whether the association of high cortisol and poor prognosis reflects adrenal regulation because of more severe CAP or adrenal dysregulation resulting in a complicated disease course cannot be concluded from our data and deserves further study.”

Comment 5: As requested another phrase now was included in the discussion section: “Recently there have been conflicting reports on benefits and risks of steroid treatment in CAP [37,38]. Given the accumulating evidence of the association of high cortisol levels with worse outcome in CAP, which is confirmed by the present data, the rationale of steroid treatment for this condition should be questioned.” Data on adjunctive steroid treatment are
conflicting, and the mentioned study on dexamethasone to our opinion does not allow a clear conclusion, moreover there are other data showing no benefit but enhanced side effects with steroid treatment in CAP (Snijders AJRCCM 2010).
Thank you very much for your valuable comments on our manuscript.

The answers to your comments are as follows:

Major comment: Thank you.

Minor comments:
1. This was corrected as requested.
2. The death rates within the CRB-65 score classes of 1 and 2 are slightly higher than those reported by previous CAPNETZ-data. We have no specific explanation for this. However, they are well within the reported mortality rates of a recent meta-analysis of Chalmers et al (Thorax 2010): mortality rate for risk score 1 and 2: Chalmers 8.3%, our cohort 10%.
3. The requested figure now is included in the manuscript (new figure 2)
4. The requested references now are included.
5. Thank you for that comment, the references now are included and the respective phrase was deleted.
6. The requested table now was included (new table 2).
7. There are no significant gender differences for cortisol values (median male 642 nmol/l, median female 588 nmol/l, p=0.06). There is no relevant sex-dependent difference for the correlation between cortisol and the CRB-65 score: R male=0.18, R female=0.21; for both correlations p=0.01
8. We think that it is not statistically sound to provide PPVs and NPVs because prevalence of endpoints cannot be generalized from study data like those of the CAPNETZ cohort to the German patient population with hospitalised CAP, which differs in terms of demographics and outcome (Ewig Thorax 2009). For your information, PPV and NPV of cortisol alone for mortality are 14/97% and for critical CAP are 18/95% from our cohort, thus resembling those of the much more complicated PSI-score from the data of the meta-analysis by Loke et al Thorax 2010: 14/98%.
Reviewer 4, Beat Müller

Thank you very much for your valuable comments on our manuscript.

The answers to your comments are as follows:

Major points:

1. We thank you for your valuable advice. The study was prospectively planned as comparison of cortisol with the CRB-65 score, which is the only recommended score by the German guideline (Höffken et al., Pneumologie 2009) for hospitalised and ambulatory CAP patients. However in other settings the CURB-65 score frequently is used. Thus we now included another post-hoc subgroup analysis of the 889 patients (90%) in whom urea measurement was evaluable in the results section and commented on the results in the discussion section. In short, substitution of age by urea (CURB-score) did not improve prediction; addition of urea to CRB65 did improve prediction (similar to cortisol). Addition of cortisol again significantly improved the diagnostic properties of both resulting scores (CURB and CURB65), which confirms its independent predictive value and is the main message of our manuscript.

2. Thank you for this comment, adrenal insufficiency was not tested in our study. This now is included in the limitations section: “Third, we did not test for adrenal insufficiency based on the response to injection of synthetic adrenocorticotropin. However previous data show a very low rate of adrenal insufficiency in patients with CAP in the absence of septic shock [21], and the association of mortality with high cortisol levels seems to contradict any major prognostic influence."

3. This was now specified in the methods section: “Venous blood samples were collected within 24 hours after first presentation and inclusion in the CAPNETZ study…”

4. The central study approval for the CAPNETZ project which includes this analysis was obtained by the ethical board of the University of Magdeburg, a former LCC of CAPNETZ.

Minor points:

1. Thank you, the definition was deleted from the background section.

2. This paragraph indeed partially would fit in the background section, however quite similar statements already have been made there. Thus the paragraph was shortened for repeated messages. However, as it leads to the rationale for introducing another biomarker mechanism, a shortened and modified part of the paragraph remained in the discussion section. We hope you agree with this modification.

3. As I understand, this figure labelling was done by the computer system within the upload process, where each file receives a sequential number, and cannot be influenced by the authors but would be accounted for during manuscript edition. File names of figures are correctly numbered.

4. The p-values were included as requested.