Author's response to reviews

Title: A latent class approach for sepsis diagnosis supports use of procalcitonin in the emergency room

Authors:

Fabián A Jaimes (fjaimesb@jhsph.edu)
Gisela De La Rosa (giseladlr@une.net.co)
Marta L Valencia (martaluzvalencia@gmail.com)
Clara M Arango (clara_arango@gmail.com)
Carlos I Gomez (cigr@une.net.co)
Alex Garcia (deorumalex@yahoo.com.ar)
Sigifredo Ospina (soox@elhospital.org.co)
Susana C Osorno (susana_ugeui@yahoo.com)
Adriana I Henao (adrisahenao@yahoo.com)

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Author's response to reviews: see over
Dear Editor
BMC Anesthesiology

We are resubmitting the manuscript entitled: “A latent class approach for sepsis diagnosis supports use of procalcitonin in the emergency room” considering the comments and corrections requested by the reviewers. Below, we are providing a point-by-point response to the concerns. In addition, specific changes are underlined in the manuscript

Reviewer 1: Iraklis Tsangaris

No changes requested. Thank you very much for your comments

Reviewer 2: Pierre Hausfater

- it is not clear when the first blood sample was drawn: as the patients were included "in the first 24-hours admission following ED admission", some patients could have been drawn at ED entry and some others 24-hours later. Is that true or were all first biomarker samples drawn at ED entry? This is important because biomarker's kinetic (notably PCT) is only 24h so that PCT levels may vary considerably during 24 hours delay. In case, this should be mentioned as a potential limitation. The same question concerning H-24 sample: drawn 24h after the first one or "just" the day after?

Thank you very much for your comments. Certainly, although blood sampling was performed immediately after the patient was admitted to the study, he/she could be in the ER any time within the last 24 hours before recruitment. So, we discuss this issue in the item of limitations. Regarding the second sample, we corrected: “CRP, PCT and DD were measured in all patients twice, at admission to the study and on the next day morning (i.e., within 24 hours after the first sample)”.

- table 3: in contrary to author's answers to reviewer 4, cluster 1 and 2 are still not clearly explicated as a legend/title

We added in the legend of Table 3 the following information: Missing = patients without information in any of PCT, CRP or DD; Cluster 1 = patients identified by LCA as a sepsis-like syndrome; Cluster 2 = the remaining of the study population

- if possible, I still not think that LCA explanation is clearly depicted in statistical method section. May be improved, maybe via a concrete example.

We rewrite this paragraph in this way: “Likelihood of sepsis in the study population according to a LCA: this analysis postulates the existence of an unobserved categorical variable that divides the population of interest into classes. Members of the population with a set of observed variables will respond differently depending on the latent class (variable) to which they belong. The problem that the outcome of interest cannot be measured directly occurs in many research situations. Examples include constructs such as intelligence, personality traits or, as in our case, the true
sepsis diagnosis. These unobservable outcomes, named also latent variables, can only be measured indirectly by eliciting responses that are related to the construct of interest. These measurable responses are called indicators or manifest variables. Latent variable models are a group of methods that use the information from the manifest variables to identify subtypes of cases defined by the latent variable. The classification appears by modeling the relationship between manifest (CRP, PCT and DD) and latent (sepsis/ no sepsis) variables in such a way that the parameters of interest (prevalence, sensitivity, specificity) are estimable from the implied relations between observable variables. In other words, LCA is just a mathematical model that identifies a subtype or a cluster of observations according to certain defined characteristics or variables that are common to those observations. In this case, we know that different expressions of inflammation and coagulation are common responses in the process of infection. Therefore, we provided these observed variables (DD, PCT and CRP) from all the study population to the model and it is able to uncover the hidden group, i.e. the latent variable, to which the patients belong. In summary, the goal of latent class analysis is to use the observed probabilities to estimate the unobserved ones.

Reviewer: Gordon P. Otto

1. Title: The title can be more specific f.e.: A latent class approach supports the use of procalcitonin in the emergency room for diagnosis of severe sepsis

Thank you very much for your comments. The title was changed according to your suggestion

2. Spelling: page 8 A # 24 for a test was considered positive in a patient if its values remain without changes or increase, and a pair was considered positive if both biomarkers were above the cut point.

We changed the sentence: “For a Δ24 test, it was considered positive in a patient if her values remain without changes or increase. For combining pair of tests, it was considered positive if both biomarkers were above the cut point”.

3. Structure of a sentence: page 14 In a secondary care hospital in Finland 539 patients admitted to the ER with suspicion of infection and with clinician’s order for blood cultures were studied [16].

The sentence was corrected: In a secondary care hospital of Finland, a population of 539 patients admitted to the ER with suspicion of infection and with clinician’s order for blood cultures was studied

4. Units abbreviation: various pages Sometimes ng/mL as well as ng/ml was used.

It was corrected
5. Spelling: page 16 A higher level of PCT…

It was corrected

Reviewer 4: Corey E Ventetuolo

No changes requested. Thank you very much for your comments

Sincerely yours,

Fabian Jaimes MD, MSc, PhD
Professor of Medicine, Clinical Epidemiology and Critical Care
School of Medicine
Universidad de Antioquia
Medellin, Colombia