# Latent class analysis-based subgroups and response to corticosteroids in hospitalised community-acquired pneumonia patients: a validation study



Received: 27 Oct 2022
Accepted: 10 Nov 2022

*To the Editor:*

Latent class analysis (LCA), a statistical method to identify "hidden" subgroups within a population, has identified clinically distinct subgroups with treatment implications in acute respiratory distress syndrome and COVID-19 [1–3]. We recently showed that LCA could also identify two clinically distinct subgroups in community-acquired pneumonia (CAP) [4]. In two independent cohorts [5, 6], LCA identified a subgroup with more excessive systemic inflammation and worse prognosis (class 2), and a subgroup with less systemic inflammation and better prognosis (class 1). In one of the two cohorts, the Ovidius cohort, we also observed a greater effect of adjunctive dexamethasone on length of stay (LOS) in class 2 compared to class 1. The aim of the present study was to validate the existence of LCA defined subgroups in a third, more recent CAP cohort. And if subgroups prove robust, to validate the finding from the Ovidius cohort that subgroups respond differently to adjunctive corticosteroids.

We conducted a LCA of data from the Santeon-CAP trial (N=401), a Dutch multicentre placebo-controlled randomised trial investigating the effect of a 4-day course of 6 mg oral dexamethasone on LOS in non-intensive care unit (ICU) patients hospitalised with CAP (www.clinicaltrials.gov identifier number NCT01743755). All patients received study medication within 24 h of hospital admission. Further details on study population characteristics, aetiologies, inclusion and exclusion criteria, and specifics of the intervention can be found in the original publication of the Santeon-CAP study [7]. Clinical and laboratory parameters on admission were available as part of the original study protocol. Concentrations of five systemic cytokines were measured in stored (at −80°C) blood samples collected at admission (prior to randomisation) using a Luminex multiplex assay (R&D Systems).

LCA was conducted using the DepmixS4 package in R 4.0.0 (R Core Team). We aimed to replicate the LCA model from the Ovidius cohort. Where available, the same class-defining variables were used. 13 out of 37 variables used in the Ovidius LCA were not available for the Santeon-CAP population: pH, arterial oxygen tension and carbon dioxide tension, duration of symptoms, glucose, lactate dehydrogenase, alkaline phosphatase, bilirubin, glucose, interleukin (IL)-5, IL-10, IL-12, and interferon-γ. Class-defining variables included in the current LCA are shown on the *x*-axis of figure 1. Missing data were accommodated by estimating model parameters based on the full information maximum likelihood [8]. For the LCA, we used the same procedures as in our previous study [4]. In short, we fitted models with two to five latent classes and subsequently identified the best-fitting model (or put differently, the optimal number of classes) using the following criteria: 1) clinical interpretability, 2) number of patients in the smallest class, and 3) model fit based on the Bayesian Information Criterion (BIC). After determining the optimal number of classes, patients were assigned to the class with the maximum probability of class assignment based on the LCA model. Next, median LOS and 30-day mortality, and ICU admission rates were compared between classes. These outcomes were chosen as they were the predefined outcomes of the Santeon-CAP study. To test for differences between subgroups, a Chi-squared test was used for categorical outcomes and a Mann–Whitney U-test was used for LOS. Lastly, we tested for interaction between class assignment and treatment allocation using a Poisson regression model for LOS and Chi-squared test for categorical outcomes.

Shareable abstract (@ERSpublications)
**In patients with community-acquired pneumonia, LCA can identify robust prognostic subgroups based on clinical and inflammatory parameters. Yet, these subgroups have not proven robust in predicting response to adjunctive dexamethasone treatment.** https://bit.ly/3O5eaxz

**Cite this article as:** Wittermans E, van der Zee PA, Qi H, *et al*. Latent class analysis-based subgroups and response to corticosteroids in hospitalised community-acquired pneumonia patients: a validation study. *ERJ Open Res* 2023; 9: 00577-2022 [DOI: 10.1183/23120541.00577-2022].

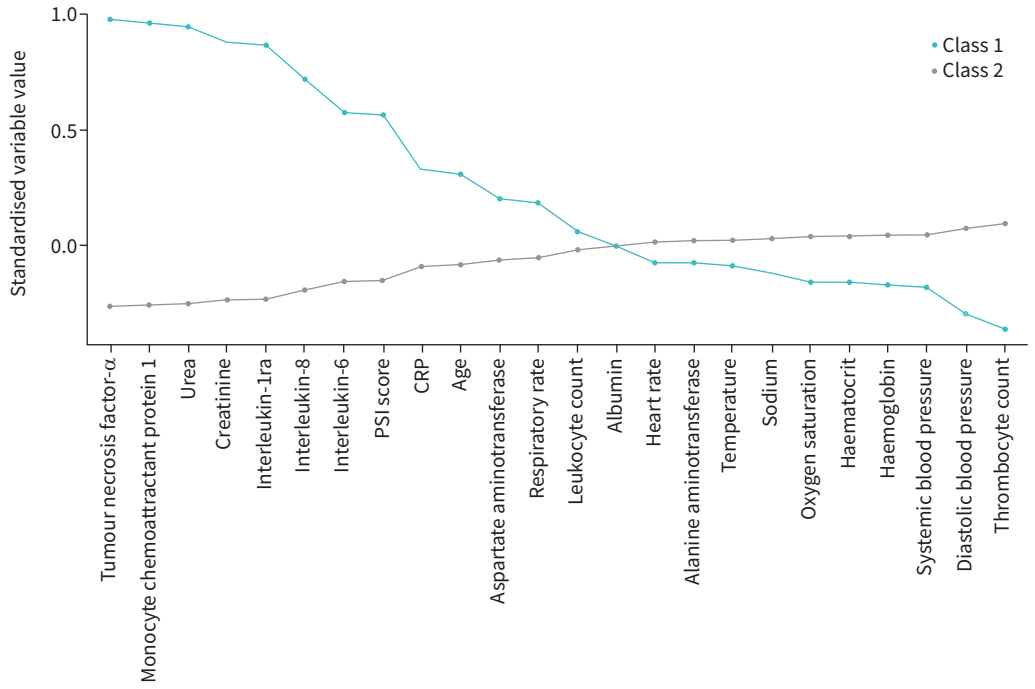


**FIGURE 1** Standardised value (*y*-axis) for each variable (*x*-axis) by class. A standardised value of 1 for a class indicates that the mean value for that variable within that class was one standard deviation higher than the mean value for that variable in the whole cohort. Variables are sorted by the degree of separation between classes: from the maximum positive separation on the left (where the standardised value of class 2 is higher than the standardised value of class 1) to the maximum negative separation on the right (where the standardised value of class 2 to is lower than the standardised value of class 1). Thus, the variables at the far left and far right of the *x*-axis are the variables that distinguish most between both classes. Variables in the middle of the *x*-axis differ least between classes or are the same in both classes (where the lines for both classes intersect). PSI: Pneumonia Severity Index; CRP: C-reactive protein.

After plotting class-defining variables for all models, the plot of a two-class model showed two clinically coherent and distinct classes (figure 1). Addition of more classes did not result in an additional clinically distinct subgroup. BIC was lowest in a four-class model (81 236.98 compared to 83 105.67 in the two-class model), indicating better model fit. Yet, addition of a third or fourth class did not result in an extra clinically distinct subgroup. So, although a data driven approach would suggest selection of a model with more than two classes, we chose to prioritise clinical interpretability and proceeded with a two-class model. 317 patients were assigned to class 1 and 84 patients were assigned to class 2. Average probability of class assignment was 99.9% for class 1 and 99.3% for class 2, indicating good model fit and robust class assignment.

Class 2 patients had higher systemic concentrations of all inflammatory cytokines, higher creatinine levels and lower diastolic blood pressure compared to class 1 patients (figure 1). In class 2, median (interquartile range) LOS was longer (6.0 (4.0–9.0) *versus* 5.0 (3.5–7.0) days; p⩽0.01), and ICU admission rate (9.5% *versus* 3.5%; p =0.04) and 30-day mortality rate (8.3% *versus* 1.3%; p =0.01) were higher. There was no difference in response to adjunctive dexamethasone treatment between classes; median LOS for dexamethasone *versus* placebo was 4.5 (3.0–6.5) *versus* 5.0 (3.5–7.0) days for class 1 and 5.8 (4.0–7.5) *versus* 7.5 (5.0–9.8) days in class 2 (p-value for interaction 0.38). ICU admission rate for dexamethasone *versus* placebo was 1.9% *versus* 5.1% in class 1 and 4.8% *versus* 14.3% in class 2 (p-value for interaction 1.00). 30-day mortality rate was 0.6% *versus* 1.9% in class 1 and 7.1% *versus* 9.5% in class 2 (p-value for interaction 1.00).

Similar to our previous study, we identified two clinically distinct CAP subgroups: one subgroup with signs of excessive systemic inflammation and worse clinical outcomes (class 2), and one subgroup with less systemic inflammation and better clinical outcomes (class 1). This indicates that subgroups identified

by our LCA model of baseline clinical and inflammatory parameters are robust. Yet, in the present study, we could not replicate our previous finding of greater response to corticosteroids in class 2 compared to class 1 despite a similar population with non-ICU patients, similar disease severity,and similar dexamethasone dose as in the Ovidius trial [9].

In line with other studies, patients with the highest inflammatory biomarker concentrations (class 2) had worse outcomes [10]. From a biological perspective, it would make sense that the effect of corticosteroids would be larger in patients in class 2 [11]. Yet in the present study, the effect of dexamethasone did not differ between classes. For this, we propose several hypotheses. First, it may be due to the small sample size in class 2 (n=84) combined with a relatively short median LOS in the Santeon-CAP cohort. This may have led to insufficient statistical power to show a difference in dexamethasone effect on LOS between classes. Second, it has been demonstrated that the host response can show signs of concurrent hyperinflammation (high plasma biomarker concentrations) and immune suppression (reduced cytokine production capacity of blood leukocytes) in CAP [12]. One could hypothesise that corticosteroid treatment in patients with concurrent immune suppression would not be beneficial.

Another hypothesis explaining the absence of differential effect of corticosteroids between classes is that only high levels of certain inflammatory mediators contribute to lung injury and sepsis while other mediators are essential for combating infection. Corticosteroids downregulate numerous inflammatory mediators and thus may also inhibit essential parts of the inflammatory response. Further research is needed to investigate whether targeted immunomodulation would be more appropriate. In sepsis, corticosteroid resistance is an issue; it has been proposed that this might contribute to the conflicting results in corticosteroid trials in patients with sepsis [13]. Yet, whether corticosteroid resistance plays a role in CAP, and specifically in our population of patients with moderate disease, is unclear.

Nonetheless, we consistently showed that LCA can identify patients with poor prognosis. The main limitations of the present study are the small number of patients in class 2 and the fact that not all class-defining variables used in the Ovidius study were available for the Santeon-CAP study. However, variables that differentiated most between class 1 and class 2 in the Ovidius cohort were included in the present study. Furthermore, inflammation is a dynamic process. Inflammatory parameters measured at admission only provide a “snapshot” of this process. It could be possible that patients with similar inflammatory values on admission are in different phases of the inflammatory response. Relative to admission, timing of the initiation of dexamethasone was the same for all patients, yet relative to the phase of the inflammatory response, timing could have differed between patients. Lastly, the Santeon-CAP study only included non-ICU patients; thus, these results might not be generalisable to ICU patients.

In conclusion, in patients with CAP, LCA can identify robust prognostic subgroups based on clinical and inflammatory parameters. Yet, these subgroups have not proven robust in predicting response to adjunctive dexamethasone treatment.

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Provenance: Submitted article, peer reviewed.

Conflict of interest: E. Wittermans has nothing to disclose. P.A. van der Zee has nothing to disclose. H. Qi has nothing to disclose. J.C. Grutters has nothing to disclose. G.P. Voorn has nothing to disclose. W.J.W. Bos reports

grants from Zilveren Kruis Insurance outside the submitted work. E.M.W. van de Garde has nothing to disclose. H. Endeman has nothing to disclose.

Support statement: This study was supported by the St Antonius Research Fund. Funding information for this article has been deposited with the Crossref Funder Registry.

## References

1 Sinha P, Furfaro D, Cummings MJ, *et al.* Latent class analysis reveals COVID-19-related ARDS subgroups with differential responses to corticosteroids. *Am J Respir Crit Care Med* 2021; 204: 1274–1285.
2 Calfee CS, Delucchi KL, Sinha P, *et al.* Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. *Lancet Respir Med* 2018; 6: 691–698.
3 Sinha P, Delucchi KL, Thompson BT, *et al.* Latent class analysis of ARDS subphenotypes: a secondary analysis of the statins for acutely injured lungs from sepsis (SAILS) study. *Intensive Care Med* 2018; 44: 1859–1869.
4 Wittermans E, van der Zee PA, Qi H, *et al.* Community-acquired pneumonia subgroups and differential response to corticosteroids: a secondary analysis of controlled studies. *ERJ Open Res* 2022; 8: 00489-2021.
5 Blum CA, Nigro N, Briel M, *et al.* Adjunct prednisone therapy for patients with community-acquired pneumonia: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2015; 385: 1511–1518.
6 Meijvis SC, Hardeman H, Remmelts HH, *et al.* Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; 377: 2023–2030.
7 Wittermans E, Vestjens SM, Spoorenberg SM, *et al.* Adjunctive treatment with oral dexamethasone in non-ICU patients hospitalised with community-acquired pneumonia: a randomised clinical trial. *Eur Respir J* 2021; 58: 2002535.
8 Cham H, Reshetnyak E, Rosenfeld B, *et al.* Full information maximum likelihood estimation for latent variable interactions with incomplete indicators. *Multivariate Behav Res* 2017; 52: 12–30.
9 Spoorenberg SMC, Deneer VHM, Grutters JC, *et al.* Pharmacokinetics of oral *vs.* intravenous dexamethasone in patients hospitalized with community-acquired pneumonia. *Br J Clin Pharmacol* 2014; 78: 78–83.
10 Ramírez P, Ferrer M, Martí V, *et al.* Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit Care Med* 2011; 39: 2211–2217.
11 Remmelts HHF, Meijvis SCA, Biesma DH, *et al.* Dexamethasone downregulates the systemic cytokine response in patients with community-acquired pneumonia. *Clin Vaccine Immunol* 2012; 19: 1532–1538.
12 Brands X, Haak BW, Klarenbeek AM, *et al.* Concurrent immune suppression and hyperinflammation in patients with community-acquired pneumonia. *Front Immunol* 2020; 11: 796.
13 Vandewalle J, Libert C. Glucocorticoids in sepsis: to be or not to be. *Front Immunol* 2020; 11: 1318.