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## Strategies to optimise the treatment of community-acquired pneumonia

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# CHAPTER 5

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

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*To the editor:*

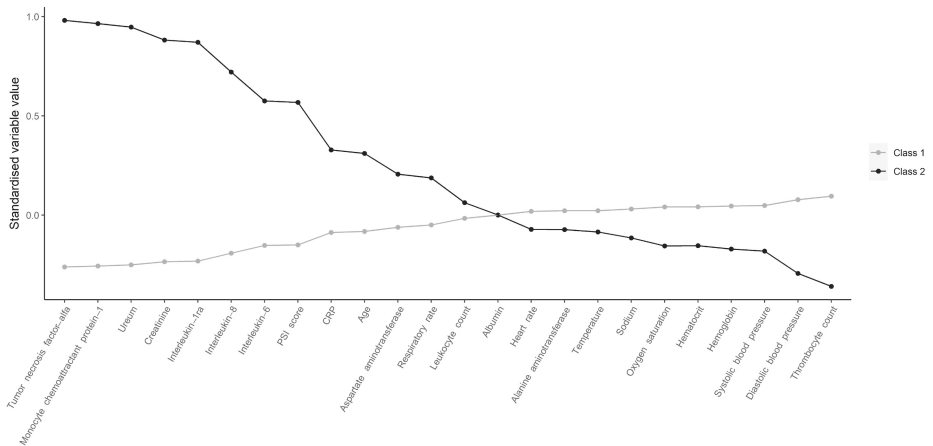
Latent class analysis (LCA), a statistical method to identify 'hidden' subgroups within a population, has identified clinically distinct subgroups with treatment implications in acute respiratory distress syndrome and COVID-19.<sup>1-3</sup> We recently showed that LCA could also identify two clinically distinct subgroups in community-acquired pneumonia (CAP).<sup>4</sup> In two independent cohorts,<sup>5,6</sup> 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 (NCT 01743755). 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.<sup>7</sup> 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, Minneapolis, USA).

LCA was conducted using the DepmixS4 package in R 4.0.0 (R core team, 2020). We aimed to replicate the LCA model from the Ovidius cohort. Where available, the same class-defining variables were used. Thirteen out of 37 variables used in the Ovidius LCA were not available for the Santeon-CAP population: pH, arterial pO<sub>2</sub> and pCO<sub>2</sub>, duration of symptoms, glucose, lactate dehydrogenase, alkaline phosphatase, bilirubin, glucose, interleukin (IL)-5, IL-10, IL-12 and interferon- $\gamma$ . 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.<sup>8</sup> For the LCA, we used the same procedures as in our previous study.<sup>4</sup> 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 these 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 was used for LOS. Last, we tested for interaction between class assignment and treatment allocation using a Poisson regression model for LOS, and Chi-squared test for categorical outcomes.

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 (81236.98 compared to 83105.67 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 >2 classes, we chose to prioritise clinical interpretability and proceeded with a two-class model. Three hundred seventeen 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.



**Figure 1** shows the 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 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).

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 LOS was longer (6.0 (IQR 4.0-9.0) vs 5.0 (IQR 3.5-7.0) days;  $p = \leq 0.01$ ), and ICU admission rate (9.5% vs 3.5%;  $p = 0.04$ ) and 30-day mortality rate (8.3% vs 1.3%;  $p = 0.01$ ) were higher. There was no difference in response to adjunctive dexamethasone treatment between classes; median LOS for dexamethasone vs placebo was 4.5 (IQR 3.0-6.5) vs 5.0 (IQR 3.5 – 7.0) days for class 1 and 5.8 (IQR 4.0 – 7.5) vs 7.5 (IQR 5.0 – 9.8) days in class 2 ( $p$ -value for interaction 0.38). ICU admission rate for dexamethasone vs placebo was 1.9% vs 5.1% in class 1 and 4.8% vs 14.3% in class 2 ( $p$  for interaction 1.00). 30-day mortality rate was 0.6% vs 1.9% in class 1 and 7.1% vs 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.<sup>9</sup>

In line with other studies, patients with the highest inflammatory biomarker concentrations (class 2) had worse outcomes.<sup>10</sup> From a biological perspective it would make sense that the effect of corticosteroids would be larger in patients in class 2.<sup>11</sup> 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 too 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.<sup>12</sup> 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.<sup>13</sup> 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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