# Ventilator Associated Pneumonia (VAP) Subphenotype Analysis

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## Introduction

Pneumonia is the second most common hospital-acquired infection in critically-ill patients. 86% of hospital-acquired pneumonias are associated with mechanical ventilation and termed **Ventilator Associated Pneumonia (VAP)**.

Factors influencing VAP outcomes remain unclear due to variability in patient populations and causative organisms. Diagnosing VAP is complex, requiring bedside assessment, imaging, and microbiologic analysis. It is uncertain **whether all VAP patients are clinically identical, and identifying molecular endotypes may help uncover subgroups with distinct outcomes.**

This project seeks to **classify VAP patients** into subphenotypes and examine their **association with mortality**, offering insights to enhance clinical management and risk stratification.

### Data Source

**466 Critically Ill Patients at Harborview Medical Center.**

- Microbiology cultures and proteomic analysis from bronchoalveolar samples for all patients.
- Electronic Health Record (EHR) data for all patients.

## Methods & Results

### Clustering

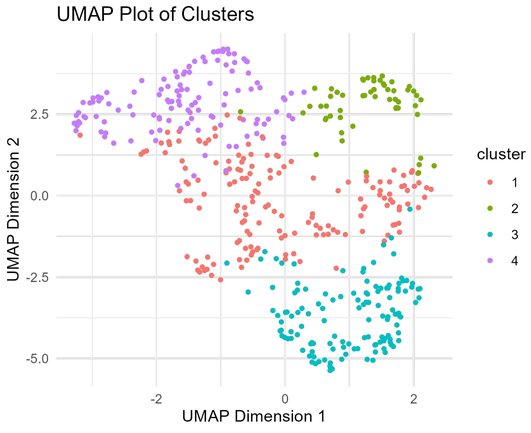
We analyzed **25 bronchoalveolar fluid biomarkers** from bronchoscopies to identify meaningful patient subgroups.

With **K-Means**, the algorithm divided the patients into two clusters of simply "high" and "low". With **GMM** selection of optimal clusters using the BIC agreed with the Latent Class models.

Using BIC, Entropy, and the Vuong-Lo-Mendell-Rubin Test (VLMR), we identified a **four-cluster** solution, leading us to adopt **Latent Class Analysis (LCA)**[1] as the most appropriate approach.

Mplus

| Classes | BIC | Entropy | VLMR p-value |
|---|---|---|---|
| 2 | 28308.9 | 0.973 | 0 |
| 3 | 26917.3 | 0.959 | 0.024 |
| 4 | 25614.6 | 0.97 | 0.0105 |
| 5 | 24973.8 | 0.968 | 0.6997 |

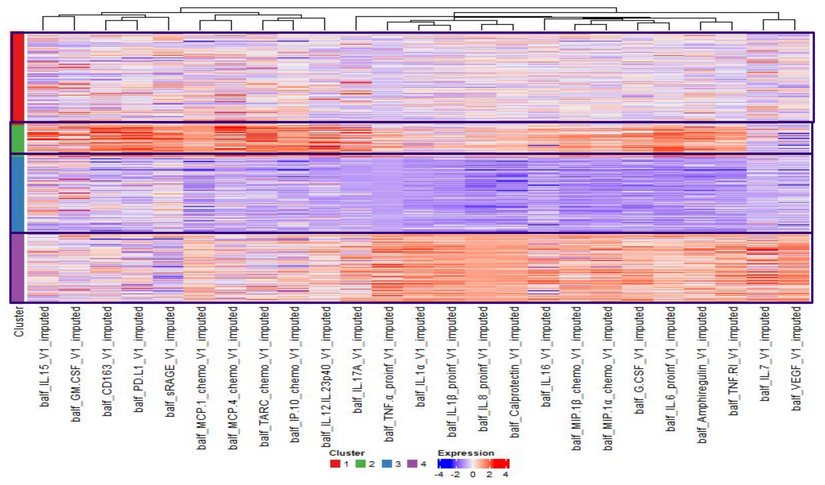



### Cluster Characteristics and Differences

**Cluster 2** consists of younger patients with lower hospital mortality and similar VFDs to Cluster 1, characterized by increased **chemokines and IL-6 expression**.

**Cluster 4** on the other hand has higher hospital mortality, lower VFDs, and is distinguished by **elevated proinflammatory biomarker expression**, suggesting a more severe inflammatory profile.

| | 1 (N=160) | 2 (N=55) | 3 (N=130) | 4 (N=121) | Total (N=466) |
|---|---|---|---|---|---|
| Age | | | | | |
| - Median | 55.476 | 38.656 | 52.550 | 49.369 | 51.522 |
| - Q1, Q3 | 38.214, 65.001 | 28.348, 54.628 | 38.925, 64.066 | 34.541, 63.003 | 35.900, 63.694 |
| Sex | | | | | |
| - Female | 43 (26.9%) | 18 (32.7%) | 32 (24.6%) | 28 (23.1%) | 121 (26.0%) |
| - Male | 117 (73.1%) | 37 (67.3%) | 98 (75.4%) | 93 (76.9%) | 345 (74.0%) |
| hospital_mortality | | | | | |
| - 0 | 134 (83.8%) | 47 (85.5%) | 101 (77.7%) | 88 (72.7%) | 370 (79.4%) |
| - 1 | 26 (16.2%) | 8 (14.5%) | 29 (22.3%) | 33 (27.3%) | 96 (20.6%) |
| vfds_bronch | | | | | |
| - Median | 16.000 | 16.000 | 14.000 | 9.000 | 14.000 |
| - Q1, Q3 | 0.000, 22.000 | 0.000, 23.000 | 0.000, 21.000 | 0.000, 19.000 | 0.000, 21.000 |




### Statistical Analysis

**Logistic Regression** evaluated whether clusters predict mortality and if these associations remain after adjusting for key clinical factors.

**hospital_mortality ~ cluster**

| Cluster | Estimate | p-value |
|---|---|---|
| Intercept | -1.77 | 3.66e-06 (***) |
| cluster1 | 0.13 | 0.76 |
| cluster3 | 0.52 | 0.23 |
| cluster4 | 0.79 | 0.068 (.) |

**hospital_mortality ~ cluster + Age + Sex**

| Cluster | Estimate | p-value |
|---|---|---|
| Intercept | -3.45 | 6.26e-08 (***) |
| cluster1 | -0.18 | 0.69 |
| cluster3 | 0.25 | 0.57 |
| cluster4 | 0.62 | 0.17 |
| Age | 0.04 | 6.59e-07 (***) |
| Sex(M) | -0.21 | 0.45 |

**Relative Risk Regression** (Modified Poisson Regression)[2] showed that **Cluster 4** has the **highest mortality risk (RR = 1.59, +59%)**, while **Cluster 1** has a **lower risk (RR = 0.89, -11%)** compared to the reference group (Cluster 2), highlighting distinct outcome differences across endotypes.

## Conclusion

We identified **four novel endotypes of VAP patients** based on **molecular biomarkers** from bronchoalveolar fluid cultures.

Although not all clusters showed statistically significant associations with hospital mortality or ventilator-free days, their **distinct biomarker profiles and varying outcomes warrant further investigation** to better understand the biological mechanisms of ventilator associated pneumonia and its impact on patients' hospital course.

(1) https://pmc.ncbi.nlm.nih.gov/articles/PMC7746621/, (2) https://pubmed.ncbi.nlm.nih.gov/15033648/