Using machine learning to identify patterns of coexisting conditions and outcomes in adults hospitalized with community-acquired pneumonia: A multicentre cohort study

Running Title: Multimorbidity patterns and outcomes in pneumonia

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Abstract

Background: Little is known about patterns of coexisting conditions and their influence on clinical care or outcomes in adults hospitalized for community-acquired-pneumonia (CAP).

Methods: We studied 11,085 adults hospitalized with CAP at 7 hospitals in Ontario, Canada. Using unsupervised machine learning, we identified patient subgroups based on clustering of the comorbidities in the Charlson index. Subgroups were derived and validated in independent cohorts (derivation: 2010-15, validation: 2015-17). Differences in medications, imaging, and outcomes were described.

Results: Patients clustered into seven subgroups. The “low comorbidity” subgroup (27.5%, N=3052) had no comorbidities. The “DM-HF-Pulm” subgroup had prevalent diabetes, heart failure, and chronic lung disease (15.4%, N=1710). One disease category defined each remaining subgroup: “pulmonary” (14.6%, N=1621), “diabetes” (11.6%, N=1281), “heart failure” (12.4%, N=1370), “dementia” (9.4%, N=1038), and “cancer” (9.1%, N=1013). Corticosteroid use ranged from 11.5% to 64.9% in the “dementia” and “pulmonary” subgroups, respectively. Piperacillin-tazobactam use ranged from 9.1% to 28.0% in the “pulmonary” and “cancer” subgroups, respectively. Thoracic computed tomography ranged from 5.7% to 36.3% in the “dementia” and “cancer” subgroups, respectively. Adjusting for patient factors, in-hospital mortality was greater in the “cancer” (aOR 2.91, 95%CI: 2.20-3.86), “dementia” (aOR 1.73, 95%CI: 1.32-2.27), “heart failure” (aOR 1.66, 95%CI: 1.27-2.16), and “DM-HF-Pulm” subgroups (aOR 1.32, 95%CI: 1.02-1.71) and lower in “diabetes” (aOR 0.65, 95%CI: 0.46-0.93) compared to “low comorbidity”.

Interpretation: Patients hospitalized with CAP cluster into clinically-recognizable subgroups based on coexisting conditions. Clinical care and outcomes vary among these subgroups with little evidence to guide decision-making, highlighting opportunities for research to personalize care.
**Key words:** Cluster analysis; Community-acquired pneumonia (CAP); Hospital medicine; Multimorbidity; Unsupervised machine learning
Introduction

Pneumonia is one of the most common reasons for hospitalization(1) and patients experience a wide range of clinical outcomes.(2, 3) The clinical care of patients with pneumonia is known to vary with respect to choice of antibiotics,(2) type of imaging use,(4) and adjunctive therapies.(5) It is not known whether patterns of coexisting conditions are associated with differences in clinical care or outcomes in patients hospitalized with pneumonia. As populations age, more people are living with multiple chronic conditions.(6) Although single coexisting diseases, such as dementia,(7) and greater comorbidity levels in general,(8-12) are known to affect clinical outcomes in patients with pneumonia, less is understood about patterns of coexisting illnesses among patients hospitalized for pneumonia. Clinical practice guidelines for pneumonia offer little guidance for how multiple coexisting conditions should affect care.(2, 13) Host phenotyping has been identified as a crucial next step in advancing the treatment of pneumonia, including calling for a focus on improving our understanding of comorbid illnesses.(14)

The objective of this study was to examine how coexisting conditions cluster in patients hospitalized with community-acquired pneumonia (CAP). We hypothesized that clinically-recognizable subgroups could be identified based on patterns of coexisting conditions, and that subgroups would differ in diagnostic imaging, medication use, and clinical outcomes. Our overall aim was to advance understanding of how multimorbidity affects CAP and to inform future research toward more personalized treatment strategies for patients hospitalized with CAP.

Methods

Design and Setting
This was a retrospective cohort study using data from seven large hospitals in Toronto and Mississauga, Ontario, Canada that were participating in the General Medicine Inpatient Initiative (GEMINI).(1) GEMINI collects administrative and clinical data from all general internal medicine (GIM) admissions. Clinical data are extracted from hospital information systems and administrative data are collected from hospitals as reported to the Canadian Institute for Health Information (CIHI) National Ambulatory Care Reporting System and Discharge Abstract Database.(15, 16) Manual validation of more than 20,000 data points within the GEMINI database demonstrated that data are highly reliable.(17) The participating hospitals serve diverse multiethnic urban and suburban populations and hospital services are publicly insured.

**Study Sample**

We included all GIM patients discharged between April 1, 2010 and October 31, 2017. At all participating hospitals, patients with CAP who are not admitted to the ICU are admitted almost entirely to GIM services rather than specialized respirology services. To identify patients with CAP, we included patients for whom the most responsible discharge diagnosis as reported to CIHI was “pneumonia”, defined by the International and Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) codes J10-J18.(1, 18, 19) We also included patients for whom pneumonia was a co-morbid diagnosis with a most responsible discharge diagnosis of Chronic Obstructive Pulmonary Disease (COPD, defined by ICD-10–CA codes J41-J44).(20) These patients were included because coding convention dictates that COPD be coded as the primary diagnosis for patients with coexisting pneumonia.(16) Prior chart abstraction studies revealed that the ICD-10 code J18 alone had a sensitivity of 80% for pneumonia(21) whereas the group of ICD-10 codes J10-J18 were found to be 98% sensitive and 97% specific for pneumonia in patients 65 years and older.(18) To enhance the specificity of case identification and to separate CAP from hospital-acquired pneumonia, we only included patients who received an antibiotic with activity against respiratory pathogens(13, 22, 23) on every day for the first four days of admission or until death or hospital discharge in accordance with a standard five-day treatment regimen for CAP (13, 23) (assuming up to one day of antimicrobial administration in the emergency
department prior to admission). We excluded patients who were not admitted from the emergency department, or who were admitted to hospital in the previous 30 days, given the possibility that their pneumonia may have been related to the prior hospitalization. For patients with multiple admissions, we included only one randomly-selected admission during the study period.

**Research Ethics Board Approval**

This study received Research Ethics Board approval with a waiver of informed patient consent from all participating hospitals.

**Measures and Outcomes**

**Patient characteristics**

Baseline patient characteristics included age, sex, residence in a long-term care facility, transport to hospital by ambulance, overall level of comorbidity estimated using the Charlson Comorbidity Index score,(24, 25) and severity of illness, estimated using the laboratory-based acute physiology score (LAPS),(26) which is a validated predictor of in-hospital mortality based on 14 laboratory tests.(27)

**Coexisting conditions**

We selected comorbid conditions of interest based on one of the most widely-used comorbidity indices, the Charlson Comorbidity Index.(24) We measured conditions that are included in this index, based on patient discharge diagnoses categorized using ICD-10 codes.(25) Sensitivity and specificity for the majority of these ICD-10 codes have been reported previously and all were >95% specific while sensitivity ranged from 25% for HIV/AIDS to 83% for metastatic cancer.(28) The Charlson Comorbidity Index defines chronic lung disease as
all obstructive and restrictive diseases. It also separates diabetes, liver disease, and malignancy into sub-categories based on disease severity and complications, which we collapsed into single categories for each disease.

Processes of clinical care

We described the use of respiratory-acting antibiotics, other medications intended to improve respiration (glucocorticoids, inhalers and furosemide), and the use of computed tomography (CT) of the thorax.

Clinical Outcomes

The study outcomes were: in-hospital mortality, ICU admission after admission to GIM, total hospital length of stay, and readmission to GIM at any participating hospital, within 30 days of discharge.

Statistical Analysis

Cluster analysis

We performed cluster analysis to identify subgroups of patients with CAP based on the presence of 14 coexisting medical condition groupings that form the Charlson Comorbidity Index (see eMethods for full methodological details). In order to assess the stability and reproducibility of the identified patient subgroups, we performed the same cluster analysis in a derivation cohort (April 1, 2010 to March 31, 2015) and validation cohort (April 1, 2015 to October 31, 2017), similar to Seymour and colleagues (29) (eFigure 1 in the Supplement). Patients who had an admission in both the derivation and validation period were excluded from the latter so that they were only captured once. Demographics, baseline characteristics and the prevalence of coexisting conditions were reported for the two cohorts. Standardized mean differences >0.10 (10%) were used
to identify any meaningful imbalance between the cohorts. After confirming a stable and reproducible clustering approach in the two cohorts, the cluster analysis was re-run using the entire study period (April 1, 2010-October 31, 2017) (eFigure 1) and all further analyses were performed on the total cohort.

We compared patient characteristics, clinical care and outcomes across subgroups using chi-square tests for categorical variables and Kruskall-Wallis tests for continuous variables. Separate logistic regression models were used to examine the effect of coexisting condition subgroups on each of: in-hospital mortality, 30-day readmission, and ICU admission. Quantile regression was used to model the non-binary outcome: median hospital length-of-stay. Models were adjusted for age, sex, hospital, and LAPS. All analyses were performed in R version 4.0.0 (R Foundation for Statistical Computing, Vienna).

Results

Overall, 11,085 patients were included in the study cohort (eFigure 1). The median age was 79 (IQR 65-87) and 52.6% were male. The mean Charlson Index score was 1.7 (SD 1.7). The five most common coexisting conditions were chronic lung disease (n=3178, 28.7%), diabetes (n=2978, 26.9%), heart failure (n=1892, 17.1%), dementia (n=1401, 12.6%) and cancer (n=1194, 10.8%).

eTable 1 summarizes demographics, baseline characteristics and prevalence of coexisting conditions in the derivation, validation and total cohorts. There were 7066 patients in the derivation cohort and 4019 patients in the validation cohort, and the two cohorts were generally similar.

Cluster analysis

Subgroups were driven primarily by the five most common comorbidities in the cohort, and 72.5% of patients had at least one of these five conditions (Figure 1). A seven cluster solution was selected as the optimal set of
subgroups from our cluster analysis (Figure 1, also see eResults and eAppendix for more details): 1) “low comorbidity” subgroup (n=3052, 27.5%), which had none of the coexisting conditions in the Charlson Index; 2) “diabetes-heart failure-pulmonary” (DM-HF-Pulm) subgroup (n=1710, 15.4%), which was a multimorbid subgroup with high prevalence of all three of those conditions; 3) “pulmonary” subgroup (n=1621, 14.6%), which included patients with either chronic obstructive or restrictive lung diseases; 4) “diabetes” subgroup (n=1281, 11.6%); 5) “heart failure” subgroup (n=1370, 12.4%); 6) “dementia” subgroup (n=1038, 9.4%), and 7) “cancer” subgroup (n=1013, 9.1%).

Patient Characteristics

Subgroups differed significantly in age, sex and other baseline characteristics (Table 1). The “cancer” subgroup was the youngest of all the subgroups (median age 72 years) while the “dementia” subgroup was the oldest (median age 86 years). The “cancer” subgroup had the most males (60.7%), while the “dementia” subgroup had the least (45.9%). The “dementia” subgroup had the highest proportion of patients from a nursing home (37.6%) and arriving to hospital by ambulance (89.5%). The “DM-HF-Pulm” group had the highest presenting LAPS (mean=27.1, SD 18.8), whereas the “low comorbidity” subgroup had the lowest (mean=20.7, SD=15.3). The “cancer” subgroup had the highest Charlson index score (mean=3.8, SD 1.9) whereas the “low comorbidity” subgroup had the lowest (mean 0.0, SD 0.0), by definition.

Clinical care

The use of respiratory-acting antibiotic classes, glucocorticoids, inhalers, furosemide, and CT of the thorax differed significantly between subgroups (Table 2). The most notable differences were the high use of piperacillin-tazobactam (28.0%) and CT thorax (36.3%) in the “cancer” subgroup, compared to the overall population (13.3% and 18.3%, respectively). Use of fluoroquinolone antibiotics was highest in the “pulmonary” subgroup (48.2%) and CT thorax use was lowest in the dementia subgroup (5.7%). Use of glucocorticoids was
greatest in the “pulmonary” subgroup (64.9%) as was use of all inhaler types. Furosemide use was greatest in the “DM-HF-pulm” subgroup (61.6%).

Clinical outcomes

Subgroups differed significantly in the four clinical outcomes examined (Figure 2, Table 3). Compared to the overall study population, the “low comorbidity” subgroup had fewer deaths (4.2% vs 6.9%), ICU admissions (6.7% vs. 8.9%), 30-day readmissions (7.7% vs. 10.0%), and shorter hospital length-of-stay (median 3.7 days, IQR 2.0 to 6.7 days vs. 4.7 days, IQR 2.6 to 8.5 days). Conversely, the “DM-HF-Pulm” subgroup had worse outcomes than the overall population on all measures: deaths 8.4%, ICU admissions 14.4%, 30-day readmission 13.2%, and median length-of-stay 6.2 days (IQR 3.4 to 10.7 days).

After adjusting for age, sex, hospital, and presenting LAPS, the risk of death was greater in the “cancer” (adjusted OR: 2.91, 95% CI: 2.20, 3.86), “dementia” (aOR 1.73, 95%CI: 1.32, 2.27), “heart failure” (aOR 1.66, 95%CI: 1.27, 2.16), and “DM-HF-Pulm” (aOR 1.32, 95%CI: 1.02, 1.71) subgroups compared to the “low comorbidity” subgroup. The “heart failure” and “DM-HF-Pulm” subgroups had worse outcomes on all four measures compared to the “low comorbidity” subgroup. The “diabetes” subgroup had lower risk of death (aOR 0.65, 95% CI: 0.46, 0.93) than the “low comorbidity” subgroup and had no significant differences in ICU admission, readmission, or length-of-stay. The “pulmonary” subgroup had greater ICU use (aOR 1.61, 95% CI 1.28, 2.02) and median length-of-stay (0.44 days longer, 95% CI 0.17, 0.71 days) than the “low comorbidity” subgroup but no significant difference in death. The “dementia” subgroup had greater risk of death (aOR 1.73 95% CI 1.32, 2.27), readmission (aOR 1.35, 95% CI 1.05, 1.75) and longer median length-of-stay (1.32 days longer, 95% CI 0.93, 1.71 days) but no significant difference in ICU use.

Interpretation
We used machine learning techniques to identify seven reproducible and clinically-recognizable subgroups of patients hospitalized with CAP based on patterns of coexisting conditions. Our study offers four major contributions to the literature. First, we found that five disease categories were the most prevalent coexisting conditions and drive the pattern of clustering: chronic lung diseases, diabetes mellitus, heart failure, dementia, and cancer. Second, we characterized the pattern of disease clustering. Five subgroups were dominated by a single disease category (pulmonary, diabetes, heart failure, dementia, and cancer). One subgroup represented a classically “multimorbid” phenotype with high prevalence of chronic lung disease, diabetes, heart failure, renal disease and prior myocardial infarction and one subgroup reflected patients with little comorbidity. Third, we found that use of diagnostic imaging, antibiotics, and other medications differed among these subgroups. Fourth, clinical outcomes differed among these subgroups, even after controlling for age, sex, and severity of illness at presentation. Examining patterns of coexisting conditions, rather than single comorbidities, offers novel insights that align with a proposed paradigm shift from single disease treatment toward “cluster medicine” for patients with multimorbidity (31) and lays the groundwork for decision-support tools to personalize care.(32)

Comparison to previous studies and implications for future research

Our study extends the previous literature related to comorbidity and CAP, which has focused on describing the prevalence of coexisting conditions,(33) associating single coexisting conditions with outcomes,(7, 34-37) and measuring comorbidity in general(8-12) rather than exploring patterns of disease. Diabetes mellitus has been associated with significantly increased mortality in patients hospitalized with pneumonia.(35-37) We found that 42.7% of patients with diabetes were part of the subgroup with high rates of chronic lung disease and heart failure, 8.3% had coexisting dementia, and 6.0% had coexisting cancer. All of these subgroups had significantly greater mortality risk, and poorer outcomes in general, than patients with no comorbidities. However, another 43.0% of patients with diabetes were in a subgroup without other Charlson comorbidities and these patients had significantly lower mortality and no significant differences in ICU use, readmission or length-of-stay compared
to patients with no comorbidities. This reveals that the relationship between diabetes, pneumonia, and mortality is not as simple as was previously understood. The association between diabetes and adverse outcomes in pneumonia may be driven by the degree of other organ-system involvement and highlights interesting opportunities for future research.

The “DM-HF-Pulm” subgroup had the most coexisting conditions and had poor outcomes overall, similar to prior studies of multimorbidity in pneumonia. The specific pattern of coexisting conditions illuminates opportunities for further research in this subgroup. For example, the use of macrolide (55.6%) and fluoroquinolone (45.8%) antibiotics was not lower in this subgroup, but these drugs cause cardiac complications. Corticosteroids were prescribed in 51.1% of patients in this group, perhaps in part to treat concomitant COPD exacerbations, but corticosteroids may also worsen heart failure and glycemic control. Corticosteroid use varied across subgroups, from 64.9% in the “Pulmonary” subgroup to 11.5% of patients in the “low comorbidity” subgroup. There may be practice variation related to the controversial literature on the benefits of corticosteroids in non-severe CAP. Further research could seek to quantify whether the risks and benefits of corticosteroids vary across subgroups, and differences in net benefits may provide opportunities for more personalized medicine.

The “pulmonary” subgroup had greater ICU use and longer hospital stays but no increased risk of mortality, consistent with prior literature. These findings correspond with the COPD GOLD guidelines, which caution against therapeutic pessimism among patients hospitalized with acute exacerbations of COPD. Mortality was greater in the dementia, cancer and heart failure subgroups than in patients with no comorbidities, which is similar to previous studies. The dementia subgroup had less ICU and thoracic CT use overall, suggesting that clinicians and patients may be opting for less intensive approaches. The cancer subgroup had a greater use of thoracic CT scans (36.3% vs 18.3% overall) and greater use of broad-spectrum antibiotics (e.g. piperacillin-tazobactam used in 28.0% of patients vs 13.3% overall), which may be related to neutropenia or risk factors for Pseudomonas infection. However, there remains limited evidence about when to
select broader antibiotic therapy or advanced diagnostic imaging in patients with cancer and CAP. Further research should seek to clarify what patient factors are associated with differences in therapeutic and diagnostic choices and determine whether there are opportunities to standardize, personalize, and improve care.

**Limitations and Strengths**

Our study has several limitations. First, we used ICD-10 CA codes to identify medical conditions in our cohort, including CAP. Although some studies suggest these codes are highly specific, their sensitivity varies.(18, 28) This may lead to misclassification, primarily by underestimating certain conditions and overestimating the prevalence of the “low comorbidity” subgroup. We augmented ICD-10 CA codes with clinical data regarding antibiotic use to increase the specificity of our definition of CAP. Second, we used the Charlson comorbidity index to define chronic conditions, but this index is not exhaustive, leaving out some potentially important conditions including psychiatric illness. We also used the same disease groupings as in the Charlson index,(25) which do not represent single diseases (e.g. chronic lung disease, cancer, dementia, heart failure, and diabetes are all heterogeneous categories, to varying degrees). Nevertheless, the prevalence of the most common conditions in our cohort was generally similar to population-based studies of pneumonia in the United States,(33) the United Kingdom,(49) and Canada,(50) including several with prospectively-collected comorbidity data, suggesting our findings are likely generalizable. Third, coexisting conditions were measured at discharge and may not have been present on admission. However the majority of these conditions are chronic diseases and it is unlikely that the admission for CAP would represent the first occurrence of this disease. For example, the incidence of cancer after hospitalization for CAP has been reported as 1.1% within 90 days of discharge and the rate of discovery during the CAP hospitalization is likely even lower.(51) Fourth, our dataset included only patients admitted to GIM. Nearly all CAP patients are admitted to GIM at participating hospitals, with the exception of a small number of patients with complex lung diseases or acute coronary syndromes who may be cared for on dedicated respirology or cardiology units. The seven participating hospitals serve diverse multiethnic populations in two of Canada’s largest cities and we used temporally-split datasets to assess the
reproducibility of clustering results. We believe our results are likely generalizable but should be externally validated.

**Conclusion**

In this study, unsupervised machine learning methods were able to identify stable and clinically-recognizable subgroups of patients hospitalized to GIM with CAP based on coexisting conditions. Clinical care and outcomes vary among these subgroups, despite no strong evidence about how comorbid illnesses should inform treatment decisions. This highlights opportunities for future research about whether and how hospital care for patients with CAP can be more personalized.
**List of abbreviations**

CAP: Community-acquired pneumonia

CIHI: Canadian Institute for Health Information

CT: Computed tomography

GEMINI: General Medicine Inpatient Initiative

GIM: General Internal Medicine

ICD-10-CA: International and Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada

LAPS: Laboratory-based acute physiology score
Declarations

Ethics Approval

Also stated above in methods. This study received Research Ethics Board approval with a waiver of informed patient consent from all participating hospitals.

Consent for Publication: Not applicable.

Availability of data

Data from this manuscript can be accessed upon request to the corresponding author, to the extent that is possible in compliance with local research ethics board requirements and data sharing agreements.

Competing interests

The authors declare that they have no competing interests.

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Author’s contributions

The study was designed by SM, AAV and FR with substantial input from all authors. SM, HYJ, MF, LL-S, TT, AW, JK, JL, FR and AAV contributed to data collection. HYJ performed data analysis. MG provided methodological support regarding cluster analysis. All authors contributed to interpretation of the results. SM wrote the first manuscript draft. All authors provided input for critical revisions, approved the final version submitted for publication, and agreed to be accountable for all parts of the study.

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Figure Legends

**Figure 1.** Subgroups of patients with community acquired pneumonia admitted to General Internal Medicine (2010-2017) identified by cluster analysis according to coexisting conditions. See text for details regarding cluster analysis. Number refers to number of patients. Conditions refer to coexisting conditions.
Pulmonary=chronic lung disease including both obstructive and restrictive, DM= diabetes mellitus, CHF=congestive heart failure, renal=renal disease, MI=myocardial infarction, Liver= liver disease, PVD=peripheral vascular disease, Rheumatic=rheumatic disease, PUD=peptic ulcer disease. Subgroups were named by the condition(s) present in all cluster members or a large proportion if no single condition was present in 100% of the patients within a subgroup. DM-HF-Pulm= subgroup composed of a large portion of patients with diabetes, congestive heart failure and chronic lung disease.

**Figure 2.** Outcomes for subgroups of patients with community acquired pneumonia admitted to General Internal Medicine (2010-2017) identified by cluster analysis according to coexisting conditions. Coloured bars are the differences in outcome (proportion or median) between the overall cohort and each subgroup. Overall cohort includes admissions that are not belonging to the subgroup being compared, e.g. the dementia subgroup admissions vs all other admissions except those in dementia subgroup. Error bars represent 95% confidence intervals (Wilson’s score based interval for proportions and percentile bootstrap interval with 2000 replications for length-of-stay). In the table, the unadjusted outcomes are reported for each subgroup.
Table 1. Baseline characteristics for subgroups of patients with community acquired pneumonia admitted to General Internal Medicine (2010-2017) identified by cluster analysis according to coexisting conditions.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Low Comorbidity</th>
<th>DM-HF-Pulm</th>
<th>Pulmonary</th>
<th>Diabetes</th>
<th>Heart Failure</th>
<th>Dementia</th>
<th>Cancer</th>
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<tr>
<td>Number</td>
<td>11085</td>
<td>3052</td>
<td>1710</td>
<td>1621</td>
<td>1281</td>
<td>1370</td>
<td>1038</td>
<td>1013</td>
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<tr>
<td>Male sex (%)</td>
<td>5832 (52.6)</td>
<td>1533 (50.2)</td>
<td>940 (55.0)</td>
<td>838 (51.7)</td>
<td>741 (57.7)</td>
<td>689 (50.3)</td>
<td>476 (45.9)</td>
<td>615 (60.7)</td>
<td>&lt;0.001</td>
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<tr>
<td>From nursing home (%)</td>
<td>1224 (11.0)</td>
<td>213 (7.0)</td>
<td>237 (13.9)</td>
<td>113 (7.0)</td>
<td>102 (8.0)</td>
<td>139 (10.1)</td>
<td>390 (37.6)</td>
<td>30 (3.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Arrived to hospital via ambulance (%)</td>
<td>6849 (61.8)</td>
<td>1672 (54.8)</td>
<td>1146 (67.0)</td>
<td>1002 (61.8)</td>
<td>765 (59.7)</td>
<td>867 (63.3)</td>
<td>929 (89.5)</td>
<td>468 (68.2)</td>
<td>&lt;0.001</td>
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<td>LAPS (mean SD)</td>
<td>23.4 (16.9)</td>
<td>20.7 (15.3)</td>
<td>27.1 (18.8)</td>
<td>22.1 (17.0)</td>
<td>25.8 (16.6)</td>
<td>25.3 (17.7)</td>
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<td>21.2 (15.8)</td>
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<td>Charlson score (mean SD)</td>
<td>1.7 (1.7)</td>
<td>0.0 (0.0)</td>
<td>3.4 (1.4)</td>
<td>1.3 (0.7)</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.1)</td>
<td>1.8 (1.0)</td>
<td>3.8 (2.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 1 legend. Number=number of patients. Age is in years, IQR=interquartile range, LAPS=laboratory acute physiology score, Charlson score=calculated Charlson comorbidity index. P=2-tailed p-value for differences between subgroups, determined by chi-square test for categorical variables and Kruskall-Wallis tests for continuous variables.
Table 2: Antibiotic use, medications and imaging use among subgroups of patients with community acquired pneumonia admitted to General Internal Medicine (2010-2017) identified by cluster analysis according to coexisting conditions.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall</th>
<th>Low Comorbidity</th>
<th>DM-HF-Pulm</th>
<th>Pulmonary</th>
<th>Diabetes</th>
<th>Heart Failure</th>
<th>Dementia</th>
<th>Cancer</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11085</td>
<td>3052</td>
<td>1710</td>
<td>1621</td>
<td>1281</td>
<td>1370</td>
<td>1038</td>
<td>1013</td>
<td></td>
</tr>
<tr>
<td>Third Gen Ceph</td>
<td>6696</td>
<td>(60.4)</td>
<td>1921</td>
<td>(62.9)</td>
<td>1021</td>
<td>(59.7)</td>
<td>885</td>
<td>(54.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Macrolide</td>
<td>6305</td>
<td>(56.9)</td>
<td>1803</td>
<td>(59.1)</td>
<td>950</td>
<td>(55.6)</td>
<td>892</td>
<td>(55.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>4592</td>
<td>(41.4)</td>
<td>1136</td>
<td>(37.2)</td>
<td>784</td>
<td>(45.8)</td>
<td>781</td>
<td>(48.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pen-derived BL</td>
<td>2131</td>
<td>(19.2)</td>
<td>614</td>
<td>(20.1)</td>
<td>310</td>
<td>(18.1)</td>
<td>357</td>
<td>(22.0)</td>
<td></td>
</tr>
<tr>
<td>Pip-tazo</td>
<td>1472</td>
<td>(13.3)</td>
<td>334</td>
<td>(10.9)</td>
<td>232</td>
<td>(13.6)</td>
<td>148</td>
<td>(9.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>862</td>
<td>(7.8)</td>
<td>253</td>
<td>(8.3)</td>
<td>110</td>
<td>(6.4)</td>
<td>104</td>
<td>(6.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MRSA</td>
<td>592</td>
<td>(5.3)</td>
<td>164</td>
<td>(5.4)</td>
<td>82</td>
<td>(4.8)</td>
<td>58</td>
<td>(3.6)</td>
<td>0.002</td>
</tr>
<tr>
<td>Simple penicillins</td>
<td>296</td>
<td>(2.7)</td>
<td>96</td>
<td>(3.1)</td>
<td>43</td>
<td>(2.5)</td>
<td>43</td>
<td>(2.7)</td>
<td>0.292</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>159</td>
<td>(1.4)</td>
<td>24</td>
<td>(0.8)</td>
<td>35</td>
<td>(2.0)</td>
<td>46</td>
<td>(2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>115</td>
<td>(1.0)</td>
<td>19</td>
<td>(0.6)</td>
<td>19</td>
<td>(1.1)</td>
<td>23</td>
<td>(1.4)</td>
<td></td>
</tr>
<tr>
<td>Carbapenems (p)</td>
<td>106</td>
<td>(1.0)</td>
<td>16</td>
<td>(0.5)</td>
<td>15</td>
<td>(0.9)</td>
<td>11</td>
<td>(0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>59</td>
<td>(0.5)</td>
<td>11</td>
<td>(0.4)</td>
<td>11</td>
<td>(0.6)</td>
<td>6</td>
<td>(0.4)</td>
<td>0.468</td>
</tr>
<tr>
<td>Carbapenems (np)</td>
<td>38</td>
<td>(0.3)</td>
<td>7</td>
<td>(0.2)</td>
<td>5</td>
<td>(0.3)</td>
<td>7</td>
<td>(0.4)</td>
<td></td>
</tr>
<tr>
<td>CT thorax</td>
<td>2032</td>
<td>(18.3)</td>
<td>609</td>
<td>(20.0)</td>
<td>241</td>
<td>(14.1)</td>
<td>341</td>
<td>(21.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Furosemide</td>
<td>3217</td>
<td>(29.0)</td>
<td>441</td>
<td>(14.4)</td>
<td>1054</td>
<td>(61.6)</td>
<td>314</td>
<td>(19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucocorticoid</td>
<td>3119</td>
<td>(28.1)</td>
<td>351</td>
<td>(11.5)</td>
<td>874</td>
<td>(51.1)</td>
<td>1052</td>
<td>(64.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SABA</td>
<td>5179</td>
<td>(46.7)</td>
<td>976</td>
<td>(32.0)</td>
<td>1245</td>
<td>(72.8)</td>
<td>1355</td>
<td>(83.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SAMA</td>
<td>3611</td>
<td>(32.6)</td>
<td>530</td>
<td>(17.4)</td>
<td>1021</td>
<td>(59.7)</td>
<td>1093</td>
<td>(67.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LABA</td>
<td>100</td>
<td>(0.9)</td>
<td>8</td>
<td>(0.3)</td>
<td>24</td>
<td>(1.4)</td>
<td>48</td>
<td>(3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAMA</td>
<td>1770</td>
<td>(16.0)</td>
<td>126</td>
<td>(4.1)</td>
<td>595</td>
<td>(34.8)</td>
<td>733</td>
<td>(45.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 2 legend. Number=number of patients. Antibiotics included only those specifically mentioned in the IDSA guidelines(13, 23) or Dragen et al.(22) Cephalexin was also included since it has the same spectrum of activity to cefazolin. Third gen Ceph= Third generation cephalosporin=Ceftriaxone, cefotaxime, cefepime, cefditoren, cefpodoxime, ceftaroline. Macrolide=Azithromycin, clarithromycin, erythromycin. Fluoroquinolone=levofloxacin, moxifloxacin, ciprofloxacin, gemifloxacin. Tetracyclines=doxycycline . Pen-derived BL=Penicillin-derived beta-lactamases=amoxicillin-clavulanic acid, ampicillin-sulbactam, ticarcillin-clavulanate. Pip-tazo=piperacillin-tazobactam. Carbapenems (p)= carbapenems (pseudomonas coverage)= meropenem, imipenem, impenem+cilastatin. Carbapenem (np)= carbapenems (no pseudomonas coverage)=ertapenem. MRSA coverage=vancomycin, linezolid. Simple penicillins=Penicillin G, amoxicillin, ticarcillin, flucloxacillin, ampicillin, piperacillin. Other=aztreonam, streptomycin, colistin, gentamicin, Septra (trimethoprim-sulfamethoxazole), 1st+2nd gen cephalosporins (cefazolin, cefprozil, cefuroxime, cephalexin). CT thorax= CT thorax performed in first 4 days of admission. SABA=short-acting beta agonist. SAMA=short-acting muscarinic antagonist. LABA=long-acting beta agonist. LAMA=long-acting muscarinic antagonist. P=2-tailed p-value for differences between subgroups, determined by chi-square test.
Table 3. Association of patient subgroup based on coexisting conditions with clinical outcomes after multivariable adjustment.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Mortality OR (95% CI)</th>
<th>p-value</th>
<th>ICU Admission OR (95% CI)</th>
<th>p-value</th>
<th>30-day readmission OR (95% CI)</th>
<th>p-value</th>
<th>Median Length of Stay Coeff (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low comorbidity</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM-HF-Pulm</td>
<td>1.32 (1.02-1.71)</td>
<td>0.036</td>
<td>2.50 (2.02-3.10)</td>
<td>&lt;0.001</td>
<td>1.58 (1.28-1.95)</td>
<td>&lt;0.001</td>
<td>1.68 (1.35-2.01)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0.83 (0.61-1.12)</td>
<td>0.230</td>
<td>1.61 (1.28-2.02)</td>
<td>&lt;0.001</td>
<td>1.20 (0.96-1.49)</td>
<td>0.112</td>
<td>0.44 (0.17-0.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.65 (0.46-0.93)</td>
<td>0.017</td>
<td>1.27 (0.98-1.65)</td>
<td>0.065</td>
<td>1.04 (0.81-1.33)</td>
<td>0.774</td>
<td>0.22 (-0.05-0.49)</td>
<td>0.112</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.66 (1.27-2.16)</td>
<td>&lt;0.001</td>
<td>1.84 (1.45-2.32)</td>
<td>&lt;0.001</td>
<td>1.32 (1.05-1.66)</td>
<td>0.017</td>
<td>1.37 (1.03-1.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia</td>
<td>1.73 (1.32-2.27)</td>
<td>&lt;0.001</td>
<td>0.90 (0.64-1.28)</td>
<td>0.571</td>
<td>1.35 (1.05-1.75)</td>
<td>0.019</td>
<td>1.32 (0.93-1.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.91 (2.20-3.86)</td>
<td>&lt;0.001</td>
<td>1.32 (0.98-1.76)</td>
<td>0.063</td>
<td>1.38 (1.06-1.78)</td>
<td>0.016</td>
<td>1.15 (0.78-1.52)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3 legend. Results for mortality, ICU admission and 30-day readmission are from binary Logistic Regression analysis. Results for length of stay are from Quantile Regression. Each subgroup was defined as a binary variable and compared to the "low comorbidity" subgroup as a reference. Models were adjusted for patient age, sex, hospital, and laboratory-based acute physiology score. OR=odds ratio. Coeff=coefficient in quantile regression. CI=confidence interval.
Subgroups of patients with community acquired pneumonia admitted to General Internal Medicine (2010-2017) identified by cluster analysis according to coexisting conditions. See text for details regarding cluster analysis. Number refers to number of patients. Conditions refer to coexisting conditions. Pulmonary=chronic lung disease including both obstructive and restrictive, DM=diabetes mellitus, CHF=congestive heart failure, renal=renal disease, MI=myocardial infarction, Liver=liver disease, PVD=peripheral vascular disease, Rheumatic=rheumatic disease, PUD=peptic ulcer disease. Subgroups were named by the condition(s) present in all cluster members or a large proportion if no single condition was present in 100% of the patients within a subgroup. DM-HF-Pulm= subgroup composed of a large portion of patients with diabetes, congestive heart failure and chronic lung disease.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Low Comorbidity</th>
<th>DM-HF-Pulm</th>
<th>Pulmonary</th>
<th>Heart Failure</th>
<th>Dementia</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1208 (50.0%)</td>
<td>726 (100.0%)</td>
<td>1208 (100.0%)</td>
<td>726 (100.0%)</td>
<td>726 (100.0%)</td>
<td>726 (100.0%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>DM</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>CHF</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>MI</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Liver</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>PVD</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>PUD</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>HIV</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1208 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

190x85mm (230 x 230 DPI)
Outcomes for subgroups of patients with community acquired pneumonia admitted to General Internal Medicine (2010-2017) identified by cluster analysis according to coexisting conditions. Coloured bars are the differences in outcome (proportion or median) between the overall cohort and each subgroup. Overall cohort includes admissions that are not belonging to the subgroup being compared, e.g. the dementia subgroup admissions vs all other admissions except those in dementia subgroup. Error bars represent 95% confidence intervals (Wilson’s score based interval for proportions and percentile bootstrap interval with 2000 replications for length-of-stay). In the table, the unadjusted outcomes are reported for each subgroup.
Supporting information for “Using machine learning to identify patterns of coexisting conditions and outcomes in adults hospitalized with community-acquired pneumonia: A multicentre cohort study”

Sarah L. Malecki, Hae Young Jung, Mark Green, Samir Gupta, Derek MacFadden, Nick Daneman, Ross Upshur, Michael Fralick, Lauren Lapointe-Shaw, Terence Tang, Adina Weinerman, Janice L. Kwan, Jessica J. Liu, Fahad Razak, Amol A. Verma

eMethods, p. 2

eResults, p. 2

eFigure 1. Cohort Creation, p. 3

eAppendix. Cluster analysis figures, p. 4-8

eTable 1. Baseline characteristics and coexisting conditions for patients with community acquired pneumonia admitted to general internal medicine (2010-2017), p. 9

eTable 2. Clustering solution for PAM with k=6 clusters (Derivation cohort), p. 10

eTable 3. Clustering solution for PAM with k=6 clusters (Validation Cohort), p. 11

References, p. 12
eMethods

Cluster analysis

We used a consensus cluster analysis approach to derive clusters in the derivation cohort, similar to that employed in recent studies describing sepsis phenotypes\(^1\) and ICU subgroups\(^2\). Using a baseline clustering algorithm, this approach consists of performing \(x\) algorithm replications to form a consensus matrix between pairs of observations. A hierarchical clustering algorithm is then run on the consensus values to obtain the final clustering solution.

We compared the performance of three different baseline clustering algorithms (K-modes,\(^3\) partitioning around mediods [PAM]\(^4\) and hierarchical agglomerative clustering [HAC]).\(^4\) These three algorithms were selected because they could each deal with binary data (an important limitation of common methods). There is no common agreement in the literature over the ‘best’ clustering algorithms. Comparing the solutions derived from three models allowed us to evaluate their performance, minimise any bias introduced by relying on a single method and selected the approach that performed best with our data. Models were run using a modified version of the R package “ConsensusClusterPlus”. We performed 100 replications of K-modes, PAM and HAC using 80% resampling of the cohort with each iteration to obtain three final consensus clustering solutions.

Unsupervised cluster analysis methods require defining the number of clusters within a model (with the algorithm then iteratively refining the allocation of cases into the selected number of groups). We did not have a priori justification of what types of clusters to expect. We took an exploratory data-driven approach to select the number of clusters that best summarised our data. Because there is no single metric to define optimal clustering, we examined numerous measures and visualizations to select the best-fitting cluster solution across \(k=2-10\) clusters. We did not consider more than 10 clusters as we wanted to find the parsimonious solution. Similar to Seymour et al. 2019,\(^1\) best fit was determined by examination of characteristics of consensus cumulative distribution function plots\(^1\) and consensus matrix heat maps to select a solution that maximized separation of clusters.\(^1\) We ensured that pairwise consensus values between cluster members was >0.8.\(^1\) We also calculated and plotted the silhouette width\(^5\) (looking for the maximum value), expected versus observed cluster size and total sum of squares (looking for the minimum value) across \(k=2-10\) clusters.

Finally, given the subjective nature of interpreting cluster analyses, we examined the clusters for identifiable clinical patterns. Study co-investigators with clinical expertise in general internal medicine and respirology were asked to provide feedback on the interpretation of cluster characteristics and if they made sense clinically, to come to a final consensus on the optimal clustering solution.

eResults

Cluster Analysis

Based on examination of the consensus plots and additional indices to evaluate different clustering solutions (see Appendix), PAM was selected as the method of choice because it yielded a better clustering solution than K-modes or HAC, regardless of the number of clusters chosen.

For the derivation cohort, clustering solution PAM \(k=7\) was the best solution based on objective indices selected (Appendix). Other candidate clustering solutions, including PAM \(k=6\) and \(k=8\) were presented to the coauthors. Qualitatively, the clusters produced by PAM \(k=5,6,7\) and \(8\) solutions were similar and PAM\(^7\) was selected as not only the best on the objective indices but also balancing clinically meaningful results with simplicity. PAM \(k=7\) was reproducible in the validation cohort (eTable 2 and 3). Therefore, \(k=7\) clusters was selected as the most clinically relevant and reproducible clustering solution.
eFigure 1. Cohort creation.

1. Derivation Cohort Creation

- All GIM admissions from April 1, 2010 to March 31, 2015
  - n=149,614
- Most responsible discharge diagnosis: Pneumonia or COPD
  - and Pneumonia
  - n=10,883
- Received respiratory acting antibiotic
  - n=9,059
- Admission to hospital in last 30 days
  - n=1,124
- Not admitted from the ED
  - n=563
- Excluded repeat admissions
  - n=706
- Final complete cohort
  - n=7,066

2. Validation Cohort Creation

- All GIM admissions from April 1, 2015 to October 31, 2017
  - n=89,582
- Most responsible discharge diagnosis: Pneumonia or COPD
  - and Pneumonia
  - n=6,239
- Received respiratory acting antibiotic
  - n=5,352
- Admission to hospital in last 30 days
  - n=540
- Not admitted from the ED
  - n=167
- Excluded repeat admissions
  - n=275
- Excluded those present in derivation cohort
  - n=351
- Final complete cohort
  - n=4,019

3. Total Cohort Creation

- All GIM admissions from April 1, 2010 to October 31, 2017
  - n=239,196
- Most responsible discharge diagnosis: Pneumonia or COPD
  - and Pneumonia
  - n=17,322
- Received respiratory acting antibiotic
  - n=14,441
- Admission to hospital in last 30 days
  - n=1,664
- Not admitted from the ED
  - n=330
- Excluded repeat admissions
  - n=1,332
- Final complete cohort
  - n=11,085
eAppendix : Cluster analysis figures

Examples of plots used when selecting the best clustering solution. For all but the first plot, the ConsensusClusterPlus package was used in R to generate plots.⁶

A. Comparison of different baseline clustering algorithms (HAC, PAM) in the derivation cohort.

Different calculated indices used to compare algorithms for k=2-10 clusters. K-modes performed poorly overall and is not pictured here. Avg.sw=silhouette width looking to maximize, exp=expected vs observed cluster size looking to minimize, and wss=within-cluster sum of squares looking to minimize.
Consensus matrix heat maps for k=7 clusters in the derivation cohort. PAM left, HAC on the right.
B. Comparing k=2-10 clusters for PAM in derivation cohort

Top panel left to right: cumulative distribution function (CDF) plot looking for the number of clusters maximizing the CDF, and pairwise consensus values between clusters, looking for at least 0.8. Bottom panel: delta area for the CDF function curve, looking for the solution with the biggest change.
C. Comparing $k=2-10$ clusters for PAM in validation cohort
D. Comparing k=2-10 clusters for PAM in total cohort

![consensus CDF graph](image1)

![cluster-consensus graph](image2)

![Delta area graph](image3)
eTable 1. Baseline characteristics and coexisting conditions for patients with community acquired pneumonia admitted to general internal medicine (2010-2017)

<table>
<thead>
<tr>
<th>Baseline characteristic or coexisting condition</th>
<th>Overall Cohort</th>
<th>Derivation Cohort</th>
<th>Validation Cohort</th>
<th>Standardized Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11085</td>
<td>7066</td>
<td>4019</td>
<td></td>
</tr>
<tr>
<td>Age (years, median [IQR])</td>
<td>79.0 [65.0, 87.0]</td>
<td>79.0 [66.0, 87.0]</td>
<td>78.0 [65.0, 87.0]</td>
<td>0.03</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>5832 (52.6)</td>
<td>3737 (52.9)</td>
<td>2095 (52.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>From nursing home (%)</td>
<td>1224 (11.0)</td>
<td>856 (12.1)</td>
<td>365 (9.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Transport via ambulance (%)</td>
<td>6849 (61.8)</td>
<td>4433 (62.7)</td>
<td>2396 (59.6)</td>
<td>0.06</td>
</tr>
<tr>
<td>LAPS (mean (SD))</td>
<td>23.4 (16.9)</td>
<td>24.0 (17.2)</td>
<td>22.4 (16.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Charlson index (mean (SD))</td>
<td>1.7 (1.7)</td>
<td>1.7 (1.7)</td>
<td>1.6 (1.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulmonary (%)</td>
<td>3178 (28.7)</td>
<td>2119 (30.0)</td>
<td>1046 (26.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>DM (%)</td>
<td>2978 (26.9)</td>
<td>1862 (26.4)</td>
<td>1113 (27.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>1892 (17.1)</td>
<td>1261 (17.8)</td>
<td>603 (15.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dementia (%)</td>
<td>1401 (12.6)</td>
<td>931 (13.2)</td>
<td>459 (11.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>1194 (10.8)</td>
<td>690 (9.8)</td>
<td>496 (12.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Renal (%)</td>
<td>703 (6.3)</td>
<td>464 (6.6)</td>
<td>229 (5.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>MI (%)</td>
<td>512 (4.6)</td>
<td>367 (5.2)</td>
<td>133 (3.3)</td>
<td>0.09</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>364 (3.3)</td>
<td>285 (4.0)</td>
<td>76 (1.9)</td>
<td>0.13</td>
</tr>
<tr>
<td>Liver (%)</td>
<td>265 (2.4)</td>
<td>159 (2.3)</td>
<td>103 (2.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>236 (2.1)</td>
<td>165 (2.3)</td>
<td>73 (1.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Rheumatic (%)</td>
<td>211 (1.9)</td>
<td>143 (2.0)</td>
<td>71 (1.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Paralysis (%)</td>
<td>125 (1.1)</td>
<td>86 (1.2)</td>
<td>40 (1.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>PUD (%)</td>
<td>75 (0.7)</td>
<td>48 (0.7)</td>
<td>23 (0.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>HIV (%)</td>
<td>12 (0.1)</td>
<td>9 (0.1)</td>
<td>4 (0.1)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

eTable 1 legend. Coexisting conditions were defined based on a previously published coding algorithm to define charlson comorbidities based on ICD-10 codes (see text). N refers to number of patients. Age is in years. LAPS=laboratory-based acute physiology score. Charlson score=calculated Charlson comorbidity index. Pulmonary=chronic lung disease including both obstructive and restrictive, DM= diabetes mellitus, CHF=congestive heart failure, renal=renal disease, MI=myocardial infarction, Liver= liver disease, PVD=peripheral vascular disease, Rheumatic=rheumatic disease, PUD=peptic ulcer disease.
### Table 2. Clustering solution for PAM with k=7 clusters (Derivation cohort)

<table>
<thead>
<tr>
<th></th>
<th>Low Comorbidity</th>
<th>DM-HF-Pulm</th>
<th>Pulmonary</th>
<th>Diabetes</th>
<th>Heart Failure</th>
<th>Dementia</th>
<th>Cancer</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>1910</td>
<td>1149</td>
<td>1060</td>
<td>758</td>
<td>918</td>
<td>693</td>
<td>578</td>
<td></td>
</tr>
<tr>
<td><strong>Age (years, median [IQR])</strong></td>
<td>75.0 [54.0, 86.0]</td>
<td>80.0 [72.0, 87.0]</td>
<td>77.0 [64.0, 84.0]</td>
<td>75.0 [66.0, 83.0]</td>
<td>82.0 [68.2, 89.0]</td>
<td>86.0 [81.0, 90.0]</td>
<td>72.0 [61.2, 83.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Male sex (%)</strong></td>
<td>958 (50.2)</td>
<td>626 (54.5)</td>
<td>571 (53.9)</td>
<td>437 (57.7)</td>
<td>693 (51.1)</td>
<td>328 (47.3)</td>
<td>348 (60.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>From nursing home (%)</strong></td>
<td>149 (7.8)</td>
<td>160 (13.9)</td>
<td>88 (8.3)</td>
<td>58 (7.7)</td>
<td>105 (11.4)</td>
<td>272 (39.2)</td>
<td>24 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Transport by ambulance (%)</strong></td>
<td>1051 (55.0)</td>
<td>768 (66.8)</td>
<td>655 (61.8)</td>
<td>454 (59.9)</td>
<td>589 (64.2)</td>
<td>627 (90.5)</td>
<td>289 (50.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>LAPS (mean (SD))</strong></td>
<td>21.2 (15.5)</td>
<td>27.7 (19.1)</td>
<td>22.7 (17.4)</td>
<td>26.2 (16.7)</td>
<td>25.2 (17.8)</td>
<td>24.5 (16.6)</td>
<td>22.6 (16.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Charlson score (mean (SD))</strong></td>
<td>0.0 (0.0)</td>
<td>3.4 (1.4)</td>
<td>1.3 (0.8)</td>
<td>1.8 (1.0)</td>
<td>1.8 (1.1)</td>
<td>1.8 (1.1)</td>
<td>3.8 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Pulmonary (%)</strong></td>
<td>0 (0.0)</td>
<td>858 (74.7)</td>
<td>1060 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>105 (15.2)</td>
<td>96 (16.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>DM (%)</strong></td>
<td>0 (0.0)</td>
<td>849 (73.9)</td>
<td>0 (0.0)</td>
<td>758 (100.0)</td>
<td>0 (0.0)</td>
<td>157 (22.7)</td>
<td>98 (17.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>CHF (%)</strong></td>
<td>0 (0.0)</td>
<td>771 (67.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>490 (53.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Dementia (%)</strong></td>
<td>0 (0.0)</td>
<td>127 (11.1)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>76 (8.3)</td>
<td>693 (100.0)</td>
<td>35 (6.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Cancer (%)</strong></td>
<td>0 (0.0)</td>
<td>73 (6.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>39 (4.2)</td>
<td>0 (0.0)</td>
<td>578 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Renal (%)</strong></td>
<td>0 (0.0)</td>
<td>97 (8.4)</td>
<td>57 (5.4)</td>
<td>52 (6.9)</td>
<td>183 (19.9)</td>
<td>49 (7.1)</td>
<td>26 (4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MI (%)</strong></td>
<td>0 (0.0)</td>
<td>119 (10.4)</td>
<td>41 (3.9)</td>
<td>36 (4.7)</td>
<td>121 (13.2)</td>
<td>32 (4.6)</td>
<td>18 (3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Stoke (%)</strong></td>
<td>0 (0.0)</td>
<td>56 (4.9)</td>
<td>24 (2.3)</td>
<td>38 (5.0)</td>
<td>98 (10.7)</td>
<td>50 (7.2)</td>
<td>19 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Liver (%)</strong></td>
<td>0 (0.0)</td>
<td>23 (2.0)</td>
<td>34 (3.2)</td>
<td>19 (2.5)</td>
<td>70 (7.6)</td>
<td>4 (0.6)</td>
<td>9 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PVD (%)</strong></td>
<td>0 (0.0)</td>
<td>48 (4.2)</td>
<td>27 (2.5)</td>
<td>17 (2.2)</td>
<td>50 (5.4)</td>
<td>11 (1.6)</td>
<td>12 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Rheumatic (%)</strong></td>
<td>0 (0.0)</td>
<td>20 (1.7)</td>
<td>23 (2.2)</td>
<td>8 (1.1)</td>
<td>79 (8.6)</td>
<td>6 (0.9)</td>
<td>7 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Paralysis (%)</strong></td>
<td>0 (0.0)</td>
<td>6 (0.5)</td>
<td>5 (0.5)</td>
<td>12 (1.6)</td>
<td>45 (4.9)</td>
<td>12 (1.7)</td>
<td>6 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>PUD (%)</strong></td>
<td>0 (0.0)</td>
<td>9 (0.8)</td>
<td>8 (0.8)</td>
<td>4 (0.5)</td>
<td>22 (2.4)</td>
<td>3 (0.4)</td>
<td>2 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>HIV (%)</strong></td>
<td>0 (0.0)</td>
<td>3 (0.3)</td>
<td>4 (0.4)</td>
<td>0 (0.0)</td>
<td>1 (0.1)</td>
<td>1 (0.1)</td>
<td>0 (0.0)</td>
<td>0.088</td>
</tr>
</tbody>
</table>

**Table 2 legend.** See text for details regarding cluster analysis. Number refers to number of patients. LAPS= laboratory-based acute physiology score. Charlson score=calculated Charlson comorbidity index. Pulmonary= chronic lung disease including both obstructive and restrictive, DM= diabetes mellitus, CHF= congregate heart failure, Renal= renal disease, MI= myocardial infarction, Liver= liver disease, PVD= peripheral vascular disease, Rheumatic= rheumatic disease, PUD= peptic ulcer disease. Subgroups were named by the condition(s) present in all cluster members or a large proportion if no single condition was present in 100% of the patients within a subgroup. DM-HF-Pulm = subgroup composed of a large portion of patients with diabetes, congestive heart failure and chronic lung disease. P=2-tailed p-value for differences between subgroups, determined by chi-square test for categorical variables and Kruskall-Wallis tests for continuous variables.
### eTable 3. Clustering solution for PAM with k=7 clusters (Validation Cohort)

<table>
<thead>
<tr>
<th></th>
<th>Low Comorbidity</th>
<th>DM-HF-Pulm</th>
<th>Pulmonary</th>
<th>Diabetes</th>
<th>Heart Failure</th>
<th>Dementia</th>
<th>Cancer</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>1156</td>
<td>533</td>
<td>567</td>
<td>532</td>
<td>456</td>
<td>343</td>
<td>432</td>
<td></td>
</tr>
<tr>
<td>Age (years, median [IQR])</td>
<td>75.0 [57.0, 86.0]</td>
<td>80.0 [69.0, 86.0]</td>
<td>77.0 [63.5, 85.0]</td>
<td>75.0 [65.0, 83.0]</td>
<td>83.0 [69.0, 90.0]</td>
<td>87.0 [82.0, 91.0]</td>
<td>80.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>585 (50.6)</td>
<td>293 (55.0)</td>
<td>278 (49.0)</td>
<td>310 (58.3)</td>
<td>224 (49.1)</td>
<td>143 (41.7)</td>
<td>262 (60.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>From nursing home (%)</td>
<td>68 (5.9)</td>
<td>75 (14.1)</td>
<td>24 (4.2)</td>
<td>42 (7.9)</td>
<td>35 (7.7)</td>
<td>113 (32.9)</td>
<td>8 (1.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Transport by ambulance (%)</td>
<td>638 (55.2)</td>
<td>347 (65.1)</td>
<td>342 (60.3)</td>
<td>320 (60.2)</td>
<td>274 (60.1)</td>
<td>301 (87.8)</td>
<td>174 (40.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LAPS (mean (SD))</td>
<td>20.0 (14.8)</td>
<td>25.7 (17.8)</td>
<td>20.5 (16.4)</td>
<td>25.2 (16.1)</td>
<td>25.7 (17.7)</td>
<td>24.0 (15.4)</td>
<td>19.5 (15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Charlson score (mean (SD))</td>
<td>0.0 (0.0)</td>
<td>3.3 (1.4)</td>
<td>1.2 (0.7)</td>
<td>1.8 (0.9)</td>
<td>1.8 (1.1)</td>
<td>1.6 (0.9)</td>
<td>3.8 (2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DM (%)</td>
<td>0 (0.0)</td>
<td>412 (77.3)</td>
<td>0 (0.0)</td>
<td>532 (100.0)</td>
<td>0 (0.0)</td>
<td>89 (25.9)</td>
<td>80 (18.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary (%)</td>
<td>0 (0.0)</td>
<td>371 (69.6)</td>
<td>567 (100.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>37 (10.8)</td>
<td>71 (16.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CHF (%)</td>
<td>0 (0.0)</td>
<td>345 (64.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>258 (56.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cancer (%)</td>
<td>0 (0.0)</td>
<td>45 (8.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>19 (4.2)</td>
<td>0 (0.0)</td>
<td>432 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dementia (%)</td>
<td>0 (0.0)</td>
<td>57 (10.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>37 (8.1)</td>
<td>343 (100.0)</td>
<td>22 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal (%)</td>
<td>0 (0.0)</td>
<td>33 (6.2)</td>
<td>26 (4.6)</td>
<td>21 (3.9)</td>
<td>113 (24.8)</td>
<td>13 (3.8)</td>
<td>23 (5.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI (%)</td>
<td>0 (0.0)</td>
<td>40 (7.5)</td>
<td>16 (2.8)</td>
<td>20 (3.8)</td>
<td>39 (8.6)</td>
<td>9 (2.6)</td>
<td>9 (2.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>0 (0.0)</td>
<td>15 (2.8)</td>
<td>10 (1.8)</td>
<td>12 (2.3)</td>
<td>29 (6.4)</td>
<td>4 (1.2)</td>
<td>6 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Liver (%)</td>
<td>0 (0.0)</td>
<td>14 (2.6)</td>
<td>19 (3.4)</td>
<td>14 (2.6)</td>
<td>38 (8.3)</td>
<td>2 (0.6)</td>
<td>16 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>0 (0.0)</td>
<td>22 (4.1)</td>
<td>4 (0.7)</td>
<td>10 (1.9)</td>
<td>21 (4.6)</td>
<td>6 (1.7)</td>
<td>10 (2.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rheumatic (%)</td>
<td>0 (0.0)</td>
<td>4 (0.8)</td>
<td>10 (1.8)</td>
<td>11 (2.1)</td>
<td>38 (8.3)</td>
<td>2 (0.6)</td>
<td>6 (1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Paralysis (%)</td>
<td>0 (0.0)</td>
<td>5 (0.9)</td>
<td>3 (0.5)</td>
<td>10 (1.9)</td>
<td>18 (3.9)</td>
<td>3 (0.9)</td>
<td>1 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PUD (%)</td>
<td>0 (0.0)</td>
<td>2 (0.4)</td>
<td>4 (0.7)</td>
<td>4 (0.8)</td>
<td>9 (2.0)</td>
<td>2 (0.6)</td>
<td>2 (0.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>HIV (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (0.5)</td>
<td>1 (0.2)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

**eTable 3 legend.** See text for details regarding cluster analysis. Number refers to number of patients. LAPS=laboratory-based acute physiology score. Charlson score=calculated Charlson comorbidity index. Pulmonary=chronic lung disease including both obstructive and restrictive, DM= diabetes mellitus, CHF=congestive heart failure, renal=renal disease, MI=myocardial infarction, Liver= liver disease, PVD=peripheral vascular disease, Rheumatic=rheumatic disease, PUD=peptic ulcer disease. Subgroups were named by the condition(s) present in all cluster members or a large proportion if no single condition was present in 100% of the patients within a subgroup. DM-HF-Pulm= subgroup composed of a large portion of patients with diabetes, congestive heart failure and chronic lung disease. P=2-tailed p-value for differences between subgroups, determined by chi-square test for categorical variables and Kruskall-Wallis tests for continuous variables.
References


