Cytokine responses, microbial aetiology and short-term outcome in community-acquired pneumonia

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Abstract

Background: The inflammatory response to community-acquired pneumonia (CAP) is orchestrated through activation of cytokine networks and the complement system. We examined the association of multiple cytokines and the terminal complement complex (TCC) with microbial aetiology, disease severity and short-term outcome.

Materials and methods: Plasma levels of 27 cytokines and TCC were analysed in blood samples obtained at hospital admission, clinical stabilization and 6-week follow-up from 247 hospitalized adults with CAP. Fourteen mediators were included in final analyses. Adverse short-term outcome was defined as intensive care unit (ICU) admission and 30-day mortality.

Results: Cytokine and TCC levels were dynamic in the clinical course of CAP, with highest levels seen at admission for most mediators. Admission levels of cytokines and TCC did not differ between groups of microbial aetiology. High admission levels of IL-6 (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.18-1.84, \(P = .001\)), IL-8 (OR 1.79, 95% CI 1.26-2.55, \(P = .001\)) and MIP-1\(\beta\) (OR 2.28, 95% CI 1.36-3.81, \(P = .002\)) were associated with a CURB-65 severity score of \(\geq 3\), while IL-6 (OR 1.37, 95% CI 1.07-1.74, \(P = .011\)) and MIP-1\(\beta\) (OR 1.86, 95% CI 1.03-3.36, \(P = .040\)) were associated with a high risk of an adverse short-term outcome.

Conclusions: In this CAP cohort, admission levels of IL-6, IL-8 and MIP-1\(\beta\) were associated with disease severity and/or adverse short-term outcome. Still, for most mediators, only insignificant variations in inflammatory responses were observed for groups of microbial aetiology, disease severity and short-term outcome.

Keywords: aetiology, complement activation, cytokines, mortality, pneumonia
1 | INTRODUCTION

Despite improvement in vaccination rates, antibiotic treatment and critical care management, morbidity and mortality of community-acquired pneumonia (CAP) remain high.\cite{1,2} For pneumonia to occur micro-organisms must reach the alveoli, multiply and elicit a host response.\cite{3} Exposure of alveolar epithelial cells and macrophages to pathogens may lead to secretion of cytokines and chemokines with subsequent recruitment of additional phagocytes, predominantly neutrophils in bacterial CAP, from the pulmonary circulation and into the site of infection.\cite{4,6} This immune response is in general beneficial for the host, but if overwhelming, the release of inflammatory mediators can cause tissue damage and harmful effects, contributing to morbidity and mortality in CAP.

In CAP, there is a release of several inflammatory cytokines including interleukin-1β (IL-1β), IL-6 and tumour necrosis factor (TNF).\cite{7,8} Simultaneous release of anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1ra) and IL-10, acts to counterbalance and compartmentalize the inflammatory response.\cite{9,11} Both the magnitude and extension of the inflammatory response are related to disease severity and clinical outcome,\cite{11-13} although conflicting data exist.\cite{8,14} Moreover, recent studies of patients with CAP have suggested that different micro-organisms exhibit diverse inflammatory responses, with distinctive cytokine activation patterns.\cite{15} However, the impact of various pathogens associated with CAP, especially respiratory viruses as well as polymicrobial infections, on cytokine production is insufficiently addressed.\cite{16} Better understanding of differences in immune responses in CAP may improve disease severity assessment, diagnostic efficiency and ultimately clinical outcome in these patients.

Considering cytokines are operating in networks, it may not be sufficient to assess only a few of these mediators during infections. Previously, we have reported that a high microbial yield was achieved in this CAP cohort.\cite{17} To further elucidate the immune response during CAP, we have in this study assessed a wide range of inflammatory cytokines and growth factors, as well as the terminal complement complex (TCC), the latter representing the last common step in the complement activation cascade, and examined the association of different cytokine network components and TCC to microbial aetiology, disease severity and short-term outcome.

2 | MATERIALS AND METHODS

2.1 | Study population and design

The study was performed in an acute care 270-bed general hospital in Drammen, Vestre Viken Hospital Trust, in South-Eastern Norway, between 1 January 2008 and 31 January 2011. A total of 267 patients aged ≥18 years admitted with suspected pneumonia to the Department of Internal Medicine were consecutively included. Within the first 48 hours of hospital admission, patients were screened for eligibility by determining the presence of CAP criteria, defined by (i) a new pulmonary infiltrate on chest radiograph, (ii) rectal temperature >38.0°C and (iii) at least 1 of the following symptoms or signs: cough (productive or nonproductive), dyspnoea, respiratory chest pain, crackles or reduced respiratory sounds. If the chest radiographic examination uncovered noninfectious causes such as pulmonary infarction, tumour or bronchiectasis, or if the patient had been hospitalized within the past 2 weeks, patients were excluded from the study. Immunocompromised patients (ie, primary or acquired immunodeficiency, active malignancy, patients using immunosuppressive drugs) defined in\cite{18} were not excluded from the study, to reflect the total population being referred to this local hospital. The inclusion process is summarized in Data S1. For the purpose of this study, patients with missing plasma cytokine concentrations at hospital admission (n = 20) were excluded, leaving a sample of 247 (ie, analysis cohort). Patients were invited to an outpatient follow-up approximately 6 weeks after hospital discharge. All patients provided written informed consent. The study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (ref. number: S-06266a), and a waiver of consent was obtained from the committee to link patient data to death certificates (2012/467 A). Reporting of the study conforms to STROBE\cite{19} and the EQUATOR guidelines.\cite{20}

2.2 | Data collection and definitions

Baseline data collection and definitions have been described elsewhere.\cite{17,18} In brief, demographic, clinical and laboratory data were collected within 48 hours of admission. Mean time from hospital admission to study inclusion was 0.6 days, and 240 of 247 (97%) patients were included within 24 hours. The microbial aetiology of CAP was established by use of extensive microbiological testing (ie, bacterial cultures, serology, urinary antigen assays and polymerase chain reaction [PCR]). In this study, clinical stabilization was evaluated daily during the first 12 days of hospitalization, with C-reactive protein (CRP) and leucocytes measured every second day, according to the following criteria (one point for each criterion): (i) unchanged antibiotic treatment the last 2 days, (ii) improvement of general condition, (iii) morning rectal temperature < 38.0°C and (iv) >25% decrease in CRP levels or leucocyte cell count. Clinical stabilization was defined as a score of ≥3 points.
2.3 | Blood sampling

Blood samples for cytokine analysis were obtained at all three time points (study inclusion, clinical stabilization (mean time 4.3 days) and at 6-week follow-up). Blood samples were drawn into pyrogen-free vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA) as anticoagulant. Plasma was separated within 60 minutes by refrigerated centrifugation at 2000 g for 12 minutes to obtained platelet-poor plasma and stored in several aliquots at −80°C. Samples were thawed only once.

2.4 | Cytokine analyses

Cytokines were measured in plasma samples by a multiplex assay (Bio-Plex Human Cytokine 27-Plex Panel; Bio-Rad Laboratories Inc., Hercules, CA, USA) containing the following interleukins, chemokines (CXC and CC chemokine ligands [CXCL and CCL]) and growth factors: IL-1β, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8/ CXCL8, IL-9, IL-10, IL-12 p70, IL-13, IL-15, IL-17, eotaxin/CCL11, basic fibroblast growth factor (bFGF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, interferon-inducible protein (IP-10)/ CXCL10, monocyte chemotactic protein (MCP-1)/CCL2, macrophage inflammatory protein (MIP)-1α/CCL3, MIP-1β/CCL4, platelet-derived growth factor-BB (PDGF-BB), regulated upon activation T cell expressed and secreted (RANTES)/CCL5, TNF and vascular endothelial growth factor (VEGF). Analyses were performed in accordance with the Bio-Plex Pro™ Human Cytokine, Chemokine, and Growth Factor Assays Instruction Manual. Only cytokines with less than 15% missing values were included for further analyses. If the cytokine concentration was below the lower detection limit, the value was set equal to the lower detection limit for data handling and statistics. RANTES and PDGF were excluded due to technical issues. Based on the criteria above, IL-1ra, IL-6, IL-7, IL-8, IL-9, IL-10, IL12 p70, IL-13, eotaxin, INF-γ, IP-10, MIP-1β, TNF were included in final analyses.

2.5 | Complement activation product

Terminal complement complex was observed using enzyme-linked immunosorbent assay (ELISA) as described in detail previously. Briefly, the assay was based on monoclonal antibodies detecting activation specific neo-epitopes. The amount of activation products is related to an international standard containing 1000 complement arbitrary units (CAU)/mL.

2.6 | Outcome measures

Based on the results of microbiological investigations, patients were categorized into four groups of aetiology; (i) pure bacterial, (ii) pure viral, (iii) viral-bacterial and (iv) unknown. Disease severity was evaluated by the validated CURB-65 scoring system; patients with a CURB-65 score of ≤ 2 were classified into low-risk and ≥ 3 into high-risk groups. Short-term outcome was defined as a composite endpoint of intensive care unit (ICU) admission and 30-day mortality.

2.7 | Statistical analysis

Categorical variables were expressed as counts (percentages) and continuous variables as mean (standard deviation [SD]) for normally distributed data or median (25th-75th percentiles) for visually skewed data. Comparison of mediators between the three time points was performed by Friedman test and Wilcoxon signed-rank test for post hoc test of differences between pair of groups, while comparison of mediators between groups of aetiology was performed by Kruskal-Wallis test. Differences between groups of aetiology were visualized using kernel density estimates. Kernel density estimates use a sliding interval and calculate the running density along the range of the variable of interest, weighing observations within the interval by 0-1 based on the distance from the interval’s centre point. As such, it is similar to a smoothed histogram plot. We used STATAs default kernel and interval width. Univariate logistic regression was used to assess the association between cytokine concentrations at hospital admission and the CURB-65 severity score and short-term outcome. Log transformations handled marked skewed distributions appropriately and were used before inclusion in regression to avoid disproportionate effect of tail values. Adjustment for multiple testing was applied for the comparison of 3 or more categories, with the P-value divided by the number of categories compared to achieve significance. A two-sided P-value <.05 was otherwise considered to be significant. Statistical analyses were performed using stata version 14.0 for Windows (Stata Corp LP, College Station, TX, USA) and spss version 23.0 for Windows (IBM Corp, Armonk, NY, USA).

3 | RESULTS

3.1 | Baseline characteristics and outcome

Data of 247 patients were analysed; the demographic, clinical and microbiological data are summarized in Table 1. Median age was 64 years, and 158 (64%) had at
least 1 comorbidity. Aetiology was established in 157 (64%) patients; 70 (28%) patients had a pure bacterial infection, 39 (16%) a viral infection, 48 (19%) a viral-bacterial infection, while 90 (36%) had CAP of unknown aetiology (Table 1). Forty-four (18%) patients were admitted to the ICU, and 10 (4%) died within 30 days of hospital admission.

3.2 Cytokine concentrations at study time points

Plasma cytokine concentrations at hospital admission (n = 247), clinical stabilization (n = 212) and 6-week follow-up (n = 227) are presented in Figure 1 and Table S1. Peak levels of TCC, IL-1ra, IL-6, IL-8, IL-9, IL-10, IL-12 p70, IFN-γ, IP-10, MIP-1β and TNF were seen at hospital admission, followed by a statistically significant reduction of concentrations of TCC, IL-1ra, IL-6, IL-8, IL-9, IL-10, IFN-γ, IP-10 and MIP-1β at clinical stabilization (P ≤ .01 for all) and for IL-12 p70 and TNF at 6-week follow-up (P < .001 for both). For IL-13, highest levels were seen at clinical stabilization (P < .001), while eotaxin concentrations were lowest in the acute phase of CAP, with significantly higher levels observed at the 6-week follow-up (P < .001). Concentrations of IL-7 (P = .12) did not differ significantly throughout the clinical course of CAP.

3.3 Admission cytokine concentrations in relation to microbial aetiology

The distributions of cytokine concentrations at hospital admission in relation to microbial aetiology are shown in Figure 2, indicating that the distributions of cytokines across the aetiological groups were quite similar. Accordingly, there were no significant differences in cytokine concentrations between the groups when tested by traditional nonparametric statistics (Table S2).

3.4 Admission cytokine concentrations in relation to the CURB-65 score

In univariate logistic regression analysis, hospital admission concentrations of IL-6 (odds ratio [OR] 1.47, 95% confidence interval [CI] 1.18-1.84, P = .001), IL-8 (OR 1.79, 95% CI 1.26-2.55, P = .001) and MIP-1β (OR 2.28, 95% CI 1.36-3.81, P = .002) were significantly associated with a CURB-65 severity score of ≥3 (Table 2). For the remaining 11 cytokines, no significant differences were seen. Excluding immunocompromised patients from analysis did not affect these results.

<table>
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<th>Missing data</th>
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<td>Demographics</td>
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<tr>
<td>Age, (years)</td>
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<td>Male gender, n (%)</td>
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<td>Nursing home resident, n (%)</td>
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<td>Comorbid conditions, n (%)</td>
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<td>Cardiovascular disease</td>
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<td>COPD</td>
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<td>Immunocompromised</td>
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<td>Autoimmune disease</td>
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<td>Diabetes mellitus</td>
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<td>Renal disease</td>
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<td>Neurological disease</td>
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<td>Dementia</td>
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<tr>
<td>Liver disease</td>
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<td>Aetiology, n (%)</td>
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<td>Bacterial</td>
<td>70 (28.3)</td>
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<tr>
<td>Viral</td>
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<tr>
<td>Unknown</td>
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<td>Vaccination status, n (%)</td>
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<td>Influenza vaccination (&lt;1 y)</td>
<td>61 (32.1)</td>
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<tr>
<td>Pneumococcal vaccination (&lt;10 y)</td>
<td>23 (12.2)</td>
<td>59</td>
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<tr>
<td>Disease severity, n (%)</td>
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<tr>
<td>CURB-65 ≥ 3</td>
<td>92 (37.6)</td>
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<tr>
<td>ICU admission</td>
<td>44 (17.8)</td>
<td></td>
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</table>

COPD, chronic obstructive pulmonary disease; CURB-65, Confusion, Urea, Respiratory rate, Blood pressure, Age ≥ 65; ICU, intensive care unit.

Data are presented as medians (25th-75th percentile) or No. (%).

*Heart failure, coronary heart disease, cerebrovascular disease and/or peripheral artery disease.


*Primary or acquired immunodeficiency, active malignancy, immunosuppressive drugs.

*Central nervous disease, neuromuscular disease.


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**Graphs showing cytokine levels across different conditions.**

- **TCC**
  - Adm Stab 6w
  - 0.0 to 2.0
  - Significant differences indicated by ***

- **IL-1ra**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **IL-6**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **IL-7**
  - Adm Stab 6w
  - (pg/mL)

- **IL-8**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **IL-9**
  - Adm Stab 6w
  - Significant differences indicated by **

- **IL-10**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **IL-12 p70**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **IL-13**
  - Adm Stab 6w
  - Significant differences indicated by *

- **Eotaxin**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **IFN-γ**
  - Adm Stab 6w
  - Significant differences indicated by **

- **IP-10**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **MIP-1β**
  - Adm Stab 6w
  - Significant differences indicated by ***

- **TNF**
  - Adm Stab 6w
  - Significant differences indicated by ***
FIGURE 2  Plasma cytokine concentrations at hospital admission in 247 hospitalized patients with community-acquired pneumonia, stratified by aetiology. Data are presented as kernel density estimates with log-transformed values (CAU/mL or pg/mL) in x-axis and density values in y-axis. IFN, interferon; IL, interleukin; IL-1ra, IL-1 receptor antagonist; IP, interferon-inducible protein; MIP, macrophage inflammatory protein; TCC, terminal complement complex; TNF, tumour necrosis factor.
3.5 | Admission cytokine concentrations in relation to short-term outcome

In all, 37 (15%) patients were survivors requiring ICU admission and a further 10 (4%) patients died within 30 days of hospital admission. An adverse outcome was thus seen in 47 (19%) patients. Increased levels of IL-6 (OR 1.37, 95% CI 1.07-1.74, \( P = .011 \)) and MIP-1\( \beta \) (OR 1.86, 95% CI 1.03-3.36, \( P = .040 \)) were significantly associated with a high risk of an adverse short-term outcome (Table 2). On the contrary, high levels of IL-7 (OR 0.57, 95% CI 0.33-1.00, \( P = .051 \)) and IL-13 (OR 0.83, 95% CI 0.52-1.25, \( P = .335 \)) were associated with a lower risk of an adverse short-term outcome. Excluding immunocompromised patients from analysis had no significant effect on the results for IL-6, IL-7 and IL-13. However, MIP-1\( \beta \) was no longer significantly associated with adverse short-term outcome (OR 1.67, 95% CI 0.84-3.34, \( P = .146 \)).

4 | DISCUSSION

In this cohort of 247 patients with CAP, several findings were revealed. First, most cytokine concentrations were high at hospital admission, with concentrations falling to clinical stabilization or the 6-week follow-up. Second, cytokine responses for groups of microbial aetiology at hospital admission were highly similar, with only nonsignificant differences observed. Third, increased concentrations of the inflammatory mediators IL-6, IL-8 and MIP-1\( \beta \) were associated with a more severe clinical presentation at hospital admission. Fourth, while elevated IL-6 and MIP-1\( \beta \) concentrations were associated with a higher risk of an adverse short-term outcome, elevated IL-7 and IL-13 concentrations were associated with a lower risk of an adverse short-term outcome. Finally, for a majority of cytokines examined, variations in cytokine responses were, in our cohort, not linked to disease severity or short-term outcome.

In the early phases of CAP, production of cytokines and other inflammatory mediators is regulated through a complex network of interactions between innate immune cells, “nonimmune” cells (eg, epithelial cells, endothelial cells and fibroblasts) and invading pathogens, with a main objective of recruiting neutrophil granulocytes necessary for local pathogen defence and clearance. As a consequence, circulating levels of inflammatory mediators are elevated in the initial stages of CAP, a finding which has been confirmed in numerous prior studies. Correspondingly, in our study, peak concentrations were seen at hospital admission for most mediators, possibly illustrating a culmination of cytokine concentrations before hospital admission or, at least, before blood samples were obtained in our study cohort.

When comparing cytokine concentrations at hospital admission between different aetiologial groups, only non-significant differences could be identified in our study. A
Spanish two-centre study of 658 hospitalized patients with CAP measured concentrations of TNF, IL-1β, IL-6, IL-8 and IL-10. In their material, a few differences in cytokine levels were reported depending on aetiology: atypical bacteria (lower IL-6), viruses (higher IL-10), Enterobacteriaceae (higher IL-8) and Legionella pneumophila (higher TNF). Of notice, in 57% of patients, aetiology of CAP was unknown, compared to 36% in our study cohort. So, even though a variety of recognized pathogens can cause CAP, aetiology remains unknown in many patients and thereby a matter of speculation. The fairly homogenous systemic cytokine responses in the present study suggest a generally shared immune reaction regardless of microbial aetiology. It is also possible that tissue damage secondary to pulmonary infection could be an important trigger of inflammation during CAP, illustrating the combination of sterile and nonsterile triggers in this condition. Our observations do not support the hypothesis that cytokine mapping has a significant clinical value in determining aetiology and as a tool for guiding antimicrobial therapy.

In our cohort, increased admission concentrations of the prototypical inflammatory cytokines IL-6, IL-8 and MIP-1β were associated with a severe clinical presentation of CAP, as evaluated by the CURB-65 severity score. For IL-6 and MIP-1β, admission concentrations were also associated with an adverse short-term outcome, defined as ICU admission and 30-day mortality. Consequently, two of three cytokines associated with severe clinical presentation were also associated with an adverse short-term outcome. This finding illustrates the interdependence between the two outcome measures in our study, the CURB-65 severity score and short-term outcome, as many of the patients with a CURB-65 score ≥ 3 at hospital admission, are at risk of ICU admission or death within 30 days. Previously, several studies have reported higher cytokine concentrations in patients with severe CAP than in nonsevere CAP when stratified by pneumonia severity assessment tools like the Pneumonia Severity Index (PSI) or the CRB-65/CURB-65 severity scores, but also when assessed by mortality. In particular, IL-6, a key regulator of the immune system with a broad range of biological effects, and IL-8, a major chemoattractant and activator of leucocytes, have been reported to be associated with a severe clinical course, ICU admission (IL-6 only), in-hospital mortality or 30-day mortality, supporting our results and underlining the substantial contribution of IL-6 and IL-8 in influencing the inflammatory response in pneumonia. Less is known about the importance of MIP-1β in pneumonia, but this natural killer cell-, monocyte- and lymphocyte-attracting chemokine has formerly been shown to correlate with disease severity in critically ill patients with the pandemic H1N1 influenza. Our study supports the possible role of MIP-1β as a prognostic factor also in CAP.

High IL-7 concentrations at hospital admission were, contrary to IL-6 and MIP-1β, associated with a lower risk of an adverse short-term outcome. IL-7 is a cytokine that stimulates proliferation of cells in the lymphoid lineage and is a key part of survival and homeostasis of lymphocytes. Interestingly, a recent study of recombinant human IL-7 therapy in patients with septic shock (primary pulmonary infection in 34% of patients) presented promising results, with improved lymphocyte functionality after treatment. In addition to IL-7, high IL-13 levels were also associated with improved short-term outcome in our CAP population. Although IL-13 has some anti-inflammatory effects, it plays a major role in IgE-mediated lung disease including asthma, and the reason for the association between high IL-13 and better prognosis in CAP is at present unclear.

4.1 | Limitations

The following limitations should be considered. First, our study was performed at a single hospital, thereby possibly limiting its generalizability. Second, the first cytokine measurements were performed until 48 hours after hospital admission, which may have resulted in lower concentrations of cytokines at this time point than earlier in the course of CAP. The statistically significant reduction of most cytokines at clinical stabilization, however, indicates relevant sensitivity for most cytokines. Third, the outcome measure short-term outcome was defined as a composite of ICU admission and 30-day mortality. A majority of patients (78%) were categorized with this softer ICU survivor outcome parameter.

5 | CONCLUSION

In summary, we examined the cytokine network in 247 hospitalized patients with CAP, with dynamic inflammatory responses seen throughout the clinical course of CAP for most cytokines. IL-6, IL-8 and MIP-1β at hospital admission were associated with disease severity and/or an adverse short-term outcome, suggesting a potential as biomarkers of severity in CAP. Nonetheless, for a majority of cytokines examined, only nonsignificant variations in inflammatory responses were observed for different aetiological groups, disease severity and short-term outcome.

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CONFLICT OF INTERESTS
The authors declare that there is no conflict of interests regarding the publication of this article.

AUTHORS’ CONTRIBUTIONS
EH, PA, TEM and LH conceived and designed the study. JCH, EH and LH collected and compiled data. WWS and SHN performed statistical analysis. WWS, JCH, SHN, TU, PA, TEM and LH analysed and interpreted the data. WWS, JCH and LH wrote the report. SHN, EH, TU, PA and TEM made substantial intellectual contributions to the work and commented and revised the report. All authors read and approved the final manuscript.

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REFERENCES


SUPPORTING INFORMATION

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