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Kinetics of inflammatory biomarkers to predict one-year mortality in older patients hospitalized for pneumonia: a multivariable analysis

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ABSTRACT

Objectives: Long-term mortality is increased in older patients with pneumonia. We aimed to test whether residual inflammation is predictive of one-year mortality after pneumonia.

Methods: Inflammation biomarkers (C-reactive protein [CRP], interleukin [IL]-6 and IL-8, tumor necrosis factor–α, serum amyloid A, neopterin, myeloperoxidase, anti-apolipoprotein A-1, and anti-phosphorylcholine IgM) were measured at admission and discharge in older patients hospitalized for pneumonia in a prospective study. Univariate and multivariate analyses were conducted using absolute level at discharge and relative and absolute differences between admission and discharge for all biomarkers, along with usual prognostic factors.

Results: In the 133 included patients (median age, 83 years [interquartile range: 78–89]), one-year mortality was 26%. In univariate analysis, the relative difference of CRP levels had the highest area under the receiver operating characteristic curve (0.70; 95% confidence interval [CI] 0.60–0.80). A decrease of CRP levels of more than 67% between admission and discharge had 68% sensitivity and 68% specificity to predict survival. In multivariate analysis, lower body mass index (hazard ratio=0.87 [CI 95% 0.79–0.96], *P*-value=0.01), higher IL-8 (hazard ratio=1.02 [CI 95% 1.00–1.04], *P*-value=0.02), and higher CRP (1.01 [95% CI 1.00–1.02], *P*=0.01) at discharge were independently associated with mortality.

Conclusion: Higher IL-8 and CRP levels at discharge were independently associated with one-year mortality. The relative CRP difference during hospitalization was the best individual biomarker for predicting one-year mortality.

Introduction

Community-acquired pneumonia (CAP) is the cause of a large number of hospitalizations and results in increased short- and long-term mortality in older patients (Martin et al., 2006; Welte et al., 2012). Pneumonia is frequently a turning point in the life of older people, leading to loss of autonomy, cognitive decline, and decompensation of other comorbidities. Indeed, studies have revealed decreased long-term survival after hospitalization for CAP in older patients (Bordon et al., 2010). Elevated biomarkers of in-

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flammation, cardiac impairment, and renal dysfunction may be associated with worse long-term prognosis after CAP (Krüger et al., 2010; Putot et al., 2016). Some older patients leave the hospital with unresolved inflammation, but the implication on prognosis remains unclear, and the association may be non-causal, as inflammaging (subclinical inflammation with elevated baseline levels of proinflammatory biomarkers) may be part of the aging process itself, with deleterious effects (Murray and Chotirmall, 2015).

Among inflammatory biomarkers, C-reactive protein (CRP) has been frequently studied for its prognostic association with adult pneumonia (Lacoma et al., 2012). Tumor necrosis factor (TNF)–α, serum amyloid A protein (SAA), neopterin (NP), myeloperoxidase (MPO), anti-apolipoprotein A-1 (anti-ApoA-1), and anti-phosphorylcholine IgM (anti-PC IgM) have been recently proposed for assessing prognosis of lower respiratory tract infections and/or cardiovascular diseases (Abo-Hagar et al., 2019; Bacci et al., 2015; Baydar et al., 2009; Davies, 2011; Pizzini et al., 2017; Schrijver et al., 2017). An association between high levels of pro- and anti-inflammatory cytokines (especially interleukin [IL]-1, -6, and -11) and CAP mortality has been described, but data in older patients are scarce (Bacci et al., 2015; Guertler et al., 2011; Kellum et al., 2007; Pinargote-Celorio et al., 2020; Yende et al., 2008). In a recent study, we found no association between biomarkers of inflammation measured at admission and one-year mortality (Malézieux-Picard et al., 2021). We aimed to explore whether the kinetics of inflammatory biomarkers during the index hospitalization and persistently elevated levels of biomarkers at discharge were predictive of one-year mortality in older patients hospitalized for pneumonia.

Methods

This is a secondary analysis of a previously described prospective observational cohort (Prendki et al., 2018). Consecutive patients aged older than 65 years with suspected pneumonia (suggestive signs and symptoms), hospitalized in Geneva University Hospitals, were included between May 1, 2015, and April 30, 2016. The diagnosis of pneumonia was adjudicated *a posteriori* by a panel of senior physicians who had access to all clinical, biological, radiological, and microbiological data. Low-dose chest computed tomography (CT) scans were obtained for all patients upon admission. Patients treated for pneumonia during the previous 6 months or admitted to the intensive care unit were excluded. Patients were managed according to local guidelines, and all were treated with antibiotics.

One-year mortality data were collected retrospectively by investigators without access to the results of biomarkers (except for CRP), using the local register of deaths.

The Institutional Review Board of Geneva University Hospitals (CER-14-250) approved the study, which was registered at ClinicalTrials.gov (NCT02467192; first submitted on May 27, 2015), and informed consent was obtained from all patients or their next of kin.

Baseline characteristics

Demographic data, comorbidities, symptoms, vital and clinical signs, severity scores, and the results of routinely obtained blood tests, including CRP, were recorded prospectively according to the protocol of the original study.

Biomarker measurement

Blood was sampled within 48 hours after admission and 48 hours before discharge from the acute care setting. Plasma CRP concentrations were measured immediately via immunoturbidimetry (cobas c702 module, F. Hoffmann-La Roche AG, Basel, Switzerland). Concentrations of IL-6, IL-8, TNF-α, SAA, NP, MPO, anti-ApoA-1 IgG, and anti-PC IgM were measured *a posteriori* using frozen plasma. IL-6, IL-8, and TNF-α were measured using the Meso Scale Discovery platform on the MESO QuickPlex SQ 120 instrument (Meso Scale Technologies, Rockville, MD, USA), SAA with electrochemiluminescence detection system using multiarray technology (SECTOR Imager 2400, Meso Scale Technologies) (Azurmendi et al., 2015), NP with a competitive enzyme-linked immunosorbent assay (ELItest® Neopterin-Screening, BRAHMS, Hennigsdorf, Germany), anti-apoA-1 IgG using frozen plasma according to a previously validated protocol (Vuilleumier et al., 2010), anti-PC IgM using a commercially available enzyme-linked immunosorbent assay kit (CVDefine™; Athera Biotechnologies, Stockholm, Sweden), and MPO with the commercial Quantikine® ELISA kit (R & D Systems, Minneapolis, MN, USA).

Definitions

Absolute difference of a biomarker was computed as the difference between blood concentrations measured at admission and discharge. Relative difference of a biomarker was computed as the concentration of the biomarker measured at admission minus concentration at discharge, divided by concentration of the biomarker at admission.

Data Analysis

We used frequencies, percentages, mean with standard deviation, and median with interquartile range for descriptive purposes. Variables were compared between patients dead or alive at one year in univariate analysis using one-way analysis of variance for continuous variables, and Fisher's exact test or chi-square test for categorical variables, as appropriate.

We constructed receiver operating characteristic curves to test the ability of biomarkers to discriminate between survivors and non-survivors at one year and computed the area under the receiver operating characteristic curve (AUROC) and C-statistics. As we were interested in assessing the prognostic implications of biomarker kinetics, we tested three different measures for each biomarker: absolute blood level at discharge, absolute difference, and relative difference between admission and discharge. As we expected that collinearity would be an issue, we computed Spearman's rank correlation between biomarkers and planned to build separate multivariate models for absolute blood level at discharge and for the difference between blood level at admission and discharge.

Biomarkers whose C-statistic significantly differed from 0.5 were introduced in two separate multivariate Cox proportional hazard models using backward conditional selection, along with clinical characteristics associated in univariate analysis with outcomes with a $P < 0.1$. Sex was added to the models. The first model used absolute levels at discharge; the second model used differences between admission and discharge. When significant correlation was evident between two biomarkers, we only introduced the biomarker with the highest AUROC into the model.

The optimal cutoff for biomarkers significantly associated with the outcome in multivariate analysis was determined with the Youden index. We plotted Kaplan-Meier survival curves at the optimal cutoff point and computed sensitivity, specificity, and positive and negative likelihood ratios. The study sample was determined by the design of the original study. All *P*-values were two-tailed and considered significant if *P*-value <0.05. No imputation was made for missing values (complete case analysis). Data were

Table 1
Baseline characteristics of the 133 patients according to one-year mortality

Characteristics	No (%), Mean (SD) or Median (IQR)		*P*-value
	Dead35 (26)	Alive98 (74)	
Demographics			
Female sex	15 (42.9)	45 (45.9)	0.76
Age (years)	85.5 (7.4)	82.0 (7.9)	0.02
Smoker (active or past)	19 (54.3)	61 (62.2)	0.41
BMI (kg/m^2)	22.7 (5.4)	24.5 (4.9)	0.03
Place of living			0.14
Home	30 (85.7)	87 (88.8)	
Nursing home	5 (14.3)	6 (6.1)	
Other	0	5 (5.1)	
Hospitalized during last 6 months	12 (27.6)	27 (34.3)	0.45
Comorbidities			
Charlson score[a]	3.25 (2.4)	3.0 (1.7)	0.52
Past myocardial infarction	8 (22.9)	14 (14.3)	0.24
Heart failure	8 (22.9)	22 (22.4)	0.96
Dementia	11 (31.4)	16 (16.3)	0.06
Chronic lung disease	8 (22.9)	21 (21.4)	0.86
Diabetes	3 (8.6)	4 (4.1)	0.31
Chronic renal disease	5 (14.3)	19 (19.4)	0.50
Active cancer	3 (8.6)	4 (4.1)	0.31
Prognostic scores			
CURB-65[b]	2.4 (1.0)	2.2 (0.8)	0.15
PSI	113 (28)	105 (25)	0.10
Vital signs			
Heart rate	95 (19)	92 (18)	0.41
Respiratory rate	24 (6)	25 (7)	0.53
Temperature (°C)	37.8 (1.0)	38.1 (1.0)	0.10
Systolic blood pressure (mmHg)	133 (26)	130 (22)	0.53
Biomarkers at discharge			
CRP (mg/l)	45.7 (16.0–78.9)	15.2 (7.9–28.4)	<0.01
IL-6 (pg/l)	3.5 (2.6–10.3)	3.2 (1.4–7.1)	0.49
IL-8 (pg/l)	22.8 (13.9–26.7)	15.6 (10.0–21.4)	0.07
MPO (pg/ml)	200.6 (95.6–300.8)	139.1 (84.0–253.0)	0.49
TNF-α (pg/ml)	3.1 (2.3–4.1)	3.0 (2.4–3.9)	0.67
SAA (μg/l)	138 (31–258)	106 (20–255)	0.44
Anti-ApoA-1 IgG (DO)	0.36 (0.19–0.60)	0.34 (0.24–0.58)	0.61
Anti-PC IgM (U/ml)	49.9 (20.8–77.8)	40.2 (21.7–70.4)	0.70
Neopterin (nmol/l)	6.5 (4.9–9.7)	5.5 (4.2–8.2)	0.97

Anti-ApoA-1, anti-apolipoprotein A-1; *anti-PC*, anti-phosphorylcholine; *BMI*, body mass index; *CRP*, C-reactive protein; *IL*, interleukin; *IQR*, interquartile range; *MPO*, myeloperoxidase; *PSI*, pneumonia severity index; *SAA*, serum amyloid A protein; *TNF-α*, tumor necrosis factor α.
[a] 23 missing
[b] Confusion, Urea >7 mmol/l, Respiratory rate ≥30 breaths per minute, Blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, age ≥65 years.

analyzed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

Of the 200 included patients , 133 were diagnosed with pneumonia (median age, 83 years [interquartile range: 78–89]), among them 35 (26%) died within one year. Baseline characteristics are displayed in Table 1. The main comorbidities were heart failure (n=30, 23%), chronic lung disease (n=29, 22%), dementia (n=27, 20%), and chronic renal failure (n=24, 18%). Most patients presented with cough (n=120, 90%), dyspnea (n=95, 71%), and lung crackles (n=114, 86%). The median duration of hospitalization was 11 days (interquartile range: 8–17).

Biomarkers at discharge and kinetics during hospitalization

Table 1 shows the levels of biomarkers at discharge according to one-year mortality, and Table 2 shows the univariate and multivariate association of each biomarker with one-year mortality. There were 16% missing data for all biomarkers except for CRP at discharge (5%).

In univariate analysis, older age, lower body mass index (BMI), higher pneumonia severity index (PSI) score, and dementia were associated with a higher risk of death, with a *P*-value of <0.1. Among biomarkers measured at discharge, higher CRP and IL-8 levels were associated with death; among the absolute and relative differences of biomarker levels, difference of CRP and MPO levels was associated with death. IL-6, SAA, NP, anti-ApoA-1, anti-PC IgM, and TNF-α were not associated with one-year mortality.

There was a correlation between the relative difference of CRP levels and the absolute difference of MPO levels (*P*-value=0.001) and between the relative difference of CRP levels and IL-8 levels at discharge (*P*-value=0.03).

The AUROCs of biomarker levels at discharge and their absolute and relative difference between admission and discharge are shown in Table 3. The AUROCs were 0.67 (95% confidence interval [CI] 0.56–0.78) and 0.67 (95% CI 0.55–0.78) for CRP and IL-8 levels at discharge, respectively. The optimal cutoff was 22 mg/l for CRP, with a sensitivity of 71% and a specificity of 61% (positive likelihood ratio was 1.89 and negative likelihood ratio was 0.48). The optimal cutoff was 19 pg/ml for IL-8, with a sensitivity of 67% and a specificity of 68% (positive likelihood ratio was 2.09 and negative likelihood ratio was 0.49). The relative difference of CRP levels (0.70, 95% CI 0.60–0.80) had the highest AUROC to discriminate one-year mortality.

Table 2
Univariate and multivariate association of predictors with one-year mortality

	Univariate analysis		Multivariate analysis			
			Model 1		Model 2	
	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value	HR (CI 95%)	*P*-value
Age (year)	1.054 (1.007–1.102)	0.02	0.871 (0.788–0.963)	0.007		
Female sex	0.944 (0.483–1.844)	0.87				
Dementia	2.143 (1.049–4.377)	0.04				
PSI score	1.011 (0.998–1.023)	0.09				
BMI (kg/m^2)	0.915 (0.849–0.986)	0.02				
CRP at discharge (mg/l)	1.010 (1.005–1.016)	<0.001	1.010 (1.002–1.017)	0.014		
IL-8 at discharge (pg/l)	1.015 (0.997–1.034)	0.10	1.023 (1.004–1.043)	0.019		
MPO absolute difference (pg/ml)	0.998 (0.997–1.000)	0.01				
CRP relative difference (mg/l)	0.984 (0.976–0.993)	<0.001			0.986 (0.978–0.995)	0.003

BMI, body mass index; *CI*, confidence interval; *CRP*, C-reactive protein; *HR*, hazard ratio; *IL*, interleukin; *MPO*, myeloperoxidase; *PSI*, pneumonia severity index.

Table 3
AUROC of biomarker levels at discharge and difference between admission and discharge levels for discriminating one-year mortality

	AUROC(95% CI)	*P*-value
CRP		
Level at discharge	0.67 (0.56–0.78)	0.003
Absolute difference[a]	0.67 (0.56–0.77)	**0.004**
Relative difference[b]	0.70 (0.60–0.80)	**0.001**
IL-8		
Level at discharge	0.67 (0.55–0.78)	**0.01**
Absolute difference	0.54 (0.41–0.67)	0.52
Relative difference	0.56 (0.44–0.68)	0.40
MPO		
Level at discharge	0.60 (0.47–0.72)	0.14
Absolute difference	0.69 (0.58–0.80)	**0.004**
Relative difference	0.67 (0.55–0.79)	**0.01**

AUROC, area under the receiver operating characteristic curve; *CI*, confidence interval; *CRP*, C-reactive protein; *IL*, interleukin; *MPO*, myeloperoxidase.

[a] Absolute difference of a biomarker is the difference between blood levels at admission and at discharge

[b] Relative difference of a biomarker is the difference between blood levels at admission and discharge, computed as (biomarker at admission minus biomarker at discharge) divided by biomarker at admission.

In the first multivariate model, CRP, IL-8 levels, and the absolute difference of MPO levels at discharge were used as predictors, additionally adjusting for age, sex, PSI, BMI, and dementia. CRP (hazard ratio [HR]=1.01 per 10 mg/l [95% CI 1.00–1.02], *P*-value=0.01), IL-8 (HR=1.02 [95% CI 1.00–1.04], *P*-value=0.02), and BMI (HR=0.87 [95% CI 0.79–0.96], *P*-value=0.01) were significantly associated with risk of death.

The second multivariate model used the relative difference of the CRP levels as the predictor, adjusting for age, sex, PSI, BMI, and dementia. The relative difference of the CRP levels remained the only variable associated with one-year mortality after backward selection (HR=0.99 [CI 95% 0.98–0.99], *P*-value=0.003). The relative difference of MPO, although significant in univariate analysis, was not introduced in the model because of a highly significant correlation with the relative difference of CRP. A decrease of CRP levels of more than 67% between admission and discharge had 68% sensitivity and 68% specificity to predict survival; positive likelihood ratio was 2.1, and negative likelihood ratio was 0.47 (Figure 1).

Discussion

In our cohort of older patients hospitalized for pneumonia, persistent inflammation at discharge, as indicated by higher IL-8 or CRP levels, was independently associated with a higher risk of death within one year. Among clinical characteristics tested, lower BMI was the only independent predictor of mortality. All other biomarkers tested (IL-6, SAA, NP, anti-ApoA-1, anti-PC IgM, TNF-α) were not associated with one-year mortality.

Among our different estimations of inflammatory biomarker kinetics (absolute or relative difference between admission and discharge; residual level at discharge), the relative decrease of CRP had the highest discrimination power, as measured by AUROC. The association remained after adjustment for clinical variables (including BMI). A 67% decrease of CRP during the index hospitalization had moderate discrimination power for one-year mortality.

Older patients hospitalized for pneumonia have a poor long-term prognosis (Kaplan et al., 2003). Inflammation, age, comorbidities, severity of pneumonia, and cardiovascular events have been described as risk factors for long-term mortality (Restrepo et al., 2013). In our study, a lower BMI was an independent predictor of one-year mortality. Malnutrition, a characteristic closely connected with functional decline and various comorbidities, is strongly associated with a poor long-term outcome in patients with CAP, particularly in the older population (Yeo et al., 2019; Yoon et al., 2019). This finding emphasizes the need to prevent, identify, and treat malnutrition in older patients in the ambulatory and hospital settings.

In our study, persisting inflammation, as measured by elevated CRP or IL-8 levels at discharge, was independently associated with a poor long-term prognosis. CRP is a traditional marker of inflammation, which is low-cost, reproducible, and readily available in most settings. In our cohort, CRP at admission was not associated with mortality (Malézieux-Picard et al., 2021), which is a finding already reported by others in different infectious diseases and settings (Póvoa et al., 2011; Ryu et al., 2015). In a prospective study of adult patients with CAP (median age, 62 years), Chalmers et al. found that a decrease of less than 50% of CRP levels at day 4 predicted an increased risk of 30-day mortality (Chalmers et al., 2008). We expand this observation to longer-term mortality. In our cohort of older patients, an elevated CRP level (>22 mg/l) at discharge was associated with one-year mortality, as was a relative decrease of CRP levels of less than 67%. Karasahin et al. reported similar findings in a cohort of older patients hospitalized in a palliative care unit (Karasahin et al., 2018). Although initial values of CRP may be irrelevant for long-term prognostication, changes in CRP levels could be more relevant, allowing clinicians to pay special attention to patients in whom CRP did not decrease by more than two-thirds of the initial value.

Although inflammation is the hallmark of the early phase of sepsis, an anti-inflammatory response develops later, dampening the deleterious effects of the inflammatory response on the host. An imbalance between the inflammatory/anti-inflammatory responses may lead either to the absence of elimination of the pathogen or to persisting inflammation (Hotchkiss et al., 2013). Persistence of chronic low-grade inflammation may be more fre-

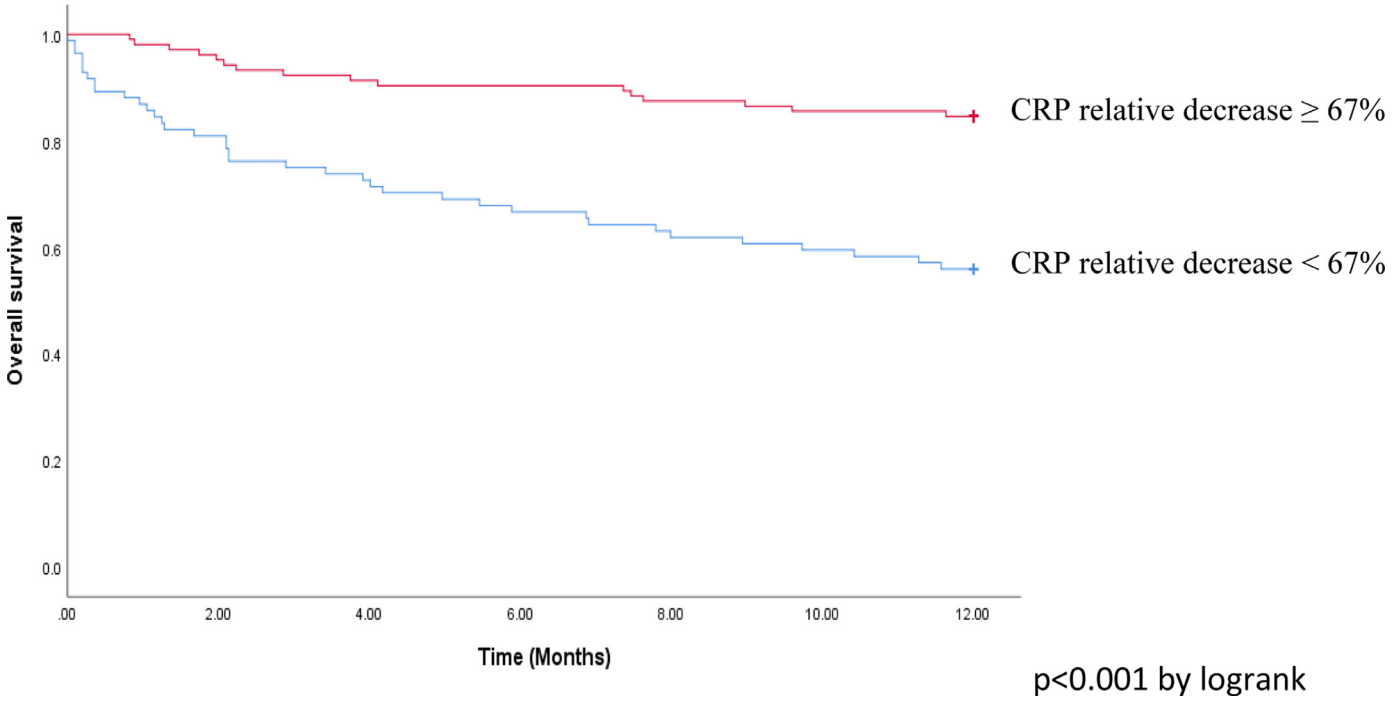

Figure 1. Survival curves according to relative difference (admission-discharge) of C-reactive protein (CRP)

quent in the aging host, promoting accelerated atherogenesis, type 2 diabetes, neurodegenerative diseases, cachexia, and death (Bruunsgaard et al., 2001; Yende et al., 2008).

In our cohort, IL-8 levels at discharge were also significantly associated with one-year mortality. IL-8 is an inflammatory chemokine that plays a key role in the recruitment and activation of neutrophils during inflammation but also in atherogenesis, atherosclerotic plaque destabilization, neovascularization, and angiogenesis (Baggiolini et al., 1989; Ramji and Davies, 2015). High levels of IL-8 in older patients without infection are associated with increased mortality (Moreno Velásquez et al., 2015). The worse prognosis conferred by a high IL-8 level at discharge in our population might be related to a higher risk of cardiovascular complications, which is a hypothesis that remains to be confirmed.

IL-6 is a cytokine of the acute-phase response and has been mostly described as a risk factor for early mortality (Bacci et al., 2015; Siljan et al., 2018). In a large prospective study, Yende et al. reported that in patients who clinically recovered from CAP, persistently elevated levels of IL-6 and IL-10 at hospital discharge were associated with all-cause mortality over one year (Yende et al., 2008). We did not confirm this observation in our study but did not test for IL-10 levels.

MPO is an enzyme released by activated neutrophils via intracellular granules, and its deficiency can lead to chronic infections due to lack of pathogen clearance (Davies, 2011). In the intensive care unit setting, MPO levels were related to 30-day mortality (Schrijver et al., 2017). Two mechanisms may explain the relationship with mortality: MPO and its by-products can lead to extracellular damage, and MPO as a marker of inflammation can lead to organ failure and thus to higher mortality. In our study, the absolute difference of MPO between discharge and admission was associated with long-term mortality. As it has not been described previously, this finding should be interpreted with caution.

One strength of our study is the prospective inclusion of very old and multimorbid patients, with assessment of many demographic, clinical, and biological variables. There were few missing values, and we assessed the presence of pneumonia using a robust reference standard, including chest CT scans in all patients. As a diagnosis of CAP based on chest X-ray has poor accuracy in this population, our reference standard may prevent misclassifications (Prendki et al., 2018). We could test several inflammatory biomarkers both at admission and discharge, allowing the assessment of the biological correlate of inflammation kinetics fitting best with long-term prognosis.

Our study is limited by its single-center design and its modest sample size. We only measured biomarkers on two occasions (the timing of testing was not fixed), which prevented us from obtaining a complete overview of their kinetics. As we did not have measurements of inflammatory biomarkers before the index pneumonia, we are unable to assess whether persisting inflammation was the consequence of CAP or merely reflected a more chronic inflammatory state. Specific causes of mortality at one year were not available. Finally, we tested nine different biomarkers, and type I error could be an issue; however, *P*-values for the described associations were fairly low, and most of our findings have been described in other contexts.

Conclusion

Persisting inflammation, as indicated by higher IL-8 and CRP levels at discharge, was independently associated with one-year mortality in older patients with pneumonia. Moreover, relative CRP decrease during hospitalization was the more discriminating factor for one-year mortality, which is an association independent of demographic and clinical characteristics. Patients with less than 67% decrease of CRP between admission and discharge have a higher risk of death, and additional interventions could be targeted toward this population. Finally, malnutrition, as indicated by lower BMI, was the only clinical risk factor for mortality in this cohort. These results suggest a stricter and more attentive clinical follow-up of relative CRP difference in older patients hospitalized with pneumonia but need to be confirmed in other studies.

Declarations of competing interest

The authors have no competing interests to declare.

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Ethical approval

The research Ethics Committee of Geneva University Hospitals approved the study. Clinical trial registration: NCT 02467092.

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent to participate

All participants gave their consent.

Consent for publication

All authors approve the manuscript.

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Author contributions

V.P. designed the study. A.M.-P., A.N., V.P., and N.G. collected the data, interpreted the results, and wrote the manuscript. L.A., S.P., N.V., and J.-C.S. performed the immunology procedures and wrote the manuscript. A.M.-P., A.N., N.G., J.S., J.-L.R, D.Z., X.R., L.A., S.P., N.V., J.-C.S., and V.P. critically revised the intellectual content of the manuscript and all approved the final version.

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