



**HAL**  
open science

## **Pneumocystis pneumonia in older non-HIV-infected patients: a French, multicentre, retrospective, cohort study**

Adrien Barraud, Romaric Larcher, Gaëtan Gavazzi, Arthur Fourmy, Renaud Verdon, Sophie Ancellin, Albert Sotto, Valéry Antoine, Alain Putot, Paule Letertre-Gibert, et al.

### ► **To cite this version:**

Adrien Barraud, Romaric Larcher, Gaëtan Gavazzi, Arthur Fourmy, Renaud Verdon, et al.. Pneumocystis pneumonia in older non-HIV-infected patients: a French, multicentre, retrospective, cohort study. *Pneumonia*, 2025, 17 (1), pp.34. <10.1186/s41479-025-00187-7>. <hal-05399910>

**HAL Id: hal-05399910**

**<https://hal.science/hal-05399910v1>**

Submitted on 14 Jan 2026

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

# **Pneumocystis pneumonia in older non-HIV-infected patients: a French, multicentre, retrospective, cohort study**

Adrien Barraud<sup>1\*</sup>, Romaric Larcher<sup>2,3</sup>, Gaëtan Gavazzi<sup>4,5</sup>, Arthur Fourmy<sup>6</sup>, Renaud Verdon<sup>7,8</sup>, Sophie Ancellin<sup>9</sup>, Albert Sotto<sup>3,10</sup>, Valéry Antoine<sup>1,11</sup>, Alain Putot<sup>12</sup>, Paule Letertre-Gibert<sup>13</sup>, Emmanuel Forestier<sup>14</sup>, Claire Roubaud-Baudron<sup>15,16</sup>, Matthieu Coulongeat<sup>17,18</sup> and Thibaut Fraisse<sup>19</sup> on behalf of on behalf GInGer (Groupe Infectio-Gériatrie)

1 Division of Geriatric Medicine, Univ Montpellier, Nîmes University Hospital, 1 Place Robert Debre, Nimes 30000, France

2 PhyMedExp, INSERM, CNRS, University of Montpellier, Montpellier, France

3 Department of Infectious and Tropical Diseases, Nimes University Hospital, 1 Place Robert Debre, Nimes 30000, France

4 T-Raig TIMC-IMAG Laboratory, CNRS 5525, Université Grenoble Alpes, Saint-Martin-d'Hères, France

5 CHU Grenoble Alpes, Department of Clinical Geriatrics, Grenoble CS-10217, France

6 Geriatrics Department, Poitiers University Hospital, Poitiers 86000, France

7 Department of Infectious Diseases, Caen University Hospital, Caen, France

8 Dynamicure INSERM UMR 1311, Normandie Université, University of Caen Normandy, Caen, France

9 Department of Infectious Diseases, Auch Hospital, Auch, France

10 VBIC, INSERM, Montpellier University, Nimes, France

11 UMR 1302, Desbrest Institute of Epidemiology and Public Health, INSERM, University of Montpellier, Montpellier, France

12 Department of Internal Medicine and Infectious Diseases, Pays du Mont-Blanc Hospitals, Sallanches F-74700, France

13 Department of Infectious and Tropical Diseases, Centre Hospitalier Alpes Léman, Contamine-sur-Arve 74130, France

14 Department of Infectious Diseases, Centre Hospitalier Métropole Savoie, Chambéry F-73000, France

15 CHU de Bordeaux, Pôle de Gériatrie Clinique, Bordeaux F-33000, France

16 INSERM UMR 1312 BRIC, University of Bordeaux, Bordeaux F-33000, France

17 Division of Geriatric Medicine, University Hospital Centre of Orleans, Orléans 45100, France

18 Division of Geriatric Medicine, Tours University Medical Centre, Tours 37044, France

19 Court Séjour Gériatrique Aigu, Centre Hospitalier Alès-Cévennes, Alès F-30100, France

**\*Correspondence:**

Adrien Barraud

**E-mail :**

[adrien.barraud@gmail.com](mailto:adrien.barraud@gmail.com)

**Keywords**

*Pneumocystis* pneumonia, Older patients, Immunosuppression, Corticosteroid therapy, Mortality

# Abstract

## Background

*Pneumocystis pneumonia* (PCP) is well-described in younger and HIV-infected populations, but limited data are available for older non-HIV-infected patients. The aim was to describe the clinical characteristics, management and outcomes of PCP in older non-HIV-infected patients and to identify factors associated with in-hospital mortality.

## Methods

This multicentre, retrospective, cohort study included patients aged  $\geq 75$  years, hospitalised for non- HIV-related PCP in 12 French university hospitals between January, 2010 and December, 2021. PCP diagnosis was confirmed by PCR or microscopy. Data on demographics, comorbidities, clinical features, management and outcomes were collected. Factors associated with in-hospital mortality were identified by univariate and multivariate analysis.

## Results

A total of 175 patients were screened and 162 were included (median age: 79 years, 57.4% male). Most patients had haematological malignancies (35.8%) or solid tumours (34.5%) and were treated with long-term corticosteroids (60%). Respiratory symptoms (87.6%) and bilateral interstitial lung involvement were common. Diagnosis was based on PCR of bronchoalveolar lavage (66.4%) or sputum samples (32.3%). In-hospital mortality was 27.8%. CRP level  $> 110$  mg/L (HR = 2.55 [95%CI: 1.35–4.83],  $p = 0.004$ ) and initiation of corticosteroids for PCP treatment (HR = 1.89 [95%CI: 1.03–3.44],  $p = 0.039$ ) were associated with mortality. Patients with higher oxygen saturation at admission (HR = 0.94 [95%CI: 0.91–0.97],  $p < 0.001$ ) had a lower risk of death.

## Conclusion

PCP in older non-HIV-infected patients has a high mortality rate, particularly in the presence of elevated CRP, hypoxaemia or corticosteroid use. Future research should focus on identifying subgroups potentially benefiting from corticosteroids and exploring safe therapeutic options for this vulnerable population.

# Introduction

*Pneumocystis pneumonia* (PCP) is an opportunistic fungal pulmonary infection that is a significant cause of morbidity and mortality in immunocompromised patients. Initially recognised in the context of HIV/AIDS, PCP has become increasingly prevalent among non-HIV populations. This includes patients with underlying conditions such as haematological malignancies, solid organ transplants, autoimmune diseases and those receiving immunosuppressive therapies, including corticosteroids [1].

As the population ages, a growing number of older patients are undergoing immunosuppressive treatments for conditions like autoimmune diseases and cancer. This has placed older individuals, especially those aged  $\geq 75$  years, at increased risk of PCP due to the combination of age-related immune dysfunction and frequent immunosuppressive conditions [2]. However, data on the presentation, management and prognosis of PCP in this population remain scarce, as much of the available evidence comes from younger non-HIV-infected cohorts [3–5]. Moreover, the older population presents a unique diagnostic and therapeutic challenge due to atypical clinical presentations [6], difficulty differentiating *Pneumocystis jirovecii* colonisation from infection [7] and reduced tolerance to high dose cotrimoxazole or corticosteroid therapy [8, 9].

The purpose of this multicentre study was to address these gaps by characterising the clinical, therapeutic and prognostic features of older non-HIV-infected patients diagnosed with PCP. Specifically, the aim was to identify factors associated with mortality, including biomarkers, disease severity at admission and treatment approaches. Through a large multicentre cohort, our aim was to generate insights that inform more tailored diagnostic and treatment strategies for this vulnerable population.

# Methods

## Study design and settings

This multicentre, retrospective, cohort study was carried out in geriatric acute care units and infectious diseases units, in 12 French university hospitals, between January 2010 to December 2021.

## Study population

At each site, investigators identified eligible patients by screening laboratory their databases for positive *P. jirovecii* samples during the study period, followed by a review of hospital discharge summaries.

All consecutive patients aged  $\geq 75$  years, hospitalised between January 1, 2010, and December 31, 2021, for non-HIV-related PCP, were included. The diagnosis of PCP was assessed retrospectively by local investigators using the following criteria: a bronchoalveolar lavage or sputum sample positive for *P. jirovecii* kyst on direct examination or by PCR with a

Ct threshold of  $\leq 35$  [7] or  $>3160$  copies/mL [10], in a patient was treated with cotrimoxazole or atovaquone for PCP.

To ensure diagnostic accuracy, all cases were independently reviewed by the principal investigators (AB and TF). In the event of a discrepancy, a discussion was carried out until a consensus was reached. Patients with more likely alternative diagnoses were excluded, as well as those who declined consent for participation.

## **Data collection**

Data were collected retrospectively from electronic medical records by local investigators. Demographic data, past medical history and comorbidities were recorded, using the updated Charlson score. Immunosuppressive treatments were documented. A comprehensive geriatric assessment was performed, including living environment (home or nursing facility), nutritional status and activities of daily living (ADL) before hospital admission. Disease severity at admission and within 24 h was assessed using SOFA score. Incident delirium during hospitalisation was recorded [6]. Clinical, biological, therapeutic and imaging characteristics were also documented. Antimicrobial treatments for PCP were recorded.

## **Outcomes**

Hospital length of stay and outcomes were recorded, including intensive care unit (ICU) admission and the primary reason for ICU admission, in-hospital all-cause mortality, admission to post-acute care or rehabilitation units, return home after discharge, 3-month post-discharge readmission rate and 3-month mortality.

## **Statistical analysis**

Continuous variables are described as median and interquartile range (IQR), and categorical variables as number and percentage. Cumulative proportions were calculated for variables with more than two categories. Normality was assessed using the Shapiro-Wilk test.

The population was divided by vital status at discharge. Categorical variables were compared using the Chi<sup>2</sup> or Fisher's exact test, and continuous variables with the Student's t-test, Wilcoxon rank-sum test, ANOVA or Kruskal-Wallis test, as appropriate.

Factors associated with in-hospital mortality were assessed using univariate and multivariable Cox regression models. Results are reported as hazard ratios (HR) with 95% confidence intervals [95%CI]. Given the number of events ( $N = 45$ ), four variables were included in the multivariate analysis [11], selected for clinical relevance and statistical significance in univariate analysis ( $p < 0.2$ ), excluding those with missing data. Conditional stepwise regression identified the most informative variables.

Sensitivity, specificity and optimal cut-off values for mortality-associated factors were assessed using the Youden index. Survival curves were generated with the Kaplan-Meier method and compared using the log-rank test.

All tests were two-sided, with  $p < 0.05$  considered statistically significant. Analyses were performed with R software (V4.2, R Foundation for Statistical Computing) using the GMRC Shiny Stat application (version 2017, Strasbourg University Hospital).

## Ethics

The study protocol (No. 22.01.05) was approved on January 5, 2022, by the Institutional Review Board of Nimes University Hospital, which waived the need for written informed consent. The study adhered to the Declaration of Helsinki and complies with French legal and ethical standards (MR004 methodology).

**Table 1** Characteristics of the study population

Characteristic	N (%) or median [IQR]
Age (years)	79 [77–82]
Sex (male)	93 (57.4)
BMI (kg/m <sup>2</sup> ) (n = 151)	24.6 [22.5–27.2]
Walking (n = 113)	
Independent	80 (70.8)
Cane	20 (17.7)
Walker	13 (11.5)
ADL score (n = 85)	6 [6–6]
IADL score (n = 28)	8 [5–8]
Previous cognitive impairment (n = 158)	9 (5.7)
Residence (n = 159)	
Home	155 (97.5)
Assisted living facility	1 (0.6)
Nursing home	3 (1.9)
<b>Comorbidities and risk factors for immunosuppression</b>	
Haematological malignancies	58 (35.8)
Solid tumour	56 (34.5)
Metastatic	16 (29.0)
Systemic rheumatic disease	45 (26.8)
Solid organ transplant	12 (7.4)
Immunosuppressive treatment	131 (80.8)
Corticosteroid therapy	96 (60.0)
Methotrexate	26 (16.0)
Rituximab	20 (12.3)
Alkylating agents (cyclophosphamide)	20 (12.3)
Calcineurin inhibitors	11 (6.8)
Mycophenolate mofetil (MMF)	8 (5.0)
Updated Charlson score	2 [2–4]
<b>Clinical and biological features</b>	
Anorexia	37 (22.8)
Falls	11 (6.8)
Delirium	8 (5.0)
Fatigue	92 (56.8)
Fever	103 (63.0)
Maximum temperature (°C)	38.1 [37.3–38.9]
Oxygen saturation (%)	94 [90–96]
Respiratory rate (/min)	28 [23–35]
Dyspnoea	120 (74.0)
Cough	90 (55.0)
Exercise-induced desaturation	46 (28.4)
Sputum	22 (13.5)
Abnormal lung auscultation	81 (50.0)
Diffuse crackles	47 (29.0)
Focal crackles	34 (21.0)
Rhonchi	7 (4.3)
Wheezing	5 (3.0)
Mean arterial pressure	91 [81.5–98.75]
Haemoglobin (g/100 mL)	10.55 [9.4–12.1]
Leukocytes (G/L) (n = 161)	8.4 [5.0–11]
Neutrophils (G/L) (n = 156)	6.4 [3.6–9.0]
Lymphocytes (G/L) (n = 155)	0.6 [0.4–1.2]
Natremia (mmol/L)	137 [134–139]

**Table 1** (continued)

Characteristic	N (%) or median [IQR]
< 135 mmol/L	48 (29.6)
C-reactive protein (mg/L)	94.8 [55.52–165.5]
Lactate dehydrogenase (IU/L) (n=51)	347 [246–454.5]
β-D-Glucan (pg/mL) (n=27)	354 [153.2–478.4]
Partial arterial oxygen pressure (mmHg)	68 [57–82.22]
Albuminemia (g/L) (n=102)	28.1 [25.0–31.9]
SOFA score	2 [1–3.75]
<b>Microbiology</b>	
Giemsa or Gomori Methenamine Silver staining	19 (11.7)
BALF	16 (84.2)
Sputum	3 (15.8)
Immunofluorescence (on BALF)	37 (22.8)
Polymerase chain reaction (PCR)	133 (82.0)
BALF	87 (66.4)
Sputum	43 (32.3)
Nasopharyngeal swab	3 (2.2)
<b>Initial management</b>	
Antimicrobials	
Cotrimoxazole	150 (92.6)
Daily dose (mg of trimethoprim)	1440 [960–4800]
Atovaquone	12 (7.4)
Daily dose (mg)	1500 [1500–1500]
Corticosteroid treatment	108 (66.6)
Newly initiated	60 (55.5)
Ongoing treatment continued	48 (45.5)
Oxygen therapy support	
None	23 (14.5)
Nasal cannula/mask	83 (52.2)
High-flow nasal oxygen therapy	25 (15.7)
Non-invasive mechanical ventilation	5 (3.1)
Invasive mechanical ventilation	23 (14.5)

Analyses used N=162, except when reduced by missing data, as noted per variable

IQR: Interquartile range; BMI: body mass index; ADL: Activities of Daily Living

IADL: Instrumental Activities of Daily Living; BALF: bronchoalveolar lavage fluid

SOFA: Sequential Organ Failure Assessment

## Results

### Population characteristics

The characteristics of the study population are summarized in Table 1. Among 175 non-HIV-infected patients aged  $\geq 75$  years screened for suspected PCP, 14 were excluded: 13 due to alternative diagnoses and one due to a lack of consent. A total of 162 patients were included in the final analysis (Fig. 1). The median age was 79 years [IQR: 77–82]. Most patients were male (57.4%), lived at home, walked without assistive devices and had a median ADL score of 6/6 [IQR: 6–6]. Median Charlson score was 2 [IQR: 2–4]. The main immunosuppressive conditions were haematological malignancies (35.8%, mainly non-Hodgkin lymphoma) and solid tumours (34.5%), followed by systemic rheumatic diseases (26.8%). Solid organ transplant patients accounted for 7.4% of the study population. Most patients (80%) were treated long-term with immunosuppressive medications: corticosteroid therapy (60%), methotrexate (16%), rituximab (12.3%) or alkylating agents (12.3%). However, 13 patients (8%) presented without any clearly identified immunosuppression risk factors.

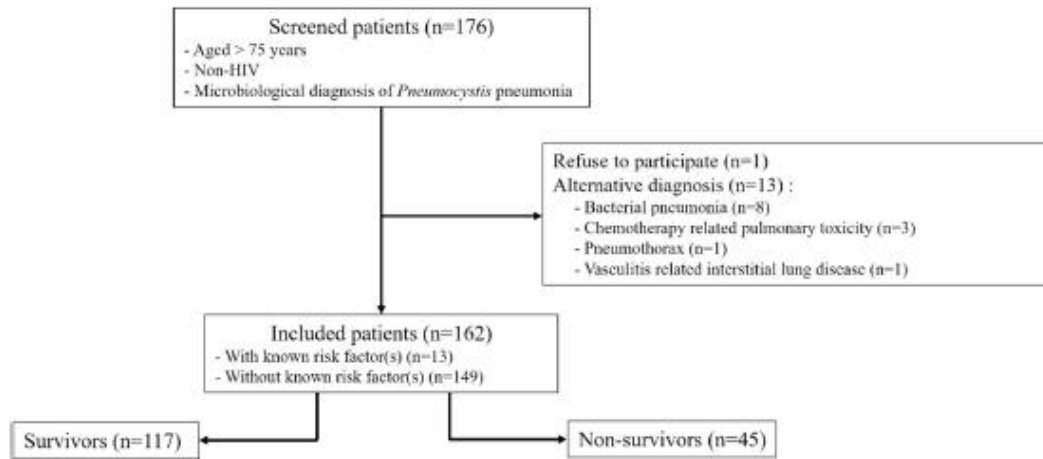


Fig. 1 Flow chart of the study population

At admission, most patients had respiratory symptoms (87.6%), with frequent dyspnoea (74%), median oxygen saturation of 94% [IQR: 90–96], and 85.5% required oxygen therapy. Auscultation was abnormal in only half of cases. Extra-respiratory symptoms (87.6%), such as fatigue, anorexia, falls, delirium and fever (62.9%), were also common. Thoracic imaging mainly showed interstitial lung disease: bilateral interstitial syndrome on chest X-ray (44/84) or ground-glass opacities on chest computed tomography scans (95/135).

Median C-reactive protein (CRP) level was 94.8 mg/L [IQR: 55.5–165.5] and median lymphocyte count was 0.6 G/L [IQR: 0.36–1.2]. Plasma  $\beta$ -D-glucan was measured in 27 patients of the cohort (16.6%), and all results were positive with elevated levels (median 354 pg/mL [IQR: 153.2–478.4]). The microbiological diagnosis relied primarily on PCR detection of *P. jirovecii*, which was performed in 133 patients (82%), using either bronchoalveolar lavage in approximately two-thirds of cases or sputum samples in one-third (Table 1). Standard staining or immunofluorescence identified the pathogen in only 56 cases (34.5%), mainly from bronchoalveolar lavage specimens.

Cotrimoxazole was the first-line therapy for most patients (150/162; 92.6%) and 108 (66.6%) also received corticosteroids. Among them, 60 (55.5%) started corticosteroids for PCP, while 48 (45.5%) continued pre-existing therapy.

## Outcomes

The short- and long-term outcomes are presented in Table 2. Initial antimicrobial therapy with cotrimoxazole was switched to atovaquone in 20.8% of patients, mainly due to acute renal failure (38.7%) or cutaneous adverse events (19.4%).

One-third of patients required ICU admission, primarily for acute respiratory failure. In-hospital mortality was 27.8%, with 45 deaths during hospitalisation. Notably, all patients originating from nursing homes or nursing facilities died ( $n = 4$ ).

Among the survivors, 70% were able to return home, while 29% were admitted to a post-acute care or rehabilitation unit. Mortality increased to 35.1% within 3 months of discharge.

At the 3-month follow-up, 39.6% of survivors had returned to their pre-hospitalisation living place, while 15% required hospital readmission.

**Table 2** Short and long-term outcomes

Characteristics	Patients (N=162)
Antimicrobial adverse events	33 (20.8)
Acute renal failure	12 (38.7)
Toxic skin reaction	6 (19.4)
Digestive intolerance	5 (16.1)
Cytopenia	3 (9.7)
Second line antimicrobials	
Atovaquone	30 (91.0)
Pentamidine Isethionate (aerosol)	3 (9.0)
Need for ICU transfer	52 (32.1)
Acute respiratory distress	48 (92.3)
Septic shock	4 (7.7)
In-hospital death	45 (27.8)
Hospital discharge	117 (72.2)
Return to previous place of living	82 (72.2)
Admission to rehabilitation	34 (26.9)
Institutionalization	1 (0.9)
Three-month follow-up	
Maintenance of previous place of living	61 (39.6)
Death	54 (35.1)
Readmission to hospital	23 (15.0)
Institutionalization	5 (3.2)
Lost to follow-up	11 (7.4)

Data shown are n (%)

ICU: intensive care unit

## Factors associated with in-hospital mortality

Univariate analysis showed a significant association between in-hospital death and living in a nursing home ( $p = 0.005$ ), lower SaO<sub>2</sub> ( $p = 0.032$ ), higher SOFA score ( $p = 0.002$ ), ICU transfer ( $p < 0.001$ ), delirium ( $p = 0.038$ ), higher leukocyte levels ( $p = 0.014$ ), neutrophils ( $p = 0.002$ ), CRP level ( $p < 0.001$ ) and initiation of corticosteroid treatment ( $p < 0.01$ ).

**Table 3** Factors associated with in-hospital mortality

	Univariate analysis			Multivariate analysis	
	Survivors (N=117)	Died (N=45)	p value	Hazard ratio	p value
Sex (male)	62 (53.0)	31 (69.0)	0.067	1.74 [0.92–3.30]	0.09
Residence			<b>0.005</b>		
Home	116 (100)	39 (91.0)			
Nursing home	0 (0)	3 (7.0)			
Assisted living facility	0 (0)	1 (2.3)			
Oxygen saturation at admission	94 [91–96]	92 [88–95]	<b>0.032</b>	0.937 [0.907–0.968]	<b>&lt;0.001</b>
Oxygen therapy support			<b>&lt;0.001</b>		
None	21 (18.0)	2 (4.5)			
Nasal cannula/mask O <sub>2</sub>	69 (60.0)	14 (32.0)			
High-flow oxygen therapy	18 (16.0)	7 (16.0)			
Non-invasive mechanical ventilation	3 (2.6)	2 (4.5)			
Invasive mechanical ventilation	4 (3.5)	19 (43.0)			
Dyspnoea	82 (70.0)	38 (84.0)	0.062		
Exertional desaturation	28 (24.0)	18 (40.0)	<b>0.042</b>		
Delirium	3 (2.6)	5 (11.0)	<b>0.038</b>		
Leukocytes	7 [5–11]	10 [8–11]	<b>0.014</b>		
Neutrophils	5.9 [3.0–8.5]	7.9 [6.0–9.2]	<b>0.002</b>		
C-reactive protein (CRP)	80 [46–126]	148 [84–226]	<b>&lt;0.001</b>		
CRP > 110 mg/L	39 (33.0)	29 (64.0)	<b>&lt;0.001</b>	2.55 [1.35–4.83]	<b>&lt;0.01</b>
Atovaquone initial antimicrobial	12 (10.0)	0 (0)	<b>0.038</b>		
Corticosteroid newly initiated	36 (31.0)	24 (53.0)	<b>0.008</b>	1.89 [1.03–3.44]	<b>0.039</b>
Corticosteroid dosage (mg/kg/d)	0.74 (0.33–0.89)	0.81 (0.65–1)	0.078		
ICU transfer	23 (20.0)	29 (64.0)	<b>&lt;0.001</b>		
SOFA	2.0 [1.0–3.0]	3.00 [1.0–5.00]	<b>0.002</b>		

Data shown are n (%) or median [IQR]

IQR: interquartile range; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment

Multivariate analysis identified CRP > 110 mg/L (HR = 2.55 [95%CI: 1.35–4.83],  $p = 0.004$ ) and initiation of corticosteroid therapy (HR = 1.89 [95%CI: 1.03–3.44],  $p = 0.039$ ) as independent predictors of mortality. Conversely, higher SaO<sub>2</sub> was associated with lower mortality (HR = 0.94 [95%CI: 0.91–0.97],  $p < 0.001$ ). The results of univariate and multivariate analyses are summarised in Table 3; Fig. 2.

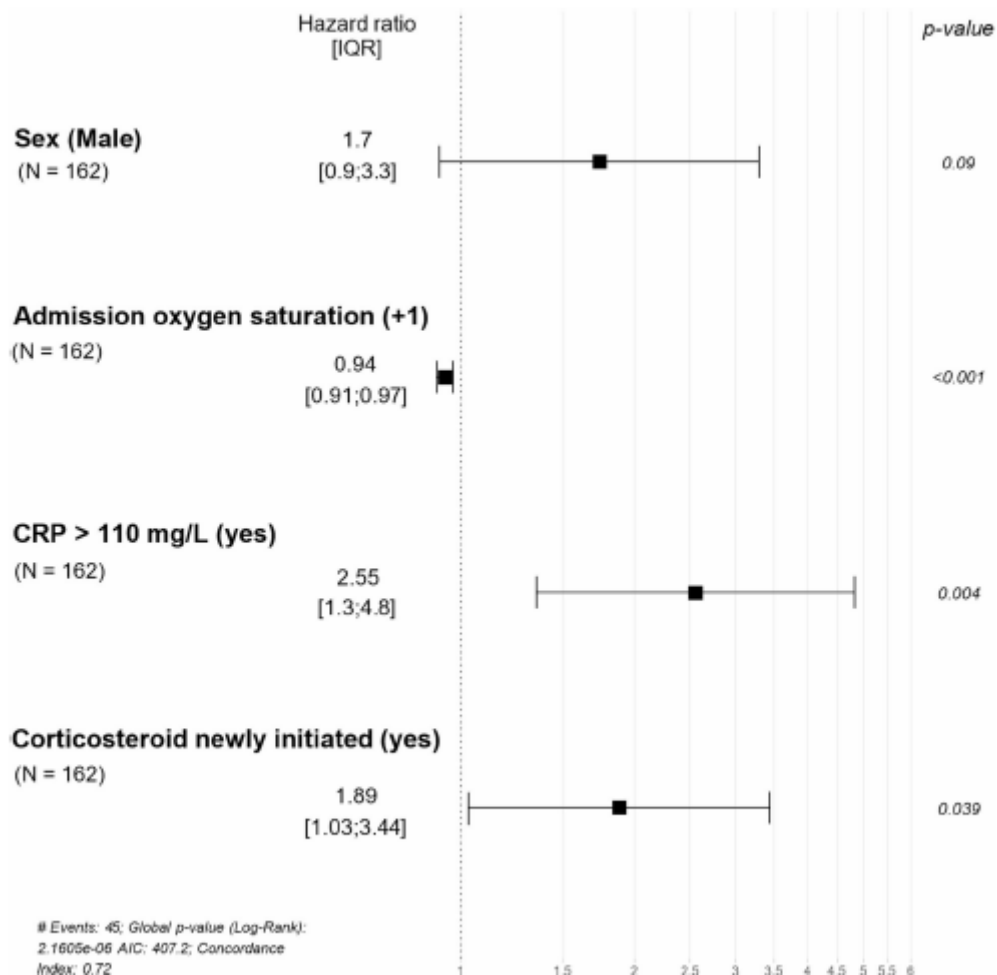


Fig. 2 Forest Plot of the factors independently associated with in-hospital mortality

## Discussion

This report describes the results of a large cohort study involving 162 non-HIV-infected patients aged  $\geq 75$  years with PCP, most of whom had immunosuppressive conditions or were receiving immunosuppressive medications. Patients commonly presented with dyspnoea, elevated CRP levels and bilateral lung involvement. PCP was primarily diagnosed by PCR testing of bronchoalveolar lavage or sputum samples, and most cases were treated with cotrimoxazole, combined with corticosteroids in two-thirds of patients. Lower oxygen saturation, CRP > 110 mg/L and corticosteroid initiation for PCP were independently linked to higher mortality.

For more than two decades, the use of corticosteroids as adjunct therapy for the treatment of PCP in non-HIV-infected populations has remained highly controversial [9, 12]. Some studies [12, 13], have highlighted adverse effects associated with corticosteroid use in this population. A retrospective cohort study [14] recently confirmed this finding, reporting increased mortality in severe cases admitted to the ICU. Consistent with these findings, our results indicate that corticosteroids may have a detrimental effect when used as adjunct therapy in older non-HIV-infected patients with PCP, as previously reported in older COVID-19 patients [15]. Older people and critically ill patients are known to be susceptible to infection [8] and the observed increase in mortality might be attributable to superinfections [9]. However, this remains unclear from the available data [9, 13] and decompensation of comorbidities induced by corticosteroids could also contribute to the increased mortality [15]. In our work, although overall mortality was higher in the corticosteroid group, the distribution of causes of death was similar in both groups (~ 2/3 PCP, ~ 1/3 other), suggesting that corticosteroid therapy did not reduce PCP-related mortality. Nevertheless, the association should be interpreted with caution given the retrospective design and the possibility of residual confounding. Further randomised controlled trials (RCTs) are needed to assess the potential benefits and risks of corticosteroids in older non-HIV patients.

Our results suggest a role of CRP or hypoxaemia severity in discriminating patients at higher risk of death. These markers [16, 17], along with others such as urea and albumin [18, 19], have already been shown to be relevant in various infectious contexts and should also be explored in PCP among older patients. Overall, the predictive factors we identified should be regarded as markers of respiratory disease severity rather than PCP-specific prognostic indicators. Nevertheless, the identification of patient subgroups likely to benefit from corticosteroids according to CRP levels should be investigated in RCTs [9]. As demonstrated in COVID-19 [20], CRP could potentially help to distinguish a highly inflammatory profile of patients who may benefit from immunomodulatory treatment, from a profile of less inflammatory patients in whom antimicrobial treatment alone should be prioritised.

Comorbid conditions, especially immunosuppression, are known to drive the prognosis of PCP and may also influence the potential impact of corticosteroid therapy [9, 12, 13]. In our cohort, comorbidities were similar to those described in younger non-HIV patients [3–5]. However, the proportion of patients with solid tumours was higher (34.5%) and the proportion of transplant patients (7.4%) was lower, as described previously in older people [21, 22]. In addition, more than a half of the patients in the current study were treated with corticosteroids (59.8%), as reported in other cohorts [3–5]. Accordingly, and despite the higher median age of our cohort, the in-hospital mortality rate was 27.8%, which is equivalent to or lower than that reported in younger non-HIV-infected adults with PCP (ranging from 30 to 60%) [23]. This could be explained by the inclusion in our study of patients with similar disease severity to those in cohorts of younger patients [3–5]. In addition, the patients included were not very old and had low frailty levels, and clinical presentations, taking into account some geriatric-specific features (delirium, falls, low fever), were similar to younger patients [3–5]. It is possible that patients with higher levels of frailty were not diagnosed and therefore not included in our retrospective cohort, raising concerns about the generalisability of our results to the whole geriatric population.

One striking finding was the greater reliance on PCR testing of sputum samples compared to other cohorts [3– 5]. PCP was confirmed by PCR testing of BALF samples in just two-thirds of cases, highlighting the limitations of invasive procedures in older patients. Frail individuals, often with severe cognitive impairments, are less likely to undergo these tests, possibly contributing to the underdiagnosis of PCP in this subgroup. Future studies on non-invasive diagnostics, such as plasma beta-D-glucan measurement [24, 25], could better define the incidence of the disease in older adults.

Cotrimoxazole is the cornerstone in the management of PCP in older patients as in young adults [9, 26]. However, cotrimoxazole-related adverse events appeared to be more common in the geriatric population [27]. In the current study, 20.8% of patients experienced adverse events, including renal toxicity and/or severe cutaneous reactions, which necessitated treatment withdrawal. This rate is three times higher than that observed in younger patients [3]. Most of these patients were subsequently treated with atovaquone as a second-line option, despite its reputation for being less effective [28]. In our cohort, none of the 12 patients treated with atovaquone died; however, the small sample size does not allow for firm conclusions (Table S1). Future research should focus on defining optimal treatment strategies for older patients. Notably, emerging evidence indicates that lower doses of cotrimoxazole may provide a safer and equally effective alternative [29, 30]. Although the effect of delayed initiation of antimicrobial therapy was not documented in our cohort, this has been demonstrated by others [14]. In the presence of severity criteria, rapid initiation of antimicrobial treatment remains a key element of management [14].

This study has several limitations, including its observational and retrospective design, which may have introduced biases in data collection and interpretation. Additionally, the limited inclusion of very frail patients or those over 85-years-old may affect the external validity of our findings to this specific population. Some diagnoses lacked robust evidence and may have been misclassified. In particular, the use of a high Ct / low copies/mL threshold to improve sensitivity at the screening stage carried a risk of overdiagnosis, a limitation that was mitigated by the adjudication process. Missing data prevented the analysis of certain frailty and diagnostic markers, such as  $\beta$ -D-glucan, or precise causes of death unrelated to PCP. Information on factors like cotrimoxazole prophylaxis in patients on long-term corticosteroids was not collected and the study design did not allow the investigation of reduced doses of cotrimoxazole. Finally, as in other studies [9, 12, 14, 26], the analysis of the impact of corticosteroid therapy is prone to bias because many patients are already receiving corticosteroids before developing PCP. To minimise this bias, we specifically focused on the effect of initiating corticosteroid therapy at the time of PCP diagnosis. Moreover, in our statistical analysis comparing outcomes of patients treated or not with corticosteroids, we adjusted for baseline severity. We also performed additional checks to ensure that both groups remained comparable in terms of severity (Table S2).

Despite these limitations, our work also has several strengths. To our knowledge, this is the first large multicentre analysis of older, non-HIV-infected patients with PCP, addressing both

short- and long-term outcomes and highlighting unique characteristics and challenges in this population. The study design allowed us to highlight the unique characteristics and challenges of this population, which is underrepresented in the literature. The large sample size provided sufficient statistical power for adjusted analyses, and we carefully accounted for baseline severity when comparing groups. Together, these strengths reinforce the validity of our findings and contribute new insights into the management of PCP in older adults. A rigorous adjudication process ensured diagnostic accuracy and minimized the risk of misclassification. The large sample size provided sufficient statistical power for adjusted analyses, and we carefully accounted for baseline severity when comparing groups. Together, these strengths reinforce the validity of our findings, which may help guide future approaches to the management of PCP in older adults.

In conclusion, this multicentre, retrospective study highlighted the clinical, microbiological and imaging characteristics of non-HIV-infected patients aged  $\geq 75$  years with PCP. The disease was prevalent among immunocompromised patients, particularly those with haematological malignancies, solid tumours or corticosteroid treatment. CRP levels  $> 110$  mg/L and severity of hypoxaemia at admission were identified as independent factors associated with increased mortality and the study suggested that the initiation of corticosteroid therapy may increase mortality in this population. Cotrimoxazole was the cornerstone antimicrobial therapy for PCP, but its management in older patients can be challenging.

These findings emphasise the need for individualised treatment strategies that consider disease severity, comorbidities and potential risks associated with corticosteroid and cotrimoxazole use, as well as the exploration of safer alternative therapies. Although PCP is primarily diagnosed through PCR testing, the use of non-invasive diagnostic tools, such as  $\beta$ -D-glucan measurement, may improve early detection in this vulnerable population. Future prospective studies are needed to refine therapeutic recommendations and enhance the diagnostic accuracy of PCP in non-HIV-infected older patients.

## **Abbreviations**

ADL Activities of Daily Living  
BALF Bronchoalveolar Lavage Fluid  
BMI Body Mass Index  
CRP C-reactive Protein  
HIV Human Immunodeficiency Virus  
HR Hazard Ratio  
IADL Instrumental Activities of Daily Living  
ICU Intensive Care Unit  
IQR Interquartile Range  
PCR Polymerase Chain Reaction  
PCP *Pneumocystis pneumonia*  
SOFA Sequential Organ Failure Assessment

## **Acknowledgements**

The authors thank Newmed Publishing Ltd. for final language editing of the manuscript.

## **Author contributions**

The first draft of the article was written by AB. Critical revision of the manuscript was performed by RL, GG, VA, CRB and TF. All authors read and approved the final version of the manuscript.

## **Funding**

No funding was received by any of the authors for this work.

## **Data availability**

AB is the guarantor for the data. The authors consent to share the collected data with others. The data will be made available by the authors, without undue reservation immediately after the main publication and indefinitely.

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the Institutional Review Board of Nimes University Hospital (reference number 22.01.05) on 5 January 2022. The requirement for written informed consent was waived by the ethics committee. The study was conducted in accordance with the principles of the Declaration of Helsinki and complied with relevant French legal and ethical standards (MR004 methodology).

### **Consent for publication**

Not applicable.

### **Generative AI and AI-assisted technologies in the writing process**

During the preparation of this report, the authors used ChatGPT-4o in order to improve the readability and language of the manuscript. After using this tool, the authors reviewed and edited the content as needed, and take full responsibility for the content of the publication.

### **Competing interests**

The authors declare no competing interests.

## **References**

1. Maschmeyer G, Helweg-Larsen J, Pagano L, Robin C, Cordonnier C, Schellongowski P, et al. ECIL guidelines for treatment of *Pneumocystis jirovecii* pneumonia in non-HIV-infected haematology patients. *J Antimicrob Chemother.* 2016;71:2405–13. <https://doi.org/10.1093/jac/dkw158>.

2. Teissier T, Boulanger E, Cox LS. Interconnections between inflammaging and Immunosenescence during ageing. *Cells*. 2022;11:359. <https://doi.org/10.3390/cells11030359>.
3. Roux A, Canet E, Valade S, Gangneux-Robert F, Hamane S, Lafabrie A, et al. Pneumocystis jirovecii pneumonia in patients with or without AIDS, France. *Emerg Infect Dis*. 2014;20:1490–7. <https://doi.org/10.3201/eid2009.131668>.
4. Fillatre P, Decaux O, Jouneau S, Revest M, Gacouin A, Robert-Gangneux F, et al. Incidence of Pneumocystis Jiroveci pneumonia among groups at risk in HIV-negative patients. *Am J Med*. 2014;127:e124211–17. <https://doi.org/10.1016/j.amjmed.2014.07.010>.
5. Grønseth S, Rogne T, Hannula R, Åsvold BO, Afset JE, Damås JK. Epidemiological and clinical characteristics of immunocompromised patients infected with Pneumocystis jirovecii in a twelve-year retrospective study from Norway. *BMC Infect Dis*. 2021;21:659. <https://doi.org/10.1186/s12879-021-06144-1>.
6. Drame M, Jovenin N, Novella JL, Lang PO, Somme D, Laniece I, et al. Predicting early mortality among elderly patients hospitalised in medical wards via emergency department: the SAFES cohort study. *J Nutr Health Aging*. 2008;12:599–604. <https://doi.org/10.1007/BF02983207>.
7. Fauchier T, Hasseine L, Gari-Toussaint M, Casanova V, Marty PM, Pomares C. Detection of Pneumocystis jirovecii by quantitative PCR to differentiate colonization and pneumonia in immunocompromised HIV-positive and HIV-negative patients. *J Clin Microbiol*. 2016;54:1487–95. <https://doi.org/10.1128/JCM.03174-15>.
8. Janssens J-P, Krause K-H. Pneumonia in the very old. *Lancet Infect Dis*. 2004;4:112–24. [https://doi.org/10.1016/S1473-3099\(04\)00931-4](https://doi.org/10.1016/S1473-3099(04)00931-4).
9. Ding L, Huang H, Wang H, He H. Adjunctive corticosteroids May be associated with better outcome for non-HIV Pneumocystis pneumonia with respiratory failure: a systemic review and meta-analysis of observational studies. *Ann Intensive Care*. 2020;10:34. <https://doi.org/10.1186/s13613-020-00649-9>.
10. Maillet M, Maubon D, Brion JP, François P, Molina L, Stahl JP, et al. Pneumocystis jirovecii (Pj) quantitative PCR to differentiate Pj pneumonia from Pj colonization in immunocompromised patients. *Eur J Clin Microbiol Infect Dis*. 2014;33:331–6. <https://doi.org/10.1007/s10096-013-1960-3>.
11. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165:710–8. <https://doi.org/10.1093/aje/kwk052>.
12. Wieruszewski PM, Barreto JN, Frazee E, Daniels CE, Tosh PK, Dierkhising RA, et al. Early corticosteroids for Pneumocystis pneumonia in adults without HIV are not associated with better outcome. *Chest*. 2018;154:636–44. <https://doi.org/10.1016/j.chest.2018.04.026>.

13. Lemiale V, Debrumetz A, Delannoy A, Alberti C, Azoulay E. Adjunctive steroid in HIV-negative patients with severe *Pneumocystis pneumonia*. *Respir Res.* 2013;14:87. <https://doi.org/10.1186/1465-9921-14-87>.
14. Kamel T, Janssen-Langenstein R, Quelven Q, Chelly J, Valette X, Le M-P, et al. *Pneumocystis pneumonia* in intensive care: clinical spectrum, prophylaxis patterns, antibiotic treatment delay impact, and role of corticosteroids. A French multicentre prospective cohort study. *Intensive Care Med.* 2024;50:1228–39. <https://doi.org/10.1007/s00134-024-07489-2>.
15. Lidou-Renault V, Baudouin E, Courtois-Amiot P, Bianco C, Esnault H, Rouet A, et al. Corticosteroid therapy in COVID-19 associated with in-hospital mortality in geriatric patients: a propensity matched cohort study. *J Gerontol Biol Sci Med Sci.* 2022;glac084. <https://doi.org/10.1093/gerona/glac084>.
16. Ticinesi A, Lauretani F, Nouvenne A, Porro E, Fanelli G, Maggio M, et al. C-reactive protein (CRP) measurement in geriatric patients hospitalized for acute infection. *Eur J Intern Med.* 2017;37:7–12. <https://doi.org/10.1016/j.ejim.2016.08.026>.
17. Kolditz M, Ewig S, Klapdor B, Schütte H, Winning J, Rupp J, et al. Community-acquired pneumonia as medical emergency: predictors of early deterioration. *Thorax.* 2015;70:551–8. <https://doi.org/10.1136/thoraxjnl-2014-206744>.
18. Shirata M, Ito I, Ishida T, Tachibana H, Tanabe N, Konishi S, et al. Development and validation of a new scoring system for prognostic prediction of community-acquired pneumonia in older adults. *Sci Rep.* 2021;11:23878. <https://doi.org/10.1038/s41598-021-03440-3>.
19. Chongthanadon B, Thirawattanasoot N, Ruangsomboon O. Clinical factors associated with in-hospital mortality in elderly versus non-elderly pneumonia patients in the emergency department. *BMC Pulm Med.* 2023;23:330. <https://doi.org/10.1186/s12890-023-02632-z>.
20. Abani O, Abbas A, Abbas F, Abbas M, Abbasi S, Abbass H, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2021;397:1637–45. [https://doi.org/10.1016/S0140-6736\(21\)00676-0](https://doi.org/10.1016/S0140-6736(21)00676-0).
21. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, et al. The European cancer burden in 2020: incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer.* 2021;157:308–47. <https://doi.org/10.1016/j.ejca.2021.07.039>.
22. Sutherland AI, IJzermans JNM, Forsythe JLR, Dor FJMF. Kidney and liver transplantation in the elderly. *Br J Surg.* 2016;103:e62–72. <https://doi.org/10.1002/bjs.10064>.
23. Quigley N, d'Amours L, Gervais P, Dion G. Epidemiology, risk factors, and prophylaxis use for *Pneumocystis jirovecii* pneumonia in the non-HIV population: a retrospective study in

Québec, Canada. *Open Forum Infect Dis.* 2024;11:ofad639. <https://doi.org/10.1093/ofad639>.

24. Senécal J, Smyth E, Del Corpo O, Hsu JM, Amar-Zifkin A, Bergeron A, et al. Non-invasive diagnosis of *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Clin Microbiol Infect.* 2022;28:23–30. <https://doi.org/10.1016/j.cmi.2021.08.017>.

25. Calvet L, Lemiale V, Mokart D, Peter S, Peter P, Demoule A, et al. Interpretation of results of PCR and B-D-glucan for the diagnosis of *Pneumocystis jirovecii* pneumonia in immunocompromised adults with acute respiratory failure. *Ann Intensive Care.* 2024;14:120. <https://doi.org/10.1186/s13613-024-01337-8>.

26. Assal M, Lambert J, Chow-Chine L, Bisbal M, Servan L, Gonzalez F, et al. Prognostic impact of early adjunctive corticosteroid therapy in non-HIV oncology or haematology patients with *Pneumocystis jirovecii* pneumonia: A propensity score analysis. *PLoS ONE.* 2021;16:e0250611. <https://doi.org/10.1371/journal.pone.0250611>.

27. Soraci L, Cherubini A, Paoletti L, Filippelli G, Luciani F, Laganà P, et al. Safety and tolerability of antimicrobial agents in the older patient. *Drugs Aging.* 2023;40:499–526. <https://doi.org/10.1007/s40266-023-01019-3>.

28. Hughes W, Leoung G, Kramer F, Bozzette SA, Safrin S, Frame P, et al. Comparison of Atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. *N Engl J Med.* 1993;328:1521–7. <https://doi.org/10.1056/NEJM199305273282103>.

29. Butler-Laporte G, Smyth E, Amar-Zifkin A, Cheng MP, McDonald EG, Lee TC. Low-dose TMP-SMX in the treatment of *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis. *Open Forum Infect Dis.* 2020;7:ofaa112. <https://doi.org/10.1093/ofa112>.

30. Sohani ZN, Butler-Laporte G, Aw A, Belga S, Benedetti A, Carignan A, et al. Low-dose trimethoprim-sulfamethoxazole for the treatment of *Pneumocystis jirovecii* pneumonia (LOW-TMP): protocol for a phase III randomised, placebo-controlled, dose-comparison trial. *BMJ Open.* 2022;12:e053039. <https://doi.org/10.1136/bmjopen-2021-053039>.