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► **To cite this version:**

Romain Lécuyer, Nahéma Issa, Fabrice Camou, Rose-anne Lavergne, Frederic Gabriel, et al.. Characteristics and Prognosis Factors of Pneumocystis jirovecii Pneumonia According to Underlying Disease. Chest, 2024, pp.S0012-3692(24)00022-9. 10.1016/j.chest.2024.01.015 . inserm-04446239

HAL Id: inserm-04446239

<https://inserm.hal.science/inserm-04446239v1>

Submitted on 8 Feb 2024

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Characteristics and Prognosis Factors of *Pneumocystis jirovecii* Pneumonia According to Underlying Disease

A Retrospective Multicenter Study

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BACKGROUND: *Pneumocystis jirovecii* pneumonia (PcP) remains associated with high rates of mortality, and the impact of immunocompromising underlying disease on the clinical presentation, severity, and mortality of PcP has not been adequately evaluated.

RESEARCH QUESTION: Does the underlying disease and immunosuppression causing PcP impact the outcome and clinical presentation of the disease?

STUDY DESIGN AND METHODS: In this multicenter retrospective observational study, conducted from January 2011 to December 2021, all consecutive patients admitted with a proven or probable diagnosis of PcP according to The European Organisation for Research and Treatment of Cancer consensus definitions were included to assess the epidemiology and impact of underlying immunosuppressive diseases on overall and 90-day mortality.

RESULTS: Overall, 481 patients were included in the study; 180 (37.4%) were defined as proven PcP and 301 (62.6%) were defined as probable PcP. Patients with immune-mediated inflammatory diseases (IMIDs) or solid tumors had a statistically poorer prognosis than other patients with PcP at day 90. In multivariate analysis, among the HIV-negative population, solid tumor underlying disease (OR, 5.47; 95% CI, 2.16-14.1; $P < .001$), IMIDs (OR, 2.19; 95% CI, 1.05-4.60; $P = .037$), long-term corticosteroid exposure (OR, 2.07; 95% CI, 1.03-4.31; $P = .045$), cysts in sputum/BAL smears (OR, 1.92; 95% CI, 1.02-3.62; $P = .043$), and SOFA score at admission (OR, 1.58; 95% CI, 1.39-1.82; $P < .001$) were independently associated with 90-day mortality. Prior corticotherapy was the only immunosuppressant associated with 90-day mortality (OR, 1.67; 95% CI, 1.03-2.71; $P = .035$), especially for a prednisone daily dose ≥ 10 mg (OR, 1.80; 95% CI, 1.14-2.85; $P = .010$).

INTERPRETATION: Among patients who were HIV-negative, long-term corticosteroid prior to PcP diagnosis was independently associated with increased 90-day mortality, specifically in patients with IMIDs. These results highlight both the needs for PcP prophylaxis in patients with IMIDs and to early consider PcP curative treatment in severe pneumonia among patients with IMIDs.

CHEST 2024; ■(■):■-■

KEY WORDS: corticosteroids; immune-mediated inflammatory diseases; *Pneumocystis jirovecii* pneumonia; outcome; solid tumors

Take-home Points

Study Question: Does the underlying disease and immunosuppression causing *Pneumocystis jirovecii* pneumonia (PcP) impact the outcome and clinical presentation of the disease?

Results: We present the findings of a cohort study involving 481 patients diagnosed with probable or proven PcP to assess the impact of various immunocompromising underlying conditions on the clinical presentation and mortality associated with PcP. This large multicenter study is the first to identify patients with immune-mediated inflammatory diseases (IMIDs), solid tumors, and prolonged corticosteroid therapy as independent factors contributing to 90-day mortality. Notably, patients with IMIDs, particularly those exposed to long-term corticosteroid therapy, exhibit the most unfavorable prognosis compared with other immunocompromised conditions.

Interpretation: These results highlight that, across all patient categories, patients with IMID and solid tumors experience the most severe forms of PcP and the highest mortality rates. Additionally, a history of prior long-term corticosteroid therapy was associated with a poor prognosis, especially among patients with IMIDs. These findings emphasize the necessity of considering PcP prophylaxis for patients with IMIDs and promptly initiating PcP treatment in cases of severe pneumonia in this specific population.

The growing number of patients undergoing immunosuppressive treatments and the development of new biotherapies for hematologic malignancies, solid organ transplantations, or immune-mediated inflammatory diseases (IMIDs) has led to the emergence of new conditions for opportunistic

ABBREVIATIONS: CMV = cytomegalovirus; IMID = immune-mediated inflammatory disease; PcP = *Pneumocystis jirovecii* pneumonia; SOFA = Sequential Organ Failure Assessment

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pulmonary fungal infections. Currently, around three-quarters of *Pneumocystis jirovecii* pneumonia (PcP) cases are diagnosed in patients who are HIV-negative in high-income countries.^{1,2} HIV-negative PcP is associated with a higher morbidity and mortality rate, and may be more challenging to diagnose than in patients who are HIV-positive; therefore, it is necessary to further improve risk reduction, diagnosis,^{Q8} and treatment procedures. In the HIV-negative population, the prognosis of PcP is highly variable, suggesting that the underlying disease and immunosuppressive therapies both have an impact on the severity and outcome of this infection.³ Prior corticosteroid therapy has been identified as a risk factor for PcP⁴⁻⁶ and has been associated with mortality.⁷ The advent of new immunosuppressive treatments raise the question of the appropriate criteria to introduce primary prophylaxis.⁸ We previously reported that the pattern of immune responses,⁹ and respiratory coinfection by cytomegalovirus (CMV)¹⁰ as a probable marker of profound immunosuppression, were associated with a worse prognosis. However, the impact of underlying disease and of specific immunologic disorders on the clinical presentation, severity, and mortality of PcP is poorly studied in the contemporary cohorts of patients. Investigating the features and the prognosis of PcP subpopulations according to the underlying disease and immunosuppressive therapies may allow an earlier diagnosis of PcP and a faster initiation of anti-*Pneumocystis* treatment. ^{Q9}

In this study, we took a large multicenter cohort of patients with probable or proven PcP from three French hospitals over 10 years of follow-up and studied the impact of the immunocompromising underlying disease and of the type of immunosuppressive treatment on the clinical presentation and mortality of PcP.

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DOI: <https://doi.org/10.1016/j.chest.2024.01.015>

Study Design and Methods

Study Design and Population

This study is a substudy from the PRONOCYSTIS cohort,¹⁰ a retrospective multicenter network involving three French hospitals. All consecutive patients admitted with a proven or probable diagnosis of PcP according to The European Organisation for Research and Treatment of Cancer and the Mycoses Study Group¹¹ consensus definitions of invasive fungal diseases from January 2011 to December 2021 were retrospectively included. Patients were followed-up for at least a year.

The study was designed in accordance with the Declaration of Helsinki and conducted in accordance with French legislation with approval obtained from the local ethics committee (groupe nantais d'éthique dans le domaine de la santé [GNEDS] No. 23-34-03-091).

Data Collection

For each case, data were collected for patient demographic characteristics, underlying disease, immunosuppressive treatment exposition during the year prior to PcP onset, use of PcP prophylaxis, nature of symptoms and time from symptoms onset to PcP diagnosis and hospital admission, laboratory findings, presence of other pathogenic microorganisms (bacteria, virus, or fungi) on diagnostic respiratory samples, use of corticosteroid therapy and its duration, oxygen requirement, and ventilatory support at admission. The Sequential Organ Failure Assessment (SOFA) and Simplified Acute Physiology Score II were retrospectively determined for each patient at the time of PcP diagnosis based on the medical records. If any parameters required were missing, the score values were treated as missing data. The retrospective assessments of FiO_2 in non-ICU patients were approximated using a concordance table (with estimated FiO_2 values for nasal oxygen = 0.3, mask oxygen = 0.4, and reservoir mask = 0.6).¹² Finally, final outcome with 90-day mortality was registered in the study database.

Definitions

Criteria for PcP diagnosis involved compatible clinical presentation (fever, respiratory symptoms, cough, dyspnea, and hypoxemia) and an interstitial syndrome on chest radiograph or CT scan, along with mycologic evidence for *P jirovecii* in respiratory samples, induced sputum, bronchial aspiration fluid, or BAL. PcP was proven when *P jirovecii* asci (cysts) were found at direct microscopic examination. Probable PcP was determined by a negative direct mycologic examination but a positive *P jirovecii* qPCR (laboratory-defined threshold) in respiratory sample,¹¹ associated with a compatible clinico-radiologic presentation. Colonization was defined as the presence of a positive real-time polymerase chain reaction without meeting the clinical and/or radiologic criteria for a proven or

Results

Patient Characteristics

Over the 10-year study period, a total of 8,508 respiratory samples were tested for *P jirovecii* across the three hospitals, with 1,238 patients having a positive *P jirovecii* qPCR. After assessment of clinical and radiologic data, 508 patients were categorized as probable or proven PcP (730 colonized patients were excluded). Of these, nine patients < 18 years of age and 18 patients with missing data during follow-up

probable diagnosis of PcP. PcP cases involving patients < 18 years of age or with mortality missing data were excluded from the study. Date of PcP diagnosis was the day of confirmation by mycologic investigation (direct examination or qPCR).

Several predisposing clinical conditions were considered, including HIV infection, hematologic malignancies, progressive cancer, solid organ transplantation, and IMIDs. Ongoing immunosuppressive or immunomodulatory treatment did not constitute an independent subgroup of predisposing condition but was an analysis parameter. Patients undergoing corticosteroid treatment were considered to be immunosuppressed if they had been receiving > 7 days at a dose \geq 1 mg/kg/d (prednisone equivalent) or for > 3 months at a lower dose. When a patient had several predisposing conditions (n = 30), the underlying disease chronologically associated with the onset of PcP was considered (eg, an immuno-virologically controlled patient who was HIV-positive receiving secondary chemotherapy for lung cancer would be classified in the solid oncology group).

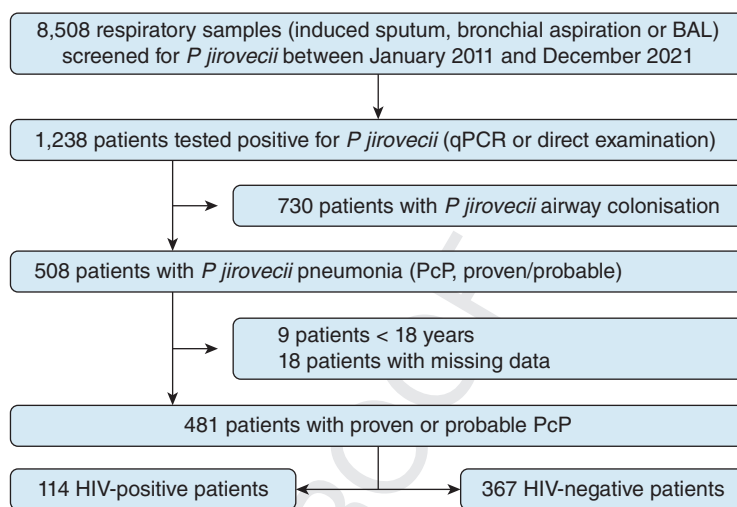
Adjuvant corticosteroid therapy was defined as any current or initiated high-dose steroid treatment justified by a PcP severe form, with a regimen similar to that used for patients with HIV with severe PcP.¹³

Statistical Analysis

Patient characteristics were described using mean \pm SD for continuous variables (or 95% CI when appropriate) and proportions for qualitative variables. Overall survival estimates were assessed using the Kaplan-Meier method. To remove potential biases associated with underlying condition impact on overall outcome in the long term, 90-day all-cause mortality was used (as previously described¹⁰). Preanalysis of the dataset did not show discrepancies across centers (n = 3) for the results, and we decided to carry on with a fixed-effect logistic regression model. All regression tests (OR estimates and CIs) for 90-day mortality were performed on variables involving > 10 events. The multivariate analysis was primarily performed to assess the respective weights of each variable, taking into account the other variables as fixed. Factors associated with 90-day mortality were identified by logistic regression analysis. Only factors reaching statistical significance ($P < .05$), with no more than 10% missing data, were included in the multivariate model. For subcategory comparisons with a low number of occurrences, numbers and percentages are given. When collinearity between covariates was detected, only the variable with the highest OR was kept in the multivariate regression model. Results were reported as log-transformed coefficients with their 95% CIs. Missing data were not interpolated. Analyses were performed on the overall population and then on the HIV-negative and IMIDs subgroups, taking into account respective missing data percentages. All analyses were conducted in R (4.3.1), using the finalfit and survminer packages.

were excluded (Fig 1). A total of 481 patients were therefore included, of which 180 (37.4%) were defined as having proven PcP and 301 (62.6%) as having probable PcP. The baseline characteristics of the included patients are shown in Table 1 (comparison according to HIV status in e-Table 1 or to other underlying diseases in e-Table 2). All patients from this cohort were immunocompromised with hematologic malignancy ranking first (n = 118, 24.5%), followed by HIV infection (n = 114, 23.7%), solid organ transplantation (n = 103, 21.4%), IMIDs

Q37 331 Q34 Figure 1 – Flowchart of the study. PcP = *Pneumocystis jirovecii* pneumonia.



(n = 87, 18.1%), solid tumor (n = 56, 11.6%), and other immunodeficiency (n = 3, 0.6%). The mean CD4 T lymphocyte count at the time of PcP diagnosis was significantly higher in the HIV-negative group than in the HIV-positive group (292 ± 360 vs $64 \pm 129/\text{mm}^3$, respectively; $P < .001$). Only 50 of 481 patients (10.4%) were given PcP prophylaxis prior to their PcP episode. Trimethoprim-sulfamethoxazole was used as first-line therapy for 443 patients (92.1%), and adjuvant corticosteroid therapy was administered to 226 patients (47.0%). The average SOFA score was 3.3 ± 3.0 . The 90-day mortality rate was 25.6% (n = 123). BAL was conducted at PcP diagnosis in 342 patients (71.1%). The detailed characteristics of BAL according to patient groups are presented in e-Table 3.

Previous Immunosuppressive Treatments

Among the overall population, 330 patients (89.9%) who were HIV-negative had received immunosuppressive treatment prior to PcP diagnosis (e-Table 4). The most common immunosuppressants were corticosteroids (n = 232, 63.2%), with an average dose of 29.2 mg/d prednisone equivalent. Prior corticosteroid therapy was more frequent in patients with IMIDs (79 of 87 [90.8%] vs 152 of 280 [54.3%]; OR, 8.25; 95% CI, 3.84-17.7; $P < .001$) and given at higher doses (31.0 vs 19.5 mg/d; $P = .008$) (e-Table 4).

Outcomes and Predictors of 90-Day Mortality

Patients with IMIDs and solid tumors had a statistically significant worse outcome at 90 days (e-Figs 1, 2; Fig 2), whereas patients who were HIV-positive had the best survival rate at 90 days (Fig 2, Table 2). Of the 56 patients with solid tumors, 36 (64.3%) had metastatic

disease, which was associated with 90-day mortality in the univariate analysis (OR, 4.71; 95% CI, 1.40-15.9; $P = .010$). Subtype of hematologic disease was not associated with 90-day mortality, as indicated in e-Table 5.

Among the overall population in multivariate analysis, solid tumor underlying disease (OR, 5.73; 95% CI, 2.25-14.84; $P < .01$), long-term corticosteroid use (OR, 2.25; 95% CI, 1.12-4.71; $P = .026$), and SOFA score at admission (OR, 1.63; 95% CI, 1.44-1.87; $P < .001$) were independently associated with 90-day mortality.

Among patients who were HIV-negative, solid tumor (OR, 5.47; 95% CI, 2.16-14.1; $P < .001$), IMIDs (OR, 2.19; 95% CI, 1.05-4.60; $P = .037$), long-term corticosteroid exposure (OR, 2.07; 95% CI, 1.03-4.31; $P = .045$), positive direct examination of sputum/BAL smears (OR, 1.92; 95% CI, 1.02-3.62; $P = .043$), and SOFA score at admission (OR, 1.58; 95% CI, 1.39-1.82; $P < .001$) were independently associated with higher 90-day mortality in multivariate analysis (Fig 3, Table 3). Prior corticotherapy was no longer associated with 1-year mortality (Fig 3). Finally, prior corticotherapy was the only immunosuppressive drug associated with 90-day mortality (OR, 1.67; 95% CI, 1.03-2.71; $P = .035$), especially for a daily dose ≥ 10 mg (OR, 1.80; 95% CI, 1.14-2.85; $P = .010$) (Table 3).

In patients who were HIV-positive, 69.3% presented positive direct examination of sputum/BAL smears without significant association with 90-day mortality (n = 74; OR, 0.47; 95% CI, 0.08-2.72; $P = .394$) nor with a neutrophilic BAL profile (n = 57; OR, 0.41; 95% CI, 0.07-2.45; $P = .317$). Conversely, only 27.5% of patients who were HIV-negative presented positive direct examination of sputum/BAL smears (e-Table 1), which was associated with high 90-day mortality

TABLE 1] Characteristics of Patients at the Time of Diagnosis of PcP and Follow-up (N = 481)

Characteristic	Value
Age, y	58.2 ± 14.7
Male	306 (63.6)
BMI, kg/m ²	22.94 ± 9.7
Albumin, g/L	27.7 ± 13.9
Chronic underlying disease	
Chronic kidney disease	166 (34.5)
Chronic pulmonary disease	101 (21.0)
Underlying cause of immunodeficiency	
Hematologic malignancy	118 (24.5)
Acute leukemia	34 (7.1)
Lymphoma	32 (6.7)
Chronic lymphoid leukemia	25 (5.2)
Multiple myeloma	15 (3.1)
Myelodysplastic syndrome	10 (2.1)
Chronic myelomonocytic leukemia	2 (0.4)
Allogeneic HSCT	32 (6.7)
Autologous HSCT	9 (1.9)
HIV infection	114 (23.7)
Therapeutic rupture	68 (14.1)
Discovery of HIV-positive status	46 (9.6)
Solid organ transplantation	103 (21.4)
Immune-mediated inflammatory disease	87 (18.1)
Solid tumor	56 (11.6)
Others ^a	3 (0.6)
Ongoing immunosuppressive therapy	334 (69.4)
Symptoms	
Dyspnea ^b	396 (82.3)
Hyperthermia	355 (73.8)
Cough	309 (64.2)
Alteration of general condition	290 (60.3)
Positive sputum/BAL direct examination (cysts in smears)	180 (37.4)
Prophylaxis prescribed	50 (10.4)
Aerosolized pentamidine	15 (3.1)
TMP-SMX	25 (5.2)
Atovaquone	9 (1.9)
Prophylaxis observance during the last 2 mo	26 (5.4)
Aerosolized pentamidine	11 (2.3)
TMP-SMX	8 (1.7)
Atovaquone	6 (1.2)
Time from symptom onset to, d	
Hospitalization	14.3 ± 27.6

(Continued)

TABLE 1] (Continued)

Characteristic	Value
Diagnostic	20.1 ± 27.1
Anti- <i>Pneumocystis</i> treatment	19.9 ± 26.9
SAPS II score	34.4 ± 16.2
SOFA score	3.3 ± 3.0
ICU admission	237 (49.3)
ICU length of stay, d	13.2 ± 11.8
Laboratory findings	
WBCs/mm ³	7,579 ± 5,000
Neutrophils/mm ³	6,093 ± 4,581
Lymphocytes/mm ³ , ^c	828 ± 800
CD4/mm ³ , ^d	182 ± 227
CRP, mg/L ^e	109 ± 100
LDH, International Units/L ^f	460 ± 250
Time from diagnosis to PcP treatment	-0.2 ± 2.4
Anti- <i>Pneumocystis</i> treatment	
TMP-SMX	443 (92.1)
Atovaquone	95 (19.8)
IV pentamidine	12 (2.5)
Respiratory support	396 (82.3)
Mechanical ventilation	109 (22.7)
Exclusive noninvasive ventilation	15 (3.1)
Exclusive high-flow nasal oxygen therapy	44 (9.2)
Exclusive simple nasal oxygen therapy	190 (39.5)
Adjunctive corticotherapy	226 (47.0)
In-hospital mortality	102 (21.2)
90-d mortality	123 (25.6)

Values are mean ± SD or No. (%). CRP = C-reactive protein; HSCT = hematopoietic stem cell transplantation; LDH = lactate dehydrogenase; PcP = *Pneumocystis jirovecii* pneumonia; SAPS II = Simplified Acute Physiology Score II; SOFA = Sequential Organ Failure Assessment; TMP-SMX = trimethoprim-sulfamethoxazole.

^aOf these three patients, two had Cushing syndrome and one had cirrhosis and lymphopenia without any immunosuppressants.

^bDecreased FEV₁ included.

^cTwenty-four missing values and 10 censored data from patients with leukemia.

^dOne hundred and seventy-four missing values.

^eThirty-nine missing values.

^fTwo hundred and thirty-two missing values.

^gEleven missing values.

(n = 257; OR, 1.94; 95% CI, 1.13-3.32; P = .016) and a neutrophilic BAL profile (n = 184; OR, 1.83; 95% CI, 0.97-3.42; P = .059) (Table 3).

Characteristics of Patients With IMIDs and Their Prognosis

An overview of the diseases of the IMIDs group (n = 87) is given in e-Table 6. The most prevalent

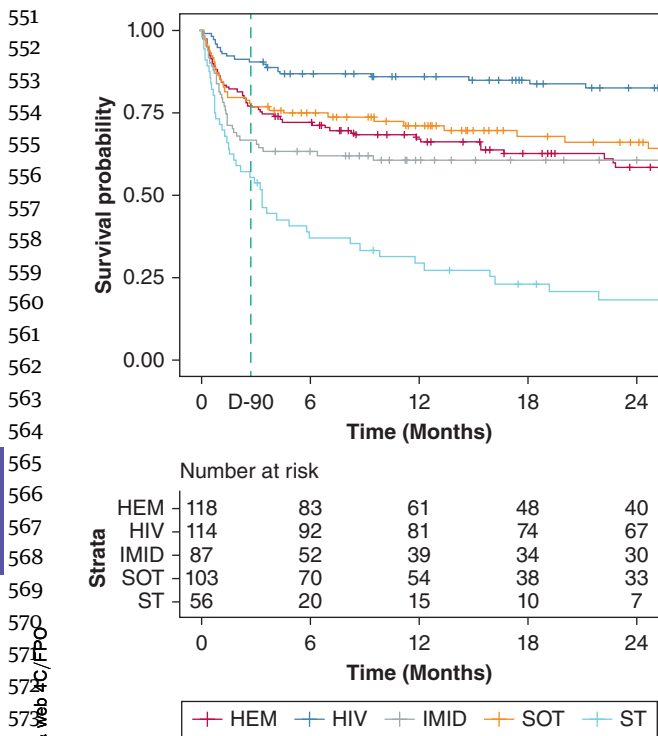


Figure 2 – Survival analysis according to the underlying cause of immunodeficiency. HEM = hematologic malignancies; IMID = immune-mediated inflammatory diseases; SOT = solid organ transplantation; ST = solid tumor.

disease was rheumatoid arthritis (n = 14, 16.1%), followed by antineutrophil cytoplasmic antibody-associated vasculitis (n = 9, 10.3%) and sarcoidosis (n = 8, 9.2%). Seventy-nine patients with IMIDs (90.8%) received long-term corticosteroid therapy, 37 (42.5%) received antimetabolite drugs, and 17 (19.5%) received anti-CD20 monoclonal antibody therapy

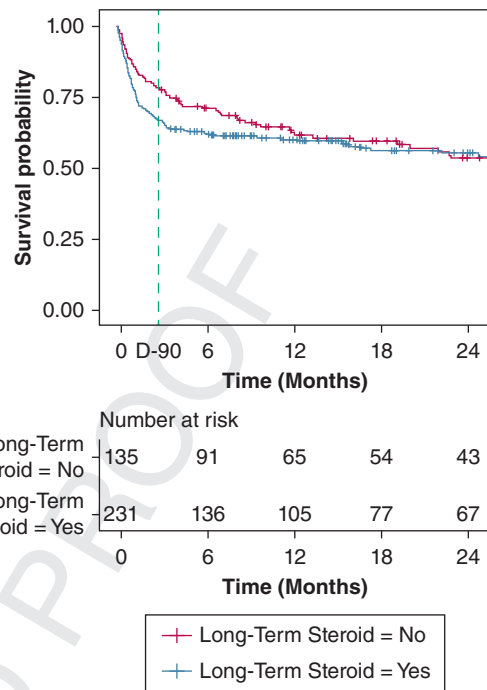


Figure 3 – Survival analysis according to long-term steroid exposure prior to *Pneumocystis jirovecii* pneumonia diagnosis in patients who are HIV-negative. D90 = day 90.

(e-Table 4) prior to PcP diagnosis. For 68 patients (78%), immunosuppressive treatment had been introduced or modified in the year prior to PcP diagnosis. The mean time between introduction or change of immunosuppressive therapy and the onset of PcP was 78 days.

Among patients who were HIV-negative, patients with IMIDs were the oldest ($P < .001$) and presented

TABLE 2] Underlying Conditions Associated With 90-Day Mortality in the Overall Population (N = 481)

Parameter	Univariate Analysis		
	OR	95% CI	P Value
Characteristic			
Age	1.04	1.02-1.05	< .001
Male	0.90	0.52-1.54	.625
Albuminemia ≤ 30 g/L ^a	3.40	1.89-6.10	< .001
Immunodeficiency			
HIV infection	0.24	0.13-0.47	< .001
Hematologic malignancy	0.88	0.54-1.43	.597
Solid tumor	3.19	1.80-5.65	< .001
Solid organ transplantation	0.86	0.51-1.43	.551
Immune-mediated inflammatory disease	1.94	1.18-3.18	.008
Immunosuppressive drug exposure			
Long-term corticosteroid therapy	2.58	1.68-3.96	< .001

^aItem with > 30% missing values.

TABLE 3] Factors Associated With 90-Day Mortality in the HIV-Negative Population

Parameter	Univariate Analysis (n = 367)			Multivariate Analysis (n = 315)		
	OR	95% CI	P Value	OR	95% CI	P Value
Characteristic						
Age	1.02	1.00-1.04	.023	1.01	0.99-1.03	.401
Male	0.90	0.52-1.54	.874
Albuminemia < 30 g/L ^a	4.36	2.33-8.18	< .001
Chronic kidney disease	0.88	0.56-1.39	.594
Chronic pulmonary disease	1.10	0.66-1.82	.713
Immunodeficiency						
Hematologic malignancy	0.61	0.37-1.00	.052
Solid tumor	2.48	1.39-4.42	.002	5.47	2.16-14.1	< .001
Solid organ transplantation	0.61	0.36-1.03	.061
Immune-mediated inflammatory disease	1.46	0.88-2.42	.146	2.19	1.05-4.60	.037
Connective tissue diseases	1.57	0.68-3.61	.286
Immunosuppressive drug exposure	1.59	0.70-3.60	0.265
Long-term corticosteroid	1.67	1.03-2.71	.035	2.07	1.03-4.31	.045
Steroid daily dose ≥ 10 mg	1.80	1.14-2.85	.010
Anticalcineurin	0.68	0.41-1.13	.132
Mycophenolic acid	0.71	0.41-1.23	.219
Antimetabolites	1.10	0.64-1.91	.724
Alkylating drug	1.31	0.70-2.45	.395
Monoclonal antibodies	1.25	0.73-2.16	.416
Anti-CD20	1.22	0.65-2.29	.543
Symptomatology						
Dyspnea	2.51	1.22-5.16	.010	1.08	0.44-2.86	.870
Hyperthermia	0.86	0.53-1.41	.556
Cough	0.79	0.50-1.24	.296
AGC	1.89	1.20-2.98	.006	1.31	0.72-2.38	.373
Sputum/BAL examination^b						
Positive direct examinations (cysts in smears) ^c	1.99	1.22-3.24	.005	1.92	1.02-3.62	.043
Neutrophilic BAL profile ^a	3.23	1.65-6.34	.001
Macrophagic BAL profile ^a	1.19	0.63-2.22	.598
Lymphocytic BAL profile ^a	0.25	0.11-0.52	< .001
CMV respiratory coinfection ^{a, d}	5.23	2.63-10.4	< .001
Laboratory findings						
Neutrophils ≥ 7,500/mm ³	1.52	0.93-24.48	.092
CD4 ≥ 200/mm ^{3a}	1.04	0.46-2.33	.930
CRP ≥ 100 mg/L ^e	1.79	1.11-2.90	.017
LDH ≥ 400 ^a	2.76	1.13-6.76	.024
Care						
Time hospitalization/treatment	1.04	1.02-1.06	.001
Adjunctive corticosteroids	1.61	1.02-2.53	.039
Exclusive nasal oxygen therapy	0.51	0.32-0.82	.005
High-flow oxygen therapy	2.47	1.42-4.31	.932
Noninvasive ventilation	2.46	1.48-4.07	.001
Mechanical ventilation	6.94	4.10-11.8	< .001

(Continued)

TABLE 3] (Continued)

Parameter	Univariate Analysis (n = 367)			Multivariate Analysis (n = 315)		
	OR	95% CI	P Value	OR	95% CI	P Value
Severity						
SOFA	1.50	1.35-1.70	< .001	1.58	1.39-1.82	< .001
ICU admission	3.42	2.17-5.51	< .001

AGC = alteration of general condition; CMV = cytomegalovirus; CRP = C-reactive protein; LDH = lactate dehydrogenase; SOFA = Sequential Organ Failure Assessment. ^{Q33}

^aItem with > 30% missing values.

^bOne hundred and seventy-two sputum examinations and 269 BAL examinations; 74 patients had both sputum and BAL examinations.

^cPositive direct examination in BAL only (OR, 1.94; 95% CI, 1.13-3.32; *P* = .016).

^dCMV polymerase chain reaction was only performed on BAL samples.

^eItem with > 10% missing values.

significantly more severe inaugural dyspnea forms of PcP (OR, 4.05; 95% CI, 1.57-10.5; *P* = .002), increased neutrophilia (*P* = .002), and more CMV respiratory coinfection (OR, 2.69; 95% CI, 1.65-6.34; *P* = .007) (e-Table 7). Patients with IMIDs reported the worst SOFA score on admission compared with the other HIV-negative subgroups (e-Table 7). These patients had less adjuvant corticosteroid therapy (OR, 0.49; 95% CI, 0.30-0.81; *P* = .005) and a higher rate of mechanical ventilation (OR, 2.01; 95% CI, 1.18-3.40; *P* = .009) to treat PcP (e-Table 7).

Patients with IMIDs with a poor outcome reported a lower albumin level (*P* < .001), were admitted to hospital earlier from their onset of symptoms (2.8 vs 15.8 days, *P* = .037) with the worst SOFA score on admission (6.9 vs 2.8, *P* < .001), but a had longer time to initiation of anti-*Pneumocystis* therapy from the time of hospitalization (7.6 vs 3.9 days, *P* = .027), a higher rate of positive direct examination of respiratory samples (*P* = .018), and a higher rate of respiratory CMV coinfection (*P* = .002) (e-Tables 8, 9). Prior prescription of anti-*Pneumocystis* prophylaxis was rarer among patients with IMIDs (five of 87, 5.7%) and solid tumors (one of 56, 1.8%) (e-Table 2). Among patients with IMIDs, only SOFA score was independently associated with 90-day mortality (OR, 1.50; 95% CI, 1.17-2.10; *P* = .007) (e-Table 9).

Discussion

To our knowledge, our work is the largest study to use a comprehensive approach of the characteristics and outcome of PcP as a function of the underlying disease and the type of immunosuppressive therapies in a large cohort of patients. We reported that PcP in patients with IMIDs presented the most severe forms of PcP at

admission, with higher SOFA score and the highest mortality rate attributable to PcP among patients who were HIV-negative. On the other hand, patients with PcP with solid tumors displayed a higher 90-day mortality rate and a poorer long-term outcome, despite a lower SOFA score at PcP diagnosis. These results suggest that these patients (most of whom had metastatic disease) may not have developed the most severe forms of PcP, but that the onset of this opportunistic infection could be a marker of their frailty.

Burghi et al¹⁴ reported in an analysis of patients who were HIV-negative (n = 321) that 30-day mortality and presentation of PcP were associated with the underlying disease. However, this study did not include patients who were HIV-positive, and did not provide details of patients with IMIDs as a specific subgroup. In our study, prior long-term corticosteroid therapy appeared to be a major risk factor and was associated with a poorer prognosis, especially in patients with IMIDs. This higher mortality rate among patients with long-term corticosteroid exposure fades at 1 year, which may be explained by the mortality related to each underlying condition among the HIV-negative group. The longer time to diagnosis and the higher severity of PcP in patients with IMIDs at admission suggest that the delayed diagnosis may be in part responsible for their poor prognosis.

Almost 90% of the patients had not been prescribed PcP prophylaxis, confirming previous findings¹⁵ which identified the lack of trimethoprim-sulfamethoxazole prophylaxis as a major risk factor for PcP in high-risk patients.¹⁶ To reduce PcP mortality in patients with IMIDs, the first step would be to improve prophylactic coverage against this preventable opportunistic infection; however, determining criteria for

881 *Pneumocystis* prophylaxis in patients with IMIDs is
 882 challenging, given the wide range of diseases
 883 involved.¹⁷⁻¹⁹ Specific prophylaxis guidelines have been
 884 developed for antineutrophil cytoplasmic antibody-
 885 associated vasculitis, scleroderma, and autoimmune
 886 inflammatory myopathies,²⁰ and for patients receiving
 887 prolonged corticosteroid therapy,^{21,22} but there are
 888 currently insufficient data for rarer IMIDs to allow
 889 specific prophylaxis recommendations to be
 890 established.²³ This study supports that high-dose
 891 corticosteroids are a major issue in patients who are
 892 HIV-negative because of the risk of PcP, and unlike
 893 patients who are HIV-positive, CD4 cell count cannot be
 894 used as an indication for prophylaxis in these patients.
 895 Rheumatoid arthritis was the most prevalent IMID in
 896 this cohort, which is consistent with a recent national
 897 study based on the French RESSIF Network.¹⁷ This
 898 highlights the difficulty in identifying the patients who
 899 would benefit from *Pneumocystis* prophylaxis and
 900 explains the lack of official recommendations/consensus
 901 guidelines for these patients. More than one-half of
 902 patients with rheumatoid arthritis in this cohort
 903 developed PcP < 6 months after initiation or
 904 intensifying their immunosuppressive therapy.
 905 Atovaquone prophylaxis during the year after the
 906 initiation of their immunosuppressive therapy could be
 907 an effective alternative²⁴ with a favorable benefit to risk
 908 ratio, while avoiding the risk of cumulative
 909 myelotoxicity of methotrexate and trimethoprim-
 910 sulfamethoxazole. Sarcoidosis seems to be another
 911 emerging condition highly exposed to corticosteroids,
 912 for which there are yet no *Pneumocystis* prophylaxis
 913 recommendations.

914
 915
 916
 917 Another important factor in improving the outcome of
 918 patients with IMIDs with PcP would be to treat them
 919 earlier. Identifying patients with IMIDs with features
 920 compatible with a severe PcP diagnosis as early as
 921 possible and ensuring prompt treatment is particularly
 922 relevant. Our work suggests that delayed treatment in
 923 patients with IMIDs has a potentially dramatic impact
 924 on their prognosis.

925
 926 Analysis of 90-day risk factors among patients who were
 927 HIV-negative in the extended cohort confirms our
 928 previous results that BAL examination can provide
 929 several important markers of mortality, including direct
 930 cyst examination, neutrophilic alveolitis profile, and
 931 respiratory coinfection with CMV at the time of PcP
 932 diagnosis. Furthermore, prior corticosteroid therapy has
 933 been reported to impair the anti-pneumocystic immune
 934 response leading to an inefficient neutrophilic alveolitis
 935

and subsequent alveolinterstitial inflammatory lesions 936
 in PcP.²⁵⁻²⁷ Indeed, positive direct examination of cysts 937
 in respiratory samples could indicate profound 938
 immunosuppression. In patients who are HIV-positive, 939
 highly active antiretroviral therapy may contribute to 940
 more rapid control of the infectious process through 941
 faster recovery of the immune system. In patients who 942
 are HIV-negative, patterns of immunosuppression, 943
 including long-term corticosteroid therapy, appear to be 944
 associated with an inappropriate inflammatory response 945
 in cases of high fungal load. 946

947
 948 Because patients with IMIDs more frequently present, at
 949 PcP diagnosis, a BAL pattern that associates
 950 immunosuppression and inflammation markers, we can
 951 hypothesize that their greater exposure to long-term
 952 corticosteroid therapy may induce dysregulation of the
 953 anti-*Pneumocystis* response, which in turn may be
 954 responsible for a more severe disease. Such prior
 955 exposure to immunosuppressive drugs in patients with
 956 IMIDs has also been shown to be associated with poor
 957 outcome of SARS-CoV-2 pneumonia.²⁸ Our study
 958 indicates that patients with the most severe IMIDs did
 959 not receive more adjuvant corticosteroids. Indeed, no
 960 evidence is available to support adjuvant corticosteroid
 961 therapy in patients who are HIV-negative presenting
 962 with severe PcP. The low use of adjuvant corticosteroid
 963 therapy to treat PcP in patients with IMIDs may be
 964 related both to the lack of guidelines for adjuvant
 965 corticosteroid therapy in patients who are HIV-negative
 966 and the high rate of prior corticosteroid exposure in
 967 these patients, which probably contributed to the
 968 development of PcP. In a previous study, we reported
 969 that adjuvant corticosteroid therapy was associated with
 970 the highest mortality rates in patients with respiratory
 971 CMV coinfection among patients who are HIV-negative,
 972 and that such CMV coinfection was more common in
 973 patients with IMIDs.¹⁰ Patients already exposed to prior
 974 long-term corticosteroid therapy may therefore not
 975 benefit from higher doses of steroids adjunctive therapy
 976 in cases of severe PcP. Therefore, to improve the
 977 management of PcP in IMIDs, there is a need to assess
 978 the benefit of immunomodulatory therapies, other than
 979 corticosteroids, to reduce the damaging pulmonary
 980 immune response. 981
 982

983
 984 This study presents several limitations because of the
 985 retrospective nature of the cohort. Indeed, this study was
 986 not designed to assess the incidence of PcP among
 987 underlying conditions, but rather to identify emerging
 988 diseases over this 10-year period. The higher rate of PcP
 989 in patients with rheumatoid arthritis could reflect a
 990

991 higher prevalence of this disease among patients with
 992 IMIDs. In addition, the lack of standardization of
 993 adjuvant corticosteroid therapy does not allow any
 994 conclusions regarding its efficacy in patients who are
 995 HIV-negative. Finally, determining the exact cause of
 996 mortality after hospital discharge represents a significant
 997 challenge, especially in a retrospective cohort of patients
 998 with severe chronic diseases that involve potential
 999 limitations in intensive care, which may have
 1000 overestimated PcP mortality in each of the subgroups.

1003 Interpretation

1004 This large multicenter PcP cohort is the first to identify
 1005 IMIDs, solid tumors, and long-term corticosteroid
 1006 therapy as independent mortality factors in patients who
 1007 are HIV-negative. Patients with IMIDs are the most
 1008 exposed to long-term corticosteroid therapy and have
 1009 the worst prognosis because of PcP when compared with
 1010 other immunocompromised conditions. The onset of
 1011 PcP in patients with solid tumors is associated with the
 1012 highest 90-day mortality and is probably related to very
 1013 advanced tumor disease. Broadening indications for
 1014 primary prophylaxis against *P jirovecii* in patients with

underlying immunocompromised conditions, earlier
 awareness, diagnosis and probabilistic treatment, and
 new therapeutic approaches for severe forms are the
 three key factors which could contribute to reducing *P*
jirovecii mortality in patients who are HIV-negative.

Funding/Support

The authors have reported to *CHEST* that no funding
 was received for this study.

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST* the following: B.
 G. reports receipt of nonfinancial support from Gilead
 Sciences, MSD, and Pfizer, outside the submitted work.
 F. R. reports receipt of personal fees from Abbvie, Astra
 Zeneca, Gilead Sciences, Janssen, Merck, Roche, and
 ViiV Healthcare, outside the submitted work. E. C.
 reports personal fees from Gilead, Sanofi-Genzyme, and
 Baxter, outside the submitted work. None declared (R.
 L., N. I., F. C., R.-a. L., F. G., F. M., D. B., A. C., M. G., Y.
 C., A. N., B. T.).

Acknowledgments

1019 **Author contributions:** R. L., N. I., F. C., B.
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 1021 data.

1022 R.-a. L., F. M., F. G., and A. C. performed
 1023 microbial analysis of bronchoalveolar fluid
 1024 samples.

1025 B. T., E. C., M. G., Y. C., A. N., D. B., and F.
 1026 R. contributed to interpretation of results and
 1027 revision of the manuscript. R. L., N. I., and B.
 1028 G. wrote the manuscript. All authors read
 and approved the final manuscript.

1029 **Role of sponsors:** The sponsor had no role in
 1030 the design of the study, the collection and
 1031 analysis of the data, or the preparation of the
 1032 manuscript.

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 Bretagne-Atlantique, Vannes); and Anne
 Cady, Myriam Auger, and Pascal Pouedras
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 Hospitalier Bretagne-Atlantique, Vannes).

Other contributions: We thank the
 physicians, microbiologists, and
 PRONOCYSTIS Study Group who
 contributed to the management of the study
 patients and for their commitment to
 providing optimal patient care.

Additional information: The e-Figures and
 e-Tables are available online under
 "Supplementary Data."

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1121 the Mycoses Study Group Education and
1122 Research Consortium. *Clin Infect Dis.*
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