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RESEARCH ARTICLE

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Mortality of *Pneumocystis jirovecii* pneumonia in intensive care units: a post-hoc analysis of an international multicenter study by ESGCIP and EFISG

Daniele Roberto Giacobbe[a,b], Silvia Dettori[a,b], Vincenzo Di Pilato[c,d], Erika Asperges[e], Lorenzo Ball[e,f], Enora Berti[g], Ola Blennow[h,i], Bianca Bruzzone[j], Laure Calvet[k], Federico Capra Marzani[l], Antonio Casabella[m], Sofia Choudaly[n], Anais Dartevel[o], Gennaro De Pascale[p,q], Gabriele Di Meco[b], Melissa Fallon[r], Louis-Marie Galerneau[o], Miguel Gallego[s,t], Mauro Giacomini[u], Adolfo González Saez[v,w,x], Luise Hänsel[y,z], Giancarlo Icardi[a,j], Philipp Koehler[y,z], Katrien Lagrou[aa,ab], Tobias Lahmer[ac], Philip Lewis White[r,ad], Laura Magnasco[b], Anna Marchese[c,d], Cristina Marelli[b], Mercedes Marín Arriaza[v,w], Ignacio Martin-Loeches[ae,af], Armand Mekontso-Dessap[g,ag,ah], Malgorzata Mikulska[a,b], Marco Muccio[a], Alessandra Mularoni[ai], Anna Nordlander[h,i], Julien Poissy[n,aj], Giovanna Russelli[ai], Alessio Signori[ak], Carlo Tascini[al,am], Louis-Maxime Vaconsin[an], Joel Vargas[p], Antonio Vena[a,b], Joost Wauters[aa,ao], Paolo Pelosi[c,f], Jean-Francois Timsit[an,ap], Matteo Bassetti[a,b] and on behalf of JIR-ICU Investigators (Collaborators), the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Diseases (ESGCIP), and the Fungal Infections Study Group of the European Society of Clinical Microbiology and Infectious Diseases (EFISG)

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ABSTRACT

Background: *Pneumocystis jirovecii* pneumonia (PJP) is a life-threatening disease. In the intensive care unit (ICU), PJP is most frequently observed among patients with several conditions not related to the human immunodeficiency virus (HIV) infection.

Methods: The primary objective of the present post-hoc analysis of a multicenter, multinational, retrospective study was to assess factors impacting prognosis in ICU patients with PJP through univariable and multivariable analyses.

Results: A total of 107 patients were included; 28 had proven PJP (26.2%), and 79 had presumptive PJP (73.8%). The overall 30-day mortality was 52.7% (95% confidence interval [CI] 42.1–62.2). In the multivariable analysis, metastatic solid tumor (hazard ratio [HR] 3.49; 95% CI 1.71–7.13, $p < 0.001$) and chronic liver disease (HR 2.44; 95% CI 1.03–5.80, $p = 0.044$) showed an independent association with 30-day mortality. The direction of effect remained consistent when center was added to the multivariable model as random effect.

Conclusion: PJP mortality remains high in ICU patients. Conditions other than HIV infection are emerging not only as non-classical risk factors for PJP development, but also as important mortality predictors. A better understanding of the reasons underlying this evolving landscape could be crucial to improve PJP management and survival.

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Pneumocystis; pneumonia; ICU; mortality; PCP; PJP

Introduction

Pneumocystis jirovecii pneumonia (PJP) is a life-threatening disease in critically ill patients admitted to the intensive care unit (ICU) [1,2]. Once most often diagnosed in patients with human immunodeficiency virus (HIV) infection, it is now frequently encountered also in patients with other reasons for immunosuppression [3–5].

Indeed, while the prevalence of PJP still remains higher in ICU patients with HIV-related immunosuppression compared to other causes of immunosuppression, the high incidence of non-HIV causes of immune system impairment in the ICU makes more likely to face PJP in non-HIV patients [6]. Therefore, there is growing interest in identifying prognostic factors that permit interventions for improving outcomes of critically ill patients with PJP, including those with underlying conditions other than HIV infection.

The primary objective of the present post-hoc analysis of a multicenter, multinational, retrospective study by the Critically Ill Patients Study Group (ESGCIP) and the Fungal Infections Study Group (EFISG) of the European Society of Clinical Microbiology and Infection Diseases was to assess factors impacting prognosis in ICU patients with PJP.

Materials and methods

Study setting and definitions

The JIRICU study was coordinated by the IRCCS Ospedale Policlinico San Martino, Italy, and was conducted in 18 participating centers across different European countries (Belgium, France, Germany, Republic of Ireland, Italy, Spain, Sweden, UK), with the primary objective to describe the characteristics of adult ICU patients with suspected PJP [7]. The retrospective study period was from 1 January 2016 to 31 December 2020. Full details of the methodology of the JIRCU study are available in the original publication [7]. The present post-hoc analysis includes the subgroup of patients with proven or presumptive PJP according to the definition of the JIRICU study. More in detail, proven PJP was defined as detection of *Pneumocystis* in respiratory specimens via conventional or immunofluorescence staining, in line with EORTC/MSGERC definitions [8]. The diagnosis of presumptive PJP was based on an independent review of completed patients' electronic case report forms by two independent medical investigators (SD and DRG), with any possible disagreement being resolved by a third investigator (AV). This approach was preferred over the classification of probable PJP according to the EORTC/MSGERC definitions, mainly to reduce incorporation bias for the evaluation of the diagnostic performance for PJP of respiratory polymerase chain reaction and serum (1,3)-β-D-glucan in the original JIRICU study [7]. This permitted an extensive global assessment of the clinical picture and disease course (e.g. concomitant presence of alternative causative agents of interstitial pneumonia, response to treatment for concomitant infections) when defining PJP beyond a proven diagnosis, conceptually in line with a more personalized risk-based approach, as recently proposed by Brown and colleagues [9].

Data were collected through a dedicated electronic case report form designed specifically for the JIRICU study [10]. All information on the type and number of collected variables is available in the original publication [7]. The JIRICU study was approved by the ethics committee of the coordinating center (Liguria Region Ethics Committee, N. Registro CER Liguria 305/2021). The collection of informed consent was waived due to the retrospective nature of the study. The other centers participating in the JIRICU study followed their local ethical committee requirements.

Statistical analysis

No a priori sample size calculation was performed for this exploratory post-hoc analysis. The demographic and baseline characteristics of patients with presumptive PJP and patients with proven PJP were descriptively compared, using the Chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Mortality up to either 30-day or 90-day in critically ill patients with PJP was initially descriptively assessed through Kaplan–Meier curves, with the time of origin set on the day of PJP diagnostic workup. For descriptive purposes, Kaplan–Meier curves of 30-day and 90-day mortality were also compared between patients with presumptive PJP vs. proven PJP and between patients with vs. without HIV infection, by means of the log-rank test. The primary study objective of the present post-hoc analysis was to determine factors associated with 30-day mortality in critically ill patients with PJP. To this aim, missing data were first imputed through Rubin's multiple imputation method [11]. Then, demographic and clinical variables were tested for their possible association with 30-day mortality in univariable Cox regression models. Subsequently, all variables potentially associated with 30-day mortality by univariable analyses ($p < 0.20$) were included in an initial multivariable Cox regression model and further selected for inclusion in a final multivariable model (model A) using a stepwise, backward procedure. In addition, variables included in model A were included in a second multivariable Cox regression (model B), including the center as a shared frailty [12]. A secondary analysis considering 90-day mortality as the outcome of interest was also performed with the same method used for assessing factors associated with 30-day mortality, without (model C) and with (model D) inclusion of center as a shared frailty [12]. The proportional hazards assumption was verified for all fixed-effect Cox regression models in the present study, employing cumulative sums of martingale residuals and a Kolmogorov-type supremum test with 1,000 simulations to check for deviations from the expected proportionality [13]. Statistical analyses were performed with SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA), and a *p*-value less than 0.05 was considered statistically significant.

Results

A total of 107 patients were included in the present post-hoc analysis (Figure 1). Of them, 28 had proven PJP (26.2%), and 79 had presumptive PJP (73.8%). The baseline demographic and clinical characteristics of the study population are reported in Table 1, showing that less than one quarter of patients had HIV infection (19.2%). As displayed in Figure 2 and Figure S1, respectively, 30-day mortality was 52.7% (95% confidence interval [CI] 42.1–62.2) and 90-day mortality was 67.9% (95% CI 56.4–77.0), with no differences in mortality according to PJP diagnosis (proven vs. presumptive) and presence of HIV infection, although a

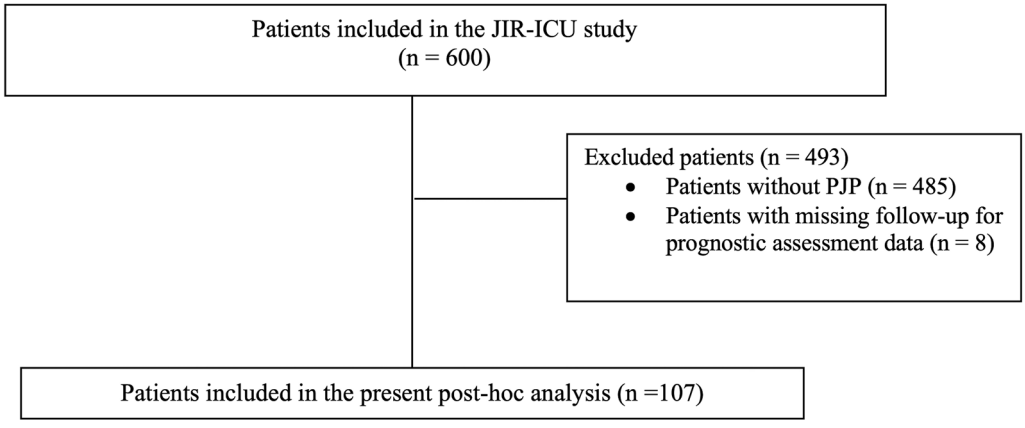

Figure 1. Flow-chart of the patients inclusion process.

non-statistically significant trend towards lower mortality was registered for patients with HIV infection compared to patients without HIV infection. The majority of patients received treatment for PJP (98.1% [105/107], in most cases with trimethoprim/sulfamethoxazole [97.1%, 102/105)] and steroid therapy (77.8% [77/99, missing = 8]).

Results of univariable and multivariable analyses of factors associated with 30-day mortality are reported in Table 2. As shown in the table, metastatic solid tumor (hazard ratio [HR] 3.49; 95% CI 1.71–7.13, $p < 0.001$) and chronic liver disease (HR 2.44; 95% CI 1.03–5.80, $p = 0.044$) showed an independent association with 30-day mortality in the final multivariable

Table 1. Baseline characteristics of the study population.

Variable*	Patients with proven/presumptive PJP $n = 107$ (100)	Patients with proven PJP $n = 28$ (26.2)	Patients with presumptive PJP $n = 79$ (73.8)	p-value
Demographic				
Age in years, median (IQR)	60 (48–70)	63.5 (47–71)	60 (48–68)	0.5026
Female sex	32 (29.9)	9 (32.1)	23 (29.1)	0.7636
Medical history				
HIV infection (missing = 2)	20 (19.1)	8 (28.6)	12 (15.6)	0.1340
AIDS (missing = 3)	17 (16.4)	6 (22.2)	11 (14.3)	0.3704
Hematological malignancy	32 (29.9)	8 (28.6)	24 (30.4)	0.8575
AML**	4 (3.8)	1 (3.6)	3 (3.9)	1.0000
ALL**	3 (2.8)	1 (3.6)	2 (2.6)	1.0000
Hodgkin lymphoma**	2 (1.9)	0 (0.0)	2 (2.6)	1.0000
Non-Hodgkin lymphoma**	16 (15.1)	4 (14.3)	12 (15.4)	1.0000
Other**	6 (5.7)	2 (7.1)	4 (5.1)	0.6568
HSCT	11 (10.3)	1 (3.6)	10 (12.7)	0.2815
Solid tumor (missing = 1)	27 (25.5)	6 (21.4)	21 (26.9)	0.5670
Metastatic solid tumor (missing = 3)	14 (13.5)	3 (10.7)	11 (14.5)	0.7542
Previous SOT	5 (4.7)	2 (7.1)	3 (3.8)	0.6043
Autoimmune disease	16 (15.0)	2 (7.1)	14 (17.7)	0.2287
COPD (missing = 1)	10 (9.4)	4 (14.3)	6 (7.7)	0.4501
Chronic pulmonary diseases other than COPD (missing = 2)	9 (8.6)	0 (0.0)	9 (11.7)	0.1083
Chronic kidney disease (missing = 1)	12 (11.3)	3 (10.7)	9 (11.5)	1.0000
Chronic liver disease (missing = 1)	9 (8.5)	2 (7.1)	7 (9.0)	1.0000
NYHA score >2 (missing = 16)	12 (13.2)	2 (7.4)	10 (15.6)	0.4985
Age-adjusted Charlson score, median (IQR)	4 (3–8)	5.5 (3.5–8)	4 (2–7)	0.0940
Previous major surgery (within 30 days) (missing = 4)	6 (5.8)	1 (3.6)	5 (6.7)	1.0000
Previous chemotherapy (within 30 days) (missing = 2)	34 (32.4)	10 (35.7)	24 (31.2)	0.6598
Previous radiotherapy (within 30 days) (missing = 2)	10 (9.5)	2 (7.1)	8 (10.4)	1.0000
Previous albumin therapy (within 30 days) (missing = 9)	7 (7.1)	0 (0.0)	7 (10.0)	0.1868
Clinical and laboratory data at PJP suspicion				
ARDS (missing = 13)	57 (60.6)	13 (46.4)	44 (66.7)	0.0662
Invasive mechanical ventilation (missing = 3)	42 (40.4)	10 (35.7)	32 (42.1)	0.5557
SOFA score, median (IQR) (missing = 4)	6 (4–10)	8 (4.5–10)	5 (3–9)	0.0789
Septic shock (missing = 5)	26 (25.5)	8 (28.6)	18 (24.3)	0.6605
CRRT (missing = 9)	7 (7.1)	2 (7.1)	5 (7.1)	1.0000
Serum BDG in pg/mL, median (IQR) (missing = 56)***	500 (256–500)	424 (224.5–500)	500 (256–500)	0.3282
Treatment of PJP				
Anti-PJP therapy	105 (98.1)	27 (96.4)	78 (98.7)	0.4567
Steroid therapy (missing = 8)	77 (77.8)	20 (76.9)	57 (78.1)	0.9028
Other concomitant infections				
COVID-19 (missing = 1)	5 (4.7)	2 (7.1)	3 (3.9)	0.6059
Concomitant candidemia (missing = 1)	5 (4.7)	1 (3.6)	4 (5.1)	1.0000
Concomitant bacteremia	28 (26.2)	7 (25.0)	21 (26.6)	0.8700
Concomitant bacterial pneumonia (missing = 3)	38 (36.5)	9 (32.1)	29 (38.2)	0.5720
Concomitant invasive pulmonary aspergillosis (missing = 3)	6 (5.8)	0 (0.0)	6 (7.9)	0.1877
Concomitant influenza (missing = 6)	1 (1.0)	0 (0.0)	1 (1.4)	1.0000
Concomitant CMV reactivation (missing = 6)	22 (21.8)	1 (3.7)	21 (28.4)	**0.0078**
Concomitant HSV reactivation (missing = 6)	11 (10.9)	2 (7.4)	9 (12.2)	0.7226

The reported p-values are from the Wilcoxon Rank Sum test for continuous variables and Chi-Square or Fisher's Exact test for categorical variables. Bold values are significant at the selected level of significance ($\alpha = 0.05$).

ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; ARDS: acute respiratory distress syndrome; BDG: β-D-glucan; CMV: cytomegalovirus; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; CRRT: continuous renal replacement therapy; CRP: C-reactive protein; CT: computer tomography; HIV: human immunodeficiency virus; HSCT: hematopoietic stem cell transplantation; HSV: herpesvirus; ICU: intensive care unit; IQR: interquartile range; IVIG: intravenous immunoglobulin; NYHA: New York Heart Association; PCT: Procalcitonin; PJP: *Pneumocystis jirovecii* pneumonia; SOFA: Sequential Organ Failure Assessment; SOT: Solid organ transplantation.

*Data reported as no. (%) unless otherwise indicated.

**Percentage calculated out of 106 patients due to $n = 1$ missing value regarding the type of hematological malignancy.

***Reported for patients tested with Fungitell assay, due to the very low number of patients undergoing serum BDG testing with other assays.

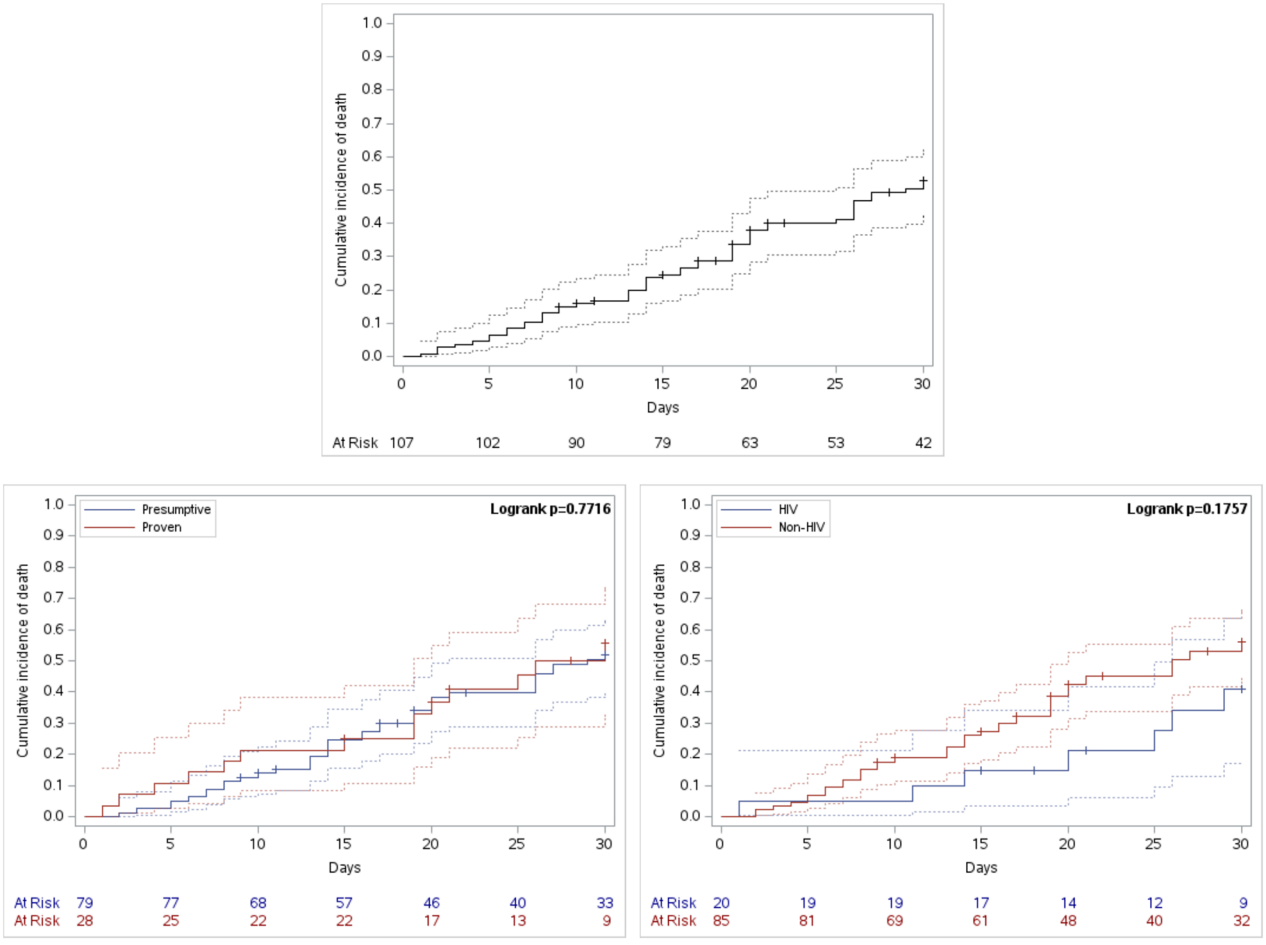

Figure 2. Cumulative incidence of death at 30 days in critically ill patients with proven/presumptive PJP. The time of origin was set at the time of PJP diagnostic workup. Right-censoring was applied at the time of hospital discharge or at 30 days after the time of PJP diagnostic workup, whichever came first. Cumulative 30-day mortality in the entire study population (proven and presumptive PJP) is displayed in the top panel, whereas bottom panels compare cumulative 30-day mortality in patients with proven PJP vs. presumptive PJP (left panel) and patients with HIV infection vs. patients without HIV infection (right panel). Dashed lines represent the 95% confidence interval.

model (model A). As shown in Supplementary Table S1, the direction of effect was consistent between models A and B (the latter including also center as random effect).

The results of univariable and multivariable secondary analyses of factors associated with 90-day mortality are reported in Table S2. As shown in Table S2, metastatic solid tumor (HR 3.24: 95% CI 1.56–6.72, $p=0.002$), chronic liver disease (HR 2.62: 95% CI 1.08–6.35, $p=0.033$), and concomitant bacteremia (HR 1.95: 95% CI 1.11–3.41, $p=0.019$) retained an independent association with 90-day mortality in the final multivariable model (model C), whereas concomitant bacterial pneumonia (HR 0.54; 95% CI 0.30–0.95, $p=0.032$) was independently associated with reduced 90-day mortality. As shown in Table S3, the directions of effect were consistent between model C and model D (the latter including the center as a random effect).

Discussion

In the present post-hoc analysis of 107 ICU patients with PJP (with PJP being mostly the reason for ICU admission instead of being developed in the ICU [7]), 30-day mortality was as high as 52%, which is notably higher than in the studies reported above, although it remains in line with other experiences, overall testifying to the persistence of an heavy negative prognostic impact of PJP in critically ill patients [1,2,14].

The development of PJP had represented a concern also outside patients with HIV infection since the last decade of the past century when a mortality rate as high as 35% was reported in a small cohort of immunocompromised HIV-negative patients [15]. In the subsequent years, several studies have continued to register a high mortality in PJP both in patients with HIV infection and in those without HIV infection,

Table 2. Results of univariable analysis, initial multivariable analysis, and final multivariable analysis after backward selection of factors associated with 30-day mortality in the study population.

	Univariable models		Initial multivariable model		Final multivariable model (Model A)	
Variable	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Proven PJP (vs. presumptive PJP as ref.)	1.09 (0.59–2.02)	0.7782				
Age in years	1.00 (0.98–1.02)	0.7548				
Female sex	1.14 (0.64–2.03)	0.6696				
HIV infection	0.54 (0.24–1.19)	0.1279	0.61 (0.26–1.43)	0.2555		
AIDS	0.66 (0.30–1.47)	0.3116				
Hematological malignancy	0.86 (0.47–1.57)	0.6241				
AML	0.98 (0.25–3.90)	0.9801				
ALL	1.79 (0.50–6.43)	0.3694				
Hodgkin lymphoma*	–	–				
Non-Hodgkin lymphoma	0.70 (0.32–1.55)	0.3831				
Other	1.08 (0.34–3.48)	0.8935				
HSCT	0.95 (0.38–2.39)	0.9129				
Solid tumor	1.42 (0.78–2.59)	0.2544				
Metastatic solid tumor	3.16 (1.57–6.34)	**0.0012**	3.27 (1.44–7.43)	**0.0047**	3.49 (1.71–7.13)	**0.0006**
SOT*	–	–				
Autoimmune disease	0.80 (0.36–1.78)	0.5844				
COPD	1.54 (0.66–3.61)	0.3203				
Chronic pulmonary diseases other than COPD	0.48 (0.15–1.54)	0.2170				
Chronic kidney disease	0.63 (0.23–1.75)	0.3793				
Chronic liver disease	2.00 (0.86–4.66)	0.1101	3.33 (1.21-9.14)	**0.0197**	2.44 (1.03-5.80)	**0.0436**
NYHA score >2	0.67 (0.27–1.67)	0.3924				
Age-adjusted Charlson score	1.02 (0.93–1.12)	0.6560				
Previous major surgery (within 30 days)	0.78 (0.23–2.67)	0.6855				
Previous chemotherapy (within 30 days)	1.57 (0.89–2.76)	0.1194	1.03 (0.52-2.06)	0.9230		
Previous radiotherapy (within 30 days)	1.46 (0.61–3.47)	0.3919				
Previous albumin therapy (within 30 days)	1.78 (0.78–4.08)	0.1716	1.90 (0.71-5.11)	0.1991		
ARDS	0.79 (0.44–1.43)	0.4422				
Invasive mechanical ventilation	1.19 (0.68–2.06)	0.5400				
SOFA score	1.06 (0.99–1.13)	0.1189	1.06 (0.98-1.15)	0.1158		
Septic shock	0.98 (0.53–1.83)	0.9527				
CRRT	0.93 (0.32–2.72)	0.8922				
Serum BDG**	1.00 (0.97–1.02)	0.7563				
Anti-PJP therapy	0.79 (0.11–5.70)	0.8124				
Steroid treatment	0.68 (0.36–1.26)	0.2192				
COVID-19	1.45 (0.52–4.04)	0.4724				
Concomitant candidemia	0.22 (0.03–1.57)	0.1298	0.16 (0.02–1.54)	0.1115		
Concomitant bacteremia	1.40 (0.78–2.49)	0.2594				
Concomitant bacterial pneumonia	0.68 (0.37–1.25)	0.2142				
Concomitant invasive pulmonary aspergillosis	0.84 (0.26–2.69)	0.7685				
Concomitant influenza	1.79 (0.25–12.60)	0.5589				
Concomitant CMV reactivation	0.77 (0.38–1.56)	0.4692				
Concomitant HSV reactivation	0.80 (0.32–1.96)	0.6199				

Analyses conducted after multiple imputation. The reported *p*-values are from the Cox regression analysis. Bold values are significant at the selected level of significance (α = 0.05). HR: Hazard Ratio; CI: Confidence Interval. ALL: Acute lymphocytic leukemia; AML: Acute myeloid leukemia; ARDS: Acute respiratory distress syndrome; BDG: β-D-glucan; CMV: Cytomegalovirus; COPD: Chronic obstructive pulmonary disease; COVID-19: Coronavirus disease 2019; CRRT: Continuous renal replacement therapy; CRP: C-reactive protein; CT: Computer tomography; HIV: Human immunodeficiency virus; HSCT: Hematopoietic stem cell transplantation; HSV: Herpesvirus; ICU: Intensive care unit; IQR: interquartile range; IVIG: Intravenous immunoglobulin; NYHA: New York Heart Association; PCT: Procalcitonin; PJP: *Pneumocystis jirovecii* pneumonia; SOFA: Sequential Organ Failure Assessment; SOT: Solid organ transplantation.
*Analysis not performed due to an insufficient number of events. ** Analysis performed on 51 patients only (multiple imputation not performed for serum BDG due to the large number of missing values); HR reflects the impact of a 10-unit increment in this variable.

especially considering severe disease with need for ICU admission. In a retrospective study of 84 PJP patients with malignancy, encompassing both hematological and solid tumors, ICU stay was reported in more than half of the cases, with an overall 32% mortality at one month [16]. An 40% mortality rate

was also registered in 5 patients with autoimmune diseases and PJP requiring ICU management, and an even higher 60% mortality was reported in another small cohort of 15 patients with rheumatology disease and PJP, although with the due limitation of the very small sample of these studies in terms of generalization of results [17,18].

It is of note that in some previous studies, also including a recent large French cohort of more than 4000 ICU patients with PJP, a higher mortality was registered in PJP patients without HIV infection than in those with HIV infection [19–21]. Although the association was not statistically significant, PJP patients with HIV infection tended to have lower mortality rates than PJP patients without HIV infection also in our post-hoc analysis, a fact deserving further investigation to assess whether such a result could be explained by any possible delay in the recognition of PJP in non-HIV patients.

In our analysis, metastatic solid tumor and chronic liver disease were associated with 30-day mortality in our primary analysis. This is partly in line with previous studies reporting an unfavorable prognostic impact of PJP on the mortality of patients with solid tumors, alongside the negative impact of older age, unawareness of the infection, the subsequent delayed diagnosis and treatment, and invasive mechanical ventilation [19,22,23]. For example, in a recent study of 481 patients with either prover or probable PJP, solid tumors showed the largest effect size in terms of unfavorable prognostic effect among underlying causes of immunodeficiency [24]. Against this background, the association between chronic liver disease and mortality in our study may also reflect an unfavorable prognostic effect related to chronic baseline diseases or conditions. Regarding invasive mechanical ventilation, the lack of association with increased mortality in our study could be explained, in our opinion, by the fact that, in our cohort of ICU patients with PJP, in most cases PJP represented the reason for admission in the ICU and subsequent initiation of mechanical ventilation. Consequently, the lack of invasive ventilation at baseline was not a strong proxy for worse conditions.

Regarding other factors showing an association with 90-day mortality in our secondary analysis (in terms of increased mortality for concomitant bacteremia and of reduced mortality for concomitant pneumonia), further large scale investigation is required. Indeed, while the direction of the effects was similar to that of the fixed model (model C), the statistical significance of the associations with increased mortality (for concomitant bacteremia) and with reduced mortality (for concomitant bacterial pneumonia) was not retained after adjusting for between-center variability (model D). It should also be noted that, while the association of concomitant bacteremia with increased mortality could be expected on a theoretical ground (given the simultaneous presence of two severe infectious conditions), the seemingly protective effect of concomitant bacterial pneumonia is less intuitive, supporting the possibility of a spurious association. However, due to the non-pathognomonic nature of lung infiltrates, bacteria could had been, in some patients, the major culprits for the lung damage fulfilling criteria for retrospective inclusion in the JIR-ICU study, thereby possibly reducing the etiological contribution of *P. jirovecii*, a fact that could have biased the assessment of its prognostic impact.

The present study has at least two additional major limitations. First, it shares the arbitrary presumptive classification of non-proven PJP as in the original JIR-ICU study [7]. This choice was necessary to improve the reliability of the results of the primary and secondary analyses of the main JIR-ICU study by reducing exclusion of non-conventional host factors and by reducing incorporation bias [7]. However, a favorable impact also on the results of the present post-hoc analysis may not be retained. Second, the very high proportion of patients treated with anti-PJP therapy and with steroid therapy, alongside with the lack of information on the exact timing of anti-PJP therapy and type of any possible previous steroid treatment (both previously reported as factors potentially impacting prognosis [21,25]), precluded the assessment of both the existence and the magnitude of a connected prognostic impact.

In conclusion, PJP mortality remains high in patients with PJP admitted to the ICU. Baseline conditions other than HIV are emerging not only as non-classical risk factors for PJP development, but also as essential mortality predictors. A better understanding of the reasons underlying this evolving landscape could be crucial to improve PJP management and survival.

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Ethical approval

The study was approved by ethics committee of the coordinating center (Liguria Region Ethics Committee, N. Registro CER Liguria 305/2021). Informed consent was waived by the Liguria Region Ethics Committee due to the retrospective nature of the study. The other participating centers followed their local ethical committee requirements. The study was conducted in accordance with the ethical standards of the declaration of Helsinki.

Authors contributions

CRediT: **Daniele Roberto Giacobbe**: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing; **Silvia Dettori**: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing; **Vincenzo Di Pilato**: Data curation, Formal analysis, Writing – review & editing; **Erika Asperges**: Data curation, Writing – review & editing; **Lorenzo Ball**: Data curation, Writing – review & editing; **Enora Berti**: Data curation, Writing – review & editing; **Ola Blennow**: Data curation, Writing – review & editing; **Bianca Bruzzone**: Data curation, Writing – review & editing; **Laure Calvet**: Data curation, Writing – review & editing; **Federico Capra Marzani**: Data curation, Writing – review & editing; **Antonio Casabella**: Data curation, Writing – review & editing; **Sofia Choudaly**: Data curation, Writing – review & editing; **Anais Dartevel**: Data curation, Writing – review & editing; **Gennaro De Pascale**: Data curation, Writing – review & editing; **Gabriele Di Meco**: Data curation, Formal analysis, Writing – review & editing; **Melissa Fallon**: Data curation, Writing – review & editing; **Louis-Marie Galerneau**: Data curation, Writing – review & editing; **Miguel Gallego**: Data curation, Writing – review & editing; **Mauro Giacomini**: Data curation, Writing – review & editing; **Adolfo González Saez**: Data curation, Writing – review & editing; **Luise Hänsel**: Data curation, Writing – review & editing; **Giancarlo Icardi**: Data curation, Writing – review & editing; **Philipp Koehler**: Data curation, Writing – review & editing; **Katrien Lagrou**: Data curation, Writing – review & editing; **Tobias Lahmer**: Data curation, Writing – review & editing; **Philip Lewis White**: Data curation, Writing – review & editing; **Laura Magnasco**: Data curation, Writing – review & editing; **Anna Marchese**: Data curation, Writing – review & editing; **Cristina Marelli**: Data curation, Formal analysis, Writing – review & editing; **Ignacio Martin-Loeches**: Data curation, Writing – review & editing; **Armand Mekontso-Dessap**: Data curation, Writing – review & editing; **Malgorzata Mikulska**: Data curation, Writing – review & editing; **Marco Muccio**: Data curation, Formal analysis, Writing – review & editing; **Alessandra Mularoni**: Data curation, Writing – review & editing; **Anna Nordlander**: Data curation, Writing – review & editing; **Julien Poissy**: Data curation, Writing – review & editing; **Giovanna Russelli**: Data curation, Writing – review & editing; **Alessio Signori**: Data curation, Formal analysis, Writing – review & editing; **Carlo Tascini**: Data curation, Writing – review & editing; **Louis-Maxime Vaconsin**: Data curation, Writing – review & editing; **Joel Vargas**: Data curation, Writing – review & editing; **Antonio Vena**: Data curation, Writing – review & editing; **Joost Wauters**: Data curation, Writing – review & editing; **Paolo Pelosi**: Conceptualization, Data curation; **Jean-Francois Timsit**: Data curation, Writing – review & editing; **Matteo Bassetti**: Conceptualization, Writing – review & editing.

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Data availability statement

The data presented in this study will be available from the corresponding author on reasonable request and provided all regulatory and privacy requirements are fulfilled.

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