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► **To cite this version:**

Benjamin Gaborit, Romain Lécuyer, Nahéma Issa, Fabrice Camou, Rose-anne Lavergne, et al.. Should We Reconsider Pneumocystis Pneumonia Presentation and Treatment According to Its Underlying Disease?. Chest, 2024, pp.S0012-3692(24)00692-5. 10.1016/j.chest.2024.04.038 . inserm-04676363

HAL Id: inserm-04676363

<https://inserm.hal.science/inserm-04676363v1>

Submitted on 23 Aug 2024

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Should We Reconsider *Pneumocystis* Pneumonia Presentation and Treatment According to Its Underlying Disease?

An Unsupervised Cluster Analysis of a Retrospective Multicenter Study

To the Editor:

Pneumocystis jirovecii pneumonia (PcP) is a fungal opportunistic disease that was first described in the 1980s during the HIV pandemic.^{1,2} The understanding

of PcP physiopathologic features and progress in effective anti-*Pneumocystis* therapies was associated closely with its specific presentation in the context of AIDS.³ However, new hosts have emerged with the advent of highly active antiviral treatments against HIV and novel immunomodulating therapies in organ transplantation and in hematology and oncology, presenting very distinct PcP patterns compared with those associated with HIV.^{4,5} Concerning prognostic factors in PcP, we previously showed that underlying disease,^{6,7} immunosuppression profiles,⁸ and respiratory coinfections⁹ directly influence patient outcomes. These findings raise challenges for improving the diagnosis and treatment of PcP, given advances in personalized medicine based on individual immunologic profiling.¹⁰

Methods

To investigate factors involved in PcP subtypes, an unsupervised analysis of clinical manifestations, laboratory features, and prognostic data from 481 patients with PcP was conducted. This study is a substudy from the Prognostic Factors in *Pneumocystis* Pneumoniae (PRONOCYSTIS) cohort,^{7,9} a retrospective multicenter network involving three French hospitals from January 2011 through December 2021, including patients with proven or probable PcP diagnosis according to the European Organization for Research and Treatment of Cancer.

Main drivers of inertia were determined by unsupervised cluster analysis using factorial analysis of mixed data analysis with R statistical software (FactoMineR package; R software version 3.2.2 [R Foundation for Statistical Computing]).¹¹ These variables encompassed 19 parameters, clinical and biological data, underlying disease, and immunosuppressive treatment exposition (including HIV, hematologic malignancy, solid tumor, solid organ transplantation, immunocompromised status, immunosuppressive treatment, long-term use of steroids, age, fever,

cough, dyspnea, general state alteration, time from onset to hospitalization, renal comorbidity, respiratory comorbidity, albuminemia, WBC count, positive direct examination for cysts, and coinfection). Several supplementary variables were added to this first construct and were considered as illustrative, either because of too many missing results or so as not to bias the interpretation and allow some degree of freedom to discover new subtypes (identification of cysts in BAL or sputum, ICU, high-oxygen flow therapy, mechanical ventilation, sex, prophylaxis observance, fibrosis, BMI, lymphocytes counts, CD3 and CD4 counts, lactate dehydrogenase (LDH), time from diagnosis, BAL profile [polymorphonuclear leukocytes, macrophagic, lymphocytic], treated coinfection, cytomegalovirus positivity, bacterial positivity in BAL, Sequential Organ Failure Assessment score, Pao₂ to Fio₂ ratio, recovery, and 90-day mortality). As a secondary objective, hierarchical clustering was performed on the coordinates of the first five axes of the analysis, leading to the identification of stable clusters that were characterized secondarily. A comprehensive overview of the data set of the PRONOCYSTIS cohort is available in the main publication.⁷

Results

A total of 481 patients were included, all of whom were immunocompromised (hematologic malignancy, n = 118; HIV infection, n = 114; solid organ transplantation, n = 103; immune-mediated inflammatory disease, n = 87; solid tumor, n = 56; and other immunodeficiency, n = 3). Three stable clusters with significantly different clinical characteristics and outcomes were identified (Fig 1A). Cluster 1 was associated predominantly with patients with positive HIV findings. Cluster 2 was associated with patients with hematologic malignancies, immune-mediated inflammatory diseases, and solid tumors. Cluster 3 corresponded to patients with solid

organ transplantation, prior long-term use of corticosteroids, and respiratory and renal comorbidities (Fig 1B). Each of these clusters was associated with a specific PcP prognosis, with cluster 1 presenting the highest survival rate, whereas cluster 2 presented the poorest outcome (Fig 1C).

Concerning biological and clinical characteristics, cluster 1 was associated with the lowest age, BMI, CD4 lymphocyte count, C-reactive protein level, and Sequential Organ Failure Assessment score, as well as the longest diagnostic delay, whereas cluster 2 was associated with the highest age, highest BMI, highest

neutrophil count, highest C-reactive protein level, and highest Sequential Organ Failure Assessment score and the shortest time to diagnosis (Fig 1D).

Discussion

To the best of our knowledge, our study provides the most detailed unsupervised cluster analysis in a large retrospective multicenter cohort of patients with PcP, including those with and without HIV infection. Burghi et

al¹⁰ suggest that clinical presentation differs between underlying diseases, with PcP related to chronic lymphocytic leukemia or autologous hematopoietic stem cell transplantation reported to be closer to that occurring in patients with HIV infection than in those with other underlying diseases. However, this study did not directly compare patients without HIV infection with those with HIV infection to confirm this hypothesis. An important finding from our study is the clear association between

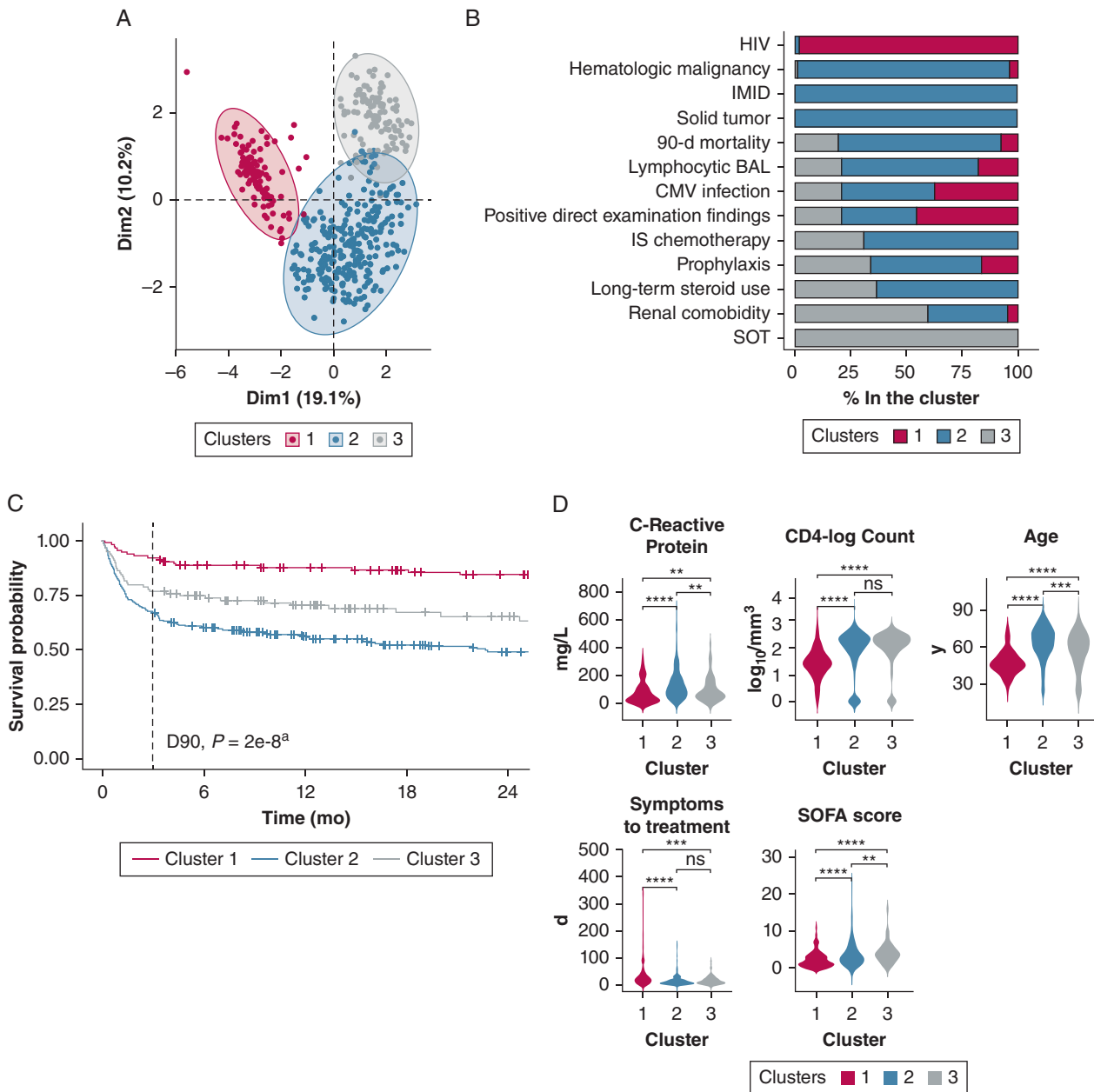


Figure 1 – Unsupervised cluster analysis of the Prognostic Factors in *Pneumocystis Pneumoniae* (PRONOCYSTIS) cohort ($n = 481$). A, Clustering grouped into three clusters according multiple correspondence analysis of clinical manifestations, laboratory features, and prognostic data. B, Analysis of statistically significant determinants of clusters 1, 2, and 3. C, Survival analysis according to *Pneumocystis jirovecii* pneumonia (PcP) cluster. D, Comparative analysis of selected clinical manifestations and laboratory features of PcP clusters. ^aLong-term administration before the PcP diagnosis. CMV = cytomegalovirus; IMID = immune-mediated inflammatory disease; IS = immunosuppressive; SOFA = Sequential Organ Failure Assessment; SOT = solid organ transplantation.

clinical features, underlying diseases, biological and diagnostic features, and phenotypes of PcP.

Cluster 1 was associated exclusively with PcP related to HIV and confirms the specific features of this disease compared with patients without HIV infection (lowest age and CD4 lymphocyte count and the longest diagnostic delay).⁷ This first cluster, already supported in the literature,^{12,13} also allowed us to confirm the findings of the cluster analysis strategy in this cohort and to highlight the underlying discrepancies between clusters 2 and 3. Exposure to corticosteroids before PcP diagnosis is an important determinant of the clusters (clusters 2 and 3) and is associated with poor outcome, although this remains a less influencing determinant than the underlying disease (oncohematology or immune-mediated inflammatory disease for cluster 2 and solid organ transplantation for cluster 3). In our study, the main characteristics that defined clustering included biological variables and clinical data, suggesting that specific immunologic characteristics might allow the identification of patient subgroups with different treatment needs and outcomes.³

Our study presents some limitations as a retrospective study covering a period of 10 years, which may have resulted in missing data and the fact that medical care has changed over this period. Additionally, the lack of standardization in diagnostic procedures and in the wide range of underlying immunosuppressive treatments may limit the analysis's power to identify clusters of interest. The unsupervised cluster analysis performed in this study loses its discriminatory ability at lower numbers of patients; in that context, the variability in immunosuppressive treatments represents a significant limitation to the study. Finally, such results need to be confirmed with a validation cohort to be more generalizable.

Interpretation

This study demonstrates that PcP phenotypes are associated strongly with underlying disease and outcomes. Clinical biological characteristics, as well as PcP prognosis, seem to be linked closely to the immune deficiency profiles of patients. Continued exploration of the immunologic profiles linked with these phenotypes may contribute to identifying individuals at higher risk better and to advancing toward more tailored therapeutic approaches.

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DOI: <https://doi.org/10.1016/j.chest.2024.04.038>

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, AstraZeneca, 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. B. T. reports receipt of nonfinancial support from Gilead Sciences and personal fees from AbbVie, Gilead Sciences, Lilly Oncology, and Incyte outside the submitted work. None declared (R. Lécuyer, N. I., F. C., R. Lavergne, F. G., F. M., D. B., A. C., M. G., Y. C., A. N.).

Acknowledgments

PRONOCYSTIS Study Group Collaborators: Francois Raffi, David Boutoille, Charlotte Biron, Maeva Lefebvre, Benjamin Jean Gaborit, Paul Le Turnier, Colin Deschanvres, Raphael Lecomte, Marie Chauveau, Romain Lécuyer, Antoine Asquier-Khati, Valentin Pineau, Marie Prime, Clarisse Delaunay, and Hakim Essid (Department of Infectious Diseases, Nantes University Hospital); Patrice Le Pape, Florent Morio, Rose-Anne Lavergne, and Fakhri Jeedi (Department of Parasitology-Myecology, Nantes University Hospital); Stéphane Corvec, Pascale Bemer, Jocelyne Caillon, Aurélie Guillouzouic, and Anne-Gaëlle Leroy (Department of Bacteriology, Nantes University Hospital); Karim Lakhali, Raphaël Cinotti, Antoine Roquilly, and Mickael Vourc'h (Department of Anesthesiology and Intensive Care Medicine, Nantes University Hospital); Jean Reignier and Emmanuel Canet (Medical Intensive Care, Nantes University Hospital); François Xavier Blanc, Cédric Bretonniere, Jean Morin, Camille Le Blanc, and Hakim Alami (Service de Pneumologie, Nantes University Hospital); Fabrice Camou, Nahéma Issa, Olivier Guisset, and Gaele Mourissoux (Intensive Care and infectious disease, Groupe Saint André, Bordeaux University Hospital); Isabelle Accoceberry, Frederic Gabriel, Noémie Coron, Laurence Delhaes, Sébastien Imbert, Maxime Lefranc, Florian Lussac-Sorton, and Amandine Rougeron (Laboratoire de Mycologie, Groupe Pellegrin, Bordeaux University Hospital); Marie Gousseff, Yoann Crabol, Grégory Corvaisier, Florent Lautredoux, and Romain Lécuyer (Department of Internal Medicine and Infectious Diseases, Centre Hospitalier Bretagne-Atlantique, Vannes); and Anne Cady, Myriam Auger, and Pascal Pouedras (Department of Microbiology, Centre Hospitalier Bretagne-Atlantique, Vannes).

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