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1 Characteristics and outcome according to underlying disease in non-AIDS patients with
2 acute respiratory failure due to *Pneumocystis* pneumonia

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42

43 Abstract (196)

44 Purpose : In the non-AIDS group, several underlying conditions and immune defects
45 could lead to different PCP presentations. This study compared PCP presentation
46 and outcome according to the underlying disease.

47 Methods : Secondary analysis of a previous published prospective observational
48 study including 544 PCP patients. Only non-AIDS patients were included. Underlying
49 disease was defined as chronic lymphocytic leukemia (CLL), organ transplantation,
50 solid cancer, allogenic hematopoietic stem cell transplant (AHSCT), other
51 hematological diseases, and immunosuppressive treatment. Clinical characteristics
52 and outcome were compared between groups. Multiple correspondent analyses
53 compared clinical characteristics at diagnosis. Day 30 (~~Day 30~~) mortality was
54 analyzed.

55 Results: Three hundred and twenty-one patients were included in the study. The
56 underlying diseases were hematological malignancy (n = 75), (~~AHSCT~~) (n = 14), CLL
57 (n = 19), solid organ transplant (n = 94), solid tumor (n = 39), and
58 immunosuppressive treatment (n = 57). Compared with other underlying diseases,
59 PCP related to CLL was closer to PCP related to AIDS presentation (long duration of
60 symptoms before diagnosis, high level of dyspnea, and low oxygen saturation at
61 diagnosis). Day 30 mortality was associated with underlying disease, oxygen flow,
62 and shock at ICU admission.

63 Conclusion: PCP presentations may vary according to the underlying reason for
64 immunosuppression. Response to treatment and adjuvant steroid therapy should be
65 analyzed regarding this result.

66

67 **Introduction**

68 *Pneumocystis jirovecii* pneumonia (PCP) remains a life-threatening, opportunistic disease
69 related to T cell suppression, macrophage defect, or other immunodeficiencies. New
70 treatments and higher life expectancies in various oncologic or immune disease illustrate
71 that PCP among non-AIDS patients is steadily increasing [1–6].

72 Several studies thus far have demonstrated significant differences between AIDS and non-
73 AIDS patients in clinical pictures, physiopathology, and mortality related to PCP. In fact,
74 non-AIDS patients experienced a shorter length of symptoms, a higher inflammation in the
75 lungs, and a significantly higher severity and mortality despite a lower pulmonary burden of
76 *Pneumocystis* [6–8].

77 However, immunosuppressive conditions leading to PCP onset remain different inside the
78 subgroup of non-AIDS patients. Immune defects for solid organ transplant recipients may
79 be different from those in chronic lymphoid leukemia (CLL) patients or solid tumor patients
80 [9–11]. The clinical presentation and response to treatment may vary between all those
81 underlying diseases, but those differences are not well established in the literature.
82 Indeed, comparing patients inside the non-AIDS group may be of importance.

83 The aim of this study was to identify different clinical profiles and mortality-related factors
84 among the different non-AIDS groups at risk for PCP.

85

86

87

88

89 **Materials and methods**

90

91 The study was a secondary analysis of an observational study. The study has already
92 been described [6]. Briefly, between January 1, 2007, and December 31, 2010, all
93 consecutive patients (AIDS infected or non-AIDS infected patients) with confirmed
94 *Pneumocystis* pneumonia were included in the study. The study was conducted in
95 accordance with French law for observational studies on retrospective data which did not
96 require patient consent for this analysis. Confirmed *Pneumocystis* pneumonia was defined
97 as having a positive result for *Pneumocystis jirovecii* by Gomori-Grocott or toluidine blue
98 stain or positive immunofluorescence test results for a broncho-alveolar lavage (BAL) fluid
99 or induced sputum specimen. Patients for whom only PCR results were positive were not
100 included in the study.

101 All clinical, biological, and imaging data were prospectively reviewed based on patients
102 hospitalization records. Clinical characteristics at admission included respiratory symptoms
103 and extra-respiratory organ failure.

104 Diagnosis criteria were assessed, and outcome during ICU stay was recorded.

105 In this secondary study, only non-AIDS patients were analyzed. Underlying diseases were
106 described as chronic lymphoid leukemia (CLL) diagnosis with or without treatment, AHSCT
107 whatever the length from transplantation, other acute hematological malignancies, active
108 solid tumor when patients had been treated within the past 5 years with chemotherapy,
109 solid organ transplantation, immunosuppressive treatment for immune disease, or other
110 reasons. Because of the high prevalence of PCP during CLL and the physiopathology
111 assumed close to the one of PCP related to AIDS, patients with CLL was firstly described
112 separately [12,13]. For CLL patients, high prevalence of PCP was usually associated T
113 cell depletion related to fludarabine treatment [9] In the further analysis, all patients with

114 hematological malignancies were analyzed in the same group. In case of several
115 underlying disease, hematological disease was first considered (for example, if patient had
116 hematological disease after solid organ transplantation (SOT), he was considered as
117 hematological patient), then the most recent underlying disease (for example if patient with
118 SOT had a recent increase of immunosuppressive treatment, he was classified as drug
119 related immune suppression).

120 Characteristics at diagnosis and outcome were analyzed. Prophylaxis was defined as an
121 antifungal therapy before PCP onset (sulfamethoxazole/trimethoprim or atovaquone or
122 pentamidine). Shock was defined with the need of vasopressors. Only day 30 mortality
123 was analyzed.

124

125 *Statistical Analysis*

126 Data from clinical or biological presentation and outcome were described according to
127 underlying disease. Quantitative variables are presented as median (interquartile range)
128 and were compared between disease groups using Kruskal-Wallis tests; categorical
129 variables are presented as count (percent) and were compared between groups using χ^2
130 tests.

131 Multiple correspondence analysis (MCA) was performed to identify profiles of clinical
132 presentation in non-AIDS *Pneumocystis* patients, possibly related to the underlying
133 diseases. For the MCA, missing data were handled by imputation using a correspondence
134 analysis procedure, with the missMDA package on R statistical platform. We report figures
135 illustrating the first two components describing variability in observations based on clinical
136 presentation signs. In figure 1, underlying diseases have been added on the plot to
137 illustrate the link between clinical variables and underlying disease. Figure 2 represents
138 the corresponding individuals factor map according to the underlying disease.

139 Factors associated with Day 30 mortality were evaluated with univariate analysis using a
140 logistic regression model estimating odds ratios and their 95% confidence intervals. in the
141 sample with available follow-up data (n=280). Variables that were significant at the 5%
142 level in univariate analysis were candidates for multivariate analysis. A multivariate model
143 was selected using a backward stepwise selection procedure based on p-values
144 (threshold = 0.05). The main analysis was performed using multiple imputations by
145 chained equations to handle missing data (50 imputations with 20 iterations). Estimates for
146 the effect of variables on mortality from imputed data were computed using Rubin's rules.
147 A sensitivity analysis was performed using a complete-cases approach, yielding consistent
148 results
149 ~~A sensitivity analysis was performed using a complete-cases approach, yielding consistent~~
150 ~~results.~~
151 All tests were two-sided, and a p-value lower than 0.05 was considered as indicating a
152 significant association. Analyses were performed on the R statistical platform, version
153 3.2.2 with the FactoMineR, missMDA, and mice packages.

154

155

156 **Results**

157

158 During the study period, 321 non-AIDS immunosuppressed patients were included in the
159 study. Median age was 59 [IQR 46–68] years, and 193 (62%) patients were male.
160 Underlying immunosuppression was related to hematological malignancy (n = 75, 23%),
161 chronic lymphoid leukemia (n = 19; 6%), AHSCT (n = 14; 4%), solid tumor (n = 39; 12%),
162 SOT (n = 94; 29%) or immunosuppressive treatment for other reasons (n = 57; 18%), and
163 other immunosuppressive reasons (n = 23; 7%). Hematological diseases were mostly non
164 Hodgkin or Hodgkin disease (n=46, including 6 autologous HSCT), multiple myeloma
165 (n=10) or acute myeloid leukemia (n=9). Solid organ transplantations were mostly kidney
166 transplantation (77/94). Immunosuppressive treatment for underlying disease as
167 connective tissue disease or systemic vasculitis was steroid (n=27), chemotherapy +/-
168 steroids (n=21), anti CD20 +/- steroids (n=4), other (n=5). Other immunosuppressive
169 conditions were pulmonary or cutaneous underlying diseases resulting in intermittent
170 steroids treatment (n=14), underlying connective tissue disease without treatment (n=6),
171 unknown reason of immunosuppression in the database (n=3). At the time of diagnosis,
172 most of the patients did not receive anti-*Pneumocystis* prophylaxis or had recently
173 withdrawn prophylaxis (n = 266; 83%).

174 The delay between respiratory symptoms and diagnosis was 5 [1–15] days, and below 7
175 days for 135(42%) patients.

176 Clinical presentations included fever over 38°C (n = 181; 83%), cough (n = 109; 54%), and
177 dyspnea (n = 151; 73%). Oxygen flow required at diagnosis was 0 [IQR 0–6] l/min. Half of
178 the patients were admitted to the ICU (n = 134; 50%). Noninvasive mechanical ventilation
179 was required for 50 (15.6%) patients, among whom 46 (92%) needed secondary invasive

180 mechanical ventilation (iMV). One-third of the patients (n = 98; 30.5%) needed iMV. Shock
181 occurred at diagnosis in 22 (6.8%) patients.

182 Pulmonary co-infections were frequent with bacteria (n = 48; 17%) or virus (n = 26; 9%).

183 Viral coinfection included 16 CMV infections and 8 herpes simplex virus infections.

184 Bacterial co-infections were mostly related to *Pseudomonas* (n=9), *Streptococcus*
185 *pneumonia* (n=9), *Escherichia Coli* (n=4), *Staphylococcus or enterococcus* (n=12).

186 The lung CT scans of 165 (51.4%) patients were analyzed. Ground-glass opacity was the
187 most frequent lesion (n = 110; 67%) but was associated with alveolar lesion in 36 (22%)
188 patients. For 3 patients (2%), the lung CT scans was normal.

189 The delay from hospital admission to treatment was 2 [0–6] days. Adjuvant steroid therapy
190 was prescribed in 106 (43%) patients.

191 Table 1 described the clinical presentation and outcome according to the underlying
192 disease. In this table, some characteristics must be highlighted. First, the duration of
193 symptoms before diagnosis was longer for CLL and AHSCT (respectively 15 [10–26] and
194 26 [12–30] days), close to the duration in AIDS patients. Prophylaxis guidelines were
195 different according to the underlying disease, and PCP occurred mostly during prophylaxis
196 vacancy. Steroid before PCP onset was differentially prescribed depending on the
197 underlying disease ($p < 0.001$); the highest frequency of steroid prescription was observed
198 in patients with solid organ transplant or immunosuppressive treatment consistent with the
199 usual treatment regimen for those underlying diseases. Although symptoms were similar
200 for all underlying diseases, cough prevalence was different according to the underlying
201 disease ($p < 0.001$); it was mostly observed in hematological diseases, including CLL and
202 AHSCT patients.

203 Age at diagnosis was different, reflecting the underlying age onset for each disease group.

204 Multiple correspondence analyses (Figs. 1 and 2) highlight those clinical differences
205 according to the underlying disease. Overall, clinical presentation variables could be
206 summarized in two main components explaining respectively 25.7% and 22.6% of
207 observations variability. The presence of a coinfection was the main characteristic
208 discriminating 2 clinical profiles.

209 Day 30 mortality was 23% (n = 64/280). Table 2 described the univariate analysis of
210 factors associated with Day 30 mortality. Table 3 described the multivariate analysis of
211 factors associated with Day 30 mortality. Higher oxygen flow at admission (OR = 1.16 per
212 1L/min increment [1.08–1.24], p < 0.001) and shock at ICU admission (OR = 7.67 [2.63–
213 22.37], p = 0.0002) were associated with higher mortality. On the contrary, solid organ
214 transplant (OR = 0.19 [0.07–0.53], p = 0.001) was associated with lower mortality rate
215 compared to patients with immune diseases or solid tumors. The sensitivity analysis on the
216 complete-case dataset was consistent with these results and is reported in table 1 suppl.

217

218 **Discussion**

219 This study is the first to compare several immunosuppressive conditions for PCP onset.
220 Although the study was mostly an exploratory analysis several points should be
221 highlighted. The study included a high number of patients with PCP. Although prevalence
222 of PCP outside the group of AIDS patients, has been increasing, the number of cases has
223 remained low, and this study included all the patients in 17 French hospitals within a three-
224 year period [6,14,15]. We found that several immune conditions lead to variable clinical
225 presentations.

226 First, PCP occurred in patients without prophylaxis, and the incidence of prophylaxis
227 varied inside the non-AIDS group. Although prophylaxis remains recommended in CLL
228 patients with treatment or in solid organ transplant patients during more than 6 months
229 (depending on the organ) after transplant [20], there are no guidelines regarding the
230 patients with solid tumor or receiving immunosuppressive treatment. However, this study
231 confirmed that prophylactic treatment should be discussed for patients with
232 immunosuppressive treatment, particularly for those who need steroid boli for rejection
233 treatment in solid organ transplant or graft-vs.-host disease [4]. Also, prophylaxis may be
234 discussed for some kinds of solid tumors for patients who receive steroids [3].

235 Second, clinical presentation seems different between underlying diseases. Presentation
236 of PCP related to CLL or AHSCT were closer to that occurring in AIDS patients than other
237 underlying diseases with a long duration of symptoms before diagnosis, high level of
238 dyspnea, and low oxygen saturation at diagnosis. Furthermore, physiopathology of
239 immunosuppression is different for those diseases. The use of fludarabine during the
240 course of treatment for CLL or before AHSCT leads to a profound T cell depletion as in
241 severe AIDS infection [9]. T cells are known to be involved in *Pneumocystis* clearance and
242 also the CD4/CD8 ratio could regulate lung inflammation. Therefore, the duration of

243 symptoms for LLC and AHSCT could be related to T cell depletion after fludarabine.
244 Secondly after fludarabine treatment, T cell recovery has been associated with a shift
245 toward Th1 cytokine secretion and could be associated with higher lung inflammation [9].
246 On the contrary, immunosuppressive treatment for immune disease or solid organ
247 transplant, mostly steroid therapy, have been associated with altered macrophage
248 function. Macrophages are highly involved in *Pneumocystis* pathogenicity. Indeed, a
249 recent study demonstrated the double role of macrophages in anti-*Pneumocystis* defense
250 [16]. This cell may recognize *Pneumocystis* and clear it from the lungs via an inflammatory
251 response leading to TNF α , IL6, IL1 β secretion. Also, macrophage could balance
252 inflammatory response via IL10 secretion. Steroids may modify the balance between
253 inflammatory and antifungal function by modifying macrophage response [10].
254 The pathogenicity of *Pneumocystis* could then be different according to the underlying
255 disease or treatment. Our study brings some arguments to explore the different type of
256 *Pneumocystis* disease. Thus, response to adjuvant therapy may be variable according to
257 the underlying disease [17,18].
258 *Pneumocystis* pneumonia in non-AIDS patients remains associated with high mortality, up
259 to 50%, according to the underlying disease [14]. Although this infectious disease was
260 associated with severe hypoxemia, shock remained rare. Consistently, in our study, only
261 8% of patients had shock during the course of *Pneumocystis* pneumonia. Only Day 30
262 mortality was analyzed to reduce the bias for the mortality related to the underlying
263 disease. However, mortality remained higher in hematological diseases patients than in
264 patients with solid organ transplant or immunosuppressive treatment. The severity of the
265 underlying disease and the possibility of treatment after *Pneumocystis* pneumonia
266 recovery may influence mortality and clinical decisions.

267 Our study had several limitations. First, this was a retrospective study, with missed data.
268 However, we used a multiple imputation approach for the analysis and performed a
269 sensitivity analysis on complete cases which did not modify results on factors associated
270 with Day 30 mortality.

271 Second, data were recorded more than 10 years ago and medical care would be modified
272 within this period. However, the primary objective of the study was to discriminate PCP
273 presentation between several underlying diseases. Although, treatments and ICU
274 procedures have been improving within the last 10 years which could have modified
275 mortality, PCP presentation at admission may remained stable according to the underlying
276 immunosuppression.

277 We also had no information about the functional status of each patient and their nutritional
278 status, or comorbidities, which are also known factors associated with the outcome of
279 these patients in the ICU and in the hospital [19]. Comorbidity scores, body mass index,
280 and functional status were probably not the same in different patient groups, all of which
281 could influence mortality.

282 Moreover we had no information about the decrease of dose or the suspension of
283 immunosuppressive treatments in each group, which may also had an impact on the final
284 outcome.

285 Finally, we separated patients in six groups according to the underlying disease, resulting
286 in a limited number of patients in each group.

287 **Conclusion**

288 To conclude, our study shows different presentations and prognoses of *Pneumocystis*
289 pneumonia according to the underlying disease. These differences may be explained with
290 the different types of alterations of the immune system. All those data should be confirmed
291 with further study. Our study added hypothesis concerning presentation and response to

292 treatment according the underlying diseases. For example, analyzing response to
293 adjunctive steroids for non-AIDS patients with PCP may include underlying disease in the
294 further study. Likewise, mortality is associated with the severity of the patients at the time
295 of diagnosis, determined by the presence of shock and higher need of oxygen.
296

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298 study

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303 GB, LB, EA, VL design the study, performed analysis and wrote the manuscript

304 AR, SV, FRG, SH, DM, AD, SLG, FD, ML, DT, CP, APB, JB, AB, XI, IDJ, DM, DP, CH, EM,
305 included patients, reviewed and approved the manuscript

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321

322 Availability of data and materials : data are availaible on reasonable request. required
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324

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384

385

Accepted manuscript

386
387 Tables and figures legend

388 **Table 1:** Characteristics at diagnosis according to the underlying disease

389

390 * Missing values: gender (n = 11), age (n = 8), prophylaxis (n = 42), duration of respiratory
391 symptoms (n = 91), temperature (n = 102), cough (n = 119), dyspnea (n = 113), SaO₂ (n =
392 184), oxygen flow (n = 144), ICU admission (n = 52), time from admission to treatment (n =
393 115), and day 30 mortality (n = 41)

394

395 **Table 2:** Univariate analysis of risk factors associated with DAY 30 mortality

396 IS: immunosuppressive treatment. CLL: chronic lymphoid leukemia

397

398 **Table 3:** Multivariate analysis of factors associated with DAY 30 mortality

399

400 **Figure 1:** Multiple correspondence analysis of clinical symptoms in non-AIDS
401 Pneumocystis patients according to the underlying disease
402 First two components could explain variability in observations up to 22.6 and 25.7%.

403
404

405 **Figure 2:** Multiple correspondence analysis of patients according to the underlying
406 disease.

407
408
409
410
411
412

Table 1

Variables	Hematological malignancy (n = 75)	Chronic lymphoid leukemia (n = 19)	Allogeneic stem cell transplant (n = 14)	Solid tumor (n = 39)	Solid organ transplant (n = 94)	Immunosuppressive treatment (n = 57)	Other immunosuppressive condition	p
Age (year) *	61 [52–73]	67 [62–76]	43 [32–57]	59 [49–64]	54 [44–61]	64 [53–74]	60 [43–68]	<0.001
Male gender*	47 (67)	12 (63)	8 (62)	21 (54)	59 (65)	30 (55)	16 (70)	0.67
No prophylaxis or recently withdrawn prophylaxis*	64 (85)	15 (79)	8 (57)	38 (97)	76 (80)	52 (96)	13 (100)	<0.001
Steroids prior to PCP	26 (35)	4 (21)	8 (57)	17 (44)	75 (80)	51 (89)	2 (9)	<0.001
Duration of respiratory symptoms (days)*	5 [0–15]	15 [10–26]	26 [12–30]	4 [0–7]	7 [0–15]	4 [0–12]	6 [4–14]	0.004
Dyspnea*	37 (79)	11 (85)	8 (89)	13 (54)	43 (68)	30 (73)	9 (82)	0.22
Cough*	29 (62)	12 (86)	5 (71)	7 (30)	34 (58)	18 (44)	4 (36)	0.013
T°>38°C*	48 (91)	13 (93)	8 (100)	15 (65)	53 (83)	35 (78)	9 (75)	0.085
SaO2 at admission (%)*	90 [87–94]	93 [87–96]	83 [74–96]	90 [86–96]	92 [90–96]	95 [89–98]	72 [64–85]	0.13
Oxygen flow at admission (L/min)*	0 [0–4]	0 [0–1]	0 [0–6]	2 [0–14]	0 [0–2]	6 [0–14]	0 [0–4]	0.069
ICU admission*	26 (42)	4 (25)	9 (69)	18 (53)	37 (47)	33 (65)	7 (47)	0.055
Time from hospital admission to treatment (days)*	2 [1–6]	2 [0–3]	0 [0–1]	2 [1–8]	2 [1–6]	2 [0–4]	7 (1–10)	0.081
D30 Mortality*	15 (22)	3 (17)	6 (50)	14 (40)	6 (8)	17 (33)	3 (17)	<0.001

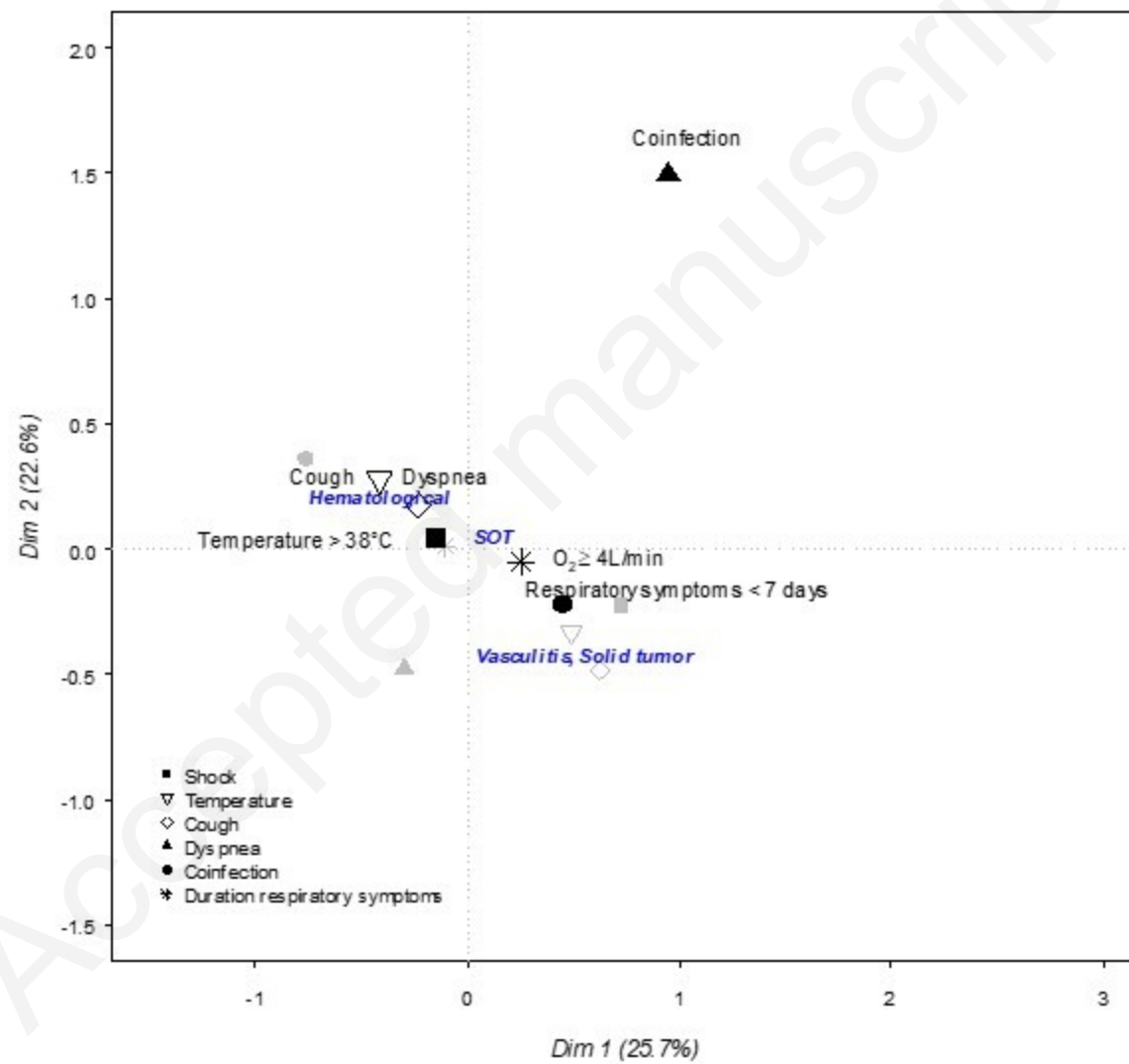
Table2

Variables	OR [CI95%]	p
Age (> or < 65 years)	2.37 [1.35–4.18]	0.003
Gender (female)	0.92 [0.52–1.64]	0.77
Underlying conditions		
Solid tumor and IS* treatment	1	
Solid organ transplantation	0.18 [0.07–0.44]	0.0002
Hematological malignancy or chronic lymphoid leukemia	0.56 [0.29–1.08]	0.083
Allogeneic stem cell transplantation	2.45 [0.77–7.83]	0.13
Prophylaxis		
None	1	
Continuous	0.25 [0.09–0.70]	0.009
Duration of respiratory symptoms		
<7 days	1	
7–21 days	0.58 [0.27–1.25]	0.17
>21 days	0.74 [0.26–2.13]	0.58
T>38°C	1.47 [0.59–3.64]	0.40
Cough	0.54 [0.27–1.09]	0.083
Dyspnea	1.32 [0.59–2.93]	0.49
SaO2 at diagnosis	0.96 [0.93–1.00]	0.029
Oxygen flow at diagnostic	1.15 [1.08–1.22]	<0.0001
Shock at admission	4.95 [2.03–12.1]	0.0005
Hospital acquired or coinfection	1.72 [0.95–3.13]	0.075
Adjuvant Steroid therapy	1.58 [0.86–2.93]	0.14

Table 3

Variables	OR [CI95%]	p
Underlying conditions		
Solid tumor and Is treatment	1	
Solid organ transplantation	0.19 [0.07–0.53]	0.001
Hematological malignancy or chronic lymphoid leukemia	0.75 [0.34–1.63]	0.47
Allogeneic stem cell transplantation	3.60 [0.93–13.9]	0.06
Oxygen flow at diagnostic	1.16 [1.08–1.24]	<0.0001
Shock at admission	7.67 [2.63–22.37]	0.0002

Dimensions 1 and 2 factor map



Dimensions 1 and 2 factor map

