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Invasive pulmonary aspergillosis in critically ill patients with hematological malignancies

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Abstract

Purpose: Invasive pulmonary aspergillosis (IPA) is a dreadful event in patients with hematological malignancies (HM). Recent advances have standardized diagnostic, prophylactic and curative therapeutic strategies. We sought to assess whether these advances actually translate into improved survival in critically ill patients with acute respiratory failure and IPA.

Methods: This was a retrospective, multicenter study. Adult patients with HM, IPA, admitted to the ICU for acute respiratory failure over a 20-year period (January 1998–December 2017) were included. A cox regression model was used to identify variables independently associated with day-90 survival.

Results: Overall, 219 patients were included [138 (63%) men, median age 55 (IQR 44–64)]. Acute myeloid leukemia (30.1%) and non-Hodgkin lymphoma (22.8%) were the most frequent malignancies, and 53 (24.2%) were allogeneic stem cell recipients. Day-1 SOFA score was 9 [7–12]. Most patients presented with probable IPA, whereas 15 (7%) underwent lung biopsies or pleurocentesis and met criteria for proven IPA. Overall ICU and day-90 mortality were, respectively, 58.4% and 75.2% (80.4% if invasive mechanical ventilation) without any significant improvement over time. By multivariable analysis adjusted on day-1 SOFA score and ventilation strategies, voriconazole use (HR 0.49, CI 95 0.34–0.73, $p < 0.001$) and an ICU admission after 2010 (HR 0.67, 0.45–0.99, $p = 0.042$) were associated with increased survival, whereas a diffuse radiologic pattern (HR 2.07, CI 95 1.33–3.24, $p = 0.001$) and delayed admission to the ICU (HR 1.51, CI 95 1.05–2.16, $p = 0.026$) were independently associated with increased mortality.

Conclusions: IPA is associated with high mortality rates in critically ill patients with acute respiratory failure. Routine voriconazole and prompt ICU admission are warranted.

Keywords: Invasive pulmonary aspergillosis, Hematological malignancies, Critically ill, Fungal infections

Introduction

Among hematology patients admitted to the ICU, invasive fungal infections remain associated with highest mortality rates [1, 2]. However, several advances outside the ICU were reported in patients with invasive pulmonary aspergillosis (IPA). Namely, a randomized trial demonstrated the superiority of voriconazole on the proportion of patients who could be cured from IPA, or survived [3]. Moreover, recognition of different clinical-CT patterns has allowed to better appraise diagnostic yield of non-invasive tests such as galactomannan or sputa culture, and to identify those patients in whom bronchoscopy and bronchoalveolar lavage (BAL) can actually assist the diagnosis [4]. Last, the use of prophylaxis in high-risk patients also modified both IPA incidence rates and clinical findings in AML patients or in recipients of allogeneic hematopoietic stem cell recipients [5, 6].

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Advances also occurred in the ICU management of hematology patients with acute respiratory failure, in whom up to 10% present with IPA [1, 7–9], a condition associated with mortality [1], particularly for patients who met ARDS criteria [10]. For instance, the use of non-invasive diagnostic tests as opposed to bronchoscopy and BAL may avoid respiratory failure. Similarly, progress in oxygenation and ventilation strategies [11] also may decrease the need for invasive mechanical ventilation [1]. Last, as suggested in an earlier study from our group, voriconazole use was associated with lower mortality in this setting [12].

Whether these non-ICU and ICU advances actually translate into improved outcomes has never been properly assessed. Data are needed to guide the clinical decision and identify patients in whom the introduction or maintaining of invasive ventilation would be unreasonable. We then sought to appraise outcomes in hematology patients admitted to the ICU for ARF in whom a diagnosis of probable or proven invasive pulmonary aspergillosis has been established.

Patients and methods

We conducted a multicentric retrospective study among the GRRR-OH study group (17 centers). All patients admitted to the ICU between January 1998 and December 2017 were included if they met the following criteria: (a) age > 18 years, (b) any hematological malignancy (HM), and (c) a recent diagnosis of IPA. IPA was diagnosed based on the 2008 EORTC criteria [13]. Only proven and probable IPA were included. Patients with proven IPA presented with a positive culture from a sterile sample or a pathological finding (needle aspiration or biopsy). Probable IPA required the combination of: host factors (neutropenia, allogeneic stem cell transplant, prolonged use of corticosteroids); clinical features including evocative CT scan lesions, tracheobronchitis observed during bronchoscopy or extrapulmonary (CNS or sinonasal) infection; a mycological criterion (positive fungal culture of respiratory samples or galactomannan antigen detection in serum or BAL).

Data presented in tables and figures were extracted from medical charts at each center. Radiologic presentation was reported from the initial chest x-ray or CT, realized in the previous or consecutive 24 h to ICU admission, and described as focal radiologic pattern, diffuse radiologic pattern or without specific pattern. Focal pattern was defined as a lesion restricted to the pulmonary lobe on chest X-ray or CT scans. Diffuse pattern affected more than one lobe. When patients presented both patterns or none of them, they were characterized as "without any specific radiologic pattern". The

Take-home messages

Invasive Pulmonary Aspergillosis in patients with hematological malignancies mostly affects patients with neutropenia and allogeneic stem cell transplant recipients. Mortality remains high and stable over the last two decades.

Sepsis-Related Organ Failure Assessment (SOFA) score was calculated at day 1 [14]. Neutropenia was defined as a neutrophil count < 500/mm^3. Non-invasive tests were defined as all tests that do not require the realization of a bronchoscopy and profound sampling: serum antigen, tracheal aspiration, sputa analysis and sinus aspiration. The threshold for positive plasma or BAL galactomannan antigen was 0.5 ng/ml [15, 16]. Regarding ventilation support, patients were allocated to one of the following groups: never ventilated, non-invasive ventilation (NIV) or high-flow nasal oxygen (HFNO) success, NIV or HFNO failure, first-line invasive mechanical ventilation (IMV). Delayed ICU admission was characterized as a time from respiratory symptoms onset to ICU admission > 5 days [17].

Statistical analysis

Mean and standard deviation (SD) or median and interquartile ranges were calculated for continuous variables, while numbers and percentages were calculated for categorical parameters. The normal distribution of each continuous variable was assessed with the use of the Shapiro–Wilk test. For univariate risk factor analysis, categorical variables were compared between independent groups using the Fisher or the Chi square tests, and continuous variables were compared using the Mann–Whitney test. Logistic regression analysis was carried out to study the association between ICU or day-90 mortality and year of admission over the 20-year follow-up. The threshold of 5 days for delayed ICU admission was set according the variable median value and previous literature.

A multivariable logistic Cox analysis was performed to identify factors independently associated with day-90 mortality. Variables associated with day-90 mortality in the univariate analysis with a $p < 0.10$ were suitable for inclusion into the multivariate model and included: cough symptom, viral pneumonia, radiologic presentation, initial SOFA score, vasopressor therapy, voriconazole treatment and ventilation strategy. Two variables were forced into the model: the time between symptoms onset and ICU admission that had previously been observed in the literature [17]; and the year of admission (before/after 2010), which offered a time-dependent variable to reduce selection bias linked with our long

inclusion period. Only variables with à $p < 0.05$ were maintained in the multivariate final model. Furthermore, the vasopressor therapy was removed because of its collinearity with the SOFA score, which presented a more complete and relevant information at ICU admission. Model assumptions for proportional hazards assumption, linear covariate relationship and lack of influential observation were tested and confirmed. To address selection bias, a sensitivity analysis was realized using a mixed-effect cox multivariable model with a random effect on the center of inclusion. Cumulative survival curves as a function of time adjusted on all variables from the cox multivariate model were presented using the Kaplan–Meier plots. All statistical analyses were performed on *R* (version 3.3.2 for Macintosh, licenses GNU GPL, The *R* foundation for statistical computing, Vienna, Austria). All tests were 2-sided and a *P* value < 0.05 was considered for statistical significance.

Results

Overall, 219 patients were included (Table 1 and Supplemental Fig. 1). Of those, 138 (63%) were of male gender and median age was of 55 (IQR 44–64). Acute myeloid leukemia (30.1%) and non-Hodgkin lymphoma (22.8%) were the most frequent malignancies. Fifty-three (24.2%) patients were allogeneic stem cell recipients, including 64.2% presenting Graft-versus-Host Disease. At admission, 134 (62%) patients were neutropenic, and 22 received antifungal prophylaxis (10%). Median SOFA score at admission was 9 [7–12]. 159 patients (72.9%)

Table 1 Patient's characteristics at ICU admission

Median (IQR) or numbers (%)	All patients *N* = 219	Day-90 survivors, *N* = 52*	Day-90 decedents, *N* = 158*	*P* value
Female gender	81 (37)	18 (34.6)	59 (37.3)	0.744
Age (years)	55 [44–64]	56 [47–62]	55 [43–64]	0.678
Underlying malignancy				0.227
Acute myeloid leukemia	66 (30.1)	19 (36.5)	45 (28.5)	
Non-Hodgkin lymphoma	50 (22.8)	9 (17.3)	40 (25.3)	
Acute lymphocytic leukemia	26 (11.9)	7 (13.5)	18 (11.4)	
Myeloma	16 (7.3)	5 (9.6)	10 (6.3)	
Chronic lymphocytic leukemia	14 (6.4)	2 (3.8)	10 (6.3)	
Burkitt lymphoma	8 (3.7)	0 (0.0)	8 (5.1)	
Hodgkin disease	8 (3.7)	4 (7.7)	4 (2.5)	
Myelodysplastic syndrome	8 (3.7)	3 (5.8)	4 (2.5)	
Chronic myeloid leukemia	5 (2.3)	0 (0.0)	5 (3.2)	
Other malignancy	18 (8.2)	3 (5.8)	14 (8.9)	
Time since diagnosis	226 [29–852]	156 [23–561]	234 [38–840]	0.254
Time since last chemotherapy	21 [11–50]	20 [9–40]	21 [12–50]	0.526
Allogeneic SCT recipients	53 (24.2)	10 (19.2)	38 (24.1)	0.570
Patients with GVHD	34/53 (64.2)	5/10 (50)	26 (68.4)	0.295
Time (days) since transplant	104 [27–245]	89 [21–402]	132 [29–242]	0.927
Autologous SCT recipients	33 (15.1)	9 (17.3)	22 (13.9)	0.652
Time (days) since transplant	29 [12–441]	16 [12–60]	52 [14–459]	0.231
Long-term steroids	100 (46)	19 (36)	77 (49)	0.149
Neutropenia	134/216 (62)	31 (59.6)	98/155 (63.2)	0.741
Antifungal prophylaxis	22 (10)	5 (9.6)	17 (10.8)	1.000
Time since symptoms onset	4.5 [1–13]	4 [1–11]	5 [1–13]	0.640
Fever	178 (81.4)	42 (80.8)	129 (81.6)	1.000
Cough	71 (32.4)	23 (44.2)	44 (27.8)	0.039
Diarrhea	53 (24.2)	16 (30.8)	34 (21.5)	0.191
Chest pain	29 (13.2)	10 (19.2)	17 (10.8)	0.150
Hemoptysis	25 (11.4)	6 (11.5)	17 (10.8)	1.000

In case of missing variables, the denominator indicates the number of patients with available data

SCT stem cell transplantation, *GVHD* graft-versus host-disease

*Day 90 mortality was unavailable for 9 patients

required vasopressors and 60 (27.8%) renal replacement therapy.

Patient were admitted to the ICU within 4.5 [1–13] days after symptoms onset. In addition to acute respiratory failure, 178 (81.3%) presented with fever, 71 (32.4%) cough, 29 (13.2%) chest pain and 25 (11.4%) presented at least one episode of hemoptysis (Table 1). Patients admitted in the ICU within 5 days after symptoms onset were diagnosed earlier for IPA compared with patient admitted after 5 days [3 (0–8) days vs. 11 [6–21], $p < 0.001$]. IPA diagnosis was based on positive serum or BAL galactomannan ($n = 74$ patients, 33.8%), fungal cultures ($n = 64$, 29.2%) or both ($n = 81$, 37%). 137 patients (62.2%) had an IPA diagnosis made by non-invasive diagnostic test. BAL was the only positive test in 11.9% of patients (Supplemental Fig. 2). IPA diagnosis was made prior to ICU admission in 125 (61%) of our patients. In patients who received invasive mechanical ventilation, 64 (53%) were diagnosed before intubation. *Aspergillus fumigatus* was the most frequent isolated strain (72.1%), followed by *Aspergillus flavus* (10.3%) and *Aspergillosis niger* (2.9%) (Supplemental Table 1). Median time from symptoms onset to IPA diagnosis was 6 days [2–12.5]. Most patients presented with probable IPA, whereas 15 (7%) underwent lung biopsies or pleurocentesis and met criteria for proven IPA.

First-line invasive mechanical ventilation was carried out in 85 (39%) patients, whereas 68 (31%) patients were intubated after failure from NIV or HFNO. In addition, 35 patients underwent non-invasive ventilation or HFNO with success, and 31 patients only received standard oxygen therapy. Time from ICU admission to IMV was 1 [0–3] day, and length of mechanical ventilation was 7 [0–16] days. Patients receiving invasive mechanical ventilation had higher day-90 mortality (80.4% vs 42.3%, $p < 0.01$). As shown in Fig. 2, need for invasive mechanical ventilation at admission or after failure of non-invasive strategies was associated with high mortality rates. Fifty-four (24.7%) patients met criteria for ARDS.

ICU and day-90 mortality rates were 58.4% and 75.2%, respectively. Case fatality remained high throughout the 20-year study period (Table 2). ICU length of stay was 12 [5–21] days. During study time, no significant association between ICU ($p = 0.21$) or day-90 mortality ($p = 0.28$) and year of admission was reported (Fig. 1).

Various changes were reported among our cohort throughout the inclusion period. Patients admitted after 2010 were older (57 vs. 51 years old, $p = 0.02$), received more allogeneic stem cell transplant (29.2% vs. 16.9%, $p = 0.04$), were more frequently treated by long-term corticosteroids (51.5% vs. 37.1%, $p = 0.04$) and showed a trend toward a longer duration of invasive mechanical ventilation (8 vs. 5 days, $p = 0.13$). However, SOFA admission scores ($p = 0.72$), number of antifungal lines of treatment ($p = 0.270$) and time between hematological diagnosis and ICU admission ($p = 0.911$) were not different (Fig. 2).

By multivariable analysis adjusted on day-1 SOFA score and ventilation strategies, use of voriconazole (HR 0.49, CI 95 0.34–0.73, $p < 0.001$) and an ICU admission after 2010 (HR 0.67, 0.45–0.99, $p = 0.042$) were associated with improved survival, whereas a diffuse radiologic pattern (HR 2.07, CI 95 1.33–3.24, $p = 0.001$) and delayed ICU admission (HR 1.51, CI 95 1.05–2.16, $p = 0.026$) were independently associated with higher day-90 mortality Table 3 and Fig. 3). The sensitivity analysis with a random effect on the center inclusion revealed similar significant results.

Discussion

This is the largest study to date that reports outcomes in critically ill hematology patients admitted to the ICU with acute respiratory failure from probable or proven IPA. These findings collected in 17 ICUs from our study group confirm clinical benefits from voriconazole in this population, and put forward outcome implications of delayed ICU management. Furthermore, the lower survival rate in patients requiring intubation and mechanical ventilation emphasizes the need to improve clinician's ability for maintaining a high level of IPA suspicion in at-risk patients, as well as to implement appropriate diagnostic workup in these patients.

In our cohort, despite a slight improvement for patients included after 2010, no significant association between ICU or day-90 mortality and time of admission was reported. This differs from recent encouraging trends of survival in hematological patients [18], in the subset admitted to the ICU [2, 19–22] and in patients with HM and IPA [12, 23, 24]. In an effort to clarify this paradox, we formulate the following hypotheses. First, the chronological beneficial effect expected from the generalization of voriconazole was diluted due to the early availability of the treatment in our cohort, as soon as 2001, 3 year after inclusion began. Second, in our cohort, patient characteristics changed over the study period for older and more immunocompromised subjects and may have impacted overall mortality. Indeed, development of specific hematological care for older patients contributed to the modification of ICU patient profile in hematological centers [25]. Moreover, our observation confirms the high severity and need for invasive and aggressive treatments in IPA patients, and emphasizes on the need for a proper assessment before an admission in the ICU. Furthermore, the introduction of invasive mechanical ventilation remains a strong predictor of mortality in hematological patients [2]. Indeed, the development of NIV [26–28] and HFNO

Table 2 Diagnostic criteria for probable or proven invasive pulmonary aspergillosis

Median (IQR) or numbers (%)	All patients *N* = 219	Day-90 survivors *N* = 52[a]	Day-90 decedents *N* = 158[a]	*P* value
IPA diagnosis				
ICU admission to IPA diagnosis (days)	1 [− 5.0 to 5.0]	0.0 [− 3.2 to 5.0]	1.0 [− 5.0 to 6.0]	0.920
Symptoms onset to IPA diagnosis (days)	6.0 [2–12]	6.5 [1.0–15.0]	6.0 [2.0, 12.0]	0.823
Positive fungal cultures	136 (62.1)	28 (53.8)	102 (64.6)	0.189
Positive serum antigen (> 0.5)	154 (70.3)	34 (65.4)	114 (72.2)	0.383
Associated infection				
Pulmonary bacterial infection	52 (23.7)	9 (17.3)	41 (25.9)	0.261
Non-pulmonary bacterial infection[b]	35 (16.0)	7 (13.5)	27 (17.1)	0.666
Associated fungal infection (%)	38 (17.4)	9 (17.3)	28 (17.7)	1.000
Pneumocystis jirovecii	12/38 (31.6)	2/9 (22.2)	10/28 (35.7)	0.687
Candida colonization	25/38 (65.8)	7/9 (77.8)	17/28 (60.7)	0.446
Viral pneumonia	30 (13.7)	11 (21.2)	17 (10.8)	0.063
Influenza infection	9/30 (30)	2/11 (18.2)	6/17 (35.3)	0.419
Radiologic presentation[c]				
Diffuse pattern	90/217 (41.5)	15 (28.8)	73/156 (46.8)	0.049
Focal pattern	58/217 (26.7)	19 (36.5)	36/156 (23.1)	
No specific pattern	69/217 (31.8)	18 (34.6)	47/156 (30.1)	
Pleural effusion (%)	85/217 (39.2)	20/52 (38.5)	63/156 (40.4)	0.871
Nodules (%)	105/217 (48.4)	29/52 (55.8)	72/156 (46.2)	0.264
CT ground glass opacity (%)	95/159 (59.7)	23/42 (54.8)	68/111 (61.3)	0.468
CT halo sign (%)	47/159 (29.6)	11/42 (26.2)	35/111 (31.5)	0.560
CT cavitation (%)	32/159 (20.1)	7/42 (16.7)	22/111 (19.8)	0.818
CT pulmonary infarction (%)	1/159 (0.6)	1/42 (2.4)	0/111 (0.0)	0.275
Aspergillus sinusitis	27/47 (57.4)	11/19 (57.9)	16/28 (57.1)	1.000
Cerebral involvement	18/39 (46.2)	3/6 (50)	14/31 (45.2)	1.000
Total SOFA score	9.00 [7.00, 12.00]	7.00 [5.00, 8.50]	10.00 [7.00, 13.00]	< 0.001
Need for vasopressors	159/218 (72.9)	26/52 (50.0)	128/157 (81.5)	< 0.001
Renal replacement therapy	60/216 (27.4)	15/51 (29.4)	44/156 (28.2)	0.860
Antifungal therapy				
Voriconazole	129 (58.9)	39 (75.0)	83 (52.5)	0.006
Ambisome (liposomal)	92 (42.0)	23 (44.2)	66 (41.8)	0.872
Amphotericin B (deoxycholate)	50 (22.8)	11 (21.2)	38 (24.1)	0.710
Caspofungine	38 (17.4)	7 (13.5)	28 (17.7)	0.528
Posaconazole	3 (1.4)	1 (1.9)	1 (0.6)	0.435
Itraconazole	2 (0.9)	1 (1.9)	1 (0.6)	0.435
Micafungin	1 (0.5)	0 (0.0)	1 (0.6)	1.000
Outcome variables				
ICU LOS (days)	12.00 [5.00, 21.00]	14.50 [5.75, 23.00]	11.00 [6.00, 20.50]	0.391
ICU mortality	128 (58.4)	0 (0.0)	128 (81.0)	< 0.001
Day-30 mortality	121/214 (56.5)	0 (0.0)	121 (76.6)	< 0.001

In case of missing variables, the denominator indicates the number of patients with available data

LOS length of stay

[a] Day 90 mortality was unavailable for 9 patients

[b] Non-pulmonary bacterial infections include 26 blood stream infections, 3 catheter related infections, 2 UTI, and 4 miscellaneous infections

[c] 212 thoracic chest radiographs, 159 thoracic CT, 47 sinus CT and 39 brain MRI were realized

[11, 29] has not yet shown its benefits for hematological patient admitted to the ICU.

The management of ICU patients suffering from HM and IPA constitutes a particular challenge as they stigmatize the most profound and complex forms of immunosuppression. In a recent study, IPA was strongly associated with the need for IMV in HM patients with ARF [1]. The development of antifungal prophylaxis

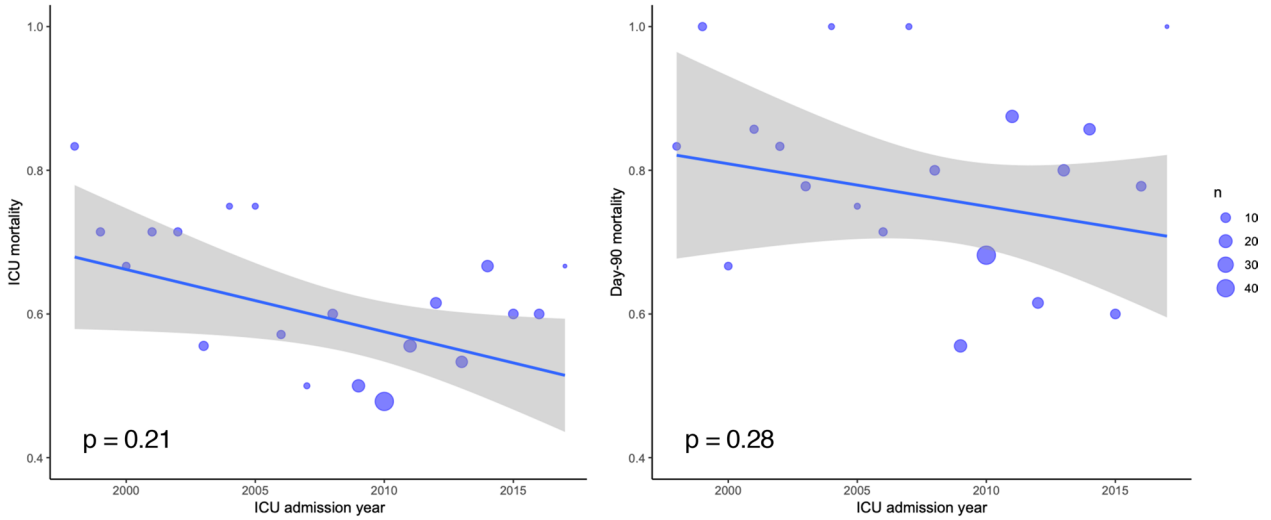

Fig. 1 Trends of ICU and day-90 mortality throughout the 20-year study period with point size relative to the number of patients included each year

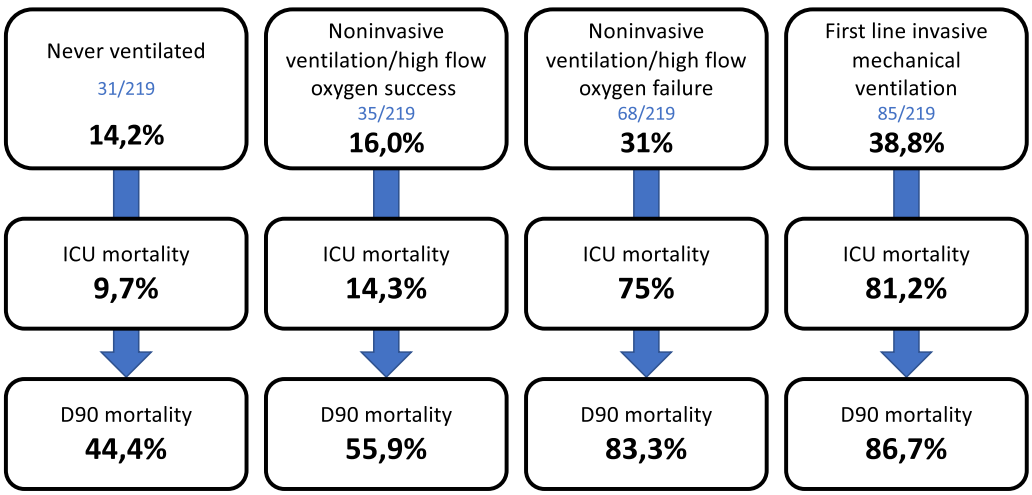

Fig. 2 Mortality according to initial ventilation strategy

for high-risk patients may have lowered the incidence of invasive fungal infections but mortality remains alarming [6]. Nevertheless, rising physician's focus on invasive fungal infections in HM patients is crucial knowing that at-risk population is constantly growing [30]. Indeed, new treatments indicated for patients with Chronic Lymphocytic Leukemia or Non-Hodgkin lymphoma may increase the incidence of opportunistic infections [31, 32]; as they may in the ageing population suffering from Myelodysplastic syndromes.

We reported that a delayed admission in the ICU of more than 5 days after respiratory symptoms onset was associated with higher day-90 mortality. This finding is consistent with the literature. Indeed, in a recent cohort of immunocompromised patients with ARF, a direct admission to the ICU resulted in a significant decrease in hospital mortality [1]. Same observation was noted among cancer patients with ARF with a lower survival rate when the time between respiratory symptoms onset and ICU admission was superior to 2 days [17]. In our cohort, patients admitted in the ICU within 5 days after symptoms onset benefited from a faster IPA diagnosis, and by proxy, a probable faster initiation of antifungal therapy. Our interpretation of these results is that faster

Table 3 Factors independently associated with 90-day mortality in IPA patients

Covariable	Hazard ratio	IC 95%	*P* value
Voriconazole use	0.49	0.34–0.73	< 0.001
SOFA score at day 1	1.07	1.02–1.12	0.005
Radiologic pattern on chest X-ray or thoracic CT (%)			
Focal pattern	Baseline		
Diffuse pattern	2.07	1.33–3.24	0.001
No specific pattern	1.13	0.70–1.83	0.619
Time between symptoms onset and ICU admission > 5 days	1.51	1.05–2.16	0.026
Year of ICU admission ≥ 2010	0.67	0.45–0.99	0.042
Ventilation strategy			
Never ventilated	Baseline		
Non-invasive ventilation/high-flow oxygen success	1.51	0.63–3.61	0.356
Non-invasive ventilation/high-flow oxygen failure	3.32	1.54–7.16	0.002
First-line invasive mechanical ventilation	3.16	1.46–6.82	0.003

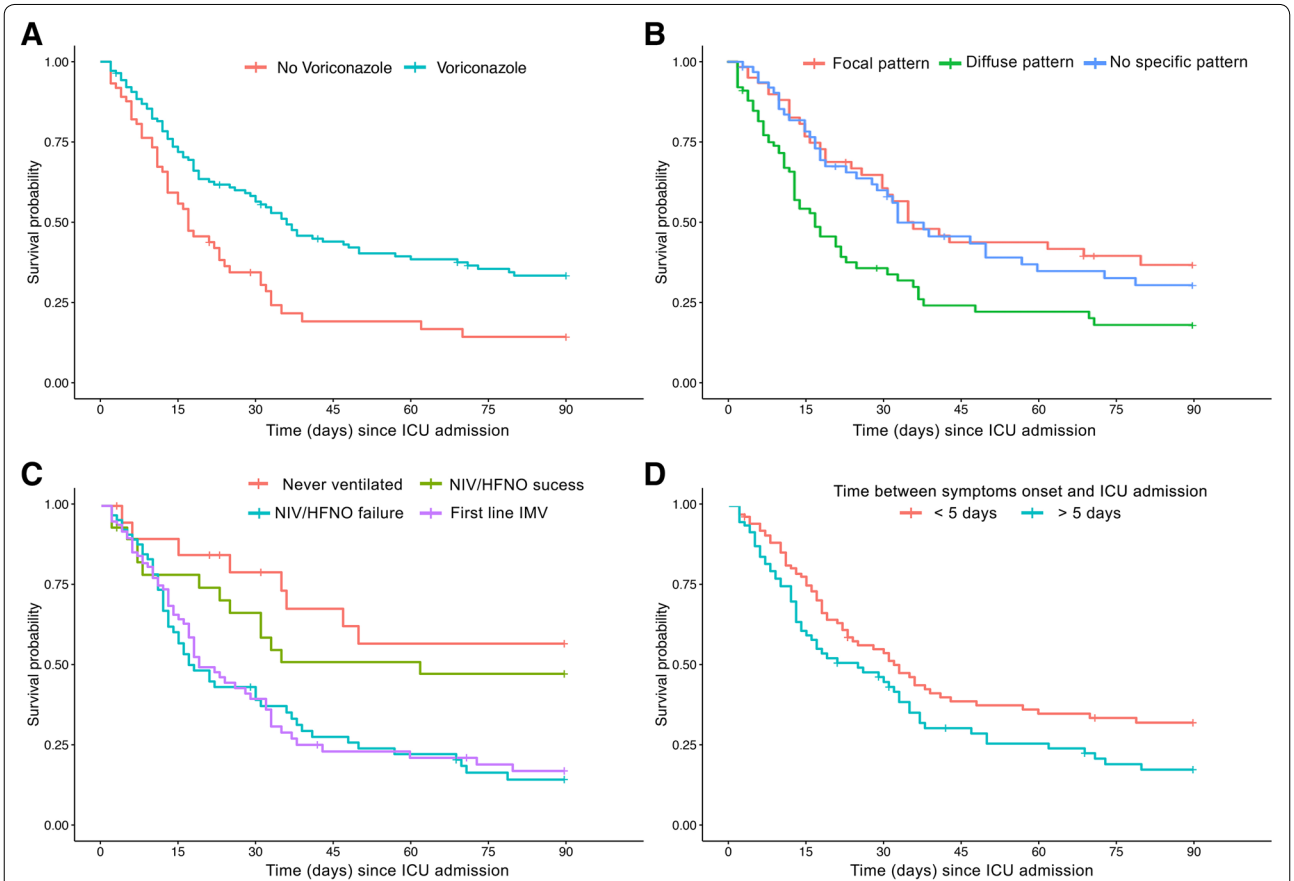

Fig. 3 Kaplan–Meier plots of adjusted cumulative survival curves as a function of time regarding voriconazole treatment (**a**), radiologic presentation (**b**), ventilation strategy (**c**) and time between symptoms onset and ICU admission (**d**). *NIV* Non-invasive ventilation, *HFNO* High-Flow Nasal Oxygen, *IMV* invasive mechanical ventilation

diagnosis and treatment initiation, made possible by accessing the technical platform available in the ICU setting, may explain partly the improved day-90 mortality associated with early admission. Faster introduction of antifungal therapy may moderate respiratory symptoms and prevent, in some cases, the introduction of invasive

mechanical ventilation, a factor highly associated with a grim prognosis. Furthermore, we believe that the time of admission in the ICU also reflects the type of IPA presentation. Late admission may be associated with more insidious and indolent forms with long term mild symptoms. These presentations could reflect a more profound or less controlled level of immunosuppression and may constitute an alarming signal announcing grim outcome. This observation is corroborated by the profound gap observed between ICU and day-90 mortality (Fig. 2), even in patients that did not require invasive respiratory support.

We also reported the negative impact of a diffuse radiologic pulmonary pattern compared to a focal pattern on patient survival. This confirms the correlation between the volume of the aspergillosis lesion and patient outcome [33]. Consequently, the necessity of conducting early CT scans on HM patients with ARF appears timely to avoid delaying diagnosis, assess treatment's response and predict patient's evolution.

Finally, voriconazole use was associated with higher survival rates in hematology patients with ARF from IPA. This is in line with a previous report from our group [12]. Hence, the superiority of voriconazole compared to other antifungal therapies is widely established and recommended outside the ICU [34, 35]. However, increasing reports mentioning azole resistance in *Aspergillus fumigatus* leading to treatment failure [36] raises concerns about the use of azole derivatives in patients previously exposed to posaconazole prophylaxis.

Strengths of our study include the large number of critically ill patients with probable or proven IPA, making this cohort the largest to date, including key messages that may remind clinicians of the specificity and complexity of critically ill hematology patients. Our results also put forward the need of early admission for at-risk patients as soon as they present signs of respiratory distress or high oxygen requirements. All physicians of hematology patients need to optimize patient trajectory and avoid delaying appropriate management, enabling a faster diagnosis and treatment initiation leading to better survival [37].

The present study has several limitations, however. First, the study design was retrospective due to the low incidence of the disease. Nevertheless, to avoid selection bias, we identified 219 patients from a dedicated study group with a majority of centers of expertise specialized in the care of hematological patients. Second, our inclusion was limited to patients in France; however, the majority of our epidemiologic observations and results are in agreement with previous data available in the literature and implies an acceptable external validity. Third, radiological signs were gathered only in exams realized in the previous or consecutive 24 h to ICU admission, which made it impossible to study the dynamic evolution of aspergillosis lesions under treatment; a useful and validated clinical information associated to patient outcomes [33, 38]. Fourth, given the retrospective study design, two major concerns had to be addressed. The first one is the inevitable omission of a few cases of probable/proven invasive aspergillosis given the high incidence of unknown cause of ARF in critically ill patients, the necessary time to identify fungal pathogen and the still insufficient number of autopsies carried out in deceased patients. Indeed, a recent study presented the results of 893 post-mortem examinations of critically ill patients over a 25-year period [39]. Only 10 of 25 (40%) patients with invasive aspergillosis were diagnosed before death. The second concern, that stems from the previous observation, is that only crude mortality, and not attributable mortality, was reported in our study. Hematological patients with ARF are often the result of multiple concomitant factors that are inseparable from each other, even in the eyes of the ICU physicians in charge of them. Assessing the causality of IPA, without an autopsy, in a deceased patient who suffered from ARF, is based on a set of arguments, including the chronology of the fungal infection and the specificity of clinical and radiological sign. To overcome this potential weakness, sustained attention was paid to report all variables that could help characterize, in the best way, the multiple factors implicated in the respiratory failure and all potential confusion factors that may have influenced patient mortality. Last, this study mentions tracheobronchial ulceration evidenced by fiberscopy or sinonasal infection as part of invasive pulmonary aspergillosis. However, according to the EORTC criteria these clinical features are suggestive of tracheobronchial aspergillosis and sinonasal aspergillosis. We do, however, consider that our patients had all invasive pulmonary aspergillosis. Indeed, all had acute respiratory failure whereas co-infections were documented in a minority of patients; data have emphasized that there were two different patterns of IPA, the halo sign being typical only in patients with neutropenia [4].; and 3/no patient had isolated sinonasal aspergillosis but only a continuum of airway-invasive aspergillosis also involving the upper respiratory tract.

In summary, IPA still mostly affects patients with neutropenia and allogeneic stem cell transplant recipients. Case fatality remains high and stable throughout the 20-year follow-up. Voriconazole treatment is associated with improved survival whereas diffuse radiologic pattern and delayed admission to the ICU are associated with a poor prognosis. Strategies to improve survival in these high-risk patients are warranted.

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
Pr. Azoulay declares having received fees for lectures and travel to conference from Pfizer, Gilead, Baxter, Alexion and Ablynx. Dr Lemiale reported being a member of a research group that has received grants from Fisher & Paykel, Alexion, Baxter, Pfizer, and Gilead. Pr. Darmon report having received consulting fees from Sanofi and Gilead-Kite, research support from Astute Medical and MSD, and speaker fees from MSD, Gilead-Kite and Astellas. Dr. De Jong reports personal fees from Baxter and Medtronic, and travel reimbursements from Fresenius-Kabi, MSD France, Astellas, Pfizer and Fisher Paykel. Other authors declare having no conflicts of interest in relation with this publication.

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