



Original Article

Elderly versus nonelderly patients with invasive aspergillosis in the ICU: a comparison and risk factor analysis for mortality from the AsplCU cohort

D. K. Matthaïou^{1,†}, G. Dimopoulos^{1,*}, F. S. Taccone², P. Bulpa³,
A. M. Van den Abeele⁴, B. Misset⁵, W. Meersseman⁶, H. Spapen⁷,
T. Cardoso⁸, P. E. Charles⁹, D. Vogelaers¹⁰, S. Blot^{10,11} and on behalf of the
AsplCU Study Investigators**

¹Department of Critical Care Medicine, Attikon University Hospital, University of Athens, Medical School, Athens, Greece, ²Department of Internal Medicine, Faculty of Medicine and Health Science, Ghent University, Ghent, Belgium, ³Department of Intensive Care, CHU Dinant-Godinne, Université Catholique de Louvain, Yvoir, Belgium, ⁴Department of Microbiology, General Hospital St. Lucas, Ghent, Belgium, ⁵Service de Réanimation Médicale, CHU de Rouen – Hôpital Charles Nicolle, Rouen, France, ⁶Medical Intensive Care Unit, University Hospital Leuven, Leuven, Belgium, ⁷Intensive Care Department, University Hospital, Vrije Universiteit, Brussels, Belgium, ⁸Department of Intensive Care (UCIP), Oporto Hospital Centre, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal, ⁹Service de Réanimation Médicale, Hôpital Bocage Central, C.H.U. Dijon, Dijon University Hospital, Dijon, France, ¹⁰Department of Internal Medicine, Faculty of Medicine & Health Science, Ghent University, Ghent, Belgium and ¹¹Burns, Trauma, and Critical Care Research Centre, The University of Queensland, Brisbane, Australia

*To whom correspondence should be addressed. George Dimopoulos, MD, PhD, Department of Critical Care Medicine, Attikon University Hospital, 1 Rimini Str., 124 62, Haidari, Greece. Tel: +30 (210) 583–2182; Fax: +30 (210) 583–2182; E-mail: gdimop@med.uoa.gr

†These authors have equally contributed to the paper.

Received 2 February 2016; Revised 1 September 2017; Accepted 17 October 2017; Editorial Decision 6 September 2017

Abstract

Data regarding the epidemiology and diagnosis of invasive aspergillosis in the critically ill population are limited, with data regarding elderly patients (≥ 75 years old) even scarcer. We aimed to further compare the epidemiology, characteristics and outcome of elderly versus nonelderly critically ill patients with invasive aspergillosis (IA) Prospective, international, multicenter observational study (AsplCU) including adult intensive care unit (ICU) patients, with a culture and/or direct examination and/or histopathological sample positive for *Aspergillus* spp. at any site. We compared clinical characteristics and outcome of IA in ICU patients using two different diagnostic algorithms. Elderly and nonelderly ICU patients with IA differed in a number of characteristics, including comorbidities, clinical features of the disease, mycology testing, and radiological findings. No difference

regarding mortality was found. According to the clinical algorithm, elderly patients were more likely to be diagnosed with putative IA. Elderly patients had less diagnostic radiological findings and when these findings were present they were detected late in the disease course. The comparison between elderly survivors and nonsurvivors demonstrated differences in clinical characteristics of the disease, affected sites and supportive therapy needed. All patients who were diagnosed with proven IA died. Increased vigilance combined with active search for mycological laboratory evidence and radiological confirmation are necessary for the timely diagnosis of IA in the elderly patient subset. Although elderly state per se is not a particular risk factor for mortality, a high SOFA score and the decision not to administer antifungal therapy may have an impact on survival of elderly patients.

Key words: galactomannan, aspergillosis, elderly, mortality, aspergillus, octogenarian.

Introduction

Invasive aspergillosis, although reported in only 1–2% of intensive care unit (ICU) patients,¹ is a diagnosis gaining increasing importance in the critical care setting.² It is associated with high mortality and considerable costs, while delays in the initiation of antifungal treatment may prolong the length of stay and further increase relevant costs.³

Thus, timely diagnosis is of paramount importance. The European Organization for Research and Treatment of Cancer (EORTC) was among the first organizations to issue diagnostic criteria for invasive fungal disease in 2002. Its most recent revision was published in 2008.⁴ According to these criteria, invasive pulmonary aspergillosis may be classified as possible, probable and proven, depending on whether host factors, clinical features and mycological criteria are present. Given that this classification was initially developed for cancer and transplanted patients, several of these criteria are not easily recognized in the critical care setting.

Other clinical scores were also developed to further facilitate the diagnosis of invasive aspergillosis. Bouza et al.⁵ developed a 5-point scale, which was based on patients hospitalized in a large tertiary teaching hospital including all types of hospitalized patients. However, this score could not be extrapolated on the critical care setting due to the differences between the general population and critically ill patients. Vandewoude et al.⁶ tried to overcome this limitation by developing an algorithm based on medical, radiological and microbiological data acquired from critically ill patients.

Recently, Blot et al. developed another clinical algorithm for the diagnosis of invasive aspergillosis, which would better fit the critically ill populations without the caveats of EORTC criteria.⁷ Under this perspective, the term “putative” aspergillosis was introduced. It was defined as such if all of the four following criteria were met: 1. There was

an *Aspergillus*-positive lower respiratory tract specimen culture as an entry criterion. 2. There were compatible signs and symptoms. 3. There was abnormal medical imaging by portable chest X-ray or CT scan of the lungs. 4. There were either host risk factors or a semi-quantitative *Aspergillus*-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae.

As data regarding the epidemiology and diagnosis of invasive aspergillosis in the critically ill population are limited, it is obvious that data regarding elderly patients, namely over 75 years old are even scarcer. Under this perspective, we aimed to further compare the epidemiology, characteristics, and outcome of elderly versus nonelderly critically ill patients with invasive aspergillosis harvested from the AspICU database, the analysis of which are extensively presented elsewhere.⁸ Additionally, we aimed to study risk factors for mortality in this particular subset population and compare two different diagnostic algorithms.

(This study was presented in part at the ESICM LIVES 2014 27th Annual Congress, Barcelona, Spain, September 2014 and at the 24th European Conference of Clinical Microbiology and Infection Diseases (ECCMID), Barcelona, Spain, May 2014.)

Methods

Study design

The data for this study come from a prospective, international, multicenter observational study that included ICU patients who had invasive aspergillosis (IA) (AspICU). There were 30 contributing ICUs from eight countries in Europe, Asia, and South America. A patient was eligible for inclusion in the study if (1) they were hospitalized in an ICU, (2) was >18 years old, (3) a culture and/or direct

examination and/or histopathological sample positive for *Aspergillus* spp. at any site. BAL galactomannan was not used as an inclusion criterion as it was not yet in practice in most centers, when the study started. For the present secondary analysis, only patients with invasive aspergillosis, proven, probable, or putative were taken into account based on the clinical algorithm. All patients judged by the principal investigators to be colonized were not included in this dataset.

The inclusion period lasted from November 2006 to January 2011. Patients diagnosed with IA *post-mortem* could be included in the study. However, patients from historical cohorts starting from January 2000 could also be included, due to the scarcity of patients in which histopathology data were available, as long as all of the requested data were available. If a patient was suspected to have IA before ICU admission, they were excluded from the study.

The study was approved by the local ethics committee/institutional review board of each participating center. No informed consent was obtained as the study was observational, and no intervention was performed regarding the management of the included patients. A complete and detailed description of the study methodology has been reported elsewhere.⁷

Collection and extraction of data

All relevant data were collected from patient medical records in each contributing center and submitted electronically to a central web-based registration system (www.aspiku.org). Data collection included demographics, comorbidities and severity scores. These scores included Acute Physiology and Chronic Health Evaluation (APACHE) II score⁹ and Sequential Organ Failure Assessment (SOFA) score.¹⁰ They were calculated on the day of ICU admission and on the day of the positive *Aspergillus* culture, respectively.

Other retrieved data included clinical signs and symptoms that were indicative of invasive fungal disease, such as refractory or recrudescing fever, pleuritic pain, dyspnea, hemoptysis or worsening lung function, techniques used to obtain samples, potentially infected sites and organs and mycological tests that would permit the diagnosis of IA, such as galactomannan (GM) measurements and *Aspergillus* polymerase chain reaction (PCR).

Data from chest X-rays and computer tomography (CT) scans were collected to suggest or make a diagnosis of probable or putative IA. When CT scans demonstrated findings such as wedge-shaped lesions, halo or air crescent-like sign, and lung cavitations or nodules, they were considered to be typical of the disease, according to EORTC criteria.⁴ Data

regarding the type and duration of antifungal therapy were also retrieved.

Definition of infection and outcomes

Acute respiratory distress syndrome (ARDS) was defined according to the criteria issued by the American-European Consensus Conference on ARDS.¹¹ Sepsis was defined according to criteria issued by the International Sepsis Definitions Conference.¹²

GM test was reported positive when it had an optical density index of more than 0.5.¹³ Other laboratory tests were interpreted according to criteria issued by international consensus groups.^{4,14}

The clinical diagnosis was decided by the attending physician. However, all diagnoses were reassessed by a central committee, which used both the EORTC⁴ and Clinical⁷ algorithms. The diagnostic criteria for IPA according to the EORTC and the Clinical Algorithm are summarized in Table 1. The diagnosis of IA was proven, probable and proven, or putative for each of the aforementioned algorithms, respectively. The classification of IA as proven is identical in both algorithms. However, the difference in the criteria of probable IA between the algorithms necessitated the renaming of probable IA to putative IA to avoid using the same term.

Various outcome parameters were collected including mortality at the end of observation, and length of ICU stay. The time of diagnosis of IA was considered as the date of the first positive *Aspergillus* culture or as the date of clinical deterioration compatible with invasive aspergillosis in case of *post-mortem* diagnosis.

Statistical analysis

Descriptive statistics are reported as number (%), mean ($\pm$ standard deviation), or median (interquartile range, i.e., 1st, 3rd quartile). The normality of distribution of the variables in each group was examined with the Kolmogorov-Smirnov test. The association of normally distributed continuous variables with a statistically significant difference between the groups was assessed with the use of Student's *t*-test, while for non-normally distributed variables Mann-Whitney *U* test was used. For dichotomous variables, χ^2 or Fisher's exact test was used. Variables found to be significantly different in the mortality bivariate analysis were entered in a multivariate logistic regression model. For all tests performed, a two-tailed $P \leq .05$ was considered to denote statistical significance. For all the analyses performed, the statistical software IBM SPSS Statistics for Macintosh, Version 22.0. (IBM Corp., Armonk, NY, USA) was employed.

Table 1. Diagnostic criteria for invasive pulmonary aspergillosis according to the European Organization for the Research and Treatment of Cancer/Mycosis Study Group and the Clinical Algorithm.**EORTC/MSG criteria***Proven invasive pulmonary aspergillosis*

Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of *Aspergillus* by culture of a specimen obtained by lung biopsy

Probable invasive pulmonary aspergillosis (all three criteria must be met)

1. Host factors (one of the following)
 - Recent history of neutropenia (<500 neutrophils/mm³) for 110 d
 - Receipt of an allogeneic stem cell transplant
 - Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for 13 wk
 - Treatment with other recognized T-cell immunosuppressants
 - Inherited severe immunodeficiency
2. Clinical features (one of the following three signs on CT)
 - Dense, well-circumscribed lesion(s) with or without a halo sign
 - Air crescent sign
 - Cavity
3. Mycological criteria (one of the following)
 - Direct test (cytology, direct microscopy, or culture) on sputum, BAL fluid, bronchial brush indicating presence of fungal elements or culture recovery *Aspergillus* spp.
 - Indirect tests (detection of antigen or cell-wall constituents): galactomannan antigen detected in plasma, serum, or BAL fluid

Possible invasive pulmonary aspergillosis

Presence of host factors and clinical features (cf. probable invasive aspergillosis) but in the absence of or negative mycological findings.

Alternative clinical algorithm*Proven invasive pulmonary aspergillosis*

Idem EORTC/MSG criteria

Putative invasive pulmonary aspergillosis (all four criteria must be met)

1. *Aspergillus*-positive lower respiratory tract specimen culture (=entry criterion)
2. Compatible signs and symptoms (one of the following)
 - Fever refractory to at least 3 d of appropriate antibiotic therapy
 - Recrudescence fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
 - Pleuritic chest pain
 - Pleuritic rub
 - Dyspnea
 - Hemoptysis
 - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs
4. Either 4a or 4b
 - 4a. Host risk factors (one of the following conditions)
 - Neutropenia (absolute neutrophil count < 500 /mm³) preceding or at the time of ICU admission
 - Underlying hematological or oncological malignancy treated with cytotoxic agents
 - Glucocorticoid treatment (prednisone equivalent, > 20 mg/d)
 - Congenital or acquired immunodeficiency
 - 4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

Aspergillus respiratory tract colonization

When ≥ 1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as *Aspergillus* colonization.

BAL, bronchoalveolar lavage; CT, computed tomography; EORTC/MSG, European Organization for the Research and Treatment of Cancer/Mycosis Study Group; ICU, intensive care unit; IPA, invasive pulmonary aspergillosis.

Results

General characteristics of the cohort

Two hundred and ninety-two ICU patients were included in our study. One hundred seventy-eight (61%) were males, and the mean age of the cohort was 61.6 ± 14.7 years. Two hundred and thirty-four (80.1%) were medical admissions, 60 (20.6%) underwent emergency or elective surgery, five (1.7%) were trauma patients, and one (0.3%) had burns. Two hundred seventy-seven (94.9%) had a comorbidity upon admission, while 138 (47.3%) were septic upon ICU admission. The median APACHE II score upon admission was 24 [17, 29], and the median SOFA score on diagnosis of IA was 10 [6, 12.75], while the median length of ICU stay was 16 [9, 34] days. Two hundred and six out of 285 (72.3%) died before the end of the observation period (data for seven patients were missing).

The affected sites were the lung in 284 cases, trachea in 37, sinus in 3, brain in 10, abdomen in 9 (liver in 5, spleen in 2, kidney in 3, pancreas in 1, gastrointestinal tract in 1, peritoneum in 2, and other in 2), skin in 1, wound in 3, empyema in 3, and intravascular in 7 (endocarditis in 7, and pericarditis in 2). The sum exceeds the total number of cases, as several of them were cases with disseminated aspergillosis.

Risk profile and clinical presentation of elderly and nonelderly

The cohort was split and further analyzed according to the limit of 75 years of age, with patients over this limit characterized as elderly. Fifty-four out of 292 (18.5%) were elderly, while 238/292 (81.5%) were nonelderly. The mean age of the two groups were 79.5 ± 4.9 and 57.5 ± 13.1 years, respectively. Thirty-nine out of 53 (73.6%) and 167/232 (72%) died before the end of the observation period, respectively. Forty-seven out of 54 (87%) and 216/238 (90.8%) needed supportive therapy. The median length of stay for each group was 16 days [6, 34] and 16 days [9, 34], respectively.

Variables that were significantly different between elderly and nonelderly ICU patients with IA in the ICU, as well as outcomes and a comparison between EORTC and the clinical algorithms are summarized in Table 2. Elderly ICU patients were more likely to suffer from diabetes mellitus and chronic obstructive pulmonary disease. Nonelderly ICU patients were more likely to have received a solid organ transplant and lung transplant, in particular. Nonelderly patients were more likely to have fever that was refractory to at least 3 days of appropriate antibiotic therapy. Furthermore, the decision to commence antifungal therapy was more likely for nonelderly patients, either empirical or

definitive depending on the certainty of diagnosis according to the definitions used.

Regarding the comparison between EORTC and the clinical algorithms, nonelderly patients were more likely to have an EORTC host factor present, namely, to receive a solid organ transplant, and be diagnosed with proven IA according to both algorithms. On the other hand, elderly patients were more likely to be diagnosed as not classifiable according to EORTC but with putative IA according to the clinical algorithm. There was no difference in validation on histology-controlled cases between elderly and nonelderly of the two algorithms.

When comparing laboratory techniques, nonelderly patients were more likely to have a broncho-alveolar lavage (BAL) performed. They were also more likely to yield a BAL positive culture. Furthermore, nonelderly were more likely to have a positive direct microscopy of any sample, as well as a positive GM test.

Elderly patients were more likely to have a normal chest X-ray, but were also more likely to manifest the air crescent-like sign, both in CT alone and in CT and chest X-ray combined. When assessing CT and chest X ray in combination, elderly patients were also more likely to manifest the halo sign. Although elderly patients were less likely to receive supportive therapy and to have antifungal treatment initiated, the mortality between the groups was similar at the end of observation.

Outcomes between survivors and non-survivors in the elderly group

Data for 53 patients out of 54 in the elderly group were available for outcome calculations. Thirty-nine (73.6%) of them died before the end of the observation period. Forty-two (79.2%) patients were medical admissions, 11 (20.8%) were surgical admissions, and 1 (1.9%) had burns. Fifty-one patients (96.2%) had a comorbidity upon admission, while 27 (50.9%) were septic upon ICU admission. The APACHE II score upon admission was 25 [20, 30.25] and the SOFA score on diagnosis of IA was 8 [5.75, 12], while the length of ICU stay was 22.8 ± 25.2 days. The mean age was 78.9 ± 4.3 years for nonsurvivors and was 81 ± 6.2 years for survivors.

Risk factors for mortality in elderly ICU patients with IA are summarized in Table 3. Nonsurvivors had a higher SOFA score and were more likely to be diagnosed as having probable or proven aspergillosis according to the clinical judgment of the attending physician, irrespective of the final diagnosis that was done by the head-investigators based on all the available data. Thus, they were more likely to start antifungal treatment. They were also more likely to have fever that was refractory to at least 3 days of appropriate

Table 2. Comparison between elderly (>75 years old) and nonelderly (<75 years old) patients with aspergillosis in the ICU.

	Elderly [n/N (%)]	Nonelderly [n/N (%)]	P
Comorbidities			
Diabetes mellitus	14/54 (25.9)	38/238 (16)	.04
COPD	25/54 (46.3)	74/238 (31.1)	.03
Solid organ transplant	1/54 (1.9)	46/238 (19.3)	.002
Lung transplant	0/54 (0)	18/238 (7.6)	.03
Immunosuppressive drug for autoimmune disease	0/54 (0)	16/238 (6.7)	.05
Clinical characteristics			
Fever refractory to at least 3 days of appropriate antibiotic therapy	12/54 (22.2)	106/238 (44.5)	.003
Decision to start antifungal therapy			.02
No, not considered necessary	19/54 (35.2)	36/238 (15.1)	
No, because of therapy withdrawal	2/54 (3.7)	9/238 (3.8)	
No, because post-mortem diagnosis	3/54 (5.6)	5/238 (2.1)	
Diagnostic algorithms			
EORTC host factor present	31/54 (57.4)	175/238 (73.5)	.02
Prolonged neutropenia	0/54 (0)	1/238 (0.4)	1
Solid organ transplant	1/54 (1.9)	46/238 (19.3)	.02
Corticosteroid prolonged use	24/54 (44.4)	115/238 (48.3)	.61
Immunosuppressive drugs	6/54 (11.1)	45/238 (18.9)	.17
HIV	0/54 (0)	2/238 (0.8)	1
Bone marrow transplant	0/54 (0)	5/238 (2.1)	.59
Diagnosis according to EORTC			
Not classifiable	38/54 (70.4)	132/238 (55.5)	.04
Probable IA	6/54 (11.1)	24/238 (10.1)	.82
Proven IA	10/54 (18.5)	82/238 (34.5)	.02
Diagnosis according to the clinical algorithm			
Colonization	1/54 (1.9)	1/238 (0.4)	.67
Putative IA	43/54 (79.6)	155/238 (65.1)	.04
Proven IA	10/54 (18.5)	82/238 (34.5)	.02
Mycology testing			
BAL performed	23/54 (42.6)	145/238 (60.9)	.01
BAL culture (+)	14/23 (60.9)	121/144 (84)	.02
Positive direct microscopy of any sample	25/51 (49)	132/206 (64.1)	.05
Galactomannan	10/25 (40)	64/94 (68.1)	.01
Radiology			
Chest X-ray normal	3/54 (5.6)	1/238 (0.4)	.02
CT chest air crescent-like sign	3/54 (5.6)	2/238 (0.8)	.05
CT or Chest X-ray air crescent-like sign	2/13 (15.4)	1/86 (1.2)	.05
CT or Chest X-ray halo sign	3/13 (23.1)	3/86 (3.5)	.03
Patient management and outcomes			
Outcome supportive therapy - none	7/54 (13)	10/238 (4.2)	.02
Antifungal therapy initiated	34/54 (63)	189/238 (79.4)	.01
Mortality at the end of observation	39/53 (73.6)	167/232 (72)	.81

BAL, broncho-alveolar lavage; COPD, chronic obstructive pulmonary disease; CT, computed tomography; IA, invasive aspergillosis; IPA, invasive pulmonary aspergillosis;

Table 3. Risk factors for mortality in elderly (>75 years old) patients with aspergillosis in the ICU.

	Dead [n/N (%)]	Alive [n/N (%)]	P
Clinical characteristics			
SOFA score	10 [6,13]	5.5 [2.75,6.25]	.001
Clinical judgement according to the attending physician			
Colonization	7/39 (17.9)	11/14 (78.6)	
Possible aspergillosis	2/39 (5.1)	2/14 (14.3)	<.001
Probable aspergillosis	20/39 (51.3)	1/14 (7.1)	
Proven aspergillosis	10/39 (25.6)	0/14 (0)	
Decision to start antifungal therapy			
Yes	27/39 (69.2)	2/14 (14.3)	
No, not considered necessary	7/39 (17.9)	12/14 (85.7)	<.001
No, because of therapy withdrawal	2/39 (5.1)	0/14 (0)	
No, because <i>post-mortem</i> diagnosis	3/39 (7.7)	0/14 (0)	
Fever refractory to at least 3 days of appropriate antibiotic therapy	11/39 (28.2)	0/14 (0)	.03
Dyspnoea	20/39 (51.3)	12/14 (85.7)	.02
Worsening respiratory insufficiency in spite of appropriate antibiotics and ventilation support	26/39 (66.7)	3/14 (21.4)	.004
Diagnostic algorithms			
Diagnosis not classifiable according to EORTC	24/39 (61.5)	13/14 (92.9)	.04
Diagnosis according to the clinical algorithm			
Colonization	0/39 (0)	1/14 (7.1)	.53
Putative invasive aspergillosis	29/39 (74.4)	13/14 (92.9)	.28
Proven invasive aspergillosis	10/39 (25.6)	0/14 (0)	.07
Histology performed (autopsy or biopsy)	14/39 (35.9)	0/14 (0)	.01
Supportive therapy			
Supportive therapy: none	1/39 (2.6)	6/14 (42.9)	.001
Supportive therapy: mechanical ventilation	38/39 (97.4)	8/14 (57.1)	.001
Supportive therapy: hemodynamic support	30/39 (76.9)	5/14 (35.7)	.01
Supportive therapy: renal replacement	18/39 (46.2)	2/14 (14.3)	.04
Antifungal therapy initiated	31/39 (79.5)	2/14 (14.3)	<.001
Mycology testing			
Sputum sample	3/39 (7.7)	5/14 (35.7)	.02
Endotracheal aspirate sample	34/39 (87.2)	7/14 (50)	.008
Affected sites			
Affected site – trachea	3/39 (7.7)	8/14 (57.1)	<.001
Supportive therapy			
Outcome Supportive therapy: none	1/39 (2.6)	6/14 (42.9)	.001
Outcome Supportive therapy: hemodynamic	36/39 (92.3)	6/14 (42.9)	<.001
Outcome Supportive therapy: mechanical ventilation	38/39 (97.4)	8/14 (57.1)	.001
Outcome Supportive therapy: renal replacement therapy	20/39 (51.3)	2/14 (14.3)	.02
Time to diagnosis			
Time from ICU admission	23.9 ± 26.1	91 ± 11.7	<.001
Time from 1st positive culture	12.9 ± 12.7	82.6 ± 1	<.001

EORTC, European Organization for Research and Treatment of Cancer; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

antibiotic therapy and to show worsening respiratory insufficiency in spite of appropriate antibiotics and ventilation support. It should be noted that all patients who were diagnosed with proven IA died.

Regarding the comparison between EORTC and the clinical algorithms, survivors were more likely to be diagnosed as not classifiable according to EORTC. On the other hand, there was no difference in the diagnosis according to the clinical algorithm, although nonsurvivors were more likely to be diagnosed with proven IA with marginal non-statistically significant difference. Besides autopsy, histology testing on biopsies was also solely performed on nonsurvivors.

As expected, nonsurvivors were more likely to receive various types of supportive therapy, including mechanical ventilation, hemodynamic support, and renal replacement therapy, if compared to survivors. Also, survivors were less likely to have antifungal therapy initiated.

Survivors were more likely to have a sputum sample, but not an endotracheal aspirate sample, tested. They were also more likely to be infected at the trachea. Lastly, survivors took longer to be diagnosed from ICU admission or from first positive culture.

A logistic regression including all potential risk factors for mortality could not be performed, as they were too many to allow a meaningful analysis. However, in a model including SOFA, which essentially depicts the patient's overall organ status, and the decision to start antifungal treatment, both of them were found to be statistically significant, with odds ratios of 1.55 (95% confidence interval [CI] 1.18–2.05, $P = .002$), and 0.27 (95% CI 0.08–0.86, $P = .03$), respectively.

Discussion

The main findings of our study were that elderly and nonelderly ICU patients with IA differed in a number of factors, including comorbidities, clinical characteristics of the disease, mycology testing, and radiological findings. However, no difference regarding mortality was found. According to the EORTC criteria, only 16 out of 54 elderly patients were diagnosed with IA (10 proven and 6 probable IA); in contrast, most of them (43/54 patients) were considered to have putative IA following the diagnostic approach of the clinical algorithm. The fact that elderly patients had less diagnostic radiological and biological findings could account for these discrepancies and suggest that IA is maybe underdiagnosed in this setting, thus emphasizing the potential interest of our clinical algorithm. Regarding the comparison between elderly survivors and nonsurvivors, there were differences in clinical characteristics of the disease, affected sites and supportive therapy needed.

There was an inconsistency in the classification of patients with IA between the two algorithms used. Elderly patients were considered as being not classifiable in 70.4%, and as having probable IA in 11.1% of the cases when EORTC classification was used. On the other hand, elderly patients were considered as being colonized in 1.9%, and as having putative IA in 79.6% of the cases when clinical algorithm was used. This discrepancy is expected, though, as the clinical algorithm has a much broader definition for putative IA, including clinical and radiological criteria, which are lacking in EORTC definitions. It should be noted that the clinical features of the EORTC are very robust findings that are very suggestive for invasive fungal disease, including dense well-circumscribed lesions with or without a halo sign or air-crescent sign or cavity on CT. The clinical algorithm is just much less strict and takes any radiologic abnormality into account. This difference may be further explained by the fact that elderly patients lacked usually reported host factors, including prolonged neutropenia, receipt of an allogeneic stem cell transplant, prolonged use of corticosteroids, treatment with immunosuppressants, and inherited severe immunodeficiency in more than 40% of the cases. Of interest is the fact that there is one patient judged by the clinical algorithm to be colonized. The same patient is the only one that had probable IPA according to EORTC but was not classified as putative due to lack of clinical signs and symptoms.

There are other clinical conditions such as chronic obstructive pulmonary disease and decompensated liver disease^{15–21} that may predispose to IA through the immunosuppression they may cause. However, these conditions are not included in any of the diagnostic algorithms, although clinical algorithm requires clinical signs that may be part of the clinical course of these diseases. Thus, the probability of elderly patients having IA goes unnoticed in the absence of other criteria.

Another important factor that may contribute to the acquisition of IA is immunosenescence that is closely related per se with aging.²² Elderly patients may not be able to manifest clear clinical symptoms that directly refer to IA. Instead, they have nonspecific symptoms such as refractory fever despite antibiotic therapy. This, combined with the reduced presence of positive mycology testing or radiological findings compared to nonelderly patients, as in our cohort, may further hinder the finding of a diagnosis. Elderly patients in our cohort were more likely to have a halo or an air crescent-like sign in the chest X-ray and CT scan. It should be noted that, although the halo sign presents early in the clinical course of the disease,^{23,24} the air crescent-like sign is a late sign that may be found 1 to 2 weeks after the appearance of the halo sign.^{25,26} Thus, early CT scans should be done in patients who do not improve despite

antibiotics. This is of great importance, given that in our cohort elderly patients were less likely to have a positive direct microscopy, a positive BAL culture or a positive GM test compared to nonelderly patients.

The risk factor analysis for mortality in the elderly subset showed that nonsurvivors were more critically ill. They had a SOFA score twice as high compared to the survivor group. As expected, they were more likely to manifest non-specific signs such as refractory fever to at least 3 days of appropriate antibiotic therapy and worsening respiratory insufficiency despite the appropriate antibiotic treatment and ventilation support. Consequently, they were in need of multifaceted supportive treatment, including mechanical ventilation, hemodynamic support and renal replacement. This fact was also reflected on the lower rates of deciding not to start antifungal therapy since a bad outcome was expected regardless of therapy. It should be noted that none of the nonsurvivors were classified as being colonized. All of them were diagnosed as having putative or proven IA, according to the clinical algorithm.

According to our results, age does not seem to be an important determinant of outcome both in elderly and nonelderly patients, as mortality was similar denoting a bad prognosis. However, the logistic regression for mortality in the elderly group found that the patient's status and the decision to start antifungal treatment are strong predictors of mortality. It should be noted that almost for one out of five elderly patients who eventually died, the clinical decision not to start antifungal therapy was based on an *Aspergillus* colonization patient status, although according to the clinical algorithm no patient of this group could be classified as such. This fact may indicate that the administration of antifungal treatment even when the elderly patients do not seem to be infected may have an important role on survival.

There have been several studies assessing various other types of infection including nosocomial bloodstream infection, and ventilator-associated pneumonia.^{27–30} However, this is the first study, to our knowledge, focusing on the differences between elderly and nonelderly patients with invasive aspergillosis in such detail, although there have been studies examining individual aspects of the disease in the elderly, such as attributable mortality and excess in length of stay,³¹ or the involvement of organs other than the lungs, such as the brain.³²

Additional strengths of this study include the large size of the cohort, which included only histopathology-controlled cases, as well as the fact that to our knowledge there are no other studies focusing on elderly critically ill patients with IA. Also, it is a multicenter study, encompassing 30 centers from eight different countries, which greatly supports the validity and the generalizability of the results.

However, there are several limitations of the study that should be considered. First, the sample size was relatively small due to several reasons. There was a selection bias due to the inclusion of cases that had a positive *Aspergillus* culture, although all patients with IA were included without a focus on lung involvement. However, patients with suspected disease based on radiological imaging or biomarkers were excluded. As a result several potentially evaluable cases may have been missed. Another criterion that could potentially increase and empower our cohort would be the routine autopsy or biopsy, as autopsy studies have shown that IA is the most frequently missed infectious diagnosis in patients requiring ICU admission.^{33–35} However, it should be noted that false-negative histology on lung biopsies may occur and could compromise our findings. Also, BAL was not routinely performed in all patients, creating the risk of missing potential cases with putative IA when no positive histology data were available. Furthermore, not all patients had CT scans and GM measurements. The reason for the scarcity of GM measurements may be attributed to the cost of the procedure and the fact that the study commenced before the publication of the most important papers assessing the role of GM in the critical care setting.^{13,36} Lastly, the study assessed overall mortality, but not attributable mortality to the infection, which could overestimate our findings.

As invasive aspergillosis is a disease of growing incidence in the critical care setting combined with the increasing age of patients admitted in the ICU, it is of great importance to acknowledge the differences between elderly and nonelderly ICU patients with IA. Elderly patients may present with IA without any clear signs that indicate the diagnosis. Interestingly, there was no difference in survival between elderly and non-elderly, indicating that elderly state per se is not a particular risk factor for mortality. In contrast, a high SOFA score and the decision not to administer antifungal therapy may have a negative impact on survival of elderly patients. Increased vigilance along with active search for mycological evidence and radiological confirmation are crucial for the timely diagnosis of in the elderly patient subset.

Acknowledgments

D.K.M. analyzed the data and drafted the manuscript. G.D., F.S.T., P.B., A.M.V.d.A., B.M., W.M., H.S., T.C., P.E.C., D.V., and S.B. had active involvement in patient recruitment, collection of data and reviewed the final version of the manuscript. H.S. served as a consultant for Pfizer and received honoraria for presentations. P.E.C. received grants from Pfizer and Sage and honoraria from Merck, Astellas, ThermoFisher Diagnostic. He also served as a speaker forum for Merck and as a consultant for ThermoFisher Diagnostic. S.B. holds a research mandate at Ghent University (Special Research Fund). The AspICU project is endorsed by an unrestricted grant by Pfizer and a research grant from the Special Research Fund of Ghent

University. The sponsor had no role in the design of the study whatsoever. All authors approved the manuscript in its final form.

Funding

Supported by an unrestricted educational grant from Pfizer Belgium and a research grant from the Special Research Fund of Ghent University. The AspICU project is endorsed by the European Critical Care Research Network (ECCRN) of the European Society of Intensive Care Medicine (ESICM).

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References

- Vincent JL, Sakr Y, Sprung CL et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006; 34: 344–353.
- Meersseman W, Van Wijngaerden E. Invasive aspergillosis in the ICU: an emerging disease. *Intensive Care Med.* 2007; 33: 1679–1681.
- Baddley JW, Stephens JM, Ji X, Gao X, Schlamm HT, Tarallo M. Aspergillosis in Intensive Care Unit (ICU) patients: epidemiology and economic outcomes. *BMC Infect Dis.* 2013; 13: 29.
- De Pauw B, Walsh TJ, Donnelly JP et al. Revised Definitions of Invasive Fungal Disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* 2008; 46: 1813–1821.
- Bouza E, Guinea J, Pelaez T, Perez-Molina J, Alcalá L, Muñoz P. Workload due to *Aspergillus fumigatus* and significance of the organism in the microbiology laboratory of a general hospital. *J Clin Microbiol.* 2005; 43: 2075–2079.
- Vandewoude KH, Blot SI, Depuydt P et al. Clinical relevance of *Aspergillus* isolation from respiratory tract samples in critically ill patients. *Crit Care.* 2006; 10: R31.
- Blot SI, Taccone FS, Van den Abeele AM et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. *Am J Respir Crit Care Med.* 2012; 186: 56–64.
- Taccone FS, Van den Abeele AM, Bulp P et al. Epidemiology of invasive aspergillosis in critically ill patients: clinical presentation, underlying conditions, and outcomes. *Crit Care.* 2015; 19: 7.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985; 13: 818–829.
- Vincent JL, Moreno R, Takala J et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996; 22: 707–710.
- Bernard GR, Artigas A, Brigham KL et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. *Intensive Care Med.* 1994; 20: 225–232.
- Levy MM, Fink MP, Marshall JC et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Intensive Care Med.* 2003; 29: 530–538.
- Meersseman W, Lagrou K, Maertens J et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. *Am J Respir Crit Care Med.* 2008; 177: 27–34.
- Ascioglu S, Rex JH, de Pauw B et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis.* 2002; 34: 7–14.
- Koulenti D, Garnacho-Montero J, Blot S. Approach to invasive pulmonary aspergillosis in critically ill patients. *Curr Opin Infect Dis.* 2014; 27: 174–183.
- Russo A, Giuliano S, Vena A et al. Predictors of mortality in non-neutropenic patients with invasive pulmonary aspergillosis: does galactomannan have a role? *Diagn Microbiol Infect Dis.* 2014; 80: 83–86.
- Aliyali M, Hedayati MT, Habibi MR, Khodavaisy S. Clinical risk factors and bronchoscopic features of invasive aspergillosis in intensive care unit patients. *J Prev Med Hyg.* 2013; 54: 80–82.
- Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax.* 2015; 70: 270–277.
- Koulenti D, Vogelaers D, Blot S. What's new in invasive pulmonary aspergillosis in the critically ill. *Intensive Care Med.* 2014; 40: 723–726.
- Lugosi M, Alberti C, Zahar JR et al. *Aspergillus* in the lower respiratory tract of immunocompetent critically ill patients. *J Infect.* 2014; 69: 284–292.
- Vandewoude K, Blot S, Benoit D, Depuydt P, Vogelaers D, Colardyn F. Invasive aspergillosis in critically ill patients: analysis of risk factors for acquisition and mortality. *Acta Clin Belg.* 2004; 59: 251–257.
- Gavazzi G, Krause KH. Ageing and infection. *Lancet Infect Dis.* 2002; 2: 659–666.
- Blum U, Windfuhr M, Buitrago-Tellez C, Sigmund G, Herbst EW, Langer M. Invasive pulmonary aspergillosis. MRI, CT, and plain radiographic findings and their contribution for early diagnosis. *Chest.* 1994; 106: 1156–1161.
- Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS. Invasive pulmonary aspergillosis in acute leukemia: the contribution of CT to early diagnosis and aggressive management. *Chest.* 1987; 92: 95–99.
- Abramson S. The Air Crescent Sign. *Radiology.* 2001; 218: 230–232.
- Horger M, Hebart H, Einsele H et al. Initial CT manifestations of invasive pulmonary aspergillosis in 45 non-HIV immunocompromised patients: association with patient outcome? *Eur J Radiol.* 2005; 55: 437–444.
- Blot S, Cankurtaran M, Petrovic M et al. Epidemiology and outcome of nosocomial bloodstream infection in elderly critically ill patients: a comparison between middle-aged, old, and very old patients. *Crit Care Med.* 2009; 37: 1634–1641.
- Blot S, Koulenti D, Dimopoulos G et al. Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old, and very old critically ill patients*. *Crit Care Med.* 2014; 42: 601–609.
- Dimopoulos G, Koulenti D, Blot S et al. Critically ill elderly adults with infection: analysis of the extended prevalence of infection in intensive care study. *J Am Geriatr Soc.* 2013; 61: 2065–2071.
- Reunes S, Rombaut V, Vogelaers D et al. Risk factors and mortality for nosocomial bloodstream infections in elderly patients. *Eur J Intern Med.* 2011; 22: e39–44.
- Vandewoude KH, Blot SI, Benoit D, Colardyn F, Vogelaers D. Invasive aspergillosis in critically ill patients: attributable mortality and excesses in length of ICU stay and ventilator dependence. *J Hosp Infect.* 2004; 56: 269–276.
- Spapen H, Spapen J, Taccone FS et al. Cerebral aspergillosis in adult critically ill patients: a descriptive report of 10 patients from the AspICU cohort. *Int J Antimicrob Agents.* 2014; 43: 165–169.
- Dimopoulos G, Piagnerelli M, Berre J, Eddafali B, Salmon I, Vincent JL. Disseminated aspergillosis in intensive care unit patients: an autopsy study. *J Chemother.* 2003; 15: 71–75.
- Robinett KS, Weiler B, Verceles AC. Invasive aspergillosis masquerading as catastrophic antiphospholipid syndrome. *Am J Crit Care.* 2013; 22: 448–451.
- Winters B, Custer J, Galvagno SM, Jr., et al. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. *BMJ Qual Saf.* 2012; 21: 894–902.
- He H, Ding L, Chang S, Li F, Zhan Q. Value of consecutive galactomannan determinations for the diagnosis and prognosis of invasive pulmonary aspergillosis in critically ill chronic obstructive pulmonary disease. *Med Mycol.* 2011; 49: 345–351.

Appendix

****The AspICU study investigators**

Miguel Blasco-Navalpotro, Hospital Universitario Severo Ochoa (Madrid, Spain), Stijn Blot, Ghent University (Ghent, Belgium), Nele Brusselaers, Ghent University Hospital, (Ghent, Belgium), Pierre Bulpa, CHU Dinant-Godinne (Yvoir, Belgium), Teresa Cardoso, Hospital de Santo Antonio (Porto, Portugal), Pierre-Emmanuel Charles, Dijon University Hospital (Dijon, France), Didier Clause, Cliniques de l'Europe (Brussels, Belgium), Patricia Courouble, Cliniques Universitaires Saint Luc (Brussels, Belgium), Emmanuel De Laere, Heilig Hartziekenhuis Roeselaere-Menen (Roeselaere, Belgium), Frédéric De Leener, CHR-St-Joseph (Warquignies, Belgium), George Dimopoulos, University Hospital Attikon (Athens, Greece), Frédéric Forêt, Centre Hôpitalier Régional Mons-Warquignies (Mons, Belgium), Dan Li, Shanghai Public Health Clinical Center (Shanghai, China), Claude Martin, Assistance publique hôpitaux

the Marseille, (Marseille, France), Shahram Mashayekhi, Centre Hospitalier Grand Hornu (Hornu, Belgium), Wouter Meersseman, Universitair Ziekenhuis Gasthuisberg (Leuven, Belgium), Benoit Misset, Hôpital Saint-Joseph (Paris, France), José Artur Paiva, Hospital de Sao Joao, (Porto, Portugal), Alessandro Pasqualotto, Santa Casa-Complexo Hospitalar (Porto Alegre, Brazil), Marcos Pérez, Vall d'Hebron University Hospital (Barcelona, Spain), Ratna Rao, Apollo Hospital (Hyderabad, India), Jordi Rello, Joan XXIII University Hospital (Tarragona, Spain) and Vall d'Hebron University Hospital (Barcelona, Spain), Jessica Souto, Vall d'Hebron University Hospital (Barcelona, Spain), Herbert Spapen, Brussels University Hospital (Brussels, Belgium), Fabio Silvio Taccone, Hôpital Erasme (Brussels, Belgium), Anne-Marie Van den Abeele, AZ Sint Lucas, (Ghent, Belgium), Koenraad Vandewoude, Ghent University Hospital, (Ghent, Belgium), Dirk Vogelaers, Ghent University Hospital (Ghent, Belgium).