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TITLE: INVASIVE PULMONARY ASPERGILLOSIS IN SOLID ORGAN TRANSPLANT PATIENTS IN THE ICU

KEYWORDS: *Aspergillus;* aspergillosis*;* solid organ recipient; transplantation; intensive care; mortality

RUNNING TITLE: Aspergillosis in solid organ transplants

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/tid.13746.

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ABSTRACT

Introduction: Solid organ transplantation (SOT) is a well-known risk factor for invasive pulmonary aspergillosis (IPA). We report on the epidemiology and outcome of SOT patients with IPA in an ICU setting.

Methods: This is a secondary study based on a subset of SOT-patients from a prospective observational multicenter cohort (the *Asp*ICU project) including ICU patients with at least one *Aspergillus* spp. positive culture. Cases were classified as proven, probable, or putative IPA, or as *Aspergillus*-colonized. Mortality was reported at 12 weeks.

Results: The study included 52 SOT-patients (of which 18 lung , 17 liver , 12 kidney and 5 heart transplants. Sixteen patients had proven IPA, 28 were categorized as putative IPA (of which only 5 reached a probable IPA diagnosis according to EORTC/MSGERC criteria) and 8 as *Aspergillus*-colonization. Among patients with IPA, 20 (45.5%) developed IPA during their ICU stay following transplantation whereas 24 patients (54.5%) had a medical ICU admission. Regarding medical imaging, nearly all IPA cases presented with non-specific findings as only 9 demonstrated robust findings suggestive for invasive fungal disease. Overall, severity of disease was reflected by a high prevalence of underlying conditions and acute organ derangements. Mortality among patients with IPA was 68%. Lung transplantation was associated with better survival (50%).

Conclusion: IPA in SOT patients in the ICU develops in the presence of an overall high severity of disease. It rarely presents with suggestive medical imaging thereby hampering diagnosis. IPA in ICU patients with SOT carries a grim prognosis.

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TWEET: International observational cohort study reports 68% mortality in invasive pulmonary aspergillosis in #ICU patients with solid organ transplantation.

ABBREVIATIONS:

SOT	Solid Organ Transplantation
SOTs	Solid Organ Transplant Recipients
IPA	Invasive Pulmonary Aspergillosis
IA	Invasive Aspergillosis
ICU	Intensive Care Unit
EORTC/MSGERC Study	European Organization for Research and Treatment of Cancer/Mycosis Group and Research Consortium
Spp.	Species pluralis
IFD	Invasive Fungal Disease
SARS CoV2	Severe Acute Respiratory Syndrome Coronavirus-2
CT	Computed Tomography
APACHE II	Acute Physiology and Chronic Health Evaluation II
GM	Galactomannan
PCR	Polymerase Chain Reaction
BAL	Bronchoalveolar Lavage
SOFA	Sequential Organ Failure Assessment Score
SPSS	Statistical Package for Social Sciences
AFT	Antifungal Therapy
OR	Odds Ratio
CI	Confidence Interval

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INTRODUCTION

Invasive pulmonary aspergillosis (IPA) is an opportunistic infection mainly observed in severely immunocompromised patients. IPA is of increasing concern due to the increasing number of patients at risk, including solid organ recipients (SOTs) [1]. Although an uncommon complication in SOT patients, IPA is the most frequent cause of invasive fungal disease (IFD) in lung transplant patients and second to invasive candidiasis in all other SOTs [2-4]. In the past two decades critically ill patients in the broader sense, including severe influenza and SARS CoV2 pneumonia have been increasingly recognized as at high-risk for invasive aspergillosis (IA) and IPA in particular [5,6]. Depending on the case-mix, the incidence of IA in the ICU varies from 0.3% to almost 7% [7]. However, any estimate of the incidence of IPA in ICU patients is hampered by diagnostic challenges due to non-specificity of clinical signs and symptoms. This often contributes to significant diagnostic delays and subsequent initiation of antifungal therapy, impacting on prognosis [8]. In addition, a systematic review of autopsy studies found IA to represent one of the most frequently missed infection-related diagnoses in the ICU [9]. Until today mortality rates for IPA remain extremely high, ranging from 60% to as much as 95% [7,10-13].

The diagnostic gold standard for proven IPA is to obtain histopathological evidence of *Aspergillus* invasion. In the absence of histopathological data the combination of host factors reflecting profound immunocompromise, medical imaging of lesions suggestive for invasive fungal disease on chest CT-scan, and any positive mycology indicating *Aspergillus* involvement represents a diagnosis of probable IPA. Possible IPA is diagnosed by a combination of host factors and the radiological criteria in the absence of positive mycology [14,15]. These EORTC/MSGERC criteria however, have proven suboptimal in ICU patients because of three reasons [16-18]. First, lung biopsies are not always considered safe due to coagulation disorders or severe respiratory distress. Second, a majority of ICU patients is not immunocompromised according to classical definitions, but yet at risk for IPA due to a combination of underlying conditions, acute organ failure and immune paralysis following sepsis. Finally, the medical imaging abnormalities suggestive for invasive fungal disease are only rarely observed in non-classically immunocompromised patients on mechanical ventilation.

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In response to these diagnostic difficulties in ICU patients a clinical algorithm was developed to discriminate colonization from IPA in patients with *Aspergillus*-positive endotracheal aspirate cultures. This algorithm leads to an alternative diagnosis coined as putative IPA and has already demonstrated its value in an ICU setting [16,19,20]. Yet, the requirement of a positive *Aspergillus* respiratory tract isolate is a limitation as such [19,21,22]. Detailed descriptions of the diagnostic criteria are reported in Appendix A & B.

Most studies focusing on IA in SOT patients report a variable time of onset, mainly within one year post-transplant [4,23,24]. However, there is only a scarce literature on the development of IPA in the ICU early after solid organ transplantation. We aimed to describe the epidemiology, clinical features and outcomes of the critically ill group of solid organ transplant patients with *Aspergillus*-positive cultures, within the *Asp*ICU observational multicenter cohort study**.**

METHODS

Patients and settings

This prospective observational study is based on a subset of the *Asp*ICU cohort, that included adult ICU patients with at least one *Aspergillus*-positive culture. The data were collected from several intensive care units (n=30) in eight countries during the period of November 2006 to January 2011. Ethics committee approval was primarily obtained at Ghent University Hospital, and later in each and every ethics committee of the institutions involved. A more comprehensive description of the study methodology can be found elsewhere [16]. For the current study only patients who received a SOT were considered.

Data collections and outcome

General information about the patients (age, sex, body mass index) and underlying conditions was available. For evaluating the health status at time of ICU admission, the Acute Physiology and Chronic Health Evaluation (APACHE) II was used [25]. Sepsis at admission was reported according to the standard definition [26]. Clinical characteristics and symptoms of IA were described according to a clinical algorithm specifically developed for the

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discrimination between infection and colonization in ICU patients with a positive endotracheal aspirate culture for *Aspergillus* spp. (i.e. proven, or putative IPA, or *Aspergillus* colonization) [27,28]. Medical imaging included both chest CT-scan or chest X-ray. Typical abnormalities suggestive of invasive fungal disease as well as non-typical findings (e.g. pleural fluid and non-specific infiltrates) on imaging were reported. Mycological data consisted of direct (culture and direct microscopy) and indirect tests (serum-galactomannan or GM, PCR) and histopathologic evidence of *Aspergillus*. GM-BAL was not yet generally implemented in the ICU during the study period but, if available, an optical density index over 0.5 was used as cut-off for a positive test. Time of culture positivity for *Aspergillus* spp. Was considered time of diagnosis. The severity of acute illness at time of diagnosis were reported by the Sequential Organ Failure Assessment (SOFA) [29] and supportive therapy for organ failure. Data on antifungal therapy was available. Mortality rates after 12 weeks of observation were reported. Classifications according to EORTC/MSGERC and ICU clinical algorithm criteria were compared.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 26.0 was used for statistical analysis. Nominal variables were reported as a frequency and their relative percentage, continuous variables as median and interquartile range. For nominal variables the Chi-squared and the Fisher exact test were used. For the continuous variables, the Kruskall Wallis and Mann Whitney U test were used. Variables that showed a relationship with mortality ($p < 0.150$) were included in a binary logistic regression model, using the "enter" procedure. Kaplan Meier survival curves were used to assess survival among different types of SOTs. The log rank test was used to compare groups. Level of significance was determined as $p<0.05$, two-sided.

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RESULTS

General characteristics of the cohort

Thirty centres from eight countries (Belgium, Brazil, China, France, Greece, India, Portugal, Spain) participated in the *Asp*ICU study. Within the original *Asp*ICU study cohort of 563 patients, 56 solid organ recipients (20 lung, 5 heart, 19 liver and 12 kidney transplants) with a positive culture for *Aspergillus* in the ICU were included. Two patients received a combined transplant (liver-lung/kidney-heart) and were reported in the liver- and heart transplant group respectively. Table 1 summarizes demographics, underlying conditions, aspects of severity of acute illness, clinical presentation, classification of IPA, *Aspergillus* species, antifungal therapy and outcomes. Figure 1 represents the occurrence of positive *Aspergillus* cultures during the ICU course. All patients with surgical admission had SOT as principle diagnosis leading to ICU admission. In contrast, patients with a medical admission had already received a SOT previously and were admitted later for other reasons such as sepsis or respiratory distress. Time to first *Aspergillus*-positive culture was shorter in patients with a medical diagnosis leading to ICU admission. Overall mortality in this cohort was 64.3%. Figure 2 depicts survival curves for distinct SOT groups. Kidney transplant patients received antifungal therapy (AFT) earlier (data not shown) but had higher mortality rates as compared to lung transplant patients.

Classification of invasive pulmonary aspergillosis

Fifty-two patients had pulmonary involvement. Sixteen patients, predominantly following lung transplant (n=7), had a histologically proven diagnosis of IPA. According to EORTC/MSGERC criteria, only 5 patients were categorized as probable, whereas 31 patients were considered as not classifiable. In contrast, the clinical algorithm identified 28 patients with putative IPA and 8 patients colonized by *Aspergillus.* In 4 patients *Aspergillus* was found in extrapulmonary sites, including single cases of brain, liver or pleural involvement In addition, one patient had a cutaneous colonization with *Aspergillus*. As this study focuses on IPA these patients were not further included in the analysis. An overview of the classification according to the ICU clinical algorithm can be found in Figure 3.

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Characteristics of SOT patients with IPA

No significant differences were observed in demographics and comorbidities between patients with IPA (n=44) and *Aspergillus* colonization (n=8). Among patients with IPA, 20 (45.5%) developed IPA during their ICU stay following transplantation whereas 24 patients (54.5%) had a medical ICU admission. The median time until IPA diagnosis was 9 days [1-15 days]. Upon diagnosis, patients with invasive disease had a higher organ failure rate than colonized patients, as evidenced by higher median SOFA scores (9 [5-14] vs. 4 [3-6]; p=0.004). Eighty percent of patients with IPA needed mechanical ventilation, 50% vasopressor support, and 47.7 % renal replacement therapy. Patients presented themselves most commonly with symptoms of dyspnoea (61.4%) and progressive respiratory insufficiency despite antibiotic therapy and ventilatory support (45%). This group of SOT patients all had a classic host risk factor (prednisone equivalent, >20mg/d), whereas only 2 patients were neutropenic.

Regarding medical imaging, non-specific infiltrates and pleural fluid were the most frequent chest CT abnormalities, present in 58.6% (17 of 29) and 55.2% (16 of 29), respectively. Only 9 patients had robust signs suggestive of IFD as formulated in the EORTC/MSGERC criteria. Due to the strict EORTC/MSGERC imaging criteria, a large proportion of patients could not be classified. Histopathologic data was available in 18 patients, resulting in a proven IPA diagnosis in 16 patients). Half of the patients with proven IPA were diagnosed by autopsy. Direct tests such as microscopy and culture on BAL were positive in 11 of 29 (37.9%) cases, indirect tests such as serum-GM in 13 of 20 (65%) cases. Eighty-one percent of patients with IPA received AFT, significantly more than in colonized patients (37.5%)(p=0.017). Voriconazole (44.4%) was the drug of choice in patients with IPA, followed by echinocandins (19.4%) and amphotericin B (19.4%). Mortality in SOT patients with IPA (68.2%) was significantly higher than in patients classified as colonized with *Aspergillus* (25.0%)(p=0.043). Figure 4 displays the survival curves for distinct diagnostic groups.

Risk factors associated with mortality in patients with proven or putative IPA

Univariate analyses of risk factors for mortality are in Table 2. Non-survivors were more often male and older, had higher APACHE II and SOFA scores, higher need for organ

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support, and were less likely to have received a lung transplant. In multivariate analysis however, only male sex (OR, 5.96; 95% CI, 1.3-27.1) and lung transplant (OR, 0.028; 95% CI, 0.05-0.99) were independently associated with mortality.

DISCUSSION

This study is one of the first describing clinical features of a critically ill cohort of SOTs with positive cultures of *Aspergillus* in the ICU. Overall, SOTs with IPA presented with poor respiratory function (despite antibiotics and ventilatory support) in combination with non-typical infiltrates on medical imaging. Apart from the cases of proven IPA, by definition identical in the EORTC/MSGERC criteria and the clinical algorithm, the latter allowed for classification of a significantly larger segment of patients with putative as opposed to probable IPA, as well as classification as *Aspergillus* colonization.

Receiving a solid organ transplant is a well-known host factor in the diagnosis of IPA [14]. Yet, when these critically ill patients are admitted to the ICU, the risk of developing this invasive fungal disease is even higher [30]. Especially when considering the degree of organ failure at time of diagnosis where the median SOFA scores were more than twice as high in patients with IPA versus patients colonized with *Aspergillus*. Studies in the past have already demonstrated the link between the high degree of organ failure and the risk of developing IPA [30-32]. Physicians should be very cautious of this invasive pulmonary disease when the combination of these factors is present.

We reported an overall mortality rate of 68.2% in patients with IPA. Mortality proved lowest in lung transplant recipients (50%). Other multicenter studies based on the Swiss Transplant Cohort and The Transplant Associated Infection Surveillance Network (TRANSNET) database also reported lower mortality rates among lung transplant patients with IA, ranging from 4.2% to 20% respectively. However this was in a non-ICU setting [31,33-35].The latter could be explained by the following. First, the inherent characteristics of lung transplant patients as they were generally younger and had lower SOFA and APACHE II scores in comparison with other SOT groups. Second, in literature 2/3 of aspergillosis infections in lung transplant patients are bronchial or anastomosis infections rather than IPA [36]. It is possible that a substantial part of these patients have been misdiagnosed by the *Asp*ICU algorithm. Third, it can be assumed that these patients had a stricter follow-up both before

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transplantation with antifungal prophylaxis and after transplantation with bronchoscopic surveillance.

Prompt initiation of antifungal therapy upon diagnosis did not contribute to a better outcome, in line with the observations by Paiva *et al.* with the suggestion that only a more timely diagnosis could improve prognosis [8]. The observation that lung transplant patients received treatment much later than other groups while survival in this subgroup was higher, seems to underscore a limited impact of antifungal therapy. However, the above mentioned explanations for a better outcome in this specific group should be taken into consideration. While awaiting faster and earlier diagnostic approaches, a low threshold of suspicion should trigger pre-emptive initiation of antifungal therapy, probably at earlier disease stages than those allowing more diagnostic certainty, in particular in highly vulnerable and critically ill patients.

A distinct difference was noticeable between the number of patients classified according to the *Asp*ICU algorithm and those classified by the EORTC/MSGERC criteria. Only a minority of SOT patients were classifiable as probable IPA. This was mainly due to the unspecificity of medical imaging. The relative absence of robust chest CT finding suggestive of IFD may be due to the systematic administration of high doses of glucocorticoids in all SOT patients, known to suppress angio-invasiveness of *Aspergillus* infection and the high degree of mechanical ventilation resulting in fewer pathognomonic signs [32,37,38]. The *Asp*ICU radiographic criteria however, may be too sensitive and lack specificity. Particularly following lung transplantation as the algorithm seems to pick up patients with likely airway colonization, and so might over-call the true burden in SOT patients.

In the literature, there is little to find about the value of the EORTC/MSGERC criteria and clinical algorithm for diagnosing invasive aspergillosis in organ transplant recipients in the ICU. The EORTC/MSG criteria, published in 2008, have been revised by a panel of specialists [15,39]. However, no recommendations could be made regarding patients in the ICU. In response, Bassetti *et al.* founded the protocol of the FUNgal infections Definitions in ICU patients (FUNDICU) project, aiming to develop a standard set of definitions to diagnose IFD in critically ill patients [21]. Recently, the FUNDICU researchers published a review of the

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existing definitions for the diagnosis of IA in the ICU, concerning only non-haematological non-SOT patients, with promising results for the *Asp*ICU clinical algorithm [19].

This study has several limitations. An obvious first limitation consists of, the observational prospective nature of the study. Second, this cohort consisted of only 56 patients. Therefore, interpretation of the statistical results should be treated with caution. Third, in the observational study design, diagnostic and therapeutic approaches were left at the discretion of the physician leading to inherent differences. GM antigen detection on BAL as well as newer diagnostics (e.g. Lateral flow device test) were not performed as these were not yet established [40]. Fourth, only patients with a positive culture for *Aspergillus* were included in the study as it was used as an entry criterion for study inclusion. This is a shortcoming as it is possible to develop IPA in the absence of positive respiratory tract cultures, obtained either by endotracheal aspirate or BAL [40]. Fifth, in patients with a medical diagnosis the timing of transplantation was not recorded. Sixth, also because of the study design, we had no data on the incidence of IPA in SOTs. Seventh, the number of patients with *Aspergillus* tracheobronchitis is not known. Eighth, data on the exact antifungal prophylaxis and therapy is lacking, no recommendations could be made in this regard.

In conclusion, the occurrence of IPA in SOT patients requiring ICU is characterised by a high rate of organ failure, non-specific imaging and poor respiratory function. Mortality rates remain worrying, despite antifungal therapy. Hence, any *Aspergillus*-positive culture should prompt further diagnostic exploration and pre-emptive antifungal therapy in these highly vulnerable patients.

CONFLICT OF INTERESTS: None of the authors declared any conflicts of interest

CONTRIBUTIONS: SB, DV, JR and GD designed the study. SB managed study registrations and the online platform for data collection. SB, JR, PB, GD provided data. JK, KB, JR and SB analysed the data. All authors interpreted the statistical analyses. JK and SB prepared the first draft. All authors reviewed and discussed the manuscript. SB and JK finalised the manuscript on the basis of comments from all authors. All authors approved the

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final version. SB has full access to all the data in the study and carries final responsibility for the decision to submit for publication.

ACKNOWLEDGMENTS:

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

The *Asp*ICU study investigators. Miguel Blasco-Navalpotro, Hospital Universitario Severo Ochoa (Madrid, Spain), Stijn Blot, Ghent University (Ghent, Belgium), Pierre Bulpa, Mont-Godinne University Hospital (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), George Dimopoulos, University Hospital Attikon (Athens, Greece), Frédéric Forêt, Centre Hôspitalier Régional Mons-Warquignies (Mons, Belgium), Dan Li, Shangai Public Health Clinical Center (Shangai, 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 Allegre, 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 (Ghent, Belgium)

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APPENDIX A

EORTC/MSGERC algorithm

Proven invasive pulmonary aspergillosis
Idem Clinical algorithm

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

1. Host factors (one of the following)
   - Recent history of neutropenia (<500 neutrophils/mm^3) >10 d
   - Receipt of an allogeneic stem cell transplant
   - Solid organ transplant
   - Hematologic malignancy
   - Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for >3 wk
   - Treatment with other recognized T-cell or B-cell immunosuppressants
   - Inherited severe immunodeficiency
   - Acute graft-versus-host disease grade III or IV refractory to first-line treatment with steroids

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

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

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APPENDIX B

Clinical algorithm

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

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
   - Recrudescent 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 at the time of ICU admission
   - Underlying hematological or oncological malignancy treated with cytotoxic agents
   - Glucocorticoid treatment (prednisone equivalent, >20mg/d)
   - Congenital or acquired immunodeficiency

   or

   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.

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Table 1: Characteristics of 56 solid organ transplants with *Aspergillus* positive cultures, clinical manifestations, antifungal therapy and outcomes

	Patients n=56	Lung Tx n=20	Heart Tx† n=5	Liver Tx‡ n=19	Kidney Tx n=12
Demographics					
Sex, male	40 (71.4)	14 (70)	4 (80)	13 (68.4)	9 (75)
Age, years *	59 (52-63)	56 (46-61)	59 (50-64)	61 (48-65)	65 (55-70)
BMI	24 (21-28)	23 (19-28)	28 (24-34)	23 (22-28)	25 (22-27)
ICU stay prior to 1st positive culture, days	4 (1-18)	4 (1-27)	1 (0-29)	4 (2-25)	5 (1-9)
Admission data					
Type of ICU admission:					
Medical	23 (41.1)	7 (35)	1 (20)	4 (21.1)	11 (91.7)
Surgical	34 (60.7)	13 (65)	4 (80)	16 (84.2)	1 (8.3)
APACHE II on admission	18 (13-28)	15 (8-24)	18 (16-30)	18 (13-28)	24 (18-29)
Diagnostic category:					
Cardiac	4 (7.1)	2 (10)	1 (20)	0	1 (8.3)
Respiratory	29 (51.8)	18 (90)	1 (20)	4 (21.1)	6 (50)
Gastro-intestinal	2 (3.6)	0	1 (20)	1 (5.3)	0
Endocrine	4 (7.1)	0	0	1 (5.3)	3 (25)
Post-operative	17 (30.4)	0	2 (40)	13 (68.4)	2 (16.7)
Sepsis on ICU admission	12 (21.4)	2 (10)	2 (40)	2 (10.5)	6 (50)
Underlying conditions					
Diabetes type I or II	15 (26.8)	2 (10)	1 (20)	5 (26.3)	7 (58.3)
ARDS	8 (14.3)	1 (5)	0	5 (26.3)	2 (16.7)
Chronic heart failure	5 (8.9)	0	3 (60)	0	2 (16.7)
Chronic renal failure	3 (5.4)	0	0	1 (5.3)	2 (16.7)
Chronic liver failure	7 (12.5)	0	0	6 (31.6)	1 (8.3)
Acute liver failure	5 (8.9)	0	0	4 (21.1)	1 (8.3)
COPD	15 (26.8)	9 (45)	1 (20)	1 (5.3)	4 (33.3)
Myelodysplastic syndrome	2 (3.6)	0	0	0	2 (16.7)
Solid tumor	2 (3.6)	1 (5)	0	1 (5.3)	0
Immunosuppressive drug use	20 (35.7)	10 (50)	1 (20)	4 (21.1)	5 (41.7)
Chronic corticosteroid use	30 (53.6)	8 (40)	3 (60)	11 (57.9)	8 (66.7)
Chronic inhalational corticosteroids	5 (8.9)	3 (15)	0	0	2 (16.7)
Alcohol abuse	3 (5.4)	0	0	3 (15.8)	0
Severity of acute illness at moment of diagnosis					
SOFA **	7 (5-12)	6 (3-7)	11 (3-13)	10 (8-16)	7 (5-12)
Supportive therapy at moment of diagnosis:					
Vasopressive or inotropic agents	27 (48.2)	3 (15)	3 (60)	14 (73.7)	7 (58.3)
Mechanical ventilation	45 (80.4)	14 (70)	5 (100)	16 (84.2)	10 (83.3)
Renal replacement therapy	26 (46.4)	6 (30)	2 (40)	9 (47.4)	9 (75)
No supportive therapy	10 (17.9)	7 (35)	0	2 (10.5)	1 (8.3)
***Aspergillus* Species**					
A.fumigatus	49 (87.5)	16 (80)	5 (100)	17 (89.5)	11 (91.7)
A.flavus	4 (7.1)	3 (15)	0	1 (5.3)	0

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A.niger		1 (1.8)	0	0	1 (5.3)	0
Other		2 (3.6)	1 (5)	0	0	1 (8.3)
Symptoms or Signs						
Fever refractory		20 (35.7)	2 (10)	1 (20)	9 (47.4)	8 (66.7)
Dyspnoea		32 (57.1)	13 (65)	1 (20)	9 (47.4)	9 (75)
Worsening respiratory insufficiency		21 (37.5)	7 (35)	2 (40)	8 (42.1)	4 (33.4)
Pleural pain		5 (8.9)	2 (10)	0	2 (10.5)	1 (8.3)
Pleural rub		1 (1.8)	0	0	1 (5.3)	0
Hemoptoe		3 (5.4)	1 (5)	0	1 (5.3)	1 (8.3)
Recrudescent fever		2 (3.6)	2 (10)	0	0	0
No signs or symptoms		5 (8.9)	2 (20)	2 (40)	1 (5.3)	0
Invasive pulmonary aspergillosis (n=52)						
Clinical algorithm:						
	Proven	16 (30.8)	7 (38.9)	0	5 (29.4)	4 (33.3)
	Putative	28 (53.8)	9 (50)	3 (60)	11 (64.7)	5 (41.7)
	Colonization	8 (15.4)	2 (11.1)	2 (40)	1 (5.9)	3 (25)
EORTC/MSGERC classification:						
	Proven	16 (30.8)	7 (38.9)	0	5 (29.4)	4 (33.3)
	Probable	5 (9.6)	0	0	2 (11.8)	3 (25.0)
	Not classified	31 (59.6)	11 (61.1)	5 (100)	10 (58.8)	5 (41.7)
Non-lung *Aspergillus* involvement (n=4)						
Proven IA						
	Brain	1	0	0	1	0
	Liver	1	0	0	1	0
	Empyema	1	1	0	0	0
Colonization						
	Skin	1	1	0	0	0
Antifungal Therapy						
Prophylactic antifungals		3 (5.4)	1 (5)	0	2 (10.5)	0
Antifungal therapy initiated		43 (76.8)	15 (75)	2 (40)	16 (84)	10 (83)
	Amphotericin B	8	2	-	6	-
	Echinocandin	7	3	-	3	1
	Voriconazole	20	10	2	4	4
	Other	6	-	-	3	3
Duration of therapy, days		17 (7-34)	25 (8-89)	20 (7-.)	14 (7-28)	9 (4-49)
Mortality						
		36 (64.3)	10 (50)	3 (60)	13 (68.4)	10 (83.3)

Data are expressed as frequency (percent) or median (interquartile range)/Mean and Standard Deviation (SD); BMI - Body Mass Index; ICU - Intensive Care Unit; APACHE - Acute Physiology And Chronic Health Evaluation; ARDS- Acute Respiratory Distress Syndrome; COPD - Chronic Obstructive pulmonary disease; SOFA - Sequential Organ Failure Assessment; EORTC/MSG- European Organization for Research and Treatment of Cancer/Mycosis Study Group and Research Consortium

† One combined Transplant: Kidney-Heart ‡One combined transplant: Liver-Lung

* $P < 0.05$ Lung transplant versus Kidney transplant ** $P < 0.05$ Lung transplant versus Liver transplant

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Table 2: Univariate risk factors for mortality in patients with proven and putative invasive pulmonary aspergillosis

Variables	Univariate Analysis		
	Non-Survivors (n=30)	Survivors (n=14)	*P*-Value
Sex, male	25 (83.3)	6 (42.9)	0.012
Age	60 (55-65)	54 (47-58)	0.025
APACHE II score	24 (17-30)	13 (8-23)	0.005
COPD	5 (16.7)	6 (42.9)	0.132
Chronic corticosteroid use	19 (63.4)	5 (35.7)	0.087
Admission type medical	18 (60)	2 (14.3)	0.010
Admission type surgical	11 (36.7)	12 (85.7)	0.020
SOFA score	11 (6-16)	6 (4-8)	0.003
Lung Tx	8	9	0.017
Kidney Tx	9	1	0.132
Pleural pain	2 (6.7)	1 (7.1)	0.029
Vasopressive support	28 (93.3)	9 (64.3)	0.025
Renal replacement therapy	23 (76.7)	5 (35.7)	0.017

Data are reported as n (%) or median (inter quartile range).
APACHE - Acute Physiology And Chronic Health Evaluation; COPD - Chronic Obstructive Pulmonary Disease; Tx - Transplant; SOFA - Sequential Organ Failure Assessment; CT - Computed Tomography; AFT - Antifungal Therapy

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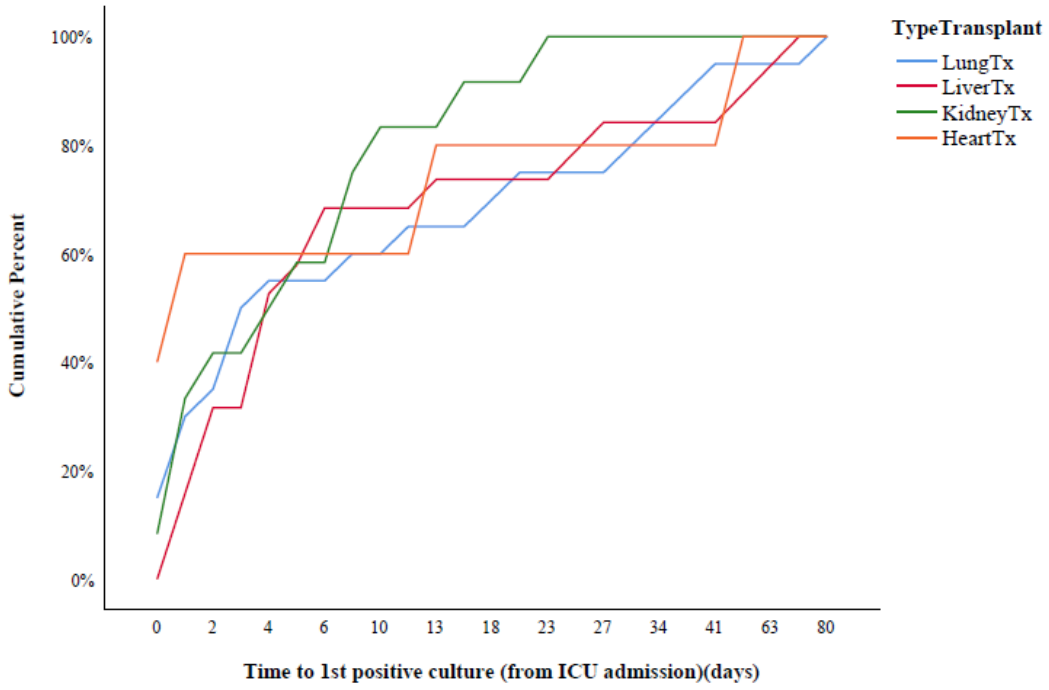

Figure 1a Cumulative incidence of positive Aspergillus cultures found in solid organ transplant patients in the ICU: The upper curve shows a steep trend at the beginning, which means that the majority of positive cultures were found shortly after admission to the ICU. It appears that positive Aspergillus spp. cultures were found quicker among kidney transplant compared to liver and lung transplant recipients. The lower curve demonstrates that SOTs with medical admission were prone to develop positive cultures sooner probably indicating the indication for ICU admission.

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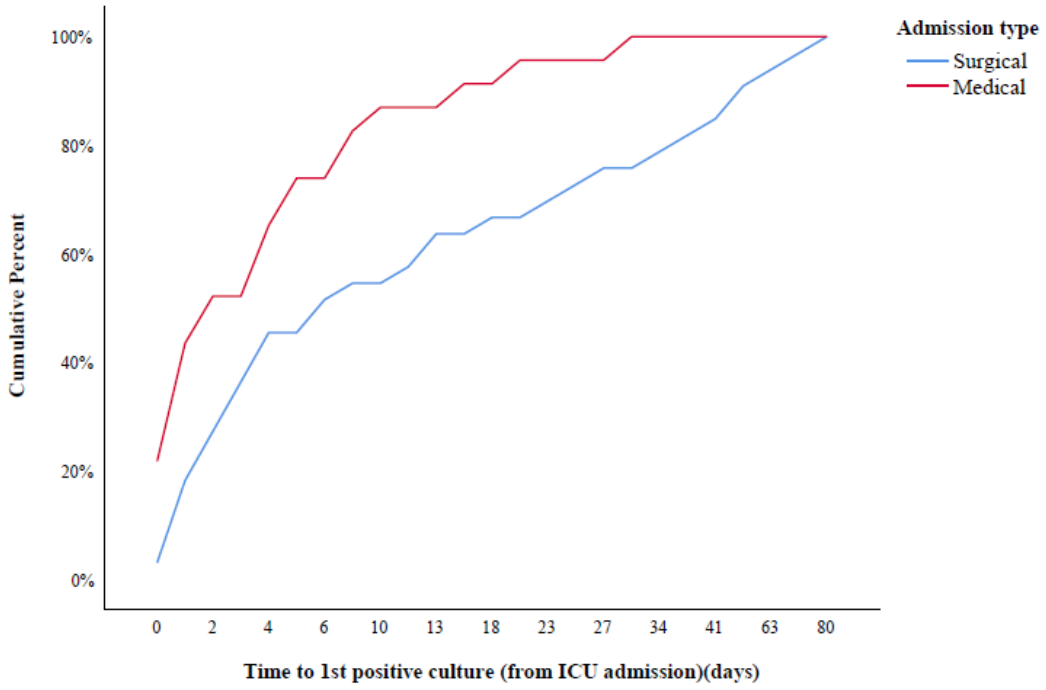

Figure 1b Cumulative incidence of positive Aspergillus cultures found in solid organ transplant patients in the ICU: The upper curve shows a steep trend at the beginning, which means that the majority of positive cultures were found shortly after admission to the ICU. It appears that positive Aspergillus spp. cultures were found quicker among kidney transplant compared to liver and lung transplant recipients. The lower curve demonstrates that SOTs with medical admission were prone to develop positive cultures sooner probably indicating the indication for ICU admission.

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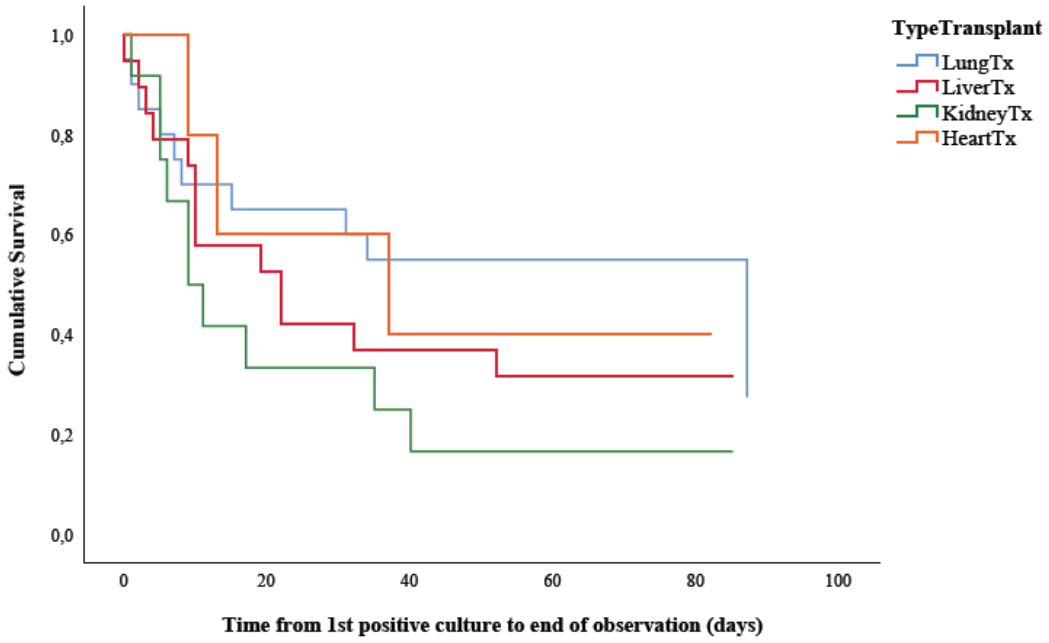

Figure 2 Survival curves of critically ill solid organ transplant recipients affected by Aspergillus (either colonization or invasive pulmonary aspergillosis): Log rank test for differences in the distribution of survival curves between solid organ transplants: p=0.232.

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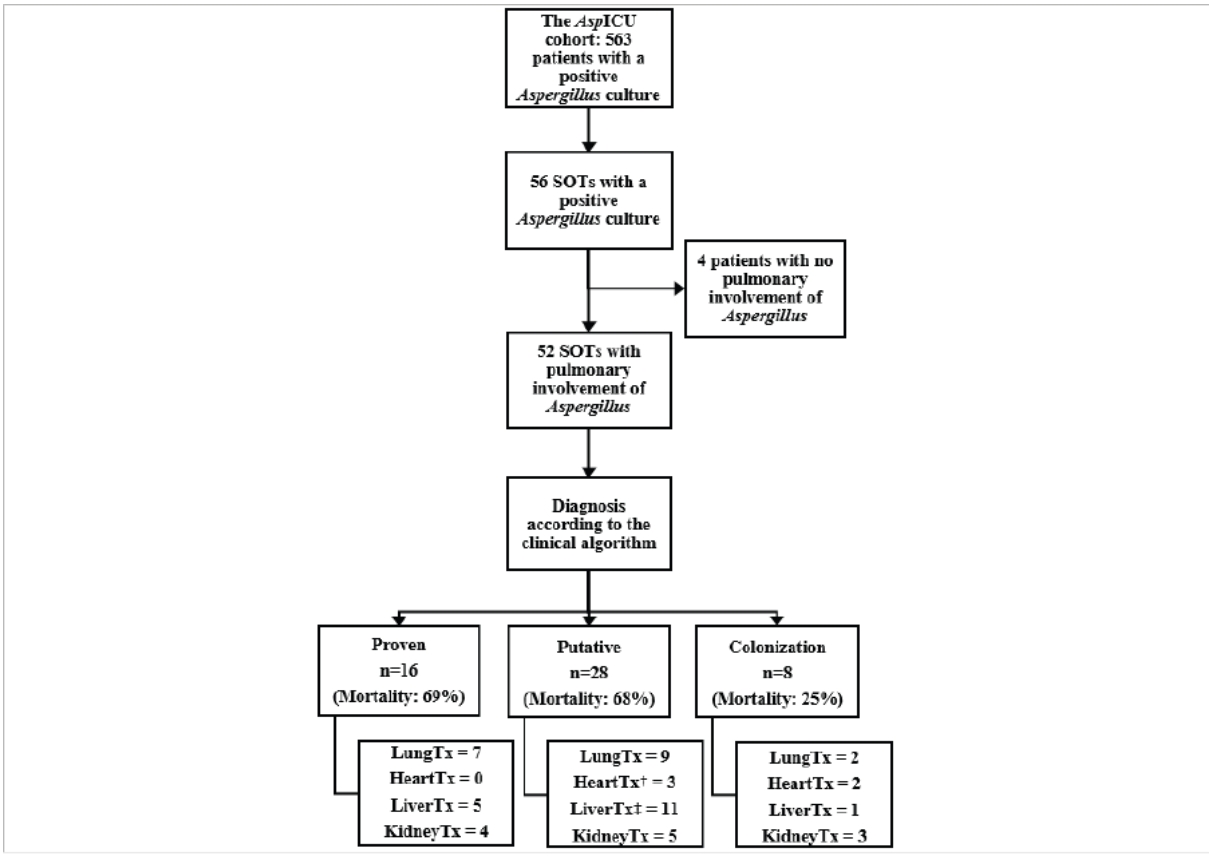

Figure 3 Overview of the Aspergillus disease classifications: One combined transplant: Kidney-Heart; One combined transplant: Liver-Lung; SOTs: Solid organ transplant recipients; Tx: Transplant. According to the EORTC/MSGERC criteria, 4 patients had probable invasive pulmonary aspergillosis. The two combined transplants were categorized as putative invasive aspergillosis.

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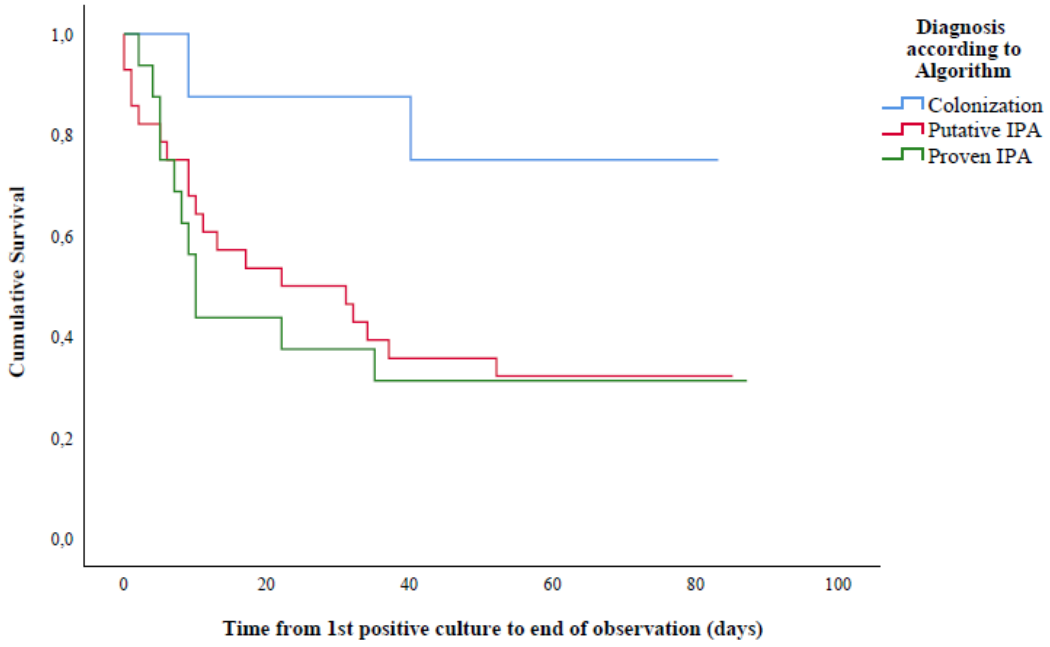

Figure 4 Survival curves of the categories of the clinical algorithm: The result of the log rank analysis: proven IPA vs. putative IPA (p=0.776), proven vs. colonization (p=0.038), putative IPA vs. colonization (p=0.041). Remarkable is the rapid decline in survival during the first 10 days after finding a positive culture in patients with proven and putative IPA.

		Patients n=56	Lung Tx n=20	Heart Tx† n=5	Liver Tx‡ n=19	Kidney Tx n=12
Demographics						
Sex, male		40 (71.4)	14 (70)	4 (80)	13 (68.4)	9 (75)
Age, years *		59 (52-63)	56 (46-61)	59 (50-64)	61 (48-65)	65 (55-70)
BMI		24 (21-28)	23 (19-28)	28 (24-34)	23 (22-28)	25 (22-27)
ICU stay prior to 1st positive culture, days		4 (1-18)	4 (1-27)	1 (0-29)	4 (2-25)	5 (1-9)
Admission data						
Type of ICU admission:						
	Medical	23 (41.1)	7 (35)	1 (20)	4 (21.1)	11 (91.7)
	Surgical	34 (60.7)	13 (65)	4 (80)	16 (84.2)	1 (8.3)
APACHE II on admission		18 (13-28)	15 (8-24)	18 (16-30)	18 (13-28)	24 (18-29)
Diagnostic category:						
	Cardiac	4 (7.1)	2 (10)	1 (20)	0	1 (8.3)
	Respiratory	29 (51.8)	18 (90)	1 (20)	4 (21.1)	6 (50)
	Gastro-intestinal	2 (3.6)	0	1 (20)	1 (5.3)	0
	Endocrine	4 (7.1)	0	0	1 (5.3)	3 (25)
	Post-operative	17 (30.4)	0	2 (40)	13 (68.4)	2 (16.7)
Sepsis on ICU admission		12 (21.4)	2 (10)	2 (40)	2 (10.5)	6 (50)
Underlying conditions						
Diabetes type I or II		15 (26.8)	2 (10)	1 (20)	5 (26.3)	7 (58.3)
ARDS		8 (14.3)	1 (5)	0	5 (26.3)	2 (16.7)
Chronic heart failure		5 (8.9)	0	3 (60)	0	2 (16.7)

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Chronic renal failure	3 (5.4)	0	0	1 (5.3)	2 (16.7)
Chronic liver failure	7 (12.5)	0	0	6 (31.6)	1 (8.3)
Acute liver failure	5 (8.9)	0	0	4 (21.1)	1 (8.3)
COPD	15 (26.8)	9 (45)	1 (20)	1 (5.3)	4 (33.3)
Myelodysplastic syndrome	2 (3.6)	0	0	0	2 (16.7)
Solid tumor	2 (3.6)	1 (5)	0	1 (5.3)	0
Immunosuppressive drug use	20 (35.7)	10 (50)	1 (20)	4 (21.1)	5 (41.7)
Chronic corticosteroid use	30 (53.6)	8 (40)	3 (60)	11 (57.9)	8 (66.7)
Chronic inhalational corticosteroids	5 (8.9)	3 (15)	0	0	2 (16.7)
Alcohol abuse	3 (5.4)	0	0	3 (15.8)	0
Severity of acute illness at moment of diagnosis					
SOFA **	7 (5-12)	6 (3-7)	11 (3-13)	10 (8-16)	7 (5-12)
Supportive therapy at moment of diagnosis:					
Vasopressive or inotropic agents	27 (48.2)	3 (15)	3 (60)	14 (73.7)	7 (58.3)
Mechanical ventilation	45 (80.4)	14 (70)	5 (100)	16 (84.2)	10 (83.3)
Renal replacement therapy	26 (46.4)	6 (30)	2 (40)	9 (47.4)	9 (75)
No supportive therapy	10 (17.9)	7 (35)	0	2 (10.5)	1 (8.3)
***Aspergillus* Species**					
A.fumigatus	49 (87.5)	16 (80)	5 (100)	17 (89.5)	11 (91.7)
A.flavus	4 (7.1)	3 (15)	0	1 (5.3)	0
A.niger	1 (1.8)	0	0	1 (5.3)	0
Other	2 (3.6)	1 (5)	0	0	1 (8.3)
Symptoms or Signs					
Fever refractory	20 (35.7)	2 (10)	1 (20)	9 (47.4)	8 (66.7)
Dyspnoea	32 (57.1)	13 (65)	1 (20)	9 (47.4)	9 (75)
Worsening respiratory insufficiency	21 (37.5)	7 (35)	2 (40)	8 (42.1)	4 (33.4)
Pleural pain	5 (8.9)	2 (10)	0	2 (10.5)	1 (8.3)
Pleural rub	1 (1.8)	0	0	1 (5.3)	0
Hemoptoe	3 (5.4)	1 (5)	0	1 (5.3)	1 (8.3)
Recrudescent fever	2 (3.6)	2 (10)	0	0	0
No signs or symptoms	5 (8.9)	2 (20)	2 (40)	1 (5.3)	0
Invasive pulmonary aspergillosis (n=52)					
Clinical algorithm:					
Proven	16 (30.8)	7 (38.9)	0	5 (29.4)	4 (33.3)
Putative	28 (53.8)	9 (50)	3 (60)	11 (64.7)	5 (41.7)
Colonization	8 (15.4)	2 (11.1)	2 (40)	1 (5.9)	3 (25)
EORTC/MSGERC classification:					
Proven	16 (30.8)	7 (38.9)	0	5 (29.4)	4 (33.3)
Probable	5 (9.6)	0	0	2 (11.8)	3 (25.0)
Not classified	31 (59.6)	11 (61.1)	5 (100)	10 (58.8)	5 (41.7)
Non-lung *Aspergillus* involvement (n=4)					
Proven IA					
Brain	1	0	0	1	0
Liver	1	0	0	1	0

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	Empyema	1	1	0	0	0
Colonization						
	Skin	1	1	0	0	0
Antifungal Therapy						
Prophylactic antifungals		3 (5.4)	1 (5)	0	2 (10.5)	0
Antifungal therapy initiated		43 (76.8)	15 (75)	2 (40)	16 (84)	10 (83)
	Amphotericin B	8	2	-	6	-
	Echinocandin	7	3	-	3	1
	Voriconazole	20	10	2	4	4
	Other	6	-	-	3	3
Duration of therapy, days		17 (7-34)	25 (8-89)	20 (7-.)	14 (7-28)	9 (4-49)
Mortality						
		36 (64.3)	10 (50)	3 (60)	13 (68.4)	10 (83.3)

Variables	**Univariate Analysis**		
	Non-Survivors (n=30)	**Survivors (n=14)**	***P*-Value**
Sex, male	25 (83.3)	6 (42.9)	0.012
Age	60 (55-65)	54 (47-58)	0.025
APACHE II score	24 (17-30)	13 (8-23)	0.005
COPD	5 (16.7)	6 (42.9)	0.132
Chronic corticosteroid use	19 (63.4)	5 (35.7)	0.087
Admission type medical	18 (60)	2 (14.3)	0.010
Admission type surgical	11 (36.7)	12 (85.7)	0.020
SOFA score	11 (6-16)	6 (4-8)	0.003
Lung Tx	8	9	0.017
Kidney Tx	9	1	0.132
Pleural pain	2 (6.7)	1 (7.1)	0.029
Vasopressive support	28 (93.3)	9 (64.3)	0.025
Renal replacement therapy	23 (76.7)	5 (35.7)	0.017

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