Initial CT manifestations of invasive pulmonary aspergillosis in 45 non-HIV immunocompromised patients: association with patient outcome?

Marius Horger\footnote{Corresponding author. Tel.: +49 7071 2987212; fax: +49 7071 295845. E-mail address: mshorger@med.uni-tuebingen.de (M. Horger).}, Holger Hebart\textsuperscript{b}, Hermann Einsele\textsuperscript{b}, Claudia Lengerke\textsuperscript{b}, C.D. Claussen\textsuperscript{a}, Reinhard Vonthin\textsuperscript{c}, Christina Pfannenberg\textsuperscript{a}

\textsuperscript{a} Department of Diagnostic Radiology, Eberhard-Karls-University, Hoppe-Seyler-Str. 3, 72076 Tübingen, Germany
\textsuperscript{b} Department of Internal Medicine-Oncology, Eberhard-Karls-University, Otfrid-Müller-Str. 5, 72070 Tübingen, Germany
\textsuperscript{c} Department of Medical Biometry, Eberhard-Karls-University Tübingen, Westbahnhofstrasse 55, 72070 Tübingen, Germany

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Abstract

Purpose: To assess early high-resolution computer tomographic (CT) signs of invasive pulmonary aspergillosis (IPA) in non-HIV immunosuppressed patients and their potential association with patient’s outcome, including frequency and severity of pulmonary hemorrhage, taking also in consideration the impact of other known risk factors contributory to IPA.

Material and methods: A retrospective review of serial CT scans was performed in 45 immunocompromised patients with a total of 46 episodes of invasive pulmonary aspergillosis. All patients underwent CT beginning with the day they showed clinical or laboratory signs of infection. Serial follow-up CT included more than two, up to 12 CT examinations. Patient’s outcome was judged by clinical and radiological follow-up and classified as survival, death by IPA, or death unrelated to IPA. The influence of patient’s age, underlying disease, hematopoietic stem cell transplantation, neutropenia, graft versus host disease, and antifungal therapy onset was also statistically considered.

Results: Three main CT findings were identified: small nodules (<1 cm) 43% (20/46), large nodules 21% (10/46) and consolidations, either in patchy ± segmental 26% (12/46), or peribronchial distribution ± tree in bud 9% (4/46). In 11 patients (24%) we found a combination of two or more of these signs: 9 (19%) patients presented concurrent small nodules accompanied by reticulation, tree in bud or peribronchial infiltrates, while 2 (4%) patients showed large pulmonary nodules accompanied by large consolidations. An accompanying “halo” sign was observed in 38 patients (82%). Crescent sign followed by cavitation was encountered in 29 patients (63%). Two patients succumbed to massive pulmonary bleeding caused by IPA. Twenty-one patients (15/46) deceased in this series, 12 of them succumbed to IPA, 1 died from cerebral invasive aspergillosis, while in 9 patients the cause of death was not primarily IPA. Manifest pulmonary hemorrhage occurred in 19% (9/46) of IPA episodes.

Conclusion: Initial CT findings of invasive pulmonary aspergillosis consist mainly of small nodules or patchy consolidations, showing in 82% of cases an early halo sign. Serious pulmonary hemorrhage was an infrequent clinical complication in our series, with an attributable mortality of 4.3%. IPA-related lethality was 26%, in our cohort. None of the early HRCT signs seemed to predict outcome.

Keywords: Pulmonary aspergillosis; HRCT; Hemorrhage; Risk factors; Outcome

1. Introduction

Invasive aspergillosis is a relatively common pulmonary complication of severely immunocompromised hosts such as patients with hematologic malignancies, especially acute and chronic myelogenous leukemia, patients who have undergone hematopoietic stem cell transplantation (HSCT), patients treated with immunosuppressive agents such as high-dose corticosteroids, as well as patients with AIDS [1]. A major predisposing factor in these patients is severe neutropenia (absolute neutrophil count of <500 cells/μL) [2–4]. Other risk factors affecting the course of IPA include host variables (age, underlying disease), immunosuppression...
associated with acute or chronic graft versus host disease (GvHD) and concomitant viral infection.

The major clinicopathological manifestations of invasive pulmonary aspergillosis include acute bronchopneumonia, angioinvasive aspergillosis, acute tracheobronchitis and chronic necrotizing aspergillosis [5]. Rare forms of IPA comprise bronchiolitis, bronchiolitis obliterans and miliar disease [6]. Although CT findings are suggestive for each type of aspergillosis, differentiation between these forms requires histologic examination.

Patients with invasive pulmonary aspergillosis have a poor prognosis with a mortality rate ranging between 30% and 80% [7–9]. Therefore, early recognition of this disease and differentiation from pulmonary complications caused by other pathogens is imperative to improve survival. Alternatively, empiric therapy with antifungals, antibiotics and sometimes additional antiviral therapy can be instituted in case that the etiology of infection remains unclear [10]. Broad-spectrum empiric antimicrobial therapy, however, has side effects, jeopardizing renal and liver function, and increasing therapy costs.

The outcome of IPA has been considered poor in immunocompromised patients, especially in allogeneic bone marrow recipients. This might be partly due to delayed diagnosis and subsequently to late onset of antifungal therapy.

In addition to the above-mentioned risk factors for IPA, early CT findings might also help in assessing risk and prognosis in patients with IPA.

Therefore, the aim of our study was to assess early CT findings of IPA and determine their eventual predictive value for clinical outcome, with emphasis on the frequency of manifest pulmonary hemorrhage and associated mortality. To this end, we also considered the potential role of other well-known risk factors for IPA.

2. Material and methods

Our patient’s cohort included 45 consecutive patients with a total of 46 infectious episodes of invasive pulmonary aspergillosis, who were diagnosed at our department from February 2000 to June 2004. Another 50 immunocompromised patients with acute pulmonary infections, clinically and radiologically judged as IPA and investigated interspersed with the 45 patients in our series within the same time interval at our department, had to be excluded from this study, due to missing microbiological validation.

The diagnosis of invasive pulmonary aspergillosis was established either by histologic demonstration of tissue invasion by the fungus using lung biopsy with video-assisted thoracoscopic surgery in 16 (35%) patients, positivity for galactomannan antigen in 5 patients (11%), positive culture for Aspergillus from the BAL in 2 patients (4%), or Aspergillus-PCR positivity in the bronchoalveolar lavage in 23 patients (50%). Clinical and radiologic features consistent with the diagnosis were present in all patients. Underlying diseases were acute myelogenous leukemia (AML) in 13 patients (13 hematopoietic stem cell transplants-HSCT, one patient presented with two episodes of IPA), chronic myelogenous leukemia in 4 (4 HSCT), chronic lymphoblastic leukemia (CLL) in 2 (1 HSCT), non-Hodgkin lymphoma in 6 (5 HSCT), multiple myeloma in 6 (5 HSCT), acute lymphatic leukemia in 6 (5 HSCT), severe aplastic anaemia in 2 (2 HSCT), myelodysplastic syndrome in 3 (3 HSCT), renal transplantation in 2, and long-term corticosteroids for Crohn’s disease in 1 patient.

The time interval between CT examination and microbiologic diagnosis ranged from 0 to 11 days (median, 1.9 days). In all patients, when the interval between CT and microbiologic diagnosis was longer than 48 h, the absence of significant interval change in the pattern of parenchymal abnormalities between the dates of CT and microbiologic diagnosis was ensured with sequential chest radiographs.

The patient cohort consisted of 32 men and 13 women (one patient had two episodes of IPA) aged 18–71 years (mean 47 years, S.D. 14 years). Associated pulmonary infections with non-fungal pathogens were excluded at that time.

CT examinations were obtained with either a single-detector row CT scanner (Somatom Plus 4, Siemens Medical Systems, Erlangen, Germany), or a multi-detector row CT scanner Volume Zoom (Siemens Medical Engineering, Forchheim, Germany). Scanning parameters for spiral CT of the chest with a single-detector row CT scanner were 120 kVp, 120 mA s, 5 mm collimation and a pitch of 1.5. Axial scans through the thorax were obtained during full inspiration. Additional thin-section CT scans were obtained with 1.0 mm collimation and at 10 mm slice interval. On the Volume Zoom scanner a collimation of 4 × 1.0 mm and a slice width of 1.25 mm were chosen. The table speed rotation was 6 mm and the rotation time was 0.75 s, with a pitch of 1.5. We used an increment of 1.2 mm. The tube voltage was 120 kV and the tube current time product was 90 mA s. Images were reconstructed with a high-spatial-frequency algorithm (high-resolution CT) B70s kernel. All scans were viewed at standard lung window setting (level, −700 HU; width, 1500 HU).

CT scans were analysed by two radiologists (H.M., P.C.A.) and decisions about the findings were reached by consensus only when discrepancies were identified. The pattern, distribution, and extent of pulmonary abnormalities were classified as large nodules or masses (>3 cm), small nodules 1–3 cm, or very small nodules <1 cm, consolidation in patchy, segmental, or peribronchial distribution ± tree in bud, reticulation, or a combination of two or more of these signs.

Consolidation and nodules were defined as areas of dense increase in attenuation with obscuration of the underlying vessels. Patchy consolidation was defined as wedge-shaped area with form and size corresponding to a secondary pulmonary lobule, or subsegment. GGO was defined as a hazy increase in lung attenuation without obscuration of the underlying pulmonary vasculature. Reticular pattern was defined as interlacing line shadow suggesting a mesh or net, and its presence was analysed in regard to association with
the above-mentioned pattern. The halo sign was defined as an area of GGO surrounding a nodule, while air crescents surrounding soft-tissue lesions were regarded as the crescent sign. Analysis of serial CT examinations was focused on the presence of the halo sign, the hypodense sign and the crescent sign or cavitation.

The sequential occurrence of the halo sign on initial CT scans and of the crescent sign and cavitation at follow-up were documented separately. Radiologic signs suggestive of pulmonary hemorrhage (GGO, crazy paving) were correlated with clinical signs and symptoms (haemoptysis), and outcome. Pulmonary hemorrhage was classified as mild (+), when manifested as recurrent short episodes of haemoptysis, or life threatening (++), in case it was followed by patient’s death.

The medical charts were reviewed for pertinent clinical data that included age, sex, and risk factors for infection. Starting at the time of first clinical symptoms and according to the absence or presence of severe neutropenia, the immune status of each patient was classified into two major risk groups (positive versus negative for neutropenia).

In every patient, the presence and duration of the antifungal therapy, as well as the time of therapy onset (early versus late) were registered and considered contributory to the outcome. Standard antifungal therapy consisted in our series of Amphotericine B deoxycholate (AmB) (1–1.5 mg/kg/day), or its liposomal form AmB (LAMB), respectively Itraconazole (400–800 mg/day). Early onset of antifungal therapy was defined as beginning either at the day the patient showed clinical signs and a CT finding suspicious of IPA, or at least 10 days before the patient succumbed to IPA. Late onset of antifungal therapy was considered whenever the administration of antifungal agents in patients with antibiotic resistant fever was delayed, despite clinical and radiological signs suggesting IPA or in cases where the disease course was fulminant resulting in therapy duration of less than 10 days, following initial diagnosis. The influence of HSCT and related acute or chronic GvHD were also considered in all hematological patients. We classified patients with respect to the presence and degree of GvHD into two main groups with a presumably different prognostic impact on patient’s outcome: a low-risk group including patients with no GvHD, grade I acute GvHD or limited chronic GvHD and a high-risk group including grade II–IV acute GvHD or extensive chronic GvHD, the latter being associated with a more intensive immunosuppressive regimen.

Statistical analysis was performed with respect to the influence of known risk factors and finally of the different initial HRCT findings on outcome by estimating the odds ratio (OR) into a 95% confidence interval (CI) for each prognostic factor and ordering them by the P-value of Fisher’s exact test. This enabled a comparison of the predictive value of all radiological signs with that of other risk factors known from the literature. We could not rely on P-values alone, as ORs had to exceed 7.3 and 13 for death by IPA and hemorrhage, respectively, to be significant on the local 5% level for a prognostic factor seen in half the affected. Since subgroups were too small, OR estimates for radiologic signs could not meaningfully be adjusted for the presence or absence of obvious risk factors like the underlying disease or the timely onset of antifungal therapy.

3. Results

Three main CT findings were identified: small nodules (<1 cm) 43% (20/46) (Fig. 1), patchy or segmental consolidations 26% (12/46) (Fig. 2), large nodules (masses) 21% (10/46) (Fig. 3) and peribronchial infiltrates (Fig. 4), associ-
ated or not with tree in bud 9% (4/46). In 1 patient (2%) we found only very small nodules (miliary pattern), in bilateral distribution (Fig. 5).

In 11 (24%) patients we found a combination of 2 or more of these signs as follows: 9 patients presented with small nodules accompanied by reticulation, tree in bud or peribronchial infiltrates, while 2 patients showed mainly large pulmonary masses, associated with bilateral reticulation (Fig. 6a and b). Multiple lesions were found in 38 cases (one patient was counted twice). In 8 patients the pulmonary aspergillosis was solitary. An accompanying “halo” sign (Fig. 7) was observed in 38 patients (82%). Crescent sign or cavitation was encountered in 29 patients (63%) at follow-up CT (Fig. 8). In the other patients the CT survey demonstrated either regression of pulmonary infiltrates or progression, in spite of ongoing antifungal therapy. One patient revealed multiple patchy consolidations with a tendency towards diffuse lung opacification, suggestive of aspergillosis-induced bronchopneumonia (Fig. 9). Manifest pulmonary hemorrhage was encountered in 9 patients (19%). Seven patients presented only one or few mild episodes of haemoptysis (Fig. 10). Two patients succumbed to massive pulmonary bleeding. The CT pattern of pulmonary infection in these two patients consisted initially of patchy consolidations and ill-defined peribronchial consolidations, respectively. Bronchial artery embolization was performed in one patient, in order to control fulminant lung hemorrhage, yet the patient deceased a few days later. Mortality by IPA was considered low (26%) in comparison to published data [11–13]. The distribution of initial CT findings among the 12 deceased patients was as follows: small nodules (n = 7), large nodules (n = 2), consolidations (n = 2) and peribronchial infiltrates (n = 1) (see Fig. 11). There was no statistically significant influence of any CT manifestation form of IPA on the clinical outcome. However, consolidations and large nodules were more frequent among the survivors. The association of the halo sign with the patient’s outcome is shown in Fig. 12. Both crescent sign and cavitation were accompanied by a higher frequency of lung hemorrhage. However, none of them had a relevant impact on the patient’s outcome (death by IPA versus survival).

The impact of the other prognostic factors is illustrated in Table 1. Notably, neither age, nor underlying disease did influence clinical outcome in our cohort.

Severe neutropenia was present in 24 patients at the time of initial clinical and radiological diagnosis of IPA. However, the impact of severe neutropenia on patient’s outcome was only moderate. Nevertheless, the probability of developing manifest lung hemorrhage was increased in neutropenic patients (OR 2.1). Twenty-six patients were HSCT recipients.
Fig. 6. (a and b) Thirty-three-year-old man with acute lymphoblastic leukemia at aplasia. A large consolidation in the right lower lung lobe accompanied by reticulation is shown on axial CT scan. Note accompanying reticulation also in the contralateral lung (black arrows). IPA was confirmed by surgery. The patient survived pulmonary aspergillosis.

Fig. 7. Sixty-six-year-old man with multiple myeloma at aplasia. Axial CT scan shows small pulmonary consolidations with air bronchogram and halo sign (black arrow). The patient survived IPA.

Fig. 8. Forty-seven-year-old man with non-Hodgkin lymphoma, following high-dose chemotherapy. Axial CT scan shows solitary pulmonary nodule with cavitation in the right upper lung lobe (black arrow), representing IPA, confirmed by surgery.

Statistically, the influence of HSCT on the clinical outcome, including pulmonary hemorrhage, was equivocal. Twelve patients had grade II-IV GvHD (+), the rest being classified as negative (−). Statistically, the influence of GvHD-positivity was reflected in ORs relatively close to 1.

Late therapy onset was more frequently associated with pulmonary hemorrhage (OR 3.0), but seemed to have had no impact on the probability of death by IPA. Two patients in this series received no therapy; both of them had a normal white blood cell count. One of them died of another cause shortly thereafter. The second patient survived.

Six patients had long-term antifungal therapy. One of them died because of IPA. Another patient died due to a cerebral fungal abscess, despite ongoing therapy. The other 4 patients survived IPA. The median duration of antifungal therapy was 40 days (inter-quartile range 97 days).

Fig. 9. Sixty-three-year-old man with MDS and AML, following intensive chemotherapy and neutropenia with new infiltrates on chest-CT. CT scan shows extensive bronchopneumonia by bronchoinvasive Aspergillosis (black arrow). The patient survived IPA.
Fig. 10. Forty-eight-year-old man with multiple myeloma, after BMT presenting with haemoptysis and new infiltrates on chest-CT. Axial CT scan reveals bilateral large areas of ground-glass-opacity, crazy-paving and parenchymal consolidation representing pulmonary hemorrhage (black arrow).

Fig. 11. Graph showing the association of early CT pattern of IPA and outcome ($P = 0.39$). Taking in consideration the different frequency of early CT findings of IPA, no trend towards favourable or unfavourable outcome can be assessed among the above-mentioned categories.

Of the 12 deceased patients, 8 had early therapy onset. In 4 patients therapy was instituted late in the disease course.

Surgery was performed in 4 patients with solitary pulmonary large masses, after long-term antifungal therapy.

Three patients survived the acute episode of IPA, 1 patient died.

4. Discussion

The pathologic and radiologic features of IPA during the course of infection have been extensively studied by different authors, who described the major patterns of manifestation, reaching from patchy infiltration, over-consolidation, up to well, or ill-defined nodules [14–17]. Rare manifestations of IPA include tracheobronchitis, bronchiolitis, as well as BOOP, or miliary forms. Histological analysis enables differentiation of the several different forms of IPA, especially of the most common manifestations including angioinvasive aspergillosis, and acute bronchopneumonia (airway-invasive aspergillosis), but this distinction is eventually not relevant for therapy. Far more, biopsy is associated with a significant risk of bleeding complication in severely thrombocytopenic patients. Nevertheless, early diagnosis of IPA is very important, because it enables early onset of antifungal therapy, and thus improves outcome. Therefore, radiological diagnosis of IPA, particularly by means of HRCT has gained popularity shortly after the introduction of CT technology [18]. Meanwhile, extensive work has been done on this diagnostic field, describing new diagnostic signs of pulmonary aspergillosis, often enabling differentiation from other pathogens, making thoracic CT scan the tool of choice to achieve the earliest and most likely diagnosis of pulmonary aspergillosis in immunocompromised patients. In the suitable clinical setting, nodular

Table 1

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prognostic factor</th>
<th>OR</th>
<th>95% CI</th>
<th>$P$-value</th>
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<tr>
<td>Death by IPA</td>
<td>Late therapy</td>
<td>0.21</td>
<td>0.015–2.1</td>
<td>0.12</td>
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<td>Underlying disease</td>
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<td>–</td>
<td>0.13</td>
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<td>0.041–1.8</td>
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<td>0.21–31</td>
<td>0.27</td>
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<tr>
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<td>CT morphology</td>
<td>–</td>
<td>–</td>
<td>0.39</td>
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<td>Underlying disease</td>
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<td>–</td>
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<tr>
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<td>–</td>
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<td>0.46</td>
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<td>0.39–15</td>
<td>0.49</td>
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<td>0.12–11</td>
<td>0.64</td>
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<td>0.66</td>
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<td>0.053–3.9</td>
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<td>Crescent</td>
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<td>0.22–4.6</td>
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</table>

No OR estimates are given for factors with more than two levels. Abbreviations: IPA (invasive pulmonary aspergillosis); GvHD (graft versus host disease); HSCT (hematopoietic stem cell transplantation).

Fig. 12. Graph showing the association between the halo sign and clinical outcome ($P = 0.18$). Patients presenting the halo sign seem to have a better prognosis, but this could be explained by earlier correct diagnosis of IPA, and correspondingly to an earlier onset of antifungal therapy.
or mass-like infiltrates surrounded by a halo of low attenuation, subsequently progressing to cavititation, or air crescent formation are considered typical for IPA. Some authors reported almost 100% positive predictive value of chest CT for IPA-diagnosis in their series [19–21].

Our results concerning frequency of CT signs of IPA are comparable with existing data [22–26]. Chen et al. reported a predominance of solitary lesions in his study; however, the nodular type was the most frequent, as in our series [27]. The accompanying halo, which is supposed to represent hemorrhage around a focus of pulmonary infarction was encountered in most of the pulmonary infiltrates, in our study, independent of their configuration, thus easing the diagnosis. This concurs with the data of Caillot et al. [18] who reported a high frequency of the halo sign early in the course of IPA, whose incidence decreased to 20%, if CT scans were performed later in the course of IPA. The favourable outcome of patients with IPA, who initially presented an associated “halo” sign, in our series, might be explained by earlier correct classification of these lesions, and subsequently by an earlier onset of antifungal therapy. Even small nodules, which sometimes are difficult to differentiate from viral bronchopneumonia, showed a high frequency of the halo sign. Because of the prevalence of small nodules in our cohort, and of early institution of antifungal therapy, the incidence of crescent sign and cavitation was low, with most of the nodules gradually decreasing over time, until they subsequently disappeared.

In the present series, mortality due to Aspergillus pneumonia was low compared to other published series reporting mortality rates of up to 85% [28,29]. This explains also some differences regarding CT pattern and size of the lesions between our study and earlier reports, presumably reflecting the effects of early diagnosis on outcome. However, our data correlate well with newer reports concerning mortality by IPA [19] that also relate their better results to an earlier employment of chest-CT in the diagnosis and earlier onset of specific therapy.

To our knowledge, the influence of early CT patterns of IPA on outcome has not yet been studied. In our study, the retrospective analysis of patient’s outcome in correlation to early CT signs of pulmonary infection did not show a statistically significant impact on the disease course. The better prognosis of patients with large masses or nodules in our study, especially if solitary, was due to the high-frequency (50%) of surgical resection. Similarly, occurrence of pulmonary hemorrhage could not be predicted by a certain CT pattern of infection (nodule, consolidation, peribronchial infiltrates), although, hemorrhage is expected to occur typically in large, cavitating nodules, or consolidations located close to larger pulmonary vessels (Table 2). However, bronchial wall infiltration with invasion of a bronchial artery branch was responsible for fatal pulmonary hemorrhage in 1 patient (50%) with Aspergillus bronchopneumonia in our series, who died following fulminant lung bleeding. Nevertheless, the presence of the crescent sign and cavitation seem to increase the propensity to hemorrhage, as stated by our data (ODs of 2.3 and 1.4, respectively). Lethality by IPA but not the probability of lung hemorrhage were also higher in patients with multiple pulmonary lesions, but this was probably due to the higher number of lesions increasing the probability of dissemination of infection (Table 3).

According to other published data, morbidity and mortality in immunocompromised patients with IPA should also be determined by other well-known risk factors such as age, underlying disease, timely onset and intensity of antifungal therapy, receipt of corticosteroids, secondary neutropenia and also transplant variables (stem cell source), and late complications (acute and chronic graft-versus-host disease, or associated infections such as cytomegalovirus or respiratory syncytial virus pneumonia), in transplant recipients [30,31]. Therefore, we also evaluated the influence of the other risk factors in our series. Hence, the late onset of antifungal therapy proved unfavourable for developing pulmonary hemorrhage in our cohort. Surprisingly, our data showed no relevant impact on the probability of death by IPA, which appears paradoxical on first site. However, proper analysis of all involved patients in our series revealed that this conclusion was artificially produced by our statistical approach, which classified patients dying of causes other than IPA together with survivors. Consequently, in 2 patients out of 5, a
long-term survey proved impossible. In most patients (82%) antifungal therapy was administered early in the course of the disease.

The impact of severe neutropenia on IPA-related mortality was not relevant in our cohort. Nevertheless, the risk for pulmonary hemorrhage was increased, which is explained by the associated thrombocytopenia.

Similar to the findings of Chen et al. [25], the influence of surgical resection of pulmonary lesions proved beneficial for outcome in patients with acute invasive aspergillosis (resection of solitary IPA lesions led to survival in 3 of 4 patients).

On the contrary, the influence of host-related risk factors such as age, underlying disease and the status of transplant recipient played in our series no relevant role, possibly due only to the relatively low number of patients.

5. Conclusion

In summary, we did not find any of the above-mentioned early CT findings of pulmonary infection to be prognostic for the outcome in immunocompromised patients with IPA. The most salient fact is that the halo seems to predict survival by IPA, about as well, as the timing of therapy onset does. Other known risk factors exhibited far less extreme ORs.

References