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Baseline chest computed tomography for diagnosis of invasive aspergillosis in patients with acute myeloid leukaemia treated with intensive chemotherapy: A retrospective single-centre cohort study

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Abstract

Background: Invasive pulmonary aspergillosis (IPA) is a relatively common infection in patients with acute myeloid leukaemia (AML), and is associated with high mortality rates. Optimising early detection is key to reduce the burden of IPA in this population. In this retrospective cohort study, we evaluated the added value of baseline chest CT before start of classical induction chemotherapy.

Methods: Adult patients receiving first-line intensive chemotherapy for AML were included if a baseline chest CT scan was available (±7 days). Data were collected from the electronic health record. IPA was classified using the EORTC/MSGERC 2020 consensus definitions.

Results: Between 2015 and 2019, 99 patients were included. During first-line treatment, 29/99 (30%) patients developed a probable IPA. Baseline chest CT was abnormal in 61/99 (62%) and 14/61 (23%) patients had typical radiological signs for IPA. An abnormal scan showed a trend towards higher risk for IPA (hazard ratio (HR): 2.12; 95% CI 0.95–4.84). Ground glass opacities were a strong predictor for developing IPA (HR 3.35: 95% CI 1.61–7.00). No probable/proven IPA was diagnosed at baseline; however, a bronchoalveolar lavage (BAL) at baseline was only performed in seven patients. Twelve-week mortality was higher in patients with IPA (7/26, 27% vs. 5/59, 8%; $p = .024$).

Conclusion: Baseline chest CT scan could be an asset in the early diagnosis of IPA and contribute to risk estimation for IPA. In patients with an abnormal baseline CT, performing a BAL should be considered more frequently, and not only in patients with radiological findings typical for IPA.

Emilie Janssens and Sammy Huygens shares first author.

KEYWORDS
acute myeloid leukaemia, computed tomography, invasive pulmonary aspergillosis, screening

1 | INTRODUCTION

Invasive aspergillosis (IA) is the most common invasive fungal infection in patients undergoing remission-induction chemotherapy for acute myeloid leukaemia (AML) and patients with high-risk myelodysplastic syndrome (MDS). Incidence rates of IA vary substantially and depend on host and environmental factors. Pulmonary infection (invasive pulmonary aspergillosis, IPA) is the most frequent phenotype.[1] Triazoles (voriconazole, posaconazole, isavuconazole) are the recommended first-line treatment for this life-threatening infection.[2–4] The overall 6-week mortality is still unacceptably high at 25%–30%.[2,5] A pivotal trial showed that the use of antimould prophylaxis (posaconazole) for AML/MDS patients receiving chemotherapy leads to lower incidence of fungal disease and improved overall survival in these patients.[6] Without prophylaxis, the incidence of IA in these populations can be as high as 10%–20%.[2,7] Recently, the EORTC consortium performed a non-inferiority study which showed that a pre-emptive antifungal strategy for high-risk neutropenic patients may also be a valid strategy with less usage of antifungals and without higher mortality or invasive fungal disease.[8] Whether a pre-emptive or a preventive strategy is chosen, optimising early detection of IA is key in order to reduce the burden of this devastating complication.[8–10]

A baseline chest CT (BCCT) may be an option for early detection of IPA; however, this is currently not recommended in guidelines. Generally, a chest x-ray is performed more frequently before initiation of chemotherapy.[11] Previously, Bitterman et al. and Ceesay et al. have prospectively analysed the value of a BCCT. Both cohorts consisted out of patients who were heavily pre-treated for their haematological malignancy.[12,13] Abnormalities on BCCT were observed in 30%–40% of these patients. Ceesay et al. showed that these abnormalities were associated with a higher risk of IPA during AML therapy.

Low dose chest CT scans are not associated with high radiation loads in contrast to older chest CT scan modalities, and are more informative than regular chest x-ray. A BCCT may also provide a reference point if the patient develops a pulmonary infection and subsequent imaging studies are needed.

At Ghent University Hospital BCCT is common practice since 2015 in newly diagnosed AML/MDS patients receiving remission-induction chemotherapy. In this centre, universal antimould prophylaxis was not applied for patients with AML receiving chemotherapy during the time of the study. Instead, a diagnostic-driven approach for invasive fungal disease was in place. In this study, we retrospectively evaluated the added value of a BCCT at time of admission in treatment-naïve AML patients.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This was a single centre retrospective cohort study performed at Ghent University Hospital. Patient data were collected from the electronic health record (EHR). Patients with AML/MDS receiving remission-induction chemotherapy were included from January 2015 to October 2019. Follow-up ended on December 31th 2020. Patients were eligible based on following characteristics: 16 years or older, newly diagnosed AML eligible for intensive chemotherapy, who underwent a CT scan around start of chemotherapy (±7 days, BCCT). Patients with myelodysplastic syndrome (MDS) or primary myelofibrosis (PMF) without intensive pretreatment, who were admitted for cytoreductive intensive chemotherapy, were also included. Patients who already received intensive regimens of chemotherapy for their underlying haematological disease were excluded. The study was approved and informed consent was waived by the Ethics Committee of Ghent University Hospital (BC-06661). Patient data were pseudonymized. The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to.

2.2 | Diagnostic-driven approach and treatment of invasive aspergillosis

Patients did not receive antimould prophylaxis systematically before 2019 in our hospital. Instead, a diagnostic-driven approach was in place. At that time, we observed a very low incidence of mould infections, probably because no major construction works took place at the campus for several years. Because intensive construction works started in April 2019 around the haematological ward, antimould prophylaxis was started in very high-risk patients based on the model by Stanzani et al.[14] or who were at higher risk because of personal history, job or hobbies. A low dose chest CT or a high resolution chest CT was performed at baseline and reviewed in real-time by a radiologist. Patients with extensive lesions were considered for a bronchoalveolar lavage (BAL). BAL fluid was sent for fungal stain (Fungi-Fluor, PolySciences, Germany), fungal culture and galactomannan (GM) antigen testing (Platelia Aspergillus Antigen, Bio-Rad, Belgium). Starting halfway through 2019, Aspergillus PCR was also performed on BAL fluid (Aspergenius®, Pathonostics, The Netherlands). During the neutropenic phase, serum GM was routinely evaluated twice weekly. There was a low threshold to perform a chest CT scan when serum GM was positive (>0.5) or if the patients

had ongoing fever despite therapy with broad spectrum antibiotics. Patients with abnormal CTs were subsequently evaluated with bronchoalveolar lavage (BAL), unless there was an elevated serum GM around the time of the chest CT scan. The diagnosis of IPA was based on the EORTC/MSGERC criteria published in 2020.[15,16]

2.3 | Follow-up

Follow-up period ranged from the start of induction chemotherapy until end of therapy (i.e. last day of the last consolidation chemotherapy or date of the allogeneic stem cell transplantation) or death depending on which event occurred first. After diagnosis of IPA subsequent CT scans were performed after 4–8 weeks and 10–14 weeks of treatment to analyse treatment effect, but these were outside the scope of this study.

2.4 | Data collection

Information on baseline characteristics and course of disease were extracted from the EHR. All BCCTs were reviewed by a radiologist and independently by two of our investigators (SH and EJ). CT abnormalities were defined according to the Fleischner Society terminology.[17] Nodular lesions were divided according to their size; micronodules were all dense, round-shaped lesions smaller than 4 mm, nodules were round-shaped lesions between 4 and 30 mm. Lesions larger than 30 mm were described as masses. In case of inter-observer disagreement, the BCCT was reviewed by another experienced thoracic radiologist until agreement was achieved. The BCCT was deemed normal if none of the above signs were present.

2.5 | Outcome parameters

We evaluated the incidence of IPA from the start of induction chemotherapy until the end of therapy as stated above. Diagnosis of IPA was based on the EORTC/MSGERC consensus definitions from 2020. Probable or proven IPA were classified as cases.[15] Risk factors for development of IPA were analysed. Six- and 12-week mortality (from the start of chemotherapy) were reported in both groups (non-IPA and IPA). We evaluated the prevalence of BCCT abnormalities and their predictive value for IPA diagnosis.

2.6 | Statistical analysis

The statistical analysis was performed using SPSS statistic version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Descriptive statistics were defined by frequencies and proportions for categorical variables. Continuous variables were defined by median and interquartile range (IQR). Differences between baseline characteristics based on presence or absence of IPA were analysed by Mann Whitney *U*-test or chi squared test for continuous and categorical variables respectively.

We created Kaplan–Meier curves and performed a log rank test and Cox regression to determine if baseline CT abnormalities were associated with a higher risk for IPA. $p < .05$ was considered statistically significant.

3 | RESULTS

In total, 129 patients received remission-induction chemotherapy between January 2015 and October 2019. Figure 1 describes the

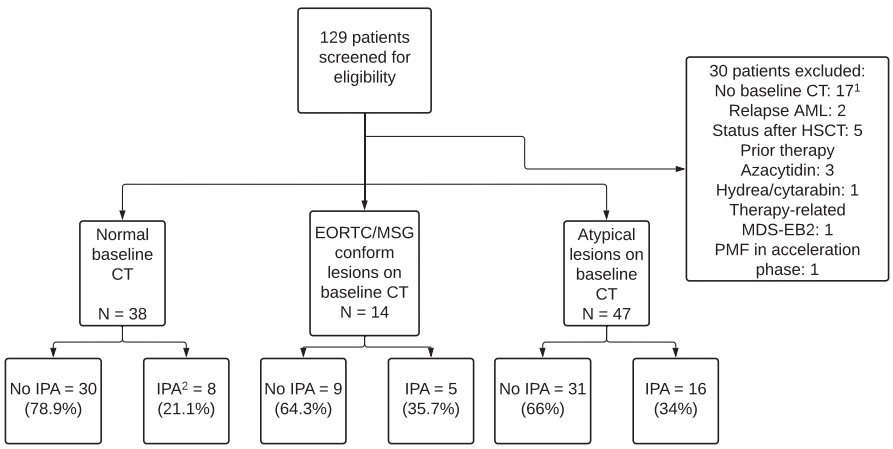

FIGURE 1 Screening and recruitment of study participants and distribution of IPA based on baseline CT. [1]Five patients were excluded because chest CT scan was performed outside the eligibility window (±7 days) of the study. Eleven patients were transferred from other centres, no chest CT images were available in these. In one patient, chest CT could not be performed because the patient was immediately transferred to the intensive care unit. [2]Probable or proven invasive aspergillosis according to the EORTC/MSGERC 2020 consensus definitions were defined as IPA cases. AML, acute myeloid leukaemia; CT, chest computed tomography; HSCT, haematopoietic stem cell transplantation; IPA, invasive pulmonary aspergillosis; MDS-EB2, myelodysplastic syndrome with excess of blasts type 2; PMF, primary myelofibrosis.

recruitment in detail. Ninety-nine patients were included in the primary analysis. Seventeen patients were excluded from the analysis since the BCCT was performed outside the window of 7 days or if the BCCT was performed in another hospital, 12 patients were pretreated and one patient had a primary myelofibrosis in acceleration phase.

Baseline characteristics are found in Table 1. BCCT showed abnormalities in 61/99 (62%) patients: 14 (23%) had signs conform to the EORTC/MSGERC criteria, all other patients (47, 77%) had atypical radiological findings.[16] Micronodules were found most frequently (30%), followed by ground glass opacities (28%), dense well-circumscribed nodules (14%), consolidations (14%) and tree-in-bud lesions (6%). No masses, air-crescent signs, cavities or reverse-halo signs were found on BCCT (Table 2).

Serum galactomannan (GM) around the time of BCCT (±2 days) was available in 38/99 (38.4%) patients, and negative in all (range 0.03–0.18). BAL was performed at baseline in 7/61 (11.5%) patients with an abnormal BCCT, 4/7 (57%) had typical EORTC/MSGERC lesions. Fungal culture and BAL GM remained negative in all BAL samples at baseline, therefore no probable IPA was diagnosed at that time.

Twenty-nine out of 99 (29%) patients developed a probable IPA according to the EORTC/MSGERC consensus definitions during follow-up.[15] No proven IPA could be identified. Extra-pulmonary fungal infection was observed in three patients: one patient had an *Aspergillus* sinusitis based on a positive culture of a nasopharynx aspirate, one patient had an erysipelas with positive culture of *Aspergillus fumigatus* on a deep skin swab and one patient had a proven invasive mucormycosis based on a leg biopsy. Patients who were diagnosed with IPA were significantly older (median age 64 (IQR 55–68) versus 53 (IQR 35–63); $p = .009$). In patients with a normal BCCT, 8/38 (21%) developed IPA in comparison to 21/61 (34%) with an abnormal BCCT, (Figure 2). A trend towards increased risk of IPA was observed in patients with an abnormal BCCT with an hazard ratio (HR) of 2.14 (95% CI 0.95–4.84, $p = .067$), (Figure 3A). In patients with an abnormal BCCT, the median time to develop IPA was significantly shorter (29, IQR 18–63 vs. 40, IQR 21–62; $p = .015$) compared to patients with a normal BCCT. No clear difference in IPA incidence was observed in patients with EORTC/MSGERC lesions (36%) compared to patients with atypical lesions (34%) at baseline. Patients with IPA had a higher prevalence of ground-glass opacities on baseline CT, 13/29 (45%) compared to 15/70 (21%) in non-IPA group ($p = .019$). When the BCCT showed ground glass opacities, the risk of developing IPA was higher with a HR of 3.35 (CI 95% 1.61–7.00), (Figure 3B). Other types of lesions did not show a statistical difference in risk for IPA.

Large construction works started on campus from April 2019, 16 (16.2%) patients were included during this period. Six patients were started on posaconazole prophylaxis, and five patients were additionally switched from fluconazole to posaconazole because of the construction works.[4] In one patient, the switch was done because of atypical radiological findings, however this patient still developed IPA during follow-up. None of the patients who were started on posaconazole developed IPA. 4/5 (80%) of the patients who received fluconazole prophylaxis developed IPA during follow-up.

Six-week overall mortality was 15% (4/26) in the IPA group compared to 7% (4/59) in the non-IPA group ($p = .24$). IPA was associated with a relative risk for six-week overall mortality of 2.3 (CI 95% 0.614–8.384). The 12-week overall mortality was higher in patients with IPA; 27% (7/26) died within 12 weeks compared to 8% in the non-IPA group (5/59) ($p = .024$). IPA was associated with a relative risk for 12-week mortality of 3.2 (CI 95% 1.111–9.086).

4 | DISCUSSION

IPA remains an important complication in haemato-oncological patients with high case-fatality rates.[18] The use of a BCCT in high-risk haemato-oncological patients could provide additional information to decide whether thorough screening or antimould prophylaxis should be initiated. Early abnormal findings can be of great importance in the pre-emptive strategy (diagnostic-drive approach), but it can also be an additional reason for administering prophylaxis in selected patients. A BCCT can also be used as a reference point for subsequent imaging if necessary. This single-centre retrospective cohort study evaluated the added value of a BCCT in patients prior to remission-induction chemotherapy. Twenty-nine (29%) of the 99 patients in our cohort developed IPA. The incidence of IPA in this cohort was very high considering an expected incidence of 10% in patients with AML receiving induction chemotherapy.[19] However, prior studies perhaps underestimated the true incidence since diagnosis of IPA can be difficult; post-mortem studies showed a higher incidence of IPA up to 30%.[2,3,13] Large construction works at our site could have been a contributing factor, especially since local incidence was much lower before start of the study.[20]

Sixty-one (62%) patients had an abnormal BCCT, of which 23% had signs that met the EORTC/MSGERC consensus criteria. Bitterman et al. conducted a prospective study to evaluate the added value of the BCCT. They included all AML patients (de novo and relapsed) and patients admitted for allogeneic stem cell transplant and performed a chest CT scan around date of admission. Ninety-one out of 295 patients (31%) had abnormal radiological findings at baseline and the incidence of IPA was higher in those patients. One-hundred and seven patients had a newly diagnosed AML, and a probable IPA was diagnosed in 10 of them at baseline.[12] Ceesay et al. also reported BCCT abnormalities in 72/198 (36%) patients, and found that these were associated with a hazard ratio for IPA of 2.52 to 4.67 depending whether the lesions were conform the EORTC/MSGERC criteria or not respectively.[13] Both studies show less abnormal findings at baseline than in our cohort, but they also report lower local incidences of IPA compared to our hospital. Patients in this cohort did not receive prior treatment for their underlying disease, as opposed to 85% and 65% in the study of Ceesay et al. and Bitterman et al., respectively. In contrast to our findings, we therefore expected a lower incidence in our cohort compared to the abovementioned groups.

TABLE 1 Baseline characteristics.

Characteristics	All (*N* = 99)	No IPA (*N* = 70)	Probable/proven IPA (*N* = 29)	Statistics (*p*-value)
Age (years)–median (IQR)	56 (44–66)	53 (35–63.25)	64 (54.5–67.5)	.009
Age category (years)–*n* (%)				.129
1–20	3 (3.0%)	3 (4.3%)	0 (0%)	-
21–40	20 (20.2%)	16 (22.9%)	4 (13.8%)	-
41–65	38 (38.4%)	29 (41.4%)	9 (31.0%)	-
65 +	38 (38.4%)	22 (31.4%)	16 (55.2%)	-
Gender– *n* (%)				.961
Male	55 (55.6%)	39 (55.7%)	16 (55.2%)	-
Female	44 (44.4%)	31 (44.3%)	13 (44.8%)	-
Charlson comorbidity index– *n* (%)				.425
0	68 (68.7%)	49 (70.0%)	19 (63.9%)	-
1	14 (14.1%)	9 (13.9%)	5 (17.2%)	-
2	8 (8.1%)	4 (5.7%)	4 (13.8%)	-
3	5 (5.1%)	4 (5.7%)	1 (3.4%)	-
4	4 (4.0%)	4 (5.7%)	0 (0%)	-
Underlying disease– *n* (%)				.280
AML with recurrent genetic abnormalities	48 (48.5%)	34 (48.6%)	14 (48.3%)	-
AML with myelodysplasia-related changes	20 (20.2%)	12 (17.1%)	8 (27.6%)	-
Therapy-related myeloid neoplasms	10 (10.1%)	8 (11.4%)	2 (6.9%)	-
AML, NOS	11 (11.1%)	10 (14.3%)	1 (3.4%)	-
Acute leukaemia of ambiguous lineage (MPAL, undifferentiated)	2 (2.0%)	1 (1.4%)	1 (23.4%)	-
CMML-1	1 (1.0%)	0	1 (3.4%)	-
CMML-2	1 (1.0%)	0	1 (3.4%)	-
MDS-EB1	2 (2.0%)	2 (2.9%)	0	-
MDS-EB2	4 (4.0%)	3 (4.3%)	1 (3.4%)	-
ELN risk stratification– *n* (%)				.435
Favourable	21 (21.2%)	17 (24.3%)	4 (13.8%)	-
Intermediate	23 (23.2%)	17 (24.3%)	6 (20.7%)	-
Adverse	44 (44.4%)	29 (41.4%)	15 (51.7%)	-
Therapy–*n* (%)				.198
Anthracyclin + cytarabine	96 (97%)	68 (97.1%)	28 (96.6%)	-
Anthracyclin + cytarabin + midostaurin	1 (1.0%)	0	1 (3.4%)	-
Anthracyclin + cytarabine + quizartinib	2 (2.0%)	2 (2.9%)	0	-
One induction	22 (23.9%)	11 (15.7%)	11 (37.9%)	
Two inductions	77 (77.8%)	59 (84.3%)	18 (62.1%)	
Prophylaxis				.226
No prophylaxis	1 (1.0%)	1 (1.4%)	0	-
Fluconazole	92 (92.6%)	63 (90.0%)	29 (100%)	-
Posaconazole	6 (6.1%)	6 (8.6%)	0	-
Neutropenia[a]	32/96 (32.3%)	21/68 (30.0%)	11/28 (37.9%)	.427
Type of chest CT scan– *n* (%)				.238
Low-dose chest CT	74 (74.7%)	24 (82.8%)	50 (71.2%)	
HRCT	25 (25.3%)	5 (17.2%)	20 (28.6%)	
Time between baseline CT and cytoreductive therapy (days)–median (IQR)[b]	0 (−1–0)	0 (−1–1)	0 (−1–0)	.697
Time between cytoreductive therapy and prophylaxis (days)–median (IQR)	0 (−1–1)	0 (−1,5–1)	0 (−1,5 – 0,5)	.821

Abbreviations: AML, acute myeloid leukaemia; CMML, chronic myelomonocytic leukaemia; CT, computed tomography; HRCT, high-resolution computed tomography; IPA, invasive pulmonary aspergillosis; IQR, interquartile; MDS-EB, myelodysplastic syndrome with excess of blasts; NOS, not otherwise specified.

[a]<500 neutrophils/mL measured around time of the baseline chest CT scan (± 2 days).

[b]The chest CT scan was performed before start of cytoreductive therapy in 75 patients. The chest CT scan was performed in six, seven and two patients on Day 1, 2 and 3 of the treatment respectively, four patients received a scan on Day 4 and one patient on Day 5. Eventually, four patients received a chest CT scan between Day 6 and 7 after start of cytoreductive therapy.

TABLE 2 overview of radiological findings on baseline CT based on occurrence of IPA during follow-up.

Radiological findings–*n* (%)	All (*N* = 99)	No IPA (*N* = 70)	Probable/proven IPA (*N* = 29)	Statistics (p-value)
Micronodules (<4 mm)	29 (29.3%)	20 (28.6%)	9 (31%)	.806
Ground-glass opacities	28 (28.3%)	15 (21.4%)	13 (44.8%)	.019
Dense, well-circumscribed lesions with/without halo (4-30 mm)	14 (14.1%)	9 (12.9%)	5 (17.2%)	.569
Wedge-shaped and segmental or lobar consolidation	14 (14.1%)	10 (14.3%)	4 (13.8%)	.949
Subsolid nodule (4-30 mm)	12 (12.1%)	6 (8.6%)	6 (20.7%)	.093
Tree-in-bud lesions	6 (6.1%)	2 (2.9%)	4 (13.8%)	.059[a]
Mass	-	-	-	-
Air-crescent sign	-	-	-	-
Cavity	-	-	-	-
Reverse-halo sign	-	-	-	-

Abbreviation: IPA, invasive pulmonary aspergillosis.

[a]Fisher's exact test.

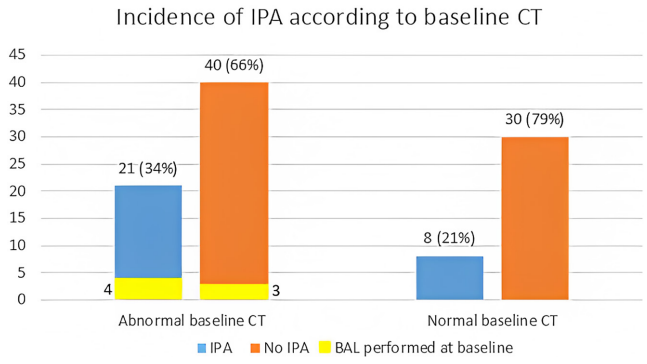

FIGURE 2 Incidence of IPA according to the overall results of the baseline chest CT scan. Galactomannan and culture on BAL was negative in all patients in whom a BAL was performed (*N* = 7), Aspergillus PCR was not performed. BAL, bronchoalveolar lavage; CT, chest computed tomography; IPA, invasive pulmonary aspergillosis.

In this cohort, we observed a trend towards higher IPA incidence when the BCCT was abnormal (34% versus 21%). Patients who presented with ground glass opacities on BCCT had a three-fold higher risk of developing IPA compared to patients who had not. We found no difference in IPA incidence in patients with atypical lesions compared to lesions concordant with the EORTC/MSGERC radiological criteria. This was also observed by Nucci et al. in a retrospective cohort study. The medical records of 125 patients were reviewed for incidence of IPA according to the EORTC/MSGERC guidelines (2020).[16] The cohort mainly consisted of patients with underlying multiple myeloma and 48% received prior stem cell transplantation. They showed that baseline characteristics, clinical manifestations, treatment, and survival of patients with atypical radiological lesions were very similar to patients presenting with nodules, cavities or air-crescent signs. Furthermore, 40% of patients with atypical radiological findings developed more specific lesions (cavities, nodules or air-cresecent signs) in the next 2 weeks. Indeed, ground glass opacities can be a very early presentation of IPA, certainly in high risk patients.[21] Girmenia et al. also recommended to add a new category in the EORTC/MSGERC criteria: probable IPA without prespecified radiological criteria based on similar findings.[22] Even though the EORTC/MSGERC criteria were developed for clinical trial purposes only, they are extensively used in clinical practice since they offer a backbone in this difficult-to-diagnose disease. In addition, they are also used for reimbursement of treatment (e.g. in Belgium).

In this cohort, no patients were diagnosed with IPA at baseline. This is in sharp contrast to the study of Bitterman et al. where 10% of the patients with newly diagnosed AML were diagnosed with IPA at baseline. The difference in pretreatment could (partially) explain this difference.[12] Presumably, the very low amount of BALs performed may also be an explanation as the performance of fungal diagnostics is better on BAL fluid than on blood.[23] We also showed that 12-week mortality was three times higher in patients who developed IPA.

Our study had several limitations. First, this study was a single centre study which only assessed high-risk haemato-oncologic patients that were not previously treated for their underlying haematological malignancy. The duration of neutropenia before inclusion could differ, from short periods in newly diagnosed AML to long periods in preceding MDS. Additional information on other patient related risk factors such as living arrangements, neighbourhood, job history and smoking were not available. Aside from the start of construction works, unknown confounders may have been present contributing to the high IPA incidence in this cohort. Whilst 75 patients received a BCCT before start of chemotherapy, 24 patients received a BCCT after, this may have induced additional confounding factors for the high incidence of radiological abnormalities. Due to the retrospective design, there was no strict adherence to a certain protocol for further investigation (e.g. bronchoscopy) in case of abnormal signs on the BCCT. Early BAL sampling may have led to earlier detection of IPA in our cohort but this was no common practice if the patient did not have symptoms suspect for infection. In the group of Bitterman

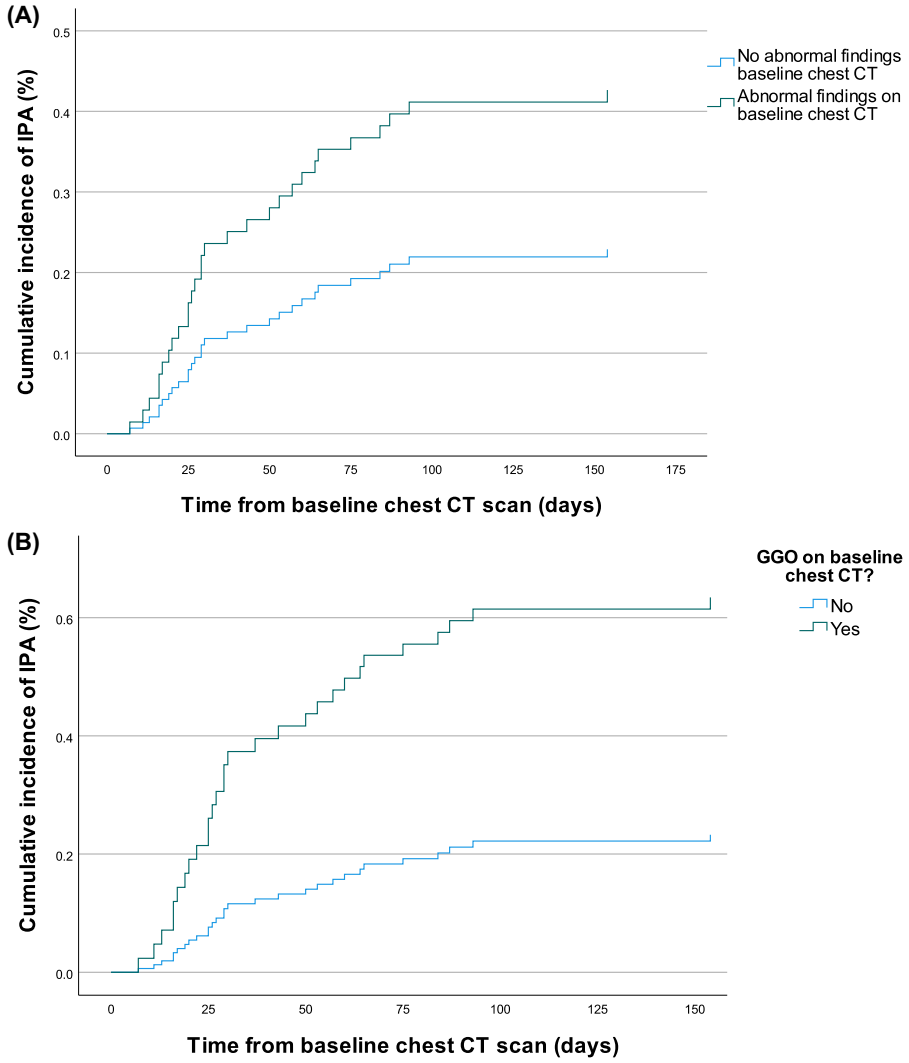

FIGURE 3 Cumulative incidence of IPA. Cox regression was performed with IPA as outcome event and radiological features were used as covariates (the presence of any abnormal CT findings in A and the presence of ground glass opacities in B). 'One minus survival' curves are represented with the covariates as group factor. Cumulative incidence of IPA based on radiological findings may not be identical to the frequencies reported in Table 2 since follow-up data were not present in all patients. The time-to-event analysis was performed in 88 patients. CT, computed tomography; GGO, ground glass opacities; IPA, invasive pulmonary aspergillosis. (A) Cumulative incidence of IPA based on baseline CT. Follow-up started at day of baseline chest CT ($d=0$). Patients with a normal baseline chest CT had a lower incidence of IPA (green line) compared to patients with an abnormal baseline CT (blue line). Log rank test showed no statistical difference between two groups ($p=.067$). Hazard ratio was 2.13 (95% CI: 0.95–4.84) for patients with abnormal chest CT findings. (B) Cumulative incidence of IPA based on baseline CT. Follow-up started at day of baseline chest CT ($d=0$). Patients without ground glass opacities on baseline chest CT had a lower incidence of IPA (green line) compared to patients with ground glass opacities present on baseline chest CT (blue line). Log rank test showed a significant difference between two groups ($p<.001$). Hazard ratio is 3.35 (95% CI: 1.61–7.00) for patients with abnormal chest CT findings.

et al. 5/49 patients in whom a BAL was performed at baseline were upgraded from possible to probable IPA. However, in our cohort, the majority did not have large EORTC/MSGERC conform lesions, and the lesions were sometimes very small (e.g. micronodules) or peripherally located. This could have decreased the diagnostic performance on BAL fluid. In addition, frequent thrombocytopenia, neutropenia and frailty, may harbour a higher risk of complications after BAL.

Until now, it remains unclear whether a pre-emptive or preventive approach should be followed in high-risk patients.[8,24] With diagnostic tests with a short turnaround time readily available (e.g. lateral flow assays, Aspergillus PCR, GM), a pre-emptive strategy may be preferred.[8,16] In case of an abnormal BCCT, a BAL should be considered after consulting an pulmonologist/endoscopist, whilst closely monitoring the diagnostic yield of those BALs. In this light, it is also important to mention that during construction works near the ward, none of the six patients who received posaconazole prophylaxis in our study were diagnosed with probable IPA during treatment, compared to four out of five patients who received fluconazole and were included in the study around the same time.[20] Improvement of imaging studies can further aid early diagnosis of IPA. Low-dose chest CT scan in combination with pulmonary angiography could provide more information since appearance of a veno-occlusive sign on angiography has a strong positive predictive value for invasive mould disease.[25] This should be further explored in the future.

5 | CONCLUSION

In conclusion, our retrospective single-centre study showed that a BCCT scan could be a valuable asset in the management of patients at high risk for IA, but further research is needed to confirm this. Early imaging studies may contribute to risk estimation for developing IPA for each patient individually. Based on these findings, we may suggest that in centres where primary prophylaxis is not used, a vigorous diagnostic-driven approach should be conducted in patients with an abnormal BCCT. A bronchoscopy should be considered in patients with abnormal radiological findings, especially in case of ground glass opacities and not only in patients with EORTC/MSGERC typical radiological findings whilst closely monitoring its diagnostic yield.

AUTHOR CONTRIBUTIONS

Emilie Janssens: Conceptualization; data curation; methodology; project administration; writing – original draft; writing – review and editing. **Sammy Huygens:** Data curation; formal analysis; methodology; project administration; writing – original draft; writing – review and editing. **Ine Moors:** Conceptualization; methodology; writing – review and editing. **Anke Delie:** Writing – review and editing. **Tessa Kerre:** Conceptualization; writing – review and editing. **Yannick Vande Weygaerde:** Resources; writing – review and editing. **Eva Van Braeckel:** Writing – review and editing. **Jerina Boelens:** Resources; writing – review and editing. **Lieve Morbée:** Resources; writing – review and editing. **Alexander Schauwvlieghe:** Conceptualization; methodology; writing – original draft; writing – review and editing; supervision.

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CONFLICT OF INTEREST STATEMENT

SH received a speaker's fee from Pfizer and was reimbursed for travel expenses by Gilead for a conference. EVB has a contract with F2G and received a speaker's fee by Pfizer (both paid to the institution). She is chair of the Chronic Pulmonary Aspergillosis Network (CPAnet, unpaid). JB received E-test material for ceftazidime-avibactam from Pfizer. All other authors declare to have no COIs.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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