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Clinical Assessment for Identifying Causes of Acute Respiratory Failure in Cancer Patients

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Running head: DIRECT approach to ARF in cancer patients.

Keywords: Acute respiratory failure; Bronchoalveolar lavage; Cancer; Fiberoptic bronchoscopy; Infectious diseases / pneumonia; Mechanically ventilated patients.

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Abbreviations list

ARF: acute respiratory failure

BAL: bronchoalveolar lavage

CI: confidence interval

FOB: fiberoptic bronchoscopy

HRCT: high-resolution computed tomography

HSCT: hematopoietic stem cell transplantation

ICU: intensive care unit

IQR: interquartile range

LOD: logistic organ dysfunction

NIV: non-invasive ventilation

OR: odds ratio

PCR: polymerase chain reaction

ABSTRACT

Purpose: In cancer patients with acute respiratory failure (ARF), early adequate therapy is associated with better outcomes. We investigate the performance of the DIRECT approach that used criteria available at the bedside at ICU admission to identify causes of ARF in cancer patients.

Methods: Cohort study of cancer patients with ARF of determined aetiology. Associations of aetiological groups with the selected criteria were evaluated using correspondence analysis.

Results: Four hundred twenty-four cancer patients were included: 201 (47%) with bacterial pneumonia, 131 (31%) with opportunistic infections, and 92 (22%) with non-infectious disorders. Mechanical ventilation (both invasive and non-invasive) was needed in 328 (77%) patients, treatment for shock in 217 (51%), and dialysis in 82 (19%). One hundred forty-two patients (34%) died in the ICU. Correspondence plots showed that bacterial pneumonia was associated with neutropenia, solid tumour, multiple myeloma, time since symptom onset <3 days, shock, unilateral crackles, and unilateral radiographic pattern. Opportunistic infections were associated with steroids, lymphoproliferative disorders, and hematopoietic stem-cell transplantation, whereas non-infectious disorders were associated with acute leukaemia

Conclusions: The selected criteria are strongly associated with causes of ARF in cancer patients and could be used to develop an algorithm for selecting first-line diagnostic investigations and empirical treatments.

INTRODUCTION

The number of cancer patients has increased over the last few decades [1, 2] as a result of survival gains achieved by intensive anti-cancer treatments and improvements in supportive care [3-7]. These survival gains have come at the cost of increases in toxic and infectious complications [6, 8, 9]. Among these complications, acute respiratory failure (ARF) occurs in up to 30% of cancer patients and is the leading reason for intensive care unit (ICU) admission in this population. ARF in cancer patients still carries a high mortality rate of 50% overall, with even higher rates in patients needing mechanical ventilation or having no identifiable cause of ARF [10-14]. Fiberoptic bronchoscopy with bronchoalveolar lavage (FOB-BAL) has long been considered the cornerstone of the aetiological diagnosis [15]. This procedure has been associated with adverse events [16-19], however, especially in the most unstable patients [20-22]. A recent study showed that FOB-BAL performed in the ICU was not associated with an increased rate of mechanical ventilation [14]. Nevertheless, compared to a non-invasive diagnostic strategy, the diagnostic strategy including FOB-BAL did not increase the proportion of patients for whom a cause was identified and had only a small impact on treatment decisions [14]. The cause of ARF is not always identifiable in cancer patients [13, 14, 23]. Clinicians must be aware that the potential benefit of identifying the cause of ARF must be balanced against the risk of adverse events related to FOB-BAL, especially in hypoxaemic ICU patients [12, 24].

The first step in the aetiological diagnosis of ARF in a patient with cancer consists in a systematic clinical evaluation [14, 24] aimed at identifying the most likely causes and, therefore, at determining which first-line diagnostic investigations and empirical treatments are most likely to benefit the patient. We have suggested that this evaluation focus on six factors, which can be listed using the mnemonic DIRECT (Table 1): *D*elay since malignancy

onset or haematopoietic stem-cell transplantation (HSCT), since symptom onset, and since antibiotics / prophylaxis implementation; pattern of *I*mmune deficiency; *R*adiographic appearance; *E*xperience and knowledge of the literature; *C*linical picture; and findings by high-resolution computed *T*omography (HRCT) of the chest [12, 25]. The DIRECT approach rests on our clinical experience with the diagnostic management of ARF in cancer patients but has never been evaluated. It consists in using criteria in each of the six above-listed categories to identify the most likely causes and help clinicians to select the urgent diagnostic investigations and appropriate empiric treatments.

The purpose of this study was to obtain preliminary information on the usefulness of DIRECT for identifying the cause of ARF in cancer patients. To this end, we assessed associations between aetiological diagnoses and DIRECT criteria.

PATIENTS AND METHODS

Patients with cancer and hypoxaemic ARF admitted to our closed ICU in a teaching hospital between November 1, 1997, and October 31, 2008, were identified in our database and included in this retrospective cohort study. The appropriate review board approved the study and waived the requirement for informed consent. Patients were excluded if they had no definite aetiological diagnosis for the episode of ARF, and if they had a documented co-infection with bacteria and opportunistic pathogen.

Cancer patients were defined as patients with active haematological malignancies or solid tumours and/or HSCT. ARF was defined by the presence of respiratory distress symptoms or PaO_2 on room air lower than 8 kPa or a need for ventilatory support. Neutropenia was defined as a neutrophil count <500 cells/mm^3 within 24 hours after ICU admission [26]. Septic shock was defined as an acute circulatory failure (systolic blood pressure lower than 90 mmHg or mean blood pressure lower than 60 mmHg combined to clinical signs of acute circulatory failure [cold extremities, skin mottling, oliguria, mental confusion]) persisting despite adequate fluid resuscitation and requiring vasopressors. Patient health before ICU admission was assessed using the Karnofsky performance status scale [27].

Microbiologically documented pneumonia was defined as an ARF episode consistent with bacterial infection and identification of pathogenic bacteria in sputum, BAL fluid, or blood cultures. Clinically documented pneumonia was defined as ARF without microbial documentation but consistent with bacterial infection, i.e., displaying at least two of the four following criteria: consolidation on chest radiography, purulent sputum and/or neutrophil alveolitis by BAL fluid analysis, and rapid resolution with antibiotics. Patients with a positive respiratory specimen but no clinical signs of pneumonia and those with sign of

pneumonia but non-pathogenic bacteria in the sputum were considered to have colonization. All other infections required microbial documentation.

Patient management was at the discretion of the attending physicians. The data reported in Tables 1 to 3 and in Figures 1 to 5 were collected for each study patient. The logistic organ dysfunction score (LOD), duration of invasive and non-invasive mechanical ventilation, time spent in the ICU, and vital status at ICU and hospital discharge were also collected [28].

All patients were investigated using a previously described diagnostic strategy that relies heavily on non-invasive tests [24]. Most of the patients underwent non-invasive tests to look for infections, such as sputum examination for bacteria, mycobacteria, and fungi; induced sputum for *Pneumocystis jirovecii* pneumonia; serum and blood tests for circulating *Aspergillus* galactomannan; blood cultures; specific polymerase chain reaction (PCR) tests for herpes viruses including Cytomegalovirus on blood and respiratory samples; PCR test for *P. jirovecii* on respiratory samples; immunofluorescence staining of respiratory samples to detect antigens of respiratory viruses (including influenza A and B viruses, respiratory syncytial virus, para-influenza viruses, and adenoviruses); and urine tests for bacterial antigens. Fiberoptic bonchoscopy with BAL was performed when deemed appropriate by the attending physician. Bronchoalveolar lavage fluid was collected as previously described [24] and was used for bacterial, mycobacterial, and fungal cultures; respiratory virus antigen detection by immunofluorescence; and cytological examination. Echocardiography, HRCT, and thoracocentesis were performed when deemed appropriate by the attending physician.

In all study patients, the aetiological diagnosis of ARF was established by the investigators based on a review of the medical charts. The diagnoses were based on clinical, radiographic, microbiological, and histological findings, according to predefined criteria [10, 23, 29]. The results of non-invasive tests (PCR for *Pneumocystis jirovecii* and

cytomegalovirus, or immunofluorescence for respiratory viruses) were not necessarily considered diagnostic, and they were interpreted according to the degree of clinical and radiological suspicion [14, 30]. For *Pneumocystis jirovecii*, a negative PCR test was used to rule out the diagnosis of pneumocystis pneumonia and a positive test was considered diagnostic only if there were radiographic criteria suggestive of the diagnosis (i.e. bilateral ground-glass opacities without pleural effusion). All other cases were considered to be contamination or airway colonization.

All invasive fungal infections were diagnosed according to criteria issued by the European Organisation for Research and Treatment of Cancer/Mycosis Study Group [31, 32]. Aetiologies of ARF were further divided into three categories requiring different treatments (i.e., antibacterial agents, antifungal and antiviral agents, or steroids and diuretics): bacterial pneumonia (either microbiologically documented or clinically documented); opportunistic pulmonary infection (*Pneumocystis jirovecii* pneumonia, pulmonary aspergillosis, viral pneumonia, and *Toxoplasma gondii* pneumonia); and non-infectious lung disorders including pulmonary oedema (with echocardiographic documentation), pulmonary drug toxicity, and pulmonary involvement with the malignancy (carcinomatous lymphangitis, leukostasis and pulmonary leukaemic infiltration, malignant pleural effusion, and lung cancer or metastasis).

The study variables were the DIRECT criteria except *E*xperience and knowledge of the literature (Table 1): *D*elay since symptom onset (less than 3 days, 4 to 7 days, or more than 7 days); pattern of *I*mmune deficiency (multiple myeloma, solid tumour, neutropenia, allogeneic HSCT, steroids, acute leukaemia, or lymphoproliferative diseases); *R*adiographic appearance (alveolar pattern, unilateral or bilateral pattern, interstitial pattern, cardiomegaly, or pleural effusion); *C*linical picture (fever, bronchial breathing, shock, and unilateral or

bilateral crackles); and HRC*T* findings (consolidation, ground-glass opacities, nodules, and/or septal lines).

Statistics

Quantitative parameters are reported as median and interquartile range (IQR) and qualitative parameters as number and percentage. Categorical variables were compared using the chi square test or Fisher's exact test and continuous variables using the Mann-Whitney U test or Wilcoxon test, as appropriate. Odds ratios (ORs) and their 95% confidence intervals (95%CIs) were computed.

We also used correspondence analysis to investigate the associations between the three above-mentioned diagnostic categories of ARF and DIRECT criteria. Correspondence analysis is a multivariate descriptive statistical technique for analysing two-way contingency tables by measuring the correlations between rows and columns. The distance between row and column points reflects the correlation between two variables: tightly correlated variables are located near each other. Thus, the association between any two variables can be depicted in a two-dimensional plane. This graphical presentation helps to detect unexpected associations between variables. Correspondence analysis provides information similar to that produced by factor analysis, although it is a non-parametric method and thus makes no assumption about distribution. The overall chi square value of the contingency table reflects the degree of departure from a purely random distribution of the distances between variables (here, diagnostic categories and DIRECT criteria). When no relationship exists, Chi square equals zero. Correspondence analysis partitions Chi square into two orthogonal dimensions. The advantage of this multivariate approach is that it analyses the data globally and takes into account the correlations among the variables, thus reducing bias in the results. The final

goal of correspondence analysis is to obtain meaningful albeit subjective interpretations of the two extracted dimensions.

Values of p smaller than 0.05 were considered significant. Statistical analyses were performed using Statview 5.0 (SAS Institute, Cary, NC, USA).

RESULTS

We included 424 cancer patients admitted to our ICU with ARF due to known causes during the study period. During the same period, 122 cancer patients were admitted with ARF of unknown cause, 97 with ARF due to suspected causes (e.g., diffuse alveolar haemorrhage) or miscellaneous causes (e.g., pulmonary embolism), and 11 patients with a documented co-infection with bacteria and opportunistic pathogen; these 230 patients were not included. Table 2 lists the main patient characteristics. All patients were admitted to the ICU for ARF and 144 (34%) also had shock at admission. At ICU admission, 149 (35%) patients had neutropenia, 193 (46%) were receiving steroids, and 292 (69%) were on antibiotics. Table 2 reports the life-supporting interventions and outcomes.

The diagnostic investigations for ARF included FOB-BAL in 277 (65%) patients and HRCT in 208 (49%). The main causes of ARF were bacterial infections in 201 (47%) patients, opportunistic pulmonary infections in 131 (31%), and non-infectious lung disorders in 92 (22%). Bacterial infections were microbiologically documented in 80 (40%) patients and clinically documented in 121 (60%). Table E1 in the online supplement lists the documented pathogens. The 131 patients with opportunistic pulmonary infections had invasive pulmonary aspergillosis (n=41, 31%), respiratory viral infections (n=37, 28%), *P. jirovecii* pneumonia (n=36, 27.5%), tuberculosis (n=6, 5%), mucormycosis (n=5, 4.5%), cytomegalovirus infection (n=2, 1.5%), fusariosis (n=2, 1.5%), *Scedosporium sp* infection (n=1, 1%), and *Toxoplasma gondii* infection (n=1, 1%). The diagnoses in the 92 patients with non-infectious lung disorders were pulmonary oedema (n=45, 49%), lung cancer or metastasis (n=45, 49%), and pulmonary drug toxicity (n=2, 2%, due to bleomycin and rituximab, respectively). Neither patient with drug toxicity underwent lung biopsy. Table 2 compares the three diagnostic groups. The prevalence of neutropenia was similar in the three

groups (35% in patients with bacterial pneumonia, 37% in those with opportunistic pulmonary infections, and 33% in those with non-infectious lung disorders; p=0.82). Patients with non-infectious lung disorders were less often on steroids at ICU admission (35% versus 46% in bacterial infections and 52% in opportunistic pulmonary infections; p=0.031) and those with bacterial pneumonia or opportunistic pulmonary infections more often received antibiotics before ICU admission (68% and 83%, respectively, versus 51%, p=0.002). Finally, patients with bacterial pneumonia more often had shock at admission (42% versus 28% in opportunistic pulmonary infection and 24% in non-infectious lung disorders; p=0.002).

Table 3 compares DIRECT criteria in the three diagnostic groups. Figure 1A shows the results of the correspondence analysis for *D*elay since symptom onset. Dimension 1 (horizontal axis) explained 29.3% and dimension 2 (vertical axis) 25.7% of the chi square value. The correspondence plot shows that patients with bacterial pneumonia more often had delays of less than 3 days since symptom onset. Figure 1B displays the correspondence analysis for the pattern of *I*mmune deficiency. Dimension 1 (horizontal axis) explained 18% and dimension 2 (vertical axis) 15.8% of the chi square value. The plot indicates associations of neutropenia, solid tumour, and multiple myeloma with bacterial pneumonia and associations of steroids, lymphoproliferative disorders, and HSCT with opportunistic pulmonary infection. Acute leukaemia was associated with non-infectious lung disorders. Figure 2A shows the correspondence analysis for *R*adiographic appearance. Dimension 1 (horizontal axis) explained 23% and dimension 2 (vertical axis) 18.7% of the chi square value. The plot shows a link between unilateral radiographic changes and bacterial infections. Figure 1C displays the correspondence analysis for *C*linical picture. Dimension 1 (horizontal axis) explained 20.3% and dimension 2 (vertical axis) 16.7% of the chi square value. Bacterial pneumonia was closely linked to shock at ICU admission and less closely

linked to unilateral crackles. Finally, Figure 2B shows the correspondence analysis for HRC*T* findings. Dimension 1 (horizontal axis) explained 22.4% and dimension 2 (vertical axis) 19.2% of the chi square value. The plot shows a link between unilateral HRCT changes and bacterial pneumonia.

DISCUSSION

Using an original methodology in a cohort of ICU patients, we investigated the usefulness of DIRECT criteria for the aetiological diagnosis of ARF in cancer patients. Strong links were documented between the three aetiological groups and DIRECT criteria.

Acute respiratory failure is a common and life-threatening event in cancer patients. It represents the leading reason for ICU admission in these patients and intensivists will be increasingly asked to managed these patients given growing incidence of cancer [1, 2] and the improved survival of cancer patients [3-9]. This condition still carries a mortality rate of about 50% overall, with even higher rates occurring in patients who require mechanical ventilation [10-14]. Studies conducted in the past decade have established that mortality in the ICU is no longer linked to the characteristics of the underlying disease but depends instead on the severity and reversibility of the ARF event [12, 33]. In particular, mortality is higher when investigations fail to identify the cause of ARF [10, 11, 13, 34]. Thus, rather than relying on broad-spectrum empirical treatments, improving the diagnostic strategy is crucial to increase survival rates [12, 24].

Based on our experience with cancer patients admitted to the ICU, we have suggested six categories of criteria for identifying the cause of ARF, which can be conveniently listed using the mnemonic DIRECT (Table 1) [12, 24, 25]. DIRECT may assist in the management of ARF in cancer patients by focusing the diagnostic investigations on the most likely causes and guiding empirical treatments [12, 24, 25, 35]. To assess the usefulness of DIRECT, we used correspondence analysis to investigate associations between three diagnostic categories of ARF having different therapeutic requirements and the DIRECT criteria. This descriptive non-parametric statistical method with a graphical display of the results showed that bacterial pneumonia was associated with rapid-onset ARF, typically occurring in patients

with neutropenia, multiple myeloma, or solid tumour and responsible for shock, unilateral crackles, and unilateral consolidations. However, these associations should be interpreted with great caution: in our experience, bacterial pneumonia is the main cause of ARF in patients with neutropenia, multiple myeloma, or solid tumour but can occur in patients with nearly all types of malignancy. We also found that opportunistic pulmonary infections occurred chiefly in patients with lymphoproliferative disorders, HSCT, or steroid therapy. These associations reflect the predominance among opportunistic pulmonary infections of invasive pulmonary aspergillosis, seen mainly in HSCT recipients [31], and pneumocystis pneumonia, a disease associated with lymphocyte dysfunction [36]. Finally, non-infectious lung disorders were associated with acute leukaemia. This association probably reflects the high proportion of patients with pulmonary leukostasis in the group with non-infectious lung disorders.

Given the multiplicity of aetiological diagnoses and of DIRECT criteria, a more detailed search for associations seems difficult because the number of comparisons would be too large for statistical validity. As stated above, correspondence analysis is useful to detect unexpected relations between variables. The main limitation of the method is that an observed association only makes sense when interpreted in the light of its clinical and pathophysiological plausibility. In our study cohort, univariate analysis was less effective in detecting associations between aetiologies of ARF and underlying malignancies. Nevertheless, not all aetiologies of ARF occur in all malignancies. This point underlines the usefulness of correspondence analysis. Correspondence analysis could be used to develop detailed clinical descriptions of each ARF aetiology in cancer patients.

Our study has several limitations. First, each item of the DIRECT approach was studied separately. The main limitation of the present study is that it was not designed to evaluate if the DIRECT approach as a whole and if it may be useful to separate patients

requiring different investigations and treatments. Second, patient management was at the discretion of the physicians in charge, and all diagnostic investigations were not done routinely in all patients. However, this study design reflects everyday clinical practice. Third, patients in whom the cause of ARF was not identified were not included in this preliminary study. Inclusion of these patients would probably have modified our results, and further studies are needed to investigate the usefulness of DIRECT criteria in unselected cancer patients with ARF. Also, the exclusion of patients who had co-infection with bacterial and opportunistic pathogen probably impacted our results. Fourth, associations detected by correspondence analysis must be interpreted with caution, in the light of pathophysiological and clinical factors. Fifth, our study did not evaluate the *E*xperience and knowledge of the literature item, which can be expected to play an important role in the effectiveness of DIRECT. Finally, our results were obtained in cancer patients and may not apply to patients with other causes of immunodeficiency.

In this cohort study, we used an original methodology to identify clear associations between groups of aetiological diagnoses and DIRECT criteria. These preliminary results suggest that an algorithm based on DIRECT criteria may be useful in clinical practice by narrowing the spectrum of possible aetiologies, thereby guiding urgent investigations and empirical treatments. Our promising results encourage further studies investigating the ability of DIRECT criteria to improve treatment decisions and patient survival.

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Authors' contributions to the study:

Study mentoring: Élie Azoulay

Study design, data collection and analysis: Élie Azoulay, Julien Mayaux, Jérôme Lambert and David Schnell.

Preparation and critical reviewing of the manuscript: all authors.

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Figure legends

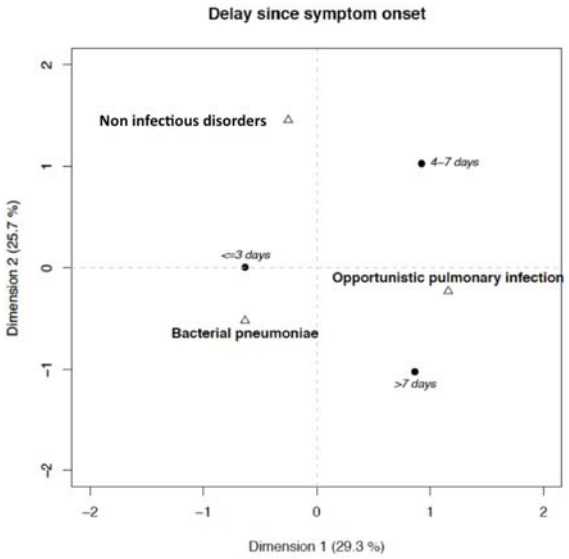
Figure 1

1-A. Correspondence plot for *D*elay since symptom onset

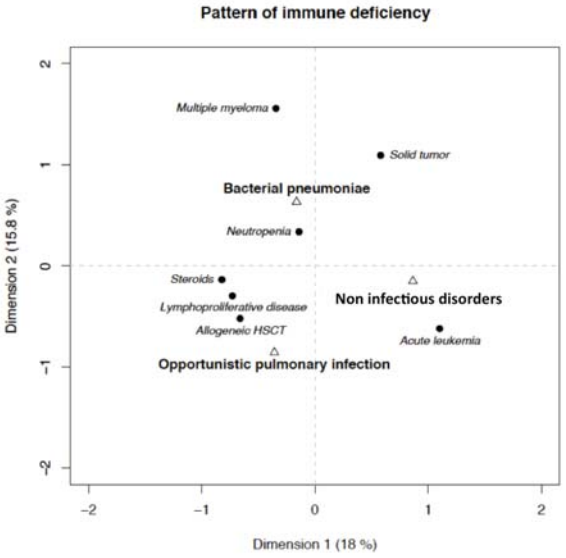
1-B. Correspondence plot for pattern of *I*mmune deficiency

1-C. Correspondence plot for *C*linical picture

1-A


Delay since symptom onset
Non infectious disorders
4–7 days
<=3 days
Opportunistic pulmonary infection
Bacterial pneumoniae
>7 days
Dimension 2 (25.7 %)
Dimension 1 (29.3 %)

1-B


Pattern of immune deficiency
Multiple myeloma
Solid tumor
Bacterial pneumoniae
Neutropenia
Steroids
Lymphoproliferative disease
Allogeneic HSCT
Non infectious disorders
Acute leukemia
Opportunistic pulmonary infection
Dimension 2 (15.8 %)
Dimension 1 (18 %)

1-C

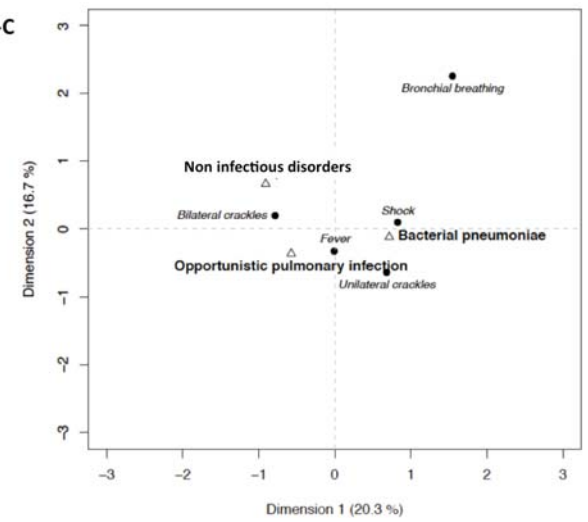
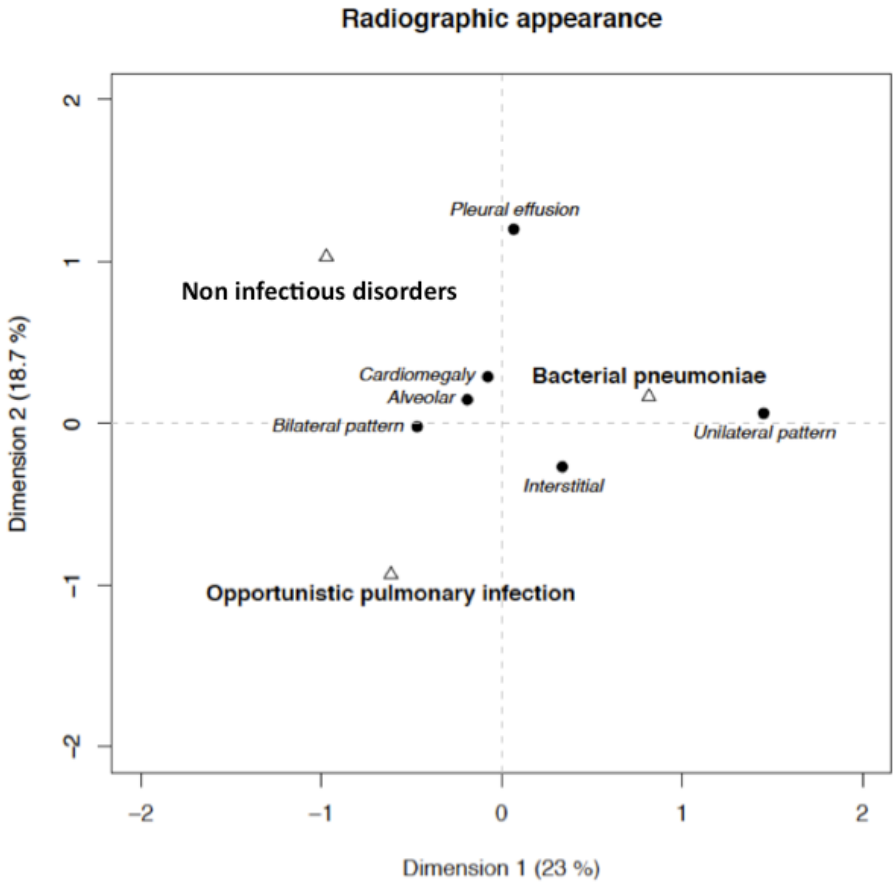

Clinical picture
Bronchial breathing
Non infectious disorders
Bilateral crackles
Shock
Bacterial pneumoniae
Fever
Opportunistic pulmonary infection
Unilateral crackles
Dimension 2 (16.7 %)
Dimension 1 (20.3 %)

Figure 2

2-A. Correspondence plot for *R*adiographic appearance

2.B. Correspondence plot for findings by high-resolution computed *T*omography of the chest

2-A


Radiographic appearance
Pleural effusion
Non infectious disorders
Cardiomegaly
Alveolar
Bilateral pattern
Bacterial pneumoniae
Unilateral pattern
Interstitial
Opportunistic pulmonary infection
Dimension 2 (18.7 %)
Dimension 1 (23 %)
2
1
0
−1
−2
−2
−1
0
1
2

2-B

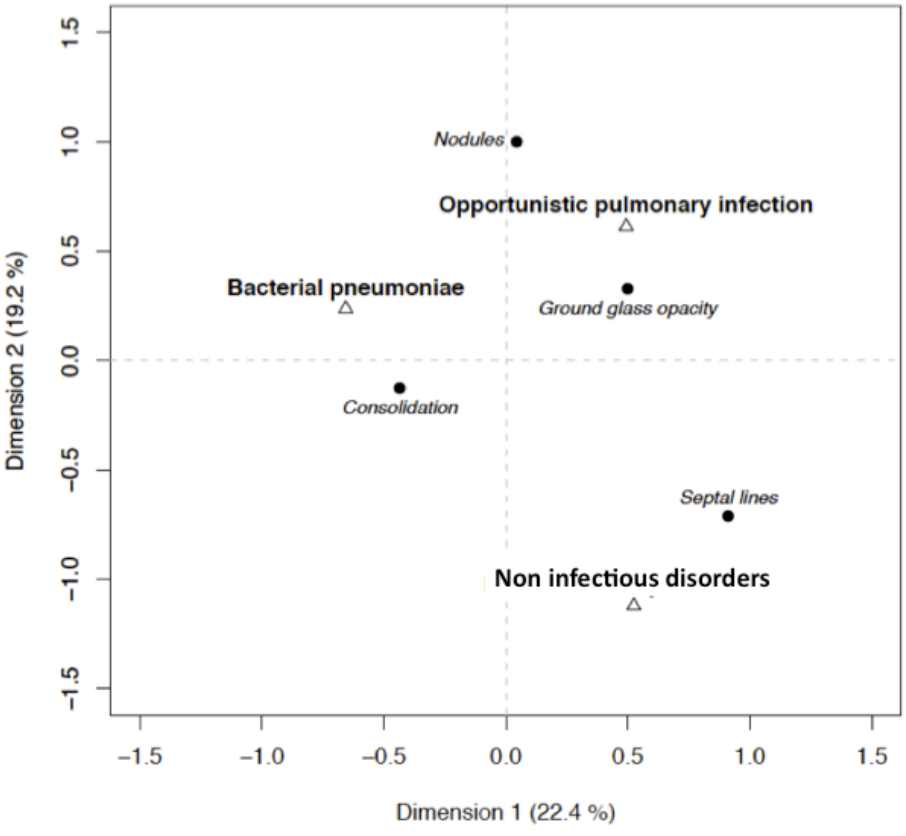

Tomodensitometry
Nodules
Opportunistic pulmonary infection
Bacterial pneumoniae
Ground glass opacity
Consolidation
Septal lines
Non infectious disorders
Dimension 2 (19.2 %)
Dimension 1 (22.4 %)
1.5
1.0
0.5
0.0
−0.5
−1.0
−1.5
−1.5
−1.0
−0.5
0.0
0.5
1.0
1.5

Table 1. DIRECT criteria for identifying the most likely causes of acute respiratory failure in cancer patients

DIRECT [12, 25]
Delay since malignancy onset or HSCT, since symptom onset, and since antibiotics / prophylaxis implementation
pattern of ***I***mmune deficiency
Radiographic appearance
Experience and knowledge of the literature
Clinical picture (including on-going chemoprophylaxis and effective antibiotic therapy)
findings by HRC***T***

HRCT, high-resolution computed tomography; HSCT, haematopoietic stem-cell transplantation.

Table 2. Baseline characteristics, underlying malignancy, need for life-supporting interventions, and outcomes of the 424 cancer patients with acute respiratory failure

Characteristics	Study cohort	Bacterial pneumonia	Opportunistic pulmonary infections	Non-infectious lung disorders	*p* value
Patients	424	201	131	92	/
Gender (male)	275 (65%)	131 (65%)	87 (66%)	57 (62%)	0.78
Age in years, median (IQR)	58 (45-67)	59 (48-69)	56 (42-65)	59 (46-67)	0.08
Hypertension	109 (26%)	56 (28%)	32 (24%)	21 (23%)	0.77
Chronic heart failure	96 (23%)	41 (20%)	38 (29%)	17 (19%)	0.73
Diabetes mellitus	52 (12%)	29 (14%)	7 (5%)	16 (17%)	0.023
Performance status 3 or 4	19 (5%)	10 (5%)	3 (2%)	6 (7%)	0.48
Delay since respiratory symptom onset[&], median (IQR)	**3 (1-6)**	**2 (1-5)**	**4 (1-8)**	**2 (1-6)**	**0.0034**
Underlying disease					
Lymphoproliferative disorder	**141 (33%)**	**65 (32%)**	**51 (39%)**	**25 (27%)**	**0.091**
Acute leukaemia	**110 (26%)**	**41 (20%)**	**35 (27%)**	**34 (37%)**	**0.012**
Multiple myeloma	**48 (11%)**	**36 (18%)**	**6 (5%)**	**6 (7%)**	**0.195**
Allogeneic HSCT	**60 (14%)**	**25 (12%)**	**25 (19%)**	**10 (11%)**	**0.15**

Solid tumours	**65 (15%)**	**34 (17%)**	**14 (11%)**	**17 (19%)**	**0.18**
Delay since malignancy diagnosis in days, median (IQR)	**237 (52-1023)**	**384 (62-1428)**	**225 (68-830)**	**167 (24-495)**	**0.0063**
Life-supporting interventions and outcomes					
Mechanical ventilation	328 (77%)	150 (75%)	119 (91%)	59 (64%)	<0.0001
NIV alone	99 (23%)	48 (24%)	37 (28%)	14 (15%)	0.065
NIV failure	123 (29%)	47 (23%)	52 (40%)	24 (26%)	0.005
Need for vasopressors	**217 (51%)**	**108 (54%)**	**69 (53%)**	**40 (44%)**	**0.24**
Renal replacement therapy	82 (19%)	43 (21%)	22 (17%)	17 (19%)	0.57
LOD at admission	6 (4-9)	6 (4-9)	6 (4-10)	5 (3-8)	0.62
Time spent in the ICU in days, median (IQR)	8 (4-15)	8 (4-15)	10 (5-19)	7 (4-12)	0.003
ICU mortality	142 (34%)	69 (34%)	57 (44%)	16 (17%)	0.0001
Hospital mortality	178 (42%)	78 (39%)	66 (50%)	34 (37%)	0.17

Data are number (percent), unless otherwise stated. Results are from the univariate analysis. Data in bold are those relevant to DIRECT criteria.

IQR, interquartile range; HSCT: haematopoietic stem cell transplantation; ICU, intensive care unit; LOD, Logistic Organ Dysfunction score; NIV, non-invasive ventilation.

Table 3. Univariate analysis of associations between DIRECT criteria and aetiological groups of acute respiratory failure in cancer patients

Characteristics	Overall population n=424	Bacterial pneumonia, n=201	Opportunistic pulmonary infections n=131	Non-infectious lung disorders n=92	*p* value
D*elay*					
Delay since malignancy onset or HSCT in days, median (IQR)	237 (52-1023)	384 (62-1428)	225 (68-830)	167 (24-495)	0.0063
Delay since symptom onset in days, median (IQR)	3 (1-6)	2 (1-5)	4 (1-8)	2 (1-6)	0.0034
*Patterns of **I**mmune deficiency*					
Lymphoproliferative disorder	141 (33%)	65 (32%)	51 (39%)	25 (27%)	0.091
Acute leukaemia	110 (26%)	41 (20%)	35 (27%)	34 (37%)	0.012
Multiple myeloma	48 (11%)	36 (18%)	6 (5%)	6 (7%)	0.195
Allogeneic HSCT	60 (14%)	25 (12%)	25 (19%)	10 (11%)	0.15
Solid tumours	65 (15%)	34 (17%)	14 (11%)	17 (19%)	0.18
Neutropenia	149 (35%)	71 (35%)	48 (37%)	30 (33%)	0.82
Steroids	193 (46%)	93 (46%)	68 (52%)	32 (35%)	0.031
R*adiographic appearance*					
Cardiomegaly	262 (62%)	124 (62%)	80 (61%)	58 (63%)	0.80

Unilateral pattern	94 (22%)	75 (37%)	15 (12%)	4 (4%)	<0.0001
Interstitial	139 (33%)	69 (34%)	41 (31%)	29 (32%)	0.77
Alveolar	246 (58%)	116 (58%)	80 (61%)	50 (54%)	0.62
Pleural effusion	102 (24%)	48 (24%)	25 (19%)	29 (32%)	0.11
C*linical picture*					
Bronchial breathing	24 (6%)	18 (9%)	3 (2%)	3 (3%)	0.016
Bilateral crackles	149 (35%)	49 (24%)	61 (47%)	39 (42%)	<0.0001
Unilateral crackles	112 (26%)	73 (36%)	21 (16%)	18 (20%)	<0.0001
Shock at admission	144 (34%)	85 (42%)	37 (28%)	22 (24%)	0.002
*Findings by HRC****T***, n (% of patients with HRCT)					
Nodules	113 (26%)	62 (31%)	33 (25%)	18 (12%)	0.35
Ground glass opacity	237 (56%)	103 (51%)	84 (64%)	50 (54%)	0.23
Consolidation	300 (70%)	156 (78%)	84 (64%)	60 (65%)	0.09
Septal lines	101 (24%)	40 (20%)	29 (22%)	32 (35%)	0.11
Halo signs	29 (7%)	18 (9%)	10 (8%)	1 (2%)	0.18

Data are number (percent), unless otherwise stated. Results are from the univariate analysis.

IQR, interquartile range; HRCT, high-resolution computed tomography; HSCT, haematopoietic stem-cell transplantation.