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In a pre-planned analysis of immunocompromised critically ill patients with acute respiratory failure, bronchoscopy was associated with better diagnosis and management but worse outcome. The decision to perform bronchoscopy should be individualised. http://bit.ly/2Dusahh

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ABSTRACT

Objective: We wished to explore the use, diagnostic capability and outcomes of bronchoscopy added to noninvasive testing in immunocompromised patients. In this setting, an inability to identify the cause of acute hypoxaemic respiratory failure is associated with worse outcome. Every effort should be made to obtain a diagnosis, either with noninvasive testing alone or combined with bronchoscopy. However, our understanding of the risks and benefits of bronchoscopy remains uncertain.

Patients and methods: This was a pre-planned secondary analysis of Efraim, a prospective, multinational, observational study of 1611 immunocompromised patients with acute respiratory failure admitted to the intensive care unit (ICU). We compared patients with noninvasive testing only to those who had also received bronchoscopy by bivariate analysis and after propensity score matching.

Results: Bronchoscopy was performed in 618 (39%) patients who were more likely to have haematological malignancy and a higher severity of illness score. Bronchoscopy alone achieved a diagnosis in 165 patients (27% adjusted diagnostic yield). Bronchoscopy resulted in a management change in 236 patients (38% therapeutic yield). Bronchoscopy was associated with worsening of respiratory status in 69 (11%) patients. Bronchoscopy was associated with higher ICU (40% *versus* 28%; p<0.0001) and hospital mortality (49% *versus* 41%; p=0.003). The overall rate of undiagnosed causes was 13%. After propensity score matching, bronchoscopy remained associated with increased risk of hospital mortality (OR 1.41, 95% CI 1.08–1.81).

Conclusions: Bronchoscopy was associated with improved diagnosis and changes in management, but also increased hospital mortality. Balancing risk and benefit in individualised cases should be investigated further.

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Introduction

In immunocompromised patients, acute hypoxaemic respiratory failure is a frequent complication leading to ∼50% 90-day mortality [1–4]. Inability to identify the cause of respiratory failure is associated with worse outcome [5]. Therefore, every effort should be made to obtain a diagnosis by noninvasive and, if necessary, invasive testing such as bronchoscopy [6]. In patients with malignancy, ∼90% of acute respiratory distress syndrome is due to infections [7]. Due to the poor tolerance to hypoxaemia, the effectiveness of bronchoscopy may be mitigated by the risk of respiratory deterioration and the need for ventilator support [5, 8]. Bronchoscopy is certainly useful in some instances, such as when a nasopharyngeal viral panel is falsely negative [9] or when induced sputum to assess, for example, *Pneumocystis jirovecii* cannot be obtained. Overall, the rate of intubation for respiratory failure can reach 35% after bronchoscopy [5] and the rate of unidentified aetiologies remains substantial [10].

Most studies regarding bronchoscopy have been performed in relatively small cohorts of patients and may have been underpowered to detect any benefit or harm associated with the bronchoscopy itself [5, 8, 10, 11]. Moreover, the yield of bronchoscopy declines rapidly with time after clinical presentation [12]. Early use of broad-spectrum antimicrobials may reduce the likelihood of a positive microbiological diagnosis. Thus, the added utility of early bronchoscopy to noninvasive testing alone is still uncertain. On the one hand, clinicians may be reluctant to perform bronchoscopy in hypoxaemic patients because of concern for respiratory deterioration. On the other hand, they may feel compelled to perform bronchoscopy in spite of a low pre-test probability for fear of missing an unrecognised pathogen or aetiology (*e.g.* alveolar haemorrhage). Therefore, a contemporary study on a larger cohort of patients offered a unique opportunity to explore the use, diagnostic capability and outcomes of bronchoscopy when added to noninvasive testing.

We performed a pre-planned secondary analysis of the Efraim study, a prospective, multinational, observational study on acute hypoxaemic respiratory failure in immunocompromised patients, performed by the Nine-I (CarIng for CrItIcally Ill Immuno-compromIsed PatIents MultInatIonal Network) investigators [13]. Our objective was to address the diagnostic utility of bronchoscopy when added to noninvasive testing, the influence of bronchoscopy results on patient management, the association between

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bronchoscopy and mortality, and to assess the complications associated with bronchoscopy including respiratory deterioration or unanticipated cardiac arrest. Our hypothesis was that bronchoscopy, with limited complications, would reduce the number of unidentified causes of respiratory failure and be associated with reduced hospital mortality.

Methods

Study methodology has been described elsewhere [13]. In brief, 1611 patients were enrolled in 62 intensive care units (ICUs) from 16 countries between October 2015 and June 2016 with a 3-month follow-up. We included adult patients with known immunosuppression (immunosuppressive drugs, solid tumour, solid organ transplant, haematological malignancies and haematological stem cell transplant) who were admitted to the ICU with acute hypoxaemic respiratory failure (respiratory rate >30 breaths·min^{-1}, laboured breathing, arterial oxygen saturation measured by pulse oximetry <90% or arterial oxygen tension (P_{aO_2}) <60 mmHg on room air or need for >4 L·min^{-1} oxygen, or need for mechanical ventilation). Patients were excluded if they were admitted to the ICU after cardiac arrest, or only to secure bronchoscopy, had elective surgery within 6 days, or had respiratory failure occurring <7 days after solid organ transplant.

The primary outcome was in-hospital mortality. The primary exposure was bronchoscopy performed in the ICU. Covariates included demographics, type of immunosuppression, comorbidities, Sequential Organ Failure Assessment (SOFA) score, symptoms and degree of respiratory failure, all measured at baseline. Two groups, those who underwent bronchoscopy in the ICU coupled with noninvasive testing and those who did not get bronchoscopy but only noninvasive testing, were compared with each other by bivariate analyses. Results are expressed as median and interquartile range or number and percentage as appropriate. Wilcoxon rank sum test or Fisher's exact test was used to compare variables between groups as appropriate. Potential confounders were defined as any available variable on admission that could be associated with bronchoscopy, had a prognostic value, and did not reside in the causal pathway between bronchoscopy and hospital mortality [14]. To adjust for any of those variables, logistic regression and propensity matching were used [15]. We developed a propensity score logistic model based on the probability of having received bronchoscopy and then matched individuals on the basis of their propensity score using a 1:1 matching algorithm without replacement within a calliper of 0.1 SD of the logit of the propensity score. To handle missing data in confounders, MICE (multiple imputation with chained equations) was used for the model, where the propensity score for each patient was averaged across 30 completed datasets (including those confounders and some auxiliary variables such as sex and tobacco use, as well as the outcomes as recommended), while matching used these averaged scores to estimate the treatment effect [16]. Imbalances, before and after matching, were measured by standardised mean differences and area under the curve of the propensity score model [17]. To test for centre effect, we plotted outcome by centre and subsequently used a funnel plot to test for heterogeneity. Several sensitivity analyses were also performed. All analyses were performed using R version 3.3.2 (www.R-project.org); all tests were two-sided with p-values $\leqslant$0.05 denoting statistical significance.

Results

Patient characteristics

Of the 1611 patients, 24 lacked information on bronchoscopy and were excluded (figure 1). Of the remaining 1587 patients, 618 (39%) underwent flexible fibreoptic bronchoscopy coupled with noninvasive investigations and 969 (61%) underwent noninvasive investigations alone (table 1).

Patients in the bronchoscopy group were younger, had a longer duration of symptoms and were admitted later to the ICU after hospital admission than those in the nonbronchoscopy group. More patients in the bronchoscopy group had haematological disease, haematopoietic stem cell transplant and solid organ transplant. They were less likely to have a solid organ tumour or chronic obstructive pulmonary disease (COPD), and more likely to have a higher Eastern Cooperative Oncology Group performance status score (supplementary tables S1 and S2). SOFA score on admission was higher, notably for its respiratory and haematological components (supplementary table S3). On admission, patients in the bronchoscopy group had more respiratory symptoms, higher arterial partial pressure of carbon dioxide and lower P_{aO_2}/inspiratory oxygen fraction (F_{IO_2}) ratio (supplementary table S4). Initial goals of care were different, with more "full-code" directives on admission in the bronchoscopy group.

Diagnosis

In the bronchoscopy group, the cause of acute respiratory failure was less often identified on admission, in spite of having more pre-ICU bronchoscopies. Although noninvasive testing was performed more often, the rate of unidentified cause by noninvasive testing alone remained higher (table 2). Specifically, there were fewer positive blood cultures and fewer positive urine antigens (*e.g. Streptococcus pneumoniae*);

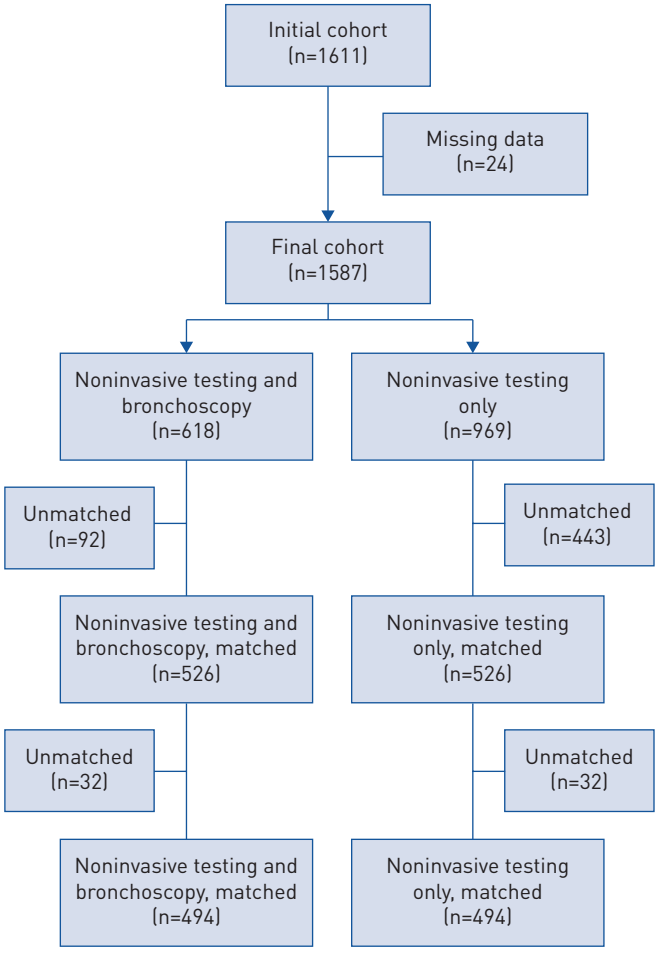

FIGURE 1 Study flowchart with initial matching (n=526) and subsequent matching (n=494) adding the variables "bronchoscopy prior to intensive care unit admission", "goal of care discussion" and "disease stage status".

C-reactive protein values were higher. On chest radiography and computed tomography scan, alveolar opacities involved more quadrants, with more evidence of fibrosis (supplementary table S5). After bronchoscopy, the rate of unidentified cause reached 13% and was identical to the nonbronchoscopy group. Open lung biopsy was rarely performed: 13 (2%) patients in the bronchoscopy group and six (1%) patients in the nonbronchoscopy group. There were more infectious causes in the bronchoscopy group, including more diagnoses for *P. jirovecii* (supplementary table S6).

Among the 618 patients who underwent bronchoscopy in the ICU (supplementary table S7), at least 90% underwent bronchoalveolar lavage and a few had either protected bacterial distal sampling (14%) or transbronchial biopsy (5%). Bronchoscopy was most commonly performed by the intensivist (55%) and less often by an external consultant (34%). It was the first-line diagnostic strategy in 45%. The majority of patients who had bronchoscopy were intubated and ventilated (61%), 13% were receiving standard oxygen, 4% high-flow nasal cannula therapy and 4% noninvasive ventilation; the type of respiratory support was not specified in 18% of patients. Respiratory status worsened after bronchoscopy in 11% of patients; clinical details of worsening respiratory status were not collected. Diagnosis was obtained by bronchoscopy in 49% of patients and achieved by noninvasive testing methods in 22% as well, giving an adjusted diagnosis yield of 27%. The therapeutic yield was 38% and prompted a change in management, adding a new treatment in 12% or withdrawing antibiotics in 26%. There was no difference in the diagnosis achieved by bronchoscopy between intensivist and external consultant, but the therapeutic yield was greater when the bronchoscopy was performed by an intensivist (48% *versus* 35%; p=0.01).

Outcome

Overall, more patients in the bronchoscopy group were intubated and were also intubated sooner than in the nonbronchoscopy group (table 3). The bronchoscopy group presented with more cases of septic shock and required more ICU support (*e.g.* fluids, vasopressors and renal replacement therapy). The bronchoscopy group was also more often on immunosuppressive medications, including corticosteroids, within the first 7 days of ICU admission. The perception of complexity of medical and ICU management

TABLE 1 Characteristics of patients according to diagnostic group

	NIT-FOB		NIT		p-value
	n	Statistics	n	Statistics	
Subjects	618		969		
Sex					
Male	356	58.3	583	60.4	0.43
Female	255	41.7	382	39.6	
Age years	587	62.3 (53.3–69.9)	927	64.7 (55.2–72.4)	0.0009
Height cm	588	170 (162–175)	889	170 (163–177)	0.073
Weight kg	610	73 (62–84)	922	72 (62–85)	0.63
Duration of symptoms days	586	2 (0–6)	936	1 (0–3)	<0.0001
Location before ICU					
Emergency room	93	16.3	251	27.5	<0.0001
Ward	347	61.0	505	55.3	
Other	129	22.7	157	17.2	
Same day ICU admission	160	26.4	355	37.0	<0.0001
SOFA score on admission	615	8 (4–10.5)	960	7 (4–10)	0.0009
Duration of disease days	344	166 (21–593)	595	113 (11–728)	0.34
Haematological malignancy any	346	56.0	482	49.7	0.017
Haematopoietic stem cell transplant					
Autologous	44	7.1	56	5.8	<0.0001
Allogeneic	82	13.3	69	7.1	
Systemic disease	124	20.1	153	15.8	0.034
Solid organ tumour	168	27.2	382	39.4	<0.0001
Solid organ transplant	78	14.1	63	7.3	<0.0001
Corticosteroid use	495	0 (0–22)	802	0 (0–15)	0.006
Neutropenia	95	16.4	154	16.4	1.00

Data are presented as % or median (interquartile range), unless otherwise stated. NIT-FOB: noninvasive testing coupled with fibreoptic bronchoscopy; NIT: noninvasive testing only; ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment.

was higher. Invasive fungal infections, drug toxicity and ventilator-associated pneumonias were more frequent. Cardiac arrest after intubation was rare: 20 (1%) patients and the frequency was the same in both groups. During ICU stay, end-of-life discussions led to more conversion to do-not-resuscitate status in the bronchoscopy group. Duration of mechanical ventilation and ICU length of stay were longer, and ICU, hospital and 90-day mortality were higher, in the bronchoscopy group (table 3). There was no difference in hospital mortality when the bronchoscopy was performed by an external consultant, with 39% ICU mortality and 47% hospital mortality *versus* 42% and 49%, respectively, when performed by an intensivist. Among 167 (27%) patients for whom bronchoscopy was both first-line diagnostic strategy and achieved diagnosis alone, 74 (31%) died in the ICU and 85 (36%) died in the hospital, which is in agreement with estimates from the whole cohort (32% and 42%, respectively). Of the 236 (38%) patients with treatment

TABLE 2 Causes and diagnosis yield of acute respiratory failure according to diagnostic group

	Total	NIT-FOB	NIT	p-value
Subjects	1587	618	969	
Infectious	938 (59)	421 (68)	517 (53)	<0.0001
Pneumocystis jirovecii	69 (4)	48 (8)	21 (2)	<0.0001
Noninfectious[#]	440 (28)	112 (18)	328 (34)	<0.0001
Diagnosis				
Identified on admission	825 (52)	263 (43)	562 (58)	<0.0001
Identified with noninvasive testing	318 (20)	135 (22)	283 (29)	0.0125
Identified with bronchoscopy alone	167 (11)	167 (27)		
Unidentified	209 (13)	85 (14)	124 (13)	0.595

Data are presented as n or n (%), unless otherwise stated. NIT-FOB: noninvasive testing coupled with fibreoptic bronchoscopy; NIT: noninvasive testing only. [#]: excluding those with unknown diagnosis.

TABLE 3 Outcome according to diagnostic group

	NIT-FOB		NIT		p-value
	n	Statistics	n	Statistics	
Subjects	618		969		
Intubation	533	86.3	446	46.0	<0.0001
Timing of intubation					
0–48 h	410	66.3	370	38.2	<0.0001
>48 h	123	19.9	76	7.8	
Length of ventilation days	351	7 (3–12)	304	3 (1–8)	<0.0001
Goal of care on admission					
Full code	522	84.5	723	74.6	<0.0001
ICU trial	20	3.2	49	5.1	
Early ICU	11	1.8	17	1.8	
DNI	3	0.5	55	5.7	
DNR	10	1.6	44	4.5	
None/unknown	52	8.4	81	8.4	
Fluids expansion on day 1 mL	554	1500 (500–3000)	873	1170 (300–2500)	0.0007
Vasopressors days 1–7	455	73.6	467	48.2	<0.0001
Low-dose steroids days 1–7	221	39.0	287	33.0	0.023
High-dose steroids days 1–7	162	28.2	169	19.0	<0.0001
Septic shock days 1–7	329	53.2	349	36.0	<0.0001
Dialysis days 1–7	142	23.0	153	15.8	0.0004
End-of-life decision					
None	421	68.1	731	75.4	0.0004
No escalation	60	9.7	79	8.2	
Withholding	33	5.3	62	6.4	
Withdrawing	104	16.8	97	10.0	
ICU length of stay days	598	11 (6–19)	955	5 (2–9)	<0.0001
Hospital length of stay days	511	28 (16–49)	835	18 (9–34)	<0.0001
ICU mortality	248	40.1	267	27.6	<0.0001
Hospital mortality	294	49	378	41	0.003
90-day mortality	325	60.5	436	53.7	0.016

Data are presented as % or median (interquartile range), unless otherwise stated. NIT-FOB: noninvasive testing coupled with fibreoptic bronchoscopy; NIT: noninvasive testing only; ICU: intensive care unit; DNI: do not intubate; DNR: do not resuscitate.

change only due to bronchoscopy, 88 (37%) died in the ICU and 103 (44%) died in the hospital, which is also close to that observed in the whole cohort.

All identifiable confounders (supplementary table S8) were imbalanced between both groups, as measured by their standardised mean difference (supplementary table S9 and supplementary figure S1), and thus were included in the model [18]. Of the 618 patients in the bronchoscopy group, 92 could not be matched, leaving a matching sample size of 526 in each group (supplementary figure S2). Before matching, performing a bronchoscopy in the ICU was associated with increased odds of death of 38% and 41% after matching for age, performance status, symptoms, severity, type of immunosuppression, type of admission and respiratory status (table 4 and figure 2). Although we found some heterogeneity in outcome among centres, there was no evidence of centre effect for diagnostic testing (supplementary figure S3). We also found no change in the result when the variable "bronchoscopy before ICU admission" was added to the model. Although hospital mortality ranged from 32% in patients whose disease was in remission up to 56% in those whose disease was uncontrolled, the odds of dying did not change, and remained 41% higher in the bronchoscopy group when goals of care and disease severity were also added to the model. Hospital mortality was 49% in the bronchoscopy group overall and 44% (55 out of 124) in patients with bronchoscopy who could not be matched and were not included in the propensity score logistic model.

Discussion

In this study of acute hypoxaemic respiratory failure in immunocompromised patients around the world, bronchoscopy was performed in less than half of patients and yielded a diagnosis in about half of the cases. Bronchoscopy influenced management in approximately one-third of patients. It was performed more often in intubated patients and was associated with some risk of respiratory deterioration. With bronchoscopy, the rate of undiagnosed causes, which was higher in that group otherwise, became, after

TABLE 4 Estimate of the effect of bronchoscopy on hospital mortality

Model	Patients n	AUC	OR (95% CI)	p-value
Original sample	618	0.726	1.38 (1.12–1.70)	0.002
Original sample, with random centre effect	618	0.698	1.51 (1.19–1.91)	0.0005
Matched sample, initial	526	0.4994	1.41 (1.08–1.81)	0.006
Matched sample, with random centre effect	526	0.699	1.11 (1.03–1.18)	0.0045
Matched also with "bronchoscopy prior to ICU" feature	526	0.5013	1.41 (1.09–1.84)	0.010
Matched also with "goals of care" and "disease status"	494	0.4980	1.41 (1.08–1.81)	0.006

AUC: area under the curve; ICU: intensive care unit.

bronchoscopy, identical to that in the nonbronchoscopy group. Bronchoscopy was associated with increased ICU and hospital mortality, even after adjusting for multiple severity criteria. Several reasons for this association are possible and could include: 1) bronchoscopy itself may increase the risk of mortality in this population, 2) bronchoscopy may be just a marker of disease severity, 3) bronchoscopy may be just a marker of underlying diagnoses with worse prognoses or without effective therapies, as eventually bronchoscopy was performed out of "desperation", or 4) one or more unmeasured confounders associated with ICU bronchoscopy are driving the increased risk of mortality.

What are some limitations of this study? First, data collection methods were predetermined [19] and therefore subject to data selection bias [20]. Second, the use of bronchoscopy was heterogeneous and may have reflected a different case mix or different practices. We did not collect data on the timing of bronchoscopy relative to ICU admission, the volume of fluid used for the lavage or the timing and severity of respiratory worsening following bronchoscopy. Third, ICU severity was assessed by SOFA score and not Acute Physiologic Assessment and Chronic Health Evaluation (APACHE), although SOFA has proven to be superior to APACHE II to predict hospital mortality in allogeneic stem cell transplant recipients [21]. Fourth, we used a propensity score approach that explicitly modelled the treatment selection assignment process using the observed background characteristics. However, this assumed that there were no unmeasured confounders. Otherwise, to remove the bias caused by unmeasured confounding, instrumental variable analysis would be an alternative approach provided that key assumptions (some of which are also untestable) were met. Notably, the effect of the instrumental variable on the dependent measure should be entirely mediated *via* its effect on exposure assignment. In ICU settings, previously used instrumental variables consisted of the bed availability at the time of assessment for ICU transfer [22, 23] or the physician's main specialisation [24]. Unfortunately, such instruments were not measured in our study. The need for reporting such variables in ICU cohorts should be highlighted for further studies.

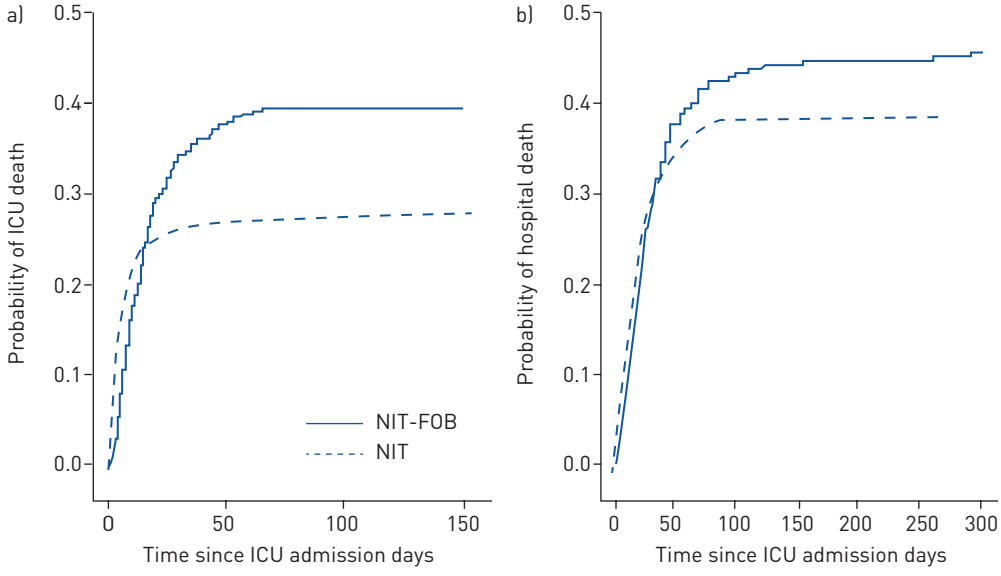

FIGURE 2 Observed cumulative risk of death in the a) intensive care unit (ICU) or b) hospital after matching on propensity score. NIT-FOB: noninvasive testing coupled with fibreoptic bronchoscopy; NIT: noninvasive testing only.

Is bronchoscopy harmful? In a prospective observational study of 148 patients with malignancy, 49% of nonintubated patients had respiratory deterioration and 36% required ventilator support [5]. In a subsequent randomised trial of 219 patients [8], the need for mechanical ventilation was no different with (35%) or without (39%) bronchoscopy and the proportion of patients that remained without diagnosis was the same with (22%) or without (20%) bronchoscopy. In both studies, hospital mortality did not differ between the two groups [5, 8]. Risk factors of death were not linked to bronchoscopy, but to disease characteristics, failure to identify the cause of acute respiratory failure and the need for mechanical ventilation or vasopressors [5]. In another study in 169 patients with acute respiratory failure, bronchoscopy was complicated by an increase in respiratory support within the subsequent 24 h in 35% of cases, of which 15% led to intubation; COPD and immunosuppression were associated with need for invasive mechanical ventilation [25]. In an observational study of 164 intubated patients, bronchoscopy and bronchoalveolar lavage were frequently associated with a decline in the P_{aO_2}/F_{IO_2} ratio (29%) within 1 h and haemodynamic instability (22%) within 24 h following the procedure [26].

Our rate of 13% unidentified cause is identical to recent data in the literature showing that failure to identify a cause is associated with a higher rate of invasive mechanical ventilation and hospital mortality [10]. In our study, bronchoscopy corrected the diagnostic gap with the noninvasive group but did not reduce further the rate of unidentified cause. Bronchoscopy was also complicated by worsening respiratory failure in some patients. Although the timing of bronchoscopy relative to intubation was not collected, more patients in this group were intubated and mechanically ventilated sooner after arrival in the ICU than in the nonbronchoscopy group and we suspect it was either for the purpose of the procedure or as a consequence, or because of their degree of respiratory failure, possible delayed ICU admissions or other conditions such as shock [2, 27]. Despite having balanced the propensity score with identifiable confounders, we may have unmasked confounders such as intubation itself which influences both bronchoscopy and outcome [28]. Although the patients in the bronchoscopy group were more severely ill, the effect of bronchoscopy persisted after adjustment for severity. Clinicians tend to underestimate harms and overestimate benefits of testing [29], and we suspect that bronchoscopy itself could be a marker of severity, *i.e.* a case of over-testing in a desperate attempt to find a diagnosis.

Can bronchoscopy be beneficial? Our findings are very similar to a small retrospective study of 35 patients with neutropenic fever and pulmonary infiltrates in which bronchoscopy yielded a diagnosis in 49% [11]. Consequently, a change in management occurred in 51% of patients. Although complications were limited (9%), the 28-day mortality was highest in patients who were mechanically ventilated prior to bronchoscopy. Similar findings were obtained in a small retrospective study of 26 bronchoscopies with a positive sampling in 23% of patients, a change in management in 38% and a low complication rate (8%) [30]. The same was also observed in a study comparing bronchoalveolar lavage alone or combined with protected specimen brushing, yielding a diagnosis in 43% and 57%, respectively [31]. Combining noninvasive testing with bronchoscopy more often yielded a diagnosis (70%) and altered management (55%) in a prospective series of 128 patients with neutropenic fever and pulmonary infiltrates, and survival was higher when the diagnosis was made early [32]. A randomised trial comparing noninvasive testing alone or coupled with bronchoscopy in nonintubated patients demonstrated that information added with bronchoscopy was relatively modest (18%), but the procedure was safe with no impact on the rate of intubation or 28-day survival rate [8]. A French expert panel recommended that the search for a diagnosis should be a primary objective in acute respiratory failure in immunocompromised and neutropenic patients, with early management being associated with a better risk/benefit ratio. It should systematically consider type of malignancy, immunosuppression, prophylaxis and clinical presentation of the failure, in order to establish a pre-test probability that will better define the respective role of noninvasive and invasive procedures such as bronchoscopy [33]. The British Thoracic Society guidelines recommended that bronchoscopy with bronchoalveolar lavage be considered in immunosuppressed patients to provide diagnostic information (Grade C) when a diagnosis is not likely to be obtained noninvasively [34]. Bronchoscopy is instrumental in identifying specific infectious causes, such as *Aspergillus* and *P. jirovecii* [35], or noninfectious causes, such as diffuse alveolar haemorrhage. Delaying diagnosis of pneumocystis pneumonia is associated with worse outcome [36]. Galactomannan testing in bronchoalveolar lavage is highly specific and more sensitive than serum testing [37]. Finding an infectious aetiology with early change in antibiotic treatment is associated with better outcomes [38]. However, in the era of empiric therapy with broad-spectrum antibiotics and antifungal agents, a recent retrospective study of 101 patients, including children, with cancers or haematopoietic stem cell transplant showed that bronchoscopy led to few changes in management (33%) and few complications except when biopsies were performed [39]. In 71 patients with haematological malignancies, bronchoscopy, indicated for respiratory failure or sepsis, led to a change in management in 45% of patients while complications occurred in 13%, some serious and leading to prolonged mechanical ventilation, need for tracheostomy and increased risk of death. Age, sex, APACHE II score and active chemotherapy did not predict management change or complications

post-bronchoscopy [40]. In our study, indiscriminate bronchoscopy itself may have contributed to worse outcome. The finding of this large prospective, multicentre, multinational observational study is likely representative and generalisable. Patients were severely ill, had a high intubation rate and high mortality. This study suggests that the use of bronchoscopy should be individualised and tailored to specific needs (*e.g.* nonbacterial infectious cause) in immunosuppressed patients.

Conclusion

In this large ICU cohort of immunosuppressed patients with acute hypoxaemic respiratory failure, bronchoscopy was associated with improved diagnosis and changes in management, but increased ICU and hospital mortality, even after adjusting for severity and other identifiable confounders. Rethinking bronchoscopy in terms of pre- and post-test probability and balancing risk and benefit in individualised cases should be investigated further.

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