Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: Prospective multicenter data*

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Objective: **To describe the diagnostic yields of test strategies with and without fiberoptic bronchoscopy and bronchoalveolar lavage (FO-BAL), as well as outcomes, in cancer patients with acute respiratory failure (ARF).**

Design: **Prospective observational study.**

Setting: **Fifteen intensive care units in France.**

Patients: **In all, 148 cancer patients, including 45 bone marrow transplant recipients (27 allogeneic, 18 autologous) with hypoxemic ARF.**

Intervention: **None.**

Results: **Overall, 146 causes of ARF were identified in 128 patients (97 [66.4%] pulmonary infections). The cause of ARF was identified in 50.5% of the 101 patients who underwent FO-BAL and in 66.7% of the other patients. FO-BAL was the only conclusive test in 34 (33.7%) of the 101 investigated patients. Respiratory status deterioration after FO-BAL occurred in 22 of 45 (48.9%) nonintubated patients, including 16 (35.5%) patients who required ventilatory support. Hospital mortality was 55.4% (82 deaths) overall and was not significantly different in the groups with and without FO-BAL. By multivariate analysis, mortality was affected by characteristics of the malignancy (remission, allogeneic bone marrow transplantation), cause of ARF (ARF during neutropenia recovery, cause not identified), and need for life-sustaining treatments (mechanical ventilation and vasopressors).**

Conclusion: **In critically ill cancer patients with ARF, a diagnostic strategy that does not include FO-BAL may be as effective as FO-BAL without exposing the patients to respiratory status deterioration. (Crit Care Med 2008; 36:100–107)**

KEY WORDS: mechanical ventilation; bronchoscopy; bronchoalveolar lavage; polymerase chain reaction; noninvasive; infection

Acute respiratory failure (ARF) is a dreaded event in patients with solid tumors or hematologic malignancies (1). ARF may occur in 10% to 50% of these patients (2, 3) and carries a mortality rate of about 50% overall and 75% when mechanical ventilation (MV) is needed (2–7). Over the last decade, studies have documented an increase in survival rates in patients with ARF receiving MV (5, 7). Survival was higher when noninvasive mechanical ventilation (8) was used for ventilatory support (6, 7, 9), and lower when investigations failed to identify the cause of ARF, indicating that both diagnostic and therapeutic strategies are urgent and worthy (3, 6, 10).

Both invasive and noninvasive diagnostic strategies can be used to identify the cause of ARF in cancer patients (1). The invasive strategy relies on fiberoptic bronchoscopy with bronchoalveolar lavage (FO-BAL), and the noninvasive strategy on imaging studies (11, 12) and on microbiological studies of blood (13–16), urine (17, 18), sputum (19), and nasopharyngeal aspirates (20). FO-BAL is currently recommended in nonhypoxemic cancer patients with pulmonary infiltrates (21, 22). However, possible harmful effects of FO-BAL have been reported, with respiratory status deterioration in 10% to 40% of cases (1, 23–25). Furthermore, the diagnostic yield of FO-BAL has been only 50% at best (1). In severely hypoxemic patients, FO-BAL has been described as inadvisable or contraindicated because of the risk of deterioration in respiratory status with a subsequent need for mechanical ventilation (26, 27).

The apparent contradiction between the need to identify the cause of ARF to improve survival and the risk of complications related to diagnostic FO-BAL has generated uncertainty about the best diagnostic strategy in hypoxemic cancer patients with ARF (1, 23–25). No specific guidelines have been established for this situation. Neither have studies evaluated

***See also p. 344.**

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Table 1. Patient characteristics

	Survivors (n = 66)	Nonsurvivors (n = 82)	*p* Value
Age	61 (50–70)	57 (45–66)	.13
Male gender	33 (50)	49 (59.7)	.18
Underlying malignancy			
Days since diagnosis of the malignancy	243 (57–1112)	202 (44–897)	.75
Acute leukemia	21 (31.8)	35 (42.7)	.23
Non-Hodgkin's lymphoma	19 (28.8)	17 (20.7)	.33
Myeloma	5 (7.5)	6 (7.3)	.95
Solid tumor	12 (18.2)	14 (17)	.86
Chronic myeloid or lymphocytic leukemia	8 (12.1)	9 (11)	.82
Complete remission	37 (56)	31 (38)	.05
Autologous bone marrow/stem cell transplantation	7 (10.6)	11 (13.4)	.62
Allogeneic bone marrow/stem cell transplantation	8 (12.1)	19 (23.2)	.05
Respiratory symptoms			
Hemoptysis	3 (4.5)	7 (8.5)	.51
Purulent sputum	11 (16.6)	7 (8.5)	.20
Chest pain	5 (7.5)	10 (12.2)	.42
Days from dyspnea onset	3 (0.5–6)	2 (1–7)	.83
Clinical examination at ICU admission			
Respiratory rate, breaths per min	31 (24–37)	30 (22–38)	.58
Heart rate, bpm	113 (101–132)	127 (105–140)	.02
Temperature, °C	39 (38.7–39.8)	39 (38.5–39.4)	.26
Diffuse crackles at lung auscultation	19 (28.8)	26 (31.7)	.72
Spo_2 on room air at admission (%)	85 (75–89)	86 (80–90)	.27
LOD Score at admission	4 (2–7)	5 (3–8)	.08
Neutropenia at ICU admission	18 (27.3)	37 (45.1)	.02
Admission to the ICU during neutropenia recovery	19 (28.8)	11 (13.4)	.03
Platelet count at ICU admission (10^3/mm^3)	84 (33–218)	51 (26–97)	.02
Ventilatory support			
NIMV only	14 (21.2)	6 (7.3)	<.0001
Intubation after failed NIMV	15 (22.7)	40 (48.8)	
Intubation as the primary method of ventilatory support	19 (28.8)	36 (43.9)	
Days from admission to intubation	0.5 (0–2)	1 (0–3)	.10
Worst Pao_2/Fio_2 during the first day of ventilation	148 (93–195)	86 (62–129)	<.0001
Criteria for ARDS	32 (48.5)	69 (84.1)	<.0001
Occurrence of pneumothorax	1 (1.5)	8 (9.7)	.04
Other organ failures			
Need for vasopressors	25 (37.9)	66 (80.5)	<.0001
Days from admission to initiation of vasopressors	0 (0–2)	0 (0–2)	.94
Need for RRT	15 (22.7)	32 (39)	.03
Days from admission to initiation of RRT	1 (0–1)	3 (1–6)	.003
Combination of organ failures			
One among invasive ventilation, vasopressors, or RRT	14 (21.2)	11 (13.4)	<.0001
Two among invasive ventilation, vasopressors, or RRT	15 (22.7)	35 (42.7)	
Invasive ventilation plus vasopressors plus RRT	10 (15.1)	31 (37.8)	

ICU, intensive care unit; LOD, Logistic Organ Dysfunction score; NIMV, noninvasive mechanical ventilation; ARDS, acute respiratory distress syndrome; RRT, renal replacement therapy.

the yield of a noninvasive diagnostic strategy used as an alternative to FO-BAL (1). We investigated practices in 15 intensive care units (ICUs) to compare diagnostic yields and mortality in cancer patients with ARF managed by noninvasive or invasive diagnostic strategies.

PATIENTS AND METHODS

The study group comprising 15 closed ICUs in university or university-affiliated hospitals in France was set up in 2003 to investigate invasive vs. noninvasive diagnostic strategies in critically ill cancer patients with ARF. The observational study reported here was approved by the appropriate ethics committee (Pitié-Salpêtrière University Hospital, Paris, France). In each ICU, an investigator used standardized forms to prospectively collect data on 10 cancer patients admitted for ARF after January 1, 2004.

ARF was defined as a respiratory rate of >30 breaths per min or respiratory distress symptoms, or Pao_2 on room air of <60 mm Hg, or the need for ventilatory support. In each of the 15 study ICUs, cancer patients are routinely managed by a multidisciplinary team that includes the referring oncologist or hematologist. For each study patient, the data reported in Tables 1–3 were collected. The Logistic Organ Dysfunction (28) score was determined at ICU admission (29). Vital status at ICU and hospital discharge and time in the ICU and hospital were recorded for all patients. Antibiotic regimens and life-sustaining treatments were used according to current recommendations.

Bronchoscopy and BAL Procedure. Fiberoptic bronchoscopy and BAL were performed routinely as described elsewhere (30, 31). The gross appearance of the recovered fluid was noted, with special attention to signs of hemorrhage. The fluid was placed on ice and processed immediately. Following centrifugation, the cell pellet was resuspended in cell culture medium, and smears were prepared. The smears were stained for differential cell counts, Perl Prussian blue for hemosiderin-containing alveolar macrophages (31, 32), Grocott stain for *Pneumocystis jiroveci* (Toluidine blue O and May-Grunwald-Giemsa), and the Papanicolaou stain. A specific immunofluorescence test for *P. jiroveci* was done, as well as immunostaining for cytomegalovirus (33). Specific polymerase chain reaction techniques were used to detect herpes viruses, syncytial respiratory viruses, and adenoviruses. Viral antigens in BAL samples were detected by a direct immunofluorescent staining method using a monoclonal antibody pool (influenza viruses A and B; parainfluenza viruses 1, 2, and 3; respiratory syncytial virus; adenovirus; and herpes simplex virus). BAL fluid aliquots were stained using Gram and Ziehl-Neelsen methods, then cultured for bacteria, mycobacteria, and fungi.

The noninvasive diagnostic strategy consisted of variable combinations of the investigations listed in Table 2 (1, 11, 13–20). Nearly all of the patients managed with FO-BAL also underwent at least one noninvasive investigation, on the basis of clinical symptoms and at the clinician's discretion.

Criteria for each Etiologic Diagnosis. Diagnoses were based on clinical, radiographic, microbiological, and cytologic findings. They were validated in each ICU by the multidisciplinary team based on predefined criteria (3, 19, 34).

Criteria for Conventional and Noninvasive Mechanical Ventilation. When use of a high-concentration oxygen mask was not associated with a significant clinical improvement (sustained high respiratory rate [>30] or oxygen saturation below 92%), noninvasive mechanical ventilation (NIMV) was delivered to the patient through a full-face mask, as previously described (7). NIMV was stopped when significant clinical improvement was documented. Patients in whom NIMV was not successful underwent endotracheal intubation and received conventional MV on predefined criteria (3, 7).

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Table 2. Noninvasive and invasive diagnostic investigations performed

Noninvasive Investigations (At Least One Investigation Performed)	141 (100) Patients (121 with Positive Results/105 with Diagnostic Results)
Blood cultures[a]	141 (100)/30 (21.3)/26 (18.4)
Sputum examination for bacteria	49 (34.7)/17 (34.7)/12 (24.5)
ELISA aspergillosis assay, blood	104 (73.7)/9 (8.6)/7 (6.7)
Sputum examination for aspergillosis	29 (20.6)/13 (44.8)/11 (37.9)
Sputum examination for other fungi	29 (20.6)/6 (20.7)/6 (20.7)
Induced sputum for Pneumocystis	24 (17)/3 (12.5)/3 (12.5)
Urine *Legionella pneumophila* antigen	94 (66.7)/3 (3.2)/3 (3.2)
Urine *Streptococcus pneumoniae* antigen	26 (18.4)/4 (15.4)/4 (15.4)
CMV circulating antigen	87 (61.7)/3 (3.4)/2 (2.3)
Nasopharyngeal aspiration	18 (12.8)/4 (22.2)/4 (22.2)
Echocardiography	113 (80.2)/25 (22.1)/23 (20.3)
Thoracentesis, 53 patients with pleural effusions[b]	20 (37.7)/4 (7.5)/4 (7.5)
FO-BAL	101 (100) Patients
Time from ICU admission to BAL	1 (0–3)
Bronchoscopy (range)	
Normal	26 (25.7)
Edema	28 (27.7)
Bloody secretions	23 (22.7)
Purulence	11 (10.9)
White coat adherent to the bronchi	4 (4)
Tumoral infiltration	2 (2)
Amount of fluid recovered/injected	0.5 (0.3–0.6)
Gross appearance of BAL fluid	
Turbid or purulent	21 (20.8)
Clear	40 (39.6)
Bloody	40 (39.6)
Alveolar cells in BAL fluid	
Total number of alveolar cells, 1000 cells/mm^3	90 (40–275)
% of neutrophils/macrophages/lymphocytes	10 (2–61)/53 (20–87)/8 (3–15)
>20% siderophages	9 (8.9)
Blasts or malignant cells	5 (4.9)
Positive bronchial biopsies, 34 biopsies performed	2 (5.9)
Impact of BAL analysis	
BAL yielded a pathogen	51 (50.5)
BAL was the only conclusive investigation	34 (33.7)
BAL fluid allowed initiation of adequate treatment	36 (35.6)
BAL fluid allowed withdrawal of useless treatments	30 (29.7)
Respiratory complications after FO-BAL in 45 patients not intubated at the time of BAL	
Increased oxygen for >12 hours	6 (13.3)
Initiation of NIMV after FO-BAL	4 (8.9)
Intubation after FO-BAL	12 (26.7)

ELISA, enzyme-linked immunosorbent assay; CMV, cytomegalovirus; FO, fiberoptic bronchoscopy; BAL, bronchoalveolar lavage; NIMV, noninvasive mechanical ventilation.

[a]Four patients had blood cultures positive for *Candida* species; [b]thoracentesis led to the diagnosis of complicated parapneumonic effusion and pleural empyema.

Table 3. Independent determinants of hospital mortality by multivariable analysis

	Odds-ratio	95% Confidence Interval	*p* Value
Related to the malignancy			
Remission of the malignancy	0.30	0.09–0.93	.03
Allogeneic bone marrow or stem cell transplantation	5.95	1.48–23.90	.01
Related to the cause of acute respiratory failure			
Admission during neutropenia recovery	0.13	0.03–0.57	.006
Undetermined diagnosis	8.65	1.39–53.56	.02
Related to the need for life-sustaining interventions			
Need for conventional mechanical ventilation	8.18	1.16–57.36	.03
Need for vasopressors	5.09	1.07–24.18	.04

Statistical Analysis. Results are reported as medians and quartiles (25th–75th percentiles) or numbers and percentages. Patient characteristics in the subgroups managed with noninvasive investigations vs. FO-BAL were compared using the chi-square test or Fisher's exact test, as appropriate, for categorical variables and the nonparametric Wilcoxon's rank-sum test or the Kruskal-Wallis test for continuous variables. To investigate associations between patient characteristics and hospital death, use of FO-BAL, and use of conventional MV, we first performed bivariate analyses to look for a significant influence of each variable on hospital mortality by logistic regression, as measured by the estimated odds ratio (OR) with a 95% confidence interval (CI). Variables yielding p values no greater than .20 in the bivariate analyses were entered into a multiple logistic regression model in which hospital mortality was the outcome variable of interest. Finally, we estimated actuarial probabilities of survival according to the Kaplan-Meier method with log-rank tests. All tests were two-sided, and p values smaller than .05 were considered statistically significant. Analyses were done using the SAS 9.1 software package (SAS Institute, Cary, NC).

RESULTS

The characteristics of the 148 patients (122 with hematologic malignancies and 26 with solid tumors) are reported in Table 1. Forty-five (30.4%) patients had received bone marrow transplants (BMT, 27 allogeneic and 18 autologous). Chest radiograph disclosed a focal alveolar pneumonia in 22 (14.9%) patients, an interstitial pattern in 41 (27.7%), a diffuse alveolar pattern in 67 (45.3%), and nodules in eight (5.4%). Ten (6.7%) patients with neutropenia had a normal chest radiograph. High-resolution computed tomography was performed in 90 patients and disclosed ground glass opacities in 55 (61.1%) patients, nodules in 23 (25.5%), septal lines in 17 (18.9%), consolidations in 63 (70%), excavations in seven (7.8%), and halo sign in six (6.7%). Pleural effusion was found in 60 (67%) patients.

The Logistic Organ Dysfunction score at admission was 5 (3–8). During the ICU stay, 75 (50.7%) patients required NIMV, 55 (37.2%) conventional MV, 91 (61.5%) vasopressors, and 47 (31.7%) renal replacement therapy. ICU mortality was 45.9% and hospital mortality was 55.4%.

Cause of Acute Respiratory Failure. At admission, all but three patients were receiving at least one antibiotic. Overall, 146 causes of ARF were identified in 128

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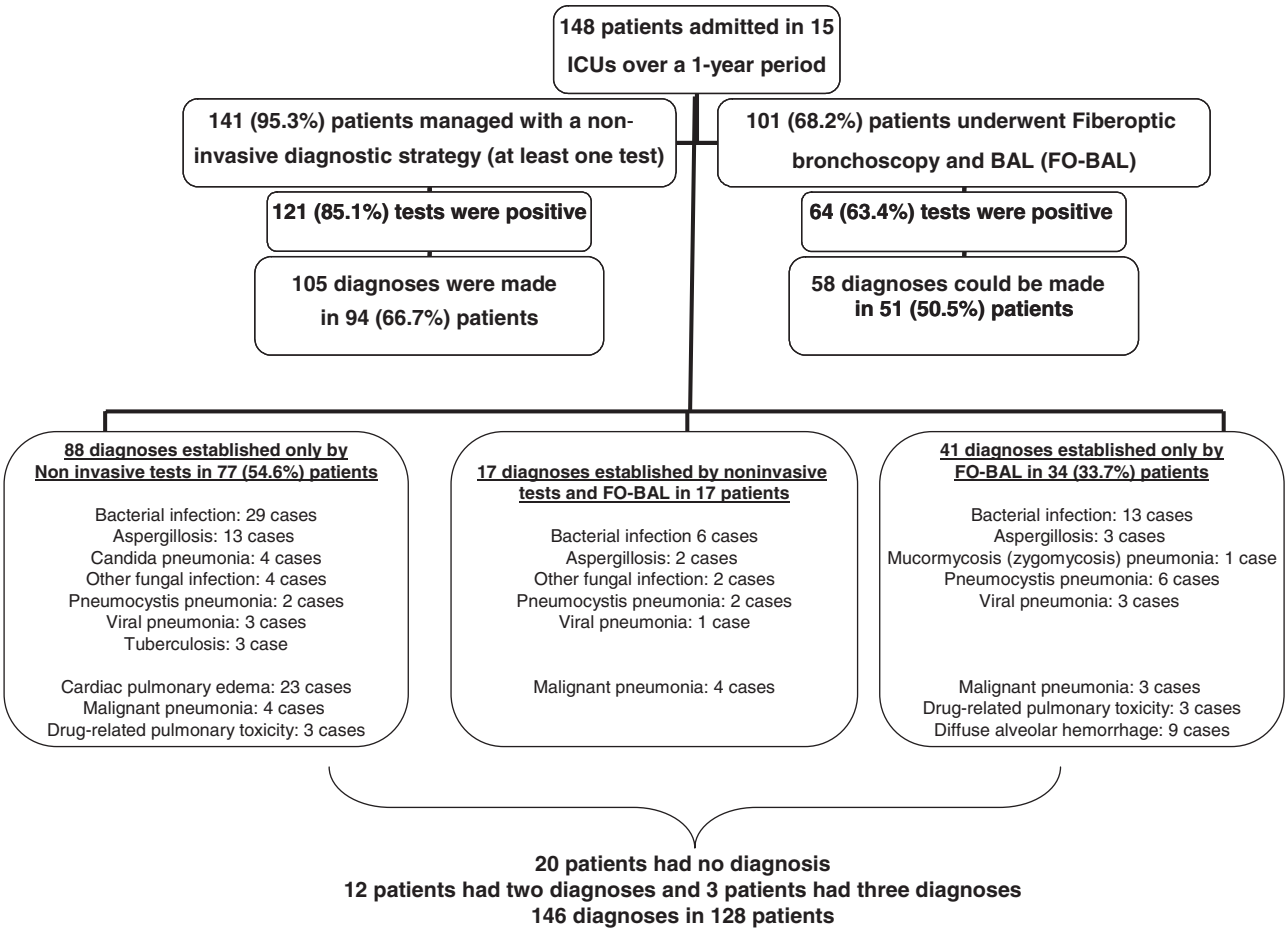

Figure 1. Diagnostic yield of invasive or noninvasive diagnostic procedures. *ICU*, intensive care unit; *BAL*, bronchoalveolar lavage.

patients, leaving 20 (13.5%) patients with an undetermined diagnosis (Fig. 1). Of the 146 identified causes, 97 were pulmonary infections, in 90 (60.8%) patients. In 23 patients, echocardiography allowed the diagnosis of cardiac pulmonary edema, and in nine recipients of hematopoietic stem cell transplantation, FO-BAL led to a diagnosis of idiopathic alveolar hemorrhage. Tests other than FO-BAL allowed the diagnosis of pulmonary involvement by the malignancy in eight patients, including five patients with pulmonary infiltration at the earliest phase of acute monocytic leukemia, two patients with bulky mediastinum and pulmonary atelectasis at the inaugural phase of lymphoma diagnosed using sternal puncture, and one patient with carcinoid lymphangitis in whom malignant cells were identified in both sputum and BAL fluid. Three patients were diagnosed with methotrexate-induced pneumonia (lymphocytic alveolitis), and in three patients beta lactam–induced pneumonia was diagnosed based on eosinophilia in the blood smears and evidence of toxic vasculitis in a skin biopsy.

Invasive and Noninvasive Diagnostic Strategies. Figure 1 reports the yields of the invasive and noninvasive diagnostic strategies. Almost all (95.3%) of the patients underwent at least one noninvasive diagnostic test, whereas FO-BAL was performed in 101 (68.2%) patients (Table 2). Patients had a median of four (3–6) noninvasive tests within 24 hrs after ICU admission.

FO-BAL was performed at ICU admission in 25 (24.7%) patients, within 24 hrs after ICU admission in 38 (37.6%) patients, and later during the ICU stay in 38 (37.6%) patients. Of the 45 (44.5%) patients who underwent FO-BAL while not intubated, 16 had the procedure with NIMV and 29 with a high-flow oxygen mask. Patients managed with FO-BAL were younger, more frequently treated for hematologic malignancies (including allogenic BMT) than solid tumors, and more frequently had diffuse pulmonary disease with severe hypoxemia. Noninvasive diagnostic tests had a diagnostic yield of 66.7% and FO-BAL of 50.5%. FO-BAL was the only investigation that provided a diagnosis in 34 (34/101; 33.7%) patients. Table 2 describes each noninvasive diagnostic test and each step of the FO-BAL. After FO-BAL, 22 (48.9%) of the 45 nonintubated patients experienced respiratory status deterioration, including 16 (35.5%) patients who required ventilatory support (four required NIMV only, six conventional MV after NIMV failure, and six primary conventional MV). Respiratory status deterioration occurred in 13 (44.8%) patients who underwent FO-BAL with high-flow oxygen and in three (18.7%) patients who had FO-BAL with NIMV ($p = .02$). Use of FO-BAL independently predicted a need for conventional MV (OR 14.73, 4.27–50.83; $p < .0001$).

Determinants of Hospital Mortality. As reported in Figure 2, survival varied with the type of ventilatory support needed. Overall mortality in the 110 patients treated with conventional MV was

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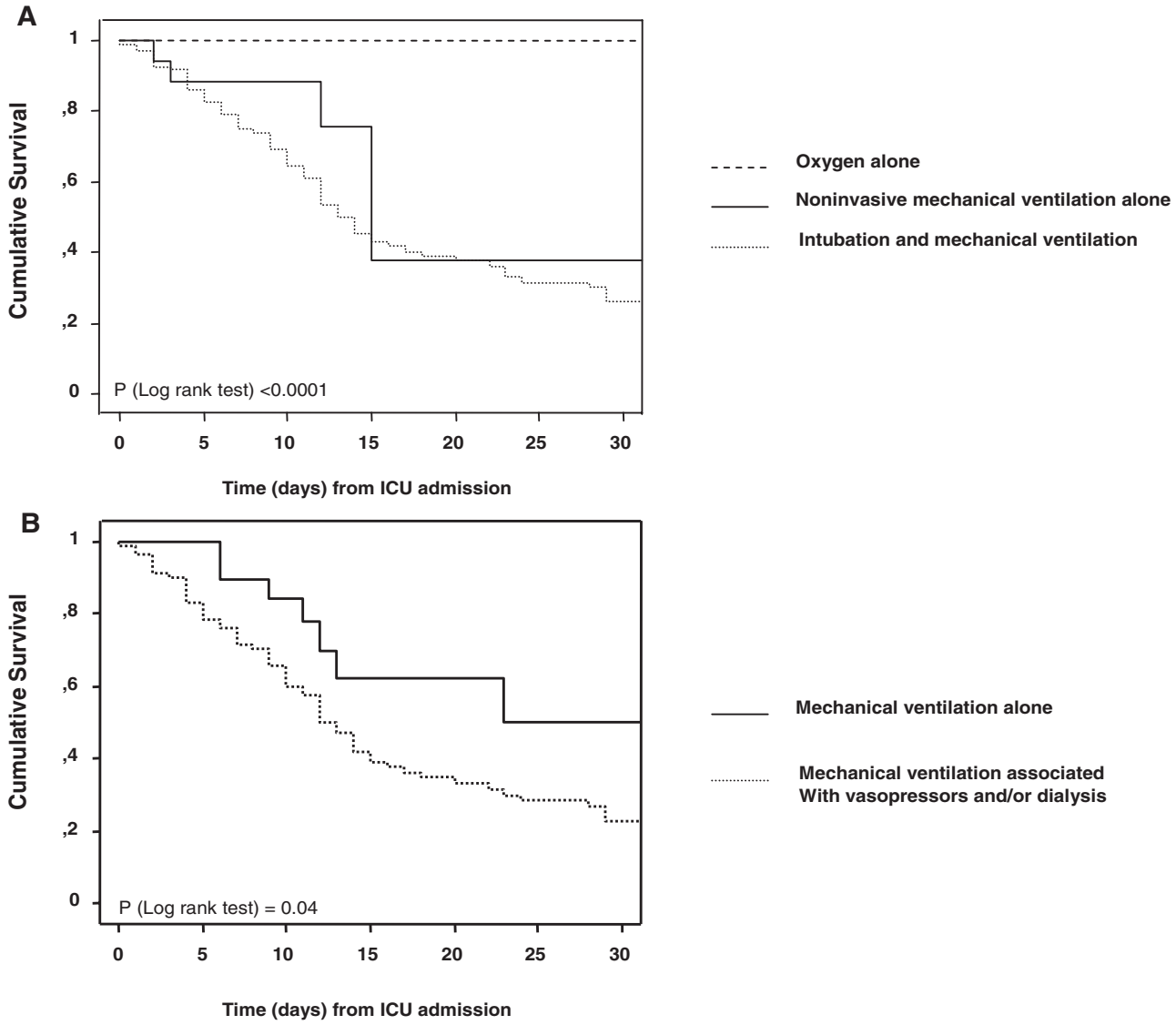

Figure 2. *A*, survival as a function of the type of ventilatory support needed, or *B*, of associated organ dysfunctions. *ICU*, intensive care unit.

69% (76 deaths). Three factors significantly influenced mortality in this subgroup: a history of BMT (81% vs. 66% mortality; $p = .04$), time of intubation (admission, 61.8%; day 1 or day 2, 73.3%; and day 3 or later, 80%; $p = .05$), and number of life-sustaining interventions (MV only, 47.6% 10/21; MV plus vasopressors or renal replacement therapy; and MV plus vasopressors and renal replacement therapy, 75.6%; $p < .0001$) (Fig. 2B).

Mortality was not significantly different between the groups with and without FO-BAL, and within the FO-BAL group, between the patients with and without a diagnosis (Fig. 3). Among the 20 (13.5%) patients with an undetermined diagnosis (six in the noninvasive group and 14 in the FO-BAL group), 14 (70%) died. In addition, patients with invasive aspergillosis had a trend toward increased mortality (15.8% vs. 7.5%, $p = .07$).

As reported in Table 3, hospital mortality was independently affected by the characteristics of the malignancy (being higher in BMT recipients and in patients with active malignant disease), the cause of ARF (being lower in ARF during neutropenia recovery and higher in patients with an undetermined diagnosis), and the nature of life-sustaining interventions (being higher in patients who needed conventional MV or vasopressors).

DISCUSSION

In this multicenter prospective observational study, diagnostic yields and outcomes were compared between cancer patients with ARF managed using invasive vs. noninvasive investigations. FO-BAL was the only conclusive investigation in only one third of patients and induced respiratory status deterioration in about half of the cases. The noninvasive strategy had a higher diagnostic yield with no complications. Even when FO-BAL provided the diagnosis, performing this investigation did not decrease mortality but independently predicted a need for conventional MV.

Several single-center studies evaluated the diagnostic and therapeutic impact of FO-BAL in patients with various types of immunodeficiency (10, 19). In our study, the diagnostic yield of FO-BAL was in agreement with previous reports (1). The rate of respiratory deterioration associated with FO-BAL was at the higher end of the range reported at other centers in non ICU-patients, indicating a need for alternatives to FO-BAL in critically ill hy-

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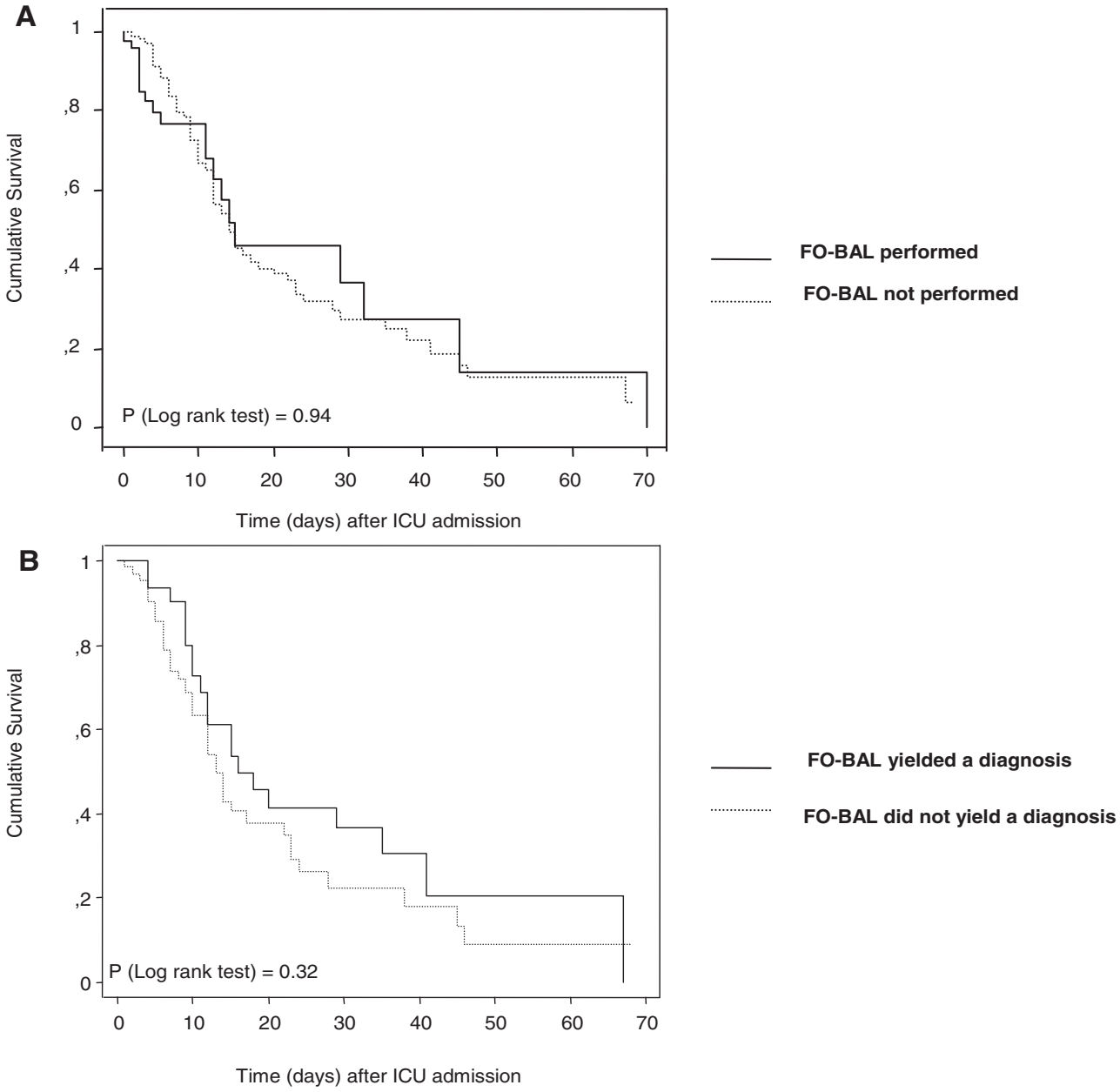

Figure 3. Impact of fiberoptic bronchoscopy and bronchoalveolar lavage (*FO-BAL*) on patients' survival. *A*, comparison between patients in whom FO-BAL was performed or not; *B*, comparison between those in whom BAL yielded a diagnosis or not. *ICU*, intensive care unit.

poxemic patients (23–25). Furthermore, our results suggest that FO-BAL may have been unnecessary in 70% of the patients or could, at the least, have been reserved for patients with inconclusive results of noninvasive investigations. The lack of improvement in survival of patients who underwent FO-BAL, even when this investigation provided the diagnosis, further supports greater reliance on noninvasive investigations.

The noninvasive diagnostic strategy included several investigations that have been evaluated individually in cancer patients (1, 11, 13–20). In addition to evaluating each noninvasive investigation, we measured the diagnostic impact of a noninvasive strategy, defined as a variable combination of noninvasive investigations without FO-BAL (1). Given the observational study design and the use of clinical judgment to select investigations—no guidelines being available—none of the investigations was performed routinely. Nevertheless, the noninvasive strategy yielded the diagnosis in 66.7% of patients and induced no adverse events, suggesting not only that clinicians performed only those noninvasive tests that were likely to confirm their clinical diagnosis, but also that in these high-risk patients, a noninvasive diagnostic strategy may help to reduce the need for FO-BAL with the attendant respiratory deterioration. Conceivably, routine use of the full range of noninvasive investigations may have a higher diagnostic yield, obviating the need for FO-BAL in a higher number of patients than in the present study. A study comparing patients managed with FO-BAL or with noninvasive investigations only would be of considerable interest. In addition, continuing advances in noninvasive diagnostic tests on various biological samples can be ex-

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pected to increase the diagnostic yield of noninvasive strategies in these high-risk hypoxemic patients (16, 35).

Our results confirm that mortality is higher when the cause of ARF remains undetermined. The corollary to this fact is that recommendations should focus on the diagnostic strategy rather than on empirical treatment (3, 6, 36). An autopsy study in BMT recipients showed that only 27 of 96 pulmonary complications were diagnosed antemortem, indicating a need for better diagnostic strategies (37).

Our study has several limitations. First, as mentioned above, the use of FO-BAL was at the clinician's discretion, and not all noninvasive investigations were performed routinely. However, previous studies also found no survival benefit with FO-BAL (3, 38). Moreover, FO-BAL was independently associated with failure of NIMV and with a need for MV, supporting an adverse effect of the invasive strategy, as previously reported (1). Second, we have focused our efforts to identify adverse events of FO-BAL in nonintubated patients. Indeed, respiratory status deterioration and subsequent need of ventilatory support clearly shifts patients' outcomes to a group with higher mortality. Third, BMT patients with pulmonary complication need to be treated aggressively, and the underlying etiology must be identified as early as possible. FO-BAL may not be the right choice, and studies are needed to investigate safety and diagnostic yield of pulmonary biopsies in this subset of patients.

In summary, in hypoxemic cancer patients with ARF, a noninvasive diagnostic strategy provides an etiologic diagnosis in a significant number of cases. FO-BAL may have an important role in the diagnostic work-up of selected critically ill cancer patients, but should be performed only after diligent analysis of its risks and benefits. Further controlled studies in nonintubated cancer patients with ARF are needed to evaluate the diagnostic yield of routinely performing the full range of noninvasive investigations, as well as the number of FO-BAL procedures and of intubations avoided with this strategy.

IN MEMORIAM

This manuscript is dedicated to Dr. Arnaud de Lassence, who was a friend, a colleague, and an artist. Dr. de Lassence taught us how to manage alveolar hemorrhage and other disorders in hematology patients. There will remain a lot of things that we could have learned from him.

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