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ORIGINAL

Acute respiratory distress syndrome in patients with malignancies

Elie Azoulay
Virginie Lemiale
Djamel Mokart
Frédéric Pène
Achille Kouatchet
Pierre Perez
François Vincent
Julien Mayaux
Dominique Benoit
Fabrice Bruneel
Anne-Pascale Meert
Martine Nyunga
Antoine Rabbat
Michael Darmon

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Take home message: Pulmonary and extrapulmonary infections were responsible for 90 % of ARDS cases in patients with solid or hematological malignancies. One-third of the underlying infections were due to opportunistic pathogens. Survival improved significantly over time. Noninvasive ventilation was attempted in 30 % of patients but failed in 70 %, and failure was associated with increased mortality. The particularly high mortality among patients with invasive fungal infections indicates a pressing need for specific studies on early antifungal therapy in high-risk patients.

On behalf of the Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique (Grrr-OH).

Electronic supplementary material
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E. Azoulay · V. Lemiale
Intensive Care Unit of the Saint-Louis University Hospital, Paris, France

D. Mokart
Intensive Care Unit of Institut Paoli Calmette, Marseille, France

F. Pène · A. Rabbat
Intensive Care Unit of Cochin University Hospital, Paris, France

A. Kouatchet
Intensive Care Unit of Angers University Hospital, Angers, France

P. Perez
Intensive Care Unit of Nancy University Hospital, Nancy, France

F. Vincent
Intensive Care Unit of Bobigny University Hospital, Bobigny, France

J. Mayaux
Intensive Care Unit of Pitié-Salpêtrière University Hospital, Paris, France

D. Benoit
Intensive Care Unit of Ghent University Hospital, Ghent, Belgium

F. Bruneel
Intensive Care Unit of Versailles Hospital, Versailles, France

A.-P. Meert
Intensive Care Unit of Brussels University Hospital, Brussels, Belgium

M. Nyunga
Intensive Care Unit of Roubaix Hospital, Roubaix, France

M. Darmon
Intensive Care Unit of Saint-Etienne Teaching Hospital, Saint-Étienne, France

E. Azoulay (✉)
Sorbonne Paris-Cité, Medical School, AP-HP, Hôpital Saint-Louis, Medical ICU, Paris-Diderot University, 1 avenue Claude Vellefaux, 75010 Paris, France
e-mail: elieazoulay.icm@sls.aphp.fr; elie.azoulay@sls.aphp.fr
Tel.: +33 142 499 421

Abstract *Purpose:* Little attention has been given to ARDS in cancer patients, despite their high risk for pulmonary complications. We sought to describe outcomes in cancer patients with ARDS meeting the Berlin definition. *Methods:* Data from a cohort of patients admitted to 14 ICUs between 1990 and 2011 were used for a multivariable analysis of risk factors for hospital mortality. *Results:* Of 1,004 included patients (86 % with hematological malignancies and 14 % with solid tumors), 444 (44.2 %) had neutropenia. Admission SOFA score was 12 (10–13). Etiological categories were primary infection-related ARDS ($n = 662$, 65.9 %; 385 bacterial infections, 213 invasive aspergillosis, 64 *Pneumocystis* pneumonia); extrapulmonary septic shock-related ARDS ($n = 225$, 22.4 %; 33 % candidemia); noninfectious ARDS ($n = 76$, 7.6 %); and undetermined cause ($n = 41$, 4.1 %). Of 387 (38.6 %) patients given

noninvasive ventilation (NIV), 276 (71 %) subsequently required endotracheal ventilation. Hospital mortality was 64 % overall. According to the Berlin definition, 252 (25.1 %) patients had mild, 426 (42.4 %) moderate and 326 (32.5 %) severe ARDS; mortality was 59, 63 and 68.5 %, respectively ($p = 0.06$). Mortality dropped from 89 % in 1990–1995 to 52 % in 2006–2011 ($p < 0.0001$). Solid tumors, primary ARDS, and later admission period were associated with lower mortality. Risk factors for higher mortality were allogeneic bone-marrow transplantation, modified SOFA, NIV failure, severe ARDS, and invasive fungal infection. *Conclusions:* In cancer patients, 90 % of ARDS cases are infection-related, including one-third due to invasive fungal infections. Mortality has decreased over time. NIV failure is associated with increased mortality. The high mortality associated with invasive fungal infections warrants specific studies of early treatment strategies.

Keywords Neutropenia · Bronchoscopy · Pneumonia · Invasive aspergillosis · Candidemia · *Pneumocystis*

Introduction

Pulmonary involvement is frequent and severe in patients with solid or hematological malignancies [1]. Acute respiratory failure occurs in up to half the patients treated for malignancies [2] and carries a variable risk of death depending on the cause, need for mechanical ventilation, concomitant organ dysfunctions, presence of graft-versus-host disease, and goals of care [3–9].

Acute respiratory distress syndrome (ARDS) in patients with malignancies exhibits several specific features, particularly in patients with neutropenia [10]. Although circulating and resident alveolar neutrophils have been considered pivotal in the pathophysiology of ARDS [11], patients with neutropenia are at high risk for ARDS [12], and alveolar macrophages play a prominent role in the response to acute lung injury [13, 14]. In patients with or without neutropenia, ARDS may be related to infectious or non-infectious causes. Causes of primary ARDS, i.e., ARDS due to a direct lung insult, include bacterial or opportunistic infections such as invasive pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia, other fungal infections, and severe viral infections [2]. Secondary ARDS is related to a systemic process such as severe sepsis or septic shock from extrapulmonary bacterial or fungal infections [15]. Non-infectious lung insults such as drug-related toxicity [16] and infiltration by malignant cells [17] may produce a clinical picture similar to ARDS, although diffuse alveolar damage is generally absent [18].

Despite the considerable improvements in outcomes achieved in recent years [19, 20], patients with malignancies and ARDS are frequently excluded from observational studies and interventional trials [21]. ARDS is more often fatal in patients with malignancies than in other patients [22, 23]. However, few studies have specifically investigated the risk factors for death among patients with malignancies and ARDS. In a single-center study of 68 patients with ARDS and hematological malignancies, multiorgan failure was an independent risk factor for death [24]. A retrospective assessment of patients in ARDS network trials showed a significantly higher risk of death in the 116 patients with cancer than in the 2,399 other patients [23]. However, outcome data are lacking from large multicenter cohort studies focusing specifically on ARDS patients with malignancies managed in high-volume centers where intensivists and oncologists/hematologists work closely together to ensure optimal management.

Our primary objective was to obtain recent data on ARDS outcomes in patients with malignancies. We used the new operational Berlin definition to define ARDS [25, 26]. Our secondary objectives were to assess how the Berlin definition of ARDS operates in this specific population, to look for associations between ARDS causes and hospital mortality, and to describe trends in outcomes over time. To meet these objectives, we conducted a large multicenter cohort study of patients managed in specialized centers.

Patients and methods

The appropriate ethics committees approved this study (CPP Pitié Salpétrière, SPLF ethics committee, and CE-ERB Bichat). We retrospectively analyzed data from six previously published prospective and retrospective outcome studies of patients with malignancies who required intensive care unit (ICU) admission [1, 4, 9, 10, 19, 27, 28]. Patients were included in these studies between 1990 and 2011 in 14 university or university-affiliated centers in France and Belgium belonging to a research network on critical respiratory diseases in patients with malignancies (*Groupe de Recherche en Réanimation Respiratoire en Onco-Hématologie*, GRRR-OH). Of the six studies, only one [10] focused specifically on patients with ARDS and malignancies, and all patients in this study had neutropenia. In each center, a senior intensivist and a senior oncologist/hematologist were available around the clock and made ICU-admission decisions together.

In the datasets of these six studies, we identified patients with malignancies who met the Berlin definition of ARDS within 3 days after ICU admission: [25, 26] (1) new or worsening respiratory symptoms over the last 7 days; (2) bilateral opacities on chest radiographs; (3) absence of suspected hydrostatic/cardiogenic pulmonary edema; and (4) $PaO_2/FiO_2 \leq 300$. ARDS severity was categorized according to the Berlin definition as mild (200 mmHg $< PaO_2/FiO_2 \leq$ 300 mmHg); moderate (100 mm Hg $< PaO_2/FiO_2 \leq$ 200 mmHg), or severe ($PaO_2/FiO_2 \leq$100 mmHg) [25, 26]. All PaO_2/FiO_2 were assessed with a PEEP level $\geq$5.

The data reported in the tables and figures were collected from the patient charts or study databases. The sequential organ failure assessment (SOFA) score was computed at ICU admission to estimate the risk of death based on organ dysfunctions. To assess the influence of ARDS on mortality, we computed a modified SOFA score (mSOFA) obtained by excluding the respiratory component.

We defined neutropenia as a neutrophil count <500/mm^3 at ARDS onset. The underlying malignancy was categorized as either in partial or complete remission or as progressive, newly diagnosed, or unknown status.

Diagnostic tests used to identify the cause of ARDS included noninvasive or invasive (i.e., bronchoscopy and bronchoalveolar lavage) investigations, as deemed appropriate by the intensivist in charge [1]. Bronchial or pulmonary biopsies were not performed routinely given the acute illness severity and bleeding risk in many patients. The cause was identified by consensus among intensivists, oncologists/hematologists, and consultants, according to recent definitions [1]. Invasive fungal infections (IFIs) met the most recent EORTC-MSG definitions [29]. Sepsis definitions and management were as published previously [28, 30]. The study patients received NIV or endotracheal mechanical ventilation (MV) according to their respiratory status and acute illness severity.

Statistical analysis

Results are reported as medians (interquartile range, IQR) or numbers (%). Categorical variables were compared using the Chi square test or Fisher's exact test, as appropriate and continuous variables using the nonparametric Wilcoxon test or Mann–Whitney test. Kaplan–Meier survival curves were plotted. We chose the log-rank test to compare the three ARDS-severity categories. We performed conditional backward logistic regression analyses to identify variables that significantly influenced hospital mortality. Variables yielding $p < 0.20$ in bivariate analyses were entered into the model, as well as variables deemed clinically relevant. Variables yielding $p \leq 0.10$ were maintained in the final model. For the multivariable analysis, missing data were handled using multiple imputation with chained equations [31]. For each variable, we computed the odds ratio (OR) for death with the 95 % confidence interval (95 % CI). Collinearity and interactions were tested. The Hosmer–Lemeshow test was used to check goodness-of-fit of the logistic regression.

We looked for changes in hospital mortality according to period of ICU admission, in four categories: 1990–1996; 1996–2000; 2001–2006; and 2006–2011.

All tests were two-sided and p values <0.05 were considered significant. Statistical tests were done using the SPSS 13 software package (IBM, Armonk, NY, USA).

Results

Over the 22-year study period, 1,004 patients with malignancies met the Berlin definition of ARDS. They accounted for 16.5 % of all ICU patients with malignancies and for 35 % of ICU patients with malignancies and acute respiratory failure (Fig. 1). Of the 1,004 study patients, 85.4 % had hematological malignancies including 115 allogeneic bone-marrow or hematopoietic-stem-cell transplants (BMT/HSCT) and 14.6 % solid tumors (Tables 1, 2). Acute leukemia and non-Hodgkin lymphoma were the most common hematological malignancies, whereas lung and breast cancers were the most common solid tumors. Over the study period, the

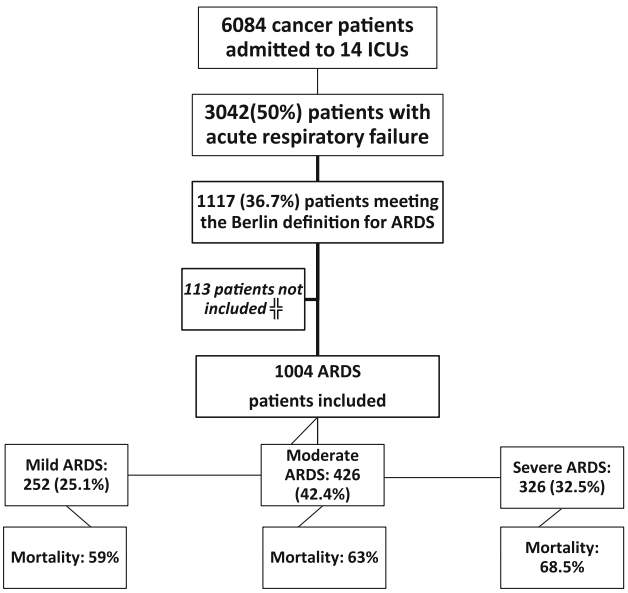

Fig. 1 Patient flow chart and distribution among in three ARDS severity categories in the Berlin definition. ╬ reasons for non-inclusion were as follows: 55 patients did not receive noninvasive or endotracheal mechanical ventilation and vital status at hospital discharge was unknown in 58 patients

Table 1 Patient characteristics at admission to the intensive care unit

Median (IQR) or *n* (%)	Study population (*n* = 1,004)	Survivors (*n* = 364)	Non-survivors (*n* = 640)	*p* value
Male gender	642 (63.9 %)	240 (65.9 %)	402 (62.8 %)	0.32
Age (years)	58 (48–67)	57 (47–67)	58 (48–67)	0.33
Underlying malignancy				
Acute leukemia	298 (29.7 %)	96 (26.4 %)	202 (31.6 %)	0.08
Non-Hodgkin's lymphoma	318 (31.7 %)	115 (31.6 %)	203 (31.7 %)	0.97
Myeloma	113 (11.3 %)	34 (9.3 %)	79 (12.3 %)	<0.0001
Solid tumor	147 (14.6 %)	60 (16.5 %)	87 (13.6 %)	0.21
Miscellaneous	95 (9.5 %)	46 (12.6 %)	48 (7.7 %)	0.01
Allogeneic BMT/HSTC[a]	115 (11.5 %)	36 (9.9 %)	79 (12.3 %)	0.23
Neutropenia	444 (44.2 %)	148 (40.7 %)	296 (46.3 %)	0.08
Stage				
Progressive	458 (45.6 %)	171 (47.0 %)	287 (44.8 %)	0.0003
Partial/complete remission	237 (23.6 %)	100 (27.4 %)	137 (21.4 %)	
Newly diagnosed	72 (7.2 %)	33 (9.1 %)	39 (6.1 %)	
Unknown	237 (23.6 %)	60 (16.5 %)	177 (27.7 %)	

[a] Bone-marrow transplantation/hematopoietic-stem-cell transplantation

Table 2 ARDS causes, severity and treatment, and hospital mortality

Median (IQR) or *n* (%)	Study population (*n* = 1,004)	Survivors (*n* = 364)	Non-survivors (*n* = 640)	*p* value
SOFA score (31) on day-1	12 [10–13]	10 [8–12]	13 [10–13]	<0.0001
mSOFA score on day-1	9 [6–11]	7 [5–10]	9 [7–11]	<0.0001
Emergency surgery	64 (6.4 %)	34 (9.3 %)	30 (4.7 %)	0.004
Sepsis	745 (74.2 %)	275 (75.5 %)	470 (73.4 %)	0.46
Cause of ARDS				
Pulmonary infection[a]	662 (65.9 %)	281 (77.2 %)	381 (59.5 %)	<0.0001
Secondary ARDS[a]	225 (22.4 %)	55 (15.1 %)	170 (26.6 %)	<0.0001
Fungal infection[b]	293 (30.7 %)	83 (23.2 %)	210 (35.1 %)	0.0001
Pneumocystis	64 (6.4 %)	30 (8.2 %)	34 (5.3 %)	0.07
No definite diagnosis[c]	41 (5.7 %)	12 (4.5 %)	29 (6.4 %)	0.29
Berlin categories				
Mild (P/F >200)	252 (25.1 %)	103 (28.3 %)	149 (23.3 %)	
Moderate (P/F 100–200)	426 (42.4 %)	158 (43.4 %)	268 (41.8 %)	0.06
Severe (P/F < 100)	326 (32.5 %)	103 (28.3 %)	223 (34.8 %)	
Organ Support				
NIV	387 (38.6 %)	174 (47.8 %)	213 (33.3 %)	<0.0001
NIV failure	276 (27.5 %)	103 (28.3 %)	173 (27.0 %)	0.67
Endotracheal MV	893 (88.9 %)	293 (80.5 %)	600 (93.8 %)	<0.0001
Vasopressors	731 (72.8 %)	241 (66.2 %)	490 (76.6 %)	0.0004
Renal replacement therapy	306 (30.5 %)	99 (27.2 %)	207 (32.3 %)	0.09

SOFA sequential organ failure assessment score, which can range from 0 to 24, *mSOFA* modified sequential organ failure assessment score, which does not take respiratory characteristics into account and can range from 0 to 20

[a] Data available for 756 patients

[b] Data available for 955 patients

[c] Data available for 717 patients

proportions of patients with acute leukemia and lymphoma increased (23 %/23 % in 1990–1995 vs 37 %/42 % in 2006–2011, respectively; $p < 0.0001$) and the proportion with myeloma decreased (28 % in 1990–1995 vs 5 % in 2006–2011, $p < 0.0001$). Proportions of patients with solid tumors and of BMT/HSCT recipients remained unchanged over time. Day-1 SOFA score was 12 (10–13) overall and decreased significantly over time (13 [11–13] in 1990–1995, 12 [10–13] in 1996–2000, 12 [10–13] in 2001–2005, and 11 [8–14] in 2006–2011; $p = 0.002$). At ICU admission, 444 (42.1 %) patients had neutropenia and 237 (23.6 %) were in partial or complete remission from their malignancy. ICU admission occurred after emergent surgery in 64 (6.4 %) patients.

Severe infection was documented clinically or microbiologically in 887 (88.3 %) patients. Vasopressors were needed in 73 % of patients and renal replacement therapy in 30.5 % (Table 2). The proportion of patients requiring dialysis increased over the four study periods (24, 25, 25 and 38 %, respectively; $p = 0.001$), whereas the proportion requiring vasopressors remained unchanged.

IFIs accounted for more than one-third of primary and secondary ARDS cases. Primary ARDS related to infection was found in 662 (65.9 %) patients, including 385 (58 %) with clinically or microbiologically documented bacterial infection and 277 (42 %) with IFI [213 with invasive pulmonary aspergillosis (17 certain, 119 probable, 77 possible) and 64 patients with certain *P. jirovecii* pneumonia]. Secondary ARDS occurred in 225 (22.4 %) patients with septic shock, including 80 (36 %) with candidemia. Noninfectious conditions were the primary cause of ARDS in 76 (7.6 %) patients. The cause of ARDS was undetermined in 41 (4.1 %) patients.

Factors independently associated with IFI were acute leukemia (OR, 1.78; 95 % CI, 1.22–2.60), lymphoma (OR, 2.01; 95 % CI, 1.37–2.95), first-line endotracheal MV (OR, 3.17; 95 % CI, 1.77–5.69), and endotracheal MV after NIV failure (OR, 2.11; 95 % CI, 1.14–3.91). Neutropenia and allogeneic BMT/HSCT were not independently associated with IFI.

Hospital mortality was 64 % overall and dropped significantly over time (from 89 % in 1990–1995 to 52 % in 2006–2011, $p < 0.0001$, Fig. 2). According to the Berlin definition, 252 (25.1 %) patients had mild, 426 (42.4 %) moderate, and 326 (32.5 %) severe ARDS (Fig. 1). Hospital mortality was 59, 63, and 68.5 % in these three groups, respectively ($p = 0.06$, Fig. 3). Mortality also dropped significantly in recipients of allogeneic stem cells transplantation (Fig. S1) or according to the type of underlying malignancy (Fig. S2).

NIV was used initially in 387 (38.6 %) patients. Among them, 276 (71 %) subsequently required endotracheal MV and 111 (29 %) did not. NIV use varied across the four study periods (14, 32, 33, and 26 %, respectively; $p = 0.0002$). The proportions of patients given NIV were similar across the three Berlin severity categories 85/252 (33.7 %) patients with mild ARDS, 173/426 (40.6 %) with moderate ARDS, and 129/326 (39.6 %) with severe ARDS ($p = 0.18$). However, NIV failed more often in the moderate and severe categories: endotracheal MV was subsequently required in 54/85

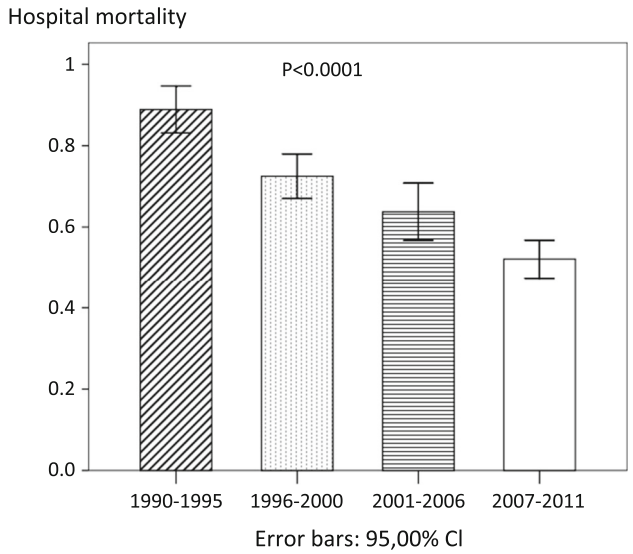

Fig. 2 Hospital mortality according to period of admission to the intensive care unit

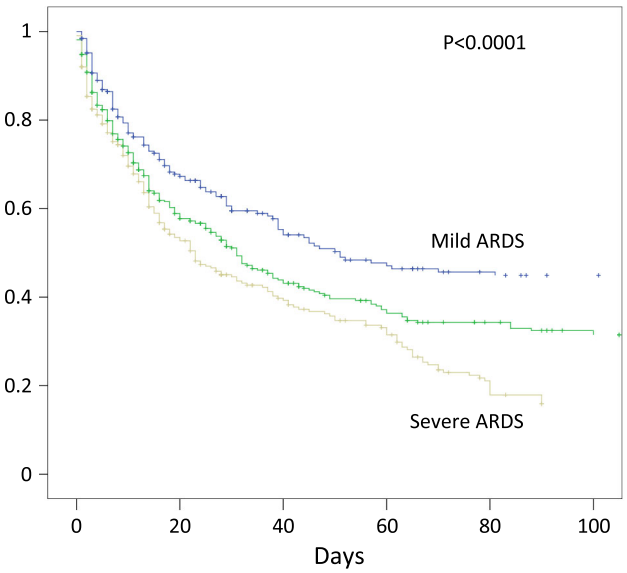

Fig. 3 Cumulative survival according to ARDS severity category in the Berlin definition. The *blue line* indicates mild ARDS, *red line* moderate ARDS and *gray line* severe ARDS. The three groups were compared using the log-rank test ($p < 0.0001$)

Table 3 Factors independently associated with hospital mortality

	OR	95 % CI	*p* value
Solid tumor	0.51	(0.34–0.77)	0.002
Need for emergency surgery	0.61	(0.35–1.05)	0.07
Allogeneic BMT/HSCT	1.71	(1.07–2.71)	0.04
mSOFA (per point)	1.11	(1.06–1.16)	<0.001
Cause of respiratory involvement			
No definite diagnosis	1	(Reference)	–
Primary ARDS	0.41	(0.20–0.88)	0.02
Secondary ARDS	0.90	(0.41–2.01)	0.80
Invasive fungal infection	1.72	(1.25–2.37)	0.001
Ventilation			
NIV	1	(Reference)	–
NIV failure	2.93	(1.80–4.79)	<0.001
Endotracheal MV	3.24	(2.02–5.24)	<0.001
ARDS severity			
Mild	1	(Reference)	–
Moderate	1.25	(0.88–1.78)	0.22
Severe	1.61	(1.10–2.36)	0.01

Hosmer–Lemeshow = 0.36; C-stat = 0.87

OR odds ratio, 95 % *CI* 95 % confidence interval, *BMT/HSCT* bone-marrow transplantation/hematopoietic-stem-cell transplantation, *mSOFA* modified sequential organ failure assessment, which does not take respiratory characteristics into account and can range from 0 to 20, *ARDS* acute respiratory distress syndrome, *NIV* noninvasive ventilation, *MV* mechanical ventilation

(63.5 %) patients with mild ARDS, 120/173 (69.4 %) with moderate ARDS and 102/129 (79.1 %) with severe ARDS ($p = 0.04$).

By multivariate analysis (Table 3), two factors were independently associated with lower hospital mortality, namely, solid tumor (versus hematological malignancy) and primary ARDS (versus undetermined ARDS etiology). Factors independently associated with higher mortality were allogeneic BMT/HSCT, worse admission mSOFA score, IFI, and NIV failure. Among the three Berlin severity categories, only severe ARDS was associated with increased mortality, whereas mortality was not significantly different between the mild and moderate categories. When period of ICU admission was entered into the multivariable model, a significant decrease in hospital mortality over time was found. With 1990–1995 as the reference, the ORs were 0.39 (95 % CI, 0.20–0.76) for 1996–2000, 0.26 (95 % CI, 0.13–0.51) for 2001–2005, and 0.16 (95 % CI, 0.09–0.30) for 2006–2011 and did not modified the final model (i.e., independent predictors of mortality).

As regard to the potential confusion bias induced by inclusion of patients with solid tumors, a sensitivity analysis was performed after exclusion of these patients (Table S2). The model was not significantly modified.

Discussion

In our large multicenter study of 1,004 patients with solid or hematological malignancies and ARDS meeting the new operational Berlin definition, about 90 % of ARDS cases were due to infections. Opportunistic organisms accounted for over one-third of all ARDS cases, with invasive aspergillosis and *Pneumocystis* pneumonia in primary ARDS and candidemia in secondary ARDS. Importantly, mortality decreased significantly over time, to 52 % during the most recent period, despite adjustment for patients' or ARDS severity, cause of the respiratory involvement or allogeneic stem cell transplantation. We found lower mortality rates in patients with solid tumors or primary ARDS and higher mortality rates in patients with allogeneic BMT/HSCT or IFIs. NIV was used initially in one-third of the patients but usually failed, with the highest failure rates occurring in the most severe ARDS category. NIV failure was associated with higher mortality.

Data on ARDS in patients with malignancies are scarce. Of two recent single-center studies in small numbers of patient, one identified multiorgan failure and the other greater acute illness severity and older age as risk factors for mortality [23, 24]; in one of these studies, NIV use was associated with lower mortality [24]. Other small studies focused on specific clinical situations such as neutropenia, neutropenia recovery, or drug-related pulmonary toxicity [10, 14, 16]. None of these studies used the Berlin definition of ARDS. In earlier studies of ARDS, SOFA scores and the need for vasopressors or renal replacement therapy were higher in patients with than without malignancies [25, 32, 33], in keeping with our data. The decreased mortality over time is also consistent with previously published studies of critically ill patients with malignancies [19]. Of note, although patient's characteristics differed across study periods (Table S1), decreased mortality over time remains significant after adjustment for patients' or ARDS severity, cause of the respiratory involvement or allogeneic stem cell transplantation. However, the 40 % decrease seen in our study is particularly large and suggests a role for optimal patient triage to ICU admission and ARDS management in ICUs that are highly experienced in managing patients with ARDS and malignancies, such as those to which our patients were admitted. Then, we believe that decreased mortality may only partially explained by the use of protective ventilation. More specifically, changes in the invasive or noninvasive diagnostic strategy for ICU patients with acute respiratory failure have increased the proportion of patients in whom the cause of ARDS is identified [1]. Primary ARDS was associated with lower mortality, indicating a need for further work on optimizing the diagnosis and treatment of secondary ARDS [17, 34, 35]. Allogeneic BMT/HSCT recipients, in particular, still have very high mortality rates if they require endotracheal MV [36].

Our study identifies two targets for improvement. The higher mortality after NIV failure is in keeping with studies of patients who had acute respiratory failure with [37] or without [38] malignancies. In one of these earlier studies, the risk of NIV failure was highest with ARDS [39]. Mortality rates of up to 90 % have been reported in patients with acute respiratory failure, immunosuppression, and endotracheal MV [40]. Overall, NIV has clearly decreased the risk of death by obviating the need for endotracheal MV in some patients. In keeping with our results, the initial enthusiasm to apply NIV was followed by a tempering that may be related to adverse events of failed NIV. Moreover, in recent years, mortality rates decreased significantly in patients managed with endotracheal MV [5, 19] and concern has been voiced that first-line NIV might be deleterious in patients with malignancies and acute respiratory failure, [41] particularly when criteria for ARDS are met [39]. Studies designed to clarify the potential benefits of early NIV in patients with malignancies and hypoxemic acute respiratory failure are warranted [41]. Our data and an earlier study [39] suggest that NIV may be best avoided in patients with malignancies and severe ARDS and should be considered only with caution in those with mild or moderate ARDS.

In our study, IFIs caused more than one-third of the ARDS cases. The main IFIs were invasive pulmonary aspergillosis and *P. jirovecii* pneumonia in primary ARDS and candidemia in secondary ARDS. IFI was independently associated with hospital mortality. Empirical antifungal therapy is the standard of care for neutropenic patients with hematological malignancies who remain febrile despite broad-spectrum antibacterial treatment [29]. In high-risk patients, primary prophylaxis is effective in preventing invasive aspergillosis and decreasing the rate of deaths related to fungal infections [42]. In a randomized trial in neutropenic patients with persistent fever despite broad-spectrum antibiotics [43], compared to empirical antifungal treatment, preemptive antifungal treatment increased the incidence of IFIs, without increasing mortality, and there was some evidence that empirical treatment decreased mortality among patients receiving induction chemotherapy [43]. However, in patients with ARDS, the frequency of invasive aspergillosis is highest during induction chemotherapy for acute leukemia or lymphoma. The role for empirical anti-aspergillosis therapy in these patients should be evaluated without delay.

Our study has several limitations. First, the participating ICUs had a high annual volume of patients with malignancies. As a volume-outcome relationship is likely in these patients, the improved outcomes over time found in our study may not apply to all ICUs. For instance, undermined ARDS etiologies occurred in only 4.1 % of the patients as most of the patients who were intubated underwent extensive diagnostic tests in highly skilled centers. However, critically ill patients with malignancies are routinely managed in specialized ICUs working closely with oncologists and hematologists. Second, the retrospective design and long study period raises the possibility of changes in diagnostic strategies and standard treatments. The improved outcomes over time are probably ascribable to advances in both the treatment of malignancies and intensive care [19]. Third, we did not collect data on tidal volumes, plateau pressures, ventilatory strategies, or rescue therapy (prone positioning, extracorporeal membrane oxygenation) and we were therefore unable to determine the extent to which improvements in these areas may have contributed to the improved survival over time [32, 44]. Until recently [32, 45], prone positioning was controversial, and extracorporeal membrane oxygenation was used in only eight of our patients. Fifth, the data used for our study were extracted from our research group database and obtained in studies that were not specifically designed to investigate ARDS [1, 9, 10, 19, 27, 46]. However, given the dearth of data on ARDS in patients with malignancies, we believe our strategy was a useful means of obtaining a sufficiently large cohort to provide convincing outcome information. Our study shows that mortality remains high in this population but has dropped significantly. Consequently, patients with malignancies should no longer be excluded from observational or interventional studies of ARDS. Last, we identified IFI as an independent predictor of death. However, advances in antifungal therapy have improved the outcomes of patients with invasive aspergillosis [6, 47], or candidemia, a fact that may have decreased the mortality in this patient group during our most recent study period.

In summary, pulmonary or extrapulmonary infections caused up to 90 % of ARDS cases in patients with malignancies. IFIs accounted for one-third of these infections. Mortality has decreased significantly over time. NIV failure occurred in 70 % of the cases and was associated with death, most notably among patients with severe ARDS, in whom initial NIV is probably unwise. Among the three ARDS categories defined in the Berlin definition, only severe ARDS was associated with increased mortality. The high mortality in patients with IFIs indicates a pressing need for specific studies of early antifungal therapy in high-risk patients.

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