Université de Poitiers
Faculté de Médecine et Pharmacie

ANNEE 2024

THESE
POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(décret du 25 novembre 2016)

Présentée et soutenue publiquement
le 8 avril 2024 à Poitiers
par Madame Mélanie Métais

Facteurs associés au pronostic à court et long terme chez les patients immunodéprimés admis en réanimation pour une insuffisance respiratoire aiguë

Factors associated with short and long-term prognosis in immunocompromised patients admitted to the intensive care unit for acute respiratory failure

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Président : Monsieur le Professeur Arnaud Thille

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Monsieur le Docteur Niels Moya
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Directeur de thèse : Monsieur le Professeur Rémi Coudroy

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UNIVERSITE DE POITIERS

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Remerciements

Au Pr Arnaud Thille, merci de me faire l'honneur de présider le jury de ma thèse. Merci de m'avoir accueilli dans votre service et formé dans cette spécialité que j'apprécie tant. C'est un réel plaisir d'être votre interne et de travailler avec vous.

Au Pr Rémi Coudroy, merci de m'accompagner depuis mes débuts d'interne et d'avoir fait naitre et grandir mon intérêt pour la recherche. Sans toi, ce travail aurait été impossible. Je te remercie pour ta patience, ta disponibilité et ta bienveillance à mon égard. C'est une fierté pour moi de t'avoir comme directeur de thèse.

Au Dr Anne Veinstein, merci de m'avoir fait l'honneur et le plaisir de faire partie de mon jury. Depuis mes premiers pas tu es un modèle pour moi, comme pour beaucoup d'autres.

Au Dr Niels Moya, toi qui m'as connu externe et pleine d'hésitations, merci de m'avoir transmis la passion de l'hématologie, c'est toujours un réel plaisir de travailler avec toi ou encore de te croiser, que ce soit dans la vie professionnelle comme personnelle.

Au Dr Camille Evrard, pour m'avoir fait l'honneur de juger ce travail. Merci pour le temps que vous avez consacré à la lecture de ce travail.

A François, Sylvain et Laura, merci à vous pour m'avoir formé et guidé sur mes premières gardes d'interne. J'ai beaucoup appris de vous et encore beaucoup à apprendre, j'espère suivre vos pas.

A Jean-Pierre, Delphine et Florence, merci pour votre bienveillance et pour tout ce que vous m'avez appris depuis le début.

A mes co-interne de la MIR, à Jérémy, Mathilde, Zofia, Corentin, Élise, Sigourney et les plus jeunes, merci pour tous ces cours et fous rire partagés ensemble. Encore de beaux moments à partager dans cette belle famille.

A toutes les infirmiers et aide soignants de la MIR, qui m'accompagne depuis mes premiers pas jusqu'à ce jour, c'est un réel plaisir de travailler avec vous dans la bonne humeur et la confiance. On ne peut rêver meilleure équipe !

A mes amis du premier jour, Mathieu C, Mathieu M, Florian, Marie R, Marie M, Camille, Pierre, Claire et Amélie, à tous les moments passés ensemble depuis le début et encore maintenant. Merci pour tous ce que vous m'apportez depuis la P2. Vous êtes les meilleurs.
Bientôt tous ultra bon docteur et pour toujours dans mon cœur.

A Mathilde, Aurélia, Clémence et Maia, j'ai trouvé en vous des co-internes en or et surtout des amis formidables. Je suis incroyablement chanceuse de vous avoir croisé. Votre soutien et votre bienveillance à mon égard est indescriptible. Vous m'inspirez au quotidien ! A notre prochaine soirée passé à refaire le monde (accompagné d'un petit verre bien sûr).

A Anne-Sophie, à nos débuts de bébé interne ensemble et à tout ce qu'on a traversé. Une co-interne puis une colocataire incroyable. Merci pour ton soutien et ta motivation au quotidien.

A Manon, Corentin, David, Garance, Clara, Constance et Louis, merci pour ces 6 mois passé ensemble, 6 mois de bonheur et de rigolade passé avec vous. Pas un jour sans fou rire, qu'est-ce que c'était cool ! On recommence ?

A Léa, Denis, Gabin, Mélanie K, Claire et Maeva, la dream team. Un de mes meilleurs semestres parmi vous. Je n'aurai pas pu espérer mieux pour commencer mon internat. Vous me manquez.

A Julien, Arnaud, Manon, Axel et Vincent, à nos consultations rage et à la douce sonnerie du téléphone voyageur avec qui on a partagé 6 mois. Heureusement que vous étiez là pour de beau moment de rire.

A Juliette et Victor, merci de m'avoir accompagné et guidé dans mes premiers jours. J'espère que tous les néo-internes ont des co-internes aussi bienveillants que vous.

A Etienne et Violaine, vous qui m'avez accompagné dans les derniers instant de ma thèse. Deux Docteurs Juniors en or !!

A l'équipe de néphrologie d'Angoulême, merci pour votre gentillesse et tous ce que vous m'avez appris. Un vrai plaisir de travailler et d'apprendre dans une équipe aussi bienveillante que la vôtre.

Au Dr Maillard et Dr Desmier, avec qui j'ai partagé 6 mois intense en greffe mais tellement passionnant. Merci d'avoir pris le temps de me transmettre une partie de vos connaissances, j'ai passé un semestre formidable à vos côtés.

A mes parents Jacqueline et Laurent, merci pour tous ce que vous m'apportez depuis toujours et pour votre soutien depuis le début de ces études difficiles et surtout longue. Vous êtes un exemple pour moi. Je vous aime.

A ma sœur et mon frère Clotilde et Vincent, à nos 400 coups faits ensemble. C'est toujours un plaisir de vous retrouver et surtout de partager une partie de Just dance. Vous me manquez et je suis fière de vous.

A mamie, merci pour tous ce que tu as fait pour nous 3. Vous nous dites sans cesse que vous êtes fière de nous, mais on vous doit ce que nous sommes devenu.
Je pense souvent à toi papi. Je sais que tu aurais été si fière de ce jour.

A Louis Poirier, merci d'être là depuis toutes ces années à mes côtés et pour ton soutien sans faille peu importe les circonstances. Je ne compte pas les choses que je n'aurai pas été capable de faire sans toi et je suis profondément reconnaissante de t'avoir à mes côtés. Je n'aurai pas pu rêver meilleur partenaire pour partager ma vie, que tu illumines.

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ABBREVIATIONS

ICU: Intensive care unit

ARF: Acute respiratory failure

IMV: invasive mechanical ventilation

NIV: noninvasive ventilation

PaO_2: Partial pressure of arterial oxygen

FiO_2: Inspired fraction of oxygen

$PaCO_2$: Partial pressure of arterial carbon dioxide

ECOG: Eastern Cooperative Oncology Group

SAPSII: Simplified Acute Physiology Score

SOFA: Sequential Organ Failure Assessment

SpO_2: Pulse oximetry

INTRODUCTION

Immunosuppression is defined as a dysfunction of the immune system, whether primary or secondary, resulting from a medical condition, such as solid cancer, hematologic malignancy, human immunodeficiency virus, or immunosuppressive drugs (1). The prevalence of immunosuppression has been steadily increasing in the recent years, primarily due to the rising incidence of cancers and the improved survival rates among these patients, resulting from the earlier detection of diseases and therapeutic advances (2). Therefore, it can be anticipated that a considerable proportion of patients will live several years with various and varying degrees of immunosuppression, exposing them to an increased risk of developing severe life-threatening infections (3). As a result, immunocompromised patients account for 15% to 25% of all patients admitted to the intensive care unit (ICU) (4).

Acute respiratory failure (ARF) is the main reason for ICU admission in this subset of patients (5). Their short-term mortality in the ICU is high, about 30% overall (6), and exceeds 50% in those requiring invasive mechanical ventilation (IMV) (7). Moreover, their long-term mortality continues to increase, reaching about 50% at 6 months and over 60% at 1 year after ICU admission (8,9). Most of studies assessing factors associated with long-term mortality in immunocompromised patients admitted to the ICU included in their analyses factors associated with short-term mortality, such as the severity of organ failure (8,9). Therefore, the risk factors of long-term mortality among ICU survivors are not clear. Additionally, although it is a major determinant to select the adequate therapeutic option in cancer patients (8,10,11), factors influencing the long-term functional status have been scarcely assessed (12). Accounting for the functional status in the long-term assessment of immunocompromised patients would be of primary importance to better understand which patient would benefit from ICU admission or readmission.

We hypothesized that factors associated with poor short-term outcomes differ from those associated with poor long-term outcomes among short-term survivors, in immunocompromised patients admitted to the ICU for acute respiratory failure.

METHODS

Study design

We performed an unplanned post-hoc analysis of a randomized controlled trial conducted in 29 centers in France and in Italy comparing two noninvasive oxygenation strategies in immunocompromised patients admitted to the ICU for acute hypoxemic respiratory failure (7). The protocol of the seminal study was approved by the Ethics Committee Ouest III (Poitiers, France) for French centers and by the local ethics committee for the Italian center. Informed consent from patients or their surrogate was obtained orally, with a written record maintained by the investigator.

Participants

Adult immunocompromised patients admitted to the ICU for acute hypoxemic respiratory failure were included. Acute respiratory failure was defined as a respiratory rate of at least 25 breaths per minute, a partial pressure of arterial oxygen (PaO_2) to inspired fraction of oxygen (FiO_2) ratio equal to or below 300 mmHg and a $PaCO_2$ not higher than 50 mmHg, while spontaneously breathing with standard oxygen (oxygen flow rate ≥ 10 L/min), with high-flow nasal oxygen therapy or with noninvasive ventilation. Immunosuppression was defined by one of the following criteria: hematological malignancy (active or remitting < 5 years), allogenic stem cell transplantation within the last 5 years, active or relapsing solid cancer, leucopenia < 1 G/L or neutropenia ≤ 0,5 G/L induced by chemotherapy, solid organ transplantation, acquired immunodeficiency syndrome, systemic steroids ≥ 0,5 mg/kg per day of prednisone equivalent for at least 3 weeks, or immunosuppressive or immunomodulatory drugs. Exclusion criteria were partial pressure of carbon dioxide higher than 50 mm Hg, contraindication to noninvasive ventilation (NIV, *i.e.* patient refusal, coma, non-drained pneumothorax, unresolved vomiting, upper airway obstruction, hematemesis or severe facial trauma), acute-on-chronic respiratory failure, cardiogenic pulmonary edema, surgery under general anesthesia less than 7 days, shock defined as a vasopressor dose of more than 0.3 µg/kg/min of norepinephrine equivalent to maintain systolic blood pressure at higher than 90 mm Hg, impaired consciousness with a Glasgow coma score of 12 or lower, urgent need for intubation (*i.e.* respiratory or cardiac arrest, respiratory pauses with loss of consciousness or gasping for air, severe hypoxemia defined as pulse oximetry [SpO_2] lower than 90% despite maximum oxygen support), and do not intubate order at time of inclusion. Pregnant women and patients under legal protection were also not included. Additionally, for the current analysis, we excluded patients whom Eastern Cooperative Oncology Group (ECOG) score at 180 days after randomization was missing.

Data collection

Demographic characteristics (such as age, gender, comorbidities, cause of immunosuppression), the cause of acute respiratory failure, severity scores at ICU admission (such as the Simplified Acute Physiology [SAPSII] score) and at randomization (such as the sequential organ failure assessment [SOFA] score, which was calculated using the worst values within the 24 hours before randomization), clinical characteristics at randomization and after 1 hour of treatment, treatments during ICU stay (randomization group, and the need for intubation, dialysis, or chemotherapy) and outcomes (mortality at day 28, at day 180, and the ECOG score at day 180) were prospectively collected.

Study Outcomes

Poor short-term outcome was defined as death at day 28 after randomization. Poor long-term outcome was defined as death or ECOG score 3 or 4 at day 180 after randomization.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (25-75th percentiles) depending on their distribution and compared using either the Student t-test or the Mann-Whitney *U* test, as appropriate. Categorical variables were expressed as number (percentage) and compared using the Chi-squared test or Fisher test, as appropriate. Two stepwise backwards stepwise logistic regression models were computed to identify early variables associated with poor short-term and long-term outcomes, respectively, including noncollinear variables associated with poor outcomes with a p-value < 0.20 in univariate analysis, and forcing variables known in the literature to be associated with poor outcomes. For the multivariable analysis of factors associated with poor short-term outcomes, we included exclusively early variables (*i.e.* clinical and biological variables occurring within the first 6 hours after randomization). A significance threshold was set at a p-value < 0.05. All statistical analyses were performed with R statistical software.

RESULTS

Characteristics of patients analyzed

From the 299 immunocompromised patients included in the seminal study, mean ± SD age was 63 ± 12 years, and 192 (64%) were males. Malignancy, either hematological or solid, was the main cause of immunosuppression in 75% of cases (224 out of 299 patients). Overall, mean ± SD ECOG score was 1 ± 1 and 16% of patients (49 out of 299) had score 3 or 4. At randomization, mean ± SD SAPSII and SOFA scores were 45 ± 16 and 6 ± 3, respectively. Randomization was performed 14 [2-38] min after ICU admission. Mean ± SD respiratory rate and PaO_2/FiO_2 at randomization were 31 ± 5 breaths/min and 147 ± 56 mm Hg, respectively. Mortality at day 28 after randomization was 36% (107 out of 299 patients).

After exclusion of the 3 patients whom ECOG score was missing at day 180, 49 out of the 189 survivors at day 28 (26%) had poor outcome at day 180, including 39 patients (21%) who died at day 180 and 10 patients (5.0%) with ECOG score 3 or 4 at day 180 (**Figure 1**).

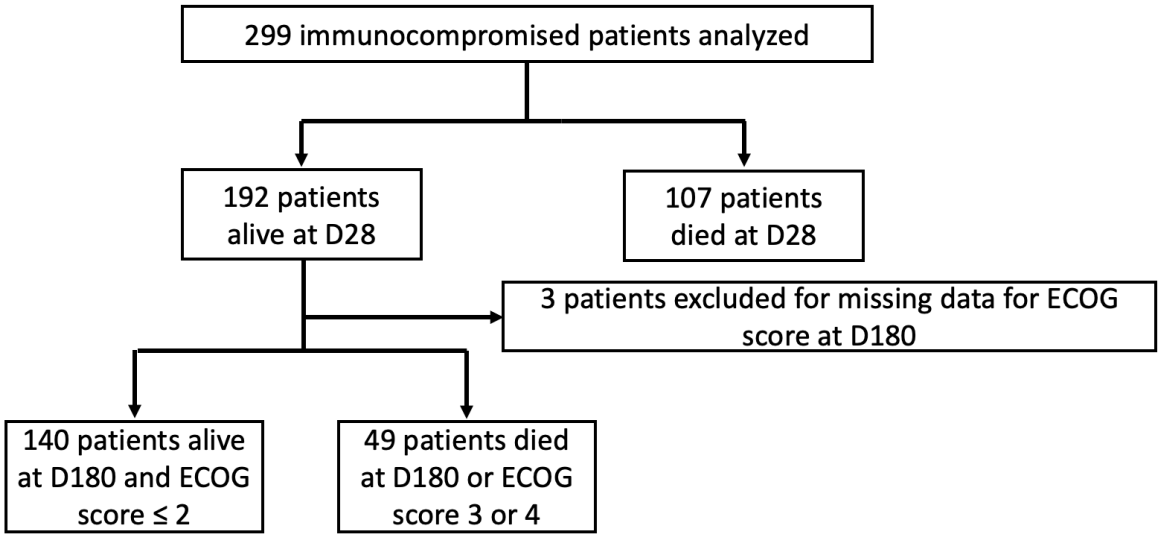


Figure 1. Flow chart of patients included in the analysis.

Factors associated with poor short-term outcome

Using univariate analysis, patients with poor short-term outcome (*i.e.* who were dead at day 28 after randomization) were more likely to have solid cancer (37% *vs.* 17% respectively, $p < 0.001$), higher severity scores at randomization (SAPSII score 49 ± 19 *vs.* 43 ± 14 respectively, $p = 0.003$; and SOFA score 6.5 ± 2.8 *vs.* 5.7 ± 2.6 respectively, $p = 0.021$), higher respiratory rate at randomization and 1 hour later (33 ± 6 *vs.* 31 ± 5 respectively at randomization, $p = 0.007$, and 30 ± 8 *vs.* 27 ± 7 respectively 1 hour later, $p = 0.016$), and lower PaO_2/FiO_2 at randomization 1 hour later (137 ± 52 *vs.* 153 ± 58 mm Hg respectively at randomization, $p = 0.012$, and 148 ± 68 *vs.* 184 ± 95 mm Hg respectively 1 hour later, $p < 0.001$) than those with good short-term outcome (**Table 1**).

Table 1. Univariate analysis of factors associated with poor short-term outcome.

Variables	Dead at day 28 (n= 107)	Alive at day 28 (n= 192)	p value
Baseline characteristics of the patients			
Age, y	65 ± 13	63 ± 12	0.268
Sex, men	64 (60%)	128 (67%)	0.289
ECOG score 3 or 4	21 (20%)	28 (15%)	0.334
Body mass index < 18,5 kg/m^2	9 (8.4%)	16 (8.3%)	1.000
Charlson comorbidity score	3.5 ± 2.5	3.4 ± 2.3	0.677
Underlying condition			
Hematological malignancy	50 (47%)	101 (53%)	0.393
Active or relapsing	43 (86%)	88 (87%)	0.411
Solid cancer active or relapsing	40 (37%)	33 (17%)	**<0.001**
Leukopenia or neutropenia	16 (15%)	28 (15%)	1.000
Allogenic stem cell transplant recipient	8 (7.5%)	15 (7.8%)	1.000
Autologous stem cell transplant recipient	3 (2.8%)	15 (7.8%)	0.136
Infected with HIV at AIDS stage	1 (0.9%)	11 (5.7%)	0.086
At intensive care unit admission			
Unit before ICU admission			0.988
Emergency department	37 (35%)	65(34%)	
Medical Unit	66 (62%)	120 (63%)	
Other ICU	4 (3.7%)	7 (3.6%)	
Simplified Acute Physiology score II	49 ± 19	43 ± 14	**0.003**
At Randomization			
Sequential organ failure assessment score	6.5 ± 2.8	5.7 ± 2.6	**0.021**
Sequential organ failure assessment score without respiratory item	3.3 ± 2.8	2.8 ± 2.5	0.095
Randomization in the high-flow nasal oxygen group	56 (52%)	98 (51%)	0.925
Respiratory rate	33 ± 6	31 ± 5	**0.007**
Respiratory rate ≥ 30 breaths/min	68 (63.55%)	96 (50%)	**0.029**
Arterial blood gases			
pH	7.43 ± 0.09	7.44 + 0.06	0.201
PaO_2/FiO_2, mmHg	137 ± 52	153 ± 58	**0.012**
$PaCO_2$, mmHg	34 ± 7	34 ± 6	0.912
Bilateral infiltrates on chest X-ray	84 (78%)	139 (72%)	0.306
Number of quadrants with infiltrates on chest X-ray	3 ± 1	3 ± 1	0.089
Norepinephrine	10 (9.3%)	8 (4.2%)	0.121
Discomfort score, mm*	47 ± 27	49 ± 28	0.559
1h after randomization			
Respiratory rate	30 ± 8	27 ± 7	**0.016**
Respiratory rate ≥ 30 breaths/min	48 (45%)	63 (33%)	**0.045**
Arterial blood gas analysis			
pH	7.43 ± 0.09	7.44± 0.06	0.255
PaO_2/FiO_2, mm Hg	148 ± 68	184 ± 95	**<0.001**
$PaCO_2$, mm Hg	34 ± 6	34 ± 6	0.553
Discomfort score, mm	46 ± 28	39 ± 27	0.060
Change between randomization and H1			
Decreased respiratory rate	64 (60%)	120 (62%)	0.873
Decreased PaO_2/FiO_2	39 (36%)	54 (28%)	0.163
Decreased $PaCO_2$	37 (35%)	58 (30%)	0.471
Decreased discomfort score	42 (39%)	84 (44%)	0.281

Qualitative variables are expressed in number (percentage), quantitative variables are expressed in mean ± standard deviation or median [25^{th}-75^{th}percentile] according to their distribution.

PaO_2 = partial pressure of arterial oxygen. FiO_2 = inspired fraction of oxygen. $PaCO_2$ = partial pressure of arterial carbon dioxide. *Discomfort score was assessed using a 100 mm visual analogue scale from no discomfort (0) to maximum imaginable discomfort (100).

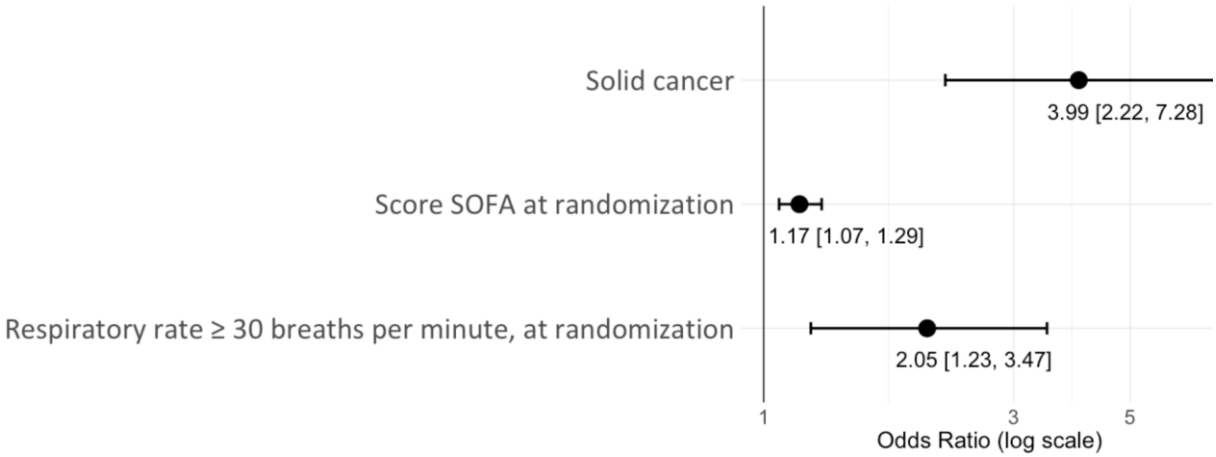
Using multivariable analysis, solid cancer and respiratory rate ≥ 30 breaths/min at randomization were associated with poor short-term outcome, independently from SOFA score at randomization (**Table 2 and Figure 2**).

Table 2. Multivariate analysis of factors associated with poor short-term outcome.

Variables[a]	Adjusted odds ratio (95% confidence interval)	p value
Solid cancer	3.99 (2.22 – 7.28)	< 0.001
SOFA score at randomization	1.17 (1.07 – 1.29)	0.001
Respiratory rate ≥ 30 breaths/min at randomization	2.05 (1.23 – 3.47)	0.007

[a]Variables included in the backwards stepwise logistic regression model were solid cancer, respiratory rate ≥ 30 breaths/min at randomization, SOFA score at randomization, discomfort score at H1 after randomization, and change in $PaCO_2$ between randomization and H1. ECOG score 3 or 4 was forced in the model.

Figure 2. Forrest plot of factors independently associated with poor short-term outcome.



Factors associated with poor long-term outcome among survivors at day 28

Using univariate analysis, patients with poor long-term outcome (*i.e.* who were dead at day 180 after randomization or who were alive with an ECOG score 3 or 4) were more likely to have an ECOG score of 3 or 4 at randomization (26% *vs.* 11% respectively, p = 0.014), lower PaO_2/FiO_2 (140 ± 54 *vs.* 159 ± 59 mm Hg respectively, p = 0.046) and higher $PaCO_2$ level at randomization (37 ± 6 *vs.* 33 ± 6 mm Hg respectively, p < 0.001), longer duration of mechanical ventilation (22 days [11-36] *vs.* 11 [6-16] days respectively, p = 0.004), increased reintubation rate (28% vs. 7% respectively, p= 0.042), longer hospital stay (31 days [18-47] vs. 19 days [13-31] respectively, p = 0.004) and were more likely to remain hospitalized at day 28 (55% vs 32% respectively, p = 0.007) than those with good long-term outcome (**Table 3**).

Table 3. Univariate analysis of factors associated with poor long-term outcome among survivors at day 28.

Variables	Died at day 180 or ECOG score 3 or 4 (n=49)	Alive at day 180 and ECOG score ≤ 2 (n=140)	p value
Baseline characteristics of the patients			
Age, y	62 ± 11	63 ± 13	0.822
Sex, men	35 (71%)	90 (64%)	0.463
ECOG score 3 or 4	13 (26%)	15 (11%)	**0.014**
Body mass index < 18,5 kg/m^2	7 (14%)	9 (6.4%)	0.165
Charlson comorbidity score	4.0 ± 3.0	3.2 ± 2.0	0.075
Underlying condition			
Hematological malignancy	25 (51%)	74 (53%)	0.956
Active or relapsing	23 (92%)	64 (86%)	1.000
Solid cancer active or relapsing	13 (26%)	20 (14%)	0.085
Leukopenia or neutropenia	9 (18%)	19 (14%)	0.562
Allogenic stem cell transplant recipient	6 (12%)	8 (5.7%)	0.236
Autologous stem cell transplant recipient	2 (4.1%)	13 (9.3%)	0.394
Infected with HIV at AIDS stage	4 (8.2%)	6 (4.3%)	0.501
At intensive care unit admission			
Unit before ICU admission			0.411
Emergency department	14 (29%)	51 (36%)	
Medical Unit	34(69%)	83 (59%)	
Other ICU	1 (2%)	6 (4.3%)	
Simplified Acute Physiology score II	45± 15	42 ± 14	0.249
At Randomization			
Respiratory rate	30 ± 6	31 ± 5	0.286
Respiratory rate ≥ 30 breaths/min	24 (49%)	70 (50%)	1.000
Arterial blood gases			
pH	7.44 ± 0.05	7.45 ± 0.07	0.311
PaO_2/FiO_2, per mm Hg	140 ± 54	159 ± 59	**0.046**
$PaCO_2$, per mm Hg	37 ± 6	33 ± 6	**<0.001**
Randomization in the high-flow nasal oxygen group	23 (47%)	73 (52%)	0.645
Bilateral infiltrates on chest X-ray	31 (63%)	107 (76%)	0.109
Number of quadrants with infiltrates on chest X-ray	2.6 ± 1.2	2.9 ± 1.1	0.160
Norepinephrine	3 (6.1%)	5 (3.6%)	0.725
During intensive care unit stay			
Bronchoalveolar lavage performed	20 (41%)	57 (41%)	1.000
CT-scan performed	30 (61%)	91 (65%)	0.763
Change in immunosuppressive drug regimen	17 (35%)	36 (26%)	0.308
Renal replacement therapy	9 (18%)	12 (8.6%)	0.107
Norepinephrine within 3 days after randomization	15 (31%)	34 (25%)	0.977
Intubation	18 (37%)	43 (31%)	0.550
Intubation before H24	9 (50%)	20 (46%)	0.496
Intubation after H24 or not intubated	40 (82%)	120 (86%)	0.496
Duration of mechanical ventilation	22 [11-36]	11 [6-16]	**0.004**
Reintubation	5 (28%)	3 (7.0%)	**0.042**
Cause of respiratory failure			0.161
Documented lung infection	23 (47%)	79 (56%)	
Pneumonia with unknown cause	12 (24%)	18 (13%)	
Specific	5 (10%)	13 (9.3%)	
Toxic cause	2 (4.1%)	8 (5.7%)	
Cardiogenic Pulmonary Edema	1 (2.0%)	9 (6.4%)	
Miscellaneous	6 (12%)	13 (9%)	
Short-term outcomes			
Length of stay in the ICU, n (%)	8 [5-21]	8 [5-14]	0.255
Length of stay in the hospital	31 [18-47]	19 [13-31]	**0.004**
Still hospitalized at day 28	27 (55%)	45 (32%)	**0.007**

Qualitative variables are expressed in number (percentage), quantitative variables are expressed in mean ± standard deviation or median [25th-75thpercentile] according to their distribution.
PaO_2 = partial pressure of arterial oxygen. FiO_2 = inspired fraction of oxygen. $PaCO_2$ = partial pressure of arterial carbon dioxide.

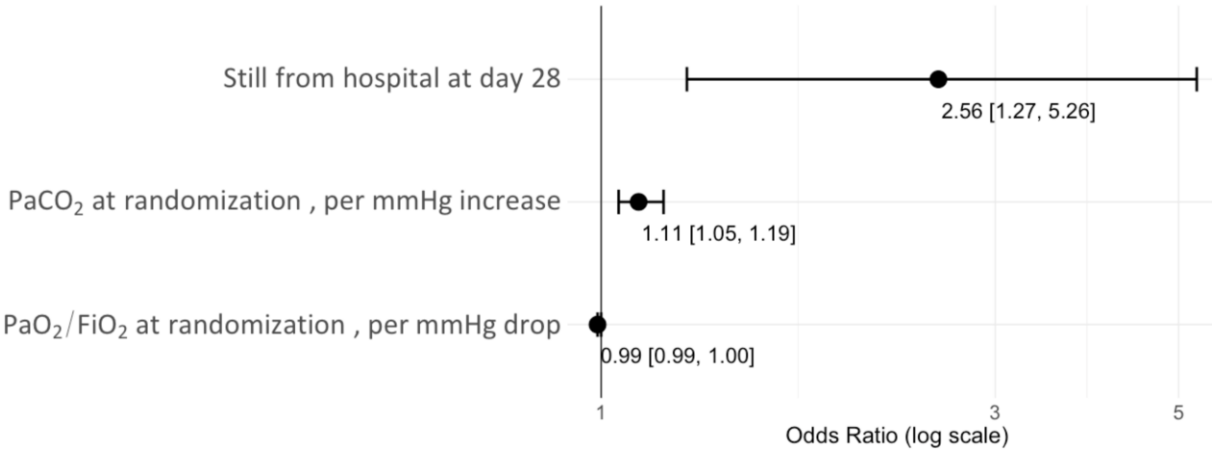
Using multivariable analysis, PaO_2/FiO_2 and $PaCO_2$ at randomization were associated with poor long-term outcome, independently from still being in the hospital at day 28 (**Table 4 and Figure 3**).

Table 4. Multivariate analysis of factors associated with poor long-term outcome among survivors at day 28.

Variables[a]	Adjusted odds ratio (95% confidence interval)	p value
$PaCO_2$ at randomization, per mm Hg increase	1.11 (1.05-1.19)	0.001
PaO_2/FiO_2 at randomization, per mm Hg drop	0.99 (0.99- 1.00)	0.030
Still hospitalized at day 28	2.56 (1.27-5.26)	0.010

[a] Variables included in the backwards stepwise logistic regression model were solid cancer, ECOG score 3 or 4, BMI < 18.5 kg/m^2, $PaCO_2$ at randomization, PaO_2/FiO_2 at randomization, renal replacement therapy, pneumonia with unknown cause, still hospitalized at day 28. Intubation and respiratory rate at randomization were forced in the model.

Figure 3. Forrest plot of factors independently associated with long-term poor outcome among survivors at day 28



DISCUSSION

In this post-hoc analysis of a randomized trial including immunocompromised patients admitted to the ICU for acute hypoxemic respiratory failure, we found that active or relapsing solid cancer, respiratory rate ≥ 30 breaths/min at randomization and the SOFA score at randomization were independently associated with mortality at day 28. Among survivors at day 28, gas exchange impairment at randomization and still being hospitalized at day 28 were independent predictors of poor long-term outcome.

In our study, short-term mortality was 36%, in keeping with that reported by Azoulay and colleagues, who reported an ICU mortality of 32% in a prospective observational international cohort study including 1611 immunocompromised patients with a population similar to ours (52% of patients had hematological malignancy and 35% had solid cancer)(6). Regarding long-term outcomes, our 6-

month mortality rate was 49% (107 patients at day 28 and 39 additional at 6 months). Although data regarding the long-term outcomes of immunocompromised patients are scarce, our results are in line with the 55% mortality rate at 6 months reported by Soares and colleagues in a multicenter observational study including 449 patients with lung cancer (8). All in all, these results reinforce the external validity of our findings.

Independent predictors of poor short-term outcomes were the severity of organ failure, respiratory rate, and solid cancer. The severity of organ failure has been extensively reported as a risk factor for short-term mortality in patients with hematological malignancy (13), lung cancer (8), or in a mixed population of immunocompromised patients admitted to the ICU for acute respiratory failure (6). Regarding respiratory rate at randomization, data on immunocompromised patients are scarce. In large cohorts including patients with acute hypoxemic respiratory failure independently from their immunosuppression status, respiratory rate is associated with increased risk of intubation in patients breathing through conventional oxygen therapy (14), NIV (15), or high-flow nasal oxygen failure (16), and with an increased risk of mortality among patients with acute respiratory distress syndrome treated with NIV (17).
In our study, active or relapsing solid cancer was associated with short-term mortality. Despite the absence of a direct comparison of outcome according to the type of immunosuppression and despite differences in prognosis according to the type of solid cancer (18), mortality of patients with solid cancer is often higher than that with other type of immunosuppression (6). Several factors associated with mortality in the literature have not been tested, such as intubation, the cause of respiratory failure or the SAPS II score. We decided not to include these variables in the model because they may require several hours or days of ICU hospitalization and therefore cannot be considered as early predictors of mortality. Additionally, SAPS II score shares collinearity with immunosuppression status (19). Other factors such as the ECOG score were not associated with poor short-term outcomes in our analysis (8,20), possibly due to the small number of patients with ECOG score of 3 or 4 at randomization in our cohort.

Impaired gas exchanges at randomization and being still hospitalized at day 28 were independent predictors of poor long-term outcome among day-28 survivors. Hypoxemia the first day of ICU admission has already been reported to be associated with hospital mortality in a mixed population of immunocompromised patients (6).

Although hypercapnia equal to or greater than 50 mmHg at randomization was an exclusion criterion in our study, increased $PaCO_2$ at randomization was associated with poor long-term outcomes. The absence of hypocapnia in patients with acute hypoxemic respiratory failure may reflect the inability of the patient to hyperventilate following lung injury. Interestingly, a different response to

noninvasive oxygenation strategies has been reported according to the $PaCO_2$ level among 109 patients with COVID-19-induced acute hypoxemic respiratory failure (21).
Still being hospitalized at day 28 after randomization was associated with a 2-fold increased risk of poor long-term outcome in our cohort. This finding highlights the importance of post-ICU care and rehabilitation to reduce the length of hospital stay. This result may also be important to consider when discussing the treatment intensity in case of readmission after ICU discharge to provide the most appropriate care to fragile patients. Some variables, such as the ECOG score, were not associated with poor long-term outcome despite being forced in the multivariable model (22). This absence of association could be due to the small proportion of patients with ECOG score 3 or 4 at randomization as mentioned above, exacerbated by the exclusion of 21 patients with ECOG score of 3 or 4 at baseline who died at day 28, or to the fact that the ECOG score measured before ICU admission may not be an actual determinant of long-term outcome among ICU survivors.

Some limitations must be acknowledged. First, the unplanned post-hoc nature of the analysis could have led to selection bias. However, baseline characteristics of patients included and their outcomes are similar to that reported in a large observational study (6). Second, the choice of variables included in the multivariate analyses is debatable. For instance, we did not include intubation in the analysis of variables associated with short-term outcome. Indeed, this event may occur later than 24 hours after ICU admission in about half of patients, and therefore is not clinically relevant. We rather decided to include only early easy-to-assess variables in the analysis of factors associated with short-term outcome. Third, data were collected at randomization and not at ICU admission. However, the time elapsed between ICU admission and randomization was very short (less than 15 min in median), suggesting that data collected at randomization correspond to data on ICU admission.

CONCLUSION

In immunocompromised patients admitted to the ICU for acute respiratory hypoxemic failure, solid cancer, respiratory rate ≥ 30 breaths/min at randomization and SOFA score at randomization were independently associated with mortality at day 28. Among survivors at day 28, impaired gas exchange and still being hospitalized on day 28 were independent predictors of poor long-term outcomes.

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Introduction

The prevalence of immunocompromised patients in intensive care unit (ICU) is increasing. Acute respiratory failure is their main reason for ICU admission. Their mortality rate is high and continues to increase after discharge from the ICU. In immunocompromised patients, factors associated with long-term outcome are dominated by risk factors of short-term mortality. Additionally, the functional status is rarely considered in these analyses, although it is a major determinant to select the adequate therapeutic option for the underlying disease. We hypothesized that factors associated with poor short-term outcomes differ from that associated with poor long-term outcomes among short-term survivors.

Methods

This is a post-hoc analysis of a multicenter randomized controlled trial comparing two strategies of non-invasive oxygenation in 299 immunocompromised patients admitted to the ICU. The objectives were to identify early factors (within 6 hours of randomization) associated with poor short-term outcome (defined as death at day 28 after randomization) and poor long-term outcome (defined as death or alive with Eastern Cooperative Oncology Group score of 3 or 4 at day 180 after randomization).

Results

Among the 299 patients analyzed, 224 (75%) had cancer (solid or hematological). Mortality rate at day 28 was 36%. In multivariate analysis, factors independently associated with poor short-term outcome were (adjusted odds ratio [95% confidence interval]) solid cancer (3.99 [2.22-7.28]), respiratory rate ≥ 30 breaths/min at randomization (2.05 [1.23-3.47]) and Sequential Organ Failure Assessment score at randomization (1.17 [1.07-1.29]). Factors associated with poor long-term outcome were analyzed in 189 survivors (3 patients excluded due to missing Eastern Cooperative Oncology Group score at day 180). Among survivors at day 28, 49 (26%) had poor prognosis at day J180, of whom 39 died (21%). In multivariate analysis, still being hospitalized at day 28 (2.56 [1.27-5.26]) was associated with poor long-term outcome, independently from PaO_2/FiO_2 (0.99 [0.99-1.00]) and $PaCO_2$ at randomization (1.11 [1.05-1.19]).

Conclusion

In this cohort of immunocompromised patient admitted to the ICU for acute respiratory failure, solid cancer was associated with short-term outcome, and still being hospitalized at day 28 of the initial ICU admission was associated with poor long-term outcome, independently from the severity of respiratory failure.

Keywords: Immunosuppression, acute respiratory failure, intensive care unit, mortality

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

RÉSUMÉ

Introduction

La prévalence des patients immunodéprimés en réanimation est en augmentation. Leur principal motif d'admission est l'insuffisance respiratoire aiguë. Leur taux de mortalité est élevé et continue d'augmenter après la sortie de réanimation. Dans cette population, les facteurs associés au pronostic à long terme sont dominés par les facteurs de risque de mortalité à court terme. De plus, le pronostic fonctionnel est rarement pris en compte dans ces analyses, alors qu'il est déterminant pour la poursuite ou non du traitement de la maladie de fond. Notre hypothèse est que les facteurs associés au mauvais pronostic à court terme diffèrent de ceux associés au mauvais pronostic à long terme chez les survivants.

Méthodes

Il s'agissait d'une analyse post-hoc d'un essai multicentrique, randomisé et contrôlé comparant deux stratégies d'oxygénation non invasive chez 299 patients immunodéprimés admis en réanimation pour une insuffisance respiratoire aiguë hypoxémique. Les objectifs étaient d'identifier les facteurs précoces (dans les 6 heures de la randomisation) associés au mauvais pronostic à court terme (défini par le décès à J28 de la randomisation) et au mauvais pronostic à long terme (défini par le décès ou la survie avec un score de l'Organisation Mondiale de la Santé de 3 ou 4 à J180 de la randomisation).

Résultats

Parmi les 299 patients analysés, 224 (75%) avaient un cancer (solide ou hémopathie). La mortalité à J28 était de 36%. En analyse multivariée, les facteurs indépendamment associés au mauvais pronostic à court terme étaient (odds ratio ajusté [intervalle de confiance à 95%]) : le cancer solide (3.99 [2.22-7.28]), une fréquence respiratoire ≥ 30 cycles/min à la randomisation (2.05 [1.23-3.47]) et le score SOFA à la randomisation (1.17 [1.07-1.29]).

Les facteurs associés au mauvais pronostic à J180 étaient analysés chez 189 survivants (3 patients exclus pour score de l'Organisation Mondiale de la Santé à J180 manquant). Parmi les survivants à J28, 49 (26%) avaient un mauvais pronostic à J180, dont 39 étaient décédés (21%). En analyse multivariée, le fait d'être toujours hospitalisé à J28 (2.56 [1.27-5.26]) était associé au mauvais pronostic à J180, indépendamment du PaO_2/FiO_2 (0.99 [0.99- 1.00]) et de la $PaCO_2$ à la randomisation (1.11 [1.05-1.19]).

Conclusion

Dans cette cohorte de patients immunodéprimés admis en réanimation pour une insuffisance respiratoire aiguë, l'existence d'un cancer solide était associée au pronostic à court terme, et le fait d'être toujours hospitalisé à J28 de l'hospitalisation princeps en réanimation était associé au mauvais pronostic à long terme, indépendamment de la sévérité de l'insuffisance respiratoire.

Mots clés : Immunosuppression, insuffisance respiratoire aiguë, réanimation, mortalité