Etiologies and Outcomes of Acute Respiratory Failure in Solid Organ Transplant Recipients: Insight Into the EFRAIM Multicenter Cohort

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ABSTRACT

Background. Respiratory complications of solid organ transplant (SOT) are a diagnostic and therapeutic challenge when requiring intensive care unit (ICU) admission. We aimed at describing this challenge in a prospective cohort of SOT recipients admitted in the ICU.

Methods. In this post hoc analysis of an international cohort of immunocompromised patients admitted in the ICU for an acute respiratory failure, we analyzed all SOT recipients and compared their severity, etiologic diagnosis, prognosis, and outcome according to the performance of an invasive diagnostic strategy (encompassing a fiber-optic

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0041-1345/20
https://doi.org/10.1016/j.transproceed.2020.02.170

bronchoscopy and bronchoalveolar lavage), the type of transplanted organ, and the need of invasive ventilation at day 1.

Results. Among 1611 patients included in the primary study, 142 were SOT recipients (kidney, n = 73; 51.4%; lung, n = 33; 23.2%; liver, n = 29; 20.4%; heart, n = 7; 4.9%). Lung transplant recipients were younger than other SOT recipients, and severity did not differ across type of received organ. An invasive diagnostic strategy was more frequently performed in lung transplant recipients with a trend toward a higher rate of bacterial etiology in lung than kidney transplant recipients. Overall ICU survival of SOT recipients was 75.4%. Invasive diagnostic strategy, type of transplanted organ, and need of invasive mechanical ventilation at day 1 did not affect ICU prognosis.

Conclusions. ICU management of hypoxemic acute respiratory failure in SOT recipients translated into a low ICU mortality rate, whatever the transplanted organ or the acute respiratory failure cause. The post-ICU burden of acute respiratory failure SOT recipients remains to be investigated.

SOLID organ transplant (SOT) is a key therapy in chronic end-stage organ failure and provides a benefit in terms of quality of life at the price of life-threatening complications, may they be transplant specific or not. However, each type of SOT carries an elevated risk for pulmonary injury [1], either related to their immunosuppressive regimens and infectious events or to other type of complications, that is, pulmonary edema, primary graft dysfunction, diffuse alveolar hemorrhage, drug-related pulmonary toxicity, or acute interstitial pneumonia from various causes [2]. The specific diagnostic workup may be challenging because the effects of immunosuppression may dampen the symptoms of infection [3]. In some cases, clinical presentation of infectious or noninfectious causes of acute respiratory failure (ARF) may widely overlap. In other patients, noninfectious causes of ARF may be associated with infectious ones. Hence, managing SOT recipients with ARF includes both a specific diagnostic workup and a dedicated oxygenation strategy. The diagnostic strategy might be invasive, including a fiber-optic bronchoscopy and bronchoalveolar lavage (FO-BAL) with the risk of worsening the respiratory status [4] or noninvasive, using sputum examinations and/or serum and urine samples. The early oxygenation challenge includes noninvasive ventilation (NIV) [5] or high-flow nasal cannula (HFNC) oxygen [6–8]. Nevertheless, 2 recent studies in immunocompromised patients with ARF showed that neither NIV [7] nor HFNC [6] therapy significantly decrease day 28 mortality or the need for intubation compared with conventional oxygen therapy (COT). Furthermore, it has been suggested that a delayed assessment of HFNC failure might cause a worse clinical outcome in patients with ARF [9,10].

Data focusing on pulmonary complications and diagnostic and therapeutic strategies in critically ill SOT recipients are scarce [11,12]. In the present study, we therefore aimed to describe the diagnostic strategy, the clinical and etiologic patterns, and the outcomes of ARF requiring intensive care unit (ICU) admission in SOT recipients and explore them according to the type of organ received.

METHODS

Study Design

We conducted a post hoc analysis of the previously published EFRAIM cohort study [13]. In brief, EFRAIM was a multinational, observational, prospective cohort study performed by the Nine-I (caring for critically ill immunocompromised patients) study group. This group includes critical care physicians from 16 countries who have extensive experience in the management of various groups of critically ill immunocompromised patients. Physician participation was voluntary, without financial incentive. Participating providers obtained Institutional Review Board approval from their institutions in accordance with local ethics regulations.

Inclusion criteria were 18 years or older; acute hypoxemic respiratory failure (PaO_2 < 60 mm Hg or oxygen saturation as measured by pulse oximetry < 90% on room air, tachypnea > 30/min, or labored breathing or respiratory distress or dyspnea at rest or cyanosis); need for more than 6 L/min oxygen; respiratory symptom duration less than 72 hours; and being nonrelated to a viral AIDS, that is, hematologic malignant neoplasm or solid tumor (active or in remission for less than 5 years, including recipients of autologous or allogeneic stem cell transplant), SOT, long-term (> 30 days) or high-dose (> 1 mg/kg/d) steroids, or any immunosuppressive drug for more than 30 days. Exclusion criteria included postoperative ARF (within 6 days of surgery), admission after a cardiac arrest, ICU admission only to secure FO-BAL, or refusal of the patient or family to participate in the study. Primary endpoints of the EFRAIM study [13] were the need for invasive mechanical ventilation (IMV) in patients not intubated on ICU admission and all-cause hospital mortality.

After Institutional Review Board approval at each center, participating ICUs enrolled patients between November 5, 2015, and July 1, 2016. A standardized paper case report was prepared by investigators and tested in 35 patients. After feedback and corrections, the case report form was sent to participating ICUs, and once completed, it was sent back to the coordinating center in Paris for data entry by specialized technicians used to handling data on critically ill immunocompromised patients. The study was funded by

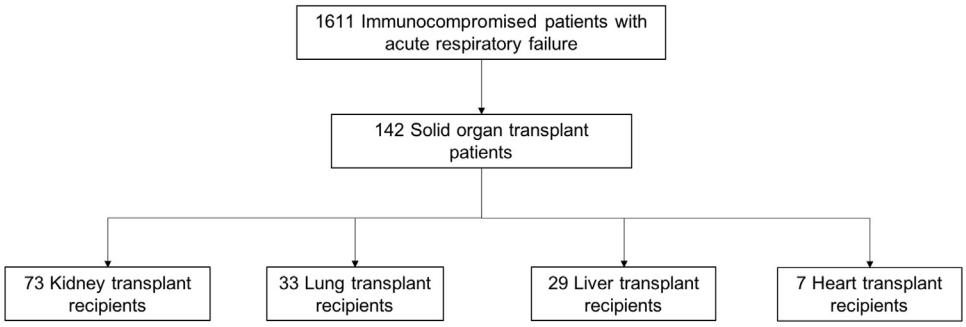

Fig 1. Flow chart of the included patients. Among 1611 immunocompromised patients enrolled over the 8-month period in the 68 participating ICUs admitted for an acute respiratory failure, 142 (8.9%) were solid organ recipients (n = 73 kidney recipients; n = 33 lung recipients; n = 29 liver recipients; and n = 7 heart recipients) included in this post hoc series.

the Groupe de Recherche en Reanimation Respiratoire Onco-Hématologique, an academic not-for-profit French organization.

Patients

Patients included in EFRAIM study and having SOT, irrespective of concurrent immune defect, were included in this post hoc analysis (Fig 1).

Study Procedures

All management decisions were independently made by the attending physicians according to standard practice in each ICU. Diagnostic tests to identify the cause of respiratory failure were noninvasive (blood and sputum cultures for bacteria and fungi, serum and urine antigens, polymerase chain reaction in blood, serum sample and nasopharyngeal aspirates, high-resolution computed tomography scan, echocardiography, serology, and specific tests according to each situation) or invasive when it encompassed FO-BAL.

All diagnoses were reviewed by 2 study investigators for coherence and for alignment with established definitions. COT was defined as the use of oxygen up to 15 L/min via nasal prongs or nonrebreathing mask. Oxygenation modalities and the use of NIV or HFNC were at the discretion of the primary team. Management of associated organ dysfunction and handling of immunosuppressive drugs or chemotherapy were done as per local preferences. The decision to intubate was not controlled by the study.

Patients were enrolled immediately at ICU admission, and the data in the tables and figures were collected prospectively using the paper case report form. Patient severity was defined according to Sequential Organ Failure Assessment (SOFA) score, recorded within 24 hours of admission, with higher score being associated with higher number or severity of organ dysfunction and with higher mortality [14]. Our primary endpoint was the description of the etiologies and outcomes of ARF in SOT recipients. Our secondary endpoints were the comparison of their epidemiologic characteristics, their prognosis according to the transplanted organ, and their prognosis according to the need of IMV at day 1, the lack of etiologic diagnosis, and the use of FO-BAL in the diagnosis strategy.

STATISTICAL ANALYSIS

Quantitative variables were described as median (interquartile range [IQR]) and were compared between groups using the nonparametric Wilcoxon rank-sum test. Qualitative variables were described as frequency (percentages) and were compared between groups using Fisher exact test.

Logistic regression model were used to assess factors independently associated with mortality. We used conditional stepwise regression with .2 as the critical *P* value for entry into the model and .1 as the *P* value for removal. It was planned a priori to force transplanted organ, IMV at day 1, lack of etiologic diagnosis, and use of FO-BAL in the final model should these variables not be selected. Interactions and correlations between the explanatory variables were carefully checked. Continuous variables for which log-linearity was not confirmed were transformed into categorical variables according to median or IQR. The final models were assessed by calibration, discrimination, and relevancy. Residuals were plotted, and the distributions were inspected. To adjust for center effect, a mixed model was then performed using variables previously selected, using center as random effect on the intercept. This model adjusting for clustering effect was planned a priori to be the main result of the analysis. The same validation methods were used as previously. Adjusted odds ratios (OR) of variables present in the final model are presented with their 95% confidence intervals.

Kaplan-Meier graphs were used to express the probability of death from inclusion to hospital discharge, censored at day 90. Influence of the transplanted organ, use of FO-BAL (ie, an invasive diagnostic strategy), oxygenation strategy at day 1, and lack of etiologic diagnosis for respiratory failure were assessed by the log-rank test.

All analyses were 2-sided, and a P value $< .05$ was considered significant. Statistical analyses were performed with R statistical software version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) and packages Survival, lme4, and lmerTest.

RESULTS

Among the 1611 immunocompromised patients with ARF enrolled over the 8-month period in the 68 participating ICUs, 142 (8.9%) were solid organ recipients. Kidney

Table 1. Demographic Data, Comorbid Conditions, Severity and ICU Course of the 142 Solid Organ Transplant Recipients

Variables	All Solid Organ Transplant Recipients N = 142	Heart Transplant Recipients n = 7	Kidney transplant Recipients n = 73	Liver Transplant Recipients n = 29	Lung Transplant Recipients n = 33	*P* Value
Age, median (IQR), y	62.0 (55.0-68.0)	63.00 (49.0-68.5)	64.0 (58.0-72.0)	61.0 (56.0-67.0)	57.0 (47.0-62.0)	< .001
Sex, No. (%), F	57 (40.7)	2 (28.6)	37 (51.4)	4 (14.3)	14 (42.4)	.007
Comorbid conditions at ICU admission, No. (%)						
- Solid tumor	24 (16.9)	0	14 (19.2)	7 (24.1)	3 (9.1)	.24
- Hematologic malignant neoplasm	8 (5.6)	0	7 (9.6)	1 (3.4)	1 (3)	.81
- Hematological stem cell or bone marrow transplant	1 (0.7)	0	1 (1.4)	0	0	.81
- Diabetes mellitus	57 (42.2)	4 (57.1)	28 (39.4)	13 (50)	12 (38.7)	.64
- Chronic kidney disease	85 (61.2)	6 (85.7)	57 (79.2)	14 (50)	8 (25)	< .001
- Cirrhosis	21 (15.4)	0	3 (4.2)	17 (63)	1 (3.2)	< .001
ECOG performance status, median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	2 (1-2)	2 (1-2)	.76
SOFA at ICU admission, median (IQR)	6 (4.0-10.0)	9 (5.5-11.0)	5.0 (3.0-10.0)	7.0 (5.0-11.0)	7.0 (4.0-9.0)	.272
Therapies administered during the first 7 days of ICU stay, No. (%)						
- Vasopressors	79 (55.6)	3 (42.9)	35 (47.9)	21 (72.4)	20 (60.6)	.12
- Renal replacement therapy	37 (26.1)	3 (42.9)	18 (24.7)	6 (20.7)	10 (30.3)	.61
Oxygenation strategy at day 1, No. (%)*						.092
- Conventional oxygen therapy	69 (48.6)	4 (57.1)	42 (57.5)	11 (37.9)	12 (36.4)	
- High-flow nasal cannula oxygen	18 (12.7)	1 (14.3)	6 (8.2)	2 (6.9)	9 (27.3)	
- Noninvasive ventilation	22 (15.5)	0	12 (16.4)	6 (20.7)	4 (12.1)	
- Invasive ventilation	33 (23.2)	2 (28.6)	13 (17.8)	10 (34.5)	8 (24.2)	
Patients who underwent FO-BAL during the etiologic workup, No. (%)	71 (50.0)	2 (28.6)	27 (37.0)	19 (65.5)	23 (69.7)	.003
ARF etiology, No. (%)						
- Bacterial	42 (29.6)	1 (14.3)	18 (24.7)	7 (24.1)	16 (48.5)	.052
- *Pneumocystis* pneumonia	6 (4.2)	0	5 (6.8)	1 (3.4)	0	.38
- Virus	25 (17.6)	2 (28.6)	13 (17.8)	3 (10.3)	7 (21.2)	.59
- *Candida*	2 (1.4)	0	1 (1.4)	1 (3.4)	0	.70
- Invasive pulmonary aspergillosis	10 (7.0)	0	6 (8.2)	2 (6.9)	2 (6.1)	.87
- Cardiac failure	11 (7.7)	1 (14.3)	7 (9.6)	2 (6.9)	1 (3.0)	.61
- Unknown	25 (17.6)	2 (28.6)	13 (17.8)	2 (6.9)	8 (24.2)	.27
Alive at ICU discharge, No. (%)	107 (75.4)	6 (85.7)	59 (80.8)	21 (72.4)	21 (63.6)	.24
Alive at hospital discharge, No. (%)	88 (63.3)	5 (83.3)	50 (68.5)	17 (60.7)	16 (50.0)	.22
Alive at day 90, No. (%)	69 (55.2)	5 (71.4)	41 (62.1)	12 (50.0)	11 (39.3)	.16

Abbreviations: ARF, acute respiratory failure; ECOG, Eastern Cooperative Oncology Group; F, female; FO-BAL, fiber-optic bronchoscopy and bronchoalveolar lavage; ICU, intensive care unit; IQR, interquartile range (25-75); SOFA, Sequential Organ Failure Assessment.

*Various oxygenation strategies might have been used for a single patient.

recipients accounted for 73 patients (51.4%), followed by lung recipients (n = 33; 23.2%), liver recipients (n = 29; 20.4%), and heart recipients (n = 7; 4.9%) (Fig 1). Their main demographics and comorbid conditions are detailed in Tables 1 and 2. Briefly, they were aged 62.0 (range, 55.0-68.0) years, and women accounted for 40.7% of those. Of note, lung transplant recipients were younger than other organ recipients, and liver recipients were less frequently female than other organ recipients (1.3% vs 46.9%; $P = .004$).

ICU Admission

Severity, as addressed by the SOFA score, did not significantly differ across different types of transplants. Vasopressors and renal replacement therapy were applied during the first 7 days of ICU stay for 55.6% and 26.1% of SOT recipients, respectively, without significant difference according to the transplanted organ.

ARF Etiologies

Diagnostic strategies differed, as an invasive strategy was performed in 2 heart (28.6%), 27 kidney (37.0%), 19 liver (65.5%), and 23 lung (69.7%) recipients ($P = .003$). The final diagnosis of the respiratory failure episodes did not significantly differ according to the transplanted organ (Table 1). In brief, bacterial ARF accounted for 42 cases (29.6%) with a trend toward higher bacterial etiologies in lung transplant recipients (n = 16; 48.5% vs n = 1; 14.3% in heart; n = 18; 24.7% in kidney; and n = 7; 24.1% in liver transplant recipients; $P = .052$). A virus was the second cause for ARF in 25 patients (17.6%) followed by cardiac failure in 11 (7.7%). Finally, the cause remained

Table 2. Demographic Data, Comorbid Conditions, Severity and ICU Course of the 142 Solid Organ Transplant Recipients According to Status at Hospital Discharge

Variables	Death at Hospital Discharge n = 51	Alive at Hospital Discharge n = 88	*P* Value
Age, median (IQR), y	62.0 (56.0-70.0)	61.00 (55.0-68.0)	.701
Sex, No. (%), F	21 (42.0)	35 (40.2)	.982
Comorbid conditions at ICU admission, No. (%)			
- Solid tumor	8 (15.7)	16 (18.2)	.887
- Hematologic malignant neoplasm	5 (9.8)	3 (3.4)	.190
- Hematologic stem cell or bone marrow transplant	0	1 (1.1)	> .99
- Diabetes mellitus	20 (40.0)	36 (43.9)	.796
- Chronic kidney disease	27 (52.9)	57 (67.1)	.145
- Cirrhosis	10 (20.4)	11 (13.1)	.358
ECOG performance status, median (IQR)	2 (1-3)	1 (1-2)	.066
SOFA at ICU admission, median (IQR)	9 (4.0-11.0)	5 (3.5-8.0)	.007
Therapies administered during the first 7 days of ICU stay, No. (%)			
- Vasopressors	38 (74.5)	39 (44.3)	.001
- Renal replacement therapy	18 (35.3)	19 (21.6)	.12
Oxygenation strategy at day 1, No. (%)*			.07
- Conventional oxygen therapy	21 (41.2)	48 (54.5)	
- High-flow nasal cannula oxygen	5 (9.8)	12 (13.6)	
- Noninvasive ventilation	7 (13.7)	14 (15.9)	
- Invasive mechanical ventilation	18 (35.3)	14 (15.9)	
Patients who underwent a FO-BAL during the etiologic workup, No. (%)	31 (60.8)	39 (44.3)	.09
ARF etiology, No. (%)			
- Bacterial	15 (29.4)	25 (28.4)	> .99
- *Pneumocystis* pneumonia	2 (3.9)	4 (4.5)	> .99
- Virus	9 (17.6)	16 (18.2)	> .99
- *Candida*	1 (2.0)	1 (1.1)	> .99
- Cardiac failure	2 (3.9)	9 (10.2)	.32
- Unknown	12 (23.5)	12 (13.6)	.21
Transplanted organ, No. (%)			.221
- Heart	1 (2.0)	5 (5.7)	
- Kidney	23 (45.1)	50 (56.8)	
- Liver	11 (21.6)	17 (19.3)	
- Lung	16 (31.4)	16 (18.2)	
Alive at ICU discharge, No. (%)	16 (31.4)	88 (85.7)	-
Alive at day 90, No. (%)	0	69 (94.5)	-

Abbreviations: ARF, acute respiratory failure; ECOG, Eastern Cooperative Oncology Group; F, female; FO-BAL, fiber-optic bronchoscopy and bronchoalveolar lavage; ICU, intensive care unit; IQR, interquartile range (25-75); SOFA, Sequential Organ Failure Assessment.

*Various oxygenation strategies might have been used for a single patient.

undetermined in 25 patients, with no differences across the different types of transplants (17.5%).

Prognosis and Outcome

In total, 107 patients (75.4%) were alive at ICU discharge, 88 (63.3%) were alive at hospital discharge, and 69 (55.2%) were alive at day 90 after admission without significance difference according to the organ received (respectively for ICU, hospital, and day 90 survival: $P = .24$, $P = .22$, and $P = .16$). Before adjustment, undetermined ARF etiology, use of specific oxygenation strategy, type of transplant, and FO-BAL performance were not associated with survival (Fig 2).

Using a hierarchical model and adjusting for center effect, mortality was associated with SOFA score and preexisting chronic kidney disease (Table 3). When forced 1 by 1 in the final model, transplanted organ (OR vs renal transplant, respectively, 0.21 [95% CI, 0.02-2.48], 0.90 [95% CI, 0.30-2.69], and 1.68 [95% CI, 0.58-4.84] for heart, liver, and lung transplants), undetermined ARF etiology (OR, 2.09; [95% CI, 0.60-7.25]), FO-BAL not performed (OR, 0.56; [95% CI, 0.23-1.36]), and oxygenation strategy at ICU admission (OR vs HFNC, respectively, 1.27 [95% CI, 0.30-5.31], 1.06 [95% CI, 0.18-6.37], and 2.21 [95% CI, 0.43-11.29] for COT, NIV, and IMV) were neither selected nor did they changed the final model.

DISCUSSION

The present study is one of the largest studies focusing on ARF in SOT recipients [11]. From this post hoc analysis of the EFRAIM cohort [13], some important findings emerged. Above all, critically ill SOT recipients with ARF are of particular severity according to their high SOFA scores and the high rate of organ supply throughout the first 7 days following ICU admission as well as the high mortality rates at ICU discharge or at day 90. Second, even though

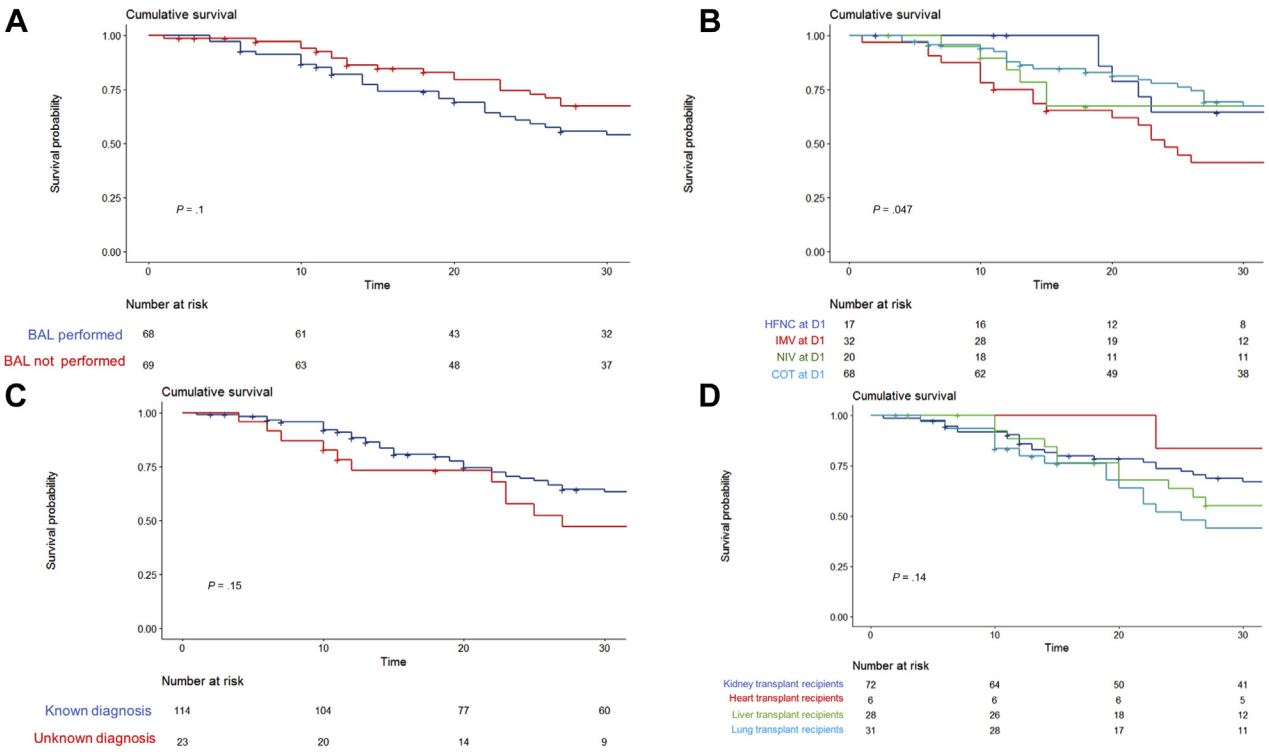

Fig 2. Cumulative survival of the transplant recipients according to **(A)** the performance of a bronchoalveolar lavage in the diagnostic strategy; **(B)** the obtention of a final diagnosis of the respiratory failure; **(C)** the oxygenation strategy at day 1; and **(D)** the type of transplanted organ. COT, conventional oxygen therapy; FO-BAL, fiber-optic bronchoscopy and bronchoalveolar lavage; HFNC, high-flow nasal cannula oxygen therapy; IMV, invasive mechanical ventilation; NIV, noninvasive ventilation.

lung transplant recipients were more frequently investigated with FO-BAL, an invasive diagnosis strategy was not associated with improved survival in the multivariable analysis. Finally, we did not find any survival difference between noninvasive oxygenation technique (NIV, COT, HFNC).

Chronic kidney disease has been significantly associated with better survival. It has to be underlined that, in comparison with other organ dysfunction, kidney failure can be easily treated with renal replacement therapy in case of a renal graft lost. In case of lung, hepatic, or cardiac graft dysfunction, only a new graft might allow a sustainable treatment of graft dysfunction. Although we did not evidence any significant differences in mortality rates according to the transplanted organs, chronic kidney disease might simply be a surrogate for the better prognosis of renal transplant recipients in the ICU. The observed survival of 81.1% at ICU discharge is in line with the 77.5% reported by Canet et al [11] in their 9-center French series. Of note in this series, 74.2% of them were dialysis free at day 90.

We found that mortality was not increased in patients remaining with an undetermined ARF etiology. One can infer that some of the nondocumented episodes were, in fact, pneumonia empirically treated. In case of respiratory failure occurring in profoundly immunocompromised patients, such as in SOT, first-line therapy encompasses an early broad-spectrum antimicrobial treatment. In that case, the absence of a documented microbial etiology does not rule out a bacterial cause. This is in line with the low number of patients with opportunistic infection or noninfectious pulmonary involvement. Another explanation to these findings might be the lack of statistical power.

The type of respiratory support at day 1 has not been found to be related to the mortality. As shown in Fig 2, no significant difference could be found in mortality according to ventilatory strategy. However, there was a trend toward higher mortality rate in patients having received mechanical ventilation. It is worth pointing that ICU survival was not affected by the noninvasive therapeutic strategy (HFNC, COT, NIV). These results are in line with those previously published by Lemiale et al [7] and Azoulay et al [6] showing that among immunocompromised patients admitted to the ICU with hypoxemic ARF, early noninvasive ventilation or HFNC compared with oxygen therapy alone did not improve survival.

In the present study, ICU survival was not affected by a noninvasive diagnosis strategy (ie, without the performance of FO-BAL) or by a determined ARF etiology. However, FO-BAL performance had no deleterious effect on mortality. These findings are highly consistent with those of prior series of immunocompromised patients admitted in the ICU for an ARF in which an invasive strategy was not associated with an increased survival or a higher diagnosis

Table 3. Final Hierarchical Logistic Regression Reporting Factors Independently Associated With Hospital Mortality (95% CI)

Variables	OR (95% CI)	*P* Value
SOFA score per point	1.19 (1.06-1.33)	.003
Chronic kidney disease	0.26 (0.09-0.71)	.03
ECOG 0	Reference	-
ECOG 1	2.14 (0.55-7.21)	.26
ECOG 2	1.70 (0.40-7.21)	.49
ECOG 3	4.26 (0.91-20.06)	.067

Center effect was included as a random effect on the intercept. Hosmer-Lemeshow goodness of fit: $\chi^2 = 3.27$; $P = .917$; C-stat = 0.70 (95% CI, 0.61-0.79).

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

rate [15,16]. Nevertheless, noninvasive strategies vs invasive strategies have mostly been evaluated in patients receiving oncohematologic treatment. Although the data we report are in this line, whether this strategy may be extended to SOT recipients remains to be investigated. Furthermore, performing a fiber-optic bronchoscopy might be necessary to determine specific causes of respiratory failure, such as airway complications in lung transplant recipients or bronchial Kaposi sarcoma, or to perform transbronchial biopsies, given the possible diagnosis [12]. Hence, we suggest not to avoid FO-BAL when needed in patients with high probability of *Pneumocystis* pneumonia, drug-related pulmonary toxicity, pulmonary graft rejection, or interstitial involvement with no obvious cause, given the fact that FO-BAL is probably safe in this population.

We found an overall ICU mortality of 24.6%, similar to mortality of all-causes immunodepression, in the Princeps publication [13]. ICU mortality was higher for lung transplant recipients (36.4%) and lower for heart transplant recipients (14.3%). Mortality rate of lung transplant recipients rises to 60.7% after 90 days of ICU admission, highlighting the severe prognosis of an ARF episode in this setting. Various recent prospective cohorts investigated the prognosis of lung transplant recipients with a viral infection [17,18]. Respiratory virus positive testing has been significantly associated with the occurrence of acute rejection, while a viral lower respiratory tract infection was a risk factor for subsequent *Pseudomonas aeruginosa* infection or colonization [17]. Moreover, the occurrence of a viral lower respiratory tract infection has been an independent risk factor for the development of chronic lung allograft dysfunction [18].

Kidney transplant recipient mortality after an ARF episode requiring ICU admission had been reported in the multicenter study performed by Canet et al [11]. In this study, ICU mortality reached 18%, which is consistent with our results (19.2% in our cohort).

In spite of its large and multicenter design, our study bears some limitations. First, the post hoc analysis of these prospectively collected data explains the limited available results when focusing on each single transplanted organ. Indeed, as the initial cohort encompassed a wide spectrum of immunodeficiencies [13], collected data were not specifically designed for SOT recipients. Thus, timing to organ transplant and the immunosuppressive regimen were not available and were not adjusted for. In addition, as per the study design, it was impossible to interpret or assess prognostic influence of delayed IMV initiation. In the same line, although no prognostic influence of transplanted organ could be demonstrated, sample size was limited, and lack of statistical power may account for these negative findings. Last, we could not identify those SOT recipients in whom FO-BAL could bear a high diagnostic or therapeutic yield.

CONCLUSIONS

ICU management of hypoxemic ARF in SOT recipients translated into a low ICU mortality rate, whatever the transplanted organ or the ARF cause. In this setting, although an invasive strategy with FO-BAL is not associated with a better prognosis, neither was it associated with a higher mortality.

The high 3-month mortality, especially in lung transplant recipients, urges reinforcement of post-ICU care in this setting. Studies to improve a rapid diagnosis of ARF, a prompt management of SOT recipients, and the analysis of the long-term consequences of ARF, especially in lung transplant recipients, are warranted.

REFERENCES

[1] De Gasperi A, Feltracco P, Ceravola E, Mazza E. Pulmonary complications in patients receiving a solid-organ transplant. Curr Opin Crit Care 2014;20:411–9.

[2] Kotloff RM, Ahya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. Am J Respir Crit Care Med 2004;170:22–48.

[3] Fishman JA. From the classic concepts to modern practice. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2014;20(Suppl. 7):4–9.

[4] Cracco C, Fartoukh M, Prodanovic H, Azoulay E, Chenivesse C, Lorut C, et al. Safety of performing fiberoptic bronchoscopy in critically ill hypoxemic patients with acute respiratory failure. Intensive Care Med 2013;39:45–52.

[5] Antonelli M, Conti G, Bufi M, Costa MG, Lappa A, Rocco M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. JAMA 2000;283:235–41.

[6] Azoulay E, Lemiale V, Mokart D, Nseir S, Argaud L, Pène F, et al. Effect of high-flow nasal oxygen vs standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. JAMA 2018;320:2099.

[7] Lemiale V, Mokart D, Resche-Rigon M, Pène F, Mayaux J, Faucher E, et al. Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. JAMA 2015;314:1711.

[8] Roca O, de Acilu MG, Caralt B, Sacanell J, Masclans JR. Humidified high flow nasal cannula supportive therapy improves outcomes in lung transplant recipients readmitted to the intensive care unit because of acute respiratory failure. Transplantation 2015;99:1092–8.

[9] Kang BJ, Koh Y, Lim CM, Huh JW, Baek S, Han M, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015;41:623–32.

[10] Ricard JD, Messika J, Sztrymf B, Gaudry S. Impact on outcome of delayed intubation with high-flow nasal cannula

oxygen: is the device solely responsible? Intensive Care Med 2015;41:1157–8.

[11] Canet E, Osman D, Lambert J, Guitton C, Heng AE, Argaud L, et al. Acute respiratory failure in kidney transplant recipients: a multicenter study. Crit Care Lond Engl 2011;15:R91.

[12] Mazo C, Pont T, Ballesteros MA, López E, Rellán L, Robles JC, et al. Pneumonia vs graft dysfunction as the cause of acute respiratory failure after lung transplant: a 4-year multicenter prospective study in 153 adults requiring intensive care admission. Eur Respir J 2019;54.

[13] Azoulay E, Pickkers P, Soares M, Perner A, Rello J, Bauer PR, et al. Acute hypoxemic respiratory failure in immunocompromised patients: the EFRAIM multinational prospective cohort study. Intensive Care Med 2017;43:1808–19.

[14] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–10.

[15] Azoulay E, Mokart D, Rabbat A, Pene F, Kouatchet A, Bruneel F, et al. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. Crit Care Med 2008;36:100–7.

[16] Azoulay E, Mokart D, Lambert J, Lemiale V, Rabbat A, Kouatchet A, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. Am J Respir Crit Care Med 2010;182:1038–46.

[17] Peghin M, Hirsch HH, Len Ó, Codina G, Berastegui C, Sáez B, et al. Epidemiology and immediate indirect effects of respiratory viruses in lung transplant recipients: a 5-year prospective study. Am J Transplant 2017;17:1304–12.

[18] Peghin M, Los-Arcos I, Hirsch HH, Codina G, Monforte V, Bravo C, et al. Community-acquired respiratory viruses are a risk factor for chronic lung allograft dysfunction. Clin Infect Dis 2019;69:1192–7.