Critical Care

RESEARCH

Open Access

Extracorporeal membrane oxygenation for tuberculosis-related acute respiratory distress syndrome: An international multicentre retrospective cohort study

Ali Ait Hssain[1], Matthieu Petit[2], Clemens Wiest[3], Laura Simon[4], Abdulrahman A. Al-Fares[5], Ahmed Hany[6], Dafna I. Garcia-Gomez[7], Santiago Besa[8], Saad Nseir[9], Christophe Guervilly[10], Wael Alqassem[11], Mathieu Lesouhaitier[12], Adrian Chelaru[13], Simon WC Sin[14], Roberto Roncon-Albuquerque Jr.[15], Marco Giani[16,17], Philipp M. Lepper[18], Jean-Rémi Lavillegrand[19], Sunghoon Park[20], Peter Schellongowski[21], Ibrahim Fawzy Hassan[1], Alain Combes[22], Romain Sonneville[13], Matthieu Schmidt[22,23*] and for the TB ECMO study group

Abstract

Objective To report the outcomes of patients with severe tuberculosis (TB)-related acute respiratory distress syndrome (ARDS) on extracorporeal membrane oxygenation (ECMO), including predictors of 90-day mortality and associated complications.

Methods An international multicenter retrospective study was conducted in 20 ECMO centers across 13 countries between 2002 and 2022.

Results We collected demographic data, clinical details, ECMO-related complications, and 90-day survival status for 79 patients (median APACHE II score of 20 [25th to 75th percentile, 16 to 28], median age 39 [28 to 48] years, PaO_2/FiO_2 ratio of 69 [55 to 82] mmHg before ECMO) who met the inclusion criteria. Thoracic computed tomography showed that 61 patients (77%) had cavitary TB, while 18 patients (23%) had miliary TB. ECMO-related complications included major bleeding (23%), ventilator-associated pneumonia (41%), and bloodstream infections (32%). The overall 90-day survival rate was 51%, with a median ECMO duration of 20 days [10 to 34] and a median ICU stay of 42 days [24 to 65]. Among patients on VV ECMO, those with miliary TB had a higher 90-day survival rate than those with cavitary TB (90-day survival rates of 81% vs. 46%, respectively; log-rank $P=0.02$). Multivariable analyses identified older age, drug-resistant TB, and pre-ECMO SOFA scores as independent predictors of 90-day mortality.

Conclusion The use of ECMO for TB-related ARDS appears to be justifiable. Patients with miliary TB have a much better prognosis compared to those with cavitary TB on VV ECMO.

Keywords Extracorporeal membrane oxygenation, Acute respiratory distress syndrome, Tuberculosis, Miliary, Outcome

TB ECMO investigators are listed in Appendix 1.

*Correspondence:
Matthieu Schmidt
matthieu.schmidt@aphp.fr
Full list of author information is available at the end of the article

Introduction

Tuberculosis (TB) remains a significant global health burden. Following the COVID-19 pandemic, the global incidence of TB rose to 10.6 million cases in 2021, equivalent to 134 cases per 100,000 population [1]. While Southeast Asia, Africa, and the Western Pacific continue to bear the highest burden of TB cases, recent trends indicate a growing incidence among migrant populations in Western countries. This has resulted in an increased number of severe TB cases requiring intensive care unit (ICU) admission in these regions. Poor hygiene, overcrowding, malnutrition, and other risk factors contribute to infection outbreaks in this population, particularly with multidrug-resistant TB in the European Union [2]. The mortality rate for acute respiratory distress syndrome (ARDS) due to TB ranges from 60 to 90%, with the most severe cases potentially requiring venovenous extracorporeal membrane oxygenation (VV ECMO) [1]. The slow progression of TB, its prolonged treatment, and the limited literature comprising only a few cases present challenges for physicians in deciding whether to utilize ECMO for patients with severe TB-related ARDS.

This international, multicenter, retrospective study aimed to address this gap by (1) reporting outcomes of ECMO-treated TB-related ARDS; (2) identifying pre-ECMO predictors of 90-day mortality; and (3) describing ECMO-related complications in this population.

Methods

Study design, patients

This study included TB patients hospitalized in 20 intensive care units (ICUs) across 13 countries between 2002 and 2022 (Fig. 1). Twenty-five ICUs with large ECMO case volumes (more than 20 ECMO cases per year) were invited to participate [3]. All participating ICUs obtained Institutional Review Board approval according to their local regulations.

All consecutive patients older than 18 years, who received extracorporeal lung support (i.e., venoarterial ECMO, VV ECMO, or veno-arteriovenous ECMO) for TB-related ARDS, were screened. Patients with end-stage chronic respiratory failure and those receiving extracorporeal CO_2 removal were excluded from the final analysis. Thus, the final analysis focused on adult patients with TB who received ECMO for moderate or severe ARDS.

Only patients with confirmed pulmonary tuberculosis due to *Mycobacterium tuberculosis* were included. Based on thoracic computed tomography findings, all included patients were classified as having either cavitary or miliary TB. A cavitary lesion was defined as a gas-filled space within a pulmonary mass, nodule, or consolidation, with the cavity wall typically measuring at least 2 mm in thickness. The presence of at least one cavitary lesion in the lungs classified a patient as having cavitary TB. Miliary TB was defined by multiple small-size (< 3 mm diameter) nodules randomly distributed throughout both lungs. The centers reported following the ELSO guidelines [4] and the mechanical ventilation protocol from the EOLIA

Fig. 1 Distribution of the number of patients included per country

trial [5] concerning ultra-lung protective ventilation practices.

Data collection

Baseline information was recorded for the time immediately preceding ECMO implantation. It included the following: age, sex, Acute Physiology And Chronic Health Evaluation II (APACHE II) score [6], Sequential Organ Failure Assessment (SOFA) score at cannulation [7], RESP (Respiratory ECMO Survival Prediction) score [8], dates of hospital and ICU admissions, immunocompromised status, and concomitant therapies before starting ECMO (e.g. nitric oxide, prone positioning..). Additionally, the start date of mechanical ventilation, ventilator settings (positive end-expiratory pressure [PEEP]), FiO_2, plateau pressure, tidal volume), arterial blood gas parameters, and standard laboratory parameters were recorded. Immunocompromised status was defined as having hematological malignancies, active solid tumors or receiving specific anti-tumor treatment within a year, solid-organ transplant, acquired immunodeficiency syndrome (AIDS), or long-term immunosuppressants or any systemic disease requiring ≥ 10 mg of prednisone dose equivalent for ≥ 3 months.

The status of being homeless or an international migrant (with residence permits, asylum seekers, or refugees) was also collected.

Tuberculosis diagnosis

Disseminated TB was defined as the involvement of two or more noncontiguous sites resulting from lymphohematogenous dissemination of *Mycobacterium tuberculosis*. Extrapulmonary involvement included central nervous system TB, cardiac and pericardial TB, or adrenal insufficiency. Drug(s)-resistant TB designed rifampicin-resistant TB or multidrug-resistant TB (i.e., resistant to both rifampicin and isoniazid) [9].

Follow-up

Follow-up variables recorded included acute kidney injury (AKI), renal replacement therapy (RRT); bleeding complications; pneumothorax, ECMO-related complications (hemolysis, ischemic stroke); ECMO and mechanical ventilation durations; length of ICU and hospital stays; and ICU and 90-day post-ICU admission survival. Major bleeding was defined as requiring at least 2 units of packed red blood cells due to an obvious hemorrhagic event, necessitating a surgical or interventional procedure, resulting in an intracerebral hemorrhage, or causing a fatal outcome. AKI was defined according to Kidney Disease Improving Global Outcomes (KDIGO) stages 1 or 2. Nosocomial infection definitions were consistent with those of the Centers for Disease Control and Prevention/National Nosocomial Infections Surveillance System [10].

Statistical analyses

This study adhered to the CONSORT recommendations for reporting cohort studies as outlined in the STROBE statement and the RECORD modification [11]. Continuous variables, expressed as median [25th; 75th percentiles], were compared using Student's t-test or the Mann–Whitney U-test, as appropriate. Categorical variables were compared using χ^2 tests. Univariable analyses were performed to test associations between patients' demographic, clinical, and pre-ECMO ventilation characteristics, as well as laboratory results, with the type of TB or death 90 days after ICU admission.

Pre-ECMO risk factors for 90-day mortality were assessed for the entire cohort and in patients on VV ECMO using multivariable Cox regression models with a complete case analysis. The variables included in the multivariable model were defined a priori (i.e., age, type of TB, drug-resistant TB, and SOFA score at ECMO cannulation) without any variable selection. An alternative model was also tested, substituting the RESP score [8] for age. Missing data were at random, and no multiple imputations were used. Log linearity was graphically assessed for the quantitative variable's effects using restricted cubic splines. Hazard ratios and their 95% confidence intervals (CIs) were estimated. Unadjusted and adjusted Kaplan–Meier survival probabilities based on the type of TB were derived from the multivariable Cox regression models and plotted in the same figure.

To better describe patients' trajectories in the ICU over time, a multi-state model was used [12]. This model considers that a patient can transition through different states during follow-up. The starting point was the day of ECMO initiation, with "On-ECMO" as the initial state for all patients. This could be followed by two intermediate states: "In-ICU & weaned-off ECMO" and "Alive & out of ICU." Since patients could die at any time during follow-up, either in the ICU or after discharge, the "Died" state was the only final "absorbing" state. In this four-state model (eFile 1), each box represents a state, and each arrow indicates possible transitions from one state to another.

After determining patient status, a Cox model, stratified by each possible transition, was used to estimate transition probabilities (from one state to another) and state occupation probabilities (for each of the four states) over time. The percentages of patients occupying each possible state were represented over time with a stacked probability plot and reported with their 95% CIs on days 28, 60, and 90 post-ECMO initiation. Mean (95% CI) state occupation times (i.e., the duration in each possible

state of the multi-state model) were also reported at the same time points. Additionally, the median on-ECMO time and length of ICU stay was determined. No data were censored. These analyses were conducted separately for cavitary TB and miliary TB.

All analyses were conducted at a two-sided alpha level of 5% using R software, version 4.0.0.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all data and the final responsibility to submit for publication.

Results

Study population and pre-ECMO characteristics

Over 20 years, a cohort of 79 patients with severe TB-related ARDS treated with ECMO was analyzed (Fig. 1). The median age of the patients was 39 years (interquartile range [IQR] 28–48 years), with a predominance of males (58%). Their median APACHE II score was 20 (16–28).

Details of patient characteristics at the time of ICU admission and before the initiation of ECMO are summarized in Table 1 and eFile 2. The SOFA score before ECMO initiation was 12 (10–15). VV-ECMO was used in 86% of cases, with a median partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of 69 (IQR 55–82) and a median plateau pressure of 30 cmH_2O (IQR 29–34 cmH_2O). ECMO was initiated after a median of 1 day (IQR 1–7 days) of mechanical ventilation, with a PEEP of 10 cmH_2O (IQR 8–14 cmH_2O). Prone positioning before ECMO was performed in 61% of patients, and 16% received inhaled nitric oxide. Before ECMO cannulation, 47% of the patients were administered corticosteroids, and 13% experienced cardiac arrest.

TB diagnosis

Pulmonary TB diagnosis primarily occurred during the ICU stay (53%, n = 39). All patients, except one who tested positive in pleural effusion, demonstrated a positive acid-fast bacillus result either through culture or molecular testing of samples obtained from tracheal aspiration or bronchoalveolar lavage. Additionally, Mycobacterium tuberculosis cultures were positive in samples from the liver (n = 2), urine (n = 2), peritoneal fluid (n = 2), pericardium (n = 1), and bone marrow (n = 1). Most patients (77%, n = 61) presented with cavitary TB, while 23% (n = 18) had miliary TB. In the miliary TB group, there was a higher incidence of disseminated TB with cardiac and neurological involvement compared to the cavitary TB group (50% vs. 13%, $p < 0.01$). The prevalence of drug-resistant TB did not differ significantly between the cavitary and miliary TB groups (Table 2).

ICU and ECMO-related complications

ECMO-related complications were not significantly different between cavitary and miliary TB. The overall incidence rates of ventilator-associated pneumonia and bacteremia were 41% and 32%, respectively, with no significant differences observed between the two study groups (Table 3). This corresponds to an incidence of ventilator-associated pneumonia and bacteremia of 46 (37–55) and 43 (35–52) episodes per 1000 ECMO days, respectively. Similarly, other ICU complications such as pneumothorax or stroke were not different between the two groups.

Patient outcomes

Complete 90-day follow-up was obtained for all patients. The estimated state-occupation probabilities (95% CI) of being on-ECMO, in-ICU & weaned-off ECMO, alive & out of ICU or dead 90 days post-ECMO initiation, respectively, were: 2% (0–11), 0% (0–0), 38% (27–51) and 61% (49–73) for patients with cavitary TB, and 0% (0–0), 0% (0–0), 61% (40–82) and 39% (21–65) for patients with miliary TB (Fig. 2 and eFile 3).

Kaplan–Meier estimates of 90-day survival in all patients of the cohort was 47% for cavitary TB and 72% for miliary TB (log-rank test $p = 0.07$). Among the 68 patients who received VV ECMO 90-day survival was 46% for cavitary TB and 81% for miliary TB (log-rank test $p = 0.02$). After adjusting for confounding factors, patients with miliary TB still showed a higher probability of survival by day 90 (hazard ratio [HR] = 0.30, 95% CI (0.09–1.02), $p = 0.053$, though this difference did not strictly reach significance (Fig. 3). Causes of death are reported in eFile 4.

The median (IQR) duration of ECMO therapy was 17 (9–35) days for patients with cavitary TB and 22 (16–32) days for those with miliary TB ($p = 0.29$). Among 90-day survivors, the median duration on ECMO was 26 (9–27) days for cavitary TB and 23 (17–31) days for miliary TB ($p = 0.15$). Mechanical ventilation duration and ICU length of stay did not significantly differ between the two groups (see Table 3).

Predictors of 90-day mortality

Patients who died within 90 days were significantly older and had higher pre-ECMO SOFA scores and a greater incidence of septic shock. The mortality by day 90 was 56% and 28% in cavitary and miliary TB, respectively ($p = 0.07$). Notably, disseminated TB was significantly more common among patients who died at day 90 (32% vs. 13%, $p = 0.03$). Furthermore, drug-resistant TB was associated with a higher likelihood of death at day 90 (eFile 2). However, initiating TB treatment before ICU admission and ECMO initiation was not associated with

Table 1 Patient and pre-ECMO characteristics according to the clinical presentation of tuberculosis on ECMO

	N	All patients *N* = 79	Cavitary TB *N* = 61	Miliary TB *N* = 18	*P* value
Age, years	79	39 (28–48)	40 (28–50)	35 (27–46)	0.35
Male	79	46 (58)	36 (59)	10 (56)	1.00
BMI, kg/m^2	71	22 (19–25)	22 (20–25)	22 (18–24)	0.56
APACHE II	49	20 (16–28)	20 (16–27)	24 (13–30)	0.59
SOFA at ICU admission	58	10 (8–13)	11 (8–13)	10 (8–12)	0.94
RESP score	58	2 (1–4)	2 (1–4)	2 (1–4)	0.71
Active smoker	79	13 (16)	9 (15)	4 (22)	0.45
Diabetes	79	10 (13)	9 (15)	1 (6)	0.44
Immunocompromised status	79	7 (9)	4 (7)	3 (17)	0.32
AIDS	79	3 (4)	2 (3)	1 (6)	1.00
IV drug user	79	1 (1)	1 (2)	0 (0)	1.00
Migrants	79	21 (27)	20 (33)	1 (5)	0.07
Homeless	79	4 (5)	3 (3)	1 (5)	0.62
Type of ECMO	79				1.00
Venovenous		68 (86)	58 (85)	16 (89)	
Venoarterial		10 (13)	8 (13)	2 (11)	
Veno-arteriovenous		1 (1)	1 (1)	0 (0)	
Before ECMO					
SOFA score	71	12 (10–15)	11 (10–15)	12 (10–16)	0.45
Cardiovascular SOFA	53	4 (1–4)	4 (1–4)	4 (3–4)	0.65
Cardiovascular SOFA > 2	53	38 (72)	28 (70)	10 (77)	0.75
Renal SOFA	53	0 (0–1)	0 (0–1)	0 (0–1)	0.54
Rena SOFA > 2	53	4 (7)	3 (7)	1 (7)	1
Blood gases					
pH	66	7.23 (7.08–7.30)	7.22 (7.04–7.30)	7.24 (7.15–7.30)	0.53
PO_2/FiO_2	66	69 (55–82)	68 (57–81)	71 (55–83)	0.89
$PaCO_2$, mmHg	66	56 (48–70)	57 (46–72)	55 (50–68)	0.95
FiO_2	66	100 (100–100)	100 (100–100)	100 (100–100)	0.89
Mechanical ventilation					
MV duration	78	1 (1–7)	1 (0–6)	4 (1–12)	0.18
Tidal volume, mL/kg PBW	58	5.9 (5.2–6.7)	5.9 (5.2–6.4)	6.2 (5.8–7.1)	0.16
Respiratory rate, breaths/min	63	28 (24–30)	28 (24–30)	29 (25–30)	0.93
Plateau pressure, cmH_2O	59	30 (29–34)	31 (29–34)	30 (28–32)	0.29
PEEP, cmH_2O	64	10 (8–14)	10 (8–14)	11 (7–12)	0.68
Prone position	77	47 (61)	34 (58)	13 (72)	0.40
Nitric oxide	79	13 (16)	11 (18)	2 (11)	0.72
Pre ECMO AKI	79	47 (59)	36 (59)	11 (61)	1.00
Pre ECMO Cardiac arrest	79	10 (13)	9 (15)	1 (6)	0.43

Data are given as numbers (percentage) or median (interquartile) range

AIDS, acquired immunodeficiency syndrome; BMI, body mass index; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology And Chronic Health Evaluation II; RESP, Respiratory ECMO Survival Prediction score; IV, intravenous; ECMO, extracorporeal membrane oxygenation; PBW, predicted body weight; PEEP, positive end-expiratory pressure; MV, mechanical ventilation; AKI, acute kidney injury; RRT, renal replacement therapy

reduced 90-day mortality (eFile 2). The multivariable Cox regression model in all patients identified older age, drug(s)-resistant TB, and higher pre-ECMO SOFA scores as factors significantly associated with increased 90-day mortality (eFile 5). As compared to cavitary TB, miliary TB was a protective factor in the multivariable model (HR 0.30, 95% CI 0.09–1.02, $p = 0.053$) when this analysis was performed in patients on VV ECMO (Table 4). Finally, the results of the second model incorporating the RESP score were closely consistent with these findings (eFile 6).

Table 2 Tuberculosis details according to the clinical presentation of tuberculosis on ECMO

	N	All patients *N* = 79	Cavitary TB *N* = 61	Miliary TB *N* = 18	*P* value
TB diagnosis	74				0.86
Before hospital admission		10 (14)	7 (12)	3 (19)	
Before ICU admission		25 (34)	20 (34)	5 (31)	
During ICU stay		39 (53)	31 (53)	8 (50)	
Disseminated TB	79	17 (22)	8 (13)	4 (50)	< 0.01
Cardiac TB	79	8 (10)	5 (8)	3 (17)	0.37
Neurological TB	79	5 (6)	2 (3)	3 (17)	0.09
Adrenal TB	79	3 (4)	1 (2)	2 (11)	0.13
Drug(s) resistant TB	79	8 (10)	5 (8)	3 (17)	0.38
Corticosteroids	79	37 (47)	26 (43)	11 (61)	0.27

Data are given as numbers (percentage)

TB, tuberculosis; ICU, intensive care unit

Table 3 ECMO-related complications and outcomes according to the clinical presentation of tuberculosis on ECMO

	N	All patients *N* = 79	Cavitary TB *N* = 61	Miliary TB *N* = 18	*P* value
In ICU complications					
Any ECMO-related complications	79	28 (35)	21 (34)	7 (39)	0.95
Pneumothorax	79	21 (27)	17 (28)	4 (22)	0.78
Stroke	79	11 (14)	8 (13)	3 (17)	1
VAP	79	32 (41)	23 (38)	9 (50)	0.51
Bloodstream infection	79	25 (32)	18 (30)	7 (39)	0.64
Massive bleeding	79	18 (23)	13 (21)	5 (28)	0.76
Need for RRT	79	26 (33)	21 (34)	5 (28)	0.81
Septic shock	79	44 (56)	32 (52)	12 (67)	0.43
Outcomes					
ECMO duration, days	79	20 (10–34)	17 (9–35)	22 (16–32)	0.29
in survivors	36	18 (12–30)	16 (9–27)	23 (17–31)	0.15
MV duration, days	78	33 (9–50)	31 (9–50)	35 (17–61)	0.59
in survivors	35	37 (11–51)	37 (9–47)	46 (28–80)	0.35
ICU length of stay, days	79	42 (24–65)	41 (22–55)	50 (38–111)	0.06
in survivors	36	48 (29–79)	47 (26–58)	54 (42–106)	0.16
ICU mortality	79	43 (54)	36 (59)	7 (39)	0.22
Hospital mortality	79	45 (57)	38 (62)	7 (39)	0.14

Data are given as numbers (percentage) or median (interquartile) range

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; MV, mechanical ventilation; RRT, renal replacement therapy; VAP, ventilator-associated pneumonia

Discussion

To our knowledge, the TB-ECMO study represents the largest international, multi-center cohort of patients with TB treated with ECMO in high-volume centers, encompassing complications and outcomes up to 90 days. The main findings were: (1) The utilization of ECMO for TB-related ARDS appears justifiable, with a maximum observed mortality rate of 53% at 90 days; (2) patients with miliary TB undergoing ECMO exhibited better outcomes compared to those with cavitary TB; (3) this vulnerable population experienced frequent infectious complications, including VAP and bloodstream infections; (4) independent predictors of 90-day mortality for the entire cohort, assessed before ECMO initiation, were advanced age, elevated pre-ECMO SOFA score, and the presence of drug-resistant TB. (5) When VV ECMO is used miliary TB is independently associated with a lower 90-day mortality.

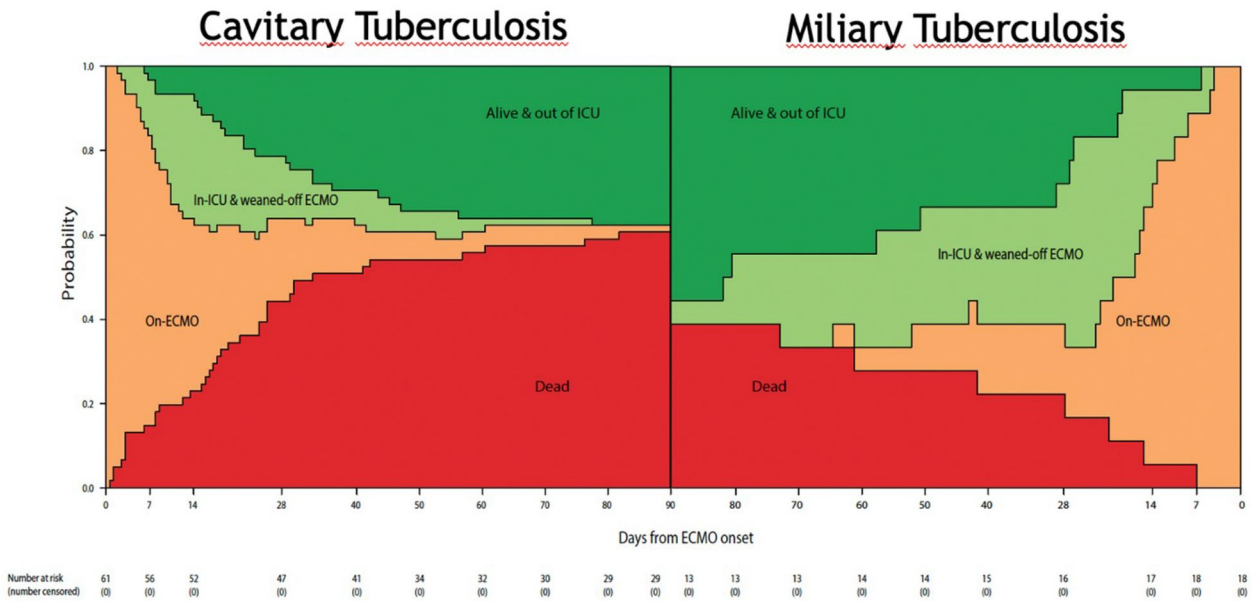

Fig. 2 Daily patient's disposition according to the type of tuberculosis. The plot illustrates the actual state occupation probabilities of being in each endpoint state—On-ECMO, In-ICU & weaned-off ECMO, Alive & out of ICU or Dead—over the 90 days following ECMO implantation. The respective probabilities and mean lengths of stay (with 95% confidence intervals) in each of these four states are reported in eFile 3. See eFile 1 for all possible transition probabilities (with 95% confidence intervals) from one state to another over time. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit

The use of ECMO in TB-related ARDS has primarily been limited to case reports and one systematic review [13–16]. This scarcity of evidence-based guidance for clinical practice poses challenges for clinicians when ECMO may needed. In a recent systematic review, Idris et al. reported the outcomes of 43 patients from 15 countries spanning 1975 to 2022, with 83.7% of these patients receiving VV-ECMO. The overall outcome was excellent, with an 81% survival rate [16]. However, this study predominantly included single case reports, which may have biased the results toward better outcomes. Our 51% overall survival at day 90 may more likely accurately reflect the expected outcome in this population. A significant finding from our cohort is the markedly better outcomes in patients with miliary TB compared to those with cavitary TB. With a 72% survival rate at day 90, this subgroup demonstrated survival rates similar to patients with bacterial or viral pneumonia (excluding COVID-19) treated with VV-ECMO [5, 17]. Thus, this acceptable outcome, despite slow improvement, should not deter clinicians from using ECMO in this context. Additionally, a better prognosis was observed in our patients with disseminated TB, and 37 (47%) patients received corticosteroids. While the use of corticosteroids in patients with tuberculosis, particularly those with pulmonary and pleural involvement, remains controversial, their adjunctive use with antituberculous therapy has been associated with reduced mortality and morbidity in cases of pericardial and central nervous system TB [18–20]. However, the effect and benefit of corticosteroids in pleural and severe pulmonary TB, as in our population, remain poorly studied. The lack of detailed information on the different corticosteroid regimens used in our population precludes definitive conclusions.

Cavitary TB was associated with higher mortality rates despite enhanced barotrauma prevention through ultra-lung protective ventilation on ECMO. The very slow improvement observed in cavitary TB, requiring prolonged ECMO support, could explain this finding. Additionally, the high incidence of VAP and bloodstream infections in our population likely contributed to the elevated mortality observed in this form of TB. Careful selection of patients with cavitary TB who may benefit from ECMO, based on identified pre-ECMO risk factors, is of paramount importance.

Drug-resistant TB continues to be a significant global health threat, with an estimated 450,000 new cases of rifampicin-resistant TB in 2021 [1]. In our cohort, eight patients had drug-resistant TB. This rare condition treated with ECMO was associated with particularly poor outcomes. Specifically, 7 out of 8 (87%) patients with drug-resistant TB died within 90 days of ECMO initiation, and drug-resistant TB was an independent risk factor for mortality at day 90. Inadequate

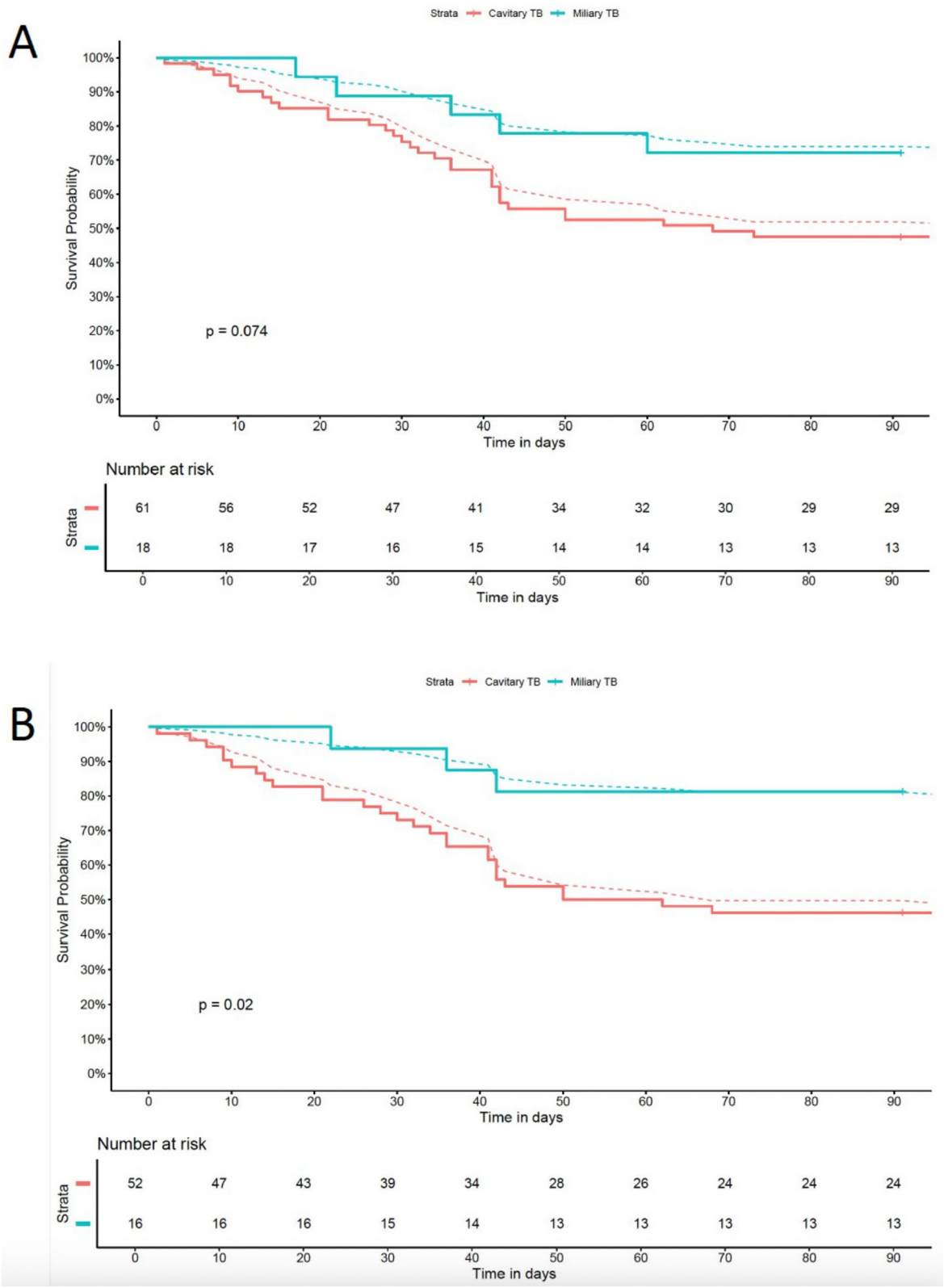

Fig. 3 Unadjusted and adjusted (dotted lines) Kaplan–Meier survival estimates according to the type of tuberculosis (cavitary vs. miliary TB) in **A** all the cohort (n = 79) and **B** patients treated with VV ECMO (n = 68)

Table 4 Predictive factors associated with 90-day mortality in critically ill adults with tuberculosis-related acute respiratory distress syndrome treated with venovenous ECMO in multivariable analysis

	Hazard ratio	95% confidence interval	*P* value
Age	1.03	1.01–1.05	0.006
Miliary tuberculosis	0.30	0.09–1.02	0.053
Drug(s) resistant tuberculosis	2.80	1.07–7.61	0.044
Pre-ECMO-SOFA	1.07	0.98–1.16	0.110

HR, hazard ratio; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; SOFA, Sequential Organ Failure Assessment

drug levels may explain this finding, as several case reports have suggested that TB patients require higher doses of standard medications during ECMO therapy [21]. Additionally, the frequent need for RRT in this critically ill population may complicate the pharmacokinetics/pharmacodynamics (PK/PD) of TB drugs on ECMO [22]. Until further PK/PD studies on ECMO are available, routine therapeutic drug monitoring seems advisable for these patients on ECMO. Our results also suggest that TB drug sensitivity should be considered in the ECMO decision-making process. Furthermore, as consistently reported in both COVID-19 and non-COVID-19-related ARDS [8, 23], age and extrapulmonary dysfunction should also be integrated into the ECMO decision process.

Our study has several limitations. Firstly, only high-volume ECMO centers participated, which may have specific patient selection criteria, limiting generalizability. In this cohort, ECMO centers from regions with a high prevalence of tuberculosis, such as Africa, India, or Indonesia, were not included. Additionally, we could not obtain the characteristics of TB patients who were denied ECMO in the participating ICUs during the study period. Secondly, the study spans 20 years, during which ECMO technology and clinical practices likely evolved. However, only 15 out of 79 (19%) patients were hospitalized before 2012. Thirdly, our follow-up was limited to survival status at day 90 and did not explore survivors' health-related quality of life and lung function tests, which would have been relevant in the context of TB [24] and prolonged ECMO runs [25]. Fourth, our sample size was limited, and 11 patients were initially managed with VA ECMO, which may indicate variations in patient severity and differences in ECMO management strategies. Lastly, we cannot rule out that some residual confounding factors may not have been considered in our predictive survival model.

Conclusion

In this retrospective study involving 79 critically ill patients with TB-related ARDS on ECMO, we reported a 51% 90-day survival rate, supporting the feasibility of ECMO for this specific disease. Better outcomes were observed in patients with miliary TB compared to those with cavitary TB. Age, drug-resistant TB, and pre-ECMO SOFA score were identified as indicators of poor prognosis, which should be carefully considered when selecting ECMO candidates in this vulnerable population. Further studies are needed to explore optimal TB drug management during ECMO.

Appendix 1: TB ECMO study investigators

Medical Intensive Care Unit, Department Of Medicine, Hamad General Hospital, Doha, Qatar

- Abdulsalam Saif Ibrahim
- Anzila Akbar

Pitie Salpetrière hospital, Paris, France

- Charles Edouard Luyt
- Guillaume Hekimian
- Marc Pineton de Chambrun
- Juliette Chommeloux
- Guillaume Lebreton

São João University Hospital, Porto, Portugal

- Paulo Figueiredo
- Gustavo Mendes

Department of Medicine I, Intensive Care Unit 13i2, Medical University of Vienna, Vienna, Austria

- Thomas Staudinger
- Nina Buchtele
- Bernhard Nagler
- Elisabeth Lobmeyr

Department of Medicine and Surgery, Department of Emergency and Intensive Care, University of Milano-Bicocca, Monza, Italy

- Roberta Garberi
- Giuseppe Foti
- Emanuele Rezoagli
- Matteo Pozzi

University Hospital of Saarland and University of Saarland, Homburg, Germany

- Sebastian Mang
- Vitalie Mazuru

Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust & Centre for Human Applied Physiological Sciences, School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King's College London

- Luigi Camporota
- Nicholas A Barrett

Hallym University Sacred Heart Hospital

- Joo-Hee Kim
- Hyoung Soo Kim

Critical Care Medicine Unit, School of Clinical Medicine, The University of Hong Kong
Department of Adult Intensive Care, Queen Mary Hospital, Hong Kong SAR

- Pauline Yeung Pui Ning
- Wallace Ngai Chun Wai

Assistance Publique Hôpitaux de Marseille (APHM), Marseille, France

- Antoine Tilmont
- Sami Hraiech
- Antoine Roch

Department of Internal Medicine II, University Hospital of Regensburg, Regensburg Germany

- Thomas Mueller,
- Matthias Lubnow
- Alois Philipp

Medical ICU, Henri Mondor Hospital, Creteil, France

- Armand Mekontso Dessap
- Keyvan Razazi
- Paul Masi
- Francois Bagate

Médecine Intensive-Réanimation, CHU de Lille, Lille 59000-F, France

- Thibault Duburcq
- Sébastien Preau
- Raphael Favory

Prince Mohammed bin Abdulaziz Hospital, Critical Care Department, Riyadh, Saudi Arabia

- Mohammed Mahdi Alfutaih,
- Mostafa Rajab
- Muhammad Ahmad Almansour

Médecine intensive – réanimation, Hôpital Bichat - Claude Bernard, Paris

- Jean Francois Timsit
- Lila Bouadma
- Etienne de Montmollin

Médecine intensive – réanimation, Pontchaillou Hospital, Rennes, France

- Félicie Belicard
- Jean Marc Tadié

Fundacion Cardiovascular de Colombia

- Leonardo Salazar
- Juan Carlos Soto

Department of Cardiac Surgery, Division of Surgery, Pontificia Universidad Católica de Chile, Santiago, Chile

- Patricio V Salas
- Sebastián M Bravo

Intensive care unit-Al-Adan hospital, Ministry of health-Kuwait

- Mohammed Shamsah
- Beena Yousef
- Huda Alfoudri

Abbreviations

ARDS	Acute respiratory distress syndrome
APACHE II	Acute physiology and chronic health evaluation II
ECMO	Extracorporeal membrane oxygenation
VV-ECMO	Venovenous-extracorporeal membrane oxygenation
ICU	Intensive care unit
COVID-19	Coronavirus disease 2019
TB	Tuberculosis
SAPS	Simplified Acute Physiology Score
SOFA	Sequential Organ-Failure Assessment

PEEP Positive end-expiratory pressure

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-024-05110-y.

Additional file 1: Four-state model.

Additional file 2: Patient characteristics according to the survival status at Day 90 in patients on ECMO for TB.

Additional file 3: Outcomes of cavitary and miliary tuberculosis on ECMO.

Additional file 4: Causes of 90-day mortality according to the type of tuberculosis.

Additional file 5: Predictive Factors Associated with 90-day Mortality in all critically ill Adult Patients with Tuberculosis-related Acute Respiratory Distress Syndrome Treated with ECMO.

Additional file 6: Predictive Factors Associated with 90-day mortality in critically ill adults with Tuberculosis-related acute respiratory distress syndrome treated with venovenous ECMO in multivariable analysis including the RESP score.

Author contributions

AAH, MP, and MS contributed to the conception of the study, data collection, data analysis, and interpretation, and drafted the manuscript. All authors contributed to data collection, and interpretation and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

Funding

Not applicable.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All participating ICUs obtained Institutional Review Board approval according to their local regulations.

Consent for publication

Not applicable.

Competing interests

Dr. Peter Schellongowski reports grants from the European Commission and the European Society of Intensive Care Medicine, and lecture fees from Fresenius Medical. Dr Romain Sonneville reports grants from the French Ministry of Health and LFB. Dr. Saad Nseir reports MSD, Pfizer, Biomérieux, Fisher and Paykel, Medtronic, and Shionogi lecture fees. Dr. Matthieu Schmidt reports lecture fees from Getinge, Dräger, Baxter, and Fresenius Medical reports lecture fees. Dr. Alain Combes reports grants from Getinge, and personal fees from Getinge, Baxter, and Xenios outside the submitted work. No other disclosures were reported.

Author details

[1]Medical Intensive Care Unit, Hamad General Hospital, Department of Medicine, Weill Cornell Medical College Doha, College of Health and Life Science, Hamad Bin Khalifa University, Doha, Qatar. [2]Medical Intensive Care Unit, Ambroise Paré Hospital, APHP, Inserm U1018, CESP, University Versailles Saint Quentin - University Paris Saclay, Guyancourt, France. [3]Department of Internal Medicine II, University Hospital of Regensburg, Regensburg, Germany. [4]Department of Critical Care, Guy's and St Thomas' NHS Foundation Trust, London, UK. [5]Department of Anesthesia, Critical Care Medicine, and Pain Medicine, Al-Amiri Center for Advanced Respiratory and Cardiac Failure, Al-Amiri Hospital, Ministry of Health, Kuwait City, Kuwait. [6]Intensive Care Unit-Al-Adan Hospital, Ministry of Health-Kuwait, Kuwait City, Kuwait. [7]Fundacion Cardiovascular de Colombia, Bucaramanga, Colombia. [8]Division of Surgery, Department of Cardiac Surgery, Pontificia Universidad Católica de Chile, Santiago, Chile. [9]Médecine Intensive-Réanimation, CHU de Lille et Inserm U1285, Université de Lille, CNRS, UMR 8576 - UGSF, 59000 Lille, France. [10]Center for Studies and Research on Health Services and Quality of Life EA3279, Aix-Marseille University, Service de Medecine Intensive et Reanimation, CHU Hopital Nord, Assistance Publique Hôpitaux de Marseille (APHM), Marseille, France. [11]Critical Care Department, Prince Mohammed Bin Abdulaziz Hospital, Riyadh, Saudi Arabia. [12]Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, 2 rue Henri Le Guilloux, UMR 1236, Univ Rennes, INSERM, Etablissement Français du Sang Bretagne, Rennes, France. [13]INSERM U1137, APHP.Nord, Médecine intensive – réanimation, Hôpital Bichat - Claude Bernard, Université Paris Cité, Paris, France. [14]The University of Hong Kong, Hong Kong, China. [15]Department of Intensive Care Medicine, São João University Hospital, Porto, Portugal. [16]Department of Medicine and Surgery, University of Milano-Bicocca, Monza, Italy. [17]Department of Emergency and Intensive Care, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy. [18]Department of Pneumology, Allergology and Critical Care Medicine, Department of Emergency Medicine, University Hospital of Saarland and University of Saarland, Homburg, Germany. [19]Medical Intensive Care Unit, Henri Mondor Hospital, Creteil, France. [20]Department of Pulmonary, Allergy and Critical Care Medicine, Hallym University Sacred Heart Hospital, Anyang 14068, South Korea. [21]Department of Medicine I, Intensive Care Unit 13i2, Medical University of Vienna, Vienna, Austria. [22]Sorbonne Université, GRC 30 RESPIRE, UMRS_1166-ICAN, Institute of Cardiometabolism and Nutrition, Sorbonne Université, 75013 Paris, France. [23]Medical Intensive Care Unit, Assistance Publique-Hôpitaux de Paris, Pitié-Salpêtrière Hospital, 47-83 Boulevard de l'Hôpital, 75013 Paris, France.

Received: 9 August 2024 Accepted: 24 September 2024
Published online: 09 October 2024

References

1. https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence.
2. Hraiech S, Pauly V, Orleans V, Auquier P, Boyer L, Papazian L, et al. Undocumented migrants in French intensive care units in 2011–2018: retrospective nationwide study. Intensive Care Med. 2022;48:290–9.
3. Combes A, Brodie D, Bartlett R, Brochard L, Brower R, Conrad S, et al. Position paper for the organization of extracorporeal membrane oxygenation programs for acute respiratory failure in adult patients. Am J Respir Crit Care Med. 2014;190:488–96.
4. Tonna JE, Abrams D, Brodie D, Greenwood JC, Rubio Mateo-Sidron JA, Usman A, et al. Management of adult patients supported with venovenous extracorporeal membrane oxygenation (VV ECMO): guideline from the extracorporeal life support organization (ELSO). ASAIO J Am Soc Artif Intern Organs. 1992;2021(67):601–10.
5. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med. 2018;378:1965–75.
6. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13:818–29.
7. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça 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.
8. Schmidt M, Bailey M, Sheldrake J, Hodgson C, Aubron C, Rycus PT, et al. Predicting survival after extracorporeal membrane oxygenation for severe acute respiratory failure. The Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score. Am J Respir Crit Care Med. 2014;189:1374–82.
9. Dheda K, Mirzayev F, Cirillo DM, Udwadia Z, Dooley KE, Chang K-C, et al. Multidrug-resistant tuberculosis. Nat Rev Dis Primer. 2024;10:22.
10. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control. 1988;16:128–40.
11. STROBE Statement: Home. https://www.strobe-statement.org/index.php?id=strobe-home. Cited 21 Aug 2020.

12. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007;26:2389–430.
13. Zakaria GS, Taufik MA, Manggala SK, Jennefer. Extracorporeal blood purification benefits in post-caesarean patient with severe acute respiratory distress syndrome due to miliary tuberculosis: a case report. J Med Case Rep. 2023;17:157.
14. Binh NG, Manabe T, Co DX, Thach PT, Tuan DQ, Cuong BV, et al. Tuberculosis-induced acute respiratory distress syndrome treated with veno-venous extracorporeal membrane oxygenation. Respir Med Case Rep. 2019;28:100900.
15. Petrillo TM, Heard ML, Fortenberry JD, Stockwell JA, Leonard MK. Respiratory failure caused by tuberculous pneumonia requiring extracorporeal membrane oxygenation. Perfusion. 2001;16:525–9.
16. Idris R, Zielbauer A-S, Koepsell J, Kloka J, Wetzstein N. Extracorporeal membrane oxygenation (ECMO) in patients with tuberculosis: systematic review and meta-analysis of 43 cases. BMC Pulm Med. 2024;24:47.
17. Schmidt M, Zogheib E, Roze H, Repesse X, Lebreton G, Luyt CE, et al. The PRESERVE mortality risk score and analysis of long-term outcomes after extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. Intensive Care Med. 2013;39:1704–13.
18. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TTO, Nguyen TCT, et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004;351:1741–51.
19. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, et al. Prednisolone and Mycobacterium indicus pranii in tuberculous pericarditis. N Engl J Med. 2014;371:1121–30.
20. Török ME, Nguyen DB, Tran THC, Nguyen TBY, Thwaites GE, Hoang TQ, et al. Dexamethasone and long-term outcome of tuberculous meningitis in Vietnamese adults and adolescents. PLoS ONE. 2011;6:e27821.
21. Kim H-S, Lee ES, Cho Y-J. Insufficient serum levels of antituberculosis agents during venovenous extracorporeal membrane oxygenation therapy for acute respiratory distress syndrome in a patient with miliary tuberculosis. ASAIO J Am Soc Artif Intern Organs. 1992;2014(60):484–6.
22. Strunk A-K, Ciesek S, Schmidt JJ, Kühn C, Hoeper MM, Welte T, et al. Single- and multiple-dose pharmacokinetics of ethambutol and rifampicin in a tuberculosis patient with acute respiratory distress syndrome undergoing extended daily dialysis and ECMO treatment. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2016;42:1–3.
23. Lebreton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guihaire J, et al. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. Lancet Respir Med. 2021;9:851–62.
24. Akalu TY, Clements ACA, Wolde HF, Alene KA. Prevalence of long-term physical sequelae among patients treated with multi-drug and extensively drug-resistant tuberculosis: a systematic review and meta-analysis. EClinicalMedicine. 2023;57:101900.
25. Chommeloux J, Valentin S, Winiszewski H, Adda M, Pineton de Chambrun M, Moyon Q, et al. One-year mental and physical health assessment in survivors after extracorporeal membrane oxygenation for COVID-19-related acute respiratory distress syndrome. Am J Respir Crit Care Med. 2023;207:150–9.

Publisher's Note