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Early View

Research letter

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Research Letter to the Editor

Extracorporeal membrane oxygenation for ARDS due to *Pneumocystis* pneumonia

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Author's contributions: KS, HS, BS, JJS and SD obtained retrospective data. KS, HS, JB, TW, CK, MMH, AH and SD analysed and discussed the data and generated the figure. SD and KS wrote the manuscript; all authors proof-read the manuscript.

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Short running title: ECMO outcome in PcP

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To the editor:

Pneumocystis jirovecii pneumonia (PcP) occurs exclusively in immunocompromised patients. About 50% of PcP is HIV-related, the other half associated with immunosuppression for other reasons [1]. If PcP progresses to an acute respiratory distress syndrome (ARDS) requiring intensive care and invasive mechanical ventilation, the prognosis is generally poor [1] and mortality is about 80% if additional veno-venous extracorporeal membrane oxygenation (VV-ECMO) support is necessary [1]. Despite lack of clear evidence [2], VV-ECMO has become an integral part in the rescue therapy of severe ARDS. Moreover, some centers start VV-ECMO at early time-points in order to rigorously follow (ultra-) protective ventilation strategies [3]. So far, VV-ECMO in patients with PcP-associated ARDS has been reported only on the basis of singular case reports, including one case of awake ECMO [4]. Using ECMO in patients who are awake and spontaneously breathing might avoid complications associated with sedation and invasive mechanical ventilation. Our group was the first to describe this awake ECMO approach in a bridge-to-transplant setting [5, 6] as well as in a small number of ARDS patients [7, 8]. However, evidence on the safety and efficacy of awake VV-ECMO strategies in this population is lacking [7]. PcP classically leads to an isolated single organ failure without accompanying systemic complications such as septic shock with hemodynamic instability or acute kidney injury (AKI). At the same time, these patients often require prolonged invasive mechanical ventilation with a high-risk of complications including ventilator-associated pneumonia and pneumothorax. Hence, patients with PcP and severe hypoxemia may be candidates for an awake ECMO strategy as bridge-to-recovery.

We retrospectively analyzed patients with PcP associated ARDS that required VV-ECMO (PaO_2/FiO_2 < 100 or pH < 7.15) in our tertiary care hospital from 2010 to 2018. Written informed consent was waived by the local ethics committee. Sixteen patients were identified of which 6 (38%) were treated with initial (no intubation prior to ECMO initiation) awake VV-ECMO when deemed cooperative and expected to tolerate the awake concept.

The 2 cohorts (intubated VV-ECMO and awake VV-ECMO) were comparable in terms of most demographic and clinical parameters. Median age of patients was 41 (33-67) years and the majority was male (75%). Primary cause for PcP infection was HIV in 6 patients (38%) and medical immuno-suppression in the other 10 patients. All patients were receiving intravenous trimethoprim-sulfamethoxazole at high daily doses of 26 (17.9-33.5) mg/kg body weight and additional daily prednisolone at 1 mg/kg body weight. With regard to organ failure, the majority of patients had predominantly singular pulmonary dysfunction indicated by rather low rates of vasopressor support (31%) and renal replacement therapy (25%) as well as physiological serum lactate concentrations (1.6 (1.3-2.2) mmol/l). Median oxygenation indices at initiation were 68 and 72 (p=0.76) with median pH values of 7.37 (7.18-7.42) and 7.38 (7.32-7.42) (p=0.46) for intubated and awake ECMO patients, respectively. Of the 6 non-intubated patients, non-invasive ventilation and nasal high flow cannula oxygenation were employed for 3 patients each. The median Sequential Organ Failure Assessment (SOFA) scores were 11 and 7, respectively, with the difference between both groups attributable to the use of sedatives in ventilated patients. Renal replacement therapy requirement was not different, as it was C-reactive protein and Lactate-dehydrogenase concentrations. The burden of comorbidities was similar in both cohorts. However, sedated patients needed vasopressors in 50% of cases at moderate doses whereas primarily awake ECMO patients were all hemodynamically stable (p=0.04).

Median respiratory rates (RR) in the awake ECMO group were 37 (31-40) /min before ECMO implantation and 22 (19-26), 26 (18-33), and 22 (20-24) /min at 4hrs, 24 hrs and 48 hrs thereafter, respectively.

The overall survival until discharge from hospital was 5/16 (31%). Four of the 6 patients who were primarily treated with the awake ECMO support survived until discharge from hospital (67%). Although, out of these 6 primarily awake ECMO patients 4 required secondary intubation after 5 (1.5 – 14) days, the survival of this awake cohort was strikingly better compared to primarily intubated ECMO patients (10%, p = 0.011, ***Figure 1***). Of note, both awake ECMO patients who died required secondary intubation during the course of their ICU stay. Causes of death in the awake ECMO group were pulmonary bleeding (n=1) and irreversible lung failure (n=1). In the intubated ECMO group progressive secondary septic shock due to superinfections (n=5) as well as lack of ARDS improvement (n=3), and fatal

pulmonary bleeding (n=1) were noted. On univariate regression analysis awake VV-ECMO strategy was a strong predictor for survival in our cohort of PcP patients (OR 18, 95% CI 1.2 – 260.9, p=0.034).

To the best of our knowledge, this is the largest cohort of PcP patients treated with ECMO reported so far. Although mortality remained high, our data suggest that the use of ECMO is not necessarily futile in this immunocompromised patient population. In addition, a primarily awake ECMO strategy seems feasible in selected patients. However, criteria to identify ideal candidates have not been established and depend on the expertise of a given center. It is not uncommon that patients who are primarily awake require later secondary intubation, mostly for agitation and delirium, or worsening of oxygenation despite maximal ECMO support.

We acknowledge the limitations of this study, in particular the small number of patients, the single center setting and the retrospective design. The sample size was too small for a matched pairs analysis or a propensity adjusted analysis to control for a possible selection bias. The observation that patients in the awake ECMO group were hemodynamically stable at baseline might represent such a bias. Thus, drawing generalizable conclusions from the comparison of outcomes between the two groups is difficult.

The comparison of ARDS severity of intubated and non-intubated patients by means of oxygenation index was confounded by the proportion of patients on high flow nasula cannula.

One advantage of awake non-intubated ECMO might theoretically be the avoidance of ventilator-induced lung injury but at the same time vigorous spontaneous breathing efforts have also been demonstrated as potentially injurious - termed *self-inflicted lung injury* [1, 9]. In this retrospective analysis, we cannot address this important concern, but we did observe that respiratory rates following ECMO implantation declined by over 40% indicating a clinical relieve of patients' respiratory distress.

Despite these limitations, our findings support the notion that ECMO support may be justified in immunocompromised patients with PcP-associated ARDS and suggest that an awake ECMO strategy might be feasible in selected patients. Whether the avoidance of intubation and mechanical ventilation is associated with better outcome,

is however unclear. We hope that these data might stimulate future prospective studies on the use of ECMO in patients with PcP-associated lung failure.

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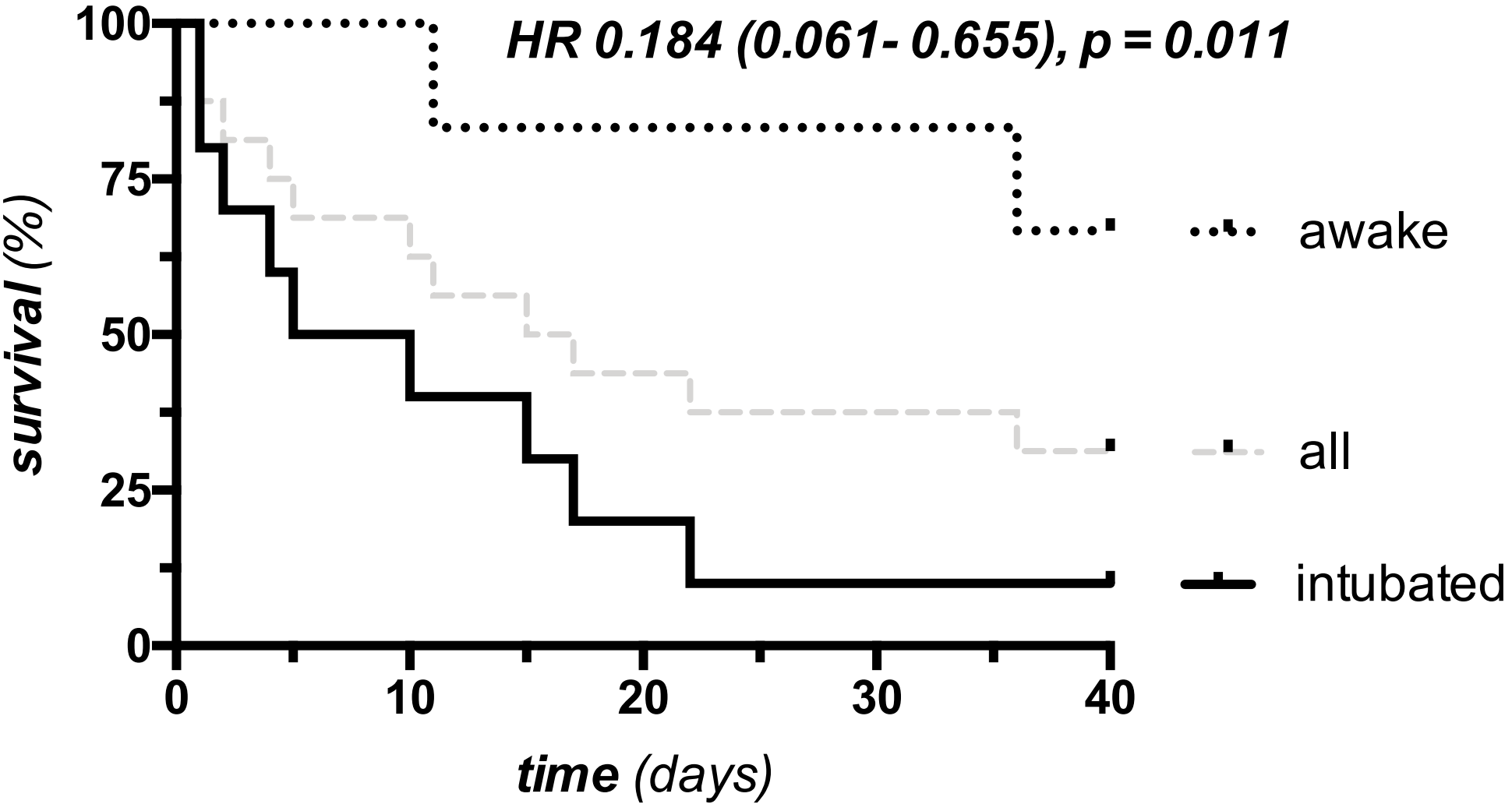
Figure 1: **Survival in intubated vs. awake VV-ECMO patients with Pneumocystis pneumonia (PcP).**

Kaplan Meier graphs showing the 40-day survival course in awake (n=6) and intubated (n=10) and all VV-ECMO patients with PcP associated ARDS (mortality awake ECMO 2/6, 33.3% vs. intubated ECMO 9/10, 90%, p=0.01)


HR 0.184 (0.061- 0.655), p = 0.011
100
75
50
25
0
survival (%)
0
10
20
30
40
time (days)
awake
all
intubated