

Midterm outcomes of venovenous extracorporeal membrane oxygenation as a bridge to lung transplantation: Comparison with nonbridged recipients

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1 **Mid-Term Outcomes of Veno-Venous Extracorporeal Membrane Oxygenation**
2 **as a Bridge to Lung Transplantation: Comparison with Non-Bridged Recipients**

3

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12

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15

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35 **Abstract**

36

37 **Objectives:** Venovenous extracorporeal membrane oxygenation (VV-ECMO) is increasingly being used in
38 acutely deteriorating patients with end-stage lung disease as a bridge to transplantation (BTT). It can allow
39 critically ill recipients to remain eligible for lung transplant (LTx) while reducing pretransplant deconditioning.
40 We analyzed early and mid-term postoperative outcomes of patients on VV-ECMO as a BTT and the impact
41 of preoperative VV-ECMO on posttransplant survival outcomes.

42 **Methods:** All consecutive LTx performed at our institution between January 2012 and December 2018 were
43 analyzed. After matching, BTT patients were compared with non-bridged LTx recipients.

44 **Results:** Out of 297 transplanted patients, 21 (7.1%) were placed on VV-ECMO as a BTT. After matching,
45 we observed a similar 30-day mortality between BTT and non-BTT patients (4.6% vs. 6.6%, $p=0.083$) despite
46 a higher incidence of early postoperative complications (need for ECMO, delayed chest closure, acute kidney
47 injury). Furthermore, preoperative VV-ECMO did not appear associated with 30-day or 1-year mortality in
48 both frequentist and Bayesian analysis (OR 0.35, 95% CI 0.03-3.49, $p=0.369$; OR 0.27, 95% CrI 0.01-3.82,
49 $P=84.7\%$, respectively). In sensitivity analysis, both subgroups were similar in respect to 30-day (7.8% vs.
50 6.5%, $p=0.048$) and 1-year mortality (12.5% vs. 18%, $p=0.154$).

51 **Conclusions:** Patients with acute refractory respiratory failure while waiting for LTx represent a high-risk
52 cohort of patients. VV-ECMO as a BTT is a reasonable strategy in adult patients with acceptable operative
53 mortality and 1-year survival comparable to non-BTT patients.

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59 INTRODUCTION

60 In patients with end-stage lung disease awaiting lung transplantation (LTx), waiting list mortality
61 remains high due to the shortage of available donor organs and the risk of acute respiratory failure in many
62 patients on the transplant list. Recent reports have demonstrated that mechanically ventilated lung recipients
63 have significantly higher post-transplant mortality when compared to non-ventilated recipients.¹⁻³

64 Veno-venous extracorporeal membrane oxygenation (VV-ECMO) is increasingly being used to bridge
65 acutely deteriorating candidates to LTx as it can allow critically ill recipients to remain eligible for LTx while
66 reducing pretransplant deconditioning.⁴⁻⁸ In particular, VV-ECMO as a bridge to transplantation (BTT) can
67 facilitate early ambulation, thus improving their condition, and may mitigate detrimental intensive care unit
68 (ICU) complications including weakness, delirium, and ventilator-associated pneumonia or lung injury.⁴
69 However, a decade ago few reports have raised skepticism for this strategy as they have suggested a negative
70 effect of bridging with ECMO on post-transplant survival.^{2,9} Since then, there is a growing evidence from
71 high-volume and experienced lung transplant centers that BTT strategy using ECMO can provide satisfactory
72 outcomes.¹⁰⁻¹⁴

73 In the present study, our aim was to analyze postoperative outcomes of patients on VV-ECMO as a
74 BTT and the impact of preoperative VV-ECMO on posttransplant survival outcomes. Early and mid-term
75 outcomes of BTT patients were evaluated and compared after matching with non-bridged LTx recipients. In
76 order to achieve the best possible matching between both subgroups, we have performed optimal full matching
77 based on Mahalanobis distance and sensitivity analysis.

78

79 METHODS

80 Study design

81 This study is a retrospective analysis of all consecutive LTx performed at Harefield Hospital (London, UK)
82 between June 2012 and December 2018. Patients who underwent heart-lung transplantation were excluded
83 from this study. Approval from the Institutional Ethics Committee was obtained, and all the patients provided
84 their written informed consent for LTx as well as for donation after circulatory death (DCD). Data were
85 extracted from the institutional electronic system. Primary endpoints were posttransplant 30-day and 1-year
86 survival. Secondary endpoints were early and mid-term postoperative outcomes.

87 Patient selection

88 All patients were listed for transplant after being reviewed by a multidisciplinary team in accordance with the
89 current guidelines. As recommended by our Institutional Ethics Committee, all patients on the LTx waiting
90 list were additionally consented for LTx from DCD donors. Donors were selected based on the current standard
91 ISHLT criteria including extended donor criteria.¹⁵ Preoperative VV-ECMO was considered as a BTT in
92 patients who were already listed for LTx, have suffered acute decompensation in their end-stage lung disease
93 and continued to deteriorate despite standard medical treatment, non-invasive or invasive mechanical
94 ventilation (MV). Further considerations for BTT included intact neurological status, the absence of active
95 bacteremia or organ failure, and the potential to participate in pretransplant physical therapy. Donor lung
96 assessment, procurement and preservation were described earlier by our group.¹⁶⁻¹⁸

97 VV-ECMO and surgical technique

98 Most patients on VV-ECMO as a BTT were awake throughout the period before the transplant and participated
99 in regular physical therapy. At our institution, awake and ambulatory ECMO protocols have been implemented
100 in order to provide rehabilitation, physical therapy, and minimization of sedation prior to LTx. Whenever
101 feasible, VV-ECMO cannulation was performed with the patient awake in the presence of two experienced
102 operators, using short-acting agents to provide anxiolysis and relying on local anesthetic to maintain patient
103 comfort. The VV-ECMO circuit consisted of a conventional centrifugal pump (Levitronix CentriMag™,
104 Thoratec, Pleasanton, CA, USA or Cardiohelp, Maquet, Rastatt, Germany) combined with an oxygenator. Our
105 preferred cannulation strategies were a dual-site (femoro-femoral or femoro-jugular) or single-site dual-lumen
106 cannula through the right internal jugular vein (Avalon Elite® bi-caval dual-lumen catheter, Maquet, Rastatt,
107 Germany). In the case of femoro-femoral configuration, a 25Fr Bio-Medicus™ multi-stage cannula
108 (Medtronic) for drainage and a 23Fr single-stage cannula were used. Our institutional anticoagulation protocol
109 involves the administration of a loading dose of 100 units/kg before ECMO cannulation on the surgeon's
110 request and then continuous intravenous infusion of unfractionated heparin. Continuous intravenous infusion
111 of unfractionated heparin was administered and regularly monitored by measuring activated partial
112 thromboplastin time (aPTT, target range 60-80 sec) and anti-Xa (target range 0.3-0.5 IU/ml for VV-ECMO or
113 0.2-0.5 IU/ml for VA-ECMO). Anti-Xa level is checked 4 hours after the initiation of heparin, 4 hours after

114 each change in rate, and every 4-6 hours until levels are stable. If heparin anti-Xa level is stable and within
115 range, heparin anti-Xa level and full blood count can be carried out once daily.

116 Surgical technique of LTx was described by our group in earlier reports.¹⁶ Intraoperative mechanical
117 circulatory support was considered in the case of severe pulmonary hypertension, inability to tolerate one-lung
118 ventilation, and hemodynamic instability after pulmonary artery clamping. Most commonly, patients who were
119 bridged to transplantation with VV-ECMO were transplanted on VV-ECMO; however, in some cases,
120 intraoperative conversion to veno-arterial (VA) ECMO was required. While ECMO was our preferred method
121 of intraoperative support, cardiopulmonary bypass (CPB) has been used depending on the surgeon's
122 preference, and in the case of severe hemodynamic instability or uncontrolled intraoperative bleeding.

123 Intraoperative VA-ECMO was used to support patients who developed primary graft dysfunction,
124 protamine sulphate-related right ventricular failure, or profound vasoplegia. In these cases, our preference was
125 the use of central cannulation.

126 If CPB was required, full heparinization (300 IU/kg) was provided before initiation of CPB to maintain
127 an activated clotting time (ACT) greater than 400 seconds during the period of CPB. After discontinuation of
128 the CPB, protamine sulphate was administered to reverse the effect of heparin. On the other hand, when ECMO
129 was used, an initial bolus of 5,000 IU intravenous heparin was given and ACT was maintained between 180
130 to 250 seconds. Protamine sulphate administration was considered after decannulation only in cases of
131 significant bleeding. Postoperatively, VV-ECMO was used to facilitate the improvement of gas exchange
132 when required. Main clinical indications for postoperative VV-ECMO were difficulties with MV leading to
133 inadequate gas exchange (primary graft dysfunction, reperfusion pulmonary oedema secondary to vasoplegic
134 syndrome or massive transfusion, and acute rejection). On the other hand, VA-ECMO was used in the case of
135 severe pulmonary hypertension to protect the new lungs from hyperperfusion or for additional hemodynamic
136 support. Among all patients requiring postoperative VV-ECMO, lung protective ventilation strategies were
137 applied with the provision of MV and lower plateau pressures. Protective MV was maintained during the post-
138 transplant ECMO support in order to avoid ventilator-induced lung injury.

139 **Data collection and analysis**

140 Data were collected retrospectively from the electronic and archived hospital medical records. We attempted
141 to specifically identify the effects of VV-ECMO as a BTT on: posttransplant 30-day mortality and

142 complications (need for postoperative ECMO, delayed chest closure, surgical re-exploration, tracheostomy,
143 chest drainage within 24 hours, chest infection, sepsis, stroke, acute kidney injury [AKI] requiring renal
144 replacement therapy [RRT]) and 1-year mortality.

145 Preoperative, intraoperative, and postoperative data are summarized for BTT and non-BTT patients.
146 In the main analysis, both subgroups were submitted to optimal full matching based on Mahalanobis distance
147 in respect to preoperative covariates. Based on their potential relevance to the observed outcomes and
148 imbalance between the two subgroups, included covariates were age, gender, body mass index (BMI), serum
149 creatinine and hemoglobin levels, platelet count $<150 \times 10^9/L$ and main diagnosis, with exact matching on the
150 gender, low platelet count and underlying diagnosis (cystic fibrosis [CF] or “other”).^{19,20} We had no patients
151 that required VV-ECMO as BTT among those with chronic obstructive pulmonary disease (COPD),
152 emphysema, bronchiolitis, bronchiectasis, pulmonary hypertension and lymphangiomyomatosis.
153 Therefore, in order to avoid aliasing between potential effects of VV-ECMO and diagnosis, a sensitivity
154 analysis (using the same methodology) was performed including only diagnoses where at least one patient was
155 bridged to LTx with VV-ECMO. To evaluate the effect of VV-ECMO as a BTT (vs. non-BTT), generalized
156 mixed models (binary distribution, logit link; subclass as a random effect [cluster]) were fitted to each binary
157 outcome with further adjustment for unbalanced covariates: frequentist (maximum likelihood estimation with
158 Gauss-Hermite quadrature approximation; classical [sandwich] robust estimator) and Bayesian (4 chains, 4000
159 iterations, 8000 samples of the posterior, vaguely informative normal priors for $\ln[\text{odds}]$ and the intercept [0,
160 2.5; scaled], and priors on the terms of a decomposition of the covariance matrices [Gamma shape=1, scale=1;
161 LKJ for correlation matrix, regularization=1; Dirichlet for the simplex vectors, concentration=1]). To evaluate
162 the effect of VV-ECMO as a BTT on the chest drainage within the first 24 hours, data were \ln -transformed
163 (since right-skewed) and the same models, although with normal distribution and identity link, were fitted. We
164 used package *MatchIt* in R for matching,²¹ SAS 9.4 for Windows *proc glimmix* (SAS Inc., Cary, NC) for fitting
165 frequentist and package *rstanarm* in R for Bayesian models.²² We evaluated susceptibility of the observed
166 effects to unmeasured confounding by determining the E-value (package *Evalue* in R).²³ Despite a large
167 number of analyzed outcomes and related formal statistical tests, we considered more appropriate not to
168 implement multiplicity adjustments as adjustments of comparison-wise alpha could have resulted in falsely
169 overlooked adverse effects of VV-ECMO as a BTT.

170 **RESULTS**

171 **Patients' perioperative characteristics, early and mid-term outcomes**

172 Out of 297 transplanted patients in the study period, 21 (7.1%) were placed on VV-ECMO as BTT. Out of
173 these 21, 13 (62%) patients were awake, non-invasively ventilated and participated in rehabilitation and
174 ambulation. There were no mechanically ventilated patients in the non-BTT group (Table 1). As compared to
175 non-BTT patients, BTT patients were younger with a slightly lower BMI and, in line with the VV-ECMO
176 support, had considerably lower preoperative hemoglobin and platelet count, longer activated partial
177 thromboplastin time and higher international normalized ratio (Table 1). The most common diagnosis in both
178 groups was cystic fibrosis (90.5% in BTT patients vs. 39.1% in non-BTT patients; Table 1). Single LTx was
179 performed only in 8 out of 276 non-BTT patients (Table 1). Intraoperative use of CPB was similar in both
180 groups, while the use of intraoperative ECMO and perioperative blood transfusion were considerably higher
181 in BTT patients (Table 1). Postoperative 30-day mortality and the incidence of early postoperative
182 complications (need for ECMO, delayed chest closure, surgical re-exploration, tracheostomy, chest drainage,
183 chest infection, sepsis and AKI requiring RRT) were higher in BTT patients compared with non-BTT patients
184 (Table 2). In the BTT group, need for postoperative ECMO was observed in 10 (47.6%) patients (4 VA-ECMO
185 and 6 VV-ECMO), while in the non-BTT group 21 (7.6%) patients required ECMO postoperatively (18 VA-
186 ECMO and 3 VV-ECMO) (Table 2.). In the BTT group, 2 patients developed dehiscence of the bronchial
187 anastomosis and only one required re-implantation of the left lung, while in the non-BTT group 3 patients had
188 dehiscence of the bronchial anastomosis with 2 requiring surgical re-exploration. One-year mortality was also
189 higher in BTT than in non-BTT patients (Figure S1.).

190

191 **Effect of VV-ECMO as a BTT on postoperative 30-day outcomes and 1-year mortality - primary** 192 **matched subgroups analysis**

193 After matching, BTT and non-BTT patients were well-balanced with respect to the age, preoperative laboratory
194 characteristics and main diagnosis (all standardized mean differences [d] <0.1; Table 3), but there was still
195 imbalance (d >0.1) in the proportion of female patients, BMI and hemoglobin levels (lower in BTT patients)
196 (Table 3). Intraoperatively, CPB was used less often, while the use of ECMO was considerably higher in BTT
197 patients than in non-BTT patients after matching (Table 3). Regarding 30-day outcomes, need for postoperative

198 ECMO (73.0% vs. 8.6%), delayed chest closure (11.9% vs. 6.3%) and incidence of AKI requiring RRT (63.6%
199 vs. 29.7%) were higher in BTT vs. non-BTT patients (Table 3). However, chest drainage within 24 hours,
200 incidence of surgical re-exploration, tracheostomy, chest infection, and 30-day mortality appeared similar in
201 the two matched subgroups, while 1-year mortality was lower in BTT patients (Table 3). With further
202 adjustment for the unbalanced covariates (gender, BMI and hemoglobin level), preoperative VV-ECMO
203 support was associated with around 20-fold higher odds of postoperative ECMO (frequentist and Bayesian
204 estimates; Table 4). It was also associated with around 4-fold higher odds of AKI requiring RRT: the Bayesian
205 estimate (95%CrI 1.31-14.2) appeared robust (a rather high E-value indicated a rather low susceptibility to
206 unmeasured confounding) and was more precise than the frequentist estimate (95%CI 0.43-39.2), leaving some
207 uncertainty about this effect (Table 4). There was also a tendency of higher odds of tracheostomy (OR 2.3),
208 but both frequentist and Bayesian estimates were imprecise (Table 4). VV-ECMO as a BTT did not appear
209 associated with other 30-day outcomes including mortality or with 1-year mortality (Table 4).

210

211 **Sensitivity analysis**

212 Patients with an underlying diagnosis of COPD, emphysema, bronchiectasis, lymphangiomyomatosis and
213 pulmonary hypertension (n = 107) were excluded, since none of them was placed on VV-ECMO (to avoid
214 aliasing between diagnosis and ECMO support), resulting in 21 BTT and 169 non-BTT patients in the
215 sensitivity analysis (Table 5). Perioperative characteristics (Table 5) and postoperative outcomes (Table 6) in
216 BTT and non-BTT patients were similar to those in the entire cohort. After matching, both subgroups were
217 well-balanced with respect to the age, low platelet count, serum creatinine and prevalence of CF, while
218 imbalance remained regarding the proportion of men, BMI, and preoperative hemoglobin levels (Table 7).
219 Intraoperatively, CPB was used less often, while the use of ECMO was considerably higher in BTT compared
220 with non-BTT patients (Table 7). Need for postoperative ECMO (62.0% vs. 8.7%), delayed chest closure
221 (16.5% vs. 5.6%), tracheostomy (50.8% vs. 34.4%), chest infection (60.8% vs. 41.2%) and AKI requiring RRT
222 (45.7% vs. 30.5%) were more common in BTT than in non-BTT patients, while the two subgroups were similar
223 in respect to 30-day mortality, surgical re-exploration, chest drainage within 24 hours, sepsis, stroke and 1-
224 year mortality (Table 7). With further adjustment for the unbalanced covariates (gender, BMI and hemoglobin
225 level), VV-ECMO as a BTT was associated with 12.8-fold higher odds of need for postoperative ECMO and

226 with 6-fold higher odds of tracheostomy, but it did not appear associated with any other early and mid-term
227 outcome (Table 8).

228

229 **DISCUSSION**

230 The use of VV-ECMO as a BTT can allow patients with decompensated end-stage lung disease to remain
231 eligible for LTx and offer a viable strategy for improving their post-transplant survival outcomes. In this study,
232 we reported our single-center experience with 297 transplanted patients, 21 (7.1%) of whom were bridged to
233 LTx with VV-ECMO. The most common diagnosis in both BTT and non-BTT recipients was CF. One of the
234 reasons is that there is a well-established CF Unit in our institution which attracts tertiary referrals from the
235 whole country. In the primary analysis, both 30-day and 1-year posttransplant mortality were considerably
236 higher in patients requiring VV-ECMO as a BTT than in non-BTT patients. In addition, the incidence of the
237 most important early postoperative complications, including need for ECMO, delayed chest closure, surgical
238 re-exploration and AKI requiring RRT, was significantly increased in the bridged patients.

239 To minimize potential effects of selection bias and decrease variability of both groups, we performed
240 further analysis comparing matched groups which were well-balanced in terms of preoperative recipients'
241 baseline characteristics. Importantly, after matching, we observed a similar 30-day mortality between the BTT
242 and non-BTT patients (4.6% vs. 6.6%, $p=0.083$) despite a higher incidence of early postoperative
243 complications (need for ECMO, delayed chest closure, AKI requiring RRT), while the 1-year mortality was
244 even lower in the BTT patients (8.0% vs. 15.6%, $p=0.238$). Furthermore, when evaluating the effect of
245 preoperative VV-ECMO on postoperative outcomes, it did not appear associated with 30-day or 1-year
246 mortality. Moreover, in the sensitivity analysis, the two subgroups were similar in respect to 30-day (BTT
247 7.8% vs. 6.5%, $p=0.048$) and 1-year mortality (12.5% vs. 18%, $p=0.154$). The clinical condition of patients
248 who were bridged to LTx with VV-ECMO is usually more critical than that among the rest of the patients who
249 were not bridged, and this may negatively influence their outcomes. However, in our experience, post-
250 transplant survival in bridged patients was comparable to that in patients who did not have pre-transplant VV-
251 ECMO. Therefore, VV-ECMO has been demonstrated to be a valuable supportive strategy to prolong life in
252 these critically ill patients while increasing the waiting period for suitable organs. Our early and mid-term
253 results are in general consistent with previous reports that have shown no significant difference in post-

254 transplant survival among BTT and non-BTT patients, especially in high-volume centers.^{4,10-12,24-29}
255 Surprisingly, we have found that 1-year mortality was even lower in the BTT group but this might be related
256 to several other factors. One of the reasons could be that the average duration of pre-transplant support with
257 VV-ECMO in our cohort was relatively short (8 days) and this could positively affect the outcomes. As
258 recently reported by *Crotti et al.*, patients who underwent LTx after a waiting period longer than 14 days had
259 significantly higher rates of post-transplant mortality and morbidity.³⁰ Furthermore, shorter waiting times after
260 urgent listing have likely contributed to these favorable outcomes. In addition, we have observed more
261 commonly intraoperative ECMO than CPB among BTT patients when compared to the non-BTT group, and
262 it is well known that the intraoperative use of ECMO might have several advantages.^{31,32} Obviously, among
263 BTT patients our preferred approach was to use VV- or VA-ECMO as intraoperative support. However, the
264 choice of intraoperative mechanical circulatory support was at the surgeon's discretion and related to the
265 patient's characteristics and specific indications as described previously. Similarly, Hoetzenecker and
266 colleagues reported recently that use of intraoperative ECMO resulted in excellent mid-term outcomes among
267 LTx recipients.³² Intraoperative use of ECMO can provide controlled reperfusion without increased risk of
268 systemic inflammatory response and early postoperative bleeding related to the use of CPB.³² In addition,
269 several high-volume LTx centers demonstrated that intraoperative use of ECMO outperforms CPB. The use
270 of ECMO has several advantages, including partial heparinization, possibility of extending the support into
271 the postoperative period and lower rates of primary graft dysfunction.³³⁻³⁵ We believe that the improved
272 survival among BTT patients can be also related to an increased experience with this strategy, early ambulation
273 of these patients, advancement in the perioperative care, and development of an experienced ECMO and
274 multidisciplinary team.

275 On the other hand, *Schechter et al.* have reported a decreased 1-year post-transplant survival among
276 patients requiring preoperative support including ECMO with MV.³ However, they have demonstrated in a
277 multivariable analysis that ECMO alone was not associated with decreased 1-year survival.³ In our study,
278 38.1% of patients were supported using both VV-ECMO and MV before LTx, but the sample size was too
279 small to perform a further analysis whether MV could have had any effect on postoperative outcomes.
280 Furthermore, *Mason et al.* have reported that survival after LTx is markedly worse (1-month and 1-year post-
281 transplantation survival were 72% and 50%, respectively) when preoperative mechanical support is necessary,

282 although they suggested that additional risk factors for mortality should be considered when selecting patients
283 for LTx in order to improve survival.² In addition, *Fischer et al.* have reported that the perioperative mortality
284 of LTx after preoperative ECMO can be even up to 60%.⁹

285 As expected, need for postoperative ECMO, delayed chest closure, tracheostomy, chest infection, and
286 AKI requiring RRT were more common among BTT patients. This can be related to the common and well-
287 known risks related to the use of ECMO such as bleeding complications, systemic inflammatory response,
288 acute kidney injury and thromboembolic complications.³⁶⁻⁴³ However, the rate of these complications was
289 lower than in some of the previous reports that demonstrated an incidence of tracheostomy in up to 77%³⁹,
290 delayed chest closure in 50%⁴⁰ and stroke in 8%³⁹ of recipients. Furthermore, nearly half of BTT patients
291 required ECMO postoperatively and we have used VV-ECMO in 6 (60%) of these patients. One of the
292 potential reasons could be that VV-ECMO was already used preoperatively and continued intraoperatively.
293 Therefore, it was easier to decide for the same modality postoperatively in the cases of difficult MV and
294 impaired gas exchange. Still, in our study it seems that both 30-day and 1-year survival have not been
295 negatively affected by the increased incidence of early postoperative complications.

296 The strength of this study is the comparison of two cohorts of patients (BTT and non-BTT) that were
297 matched. However, we acknowledge several study limitations. First, the analysis was performed
298 retrospectively and designed as a single-center study, although the study period was up to 7 years and included
299 moderate sample size with 1-year follow-up. The present study also lacks donor data as we were not able to
300 collect these data for the majority of the study period. For the same reason, it was not possible to obtain or
301 compare data regarding DCD donation for the majority of recipients, including warm ischemic time. However,
302 recent analysis from the ISHLT DCD Lung Transplant Registry reported that current experience with DCD
303 category III LTx did not show a relationship between the duration of donor warm ischemic time up to 60
304 minutes and early survival.⁴⁴ Further studies with analysis of donor data and type of organ donation would be
305 needed. Regarding the need for postoperative ECMO, due to the fact that the subgroups (postoperative VA-
306 and VV-ECMO) were too small, it was not possible to include them in our matching analysis. In addition, it
307 would be interesting to expand the research and study primary graft dysfunction and rejection rate as we did
308 not have this data. Further studies with long-term follow-up would be useful in order to analyze occurrence of
309 late complications. Lastly, we were not able to extend our analysis including patients bridged with other

310 devices (VA-ECMO, Novalung) due to a small sample size and different clinical characteristics some of these
311 patients.

312

313 **CONCLUSIONS**

314 End-stage lung disease patients with acute refractory respiratory failure while waiting for LTx represent a
315 challenging and high-risk cohort of patients. However, VV-ECMO is our favored bridging strategy and we
316 have observed that these patients can be successfully bridged to LTx and can have post-transplant mortality
317 comparable to non-BTT patients. The results of this study provide further insight into early and mid-term
318 outcomes and evidence for the clinical use of VV-ECMO as a bridging strategy for patients with refractory
319 respiratory failure, especially in carefully selected recipients and high-volume ECMO and lung transplant
320 centers. VV-ECMO as a BTT is a reasonable strategy in adult patients with acceptable operative mortality and
321 1-year survival comparable to non-BTT patients.

322

323 **Author contributions:** Davorin Sef and Alessandra Verzelloni Sef: Conceptualization, Formal analysis,
324 Investigation, Methodology, Validation and Writing—original draft. Davorin Sef, Alessandra Verzelloni Sef,
325 Vladimir Trkulja and Binu Raj: Data curation, Formal analysis, Investigation, Methodology and Validation.
326 Vladimir Trkulja: Statistical analysis. Vladimir Trkulja, Nicholas James Lees, Christopher Walker, Jerry
327 Mitchell, Mario Petrou, Fabio De Robertis, Ulrich Stock, Ian McGovern: Conceptualization; Writing—Review
328 and Editing.

329

330 **Data Availability Statement**

331 Data available on request due to privacy/ethical restrictions.

332

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334

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- 445

446 **Table 1.** Patients' preoperative and intraoperative characteristics.

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	BTT with VV-ECMO	Non-BTT	<i>p</i> ¹
N	21	276	---
<i>Preoperative characteristics</i>			
Age, years	30.5 (23-34.8; 19-56)	49 (30.2-57.8; 19-71)	<0.001
Male gender	13 (61.9)	152 (55.1)	0.544
Body mass index, kg/m ²	20.2 (19-23; 17.7-27.9)	22.1 (19.5-25.5; 14.7-58.1)	0.062
Hemoglobin, g/L	84 (78-91; 71-103)	137 (121-149; 59-196)	<0.001
Hemoglobin <90 g/L	16 (76.2)	11 (4.0)	<0.001
Platelet count, x10 ⁹ /L	153 (84-257; 37-550)	273 (221-357; 52-659)	<0.001
Platelet count <150 x10 ⁹ /L	11 (52.4)	19 (6.9)	<0.001
aPTT, seconds	49.5 (43.8-66.2; 34.5-97.1)	32 (29-34.5; 17.7-108.5)	<0.001
INR	1.2 (1.1-1.4; 0.9-1.7)	1.0 (0.9-1.1; 0.8-2.5)	<0.001
Creatinine, μmol/L	58 (33-70; 19-94)	59 (50-72.5; 24-142)	0.237
FVC, L	1.62 (1.36-2.18; 0.73-3.23)	1.88 (1.43-2.37; 0.39-4.98)	0.316
FEV1, L	0.97 (0.62-1.36; 0.41-2.30)	0.73 (0.55-0.92; 0.20-3.61)	0.037
Renal replacement therapy	1 (4.8)	1 (0.4)	0.100
Mechanical ventilation	8 (38.1)	0	---
<i>Diagnosis</i>			
Cystic fibrosis	19 (90.5)	108 (39.1)	<0.001
COPD/emphysema/bronchiectasis	0	99 (35.9)	---
α1-antitrypsin deficiency	1 (4.8)	34 (12.3)	0.300
Pulmonary fibrosis/ILD	1 (4.8)	27 (9.8)	0.448
Lymphangioleiomyomatosis	0	5 (1.8)	---
Pulmonary hypertension	0	3 (1.1)	---
Preoperative VV-ECMO duration, d	8 (6.5-16; 1-53)	---	---
<i>Intraoperative characteristics</i>			
Bilateral lung transplant	21 (100)	268 (97.1)	---
Cardiopulmonary bypass	6 (28.6)	94 (34.1)	0.608
ECMO	15(71.4)	15 (5.4)	<0.001
<i>Transfusion (24h)</i>			
Red blood cells, units	13.5 (8.2-41.8; 5-53)	3 (1-3, 0-71)	<0.001
Platelets, pools	3.5 (1.2-8.5; 0-21)	1 (0-2; 0-18)	<0.001
Fresh frozen plasma, units	6 (2.5-11; 0-37)	2 (0-4; 0-32)	<0.001
Cryoprecipitate, units	8 (38.1) (median 3.5 units)	45 (16.3) (median 2 units)	0.022

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Data are median (quartiles; minimum-maximum) or count (percent)

aPTT, activated partial thromboplastin time; BTT, bridge to transplantation; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal mechanical oxygenation; FEV1, forced expiratory volume (1st second); FVC, forced vital capacity; ILD, interstitial lung disease; INR, international normalized ratio; VV, veno-venous.¹ Mann-Whitney U-test or likelihood ratio test

455 **Table 2.** Early and mid-term postoperative outcomes.
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Outcomes	BTT with VV-ECMO	Non-BTT	<i>p</i> ¹
N	21	276	---
<i>30-day outcomes</i>			
30-day mortality	5 (23.8)	15 (5.4)	<0.001
Postoperative ECMO	10 (47.6)	21 (7.6)	<0.001
VV-ECMO/VA-ECMO	6/4 (60.0/40.0)	3/18 (14.3/85.7)	---
ECMO duration, days	9 (1-15; 1-19)	7 (2.2-26; 2-49)	---
Delayed chest closure	9 (42.8)	18 (6.5)	<0.001
Chest drainage within 24h, mL	2225 (975-3450)	1125 (825-1725)	0.006
Surgical re-exploration	8 (38.1)	35 (12.7)	<0.001
AKI requiring RRT	12 (57.1)	81 (29.4)	0.001
Tracheostomy	12 (57.1)	94 (34.1)	0.037
Chest infection	12 (57.1)	108 (39.1)	0.109
Sepsis	12 (57.1)	84 (30.4)	0.015
Stroke	0	12 (4.3)	---
ICU length of stay, d	19 (12-22.5; 1-52)	7 (4-21; 1-98)	0.011
<i>1-year all-cause mortality</i>	7 (33.3)	40 (14.5)	0.023
<i>Cause of death</i>			
Multiorgan failure	5/7 (71.4)	19/40 (47.5)	---
Primary graft dysfunction	1/7 (14.3)	0	---
Acute rejection	0	1/40 (2.5)	---
Chronic rejection	1/7 (14.3)	6/40 (15.0)	---
Infectious complications	0	6/40 (15.0)	---
Pulmonary embolism	0	1/40 (2.5)	---
Malignancy	0	2 (5.0)	---
Cardiac arrest	0	1 (2.5)	---
Other causes	0	4 (10.0)	---

457 Data are median (quartiles; minimum-maximum) or count (percent)

458 AKI, acute kidney injury; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; ICU, intensive care unit;
 459 RRT, renal replacement therapy; VV, veno-arterial; VV, veno-venous.

460 ¹ Mann-Whitney U-test or likelihood ratio test

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463 **Table 3.** Patients' preoperative and intraoperative characteristics, 30-day outcomes and 1-year mortality before
 464 and after matching – primary analysis. Variables used for matching are shaded. Standardized mean differences
 465 (d) <0.1 indicate irrelevant differences between BTT and non-BTT lung transplant recipients.

Characteristics	Before matching			After matching		
	BTT with VV- ECMO	Non-BTT	d	BTT with VV- ECMO	Non-BTT	d
N	21	276	---	21	276	---
<i>Preoperative</i>						
Age, years	30.5 (23-34.8)	49 (30.2-57.8)	-1.064	44.0±14.0	44.4±14.7	-0.035
Male gender	13 (61.9)	152 (55.1)	0.139	16.3 (77.8)	152.5 (55.3)	0.458
BMI, kg/m ²	20.2 (19-23)	22.1 (19.5-25.5)	-0.495	21.6 (20.2-21.6)	21.9 (19.5-25.2)	-0.517
Hemoglobin, g/L	84 (78-91)	137 (121-149)	-2.910	82 (82-87)	136 (119-148)	-2.804
Platelets <150 x10 ⁹ /L	11 (52.4)	19 (6.9)	1.149	2.1 (10.1)	27.9 (10.1)	0.000
Creatinine, μmol/L	58 (33-70)	59 (50-72.5)	-0.434	70 (57-70)	58 (50-71)	0.071
Cystic fibrosis	19 (90.5)	108 (39.1)	1.275	9.0 (42.8)	118 (42.8)	0.000
<i>Intraoperative</i>						
CPB	6 (28.6)	94 (34.1)	-0.118	2.6 (12.5)	94.9 (34.4)	-0.533
ECMO	15 (71.4)	15 (5.4)	1.846	18.4 (87.5)	15.6 (5.6)	2.866
<i>30-day outcomes</i>						
30-day mortality	5 (23.8)	15 (5.4)	0.539	0.97 (4.63)	18.1 (6.55)	-0.083
Postop ECMO	10 (47.6)	21 (7.6)	1.120	15.3 (73.0)	23.7 (8.6)	1.735
Delayed chest closure	9 (42.8)	18 (6.5)	0.929	2.5 (11.9)	17.3 (6.3)	0.196
Chest drainage 24h, mL	2225 (975-3450)	1125 (825-1725)	0.745	975 (975-1100)	1150 (825-1750)	0.045
Re-exploration	8 (38.1)	35 (12.7)	0.611	2.3 (11.2)	39.2 (14.2)	-0.090
AKI requiring RRT	12 (57.1)	81 (29.4)	0.584	13.3 (63.6)	81.9 (29.7)	0.722
Tracheostomy	12 (57.1)	94 (34.1)	0.476	7.03 (33.5)	92.2 (33.4)	0.002
Chest infection	12 (57.1)	108 (39.1)	0.366	8.45 (40.2)	111.1 (40.2)	-0.000
Sepsis	12 (57.1)	84 (30.4)	0.559	4.48 (21.4)	88.2 (32.0)	-0.241
Stroke	0	12 (4.3)	-1.395	0	11.4 (4.2)	-0.535
<i>1-year mortality</i>	7 (33.3)	40 (14.5)	0.453	1.68 (8.0)	43.1 (15.6)	-0.238

466 Data are count (percent), median (quartiles) or mean±SD.

467 AKI, acute kidney injury; BMI, body mass index; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; ECMO,
 468 extracorporeal mechanical oxygenation; RRT, renal replacement therapy; VV, veno-venous

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472 **Table 4.** Adjusted (for gender, body mass index and hemoglobin level) odds ratios and geometric means ratios
 473 (GMR)¹ (for chest drainage within the first 24 hours): BTT with VV-ECMO vs. non-BTT recipients in the
 474 matched subgroups – primary analysis.

	Frequentist		Bayesian		E-value ²
	OR (95% CI)	<i>p</i>	OR (95% CrI)	P(OR≠1)	
<i>30-day outcomes</i>					
30-day mortality	0.35 (0.03-3.49)	0.369	0.27 (0.01-3.82)	84.7%	---
Postoperative ECMO	19.3 (1.38-270)	0.028	22.3 (4.35-113)	100%	8.91; 3.59
Delayed chest closure	2.31 (0.63-8.52)	0.209	2.35 (0.31-14.4)	81.2%	---
Chest drainage 24h, mL	1.38 (0.86-2.23)	0.177	1.16 (0.56-2.25)	67.2%	---
Re-exploration	1.18 (0.26-5.41)	0.834	1.10 (0.14-6.17)	54.2%	---
AKI requiring RRT	4.09 (0.43-39.2)	0.220	4.18 (1.31-14.2)	99.2%	3.51; 1.55
Tracheostomy	2.28 (0.41-12.6)	0.343	2.34 (0.71-8.00)	91.4%	---
Chest infection	0.92 (0.16-5.43)	0.926	1.16 (0.36-3.90)	60.6%	---
Sepsis	0.60 (0.11-3.19)	0.546	0.83 (0.19-3.10)	59.9%	---
Stroke	---	---	---	---	---
<i>1-year mortality</i>	0.48 (0.10-2.30)	0.360	0.41 (0.04-3.13)	81.2%	---

475 AKI, acute kidney injury; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement
 476 therapy

477 ¹Chest drainage volume data were right-skewed and were ln-transformed. The BTT vs. non-BTT difference is geometric means ratio
 478 (GMR)= exp[mean ln(BTT) – mean ln(non-BTT)]

479 ²Lowest unmeasured confounder effect (on the relative risk scale) needed to shift the (Bayesian) point estimate (first value) or the
 480 lower limit of the 95% CrI to 1.0 (second value).

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484 **Table 5.** Patients' preoperative and intraoperative characteristics – subgroups included in the sensitivity
 485 analysis.

	BTT with VV-ECMO	non-BTT	<i>p</i> ¹
N	21	169	---
<i>Preoperative characteristics</i>			
Age, years	30.5 (23-34.8; 19-56)	38 (26-53; 19-70)	0.048
Male gender	13 (61.9)	99 (58.6)	0.770
Body mass index, kg/m ²	20.2 (19-23; 17.7-27.9)	20.6 (18.9-24.2; 15.8-58.1)	0.586
Hemoglobin, g/L	84 (78-91; 71-103)	132 (115-146; 70-196)	<0.001
Hemoglobin <90 g/L	16 (76.2)	9 (5.3)	<0.001
Platelet count, x10 ⁹ /L	153 (84-257; 37-550)	293 (217-376; 52-659)	<0.001
Platelet count <150 x10 ⁹ /L	11 (52.4)	14 (8.3)	<0.001
aPTT, seconds	49.5 (43.8-66.2; 34.5-97.1)	31.9 (29.5-34.6; 21.4-108)	<0.001
INR	1.2 (1.1-1.4; 0.9-1.7)	1.0 (1.0-1.1; 0.8-2.5)	<0.001
Creatinine, µmol/L	58 (33-70; 19-94)	57 (46-69.5; 27-142)	0.333
FVC, L	1.62 (1.36-2.18; 0.73-3.23)	1.83 (1.35-2.33; 0.39-4.98)	0.561
FEV1, L	0.97 (0.62-1.36; 0.41-2.30)	0.78 (0.63-0.99; 0.28-3.21)	0.217
Renal replacement therapy	1 (4.8)	1 (0.6)	0.168
Mechanical ventilation	8 (38.1)	0	---
<i>Diagnosis</i>			
Cystic fibrosis	19 (90.5)	108 (63.9)	0.015
α1-antitrypsin deficiency	1 (4.8)	34 (20.1)	0.087
Pulmonary fibrosis/ILD	1 (4.8)	27 (16.0)	0.171
Preoperative ECMO duration (days)	8 (6.5-16; 1-52)	---	---
<i>Intraoperative characteristics</i>			
Bilateral lung transplant	21 (100)	162 (95.9)	---
Cardiopulmonary bypass	6 (28.6)	60 (35.5)	0.529
ECMO	15 (71.4)	12 (7.1)	<0.001
<i>Transfusion (24h)</i>			
Red blood cells, units	13.5 (8.2-41.8; 5-53)	4.0 (2.0-8.0; 0-71)	<0.001
Platelets, pools	3.5 (1.2-8.5; 0-21)	1.0 (0-2.0; 0-18)	<0.001
Fresh frozen plasma, units	6 (2.5-11; 0-37)	2.0 (0-4.5; 0-32)	<0.001
Cryoprecipitate, units	8 (38.1) (median 3.5 units)	27 (16.0) (median 2 units)	0.023

486 Data are median (quartiles; minimum-maximum) or count (percent)
 487 aPTT, activated partial thromboplastin time; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; FEV1,
 488 forced expiratory volume (1st second); FVC, forced vital capacity; ILD, interstitial lung disease; INR, international normalized ratio; VV,
 489 veno-venous.

490 ¹ Mann-Whitney U-test or likelihood ratio test

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494 **Table 6.** Early and mid-term postoperative outcomes – subgroups included in the sensitivity analysis.

Outcomes	BTT with VV-ECMO	non-BTT	<i>p</i> ¹
N	21	169	---
<i>30-day outcomes</i>			
30-day mortality	5 (23.8)	8 (4.7)	0.001
Postoperative ECMO	10 (47.6)	12 (7.1)	<0.001
ECMO duration, days	9 (1-15; 1-19)	3 (2-27.5; 2-49)	
Delayed chest closure	9 (42.8)	10 (5.9)	<0.001
Chest drainage 24h, mL	2225 (975-3450)	1125 (719-1750)	0.005
Surgical re-exploration	8 (38.1)	24 (14.2)	0.006
AKI requiring RRT	12 (57.1)	50 (29.6)	0.011
Tracheostomy	12 (57.1)	60 (35.5)	0.058
Chest infection	12 (57.1)	66 (39.1)	0.112
Sepsis	12 (57.1)	52 (30.8)	0.019
Stroke	0	7 (4.1)	---
ICU length of stay, days	19 (12-22.5; 1-52)	7 (3.5-21.5; 1-97)	0.013
<i>1-year all-cause mortality</i>	7 (33.3)	27 (16.0)	0.050
<i>Cause of death</i>			
Multiorgan failure	5/7 (71.4%)	13/27 (48.2%)	---
Primary graft dysfunction	1/7 (14.3%)	0	---
Acute rejection	0	1/27 (3.7%)	---
Chronic rejection	1/7 (14.3%)	5/27 (18.5%)	---
Infectious complication	0	5/27 (18.5%)	---
Other causes	0	3 (11.1%)	---

495 Data are median (quartiles; minimum-maximum) or count (percent)

496 AKI, acute kidney injury; BTT, bridge to transplantation; ECMO, extracorporeal mechanical oxygenation; ICU, intensive care unit;

497 RRT, renal replacement therapy; VV, veno-venous

498 ¹Mann-Whitney U-test or likelihood ratio test

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501 **Table 7.** Patients' preoperative and intraoperative characteristics, 30-day outcomes and 1-year mortality before
 502 and after matching – sensitivity analysis. Variables used for matching are shaded. Standardized mean
 503 differences <0.1 indicate irrelevant differences between BTT and non-BTT lung transplant recipients.

Characteristics	Before matching			After matching		
	BTT with VV- ECMO	Non-BTT	d	BTT with VV- ECMO	Non-BTT	d
N	21	169	---	21	169	---
<i>Preoperative</i>						
Age, years	30.5 (23-34.8)	38 (26-53)	-0.599	37.9±13.3	38.8±14.5	-0.079
Male gender	13 (61.9)	99 (58.6)	0.068	14 (66.8)	98.8 (58.5)	0.172
BMI, kg/m ²	20.2 (19-23)	20.6 (18.9-24.2)	-0.212	20.2 (18.6-21.6)	20.6 (18.8-24.1)	-0.365
Hemoglobin, g/L	84 (78-91)	132 (115-146)	-2.555	85 (82-92)	131 (111-144)	-2.354
Platelets <150 x10 ⁹ /L	11 (52.4)	9 (5.3)	1.093	2.8 (13.2)	22.2 (13.2)	0.000
Creatinine, μmol/L	58 (33-70)	57 (46-69.5)	-0.306	66 (53-70)	57 (46-68)	0.016
Cystic fibrosis	19 (90.5)	108 (63.9)	0.668	14 (66.8)	113 (66.8)	0.000
<i>Intraoperative</i>						
CPB	6 (28.6)	60 (35.5)	-0.149	3.9 (18.5)	60.4 (35.7)	-0.394
ECMO	15 (71.4)	12 (7.1)	1.751	17.1 (81.5)	12.3 (7.3)	2.245
<i>30-day outcomes</i>						
30-day mortality	5 (23.8)	8 (4.7)	0.567	1.6 (7.8)	11 (6.5)	0.048
Postoperative ECMO	10 (47.6)	12 (7.1)	1.140	13.0 (62.0)	14.7 (8.7)	1.342
Delayed chest closure	9 (42.8)	10 (5.9)	0.953	3.4 (16.5)	9.4 (5.6)	0.352
Chest drainage 24h, mL	2225 (975-3450)	1125 (719-1750)	0.727	975 (975-3450)	1150 (750-1925)	0.382
Re-exploration	8 (38.1)	24 (14.2)	0.565	3.2 (15.4)	27.9 (16.5)	-0.030
AKI requiring RRT	12 (57.1)	50 (29.6)	0.579	9.6 (45.7)	51.5 (30.5)	0.316
Tracheostomy	12 (57.1)	60 (35.5)	0.445	10.6 (50.8)	58.1 (34.4)	0.336
Chest infection	12 (57.1)	66 (39.1)	0.368	12.8 (60.8)	69.6 (41.2)	0.340
Sepsis	12 (57.1)	52 (30.8)	0.551	6.7 (31.8)	55.9 (33.1)	-0.026
Stroke	0	7 (4.1)	-1.405	0	6.6 (3.9)	-0.783
<i>1-year mortality</i>	7 (33.3)	27 (16.0)	0.411	2.6 (12.5)	30.5 (18.0)	-0.154

504 Data are count (percent), median (quartiles) or mean±SD.
 505 AKI, acute kidney injury; BMI, body mass index; BTT, bridge to transplantation; CPB, cardiopulmonary bypass; ECMO,
 506 extracorporeal mechanical oxygenation; RRT, renal replacement therapy, VV, veno-venous
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509 **Table 8.** Adjusted (for gender, body mass index and hemoglobin level) odds ratios and geometric means ratios
 510 (GMR)¹ (for chest drainage within the first 24 hours): BTT with VV-ECMO vs. non-BTT recipients in the
 511 matched subgroups – sensitivity analysis.

Outcomes	Frequentist		Bayesian		E-value ²
	OR (95%CI)	<i>p</i>	OR (95%CrI)	P(OR≠1)	
<i>30-day outcomes</i>					
30-day mortality	0.96 (0.06-14.3)	0.977	0.85 (0.06-9.68)	55.4%	---
Postoperative ECMO	10.3 (1.37-77.0)	0.023	12.8 (2.86-77.5)	99.99%	6.61; 2.27
Delayed chest closure	3.08 (0.85-11.2)	0.087	3.59 (0.52-21.7)	91.2%	---
Chest drainage 24h, mL	1.58 (0.80-3.10)	0.183	1.33 (0.64-2.94)	77.8%	---
Re-exploration	0.94 (0.17-5.04)	0.939	0.48 (0.17-5.10)	53.5%	---
AKI requiring RRT	2.11 (0.32-13.6)	0.432	2.15 (0.66-7.32)	89.9%	---
Tracheostomy	5.66 (1.19-26.9)	0.029	6.06 (1.79-20.9)	99.9%	4.36; 2.01
Chest infection	2.16 (0.42-11.3)	0.357	2.48 (0.75-8.00)	94.3%	---
Sepsis	1.44 (0.24-8.72)	0.690	1.53 (0.44-6.62)	73.4%	---
Stroke	---	---	---	---	---
<i>1-year mortality</i>	0.90 (0.17-4.91)	0.905	0.84 (0.11-5.53)	57.7%	---

512 AKI, acute kidney injury; ECMO, extracorporeal mechanical oxygenation; RRT, renal replacement therapy; VV, veno-venous
 513 ¹Chest drainage volume data were right-skewed and were ln-transformed. The BTT vs. non-BTT difference is geometric means ratio
 514 (GMR)= exp[mean ln(BTT) – mean ln(non-BTT)]

515 ²Lowest unmeasured confounder effect (on the relative risk scale) needed to shift the (Bayesian) point estimate (first value) or the
 516 lower limit of the 95% CrI to 1.0 (second value).
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