Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Should extracorporeal membrane oxygenation (ECMO) be used in the management of Acute Respiratory Distress Syndrome (ARDS) among COVID-19 patients?

Update by: Maria Cristina H. Lozada, MD, Vaneza Leah A. Espino, MD, Christopher G. Manalo, MD, Leonila F. Dans, MD, MSc

Initial review by: Belen L Dofitas, MD MSc, Paoline Nicole Villanueva, RMT, MD, Dan Louie Renz P. Tating, MS (cand), RN

RECOMMENDATION

We suggest the use of Extracorporeal Membrane Oxygenation (ECMO) for judiciously selected COVID-19 patients with severe Acute Respiratory Distress Syndrome (ARDS) based on the ELSO criteria. *(Very low certainty of evidence; Weak recommendation)*

PREVIOUS RECOMMENDATION

We suggest the use of VV-ECMO for judiciously selected COVID-19 patients with severe ARDS based on the ELSO criteria *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues
VV-ECMO is not indicated for all severe COVID-19 patients with ARDS. The general guidelines for the use of ECMO among non-COVID patients must be followed given that there are no guidelines for the use of ECMO among patients with COVID-19. Likewise, standard selection criteria, indications and contraindications should be followed in recommending the use of ECMO. The protocol for the treatment of severe ARDS must be followed. VV-ECMO is used once other modalities (e.g., proning, mechanical ventilation and lung protective strategies) did not work and the patients are qualified for ECMO.

There is a limited number of ECMO machines that are locally available. In addition, manipulation of this machine requires manpower, training and additional medical equipment. The use of ECMO must be judicious due to the considerable concern on the high cost and local availability of ECMO. ECMO is also used for the treatment of ARDS caused by leptospirosis and cytokine adsorption among COVID patients. The use of ECMO is included in the COVID fund and it costs around Php 2,000,000.00 per day, however, the costs are not fully covered. The results of ongoing trials are needed to show that the use of ECMO is effective and safe among patients with COVID-19 infection.

What's new in this version?

- Four cohort studies on the use of extracorporeal membrane oxygenation (ECMO) among patients with critical COVID-19 or COVID-19 acute respiratory distress syndrome (ARDS) were included in this review update.

Key Findings

Four cohort studies on the use of ECMO in adult patients with critical COVID-19 or COVID-19 ARDS were reviewed in this evidence update. Pooled results from four studies showed inconclusive mortality benefit with the use ECMO versus standard of care. In one study, occurrence of procedure-related infection reported as a serious adverse event was significantly associated with ECMO therapy. The certainty of evidence is very low because of the risk of bias attributed to lack of randomized studies, inconsistency due to significant heterogeneity, and imprecision due to small study sample sizes.

Introduction

In patients with COVID-19 acute respiratory distress syndrome (ARDS), severe hypoxemia complicated by respiratory or circulatory failure may persist despite optimal mechanical ventilation strategies.[1] Extracorporeal Membrane Oxygenation (ECMO) is indicated for patients with acute severe cardiac or respiratory failure with high mortality risk.[2] Initiation of ECMO in cases of COVID-19 ARDS refractory to mechanical ventilation and salvage therapy (such as prone positioning or nitric oxide) may lead to improvement in oxygenation and decrease in mechanical power through a homogeneous ultraprotective ventilation strategy.[3,4] Current practice takes into consideration referring patients with COVID-19 ARDS refractory to lung-protective ventilation for ECMO initiation. However, several practical concerns such as institutional ECMO capability, trained personnel availability, and costs should be considered prior to its initiation. Latest guidance from Philippine COVID-19 Living Clinical Practice Guidelines suggested the use of ECMO for judiciously selected COVID-19 patients with severe ARDS based on very low certainty of evidence. Given the evidence gap and local resource limitations on the use of ECMO, this review aims to update and summarize current literature on outcomes associated with the use of ECMO among COVID-19 patients with severe ARDS.

Review Methods

An exhaustive literature search was conducted in PUBMED, Cochrane Library, clinicaltrials.gov and MedRxiv (for pre-print articles) databases for articles relating to the use of ECMO in patients with COVID-19. The following keywords were used in the search: "extracorporeal membrane oxygenation", "acute respiratory distress syndrome", "COVID-19" and "cohort". No restrictions were applied as to the language or date of publication. The retrieved titles and abstracts were screened for possible inclusion. Studies which determined the use of ECMO on COVID-19 ARDS or critical COVID-19 and its outcomes in terms of mortality and/or adverse events were retrieved for full-text review. Irrelevant studies which did not address the PICO question, case reports, case series, systematic reviews, and commentary articles were excluded. Four full-text articles were reviewed and included in the qualitative and quantitative analysis. The PRISMA Flow Diagram [5] is shown in Figure 1 (see Appendix 2). The quality of the included studies was evaluated based on the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort Studies.[6]

Results

Four cohort studies compared a total of 1,301 adult patients with critical COVID-19 and COVID-19 ARDS who received ECMO and standard of care with 16,548 adult patients with critical COVID-19 and COVID-19 ARDS who received standard of care alone without ECMO therapy [7-10]. In three studies [7-9], venovenous ECMO (VV-ECMO) was used. In one study, [10] the type of ECMO therapy used was not explicitly specified. The studies were done in China [7,8] and the USA [9,10]. Characteristics of included studies are presented in detail in Table 2 (see Appendix 3). The general methodological quality of the included studies was assessed to be of good quality based on the NHLBI quality assessment tools.

All-Cause Mortality

Pooled analysis from four cohort studies [7-10] showed inconclusive reduction in all-cause mortality with the use of ECMO (RR 0.70, 95% CI 0.47-1.07; I2=95%; very low certainty). In two studies [7,10], younger age was found to have lower mortality rates. The cohort study by Cheng and coworkers [7] demonstrated that in-hospital mortality among patients with critical COVID-19 placed on ECMO was significantly lower compared to patients who were not placed on ECMO and received standard of care (RR 0.84, 95% CI 0.71-0.99; low certainty). In this study, patients who were placed on ECMO were significantly younger compared to those who did not receive ECMO (58 versus 66 years old, $p<0.003$). Similarly, the cohort study by Nguyen and colleagues [10] reported that in-hospital mortality was found to increase with age. Patients under 30 years old who received ECMO had the lowest in-hospital mortality (34/125, 25.2%). In-hospital mortality rates were higher in the 31-50 (232/550, 42.2%) and 51-64 (234/440, 53.2%) age groups. Patients aged 65 years old and above had the highest in-hospital mortality rate (42/57, 73.7%).

Other Outcomes: Length of Hospital Stay, & Direct Cost

The mean length of stay was longer for ECMO (37.1±24.9 days) versus the non-ECMO (23.1 ±18.8 days) group (MD 14.0 days, 95% CI 12.51-15.49; low certainty). Direct hospitalization cost was likewise higher in the ECMO group ($138,403 ±99,173) compared to the non-ECMO ($48,419 ± 44,799) group (MD $89,984.00, 95% CI $84,117.34-95,850.66; low certainty).[10]

Adverse Events

In the study by Cheng et al. [7], the presence of bacterial co-infections was observed in 34/74 patients (45.9%) compared to 26/94 patients (27.7%) among those who received ECMO and those who received standard of care, respectively (RR 1.66, 95% CI 1.10-2.50; very low certainty).[7] On the other hand, Li et al. [8] reported that of the 34 patients with COVID-19 who were placed on ECMO, bleeding at different sites (intracranial, gastrointestinal, pulmonary or airway) was observed in 26/34 patients (76.4%), infections in eight patients, and pneumothorax in four cases. The study did not provide a comparison of the adverse events for the non-ECMO group.

Summary of Certainty of Evidence

The GRADE evidence profile is shown in Appendix 4. The certainty of evidence was very low because of the risk of bias attributed to non-randomized study designs, inconsistency due to significant heterogeneity, and imprecision. Significant heterogeneity may be attributed to several clinical factors such as patients' age, duration of ECMO therapy, duration of mechanical ventilation prior to ECMO initiation, differences in institutional ECMO protocols, and co-interventions (see Appendix 5).

At present, a nationwide cohort study on the use of ECMO as a therapeutic option in severe COVID-19 is being conducted in France [11]. The characteristics of this study are shown in Table 3 (see Appendix 6). No ongoing clinical trials were identified at the time of this review.

Evidence to Decision

In dedicated ECMO referral institutions, patients with severe COVID-19 ARDS who are not clinically responding to optimal lung protective ventilation may safely be initiated on ECMO.[4] However, hospital capability should be considered prior to ECMO initiation.[12] Cost of ECMO initiation and daily use should also be considered. The average direct cost for adult COVID-19 patients who were managed with ECMO therapy was $138,403.00.[10] Thus, practical considerations should include the availability and capacity of medical centers equipped with facilities and specialized personnel or teams for ECMO and the financial limitations for patients and their families.

Recommendations from Other Groups

According to the Extracorporeal Life Support Organization (ELSO) guidelines for ECMO use in COVID-19, contraindications for ECMO use should become more stringent as ECMO capacity diminishes. Based on the ELSO guidelines, ECMO should not be initiated for patients with end-stage chronic organ failure without anticipated recovery and who are not candidates for durable device or transplant, in severe acute multiple organ failure with anticipated death despite ECMO support, and in severe acute neurologic injury with poor prognosis for recovery. Potential additional contraindications also include long invasive mechanical duration of more than 10 days, patient or surrogate refusal of blood products, inability to receive systemic anticoagulation, ongoing cardiopulmonary resuscitation, significant underlying comorbidities, advanced age, and immunocompromised condition.” [12]

The World Health Organization (WHO) living guidance on COVID-19 recommended that in settings with adequate ECMO resources and expertise, a consideration of referring patients with refractory hypoxemia for initiation of ECMO should be made.[13]

The Australian guidelines on COVID-19 gave a conditional recommendation on the use of ECMO for adult patients with critical COVID-19. The decision regarding ECMO initiation should consider the preferences and values of the patients as well as the benefits and risks associated with this form of invasive and resource-intensive treatment [14].

Research Gaps

Presently, there are no randomized controlled trials on the use of ECMO for patients with critical COVID-19. There is also a lack of evidence on long-term clinical outcomes, including pulmonary function, of patients who were successfully discharged after ECMO therapy.

References

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=5)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (5)					• Initiation of ECMO in cases of COVID-19 ARDS refractory to mechanical ventilation and salvage therapy may lead to improvement in oxygenation.
Benefits	Large (1)	Moderate (2)	Small (1)	Uncertain (1)			• Reduction in all-cause mortality (RR 0.70; 95% CI 0.47, 1.07; I2=95%; Very Low Certainty)
Harm	Large (2)	Small (1)	Uncertain (2)	No response			• The presence of bacterial co-infections was observed in 34/74 patients (45.9%) compared to 26/94 patients (27.7%) who received ECMO and those who received standard of care, respectively (RR1.66, 95% CI 1.10, 2.50) Cheng et al. [7]
Certainty of Evidence	High	Moderate	Low (2)	Very low (3)			• Very low: risk of bias attributed to lack of randomized studies, inconsistency due to significant heterogeneity, and imprecision due to small study sample sizes.
Balance of effects	Favors drug (5)	Does not favor drug	Uncertain				
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (5)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• Direct hospitalization cost was higher in the ECMO group ($138,403 ±99,173) compared to the non-ECMO ($48,419 ±

							44,799) group (MD $89,984.00; 95% CI $84,117.34,95,850.66; Low Certainty) [10]
Certainty of evidence of required resources	No included studies	Very low (1)	Low (3)	Moderate (1)	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (1)	Reduced (2)	Probably no impact	Increased (2)			
Acceptability	Uncertain (2)	No	Yes (3)				
Feasibility	Uncertain (5)	No	Yes				

Appendix 2. Search Yield and Results

SEARCH Strategy for Extracorporeal Membrane Oxygenation in COVID-19
Date of Last Search: 09 November 00:38H

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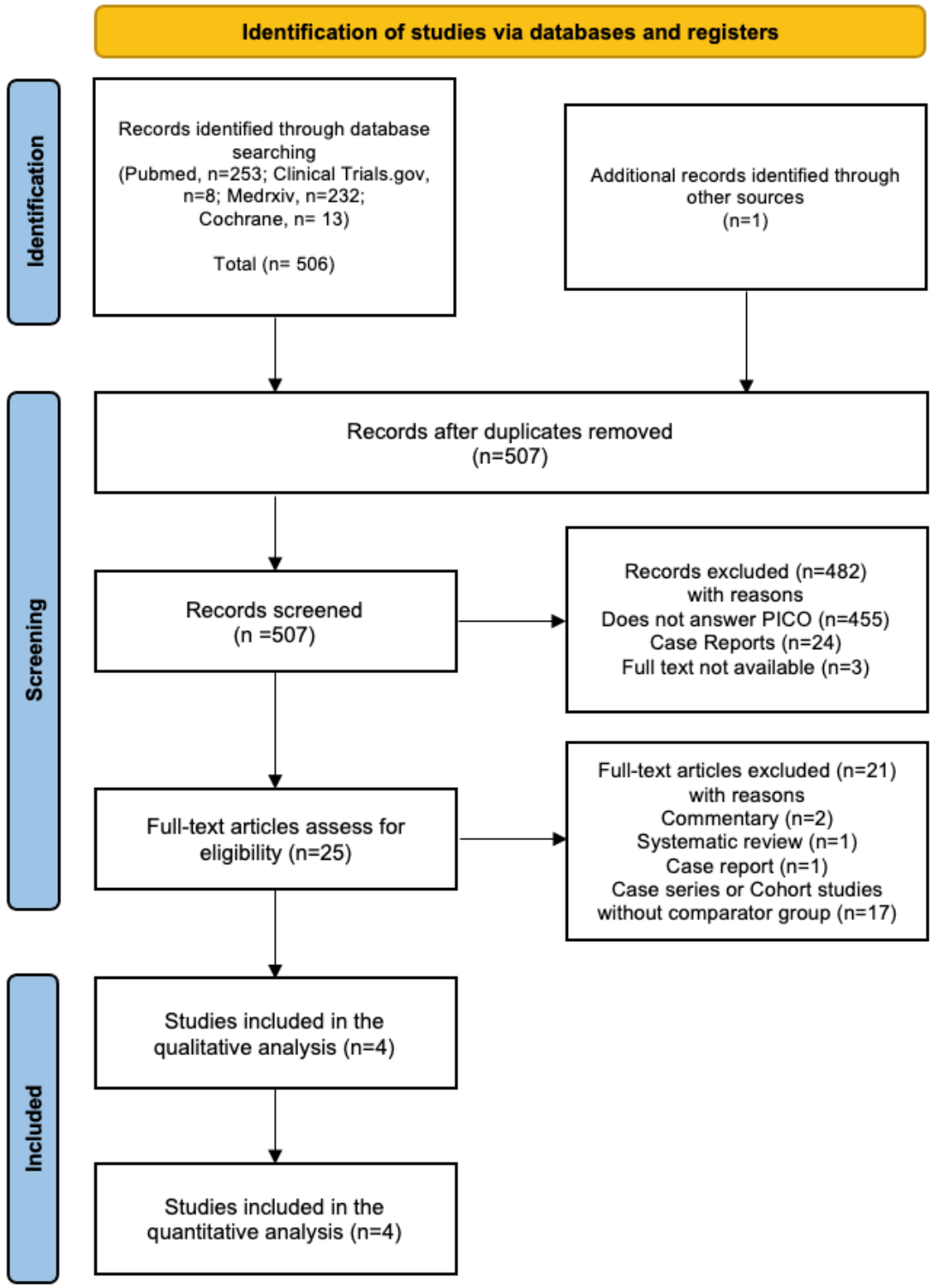
#1	Search: **extracorporeal membrane oxygenation** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields] **Translations** **extracorporeal membrane oxygenation:** "extracorporeal membrane oxygenation"[MeSH Terms] OR ("extracorporeal"[All Fields] AND "membrane"[All Fields] AND "oxygenation"[All Fields]) OR "extracorporeal membrane oxygenation"[All Fields]	18,102	10:34:31

Figure 1. PRISMA Flow Diagram



Appendix 3. Characteristics of Included Studies

Table 2. Study Characteristics of Included Studies (n=21)

Study ID Title Author	Study Design	Setting /Country	Population	Intervention	Comparator/Control	Outcomes
Cheng 2021 [7]	Retrospective Cohort	Wuhan, China	Patients with critical COVID-19	VV ECMO (n=74)	Standard of Care + No ECMO (n=94)	**Mortality** In-hospital mortality ECMO=53/74 (71.6%) Non-ECMO=80/94 (85.1%) **Length of Stay** Length of Hospital Stay ECMO=32 (16-45) days Non-ECMO= 21.5 (12-34) Length of ICU stay ECMO=21 (12.75-33) Non-ECMO=15 (5-30) **Adverse events** Co-Infection ECMO=34/74 Non-ECMO=26/94 RR=1.4530 95% CI 0.9362, 2.2549 P=0.0957
Li 2021 [8]	Retrospective Cohort	Wuhan, China	patients with critical COVID-19	VV ECMO (n=34)	Conventional Ventilatory Support (n=31)	**Mortality** In-hospital mortality ECMO=20/34 (58.8%) Non-ECMO=29/31 (93.5%)
Mustafa 2021 [9]	Prospective Cohort with Propensity-Matching	Illinois, USA	Patients with Critical COVID-19	VV ECMO(n=80)	Maximum Ventilatory Alone (MVA; n=80)	**Mortality** Overall mortality ECMO=20/80 (25%) MVA=59/80 (93.5%) Discharged alive ECMO=54/80 (67.5%) MVA=21/80 (26.3%)
Nguyen 2021 [10]	Retrospective Cohort	California, USA	Patients with COVID-19 ARDS	ECMO (n=1113)	Standard of Care + No ECMO (n=16,343)	**Mortality** In-hospital mortality ECMO=497/1113 (44.7%) No ECMO=6191/16,343 (37.9%) **Length of Hospital Stay** Mean Hospital LOS ECMO=37.1±24.9 Non-ECMO=23.1±18.8 Cost ECMO=$138,403 ±99,173 No ECMO=$48,419 ± 44,799

Appendix 4. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ECMO	standard of care	Relative (95% CI)	Absolute (95% CI)		
Mortality												
4	observational studies	serious[a]	serious[b]	not serious	serious[b]	none	590/1301 (45.3%)	6359/16548 (38.4%)	**RR 0.70** (0.47 to 1.07)	**115 fewer per 1,000** (from 204 fewer to 27 more)	⨁◯◯◯ Very low	CRITICAL
Mean Length of Stay												
1	observational studies	serious[a]	not serious	not serious	not serious	none	1113	16343	-	MD **14 days higher** (12.51 higher to 15.49 higher)	⨁⨁◯◯ Low	CRITICAL
Direct Cost												
1	observational studies	serious[a]	not serious	not serious	not serious	none	1113	16343	-	MD **89984 USD higher** (84117.34 higher to 95850.66 higher)	⨁⨁◯◯ Low	CRITICAL
Adverse Events: Bacterial Infection												
1	observational studies	serious[a]	not serious	not serious	serious[c]	none	34/74 (45.9%)	26/94 (27.7%)	**RR 1.66** (1.10 to 2.50)	**183 more per 1,000** (from 28 more to 415 more)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. non-randomized studies
b. significant heterogeneity
c. small sample sizes / optimal information size not met

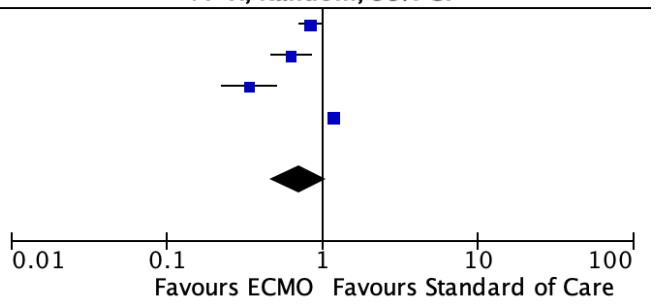
Appendix 5. Forest Plot

Figure 2. Forest Plot of Pooled Studies on Mortality among patients with COVID-19 who were placed on ECMO versus Standard of Care

Study or Subgroup	ECMO Events	ECMO Total	Standard of Care Events	Standard of Care Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheng 2021	53	74	80	94	26.4%	0.84 [0.71, 0.99]
Li 2021	20	34	29	31	24.2%	0.63 [0.47, 0.85]
Mustafa 2021	20	80	59	80	21.9%	0.34 [0.23, 0.51]
Nguyen 2021	497	1113	6191	16343	27.4%	1.18 [1.10, 1.26]
Total (95% CI)		**1301**		**16548**	**100.0%**	**0.70 [0.47, 1.07]**
Total events	590		6359			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 59.88$, df = 3 ($P < 0.00001$); $I^2 = 95\%$

Test for overall effect: Z = 1.65 (P = 0.10)



Appendix 6 - Study Characteristics of Ongoing Studies

Table 3. Study Characteristics of Ongoing Studies (n=1)

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
Extracorporeal Membrane Oxygenation (ECMO) as a Therapeutic Option in Severe Form of COVID-19: a Nationwide Cohort Study France NCT04397588 [11] Ongoing recruitment	VV or VA ECMO	None	All COVID-19 patients, adults or children, Tested positive by RT-PCR for SARS-CoV2 (nasopharyngeal swabs, sputum, endotracheal aspiration, bronchoalveolar lavage or stool sample) and / or with a diagnosis made on chest CT findings, Supported by venovenous or venoarterial ECMO	Primary Outcome Measures : 1. Hospital mortality (Time Frame: up to 90 days) Secondary Outcome Measures : 1. Mortality Day 28 2. Mortality Day 90 3. Ventilator-free days 4. Intensive care unit-free days 5. Hospital-free days