Economic Evaluation of VV-ECMO for Severe Acute Respiratory Distress Syndrome

Kali A Barrett

Neil Hawkins

Eddy Fan

Online Data Supplement

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# Cohort State Transition Model

For the cost-utility analysis a cohort state transition model was constructed to determine total costs and quality-adjusted life years (QALYs) associated with VV-ECMO and the comparator. The three health-states used in the model were: 1) ARDS; 2) Recovered; and 3) Dead. The target population is adults with severe ARDS aged 45 years old. This is the mean age of patients in the literature used to inform treatment efficacy, suggesting that patients of this age are most likely to be considered for VV-ECMO in real-world situations(1-3). Patients started in the ARDS health-state, which was assumed to include the acute illness period including hospitalization, time spent in the intensive care unit (ICU), as well as the acute recovery period up to one year. The cohort transitioned to the Recovered or Dead health-states based on the efficacy of treatment used for ARDS. Those who survived ARDS remained in the Recovered health-state until they progressed to death based on annual transition probabilities of death reflecting population norms for the age of the patient while in the cycle. We assumed that ARDS is a “one-hit” disease with no long-term incremental impact on mortality. This was supported by recent analysis of the long-term outcomes in a cohort of Canadian survivors of ARDS which showed that death beyond 6 months in this cohort was due to causes unrelated to ARDS(4). Death was an absorbing state. Transition between states, and the accumulation of costs and QALYs gained during the cycle occurred at the end of the cycle. Half-cycle corrections were not performed.

Although the immediate hospitalization and ICU stay associated with an episode of ARDS is typically less than a year, the immediate recovery and rehabilitation process takes months(4). Cycle length for the model was set at one year. This corresponded to the time interval at which mortality rates were reported and the time point at which post-ICU admission costs and quality of life were reported (5, 6). Successive cycles were run until 99% of patients in the cohort had entered the dead health-state. Deterministic sensitivity analyses and probabilistic sensitivity analyses using Monte Carlo simulation were performed to determine the degree of uncertainty around the model and its results. The results of the probabilistic sensitivity analysis were displayed on the cost-effectiveness plane, with each point on the graph representing the ICER of VV-ECMO compared to lung protective ventilation for one of the 30,000 simulations. Each simulation was conducted with different model parameters drawn randomly from the range of possible values for the stochastic variables.

## Model Parameters

The allocation of parameter values for the cycles are displayed in **Table E1** (Supplemental Digital Content 2, http://links.lww.com/CCM/E51).

## Transition probabilities

### From the ARDS State

To determine the baseline probability of death for the comparator therapy and treatment effect of VV-ECMO therapy, a literature search was conducted to identify studies describing the efficacy of VV-ECMO for ARDS compared to lung-protective ventilation. Two systematic reviews and meta-analyses were identified that describe the treatment effect of ECMO for patients with severe ARDS: one by Munshi et al. published in 2014, and one by Zampieri et al. published in 2013(7, 8). Please see **Table E2** (Supplemental Digital Content 3, http://links.lww.com/CCM/E52) for details regarding the two meta-analyses. Both of these meta-analyses limited studies to those that were of high quality, reported results for patients who received VV-ECMO, and reported the use of lung protective ventilation in the comparison group, thus meeting the requirements of this economic evaluation. They both identified the same three studies that met their criteria inclusion: the 2009 CESAR randomized control trial by Peek et al., and two observational cohort studies of A(H1N1) patients published by Pham et al. in 2013, and Noah et al. in 2011(1-3). The two meta-analyses differed in the way they pooled patients for analysis based on matching used in the observational trials, and whether the outcomes were analysed using per-protocol versus intention-to-treat analysis for the randomized control trial. Please see Table E2 (Supplemental Digital Content 3, http://links.lww.com/CCM/E52) for a summary of how patients were pooled in the different analyses.

In order to identify more recent relevant randomized control trials or observational studies, MEDLINE, EMBASE and CENTRAL electronic databases were searched from September 2013 to July 2015 using the same strategy described by Munshi et al.(7). Inclusion criteria were pre-defined and limited to studies that: 1) enrolled adult patients with severe ARDS, 2) compared VV-ECMO to lung-protective mechanical ventilation, and 3) used mortality as an outcome. The electronic database search retrieved 150 citations, of which 3 were retrieved in full text for additional review. None of these studies met criteria for inclusion: one did not report results for patients who received ECMO, one was not limited to VV-ECMO, and one did not report the use of lung-protective ventilation in the comparison group(9-11). Therefore, no additional studies were incorporated into the meta-analysis.

The probability of death from ARDS with lung-protective ventilation and the treatment effect of ECMO for the base case analysis were based on the VV-ECMO analysis presented by Munshi et al.(7). This meta-analysis reported a relative risk of death of 0.64 (95% CI 0.51-0.79) with the use of VV-ECMO for patients with severe ARDS compared to lung-protective mechanical ventilation and incorporated data from the CESAR trial and two observational cohort studies(1-3).

This analysis was chosen for several reasons. First, it used per protocol analysis of the results of the CESAR trial, meaning it only included patients from the ECMO arm of the CESAR trial who had received VV-ECMO. It was also selected because it pooled patients from the two observational studies according to the GenMatch method. The GenMatch method has been argued as superior to propensity score matching when using matched samples for cost-effectivness analyses using non-randomised samples and randomized control trials(12). Sekhon et al. describe that the method “automates the process of maximizing balance on observed covariates in the matched sample…by performing multivariate matching using an evolutionary search algorithm to determine the weight each individual covariate is given”(12). It thereby reduces the likelihood of bias resulting from an imbalance of covariates and confounders(2). Munshi et al. report that their analysis using the GenMatch pooling technique resulted in “the most inclusive cohort of patients undergoing ECLS”(7). Therefore this analysis likely had less bias and confounding, in addition to being more generalizable to real-world situations. The results of this meta-analysis revealed a baseline probability of death for those with ARDS receiving standard lung-protective ventilation of 0.52, with a treatment effect of VV-ECMO therapy as a risk ratio of 0.64 (95% CI 0.51-0.79)(7). The baseline probability of death reported in the meta-analysis was assigned as the transition probability from ARDS to death for the mechanical ventilation cohort. The probability of death from ARDS for the ECMO cohort was calculated by multiplying the baseline probability of death by the treatment effect (0.52 x 0.64 = 0.33)(13).

The three primary studies incorporated into the meta-analysis reported all-cause mortality for patients; therefore, the probabilities of death were assumed to include both the background age-related probability of death for patients, in addition to the additional deaths associated with ARDS and treatment failure. The three studies reported different time points for all-cause mortality: 90 days, 6 months, and in-hospital(1-3). In the absence of sufficient evidence to further inform time-to survival, it was assumed that those who survived ARDS, survived for the length of the entire one-year cycle they spent in the ARDS Markov state, and that those who died did so at the six-month point in the cycle. This assumption was supported by observations that non-survivors of ARDS died within the first 6 months of their illness(5, 14).

During the process of revising this paper, the results of the EOLIA study were released(15). We considered attempting to pool the results of this trial with those from the Munshi analysis. However, the results of the EOLIA study are challenging to pool as a large percentage (28%) of the control group, who appeared to have more severe ARDS, crossed over to the VV-ECMO group and received ECMO as a rescue therapy(15). We therefore chose to incorporate the EOLIA results as a sensitivity analysis using the intention-to-treat 60 day mortality as the transition probability for the ARDS to Recovered or Dead health-states for patients in the VV-ECMO and standard lung protective mechanical ventilation cohorts.

### From the Recovered Markov States

Transition probabilities from the Recovered Markov state to death were allocated according to the age of the patient in each successive cycle, and based on age and sex-specific annual transition probabilities reported in the Canadian Life Tables(16). The simulation was run separately for cohorts of male and female patients using the sex-specific annual transition probabilities, and the results were pooled for analysis.

## Utility Values

A literature search was conducted to identify utility values for ARDS patients who had received conventional lung-protective mechanical ventilation and VV-ECMO. Results of the literature search did not identify an abundance of data to inform utility values for this analysis. The CESAR trial collected EQ-5D data from patients at 6 months post-randomization to inform their cost-utility analysis, but did not report the mean utility values(3). The study reported that there was no significant difference in EQ-5D scores between patients randomized to referral to an ECMO center and patients randomized to conventional treatment(3).

A French study was identified that reported one-year outcomes in patients with ARDS secondary to the pandemic influenza A(H1N1)(17). The patients in this study were drawn from the same registry of A(H1N1) patients used to derive the cohorts for the French observational study of A(H1N1) patients described above(1). This study did not report preference-based health-related quality of life utility values. However, they did report mean scores from the non-preference based Short Form-36 (SF-36). Similar to the results reported by the CESAR trial, they found no statistically significant difference in SF-36 scores between patients who received ECMO therapy compared to those who received conventional mechanical ventilation(17). Based on these two studies, it was assumed that health-related quality of life in ARDS survivors was not affected by treatment with ECMO, and utility scores for ARDS survivors who had received mechanical ventilation could also be applied to those who received ECMO therapy.

Only one study was identified that reported preference-based utility values in survivors of ARDS. This study was conducted in Australian patients who had survived ARDS secondary to the 2009 pandemic Influenza A(H1N1) outbreak(6). The patients in this study received both ECMO therapy and conventional lung-protective ventilation, however, utility values were not reported separately for the two groups. The study used the Assessment of Quality of Life (AQoL-4D) scale, which is a multi-attribute scoring tool that measures health-related quality of life across five domains: Psychological Well-Being, Social Relationships, Physical Senses, Independent Living, and Illness(18). Utility weights were derived using the time trade-off method in a representative sample of the Australian population(19). The tool has been validated in the critical care setting(20). The mean utility weight reported for the cohort of ARDS survivors at 6-months post ICU discharge was 0.66 (95% CI 0.53-0.79), and was 0.68 (95% CI 0.58-0.78) at 12-months post ICU discharge(6).

Patients with ARDS were assumed to enter the model with a utility value of zero. The utility weight assigned to the survivors of the ARDS Markov state was taken as the 6-months post-ICU discharge utility value reported by Skinner et al.(6). Those who died were assumed to have made no health-related quality of life gains, and assigned a utility value of 0 for their time spent in the ARDS state. This was based on the clinical knowledge that death from ARDS most often occurs when patients are comatose, intubated and mechanically ventilated, which is similar to their quality of life at the initiation of therapy.

The utility value for survivors of ARDS at 12-months post ICU discharge reported by Skinner et al was allocated to the first cycle in the Recovered health-state.

The allocation of utility values for the second to fifth cycles in the Markov state was based on assumptions. The authors of the economic evaluation for the CESAR trial assumed that health-related quality of life in ARDS survivors gradually improved, and that by two-years post ICU discharge, survivors would have attained a quality of life as could be predicted by the age and sex-based norms for the UK population(21). This assumption likely overestimated quality of life for ARDS survivors. The largest and most comprehensive follow up study of ARDS patients published outcome data for a cohort of ARDS patients five years after ICU discharge(5). This study showed that ARDS survivors experienced gradual improvements in quality of life over the first five years after discharge from the ICU. However, at five years post discharge they still had a small residual deficit in health-related quality of life, with mean scores on the physical component section of the SF-36 tool one standard deviation below age and sex-matched population based values(5). Therefore, for this analysis it was assumed that survivor quality of life gradually increased over time and would return to a level predicted by population-based normative data, but that this would not be achieved until the sixth cycle in the Recovered Markov state. Utility values for the second to fifth cycles of the Recovered Markov state were calculated based on a linear increase from the 12 month utility value reported by Skinner et al. assigned to the first cycle in the Recovered state, to the Canadian age-based population normative utility value that was assigned to the sixth cycle in the Recovered state.

Subsequent cycles in the Recovered Markov state were assigned utility values according to age-related normative values derived from the Canada National Population Health Survey(22). These utility values were derived using the Health Utilities Index Mark 3 (HUI3), which is a widely accepted, preference-based utility scoring tool based on preferences derived from a Canadian population(22, 23).

## Costs

Treatment costs for ARDS and recovered states were identified by literature search.

Mean healthcare costs for the first six months of therapy during the ARDS cycle were obtained from the CESAR Trial(3). The mean health care costs up to six months post hospitalization were reported as £73979 for the ECMO group, and £33435 for the conventional management group(3). Costs were reported in 2005 GBP. These costs were based on the results of a concurrent multicenter study of critical care expenditure that determined case-mix-adjusted average daily costs for critical care patients based on the number of organs being supported(3). Reported costs included those accrued as a result of hospitalization, for the transport of patients to the ECMO center, staffing, capital expenditure required for equipment, rehabilitation, psychological counseling and outpatient nursing care(21, 24). Hospital overhead and trial-related costs were not included(21, 24).

Mean costs reported for the conventional mechanical ventilation arm of the CESAR trial were taken as the costs for the first six months in the ARDS cycle for the cohort receiving mechanical ventilation. The mean healthcare costs reported for the ECMO group included 24% of patients who never went on to receive ECMO therapy, therefore this value is likely an underrepresentation of the true costs associated with ECMO therapy. To better estimate the true costs of ECMO therapy, the average cost of ECMO therapy was recalculated assuming that the 24% of patients in the ECMO arm who did not receive ECMO had contributed costs equaling the mean costs reported for the comparison arm of the trial [73,979=(0.76\*C\_ECMO)+(0.24\*33,435)]. This new calculated value for mean healthcare costs of ECMO was £86,782.37.

A study by Herridge et al. reported health care costs that were accumulated by ARDS patients from hospitals in Ontario, Canada over the five years following their initial hospitalization(23). These survivors required additional medical care and rehabilitation for complications of their critical illness such as: tracheal stenosis secondary to tracheal intubation, soft tissue injuries due to pressure sores, physical deconditioning, and critical illness neuropathies and myopathies(5). The costs reported in this trial were ascertained via prospective data collection of health-care resource use, and allocation of average unit costs based on Canadian and Ontario reference pricing(25). Costs were reported in 2009 Canadian dollars. The study reported mean health-care costs for the time period spanning after the initial hospitalization up to one year, and for each of the next four years(5).

The six-month mean costs for the provision of ECMO and lung protective mechanical ventilation reported in the CESAR trial were assigned to the first six months of the ARDS Markov state. It was assumed that the only increase in costs associated with the provision of ECMO therapy occurred during this initial six-month period. Any additional health-care costs associated with the treatment of ARDS would be the same for those who received ECMO or standard lung-protective mechanical ventilation. The costs assigned to the second six months in the ARDS Markov state were taken from the reported mean costs in the Canadian study from the time point after initial hospitalization up to one-year post admission(5). It was assumed that these costs were accrued between six and 12 months post hospital admission. For the model it was previously assumed that non-survivors of ARDS died at the six-month point in the cycle, and therefore would only accumulate the costs associated with the first six months in the health-state. It was assumed that patients who survived ARDS accumulated costs associated with the entire 12 months spent in the ARDS state. The mean costs reported at 2, 3, 4 and 5 years post hospitalization by Herridge et al. were allocated to the first four cycles in the Recovered state(5).

Average healthcare costs in the fifth and subsequent cycles in the Recovered state were based on data reported by Wodchis et al., which estimated the total attributable health care spending per resident of Ontario from 2009-2011, and categorized patients into percentiles based on the number of dollars spent on their care(26). In Herridge’s cohort, mean health care costs accrued by ARDS survivors four and five years post hospitalization are consistent with the values representing the 95th percentile in Wodchis’ paper. Based on this, an assumption was made that survivors of ARDS continue to have high cost health care needs, consistent with those among the top 5% of health care users. The cost threshold for the top 5% cost category for adults aged 18-64 was used as the cycle costs until the cohort was aged 65(26). It was assumed that ARDS survivors gradually recover and that their health care costs return to population norms by the age 65. For cycles beyond age 65, the median annual healthcare costs for adults over 65 years was used as the cycle costs(26). Mean costs per patient were not reported so the median cost was used.

All costs were converted to a common currency using best practices(23, 27, 28). Costs reported in GBP were converted to 2016 GBP using the World Bank GDP Deflator and converted to Canadian Dollars using Purchasing Power Parity conversion rates published by the World Bank(29, 30). Costs reported in Canadian Dollars were converted to 2016 Canadian Dollars using the World Bank GDP Deflator(29).

# Collection of Costs and QALYs

To determine total lifetime costs and QALYs associated with ECMO therapy, the state transition cohort model was run for a cohort of 1,000 male and female patients using the ECMO-specific model parameters. To determine the total lifetime costs and QALYs associated with lung-protective mechanical ventilation, the model was run for a cohort of 1,000 male and female patients using the comparator model parameters. This data was used to calculate the ICER for ECMO therapy compared to conventional lung-protective mechanical ventilation.

# Uncertainty

Sensitivity analyses were undertaken as a part of this analysis to explore the relationship between uncertainty and the robustness of the results. The ISPOR-SMDM classifications of uncertainty and best practices recommendations were used to inform the sensitivity analyses for this evaluation(31).

## Deterministic Sensitivity Analyses

To determine how the outcomes of the model changed based on parameter variation, one-way deterministic sensitivity analyses (DSA) were performed. The model was re-run with a different value for one or more parameters of the model, holding the other parameters unchanged. The results of the DSA are shown in **Table E3** (Supplemental Digital Content 4, http://links.lww.com/CCM/E53).

To explore the how changes in the efficacy of ECMO therapy affected the outcome of the model, a one-way DSA exploring this parameter were performed. A DSA was performed using the high and low values of the 95% confidence intervals for the relative risk reported in the meta-analyses by Munshi et al. Additional DSA were performed using the efficacy data of VV-ECMO as reported in the three analyses presented in the meta-analysis by Zampieri et al.(8). The transition parameters from ARDS to Recovered state were calculated from this data using the same method used for the base case analysis. As mentioned above, we also ran a DSA using the results of the EOLIA trial. Specifically, we used the intention-to-treat 60 day mortality as the transition probability for the ARDS to Recovered or Dead health-states for patients in the VV-ECMO and standard lung protective mechanical ventilation cohorts(15).

The costs associated with the initial treatment of ARDS, as well as the ongoing long-term rehabilitation and related healthcare costs were analyzed in a one-way DSA as these contributed all of the costs to the analysis. There was no data reported on the variance or distribution of these costs, therefore a plausible range of estimates of 50% higher and 20% lower for all costs were used(23).

The utilities reported at 6 and 12 months post hospitalization were included in a one-way DSA as they were the basis from which the utility parameters for the following four cycles were calculated, and therefore may have introduced a great deal of uncertainty into the model. The high and low values of the 95% confidence intervals of the parameter were used for these analyses, and the utility values for the subsequent four cycles in the Recovered state recalculated using these new values.

The variation in the discount rate was explored using values of 0% and 3%, as recommended in the Canadian reference case(28, 32).

Parameters of population normative health related quality of life and life expectancy were not subjected to sensitivity analyses, as they were based on very large sample sizes, had extremely small 95% confidence intervals, and were therefore felt to have the least sampling variability and associated uncertainty(16, 22).

## Probabilistic Sensitivity Analysis

To simultaneously assess the effects of uncertainty across all the stochastic model parameters, a probabilistic sensitivity analysis was performed. Model parameters were assigned a plausible range of values. Transition probabilities, utility values and costs were assumed to be stochastic. Discount rates and probabilities of death and utility values derived from Canadian population data were considered deterministic and not assigned distributions for the PSA.

The model parameters were assigned distributions as follows. Transition probabilities are binomial, can only fall between the range of 0 and 1, and were therefore assigned a beta distribution(13). The values for alpha and beta were determined from the number of events and total observations reported in the meta-analysis as described by Briggs et al.(13). As the values were far from zero, a pragmatic approach was used to assign the beta distribution to the utility values for ARDS survivors at 6 and 12 months(13). The standard error was calculated from the range of the 95% CI, and the method of moments approach described by Gray et al. was used to estimate the alpha and beta values for the distribution(23). Costs by definition are bound by zero and infinity, and were thus assigned a gamma distribution as recommended by modeling best practices(13). There was no reported variance for the costs used to inform the model parameters. Therefore, as Briggs et al. suggests in this scenario, the assumption was made that the standard error of the costs is equal to the mean, and the alpha and beta values for the distribution were determined by the method of moments approach(13).

Parameter values were randomly selected from the possible range of values, and simultaneously propagated through the model using Monte Carlo simulation. The simulation was run 30,000 times. The mean of the 30,000 results from the Monte Carlo simulation was determined, and compared to the value from the base case analysis. The results of the PSA were plotted on the cost-effectiveness plane (**Fig. E1**, Supplemental Digital Content 5, http://links.lww.com/CCM/E54). In order to expand the generalizability of the results, no single cost-effectiveness threshold was used, and the expected value of information was therefore not presented(28, 31, 32). Instead, the results of the PSA were plotted on the cost-effectiveness acceptability curve using the net-benefit method as recommended by ISPOR-SMDM best practices (23, 31).

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