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# The economic effect of extracorporeal membrane oxygenation to support adults with severe respiratory failure in Brazil: a hypothetical analysis

*Efeito econômico do uso da oxigenação extracorpórea para suporte de pacientes adultos com insuficiência respiratória grave no Brasil: uma análise hipotética*

## ABSTRACT

**Objective:** To analyze the cost-utility of using extracorporeal oxygenation for patients with severe acute respiratory distress syndrome in Brazil.

**Methods:** A decision tree was constructed using databases from previously published studies. Costs were taken from the average price paid by the Brazilian Unified Health System (*Sistema Único de Saúde*; SUS) over three months in 2011. Using the data of 10,000,000 simulated patients with predetermined outcomes and costs, an analysis was performed of the ratio between cost increase and years of life gained, adjusted for quality (cost-utility), with survival rates of 40 and 60% for patients using extracorporeal membrane oxygenation.

**Results:** The decision tree resulted in 16 outcomes with different life support techniques. With survival rates of 40 and 60%, respectively, the increased costs were R\$=-301.00/-14.00, with a

cost of R\$=-30,913.00/-1,752.00 paid per six-month quality-adjusted life-year gained and R\$=-2,386.00/-90.00 per quality-adjusted life-year gained until the end of life, when all patients with severe ARDS were analyzed. Analyzing only patients with severe hypoxemia (i.e., a ratio of partial oxygen pressure in the blood to the fraction of inspired oxygen <100mmHg), the increased cost was R\$=-5,714.00/272.00, with a cost per six-month quality-adjusted life-year gained of R\$=-9,521.00/293.00 and a cost of R\$=-280.00/7.00 per quality-adjusted life-year gained.

**Conclusion:** The cost-utility ratio associated with the use of extracorporeal membrane oxygenation in Brazil is potentially acceptable according to this hypothetical study.

**Keywords:** Extracorporeal membrane oxygenation/economy; Costs and cost analysis; Respiratory insufficiency; Respiration, artificial; Intensive care units

## INTRODUCTION

The use of extracorporeal membrane oxygenation (ECMO) to support patients with severe acute respiratory distress syndrome (ARDS) has increased significantly over recent years.<sup>(1-7)</sup> The most consistent evidence on the effectiveness of ECMO with regard to increasing the survival of patients with severe ARDS comes from a randomized study in the UK<sup>(4)</sup> and two case series paired with propensity score matching among patients suffering from influenza A H1N1 virus.<sup>(8)</sup> A recent meta-analysis supported these studies' findings, but the use of propensity scores has been criticized.<sup>(8)</sup>

The additional cost of using ECMO to support patients with severe ARDS has only been analyzed properly in the UK,<sup>(4)</sup> where the incorporation of this technology was considered cost-effective: £128,621.00 to save one quality life

year, a measure adjusted six months after admission to the intensive care unit (ICU). Despite the widespread use of ECMO, no additional detailed economic evaluations have been made. Certain centers in Brazil have been developing the use of ECMO to support the most severe patients, and their results have been published.<sup>(9-15)</sup> Recently, an epidemiological study of respiratory failure, i.e., the epidemiology of respiratory distress in critical care (ERICC) study, was published in Brazil.<sup>(16)</sup> The ERICC study mapped patients with respiratory distress who required mechanical ventilation for two months, exploring different diagnoses, severities, incidence, and clinical outcomes.

The cost of this technology in a developing country can have significant repercussions, as is the case in Brazil. In this sense, the objective of the current manuscript was to analyze the hypothetical economic effect of the inclusion of ECMO in Brazil using cost-utility ratios.

## METHODS

This study randomly simulated decisions to treat hypothetical patients distributed based on the most common forms of respiratory and renal support given to patients with severe ARDS. To that end, a tree of the possible distributions of respiratory and renal support was constructed (Figure 1), and each hypothetical patient had a predetermined probability of meeting the outcomes displayed on the different branches of the tree. The tree has eight possible binary outcomes (e.g., death or survival) and each of the 18 branches associated with an outcome passes through different combinations of support techniques. Each of the 16 outcomes had a cost based on the average time (days) of the ERICC studies and case series of patients with ECMO. The costs of each procedure (electronic supplementary material - Tables 1 to 20) allowed us to calculate the hypothetical economic cost of each scenario at the end of simulation. The hypothetical survival rate of patients was used as the dependent variable and adjusted based on quality-adjusted life-years (QALYs).

### The decision tree regarding different support techniques for critical patients

The outcome distribution tree was constructed as previously described.<sup>(17-19)</sup> The procedures included were those most commonly used in clinical practice to support patients with severe respiratory failure. To consolidate these states and generate the distribution probabilities

according to the tree, the events recorded in the ERICC study were used,<sup>(16)</sup> in which 242 patients were diagnosed with ARDS. The initial tree is shown in panel B of figure 1. Patients who were admitted to the ICU with a ratio of partial pressure of oxygen in the blood to fraction of inspired oxygen (P/F) <100 mm Hg and who died in the ICU were classified as having refractory hypoxemia.

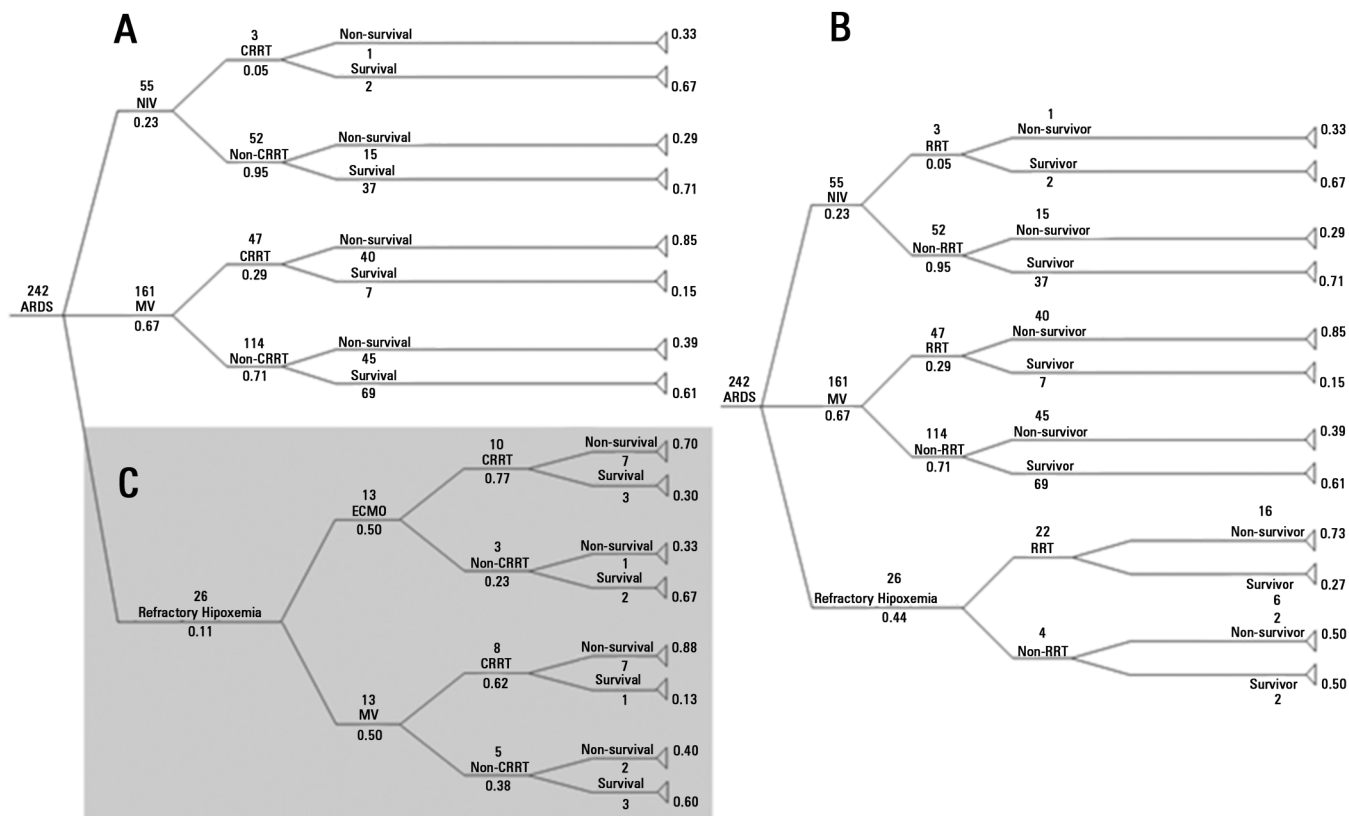
Because the use of ECMO for respiratory support in Brazil is only episodic, we adopted the premise that half of the patients with refractory hypoxemia would receive support via this treatment in the simulations (Panel C of Figure 1). Within the group receiving respiratory support via ECMO, other events were removed from the initial extracorporeal respiratory support sample.<sup>(20)</sup> In that publication, the survival rate was 40% among patients with expected mortality rate of 95%. Importantly, however, the Campinas (SP) cardiovascular surgery group of the *Hospital e Maternidade Celso Pierro* of the *Pontifícia Universidade Católica de Campinas* currently has a survival rate of 60%. These data are consistent with those reported in the literature for patients undergoing extracorporeal respiratory support.<sup>(21)</sup>

Given that mortality might be more likely when beginning the activity than when conditions subsequently improve, two simulations were planned: an initial one that simulated a novice center with an ECMO patient survival rate of 40%, and a second simulation of an advanced center with a survival rate of 60% (Panels A and C of Figure 1). In Figure 1, the black arrow shows the events that were modified to increase the probability of survival. These simulations examined the hypothetical economic effect of experience with ECMO on a center initially and after some time.

Although all patients died in the ERICC study upon which the probabilities of refractory hypoxemia diagnoses were based,<sup>(16)</sup> we assumed a survival rate of 9% for this group using the tree based on a Canadian study of patients with severe ARDS and refractory hypoxemia.<sup>(22)</sup>

The Markov model has a few features to keep in mind: (1) its probabilities are fixed; (2) these probabilities are mutually exclusive in relation to events (i.e., it is not possible to take different paths simultaneously); and (3) past events do not influence future ones (i.e., the Markov model does not have a memory).

Electronic supplementary material - tables 1, 2, and 20 show the events in relation to survival and support, support periods for organ dysfunction, ICU admittance, and hospital stay.



**Figure 1** - General decision trees used in the simulations. Panel (A): the structure of the strategy tree that considers the use of extracorporeal membrane oxygenation (ECMO) for patients with respiratory failure. Panel (B): the structure of the strategy tree that does not include the use of ECMO for patients with respiratory failure. Subpanel (C) the region studied for a sensitivity analysis between the use and non-use of ECMO support for the patients with refractory hypoxemia upon arrival to the intensive care unit. The numbers above the ratings represent the number of patients from the ERICC study and the Brazilian series of patients who received ECMO. The other numbers (with decimal places) represent the probabilities of occurrence of the route in question according to figures cited. Patients who received ECMO also received conventional mechanical ventilation. The black arrow shows the region changed for the analysis with a survival probability of 60% for patients receiving ECMO. In this analysis, the number of survivors was increased to six, and the number of non-survivors was reduced to four. ARDS - acute respiratory distress syndrome; NIV - noninvasive ventilation; CMV - conventional mechanical ventilation; RRT - renal replacement therapy.

### Calculation of costs per patient

The costs used for the analysis were collected from payments by the SUS for the necessary inputs over an average of three months in 2012, without accounting for the cost of medical professionals. This survey was conducted by the Center for Technology Assessment in Health (*Núcleo de Avaliação de Tecnologias em Saúde; NATS*) of the *Instituto do Coração* and *Hospital das Clínicas* of the *Faculdade de Medicina* of the *Universidade de São Paulo*, a member of the Brazilian Network for Health Technology Assessment (*Rede Brasileira de Avaliação de Tecnologias em Saúde*) of the Ministry of Health. The cost statistics are shown in electronic supplementary material - tables 12 to 20.

In the cost survey, each support method was evaluated and accounted for in terms of initiation and maintenance

(price per day; electronic supplementary material - table 3). Each of the 16 outcomes had a scenario that was economically evaluated in isolation, totaling an individual cost for each of the 16 branches relative to the support methods.

The costs for each patient associated with each outcome were calculated by adding the individual costs of the items used related to his or her support (electronic supplementary material - tables 4 to 9 and 12 to 19) in accordance with the support and number of days over which that support was received.

### Quantitative QALY survival adjustment

The quantitative survival result was adjusted for survival time with good patient quality of life; to that end, the QALY concept was used. The QALY value can be positive

or negative and range from -1 to 1, where 1 denotes a high quality of life. A patient who is alive but whose life condition is poor is assigned a negative QALY value.<sup>(23)</sup>

The current paper performs two sub-analyses in relation to QALYs: one that focuses on QALYs six months after admission to the ICU (i.e., the primary analysis) and the other that considers the amount of time during which the patient had a good quality of life until his or her natural death. A six-month timeframe was chosen for the primary analysis because the only existing ECMO cost-utility measurement in the literature (i.e., the CESAR study,<sup>(4)</sup> conducted in the UK) adjusted their cost-utility evaluation for six months. Thus, we have an economic point of comparison.

Because the Brazilian literature concerning the quality of life of people with ARDS is scarce, three papers were used to simulate data regarding the quality of life of patients with refractory hypoxemia, with or without ECMO. Two of the studies cited are Brazilian,<sup>(20,24)</sup> and the third is Australian.<sup>(25)</sup> Two post-ECMO studies predominantly evaluated young patients after the acute phase of influenza A H1N1.<sup>(24,25)</sup> The remaining cases included post-ARDS follow-up evaluations of Americans<sup>(26-28)</sup> and Canadians.<sup>(29,30)</sup>

As suggested by the National Institute for Health and Clinical Excellence (NICE), the QALY scores were evaluated based on the EQ-5D quality of life questionnaire.<sup>(31)</sup> If the values recorded in the aforementioned follow-up samples of post-ARDS patients for each EQ-5D dimension were greater than or equal to the normal population, then a 1 was assigned on the EQ-5D questionnaire; if the value was  $\geq 50\%$  but lower than the normal value, then it was assigned a 2; and if the observed value was  $< 50\%$  of the normal value, then it was assigned a 3. The visual analog scale of the EQ-5D was not used. A weight was used as previously described for each of the three scores of each EQ-5D dimension.<sup>(32)</sup> We used the survival tables of the *Instituto Brasileiro de Geografia e Estatística* (IBGE), which is freely accessible via the Internet, to estimate quality of life after discharge from the hospital.<sup>(33)</sup> We used the average patient age recorded by the ERICC study (62 years old), which resulted in an average of 21 years of survival for our patients.

### Economic evaluation

We used the difference in cost-per-patient in each of the designed situations as well as the concepts of cost-effectiveness and cost-utility for the economic evaluation in the simulations.<sup>(18,23)</sup>

Thus, the calculations included the ratio of cost increase-effectiveness = (cost difference with ECMO - without ECMO)/number of lives saved; the ratio of cost-utility increase = (cost difference with ECMO - cost difference without ECMO)/(difference in QALYs with ECMO - QALYs without ECMO).

### Decision tree flow simulations

A total of 242 patients with ARDS were admitted during the two months of data collection across the 45 ICUs involved in the ERICC study.<sup>(16)</sup> Because admissions due to ARDS change for various reasons (e.g., seasonality), 1,000 simulations were performed to reproduce the movement of patients within these ICUs over one year. These 1,000 admissions were randomly distributed according to the Markov chain trees (Figure 1). The simulations were performed on an Excel 2013 spreadsheet using the = rand() command to randomly generate numbers. A discount rate of 1% was used for these simulations.

Based on the assumption that several consecutive years would show a movement similar to those for organ dysfunction support in terms of probability, 10,000 entries of 1,000 admissions (i.e., 10,000,000 entry repetitions in the tree) were performed to generate 16 possible outcomes for the different support methods. Each new entry in the tree generated both the branch in panel A and the one in panel B (Figure 1). In addition, panel C of figure 1 (in gray) was independently evaluated because it represented the branch of patients with refractory hypoxemia who received ECMO during support or conventional ventilation. The same simulation was repeated twice with different survival rates (40 and 60%) for the group receiving ECMO as described above.

### Statistical analyses

The generated data were tested for normality using the Kolmogorov-Smirnov goodness-of-fit model. After confirming normality, the quantitative data are presented as the means  $\pm$  standard deviations, and the qualitative data were presented as the number of events. The means of the different groups were tested using Student's *t*-test for independent samples. Scatterplots were constructed to demonstrate the difference in cost versus the time difference with good quality of life, adjusted for the first six months after ICU admission. Graphs were created and statistical analyses were performed using R, the freeware statistical package.<sup>(34)</sup>



## RESULTS

Table 1 shows the results of the 10,000 simulations that evaluated the economic effect regarding the use of ECMO over one year, performed with 1,000 patients who had a 40% probability of survival. Given the greater clinical relevance of using ECMO on the patients with refractory hypoxemia, the economic effect associated with these patients was also estimated (Subpanel C of Figure 1). A survival increase of 7% (4/54 patients) was observed. A QALY value of 3.019 was correlated with an acceptable cost differential. The simulation results with a survival probability of 60% among patients receiving ECMO are shown in table 2 (Subpanel C in Figure 1). In this case, a 29% survival increase (16/54 patients) represented 7.098 QALYs, which was correlated with an average increase of 0.4% in costs.

Electronic supplementary material - tables 10 and 11 shows the results for the simulation of the economic effect regarding respiratory support using ECMO for all patients with ARDS. In this overall strategy, patients received noninvasive and conventional mechanical ventilation (Panels A and B of Figure 1). Likewise, electronic supplementary material - table 10 shows the simulation with a 40% survival probability for patients with ECMO. Electronic supplementary material - table 11 shows results for the simulation with 60% survival probability among patients who received ECMO, with a slight increase in costs.

After adjusting for six months, the QALYs were correlated with an acceptable cost increase dispersion for the 40% survival rate (Figure 2), both for the

**Table 1** - A comparative evaluation of patients who developed severe chronic hypoxemia, with or without the use of extracorporeal membrane oxygenation; the expected survival rate of patients receiving extracorporeal membrane oxygenation was 40%

Characteristics	Without ECMO	With ECMO	p-value
Evaluated patients (N/year)	54 ± 7	54 ± 7	-
Average cost/patient (R\$/year)	57,044 ± 1,868	51,334 ± 1,734	<0.001
QALY/patient adjusted for six months	0.111 ± 0.012	0.226 ± 0.034	<0.001
QALY	9.35 ± 1.02	12.37 ± 1.924	<0.001
Survivors (N)	17 ± 4	21 ± 4	<0.001
Lives saved (N/year)		4 ± 6	
Six-month adjusted QALY		0.115 ± 0.033	
QALY gain		3.019 ± 1.918	
Cost increase (R\$)		-5,714 ± 2,545	
Cost-utility ratio (R\$/six-month adjusted QALY)		-59,521 ± 2,545	
Cost-utility ratio (R\$/QALYs)		-280 ± 235192	
Cost per life saved (R\$/life)		-340 ± 2821	

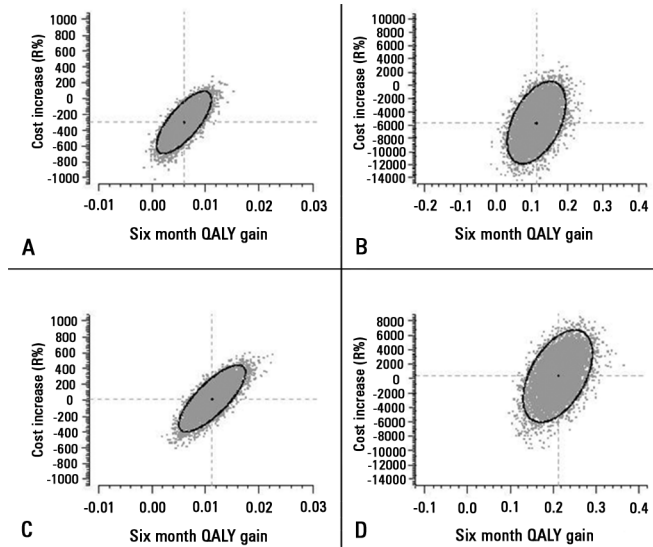
ECMO - extracorporeal membrane oxygenation; QALY - quality-adjusted life-years.

**Table 2** - A comparative evaluation of patients developing severe chronic hypoxemia, with or without the use of extracorporeal membrane oxygenation, with an expected survival rate of 60% among patients receiving extracorporeal membrane oxygenation

Characteristics	Without ECMO	With ECMO	p-value
Evaluated patients (N/year)	54 ± 7	54 ± 7	-
Average cost/patient (R\$/year)	57,024 ± 1,880	57,296 ± 1,797	<0.001
QALY/patient adjusted over six months	0.111 ± 0.012	0.323 ± 0.033	<0.001
QALY	9.34 ± 1.02	16.44 ± 1.88	<0.001
Survivors (N)	17 ± 4	33 ± 6	<0.001
Lives saved (N/year)		16 ± 7	
Six-month adjusted QALY		0.212 ± 0.033	
QALY gain		7.098 ± 1.880	
Cost increase (R\$)		272 ± 2612	
Cost-utility ratio (R\$/six-month adjusted QALY)		293 ± 13038	
Cost-utility ratio (R\$/QALY)		7 ± 439	
Cost per life saved (R\$/life)		-56 ± 470	

ECMO - extracorporeal membrane oxygenation; QALY - quality-adjusted life-years.

overall strategy and patients with refractory hypoxemia. The six-month QALY associated with a 60% survival probability produced a slight cost increase. These same results were observed in the lifetime simulation (Figure 3) using the two probabilities of survival, both for those with refractory hypoxemia and the overall strategy.

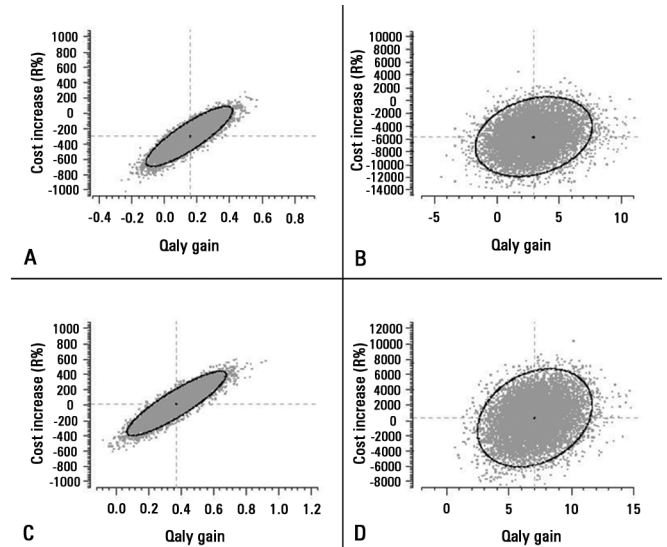


**Figure 2** - Graphs showing the correlations between the cost increase per patient and QALY after using extracorporeal membrane oxygenation (ECMO). Panel (A): the correlation when the total spent per the 1,000 patients (one year) in the overall strategy was estimated, with a survival rate of 40% among patients receiving ECMO. Panel (B): the same type of correlation evaluating only the patients who developed refractory hypoxemia, again with a survival rate of 40% among patients receiving ECMO. Panel (C): the correlation when total cost per the 1,000 patients (one year) in the overall strategy was estimated, with a survival rate of 60% among patients receiving ECMO. Panel (D): the correlation when evaluating only those patients who developed refractory hypoxemia, with a survival rate of 60% among patients receiving ECMO. The graphs were constructed with 10,000 hypothetical years, replicated with randomization. QALY denotes the years of good quality of life gained. Ellipses represent the 95% confidence intervals. The central black dots represent the intersection of the average cost increase with the average QALY.

Electronic supplementary material - table 20 revealed an interesting finding: Whereas patients undergoing ECMO died after five days on average, patients who used only conventional mechanical ventilation died after 12 days in the ICU.

## DISCUSSION

The major finding of this study was the protective value of the cost-utility ratio when the patient survival rate associated with ECMO was 40%. Supporting this idea, the dispersion graph of the incremental cost value for each QALY also resulted in a protective average (Figures 2 and 3).



**Figure 3** - Graphs showing the correlations between cost increase per patient and QALY using extracorporeal membrane oxygenation (ECMO). The graphs were constructed with 1,000 patients (one year), replicated 10,000 times (i.e., for 10,000 years). Panel (A): the correlation when the total spent for the total respiratory support strategy was estimated, with a survival rate of 40% among patients receiving ECMO. Panel (B): the correlation when evaluating only those patients who developed refractory hypoxemia, again with a survival rate of 40% among patients receiving ECMO. Panel (C): the correlation when total cost per 1,000 patients (one year) in the overall strategy was estimated, and the survival rate was 60% among patients receiving ECMO. Panel (D): the correlation when evaluating only those patients who developed refractory hypoxemia, and the survival rate was 60% among patients receiving ECMO. The graphs were constructed with 10,000 hypothetical years, replicated with randomization. QALY denotes the years of good quality of life gained. Ellipses represent the 95% confidence intervals.

However, when the survival rate was simulated at 60%, the cost-utility ratio of patients who developed refractory hypoxemia became positive, both adjusted for six months and overall. This finding is also shown in the scatterplot of cost variation by QALY (Figures 2 and 3).

According to the ERICC study, all patients hospitalized in the ICUs with P/F ratio of <100mmHg (and who died) were included in the refractory hypoxemia group. By itself, this fact does not guarantee that non-simulated patients would receive ECMO support even in a center with the necessary equipment. Because of this fact, we arbitrarily decided that half of these patients would receive support using ECMO. In a real situation, we believe that fewer patients would be genuine candidates for ECMO. This high estimation might raise the costs of ECMO for patients with severe ARDS. In turn, however, our simulation more consistently expresses the effectiveness of the methodology. We emphasize that the quoted 50% of patients who received ECMO are part of the 11% who developed refractory hypoxemia.

The severe chronic hypoxemia criterion might be considered late in terms of considering the indications for ECMO. When the methodology was tested only among patients with hypoxemia and severe ARDS, no satisfactory effects were found with regard to patient mortality.<sup>(35)</sup> However, when ECMO was used for ultraprotective mechanical ventilation (with current volumes between 1 and 2mL/kg as well as very low pressure in the airways),<sup>(36,37)</sup> the mortality rates of more severe patients receiving ECMO has consistently fallen,<sup>(4)</sup> currently reaching numbers as low as 14% in Australia.<sup>(25)</sup>

Our results revealed a negative increase in cost, so that when the survival of patients who received ECMO was 40%, the cost per QALY ratio was negative. This negative finding is of little real economic significance, and we can only interpret it as an indication that these costs are not prohibitive. This result was obtained because the costs of shorter ICU stays associated with ECMO were used. Regarding the expected mortality rate of 95% and the 60% observed in our sample group,<sup>(10)</sup> these values might seem disproportionate; however, they are similar to those described in the literature.<sup>(38)</sup> A significant increase in cost was found when the survival was increased to 60%. Importantly, the literature describes that increased experience is associated with improved outcomes.<sup>(39)</sup> The improvement of the results from the ERICC study map is associated with more hospitalization days for survivors, which resulted in increased costs. Despite these increased costs, the cost per QALY was much lower than that which is considered optimal and acceptable in the UK.<sup>(4)</sup>

The cost associated with six months of QALY in the UK (£128,621.00) is very high for the Brazilian economy; however, this figure included the transport of 62 of 90 (69%) patients by air, regardless of ECMO use. In Brazil, patients using ECMO are transported by land<sup>(15,20)</sup> and air,<sup>(13,20)</sup> but these costs were not included in the current analysis.

As mentioned above, a respiratory support center's experience with ECMO is important for the results.<sup>(39)</sup> Currently, finding a group in Brazil with extensive experience is difficult because no certain funding source exists for this procedure; therefore, centers are scarce and have limited movement. The results of the Campinas center, which is one of those with the most experience in Brazil (and one with municipal financial support), should be highlighted. ECMO involves a simple technique, but it requires training; moreover, patients must be attended because it involves high blood flow in the extracorporeal

circuit (2,000 to 5,000mL/minute). This high flow can cause hemolysis and coagulopathy from the breakdown of coagulation factors; furthermore, any leak can be fatal. The group responsible for extracorporeal support should be clear regarding the rationale for respiratory support with ECMO (i.e., to protect severely damaged lungs from the mechanical ventilator) and not just treat patients' hypoxemia and respiratory acidemia.

Another interesting finding was that the average age of our patients was 62 years old. According to the IBGE survival tables, this age resulted in an average survival of 21 years. Therefore, we can expect that younger patients would have more QALYs.

Currently, economic analyses are receiving widespread criticism because of the scarce resources for their methodologies.<sup>(40)</sup> However, the desire to make medical decisions more rationally means that some economic basis is necessary.<sup>(19,40)</sup> For this reason, the Health Technology Assessment program (HTA) was created in the UK. This program is responsible for high-impact analyses in terms of cost, utility, and the local effect on the inclusion of technology. The HTA's research has had a great deal of influence on the NICE. Currently, the Brazilian Network for Health Technology Assessment, the body to which this material was submitted, subsidizes the National Commission on Technology Incorporation (*Comissão Nacional de Incorporação de Tecnologias*; CONITEC) in the SUS, Ministry of Health.

This study has several limitations. The first is the low degree of freedom with regard to possible regional variations, time dependence, experience, and seasonality.<sup>(40)</sup> Baseline data were derived from a group of 252 patients, few of whom received respiratory support using ECMO, and this support was received during the learning curve. This hypothetical analysis is not intended to serve as a basis for economic decision making. Although the flow data concerning ICU support were based on real data, the analysis was performed as an extrapolation of a sample to a "population". The view that 50% of patients with severe and refractory respiratory failure would receive ECMO is optimistic; according to the hypothesis of this study, 50% of patients receiving ECMO would increase costs. However, because cost reduction was an unexpected result, this optimistic figure of 50% might be responsible for a reduction in costs that will not be true in practice. The support costs associated with other organ dysfunctions and post-discharge costs were not included in the current analysis.

## CONCLUSIONS

This hypothetical analysis of the economic effect of the use of extracorporeal membrane oxygenation in Brazil demonstrates that its costs might be acceptable. However,

the absence of more robust data concerning the morbidity and mortality rates associated with these patients and the actual costs in Brazil likely limit this evaluation. Structured planning is necessary to incorporate and use extracorporeal membrane oxygenation in Brazil.

## RESUMO

**Objetivo:** Analisar o custo-utilidade do uso da oxigenação extracorpórea para pacientes com síndrome da angústia respiratória aguda grave no Brasil.

**Métodos:** Com bancos de dados de estudos previamente publicados, foi construída uma árvore encadeada de decisões. Os custos foram extraídos da média de 3 meses do preço pago pelo Sistema Único de Saúde em 2011. Com 10 milhões de pacientes simulados com desfechos e custos predeterminados, uma análise da relação de incremento de custo e de anos de vida ganhos ajustados pela qualidade (custo-utilidade) foi realizada com sobrevida de 40 e 60% dos pacientes que usaram oxigenação extracorpórea.

**Resultados:** A árvore de decisões resultou em 16 desfechos com técnicas diferentes de suporte à vida. Com a sobrevida de 40/60%, respectivamente, o incremento de custos foi de R\$ -301,00/-14,00, com o preço pago de

R\$ -30.913,00/-1.752,00 por ano de vida ganho ajustado pela qualidade para 6 meses e de R\$ -2.386,00/-90,00 por ano de vida ganho ajustado pela qualidade até o fim de vida, quando se analisaram todos os pacientes com síndrome da angústia respiratória aguda grave. Analisando somente os pacientes com hipoxemia grave (relação da pressão parcial de oxigênio no sangue sobre a fração inspirada de oxigênio <100mmHg), o incremento de custos foi de R\$ -5.714,00/272,00, com preço por ano de vida ganho ajustado pela qualidade em 6 meses de R\$ -9.521,00/293,00, e com o custo de R\$ -280,00/7,00 por ano de vida ganho ajustado pela qualidade.

**Conclusão:** A relação de custo-utilidade do uso da oxigenação extracorpórea no Brasil foi potencialmente aceitável neste estudo hipotético.

**Descritores:** Oxigenação por membrana extracorpórea/economia; Custos e análise de custo; Insuficiência respiratória; Respiração artificial; Unidades de terapia intensiva

## REFERENCES

1. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. *JAMA*. 2009;302(17):1888-95.
2. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA*. 2011;306(15):1659-68.
3. Pham T, Combes A, Rozé H, Chevret S, Mercat A, Roch A, Mourvillier B, Ara-Somohano C, Bastien O, Zogheib E, Clavel M, Constan A, Marie Richard JC, Brun-Buisson C, Brochard L; REVA Research Network. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-85.
4. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, Hibbert CL, Truesdale A, Clemens F, Cooper N, Firmin RK, Elbourne D; CESAR trial collaboration. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-63.
5. Combes A, Bacchetta M, Brodie D, Müller T, Pellegrino V. Extracorporeal membrane oxygenation for respiratory failure in adults. *Curr Opin Crit Care*. 2012;18(1):99-104. Review.
6. Gattinoni L, Carlesso E, Langer T. Clinical review: Extracorporeal membrane oxygenation. *Crit Care*. 2011;15(6):243. Review.
7. Gattinoni L, Carlesso E, Langer T. Towards ultraprotective mechanical ventilation. *Curr Opin Anaesthesiol*. 2012;25(2):141-7.
8. Zampieri FG, Mendes PV, Ranzani OT, Taniguchi LU, Pontes Azevedo LC, Vieira Costa EL, et al. Extracorporeal membrane oxygenation for severe respiratory failure in adult patients: a systematic review and meta-analysis of current evidence. *J Crit Care*. 2013;28(6):998-1005.
9. Colafranceschi AS, Monteiro AJ, Canale LS, Campos LA, Montera MV, Silva PR, et al. Adult extracorporeal life support: a failed or forgotten concept? *Arq Bras Cardiol*. 2008;91(1):34-41.
10. Park M, Azevedo LC, Mendes PV, Carvalho CR, Amato MB, Schettino GP, et al. First-year experience of a Brazilian tertiary medical center in supporting severely ill patients using extracorporeal membrane oxygenation. *Clinics (São Paulo)*. 2012;67(10):1157-63.
11. Bassi E, Azevedo LC, Costa EL, Maciel AT, Vasconcelos E, Ferreira CB, et al. Hemodynamic and respiratory support using venoarterial extracorporeal membrane oxygenation (ECMO) in a polytrauma patient. *Rev Bras Ter Intensiva*. 2011;23(3):374-9.
12. Park M, Costa EL, Azevedo LC, Afonso Junior JE, Samano MN, Carvalho CR; ECMO Group. Extracorporeal membrane oxygenation as a bridge to pulmonary transplantation in Brazil: are we ready to embark upon this new age? *Clinics (São Paulo)*. 2011;66(9):1659-61.
13. Mendes PV, Moura E, Barbosa EV, Hirota AS, Scordamaglio PR, Ajar FM, Costa EL, Azevedo LC, Park M; ECMO Group. Challenges in patients supported with extracorporeal membrane oxygenation in Brazil. *Clinics (São Paulo)*. 2012;67(12):1511-5.



14. Maksoud-Filho JG, Diniz EM, Ceccon ME, Galvani AL, Chamelian MD, Pinho ML, et al. Circulação extracorpórea por membrana (ECMO) em recém-nascido com insuficiência respiratória por síndrome de aspiração meconial: efeitos da administração de surfactante exógeno. *J Pediatr (Rio J)*. 2001;77(3):243-8.
15. Azevedo LC, Park M, Costa EL, Santos EV, Hirota A, Taniguchi LU, Schettino Gde P, Amato MB, Carvalho CR; Extracorporeal Support Study Group. Extracorporeal membrane oxygenation in severe hypoxemia: time for reappraisal? *J Bras Pneumol*. 2012;38(1):7-12.
16. Azevedo LC, Park M, Salluh JI, Rea-Neto A, Souza-Dantas VC, Varaschin P, Oliveira MC, Tierno PF, Dal-Pizzol F, Silva UV, Knibel M, Nassar AP Jr, Alves RA, Ferreira JC, Teixeira C, Rezende V, Martinez A, Luciano PM, Schettino G, Soares M; The ERICC (Epidemiology of Respiratory Insufficiency in Critical Care) investigators. Clinical outcomes of patients requiring ventilatory support in Brazilian intensive care units: a multicenter, prospective, cohort study. *Crit Care*. 2013;17(2):R63.
17. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993;13(4):322-38.
18. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. *Pharmacoeconomics*. 1998;13(4):397-409.
19. Briggs AH. Handling uncertainty in cost-effectiveness models. *Pharmacoeconomics*. 2000;17(5):479-500.
20. Park M, Azevedo LC, Mendes PV, Carvalho CR, Amato MB, Schettino GP, et al. First-year experience of a Brazilian tertiary medical center in supporting severely ill patients using extracorporeal membrane oxygenation. *Clinics (São Paulo)*. 2012;67(10):1157-63.
21. Extracorporeal Life Support Organization - ECLS Registry Report 2014. Available from: [http://www.else.org/index.php?option=com\\_content&view=article&id=85&Itemid=653](http://www.else.org/index.php?option=com_content&view=article&id=85&Itemid=653).
22. Meade MO, Cook DJ, Guyatt GH, Slutsky AS, Arabi YM, Cooper DJ, Davies AR, Hand LE, Zhou Q, Thabane L, Austin P, Lapinsky S, Baxter A, Russell J, Skrobik Y, Ronco JJ, Stewart TE; Lung Open Ventilation Study Investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008;299(6):637-45.
23. Siegel JE, Torrance GW, Russell LB, Luce BR, Weinstein MC, Gold MR. Guidelines for pharmacoeconomic studies. Recommendations from the panel on cost effectiveness in health and medicine. *Panel on cost Effectiveness in Health and Medicine. Pharmacoeconomics*. 1997;11(2):159-68.
24. Toufen C Jr, Costa EL, Hirota AS, Li HY, Amato MB, Carvalho CR. Follow-up after acute respiratory distress syndrome caused by influenza a (H1N1) virus infection. *Clinics (São Paulo)*. 2011;66(6):933-7.
25. Hodgson CL, Hayes K, Everard T, Nichol A, Davies AR, Bailey MJ, et al. Long-term quality of life in patients with acute respiratory distress syndrome requiring extracorporeal membrane oxygenation for refractory hypoxaemia. *Crit Care*. 2012;16(5):R202.
26. Needham DM, Dinglas VD, Morris PE, Jackson JC, Hough CL, Mendez-Tellez PA, Wozniak AW, Colantuoni E, Ely EW, Rice TW, Hopkins RO; NIH NHLBI ARDS Network. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. *Am J Respir Crit Care Med*. 2013;188(5):567-76.
27. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med*. 2012;185(12):1307-15.
28. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171(4):340-7.
29. Herridge MS, Cheung AM, Tansey CM, Matte-Martyn A, Diaz-Granados N, Al-Saidi F, Cooper AB, Guest CB, Mazer CD, Mehta S, Stewart TE, Barr A, Cook D, Slutsky AS; Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-93.
30. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, Guest CB, Mazer CD, Mehta S, Stewart TE, Kudlow P, Cook D, Slutsky AS, Cheung AM; Canadian Critical Care Trials Group. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364(14):1293-304.
31. Baker R, Bateman I, Donaldson C, Jones-Lee M, Lancsar E, Loomes G, Mason H, Odejar M, Pinto Prades JL, Robinson A, Ryan M, Shackley P, Smith R, Sugden R, Wildman J; SVQ Research Team. Weighting and valuing quality-adjusted life-years using stated preference methods: preliminary results from the Social Value of a QALY Project. *Health Technol Assess*. 2010;14(27):1-162.
32. Dolan P. Modeling valuations for EuroQol health states. *Med Care*. 1997;35(11):1095-108.
33. Instituto Brasileiro de Geografia e Estatística (IBGE) - Diretoria de pesquisas. Tabela de expectativa de sobrevida no Brasil - Ambos os sexos 2012 [Internet]. [citado 2014 Mai 20]. Disponível em: <http://www010.dataprev.gov.br/cws/contexto/conrmi/tabES.htm>.
34. Team RDC. R: A language and environment for statistical computing. R Foundation for Statistical Computing; 2009.
35. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA*. 1979;242(20):2193-6.
36. Peek GJ, Moore HM, Moore N, Sosnowski AW, Firmin RK. Extracorporeal membrane oxygenation for adult respiratory failure. *Chest*. 1997;112(3):759-64.
37. Lindén V, Palmér K, Reinhard J, Westman R, Ehrén H, Granholm T, et al. High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation. *Intensive Care Med*. 2000;26(11):1630-7.
38. Zampieri FG, Mendes PV, Ranzani OT, Taniguchi LU, Pontes Azevedo LC, Vieira Costa EL, et al. Extracorporeal membrane oxygenation for severe respiratory failure in adult patients: a systematic review and meta-analysis of current evidence. *J Crit Care*. 2013;28(6):998-1005.
39. Karamlou T, Vafaeezadeh M, Parrish AM, Cohen GA, Welke KF, Permut L, et al. Increased extracorporeal membrane oxygenation center case volume is associated with improved extracorporeal membrane oxygenation survival among pediatric patients. *J Thorac Cardiovasc Surg*. 2013;145(2):470-5.
40. Williams I, McIver S, Moore D, Bryan S. The use of economic evaluations in NHS decision-making: a review and empirical investigation. *Health Technol Assess*. 2008;12(7):iii, ix-x, 1-175.

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