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

INTRODUCTION

The use of extracorporeal membrane oxygenation (ECMO) to support patients with severe acute respiratory distress syndrome (ARDS) has increased significantly over recent years. 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, and two case series paired with propensity score matching among patients suffering from influenza A H1N1 virus. A recent meta-analysis supported these studies’ findings, but the use of propensity scores has been criticized.

The additional cost of using ECMO to support patients with severe ARDS has only been analyzed properly in the UK, where the incorporation of this technology was considered cost-effective: £128,621.00 to save one quality life-year gained.

The economic effect of ECMO with regard to increasing the survival of patients with severe ARDS has increased significantly over recent years. 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, and two case series paired with propensity score matching among patients suffering from influenza A H1N1 virus. A recent meta-analysis supported these studies’ findings, but the use of propensity scores has been criticized.

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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.\(^\text{[9-15]}\)

Recently, an epidemiological study of respiratory failure, i.e., the epidemiology of respiratory distress in critical care (ERICC) study, was published in Brazil.\(^\text{[16]}\) 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.\(^\text{[17-19]}\) 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,\(^\text{[16]}\) 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.\(^\text{[20]}\) 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.\(^\text{[21]}\)

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,\(^\text{[16]}\) 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.\(^\text{[22]}\)

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.
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 (Centro 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.\(^{(23)}\)

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,\(^{(4)}\) 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,\(^{(20,24)}\) and the third is Australian.\(^{(25)}\) Two post-ECMO studies predominantly evaluated young patients after the acute phase of influenza A H1N1.\(^{(24,25)}\) The remaining cases included post-ARDS follow-up evaluations of Americans\(^{(26–28)}\) and Canadians.\(^{(29,30)}\)

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.\(^{(31)}\) 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 ≥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.\(^{(32)}\) 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.\(^{(33)}\) 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.\(^{(18,23)}\)

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.\(^{(16)}\) 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 mean±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.\(^{(34)}\)
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.

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%

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

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Without ECMO</th>
<th>With ECMO</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluated patients (N/year)</td>
<td>54±7</td>
<td>54±7</td>
<td>-</td>
</tr>
<tr>
<td>Average cost/patient (R$/year)</td>
<td>57,024±1,880</td>
<td>57,296±1,787</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QALY/patient adjusted over six months</td>
<td>0.111±0.012</td>
<td>0.323±0.033</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>QALY</td>
<td>9.34±1.02</td>
<td>16.44±1.88</td>
<td>&lt;0.001</td>
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<tr>
<td>Survivors (%)</td>
<td>17±4</td>
<td>33±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lives saved (N/year)</td>
<td>16±7</td>
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<td></td>
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<tr>
<td>Six-month adjusted QALY</td>
<td>0.212±0.033</td>
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<tr>
<td>QALY gain</td>
<td>7.098±1.880</td>
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<tr>
<td>Cost increase (R$)</td>
<td>272±2612</td>
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<td></td>
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<tr>
<td>Cost-utility ratio (R$/six-month adjusted QALY)</td>
<td>293±13038</td>
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<td>Cost-utility ratio (R$/QALY)</td>
<td>7±439</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per life saved (R$/life)</td>
<td>-56±470</td>
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</table>

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.

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).

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.\(^{(35)}\) 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),\(^{(36,37)}\) the mortality rates of more severe patients receiving ECMO has consistently fallen,\(^{(4)}\) currently reaching numbers as low as 14% in Australia.\(^{(25)}\)

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,\(^{(10)}\) these values might seem disproportionate; however, they are similar to those described in the literature.\(^{(38)}\) 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.\(^{(39)}\) 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.\(^{(40)}\)

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\(^{(15,20)}\) and air,\(^{(13,20)}\) 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.\(^{(39)}\) 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.\(^{(40)}\) However, the desire to make medical decisions more rationally means that some economic basis is necessary.\(^{(19,40)}\) 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 HTAs 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.\(^{(40)}\) 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.
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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


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