

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

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

To the Editor,

This letter regards the study published by Park et al.,⁽¹⁾ which deserved an interesting editorial.⁽²⁾ The initiative of health technology economic evaluation is of great importance. Nevertheless, some issues of this study need further discussion.

The authors of the study performed a cost-effectiveness analysis, comparing the treatment of adults with severe respiratory failure with and without extracorporeal membrane oxygenation (ECMO), and reached the following surprising result: ECMO would probably not only be cost-effective, but, in one scenario, it could even be cost-saving in Brazil.⁽¹⁾ However, from a conceptual point of view, an economic evaluation should be conducted after a new intervention is proven effective.

The only randomized clinical trial regarding this matter published after the lung protective ventilation era⁽³⁾ has several methodological problems. One of them is that patients randomized to ECMO were treated in a single specialized center, while controls were treated in up to 92 different centers, using different treatment protocols. Consequently, the survival of patients allocated to the control group (50%) was much lower than that of patients randomized to ECMO, who were treated in the ECMO center without receiving ECMO (82%). Another problem is that while ECMO was better than the control strategy regarding survival or severe disability (compound outcome), there was no significant difference between treatments in terms of the survival, and severe disability was detected in a single patient of the control group.⁽³⁾

Moreover, in a meta-analysis published by some of the authors responsible for this economic evaluation, the main analysis did not find a significant difference between ECMO and conventional therapy regarding survival (odds ratio = 0.71, 95% confidence interval = 0.34 - 1.47, $p = 0.358$). The authors concluded that there was insufficient evidence to recommend ECMO.⁽⁴⁾

Considering the abovementioned, we understand that it is rather soon to perform an economic evaluation regarding ECMO, and we think efforts should be concentrated on defining whether this is an effective treatment option for adult respiratory distress syndrome.

Regarding the results of the Brazilian cost-effectiveness analysis,⁽¹⁾ the ECMO costs were substantially lower than those presented in the piggy-back economic evaluation by Peek et al.⁽³⁾ Although some differences could be explained by the

Conflicts of interest: None.

Corresponding author:

Ângelo Zambam de Mattos
Rua Professor Annes Dias, 154/1.103
Zip code: 90020-090 - Porto Alegre (RS), Brazil
E-mail: angmattos@hotmail.com

DOI: 10.5935/0103-507X.20150015

specific characteristics of each country, it is not reasonable to think that while ECMO would be associated to an incremental cost-effectiveness ratio (ICER) of 31,112 US dollars per QALY in the United Kingdom (UK),⁽³⁾ it would be associated with an ICER between -280 and 7 Brazilian reais per QALY in Brazil.⁽¹⁾ This difference could be explained by the Brazilian study not accounting for medical professional costs or costs related to the transportation of the patients to the ECMO center. In this context, it would also be interesting to understand why Brazilian patients undergoing ECMO spent less time

in the intensive care unit and in the hospital than patients who did not use ECMO,⁽¹⁾ which is the exact opposite of what happened in the UK.⁽³⁾ Moreover, it would have been interesting to evaluate, in the decision tree, the role of the prone positioning strategy, which has positive outcomes with low incremental costs.⁽⁵⁾

Therefore, the results of this cost-effectiveness analysis should be interpreted with caution.

Ângelo Zambam de Mattos, Diego Silva Leite Nunes - Secretaria Municipal de Saúde de Porto Alegre - Porto Alegre (RS), Brazil.

REFERENCES

1. Park M, Mendes PV, Zampieri FG, Azevedo LC, Costa EL, Antoniali F, Ribeiro GC, Caneo LF, Cruz Neto LM, Carvalho CR, Trindade EM; Grupo de investigadores ERICC; grupo de ECMO do Hospital Sírio Libanês e do Hospital das Clínicas de São Paulo. The economic effect of extracorporeal membrane oxygenation to support adults with severe respiratory failure in Brazil: a hypothetical analysis. *Rev Bras Ter Intensiva*. 2014;26(3):253-62.
2. Zigaib R, Noritomi DT. Critical care medicine: extracorporeal oxygenation is feasible in Brazil? *Rev Bras Ter Intensiva*. 2014;26(3):200-2.
3. 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. Erratum in *Lancet*. 2009;374(9698):1330.
4. 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.
5. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, Mercier E, Badet M, Mercat A, Baudin O, Clavel M, Chatellier D, Jaber S, Rosselli S, Mancebo J, Sirodot M, Hilbert G, Bengler C, Richecoeur J, Gainnier M, Bayle F, Bourdin G, Leray V, Girard R, Baboi L, Ayzac L; PROSEVA Study Group. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-68.

AUTHORS' RESPONSE

We thank Mattos and Nunes for their careful reading, comments and concerns about our study.⁽¹⁾ Since April 2011, the Brazilian Health Ministry has created a system devoted to the care for health technology assessment, which is called “*Comissão Nacional de Incorporação de Tecnologias para o SUS (CONITEC)*”. Moreover, the method for technology incorporation is positively complex and accomplishes an extensive and detailed literature review (efficacy analysis) of the potential long-term impact in quality of life (utility analysis), cost analysis, cost-utility analysis, public consultation and a re-analysis of all cited steps. Undoubtedly, it consists of a step towards developing health, economy and culture in Brazil. Brazil is a middle-income country where health costs and cost utility are considered before any technology is incorporated

in the public healthcare system because health technology can potentially add unnecessary or disproportional costs in spite of the utility, resulting in further inequalities to our nation. This is a very important open debate.

In answer to the letter authors' concerns:

1. The study in question⁽¹⁾ was based on real Brazilian epidemiological data⁽²⁾ and local experience with respiratory extracorporeal membrane oxygenation (ECMO).⁽³⁾ In spite of the representative data, the assumptions of a modeled decision tree analysis produce estimated conclusions; therefore, the study was considered a hypothetical one.
2. The finding of a negative cost-utility ratio classifies a procedure as an acceptable cost or as a cost-saving one; however, it ascertains the degree of uncertainty

around the estimate. Moreover, the manuscript discusses its economic significance.

3. About the ECMO efficacy: the European, USA and *Agência Sanitária de Vigilância Sanitária* (ANVISA) regulators accepted those published trials as having sufficient efficacy evidence to allow for market approval. Effectiveness, however, depends on the team skills.
4. The authors expressed methodological concerns about the CESAR trial.⁽⁴⁾ We would like to highlight that CESAR was a pragmatic trial about efficacy and economical evaluation in the United Kingdom.
 - a. Severe acute respiratory distress syndrome patients were transferred to a referral center, where, after an initial observational period, the patient was only placed on ECMO if improvement on conventional support was not observed. (Therefore, it is intuitive that of transferred hypoxemic patients who improved without ECMO, 18%, were indeed less severe patients, explaining the low mortality of this subgroup. Furthermore, the natural history of this disease observed in the control arm of the three randomized studies demonstrates all-cause mortality of 50%-92%.) This strategy of transference, observation, and, if necessary, ECMO support was cost-effective for this UK health technology assessment.⁽⁴⁾
 - b. The combined analysis of death and severe disability in the CESAR trial is straightforward once the severe acute respiratory distress syndrome (ARDS) patients commonly have severe long-term disabilities.⁽⁵⁾ Furthermore, the conceptual frame of cost-utility analysis focuses on the lifetime gained with quality, QALY.
 - c. Although the control groups were from 92 different centers, each center was strongly advised to apply low tidal volumes of 6 - 8mL/kg with a plateau pressure lower than 30cmH₂O according to the ARDS network guidelines and group trial.⁽⁶⁾ The resulting low

number of events of severe disability shows that the best support was offered for patients enrolled in both groups.

5. The letter authors also quote lack of evidence of ECMO efficacy, which was cited in a recent Brazilian systematic review and metanalysis⁽⁷⁾ about adult patients with three studies. Two of these studies evaluated patients with severe influenza A (H1N1) pneumonitis in France⁽⁸⁾ and the United Kingdom.⁽⁹⁾ These studies had retrospective data analysis with propensity score matching. Both studies were positive when all ECMO supported patients were analyzed. However, due to the extreme severity of the ECMO group and absence of pairs with such severity in the control group, some patients in the control group were replicated. When replications were excluded, the final results of this metanalysis did not favor the use of ECMO. Additionally, the pregnant and more severe patients of the ECMO supported group were excluded from such negative analysis.⁽⁸⁾ It is notable that ECMO selection criteria include those more severe patients and pregnant women. Therefore, such results are sensitive to the analysis.

In summary, the first Brazilian ECMO technology costs required hypothetical analysis; however, the data analysis is ongoing in the Brazilian environment. The best currently available evidence shows that ECMO is a salvage therapy for selected patients. There were current examples in the influenza A H1N1 epidemics and in Porto Alegre after the Santa Maria Boate Kiss disaster when a Canadian assistance team offered ECMO support for three surviving patients. The model of the ECMO reference centers was and is being adopted internationally. ECMO is a complex technology requiring in-depth training. It is worth evaluating severely ill patients,^(4,9) which can help to answer this question for the Brazilian citizens.

Marcelo Park, Pedro Vitale Mendes, and Evelinda Marramon Trindade, on behalf of authors - Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo - São Paulo (SP), Brazil.

REFERENCES

1. Park M, Mendes PV, Zampieri FG, Azevedo LC, Costa EL, Antoniali F, et al. The economic effect of extracorporeal membrane oxygenation to support adults with severe respiratory failure in Brazil: a hypothetical analysis. *Rev Bras Ter Intensiva*. 2014;26(3):253-62.
2. 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.
3. 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 (Sao Paulo)*. 2012;67(10):1157-63.
4. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. 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. 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.
6. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-8.
7. 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.
8. 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.
9. 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.