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The Cost-Effectiveness of Interventions to Increase Utilization of Prone Positioning for Severe Acute Respiratory Distress Syndrome

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Abstract

Objective: Despite strong evidence supporting proning in acute respiratory distress syndrome (ARDS), few eligible patients receive it. This study determines the cost-effectiveness of interventions to increase utilization of proning for severe ARDS.

Design: We created decision trees to model severe ARDS from intensive care unit admission through death (societal perspective) and hospital discharge (hospital perspective). We assumed patients received low tidal volume ventilation. We used short-term outcome estimates from the PROSEVA trial and longitudinal cost and benefit data from cohort studies. In probabilistic sensitivity analyses we used distributions for each input that included the 5th-95th percentile of its confidence interval (CI).

Setting: Intensive care units that care for patients with ARDS.

Subjects: Patients with moderate to severe ARDS.

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Interventions: The implementation of a hypothetical intervention to increase the appropriate utilization of prone positioning.

Measurements and Main Results: In the societal perspective model, an intervention that increased proning utilization from 16% to 65% yielded an additional 0.779 (95% CI 0.088-1.714) quality-adjusted life years (QALYs) at an additional long-term cost of \$31,156 (95% CI -\$158 - \$92,179), [incremental cost-effectiveness ratio (ICER) = \$38,648 per QALY (95% CI \$1,695-\$98,522)]. If society was willing to pay \$100,000 per QALY, any intervention costing less than \$51,328 per patient with moderate to severe ARDS would represent good value. From a hospital perspective, the intervention yielded 0.072 (95% CI 0.008-0.147) more survivals-to-discharge at a cost of \$5,242 (95% CI -\$19,035-\$41,019) (ICER = \$44,615 per extra survival (95% CI -\$250,912-\$558,222)). If hospitals were willing to pay \$100,000 per survival-to-discharge, any intervention costing less than \$5,140 per patient would represent good value.

Conclusions: Interventions that increase utilization of proning would be cost-effective from both societal and hospital perspectives under many plausible cost and benefit assumptions.

Keywords

Respiratory Distress Syndrome; Adult; Cost-Benefit Analysis; Prone position; Economics; Hospital; Decision Trees

Introduction:

Despite recent advances, survival following the acute respiratory distress syndrome (ARDS) remains 50-60% in many settings (1–4). Prone positioning (PP) in moderate-severe ARDS has been shown in randomized trials to substantially improve survival, and, like low-tidal-volume ventilation (LTV), is a core component of ARDS management guidelines (5–8). As an inexpensive intervention requiring no complex technology, PP is feasible across high and middle income countries (9). However, a 2017 Canadian study showed that only 10% of appropriate patients receive PP, and the LUNG-SAFE study found that 16% of severe cases globally received PP (1, 3). A regional analysis of the LUNG-SAFE data showed that in middle income countries rates of proning were considerably lower (10). Yet improvements are clearly possible, as the Canadian study found that centers with PP protocols had higher rates of PP, and the 2017 multinational APRONET study demonstrated PP in 33% of severe ARDS cases (1, 3, 11).

Prior work has shown that interventions to overcome barriers to utilization of LTV would be cost-effective (12), but ways to improve utilization of PP have not been examined. The barriers to PP uptake have been described as including staff training, physician awareness of patient eligibility, and cultural factors around ventilator management (11, 13). Constrained nursing and other staffing resources are almost certainly major barriers as well, but the most appropriate intervention to surmount these barriers likely varies by setting.

Thus, to guide hospitals in how to select an intervention to facilitate greater PP adoption, and to inform payers regarding reimbursement for the care of patients requiring PP, we evaluated the cost-effectiveness of putative interventions, such as adding a dedicated nurse specialist, from both the hospital and societal perspectives. In performing this evaluation, we note that

an intervention that increases survival of ill patients results in a greater number of patients consuming healthcare resources, both through longer lengths of stay (LOS) in the hospital and greater healthcare utilization following discharge. As such, even if an intervention that increased utilization of PP was free, such as an electronic reminder, it still might be more expensive due to additional survivors consuming resources. Such costs of greater survivorship might be considered reasonable or even desirable. Nonetheless, quantifying the overall cost-effectiveness of interventions with different implementation costs would help hospitals choose which interventions to prioritize. This may help hospitals choose between interventions to augment relatively inexpensive interventions such as PP versus more expensive interventions such as extracorporeal membrane oxygenation (ECMO) (8, 14).

Materials and Methods:

Following recommendations from the second panel on cost-effectiveness in health and medicine, we created two decision trees to separately model the decisions to implement an intervention from the societal and hospital perspectives (15). Each tree had a base-case for the care and outcomes of patients with moderate-severe ARDS based on the age and comorbidity distributions from LUNG-SAFE or PROSEVA (1, 16). An intervention-case was modeled where the only differences from the base-case was the percentage of patients receiving PP and costs associated with the intervention. We assumed the intervention would increase utilization from a base level of 16% to 65%, approximately the current uptake of LTV in the LUNG-SAFE study (1). We varied the ultimate uptake from 24% to 65% in sensitivity analyses.

The societal model assigned a proportion of moderate-severe ARDS patients to either sepsis or a non-sepsis etiology for ARDS based on studies showing increased mortality for sepsis (17). It accumulated costs and calculated mortality through ICU stay, inpatient ward stay, followed by outpatient healthcare and quality-adjusted life years (QALY) until death or age 100 (Supplemental Figure 1). Per the recommendations of the consolidated health economic evaluation reporting (CHEERS) document and the second panel on cost-effectiveness in health and medicine, the societal model used the QALY as the outcome of interest, with QALY data drawn from cohort studies following survivors of ARDS beyond hospital discharge (15,18–20).

Since there is currently no direct reimbursement for PP, any costs associated with an intervention would be borne directly by the hospital. From a budgetary standpoint, hospitals would want to account for any differences in costs to the hospital as well as changes to survival, when deciding whether to adopt an intervention. Thus, we also conducted a cost-effectiveness analysis (CEA) from the hospital perspective, measuring effectiveness using survival-to-hospital-discharge as the outcome and included only costs directly associated with hospitalization and interventions (Supplemental Figure 2).

To understand the acceptable cost of the proposed hypothetical intervention, a variable in the model to represent per patient intervention costs was created. Initially this variable was set to \$0, and then was increased until the cost effectiveness equals one of several previously described thresholds for a willingness to pay ratio (21,22). The complete set of outcome

assumptions and resources for the models can be found in Table 1 and cost inputs can be found in Table 2 (1,3,12,16–19, 23–26). For a better understanding of the methods and rationale used in the construction of the models and analyses please review the Supplemental Methods available online. All costs were adjusted to 2012 US dollars using the bureau of labor statistics calculator (27). Future costs and QALY accumulation were depreciated by 3% annually to account for inflation and future discounting (15). Incremental cost-effectiveness ratios were calculated to quantify the increased cost for one additional QALY or survival to discharge depending on the model perspective.

For both models, one-way sensitivity analyses were performed for all variables. To address the interactions of the uncertainty between each of the model inputs, a probabilistic analysis was performed using a second-order Monte Carlo simulation on 100,000 iterations to generate CIs around the point estimates for the results reported (28). Confidence intervals that cross 0 in such analyses include values suggesting cost savings rather than added costs. All computations were performed using TreeAge (Williamstown, MA) and Stata Version 14.1(StatCorp LP, College Station, Tx). The University of Pennsylvania Institutional Review Board approved this protocol as exempt.

Results:

In the societal perspective model, an intervention that increased proning utilization from 16% to 65% yielded an additional 0.779 (95% CI 0.088-1.714) QALY at an additional long-term cost of \$31,156 (95% CI -\$158 - \$92,179), [ICER = \$38,648 per QALY (95% CI \$1,695-\$98,522)]. In this case, all extra costs accrue due to lives saved and increased LOS for non-survivors. Calculating this another way, the number of patients needed to treat (NNT) for an additional QALY would be 1.3. If society was willing to pay \$100,000 per QALY, the cost of the intervention could be increased to \$51,328 per patient with moderate to severe ARDS while still representing good value. Corresponding thresholds under which interventions would represent good value are \$12,331 per patient if society was willing to spend \$50,000 per QALY, and \$129,324 per patient if society was willing to spend \$200,000 per QALY. Figure 1 quantifies the effect of the variables with the greatest impact in multiple one-way sensitivity analyses for the societal model. Supplemental Figure 3 plots the ICER distribution of the probabilistic sensitivity analyses.

From a hospital perspective, the same base-case intervention yielded 0.072 (95% CI 0.008-0.147) more survivals-to-discharge at a cost of \$5,242 (95% CI -\$19,035-\$41,019) (ICER = \$44,615 per extra survival (95% CI -\$250,912-\$558,222)). Extrapolating this, for every 100 severe ARDS patients in a hospital that invests in an intervention to increase prone positioning rates, an additional 7.2 would survive to discharge compared with current standards of care, at a cost of \$524,000. Phrasing this another way, the NNT for an additional survival would be 13.9. Changing the final utilization of PP did not significantly affect the ICER between a final rate of 24% and 95%, although at higher rates a larger number of survival-to-discharges were accumulated. There is no standard threshold at which to value an extra survival-to-discharge, but using a similar framework to the societal analyses of QALY, if hospitals were willing to pay \$100,000 per survival-to-discharge, the cost of the intervention could be increased to \$5,140 per patient while still representing good

value. The intervention would similarly represent good value at \$1,557 per patient for a willingness to pay \$50,000 per survival-to-discharge, and at \$12,306 per patient for a willingness to pay \$200,000 per survival-to-discharge. Figure 3 shows the variables with the greatest impact in one-way sensitivity analyses for the hospital model. Supplemental Figure 4 plots the ICER distribution of the probabilistic sensitivity analyses.

Discussion:

This study quantifies the cost-effectiveness across a broad range of assumptions from a societal and hospital perspective of a hypothetical intervention to increase PP utilization for patients likely to benefit. This is of interest for decision makers attempting to improve on observed to expected survival for patients with ARDS, and we found a NNT of approximately 14 to achieve one additional survival. We assumed that such an intervention would, at best, increase utilization to 65% of patients who would benefit, given that is the current LTV utilization rate, although sensitivity analysis showed that the ICER was relatively unchanged even if that target ranged from 24% to 95%, indicating that more QALYs would be accumulated at correspondingly increased costs. If interventions with fixed annual costs to promote PP were even more effective at increasing utilization, their cost-effectiveness would be even more favorable. Similarly, if interventions to promote PP also increased rates of other appropriate interventions, including LTV, it might be even more favorable. The specific selection of an intervention (eg., paying for increased nurse staffing, incentivizing physician behavior, educational campaigns, or other behavioral modification efforts) was not a part of this analysis.

Although data about the actual impact of such an intervention on ICU LOS and costs has not been studied, the PROSEVA trial provides guidance: survivors in the PP and supine arms had similar LOS, but decedents in the PP arm had significantly longer LOS. This results in increased cost for any intervention that increases the number of prone patients. Additionally, from an economic perspective, the larger number of survivors, who have greater subsequent healthcare utilization, increase costs. Because we incorporated the best available estimates of these additional costs into our analyses, these results provide “complete” estimates of the intervention’s costs and effects to most usefully guide hospitals, payers, and policymakers.

To put the results of this study in context, we convert the per-patient costs that were found in our analysis in terms of several systems that would benefit from these data. Consider a hospital that currently utilizes PP for 16% of eligible patients and is considering hiring a practitioner whose sole mission would be identifying eligible patients and ensuring that PP is utilized. If this practitioner enabled PP to be used for 65% of appropriate patients, the hospital admits 50 such patients each year, and hospital leaders believe an additional patient surviving to discharge is worth \$75,000, then it would be good value for this hospital to hire any practitioner costing less than \$3,348 per patient, or \$167,400 annually. If the hospital admitted more patients with moderate-severe ARDS, or placed greater value on saving one additional life, then it should be willing to spend even more. Similarly, if a less expensive intervention were developed that proved to be similarly effective, such as a default order

entered automatically for patients identified by the electronic health record as being eligible for PP, then hospitals who admitted few eligible patients should be willing to support it (29).

Alternatively, an integrated health system that also insures its beneficiaries might consider all costs, including additional downstream costs of survivors, making the results of our societal model more relevant. Suppose such a system was willing to pay \$50,000 per QALY gained and admitted 200 patients with moderate-severe ARDS annually. Our results suggest that this health system should be willing to budget up to \$12,331 per patient, or \$2,466,200 annually, for a combination of technological decision aids, financial incentives, and staff support. Again, health systems that place greater value on QALYs gained or admit more patients with severe ARDS, should be willing to expend greater resources on PP implementation.

This study is designed to aid in decision-making for allocating healthcare resources. For decision makers, our results demonstrate that investment in a program to improve appropriate PP utilization is a rational use of resources societally given other accepted interventions (30). This study also highlights the challenge of using the hospital perspective in cost effectiveness analyses; it is unclear what value should be placed on an additional patient surviving to discharge. However, these results do provide a starting place for hospital directors to make informed decisions about fund allocation among different interventions impacting diverse patient populations. A recent clinical trial assessing the effect of ECMO on ARDS survival demonstrated the possibility of clinical benefit, and a future CEA comparing ECMO to increased PP utilization would certainly be interesting (31). Currently the lack of data concerning ECMO costs in ARDS patients, the limitation of the previously cited trial to patients with more severe ARDS than in PP trials, and the effect of ECMO exposure on survivor outcomes prohibit including it in this model.

This analysis has several strengths. First, the data inputs to the study come from recent and reliable sources, as several cohort studies following patients with ARDS have been published in the past two years, allowing considerable specificity in our downstream survival and cost estimates (18, 19, 26, 32, 33). Similarly, a recent epidemiological study and subsequent analyses allowed an understanding of the current geographic treatment patterns and demographics of ARDS globally (1, 10). Second, the availability of the raw, patient-level data of the PROSEVA trial allowed quantification of the specific differences in the clinical course between a prone arm and a supine arm when other factors were controlled, as per the recommendations for CEA from the American Thoracic Society (16, 29). Third, by performing the analyses from both societal and hospital perspectives, these analyses follow modern recommendations for CEA (15) and provide guidance to health systems, payers, and policymakers alike.

An additional strength is that the analyses reveal which specific model inputs most affect the predicted value of an intervention. For example, the one-way sensitivity analyses reveal that the variables whose uncertainty most impacted the estimates of cost-effectiveness in the societal model were the relative LOS values for survivors and decedents, the cost of lost income, the effectiveness of PP at reducing mortality, and the mean age of patients. The LOS variables were taken directly from the PROSEVA trial, in which patients experienced a wide

range of LOS. This makes the CIs around our point estimates for LOS wide, though similar to those found in other papers evaluating the cost of hospitalization for survivors of ARDS (18, 34, 35). Negative values for costs should be interpreted as demonstrating that a certain percentage of the simulations suggested a profit to the intervention instead of a cost, and not as a lack of statistical significance. The cost of lost income was generated from a single small cohort study, giving large CI, resulting in a large impact on the final confidence intervals. The effectiveness of PP includes wide CIs consistent with the meta-analysis (24). Patient age is expected to have an effect when QALY is the outcome of interest. However, this analysis demonstrates that for the entire range of uncertainty around the effectiveness of PP, the point estimate of the ICER remains below \$50,000 per QALY.

Nonetheless, like all CEAs, limitations of the data sources used to generate model inputs must be considered in interpreting this study's results. With only a single prospective randomized controlled trial to draw from, it is unclear how reliable the values for ICU LOS are when forecasting for other institutions. From a point-estimate standpoint, however, the values for ICU LOS and cost are similar to previously published studies (24, 34–36). The cohort studies used for outpatient QALY and cost estimations in the first 5 years were not stratified by ARDS severity, but are the most complete sources of data available (18, 34). It is unclear what the actual nursing costs are for proning a patient, although based on the experience of the authors, the estimate of an additional nurse for the entire time proned is conservative. Opportunity costs for the hospital were not included in our hospital perspective model, but this was a conservative decision given the decrease in ICU LOS among PP survivors. Another limitation in this study is the method used to calculate hospital costs. Deriving total cost from LOS and mechanical ventilation allowed differentiation between the individual costs of each ICU day, which is more precise than simply using a cost per day formula (25). It does not, however, allow for a more sophisticated breakdown of costs into variable and fixed costs, or attempt to quantify the opportunity costs of an occupied bed, which would potentially be more useful for a decision-maker (35, 37). Perhaps most relevantly, this analysis does not attempt to describe the specific method of fund utilization that would be most effective, although there is a growing body of evidence in critical care implementation science that could be used for guidance (38, 39).

Conclusion:

Critical care represents a highly resource intensive area in healthcare, with few interventions that have been shown to be cost-effective. The high mortality from ARDS makes it an attractive target for intervention and PP has been shown to be clinically effective. This analysis allows decision makers to determine the range of interventions to increase PP utilization that would be cost-effective under commonly accepted thresholds. Applying a similar analytic framework to other ICU interventions would help improve the overall cost-effectiveness of critical care in diverse settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Societal Model Tornado Diagram showing one-way sensitivity analyses for cost effectiveness of an intervention. Bars to the left of the point estimate indicate that the intervention becomes more cost effective at the limits of the range for that variable. Bars to the right of the point estimate indicate that the intervention becomes less cost effective at the limits of the range for that variable.

Figure 2:

Hospital model tornado diagram showing one-way sensitivity analyses for cost effectiveness of an intervention. Bars to the right of the point estimate indicate that the intervention becomes less cost effective at the limits of the range for that variable. Bars to the left of the point estimate indicate that the intervention becomes more cost effective at the limits of the range for that variable.

Table 1:**Model Outcome Measures Inputs and Sources**

Value	Survivors	Non-survivors	Standard Deviation	95% CI or IQR	Distribution	Citation
Age	Mean = 61.5		9.6	IQR 55.0-80.2	Normal	(1, 3)
Percent of patients with ARDS from sepsis	75.4%		0.05	0.66 – 0.85	Normal	(1)
Increased odds of mortality with sepsis as etiology of ARDS	1.2		1.2 – 1.3		Normal	(17)
Base-case probability of prone positioning	16.3%		0.1	0.1 – 0.2	Beta	(1)
Effectiveness of prone positioning on ICU mortality	45.5% reduction		11.1%	5.0% – 71.0%	Normal	(16, 23)
Probability of dying in the ICU	34.9% (control in PROSEVA)			26.4% – 52.0%	Direchlet	(1, 16)
Probability of dying on the ward	3.2%			2.0% – 4.5%	Log normal	(1, 16)
Ward length of stay (days)	Median = 12.0	Median = 5.0		IQR Survivors 7.0-20.0 Non-survivors 1.0-12.0	Exponential	(1, 16)
ICU length of stay in supine patients (days)	24.9	18.9	SD Survivors 24.7 Non-survivors 19.9		Exponential	(16)
Change in ICU length of stay in prone patients (days)	-1.2	2.2	SD Survivors 2.5 Non-survivors 3.6		Normal	(16)
Percent of ICU days mechanically ventilated	Prone: 73.8% Supine: 75.8%	Prone: 92.2% Supine: 92.7%	Prone survivors 2.6% Supine survivors 1.7% Prone non-survivors 3.5% Supine non-survivors 2.8%		Normal	(16)
Probability of outpatient death	First 5 years: per findings in Herridge et al: 2.5-11.0% After, life tables based on age		---		---	(16)
Quality-adjusted life year accumulation per year	First year: 0.5 2 nd -5 th : interpolation between 0.6 and 0.8 >5 years, between 0.8 and 1.0		First year 0.15 Others 0.1		Normal	(17,19,23)

Table 2:**Model Cost Inputs and Sources**

Costs (2012 dollars)	Survivors		Non-survivors	Range	Distribution	Citation
Prone positioning	\$0 / day			0 – \$500	Uniform	
Cost of ICU day 1 with mechanical ventilation (MV)	\$6,845			\$6,713 – \$6,979	Log normal	(24)
Cost of ICU day 2 with MV	\$5,493			\$5,378 – \$5,610	Log normal	(24)
Cost of ICU day 2 without MV	\$4,022			\$3,956 – \$4,090	Log normal	(24)
Cost of ICU day 3 with MV	\$4,795			\$4,506 – \$4,845	Log normal	(24)
Cost of ICU day 3 without MV	\$3,583			\$3,547 – \$3,620	Log normal	(24)
Cost of ward day	\$1,792			\$1,774 – \$1,810	Log normal	(12)
Cost of death	---		\$10,000	\$2,500 – \$15,000	Uniform	
Lost labor	\$25,707 in 71% of patients		---	\$9,800 – 67,500	Log normal	(25)
Healthcare costs of first year after ARDS	\$18,058		0	\$1,500 – \$240,000	Log normal	(28)
Healthcare costs of the 2 nd -5 th years after ARDS	2 3 4 5	\$15,042 \$9,773 \$8,422 \$7,430	0	---	---	(18)