ARTICLE

Cost-effectiveness analysis of multimodal prognostication in cardiac arrest with EEG monitoring

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Abstract

Objective

To determine cost-effectiveness parameters for EEG monitoring in cardiac arrest prognostication.

Methods

We conducted a cost-effectiveness analysis to estimate the cost per quality-adjusted life-year (QALY) gained by adding continuous EEG monitoring to standard cardiac arrest prognostication using the American Academy of Neurology Practice Parameter (AANPP) decision algorithm: neurologic examination, somatosensory evoked potentials, and neuron-specific enolase. We explored lifetime cost-effectiveness in a closed system that incorporates revenue back into the medical system (return) from payers who survive a cardiac arrest with good outcome and contribute to the health system during the remaining years of life. Good outcome was defined as a Cerebral Performance Category (CPC) score of 1–2 and poor outcome as CPC of 3–5.

Results

An improvement in specificity for poor outcome prediction of 4.2% would be sufficient to make continuous EEG monitoring cost-effective (baseline AANPP specificity = 83.9%). In sensitivity analysis, the effect of increased sensitivity on the cost-effectiveness of EEG depends on the utility (u) assigned to a poor outcome. For patients who regard surviving with a poor outcome (CPC 3–4) worse than death ($u = -0.34$), an increased sensitivity for poor outcome prediction of 13.8% would make AANPP + EEG monitoring cost-effective (baseline AANPP sensitivity = 76.3%). In the closed system, an improvement in sensitivity of 1.8% together with an improvement in specificity of 3% was sufficient to make AANPP + EEG monitoring cost-effective, assuming lifetime return of 50% (USD $70,687).

Conclusion

Incorporating continuous EEG monitoring into cardiac arrest prognostication is cost-effective if relatively small improvements in sensitivity and specificity are achieved.

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Glossary

AANPP = American Academy of Neurology Practice Parameter; **CPC** = Cerebral Performance Category; **GCS** = Glasgow Coma Scale; **HUI-3** = Health Utility Index Mark 3; **NSE** = neuron-specific enolase; **QALY** = quality-adjusted life year; **SSEP** = somatosensory evoked potentials; **WTP** = willingness to pay.

More than $11 billion is spent annually in post–cardiac arrest care in the United States.[1] Survival of out-of-hospital cardiac arrest has steadily improved over the last 15 years, causing an increased demand for neurocritical care services and prognostication consultations for these patients.[2–5] Recent guidelines in post–cardiac arrest care specifically recommend EEG for the diagnosis and treatment of seizures and prognostication.[5] Despite strong recommendations for early and frequent brain monitoring with EEG after cardiac arrest, real-world utilization of EEG in this context is low.[6]

Proposed reasons for the low adherence to expert consensus recommendations for EEG monitoring after cardiac arrest include costs related to intermittent and continuous EEG monitoring, low availability of experts with adequate training to interpret critical care EEG records, and the fact that it is not known if seizures after cardiac arrest are exclusively hallmarks of severe brain injury or if these patterns are amenable to treatment.[6,7] Limited information is available on the cost-effectiveness of adding EEG to standard prognostication in cardiac arrest.[8] Previous studies have shown increased seizure diagnosis yield with continuous vs intermittent EEG monitoring, but no improvement in outcomes was observed with more monitoring despite substantial increase in costs.[7,9]

Using a decision analysis framework that incorporates the patient's perspective about neurologic outcomes and prognostication accuracy, we aimed to examine the cost-effectiveness of adding continuous EEG monitoring to the American Academy of Neurology Practice Parameter (AANPP) decision algorithm for hypoxic–ischemic coma prognostication, which includes clinical examination, somatosensory evoked potentials (SSEP), and serum neuron-specific enolase (NSE).

Methods

Model structure

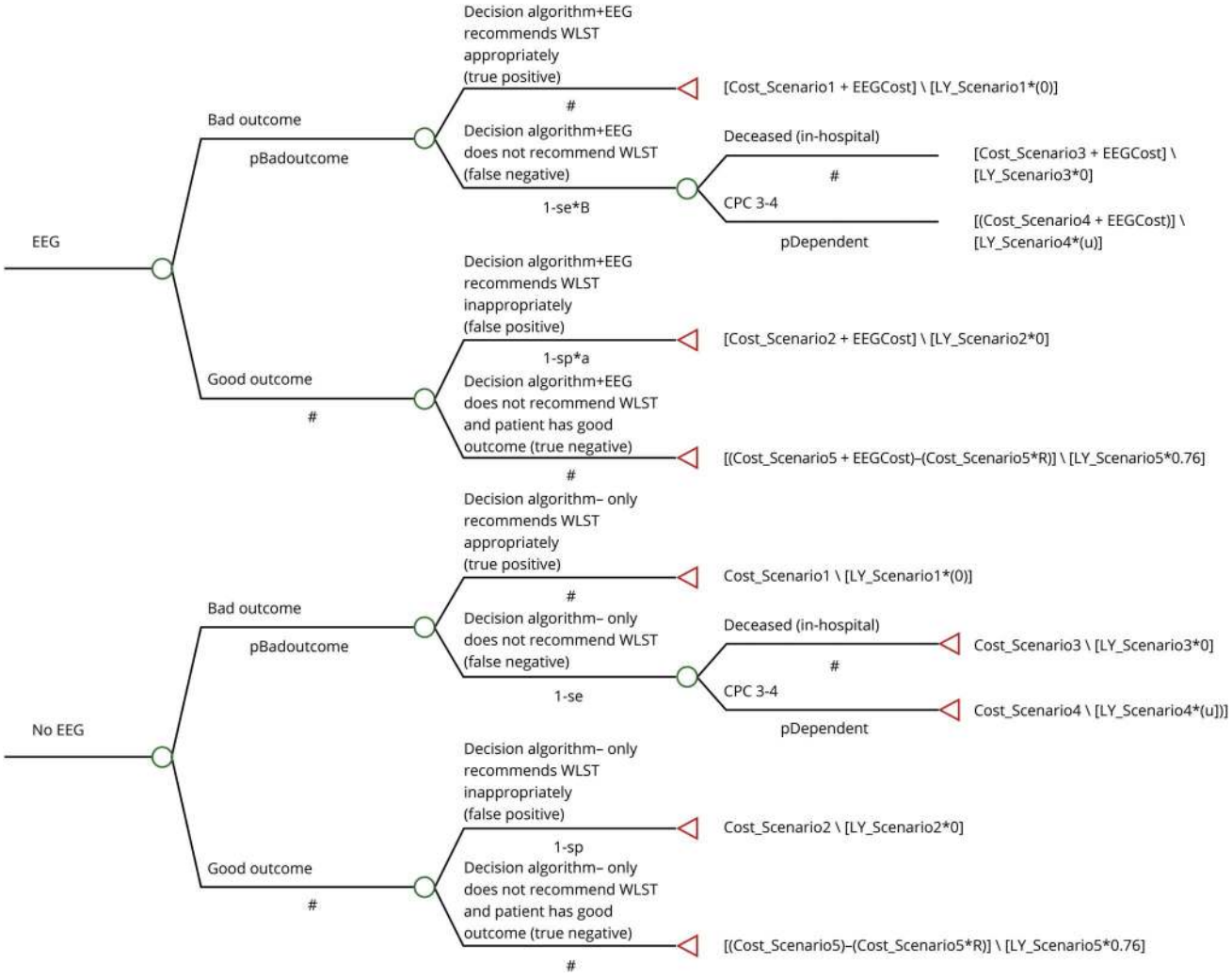
Our decision tree model focuses on 2 strategies for cardiac arrest coma prognostication: (1) the AANPP decision algorithm, termed decision algorithm–only prognostication,; and (2) EEG monitoring in addition to the AANPP decision algorithm, termed decision algorithm + EEG. We also compare the decision algorithm–only to the decision algorithm + brain MRI strategy (supplementary materials). In both the decision algorithm–only and decision algorithm + EEG arms, each patient's true status is classified as binary, either a poor outcome with probability pPO, or good outcome with probability 1 − pPO. Poor outcome is defined as death, equivalent to a Cerebral Performance Category (CPC) score of 5, or a dependent state due to severe neurologic disability, CPC 3, or vegetative state, CPC 4. Good outcome indicates that the patient is able to perform independent activities of daily living, that is, CPC of 1–2.[10]

The AANPP decision algorithm makes a determination of poor outcome when clinical examination, SSEP, or serum NSE results indicate severe brain injury. If no conditions are satisfied, the AANPP suggests an indeterminate outcome. Because no criteria for good outcome prediction are incorporated in the AANPP algorithm, our prognostication classification is also similarly binary: it predicts either poor or indeterminate outcome. A poor outcome prognostication means that the patient satisfies criteria for withdrawal of life-sustaining therapies based on either decision algorithm–only or decision algorithm + EEG prognostication methods, and that life-sustaining therapies are withdrawn (figure 1). The assumption is made that once life-sustaining therapies are stopped, the patient necessarily dies. By contrast, an indeterminate outcome prognostication means criteria for withdrawal of life-sustaining therapies have not been satisfied and life support will continue indefinitely.

Coupling the medical outcome (poor outcome or good outcome) with the prognostication outcome (poor outcome prognostication or indeterminate outcome prognostication), our model has 5 potential patient outcomes per prognostication arm (cost scenarios, figure 1): (1) withdrawal of life-sustaining therapies appropriately (poor outcome with poor outcome prognostication); (2) withdrawal of life-sustaining therapies inappropriately (good outcome with poor outcome prognostication; i.e., the patient would have survived with good outcome if life-sustaining therapies were not stopped); (3) in-hospital death despite continuation of life support (poor outcome with indeterminate outcome prognostication and probability, 1 − pDep); (4) dependent state with continuation of life support (poor outcome with indeterminate outcome prognostication and probability pDep); and (5) independent state (good outcome with indeterminate prognostication).

In our model, Se and Sp indicate the baseline sensitivity and specificity of the AANPP decision algorithm–only prognostication. In the setting of decision algorithm–only prognostication, we define Se as the probability that poor outcome prognostication occurs in a patient whose natural outcome would be a poor outcome (true positive/condition positive).

Figure 1 Decision tree model for cost-effectiveness analysis comparing multimodal prognostication with and without continuous EEG monitoring



Cost-effectiveness for the decision algorithm–only (clinical examination + somatosensory evoked potentials [SSEP] + serum neuron-specific enolase [NSE]) and the decision algorithm + continuous EEG monitoring are evaluated in 5 outcome scenarios: (1) appropriate withdrawal of life-sustaining therapies (poor outcome with poor outcome prognostication); (2) withdrawal of life-sustaining therapies inappropriately (good outcome with poor outcome prognostication); (3) dependent state (poor outcome with indeterminate outcome prognostication and probability pDep); (4) in-hospital death despite continuation of life support (poor outcome with indeterminate outcome prognostication and probability, 1 − pDep); and (5) independent state (good outcome with indeterminate prognostication). a = improvement in specificity from baseline; B = improvement in sensitivity from baseline; CPC = Cerebral Performance Category; LY = life-years; Se = sensitivity; Sp = specificity; u = utility; WLST = withdrawal of life-sustaining therapies.

Sp was defined as the probability that an indeterminate outcome prognostication occurs in a patient whose natural outcome would be a good outcome (true negative/condition negative). Our model explores the parameter space in which addition of EEG monitoring to the AANPP decision algorithm can improve poor outcome prediction, i.e., increase the area under the curve by improving Se or Sp, or both. To examine this, we model tune-able Se and Sp coefficients to account for each of these possible conditions. Assuming an increase in Se is possible, and noting that Se must be a value between 0 and 1, we define the sensitivity coefficient of decision algorithm + EEG prognostication as B, where $1 < B < 1/Se$. B can be interpreted as the percentage improvement in Se due to adding EEG monitoring, e.g., B = 1.1 means that the addition of EEG (decision algorithm + EEG) improves the sensitivity of baseline decision algorithm–only prognostication by 10%. Similarly, a is the specificity coefficient of the decision algorithm + EEG prognostication approach, defined as $1 < a < 1/Sp$. Thus, in the setting of the decision algorithm + EEG, Se × B is the probability that poor outcome prognostication occurs in a patient whose natural outcome is a poor outcome, and Sp × a is the probability that indeterminate outcome prognostication occurs in a patient whose natural outcome would be a good outcome.

In order to understand the model, we must couple interpretation of sensitivity and specificity improvements with cost scenarios. Increasing sensitivity means identifying more

patients who would have a poor outcome and, consequently, increase in appropriate withdrawal of life-sustaining therapies (scenario 1). This would lead to fewer patients with indeterminate outcome predictions ending up in scenario 3, death during that hospital stay despite intensive medical care, or scenario 4, survival in a dependent state. On the other hand, increasing specificity means identifying more patients who would have a good outcome, i.e., avoid withdrawal of life-sustaining therapies by providing an indeterminate outcome prognostication (scenario 5). This would lead to fewer patients dying after having inappropriate withdrawal of life-sustaining therapies (scenario 2).

Costs or return

To examine cost-effectiveness, specifically the relative cost per quality-adjusted life year (QALY) gained by improved prognostication, we assign to each scenario an associated total medical cost and QALY based on the product of mean life years post cardiac arrest with the outcome utility from the patient's perspective (table 1).

We also define a nonzero returns term, defined as R, for scenario 5 (independent state), to allow for our model to assume 2 different modes: (1) open system, where $R = 0$ and (2) closed system, where $R > 0$. In the open system, we assume no return of capital into the medical system by patients who had a good outcome on discharge. Thus, we restrict our analysis to examining the ratio of net cost for the hospital system relative to QALYs gained.

In the closed system, we allow $R > 0$ so patients in scenario 5, survival with good outcome, have the potential to bring revenue back into the system following hospital discharge during their remaining years of life. In a single-payer medical system, this could be through paying taxes and in a multipayer system via additional insurance premiums or other health care spending. Return could also be evaluated based on the opportunity cost of surviving with good outcome and continued employment after discharge, e.g., wages. Thus, in a closed system, we can examine the range of values of R that still result in EEG monitoring being overall cost-effective. Return can be interpreted as how many times the cost of care for survivors (both independent and dependent) must bring back into the system for adding EEG to the prognostication approach with the decision algorithm–only to be financially justifiable to the health care system. The complete decision tree is shown in figure 1.

Model parameters and assumptions

Model parameters (tables 1 and 2) were adapted from published estimates of health care costs, mean post cardiac arrest life-years, patient-perceived utility of outcomes, and prognostication probabilities.[11–18] Costs were adjusted for inflation from the year of publication to December 2018.[19] The total number of patients who develop a cardiac arrest yearly in the United States and respective outcomes were estimated from a summary of national databases.[20]

We chose utility base case values for the model based on the Health Utility Index Mark 3 (HUI-3).[21] A HUI-3 score of 1 is equivalent to perfect health and a score of 0 is equivalent to death. The utility values used in this study have been validated in the cardiac arrest population: patients with a good outcome (CPC 1–2) had a utility score of 0.76; patients surviving with a CPC of 3 had "better than death" utility ($u = 0.3$), but survivors with a CPC of 4 were considered to have "worse than death" utility ($u = -0.34$).[22,23] As individual patients' views about the utility of surviving in a dependent state, i.e., CPC 3–4, might vary, we performed a sensitivity analysis based on a range of utility values that patients might assign to a dependent state (figure 1).

Total health care costs (including hospitalization, prognostication without EEG-related costs, and postdischarge care) per scenario ranged from $36,343 to $163,666 (USD). Costs related to continuous EEG monitoring for 48 hours postarrest using conventional 21- or 4-channel montages were used as base-case values for EEG monitoring. The estimated cost of continuous 21-channel EEG monitoring for 48 hours is $5,080, while the estimated cost of a single short-term 21-channel EEG monitoring for <60 minutes is $1,645 (local EEG laboratory costs), and continuous 4-channel EEG monitoring for 48 hours is $626 (Bispectral Index, Medtronic, Minneapolis, MN).[24] We also investigated the cost-effectiveness of adding brain imaging with MRI to the decision algorithm independently or in addition to EEG monitoring.

Further, we assumed that changes in *u(dependent)*, CPC 3–4, do not affect a in our sensitivity analyses. This assumption appears reasonable since there is no clear relationship between decision algorithm–only specificity and the patient's perspective about the utility of surviving in a dependent state, as these patients would have died after withdrawal of life support. The presence of a Glasgow Coma Scale (GCS) motor score <3 was used as the performance proxy for multimodal prognostication using the AANPP decision algorithm, since exact outcome distributions for all possible combinations of predictors could not be determined—the frequency of predictors combinations stratified by outcome is not reported in the literature. Willingness to pay (WTP) was assumed to be $50,000 per QALY in all of our analyses. All analyses were conducted using TreeAge Pro 2.1 (TreeAge Software, Inc., Williamstown, MA).

Data availability

All data analyzed during the current study are included in this published article and its supplementary files.

Results

We evaluated the cost-effectiveness of implementing continuous EEG monitoring in addition to the AANPP decision algorithm for prognostication in hypoxic-ischemic coma by

Table 1 Base-case cost parameters per patient and discharge disposition

	Base case (USD, $)	Assumptions	References
Decision algorithm–only (total cost)	1,059	Serial neurologic examination, SSEP, and NSE	Wijdicks et al.[11]
Neurologic examination	0	Neurologic examination does not require separate charge	Not applicable
Serum NSE	170	Measured once	Estimation from local EEG laboratories
SSEP	889	Measured once	Estimation from local EEG laboratories
Hospitalization costs per day according to level of care			
ICU	13,801	Patient on mechanical ventilation	Kahn et al.[12]
Hospital ward	5,867.8		Kahn et al.[12]
Total hospitalization costs			
Nonsurvivor (despite continuing life support)	35,284	1.6 days ICU stay and 2.25 days in hospital ward; 31.4% of in-hospital deaths	Carr et al.,[13] Elmer et al.[14]
Nonsurvivor (WLST)	40,271	1.6 days ICU stay and 3.1 days in hospital ward; 68.6% of in-hospital deaths	Carr et al.,[13] Elmer et al.[14]
Survivor	131,775	3.8 days ICU stay and 13.5 days in hospital ward	Carr et al.,[13] Elmer et al.[14]

Initial post-discharge care placement	Independent (CPC 1–2), %	Dependent (CPC 3–4), %	References
Acute rehabilitation (inpatient facility)	26.1	29.6	Amorim et al.[15]
Skilled nursing facility	17.4	33.8	Amorim et al.[15]
Long-term acute care	2.2	9.9	Amorim et al.[15]
Hospice	0	7	Amorim et al.[15]
Home	54.3	19.7	Amorim et al.[15]

	Base case (USD, $)	Assumptions	References
Annual postdischarge costs stratified by placement			
Acute rehabilitation (inpatient facility)	19,721	Average Medicare payment per patient in 2014	MEDPAC[16]
Skilled nursing facility	14,052	Average Medicare payment per day $312 and average length of stay of 42 days in 2014	MEDPAC[16]
Long-term acute care	42,997	Average Medicare payment per patient in 2014	MEDPAC[16]
Hospice	12,249	Average Medicare payment per patient in 2014	MEDPAC[16]
Lifetime postdischarge cardiac arrest care costs and return			
Independent (CPC 1–2)	8,538	Mean survival of 10.5 years	Phelps, 2013[25]
Dependent (CPC 3–4)	30,832	Mean survival of 2.68 years	Phelps, 2013[25]
Health insurance premium per year	6,896	Average annual premium for employer-sponsored health insurance	Kaiser family foundation[18]
Annual salary estimate per year	50,620	Average annual mean wage for all occupations in the United States	US Department of Labor[19]
Out-of-hospital cardiac arrest national yearly estimates, n patients			
Death prior to hospital admission	246,528		Benjamin et al.[20]
In-hospital death	63,194		Benjamin et al.[20]
Discharged alive with good outcome	31,250		Benjamin et al.[20]
Discharged alive with poor outcome	6,250		Benjamin et al.[20]

Abbreviations: CPC = Cerebral Performance Category; ICU = intensive care unit; NSE = neuron serum enolase; SSEP = somatosensory evoked potentials; WLST = withdrawal of life-sustaining therapies.

Table 2 Model cost, parameters, and prognostication scenarios

EEG monitoring modality cost	Base case (USD, $)	Assumptions	References
Continuous 21-channel EEG	5,080	48 hours monitoring and interpretation	Estimation from local EEG laboratories
Short-term (<60 min) 21-channel EEG	1,645	<60 minutes monitoring and interpretation	Estimation from local EEG laboratories
Limited montage 4-channel EEG (BIS)	626	48 hours monitoring (sensor cost per day = $24 and interpretation cost per day = $289)	Pati et al.[24]
Brain MRI without contrast	4,086		Estimation from local Radiology centers

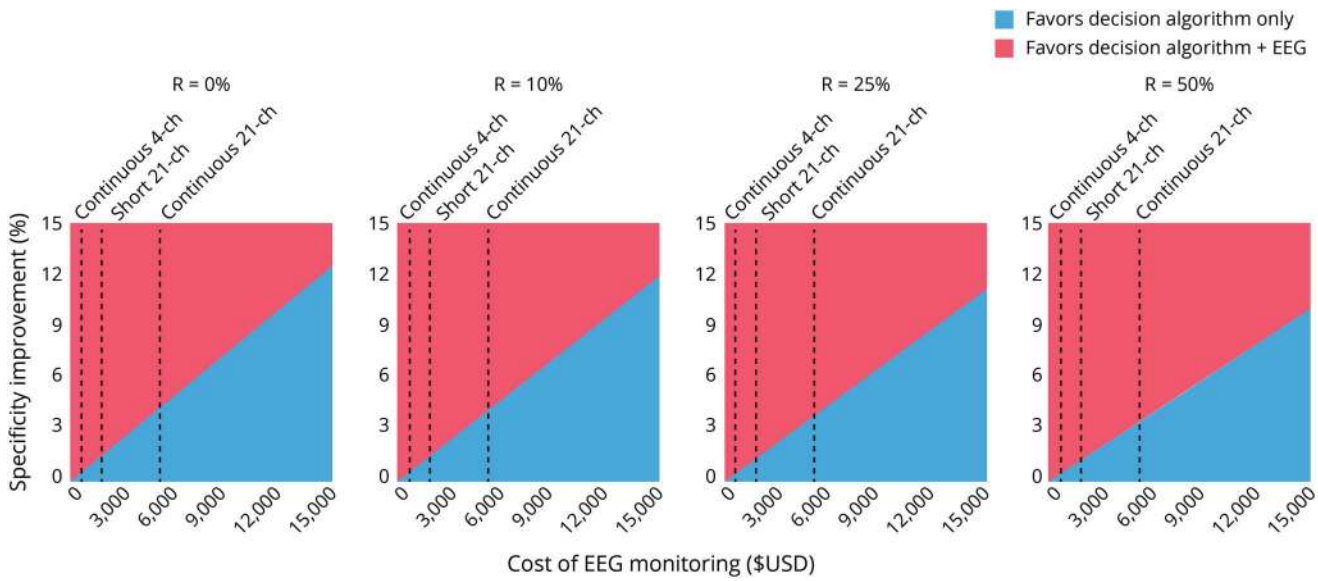
	Rate	Definition	Reference
Prognostication decision algorithm for poor outcome prediction[a]			
Probability of poor outcome (pPO+),	49.6%	Poor outcome defined as CPC 3–5	Rossetti et al.[32]
Probability of a false-negative prediction for survivor with poor outcome (pDependent)	57.1%	Survivor who becomes dependent (CPC 3–4) despite not having a poor outcome predicted on the decision algorithm	Rossetti et al.[32]
Specificity of AAN only	83.9%	Specificity for GCS-motor <3	Rossetti et al.[32]
Sensitivity of AAN only	76.3%	Specificity for GCS-motor <3	Rossetti et al.[32]

Decision model scenarios per prognostication arm	Total cost (USD, $)	Utility to patient	Life-years	QALYs	Assumptions	References
Total cost, utility, and QALYs of model scenarios						
Scenario 1: withdrawal of life-sustaining therapies appropriately (poor outcome with poor outcome prognostication)	41,330	0	0.013	0	Total cost includes cost of decision algorithm and nonsurvivor hospitalization costs in the setting of withdrawal of life-sustaining therapy	Elmer et al.[14]
Scenario 2: withdrawal of life-sustaining therapies inappropriately (good outcome but poor outcome prognostication)	41,330	0	0.013	0	Total cost includes cost of decision algorithm and nonsurvivor hospitalization costs in the setting of withdrawal of life-sustaining therapy	Elmer et al.[14]
Scenario 3: in-hospital death despite continuation of life support (poor outcome with indeterminate outcome prognostication and additional probability, 1 − pDependent)	36,343	0	0.011	0	Total cost includes cost of decision algorithm and nonsurvivor hospitalization costs in the setting of continuing life support	Elmer et al.[14]
Scenario 4: dependent state (poor outcome with indeterminate outcome prognostication and additional probability, pDependent)	163,666	−0.34 to 0.3	2.68	−0.1 to 0.8	Total cost includes cost of decision algorithm, survivor hospitalization costs, and dependent postdischarge costs	Rania et al.[22]; Stiell et al.[23]; Phelps, 2013[25]
Scenario 5: independent state (good outcome with indeterminate outcome prognostication)	141,373	0.76	10.05	7.6	Total cost includes cost of decision algorithm, survivor hospitalization costs, and independent postdischarge costs	Stiell et al.[23]; Phelps, 2013[25]

Abbreviations: AAN = American Academy of Neurology; BIS = bispectral index; GCS = Glasgow Coma Scale; QALYs = quality-adjusted life-years.

comparing 2 distinct hypothetical post–cardiac arrest patient cohorts who received either decision algorithm–only or decision algorithm + EEG prognostication. The total cost of prognostication with the decision algorithm–only approach was $1,059 per patient, and total cost for the decision algorithm–only + continuous 21-channel EEG monitoring was $6,139. The costs of decision algorithm–only and decision algorithm + continuous 21-channel EEG monitoring represent 0.8% and 4.3% of the total hospitalization cost for surviving patients with good outcome, respectively. We conducted a series of 2-way sensitivity analyses, in each case varying important factors that may shape decision-making by health policy makers: the sensitivity coefficient, B, specificity coefficient, a, return, *R*, EEG cost. This allowed exploration of a wide range of values in the parameter space (figures 2 and 3). Varying the utility parameter only affects cost-effectiveness

Figure 2 Two-way sensitivity analysis for multimodal prognostication in an open system or closed system using different levels of return



Cost-effectiveness for the decision algorithm–only (clinical examination + somatosensory evoked potentials + serum neuron-specific enolase) and the decision algorithm + EEG monitoring (continuous 4-channel, short-term, or continuous 21-channel EEG montage) using different return values. The 4 return values provided indicate different levels of lifetime return to the health care system from survivors with good outcome. Improvement in specificity of the decision algorithm + EEG approach is compared to the baseline decision algorithm–only (y-axis). Cost of multimodal prognostication varies on the x-axis. ch = channel; CPC = Cerebral Performance Category.

with sensitivity change while varying the return parameter only affects cost-effectiveness specificity, therefore figure 2 does not include varying utility and figure 3 does not include varying returns.

Open system

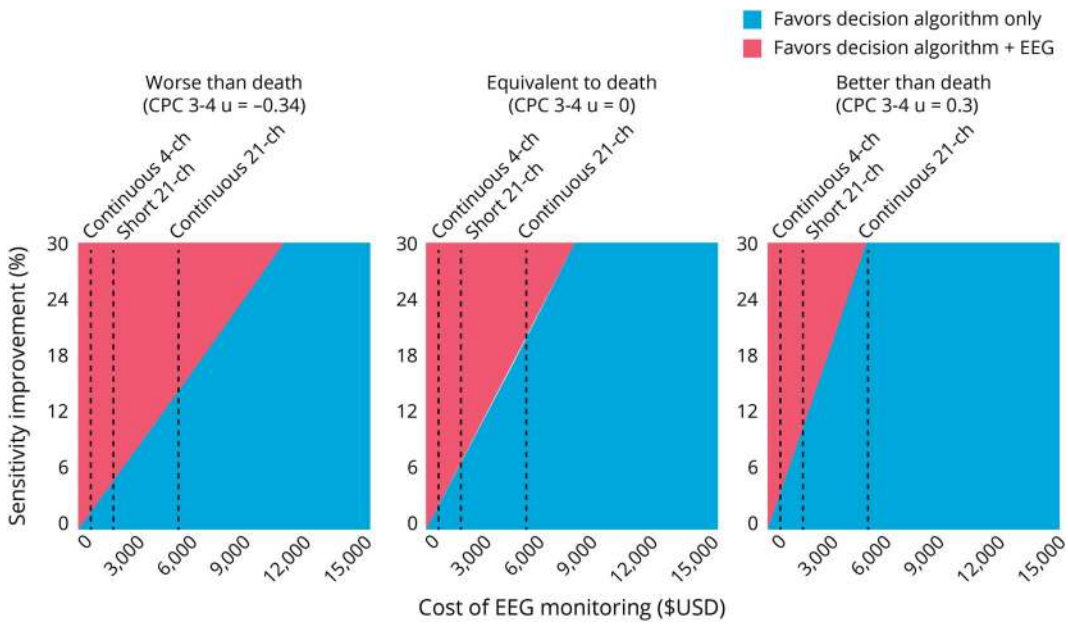
Our analysis showed that an increase of 4.2% in prognostication specificity with correspondingly more patients in scenario 5 due to appropriate continuation of life-sustaining therapies and less in scenario 2 is sufficient for cost-effectiveness of using the AANPP decision algorithm + continuous 21-channel EEG monitoring – assuming no change in sensitivity (R = 0, WTP = $50,000/QALY, and baseline Sp of 83.9%, figure 2). For continuous 4-channel EEG monitoring, an improvement in specificity of less than 1% is sufficient and for short-term 21-channel EEG, 1.5%. Figure 2 summarizes the results of this sensitivity analysis for an open system (R = 0), and it also details trade-offs for a closed system with varying returns to the health care system (R = 10–50%).

Figure 3 summarizes the results of sensitivity analyses for the utility $u(dependent)$ assigned to surviving with a poor outcome (CPC 3–4). Based on prior literature, the utility of surviving with poor outcomes depends on CPC score: better than death (u = 0.3) for CPC 3 and worse than death (u = −0.34) for CPC 4. We also evaluated cases in which the utility of a poor outcome is considered equivalent to death (u = 0). For the base-case value of $u(dependent)$ = −0.34, an increase in sensitivity of 13.8% (with correspondingly more patients in scenario 1 due to appropriate withdrawal of life-sustaining therapies, and less in scenario 3 or 4) is necessary for continuous 21-channel EEG monitoring to be cost-effective, while less than 1% increase is necessary for prognostication with continuous 4-channel EEG and 4.5% for short-term 21-channel EEG. When $u(dependent)$ = 0.3, the needed sensitivity improvement for cost-effectiveness is 30.5% for continuous 21-channel EEG, 9.6% for short-term 21-channel EEG, and less than 2% for continuous 4-channel EEG.

Closed system

We explored cost-effectiveness of adding continuous EEG monitoring using continuous 21-channel EEG monitoring to the AANPP decision algorithm in a closed system by evaluating the interaction between improvement in sensitivity and specificity at various return levels. A closed system analysis examines the realistic hypothetical scenario where patients who are discharged in an independent state after recovering from a cardiac arrest have the potential to bring capital back into the health care system, e.g., by premium insurance payment or wages through continued employment. Our base-case patient with a good outcome after a cardiac arrest who remained employed would have paid throughout the lifetime $69,305 in health insurance and have earned $540,622 in wages on average. In figure 4, we evaluate 12 different scenarios with R values ranging from an open system (R = 0, figure 4A) to a closed system with R = 10%–50% (figure 4, B–D), while varying the utility of survival in the dependent state (CPC 3–4). The required improvement in sensitivity

Figure 3 Two-way sensitivity analysis for multimodal prognostication using different utilities values for surviving on a dependent state outcome (Cerebral Performance Category [CPC] 3–4)



Cost-effectiveness for the decision algorithm–only (clinical examination + somatosensory evoked potentials + serum neuron-specific enolase) and the decision algorithm + EEG monitoring (continuous 4-channel, short-term or continuous 21-channel EEG montage) using different utility values for a dependent state (CPC 3–4). The 3 utility values provided indicate the patient's perspective about the utility of surviving in a dependent state (i.e., surviving with CPC 3–4 is "worse than death," "equivalent to death," or "better than death"). Improvement in sensitivity of the decision algorithm + EEG approach is compared to the baseline decision algorithm–only (y-axis). Cost of multimodal prognostication varies on the x-axis. ch = channel.

and specificity to justify the cost of adding continuous 21-channel EEG monitoring to the decision algorithm decreases as *R* increases. For example, assuming an *R* of 50% ($70,687), an improvement in sensitivity of approximately 2.3% (increased scenario 1, decreased scenarios 3 and 4) together with an improvement in specificity of 3% (increased scenario 2, decreased scenario 5) is cost-effective for *u(dependent)* = 0. For *u(dependent)* = 0.3 and *R* of 50%, an improvement in (sensitivity and specificity) of 3.4% and 3% are needed. For *u(dependent)* = −0.34 and *R* of 50%, an improvement in (sensitivity and specificity) of 1.8% and 3% is cost-effective. If we set *R* to 10% ($14,138), larger improvements in performance are needed (figure 4). In figure 5, we evaluate cost-effectiveness of the decision algorithm + continuous EEG monitoring using a 4-channel EEG montage. For the 4-channel montage, the improvements in sensitivity and specificity required for cost-effectiveness are mainly below 1%. Improvements in sensitivity–specificity trade-offs required for cost-effectiveness in the decision algorithm + brain MRI prognostication approach are inferior but comparable to the decision algorithm + continuous EEG monitoring using a 21-channel EEG montage.

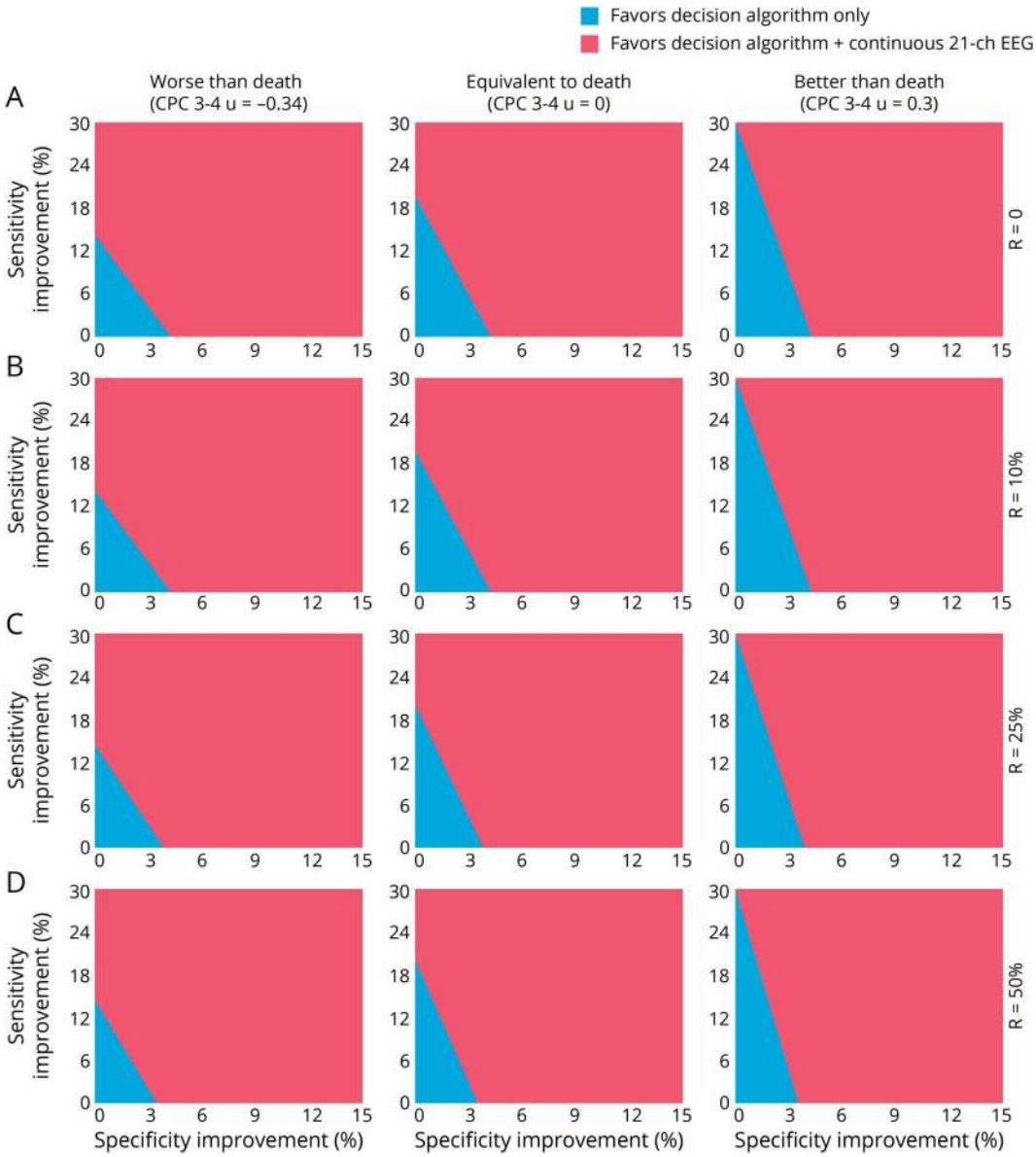
National estimates of post–cardiac arrest care costs and multimodal prognostication

We estimate that approximately 100,694 patients are admitted due an out-of-hospital cardiac arrest every year in the United States (table 1).[20] The projected annual health care–associated costs for post–cardiac arrest care accrued in this patient population would be $8.8 billion. In the hypothetical scenario that all patients admitted to the hospital for post–cardiac arrest in the United States underwent multimodal prognostication, the total annual cost of the decision algorithm–only (clinical examination, somatosensory evoked potentials, and NSE) approach would be $106,634,946, whereas for the decision algorithm + continuous EEG costs would be $169,699,598 (4-channel) or $618,160,466 (21-channel). Assuming all survivors with good outcome remain employed throughout their lifetime (10.5 years), the population-level total return to the system through health insurance premiums and wages would be $2.2 billion (24.6% return) and $15.9 billion (180.5% return) on investment, respectively.

Discussion

Using a 2-way sensitivity analysis, we demonstrated that continuous EEG monitoring in post–cardiac arrest care can be cost-effective with relative small improvements in prognostication performance. We incorporated in our estimates the patient's perspective about surviving with long-term neurologic disability and how these perspectives might influence cost-effectiveness trade-offs in prognostication with and without continuous EEG monitoring. The cost-effectiveness of continuous EEG monitoring for prognostication was influenced by both its ability to rule out survival with poor functional outcomes and to avoid

Figure 4 Two-way sensitivity analysis for multimodal prognostication with continuous EEG monitoring (21-channel) in a closed system

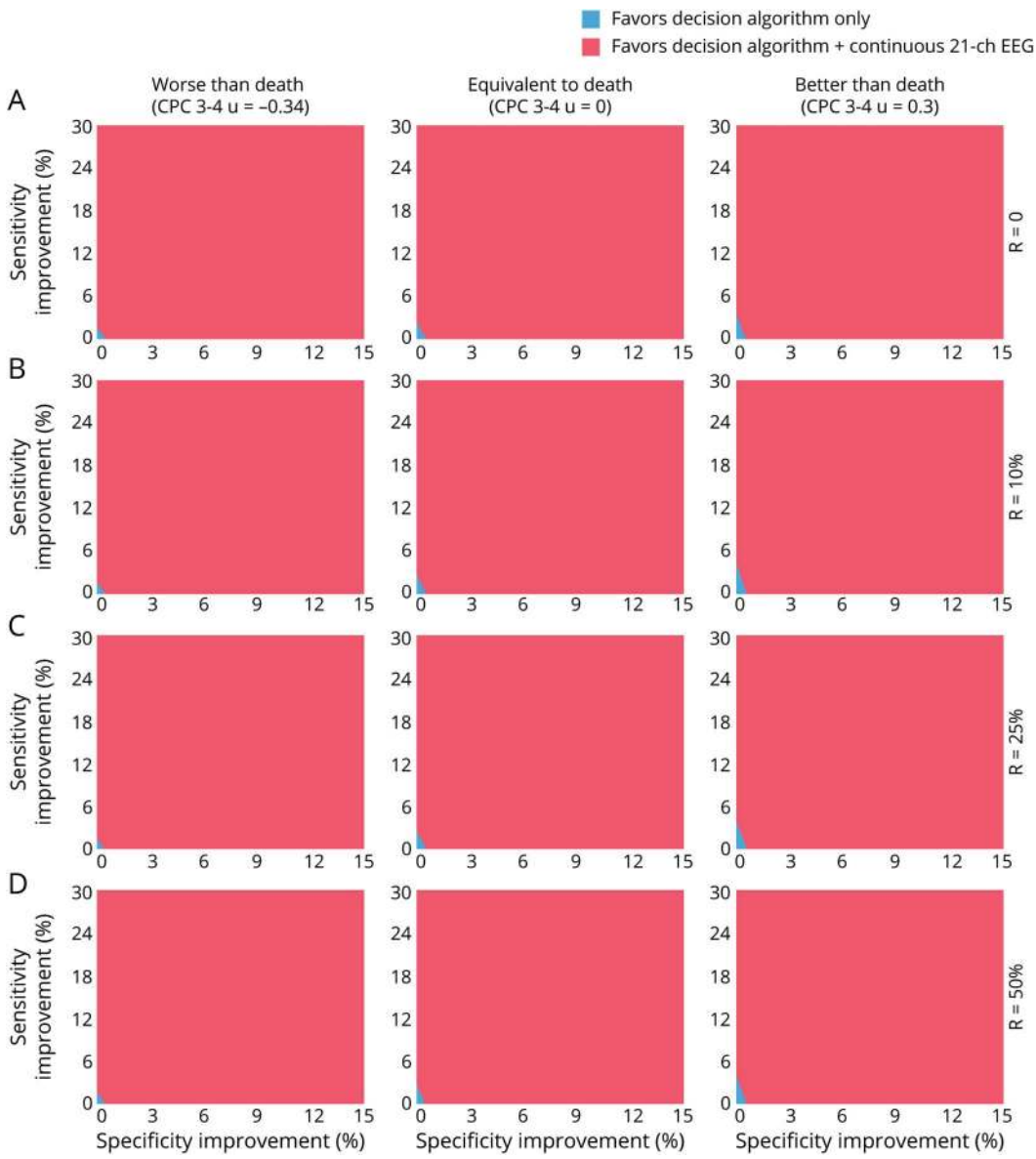


Cost-effectiveness for the decision algorithm–only (clinical examination + somatosensory evoked potentials + serum neuron-specific enolase) and the decision algorithm + continuous EEG monitoring (21-channel) is evaluated in a closed system (i.e., return back into the medical system across lifetime is incorporated). Several levels of return (0%, 10%, 25%, and 50%) are assessed (A–D). The 3 utility values provided indicate the patient's perspective about the utility of surviving on a dependent state (i.e., surviving with Cerebral Performance Category [CPC] 3–4 is "worse than death," "equivalent to death," or "better than death"). Improvement in sensitivity and specificity of the decision algorithm + EEG (21-channel) compared to the baseline decision algorithm–only is varied on the y-axis and x-axis, respectively. ch = channel; R = return.

withdrawal of life-sustaining therapies in patients without definite indicators of poor outcome. These results serve to emphasize that prognostication strategies focused on only preventing false-positive predictions of poor outcome are insufficient, and that improving both sensitivity and specificity of multimodal prognostication are valued by patients and society.

Even though continuous EEG monitoring is a well-established tool for seizure detection and prognostication in cardiac arrest, concern about financial costs remains a barrier for implementation.[5,7,15,26] Our analysis suggests that adding EEG monitoring to the AANPP decision algorithm for cardiac arrest prognostication could be cost-effective when improvements in sensitivity and specificity as low as 4% are observed. Whereas value analyses using long-term EEG monitoring in post–cardiac arrest care prognostication have been done, no cost-effectiveness study has compared different outcome scenarios with and without inclusion of continuous EEG monitoring in prognostication protocols or incorporated QALY to evaluate the

Figure 5 Two-way sensitivity analysis for multimodal prognostication with continuous EEG monitoring (4-channel) in a closed system



Cost-effectiveness for the decision algorithm–only (clinical examination + somatosensory evoked potentials + serum neuron-specific enolase) and the decision algorithm + continuous EEG monitoring (4-channel) is evaluated in a closed system (i.e., return back into the medical system across lifetime is incorporated). Several levels of return (0%, 10%, 25%, and 50%) are assessed (A–D). The 3 utility values provided indicate the patient's perspective about the utility of surviving on a dependent state (i.e., surviving with Cerebral Performance Category [CPC] 3–4 is "worse than death," "equivalent to death," or "better than death"). Improvement in sensitivity and specificity of the decision algorithm + EEG (21-channel) compared to the baseline decision algorithm–only is varied on the y-axis and x-axis, respectively. ch = channel; R = return.

long-term economic impact of prognostication performance.[7,8] One of the main advantages of our approach is that we did not assume an a priori improvement in prognostication performance from adding EEG monitoring to the AANPP decision algorithm. Instead we estimated the cost-effectiveness of EEG monitoring across a wide possible range of plausible specificity and sensitivity improvements to estimate the minimal performance improvement requirements needed for cost-effectiveness (figures 2 and 3). These results could serve to guide effect size calculations for future studies evaluating different prognostication strategies.

It is estimated that approximately 1 out of 4 patients who had life-sustaining therapies withdrawn within 72 hours from cardiac arrest due to perceived poor neurologic prognosis might have survived if intensive care had been continued.[14] On the other hand, lifetime postdischarge costs related to caring for patients with cardiac arrest in a dependent state are high and most patients consider surviving with substantial disability to be worse than death.[22,27] In our model, we incorporated postdischarge medical costs for different outcome scenarios using a patient-centered approach that included utility values based on the patient's perspective about

surviving with major disability. A recent study evaluated the potential value of using EEG to guide early withdrawal of life-sustaining therapies after cardiac arrest, and identified potential to reduce costs from unnecessary intensive care unit stay by withdrawing life-sustaining therapies when EEG markers with 100% specificity were present.[8] Our approach complements this previous analysis by evaluating the patients' WTP for EEG monitoring to avoid outcome predictions that could lead to survival with severe disability, i.e., false-negatives. Furthermore, our model has the flexibility to evaluate the cost-effectiveness of incremental improvements in specificity or sensitivity–specificity relationship without assuming that 100% specificity is a requirement for prognostication.

We also considered in our analysis the fact that cardiac arrest survivors with good outcome can bring capital back into the system from continued insurance coverage throughout their lifetime or wages from continued employment. We compared prognostication performance using QALYs in an open system (no capital return into the medical system after patient discharge is considered) and in a closed system (capital return into the medical system after patient discharge is considered). We found that in a closed system using 21-channel long-term EEG monitoring, identifying an additional 4% of patients who would have died due to inaccurate prognostication, i.e. improvement in specificity, is adequate for cost-effectiveness assuming a 10% return of total inpatient health care costs from the additional surviving patients with good outcome (R = 10%). For limited 4-channel EEG monitoring, a specificity improvement of less than 1% would be sufficient for cost-effectiveness given an R = 10%. The results from our closed system analysis reiterate the open system findings, which demonstrate that small improvements in prognostication performance from EEG monitoring in cardiac arrest coma prognostication could provide overall financial benefit to patients, health care systems, and society. Incorporating both in-hospital and postdischarge costs enables a more representative evaluation of cost-effectiveness by considering additional financial routes beyond direct in-hospital costs and by considering the post–cardiac arrest care from patient, payers, and health system perspectives.

We compared cost-effectiveness trade-offs for a wide range of EEG monitoring implementation costs and highlighted 2 long-term monitoring strategies: 21-channel and 4-channel EEG systems in addition to short 21-channel EEG monitoring and brain imaging with MRI. For open or closed systems, both continuous EEG monitoring strategies appear potentially cost-effective with relatively small improvements in prognostication performance metrics and, as expected, the 4-channel system always overperformed the 21-channel system given the lower implementation costs. Despite not being conventionally performed in post–cardiac arrest care, we included a model utilizing a 4-channel montage given encouraging preliminary data showing that a limited montage EEG system may have equivalent performance to traditional 21-channel EEG in cardiac arrest prognostication.[24,28–31] Improvement in sensitivity or specificity as low as 1% could be sufficient for cost-effectiveness in various scenarios utilizing 4-channel EEG monitoring. Improvements in specificity as low as 1.5% would make a short-term EEG cost-effective, assuming that a single short-term EEG is done. Centers without continuous EEG capabilities often have to pursue serial short-term EEGs in cardiac arrest coma monitoring, and cost-effectiveness of employing repeated short-term EEGs can be abstracted from figures 2 and 3. Only one previous cost analysis in cardiac arrest has investigated the value of short-term and continuous EEG strategies using 21-channel systems.[7] Implementing continuous EEG during hypothermia in their institution was associated with a 3-fold increase in costs without any change in outcomes. Although we did not explicitly explore cost-effectiveness trade-offs of adding brain imaging with MRI to the AANPP in our study, cost-effectiveness of combining MRI with the AANPP for prognostication could be assessed using the specificity and sensitivity charts provided in figures 2 and 3. In fact, these charts could be used to assess the cost-effectiveness trade-offs for implementation of any ancillary test in addition to the AANPP assuming costs used here are comparable across institutions.

Our analysis has important limitations. First, our model is the approximation of the sensitivity and specificity of the AANPP decision algorithm. Data at the patient level from previous studies are unavailable; therefore estimating the joint sensitivity and specificity of a multimodal assessment combining all predictors part of the AANPP was not possible. GCS motor score <3 at 72 hours was selected as the proxy for the overall algorithm as it had the largest sensitivity for poor outcome prediction compared to other markers part of the AANPP despite having a larger false-positive rate.[32,33] Prognostication scenarios in which all poor outcome predictors are concordant (i.e., GCS <3, absent brainstem reflexes, and bilateral absent SSEP) would have higher specificity, but would likely have limited sensitivity. Moreover, several studies have highlighted that sensitivity and specificity of prognostic tests part of the AANPP, as well as EEG, may be affected by use of targeted temperature management, sedatives use and metabolism, variability of electrophysiologic tests technique and interpretation, and self-fulfilling prophecies from premature withdrawal of life-sustaining therapies. A recent study from our group utilizes the AANPP outcome predictor of absent bilateral cortical responses on SSEP as a use-case to highlight how estimating unbiased sensitivity and specificity of prognostic tests is challenging given the risk for attrition bias from self-fulfilling prophecies due to withdrawal of life-sustaining therapies in several studies in cardiac arrest prognostication published to date.[34] Second, the added benefit of EEG monitoring compared to prognostication without EEG monitoring has not been formally tested in a prospective randomized clinical trial, therefore the specific improvement in sensitivity and specificity from each type of EEG monitoring modality in addition to the AANPP is not known. Several large nonrandomized studies have evaluated the

sensitivity and specificity of individual tests and multimodal prognostication with intermittent or continuous EEG monitoring, which serve to provide an approximate estimate of the added sensitivity and specificity of EEG testing compared to clinical examination and other prognostication tests.[35–37] Third, we estimated hospital cost for nonsurvivors to range from $36,000 to $41,000 and for survivors to be roughly $141,000–$163,000, which is less than a recent report of $80,000 per nonsurvivor and $180,000 for survivors.[1] Our projections for total annual direct cost of post–cardiac arrest costs for out-of-hospital cardiac arrests in the United States of above $8.8 billion is inferior to estimated costs for 2011–2012 of $11.1 billion.[1] The difference observed could be accounted for by our choice of not including other inpatient costs from invasive procedures such as coronary angiography, intraaortic balloon pump, extracorporeal membrane oxygenation, pacemaker placement, or therapeutic hypothermia. We also utilized the direct cost to our local institution for EEG, MRI, and AANPP protocol ancillary tests, which could vary between institutions and limit the external validity of our prognostication cost estimation. In estimating postdischarge costs, we relied on Medicare rates not specific to the post–cardiac arrest patient subpopulation as those data are unavailable. Fourth, as yearly trends on postdischarge disposition and costs for this patient population are unavailable, we utilized the costs from the first year after hospital discharge and assumed that patients with CPC of 3 or 4 who were discharged to skilled nursing facilities, long-term acute care facilities, or hospice remained in these settings for the remainder of their lifetime. Fifth, survivors might have medical complications during their index admission for cardiac arrest, which would lead to readmissions and increased health care costs. We could not precisely account for these additional postdischarge lifetime costs in our model, therefore our model underestimates lifetime costs in this patient population. Sixth, estimates of lifetime return, *R*, from insurance premium payment or wages by survivors with good outcome who remain employed are necessarily tentative. A study from Denmark found that up to 76.6% of survivors returned to work after an out-of-hospital cardiac arrest, but there is limited information about postdischarge employment status for cardiac arrest survivors in the United States.[38] Furthermore, a significant number of cardiac arrest survivors would become eligible for Medicare benefits at age 65, complicating estimates of *R* in this patient population. Seventh, access to inpatient EEG monitoring, especially continuous EEG, is limited in many settings, and is very labor intensive. We were not able to account in our model for the costs involving infrastructure of expanding EEG laboratory services to monitor patients presenting with acute brain injury after cardiac arrest. Decision about who to monitor, and for how long, has to be individualized when capacity for EEG monitoring is limited, but our model provides some guidance to providers and health care management about the cost-effectiveness for EEG monitoring in this setting. Eighth, decisions for continuing or withdrawing life-sustaining therapies are not exclusively influenced by cost—individual, family, religious, and other more personal values have to be carefully taken into consideration. Whereas our model cannot account for these factors, we attempt to incorporate the concept of "what a meaningful outcome means" for individual patients and families by varying utility values for independent, dependent, or death outcomes in our cost-effectiveness model. These utility values were generated by interviewing several cardiac arrest survivors in previous studies, providing a window about long-term quality of life after cardiac arrest.[22,23] Finally, all parameters in our analysis were selected from studies involving cardiac arrest prognostication, which are inherently tinted by the bias of self-fulfilling prophecies in determining patient outcomes. Physicians involved in decision-making regarding continuation or withdrawal of life-sustaining therapies in these studies were not blinded to test results, therefore determining the actual sensitivity and specificity of prognostic tests will not be possible until prospective clinical studies focused on prognostication and designed to avoid early withdrawal of life-sustaining therapies are conducted.

Small increments in outcome prediction performance by incorporating continuous EEG monitoring in cardiac arrest prognostication could lead to cost-effectiveness by avoiding inappropriate withdrawal of life-sustaining therapies or protracted continuation of intensive care measures. Future prospective studies employing multimodal prognostication in cardiac arrest should incorporate performance and cost-effectiveness assessment of EEG monitoring in prognostication strategies and individualize prognostication by evaluating perspectives about quality of life for surviving patients and families.

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Shirley S. Mo, MD	Harvard Medical School, Boston, MA	Conceptualized and designed the study, completed the statistical analysis, drafted the original manuscript, contributed to data production and collection, reviewed and revised the manuscript
Sebastian Palacios, MS	Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge	Conceptualized and designed the study, completed the statistical analysis, drafted the original manuscript, contributed to data production and collection
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Wei-Hung Weng, MD, MMSc	Department of Electrical Engineering and Computer Science, Massachusetts Institute of Technology, Cambridge	Reviewed and revised the manuscript
Sydney S. Cash, MD, PhD	Harvard Medical School; Department of Neurology, Massachusetts General Hospital, Boston	Reviewed and revised the manuscript
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