Extracorporeal CPR for Refractory Out-of-Hospital Cardiac Arrest
A Bayesian Perspective

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Abstract

A recent randomized clinical trial reported in patients with refractory out-of-hospital cardiac arrest, extracorporeal CPR and conventional CPR had similar effects on survival with a favorable neurologic outcome. Herein, it is examined whether a Bayesian perspective allows any additional insights into the interpretation of this trial.

Keywords: extracorporeal CPR, Bayesian statistics

1. Introduction

Out-of-hospital cardiac arrest is a frequent event and fortunately its devastating consequences can be partially mitigated by rapid commencement of basic life support with high-quality chest compressions and external defibrillation (conventional cardiopulmonary resuscitation (CPR)). However, there remains a substantial subset of individuals who do not respond rapidly to these measures and whether more invasive measures. Whether the addition of more aggressive measure including extracorporeal CPR (the addition of extracorporeal membrane oxygenation to standard advanced cardiac life support (eCPR)) can improve survival and diminish anoxic brain injury is a current topic of research. The largest randomized clinical trial (RCT) examining this question recently published their results[1]. For the primary outcome, 30 day survival without significant neurological deficit, the authors observed an odds ratio of 1.4 (95% confidence interval, 0.5 to 3.5; P = 0.52) in favor of extracorporeal CPR for leading to their conclusion "In patients with refractory out-of-hospital cardiac arrest, extracorporeal CPR and conventional CPR had similar effects on survival with a favorable neurological outcome".[1]

This communication does not reiterate the many reasons to be wary of null hypothesis significance testing (NHST), p values and confidence intervals[2]. Rather it assumes the reader has perhaps heard that Bayesian methods mirror our intuitive learning process and is curious about its potential application to RCT interpretations.

Therefore the goal of this communication is to examine whether a Bayesian perspective permits additional insights into the specific clinical question regarding any added value of extracorporeal CPR following an out-of-hospital arrest in patients refractory to standard CPR.

2. Methods

The data for the primary outcome, 30 day survival with intact neurological status, based on an intention to treat (ITT) analysis was abstracted from the original INCEPTION trial[1] and used for the primary analysis.

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[1] JMB is a research scholar supported by Les Fonds de Recherche Québec Santé

The ITT analysis has the advantage of minimizing bias by preserving the prognostic balance afforded by randomization as well as assuring the validity of the statistical analyses.

Bayesian analytical approaches provide a number of benefits over the classical NHST approach, including parameter estimation accompanied by direct probability statements about parameters of interest (herein the risk of survival with intact neurological status), and the incorporation prior knowledge[3,4].

These probability statements arise from the posterior distribution according to the following equation:

$$\text{Posterior} = \frac{\text{Probability of the data} * \text{Prior}}{\text{Normalizing Constant}}$$

Therefore, in addition to the current data summarized by the probability of the data (likelihood function) one requires a prior probability distribution for each parameter. The mechanics of the Bayesian analyses were performed using the Stan programming language[5] through the R package rstanarm[6] and fit a logistic regression model with a single treatment parameter, θ. Because our focus is the interpretation of the INCEPTION trial alone, our primary analysis used rstanarm's default vague parameter priors ($log(\theta) \sim Normal[0, 2.50]$, thereby assuring that the posterior distribution is dominated by the observed INCEPTION data.

The robustness of the Bayesian approach is often assessed by sensitivity analyses that examine the variation in the posterior probability as a function of the choice of different prior distributions. Using prior information also underscores the important advantage of Bayesian analyses to learn sequentially. There were two previous RCTs examining extracorporeal CPR[7,8] and while the protocols are not identical, it may be reasonable to allow this data to serve as informed priors for the eCPR parameter, which can be updated with the INCEPTION data.

This prior information of the probability of eCPR success in each previous trial, X_i, can be summarized as a normal distribution with a mean equal to the proportion of successes, $\hat{p}_i$ with a standard deviation equal to

$$\sqrt{\hat{p}_i * (1 - \hat{p}_i)}$$

As baseline success rates for standard CPR varies markedly between the three studies, it was decided to maintain the INCEPTION control baseline with the vague prior for all analyses and to update only the eCPR arm with prior information.

Posterior distributions are summarized with medians and 95% highest-density intervals (credible intervals), defined as the narrowest interval containing 95% of the probability density function[9]. We not only calculated the posterior probability of any additional survival with eCPR (OR >1.00), but also of clinically meaningful benefits (defined as OR >1.10).

ITT assesses subjects based on the group they were initially (and randomly) allocated to, regardless of whether or not they dropped out, were fully adhered to the treatment or switched to an alternative treatment. ITT analyses can therefore be seen as a conservative estimate which mirrors clinical effectiveness. In contrast, a per protocol (PP) analysis involves a comparison of treatment groups in a trial that includes only those patients who completed the treatment they were originally allocated to. Similarly an "as treated" analysis considers only which treatments subjects received, regardless of their randomization status and protocol adherence. While both PP and as-treated analyses alone may lead to bias, in conjunction with an ITT analysis they may provide additional insights into efficacy and have also been examined from a Bayesian perspective.

All analyses were executed using `R`[10] within the integrated development environment of RStudio. Bayesian analyses were performed using the front end `rstanarm` package[6] to the `Stan` programming language[stan]. The statistical code can be found on Github (https://github.com/brophyj/eCPR).

3. Results

ITT data from the INCEPTION trial[1] and two other pertinent trials[8,7] that also randomized CPR to eCPR are shown in Table 1. Performing a Bayesian analysis on the INCEPTION trial, using the default vague prior, produces an odds ratio (OR) 1.32 (95% Credible Interval (CrI) 0.54 - 3.22). The closeness of this result to the original analysis (OR, 1.4; 95% CI 0.5 - 3.5) confirms no impact of the vague prior and shows this Bayesian analysis is completely dominated by the observed INCEPTION data.

One of the advantages of a Bayesian approach is the ability to make direct probability statements about the estimand of improved survival with eCPR. The eCPR probability density function for improved survival from INCEPTION data with the default vague prior is displayed in Figure 1 and reveals that the probability of enhanced survival with eCPR is 72.72%. The probability that the improved survival exceeds a 10% improvement is 0.66%.

Another advantage of a Bayesian approach is the possibility of including previous evidence as informed priors. We considered three possible scenarios i) using all the available prior RCT data[8,7] to create a combined prior which was expressed as a N(0.32, 0.47)
ii) using only the ARREST data, labelled an enthusiastic prior, as this trial was stopped prematurely for efficacy, expressed as a N(0.43, 0.49)
iii) using only the PRAGUE data, labelled a skeptical prior, as this trial was stopped prematurely for futility, expressed as a N(0.31, 0.46)

These different prior probabilities can be updated using the INCEPTION to create posterior distributions that are summarized in Table 2. Basically, in all cases the point estimate for the enhanced eCPR survival remains fairly constant but the associated uncertainty is reduced with the additional data as reflected by the narrower 95% CrI. The posterior probability of improved eCPR survival goes from 80% with a skeptical prior to 85% with the enthusiastic prior. The graphical presentation of these results is shown in Figure 2.

Although INCEPTION did not report a per-protocol analysis, just an analysis may be revealing concerning treatment efficacy, at the risk of an increased risk of bias by not respecting the ITT. From INCEPTION Figure S4[1], it appears that the per protocol data for mortality is 13 survivors from 61 patients in the CPR group compared to 5 survivors from 46 patients receiving eCPR. With a vague prior, the probability of increased survival with eCPR is decreased compared to CPR but with wide CrI (OR 0.45, 95% CrI 1.5 - 1.35), limiting any definitive conclusions. The probabilities of increased eCPR survival incorporating the previous identified priors is shown in Table 3.

4. Tables

Table 1 Extracted ITT trial data

Trial	Fail CPR (n)	Fail eCPR (n)	Success CPR (n)	Success eCPR (n)
INCEPTION	52	56	10	14
ARREST	15	8	0	6
PRAGUE	108	86	24	38

eCPR = extracorporeal cardiopulmonary resuscitation

Table 2 eCPR odds ratios, 95% credible intervals and probabilities with various priors

Priors	OR	95% CrI		Probabilities	
	point estimate	lower limit	upper limit	p(OR) >1	p(ROPE)
Vague	1.32	0.543	3.21	0.727	0.134
Combined	1.35	0.705	2.58	0.817	0.153
Enthusiastic	1.40	0.738	2.67	0.849	0.138
Skeptical	1.32	0.700	2.50	0.804	0.168

Vague: default vague prior
Combined: prior eCPR data from ARREST + PRAGUE
Enthusiastic: prior eCPR data from ARREST alone
Skeptical: prior eCPR data from PRAGUE alone
ROPE: range of practical equivalence = + / - 10% OR (odds ratio)

Table 3 eCPR (per protocol) odds ratios, 95% credible intervals and probabilities with various priors

Priors	OR	95% CrI		Probabilities	
	point estimate	lower limit	upper limit	p(OR) >1	p(ROPE)
Vague	0.451	0.151	1.35	0.0698	0.0473
Combined	0.859	0.430	1.71	0.33	0.2022
Enthusiastic	0.870	0.437	1.73	0.345	0.2013
Skeptical	0.858	0.419	1.75	0.327	0.1970

Vague: default vague prior
Combined: prior eCPR data from ARREST + PRAGUE
Enthusiastic: prior eCPR data from ARREST alone
Skeptical: prior eCPR data from PRAGUE alone
ROPE: range of practical equivalence = + / - 10% OR (odds ratio)

5. Figures

Figure 1 INCEPTION ITT analysis with vague prior

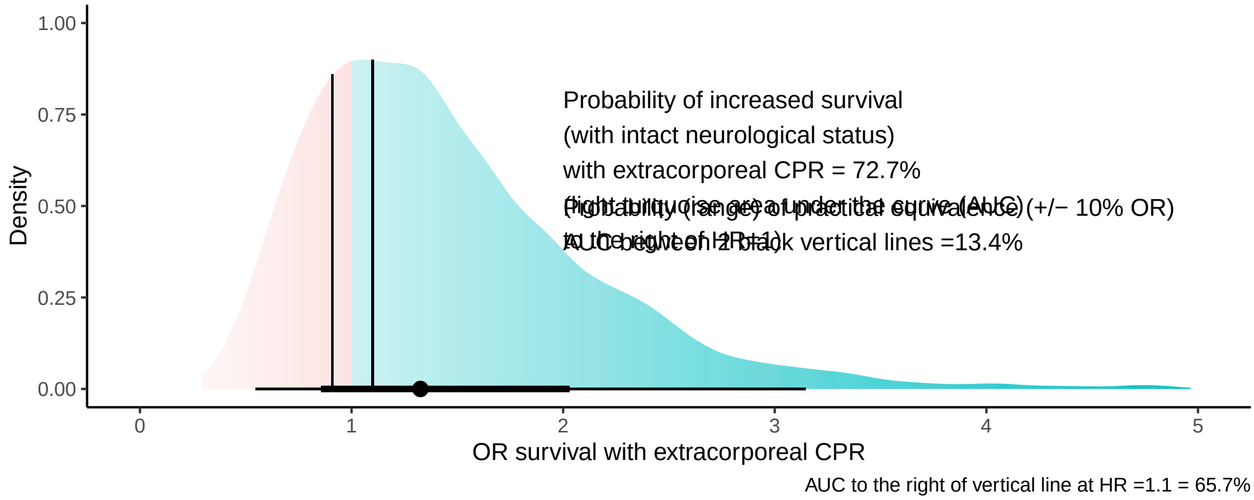
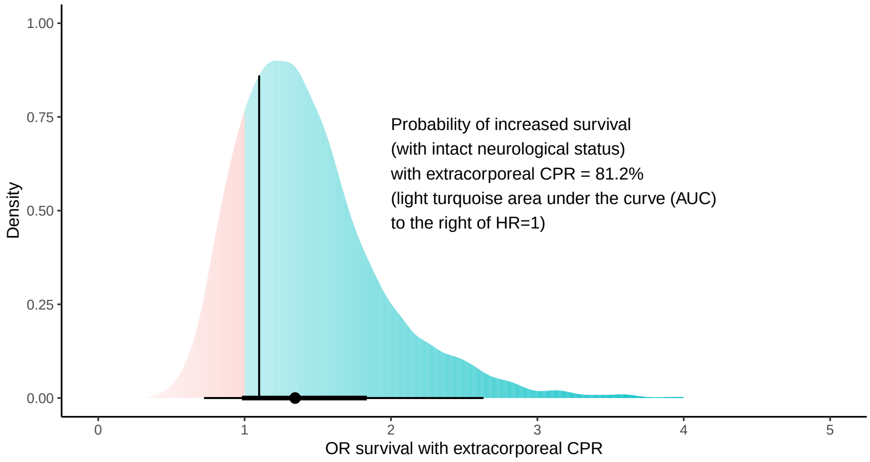


Figure 2. Probability density plots with informative priors

Figure 2a INCEPTION ITT analysis with combined prior*

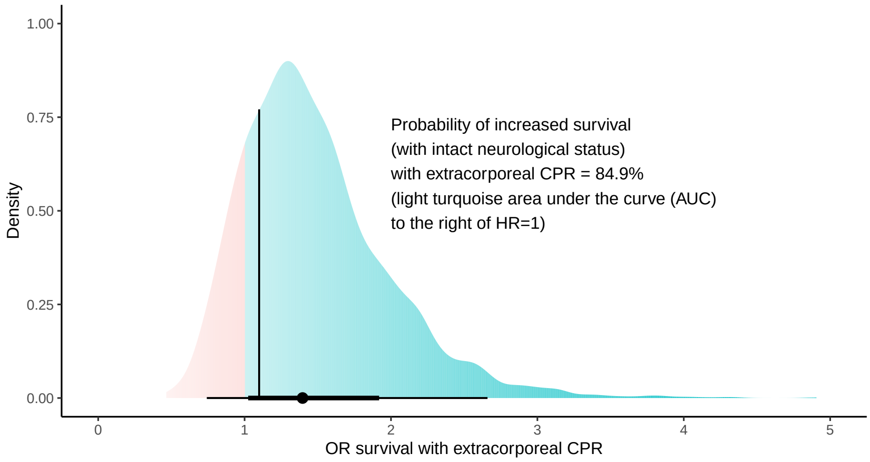
*data from ARREST and PRAGUE



AUC to the right of vertical line at HR =1.1 = 73.2%

Figure 2b INCEPTION ITT analysis with enthusiastic prior*

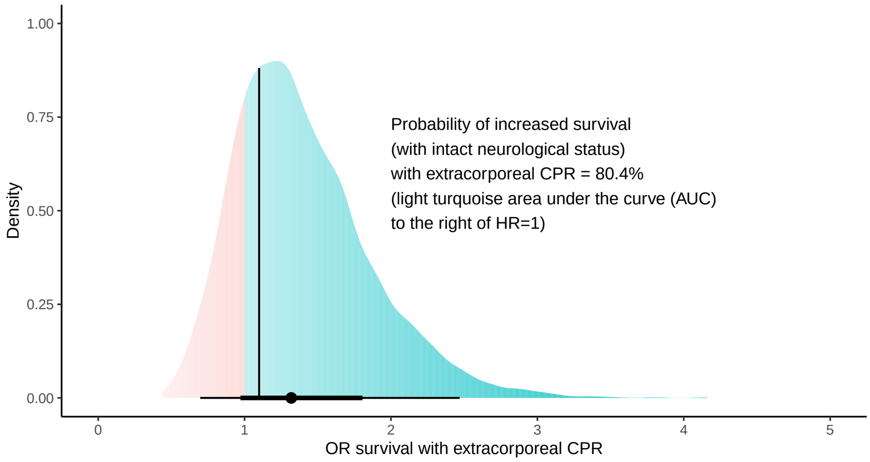
*data from ARREST alone



AUC to the right of vertical line at HR =1.1 = 77.0%

Figure 2c INCEPTION ITT analysis with skeptical prior*

*data from PRAGUE alone



AUC to the right of vertical line at HR =1.1 = 71.0%

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