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Incorporating Covariates in Healthcare Decision-Making. Empirical Application of Methods in a Cost-Effectiveness Model for IVIG in Severe Sepsis

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Introduction

- Cost-effectiveness models typically depend on several patient and disease characteristics(i.e., covariates).
- To estimate results at the population level the model needs to average over the joint covariate distribution at each evaluation of the model. This requires nested numerical integration, which can be computationally challenging[1,2]. We aim to explore the bias with two commonly used approximations.

Methods

- We compare the results from three different approaches to covariate adjustment in an economic model for intravenous immunoglobulin (IVIG) compared with standard care in patients with severe sepsis[3]:
  - The mean of covariate method obtained by plugging in the average value of each covariate.
  - The predictive distribution method that is based on simulating from the joint covariate distribution with a single simulation for each evaluation of the model in a probabilistic sensitivity analysis (PSA).
  - Averaging over the covariate distribution by integrating over the joint covariate distribution at each iteration of the PSA (gold standard approach). A Gauss Kronrod integration routine is used with a maximum of 100 subintervals[4].
- We present results for the overall population and for subgroups based on ICNARC physiology score.
- Cost-effectiveness results are reported as incremental net monetary benefits (INMBs) estimated at a willingness-to-pay threshold (WTP) of £20,000/QALY as follows:
- $INMB = \left(QALYs_{int} - QALYs_{comp}\right) * WTP - \left(Costs_{int} - Costs_{comp}\right)$

Results

- Overall population estimates depend on patient age and gender. Expected INMB at a cost-effectiveness threshold of £20,000/QALY is estimated at -£293, -£555 and -£556 based on the mean of covariate method, the predictive distribution method and averaging over the covariate distribution, respectively. The probability of being cost-effective is overestimated from the mean of covariate method (51.4%) and underestimated from the predictive distribution method (41.2%), as the probability of being cost-effective from averaging over the covariate distribution is estimated at 47.9%.
- Population EVPI for severe sepsis patients in the United Kingdom for a 10-year time horizon is estimated at £415 million based on the mean of covariate method and £462 million based on the predictive distribution method, with both methods overestimating the value of further research, as population EVPI based on averaging over the covariate distribution is estimated at £359 million.
- Cost-effectiveness results depend on disease severity as defined by ICNARC scores (Figure 1 and Figure 2).
- The mean of covariate method overestimates the expected INMB by up to £1,000 (Figure 1) and the probability of IVIG being cost-effective by up to 14% compared to averaging over the covariate distribution (Figure 2). That is, for a patient with an ICNARC score of 28, IVIG has a 55% probability of being cost-effective under the mean of covariate approach and a 41% probability of being cost-effective under the average over the covariate distribution approach.
- The predictive distribution method provides cost-effectiveness estimates aligned to averaging over the covariate distribution method (Figure 1) but slightly over- or under-estimates the probability of IVIG being cost-effective at different ICNARC scores (Figure 2).

Table 1: Cost-effectiveness and value of information results for overall population with severe sepsis

Model outcome	Mean of covariate method	Predictive distribution method	Average over the covariate distribution method
Expected INMB*(£)	-293	-555	-556
Probability of being cost-effective* (%)	51.4%	41.2%	47.9%
Per person EVPI* (£)	1,453	1,618	1,259
Population EVPI in UK* (£million)	415	462	359

*At a cost-effectiveness threshold of £20,000/QALY. INMB, incremental net monetary benefit; EVPI, expected value of perfect information

Figure 1: Expected incremental net benefit at £20,000/QALY for specific ICNARC scores based on averaging over covariate distribution, at mean covariate values and the predictive covariate distribution.

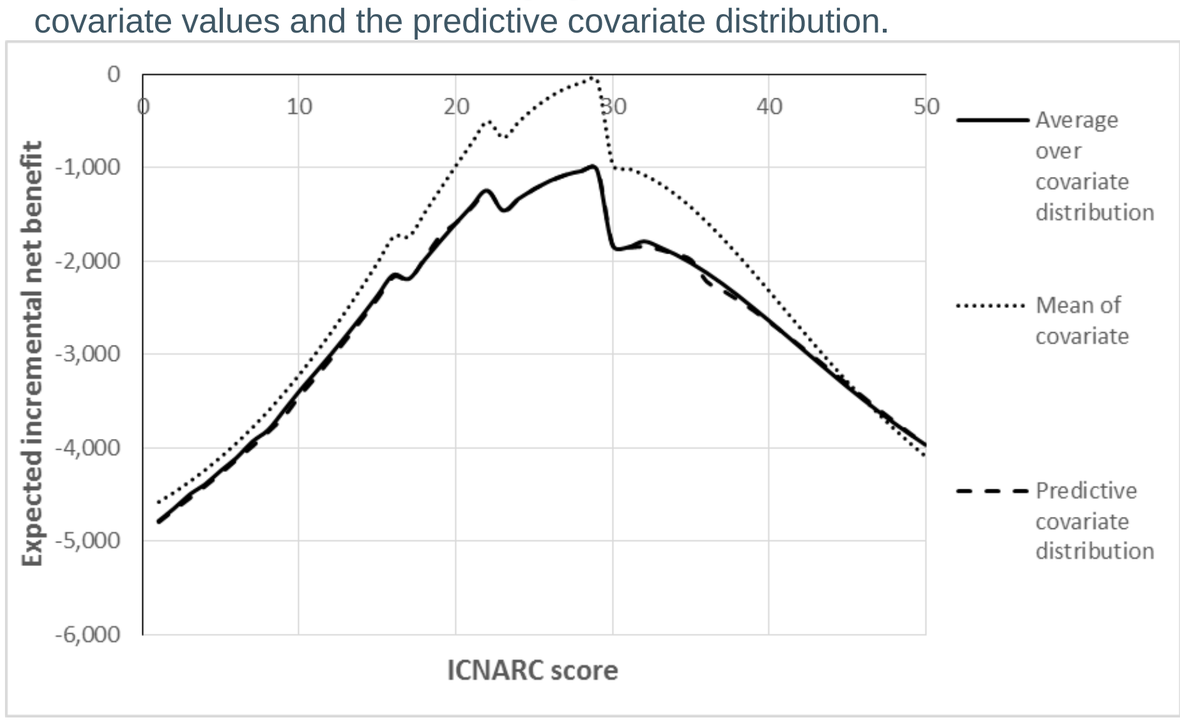
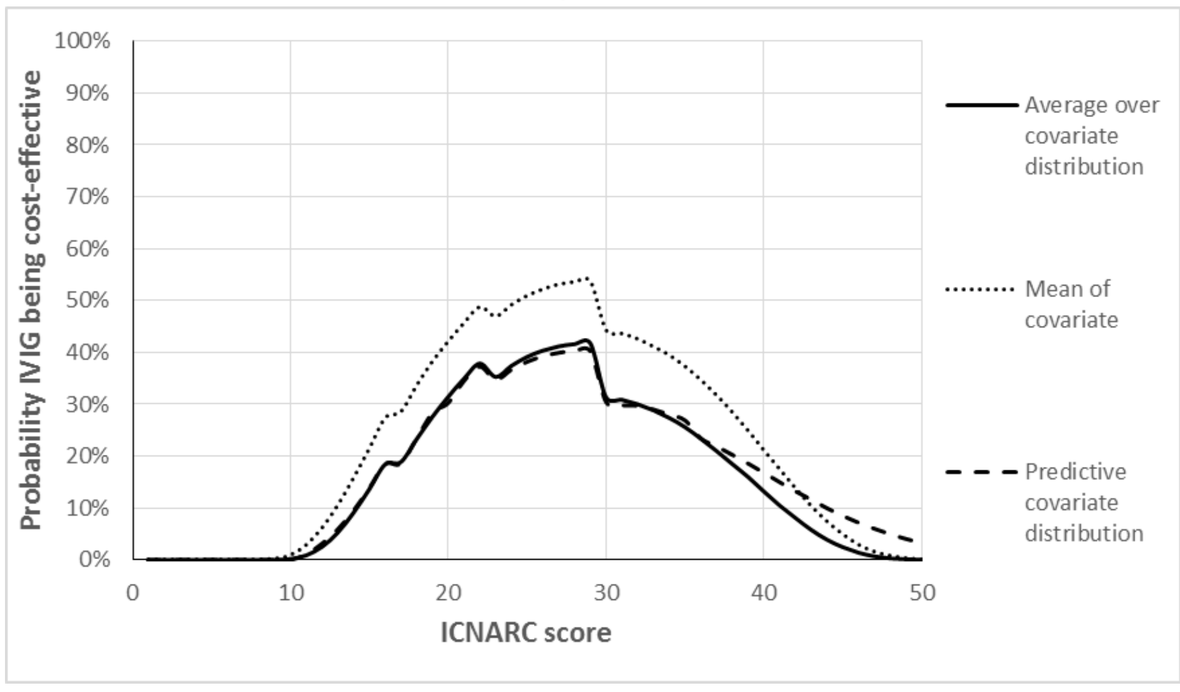


Figure 2: Probability IVIG being cost-effective at £20,000/QALY for specific ICNARC scores based on averaging over covariate distribution, at mean covariate values and the predictive covariate distribution.



Conclusions

The mean of covariate method provides biased cost-effectiveness results due to the non-linear structure of the economic model. The predictive distribution method provides unbiased cost-effectiveness results but does not accurately capture uncertainty and the value of further research. Averaging over the joint covariate distribution is required to accurately capture uncertainty and the value of information.

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