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An Integrated Approach to Evaluating Alternative Risk Prediction Strategies: A Case Study Comparing Alternative Approaches for Preventing Invasive Fungal Disease

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ABSTRACT

Objectives: This article proposes an integrated approach to the development, validation, and evaluation of new risk prediction models illustrated with the Fungal Infection Risk Evaluation study, which developed risk models to identify non-neutropenic, critically ill adult patients at high risk of invasive fungal disease (IFD). **Methods:** Our decision-analytical model compared alternative strategies for preventing IFD at up to three clinical decision time points (critical care admission, after 24 hours, and end of day 3), followed with antifungal prophylaxis for those judged "high" risk versus "no formal risk assessment." We developed prognostic models to predict the risk of IFD before critical care unit discharge, with data from 35,455 admissions to 70 UK adult, critical care units, and validated the models externally. The decision model was populated with positive predictive values and negative predictive values from the best-fitting risk models. We projected lifetime cost-effectiveness and expected value of partial perfect information for groups of parameters. **Results:** The risk prediction models performed well in internal and external validation. Risk assessment and prophylaxis at the end of day 3 was the most cost-effective strategy at the 2% and 1% risk threshold. Risk assessment at each time point was the most cost-effective strategy at a 0.5% risk threshold. Expected values of partial perfect information were high for positive predictive values or negative predictive values (£11 million–£13 million) and quality-adjusted life-years (£11 million). **Conclusions:** It is cost-effective to formally assess the risk of IFD for non-neutropenic, critically ill adult patients. This integrated approach to developing and evaluating risk models is useful for informing clinical practice and future research investment.

Keywords: cost-effectiveness analysis, critical care, invasive fungal disease, risk prediction, value of information analysis.

Introduction

Risk prediction models have great potential to support clinical decisions and the development of clinical guidelines [1–5]. For example, the decision to initiate statin therapy for the primary prevention of cardiovascular disease may be informed by risk equations from the Framingham study [6]. Treatment choice for patients with breast cancer can be guided by estimates of the long-term risk of cancer recurrence or death, for example, from the Nottingham prognostic index [7]. Clinical decision making in critical care units may be informed by estimates of the predicted risk of death, based, for instance, on the acute physiology and chronic health evaluation score [8,9]. In many circumstances, however, it is unclear whether using risk prediction approaches to initiate prevention and treatment strategies is cost-effective.

Risk prediction models can be used in cost-effectiveness analysis (CEA) to identify which patient subgroups are the most cost-effective to receive a particular treatment or prevention strategy [10–12]. For example, Grieve et al. [13] considered alternative Framingham equations to evaluate strategies for preventing cardiovascular disease, and Williams et al. [14] outlined the use of a prognostic model to select patients with breast cancer for systemic therapy. Longworth et al. [15] used published risk prognostic models to evaluate the cost-effectiveness of liver transplantation. None of these studies, however, evaluated whether a strategy of formal risk assessment with a prognostic model was cost-effective. Furthermore, previous CEAs have taken a published risk prediction model and assumed that it is valid for the decision context. The population characteristics in the decision context are often different from those of the population, on

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which the risk prediction model was developed, leading to unreliable extrapolations. To assess whether a risk prediction model is valid in the specific decision context requires a careful assessment of the statistical performance of the model for the relevant population and time points. In particular, it is important to consider whether the risk prediction model accurately predicts events not only for the original population on which it was developed (internal validation) but also for alternative populations of prime interest for the decision problem (external validation). Of greatest importance for decision making is the discrimination of the risk model. If a risk model has perfect discrimination, then there is a threshold risk that divides the patients into those who will versus those who will not experience an event, leading to the optimal treatment decision for every patient. In practice, perfect discrimination will not be achieved, but improved discrimination will lead to better decision making, reflected through the positive predictive value (PPV) and the negative predictive value (NPV) of the decision rule. In addition to developing risk models that are accurate, it is important to evaluate the relative cost-effectiveness of alternative risk prediction approaches.

There is growing appreciation of the need to evaluate risk prediction models, but only a few studies have done this, and only to a limited extent. Henriksson et al. [16] developed a risk prediction model and assessed the cost-effectiveness of prognostic biomarkers and risk scores to inform prioritization for coronary artery surgery. Rapsomaniki et al. [17] evaluated the net benefit from using a prognostic model, illustrated in the context of the prevention of cardiovascular disease. But none of the above studies has fully assessed the uncertainty in the decision problem by assessing the value of information to help support decision making. Value of information analysis provides an important framework for determining the expected payoff of conducting further research to resolve the parameter uncertainties that pervade the cost-effectiveness estimates [18]. We propose an integrated approach to considering risk prediction models in decision making. The integrated approach considers developing, validating, and evaluating the cost-effectiveness of a risk prediction approach for the relevant decision context, for example, according to the specific population and time point of interest. This integrated approach also requires that the ensuing decision uncertainty be fully recognized by providing an assessment of the priorities for further research.

The integrated approach is illustrated with the Fungal Infection Risk Evaluation (FIRE) study, which developed prognostic models to identify non-neutropenic, critically ill adult patients at high risk of invasive fungal disease (IFD). For critically ill patients, IFD is associated with increased morbidity, mortality, and cost [19–21]. Randomized controlled trials have reported that antifungal prophylaxis with either fluconazole or ketoconazole reduces the subsequent risk of IFD and mortality [22]. These randomized controlled trials were conducted in high-risk patients, and concerns about the costs of prophylaxis and possible drug resistance have discouraged the widespread adoption of antifungal prophylaxis. In the United Kingdom, risk models are not routinely used to identify those non-neutropenic, critically ill adult patients who are at high risk of IFD. Antifungal prophylaxis is prescribed only on an ad-hoc basis for those patients who, according to clinical judgment, are at very high risk of IFD. In the FIRE study, only 1% of eligible patients received systemic antifungal therapy at admission to the critical care unit [23]. For the vast majority of patients admitted to critical care units who do not currently receive antifungal prophylaxis, it is unknown whether it is cost-effective to formally assess the risk of IFD at different clinical decision time points, and to initiate antifungal prophylaxis for those judged high risk.

The objective of this article was to illustrate an integrated approach to the development, validation, and CEA of risk prediction models through the FIRE case study. We use these risk prediction models to report the relative cost-effectiveness of alternative risk assessment and prophylaxis strategies for preventing IFD and assess the relative value of further research.

The article proceeds as follows. The next section outlines the decision, problem, and the CEA model, followed by a summary of risk model development and validation. Following this are sections on methods and results of CEA, scenario analysis, and value of information (VOI) analysis. In the final section, we discuss the approach taken and suggest a research agenda.

Overview of the Decision Problem and the CEA Model

The CEA aimed to assess the relative cost-effectiveness of alternative strategies for assessing the risk of IFD and initiating antifungal prophylaxis in non-neutropenic, adult patients admitted to National Health Service critical care units in the United Kingdom. The CEA reported cost-effectiveness over the patients' lifetime and assessed costs from the National Health Service perspective. The alternative prevention strategies comprised "formal risk assessment" according to the predicted risk of IFD at up to three clinical decision time points (from herein termed "risk assessment"). These time points were at critical care unit admission, after 24 hours, and at the end of the third calendar day in the critical care unit (Table 1).

At any clinical decision time point, risk assessment was considered only for those patients who were still in the critical

Table 1 – Alternative treatment strategies for non-neutropenic, critically ill adult patients.

Strategy	Decision node		
	On admission	At end of 24 h	At end of day 3
1	Do not assess risk	Do not assess risk	Do not assess risk
Risk assessment at a single time point			
2	Assess risk, Prophylaxis if risk > P_T	Do not assess risk	Do not assess risk
3	Do not assess risk	Assess risk, Prophylaxis if risk > P_T	Do not assess risk
4	Do not assess risk	Do not assess risk	Assess risk, Prophylaxis if risk > P_T
Risk assessment at multiple time points			
5	Assess risk, Prophylaxis if risk > P_T	Assess risk, Prophylaxis if risk > P_T	Do not assess risk
6	Do not assess risk	Assess risk, Prophylaxis if risk > P_T	Assess risk, Prophylaxis if risk > P_T
7	Assess risk, Prophylaxis if risk > P_T	Do not assess risk	Assess risk, Prophylaxis if risk > P_T
8	Assess risk, Prophylaxis if risk > P_T	Assess risk, Prophylaxis if risk > P_T	Assess risk, Prophylaxis if risk > P_T

P_T, risk threshold.