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Methods for estimating costs of healthcare-associated Infections

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Εκτίμηση κόστους λοιμώξεων

Περίληψη στο τέλος του άρθρου

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Introduction: **Healthcare-associated infections (HCAIs) cause significant clinical and economic burdens worldwide, making accurate cost estimation critical for effective prevention and resource allocation. Several methodologies exist to estimate the attributable costs and hospital length of stay due to HCAIs, each with its own strengths and limitations. Case studies are simple and inexpensive but subjective and less reliable, while unmatched case-control studies provide quick estimates but may overestimate costs by not controlling for confounders. Matched case-control studies offer improved accuracy by pairing infected patients with similar controls, although they face challenges related to matching complexity and time-dependent biases. Regression analysis allows for multivariable adjustment and reduces selection bias by including nearly all patients, but it requires detailed clinical data and expert analysis. Multistate models provide the most comprehensive insight by modeling patient transitions between health states over time, effectively addressing time-dependent bias, yet they require extensive data collection and complex modeling efforts. In conclusion, the choice of methodology depends on research objectives, data availability, and desired precision, and often a combination of approaches delivers the most accurate and actionable information for healthcare policy and infection control strategies.**

Key-words: *Case-control studies, Cost estimation, Healthcare-associated infections, Multi-state models, Regression analysis*

Introduction

Approximately 1.7 million healthcare-associated infections (HCAIs) occur annually, resulting in 99,000 patient deaths, while the estimated direct cost is around $10 billion.[1] The total direct and indirect costs of HCAIs are estimated to range from $96 billion to $147 billion annually, including lost work productivity and other expenditures.[2] The average cost per type of HCAI ranges between $1,479 and $9,807 for catheter-associated urinary tract infections,[3-5] between €3,227 and $6,775 for ventilator-associated events,[6,7] and between $13,727 and $48,000 for central line-associated bloodstream infections.[8-11]

The continuous evolution of healthcare systems, technological advancements, and the need to optimize resource allocation require accurate estimation of the cost of HCAIs. The evaluation of the social and economic impacts of HCAIs plays an increasingly critical role in implementing prevention and surveillance systems. Therefore, the design of cost-assessment studies on infections is essential in order to adopt effective intervention strategies aimed at saving healthcare resources.[12]

The overwhelming majority of economic evaluations and cost analyses related to HCAIs focus primarily on direct hospital costs, as these directly affect healthcare institutions. Most researchers conduct their analysis exclusively from the hospital perspective to demonstrate the financial benefits of investing in infection control programs. However, there are broader analytical approaches that incorporate wider interpretations of infection costs, especially regarding economic consequences resulting from decreased productivity among infected patients (due to additional morbidity) or even death. Although these effects impact both patients and society at large, there is limited evidence concerning the costs associated with these long-term outcomes.[12]

Cost Estimation Methodologies for Healthcare-Associated Infections

According to the Centers for Disease Control and Prevention, the main methodologies for estimating attributable length of stay and cost of HCAIs include: case studies, matched and unmatched case-control studies, regression analysis and multi-state model (See Table 1).[13-19]

Table 1. Characteristics of Cost Estimation Methodologies for HCAIs

Methodology	Advantages	Limitations	Quality
Case Study	Easy to perform, low cost	Subjective method, not standardized	Moderate
Unmatched Case-Control Study	Easy to conduct, shorter duration, low cost	Subjective, non-standardized, lacks control for confounders	Low
Matched Case-Control Study (Non-time-dependent)	Reduces confounding compared to unmatched controls	Matching criteria may limit available controls, some patients excluded	Moderate
Matched Case-Control Study (Time-dependent)	Controls for time-dependent bias	Matching criteria may still reduce available controls	High
Regression Analysis	Includes nearly all patients and controls	Requires highly trained personnel, availability of detailed clinical data	High
Multistate Model	Includes nearly all patients and controls, accounts for time-dependence	Requires highly trained personnel, availability of detailed and continuous clinical data	High

Case Study Method

The case study method is a subjective approach in which the healthcare professional, based on clinical information and patient data, decides whether each hospital day is attributable to the infection. This method is simple and resource-efficient. Unlike comparative methods, it includes only infected patients without the need for a control group. The major limitations include high subjectivity and low reliability regarding the estimation of infection-attributable length of stay. This method tends to attribute fewer days to the infection than other methodologies and is believed to underestimate the true burden, since the reviewer only attributes days clearly resulting from the infection.[18-20]

Unmatched Case-Control Studies

Unmatched case-control studies estimate the attributable cost by comparing two groups of patients: those with HCAIs and those without. The difference in overall length of stay between the two groups is attributed to the infection. This methodology assumes that any difference in length of stay, and consequently in cost, is due to the HCAI. Generally, the comparison is made using the average cost of patients and controls.[18-22]

The main advantage of this method is the use of inexpensive, readily available data on the length of stay. The major drawback is the assumption that any additional length of stay is exclusively due to the infection and not related to any other inherent differences between the two groups. Therefore, it appears that unmatched case-control studies overestimate the attributable length of stay due to the infection. However, they may be useful in situations where a quick estimation of attributable cost is necessary, provided that they are followed by more accurate and detailed studies.[18-22]

Matched Case-Control Studies

Matching overcomes the limitations of simple case-control studies by comparing patients with HCAIs to similar controls (without HCAIs), based on potential confounding factors such as age, sex, diagnosis, risk factors, and severity scoring systems (e.g., APACHE II score). The attributable length of stay is calculated by subtracting the length of stay of the control from that of the infected patient. The resulting difference is attributed to the infection.[18-21]

The diverse characteristics of patients make matching particularly difficult. The likelihood of selection bias may increase due to the exclusion of patients and controls who could not be matched. Reducing the strictness of matching criteria increases the number of pairs but may fail to account for important patient characteristics, such as disease severity.[14,18-22]

This method assumes that patients have no additional predisposition—other than the infection—for longer hospitalization. An ideal matching process should include the full range of potential confounding variables, which are not always available. Thus, as the number of matching variables increases, the pool of potential controls may become insufficient, leading to the exclusion of patients for whom no match can be found. Full matching results in the distribution of confounders being the same between cases and controls. Therefore, when several confounders are used for matching, the controls become "identical" to the cases. [14,18-22]

Among the various methods used to estimate the attributable length of stay and cost of HCAIs, matched case-control studies are among the most appropriate. However, they are generally thought to slightly overestimate the attributable length of stay and cost. To improve the matching process, some researchers have introduced scoring systems that measure the appropriateness of the control match. Others included additional criteria: the length of stay of controls must not be shorter than the time between hospital admission and onset of infection in the case patient. Although this criterion does not fully eliminate time-dependent bias, it significantly reduces it.[18,19]

Regression Analysis

Matching presents some limitations. When multiple variables are used, a substantial increase in the control pool size is required, which is not always feasible. Matching too few variables can result in residual confounding due to the omission of important cost-related factors. As a result, the attributable cost of HCAIs may be overestimated or underestimated. Furthermore, if patients are later excluded from the study to allow more variables for matching (i.e., to reduce omitted variable bias), selection bias may occur, as not all patients have the same chance of being included in the cost comparison.

By using regression analysis for a patient cohort, selection bias can be completely avoided, and it offers an opportunity to reduce confounding from omitted variables.[18,19]

Regression analysis can be used to estimate the value of a dependent variable (e.g., hospital cost) by developing predictive models. A mathematical predictive mod-

el yields an equation used to estimate the dependent variable for an individual. For example, a mathematical model can estimate the hospitalization cost of an individual based on age, sex, comorbidities, length of stay, duration of mechanical ventilation, type of infection, and type of pathogen. The regression coefficients for each of these predictors can be inserted into an equation to predict the hospitalization cost.[18,19]

Linear regression, analysis of variance, and certain survival analysis models are generalized linear models widely used in financial data analysis. Multivariable regression is a mathematical method that ensures validity, as it allows the effect of each variable to be isolated from the influence of others—thereby eliminating confounding from multiple variables. This method enables the inclusion of nearly all patients and controls in the analysis and thus avoids selection bias.[14,18,19,23]

For the final multivariable linear regression model, assumptions must be checked: independence of observations, presence of outliers, linearity between the dependent and independent variables, normal distribution of residuals, and homoscedasticity (constant variance of residuals).[15]

The simplest way to handle data that violate linear regression assumptions is by transforming the dependent variable, which theoretically can make the data distribution more symmetric. However, this transformation has a major drawback: if the dependent variable is transformed (e.g., logarithmically), then the resulting estimates will also be on the transformed scale. Nonetheless, this issue can be addressed by reporting the results in their natural units through back-transformation using a conditional mean.[24]

Multistate Models

A multistate model is defined as a model for a continuous-time stochastic process, in which at any given time, individuals occupy one of a finite number of discrete states and are allowed to move between them.[18,25-29] In epidemiology, states may describe statuses such as healthy, ill, ill with complications, and deceased. A change in state is referred to as a transition or event. It is important to distinguish between an event (e.g., death) and a state (e.g., the state of being deceased). The structure of states defines which transitions are possible between states. The complexity of multistate models depends significantly on the number of states and possible transitions.[25-30] Multistate models can be considered a generalization of the basic survival data framework, allowing for multiple (possibly competing) events to occur over time and thus enabling the handling of competing risks. These models have proven useful and easy-to-understand frameworks for defining and estimating HCAI-attributable mortality and length of hospital stay. They are suitable for avoiding time-dependent bias, as they account for the timing of admission, infection onset, discharge, or death.[18,19]

However, multistate models also have some limitations. First, because the model represents events as they occur over time, daily individual-level data must be collected, which can be expensive and time-consuming. Second, multistate models rely on two restrictive assumptions: the probability of transition to the next state depends only on the current state and the patient's future trajectory (e.g., discharge or death) depends solely on the current infection state—not the exact timing of infection diagnosis. The first limitation can be addressed by including the time since infection diagnosis in the model. The second assumption may be more relevant in clinical trials with periodic outpatient follow-ups, where daily data are available.[18,19]

The structure of states is not unique. The common state structures are five:

i. The mortality model with states alive-dead and only one possible transition is the simplest possible multistate model.

ii. The alternating state model relates to reversible diseases where individuals move back and forth between health and illness.

iii. The disability model with states healthy, ill, dead relates to irreversible diseases, specifically when the disease increases the risk of death. It is also called the illness-death model. It is used to study the occurrence of HCAI and the death rate, while also estimating whether those previously ill have the same risk of death as those who were healthy. This can be modeled by allowing the risk of death to depend on whether the history of the process includes illness. In this model, it is clear that the risk of death for those previously ill is possibly different from the risk of death for those never ill.

iv. The bivariate model is the multistate model for bivariate parallel data with states: both alive, the 1st person dead, the 2nd person dead, and both dead.

v. The recurrent events model is the model which describes populations that experience the same event multiple times, e.g., hospital admissions, childbirths, infections, etc.[31,32]

Conclusions

Healthcare-associated infections represent a major clinical and economic burden on modern health systems. Estimating their true cost is critical for designing and implementing effective infection prevention and control strategies. A wide array of methodologies is available to estimate the cost and burden of HCAIs, ranging from simple case studies to complex multistate models. Each method offers specific strengths and limitations in terms of precision, data requirements, time sensitivity, and resource intensity. Case studies and unmatched controls may provide quick, low-cost approximations but risk bias. Matched case-control studies offer more reliability, particularly when accounting for time-dependency. Regression analysis presents a flexible and powerful tool for multivariable adjustment, while multistate models offer the most comprehensive temporal insight—though at the cost of complexity and data demands. Choosing the appropriate cost estimation method depends on the research question, available data, and required level of precision. A combination of methodologies, tailored to context, may often provide the most accurate and actionable insights for healthcare policy and resource allocation.

ΠΕΡΙΛΗΨΗ

Μεθοδολογίες εκτίμησης κόστους λοιμώξεων σχετιζόμενων με τη φροντίδα υγείας

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Οι λοιμώξεις που σχετίζονται με τη φροντίδα υγείας (ΛΣΦΥ) προκαλούν σημαντική κλινική και οικονομική επιβάρυνση παγκοσμίως, καθιστώντας την ακριβή εκτίμηση του κόστους κρίσιμη για την αποτελεσματική πρόληψη και την κατανομή των πόρων. Υπάρχουν διάφορες μεθοδολογίες για την εκτίμηση του αποδιδόμενου κόστους και της διάρκειας νοσηλείας λόγω ΛΣΦΥ, καθεμία με τα δικά της πλεονεκτήματα και περιορισμούς. Οι μελέτες περιπτώσεων είναι απλές και φθηνές, αλλά υποκειμενικές και λιγότερο αξιόπιστες, ενώ οι μελέτες ασθενών-μαρτύρων χωρίς εξομοίωση παρέχουν γρήγορες εκτιμήσεις αλλά μπορεί να υπερεκτιμήσουν το κόστος επειδή δεν ελέγχουν για συγχυτικούς παράγοντες. Οι μελέτες ασθενών-μαρτύρων με εξομοίωση προσφέρουν βελτιωμένη ακρίβεια αντιστοιχίζοντας ασθενείς με λοιμώξεις με παρόμοιους μάρτυρες, αν και αντιμετωπίζουν προκλήσεις που σχετίζονται με την πολυπλοκότητα της αντιστοίχισης και τις χρονοεξαρτώμενες μεροληψίες. Η ανάλυση παλινδρόμησης επιτρέπει πολυμεταβλητή προσαρμογή και μειώνει τη μεροληψία επιλογής συμπεριλαμβάνοντας σχεδόν όλους τους ασθενείς, αλλά απαιτεί λεπτομερή κλινικά δεδομένα και εξειδικευμένη ανάλυση. Τα μοντέλα πολλαπλών καταστάσεων παρέχουν την πιο ολοκληρωμένη εικόνα προσομοιώνοντας τις μεταβάσεις των ασθενών μεταξύ καταστάσεων υγείας με την πάροδο του χρόνου, αντιμετωπίζοντας αποτελεσματικά τη χρονοεξαρτώμενη μεροληψία, όμως απαιτούν εκτενή συλλογή δεδομένων και σύνθετη μοντελοποίηση. Συμπερασματικά, η επιλογή της μεθοδολογίας εξαρτάται από τους στόχους της έρευνας, τη διαθεσιμότητα δεδομένων και την επιθυμητή ακρίβεια, και συχνά ένας συνδυασμός μεθόδων παρέχει τις πιο ακριβείς και εφαρμόσιμες πληροφορίες για την πολιτική υγείας και τις στρατηγικές ελέγχου λοιμώξεων.

Λέξεις-ευρετηρίου: *Ανάλυση παλινδρόμησης, Εκτίμηση κόστους, Λοιμώξεις σχετιζόμενες με τη φροντίδα υγείας, Μελέτες ασθενών-μαρτύρων, Μοντέλα πολλαπλών καταστάσεων*

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