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SPECIAL ARTICLE

Analysis of causality from observational studies and its application in clinical research in Intensive Care Medicine☆

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Abstract Random allocation of treatment or intervention is the key feature of clinical trials and divides patients into treatment groups that are approximately balanced for baseline, and therefore comparable covariates except for the variable treatment of the study. However, in observational studies, where treatment allocation is not random, patients in the treatment and control groups often differ in covariates that are related to intervention variables. These imbalances in covariates can lead to biased estimates of the treatment effect. However, randomized clinical trials are sometimes not feasible for ethical, logistical, economic or other reasons. To resolve these situations, interest in the field of clinical research has grown in designing studies that are most similar to randomized experiments using observational (i.e. non-random) data. Observational studies using propensity score analysis methods have been increasing in the scientific papers of Intensive Care. Propensity score analyses attempt to control for confounding in non-experimental studies by adjusting for the likelihood that a given patient is exposed. However, studies with propensity indexes may be confusing, and intensivists are not familiar with this methodology and may not fully understand the importance of this technique. The objectives of this review are: to describe the fundamentals of propensity index methods; to present the techniques to adequately evaluate propensity index models; to discuss the advantages and disadvantages of these techniques.

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Análisis de la causalidad desde los estudios observacionales y su aplicación en la investigación clínica en Cuidados Intensivos

Resumen Una de las características fundamentales de los ensayos clínicos es la asignación aleatoria de un tratamiento o intervención sobre los pacientes. Esta asignación divide los pacientes en dos grupos que, aunque difieran por el tratamiento recibido, presentan unas características basales homogéneas haciendo que ambos grupos sean comparables y se pueda evaluar el efecto causal del tratamiento. Por otro lado, los estudios observacionales se caracterizan por la asignación no aleatoria del tratamiento y por lo tanto que los grupos de pacientes no solo difieran por el tratamiento recibido, sino también por otras características basales, a menudo relacionadas con la variable de intervención. En numerosas ocasiones, los ensayos clínicos aleatorizados no son factibles por razones éticas, logísticas, económicas o de otro tipo. Uno de los retos de la investigación clínica en Cuidados Intensivos debería ser aprovechar los datos que provienen de la práctica clínica habitual y analizarlos como si fueran ensayos clínicos. Los estudios observacionales utilizando métodos de análisis con índices de propensión *(propensity score)* han ido en aumento en los artículos científicos de Cuidados Intensivos. Los análisis de índices de propensión intentan controlar la confusión en estudios observacionales ajustando la probabilidad de que un determinado paciente esté expuesto. Sin embargo, los estudios con índices de propensión pueden ser confusos, y los intensivistas no están familiarizados con esta metodología y pueden no comprender plenamente la importancia de esta técnica. Los objetivos de esta revisión son: describir los fundamentos de los métodos del índice de propensión; presentar las técnicas para evaluar adecuadamente los modelos de índices de propensión, y discutir las ventajas y los inconvenientes de estas técnicas.

Introduction

In clinical research carried out in Intensive Care Units (ICUs), one of the common objectives is to evaluate the causal relationship between a given treatment or intervention (exposure) and the health outcome of a patient (death, healing, discharge from the ICU). Clinical trials are the reference research design when assessing the efficacy of a treatment in relation to the event of interest, since they reduce the risk of confounding influences or selection bias. Clinical trials involve the random assignment or allotment of a series of patients with a similar disease stage in order to assess the impact of such treatment upon the outcome. In the ICU setting, this outcome is usually defined as mortality during admission to the Unit or during the first 28 days after admission, or as the need for more aggressive treatment (e.g., tracheotomy).[1–3]

Assignment to treatment is the principal characteristic of clinical trials. The type of treatment for each patient is determined on a random basis in order to ensure that both the treated and the untreated patients present homogeneous features, thereby preventing the effect of the treatment from being confounded by the characteristics of the patients.

Although clinical trials are considered to be the highest quality studies for estimating causality, they also have some limitations: the sample size is typically of limited size and difficult to achieve; external validity is low; the application of inclusion criteria narrows down the population analyzed (since elderly patients, individuals with comorbidities or pregnant women tend to be excluded); ethical issues must be taken into account; and the duration of follow-up is limited.[4]

In the case of the ICU there are additional factors that make the designing of clinical trials in this setting particularly difficult, such as nosographic shortcomings (patients admitted to the ICU present syndromes such as for example acute respiratory distress syndrome [ARDS] instead of diseases); problems in defining adequate control groups; the concomitant use of different treatments (in many cases the intervention is not a drug but a therapeutic approach); randomization prior to treatment; or the obtainment of informed consent (which poses problems due to the moment in which consent is required).[5]

A possible solution to some of the difficulties of clinical trials is the conduction of observational studies. These represent a type of research in which treatment selection is conditioned to the baseline characteristics of the patient. The supervising physician decides the type of treatment according to the patient features. This is one of the main differences between observational studies and clinical trials.[6–9]

Observational studies have a number of advantages with respect to clinical trials: the population setting is broader; the duration of follow-up is longer; and the sample size is greater. In contrast, the fact that treatment allocation is not randomized implies that the estimation of causality is biased, and that the treated patients and untreated patients therefore differ not only in the treatment received but also in their baseline characteristics. If these baseline variables