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Longitudinal observational studies and causality

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Results from randomised clinical trials (CT) and CT meta-analyses provide the best scientific evidence for evaluating the effect of a treatment according to the hierarchical rankings for clinical research methods. Observational studies (OS) hold a lower position in the evidence rankings, and are considered to have less probative force for the following reasons: a) they may overestimate the effects of the treatment due to patient heterogeneity; b) they may contain biases that are inherent to their design and nature; and c) on some occasions, the interpretation of results may be confusing. However, the controlled conditions found in a CT mean that their results may not be directly applicable to patients in clinical practice. An OS, on the other hand, measures effectiveness that cannot feasibly be obtained in any other way. In clinical research, and in the field of nephrology in particular, the analysis of large patient registers or clinical databases provides information whose usefulness should not be underestimated,[1,2] and which may complement CT results. Using this strategy, we can perform medical research that is closer to daily clinical practice, and focuses on the normal conditions experienced by the patients themselves.[3]

Generally speaking, OS, and cohort studies in particular, are useful for assessing the effect of a treatment that was not assigned at random. Here, treatment is established based on common medical practice or on the patient's individual characteristics. Establishing a link between a treatment and a certain result may depend on a number of biases, including confounding by indication, since in this type of study, treatment is not assigned at random and may be related to health results. One obvious example is when the indication for the treatment in some situations is determined based on clinical guidelines or consensus for a specific disease.

A number of statistical models have been created to assess the effect of a treatment and to check for potentially confounding co-variables. For example, regression models can offer measures to associate a treatment with a result, but they cannot establish causality measures due to the lack of interchangeability among patients. Causal relationships can be established in a CT, since the patients are interchangeable and assigned to different groups at random. Interchangeability cannot be assumed in an OS, since the assigned group depends on the patient's conditions, expressed as co-variables that change over time, and on the treatment the patient receives according to the co-variables that were analysed. It may therefore occur that time-dependent variables are affected by the treatment itself. This means that both the co-variables and the treatment may change the patient's prognosis.

Marginal structural models (MSM) were proposed in the late 1990s by members of the Harvard School of Public Health[3,4] to evaluate causal relationships and avoid biases in longitudinal studies. MSM are an alternative to classical regression models when there is a time-dependent confounder that is associated with the event in question, but it is also related to the treatment being evaluated. These models are called "structural" because they study causality, rather than simple association. Causal inference is performed by means of comparing, theoretically, the results of treating all patients with the results of treating none of the patients. Marginal structural models use a weighted form of the propensity score, called IPTW (inverse probability of treatment weight), in such a way as to simulate a population in which treated and untreated patients do not differ in any of their co-variables, therefore allowing us to assume interchangeability for treated and untreated patients. MSM are used in clinical research in order to resolve questions of causality. As noted by Hernan, the scenario is typically represented by observational studies that are analysed like CT.[5] This type of model can be implemented by using common statistical software applications. The journal NBE published an article entitled "*Modelos estructurales marginales: una herramienta útil que proporciona evidencia a los estudios observacionales*" (marginal structural models: a tool for studying causal relationships in observational studies)[6] which provides

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practical information about this type of statistical tool. This article also provides an in-depth account of the conceptual bases of an MSM, the assumptions and conditions it must contain, and the way to implement it by using specifically designed statistical software.

In many medical specialties, including nephrology, patients are monitored over long periods of time as part of their care requirements, and they receive a number of treatments that are added according to their condition at a specific time. An MSM is ideal in this type of situation for avoiding confounding by indication biases. To cite an example, MSM were applied in OS of HIV-positive patients receiving antiretroviral drugs[7-10]; in patients taking aspirin due for cardiovascular disease[11]; and in patients who received corticosteroids for asthma[12] or rheumatoid arthritis.[13]

In nephrology, MSM have also been used to determine the causal relationship between multiple treatments or exposures and the final outcome of a disease. In this respect, multiple OS have shown that patients on high doses of erythropoietin (EPO) could have higher mortality rates, although it was also suspected that patients requiring higher doses of EPO could have more co-morbidities. Likewise, the efficacy of restricting phosphorus in a diet or using a certain dialysis technique (haemodialysis vs peritoneal dialysis) to decrease mortality in kidney patients are also topics of considerable debate.

Although a preliminary analysis shows that very high doses of EPO are associated with higher mortality, this effect disappeared with the implementation of a more complete MSM.[14] Use of MSM also revealed that neither restricting dietary phosphate in these patients nor the type of dialysis (haemodialysis or peritoneal dialysis) had a decisive influence on mortality in this patient group.[15,16] Lastly, the use of MSM in a multi-centre OS from the Netherlands showed that loss of residual renal function was associated with higher mortality rate,[17] which supports the possibility of implementing kidney replacement therapy that is personalised according to the urinary volume of the patient at the start of chronic dialysis.

In the field of kidney transplantation, the main purpose of MSM is to estimate the impact of metabolic changes on mortality and to evaluate the efficacy of immunosuppressive and cardioprotective drugs on both patient and kidney graft survival. In fact, the use of Cox regression models and MSM, adjusted for confounders, showed that high glycaemia and more intense insulin treatment was associated with higher mortality.[18] At the same time, with the help of MSM, it was shown that the use of mycophenolate mofetil was a more effective aid to kidney graft survival than azathioprine.[19] Lastly, a recent OS performed by our group by MSM found that the use of renin-angiotensin system blockers in kidney transplant patients is associated with a lower risk of mortality, but does not guard against losing the graft.[20] These findings confirm the usefulness of implementing an MSM in cohort OS of renal patients, but it remains unclear whether carrying out randomised CT on these patients will support these results.

As we await new evidence, use of MSM in cohort OS employing time-dependent variables provides results that are valid and complementary to CT results for evaluating the clinical efficacy of specific treatments.

KEY CONCEPTS

1. OS results may be comparable to those from clinical trials in terms of therapeutic efficacy, given adequate, rigorous OS design and data analysis methods.
2. The presence of time-dependent clinical confounders can result in overestimating or underestimating the effect of treatment when conventional regression models are used, due to confounding by indication.
3. MSM can prevent confounding by indication biases, but their assumptions and conditions must be verified.
4. The choice of confounders for implementing MSM must be done from a clinical standpoint, using the appropriate statistical support. Faulty choice of these variables can result in a bias that changes the estimator variance.
5. When using an OS to assess the efficacy of a treatment, employing MSM can increase the level of evidence, making it applicable and extendable to daily clinical practice.

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Conflict of interest

The authors declare they have no potential conflicts of interest related to the contents of this article.

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