How Important is the Sample Size?

To the Director

We have read the recently published article "Cystatin C as a predictor of cardiorenal syndrome and poor prognosis in patients hospitalized for acute heart failure and normal renal function", by Constantin et al, which was granted the 2015 Dr. Pedro Cossio Foundation Award. (1)

The lack of consistency between the title, the methodology, and the conclusions is particularly striking. The authors try to analyze the predictive value of cystatin C in patients hospitalized for acute heart failure, but focusing their study on a population with normal renal function (as stated in its title). In the Discussion section, the researchers admit that at least 25% of the patients studied did not have normal renal function (GFR <60 ml/min); however, they were included in the analysis. Enrolling patients who do not meet the selection criteria is a significant methodological flaw. Excluding this group of patients from the analysis would have further reduced the sample size, and therefore its statistical power.

Once the sample size was calculated with the corresponding formula, its final number should have been adjusted by taking into account a loss-to-follow-up percentage –usually between 10% and 15%– and not 25%, which a priori invalidates the results. (2)

Despite the importance of calculating sample size, it is surprising how often researchers fail to perform any systematic sample size calculation, or do not report having performed one, as in this case. In this sense, it is not uncommon for decisions of this sort to be made arbitrarily on the basis of convenience, available resources, or the number of easily available subjects. (2) A study by Moher et al. reviewed randomized controlled trials published in three important journals (*Journal of the American Medical Association, The Lancet and The New England Journal of Medicine*) in order to examine the level of statistical power in published trials. (3) Out of 102 trials studied, the investigators found that only 36% had 80% power to detect a relative difference of 50% among groups and only 32% of trials reported adequate sample size calculation in the published report. More recently, Charles et al., with the same methodology but analyzing six high impact factor journals, also found that only 34% of published articles reported all the necessary data to calculate sample size. (4)

The situation is slowly improving. Many agencies sponsoring clinical trials require sample size calculations before starting any study. However, many studies with poor statistical power continue to be published, and it is important for readers to become aware of the problem to have a proper critical interpretation.

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Authors´reply

We are glad you have read with great interest our work "Cystatin C as a predictor of cardiorenal syndrome and poor prognosis in patients hospitalized for acute heart failure and normal renal function", which received the 2015 Dr. Pedro Cossio Foundation Award. (1) We hope to resolve your concerns in these lines.

The strength of the work is based, as pointed out, on the consistency between the title, the methodology, and the conclusions. The title specifies that the effectiveness of cystatin will be assessed in patients with acute heart failure and normal renal function. Regarding methodology, a creatinine value <1.3 mg/dl on admission was considered normal renal function. The conclusion, supported by the results, highlights the independent association between cystatin C on admission and the final endpoints assessed in this population. Therefore, all the sections are consistent. The concern raised by Dr. Espinoza et al. is based on the fact that 25% of the patients with creatinine values <1.3 mg/dL had glomerular filtration rate <60 ml/min/1.7m². Whenever there are two different ways to estimate the same phenomenon (in this case, renal function), this problem may arise, particularly when both forms are imperfect. For instance, Leon et al. have recently published a study in *The New England Journal of Medicine* on the usefulness of percutaneous aortic valve replacement in intermediate risk patients. (2) Risk estimation was based on the risk score developed by the Society of Thoracic Surgeons (STS). Probably, if we applied a different risk score on the same population (for example, EuroSCORE), a percentage of patients would be classified as high-risk subjects, without implying that the trial is not valid. As mentioned in the Discussion section of our work, both creatinine and glomerular filtration rate have limitations. Our decision to consider creatinine values <1.3 mg/dl as normal renal function was based on the fact that creatinine is the most widely used method to estimate renal function, and on the inaccuracies presented by equations to estimate glomerular filtration rate in the studied population (elderly patients with acute heart failure).

Considering that the sample power is the probability of not incurring in a false negative study (i.e. the probability of detecting a difference, if it exists), (3) it is surprising that the sample size in our study with positive results is being questioned. In any case, considering 40% incidence of cardiorenal syndrome in patients with high

cystatin and 20% incidence in patients with low cystatin, with 5% alpha error and 80% power, it would be necessary to include 162 patients. Our loss-to-follow-up was 3.6%. The 166 enrolled patients met the inclusion criteria and therefore were properly included in the analysis.

We hope to have clarified that while our study has its limitations (detailed in the Discussion section), its methodology does not call into question both its internal and external validity.

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