META-ANALYSIS OF PATIENT-REPORTED OUTCOMES: METHODOLOGICAL PROPOSAL AND APPLICATION TO RANDOMIZED CLINICAL TRIALS IN HEART FAILURE

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Introduction

Randomized clinical trials (RCTs) are increasingly utilizing patient-reported outcomes (PROs) to ensure a patient-focused approach to treatment development and regulation.
However, due to the lack of standardization in PROs collection and analysis in RCTs, it can be challenging to summarize the evidence using a meta-analytic approach. To facilitate a more robust and comprehensive evaluation of treatment outcomes in terms of health-related quality of life (HRQoL) improvement, efforts are needed to establish a consistent methodology for analyzing and synthesizing PROs data.

Aims

This study aims to propose a meta-analytical methodology that enables the comparison of continuous PROs between treatment groups. As a motivating example, we applied the proposed methodology to PROs data from published RCTs testing SGLT2 inhibitors (SGLT2i) versus standard therapy in heart failure patients.

Methods

Although meta-analysis of individual patient data (IPD) is considered the most reliable method for synthesizing results from different trials, obtaining IPD can be a challenging and resource-intensive process. As an alternative, we suggest, using the algorithm proposed by Papadimitropoulou et al [1], to reconstruct pseudo-IPD for a continuous PRO at baseline and at pre-specified follow-up timepoints from available published aggregate data. The generated pseudo-IPD can then be analyzed in the same way as the original IPD [1]. However, the necessary input data, including group means (μ), standard deviations (SD), and sample sizes (N) within each study, are not always available in the original papers and must be either imputed or derived. If PRO scores are available only at timepoints other than the one(s) chosen for pooled synthesis, we recommend estimating the PRO score needed using techniques like linear interpolation between the previous and subsequent timepoints.
Once pseudo-IPDs are obtained, we propose, using the one-stage approach for IPD meta-analysis based on linear mixed-effects regression models [1], to obtain pooled estimates of treatment differences at the pre-specified timepoints while adjusting for baseline score, and to explore the interaction between time and treatment effect. Alternatively, a two-stage approach can be performed, in which study-specific estimates are firstly obtained from the pseudo-IPD separately for each study and then combined by a traditional meta-analytical model.
In our motivating example, we applied the proposed methodology considering as primary endpoint the difference in mean change of the Kansas City Cardiomyopathy Questionnaire [2] overall score between the SGLT2i group and the standard therapy group at 3 and 6 months from baseline. The KCCQ is a widely used and validated instrument designed to assess HRQoL in patients with cardiomyopathy. It includes multiple domains and provides a comprehensive measure of well-being, with scores ranging from 0 to 100. Higher scores indicate better HRQoL.
All analyses were conducted using SAS v9.4 and R v4.2.1.

Results

Fourteen RCTs on SGLT2i were included in the meta-analysis, for a total number of 21 737 individual PROs assessment recorded at baseline and at 3 months of follow-up and 17 132 at 6 months.

Results showed with the two-stage approach an estimated difference in mean change of 2.06 (standard error (SE)=0.29) at 3 months and 1.70 (SE=0.41) at 6 months, whereas with the one-stage approach 1.68 (SE=0.16) at 3 months and 1.81 (SE=0.18) at 6 months. Both methods suggested a significant benefit of taking SGLT2i compared to standard therapy alone in terms of HRQoL improvement, although the effect size might be too small to be considered clinically relevant [3]. The one-stage approach provided a more detailed understanding of the treatment effects, revealing a significant improvement in QoL over time ($p<0.001$) in both groups. The time-dependent impact of SGLT2 inhibitors did not substantially differ from that of standard therapy alone (interaction $p=0.6$), even though patients in the SGLT2i group showed a tendency towards a faster rate of improvement over time.

Conclusions

In our earlier publication [4], we showed the utility and feasibility of conducting a meta-analysis by using pseudo-IPD derived from available aggregate PROs data in the field of oncology. Building upon this previous work, we conducted a new study focused on the cardiovascular setting, where we meta-analyzed PROs from more than 20 000 patients to specifically compare results obtained by employing both the one-stage and the two-stage approaches. Notably, the one-stage approach provided lower SEs of the treatment effect compared with the two-stage. Further simulation-based analyses are needed to assess whether this method could also reduce the bias in estimating the effect and improve statistical power. Overall, the one-stage approach based on linear mixed-effects models and pseudo-IPD could be a powerful approach for meta-analyzing continuous PROs in clinical studies. Its flexibility and ability to potentially improve statistical power and reduce bias make it a valuable tool for conducting comprehensive meta-analyses.

Bibliography

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