VALIDATION OF DISEASE STATES IN SCHIZOPHRENIA: COMPARISON OF CLUSTER ANALYSIS BETWEEN THE UNITED STATES AND EUROPEAN POPULATIONS

Takayuki Kitagawa, Kenneth M. Miller, Lambert S. Lentz, Siddharth S. Moreno, and Brian J. Murray

OBJECTIVES: A set of disease states for patients with schizophrenia was previously published using a statistical clustering method, applied to Positive and Negative Syndrome Scale (PANSS) data from US patients. While factor analyses of the PANSS have shown remarkable stability of the structure across international populations, it is unknown whether similar multidimensional disease states would also be replicable. Using data from the European Schizophrenia Cohort (Europe), a 2-year observational study in 1,208 schizophrenia patients, we examined the factor structure of the PANSS and identified disease states using the same clustering method.

RESULTS: A principal component analysis (PCA) was conducted using the Kaiser criterion and varimax rotation on PANSS items, followed by a k-means cluster analysis on PANSS scores for items most strongly correlated with the PCA domains. For each cluster, a level (low, moderate, high) was assigned to measure the agreement in assignment between the published and the derived states set.

RESULTS: Five factors accounting for 56% of total variance were obtained from the PCA (positive symptoms, negative symptoms, cognitive impairment, mood disorder, and hostility). As in the analysis of patients in the initial US study, rates of change in root mean squared distance became small after six clusters. When using the European Schizophrenia Cohort (Europe), the statistical characteristics of the clusters were very similar to those of the published set but revealed differences in the distribution of patients across clusters.

PREDICTORS OF CLUSTER ASSOCIATION WITH HEALTH OUTCOMES

We demonstrate three techniques that may help to counteract these biases: graphical inference methods clearly illustrate the inherent uncertainty in subgroup analysis, Bayesian shrinkage estimation can reduce the effect of anchoring the observed subgroup effects and encourage consideration of regression to the mean, and reframing exercises (for example, considering the credibility of biological plausibility arguments as if they had been mooted a priori) may counter optimism bias.

PARAMETER IMPORTANCE ASSESSMENT IN A HEALTH ECONOMIC EVALUATION MODEL FOR HEART FAILURE

Sagdas Kuyukbaramish, 1Nicholas M. Gough, 1Matthew J. Lambert, and Philip R. Boucher

OBJECTIVES: This review of T&M studies revealed that methods with data from the Lux Lung 1 trial of the tyrosine kinase inhibitor afatinib applied an analytical design aiming to defect statistical differences, and 2 reported pooling data (3 of which used a “mean of centre averages” approach). Eleven studies (52%) compared two groups, of which 3 applied a fixed-effect statistical model. We reported a sample size calculation.

CONCLUSIONS: This review of T&M studies revealed that descriptive designs are most common (analytical designs using power calculations are rare). Multi-centre comparator studies rarely use random effects regression models to account for “centre clustering”, though considered the method of choice to produce valid confidence intervals around point estimates. In general, statistical methodology is scarcely reported, affecting overall study credibility.

PARAMETER IMPORTANCE ASSESSMENT IN AHEALTH ECONOMIC EVALUATION MODEL FOR HEART FAILURE

Sagdas Kuyukbaramish, 1Nicholas M. Gough, 1Matthew J. Lambert, and Philip R. Boucher

OBJECTIVES: To reduce the potential to confound assessment of overall survival (OS) in oncology trials, in particular for trials in early lines of treatment, we undertook a systematic review of different techniques with several example applications. Standard intent-to-treat analysis is biased, since treatment choices are likely to be influenced by events associated with mortality risk, such as disease progression. We review and compare available statistical methods to obtain unbiased estimates of OS effects in presence of subsequent therapies.

RESULTS: The methods that correct for the potential OS benefit from afatinib, but the hazard ratio varied from 0.58 (95% CI:0.38-0.89) with the pre-specified IPCW method to 0.89 (0.28) with RSPTF/IPE. Conclusions: The proposed methods for obtaining unbiased OS estimates in presence of subsequent therapies are robust to the choice of OS model and are therefore valid as well as testing alternative methods. Care should be taken to avoid imbalance in subsequent therapy and to record specific information on administered treatments with potential OS effects.