RESEARCH ON MODELING METHODS STUDIES

M01 REDUCING AND QUANTIFYING OVER-FITTING IN REGRESSION MODELS
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OBJECTIVES: Regression models are the mulitvariable analytical method of choice for epidemiologists and statisticians. It is widely recognized that these models may suffer from over-fitting where the sample estimates fail to generalize to other samples. Systematic approaches to minimize over-fitting are seldom adopted and there is a reluctance to hold data back for independent assessment of model performance. This study assesses penalized regressions for reducing over-fitting, cross-validation on training data for estimating over-fitting, and the extent to which over-fitting produces misleading conclusions. METHODS: Data were extracted from the IMS PharMetrics Plus US medical claims database for patients with Multiple Sclerosis receiving treatments. Cohorts were matched using propensity scores producing 3,348 matched pairs. The probability of relapse and persistence were estimated using standard, stepwise and (LASSO) penalized regression. Over-fitting was measured as the difference between the Area Under Curve (AUC) for training and test data and additionally estimated using cross-validation on training data alone. RESULTS: Penalized logistic regressions greatly reduced over-fitting compared to standard and stepwise alternatives, irrespective of the choice of response variable and degrees of freedom: for example, modelling relapse with 50% of the data used for training and 50% used for testing showed overfitting of 9.9% with standard, 8.0% with stepwise and 3.9% with penalized logistic regression. Cross-validation provided reasonable approximations for over-fitting, estimated over-fitting of 10.4% using standard logistic models and 10.4% using penalized logistic models. Over-fitting inflated the estimated treatment effect by 25% (OR=2.03 vs. 1.64; standard logistic model vs. penalized model). CONCLUSIONS: Penalized logistic regression models had substantially lower over-fitting. Moreover, good estimates of over-fitting can be derived without withholding data. Both penalized regressions and cross-validation are straightforward to implement in most statistical packages and greater adoption of these methods is encouraged to ensure more reliable estimates of risk factors.

M02 A COMPARISON OF STATE TRANSITION AND DISCRETE EVENT MODELING APPROACHES FOR COST-EFFECTIVENESS ANALYSIS IN THE PREVENTION OF THROMBOTIC EVENTS AFTER MYOCARDIAL INFARCTION (MI)
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OBJECTIVES: A state transition model (STM) and a discrete event simulation (DES) were developed to evaluate the health outcomes associated with antiplatlet treatment following a secondary prevention of coronary heart disease event among patients with a recent myocardial infarction (MI) in the UK. METHODS: The STM and DES were developed with similar assumptions about which events altered risk. In both models, results were compared between the vorapaxar plus standard care (VOR) and the standard care (SC) arms. Individual patient characteristics at baseline from the qualifying MI cohort of TRIA 2/7F-TIMI 50 trial were used to define patient profiles in both models; risk equations developed from the trial were used to estimate MI, stroke, and cardiovascular-related death risk. Bleeding event risks, case fatality rates, non-cardiovascular mortality, and utilities were taken from published studies or UK statistics. RESULTS: In the base case, for the VOR and SC arms, the DES predicted 13.93 CV-deaths, 13.93 strokes, and 13.93 MIs; the STM predicted 0.226 MIs, 0.132 strokes, and 0.417 CV-deaths per patient lifetime. The probability of relapse and persistence were compared between the vorapaxar plus standard care (VOR) and the standard care (SC) arms. The STM predicted 0.226 MIs, 0.132 strokes, and 0.417 CV-deaths per patient lifetime, producing 3,348 matched pairs. The probability of relapse and persistence were estimated using standard, stepwise and (LASSO) penalized logistic regressions. Over-fitting was measured as the difference between the Area Under Curve (AUC) for training and test data and additionally estimated using cross-validation on training data alone. RESULTS: Penalized logistic regressions greatly reduced over-fitting compared to standard and stepwise alternatives, irrespective of the choice of response variable and degrees of freedom: for example, modelling relapse with 50% of the data used for training and 50% used for testing showed overfitting of 9.9% with standard, 8.0% with stepwise and 3.9% with penalized logistic regression. Cross-validation provided reasonable approximations for over-fitting, estimated over-fitting of 10.4% using standard logistic models and 10.4% using penalized logistic models. Over-fitting inflated the estimated treatment effect by 25% (OR=2.03 vs. 1.64; standard logistic model vs. penalized model). CONCLUSIONS: Penalized logistic regression models had substantially lower over-fitting. Moreover, good estimates of over-fitting can be derived without withholding data. Both penalized regressions and cross-validation are straightforward to implement in most statistical packages and greater adoption of these methods is encouraged to ensure more reliable estimates of risk factors.

M03 DOES THE USE OF EFFICACY OR EFFECTIVENESS EVIDENCE IN COST-EFFECTIVENESS ANALYSES MATTER?
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OBJECTIVES: Clinical efficacy or effectiveness (the “C”) is one driver of cost-effectiveness analysis (CEAs). The type of “C” used in each CEA depend on the objectives and corresponding data sources. Applying different types of the “C” may affect CEA conclusions, but little is known. We aim to test the association of type of “C” and cost-effectiveness conclusions using asthma CEAs as an example. METHODS: A systematic review was performed with 5 electronic databases from 2009 to 2014. All CEs that included the use of asthma medications for maintenance reporting incremental costs and effectiveness against a non-pharmaceutical comparator. Descriptions of CEs were extracted from published reports or, if unavailable, from the study authors. RESULTS: A total of 17 CEs were included. Nine studies (52.9%) used efficacy evidence, while 8 studies (47.1%) used effectiveness evidence. Ten studies (58.8%) were modeling-based studies, while 7 studies (41.2%) were CEA alongside-clinical trials. The “C” of 5 studies (29.4%) were derived from explanatory RCTs, 4 studies (23.5%) from meta-analysis of RCTs, 4 studies (23.5%) from pragmatic trials, and another 4 studies (23.5%) from observational studies. The odds ratio for effectiveness being cost-effective was 8.75 (95% confidence interval; 0.74 to 103.82). CONCLUSIONS: Most CEA studies in asthma used efficacy data to inform CEA. Studies using effectiveness data trend toward being more likely to disseminate cost-effective findings than those using efficacy data. Health policy decisions and researchers should pay attention to the type of “C” evidence used in CEAs for accurate interpretation and application.

M04 EXTRAPOLATING ALL-CAUSE MORTALITY ESTIMATES IN ECONOMIC EVALUATIONS: A SIMULATION ANALYSIS
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OBJECTIVES: A cost-effectiveness model can be populated using mortality rates from a period’s life-table or using extrapolations of mortality based on historical life-tables. Current decision models use the first method. This simulation study aims at identifying the impact of mortality methods used on cost effectiveness analyses. METHODS: A simulation study was designed based on a two-state Markov model (alive-death) that compared a hypothetical intervention against no intervention. The model was populated with age-specific, all-cause mortality probabilities from the estimation methods presented above. The mortality extrapolations were estimated using a smoothed Lee-Carter method. The model outcomes were incremental costs, life-years gained (LYG) and incremental net benefit (INB). The proportional difference (PD) of the model outcomes between the two mortality estimation methods was the outcome of each simulation. The following parameters were simultaneously varied: discounting rate (0 – 0.05), intervention effect (relative risk of mortality: 0.9 – 0.99), age at intervention (birth- 80 years old), duration of intervention effect (1 year/10 years/ lifelong), estimation of intervention administration. Simulations were conducted using Canadian life-tables. The impact of each parameter on the simulation outcomes was estimated using descriptive and graphical methods. RESULTS: The cohorts’ age and the duration of intervention had the most impact on the PD in all 3 cost and LYG. The duration of intervention effect and administration were more influential on the effect of method on the PD of incremental costs and INB. Large variation was observed among the scenarios within parameter values, for the PD of all outcomes. CONCLUSIONS: Allowing mortality projection methods, substantial differences were observed in CEA model outcomes. Given that the magnitude and the direction of the impact of mortality estimation methods on the model outcomes is multi-factorial, decisions on mortality estimation method used in economic evaluations should be considered after conducting sensitivity analyses using both methods.

RESEARCH PODIUM PRESENTATIONS - SESSION II

CANCER OUTCOMES RESEARCH STUDIES

C01 THE IMPACT OF CHRONIC CONDITIONS ON THE ECONOMIC BURDEN OF CANCER SURVIVORSHIP IN THE UNITED STATES
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OBJECTIVES: The objective of this study is to examine the prevalence of chronic conditions and their impact on the economic burden among cancer survivors in the United States (US). METHODS: Using the 2008-2012 Medical Expenditure Panel Survey (MEPS) we identified 8,617 cancer survivors and 111,695 individuals without a history of cancer. Medical expenditures for cancer survivors with other chronic conditions, particularly those with MCCs were higher than among cancer survivors without any of the chronic conditions studied. The largest increase in medical expenditures was associated with heart disease ($4,287) and stroke ($4,210). Having ≥4 chronic conditions was associated with increased expenditures of $9,082 per cancer survivor. Low productivity was greater among cancer survivors with other chronic conditions. The largest increase in lost productivity was associated with stroke ($4,146) and arthritis ($3,420). Having ≥4 chronic conditions was associated with increased lost productivity of $9,245 per cancer survivor. CONCLUSIONS: Chronic conditions, especially the presence of MCCs, are associated with higher medical expenditures and lost productivity among cancer survivors. Efforts to reduce the health and economic burden caused by chronic conditions among cancer survivors are important given their substantial impact on medical expenditures and lost productivity.

C02 A COMPARATIVE COST UTILITY ANALYSIS FOR FIRST LINE TREATMENT OF METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH EGFR EXON 19 DELETIONS OR EXON 21 (L858R) SUBSTITUTION MUTATIONS
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Objective: To perform a cost-utility analysis for first-line treatment of metastatic NSCLC patients with EGFR exon 19 deletions or L858R substitution mutations. Method: We performed a cost-utility analysis using a Markov decision model. Life years (LY), quality-adjusted life years (QALY), and costs were calculated. RESULTS: The ICER for gefitinib versus amrubicin was $130,024/QALY for patients with EGFR exon 19 deletions and $190,594/QALY for patients with L858R substitution. CONCLUSION: Both gefitinib and amrubicin are cost effective compared to the current standard of care. However, gefitinib is the preferred treatment option for patients with EGFR exon 19 deletions.