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THE INTERNATIONAL PROJECT FOR DEVELOPING A PROGNOSTIC INDEX FOR SYMPTOMATIC WALDENSTRÖM'S MACROGLOBULINEMIA.

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In October 2002, 11 cooperative groups or institutions have decided to join their patients populations in order to develop an international prognostic index for symptomatic WM, requiring therapy (according to Athens workshop recommendations). The main inclusion criteria include: (i) a date of diagnosis before January 1st, 2002; (ii) a minimal follow-up of surviving patients posterior to December 2002; (iii) the availability of serum β 2-microglobulin (b2-m) concentration before initiating therapy. The main endpoint is overall survival from initiating therapy to last follow-up. By June 2004, 957 records have been collected, including 678 patients with available serum b2-m. The validation process rests on four steps with the aim to obtain less than 10% missing data or patients lost to follow-up. (i) A descriptive analysis of demographics, dates and covariates identified 3 covariates and 2 date items with out of range values. (ii) These 5 items were included in a check list of 36 controls. Using these controls and the 678 records with available b2-m, a SAS program produced 1445 queries that have been sent to investigators. (iii) Using, a multivariate classification analysis, 6 observations appeared very different from the other and they have been completely verified. (iv) Once response to queries will be collected, the French and the Italian databases will be compared to detect input mistakes, before closing the final database. An agreement of all investigators on the statistical plan and decision rules should also be obtained before conducting the analyses. We propose the following steps: (i) Descriptive statistics will include all clinical and demographic characteristics. These covariates will be compared in pairs. The relationship between the different covariates will be investigated using Pearson correlation coefficient for numeric variables and chi-square test otherwise. (ii) Univariate analyses of survival will identify the optimal cut-off values according the following rules: Litterature based cut-off values will be assessed, then a recursive partitioning analysis, and Fisher algorithm will be used, Finally the choice of cut-off values will be done through expert meeting, using the delphi method. (iii) Cox model analysis of survival will be conducted after assessment of Cox model hypothesis using both graphical (Schoenfeld residuals) and test (Grambsch and Therneau) methods. (iv) In case of departure from the Cox model hypothesis, cubic spline functions will be employed to model the time by covariate interaction. (v) Regression tree analysis using the CART algorithm will be also performed. (vi) The final model will be chosen after the identification of the expected clinical criteria of quality of the model by clinician experts. The separation methodology described by Royston et al (Statist Med, 2004, 23, 723-48) will be used, with simplification of the model according to Ambler et al (Statist Med, 2002, 21, 3803-22). (vii) In case of selection of age as covariate in the final model, the analyses will be repeated in subgroups of younger and older patients (viii) Because of the rarity of the disease, it is unlikely to obtain a simultaneous external validation data set. Therefore, we propose to conduct two validation procedures: first a cross validation or bootstrap analysis will be performed, second the validation of the prognostic index using a series of patients fulfilling the same inclusion criteria and diagnosed after January 1st 2002. We conclude with the hope that beyond statistical methodology, the quality of the data, and decision rules defined "a priori" will result in a workable tool despite the rarity of the disease.