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Logistic regression in the medical literature: Standards for use and reporting, with particular attention to one medical domain

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Abstract

Logistic regression (LR) is a widely used multivariable method for modeling dichotomous outcomes. This article examines use and reporting of LR in the medical literature by comprehensively assessing its use in a selected area of medical study. Medline, followed by bibliography searches, identified 15 peer-reviewed English-language articles with original data, employing LR, published between 1985 and 1999, pertaining to patient interest in genetic testing for cancer susceptibility. Articles were examined for each of 10 criteria for proper use and reporting of LR models. Substantial shortcomings were found in both use of LR and reporting of results. For many studies, the ratio of the number of outcome events to predictor variables (events per variable) was sufficiently small to call into question the accuracy of the regression model. Additionally, no studies reported validation analysis, regression diagnostics, or goodness-of-fit measures. It is recommended that authors, reviewers, and editors pay greater attention to guidelines concerning the use and reporting of LR models. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Logistic regression; Genetic testing; Cancer susceptibility; Regression analysis; Validation; Statistical methods

1. Introduction

Multivariable methods have become routine in statistical analyses appearing in the medical literature. Common to all multivariable methods is a relation between two or more predictor (independent, exposure) variables, and one outcome (dependent, response) variable. Formally, the model expresses the predicted value of the outcome variable as a sum of products, each product formed by multiplying the value of the variable and its coefficient. The coefficients are computed from the data. A regression model serves two purposes: (1) it can predict the outcome variable for new values of the predictor variables, and (2) it can help answer questions about the area under study, because the coefficient of each predictor variable explicitly describes the relative contribution of that variable to the outcome variable, automatically controlling for the influences of the other predictor variables.

Logistic regression (LR) is a multivariable method that was devised for dichotomous outcomes [1–4]. It is particularly appropriate for models involving disease state (diseased/healthy) and decision making (yes/no), and therefore is widely used in studies in the health sciences. In LR one obtains the logarithm of the odds of a positive outcome (where "positive" is defined by the encoding of the outcome variable, that is, $Y = 1$); a straightforward algebraic manipulation transforms this into the outcome's probability.

In multivariable methods, the calculation of the coefficients from the original data is more complex than can be conveniently performed by hand. The calculation of the coefficients for logistic models involves equations that cannot be solved explicitly but can be solved by an iterative procedure, easily expressed in computational form, and now widely available in statistical software packages. The quality of the regression analysis depends heavily on researchers understanding the assumptions inherent in the method and following principles developed to ensure their sound application [4–7]. Explicitness in modeling is also necessary for reporting the results to other researchers for verification and replication. The use of LR has been analyzed in informal [5] and random [7] samples of the medical literature, and across

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a collection of specialty journals [8]. Here we extend these analyses to a systematic review of a specific area with both considerable research activity and public concern, namely, patient interest in genetic testing for cancer susceptibility. Because the decision to seek testing for cancer susceptibility genes is complex, the relevance of LR in unraveling the intertwined psychosocial and demographic factors that may affect patients' decisions to seek testing is obvious. The purpose of this article is to examine the use of LR for modeling patients' interest in genetic testing for cancer susceptibility by comparing the actual use of LR with published criteria for use and reporting.

2. Methods

Articles about patient interest in genetic testing for cancer susceptibility were identified as part of a systematic review of that literature by searching the Medline database for peer-reviewed articles published in English between 1985 and 1999 matching the following keywords or keyword prefixes: "neoplasms," "genetic," and "psycholog." The search was executed in the Medline database on 3 January 2000. The resulting list of articles was processed by hand to retain only articles that: (1) contained results of original studies (removing reviews), (2) measured patients' interest in genetic testing for cancer susceptibility, and (3) contained explicit mention of LR modeling. This list was augmented by articles found through searches of bibliographies in previously identified articles, ultimately producing a list of 15 publications containing a total of 21 LR analyses. All of the identified articles are observational studies in which LR is used to predict patient interest in genetic testing given a set of demographic, clinical, and patient knowledge variables.

To evaluate the research reports, a list of criteria for the proper use and description of LR was created from the available literature [4–7,9–13]. The criteria were chosen both to summarize widely accepted statistical practice and to highlight common problems in regression analysis. The criteria have been divided, somewhat arbitrarily, into those that concern the qualities of the regression model ("analytic"), and those that principally involve the reporting of the results of the regression ("documentation").

2.1. Analytic criteria

2.1.1. Sufficient events per variable

Although it is important that the model include all relevant variables, it is also important the model not start with more variables than are justified for the given number of observations [7,9,10,14]. (For a given set of data, introducing more variables will generally produce a model better fit to the data; with excessive numbers of variables, idiosyncrasies of the particular data set unduly influence the coefficients in the model, which is said to be "overfit.") For LR, a useful rule of thumb comes from simulation experiments [14] which suggest that the number of the less common of the two possible outcomes ("events") divided by the number of predictor variables should be at least 10, and preferably greater. (In these simulation experiments, no sequential selection of variables was performed, so the final, "full" model included all the independent variables; the interaction of variable selection methods and the number of events per variable has been studied in [15].) The fewer events per variable, the greater the opportunity for the estimates of the regression coefficients to be unreliable; the sample variance of the model coefficients, and confidence intervals will also be less accurate [14]. The validity of statistical inference may also be adversely affected by having a small number of events per variable.

2.1.2. Conformity with linear gradient for continuous variables

For best results from the use of standard LR, any given change in a continuous predictor variable should have an effect on the log-odds of a positive outcome that is the same magnitude, regardless of the value of the predictor variable [7]. This is not an issue for dichotomous predictor variables for which necessarily there are only two values and one possible change, but for continuous variables it is important to check this assumption.

2.1.3. Tests for interactions

Interactions are represented as product terms: the term in the regression model is not a single predictor variable but the product of two predictor variables [4,6]. Generally, with samples of modest size the decision to consider interaction terms should be governed by prior knowledge of the domain. If interactions are included, then the significance of the interaction should be measured and reported.

2.1.4. Collinearity

Two predictor variables that are highly correlated (with each other) present a problem for any regression analysis [5]. If two highly correlated variables are included in the model, then their estimated contributions (as measured by the reported regression coefficients)—and those of all the other variables—may be imprecise. The variance associated with these coefficients will be increased, with a consequent loss of statistical significance. Although some software packages may include automatic checks, explicit tests for collinearity are more convincing and should be undertaken.

2.1.5. Validation

Even if the model coefficients have been computed following standard procedures, the resulting model may not be useful in making inferences about the population from which the data were sampled. It is therefore desirable to validate the model [5]. A simple validation procedure is to split the data in half; the model coefficients are calculated using one half and the model's goodness of fit is evaluated on the other half. Alternatively, the cross-validation technique can be employed: a subset of observations is withheld during training to serve as test cases; the process is repeated for each of the observation subsets, and model goodness of fit is evaluated by averaging over the withheld subsets. Although

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these strategies do not solve all problems pertaining to external validation (such as those related to the sample having systematic differences from the "base" population it is intended to reflect, due to sampling practices), they do provide protection against spurious associations occurring by chance within the sampled population.

2.1.6. Statistical significance

Statistical tests of significance can be applied to each variable's coefficients and to the entire model [3,4,6,16,17]. For each coefficient, the null hypothesis that the coefficient is zero can be tested using, for example, a Wald test. A Wald test can also be used to compare a full model containing all the predictor variables with a reduced model with some coefficients set to zero. (Alternative formulations of statistical significance for LR models and variables, such as the likelihood ratio test, are also available [2].)

2.1.7. Goodness-of-fit measures

Because the model will not fit the data set exactly, some indication of how well it does fit should be given. Summary goodness-of-fit measures describe how well the entire model matches the observed values; in addition, regression diagnostics (including residual, leverage, and influence measures) are important in revealing the effect of individual subjects on the estimated model [3,4,6,16,17].

2.2. Documentation criteria

2.2.1. Selection of predictor variables

Does the article explain how variables were selected for inclusion into the model? Usually the variables are chosen based on earlier research; sometimes they are selected by virtue of significant association in a bivariate analysis with the outcome variable [4]. (Problems associated with use of bivariate analysis for variable selection are discussed in [15].)

2.2.2. Coding of variables

The coefficient for a predictor variable depends on how that variable is coded (i.e., how each possible value is represented numerically) [5]. The effect of the coding on the interpretation of the regression coefficients is especially important when interaction terms are reported. Studies were evaluated for whether they provided an appropriate description of the coding.

2.2.3. Fitting procedure

The variables included in the model may be either determined by an automatic procedure (usually one of forward inclusion, backward elimination, or best-subset) or be specified *a priori*, either collectively or in "hierarchically" grouped subsets. Regardless of the procedure, it should be explicitly stated, preferably with some motivation for the appropriateness of that choice. If one of the automatic procedures is used, the user should be aware that the coefficient estimates no longer have the classic properties and the usual statistical error estimates no longer necessarily apply [15].

Each LR analysis appearing in the identified research reports was examined to determine which of the criteria listed above were satisfied.

3. Results

Table 1 shows the adherence to the guidelines for using and reporting LR for each of the 21 analyses. None of the studies reported any validation or conformity with a linear gradient where appropriate, so those columns have been omitted.

3.1. Analytic criteria

3.1.1. Sufficient events per variable

The number of events-per-variable (for the less-common outcome, as defined above) ranged from 2.4 to 25.7. Only 8 of 21 of the analyses had an events-per-variable ratio above 10, and only 2 studies had a ratio above 20.

3.1.2. Conformity with linear gradient (for continuous or ranked variables)

In all the studies in which continuous or ranked variables appeared, none tested to assure conformity with the linear gradient.

3.1.3. Tests for interactions

Interactions were reported in only five studies. For the studies not reporting interactions, it is unclear whether interactions were considered but not found to be significant or whether interactions were not considered.

3.1.4. Collinearity

Only two studies mentioned collinearity. The details of testing for collinearity were not reported.

3.1.5. Validation

As noted above, no validation was performed in any of the analyses.

3.1.6. Statistical significance

All of the studies reported measures of statistical significance, typically confidence intervals and P-values for each of the predictor variables (sometimes, only for those variables found to be significant). The statistical significance for the entire model was reported for 6 of the 21 analyses.

3.1.7. Goodness-of-fit measures

Summary measures of goodness of fit and regression diagnostics were not mentioned in any of the articles.

3.2. Documentation criteria

3.2.1. Selection of predictor variables

Nearly all the articles provided some motivation—usually informally via review of previous research—for including each predictor variable in the model; only 9 of 21 reported performing any statistical tests (such as bivariate analyses) before considering the variables for the models.

Table 1
Adherence to guidelines for using and reporting LR

Author and reference	Events per variable	Interactions	Collinearity	Statistical tests	Variable selection[a]	Fitting procedure
Andrykowski [29][b]	84/11 = 7.6	NR	NR	Variables: CI, P Model: Chi-square, P	Informal	NR
Andrykowski [29][c]	25/10 = 2.5	NR	NR	Variables: CI, P Model: Chi-square, P	Informal	NR
Andrykowski [30][d]	78/16 = 4.9	NR	NR	Variables: CI, P Model: Chi-square, P	Informal	NR
Andrykowski [30][e]	108/16 = 6.8	NR	NR	Variables: CI, P Model: Chi-square, P	Informal	NR
Cappelli [31][f]	44/6 = 7.3	NR	NR	Variables: CI, P Model: NR	Yes, P<0.15	NR
Cappelli [31][g]	23/7 = 3.3	NR	NR	Variables: CI, P Model: Chi-square, P	Yes, P<0.15	NR
Codori [32]	77/8 = 9.6	Considered two interactions	NR	Variables: SE, CI, P Model: NR	Informal	NR
Croyle [33]	69/5 = 13.8	NR	NR	Variables: Wald, P Model: Chi-square, P	Informal	Forward stepwise
Durfy [34][h]	64/10 = 6.4	NR	NR	Variables: SE, P, CI Model: NR	Informal	All variables entered simultaneously
Durfy [34][i]	102/10 = 10.2	NR	NR	Variables: SE, P, CI Model: NR	Informal	All variables entered simultaneously
Glanz [35][j]	186/17 = 10.9	NR	NR	Variables: CI, P Model: NR	Yes, P<0.1	In 3 blocks
Glanz [35][k]	109/17 = 6.4	NR	NR	Variables: CI, P Model: NR	Yes, P<0.1	In 3 blocks
Lerman [36][l]	30/6 = 5	NR	NR	Variables: CI, P Model: NR	Yes, P<0.1	Backward stepwise
Lerman [37]	77/7 = 11	NR	Mentioned, tested by leaving out affected subjects and re-running	Variables: SE, CI Model: NR	Yes, P<0.1	NR
Lerman [38]	63/6 = 10.5	NR	NR	Variables: CI, Chi-square for each block Model: NR	Informal	Hierarchical, in 3 blocks
Lerman [39]	165/8 = 20.6	Considered interaction for one variable	NR	Variables: CI for each variable, Chi-square for each block Model: NR	Informal	Hierarchical, in 4 blocks
Lipkus [40]	86/12 = 7.2	Considered interaction for one variable	NR	Variables: CI, P Model: NR	Informal	Hierarchical in 3 blocks
Smith [41]	181/12 = 15.1	NR	NR	Variables: CI Model: NR	No	NR
Tambor [42][m]	231/9 = 25.7	Considered interaction for one variable	NR	Variables: CI, P Model: NR	Yes, included variables with significant Chi-square values	NR
Tambor [42][n]	147/15 = 9.8	Considered interaction for one variable	NR	Variables: CI, P Model: NR	Yes, included variables with significant Chi-square values	NR
Vernon [43]	26/11 = 2.4	NR	Mentioned, addressed by building separate models with the collinear variables	Variables: CI, SE Model: NR	Yes, P<0.25	Hierarchical, in 3 blocks

Abbreviations: CI: confidence interval; NR: not reported; P: p-value; SE: standard error

[a]A P-value is listed when only variables significant at that level in bivariate analyses were entered into the model.

[b]All subjects.

[c]Women only (for breast cancer questions).

[d]Predicting interest in cancer risk notification.

[e]Predicting interest in genetic testing.

[f]Predicting intent to be tested.

[g]Predicting genetic counseling follow-up.

[h]Predicting interest in genetic testing.

[i]Predicting candidacy for genetic testing.

[j]Predicting interest in genetic testing. Number of events is unclear in paper; 186 is the maximum (most favorable assumption) that can be assumed from the presentation.

[k]Predicting intention to obtain genetic testing. Number of events is unclear in paper; 109 is the maximum (most favorable assumption) that can be assumed from the presentation.

[l]Number of events is unclear in paper; 30 is the maximum (most favorable assumption) that can be assumed from the presentation.

[m]Predicting awareness of breast cancer gene.

[n]Predicting interest in genetic testing.

3.2.2. Coding of variables

None of the articles provided complete details on the coding for all the variables. In some cases when binary variables were used, it was possible to infer the coding from the textual description (e.g., "male vs. female" suggests that male was coded as gender = 1, and female coded as gender = 0). Occasionally, dummy variables were introduced without explicit mention of how they were coded.

3.2.3. Fitting procedure

Ten studies mentioned the fitting procedure.

4. Conclusions

Logistic regression is a type of multivariable analysis used with increasing frequency in the health sciences because of its ability to model dichotomous outcomes. Proper use of this powerful and sophisticated modeling technique requires considerable care both in the specification of the form of the model and in the calculation and interpretation of the model's coefficients. (Incorrect statement of the model's form is called "misspecification"; the technical issues associated with misspecification have been explored at a relatively advanced level elsewhere [18,19].) In the resulting model, the coefficients of the predictor variables are interpreted as signifying the relative contribution of their respective variables toward the predicted probability of a positive outcome. The criteria considered in this article can affect the regression coefficients, in different ways and at different stages of the model-building process. Although many parts of the process have been effectively automated, the authority of the final model depends on the attempts by investigators to rule out sources of bias or inaccuracy toward which each of the criteria contributes. Because the coefficients are used for guiding decisions about patient care and treatment (e.g., the design of counseling strategies and protocols for patients seeking genetic testing), their accuracy is of paramount importance to the "consumers" of these results, and ultimately, to patients.

In the collection of articles we studied, there were substantial shortcomings in the use and reporting of LR results. Most notably: (1) none reported any goodness-of-fit measures or regression diagnostics; (2) the majority of the studies had events-per-variable ratios near or below 10, suggesting that those regression results themselves may be particularly unreliable; and (3) none of the studies reported any validation analysis. Validation is an important test of the regression's internal validity, a crucial step in the argument that the regression model is not an idiosyncratic artifact but instead that it has captured essential relationships in the domain of study. The problems we identified may be limited to failures to *report* details of the regression analysis; alternatively, they represent failures to *perform* important aspects of the regression analysis, and in almost all cases, the authors did not provide enough information to distinguish those two possibilities. (Some of the papers reported multiple analyses, and some researchers appear as author of more than one paper making the data in our sample not independent; this has no bearing on the accuracy of our conclusions. In passing, we note that failure to report, when due to space limitations of the print journals, may be remedied by publication of electronic appendices on author or journal websites.

Because regression is a relatively sophisticated technique, and specifically because it has potential to control for other explanatory variables, regression results often find privileged positions in literature reviews. Published literature reviews in the area of patient interest in genetic testing for cancer susceptibility have, to date, accepted the conclusions of these primary studies as stated, and not addressed the accuracy and appropriateness of the statistical analyses or other methodological issues [20–24]. While the conclusions of these reviews may be valid, it would be unfortunate if counseling guidelines and testing protocols were founded on results that had not been more rigorously tested through independent analysis and external validation. Without such reanalyses in hand, it is impossible to identify specific errors in statistical inference, but common sense suggests that some caution is advised.

The results we report here confirm and extend conclusions about LR analysis drawn by other observers of the medical literature (in research articles [5,7,8] and letters [25,26]). This existing literature has examined informal and random samples of journals across medical specialty areas and a collection of specialty journals in the area of obstetrics and gynecology. Our extension focuses on a single area of research with considerable public interest, patient interest in genetic testing for cancer susceptibility. This choice of focus has the following desirable properties:

1. It is a high visibility domain of clinical importance in which recent research affects practice.
2. The choice to examine comprehensively the literature in a specific recent field removes the problem of uncited literature which might "offset" the clinical impact of the cited papers; any flaws engendered by statistical reasoning errors in the cited literature may propagate to practice. In contrast, examination of articles across fields (which complements the present approach by enhancing external generalizability) may arouse concerns that papers selected are not representative of their field; and problems detected in each examined paper might be mitigated in their effect on practice by uncited literature.
3. Choice of a comparatively new field implies most papers are recent, which reflect current use of LR in the literature; statistical deficiencies identified cannot be criticized for reflecting outmoded statistical practice and reporting patterns.

Although the conclusions from this study corroborate and extend those of similar prior studies focusing on other research areas or sampling across such areas, neither this

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nor other studies constitute a representative examination of all uses of LR in the medical literature, and the conclusions are therefore subject to the usual cautions about external generalizability. Nonetheless, there is no reason to believe that the area studied here, patient interest in genetic testing for cancer susceptibility, is in any way unique with respect to the use and reporting of LR.

Most journals' instructions to authors make no mention of these statistical issues (including the widely disseminated Uniform Requirements [27]), although the AMA's current *Manual of Style* [28] does state that articles should describe " . . . steps used for developing a model in multivariate analysis . . . " and the entry for "logistic regression" states with reference to the adequacy of the sample size that at least 25 individuals be included for each predictor variable (which is not the same as the EPV criterion used here). Our results point to the need for greater scrutiny by authors, reviewers, and editors, to both the use and reporting of logistic regression.

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