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Journal of Clinical Epidemiology ■ (2015) ■

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

A nomogram was developed to enhance the use of multinomial logistic regression modeling in diagnostic research

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Accepted 28 October 2015; Published online xxxx

Abstract

Objectives: We developed a nomogram to facilitate the interpretation and presentation of results from multinomial logistic regression models.

Study Design and Setting: We analyzed data from 376 frail elderly with complaints of dyspnea. Potential underlying disease categories were heart failure (HF), chronic obstructive pulmonary disease (COPD), the combination of both (HF and COPD), and any other outcome (other). A nomogram for multinomial model was developed to depict the relative importance of each predictor and to calculate the probability for each disease category for a given patient. Additionally, model performance of the multinomial regression model was assessed.

Results: Prevalence of HF and COPD was 14% (n = 54), HF 24% (n = 90), COPD 20% (n = 75), and Other 42% (n = 157). The relative importance of the individual predictors varied across these disease categories or was even reversed. The pairwise C statistics ranged from 0.75 (between HF and Other) to 0.96 (between HF and COPD and Other). The nomogram can be used to rank the disease categories from most to least likely within each patient or to calculate the predicted probabilities.

Conclusions: Our new nomogram is a useful tool to present and understand the results of a multinomial regression model and could enhance the applicability of such models in daily practice.

Keywords: Multinomial; Regression analyses; Nomogram; Heart failure; Chronic obstructive Pulmonary disease; Diagnostic research

1. Introduction

The starting point in clinical practice is a patient with certain symptoms and/or signs, and nearly always, different disorders can be responsible. This is known as the differential diagnosis. Additionally, several disorders can be present simultaneously in a single patient. In diagnostic research, the presence or absence of a single disease is usually modeled using dichotomous logistic regression. In such models, there is one disease of interest and patients with no or alternative diseases are combined into the disease absent category. Consequently, the multinomial aspect of clinical diagnosis is ignored [1,2]. To mimic the diagnostic process in real-life clinical practice more closely, multinomial logistic regression modeling could be applied, considering multiple diseases and their combination as potential outcomes simultaneously [3−7].

Multimorbidity is common in the elderly, and diseases often result in overlapping symptoms and signs. Patients presenting with dyspnea form a typical example. More than 30 diseases can be the underlying cause; in the elderly, chronic obstructive pulmonary disease (COPD) and heart failure (HF) alone or in combination are the most likely explanation of dyspnea [8−10]. When multiple disorders may be present in a single patient, multinomial logistic regression modeling seems an attractive method in diagnostic research, as it models estimates for all outcomes of interest simultaneously.

In the previously mentioned situation, the use of a multinomial regression model seems more natural than the use of multiple dichotomous regression models. However, multinomial regression modeling is not frequently applied in clinical research, despite the statistical advantages of using such

Funding: The study was conducted as part of the Dutch National Care for the Elderly Program (ZonMw-NPO) and funded by a research grant from the "Netherlands Organization for Health Research and Development" (ZonMw grant 311040302) and a grant from the Netherlands Organization for Scientific Research (project 918.10.615).

Conflict of interest: None.

Trial registration: ClinicalTrails.gov NCT01148719.

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http://dx.doi.org/10.1016/j.jclinepi.2015.10.016
0895-4356/

What is new?

Key findings

- The multinomial nomogram helps visualizing the relative importance of predictors for the different disease categories and assists in the calculation of absolute probabilities for the various outcome categories for a specific patient.

What this adds to what was known?

- We developed a nomogram for multinomial models to facilitate the interpretation and presentation of the results from multinomial regression models.

What is the implication and what should change now?

- The multinomial model should be used more in diagnostic research, especially in situations where multiple diseases are considered including the likelihood that a combination of those diseases is present.

models [4,5]. One possible reason is that the presentation and calculation of predicted probabilities from a multinomial logistic regression model is more complex than from a binary regression model. Nomograms are increasingly being used in binary logistic regression models and Cox survival models to facilitate the interpretation of their results [11]. Given the more complex interpretation of regression coefficients from multinomial logistic regression models, the usefulness of nomograms is likely to be higher.

Therefore, we aim to improve the use of multinomial regression models for clinical practice by describing a nomogram to present the results of a multinomial logistic regression model. We will use data from a diagnostic study in frail elderly patients with dyspnea and/or reduced exercise tolerance who were examined for the presence of HF, COPD, or both [12,13].

2. Methods

2.1. Case study

2.1.1. Participants

The study population was derived from a cluster randomized trial in which community-dwelling frail elderly with complaints of dyspnea and/or reduced exercise tolerance were evaluated (triage of reduced exercise tolerance in frail elderly) [12,13]. In this study, frailty was defined as three of more comorbidities or the chronic use of five or more drugs. For the present study, we used data from those randomized to the screening arm of the trial. All these participants underwent a diagnostic strategy, including history taking, physical examination, electrocardiography, spirometry, blood tests, and echocardiography. The study complied with the Declaration of Helsinki, and the Medical Ethical Committee of the University Medical Centre Utrecht approved the study (trail registration: ClinicalTrails.gov NCT01148719). All participants gave their written informed consent.

2.1.2. Outcome

The outcome consisted of four categories: COPD alone, HF alone, the combination of HF and COPD (HF and COPD), and another or no disease (Other). These final diagnoses were established by a panel of experts during a consensus meeting. The panel always consisted of a general practitioner (F.H.R.), a pulmonologist (alternating: J.W.J.L. or H.J.H.), and a cardiologist (alternating: M.J.M.C., M.A.N.S., or C.G.K.M.F.). Signs, symptoms, and test results from the diagnostic strategy, including spirometry and echocardiography, from each patient were discussed before reaching a consensus decision on the presence or absence of a particular diagnosis.

2.1.3. Potential diagnostic predictors

Based on the literature, nine variables were selected as potential diagnostic predictors for the presence of HF and/or COPD: gender, body mass index (BMI), signs of fluid overload (a composite of peripheral edema, pulmonary crepitations, nocturnal dyspnea, orthopnea, and elevated jugular venous pressure), displaced apex beat, NT-proBNP levels, pack years of smoking, breathing sounds (a composite of wheezing on history and physical examination and rhonchi), cough, and forced expiratory volume in 1 second as percentage of the population-specific predicted values (FEV1) [9,14–19]. BMI, number of pack years of smoking, NT-proBNP, and FEV1 were treated as continuous variables.

2.2. Missing data

Overall, very few values were missing in our data set. In three patients, the spirometry data were unreliable due to poor technical performance, and presence or absence of COPD could not be determined in these patients. In 10 patients, echocardiography was missing, and presence or absence of HF could not be determined. For the present study, these 13 patients were excluded. Of the determinants, 17 values of NT-pro-BNP were missing, and six missing values were of postbronchodilator FEV1 measurements. These values were imputed using multiple imputation (10 rounds of imputation), and Rubin's rules were applied to come to the overall estimates in the regression models [20,21].

2.3. Multinomial logistic regression model

A multinomial logistic regression model was fitted in which the probability of each of the four disease categories (HF and COPD, HF, COPD, and Other) was estimated in a single model using maximum likelihood techniques [4,7].