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Age and sex are sufficient for predicting fractures occurring within 1 year of hemodialysis treatment☆

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Abstract

Background: The incidence of fractures averages 20 per 1000 hemodialysis patient years at risk. This study sought to design and evaluate the utility of a simple prediction rule for fractures in dialysis patients using only standard demographical and biochemical information.
Methods: 1777 prevalent hemodialysis patients of the Austrian dialysis and transplant database who had an evaluation of fractures in 2004 and 2005 were included into analysis. Validation of the prediction rule model by a test set was performed using three different resampling techniques, the split sample approach, a 100-fold cross validation and a 100× bootstrap. Calibration of the model was performed visually by comparing the observed to the expected number of outcomes in each category and by calculating the Hosmer and Lemeshow goodness-of-fit statistic.
Results: A multivariable logistic regression model built on clinical expertise yielded a discrimination of $c=0.73$ (AUC of ROC). Further reduction of the covariables to age and sex as the only predictive variables did not result in loss of discrimination ($c=0.71$) and at the same time provided adequate calibration ($p=0.69$). The probability of fractures (PF) occurring within the next year of hemodialysis can be calculated from our prediction model as, $PF = \frac{e^{-6.25+0.4*\text{age (in decades)}-0.93(\text{if male})}}{1+e^{-6.25+0.4*\text{age(in decades)}-0.93(\text{if male})}}$, e.g., a 70-year-old male would have a fracture probability of 0.01 or 1%, a female 3%.

The optimism derived by all resampling techniques was between 1% and 2% suggesting adequate generalizability of the prediction rule.
Conclusion: A sufficient and parsimonious prediction rule for fractures in hemodialysis patients consists of the independent variables age and sex.

Keywords: Bone; Fracture; Hemodialysis; Logistic regression model; Prediction rule

Introduction

Patients with end-stage renal disease (ESRD) treated by hemodialysis have a dramatically increased risk of bone fractures. According to the United States Renal Data System (USRDS) annual data report, the incidence of fractures is roughly 20 per 1000 patient years on dialysis [1]. The high incidence is not surprising given the fact that almost every patient on hemodialysis suffers from renal osteodystrophy (ROD) [2]. The causes of ROD are multifactorial, but disturbances of calcium and phosphate with consecutive dysregulation of parathyroid hormone are among the key features. The recommended ranges of serum calcium, phosphate and intact parathyroid hormone (iPTH) levels seem reasonable from a pathophysiological point of view, but it remains unclear whether values outside the reference range are associated with a higher rate of fractures within the next year.

Furthermore, almost all dialysis patients receive prescriptions for medication labeled for maintaining calcium, phosphate and iPTH homeostasis. There is almost uniform use of first to third generation vitamin D analogs, calcium-free and calcium-containing phosphate binder as well as newer products such as

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calcimimetics. These drugs can effectively reduce the serum level of their respective target, but no data exist on whether these medical interventions lead to a reduction in the rate of fractures.

Besides the disturbances of the calcium and phosphate homeostasis, other very important entities contribute to ROD and fractures in hemodialysis patients. Many of the patients with ESRD received potential bone toxic medication for the treatment of their underlying renal disease, such as prolonged use of high dose corticosteroids [3,4]. Furthermore, the major cause of ESRD in industrialized countries is diabetes. It is well known that patients with long standing diabetes have a substantially increased risk of fractures even if not uremic [5,6]. Most of the patients who present with ESRD suffer from chronic kidney failure for years. The majority of them, especially those with a nephrotic kidney disease, use loop diuretics to control water balance and edema. However, these loop diuretics lead to a negative calcium balance and thus aggravate renal osteodystrophy [7]. An almost obligatory hypogonadism in hemodialysis patients further contributes to bone loss and increases the risk of fractures [8]. Most importantly for the primary prevention of fractures in the general population is physical activity. Because dialysis patients are multimorbid, physical activity is severely limited in almost all cases.

In order to adequately guide patients on hemodialysis and prevent future fractures, we sought to identify predictive parameters and design and evaluate a parsimonious prediction rule for fractures based on these findings. A prediction rule is an algorithm for obtaining these likelihoods based on values of selected predictors for fractures.

Methods

Patient population and outcomes

The Austrian dialysis and transplant registry (OEDTR) is a nationwide database of all patients with ESRD treated in the 65 dialysis units in Austria. This database was established in 1965 and has complete annual follow up of all patients on hemo- or peritoneal dialysis as well as patients that received a renal transplant since then. The variables recorded are patient demographics, biochemical laboratory readings, comorbidities, organ/disease-specific cause of mortality and since September 2003 also bone fractures and extraosseal calcifications. Serological parameters such as electrolytes, creatinine, BUN, iPTH, albumin, CRP, alkaline phosphatase, hemoglobin, hematocrit, ASAT, ALAT and cholesterol are obtained annually. Furthermore, concentration of dialysate calcium and medications such as type of phosphate binders, vitamin D preparations and calcimimetics are recorded as well to be found at www.nephro.at. [9].

Bone fractures were counted if either clinically or radiologically evident or if a decrease in any vertebral height of >20% (at least more than 4mm) occurred within the twelve months [10].

Analytical methods

Initially, we built multivariable models using three different strategies to evaluate significant predictors of fractures occurring within the next year on hemodialysis. Only the first fracture was analyzed.

First, we used an automated backward elimination algorithm including all biochemical variables as well as patient's age, sex, cumulative time on renal replacement therapy, comorbidities, extraosseal calcifications, use of vitamin D analogs and calcimimetics. This variable selection approach begins with a model that contains all of the factors of interest (as listed above). In the first step, the algorithm eliminates the factor with the least significant relationship to the outcome. A p-value of 0.25 was predefined as threshold for variables remaining in the model.

Secondly, we applied an automated stepwise procedure using the same variables for selection as in the backward procedure, now with a predefined p-value of 0.25 for model entry and a p-value of 0.05 for remaining in the model. The stepwise algorithm has a forward direction in which one variable at a time is entered into the model if it shows evidence of independent association with the outcome at a p-value defined above (<0.25), conditional on all other factors. However, in the elimination steps, variables that no longer possess significant associations with the outcome (at a $p<0.05$ defined above) are eliminated in a later step.

Thirdly, a model was built on the basis of clinical expertise including the variables age, sex, cumulative time on dialysis, number of renal transplants, diabetes status, serum concentrations of alkaline phosphatase, calcium, phosphate, iPTH, presence of extraosseal calcifications and use of vitamin D analogs. In this model, all variables were included that have been shown to be associate with bone disease in other trials.

Based on the results from the various approaches, we designed a parsimonious and simple to use prediction rule for fracture forecasting and validated this model. We assessed the ability of the prediction rule to discriminate between the binary outcome (fracture) by calculating the area under the ROC curve using the Sommer's D statistic. The relation between the area under the ROC and Sommer's D is AUC=(1+Sommer's D)/2.

Calibration, also known as criterion-related validity of the model, was performed visually by comparing the observed to the expected number of fractures in each category and by calculating the Hosmer and Lemeshow goodness-of-fit statistic [11].

Validation was performed by evaluating the reproducibility of the accuracy in patients from the same population. For that means, we used three different resampling methods of obtaining a training and a test data set. First, we used a split sample approach, secondly a 100-fold cross validation was performed and thirdly a bootstrap with 100 resampling steps was applied [12].

Statistical analysis

Statistical analysis was conducted using the SAS for Windows software, version 9.1.3 (The SAS Institute, Inc., Cary, North Carolina, USA). Continuous data are presented as mean±SD or median and IQR when appropriate. Categorical data are shown as counts or fractions respectively. Differences between patients with and without fractures were evaluated by the t-test and Wilcoxon rank sum test when appropriate. The chi-square test was used to estimate differences of categorical data according to fracture status. Results of the multivariable logistic regression models are provided as parameter estimates and p-values or risk ratio and 95% confidence interval.

Results

Of the prevalent hemodialysis patients, 1777 were available for analysis and had all variables measured as well as the outcome of fractures determined in the years 2004 and 2005. Patients' demographics, procedure-related variables as well as bone-specific medications are listed in Table 1. In the 1777 patients, a total of 73 fractures occurred within 1 year yielding an incidence density of 41 per 1000 patient years at risk.

Table 2a shows the multivariable regression model that was built on the basis of clinical experience. The only predictive variables that were significantly associated with the occurrence of fractures were age and sex, regardless of the model building strategies used (backward, stepwise). This two