Predicting the Effect of Parathyroidectomy on Patient Survival in Secondary Hyperparathyroidism with Machine Learning

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***Abstract*—The main goal of parathyroidectomy (PTX) is to remove the offending gland(s) while protecting the remaining normal parathyroid glands as well as the recurrent laryngeal nerves and the thyroid gland. In this study, the writer hypothesized that Machine Learning (ML) could predict the effect of PTX based on readily available clinical and laboratory indicators. There were 158 consecutive HD patients who underwent PTX before 2009 and 275 consecutive hemodialysis (HD) patients without PTX as controls from those visiting the Kaohsiung Chang Gung Memorial Hospital, Taiwan between 2009 and 2013. The study first held by testing several categories of supervised ML classifiers: 1) Bayesian network classifier, 2) k-Nearest Neighbors, 3) rule-based classifiers, and 4) tree-based classifiers. All ML classifiers were tested using 10-fold cross validation. The performance of each classifier was evaluated based on sensitivity (recall), specificity, positive predictive value (precision), area under the Receiver Operating Characteristic (ROC) curve, and overall accuracy. After testing >20 different algorithms, we selected tree-based classifier (Random Forest) that has the highest value of correctly classified instances, namely 76.91% (area under receiver operating characteristic = 0.78).**

***Index Terms*—parathyroidectomy, machine learning, classifier, random forest**

I. Introduction

Secondary hyperparathyroidism (HPT) means the parathyroid glands are overproducing parathyroid hormone in an attempt to help body increase the amount of calcium in the blood. It is the only job of the parathyroid glands to maintain calcium levels and the four parathyroid glands will increase the production of their hormone (parathyroid hormone PTH) if the calcium is too low [1]. Secondary HPT occurs most commonly “secondary” to chronic renal failure (CRF). For this reason, secondary HPT is frequently referred to as renal HPT [2]. Secondary HPT can be treated by PTX operation which can remove one or more of the parathyroid glands.

Parathyroidectomy is necessary when calcium levels are elevated, if there is a complication of HPT (such as kidney stone, osteoporosis, and bone fractures), or if a patient is relatively young. The main goal of PTX is to remove the offending gland(s) while protecting the remaining normal parathyroid glands as well as the recurrent laryngeal nerves and the thyroid gland [3]. The effect of PTX can be predicted with Machine Learning (ML). There are many possibilities for how ML can be used in healthcare, and all of them depend on having sufficient data and permission to use it [4]. An example of healthcare providers can take advantage of ML is being able to classify the quality of Electrocardiogram (ECG) signal. Tanatong [5] proposed an approach for signal quality classification in continuous cardiac monitoring using wireless sensors. ECG signal recordings captured while subjects are performing Activities of Daily Living (ADLs). Using a *k*-Nearest Neighbor (*k*NN) algorithm and statistical features, 5-second ECG segments were classified into good-quality and bad-quality levels.

Machine Learning (ML) aims at providing computational methods for accumulating, changing and updating knowledge in intelligent systems, and in particular learning mechanism that will help us to induce knowledge from examples or data. ML provides methods, techniques, and tools that can help solving diagnostic and prognosis problems in a variety of medical domains. It is argued that the successful implementation of ML methods can help the integration of computer-based systems in the healthcare environment providing opportunities to facilitate and enhance the work of medical experts and ultimately to improve the efficiency and quality of medical care [6]. In this study, it is hypothesized that ML could predict the effect of PTX based on readily available clinical and laboratory indicators.

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II. Methods

Scheduling regular treatments are applied to outpatient hemodialysis (HD) who attended the Kaohsiung Chang Gung Memorial Hospital, Taiwan. There were 665 patients who got treatment 3 times a week. Their laboratory blood values were recorded from January 1, 2009 to December 31, 2013. Based on the exclusion criteria reported in [7], the invalid HD patients were (1) patients who had initiated regular HD after January 1, 2009; (2) patients who were older than 90 years; (3) patients who received PTX after January 1, 2009; (4) patients transferred to other medical facilities; and (5) patients whose information was incomplete and/or those who were lost to follow-up during the study period. After eliminating those which fell out because of the exclusion criteria, the final sample was 433 patients. There were 158 consecutive HD patients who underwent PTX before 2009 and 275 consecutive hemodialysis (HD) patients without PTX as controls.

Machine Learning (ML) is a collection of different methods or algorithms, each with differing mechanisms of classification [8]. An algorithm can model a problem from an input data. Input data is called training data and has known label or result such as patients who underwent PTX and patients without PTX. A model is prepared through a training process in which it is required to make predictions and is corrected when those predictions are wrong. The training process continues until the model achieves a desired level of accuracy on the training data. In order to accomplish the task, the ML software platform available is used from the Waikato Environment for Knowledge Analysis (version 3.7.12, Weka). The Weka software suite contains a library of algorithms that build predictive models by learning from examples provided in supplied datasets. Each algorithm was trained using our patient dataset, which included 20 attributes. A 5-year average value was calculated for each blood analysis variable. Ten blood analysis variables were considered as continuous variables (Hb, albumin, blood urea nitrogen, creatinine [Cr], potassium [K], corrected serum calcium [Ca], phosphate [P] levels, intact-parathyroid hormone [iPTH] levels, ferritin levels, and Kt/V), whereas the remaining variables (URR, CT ratio) were considered categorical variables. URR was categorized as either less than 65% or ≥65%, whereas the CT ratio was categorized as either less than 50% or ≥50%.

The study began by testing several categories of supervised ML classifier : 1) Bayesian network classifier, 2) *k*-Nearest Neighbors, 3) rule-based classifiers, and 4) tree-based classifiers. After testing >20 different algorithms, we selected tree-based (Random Forest) for additional study as it maximized accuracy and transparency. Random Forest is one of the most popular and most powerful machine learning algorithms. It is a type of ensemble machine learning algorithm called Bootstrap Aggregation or bagging. Random forest changes the algorithm for the way that the sub-trees are learned so that the resulting predictions from all of the subtrees have less correlation.

All ML classifiers were tested using 10-fold cross validation. The performance of each classifier was evaluated based on sensitivity (recall), specificity, positive predictive value (precision), area under the Receiver Operating Characteristic (ROC) curve, and overall accuracy. Continuous variables were estimated by independent 2-sample t-test. The effects of PTX on clinical variables were tested by multivariate linear regression, after adjusting for age, gender, diabetes mellitus, and hemodialysis duration. Categorical variables were statistically compared using chi-square test. The 95 % confidence interval (95% CI) and a *P* value were used to determine statistical significance. A *P* value less than 0.05 was considered statistically significance.

III. Result

The baseline characteristics of the study participants are presented in Table I. A total of 158 PTX patients with 14.54 years mean HD duration and 275 controls (without PTX) with 9.85 years mean HD duration were enrolled between 2009 and 2013. The PTX patients showed significant differences in HD duration, age groups, diabetes mellitus, iPTH levels, Hct, BUN, Cr, and Ca compared with those without PTX. For PTX patients, BUN, Cr, and Hct were higher, whereas Ca and iPTH levels were lower than those without PTX.

PTX patients had a much lesser mean calcium and iPTH levels (9.11 ± 0.0085 mg/dL and 221.32 ± 3.44 pg/mL, respectively) compared with that of controls (9.40 ± 0.0077 mg/dL and 430.11 ± 5.29 pg/mL, respectively). Table II summarizes the effect of PTX on clinical variables adjusted for age, sex, diabetes mellitus, and HD duration. It showed significant differences in Hb, BUN, Cr, Hct, Ca and iPTH levels between PTX patients and controls.

After testing a variety of ML methods, it is found that a Random forest predicted the effect of parathyroidectomy more accurate. A graphic representation of the network structure is shown in Fig. 1. The Random forest resulted in a test set accuracy of 78.98% and area under the ROC curve of 0.786 (Table III).

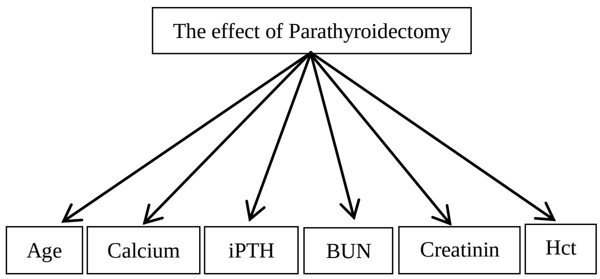

Figure 1. Graphic structure of the random forest classifier. Each arrow represents a conditionally dependent relationship.

IV. Discussion

During a 5-year cohort study, it is found that PTX patients had higher level of Hb, BUN, Cr, and Hct, as well as lower blood Ca and iPTH levels, compared with those who did not undergo PTX. The findings of the present study provide further evidence for the benefits of PTX in HD patients. For patients on dialysis, levels of iPTH that are within or below the normal range of the assay area generally indicative of low bone turnover and levels of iPTH that are greater than 2-3 times the upper normal range of the assay are generally indicative of high bone turnover [9]. No change was detected in fracture rates up to 1 year after parathyroidectomy, given that fractures occurred infrequently [10].

Both high calcium and phosphate are implicated in contributing to an increased cardiovascular calcification in patients on renal replacement therapy (RRT) and an increased cardiovascular and all-cause mortality. PTX was associated with improved survival in patients on maintenance dialysis but not in patients with renal allograft. Moreover, PTX improves calcium and phosphate balance [11].

Several studies have found that parathyroidectomy is underutilized [12], and the undertreatment seems to hinge on at least 2 factors : first, a lack of diagnostic awareness, and second, deferment of evaluation [13], [14]. The informatics tools reported here can prompt timely referral for further evaluation and treatment. Importantly, this tool utilizes readily available clinical data and provides automated prediction without additional cost or invasive testing. Our Random forest to predict the effect of PTX could become even more accurate as it is “trained” on more patients. Although the present study provided promising evidence for PTX in HD patients, it presents some limitations. First, the study was conducted in just one HD unit. The surgeon’s skill, preoperative assessment, and quality of care by nephrologists will affect the outcomes of PTX in HD patients. Second, the determination of test-set accuracies by cross-validation within the dataset, thus making it difficult to predict how the algorithm would perform a different population. Finally, future analysis of the tool should include laboratory values taken at multiple time points to reflect actual clinical practice which may potentially increase the accuracy for the most challenging cases.

TABLE I. BASELINE CHARACTERISTIC OF STUDY COHORT (N =433)

	Control (n = 275)		Case (n = 158)		
Variables	Mean (n)	SD (%)	Mean (n)	SD (%)	P value
Hemodialysis duration (y)	9.85	4.24	14.54	5.32	<0.001
Age group					0.031
17-44	29	6.95	19	4.00	
45-64	164	5.20	106	5.28	
65-74	60	2.93	28	2.87	
≥75	22	4.04	5	2.79	
Gender					0.122
Male	122		58		
Female	153		100		
Diabetes mellitus					0.001
No	221		144		
Yes	54		14		
Clinical variables (in first calendar year)					
Hb (g/dL)	10.68	0.95	10.79	1.07	0.277
Hct (%)	32.79	2.93	33.26	3.35	0.137
Albumin (g/dL)	3.84	0.26	3.91	0.25	0.004
BUN (mg/dL)	69.27	13.78	72.28	12.34	0.020
Cr (mg/dL)	10.71	2.09	11.20	2.09	0.021
K (meq/L)	4.97	0.55	5.00	0.47	0.556
Ca (mg/dL)	9.60	0.67	9.34	0.69	<0.001
P (mg/dL)	5.04	0.99	5.12	1.10	0.476
iPTH (pg/mL)	458.50	394.55	245.83	325.14	<0.001
Feritin (ng/mL)	426.92	224.42	409.27	226.83	0.436
Kt/V	1.71	0.26	1.83	0.62	0.021
URR					0.649
<.65	5	2.25	2	0.35	
≥.65	270	5.32	156	5.39	
Cardiothoracic ratio					0.002
<0.5	107	2.80	87	3.28	
≥0.5	168	4.25	71	3.87	

Control, subjects without parathyroidectomy; Case, subjects with parathyroidectomy.
iPTH = intact parathyroid hormone; Ca = corrected serum calcium; Hct = hematocrit; Cr = creatinine; Hb = hemoglobin; BUN = blood urea nitrogen; P = phosphorus; K = potassium; URR= urea reduction ratio.

TABLE II. MULTIVARIATE LINEAR REGRESSION MODEL TO EVALUATE THE EFFECT OF PARATHYROIDECTOMY

Dependent variables	Coef.	SE	P^a value	95 % CI	R-squared	RMSE
iPTH (pg/mL)	458.502	22.387	<.001	414.501 to 502.503	0.072	370.568
Ca (mg/dL)	9.602	0.041	0	9.521 to 9.682	0.033	0.679
Hct (%)	32.785	0.186	0	32.419 to 33.152	0.006	3.087
Cr (mg/dL)	10.714	0.126	<.001	10.466 to 10.962	0.012	2.090
Hb (g/dL)	10.676	0.060	0	10.558 to 10.794	0.003	0.996
BUN (mg/dL)	69.269	0.801	<.001	67.695 to 70.844	0.012	13.262
Kt/V	1.706	0.026	<.001	1.656 to 1.659	0.018	0.426
Albumin (g/dL)	3.836	0.016	0	3.805 to 3.867	0.017	0.259
P (mg/dL)	5.044	0.062	<.001	4.921 to 5.166	0.001	1.029
Ferritin	426.922	13.595	<.001	400.201 to 453.644	0.001	225.040
K (meq/L)	4.971	0.032	0	4.909 to 5.034	0.001	0.525
Cardiothoracic ratio	0.609	0.030	<.001	0.551 to 0.668	0.024	0.493
URR	0.982	0.008	0	0.967 to 0.997	0.000	0.127

Age, gender, diabetes mellitus, and hemodialysis duration were adjusted in this model.
P^a : P value for linear regression coefficient.
SE = standard error; RMSE = root-mean-square-error.

TABLE III. ACCURACY OF RANDOM FOREST FOR PREDICTING THE EFFECT OF PARATHYROIDECTOMY

	Correctly classified instances	Sensitivity	Specificity	Positive predictive value	Area under ROC
All patients (N = 433)	76.91%	89.1%	55.7%	76.6%	78%

Present study provide further evidence for the benefits of PTX in HD patients. For patients on dialysis, levels of IPTH that are within or below the normal range of the assay area generally indicative of low bone turnover and levels of IPTH that are greater than 2-3 times the upper normal range of the assay are generally indicative of high bone turnover [9]. No change was detected in fracture rates up to 1 year after parathyroidectomy, given that fractures occurred infrequently [10].

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V. CONCLUSIONS

The findings of the present study provide further evidence for the benefits of PTX in HD patients. Incorporation of machine learning (ML) into the healthcare environment can provide opportunities to facilitate and enhance the work of medical experts and ultimately to improve the efficiency and quality of medical care. Moreover, ML can predict the effect of parathyroidectomy on patient survival in secondary hyperthyroidism.

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