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Use of Neural Networks in Predicting the Risk of Coronary Artery Disease

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Artificial neural networks were created to predict the occurrence of coronary artery disease based on information from the serum lipid profile. The development of the networks involved a strategy which permitted learning from censored observations. The networks were developed with data from the Cholesterol Lowering Atherosclerosis Study, which followed serum lipoprotein levels and clinical events in 162 patients over a period of up to 10 years. Inputs consisted of seven different mean lipid values, and the desired output was the time period during which a complication of coronary artery disease was predicted to occur. Cross-validation was performed by splitting the data into separate training and testing sets, scoring the performance of the neural network strategy on the testing sets, and comparing scores with those obtained from Cox regression models developed on the same training data. Performance of the neural network strategy exceeded that of Cox regression in predicting clinical outcomes (66% vs 56%, McNemar's test $P = 0.005$). The network design provided an effective approach to predicting outcomes from a clinical trial with variable follow-up times.

INTRODUCTION

There are several different serum lipids which correlate with the development and progression of coronary artery disease (*1*). Rather than relying only on total cholesterol, the physician may evaluate high-density lipoprotein (HDL), low-density lipoprotein (LDL), or the HDL/LDL ratio in order to assess the risk of coronary artery disease (*2*). The physician faces the task of integrating the results of several different lipid levels into one overall estimate of disease risk.

Neural networks are promising tools for multivariate analysis which can be applied to estimate disease risk. Their clinical use has frequently been in the analysis of outputs of medical diagnostic instruments (*3–10*), but they have also been applied in several different situations to diagnose acute illness or to predict clinical outcomes (*11–20*). A body of theoretical work suggests that

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neural networks have the ability to consistently match or exceed the performance of other statistical methods (21, 22).

The application of neural networks to predict the risk of coronary artery disease requires the development of a strategy to address the time course of a chronic disease process and include censored data. Outcomes may be best classified in terms of the time to an event, rather than simply the presence or absence of an event. Simple exclusion of censored observations from the available training set would limit the amount of data available for network development and could lead to significant biases in event predictions.

Cox regression analysis is an accepted solution to the problem of analyzing censored data. Patients who exit a study early without a clinical event still provide important information to the Cox regression analysis. The performance of Cox regression models, when compared directly to those of neural networks, can provide a useful perspective on the success of a neural network approach.

This paper presents a neural network which effectively integrates data from several different lipid levels in order to predict outcomes in patients with coronary artery disease. A method is developed which allows the neural network to learn from censored observations in a long-term study. Cross-validation is performed with comparison of the neural network performance to that of Cox regression models developed on the same data.

Background

The Cholesterol Lowering Atherosclerosis Study

The Cholesterol Lowering Atherosclerosis Study (CLAS) was a randomized, placebo-controlled clinical trial which evaluated the effects of lipid-lowering drugs on angiographic changes and clinical outcomes in patients with known coronary artery disease (*23*, *24*). The study included 188 male patients between 40 and 59 years of age, each of whom had undergone previous coronary artery bypass surgery. Additional entry criteria included cholesterol levels between 185 and 350 mg/dl and confirmed lipid-lowering response to study medications prior to randomization. Patients were randomized to treatment with cholesterol-lowering drugs (colestipol and niacin) and a low-cholesterol diet or to treatment with a low-cholesterol diet and placebo. Atherosclerosis change on 2-year coronary angiography was evaluated in 162 of the patients. For these subjects follow-up data on clinical events are available up to 10 years after the 2-year angiogram. Clinical events included coronary deaths, myocardial infarction, and angioplasty or repeat coronary artery bypass.

Methods

Input and Output Variables

In order to select input variables for the neural network and Cox regression models the on-trial lipid levels were examined for significant differences between patients who had events and those who remained event free. An independent-sample t test was applied to compare mean on-trial lipid levels in patients who

were followed through the beginning of Year 7. This point in time was used for comparisons because afterward the number of censored cases increased rapidly.

Seven significant variables ($P < 0.05$) were chosen, consisting of cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride (TG), apolipoprotein B (Apo B), apolipoprotein C-III measured in heparin-precipitate (Apo CHP), and the ratio of apolipoprotein C-III measured in heparin-supernate to apolipoprotein C-III measured in heparin-precipitate (Apo CR). These lipids were the input variables for both the Cox regression model and the neural network.

Output variables represented the time of occurrence of clinical coronary events. The duration of the study was divided into three periods of 40 months each. Four possible outcomes were considered, an initial coronary event in period 1 (0–39 months), an initial event in period 2 (40–79 months), an initial event in period 3 (80–120 months), or no event at all during the 120 month study. The output variable for the neural network was therefore a vector $[x_1, \ldots, x_4]$ corresponding to outcomes at periods 1, 2, 3, or no event at all, respectively. Initial values for x_i were 1, 0, or the symbol "?", corresponding to an initial event, no event, or censorship.

Organization of Training and Testing Sets

In order to permit cross-validation the data was organized into training and testing sets by the m items out approach, which is a modification of the jackknife. In the m items out approach a database of size n is divided into n/m separate training and testing sets. Each training set consists of the $n - m$ cases which remain after the m items of a corresponding testing set are excluded from the data. A model is developed on each training set and evaluated on the corresponding testing set.

In this manner external validation on a total of n cases is done, reflecting the performance of one strategy that was applied to develop several similar models on data sets of size $n - m$. The m items out approach can be a useful validation technique (*25*, *26*), and it does not introduce significant biases into estimates of model performance (*27*, *28*). It has been applied in other neural network studies (*6*, *8*, *12*, *16*, *20*).

The m items out approach was applied to the CLAS data by dividing the 162 patients randomly into four separate groups (A, B, C, and D), where m was approximately 41 patients. The training sets were therefore A + B + C, A + B + D, A + C + D, and B + C + D, and the corresponding testing sets were D, C, B, and A, respectively. Neural network and Cox regression models were developed in parallel on these training and testing sets. The aggregate results of groups A, B, C, and D provided external validation on 162 patients for each strategy.

Cox Regression Analysis

Cox regression analysis was performed by use of EPILOG PLUS data analysis software (*29*). All seven of the selected variables (the lipid profile) for the

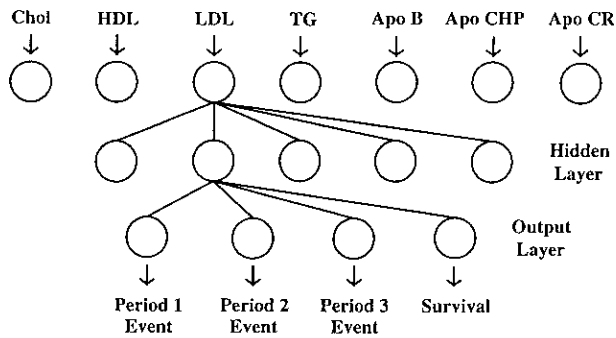

FIG. 1. The Predictor neural network. Seven different variables from a patient's lipid profile constitute the input neurons. There are five neurons in the hidden layer and four in the output layer. Outcomes are classified by the four neurons in the output layer, which represent the occurrence of a coronary event in period 1 (0–39 months), an event in period 2 (40–79 months), an event in period 3 (80–120 months), or no event at all. Because of the large number of neurons not all the network connections are shown.

training set patients were entered into the regression in a single step approach, creating Cox models with the same input variables as the neural networks.

Evaluation of Cox regression models was performed with EPILOG PLUS by plotting individual survival curves for patients of the testing sets, given their individual lipid profiles. The predicted survival at the time of exit from the study was determined. If the result was less than 0.5 then Cox regression was considered to predict the occurrence of a coronary event before the exit time. Otherwise, Cox regression was considered to predict no event. This method has been applied previously toward the use of Cox regression models as predictors of clinical outcomes (*30*, *31*).

The Neural Network Strategy

All neural networks were designed with NeuralWorks Profession II/Plus v5.0 software obtained from NeuralWare, Inc. (*32*). Each network was feed-forward with back-propagation and consisted of an input layer, a hidden layer, and an output layer. A principal Predictor network (Fig. 1) had seven input neurons, five neurons in its hidden layer, and four output neurons. Another type of network described below, the Period 2 or Period 3 network, had seven input neurons, four hidden neurons, and two output neurons. Sigmoid transfer functions were selected, and a normalized cumulative delta learning rule was applied.

The neural network strategy began with a procedure for imputing results for early censored cases in each training set. This procedure itself included the use of two initial neural networks, the Period 2 and Period 3 networks. The imputation process allowed a complete training set to be subsequently provided to the Predictor network. The entire strategy, beginning with the imputation of training set data and ending with the results of a Predictor network, was applied in a consistent manner so that training and testing sets were always

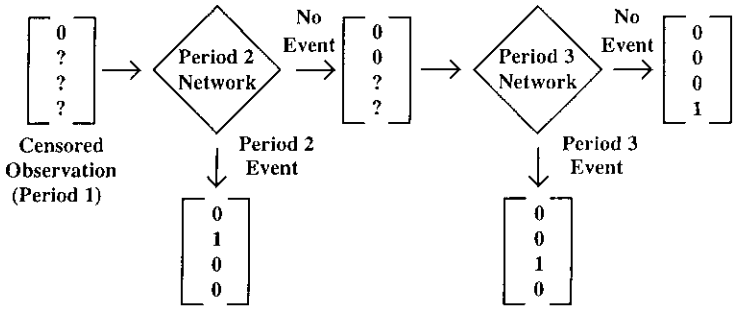

FIG. 2. A strategy for classifying outcomes for early censored cases. On the left is the outcome vector of a patient lost to follow-up during period 1. It is an array of numbers reflecting (from top to bottom) the presence or absence of an initial period 1 event, period 2 event, period 3 event, or no event at all. Question marks are placed in the array because the period 2 and period 3 outcomes are unknown for this individual. The lipid profile is presented to the Period 2 network. If the network predicts no event, then further classification by the Period 3 network is done. The imputation process provides a completed outcome array for Predictor network training.

kept separate. The imputation of results was not performed with any testing set data.

A training set patient lost to follow-up in period 1 would begin with an incomplete outcome vector of [0, ?, ?, ?]. In order to provide a completed vector for Predictor network training it was first considered whether such a patient had a lipid profile most similar to those patients with initial period 2 events, those with initial period 3 events, or those who remained event free.

The Period 2 network was developed only with training set cases whose period 2 outcomes were known. It predicted the likely period 2 outcome of training set patients lost to follow-up in period 1. Its seven input neurons corresponded to the lipid profile and its two output neurons corresponded to the presence or absence of a coronary event in period 2. The Period 3 network was organized in the same way, but it was developed instead with only training set cases that had known period 3 outcomes. It predicted period 3 outcomes of training set patients lost to follow-up in periods 1 or 2.

For example, if 122 patients were initially provided for network training but 5 were lost to follow-up in period 1 and 21 were lost to follow-up in period 2, then the Period 2 network was trained on the 117 examples of known period 2 outcomes and the Period 3 network was trained on the 96 examples of known period 3 outcomes. The Predictor network in contrast was developed with the full set of 122 patients, 26 of them having some imputed results.

The imputation approach is summarized in Fig. 2. A training set patient who was lost to follow-up in period 1 began with an incomplete output, described as [0, ?, ?, ?]. His lipid profile was then submitted to the Period 2 network. If the Period 2 network predicted a coronary event in period 2 then the output was now classified as [0, 1, 0, 0]. If the Period 2 network predicted no event, then the output was now [0, 0, ?, ?] and needed to be submitted to the Period

3 network. The same lipid profile was submitted to the Period 3 network, and if a coronary event was predicted for period 3 then the output was completed as [0, 0, 1, 0]. Otherwise it was completed as [0, 0, 0, 1] (no event during the study).

After training was complete the Predictor network was given the lipid profiles of the testing set cases. The four output neurons of the Predictor network corresponded to a period 1 event, a period 2 event, a period 3 event, and no event at all. The output of each neuron was a number approximately between 0 and 1. The output neuron with the highest value indicated the most likely outcome. As with the Cox regression models, the exit time and outcome of a patient were first considered, and the network results were scored according to whether or not an event was predicted to occur before or after the exit time.

Since the imputation process was never applied to any testing set data, there was no associated bias in scoring neural network predictions. For an early censored case the 120-month outcome was unknown, but the Predictor network and the Cox models were each scored as correct if they indicated that an event was unlikely to occur before the patient left the study.

Additional Models

Additional models were developed to examine more closely different elements of the neural network strategy. A simpler neural network approach developed on smaller training sets which excluded early (period 1 or 2) censored observations was applied. Outcomes were still classified according to four alternatives (initial events in period 1, 2, or 3, or no event at all). However, instead of 121 or 122 patients in the training set, these networks were developed on only 85 to 96 patients. No imputation process was used. Comparison with the initial Predictor networks served to determine whether the incorporation of early censored observations had played an important role in the Predictor network strategy success.

Furthermore, a second series of Cox regression analyses was performed. This Cox model utilized the same imputed results that had been provided to the Predictor networks, and its inputs and outputs were categorized and scored in an identical manner. A comparison of this second series of Cox regression models with the initial Predictor network served to examine whether the imputation of training set values and the classification and scoring of testing set predictions created a significant bias favoring the Predictor network approach.

Evaluation of Strategy Performance

Differences in performance were evaluated by McNemar's test for correlated proportions (*33*) on the 162 aggregate results obtained from testing sets A, B, C, and D. McNemar's test compared the relative numbers of discordant cases in paired strategies. Discordant pairs included those cases where Cox regression predicted correctly while the Predictor network erred and cases where the Predictor network estimated correctly while Cox regression erred. The null

TABLE 1

MEAN (±SD) LIPID VALUES, FOLLOW-UP TIMES, AND EVENT RATES

Variable[a]	Group A (n = 40)	B (n = 40)	C (n = 41)	D (n = 41)	P^b
Chol	204 ± 48	203 ± 37	204 ± 36	214 ± 41	0.59
HDL	54 ± 13	54 ± 14	52 ± 15	50 ± 11	0.58
LDL	124 ± 46	126 ± 40	127 ± 38	138 ± 41	0.42
Triglycerides	134 ± 88	117 ± 48	124 ± 56	128 ± 67	0.71
Apo B	99 ± 27	101 ± 28	102 ± 29	112 ± 32	0.17
Apo CHP	4.1 ± 2.7	3.8 ± 2.0	4.0 ± 2.4	4.4 ± 2.3	0.76
Apo CR	2.5 ± 1.9	2.3 ± 1.6	2.3 ± 1.3	1.9 ± 1.0	0.26
Follow-up	66 ± 28	74 ± 33	74 ± 27	67 ± 30	0.50
Coronary events	12	13	16	14	0.87

[a] Lipid values are mg/dl, follow-up time is in months.
[b] ANOVA P-value for comparison of means, Fisher's exact test for number of events.

hypothesis was that paired strategies performed equally well and that the relative numbers of discordant pairs were similar. McNemar's test has been previously used to evaluate neural network performance (*11*).

Neural network performance was also examined by providing the Predictor network with hypothetical cases of patients with various lipid profiles. The effects of individual aberrant values on network performance were identified and compared with changes in Cox regression estimates of survival. Combinations of different hypothetical lipid abnormalities were applied to identify whether interactions between variables affected network performance.

RESULTS

The mean on-trial lipid values for the 162 patients of the CLAS study are presented in Table 1 along with a comparison of the four groups A, B, C, and D which were the components of the training and testing sets. The lipid profiles of the patients in the four sets were similar. The mean length of follow-up and the number of coronary events were also similar.

Comparison of the Neural Network and Cox Regression Models

As shown in Table 2, the Predictor network strategy predicted 107 of 162 results correctly (66%). Cox regression analyses predicted 91 of 162 outcomes (56%). There were 22 cases where the Predictor network strategy led to correct predictions but the Cox regression strategy erred. There were only 6 cases where the Predictor network erred and the Cox strategy was correct. McNemar's test of correlated proportions resulted in $P = 0.005$.

A neural network strategy based on smaller training sets which excluded

TABLE 2

PERFORMANCE OF THE PREDICTOR NETWORK AND ALTERNATE METHODS

Predictor network or alternate method	Success rate (%)	Discordant pairs[a]		P^b
		PN correct AM incorrect	PN incorrect AM correct	
Predictor network	66	—	—	—
Cox regression	56	22	6	0.005
Neural network developed without early censored cases[c]	64	14	10	0.54
Cox regression using imputed values	57	21	7	0.01

[a] PN, Predictor network; AM, alternate method.

[b] McNemar's test on discordant pairs.

[c] Early censored case, period 1 or 2 censorship.

cases lost to early follow-up had a performance which was still above that of the Cox regression strategy, but less than the Predictor network. The neural network developed without early censored observations predicted 103 of 162 outcomes correctly for a success rate of 64%.

The Cox models provided with identical imputed data and the same categorization of inputs and outcomes as the Predictor networks had a success rate of 57% vs 56% for the initial Cox regression strategy. McNemar's test for discordant pairs, comparing the Predictor network approach with the Cox strategy developed on imputed values, resulted in $P = 0.01$. All the evaluated strategies are compared with Predictor network performance in Table 2.

With application of the m items out technique the successful predictions of each strategy were equally distributed across the four testing sets. χ^2 Tests showed that no strategy had a significant difference in the distribution of its correct predictions among groups A, B. C, and D (Predictor network $P = 0.85$; Cox regression $P = 0.29$; Neural network developed without early censored cases $P = 0.86$; Cox model developed with imputed data $P = 0.42$).

Performance Characteristics of the Predictor Network

The effects of individual aberrant values on Predictor network performance are shown in Table 3. A hypothetical patient with approximately mean values of all serum lipids is presented in the top row of the table. Both the Predictor network and the Cox regression strategies predict no coronary events in periods 1, 2, or 3. In the second row the cholesterol is elevated by 50%, without any changes in other variables. The network continues to predict survival, but the Cox regression strategy changed substantially, predicting a 120-month survival of essentially 0. In general, individual aberrant values had a greater impact on the Cox model. Only HDL had a significant effect on Predictor network output.

The effect of a combination of lipid abnormalities on Predictor network

TABLE 3

EFFECTS OF ABERRANT VALUES ON PREDICTOR NETWORK OUTPUT AND COX SURVIVAL

Lipid values (mg/dl)							Predictor network output				Cox survival at 120 months
Chol	HDL	LDL	TG	Apo B	Apo CHP	Apo CR	Period 1 event	Period 2 event	Period 3 event	No event	
204	52	127	124	102	4.0	2.3	0.15	0.1	0.06	0.7	0.51
306	52	127	124	102	4.0	2.3	0.15	0.1	0.06	0.7	0.00
204	**26**	127	124	102	4.0	2.3	**−0.05**	**0.49**	**−0.1**	**0.41**	0.00
204	52	**190**	124	102	4.0	2.3	0.15	0.1	0.06	0.7	1.00
204	52	127	**186**	102	4.0	2.3	0.15	0.1	0.06	0.7	0.99
204	52	127	124	**153**	4.0	2.3	0.15	0.1	0.06	0.7	0.37
204	52	127	124	102	**6.0**	2.3	0.15	0.1	0.06	0.7	0.56
204	52	127	124	102	4.0	**3.5**	0.15	0.1	0.06	0.7	0.53

Note. Boldface values highlight aberrant lipid profile values and changes in network output. The Predictor network shown was trained on sets A + B + D.

performance is shown in Table 4. The first row shows approximately normal lipid values, and the network predicts no event. Although a lower HDL of 32 mg/dl does affect network output, the network still predicts no event. Increasing the triglyceride level to 250 mg/dl has no effect if the other lipid values are normal (row 3). However, the elevated triglyceride level does have an effect if the patient also has a low HDL (row 4), and the network now favors a period 2 event. The network performance is nonlinear, the response to triglyceride elevations being affected by the HDL level.

The aggregate success rates for event predictions according to each period are presented in Table 5. Although both models had difficulty predicting early events, the success of the Predictor network was not simply from an increased likelihood of predicting long-term survival. It was a combination of success in predicting both the presence and the absence of events. There was no relative advantage in predicting survival for the censored cases. Many of these patients exited the study during periods 1 and 2, for which either model was likely to predict survival.

For early periods the baseline survival was very high (as much as 0.99 in period 1), and the Cox regression estimate of relative risk did not affect these survival rates enough to predict events effectively. The Predictor network was able to predict correctly seven events in periods 1 through 3, while the Cox regression strategy predicted only one of them.

For period 3 the baseline survival rate in the training set approached 0.57, so small changes in relative risk did have a significant impact on the Cox regression strategy predictions. This led the Cox model to incorrectly predict period 3 events in some instances of long-term survival. The Cox regression strategy predicted long term survival correctly 47 times, whereas the Predictor network was correct 57 times.

Discussion

The neural network strategy performed better than the Cox regression strategy, even when the Cox models were developed on the same imputed data as the networks. Cox regression performance did not change significantly when the imputed data was provided, suggesting that the imputation process did not alter the data in a way that biased model predictions.

The imputation technique did allow the Predictor network to be trained on a larger database (121 or 122 patients instead of 85 to 96). Although this may have contributed to Predictor network success, the difference between neural networks developed with and without early censored cases did not reach statistical significance ($P = 0.54$). Nevertheless, the imputation technique helps address the problem of incorporating censored data in neural network analysis. In many settings exclusion of uncensored data could otherwise bias network performance.

Other imputation techniques could have been used in network development. A discriminant analysis approach could have classified the input vectors of

TABLE 4

NONLINEAR BEHAVIOR OF THE PREDICTOR NETWORK

Lipid values (mg/dl)							Predictor network output			
Chol	HDL	LDL	TG	Apo B	Apo CHP	Apo CR	Period 1 event	Period 2 event	Period 3 event	No event
200	50	125	125	100	4	2	0.15	0.1	0.06	0.7
200	**32**	125	125	100	4	2	**0.03**	**0.31**	**−0.04**	**0.54**
200	50	125	**250**	100	4	2	0.15	0.1	0.06	0.7
203	**32**	125	**250**	100	4	2	**−0.04**	**0.45**	**−0.09**	**0.41**

Note. Boldface values highlight changes in lipid profile and network output. The Predictor network shown was trained on sets A + B + D.

TABLE 5

PREDICTOR NETWORK AND COX REGRESSION PERFORMANCE ACCORDING TO PERIOD

	No. of cases	Predictor network correct	Cox regression correct	Network without censored cases correct	Cox model with imputed data correct
Period 1 event	24	0	1	3	1
Period 2 event	22	5	0	1	1
Period 3 event	9	2	0	2	4
No event (period 4)	64	57	47	56	49
Censored events	43	43	43	41	38

Note. Scores reflect aggregate performances of strategies on testing sets A, B, C, and D.

censored cases in a similar manner. However, the neural network imputation technique is novel, it is relatively easy to apply with the available software, and it does not require any assumptions about the distribution of input or output variables.

In this study the differences in Predictor network and Cox regression strategies may have existed because the Cox model requires specific assumptions about hazard, survival, and the variables which affect them. The Cox regression strategy could be described as an application of one specific function which attempts to describe data. The neural network, on the other hand, has the potential to reproduce any continuous function. When the data does not follow a particular Cox regression model closely then the neural network can show superior performance.

It would certainly be possible to apply the Cox regression model in several different ways (*34–37*) in search of better performance. An exhaustive search for the best possible Cox model could include repeated attempts to either stratify the database or experiment with different interaction terms in the model. On a larger database these alternatives might be very effective. Further comparisons with several different types of Cox models developed on other data sets will help provide a good perspective on the differences between neural network and Cox regression strategies.

One advantage of the Cox model is that when successful it can provide a theoretical framework to explain results, one of proportional hazards and relative risk. The network, although it promises performance, does not offer a specific theory of variable interrelationships. Hypotheses about significant variables are often developed instead by providing the network with theoretical cases and examining its response. Individual connections between neurons in a complicated network usually do not provide an easy understanding of relationships between input and output.

The Predictor network successfully predicted outcomes in 66% of patients. This performance could be improved by adding other important variables that affect the progression of coronary artery disease. Information on smoking status, blood pressure, the presence or absence of diabetes, and baseline disease severity could increase the ability of both neural network and Cox regression models to predict clinical coronary events.

Neural network performance of 66% does not appear to be very high, but it can be contrasted with that of a hypothetical random predictor. From Table 5 it can be seen that among uncensored observations 54% were no event, 8% were period 3 events, 18% were period 2 events, and 20% were period 1 events. A random predictor which utilizes this distribution to predict outcomes would be relatively poor at predicting period 1, 2, and 3 events because of their lower frequency. For example, a period 3 prediction would be made only 8% of the time, and these predictions would in turn have only an 8% chance of being correct. Overall performance among all categories would be only 37%, much less than that of the Predictor network. A certain amount of difficulty in predicting earlier events is inherent in the distribution of the data.

The Predictor network, however, is not simply a model that always predicts no event. Its response to abnormal lipid values can reflect disease risk (as shown in Table 3). In cases with complete follow-up the Predictor network predicted events 17 times, and coronary events were indeed observed in 10 of these patients, a majority. Predictor network performance was scored with strict criteria that the period of an event prediction must reflect the observed exit time, and as a result the 66% performance described did not include all 10 of these cases.

The neural network approach developed here can be applied to other clinical trials with censored data. Similar settings would include epidemiological studies which evaluate variables that affect the risk of cancer, diabetes, and other conditions, or clinical trials which follow time-related variables such as disease-free survival. In an area such as lipid profiles it has the advantage of integrating several laboratory parameters into a single evaluation of disease risk. With the availability of larger databases neural networks developed in this manner could serve as a useful clinical tool.

Conclusion

Neural networks were used to associate lipid profiles with the presence or absence of coronary events in data from the Cholesterol Lowering Atherosclerosis Study. A novel strategy for imputing the eventual outcomes of early censored cases allowed all the available training data to be used in developing a Predictor network. With cross-validation the Predictor network was shown to outperform Cox regression strategies in predicting coronary events. This neural network approach can be applied to data from other clinical trials and epidemiological studies with censored observations.

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