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Artificial Neural Networks and risk stratification in Emergency department

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ABSTRACT: The primary goal of the Emergency Department physician is to discriminate individuals at low risk, who can be safely discharged, from patients at high risk, who deserve prompt hospitalization for monitoring and/or appropriate treatment. Obviously, the problem of a correct classification of patients, and the successive hospital admission, is not only a clinical issue but also a management one since ameliorating the rate of admission of patients in the emergency departments could dramatically reduce costs and create a better health resource use.

Considering patients at the emergency departments after an event of syncope, this work propose a comparative analysis between multivariate logistic regression model and Artificial Neural Networks (ANNs), highlighting the difference in correct classification of severe outcome at 10 days and 1 year. According to results, ANNs can be very effective in classifying the risk of severe outcomes and it might be adopted to support the physician decision making process reducing, at least theoretically, the inappropriate admission of patients after syncope event.

KEYWORDS: Artificial Neural Networks (ANNs); Syncope; Emergency Departments; Risk stratification; Area Under the Curve, referring to the Receiver Operating Characteristics (ROC) Curve; correct classification;

JEL Codes: I12; D81;

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SUMMARY

1. INTRODUCTION

Syncope can be defined as a transient loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery.

Syncope is a common presenting problem accounting for 1–3% of Emergency Department (ED) visits and 1–3% of hospital admissions (Brignole *et al.*, 2006; Day *et al.*, 1982; Silverstein *et al.*, 1982). The overall risk for a patient entering the ED because of syncope spans between 5% and 15%, and the mortality rate at one week is about 1%. The primary goal of the ED physician is thus to discriminate individuals at low risk, that can be safely discharged, from patients at high risk, who deserve prompt hospitalization for monitoring and/or appropriate treatment.

Unfortunately, undetermined syncope is frequent after the first assessment in ED. Thus, in the absence of a certain diagnosis the doctor's main goal should shift from the effort to further identify a syncope cause to the attempt to stratify the patient risk. This can be done on the basis of the patient's history and the characteristics of the syncope. Of notice, risk stratification can be obtained by the simple clinical experience (clinical judgment) or by using appropriate rules or risk scores. These latter may help the ED physician in the decision making, although so far there is no compelling evidence that any score or rule is indeed performing better than the personal clinical judgment in affecting the patient clinical outcome (Costantino, 2014).

Moreover, as suggested in the First International Workshop on Syncope Risk Stratification (Ben Sun et al., 2014), there are several problems related to the use of clinical decision rules including the fact that e they are suited on average values belonging to groups of patients while in clinical practice decisions must be taken on the single patient. At the same time, external validity may be weak, as decision rules are often derived from data obtained from single clinical centers. Finally, syncope adverse events are rare and thus a huge number of events is required to build a consistent statistical model if we take the current statistical tools into account.

Obviously, the problem of a correct classification of patients, and the successive hospital admission, is not only a clinical issue but also a management one (Eriksen *et al.*, 2000). Indeed, ameliorating the management and rate of admission of syncope patients in the emergency departments could dramatically reduce costs and optimize the use of health system resources.[6] This is even more pertinent if we consider the current worldwide age of austerity and the common policy of spending review in the health care sector.

According to the proposed background, a new methodology might be desirable to identify, with high sensitivity and an appropriate specificity, those patients referred for syncope likely to have serious adverse events in the short- and long-term, as well to support the physician decision making process. In the present study we propose the Artificial Neural Networks (ANNs) as a suitable tool for syncope risk stratification.

[6] See McDonagh *et al.* (2000) for a deeper analysis of inappropriateness hospital admission. Authors propose a systematic review of the methods used to assess appropriateness of acute bed use and the evidence on the scale of inappropriate use in different patient groups. See also Fellin *et al*. (1995) for a background of the Italian reality, both considering emergency departments and others hospital structures.

This approach has never been used, at the best of our knowledge.

Literature shows that ANNs may simulate or forecast an event or an agent behavior (Lin *et al*., 2009).Moreover, ANN are more effective than logistic and probabilistic models in classifying elements (Lin *et al*., 2009; Huang *et al*., 2007; De Andres, 2005; Lin and McClean, 2001). These methodologies have been applied in several fields from finance to electronic (Jain and Srivastava, 2013; Falavigna, 2008; Patterson, 1998) and, of course, in medical diagnosis (Amato *et al*., 2013). Indeed, among others, Artificial Neural Networks have proven useful in the analysis of blood and urine samples of diabetic patients (Catalogna *et al*. 2012, Fernandez de Canete *et al*. 2012), diagnosis of tuberculosis (Er *et al.* 2008, Elveren and Yumuºak 2011), leukemia classification (Dey *et al.* 2012) and emergency departments (e.g. Bektaş *et al.*, 2008; Harrison and Kennedy, 2005; Baxt *et al.*, 2002).

Technically, ANNs are complex tools that start from data in order to extract rules and relationships among input variables, which are the determinants of bad outcome in case of syncope. Their framework is non linear and then they do not require specific hypotheses on distributions of variables, increasing the powerfulness of the proposed methodology. For these reasons, authors expect better results by ANNs in the risk stratification, supporting properly the physicians' decision making process. In other words, we expect higher correct classification (i.e. higher value of specificity and sensitivity) with respect to the common statistical tools adopted up to now (e.g. *logistic multivariate regression model*).

In order to achieve the proposed goal, we implement a comparative analysis on the same dataset, highlighting the difference in correct classification. Specifically, we here present results obtained by comparing a model based on multivariate logistic regression approach with another model based on ANNs.

This work is organized in four sections. After this first introductive section, there will be data and methodology sections. The third section shows the results of the comparative analysis between the innovative methodology and the current one while, in the fourth section, some conclusions are suggested.

2. DATA AND METHODOLOGY

Data used in the analysis are extracted from the STePS study (Short-Term Prognosis of Syncope) and published by Costantino et al. (2008). Applied methodologies in that work are univariate, multivariate analyses and the logistic multivariate stepwise backward regression. These applications allowed authors to evaluate the level of significance of patients' information in determining severe short- and long-term outcomes, through a stepwise backward algorithm. This might be considered a representative methodology of the current knowledge. In the present work authors apply an innovative technique for risk stratification in case of syncope: Artificial Neural Networks (ANNs).

In order to compare previous methodologies, authors adopt Receiver Operator Characteristics (ROC) Curves and correct classification.

2.1 Methodology: Artificial Neural Networks (ANNs)

Artificial Neural Networks (ANNs) are complex models organized by layers (multilayer) formed by neurons (also called perceptrons) interconnected by synapsis (weights), as depicted in Figure 1.

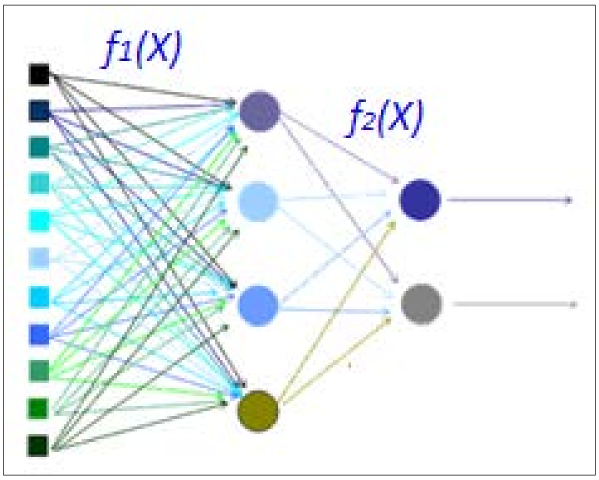
The first layer is called “input layer” and it is composed by a number of neurons (or nodes) equal to that of variables analyzed (in our specific case, the model has the same number of neurons of patients’ information). The last layer is the “output layer”, from which derives the result of model.

The number of nodes in this layer depends from the type of expected answer. Usually, there is only one neuron because results are expressed in a dichotomous form.Between the input layer and the output one there are hidden layers that can be more than one. Nevertheless, Hornick et al. (1989) prove that a single hidden layer is able to approximate any functional form. The number of neurons of hidden layers has to be found empirically (Kim, 2003; Min and Lee, 2005), even if some authors tried to define rules, as Patuwo et al. (1993), Nath et al. (1997) Chauhan et al. (2009) that suggested to use the formula $(2i + 1)$ where $i = 1, \dots, I$ represents the number of considered variables.

A more performant criterion in terms of time-consuming has been validated by Salchenberger at al. (1992) and Olmeda and Fernandez (1997) that proposed the proportion 0.75i.

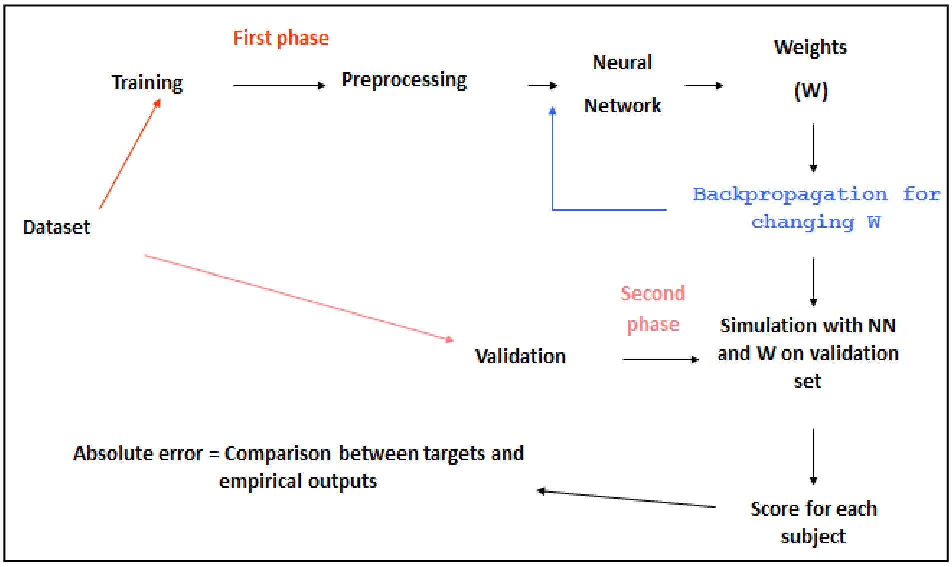
Links between layers are “synapsis”, mathematically called weights, and they collect information between input variables and the expected outputs.

These relationships are formalized through functions that, in the majority of cases, are not linear (i.e., logsigmoidal, tansigmidal, hardlim and so on).



Source: adjusted from Falavigna (2012)

Figure 1: Feed-forward MultiLayer Perceptron framework



Source: adjusted from Falavigna (2012)

Figure 2: Supervised learning of MLP with back-propagation algorithm

Activation functions used in this model are linear from the input layer to the hidden one and tansigmoidal from the hidden layer to the output one[7].

Relationships between layers are collected in weight matrixes and from their analysis, it is possible to evaluate the contribution of each information in the definition of expected output (Garson, 1991; Nath et al., 1997).

The MultiLayer Perceptron (MLP) network is represented in Figure 1 and its links are feed-forward because connections come from input layer to hidden one and from hidden layer to output one. Backward relationships or recursive are not considered in this framework.

Feed-forward MultiLayer Perceptron works with a supervised learning through a back-propagation algorithm[8]. Figure 2 represents the working plan of the supervised learning with back-propagation algorithm. Initial sample is subdivided into two sub-samples: the training and the validation. In the first phase, only elements of training are presented in the model and through the back-propagation algorithm, ANN computes weights matrixes until a predefined error threshold is reached. In this step, in the model are introduced information about patients but also their “target”, so that their health status (severe short-long-term outcomes). This stage is very important because ANN learns from data and collects in weight matrixes information about relationships between variables. From this consideration, it is clear that the subdivision of initial sample into training and validation is very critical: the training set must represent all possible types of patients with their specific characteristics. In our case we have set the proportion of 4/5 in the training set and 1/5 in the validation one.

[7] Tansigmoidal function has a logsigmoidal form with a codomain range from -1 to +1.

[8] Notice that there are some network frameworks that use an unsupervised procedure, i.e., Self-Organizing Map or Kohonen networks (Kohonen, 1990).

Table 1: Descriptive statistics on STePS Database

Variables	Severe short-term outcomes (Outcome=< 10 days)		Severe long-term outcomes (10days<Outcome<1years)		Total
	No	Yes	No	Yes	
Female	365	14	354	25	379
Age<65 yrs	196	1	196	1	197
Age>=65 yrs	169	13	158	24	182
Male	270	27	277	20	297
Age<65 yrs	140	8	147	1	148
Age>=65 yrs	130	19	130	19	149
Total	635	41	631	45	676

Once defined weights and ANN framework (i.e., type of activation functions between layers; number of hidden layers and their nodes; other technical parameter as the search function for the optimal gradient, etc…), these parameters are applied to the validation sample that is introduced in the ANN without the information on the severe short-long-term outcomes. In this manner, ANN applies previous framework to new data in order to evaluate results and the classification ability of the model.

In our model, information about patients are introduced in the input layer with the aim to obtain an outcome for each patient indicating the possibility of a severe short- or long-term outcome (1 if there is the possibility, 0 if not).

2.2 Data

Data used in the analysis are from the STePS study (Short-Term Prognosis of Syncope) and collects information about 676 patients that have suffered from syncope. The same database has been analyzed by Costantino et al. (2008) through a step-wise multivariate regression model with the aim to evaluate which patients' information are determinant in forecasting serious outcome (or death) after the syncope event.

The analysis has been conducted both for severe short-term outcomes within 10 days and for severe outcomes from the 11th day up to 1 year after the Emergency Department visit. Table 1 presents a preliminary descriptive statistics on analyzed data.

In particular, we present short- and long-term outcomes subdivided by Sex and Age variables.

These are exactly the interested variables of the models proposed in this work.

Collected information in the database refer to physical and biological characteristics of patients (i.e. sex, age, diabetes, hypertension, ECG values, and so on).

In the paper of Costantino *et al.* (2008), authors study which risk factors can affect severe short and long-term outcomes, as well long-term mortality, considering the following information on patients: age older than 65 years, male gender, the coexistence at presentation of structural heart disease, heart failure, chronic obstructive pulmonary disease, trauma, abnormal ECG, and the absence of preceding symptoms.

Table 2: Results – Logistic multivariate regression model and Artificial Neural Networks (variables according to Costantino et al., 2008)

Model	AUC (Area Under the Curve)	Correct classification
Logistic multivariate regression short-term (10 days)	0.8844	94.07%
Logistic multivariate regression long-term (1 year)	0.7116	89.66%
Artificial Neural Network short-term (10 days)	0.8258	94.07%
Artificial Neural Network long-term (1 year)	0.9127	97.67%

Results, which are in line with those obtained from previous literature, suggest that statistically significant risk factors for severe short-term outcomes (within 10 days) are: abnormal electrocardiogram at presentation, trauma, absence of symptoms preceding syncope, and male gender. Severe long-term outcomes (from the 11th day up to 1 year after the ED visit) are affected by age>65 years, neoplasm, cerebrovascular disease, structural heart disease, and ventricular arrhythmias.

In the next section authors compares the current methodology and the innovative one, highlighting the difference in terms of Area Under the Curve, referring to the Receiver Operating Characteristics (ROC) Curve. Therefore, results will suggest the most appropriate methodology for patients' risk stratification in case of syncope.

3. RESULTS

Authors have compared results obtained with a logistic multivariate regression model (Costantino *et al.*, 2008) and those found through the ANN framework, recalling the idea of ROC Curve and correct classification. Moreover, Garson indexes (Garson, 1991) for input variables have been calculated in order to evaluate the percentage weight for each patient's characteristics and, in this way, to analyze the main differences.

Two main steps are implemented. In the first step, authors run ANNs using significant variables obtained through the multivariate analysis, as well applied in Costantino et al. (2008).

Table 2 compares results in terms of Area Under the Curve, referring to the Receiver Operating Characteristics (ROC) Curve, as well correct classification of the sample of patients. Authors considered both short- and long-term, represented respectively by outcome at 10 days and 1 year.

Moreover, in figure 3 and 4, authors show the AUC with respect the short and long-term.[9] Obviously, the greater the area under the curve (AUC), the more accurate the test.

[9] The diagonal line represents the AUC with a value equal to 0.5, which is the minimum benchmark in terms of accuracy for the test.

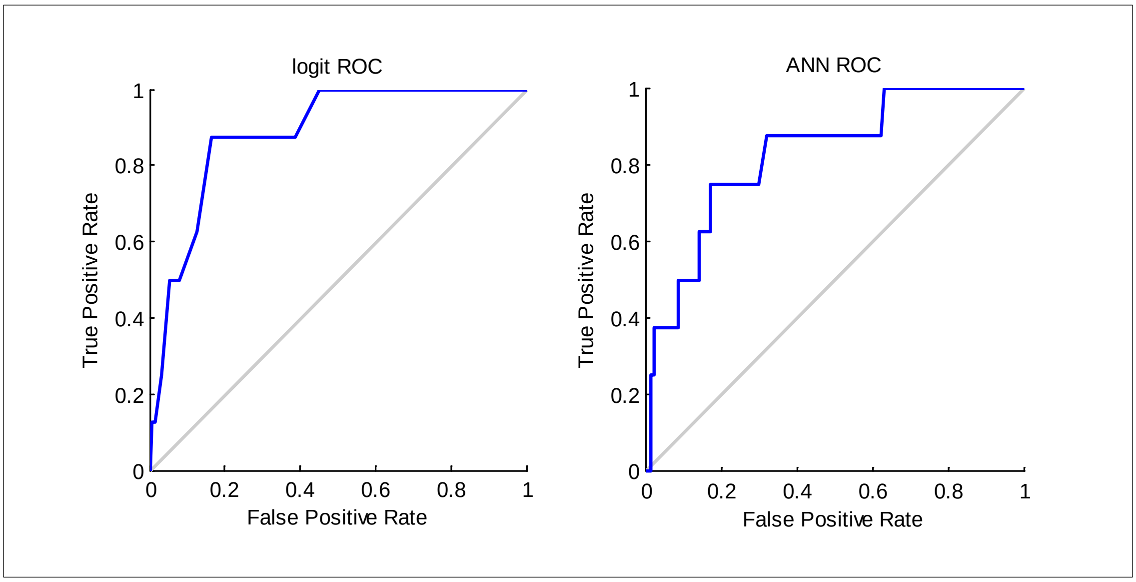


Figure 3: ROC curves: logit model vs ANN in the short-term

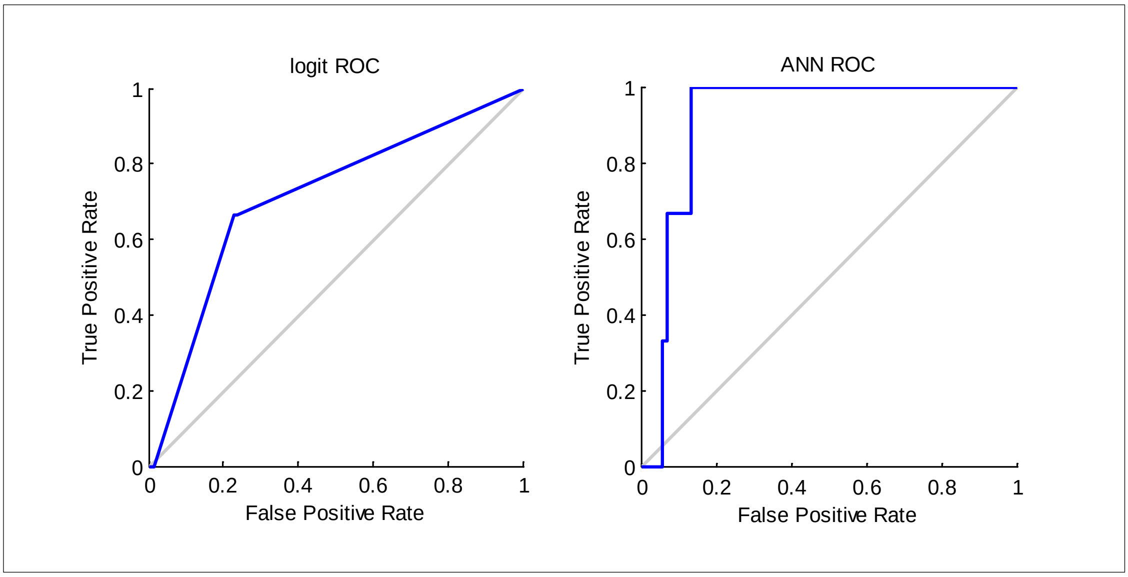


Figure 4: ROC curves: logit model vs ANN in the long-term

On the one hand, results suggest that the model applies multivariate logistic regression model is more accurate than the model applies ANNs, if we consider the analysis at short-term (i.e. after 10 days of the visit in the emergency department). However, the estimated difference is irrelevant and there is no difference if we take the correct classification into account.

Table 3: Results – Artificial Neural Networks
(variables selected by ANN)

Model	AUC (Area Under the Curve)	Correct classification
Logistic multivariate regression short-term (10 days)	0.8874	94.07%
Logistic multivariate regression long-term (1 year)	0.9960	96.40%
Artificial Neural Network short-term (10 days)	0.8938	98.30%
Artificial Neural Network long-term (1 year)	0.9848	97.67%

* *one-sided, 97.5% confidence interval*

On the other one, taking long-term into account (i.e. after 1 year from the visit in the emergency department), results suggest that the model which applies ANNs is more accurate than the model that use the multivariate logistic regression model. In this case the difference is significant (97.67 vs. 89.66 % of correct classification[10]).

This means that the model whit the innovative methodology (i.e. ANNs) is more appropriate in ruling-out the severe outcome in the long-term. Nevertheless, from a clinical point of view, the results at short terms are more relevant and thus a deeper study might be desirable. Considering the proposed analyses and the collected values, we can imagine that the estimation might be affected by the variables selection and there could be clear opportunities to increase these values. The second step is aimed at establishing if the hypothesis is correct or not.

According to the proposed idea, the second analysis has been conducted introducing all available variables in the ANN model and in the logistic multivariate regression model[11]. Table 3 proposes the results (percentage of correct classification and AUC).

Observing results, in both cases there is an increasing of all values, clearly affected by the number of variables, i.e. the amount of information used by the models. In other words, the selection variables induced by the stepwise option has a significant impact on the results.

Thinking in terms of test aimed at deciding whether admitting a patient after a visit to the emergency department, the model based on the ANNs would identify correctly patients with severe outcome both in the short and in the long term. In other words, a high percentage of appropriate admission/rejection

[10] A two-sample test of proportions has been calculated in order to evaluate if the difference between correct classification results is statistically significant. Test result suggests that the proportions are statistically different from each other at any level greater than 0.58%. This means that the null hypothesis on statistical significance of the equality is rejected.

[11] All missing values are not considered in the ANN model, which means that a sample of 588 patients is considered in the short term and 566 in the long one.

to the hospital would be achievable through the proposed model (98.30 and 97.67 %).

Notice that the present model has been built in order to maximize the percentage of correct classification, without considering sensitivity and specificity or other performance indexes. Referring to this, the model must be improved considering sensitivity and specificity in the definition of parameters.

Also in this case authors show the graphic representation of the AUC, as well proposed in figure 4 and 5.

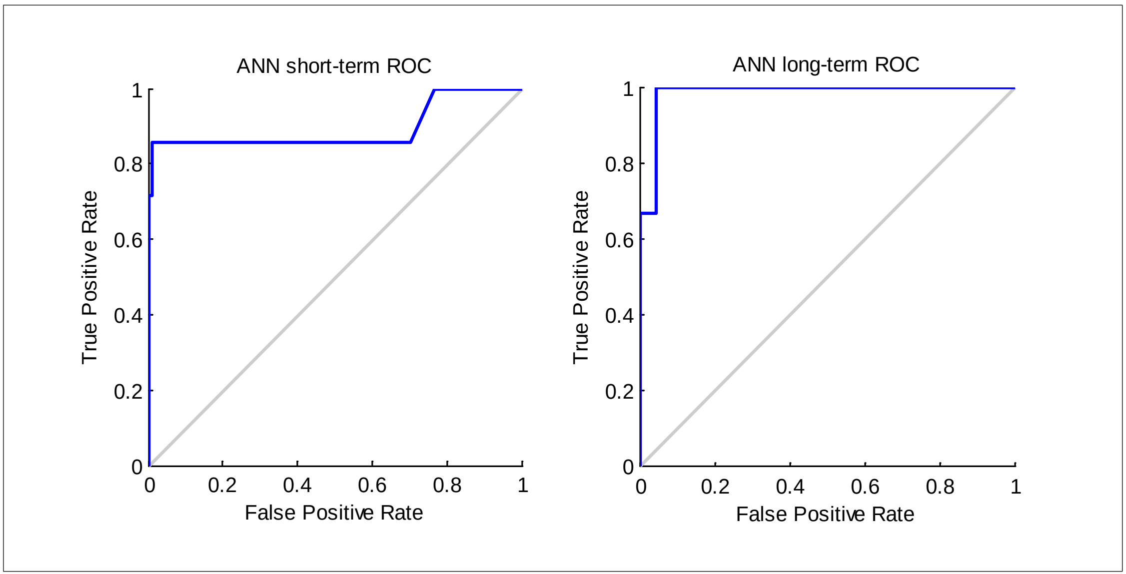


Figure 5: ROC curves: ANN results in the short- and long-term

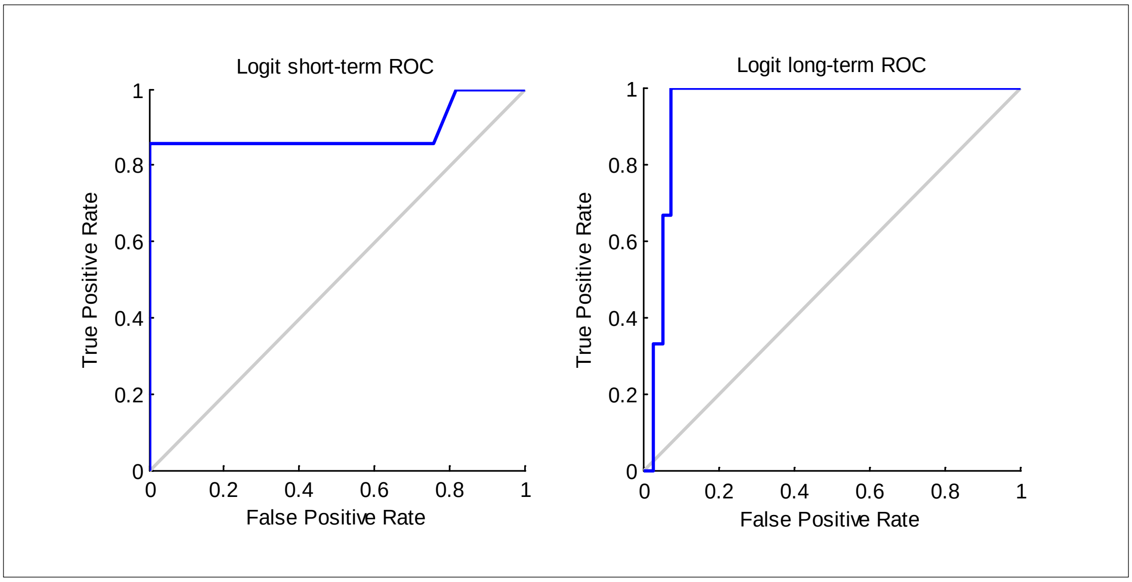


Figure 6: ROC curves: Logit results in the short- and long-term

Table 4: Multivariate logistic regression model, results in short- and long-term considering all variables

VARIABLES	(1) Short-term	(1) Long-term
Age	0.0845***	0.166***
	(0.0214)	(0.0571)
Sex	0.634	0.219
	(0.449)	(0.770)
Hypertension	-0.405	1.198
	(0.438)	(0.869)
Diabetes mellitus	-0.459	-0.797
	(0.781)	(1.267)
CRD^	-	1.559
		(1.294)
COPD*	-0.0268	1.227
	(0.622)	(0.841)
Chronic anemia	0.290	-0.316
	(0.747)	(1.080)
Hemolytic anemia	-0.0355	0.743
	(1.117)	(1.253)
Neoplasm	-0.763	0.0423
	(0.780)	(1.180)
Cerebrovascular	-0.0166	-0.760
	(0.514)	(0.859)
Neurological diseases	-1.910*	1.413*
	(1.061)	(0.828)
Structural heart diseases	0.791*	0.705
	(0.456)	(0.732)
Pacemaker	-0.526	-
	(0.932)	
Constant	-9.062***	-18.17***
	(1.686)	(4.936)
Observations	451	445

^ CRD: Chronic renal disease

* COPD: chronic obstructive pulmonary disease

Standard errors in parenthesis

*** $p<0.01$, ** $p<0.05$, * $p<0.1$

Table 4 summarizes the results of the empirical analysis with multivariate logistic regression model. According to results, the unique statistically significant coefficient is the age (*p value < 0.01*).

As conclusion of the analysis, authors have estimated Garson indexes (Garson, 1991), which represent the percentage contribution of each variable introduce in the ANN to the result (i.e. severe outcomes). Afterwards, these indexes are compared with the results obtained in the multivariate logistic regression model (table 4). Table 5 presents these percentages, considering both short- and long-term. By comparing significant variables of both models, authors can show how much different might be the physicians' conclusions in the diagnostic phase, i.e. how different might be the determinants of sever outcomes in the long and short term that the physician

Table 5: Garson indexes for short- and long-term

Variables	Weights – 10 days (% values)	Weights – 1 year (% values)
Age	11.31	2.60
Sex	2.18	3.71
Hypertension	8.10	7.69
Diabetes mellitus	11.39	5.36
CRD^	6.28	9.07
COPD*	5.79	5.72
Chronic anemia	10.78	3.80
Hemolytic anemia	2.11	22.11
Neoplasm	9.12	9.12
Cerebrovascular	3.02	2.88
Neurological diseases	9.63	9.95
Structural heart diseases	9.53	8.34
Pacemaker	10.75	9.66

^ CRD: Chronic renal disease

* COPD: chronic obstructive pulmonary disease

should consider in the admission of the patient.

Taking the short-term into account (Costantino *et al*., 2008), multivariate logistic methodology found a significant relationship between severe outcome and four variables: abnormal electrocardiogram at presentation, trauma, absence of symptoms preceding syncope, and the sex (*male gender*). Implementing the new model with available data and without the stepwise option, only one significant variable is collected, the age of patients; whereas Garson indexes suggest that the most significant variables are: age, diabete mellitus, the presence of the pacemaker and chronic anemia. This means that only one variable is common for both models (i.e. age).

Concerning long-term outcomes, significant variables found by Costantino *et al*. (2008) were age (*patients>65 years*), neoplasm, cerebrovascular disease, structural heart disease, and ventricular arrhythmias. Also in this case, ANN suggests that other variables are relevant: hemolytic anemia, neurological disease, the presence of the pacemaker and neoplasm; whereas, considering the multivariate regression model without the stepwise option, only one variable is statistically significant (i.e. age). Comparing results, only one variable is common for both models: neoplasm, if we consider Costantino *et al.* (2008), and age, if we take the model without stepwise option into account.

These results suggest that other clinical information should be considered in the estimation of the likelihood of a severe outcome in the short- and long-term according to the proposed model. In other words, a different model should be considered by physicians in order to decide the appropriateness of patients admission to the hospital.

4. CONCLUSIONS

The primary goal of the emergency department physician is to discriminate individuals at low risk, who can be safely discharged, from patients at high risk, who deserve prompt hospitalization for monitoring and/or appropriate treatment. Considering patients at the emergency departments after a syncope event, this work proposes a comparative analysis between multivariate logistic regression models and Artificial Neural Networks (ANNs), highlighting the difference in the correct classification of severe outcome at 10 days and 1 year from that event.

Results shown in this paper confirm there are several opportunities to implement alternative successfully risk stratification tools based on ANNs, increasing the correct classification of the risk of severe outcome at short and long term.

Obviously, from a management point of view, the main implications of our work concerns the correct classification of patients, and the successive hospital admission. Indeed, a decisional making process based on ANNs might represent an opportunity in the health care sector, ameliorating the management and rate of admission of syncope patients in the emergency departments and, in this way, reducing dramatically the costs and creating a better health resource use.

However, even if these results are interesting and relevant, there are still opportunities to improve the proposed methodology according to the specific necessity of the final user. Indeed, the paper adopt an algorithm aimed at maximizing the percentage of correct classification but, in medical field, the type of error is more relevant than the number of misclassification (Weingart and Wyer, 2006). In other words, there is a significant difference between false positives and negatives. For this reason, authors are working on an algorithm able to select the best setting of ANN parameters on the basis of predefined values of sensitivity and specificity. With this approach, ED physicians can decide a priori the level of expected performance in terms of sensitivity and specificity and the model learn from data in order to satisfy this request.

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