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• *BRIEF REPORTS* •

Possible contribution of advanced statistical methods (artificial neural networks and linear discriminant analysis) in recognition of patients with suspected atrophic body gastritis

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Abstract

AIM: Diagnosis of atrophic body gastritis (ABG) is based upon histological examinations of body mucosa biopsies obtained during gastroscopy. However, gastroscopy is invasive and expensive, and biopsy sampling of body mucosa prolongs the procedure increasing discomfort to the patient. Artificial neural networks (ANNs) and linear discriminant analysis (LDA) may be used as computer-based decision-support systems. Thus, this pilot study aimed at investigating whether ANNs and LDA could recognize patients with ABG in a database, containing only clinical and biochemical variables, of a pool of patients with and without ABG, by selecting the most predictive variables and by reducing input data to the minimum.

METHODS: Data was collected from 350 consecutive outpatients (263 with ABG, 87 with non-atrophic gastritis and/or celiac disease [controls]). Structured questionnaires with 22 items (anagraphic, anamnestic, clinical, and biochemical data) were filled out for each patient. All patients underwent gastroscopy with biopsies. ANNs and LDA were applied to recognize patients with ABG. Experiment 1: random selection on 37 variables, experiment 2: optimization process on 30 variables, experiment 3: input data reduction on 8 variables, experiment 4: use of only clinical input data on 5 variables, and experiment 5: use of only serological variables.

RESULTS: In experiment 1, overall accuracies of ANNs and LDA were 96.6% and 94.6%, respectively, for predicting patients with ABG. In experiment 2, ANNs and LDA reached an overall accuracy of 98.8% and 96.8%, respectively. In experiment 3, overall accuracy of ANNs was 98.4%. In experiment 4, overall accuracies of ANNs and LDA were, respectively, 91.3% and 88.6%. In experiment 5, overall accuracies of ANNs and LDA were, respectively, 97.7% and 94.5%.

CONCLUSION: This preliminary study suggests that advanced statistical methods, not only ANNs, but also LDA, may contribute to better address bioptic sampling during gastroscopy in a subset of patients in whom ABG may be suspected on the basis of aspecific gastrointestinal symptoms or non-digestive disorders.

Key words: Atrophic body gastritis; Computer-based decision support; Gastroscopy; Artificial neural networks

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INTRODUCTION

Atrophic body gastritis (ABG), a condition characterized by atrophy of the gastric oxyntic mucosa, hypo/achlorhydria, and, in turn, hypergastrinemia, is a disorder considered as increased risk for gastric neoplasms[1,2].

In general, ABG does not give rise to symptoms of the upper gastrointestinal tract, such as epigastric pain or burning. Some patients may complain of dyspeptic symptoms, such as epigastric discomfort or postprandial bloating, complaints which are frequently found in the general population[1]. More frequently, the only relevant clinical finding is the presence of anemia[3-5], and, indeed, ABG is often considered synonymous with the presence of pernicious anemia[6,7]. Moreover, ABG may also present with iron-deficiency anemia, a consequence of the impaired iron absorption due to hypo/achlorhydria[8]. Finally, ABG may be associated with autoimmune disorders, such as autoimmune thyroid disease, vitiligo, and alopecia[7], and, in the presence of vitamin B_{12} deficiency, also with neurological symptoms[9].

However, the gold standard for the diagnosis of ABG is based, despite its limits, such as sampling error and inter-observer variability, on the histological examination of biopsy specimens of body mucosa obtained during gastroscopy[10,11]. Gastroscopy, however, is an invasive and expensive procedure, which is often accepted with reluctance

by patients without gastric symptoms. Moreover, the biopsy sampling of body and antral mucosa prolongs the endoscopic procedure increasing discomfort to the patient. Furthermore, the processing of multiple gastric biopsy specimens for histological examination is time- and cost-consuming.

Non-invasive screening methods, such as serum levels of gastrin and pepsinogen I and II, have been tested for gastric antral and body atrophy, respectively. Unfortunately, however, because of the high specificity but low sensitivity[12-14], these methods need to be further improved before their use in serological screening for atrophic gastritis can be considered feasible[15].

Thus, reliable tools to select patients with suspected ABG requiring gastroscopy with collection of body mucosa specimens for histological diagnosis of ABG are still lacking. Decision-support systems, based on conventional statistical methods, made their entry into medicine several years ago[16,17]. Recently, efforts to improve predictive and prognostic performance of these systems have led to the application of artificial neural networks (ANNs) as tools for clinical decision-making[17-19]. ANNs are highly flexible computerized mathematical models for understanding and predicting complex and chaotic dynamics in complex biological systems, and have been effectively used to solve non-linear problems related to diagnostic or prognostic queries even for single patients, and not necessarily for the groups of patients as in the case with conventional statistics[17,20]. Thus, ANNs would appear to be a promising tool for clinical decision-making and have been applied in various areas of medical research[21-24]. Recently, the role of ANNs has been investigated in two important aspects of clinical decision-making in gastroenterology: Das *et al*.[25], have proposed a prediction model of outcome in acute lower gastrointestinal hemorrhage based on ANNs; and Selaru *et al*.[26], have reported that ANNs are able to distinguish among subtypes of neoplastic colorectal lesions. To our knowledge, studies applying advanced statistical methods in patients with suspected ABG have not yet been performed. This pilot study, therefore, aimed to investigate the role of ANNs and LDA in recognizing patients with ABG in the database of a pool of patients with ABG comprising only clinical and biochemical variables, by selecting the most predictive variables and by reducing input data to the minimum.

MATERIALS AND METHODS

Patients

This study was carried out using a database prepared ad hoc, comprising data from 350 consecutive outpatients (86 male, 264 female, median age 53 years, range 20-81 years), with a diagnosis of ABG (n = 263), chronic non-atrophic gastritis (n = 42), and celiac disease with or without chronic non-atrophic gastritis (n = 45). The 87 patients without ABG were considered as controls. These patients were evaluated, from 1994 to 1998, for long-standing dyspepsia, microcytic or macrocytic anemia, presence of autoimmune diseases or neurological disorders in our gastroenterology unit, which is part of an academic, urban, tertiary-care medical institution.

For each of these patients, a structured questionnaire was filled out, composed of 22 items concerning anagraphic, anamnestic, clinical, and biochemical data. The items with their respective variables of the structured questionnaire are shown in Table 1. Replies of the patients to questionnaire items regarding symptoms were considered positive, when present for at least three consecutive months during the previous year.

All patients underwent gastroscopy with standardized biopsy sampling from the antrum (n = 3), body (n = 3), and duodenum (n = 2) for conventional histopathological examination, as previously described[3,4,27,28]. The degree of gastritis was assessed according to the Updated Sydney System[10]. Atrophy of the body and antral mucosa was defined as focal or complete replacement of oxyntic or pyloric glands by metaplastic pyloric or intestinal glands, respectively, as previously described[3,4]. Celiac disease was diagnosed and classified according to the classification of Marsh[29].

Furthermore, all patients also underwent serological studies: fasting gastrin levels were evaluated by means of a specific radioimmunoassay (RIA) using polyclonal antibody (No. 4562, kindly provided by Prof. J. Rehfeld, Copenhagen), which is able to detect the entire pool of molecular forms of gastrin, as described earlier (normal values $\leqslant$40 ng/L)[3]. Pepsinogen I levels were measured using a commercial RIA kit (Pepsik, Sorin, Saluggia, Italy), as previously reported (normal values 20-80 ng/mL)[3]. Antibodies against anti-parietal cells were assayed using a commercial kit (Autostat, Cogent Diagnostic Ltd, Edinburgh, UK), as previously described[3,4].

All patients gave written informed consent to the study, which was approved by the Local Ethics Committee.

Statistical methods

Artificial neural networks (ANNs) ANNs were applied to the data set from a structured questionnaire containing 22 clinical and biochemical items for each of the 350 patients (263 with ABG, 87 without ABG [controls], Table 1). The items with three or more levels were recoded in binary variables. The final data set was thus composed of 37 variables for each of the 350 patients, these being considered as independent variables (input). As dependent variable (output), we considered the presence or absence of diagnosis of ABG based on the histological examination of gastric biopsies obtained during gastroscopy. Endoscopic and histological data were not included in the data set.

Since the aim of our investigation was to study ANNs as a tool to recognize the presence of ABG on the basis of clinical and biochemical data, which in mathematical language is referred to as "classification problem", we applied the hetero-associated ANNs[19,20]. Thus, the samples of 350 patients were randomly subdivided several times into two equal and balanced sub-samples of patients with ABG and controls (random selection) as follows: one for the training phase (training) and one for the prediction phase (testing). During training phase, ANNs learn, on the basis of linear and non-linear relations existing between the variables of the data set, including the outcome variable, to perform the required classification, i.e., to correctly recognize the patients with ABG with respect to controls. ANNs were used with the following learning methods: (i) feed forward back propagation (BP)[30] e sine learning law (SP)[31]; (ii)

auto-recurrent (ARCR) and cluster recurrent (TASM)[32,33]. After several training cycles, the dependent variables (presence/absence of ABG) were excluded from the data set, and the ANNs showing the best performance during the training phase were applied to the second sub-sample of patients, not previously exposed to the network, whereby ensuring an unbiased testing phase during which the capability of trained ANNs to recognize patients with ABG with respect to controls was evaluated.

In order to reduce the number of input variables, selecting those most informative to predict the output, we used the "Training and Testing" (T&T) model, associated with the input selection (IS) system[34]. The T&T algorithm is a population of ANNs managed by an evolutionary system, in which a separate ANN represents a model of distribution of the complete data set in a training and a testing set. The score that each ANN reaches in the testing phase represents its goodness-of-fit and, consequently, its probability of evolution. The evolutionary algorithm called "Genetic Doping Algorithm" (GenD)[35], at each generation, combines the different hypotheses of distribution of each ANN according to the goodness-of-fit criterion. In this way, the best distribution of the entire data set, in a training set and in a testing set, is reached after a finite number of generations. The IS system becomes operative on a population of ANNs, each of them with the ability to select independent variables for the validation set. Each ANN learns from the training set, and is evaluated on the testing set[34]. Through the GenD evolutionary algorithm, different hypotheses of each ANN change over time, and generation after generation. When the evolutionary algorithm no longer improves, the process stops, and the best hypothesis of the input variables is selected and employed on the validation subset. The goodness-of-fit rule of GenD promotes, at each generation, the best testing performance with the minimal number of inputs[34].

All software used for the ANNs analysis, including the T&T model associated with the IS system, and the GenD have been developed and were applied by the Semeion Research Center, Rome, Italy[36].

Linear discriminant analysis (LDA) LDA was also used to analyze the predictive performance of conventional statistics. In order to optimize the predictive ability, different models were assessed and, as for the ANNs procedure, the samples were randomly divided into two sub-samples for the training and testing phases. For the analysis of LDA, the SAS version 6.04 (SAS Institute, Cary, NC, USA) using forward stepwise procedure was employed. This was performed by the Semeion Research Center, Rome, Italy. The application protocols of ANNs and LDA are schematically illustrated in Figure 1.

Study design

The first experiment was performed by random selection on the original database using all independent input variables. In the second experiment, the T&T algorithm, associated with the IS system, was applied using the independent input variables, which were reduced to the most informative ones.

The application of statistically-based decision supports, in clinical practice, should be simple and require little time for data entry. Thus, the number of inputs should be reduced to the bare minimum. Therefore, in order to verify the prediction capability of ANNs by using a reduced amount of input data, ANNs, in the third experiment, were performed using only the eight independent variables identified by LDA in the second experiment as having the most predictive power for the diagnosis of ABG. In the fourth experiment, the serological variables were removed from the eight independent variables used in the third experiment, thus verifying the prediction capability of ANNs and LDA for the presence of ABG by using only five clinical input variables. Finally, in the fifth experiment, only the serological variables were used. The study design is outlined in Figure 2.

RESULTS

Experiment 1

After random selection of patients, the ANNs training sets were used on a sub-sample of 175 patients (132 with ABG

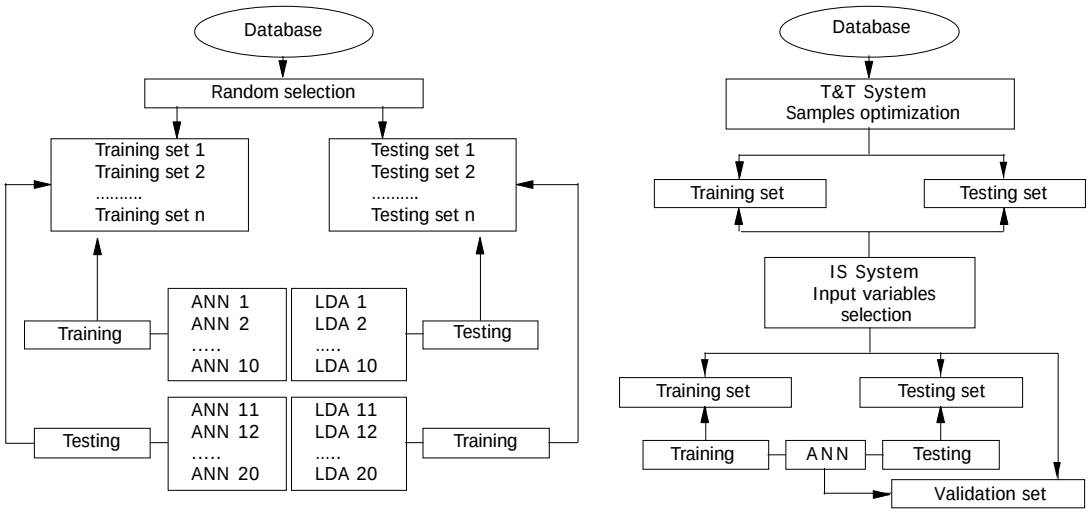

Figure 1 Application protocol of ANNs, LDA, T&T, and IS.

and 43 controls), and the ANNs tests were employed on the second sub-sample of 175 patients (131 with ABG and 44 controls) by using the original data set (37 independent variables). The best ANNs identified 128 of the 131 patients with ABG (sensitivity 97.7%), and correctly matched 42 of the 44 controls (specificity 95.5%), yielding an overall accuracy of 96.6%. The yield of LDA was slightly lower with a sensitivity of 95.4% (identifying 125 of the 131 patients with ABG), a specificity of 93.2% (recognizing 41 of the 44 controls), and the overall accuracy being 94.6% (Table 2).

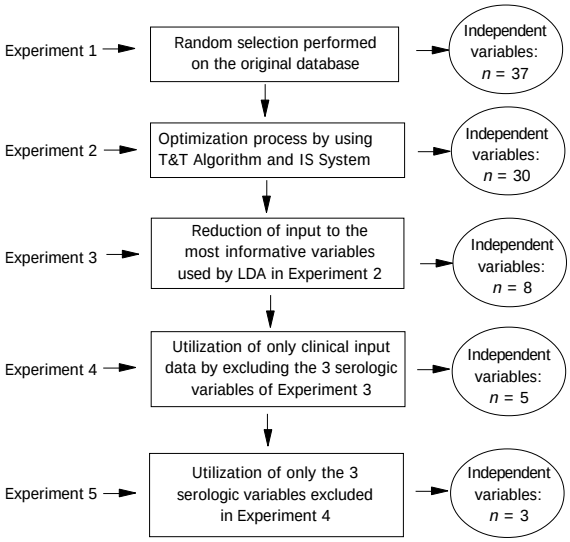

Figure 2 Study design: progressive reduction of independent input variables.

Experiment 2

The T&T algorithm, associated with the IS system, selected as the most informative 30 out of the 37 initial independent variables, removing the 7 variables such as mean corpuscular volume, absence of gastrointestinal symptoms, association with thyroid disease, family history for gastric ulcer, referred from the Department of Hematology, motility-like dyspepsia and hemoglobin was carried out.

The sub-samples of ANNs training, testing, and validation sets comprised 78, 60, and 125 patients with ABG, and 30, 17, and 40 controls, respectively. Following the optimization process, the performance of both the ANNs and the LDA increased with respect to the first experiment. In fact, on the validation set, ANNs' sensitivity rose to 98.4% (identifying 123 of the 125 patients with ABG) and specificity to 100% (correctly matching all 40 controls), thus yielding an overall accuracy of 98.8%. LDA recognized 119 of the 125 patients with ABG and failed to recognize only one out of the 40 controls, thus achieving a sensitivity, a specificity, and an overall accuracy of 96%, 97.5%, and 96.75%, respectively (Table 2).

Experiment 3

The eight independent variables used in this experiment are shown in Table 3. The performance of ANNs was good (overall accuracy 98.4%): only 4 out of the 125 patients with ABG (sensitivity 96.8%) were misclassified, but all 40 controls (specificity 100%) were correctly matched. The performance of LDA, which was the same as in the previous experiment, was slightly lower than that of ANNs (Table 2).

Table 1 Structured questionnaire containing anagraphic, anamnestic, clinical, and biochemical variables considered as independent variables (input)

Variables	Independent variables (input) levels
1. Sex (2)	Male; female
2. Age[1] yr	
3. Referred from the Department of… (5)	Hematology, gastroenterology, dermatology, endocrinology, other
4. Presentation symptom (5)	Anemia, GI symptoms/disorders, dermatological symptoms/disorders, endocrinological symptoms/disorders, other
5. Onset of presentation symptom (mo)	
6. GI symptoms (4)	Dyspepsia motility-like, dyspepsia ulcer-like, other GI symptoms, absence
7. Neurological symptoms (2)	Yes/no
8. Other symptoms (2)	Yes/no
9. Family history (1st degree relatives) autoimmune diseases (2)	Yes/no
10. Family history (1st degree relatives) for gastric neoplasms (2)	Yes/no
11. Family history (1st degree relatives) for duodenal ulcer or gastric ulcer (3)	No family history, family history for duodenal ulcer, family history for gastric ulcer
12. Association with thyroid disease (2)	Yes/no
13. Association with dermatological disease (2)	Yes/no
14. Association with neoplasms (2)	Yes/no
15. Association with duodenal ulcer or gastric ulcer (2)	Yes/no
16. Association with other diseases not mentioned previously (2)	Yes/no
17. Anemia (3)	No anemia, macrocytic (pernicious) anemia, microcytic (iron-deficiency) anemia
18. Hemoglobin[1]	
19. Mean corpuscular volume (MCV[1])	
20. Fasting gastrin[1]	
21. Pepsinogen I[1]	
22. Parietal cell antibodies (2)	Presence/absence

GI, gastrointestinal; ABG, atrophic body gastritis; [1]continuous variables. The number of levels of each variable is indicated in the brackets.

Table 2 Performance of ANNs and LDA for diagnosis of ABG

Experiments	ANNs			LDA		
	Accuracy (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	Sensitivity (%)	Specificity (%)
Experiment 1	96.6	97.7	95.5	94.6	95.4	93.2
Experiment 2	98.8	98.4	100	96.8	96.0	97.5
Experiment 3	98.4	96.8	100	96.8	96.0	97.5
Experiment 4	91.3	91.7	90.9	88.6	93.2	84.1
Experiment 5	97.7	95.4	100	94.5	94.9	94.2

Experiment 4

In this experiment, of the eight variables used in the previous experiment, the three serological variables, namely gastrin, pepsinogen I, and anti-parietal cell antibodies, were excluded. Using only the five clinical variables (Table 3), ANNs showed a sensitivity of 91.7% (121 of the 132 ABG patients identified), a specificity of 90.9% (40 of the 44 controls recognized), and an overall accuracy of 91.3%. On the other hand, LDA showed a sensitivity of 93.2% (123 of the 132 ABG patients identified), a specificity of 84.1% (37 of the 44 controls correctly matched), and an overall accuracy of 88.6% (Table 2).

Table 3 Independent variables identified by LDA as most predictive for the diagnosis of ABG with respective correlation coefficients

Independent variables	Correlation coefficients
Pepsinogen I[1]	0. 42
Gastrin[1]	–0.40
Age, yr	–0.37
Association with other diseases not previously mentioned[2]	0.35
Other (not gastrointestinal) symptoms[3]	0.34
Onset of presentation symptoms (mo)	0.25
Other gastrointestinal symptoms[4]	0.25
Antibodies against parietal cells[1]	0.23

[1]Serological variables; [2]represented in data set by cardiovascular diseases, diabetes type II and other causes of iron-deficiency anemia; [3]represented in data set by asthenia, fatigue, and headache; [4]represented in data set by diarrhea, abdominal pain, and bloating.

Experiment 5

In the final experiment, using only the three serological variables (gastrin, pepsinogen I, and anti-parietal cell antibodies), ANNs showed a sensitivity of 95.4%, a specificity of 100%, and an overall accuracy of 97.7%. LDA showed a sensitivity of 94.9%, a specificity of 94.2% and an overall accuracy of 94.5% (Table 2).

DISCUSSION

The results emerging from this pilot study suggest that advanced statistical methods, not only ANNs, but also LDA, are able to predict, with great accuracy, the presence of ABG using only clinical and serological variables. These methods may thus, after appropriate validation, be taken into consideration as potential clinical decision-support tools for identifying those patients with suspected ABG requiring gastroscopy with body mucosa biopsy sampling for the assessment of atrophy of the oxyntic mucosa. However, gastroscopy is an invasive and expensive procedure, which is often accepted with reluctance by patients without specific gastrointestinal symptoms or presenting with non-digestive disorders, such as thyroiditis, anemia or neurological symptoms. Furthermore, in this particular clinical setting, the cost-effectiveness of bioptic sampling during gastroscopy still needs to be determined[37]. Thus, a computer-based decision-support system, which is able to select with a high predictive accuracy, those patients with a high probability of having ABG, would enable the endoscopic/histologic investigation to be better addressed. Indeed, in the third experiment, the advanced statistical systems correctly identified all patients without ABG.

For the clinical applicability of computer-based decision support systems and their acceptance by physicians, it is necessary to offer a system, which is simple, with entry of data that requires little time, thus using a limited number of variables, which are readily available to the clinician. In the present study, we, therefore, progressively decreased the input variables in order to use less input data with a high predictive power for ABG. It is of interest that, despite the reduction in the number of input variables from the initial 37 to only 8, the accuracies of ANNs and LDA were still 98.4% and 96.8%, respectively. Surprisingly, the performance of ANN and LDA was still acceptable (91.3% and 88.6%, respectively) despite the reduction in the input variables to only five variables, readily available in the clinician's office by clinical history. However, four of these five clinical variables are non-specific, such as other gastrointestinal symptoms, namely diarrhea, abdominal pain and bloating, and other non-gastrointestinal symptoms, such as headache and asthenia. Thus, these findings need to be confirmed by a prospective study using these systems.

It was not surprising that of the most informative variables for the prediction of ABG, we find gastrin and pepsinogen I, which are parameters previously tested as serological screening tools for ABG[12-14]. In fact, in these studies, an overall accuracy of about 80% for the diagnosis of atrophic gastritis had already been obtained. The results of the present study support these findings: indeed, by using only the serological variables, gastrin and pepsinogen I together with parietal cell antibodies, the overall accuracy of ANNs was almost 98%. However, our study also shows that the accuracy of these serological markers for the identification of patients with suspected ABG may potentially be improved by almost 100%, associating them with a few clinical data and applying advanced statistical systems.

Albeit the clinical variables identified as those having the highest predictive power for the diagnosis of ABG were quite unexpected: age, onset of presentation symptoms, other gastrointestinal symptoms (diarrhea and bloating),

other non-gastrointestinal symptoms (headache, asthenia), and the association with other,not previously mentioned diseases(cardiovascular diseases and diabetes) . In general, the presence of a statistical relationship between a predictor variable and the outcome alone does not imply causality[38]. This is even more the case for ANN-based models, which process data in a non-linear way, and the network logic of prediction cannot be broken down into simple elements of clinical reasoning[17,18]. Thus, the variables with the most predictive power selected by the advanced statistical systems should not be viewed as independent predictive variables as perceived by a clinician[17,38].

However, these findings also show the crucial importance of coding variables during the setting up of a database to be used for advanced statistical analysis, which obviously affects the results of analyses. In fact, in our data set, three out of the five most informative variables were coded as cumulative variables (other gastrointestinal symptoms, other non-gastrointestinal symptoms, and association with other diseases not previously mentioned) and thus considered of little importance at the time of data collection. On the contrary, these five variables alone were able to distinguish between patients with and without ABG with an overall accuracy of approximately 90%. Thus, data sets for the use of advanced statistical methods need to be developed without considering a single data a priori as less important, but all available data should be entered in detail, since advanced statistical methods recognize complex linear and non-linear relationships, not valuable a priori[39].

It is of interest that, although a comparison of the two statistical approaches was not performed, ANNs somewhat outperformed LDA, but both technologies showed good predictive results. In fact, in 24 out of the 37 independent variables (64.9%), a non-linear relationship with the output (diagnosis of ABG) was observed, as shown by the values of the correlation coefficients, which were less than 0.06 (data not shown). However, the values of correlation coefficients of the remaining 13 independent variables ranged between 0.063 and 0.302, showing that these variables were, to some extent, related in a linear way to the output. This finding is in agreement with that of previous studies in which conventional statistical methods were compared to neural networks and no differences in overall predictive performance were observed[38,40,41]. However, it has been argued that performance improves merely by structuring information, making it difficult to assess how much improvement could be related to any specific statistical analysis[42].

However, the aim of the present study has been not to emphasize that advanced statistical decision support systems should replace or substitute experienced clinicians, but to stress that, in our opinion, these systems should be viewed as a potential decision aid, particularly in times of shortages of financial resources, in order to better address invasive investigations to save costs and to use resources when effectively necessary, as described in other fields of medical settings[43].

We are aware that the current study had some pitfalls, including the fact that external validation has not yet been carried out; in fact, our results need to be considered as preliminary and be validated in a prospective and large-population study. Secondly, these findings may not be generalized "tout-court" to the general population, since, in this pilot study, the frequency of ABG was higher than that of controls.

In conclusion, this preliminary study suggests that advanced statistical methods, not only ANNs, but also LDA, may contribute to better address bioptic sampling during gastroscopy in a subset of patients in whom ABG may be suspected on the basis of aspecific gastrointestinal symptoms or non-digestive disorders.

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