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An Easy Affordable Statistical and Economic (EASE) approach to avoid unnecessary and expensive exams to monitor patients with small AAA

Vezzoli Marika[1], Archetti Claudia[2], Bianchessi Nicola[3], Bonardelli Stefano[4], Garrafa Emirena[1*]

[1]Department of Molecular and Translational Medicine, University of Brescia, Brescia, 25123, Italy.
[2]IDS Department, ESSEC Business School in Paris, Paris, 95021 Cergy-Pontoise Cedex, France.
[3]Department of Informatics "Giovanni degli Antoni", University of Milan, Milan, 20133, Italy.
[4]Department of Clinical and Experimental Sciences, University of Brescia, Brescia, 25123, Italy.

ABSTRACT

Abdominal Aortic Aneurysm (AAA) is a localized enlargement of the abdominal aorta, such that the diameter exceeds 30 mm. AAA is a progressive growth leading to rupture, with high risk of mortality, therefore elective surgical repair is indicated when AAA diamenter is >55 mm. Screening programs, that use morphological imaging, have been developed internationally with the aim of detecting AAA before rupture with important limitations in term of cost and benefit for patients. Furthermore, different biochemical markers have been proposed to monitor AAA progression to overcome the above-mentioned limitations but none of them is used in the clinical practice. In fact, most of the biomarkers proposed are expensive and not feasible in the majority of laboratories. Combining different methodologies coming from Statistics and Operational Research fields, we developed an algorithm able to assess the importance of common biomarkers, requested in the clinical practice to evaluate the health of patient, and therefore no exams are required. Furthermore, we develop an Easy, Affordable Statistics and Economic (EASE) model able to identify if the AAA remain below the cut off for surgical repair. This prediction can provide guidance to how closely the patient's abdominal aorta should be monitored avoiding additional and expensive exams.

Keywords: Abdominal Aortic Aneurysm, EASE

***Correspondence to Author:**
Emirena Garrafa
Department of Molecular and Translational Medicine, University of Brescia, Brescia, 25123, Italy.

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Introduction

Abdominal Aortic Aneurysm (AAA), a dilatation that exceed 30 mm of the distal aorta, is among the 10 leading causes of death for people aged 60-84 years in industrialized countries [1]. It is considered a life-threating condition since the ultimate complication of AAA is rupture of the aneurysm [2; 3], with an approximate overall mortality rate of at least 80% [1]. Depending on their diameter, AAA are classified as Small (< 45 mm), Medium (45 mm $\leq$ diameter $<$ 55 mm) and Large (≥ 55 mm) [4; 5].

International screening programs that recommend conservative management and imaging surveillance of Small AAA have been developed. Lack of established prognostic indexes or drug treatment make repeating imaging necessary to monitor [6] vessel dilatation that is often progressive in patients that are usually asymptomatic. In fact, timely elective AAA repair is currently the only available effective therapy and is related to AAA diameter [7; 1].

When AAA are diagnosticated and result < 55 mm, survey program provides the execution of an ultrasound or a TAC; in detail, every 2 years in case of Small AAA and every 6-12 months in case of Medium AAA. Surveillance continues until aortic diameter increases (≥ 55 mm), at which point surgical intervention is usually undertaken, since risk of rupture outweighs preoperative risks for the majority of patients [8; 6; 1]. In patients with a not yet surgical AAA, there are no clear predictors of a fast or slow progression, and the best interval between an imaging check and the next step is not defined with important consequences in terms of risk for patients and cost-effectiveness [8]. Furthermore, the use of morphologic imaging as a stand-alone approach to diagnose and provide prognostic information regarding AAA, has a number of limitations: imaging may not always be visible as variations in patient characteristics (obesity, renal impairment etc) and, more importantly, imaging assessments do not provide complete data to identify which AAA will remain below the cut-off of 55 mm [3; 9]. This oblige patients to undergo unnecessary imaging exams, that require waiting time, specialized staff to perform and evaluate the results together with important cost for sanitary service and indirect cost on life of patients [3; 9; 10].

Many authors have investigated the role of biochemical markers able to follow AAA progression and that potentially could help in triaging patients in order to discriminate those who should undergo rapid imaging to allow a prompt initiation of treatment [11; 12; 13]. Most of the molecules studied are molecules potentially involved in mechanism that could be critical in AAA formation and progression. Most of them may be expressed within diseased tissues, even if those that can be detected within body fluids, such as serum and plasma, are highly desirable, for diagnostic, prognostic and monitoring purpose, due to relative ease of sample collection. Between the most studied markers of thrombosis, such as inflammatory markers, and selected proteolytic enzymes, conflicting results often emerge [14; 15; 7]. Furthermore, most of the markers analyzed are sophisticated and their detection requires complex and expensive analyzers, specialized staff, while other markers are easier to detect and often part of a routine required by the medical service to assess patient's health [14; 16; 17]. Some of these biomarkers have been used to build or integrate previous mathematical models able to predict risk of rupture of AAA [18; 19]. Nevertheless, in the clinical practice none of the models proposed by the literature is used probably because a focused hypothesis-led approach may miss important molecular changes if such molecules are not a direct target of the investigation.

The combination of different methodologies coming from the field of Statistic and Operational Research through the development of increasingly powerful technologies permit the simultaneous analysis of thousands of candidates from a single biological specimen could bypass this shortfall. By using these approaches, the likelihood of identifying key physiological changes is supposed to greatly increased. For this reason,

we combine different statistic and operational research approaches in order to assess the importance of biomarkers requested in the clinical practice to evaluate the health of patients, and therefore do not require additional exams.

We select the biomarkers using an innovative algorithm and build an Easy, Affordable Statistical and Economic (EASE) mathematical model able to define if the AAA remain below the cut off for surgical repair. This is very important since if AAA is < 55 mm, the patients can cease with unnecessary exams with benefit for health care system and patients itself. In the first part of our analysis, we combine non-parametric methods and machine learning techniques, such as Variable Importance Measures (VIM) extracted from Random Forest (RM), to select key biochemical marker(s). Afterwards, we build a classification tree through an approach based on the sequential solution of Linear Programming (LP) models that identify combinations of molecules and threshold values. The resulting tree is then transformed into an easy tool, the EASE score, which provides an immediate answer given the values of the identified molecules.

With the EASE score we were able to identify 79% of patients with Small/Medium AAA that do not turn into Large, avoiding unnecessary and expensive exams.

Materials and Methods

Patients and specimens

Among the 700 consecutive male patients who were enrolled between 2017-2019 for the study admitted to the Vascular Surgery Unit of Brescia University “Spedali Civili” hospital in Brescia, Northern Italy, 37 (5.3%) were rejected because had recent infections, fever, or traumas, inflammatory aneurysm based on CT findings, symptomatic or ruptured aneurysm, inflammatory or infectious aneurysm, or anastomotic pseudoaneurysm and malignant disease. We obtain a consecutive sample of 423 male Caucasian patients (mean age 72.6$\pm$ 7.68; median age 72) admitted to the Vascular Surgery Unit of Brescia University “Spedali Civili” hospital in Brescia, Northern Italy, for AAA resection.

Based on CT findings, we found that 39 out of the 423 patients selected for the study, were classified as having a Small AAA (diameter <45 mm), 202 as Medium (45 mm $\leq$diameter <55 mm) and 182 as Large (diameter $\geq$ 55 mm). Since the number of Small aneurisms were unbalanced with respect the others, we join the categories Small and Medium in a unique group that we renamed “S/M” for a total of 241 patients.

The study is conformed to the ethical guidelines of the “World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects” adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, and revised in Tokyo in 2004. Institutional ethic committees approved the study, and all patients provided a written informed consent (Ethics Committee of ASST Spedali Civili di Brescia, approval reference number: 1353) [7]. Participants did not receive any form of financial compensation.

As mentioned above, these patients performed numerous blood tests, and for some of them a maximum of 77 biomarkers were collected. To obtain a homogeneous sample, from our data we selected those biomarkers with less than 55% of missing values obtaining a data matrix with 423 man for 55 biomarkers.

Since we deal with a consistent sample, we decided to split the data in two subsets: the first containing 90% of subjects for training the classificator proposed in our analysis and the remaining fresh data for testing the accuracy of the output obtained.

We compute the percentage of diameters classified as S/M or L ($\cong 57\%$ and $\cong 43\%$, respectively), then we sample 90% of the data stratifying for the dichotomized diameter. Hence, we obtained a training set of 381 patients that reflected the same percentage of S/M and L diameter: 217 (57%) and 164 (43%) patients, respectively. The same holds for the test set: S/M=24 patients (57%) versus L=18 patients (43%).

Blood collection and laboratory measurements

Venous blood samples were obtained from fasting overnight patients via an anticubital vein puncture without venous stasis before AAA resection (no longer than one month from imaging and resection). Commercially available assays were used according to manufacturer's instruction on instruments calibrated against appropriate proprietary reference standard material and verified by using the registered quality controls [7].

Statistical approach

We applied a new combination of different methods to test and prove the connection and interrelationship among the many faces of a complex pathological state to discover missing pieces in the current knowledge. The different approaches that we merged come from different fields, namely, statistics (with non-parametric and machine learning methods) and operational research. The choice of combining methodologies coming from different disciplines is due to the complexity of the problem and the variety of the dataset. This allowed us, on one side, to deal with complex data (as in our case) such as outliers, missing values, extremely asymmetric variables (positive and negative) and, on the other side, to use optimization when determining the best predictive molecules and their interrelations.

Non-parametric method

Since biomarkers have a not-normal distribution (data not shown but available upon request), for understanding if one of them is able to discriminate whether a patient can be classified as having S/M or L AAA, we use a well-known non-parametric test like the Wilcoxon Rank Sum test with a significance level of 0.05.

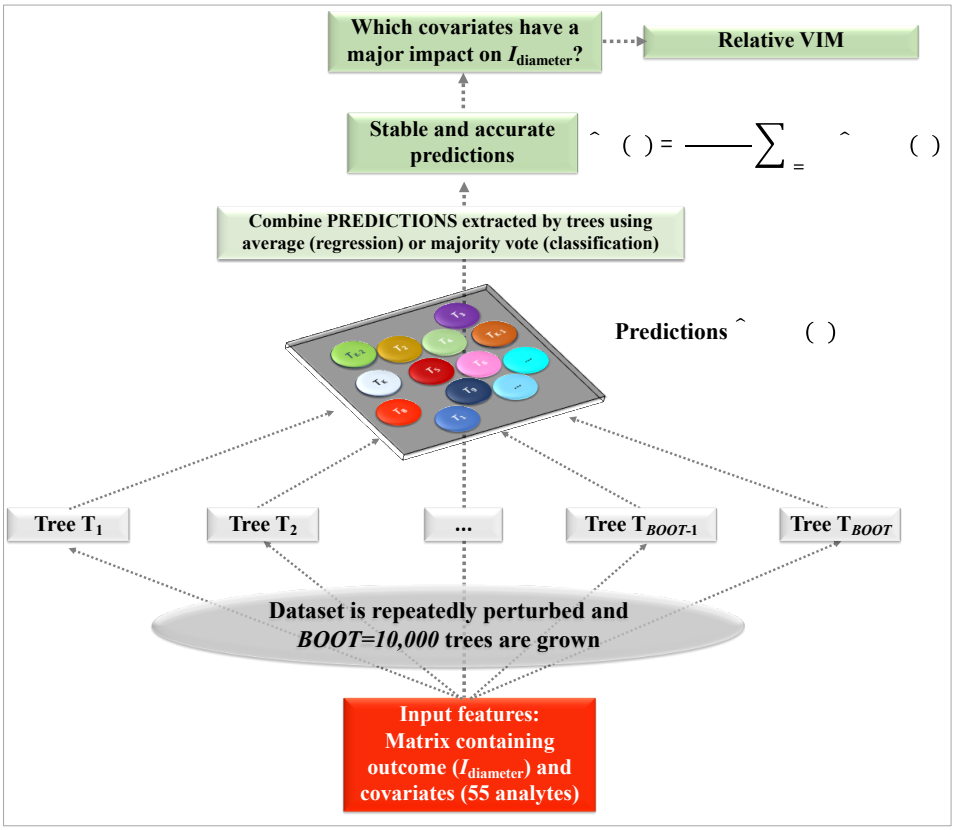

Figure 4: How ensemble methods (e.g. Random Forest) work

This figure summarizes the functioning of the ensemble method and can be read from the bottom up.

In case of Random Forest, used in this study for extracting the relative VIM jointly with the Wilcoxon test, starting from the matrix containing outcomes and covariates, the training set is repeatedly perturbed (10,000 bootstrap samples). On each perturbed set, a single regression tree (weak learner) is grown selecting only a limited number ($\sqrt{55}$) of covariates at each split. Its performance is measured on a test set not used in the training procedure, called Out of Bag (OOB). From each tree, the algorithm extracts the predictions and combines them (average in case of regression or majority vote in case of classification) in order to generate a stable and accurate predictor.

Machine learning

To identify biomarkers that most impact on the prediction of AAA dimensions, we use machine learning techniques. In detail, we use ensemble method where the weak learner is the regression tree [33]. In fact, as suggested in [20], when the outcome is dichotomic, you can use regression instead of classification.

Ensemble methods [20], and in particular Random Forest [34] technique used in this paper, are an extension of trees, combines the predictions obtained from many regression trees grown on perturbed versions of the dataset. RF deals with the missing values by means of *imputation on the fly* algorithm. The algorithm below quickly explains how Random Forest works, providing details on parameters setting. Moreover, Figure 4 syntheses the idea under the perturbation and combination method. The prediction error of Random Forest is measured with the Out-Of-Bag procedure which is the mean prediction error on each training sample, x_i, based on trees that do not contain x_i in their bootstrap sample.

From Random Forest we extracted a variable importance measure, called Mean Decrease in Accuracy (MDA), which identified the covariates that most impact on the prediction of the response variable (AAA dimension). This measure is relativized respect its maximum. Hence, the most important variable has a VIM=100 and to the remaining covariates a decreasing value is assigned. Using this procedure, we selected analytes with a VIM>57, since this threshold is closed to 60, as suggested in [22].

All the statistical analyses were performed with R 4.0.

Random Forest Algorithm – Regression

Set parameters

N=423 # number of observations in the dataset

X=data matrix with 423 patients for $r = \{1, \dots, R\}$ columns, where *R*=55 analytes in our dataset

BOOT=10,000 #number of replications (10,000)

n_{min}=10% of observation=0.1*423≅ 42 # minimum node size (fourty-two subjects)

#number of variables selected by the algorithm at each node of the tree

r AAA $\Rightarrow I_{diameter} = \begin{bmatrix} 1 \text{ if diameter } \geq 55 \text{ mm} \Rightarrow \text{L} \\ 0 \text{ otherwise (diameter} < 45 \text{ mm} \Rightarrow \text{S/M)} \end{bmatrix}$

For *i*=1 to *BOOT* {

(a) Draw a bootstrap sample, called $boot_i$, of size *N* from the dataset

(b) Grow a regression tree T_{boot_i} $(Y \sim X)$ to the bootstrapped data, by recursively repeating the following steps for each node of the tree, until the minimum node size n_{min} is reached:

(*i*) Select *g* variables at random from the *r* covariates

(*ii*) Take the best split/variable among the *g* variables available

(*iii*) Split the node in two child nodes.

Each T_{boot_i} produces a vector of predictions $\hat{f}_{rf_{boot_i}}(x)$ validated Out-Of-Bag (OOB), namely on observations not used in the training step}

From the ensemble of trees, the prediction at a new point *x* is:

$$\hat{f}_{rf}^{B}(x) = \frac{1}{BOOT}\sum_{i=1}^{BOOT} \hat{f}_{rf_{boot_i}}(x)$$

Score

EASE-Score is a simple and easy tool which enables to immediately know the classification of the AAA (S/M or L) given the value of the molecules identified by the two non-parametric approaches used in this study. Specifically, once executed the blood tests on a patient, the molecule values are inserted in the score which provides the classification. The EASE score was developed as an Excel-file based macro and it is available upon request (Figure 3.A and 3.B reports report the interface of the score and an example of classification computed on a real patient of our sample, respectively). Missing values are not recommended but, just in case of an omitted value, the macro automatically imputes

the median value of the missing analyte computed on the original dataset.

The EASE Score is programmed starting from a Linear Programming (LP)-based tree where the outcome is the $I_{diameter}$ and covariates are the analytes previously identified. It is inspired by classification trees since, at each interaction, it splits subjects in two subsets [33]. Unlike the classification tree, it identifies splits, thresholds and, consequently, final nodes using a completely innovative approach based on sequentially solving linear programming models [35; 36]. Relative to well-known decision tree (that generates a local optimum since the final partition is conditioned from the rules of thumb at each node), the resulting partition represents a global optimum, since all the splitting variables and corresponding thresholds, induce the best path from the treetop to the final nodes, where patients, classified respect the most representative class in the node, fall. Moreover, the running time of the LP-based tree is very long; for this reason, the first step that select most important covariates (reducing the dataset dimension) is of primary importance. Here follows a brief description of how LP-based tree works.

Consider two disjoint sets S_1 and S_2 that we wish to discriminate, with $|S_1|= n_1$ and $|S_2|= n_2$.The available training values for sets S_1 and S_2 are represented as matrices A_1 and A_2 of dimension $n_1 \cdot r$ and $n_2 \cdot r$, respectively, where r is the number of variables involved in the analysis. Let w be an r-dimensional weight vector in R^r, and γ be a real number. We would like to identify a separating plane $x^T \cdot w = \gamma$ in the attribute space of the examples, where x^T is the transpose of x. Ideally, such a plane would be such that all the points of A_1 lie on one side of the plane and all the points of A_2 lie on the other. This is in general not possible to achieve. Thus, in [35], the author proposes to minimize the average distance between the plane and the misclassified points. This results in optimizing the following linear programming problem:

$$\min_{w,t,z}\left\{\frac{et}{n_1}+\frac{ez}{n_2}|t \geq -A_1 \cdot w + e \cdot \gamma + e, z \geq A_2 \cdot w - e \cdot \gamma + e, t \geq 0, z \geq 0\right\} \quad (1)$$

where t and z are variables measuring the distance between the plane and the misclassified points and e is the identity vector.

For each node in the tree, the best split (w^*, γ^*) of the points reaching that node is found by solving (1). The node is then split into two branches. In the first branch a node is defined for the points $a_i \in A_1 \cup A_2$ such that $a_i \cdot w^* \leq e \cdot \gamma^*$, while points $a_i \in A_1 \cup A_2$ such that $a_i \cdot w^* > e \cdot \gamma^*$ are associated with the node of the second branch. The procedure is recursively applied until there are mostly points of one class at the node or there are too few points at the node. The node is classified by means of the majority vote (indirectly we compute the node mode). The procedure is also adapted to the case where at most k attributes (where $k<<r$) are chosen in (1) by imposing an additional inequality in each LP model.

In this study on AAA classification, starting from the training set of 381 patients for 7 variables ($I_{diameter}$ (outcome) + 6 biomarkers selected by Wilcoxon-test and Random Forest), S_1 corresponds to the set of patients with a S/M AAA, where $n_{S/M}$=217 (57%), while S_2 corresponds to set of patients with a L AAA, where n_L=164 (43%). LP-based trees are then built following the procedure described above.

Two options are proposed. The first one shows the tree obtained in the special case where only one biomarker is considered in the inequalities shown in (1). Graphically, it recalls the classic decision tree where grey branches reported splitting variables and corresponding threshold, and final nodes (grey ovals) contains the classification for each subject fallen inside them. The second option contains the LP-based tree where, for each node, a linear combination of biomarkers is chosen. In this case, the graphical representation of a single tree is completely lost but the ability of detecting S/M AAA out of sample increases. In fact, since the aim of our study is to detect the AAA progression, for each LP-tree we evaluated the specificity and

corresponding 90% Confidence Interval (CI) computed with 10000 stratified bootstrap replicates.

Concluding, we focused our attention on the second LP tree, programming our EASE score from it.

Results

Patients and specimens

We selected a consecutive sample of 423 male Caucasian patients (mean age 72.6±, 7.68 median 72) admitted to the Vascular Surgery Unit of Brescia University "Spedali Civili" hospital in Brescia, Northern Italy, for AAA resection. This sample is the result of a selection from a bigger cohort where patients have performed a CT angiography to classify AAA as Small (S), Medium (M) or Large (L) within one month before or after blood tests. Due the exiguous number of S AAA (39 patients), we dichotomized the diameter in S/M (249 patients, namely 57%) and L (182 patients, namely 43%). Furthermore, depending on the patients, laboratory data were different since, for some of them consisted of 77 biomarkers, for others were collected a smaller number of analytes. To overcome this limitation, we selected only biomarkers with less than 55% of missing values. The result is a data matrix with 423 man for 55 biomarkers. First, using two non-parametric methods (Wilcoxon test and Relative VIM for Random Forest) we selected a limited number of analytes. Then, using 90% of the sample (training set with 381 patients) we trained a Linear Programming based tree obtaining a AAA classificator and validating it on the remaining 10% of patients (42 subjects). Obviously, the training set reflects the percentage of S/M and L AAA of the entire sample. In Table 1 are reported the 55 biomarkers used in our analyses (in alphabetical order) together with normal range values, descriptive statistics (mean ± SD, median, min-max) and number (%) of missing values. Table 2 reports descriptive statistics on the diameter (entire sample or stratified for S, M, S/M, and L).

Table 1: Descriptive statistics on 55 analytes (in alphabetical order) considering the entire sample of 423 patients

Analytes (Variables, Biomarkers, test)	Normal range values	Media ± SD *GeoMean with Boot interval	Median	Range (min-max)	Missing values *n* (%)
A/G	1.08 – 1.86	1.21 ± 0.21	1.19	0.64 - 1.84	14 (3.31%)
Albumin	3.4 – 4.6 g/dL	3.89 ± 0.35	3.93	2.19 - 4.69	14 (3.31%)
Albumin %	55.80 – 66.10 %	54.46 ± 4.32	54.40	39.10 - 64.80	14 (3.31%)
Alfa 1	0.15 – 0.4 g/dL	0.18 ± 0.07	0.18	0.08 - 1.34	14 (3.31%)
Alfa 1 %	1.0 – 3.0 %	2.56 ± 0.76	2.50	1.10 - 7.90	14 (3.31%)
Alfa 2	0.45 – 1.0 g/dL	0.93 ± 0.17	0.91	0.25 - 1.60	14 (3.31%)
Alfa 2 %	9.5 – 14.4 %	13.01 ± 2.10	12.80	6.30 - 23.40	14 (3.31%)
ALP	40 – 129 U/L	80.94 ± 36.09	75.00	24.00 - 453.00	11 (2.60%)
ALT	5.0 – 50 U/L	26.57 ± 14.95	23.00	7.00 – 163.00	0 (0.00%)
APTT (sec)	24 – 38 sec	31.57 ± 8.57	30.50	0.19 - 178.10	14 (3.31%)
APTT ratio	0.7 – 1.28	1.06 ± 0.57	1.00	0.41 - 11.04	14 (3.31%)
AST	5.0 - 50 U/L	19.74 ± 19.59	17.00	3.00 – 283.00	1 (0.24%)
Basophilis	0 – 0.20 $\times 10^3/\mu L$	0.04 ± 0.03	0.04	0.00 - 0.17	119 (28.13%)
Basophilis %	0 – 1.5 %	0.61 ± 0.33	0.55	0.00 – 3.20	119 (28.13%)
Beta	0.55 – 1.10 g/dL	1.05 ± 0.17	1.05	0.52 - 1.76	14 (3.31%)
Beta %	8.6 – 15.6 %	14.66 ± 1.78	14.60	10.10 - 23.80	14 (3.31%)
Calcium	8.6 – 10.6 mmol/L	9.08 ± 0.55	9.10	3.00 – 10.36	8 (1.89%)

Analytes (Variables, Biomarkers, test)	Normal range values	Media ± SD *GeoMean with Boot interval	Median	Range (min-max)	Missing values *n* (%)
Cholesterol	120 – 200 mg/dL	175.50 ± 40.95	173.00	74.00 - 322.00	2 (0.47%)
Cholinesterase (CHE)	6400 – 15500 U/L	11,100.35 ± 3198.62	11,274.00	144.00 – 21,375	33 (7.80%)
CK	20 – 170 U/L	87.10 (81.57 - 92.89)*	82.00	13.00 - 13201.00	7 (1.65%)
Cloryte	95 – 110 mmol/L	104.90 ± 5.68	105.00	8.67 - 116.00	7 (1.65%)
Creatinine	0.5 – 1.2 mg/dL	1.18 ± 0.89	0.99	0.55 – 9.85	0 (0.00%)
Eosinophilis	0 – 0.80 $\times 10^3/\mu L$	0.29 ± 1.26	0.17	0.00 – 22-00	119 (28.13%)
Eosinophilis %	0 – 8 %	2.99 ± 2.23	2.50	0.00 – 15.10	119 (28.13%)
ESR	< 20 mm/h	14.96 ± 13.79	11.00	2.00 – 83.00	32 (7.57%)
Fibrinogen	170 – 410 mg/dL	341.51 ± 84.67	325.00	105 - 856	50 (11.82%)
Gamma %	10.7 – 20.3 %	15.29 ± 3.55	14.90	4.60 - 33.50	14 (3.31%)
GGT	5.0 – 50 U/L	43.33 ± 52.96	31.00	5.00 - 767.00	3 (0.71%)
Glucose	70 – 100 mg/dL	104.00 ± 25.15	98.00	60.00 – 294.00	2 (0.47%)
Hematocrite (Hct)	42 – 52 %	43.12 ± 18.10	42.70	24.30 - 401.00	0 (0.00%)
Hemoglobin (Hgb)	14 – 18 g/dL	14.11 ± 1.65	14.30	7.60 – 18.60	0 (0.00%)
INR	0.2 – 1.2	1.11 ± 0.36	1.00	0.80 - 4.20	11 (2.60%)
LDH	125 – 220 U/L	177.82 ± 42.97	171.00	41.00 - 403.00	9 (2.13%)
Linphocytes	0.9 – 4.0 $\times 10^3/\mu L$	1.83 ± 0.70	1.77	0.54 - 8.11	119 (28.13%)
Linphocytes %	20 – 45 %	25.25 ± 7.80	24.50	6.60 - 61.20	119 (28.13%)
MCH	27 – 31 pg	31.00 ± 2.21	31.20	18.10 – 37.00	0 (0.00%)
MCHC	32 – 37 g/dL	33.30 ± 1.64	33.40	3.70 – 35.50	0 (0.00%)
MCV	82 – 94 fL	92.83 ± 5.70	93.10	61.80 - 106.90	0 (0.00%)
Monocyte	0.2 – 1.0 $\times 10^3/\mu L$	0.63 ± 0.19	0.59	0.12 - 1.26	119 (28.13%)
Monocytes %	3.4 – 9 %	8.59 ± 1.99	8.40	1.30 - 15.20	119 (28.13%)
Neutrophils	1.50 – 8 $\times 10^3/\mu L$	4.68 ± 1.67	4.39	1.96 - 12.48	119 (28.13%)
Neutrophils %	40 – 74 %	62.55 ± 8.89	63.25	29.40 - 91.30	119 (28.13%)
Phosphorous	2.7 – 4.5 mmol/L	3.26 ± 10.17	2.70	1.00 – 209.00	10 (2.36%)
Platets (PTL)	130 – 400 $\times 10^3$ U/L	193.30 ± 57.40	188.00	11.00 – 449.00	0 (0.00%)
Potassium	3.5 – 5 mmol/L	4.39 ± 5.08	4.10	2.80 – 108.00	3 (0.71%)
PT (seconds)	9.5 – 13.5 seconds	12.65 ± 6.43	11.30	9.30 - 109.00	13 (3.07%)
PT %	80 – 120%	98.28 ± 22.07	103.00	14.00 - 151.00	13 (3.07%)
RDW	12.0 – 17.0 %	14.44 ± 1.43	14.20	12.10 - 26.40	0 (0.00%)

Analytes (Variables, Biomarkers, test)	Normal range values	Media ± SD *GeoMean with Boot interval	Median	Range (min-max)	Missing values *n* (%)
Red blood cell count (RBC)	4.5 – 5.5 ×10^6/µL	4.57 ± 0.56	4.60	2.55 - 6.55	0 (0.00%)
Sodium	135 – 145 mmol/L	141.00 ± 7.09	141.00	3.80 – 149.00	2 (0.47%)
Total Bilirubin	0.30 – 1.20 mg/dL	0.78 ± 1.87	0.60	0.21 – 38.00	5 (1.18%)
Total protein	6.0 – 8.0 g/dL	7.13 ± 0.65	7.20	0.79 – 9.40	13 (3.07%)
Tryglicerides	< 150 mg/dL	129.24 ± 68.89	111.00	34.00 - 467.00	2 (0.47%)
Uric acid	3.4 – 7 mg/dL	5.47 ± 1.41	5.30	2.09 – 11.90	3 (0.71%)
White blood cell (WBC)	4.00 – 10.80 ×10^3/µL	7.39 ± 2.05	7.05	3.15 - 16.68	0 (0.00%)

Table 2: Descriptive statistics on AAA diameter: entire sample (S+M+L) and stratified respect S, M, S/M, and L

Diameter	Entire sample (S+M+L) N=423	S (n_S=39)	M (n_M=202)	S/M ($n_{S/M}$=241)	L (n_L= 182)
Mean ± sd	55.18 ± 10.26	38.95 ± 4.39	50.71 ± 2.54	48.81 ± 5.22	63.61 ± 9.17
Median	53.80	40.00	51.00	50.00	60.00
Min-Max	28.00-106.00	28.00 – 44.00	45 - 54.50	28 - 54.50	55.00 – 106.00

**Denotes variables not normally distributed (Shapiro test>0.05). Data shown upon request. In third column, in bold and italics Wilcoxon p-values $\leq$ 0.05. In fourth column, in bold VIM values >57.

Statistical analysis

In this research we merged approaches coming from different fields, namely, statistics (non-parametric and machine learning methods) and operational research (Linear Programming -LP-models). The choice of combining methodologies coming from different disciplines is due to the complexity of the problem and the typology of the dataset. On one side, the use of machine learning allowed us to deal with complex data non-normally distributed, containing outliers, high percentages of missing values, and with multicollinearity problems (data shown upon request). On the other side, by means of the LP-based model, we determine the interrelations between the best predictive molecules identified by the machine learning approach.

Table 3: Descriptive statistics on each analyte stratified for AAA diameter (S/M vs L) and relative VIM
Variables are ordered respect the relative VIM extracted from the Random Forest (values in the last column), from the most (CK, VIM=100) to the less important variable (Basophilis %, VIM=31.21).
The table has a grey background in correspondence of the 6 analytes (CK, ALT, MCV, Hemoglobin (Hgb), RDW, Hematocrite (Hct)) jointly selected by the Wilcoxon test and the relative VIM.

Analytes (Variables, Biomarkers, covariates)	Analytes (Variables, Biomarkers, covariates)	Diameter ≥ 55 (L) nL=182	p-value	Relative VIM
CK (20-170 U/L)**				
Mean ± SD	109.64 ± 102.97	181.99 ± 984.58		**100**
Median	85	77	0.0341	
Min - Max	13 – 1061	23 - 13201		
ALT (5-50 U/L)**				
Mean ± SD	26.81 ± 12.67	26.24 ± 17.56		96.43
Median	24.00	21.50	0.0089	
Min - Max	8 - 123	7 - 163		
Plates (PTL) (130-400 × 103 U/L)**				86.54
Mean ± SD	189.91 ± 54.30	197.85 ± 61.24		

Median **Min - Max**	188.00 78 - 420	188.50 11 - 449	0.3625	
Cholinesterase (CHE) (6400-15500 U/L)** **Mean ± SD** **Median** **Min - Max**	11287.03 ± 2967.11 11274.00 144 - 20363	10884.63 ± 3198.03 11133.00 1224 - 21375	0.1538	78.86
Glucose (70-100 mg/dL)** **Mean ± SD** **Median** **Min - Max**	104.76 ± 25.29 98.00 67 - 294	102.91 ± 24.86 97.00 60 - 220	0.3346	78.25
Calcium (8.6-10.6 mmol/L)** **Mean ± SD** **Median** **Min - Max**	9.10 ± 0.60 9.10 3.00 - 10.36	9.07 ± 0.47 9.05 7.40 - 10.31	0.2190	77.83
Gamma % (10.7-20.3%)** **Mean ± SD** **Median** **Min - Max**	15.05 ± 3.21 14.80 7.30 - 27.40	15.57 ± 3.81 15.10 4.60 - 33.50	0.0669	66.04
Total Protein (6.0-8.0 g/dL)** **Mean ± SD** **Median** **Min - Max**	7.12 ± 0.54 7.20 4.00 - 8.50	7.14 ± 0.75 7.20 0.79 - 9.40	0.837	
LDH (125-220 U/L)** **Mean ± SD** **Median** **Min - Max**	173.61 ± 38.85 171.00 41 - 397	183.05 ± 46.51 172.50 91 - 403	0.1236	63.20
MCV (82-94 fl)** **Mean ± SD** **Median** **Min - Max**	93.40 ± 5.71 94.00 65.30 - 106.90	92.09 ± 5.64 92.65 61.80 - 104.60	0.0044	59.02
Hemoglobin (Hgb) (14-18 g/dl)** **Mean ± SD** **Median** **Min - Max**	14.31 ± 1.59 14.50 8.20 - 18.6	13.83 ± 1.70 14.10 7.60 - 18.0	0.0042	58.22
RDW (12-17%)** **Mean ± SD** **Median** **Min - Max**	14.28 ± 1.41 14.00 12.10 - 26.40	14.64 ± 1.44 14.30 12.40 - 21.00	0.0020	57.74
Hematocrite (Hct) (42-52%)** **Mean ± SD** **Median** **Min - Max**	42.84 ± 4.73 43.10 24.30 - 55.90	43.50 ± 27.12 42.40 25.80 - 401.00	0.0189	57.40
Red blood cell count (RBC) (4.5-5.5 × 106/L)** **Mean ± SD** **Median** **Min - Max**	4.60 ± 0.56 4.63 2.55 - 6.55	4.52 ± 0.56 4.56 2.93 - 6.29	0.1955	56.06
Albumin (3.4-4.6 g/dL)** **Mean ± SD** **Median** **Min – Max**	3.90 ± 0.35 3.93 2.19 – 4.69	3.88 ± 0.34 3.91 2.68 – 4.67	0.3425	56.02
PT (9.5-13.5 seconds)** **Mean ± SD** **Median** **Min - Max**	12.56 ± 7.37 11.20 9.30 - 109.00	12.67 ± 4.63 11.45 9.70 - 41.70	0.0013	55.56
Cholesterol (120-200 mg/dL)** **Mean ± SD** **Median** **Min - Max**	179.02 ± 41.54 177.00 92 - 322	170.84 ± 39.56 169.50 74 - 314	0.0636	54.78
MCH (27-31 pg)**				

Mean ± SD **Median** **Min - Max**	31.23 ± 2.23 31.30 20.20 - 37.00	30.69 ± 2.17 30.75 18.10 - 35.60	0.0034	54.26
White blood cell (WBC) (4.0-10.8 × 103/l) **Mean ± SD** **Median** **Min - Max**	7.36 ± 2.13 7.08 3.15 - 16.68	7.43 ± 1.96 7.02 3.67 - 14.80	0.6376	54.19
GGT (5.0-50 U/L)** **Mean ± SD** **Median** **Min - Max**	44.02 ± 58.30 31 5 - 767	42.21 ± 44.56 30 9 - 377	0.3761	53.43
ALP (40-129 U/L)** **Mean ± SD** **Median** **Min - Max**	77.98 ± 31.32 71 24 - 331	77.98 ± 31.32 71 24 - 331	0.0251	52.84
PT % (80-120%)** **Mean ± SD** **Median** **Min - Max**	100.06 ± 21.96 104 14 - 151	96.25 ± 21.32 100 18 - 137	0.0027	52.77
Albumin % (55.80-66.10%)** **Mean ± SD** **Median** **Min - Max**	54.70 ± 4.06 54.60 39.10 - 64.50	54.14 ± 4.48 54.25 39.80 - 64.80	0.1348	51.90
Uric acid (3.4-7 mg/dL)** **Mean ± SD** **Median** **Min - Max**	5.43 ± 1.39 5.30 2.30 - 11.90	5.52 ± 1.42 5.40 2.09 - 10.40	0.5175	51.60
Tryglicerides (<150 mg/dL)** **Mean ± SD** **Median** **Min - Max**	130.86 ± 73.63 115.00 34 - 467	126.90 ± 61.80 105.50 38 - 356	0.8841	49.64
Alfa 1 (0.15-0.40 g/dL)** **Mean ± SD** **Median** **Min - Max**	0.18 ± 0.04 0.17 0.08 - 0.36	0.20 ± 0.10 0.18 0.09 - 1.34	0.0006	49.20
AST (5.0-50 U/L)** **Mean ± SD** **Median** **Min - Max**	19.48 ± 14.63 17 6 - 196	20.08 ± 24.66 16 3 - 283	0.0481	49.01
Potassium (3.5-5.0 mmol/L)** **Mean ± SD** **Median** **Min - Max**	4.57 ± 6.70 4.10 2.80 - 108.00	4.15 ± 0.46 4.10 2.82 - 5.60	0.669	48.49
ESR (< 20 mm/h)** **Mean ± SD** **Median** **Min - Max**	12.67 ± 11.61 10 2 - 83	17.31 ± 14.88 12 2 - 83	0.0005	46.00
Alfa 1 % (1.0-3.0%)** **Mean ± SD** **Median** **Min - Max**	2.49 ± 0.74 2.40 1.10 – 7.80	2.65 ± 0.76 2.55 1.20 – 7.90	0.0015	45.85
Creatinine (0.5-1.2 mg/dL)** **Mean ± SD** **Median** **Min - Max**	1.10 ± 0.57 0.98 0.59 - 6.40	1.29 ± 1.18 1.00 0.55 - 9.85	0.1980	45.45
Alfa 2 % (9.5-14.4%)** **Mean ± SD** **Median** **Min - Max**	12.94 ± 2.01 12.80 7.70 - 23.40	13.08 ± 2.13 12.90 6.30 - 20.80	0.4256	44.53
Alfa 2 (0.45-1.0 g/dL)**				

Mean ± SD **Median** **Min - Max**	0.92 ± 0.17 0.91 0.25 - 1.59	0.94 ± 0.17 0.91 0.47 - 1.60	0.3132	44.47
Fibrinogen (170-410 mg/dL)** **Mean ± SD** **Median** **Min - Max**	329.51 ± 67.36 325 198 - 554	351.62 ± 90.86 325 105 - 856	0.0158	43.87
Beta (0.55-1.10 g/dL)** **Mean ± SD** **Median** **Min - Max**	1.05 ± 0.16 1.05 0.52 - 1.76	1.05 ± 0.16 1.05 0.52 - 1.76	0.5053	0.5053
Beta % (8.6-15.6%)** **Mean ± SD** **Median** **Min - Max**	14.75 ± 1.77 14.60 10.1 - 23.80	14.54 ± 1.73 14.50 10.4 - 19.90	0.2269	43.06
A/G (1.08-1.86)** **Mean ± SD** **Median** **Min - Max**	1.22 ± 0.20 1.20 0.64 - 1.82	1.20 ± 0.22 1.18 0.66 - 1.84	0.1119	41.76
Eosinophilis (0-0.80 × 103/L)** **Mean ± SD** **Median** **Min - Max**	0.19 ± 0.13 0.17 0.00 - 1.30	0.34 ± 1.62 0.17 0.00 - 22.0	0.0850	41.52
Phosphorous (2.7-4.5 mmol/L)** **Mean ± SD** **Median** **Min - Max**	3.59 ± 13.30 2.70 1.00 - 209.00	2.79 ± 0.62 2.70 1.70 - 6.30	0.6103	41.27
Linphocytes **(0.9-4.0 × 103/L)**** **Mean ± SD** **Median** **Min - Max**	1.83 ± 0.54 1.77 0.70 - 3.76	1.78 ± 0.67 1.77 0.54 - 8.11	0.3852	40.66
Monocytes % (3.4-9%)** **Mean ± SD** **Median** **Min - Max**	8.51 ± 1.71 8.40 1.30 – 15.20	8.58 ± 1.66 8.40 4.70 – 15.1	0.9987	37.65
Neutrophils **(1.50-8 × 103/L)**** **Mean ± SD** **Median** **Min - Max**	4.57 ± 1.47 4.38 1.96 - 12.48	4.62 ± 1.37 4.38 2.07 - 11.78	0.7579	37.32
Monocytes (0.2-1 × 103/L)** **Mean ± SD** **Median** **Min - Max**	0.61 ± 0.17 0.59 0.12 - 1.21	0.62 ± 0.16 0.59 0.34 - 1.26	0.4575	36.86
Sodium (135-145 mmol/L)** **Mean ± SD** **Median** **Min - Max**	140.72 ± 9.14 141.00 3.80 – 149.00	141.40 ± 2.44 141.0 132.00 – 148.00	0.5823	36.37
Eosinophilis % (0-8%)** **Mean ± SD** **Median** **Min - Max**	2.71 ± 1.72 2.50 0.00 - 15.10	3.04 ± 2.11 2.50 0.00 - 14.10	0.0993	36.09
Linphocytes % (20-45%)** **Mean ± SD** **Median** **Min - Max**	25.47 ± 6.46 24.50 7.20 - 49.00	24.47 ± 6.80 24.50 6.60 - 61.20	0.0925	36.09
MCHC (32-37 g/dL)** **Mean ± SD** **Median** **Min - Max**	33.29 ± 2.08 33.40 3.70 - 35.50	33.32 ± 0.76 33.30 29.30 - 35.50	0.3241	35.17

Basophilis (0-0.20 × 103/L)**				
Mean ± SD	0.04 ± 0.02	0.04 ± 0.02		34.78
Median	0.04	0.04	0.3140	
Min - Max	0.01 - 0.13	0.00 - 0.17		
Neutrophils % (40-74%)**				
Mean ± SD	62.51 ± 7.46	62.51 ± 7.46		34.19
Median	63.25	63.25	0.4632	
Min - Max	36.4 - 91.30	36.4 - 91.30		
APTT (24-38 seconds)**				
Mean ± SD	31.70 ± 10.38	31.32 ± 4.75		33.43
Median	30.50	30.30	0.5361	
Min - Max	0.19 - 178.10	23.00 - 68.10		
INR (0.2-1.2)**				
Mean ± SD	1.09 ± 0.34	1.13 ± 0.39		32.48
Median	1.00	1.00	0.7037	
Min - Max	0.80 - 4.20	0.90 - 3.70		
Cloryte (95-110 mmol/L)**				
Mean ± SD	104.71 ± 6.92	105.15 ± 3.25		32.30
Median	105.00	105.00	0.7649	
Min - Max	8.67 – 114.00	91.00 – 116.00		
APTT ratio (0.70-1.28 ratio)**				
Mean ± SD	1.08 ± 0.73	1.03 ± 0.15		32.03
Median	1.00	1.00	0.7032	
Min - Max	0.41 - 11.04	0.76 - 2.13		
Basophilis % (0-1.50%)**				
Mean ± SD	0.58 ± 0.22	0.58 ± 0.22		31.21
Median	0.55	0.55	0.5283	
Min - Max	0.10 - 1.70	0.10 - 1.70		

**Denotes variables not normally distributed (Shapiro test>0.05). Data shown upon request.
In third column, in bold and italics Wilcoxon p-values ≤ 0.05. In fourth column, in bold VIM values >57.

In Table 3, using the entire sample of 423 patients, we first compute the descriptive statistics (mean ± SD, median, min-max) for each biomarker stratifying for the dichotomized diameter:

$$I_{diameter} = \begin{cases} 1 \text{ if diameter is } \geq 55 \text{ mm} \Rightarrow \text{L AAA} \\ 0 \text{ otherwise} \Rightarrow \text{S/M AAA} \end{cases}$$

Then, we perform the Wilcoxon test, identifying 15 biomarkers (out of 55) which are significantly different (*p-value* < 0.05) in the two sub-populations defined by $I_{diameter}$ (in Figure 1 they are identified by bars with grey background). Second, we run an ensemble method where each weak learner is a tree which partitions the covariates space into disjoint regions (called nodes), homogeneous respect the outcome by means of a series of subsequent splits. In detail, we use the Random Forest, namely a robust method [[20]; [21]], where $I_{diameter}$ is the outcome and *X* is the matrix of 423 patients for 55 biomarkers. We then extract the relative Variable Importance Measure (VIM) identifying the biomarkers that more impact on the prediction of $I_{diameter}$. The algorithm selects 14 biomarkers with a VIM >57 as shown in the last column of Table 3 (values in bold) and in Figure 1 (bars with black dots). The cut-off (VIM>57) chosen for the variable selection is close to 60 (as suggested in [[22]]), selecting 25% of the variables. When comparing results obtained by these two different procedures (*p*-value<0.05 for Wilcoxon test and VIM>57 for Random Forest), only six biomarkers were jointly chosen: CK, ALT, MCV, Hemoglobin (Hgb), RDW, Hematocrite (Hct) The selected biomarkers are used as covariates in a new optimization algorithm (belonging to the operational research field), the LP-based classification trees, grown on the training set of 381 patients, in order to classify the dichotomic variable $I_{diameter}$.

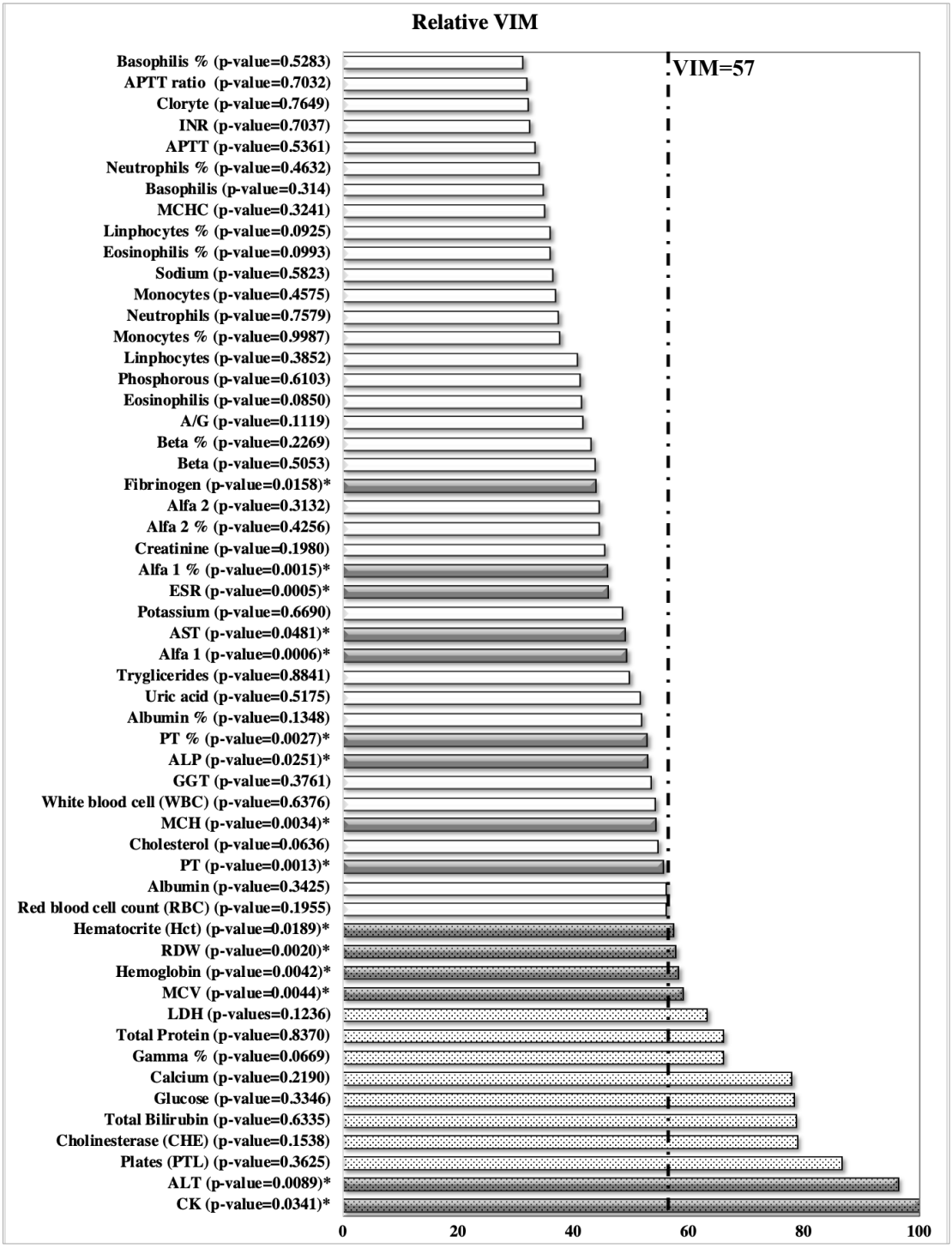

Figure 1: Barplot for the Relative Variable Importance extracted from the Random Forest

This Figure visualizes the Relative Variable Importance Measure (VIM) extracted from a Random Forest where the outcome is the dichotomized diameter (I_{diameter}) and the covariates are the 55 analytes. It is grown on a training set of 381 patients which contains the same percentage of S/M and L diameter of the entire sample. It represents a ranking from the most (CK with a VIM=100) to the less (Basophilis % with a VIM=31.21) important variable. Near the analyte name, we report the p-value obtained by the Wilcoxon test applied in the two sub-populations defined by I_{diameter} (patient with S/M vs L AAA). Asterisk denotes the significative p-values (<0.05).

In detail:

- The 14 bars with black dots are in correspondence of the analytes with a relative VIM>57. We choose this cut-off in order to maintain the 25% of the variables.
- The 15 grey bars are in correspondence of the analytes with Wilcoxon *p*-values < 0.05 (denoted also by an asterisk).
- When bars have both gray background and black dots, it means that the corresponding analytes (CK, ALT, MCV, Hgb, RDW, Hct) are jointly selected by the relative VIM>57 and the Wilcoxon test (*p*-values < 0.05).
- The 32 white bars denote analytes that have a relative VIM<57, jointly with Wilcoxon *p*-values > 0.05.

Table S.1 an S.2 of Supplementary Materials, report the descriptive statistics (mean ± SD, median, min-max) computed in training and test set, respectively, for each biomarker stratifying for $I_{diameter}$. It is evident that, training reproduces accurately what observed in the entire sample. In detail, the Wilcoxon test identifies almost the same biomarkers as significantly different (p-value < 0.05) in the two sub-populations defined by $I_{diameter}$. On the contrary, the test set does not reflect what happens in the training set. In fact, only five biomarkers are significantly different in the two subpopulation's S/M and L: PT, PT%, ESR, INR and Fibrinogen (the latter arises only in the test set) and none of them correspond with the six analytes identified by VIM and Random Forest.

We proposed two options: the first LP-tree was grown using only one biomarker at each node (see Figure 2 which is similar to the output of a decision tree); the second using a linear combination of the six biomarkers at each node for defining splits and thresholds. In the first case, we obtained an interpretable classifier whose specifity (ability to detect patients with S/M AAA) is 81% (CI: 77%- 85%) in the training set but decreases to 75% (CI: 58%- 88%) in the test set (42 patients not used during the training). In the second case, the LP-based tree loses the interpretability (representation) of a single tree and it correctly identifies 73% (CI: 68%- 78%) of S/M AAA patients in the training set. But, most important, when it is validated on the test set, surprisingly, the specificity increases up to 79% (CI: 67%- 92%), validating our score on fresh data. Note that test set is not homogeneous respect the training set and, regardless of this aspect, the performance of last LP-tree is good in detecting S/M AAA. Hence, due to the aim of this study, we focused our attention on this second output.

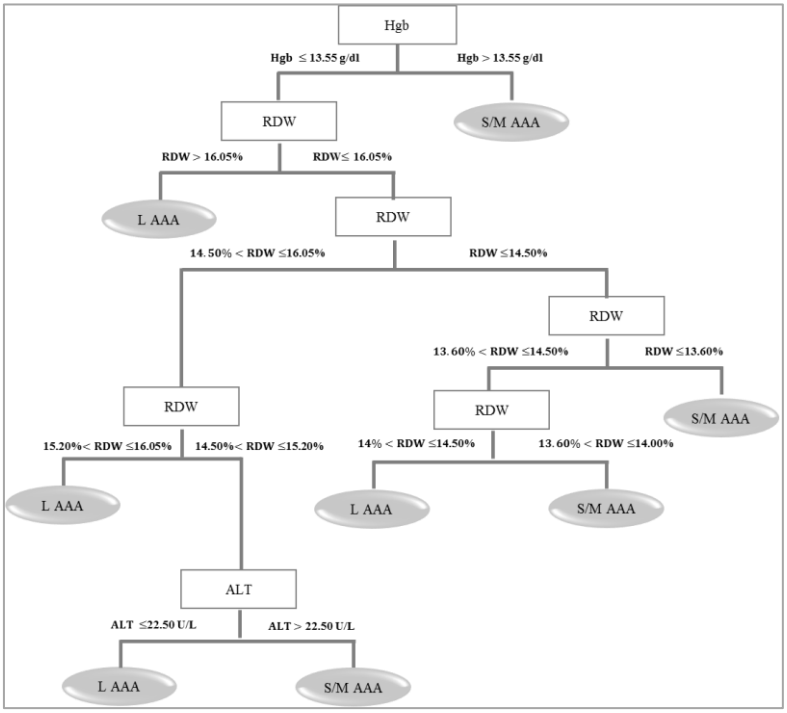

Figure 2: The LP-based classification trees where only one biomarker is chosen at each node

This figure reports the LP-tree obtained in the special case when we use only one biomarker for each split.

Relative to the more popular classification tree, the resulting partition represents a global optimum, since the splitting variables, and corresponding thresholds, are computed by solving a linear programming problem. In more depth, white rectangles display the selected variables, while grey branches the corresponding thresholds which split (at each step) the observations within the two subsamples. Grey ovals (which corresponds to the "nodes" in the decision tree theory) represent the final partition; they report the classification attributed to each observation that fell into that node.

This model was not used in the discussion, since its specificity (aim of this paper) out of sample was lower (75%) respect the specificity of the LP-tree where at each node a linear combination of biomarkers is chosen (79%).

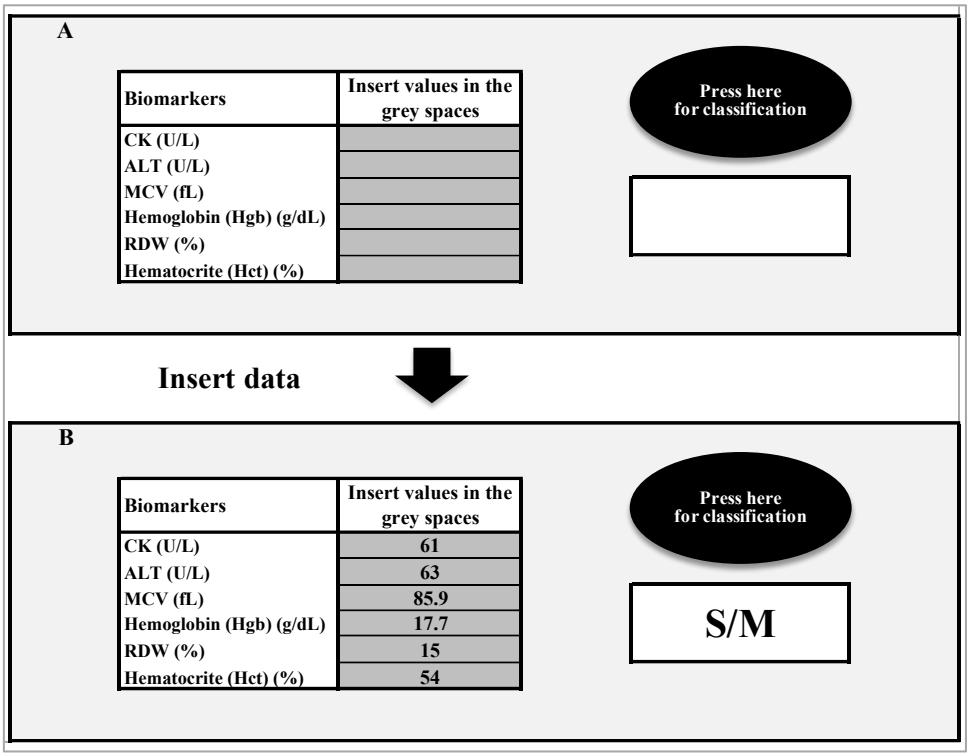

Figure 3: The interface of the EASE Score

The EASE Score is an Excel-file based macro (file available upon request). It is programmed starting from the LP-tree that uses at each node a linear combination of the 6 biomarkers selected in previous analyses. It has been designed to remedy the loss of interpretability of a single tree.

Panel A reports the interface of the macro. In grey cells, physicians insert analytes values; then, pressing the black button, they obtain the AAA classification of a patient.

Panel B reports a real example of a patient: after inserting the values of its exams, we obtain the classification of his/her AAA (in this case S/M).

Missing values are advised but, just in case, they are imputed with the median value of the missing analyte computed on the entire sample of 423 patients.

To overcome the loose of interpretability, the LP-based tree is traduced into an easy tool useful for physicians, called EASE score (Figure 3). It is a macro contained in an Excel file. For each new patient, the physician inserts the six biomarkers values (CK, ALT, MCV, Hgb, RDW, Hct) in the corresponding grey cells, and, pressing the black button, obtains the AAA classification as S/M or L. Obviously, missing values are not recommended but, just in case of an omitted value, the macro automatically imputes the median value of the missing analyte computed on the 423 patients. Figure 3.A and 3.B reports report the interface of the score and an example of classification computed on a real patient, respectively.

Discussion

In this paper we propose an Easy Affordable Statistical and Economic method that use routine blood analysis for the follow up of patients with S/M AAA and avoid unnecessary cost for health care system since the current strategy of using morphologic imaging as a stand-alone approach has a number or limitations, in particular for S/M AAA [3; 10]. First, imaging may not always be feasible, as variations in patient characteristics, such as obesity, meteorism or renal impairment, may prove prohibitive. Second ultrasound is a method that is operator dependent while CT is more accurate but has the drawback of exposing the patient to ionizing radiation and intravenous contrast and is also more expensive [23; 24]. Furthermore, both the approach above mentioned are exams that require waiting time with indirect costs for patients but also for health care system since, different authors have demonstrated that S/M AAA with similar initial diameter can vary significantly in growth pattern

[25; 23]. A more complete ability to monitor S/M AAA may allow significant streamlining of current management practice, which involves prolonged intermittent imaging. Different authors have used mathematical model using more complex factors as expansion rate, mechanical stress, wall stiffness [2; 26]. These variables have technical limitations mainly due to the difficulties of the analyses that require trained operators not available in all hospitals. Hence, since we were looking for something economic and easy to use and understandable, we decide to focus our attention on routine exams performed by these patients to build our score. We avoid the search in the biological matrix of extra lead markers that are mostly represented in the literature since, at the time of this writing, the clinical value of these markers remains unknown and none of them is used in the clinical practice even if different models have been proposed [16; 14]. In order to determine the biomarkers that identifies S/M or L AAA, we used (jointly with the Wilcoxon test) a Random Forest of regression trees. It extrapolates information from a dataset where each subject is composed by a set of features associated to a class (S/M or L). Many methodologies have been proposed to deal with problems of this type. For example, in [27] authors evaluated 179 classifiers arising from 17 families over 121 data sets. One of the main findings is that Random Forest is the best classifiers since it achieves 94.1% of the maximum accuracy overcoming 90% in the 84.3% of the data sets.

One of the innovations of our process is that the biomarkers used in this paper are jointly selected by the Wilcoxon test and Random Forest, without considering the previous literature. Differently from most of the approaches that have investigated specific molecules believed to be critical in AAA formation and progression, such as inflammatory markers or proteolytic enzymes, we decide to use high-throughput techniques to test different putative markers in an unbiased manner.

Recently, many papers use the machine learning approach for analysing clinical data [28; 29; 30; 21], but we are pioneers in the AAA field in combining approaches coming from machine learning and operational research. Our new LP-tree based algorithm provides, for each patient, the diameter classification (S/M or L) based on the selected biomarkers. This is an easy and effective tool to quickly and cheaply obtain predictions based on basic information collected on patients.

Relative to the more popular classification tree, the resulting partition represents a global optimum, since all the splitting variables, and corresponding thresholds, are computed by solving iteratively a linear programming problem that provide the best path from the treetop to the final nodes. As in decision tree, at each split, patients are separates in two classes. Final nodes provide a classification of each subject, minimizing the error in predicting the right class (S/M or L). The approach extends those proposed in [31] and [32].

Armed with the small but robust panel of biomarkers and the LP-based classification tree, we obtain a classificator able to identify (out of sample, namely on fresh data) 79% (CI: 67%-92%) of S/M AAA patients that do not progressed into L AAA and therefore do not require useless exams.

The advantages of our procedure are different: first, we use, as biological matrix, blood (entire blood and plasma) that differently from molecules expressed within diseased tissue are easier to be sample. Furthermore, we did not choose new biomarkers, but we build our score by using routine exams that these patients afford in their follow up with no additional cost for health care system neither for patients. Moreover the 6 biomarkers that we use for our score can be prescribed by a generalist doctor and can be performed also in small and periphery laboratories since are commonly request and the commercialization of common reagents has contributed to the standardization and reproducibility. Furthermore, these exams are not expensive and patients do not waste time on waiting list. Very intriguing, the biomarkers we found to be important for the prediction of the AAA diameter, are not the most cited in the literature and the

value of biomarkers are often in the normal range: none of them must be necessary out of the reference range. This could be due the fact that most researches are based on case-control studies, furthermore, in a multifactorial disease such as AAA, it seems unlikely that observed pathologies result from an important change in the expression of a single molecules. Rather, we believe that the AAA phenotype results from the concerted actions of large numbers of molecules over a prolonged period that could be detected, in part, by our approach.

A limit of this study is the 21% of false positive (patients S/M classified as L). Probably, introducing more sophisticated markers or other attributes, we will reduce this percentage.

Anyhow, given the international opinion regarding the importance of biomarkers in AAA, the finding of this study serves as a primer to stimulate interest for further validation by external cohorts. In fact, we could not divide our cohort in 3 subsamples (training, test and validating) since it does not reach 1000 subjects that is the number recommended for this procedure. For Anyhow, using our score, it is possible to avoid, for 79% of patients with S / M AAA, unnecessary examinations or to use the classification for scheduling the imaging timing, personalizing the surveillance intervals. To deliver on this promise, more comprehensive screening studies with large-scale validation of identified putative biological markers are needed.

References

[1] Sakalihasan, N. *et al.* Abdominal aortic aneurysms. *Nat. Rev. Dis. Primer* 4, 34 (2018).

[2] Tang, A. *et al.* Morphologic evaluation of ruptured and symptomatic abdominal aortic aneurysm by three-dimensional modeling. *J. Vasc. Surg.* 59, 894-902.e3 (2014).

[3] Thompson, S. G. *et al.* Systematic review and meta-analysis of the growth and rupture rates of small abdominal aortic aneurysms: implications for surveillance intervals and their cost-effectiveness. *Health Technol. Assess. Winch. Engl.* 17, 1–118 (2013).

[4] Lederle, F. A. *et al.* Multicentre study of abdominal aortic aneurysm measurement and enlargement. *Br. J. Surg.* 102, 1480–1487 (2015).

[5] Flondell-Sité, D., Lindblad, B., Kölbel, T. & Gottsäter, A. Cytokines and systemic biomarkers are related to the size of abdominal aortic aneurysms. *Cytokine* 46, 211–215 (2009).

[6] Wanhainen, A. *et al.* Editor's Choice - European Society for Vascular Surgery (ESVS) 2019 Clinical Practice Guidelines on the Management of Abdominal Aorto-iliac Artery Aneurysms. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* 57, 8–93 (2019).

[7] Garrafa, E. *et al.* Prediction of abdominal aortic aneurysm calcification by means of variation of high-sensitivity C-reactive protein. *JRSM Cardiovasc. Dis.* 5, 2048004016682177 (2016).

[8] Mussa, F. F. Screening for abdominal aortic aneurysm. *J. Vasc. Surg.* 62, 774–778 (2015).

[9] Guirguis-Blake, J. M., Beil, T. L., Senger, C. A. & Whitlock, E. P. Ultrasonography screening for abdominal aortic aneurysms: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann. Intern. Med.* 160, 321–329 (2014).

[10] Lindholt, J. S., Vammen, S., Fasting, H. & Henneberg, E. W. Psychological consequences of screening for abdominal aortic aneurysm and conservative treatment of small abdominal aortic aneurysms. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* 20, 79–83 (2000).

[11] Garrafa, E. *et al.* Association between human parainfluenza virus type 1 and smoking history in patients with an abdominal aortic aneurysm. *J. Med. Virol.* 85, 99–104 (2013).

[12] Stather, P. W. *et al.* Meta-analysis and meta-regression analysis of biomarkers for abdominal aortic aneurysm. *Br. J. Surg.* 101, 1358–1372 (2014).

[13] Vezzoli, M., Bonardelli, S., Peroni, M., Ravanelli, M. & Garrafa, E. A Simple Blood Test, Such as Complete Blood Count, Can Predict Calcification Grade of Abdominal Aortic Aneurysm. *Int. J. Vasc. Med.* 2017, 1370751 (2017).

[14] Moris, D. *et al.* Novel biomarkers of abdominal aortic aneurysm disease: identifying gaps and dispelling misperceptions. *BioMed Res. Int.* 2014, 925840 (2014).

[15] Jalalzadeh, H. *et al.* Inflammation as a Predictor of Abdominal Aortic Aneurysm Growth and Rupture: A Systematic Review of Imaging Biomarkers. *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* 52, 333–342 (2016).

[16] Wanhainen, A., Mani, K. & Golledge, J. Surrogate Markers of Abdominal Aortic Aneurysm Progression. *Arterioscler. Thromb. Vasc. Biol.* 36, 236–244 (2016).

[17] Garrafa, E. & Bonardelli, S. Re 'Calcification of Thoracic and Abdominal Aneurysms is Associated with Mortality and Morbidity'. Abdominal Aortic Aneurysm Calcification: Are Biochemical Markers a Missing Piece of the Puzzle? *Eur. J. Vasc. Endovasc. Surg. Off. J. Eur. Soc. Vasc. Surg.* 55, 900

(2018).
[18] Lindberg, S., Zarrouk, M., Holst, J. & Gottsäter, A. Inflammatory markers associated with abdominal aortic aneurysm. *Eur. Cytokine Netw.* 27, 75–80 (2016).
[19] Hao, W. *et al.* A mathematical model of aortic aneurysm formation. *PloS One* 12, e0170807 (2017).
[20] Savona, R. & Vezzoli, M. Fitting and Forecasting Sovereign Defaults using Multiple Risk Signals. *Oxf. Bull. Econ. Stat.* 77, 66–92 (2015).
[21] Doglietto, F. *et al.* Factors Associated With Surgical Mortality and Complications Among Patients With and Without Coronavirus Disease 2019 (COVID-19) in Italy. *JAMA Surg.* (2020) doi:10.1001/jamasurg.2020.2713.
[22] Carpita, M. & Vezzoli, M. Statistical evidence of the subjective work quality: the fairness drivers of the job satisfaction. *Electron. J. Appl. Stat. Anal.* 5, 89–107 (2012).
[23] Evangelista, A. Imaging aortic aneurysmal disease. *Heart Br. Card. Soc.* 100, 909–915 (2014).
[24] Collins, J. T., Boros, M. J. & Combs, K. Ultrasound surveillance of endovascular aneurysm repair: a safe modality versus computed tomography. *Ann. Vasc. Surg.* 21, 671–675 (2007).
[25] Armstrong, P. A. *et al.* Optimizing compliance, efficiency, and safety during surveillance of small abdominal aortic aneurysms. *J. Vasc. Surg.* 46, 190–195; discussion 195-196 (2007).
[26] Salman, H. E., Ramazanli, B., Yavuz, M. M. & Yalcin, H. C. Biomechanical Investigation of Disturbed Hemodynamics-Induced Tissue Degeneration in Abdominal Aortic Aneurysms Using Computational and Experimental Techniques. *Front. Bioeng. Biotechnol.* 7, 111 (2019).
[27] Fernandez-Delgado, M., Cernadas, E., Barro, S. & Amorim, D. Do we Need Hundreds of Classifiers to Solve Real World Classification Problems? *J. Mach. Learn. Res.* 15, 3133–3181 (2014).
[28] Deo Rahul C. Machine Learning in Medicine. *Circulation* 132, 1920–1930 (2015).
[29] Giger, M. L. Machine Learning in Medical Imaging. *J. Am. Coll. Radiol. JACR* 15, 512–520 (2018).
[30] Vezzoli, M. *et al.* RERT: A Novel Regression Tree Approach to Predict Extrauterine Disease in Endometrial Carcinoma Patients. *Sci. Rep.* 7, 10528 (2017).
[31] Bennett, K. P. Decision Tree Construction Via Linear Programming. in *Proceedings of the 4th Midwest Artificial Intelligence and Cognitive Science Society Conference* 97–101 (M. Evans, 1992).
[32] Street, W. N. Oblique Multicategory Decision Trees Using Nonlinear Programming. *Inf. J. Comput.* 17, 25–31 (2005).
[33] Breiman, L., Friedman, J., Stone, C. J. & Olshen, R. A. *Classification and Regression Trees*. (Taylor & Francis, 1984).
[34] Breiman, L. Random Forests. *Mach. Learn.* 45, 5–32 (2001).
[35] Mangasarian, O. L. Linear and Nonlinear Separation of Patterns by Linear Programming. *Oper. Res.* 13, 444–452 (1965).
[36] Mangasarian, O. Multisurface method of pattern separation. *IEEE Trans. Inf. Theory* 14, 801–807 (1968).

Analytes (Variables, Biomarkers, co-variates)	**Diameter < 55 (S/M)** $n_{train\ S/M}$**=217**	**Diameter ≥ 55 (L)** $n_{train\ L}$**=164**	**TOTAL** N_{train}**=381**	***p-value***
Creatine kinase (CK) (20-170 U/L)**				
Mean ± SD	109.20 ± 103.12	189.55 ± 1036.61	143.79 ± 684.52	
Median	86.00	77.00	82.00	***0.0355***
Min - Max	13 - 1061	23 - 13201	13 - 13201	
Alanine transaminase (ALT) (5-50 U/L)**				
Mean ± SD	27.02 ± 13.04	26.21 ± 17.93	26.67 (15.32)	
Median	24.00	22.00	23.00	***0.0096***
Min - Max	11 - 123	7 - 163	7 - 163	
Platelet (PTL) (130-400 × 10^3 U/L)**				
Mean ± SD	190.42 ± 54.79	197.07 ± 62.32	193.28 ± 58.16	
Median	188.00	187.50	188.00	0.5504
Min - Max	78 - 420	11.00 - 449.00	11 - 449	
Cholinesterase (CHE) (6400-15500 U/L)**				
Mean ± SD	11275.04 ± 2945.56	10841.30 ± 3045.02	11088.34 ± 2992.55	
Median	11274.00	11133.00	11274.00	0.1558
Min - Max	144 - 20363	1288 - 19531	144 - 20363	
Total Bilirubin (0.30-1.20 mg/dL)**				
Mean ± SD	0.70 ± 0.42	0.90 ± 2.94	0.78 ± 1.95	
Median	0.60	0.57	0.59	0.4250
Min - Max	0.21 - 3.08	0.23 – 38.00	0.21 – 38.00	
Glucose (70-100 mg/dL)**				
Mean ± SD	105.29 ± 25.91	102.93 ± 24.49	104.27 ± 25.30	
Median	98.00	97.00	98.00	0.2939
Min - Max	67 - 294	60 - 220	60 - 294	
Calcium (8.6-10.6 mmol/L)**				
Mean ± SD	9.09 ± 0.62	9.07 ± 0.46	9.08 ± 0.55	
Median	9.10	9.08	9.10	0.3720
Min - Max	3.00 - 10.36	7.40 - 10.11	3.00 - 10.36	
Gamma % (10.7-20.3%)**				
Mean ± SD	15.10 ± 3.20	15.54 ± 3.77	15.29 ± 3.46	
Median	14.90	15.10	14.90	0.1260
Min - Max	7.30 - 25.90	4.60 - 33.50	4.60 - 33.50	
Total Protein (6.0-8.0 g/dL)**				
Mean ± SD	7.14 ± 0.55	7.15 ± 0.76	7.14 ± 0.65	
Median	7.20	7.20	7.20	0.8858
Min - Max	4.00 - 8.50	0.79 - 9.40	0.79 - 9.40	
Lactate Dehydrogenase (LDH) (125-220 U/L)**				
Mean ± SD	174.09 ± 37.86	180.65 ± 41.57	176.91 ± 39.58	
Median	171.00	172.00	171.00	0.2967
Min - Max	41 - 397	91 - 379	41.00 - 397.00	
Mean Corpuscular Value (MCV) (82-94 fl)**				
Mean ± SD	93.24 ± 5.85	91.91 ± 5.73	92.67 ± 5.83	
Median	93.80	92.65	92.90	***0.0070***
Min - Max	65.30 - 106.90	61.80 - 102.70	61.80 - 106.90	

Hemoglobin (Hgb) (14-18 g/dl)**				
Mean ± SD	14.30 ± 1.58	13.79 ± 1.73	14.08 ± 1.66	
Median	14.50	14.05	14.30	***0.0049***
Min - Max	8.20 - 18.60	7.60 - 18.00	7.60 - 18.60	
RDW (12-17%)**				
Mean ± SD	14.31 ±1.45	14.64 ± 1.44	14.46 ± 1.45	
Median	14.00	14.30	14.20	***0.0043***
Min - Max	12.10 - 26.40	12.40 - 21.00	12.10 - 26.40	
Hematocrite (Hct) (42-52%)**				
Mean ± SD	42.81 ± 4.67	43.59 ± 28.55	43.15 ± 19.03	
Median	43.10	42.40	42.70	***0.0215***
Min - Max	24.30 - 55.90	25.80 - 401.00	24.30 - 401.00	
Red blood cell count (RBC) (4.5-5.5 × 10^6/mL)**				
Mean ± SD	4.61 ± 0.55	4.51 ± 0.58	4.57 ± 0.56	
Median	4.63	4.58	4.61	0.1852
Min - Max	2.55 - 6.55	2.93 - 6.29	2.55 - 6.55	
Albumin (3.4-4.6 g/dL)**				
Mean ± SD	3.90 ± 0.34	3.88 ± 0.33	3.89 ± 0.34	
Median	3.93	3.91	3.93	0.3455
Min – Max	2.19 - 4.66	2.68 - 4.67	2.19 - 4.67	
PT (9.5-13.5 seconds)**				
Mean ± SD	12.72 ± 7.75	12.52 ± 4.44	12.63 ± 6.52	
Median	11.20	11.40	11.30	***0.0139***
Min - Max	9.30 - 109.00	9.70 - 41.70	9.30 - 109.00	
Cholesterol (120-200 mg/dL)**				
Mean ± SD	179.06 ± 41.62	169.94 ± 38.70	175.13 ± 40.59	
Median	176.00	169.50	173.00	0.0543
Min - Max	92.00 - 322.00	74.00 - 314.00	74.00 - 322.00	
MCH (27-31 pg)**				
Mean ± SD	31.16 ± 2.29	30.63 ± 2.23	30.93 ± 2.28	
Median	31.30	30.70	31.20	***0.0068***
Min - Max	20.20 - 37.00	18.10 - 35.60	18.10 - 37.00	
White blood cell (WBC) (4.0-10.8 × 10^3/ml)**				
Mean ± SD	7.42 ± 2.16	7.36 ± 1.87	7.39 ± 2.04	
Median	7.08	6.98	7.04	0.9993
Min - Max	3.15 - 16.68	3.67 - 14.37	3.15 - 16.68	
GGT (5.0-50 U/L)**				
Mean ± SD	43.31 ± 59.66	40.67 ± 38.09	42.17 ± 51.45	
Median	31.00	30.00	31.00	0.5249
Min - Max	11 - 76	9 - 289	9 - 767	
ALP (40-129 U/L)**				
Mean ± SD	77.35 ± 30.38	84.85 ± 41.52	80.58 ± 35.75	
Median	71.00	78.00	75.00	***0.0164***
Min - Max	24 - 331	39 - 453	24 - 453	
PT % (80-120%)**				
Mean ± SD	98.98 ± 22.25	96.98 ± 20.51	98.12 ± 21.52	
Median	103.00	100.00	103.00	***0.0279***
Min - Max	14 - 151	18 - 137	14 - 151	
Albumin % (55.80-66.10%)**				
Mean ± SD	54.64 ± 3.96	54.10 ± 4.52	54.41 ± 4.21	
Median	54.40	54.05	54.40	0.1558
Min - Max	39.10 - 64.50	39.80 - 64.80	39.10 - 64.80	

Uric acid (3.4-7 mg/dL)**				
Mean ± SD	5.42 ± 1.42	5.48 ± 1.45	5.45 ± 1.43	
Median	5.29	5.30	5.30	0.7511
Min - Max	2.30 - 11.90	2.09 - 10.40	2.09 - 11.90	
Tryglicerides (<150 mg/dL)**				
Mean ± SD	127.80 ± 70.83	126.05 ± 61.92	127.05 ± 67.06	
Median	112.00	105.00	111.00	0.9341
Min - Max	34 - 453	38 - 356	34 - 453	
Alfa 1 (0.15-0.40 g/dL)**				
Mean ± SD	0.18 ± 0.04	0.20 ± 0.10	0.19 ± 0.07	
Median	0.17	0.19	0.18	***0.0006***
Min - Max	0.08 - 0.36	0.09 - 1.34	0.08 - 1.34	
AST (5.0-50 U/L)**				
Mean ± SD	19.65 ± 15.26	19.99 ± 25.66	19.80 ± 20.37	
Median	17.00	16.00	16.00	***0.0299***
Min - Max	7 - 196	3 - 283	3 - 283	
Potassium (3.5-5.0 mmol/L)**				
Mean ± SD	4.61 ± 7.07	4.16 ± 0.47	4.42 ± 5.34	
Median	4.10	4.19	4.10	0.3559
Min - Max	2.80 - 108.00	2.82 - 5.60	2.80 - 108.00	
ESR (< 20 mm/h)**				
Mean ± SD	12.54 ± 10.89	17.20 ± 15.08	14.55 ± 13.05	
Median	10.00	12.00	11.00	***0.0028***
Min - Max	2.00 - 75.00	2.00 - 83.00	2.00 - 83.00	
Alfa 1 % (1.0-3.0%)**				
Mean ± SD	2.50 ± 0.75	2.67 ± 0.78	2.58 ± 0.76	
Median	2.40	2.60	2.50	***0.0022***
Min - Max	1.10 - 7.80	1.20 - 7.90	1.10 - 7.90	
Creatinine (0.5-1.2 mg/dL)**				
	1.11 ± 0.59	1.32 ± 1.24	1.20 ± 0.93	
	0.98	1.00	0.99	0.1327
	0.59 - 6.40	0.55 - 9.85	0.55 - 9.85	
Alfa 2 % (9.5-14.4%)**				
Mean ± SD	12.91 ± 1.91	13.11 ± 2.05	13.00 ± 1.97	
Median	12.80	12.95	12.80	0.2898
Min - Max	7.70 - 18.70	6.30 - 19.40	6.30 - 19.40	
Alfa 2 (0.45-1.0 g/dL)**				
Mean ± SD	0.92 ± 0.16	0.94 ± 0.16	0.93 ± 0.16	
Median	0.91	0.92	0.91	0.1835
Min - Max	0.25 - 1.46	0.47 - 1.60	0.25 - 1.60	
Fibrinogen (170-410 mg/dL)**				
Mean ± SD	330.96 ± 68.54	351.30 ± 93.45	339.72 ± 80.73	
Median	325.00	325.00	325.00	0.0630
Min - Max	198 - 554	105 - 856	105 - 856	
Beta (0.55-1.10 g/dL)**				
Mean ± SD	1.06 ± 0.16	1.05 ± 0.17	1.05 ± 0.16	
Median	1.05	1.05	1.05	0.5419
Min - Max	0.52 - 1.76	0.71 - 1.48	0.52 - 1.76	
Beta % (8.6-15.6%)**				
Mean ± SD	14.78 ± 1.77	14.57 ± 1.70	14.69 ± 1.74	
Median	14.60	14.50	14.60	0.2736
Min - Max	10.10 - 23.80	11.10 - 18.80	10.10 - 23.80	
A/G (1.08-1.86)**				
Mean ± SD	1.22 ± 0.19	1.20 ± 0.22	1.21 ± 0.21	
Median	1.19	1.17	1.19	0.1287

Min - Max	0.64 - 1.82	0.66 - 1.84	0.64 - 1.84	
Eosinophilis (0-0.80 × 10^3/mL)**				
Mean ± SD	0.20 ± 0.14	0.35 ± 1.71	0.26 ± 1.13	
Median	0.17	0.17	0.17	0.1436
Min - Max	0.00 - 1.30	0.00 - 22.00	0.00 - 22.00	
Phosphorous (2.7-4.5 mmol/L)**				
Mean ± SD	2.72 ± 0.60	2.82 ± 0.63	2.77 ± 0.62	
Median	2.70	2.70	2.70	0.2261
Min - Max	1.00 - 8.00	1.70 - 6.30	1.00 - 8.00	
Linphocytes (0.9-4.0 × 10^3/mL)**				
Mean ± SD	1.86 ± 0.54	1.79 ± 0.69	1.83 ± 0.61	
Median	1.77	1.77	1.77	0.2180
Min - Max	0.70 - 3.76	0.54 - 8.11	0.54 - 8.11	
Monocytes % (3.4-9%)**				
Mean ± SD	8.49 ± 1.68	8.62 ± 1.68	8.55 ± 1.68	
Median	8.40	8.40	8.40	0.8799
Min - Max	1.30 - 15.00	4.70 - 15.10	1.30 - 15.10	
Neutrophils (1.50-8 × 10^3/mL)**				
Mean ± SD	4.59 ± 1.50	4.53 ± 1.22	4.56 ± 1.39	
Median	4.38	4.38	4.38	0.9262
Min - Max	2.04 - 12.48	2.07 - 11.18	2.04 - 12.48	
Monocytes (0.2-1 × 10^3/mL)**				
Mean ± SD	0.61 ± 0.17	0.62 ± 0.16	0.62 ± 0.17	
Median	0.59	0.59	0.59	0.6959
Min - Max	0.12 - 1.21	0.34 - 1.26	0.12 - 1.26	
Sodium (135-145 mmol/L)**				
Mean ± SD	140.66 ± 9.61	141.49 ± 2.40	141.02 ± 7.43	
Median	141.00	141.00	141.00	0.4569
Min - Max	3.80 - 149.00	132.00 - 148.00	3.80 - 149.00	
Eosinophilis % (0-8%)**				
Mean ± SD	2.74 ± 1.77	3.09 ± 2.19	2.89 ± 1.97	
Median	2.50	2.50	2.50	0.1079
Min - Max	0.00 - 15.10	0.00 - 14.10	0.00 - 15.10	
Linphocytes % (20-45%)**				
Mean ± SD	25.63 ± 6.52	24.73 ± 6.76	25.24 ± 6.63	
Median	24.50	24.50	24.50	0.1467
Min - Max	7.20 - 49.00	6.70 - 61.20	6.70 - 61.20	
MCHC (32-37 g/dL)**				
Mean ± SD	33.40 ± 0.83	33.32 ± 0.77	33.36 ± 0.81	
Median	33.40	33.30	33.30	0.4705
Min - Max	30.30 - 35.50	29.30 - 35.50	29.30 - 35.50	
Basophilis (0-0.20 × 10^3/mL)**				
Mean ± SD	0.04 ± 0.02	0.04 ± 0.03	0.04 ± 0.02	
Median	0.04	0.04	0.04	0.6511
Min - Max	0.01 - 0.13	0.00 - 0.17	0.00 - 0.17	
Neutrophils % (40-74%)**				
Mean ± SD	62.34 ± 7.47	62.71 ± 7.57	62.50 ± 7.50	
Median	63.25	63.25	63.25	0.5113
Min - Max	36.40 - 91.30	29.40 - 86.80	29.40 - 91.30	
APTT (24-38 seconds)**				
Mean ± SD	31.92 ± 10.70	31.35 ± 4.84	31.68 ± 8.67	

Median	30.50	30.30	30.50	0.5854
Min - Max	24.00 - 178.10	23.00 - 68.10	23.00 - 178.10	
INR (0.2-1.2)**				
Mean ± SD	1.10 ± 0.35	1.11 ± 0.37	1.10 ± 0.36	
Median	1.00	1.00	1.00	***0.0387***
Min - Max	0.80 - 4.20	0.90 - 3.70	0.80 - 4.20	
Cloryte (95-110 mmol/L)**				
Mean ± SD	104.67 ± 7.24	105.22 ± 3.27	104.90 ± 5.87	
Median	105.00	105.00	105.00	0.6355
Min - Max	8.67 - 114.00	91.00 - 116.00	8.67 - 116.00	
APTT ratio (0.70-1.28 ratio)**				
Mean ± SD	1.09 ± 0.77	1.03 ± 0.15	1.06 ± 0.59	
Median	1.00	1.00	1.00	0.7290
Min - Max	0.76 - 11.04	0.76 - 2.13	0.76 - 11.04	
Basophilis % (0-1.50%)**				
Mean ± SD	0.58 ± 0.21	0.62 ± 0.35	0.60 ± 0.28	
Median	0.55	0.55	0.55	0.9211
Min - Max	0.10 - 1.50	0.00 - 3.20	0.00 - 3.20	

**Denotes variables not normally distributed (Shapiro test>0.05). Data shown upon request.

In fourth column, in bold and italics Wilcoxon p-values ≤ 0.05.

Tabella S.1 Descriptive statistics on each analyte stratified for AAA diameter (S/M vs L) computed in the training sample (381 subjects)

Analytes maintain the same order of Table 3 in the main text. In detail, the Wilcoxon test confirms same results obtained in the entire sample (423 observations), identifying almost the same biomarkers (15 out of 55) significantly different (*p-value* < 0.05) in the two sub-populations defined by $I_{diameter}$.

Analytes (Variables, Biomarkers, co-variates)	**Diameter < 55 (S/M)** $n_{test\ S/M}$**=24**	**Diameter ≥ 55 (L)** $n_{test\ L}$**=18**	**TOTAL** N_{test}**=42**	***p-value***
CK (20-170 U/L)**				
Mean ± SD	113.62 ± 103.69	113.17 ± 111.58	113.43 ± 105.80	
Median	83.00	77.00	82.00	0.7894
Min - Max	34 - 552	41 - 519	34 - 552	
ALT (5-50 U/L)**				
Mean ± SD	24.92 ± 8.55	26.44 ± 14.16	25.57 ± 11.17	
Median	24.00	20.50	22.00	0.6102
Min - Max	8 - 46	14 - 71	8 - 71	
Platelet (PTL) (130-400 × 10^3 U/L)**				
Mean ± SD	185.25 ± 50.47	205.00 ± 51.35	193.71 ± 51.19	
Median	185.00	198.50	189.00	0.2223
Min - Max	87 - 309	119 - 290	87 - 309	
Cholinesterase (CHE) (6400-15500 U/L)**				
Mean ± SD	11395.50 ± 3220.16	11279.39 ± 4450.26	11345.74 ± 3745.95	
Median	11274.00	11055.50	11274.00	0.7895
Min - Max	5297 - 18101	1224 - 21375	1224 - 21375	
Total Bilirubin (0.30-1.20 mg/dL)**				
Mean ± SD	0.72 ± 0.41	0.79 ± 0.36	0.75 ± 0.39	
Median	0.65	0.73	0.65	0.3402
Min - Max	0.22 - 2.21	0.22 - 1.64	0.22 - 2.21	
Glucose (70-100 mg/dL)**				
Mean ± SD	100.00 ± 18.56	102.67 ± 28.80	101.14 ± 23.21	
Median	100.00	100.00	100.00	0.9696
Min - Max	7 - 15	61 - 163	61 - 163	
Calcium (8.6-10.6 mmol/L)**				
Mean ± SD	9.14 ± 0.42	9.01 ± 0.60	9.08 ± 0.50	
Median	9.25	8.85	9.14	0.3468
Min - Max	8.30 - 9.76	8.15 - 10.31	8.15 - 10.31	
Gamma % (10.7-20.3%)**				
Mean ± SD	14.62 ± 3.39	15.86 ± 4.24	15.15 ± 3.78	
Median	14.10	15.20	14.85	0.1776
Min - Max	10.70 - 27.40	11.30 - 30.60	10.70 - 30.60	
Total Protein (6.0-8.0 g/dL)**				
Mean ± SD	7.01 ± 0.47	7.07 ± 0.61	7.04 ± 0.53	
Median	7.00	7.20	7.05	0.7595
Min - Max	5.70 - 7.70	5.80 - 8.20	5.70 - 8.20	
LDH (125-220 U/L)**				
Mean ± SD	169.25 ± 47.56	205.00 ± 76.82	184.57 ± 63.54	
Median	169.00	175.50	170.50	0.1335
Min - Max	122 - 332	118 - 403	118 - 403	
MCV (82-94 fl)**				
Mean ± SD	94.78 ± 4.06ì	93.69 ± 4.57	94.31 ± 4.26	
Median	94.95	93.50	94.45	0.3215
Min - Max	85.60 - 103.00	86.60 - 104.60	85.60 - 104.60	
Hemoglobin (Hgb) (14-18 g/dl)**				
Mean ± SD	14.45 ± 1.70	14.25 ± 1.40	14.36 ± 1.56	
Median	14.40	14.30	14.35	0.5667

Min - Max	11.30 - 18.00	12.10 - 17.70	11.30 - 18.00	
RDW (12-17%)**				
Mean ± SD	14.01 ± 0.88	14.61 ± 1.56	14.27 ± 1.24	
Median	14.00	14.20	14.15	0.2627
Min - Max	12.70 - 16.20	12.50 - 19.00	12.50 - 19.00	
Hematocrite (Hct) (42-52%)**				
Mean ± SD	43.08 ± 5.34	42.69 ± 3.99	42.92 ± 4.76	
Median	43.05	42.45	42.50	0.6564
Min - Max	33.80 - 53.60	36.50 - 53.60	33.80 - 53.60	
Red blood cell count (RBC) (4.5-5.5 × 10^6/mL)**				
Mean ± SD	4.56 ± 0.65	4.56 ± 0.44	4.56 ± 0.57	
Median	4.52	4.52	4.52	0.8888
Min - Max	3.41 - 5.78	3.95 - 5.40	3.41 - 5.78	
Albumin (3.4-4.6 g/dL)**				
Mean ± SD	3.88 ± 0.45	3.85 ± 0.38	3.86 ± 0.42	
Median	3.90	3.88	3.90	0.7314
Min – Max	2.93 - 4.69	2.90 - 4.44	2.90 - 4.69	
PT (9.5-13.5 seconds)**				
Mean ± SD	11.18 ± 1.04	14.00 ± 6.09	12.39 ± 4.24	
Median	10.95	11.95	11.40	***0.0067***
Min - Max	9.80 - 14.30	10.20 - 32.30	9.80 - 32.30	
Cholesterol (120-200 mg/dL)**				
Mean ± SD	178.75 ± 41.77	179.00 ± 47.12	178.86 ± 43.58	
Median	177.50	171.50	175.50	1.0000
Min - Max	120 - 284	104 - 274	104 - 284	
MCH (27-31 pg)**				
Mean ± SD	31.83 ± 1.43	31.24 ± 1.47	31.58 ± 1.46	
Median	31.55	31.35	31.45	0.2221
Min - Max	29.20 - 34.30	28.90 - 34.20	28.90 - 34.30	
White blood cell (WBC) (4.0-10.8 × 10^3/ml)**				
Mean ± SD	6.82 ± 1.71	8.11 ± 2.63	7.37 ± 2.22	
Median	6.95	8.02	7.22	0.1304
Min - Max	4.06 - 10.40	4.43 - 14.80	4.06 - 14.80	
GGT (5.0-50 U/L)**				
Mean ± SD	50.42 ± 44.72	56.28 ± 83.68	52.93 ± 63.51	
Median	40.50	30.50	33.50	0.4608
Min - Max	5 - 222	14 - 377	5- 377	
ALP (40-129 U/L)**				
Mean ± SD	83.67 ± 39.07	81.28 ± 29.48	82.64 ± 34.90	
Median	81.50	74.00	74.50	0.9190
Min - Max	41 - 217	35- 141	35 - 217	
PT % (80-120%)**				
Mean ± SD	11.18 ± 1.04	14.00 ± 6.09	12.39 ± 4.24	
Median	10.95	11.95	11.40	***0.0067***
Min - Max	9.80 - 14.30	10.20 - 32.30	9.80 - 32.30	
Albumin % (55.80-66.10%)**				
Mean ± SD	55.26 ± 4.91	54.49 ± 4.23	54.93 ± 4.59	
Median	55.65	55.75	55.75	0.5168
Min - Max	41.90 - 61.90	44.00 - 59.50	41.90 - 61.90	
Uric acid (3.4-7 mg/dL)**				
Mean ± SD	5.48 ± 1.09	5.88 ± 1.14	5.65 ± 1.12	
Median	5.40	5.70	5.55	0.1900
Min - Max	3.40 - 7.60	3.70 - 7.60	3.40 - 7.60	

Tryglicerides (<150 mg/dL)**				
Mean ± SD	158.54 ± 92.51	134.56 ± 61.91	148.26 ± 80.84	
Median	138.50	121.50	131.00	0.3945
Min - Max	61 - 467	57- 252	57 - 467	
Alfa 1 (0.15-0.40 g/dL)**				
Mean ± SD	0.17 ± 0.05	0.17 ± 0.04	0.17 ± 0.04	
Median	0.16	0.17	0.17	0.3251
Min - Max	0.12 - 0.31	0.13 - 0.29	0.12 - 0.31	
AST (5.0-50 U/L)**				
Mean ± SD	17.96 ± 6.70	20.89 ± 12.64	19.21 ± 9.67	
Median	17.50	17.00	17.00	0.9592
Min - Max	6 - 38	13 - 65	6 - 65	
Potassium (3.5-5.0 mmol/L)**				
Mean ± SD	4.15 ± 0.36	4.00 ± 0.36	4.09 ± 0.37	
Median	4.15	3.95	4.05	0.0973
Min - Max	3.50 - 5.10	3.40 - 5.00	3.40 - 5.10	
ESR (< 20 mm/h)**				
Mean ± SD	13.83 ± 17.04	18.28 ± 13.34	15.74 ± 15.55	
Median	9.00	14.00	11.00	***0.0104***
Min - Max	2 - 83	2 - 61	2 - 83	
Alfa 1 % (1.0-3.0%)**				
Mean ± SD	2.42 ± 0.66	2.48 ± 0.53	2.44 ± 0.60	
Median	2.25	2.50	2.45	0.3375
Min - Max	1.60 - 4.50	1.70 - 4.20	1.60 - 4.50	
Creatinine (0.5-1.2 mg/dL)**				
	1.08 ± 0.24	1.02 ± 0.21	1.05 ± 0.23	
	1.02	1.00	1.02	0.4923
	0.78 - 1.75	0.74 - 1.69	0.74 - 1.75	
Alfa 2 % (9.5-14.4%)**				
Mean ± SD	13.21 ± 2.83	12.79 ± 2.78	13.03 ± 2.78	
Median	13.00	12.75	12.75	0.5584
Min - Max	8.30 - 23.40	8.10 - 20.80	8.10 - 23.40	
Alfa 2 (0.45-1.0 g/dL)**				
Mean ± SD	0.93 ± 0.20	0.90 ± 0.20	0.91 ± 0.20	
Median	0.90	0.84	0.89	0.4230
Min - Max	0.59 - 1.59	0.59 - 1.38	0.59 - 1.59	
Fibrinogen (170-410 mg/dL)**				
Mean ± SD	316.46 ± 55.06	354.44 ± 64.50	332.74 ± 61.54	
Median	319.00	332.00	325.00	***0.0145***
Min - Max	211 - 449	214 - 480	211 - 480	
Beta (0.55-1.10 g/dL)**				
Mean ± SD	1.02 ± 0.14	1.01 ± 0.16	1.01 ± 0.15	
Median	1.02	1.04	1.03	0.8189
Min - Max	0.76 - 1.26	0.74 - 1.31	0.74 - 1.31	
Beta % (8.6-15.6%)**				
Mean ± SD	14.49 ± 1.72	14.29 ± 2.06	14.40 ± 1.85	
Median	14.50	14.50	14.50	0.6022
Min - Max	10.90 - 17.40	10.40 - 19.90	10.40 - 19.90	
A/G (1.08-1.86)**				
Mean ± SD	1.26 ± 0.23	1.21 ± 0.19	1.24 ± 0.21	
Median	1.25	1.26	1.26	0.5250
Min - Max	0.72 - 1.62	0.79 - 1.47	0.72 - 1.62	
Eosinophilis (0-0.80 × 10^3/mL)**				
Mean ± SD	0.17 ± 0.08	0.20 ± 0.10	0.18 ± 0.09	

Median	0.17	0.17	0.17	0.2782
Min - Max	0.05 - 0.38	0.02 - 0.39	0.02 - 0.39	
Phosphorous (2.7-4.5 mmol/L)**				
Mean ± SD	11.41 ± 42.09	2.50 ± 0.31	7.60 ± 31.84	
Median	2.80	2.45	2.70	0.0576
Min - Max	1.60 - 209.00	1.90 - 2.95	1.60 - 209.00	
Linphocytes (0.9-4.0 × 10^3/mL)**				
Mean ± SD	1.63 ± 0.41	1.69 ± 0.42	1.66 ± 0.41	
Median	1.75	1.77	1.77	0.2883
Min - Max	0.86 - 2.56	0.75 - 2.39	0.75 - 2.56	
Monocytes % (3.4-9%)**				
Mean ± SD	8.65 ± 2.00	8.13 ± 1.38	8.43 ± 1.76	
Median	8.35	8.40	8.40	0.6797
Min - Max	6.10 - 15.20	5.80 - 11.00	5.80 - 15.20	
Neutrophils (1.50-8 × 10^3/mL)**				
Mean ± SD	4.44 ± 1.14	5.42 ± 2.20	4.86 ± 1.73	
Median	4.38	4.38	4.38	0.1635
Min - Max	1.96 - 6.37	3.44 - 11.78	1.96 - 11.78	
Monocytes (0.2-1 × 10^3/mL)**				
Mean ± SD	0.58 ± 0.11	0.64 ± 0.12	0.61 ± 0.12	
Median	0.59	0.59	0.59	0.2455
Min - Max	0.34 - 0.79	0.41 - 0.87	0.34 - 0.87	
Sodium (135-145 mmol/L)**				
Mean ± SD	141.29 ± 2.10	140.56 ± 2.71	140.98 ± 2.37	
Median	141.50	141.00	141.00	0.5963
Min - Max	136 - 145	133 - 143	133 - 145	
Eosinophilis % (0-8%)**				
Mean ± SD	2.50 ± 1.11	2.62 ± 1.08	2.55 ± 1.08	
Median	2.50	2.50	2.50	0.6676
Min - Max	0.80 - 5.30	0.20 - 4.80	0.20 - 5.30	
Linphocytes % (20-45%)**				
Mean ± SD	24.03 ± 5.82	22.04 ± 6.88	23.18 ± 6.29	
Median	24.50	24.50	24.50	0.3081
Min - Max	14.20 - 35.30	6.60 - 33.00	6.60 - 35.30	
MCHC (32-37 g/dL)**				
Mean ± SD	32.33 ± 6.12	33.37 ± 0.68	32.78 ± 4.64	
Median	33.45	33.35	33.40	0.3393
Min - Max	3.70 - 34.40	32.30 - 35.20	3.70 - 35.20	
Basophilis (0-0.20 × 10^3/mL)**				
Mean ± SD	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02	
Median	0.04	0.04	0.04	0.0893
Min - Max	0.01 - 0.11	0.01 - 0.11	0.01 - 0.11	
Neutrophils % (40-74%)**				
Mean ± SD	64.07 ± 7.41	66.28 ± 7.91	65.01 ± 7.61	
Median	63.25	63.25	63.25	0.7180
Min - Max	46.60 - 77.30	54.60 - 83.70	46.60 - 83.70	
APTT (24-38 seconds)**				
Mean ± SD	29.73 ± 6.73	31.04 ± 3.90	30.29 ± 5.67	
Median	31.15	30.40	30.60	0.6471
Min - Max	0.19 - 37.00	24.40 - 41.00	0.19 - 41.00	
INR (0.2-1.2)**				
Mean ± SD	1.00 ± 0.10	1.23 ± 0.52	1.10 ± 0.36	

Median	1.00	1.06	1.00	***0.0050***
Min - Max	0.88 - 1.30	0.90 - 2.80	0.88 - 2.80	
Cloryte (95-110 mmol/L)**				
Mean ± SD	105.12 ± 2.80	104.50 ± 3.09	104.86 ± 2.91	
Median	105.50	105.00	105.50	0.6432
Min - Max	99 - 112	98 - 109	98 - 112	
APTT ratio (0.70-1.28 ratio)**				
Mean ± SD	0.99 ± 0.14	1.02 ± 0.13	1.00 ± 0.14	
Median	1.01	0.99	1.01	0.7311
Min - Max	0.41 - 1.20	0.78 - 1.32	0.41 - 1.32	
Basophilis % (0-1.50%)**				
Mean ± SD	0.56 ± 0.33	0.61 ± 0.25	0.58 ± 0.29	
Median	0.53	0.55	0.55	0.1148
Min - Max	0.20 - 1.70	0.10 - 1.10	0.10 - 1.70	

**Denotes variables not normally distributed (Shapiro test>0.05). Data shown upon request.

In fourth column, in bold and italics Wilcoxon p-values $\leq$ 0.05.

Tabella S.2 Descriptive statistics on each analyte stratified for AAA diameter (S/M vs L) computed in the test sample (42 subjects)

Analytes maintain the same order of Table 3 in the main text.

The test set does not reflect what happens in the entire sample and in the training set. In fact, Wilcoxon test identify only 5 biomarkers as significantly different (p-values>0.05) in the two sub-populations S/M AAA vs L AAA. Four of them coincide with those identified in the entire sample of 423 observations, while one differs (Fibrinogen). Anyhow, the LP-based tree grown on linear combination of biomarkers, was validated on this data (not homogeneous with training set), showing good performance in terms of specifity.