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Novel computational model for survey and trend analysis of patients with endometriosis : a decision aid tool for EBM

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Endometriosis Index, Homothety, meta-analysis, bioinformatics, survey consensus model

Abstract

Endometriosis is increasingly collecting a worldwide attention due to its medical complexity and social impact. Recently, the European community has identified this as a "social disease".
A large amount of information comes from numerous works, yet several aspects of this pathology as well as evaluation criteria need to be clearly defined on a suitable number of individuals. In fact, available studies on endometriosis are not easily comparable due to a lack of standardized criteria to collect patients' informations and scarce definitions of symptoms. So far, only retrospective surgical stadiation is used to measure pathology intensity, while the Evidence Based Medicine (EBM) requires sharable methods and correct statistical models for disease classification and prognostic indication.

We addressed this issue by setting up a unified evaluation model designated "Endometriosis Index" (EI), obtained from a real-time software using 32 clinical indicators after homotetic transformation. The indicators, collected by the gynecologist are expressed as normalised scores. Subsequently, such normalised variables are cumulated to obtain the EI value. The entire panel of individual variables is then expressed by a unique number to possibly suggest a) a grade of the disease, b) indication to surgery, c) a trend of disease recurrence and d) prognostic indications .

The model of the EI construction has been conceived to be easily applicable and interpretable by all doctors under different clinical protocols. All variables were considered as discrete scores, computed to reliably and simultaneously express three concurrent elements: a) patient pain self-assessment, b) physician examination and 3) laboratory assays and Rx results.

This work briefly explains the mathematical mode, describes its software functional features and reports its practical application in a group of patients with endometriosis. A summary of the statistics of an observational study is also cited in order to explain the multi-centre consensus validation of the model.

Keywords *:Endometriosis Index, Records Matching, Unique Factorisation Domain, Bioinformatics, Evidence Based Medicine*
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INTRODUCTION

The pathogenesis of endometriosis is partially understood and there is no definitive cure for this pathology. One of the practical needs of a gynecologist is to collect and interpret clinical information to identify similarities and differences under a common criteria.

Extensive publications [5] have emphasized how important is to homogenise methods and standardize measurements to give the possibility that more studies could be included in a meta-analysis and the results could offer a predictive indication concerning surgery choice or fertility impairment [20, 23].
The endometriosis has multi-faceted aspects and very likely a multi-factorial basis. Intense literature is especially concentrated on the association between endometriosis and pain [11, 12, 26] or recursive surgical interventions [27] in chronic patients.

According with the available literature, McGill at Al have proposed a quite limited approach by a questionnaire built in for endometriosis patients [13]. The American Society for Reproductive Medicine (ASRM) has also delivered a schematic surgical classification of endometriosis types [2]. These scheme do not provide a precise status of the pathological course and can not be used as prognostic indication on a regular basis.

To overcome these limits, we have studied a Clinical Computation Algorithm model (CCA) and created a software specific for endometriosis, to provide an every-day tool for the evaluation of the disease evolution by either observational, laboratory and instrumental data analysis.

Something on which all exert appear to convene is that three different main components should be considered to achieve a clear picture of an endometriosis case: **a)** patient perception of pain, **b)** physician clinical evaluation and **c)** evidences from instrumental diagnostic. Therefore, any hypothetical predictive index for endometriosis should take into account these aspects on contemporary. At the time of this work, no endometriosis index has been officially proposed and accepted by the scientific community.

We have considered each one of the elements cited above and defined them as separate "Component" of a cumulative Endomentriosis Index. Such unique value represents a level of the pathological *status of a woman* at a specific time.
Based on a standard questionnaire, all information collected is characterised and classified as scalar or discrete variables and translating variables and parameters (indicators) validation into a matrix. Taken together, the indicators were then used to train a set of heuristic rules [15, 16]

The model is generated so that it could not be susceptible to *bias* caused by both physician interpretation or patients' misleading information. Any *bias* was considered as physiological standardised error, hence always present and cumulatively distributed among the components [1, 3, 6, 8].

The need of a standardised method for evaluating endometriosis is largely requested. This work provides a unique score named Endometriosis Index (EI), able to numerically express all information collected during a patient consultation. Authors have already applied the Unique Factorisation Domain theory to biological-clinical datasets for computational purposes and for record's matching on experimental and clinical microbiology [21].

The model and its coded software implementation is applied to endometriosis records profiles to calculate the EI of women which underwent interviews. Each single EI, or its serial follow-up, was then statistically used for a possible disease quantification, indication on surgery, prediction of disease recurrences and epidemiological analyses with homogeneous data.

MODEL DESCRIPTION

Endometriosis is a complex, multi-factorial pathology. A complete evaluation of the patient can be accomplished by analysing pain symptoms, habit limitations, physical and biological alterations, medical visit and instrumental diagnostics.

Informatics with evolute expert systems based on neural network, fuzzy logics and bayesian modelling [1, 7, 10] may today help to manage multi-factorial diseases and protocols needing multivariate data analysis. To be really effective, these methodologies have to be used on a specific and well characterised dataset, and practitioners need a skilled insight to classify clinical data modelling. Real effective and powerful mathematical tools are available to scientist but they presume a high competence on informatics to formalise algorithm logics and to correctly design an experiment.

We here introduce a CCA model which can be used with a simple software and does not presume any statistical assumption. It is indeed possible to elaborate data according to concepts such as similarity, correlation and phenotype variability by treating descriptive variables and parameters, if proficiently calculated as normalised scores.

Our model is formalised in an intuitive software interface which calculate the EI, while physicians provide data-entry. The software uses a heuristic knowledge which contains a weighted-matrix for 32 endometriosis indicators and the physician simply move a slider to indicate the relevance of a character of the record profile [i.e.: Figure 2]. Several patients can be followed over time so that an auto-correlation and a trends analysis gives an epidemiological prospect. The software can persist a storage template of the heuristic weighted knowledge for further uses. A complete listing of the indicators are grouped in the Table 1 pending on the component's panel to which they belong.

Each record profile is compiled through a sequential data-entry of four panels, for which the model algorithm on real-time calculates EI and plots a nomogram [Figure 1].In a first phase of use, the physicians can adapt the evaluation's scale simply changing the indicators' weights, on the base of their clinical experience.

Because of the inherent model feature [21], the algorithm calculates meaningful EI values, even in the case of missing or incomplete information. In fact, in the real practise, it is unlikely to cover all the data-entry panels when interviewing many patients.
Beside logistic reasons or practical limitations for having incomplete information, the model treats also these critical events and allows the data validation. For instance, it is not possible to consider the indicator score for sexual intercourse pain when a young patient is virgin (a case where it would not make sense to consider a zero score for this type of pain, because there were no sexual intercourses).

EI software considers several approximation possibilities and let the physician to decide whether to exclude or emphasise a specific information. This is allowed because the algorithm treats the contribute of an indicator (either variable or parameter) by discriminating between zero and *nil* values, so distinguishing a zero scalar number from the absence of indicator (when not applicable or not meaningful). In this latter case, the redistribution of the algebraic, cumulative sum of indicators will only take into account the meaningful values and the EI will be calculated accordingly.

THE ENDOMETRIOSIS INDEX

Table 1 lists the panel of indicators for endometriosis processed by the model; the variables and parameters were distributed over three components: A) woman pain self assessment, B) physician visit and C) data from laboratory and Rx diagnostics. This design is adherent with the model structure and the foreseen questionnaire can be filled up on paper or inserted directly on the computer.

Each component has a collection of values (indicators) grouped according to a logical cascade of questions in the following sections :

- *Patient Pain Self-assessment (DOL as result of subitems IDM + IDP + DRS + CDD),*
- *Pain types and quality of life limitation (LDD),*
- *Induced dysfunction and physical alteration (SPA),*
- *Medical judgement and instrumental diagnosis (VM and IS).*

Acronims are related to the Figure 6.

The information hierarchy is treated by the model so that the EI values can still be calculated even when entire sections are not compiled. A single indicator is sufficient to calculate the EI score. For instance, Pain evaluation is expressed as a unique score, calculated as a weighted average of three indicators: Menstrual pain, Pelvic Pain and Pain during Sexual intercourse.

The structured cascade of information can be schematically summarised as follows:

Section *(i.e. : LDD)*
➔ **Collection** *(i.e. : pulsed, trafittive, cricked, burning, staleness, swelling)*
➔ **Indicator (*value * weigth*)** *(i.e. : 7 * 2.5)*

With the exception of few cases discussed beyond, all indicators are expressed by a score from 0 to 10, and each score also has a specific weight (Indicator weight, Iw), allowing to reduce or emphasise the relevance of a variable or parameter (Figure 2).
In the case of diagnostics assay collection (IS), the score is the sum of contributions of each analysis. When considering the diagnostics results, both positive and negative responses were included, therefore the last scores can assume a negative value (Figure 3).
Each indicator contributes to its collection proportionally to its weight. In turn, the collection score has a weight for calculating the section index that is identified by a unique section acronym, (for example, CDD in Figure 2 and IS in Figure 3.

Total EI is a cumulative value which is concomitantly a qualitative and a quantitative contribute of all sections. In conclusion, EI is the numerical expression of the overall clinical profile of obtained by questionnaire. The more each section is relevant, the more EI value is scaled-up; on the contrary, lower or absent section values will down-adjust the overall EI level. EI normalisation is achieved by homothetic transformation of all collection scores [17, 18, 19].

The final interpretation of EI is quite simple: 0 (zero) value means no pathology whereas 100 is the maximum pathological grade as visualised in a nomogram (Figure 1). The red area extension in the radial chart is proportional to the section values and mathematically expresses a fraction of the EI integral. In fact, the area would be entirely covered if all sections should get their maximum values.
The final nomogram (Venn diagram) emphasizes each component by colouring separated bubbles; each bubble being proportionate to its section weight (Figure 6).

METHODS AND DISCUSSION

Authors' intent was creating a software tool for a bio-medical registry on endometriosis and its clinical survey. The software has today a freely testable release for consensus groups.

All examples and figures reported derive from an Italian experimental prototype, created in Genoa for the "Galliera Hospitals". The software architecture is generated by means of the theoretical work and subsequent mathematical formalisation already described [22]. The previous general model was adapted to clinically evaluate endometriosis patients.

INDICATORS

The information units, namely Indicators, taken together, describe the clinical profile of a case in the EI model. This scheme can be treated as field of a record profile (column). Such a record structure can be expressed as a theoretical unique number accordingly to Unique Factorisation Domain documented by authors in the theoretical model [21]. This method has the peculiar feature of unifying either qualitative descriptive or quantitative numerical data.

Either scalars numbers or discrete attributes of the records can be expressed as scores and this transformation leads to a range of scores varying from 0 to10 for each single variable/parameter. For example, Pain categories seen in Table 1 can be defined as an adjectival parameter, which can more specifically be described with detailed indicators such as *burning* or *swelling* and other. Essentially, also discrete entities can be linearised.

The possible indicators for the the Pain categories are represented as collection CDD and its final score is the weighted average of all the Indicators. Going deeper, each indicator is the product of a 0 to10 scaled scores multiplied by their weights (*Iw*).

The field Pain type mentioned above is a phenotypical character that can be intimately and much precisely be expressed through several descriptive characterisations of symptoms, each of them being ranked as score. The software *front-end* facilitate the *data-entry* of the user. In fact, a simple scale of descriptive levels is offered: *none, mild, high* and *severe* (Figure 2 shows the Italian equivalent terms: *nessuno, lieve, moderato, severo: meglio eliminare*).

This encapsulated parentage of a variable expression describes better than the simple *True/False boolean* factor. Therefore, the analysis will result in a sensitive and accurate measure of that specific variable and then longitudinal statistics may be applied for a trend over the time.

Another useful property of the EI model is the usage of *weighted-indicator*. Many indicators are binary measures and this is rendered by the model in a numerical way; thus variables can be normalised even in the case of binary parameters. In addition, instead of using two possibilities such as y*es/no* or *true/false*, we also consider a third *nil* value, distinguishing a third state: unknown variable and/or parameter (not available, not answered or not applicable) (Figure 8).

Figure 3 shows IS score, which accounts for the collection of indicators concerning laboratory equipment results (IS stands for the Italian "Indagini Strumentali", namely "Instrumental Diagnostics Assays"). In this case, all the variables were registered as a binary (Positive or Negative) responses. Note that the homothety of the model will be re-normalised in an "always positive" range of EI value.

One simplification of the model consists on the unification (pooling evaluation and measurement) of some blood markers. This is a convenient solution to express the levels of CA-125 and CA19.9 tumour markers. In fact, in our model, their titration values does not add information to the general clinical profile. Furthermore, original values cannot be considered standardised, because these values come from diversely calibrated instruments and different kits.

INDEXES AND INDICATORS. MULTIVARIATE STATISTICS

According to hierarchy graph showed in the formula (1), weighted indicator values are cumulated to originate the collection score and these values are later normalised to be expressed, according to an homogeneous scale, as section index. Lastly, all section indexes are normalised again, to be weighted proportionally to their relevance in a final unique EI with unified range value varying between 0 and 100.

To test the model performance and discrimination hability, an EI trial was designed to study endometriosis patients.

A total of 65 women were interviewed 35 of which had a "before surgery" and "after surgery" (PRE/POST scores) EI levels. Figure 10 shows the highly significant difference of the EI values of the two samples. The POST EI values were correlated with the improvement of the clinical situation (and quality of life) after laparoscopy (Pre/Post EI with a $P < 0.0001$) while PRE EI did not.

Because EI values derive from the homothetic sum of distinct normalised indicators, we also evaluated all the possible correlations with the individual components and verified all the univariate distributions of the different section indicators (manuscript in preparation). EI was very sensitive to detect disease intensity, in women refractory to surgical treatment, in misdiagnoses and in relapses.

The Figure 7 shows a Principal Component Analysis chart (PCO/PCA): categorical discrete classification of Pre/Post paired samples is clearly identifiable (Black dot and Red cross). In the same figure, there are also visible the PCA loading bars, which indicate how the Instrumental Diagnostics component is the most discriminant for EI. Therefore, EI model can be effective and predictive even when pain related indicators (DOL, LDD) are not assigned or if the patient is asymptomatic. Very often, older women appear to be less susceptible to pain, that is they can tolerate pain better than young women, and in such cases it is essential that the model could still recognize the patient from the normal population by considering the gynecologist evaluation and the diagnostics results.

We also verified which indicators were related each to the other and what was the sorted relevance in the contribution of an indicator to the global EI. We addressed this point with a cluster analysis on the same PCO/PCA sample (Figure 9). As clearly indicated, the lower dendrogram segregate the same PCO/PCA population (Eucledian and likelihood values) while the parentage dendrogram (upper right) shows the hierarchy of the EI indicators according to their discriminant/correlating relationships.

DOL indicator is strictly related to EI itself; as expected a strong parentage links DOL (Patient Pain Self-Assessment) with LDD (limitation of the quality of life). Interestingly, gynaecological judgement and physical disfunction (GIN and SPA) are also related each other. The IS (Instrumental Diagnostics) is phenetically the more distant factor.
No significant correlation was observed between EI and ASRM post-surgical stadiation.

TREND AND MONITORING PATHOLOGY

A single EI value concerns with a clinical situation at a specific date time: this means that sequential EI values are collected as follow-up, each time a woman is visited. Time to time, case by case, several records of a patient are available with anamnesis and updated information. Every follow-up reports the EI, so it is possible to study a trend and a survey analysis on a single as well as on a group of patients to monitor EI levels and clustering potential risk of a disease relapse [18].

To study longitudinal follow-up trend curves, EI values were analysed with both Patrick Royston's *ptrend* and Cochran–Armitage test was used as reference [Res.: http://www.stata.com/support /faqs/stat/trend.html]. For non-parametric comparison of multiple EI patient profiles were also evaluated with modified Chi-square test based on distribution of Pearson's correlation coefficient (TANAGRA Software).

CONCLUSION

Epidemiology of endometriosis requires to be studied with a wide range of multi-disciplinary aspects that can be aggregated for longitudinal as well in cross-population statistics.
We have provided a model to classify the patients according to an Endometriosis Index so that gynecologists can have a trend perspective in long-term treatments as well as a possible predictive indication for prognosis. Either software and theoretical methodology of the model has been divulgated by Authors so that any interested group can have the possibility to evaluate it in their clinical routines.

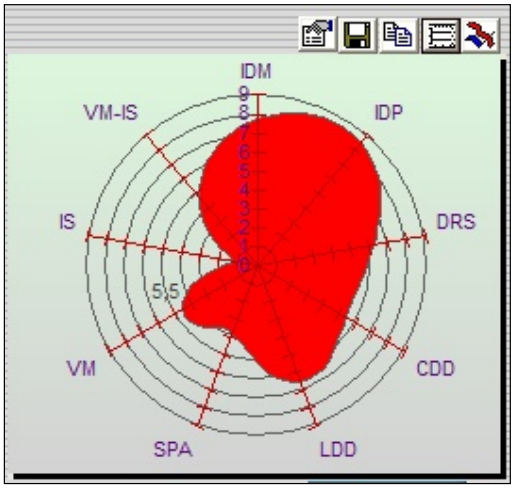
Multiple survey studies conducted according to our method could lead to a uniform and coherent meta-analysis, to improve the medical insight on endometriosis and to become a common consensus paradigm.

Once statistically validated, our pilot model can be further investigated to determine optimal ranges of EI values in order to early detect this pathology as well as the possibility to recognize the first signs of disease worsening in chronically treated patients or early relapses after surgery.

Table 1 : List of endometriosis indicators according to sections scheme of EI model component

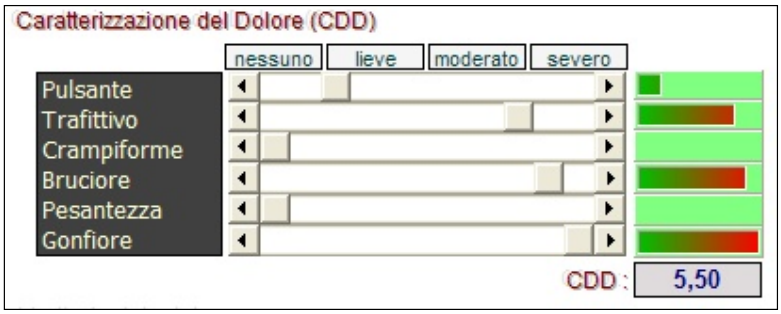
COMPONENT A PATIENT SELF ASSESSMENT	**Pain intensity [IDM, IDP, DRS] :** *menstrual, pelvic, during sexual intercourse (if applicable)* **Pain typification [CDD]**: *pulsed, trafittive, cricked, burning, staleness, swelling* **Pain induced limitation [LDD]** : *physical activity, intellectual activity, sleep disease* **Alvo's alteration [SPA]:** *constipation and diarrhea, tenesm, constipation, diarrhea, hematochezia* **Urinary alteration [SPA]:** *strangury, vesical tenesm, pollachiuria, dysuria* **Headache [SPA]:** *headache , migraine, cephalalgy*
COMPONENT B PHYSICIAN JUDGEMENT	**Gynaecological examination [VM] :** *fixed uterine, ovarian cyst, Douglas endangerment , vaginal nodule*
COMPONENT C DIAGNOSTICS EVIDENCE	**Instrumental evidences [IS]** : *CA-125, echography, CA-19.9, RMN, Tomography, Colonoscopy*

Figure 1 - Nomogram of collections and indicators scores during real-time EI computation



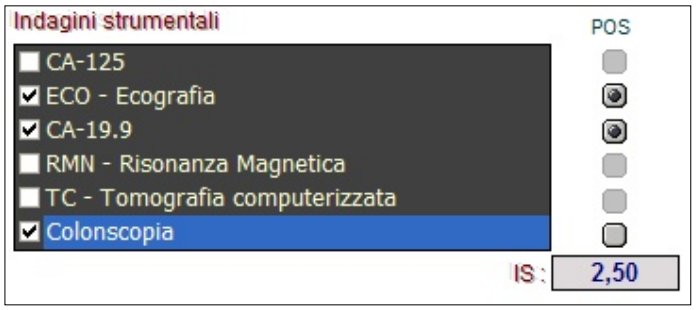
NOTE : Indicator's acronyms are associated to Table 1 list with square brackets.

Figure 2 - CDD score resulting from weighted average of indicators



Legend : image reports a screen-shot of Italian version of the software prototype

Figure 3 - Binary to weighted scalar score of diagnostic exams
The check-list indicates whether or not an examination was done while the [POS] column on the right will be flagged to signify a positive response. Eventually, pending on the response of the assay collection of indicators, this section IS might assume negative values.



Legend : image report a screen-shot of Italian version of the software prototype

Figure 4 - Negative collection's score of diagnostic exams outcomes
The check-boxes flagged indicate accomplished or available investigation report. The [POS] column shows only one suspicious CA19.9 flag while other result are negative. Because each exam has a relative 2.5 value (2 times and an half fold), this will be summarised when positive and subtracted if negative; this explain why the IS collection score is negative. Note that the colonoscopy was ignored in that was not considered and this account for the case in which a variable assumes the *nil* meaning.

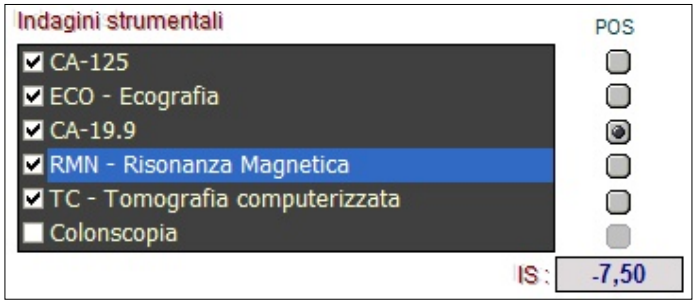


Figure 5 - Trend analysis of EI patient follow-up
Curve is a smooth plot according to polynomial square fitting of values series (red curve). The software can optionally visualise the ordinary linear regression curve (blu line)

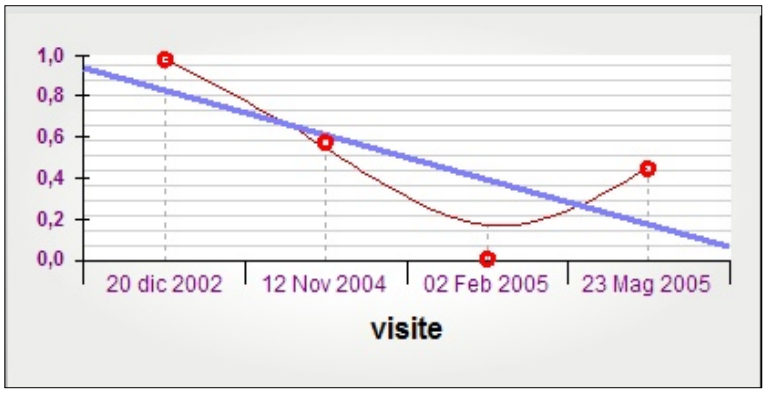


Figure 6 - Trend analysis of EI patient and follow-up of normalised chart
A summary panel of one case follow-ups graphically shows the complete pattern of a case; starting from its first interview the patient is monitored and the endometriosis evolution can be visualised either quantitatively or qualitatively over a periodic outcome EI

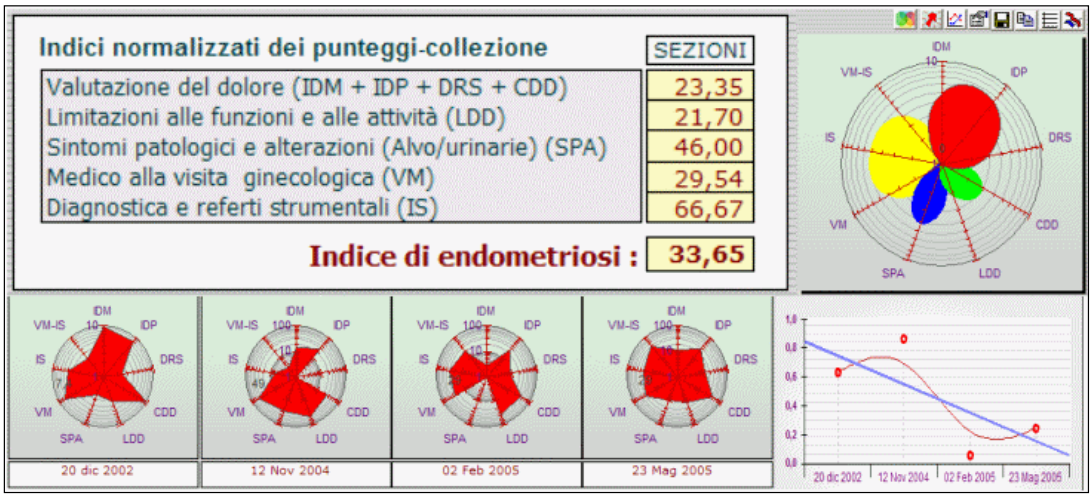


Figure 7 - PCO and PCA on EI and its indicators multi-variate Per/Post samples
A discriminant contribute of the EI indicators was evaluated on the pre/post (black dots and red cross) EI comparison according their bi-dimensional segregation of derivative covariates (second component, 1+2 effects of Eigenvalues).
The chart shows the PCO plot while the bars in the upper right comes from the PCA loadings of second component of Eigen values. Statistics and graphics were achieved by using PAST free software [9].

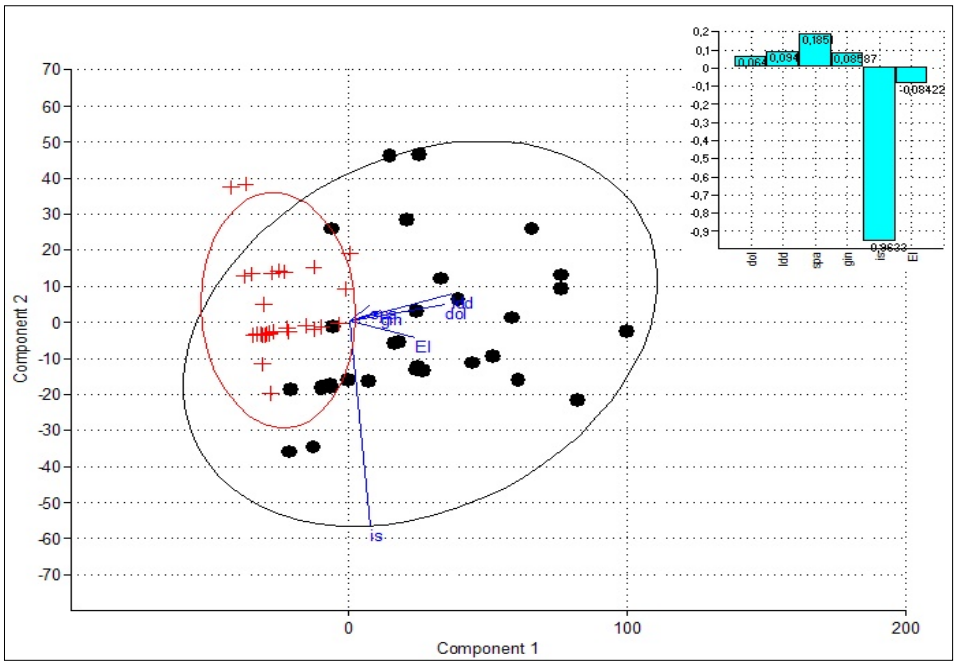


Figure 8 – Section/indicators data-entry panel with information on endometriosis induced dysfunctions
The figure shows the panel which collects the information related to symptoms and physiological alteration. The model will calculate a unique section score (SPA) considering either scalar or binary data. The software adjusts *true/false* variables according to internal heuristic rules. Each indicator will assume a value that proportional to its weight (see. *Headache*, italian "*mal di testa*"). Binary parameters are also used in the software to "*enhance*" special indicator relevance under contextual circumstances. For instance the *tenesm* and *migraine* phonomena can be enphasised if they occur in synchronous with menstrual cycle.

Figure 9 – Two-ways Cluster Analysis dendrogram for EI indicators parentage
Multi-factorial analysis was demonstrated with dendrogram by using the sample studied in Figure 7 (black and Red labels refre to Pre/Post EI values of 35 patients). Pink elliptic area shows the components hierarchy.

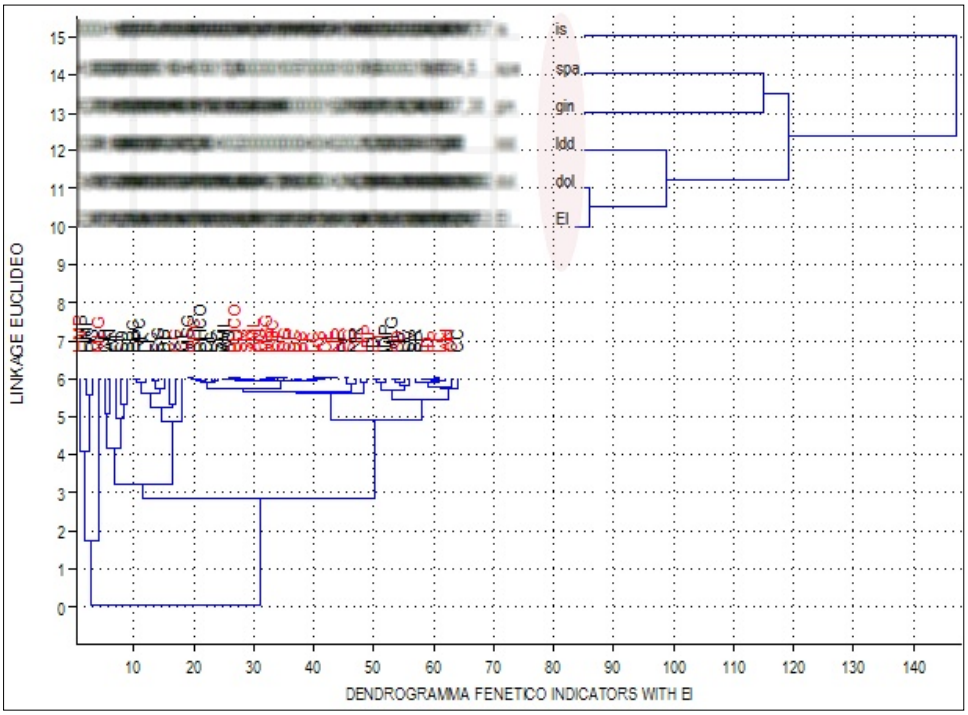
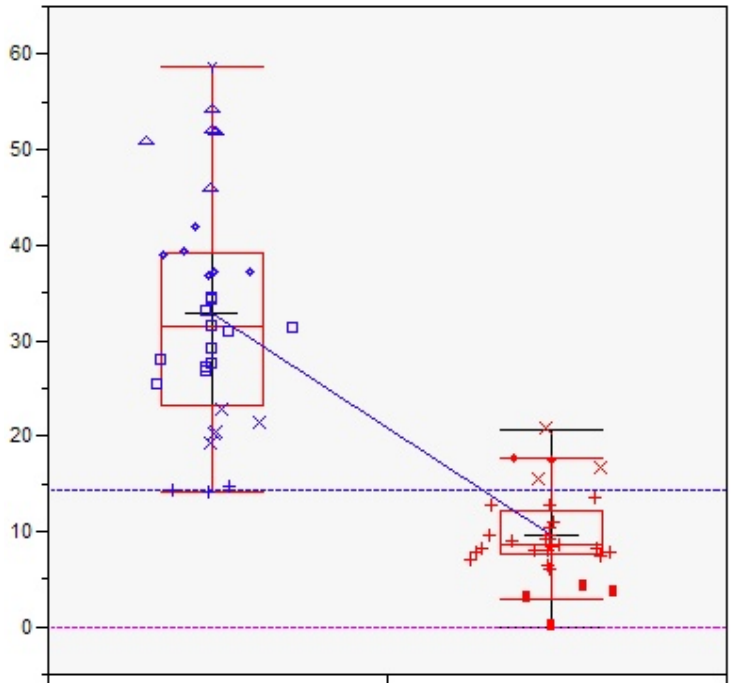


Figure 10 – Before surgery and after surgery EI follow-up
PRE/POST EI values are plotted to demonstrate the before/after (left/right or triangle/cross) surgery EI score which is strongly associated with the improvement of the quality of life due to a successful laparoscopy.



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