Artificial intelligence for target prostate biopsy outcomes prediction the potential application of fuzzy logic

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Running title: artificial intelligence predicts target biopsy outcomes

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ABSTRACT:

Background: In current precision prostate cancer (PCa) surgery era the identification of the best patients candidate for prostate biopsy still remains an open issue. The aim of this study was to evaluate if the prostate target biopsy (TB) outcomes could be predicted by using artificial intelligence approach based on a set of clinical prebiopsy.

Methods: Prebiopsy characteristics in terms of PSA, PSA density, digital rectal examination (DRE), previous prostate biopsies, number of suspicious lesions at mp-MRI, lesion volume, lesion location and Pi-Rads score were extracted from our prospectively maintained TB database from March 2014 to December 2019. Our approach is based on Fuzzy logic and associative rules mining, with the aim to predict TB outcomes.

Results: A total of 1448 patients were included. Using the Frequent-Pattern growth algorithm we extracted 875 rules and used to build the fuzzy classifier. 963 subjects were classified whereas for the remaining 484 subjects were not classified since no rules matched with their input variables. Analyzing the classified subjects we obtained a specificity of 59.2% and sensitivity of 90.8% with a negative and the positive predictive values of 81.3% and 76.6%, respectively. In particular, focusing on ISUP $\geq$ 3 PCa, our model is able to correctly predict the biopsy outcomes in 98.1% of the cases.

Conclusions: in this study we demonstrated that the possibility to look at several prebiopsy variables simultaneously with Artificial Intelligence algorithms can improve the prediction of TB outcomes, outclassing the performance of PSA, its derivates and MRI alone.

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In precision prostate cancer (PCa) surgery era [1], an early recognition of subjects with the risk of developing PCa still remains an unmet need. In the last years, notwithstanding the advent of mp-MRI the excessive variability in the performance and interpretation of its findings together with the intrinsic biological heterogeneity of PCa features cause 40% of the patients who underwent mp-MRI guided target biopsy (TB) to have a negative pathological report. Hence the necessity to better identify the ideal candidate for TB with risk of PCa. Nowadays, artificial intelligence (AI) helps physicians to build personalized predictive models (PPMs), which are gaining a wide diffusion even in urology [2–4]. The possibility of analyzing several variables at the same time and focusing on underlying patterns by including whole data packets simultaneously, makes this technology very appealing [5,6]. As mentioned in a recently published systematic review that included 55 papers, 26 studies explored the role of AI in prostate cancer diagnosis; the majority of them were focused on the distinction between benign and malignant samples at pathological analysis or on mp-MRI images [7], whilst the role of AI as predictive tool by using the clinical variables was less explored.

Fuzzy logic (FL) is a powerful tool belonging to the AI allowing to manage uncertainty that affects most real-world problems and characterizes human reasoning, representing uncertain information in a form that can be understood by a computer and, thus, it is suitable for developing PPMs in many medical fields [8].

In this study we evaluate the role of FL-based PPM in the identification right candidate for TB, based on a set of clinical prebiopsy variables.

For this study, we retrospectively reviewed our prospectively maintained TB database from March 2014 to December 2019. Prebiopsy features in terms of PSA, PSA density, digital rectal examination (DRE), previous prostate biopsies, number of suspicious lesions at mp-MRI, lesion volume, lesion location and Pi-Rads score were collected [9, 10]. A total of 1447 patients were finally included in this analysis: 824 patients with positive TB outcome, 623 with negative TB outcome.

The proposed PPM was based on a Fuzzy Inference System (FIS), requiring the definition of a set of fuzzy input and output variables and a list of rules. Specifically, the 8 prebiopsy variables were used as input and described in fuzzy terms according to the

thresholds/categories showed in Figure 1A, using trapezoidal or triangular membership functions. The output variable of the FIS represented the patient classification, and it was described using two triangular membership functions corresponding to the negative (no risk of PCa) and positive class (risk of PCa), respectively. In order to connect input and output variables and to obtain the final patient classification, a set of IF-THEN rules is required by the FIS. In this study, a total of 875 rules were automatically extracted from the entire dataset of patients, using the FP-Growth (frequent-pattern growth) algorithm, that is a basic algorithm for association rules mining [11]. The patient classification was than obtained by entering in the PPM the values of his prebiopsy variables: if one or more rules matched with his input values, one of the two classes (positive or negative) was assigned by the FIS, otherwise the patient was labeled as not classified.

Our Personalized Predictive Model (PPM) was tested on the entire dataset and the results are summarized in Figure 1.B. 963 subjects were classified whereas for the remaining 484 subjects were not classified. Focusing on the classified subjects, 231 out of 390 patients (specificity; Sp = 59.2%) were correctly classified as negative and 520 out of 573 patients (sensitivity; Se = 90.8%) were correctly recognized as positive. The negative and the positive predictive values (NPV and PPV) of the PPM were 81.3% and 76.6%, respectively. The distribution of the ISUP score among the positive patients is showed in Figure 1.C. The ROC curve obtained for the 963 classified patients, corresponding to an AUC value of 0.77 (Figure 1D).

The results presented above show how taking together 8 pre-biopsy characteristics makes it possible to correctly classify patients with suspicious PCa by using AI algorithms.

Our findings are particularly noteworthy if we focus on more aggressive PCa, defined as ISUP $\geq$ 3, for which our PPM is able to correctly predict the biopsy outcomes in 98.1% of the cases. These results outclass the performance of PSA and its derivates such as PSA density or free PSA, which Sp ranging from 30-40% and Se between 70% and 80%. Similarly, considering the indication to perform TB with respect to mp-MRI findings [12], the PPV of suspicious mpMRI for csPCa was 40% (95% confidence interval 36–43%), with large heterogeneity between the studies analyzed in a recent metanalysis (I^2 94%, $p < 0.01$) [13].

If these are the findings that analyzed one single variable (serum markers or images) alone, different risk calculators (RC) were already published with the aim to better identify the

patients with risk of Pca taking together multiple variables. However, none of them have clearly shown superiority, therefore it remains a personal decision as to which one to use [14]. A comparative analysis showed RCs containing MRI to be most predictive.

In fact, the discriminative ability of MRI RCs for the detection of csPCa was superior (AUC 0.81-0.87) to the traditional RCs (AUC 0.76-0.80) [15]

On the other side, few studies explored the role of AI in the creation of a predictive models [7]. Roffman et al. published the largest series of data [16] including 2016 patients with the aim to create and validate a multi-parametric Artificial Neuronal Network model, able to simultaneously examine anamnestic details of each patients in order to predict PCa risk and stratification. They showed a Se of 23%, Sp of 89%, AUC of 0.72, and positive predictive value of 27%.

We think that the possibility of correctly prioritizing the patients who require TB by using AI is particularly appealing for two reasons: firstly because, especially in re-biopsy setting (a fortiori after previously negative TB), the correct indication to a further biopsy is an unsolved issue of the current literature; secondarily, because in actual COVID-19 pandemic era, characterized by limited access to medical facilities and limited resources, the individuation of patients with higher risk of PCa could lead to a better assignment of the assets [17, 18].

Under a technical point of view, one of the main strengths of such approach for PPMs construction lies in the understandability of FIS results that allow to know the subset of rules matching with the input parameters and, thus, to evaluate the confidence in the obtained result.

The main limit of our study is the presence of patients that were not classified. This finding encourages the reflection on the huge biological heterogeneity of PCa and further studies are warranted trying to reclassify also this rate of missed patients using other supervised AI techniques such as Random Forest.

Notwithstanding the above-mentioned limitation, together with the unavailability of a validation cohort, the proposed PPMs based on AI FL algorithms showed how looking at multiple prebiopsy variables simultaneously is possible to improve the prediction of TB outcomes.

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CONFLICTS OF INTEREST

None declared.

ETHICAL APPROVAL:

The study was conducted in accordance with good clinical practice guidelines, and informed consent was obtained from the patients. According to Italian law (Agenzia Italiana del Farmaco Guidelines for Observational Studies, March 20, 2008), no formal institutional review board or ethics committee approval was required.

FIGURE LEGEND:

Figure 1. Overview of study results**.** A): Distribution of 1448 classified patients with negative and positive TB for the 8 prebiopsy variable, according to the thresholds/categories used for PPM construction. B): Confusion matrix reporting the results of our PPM with respect to the TB outcome. C): Distribution of false negative (red) and true positive (green) patients by ISUP. Focusing on the 53 false negative patients, the distribution of ISUP score was: 30.18% (16/53) with ISUP 1, 60.3% (32/53) with ISUP 2, 3.7% (2/53) with ISUP 3, 5.6% (3/53) with ISUP 4, 0% (0/53) with ISUP 5. D): ROC Curve obtained for the 983 classified patients