

EXPLAINABLE MACHINE LEARNING FOR NON-INVASIVE PROSTATE CANCER DETECTION USING SIGNAL-DERIVED VOC FEATURES

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Received: October 03, 2025; Revised: February 27, 2026; Accepted: March 16, 2026

Abstract

The present study aimed to develop an explainable artificial intelligence (AI) model by using urinary volatile organic compound (VOC) profiles for non-invasive prostate cancer (PCa) detection. A total of 123 participants were included: 29 with PCa, 67 with benign prostatic hyperplasia (BPH), and 27 healthy controls. Urinary VOC signals were recorded by metal oxide semiconductor sensors across six thermal cycles, generating 120 features per subject. Mutual Information and Random Forest importance identified 15 key features. Five classifiers—logistic regression (LR), decision tree (DT), random forest (RF), naïve Bayes (NB), and ensemble voting (EV)—were optimized with GridSearchCV and evaluated by using stratified cross-validation with SMOTE. The NB classifier provided the best discriminative performance on the independent test set, achieving an ROC-AUC of 0.90, while its accuracy, precision, recall, and F1-score were comparable to those of LR and RF under stratified 5-fold cross-validation. Importantly, explainability in this model arises from the probability-based decision structure of NB, which generates two distinctly separated probability clusters for PCa and non-PCa. This bimodal distribution enables direct interpretation of risk estimates, offering transparent and easy-to-communicate clinical meaning an advantage over black-box models. LR showed comparable utility (ROC-AUC = 0.81), whereas RF (0.76) and EV (0.77) demonstrated moderate discriminative performance, and DT produced the weakest results (0.67). These findings indicate that urinary VOC-derived features, analyzed with interpretable AI, can differentiate PCa from benign and control cases with reproducible performance across cross-validation folds. NB emerged as the most robust and transparent approach in this study, supporting the potential of VOC-based AI as a low-cost adjunct to clinical assessment and diagnostic pathways. Multi-center validation is recommended to confirm generalizability.

Keywords: Interpretable machine learning; Naïve Bayes classifier; Prostate cancer; Urinary biomarkers; Volatile organic compounds (VOCs)

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DOI: <https://doi.org/10.55766/sujst11714>

Suranaree J. Sci. Technol. 33(4):030405(1-9)

Abbreviations

VOC – Volatile Organic Compound, ML – Machine Learning, PCa – Prostate Cancer

Introduction

Prostate cancer remains one of the most common malignancies among men aged 45-60 years and continues to be a major cause of cancer-related mortality worldwide (Chen *et al.*, 2013). Current diagnostic strategies rely on digital rectal examination (DRE), serum prostate-specific antigen (PSA) testing, magnetic resonance imaging (MRI), and histopathological confirmation through biopsy.

Its development is shaped by both inherited and lifestyle-related factors. Advancing age strongly increases risk, rising from 1.8% in men aged 60-69 to 12.5% in those over 70 years. Ethnic variation is also evident. African American men, for instance, experience disproportionately higher incidence and mortality compared with White men (Siegel *et al.*, 2022). A positive family history, particularly among first-degree relatives, increases risk approximately 2.5-fold, while the presence of breast cancer in the family further augments susceptibility (Johns & Houlston, 2003). Modifiable exposures, including dietary habits and smoking, further contribute to disease risk (Li *et al.*, 2021; Parra-Soto *et al.*, 2022; Rowles *et al.*, 2017, 2018).

Despite the widespread use of PSA, either alone or in combination with DRE, its specificity and predictive accuracy remain limited. Values in the 4-10 ng/mL range fall into a diagnostic “gray zone,” while biopsy, although definitive, carries important drawbacks false-negative rates up to 20% and complications, such as sepsis, bleeding, and patient reluctance due to its invasive nature (Babaian *et al.*, 2000; Presti *et al.*, 2003; Ferlay *et al.*, 2010; Altwaijry *et al.*, 2018; Ozah & Imasogie, 2023). In light of these limitations, alternative strategies that can supplement or partially replace histopathology are of increasing importance. New diagnostic technologies are frequently evaluated against established reference standards, with agreement-based approaches serving as benchmarks for clinical adoption (Kreepala *et al.*, 2017, 2025).

The search for less invasive yet reliable biomarkers has expanded from traditional genomic and proteomic markers to include metabolic byproducts. Volatile organic compounds (VOCs) have emerged as particularly attractive candidates, as they reflect biochemical processes and can be collected non-invasively with good reproducibility (Halloran *et al.*, 2015; Kreepala *et al.*, 2018;

Tangkiatkumjai & Kreepala, 2018; Kreepala *et al.*, 2021; Suthat Na Ayutaya *et al.*, 2024). Specific VOCs, including methane, iso-butane, hydrogen, and ethanol, have been linked to urologic malignancies when detected by using metal oxide semiconductor sensors, platforms that have also been successfully applied in renal and metabolic disease contexts (Kreepala *et al.*, 2019; Suthat Na Ayutaya *et al.*, 2024).

In our earlier exploratory analysis (Suthat Na Ayutaya *et al.*, 2024), urinary VOC features were examined by using statistical filtering and univariate comparisons to highlight parameters with potential discriminative value. However, that analysis remained descriptive and did not extend to predictive modeling. Building on these preliminary findings, the present work applies an artificial intelligence (AI)-based framework to evaluate whether composite VOC feature patterns can improve diagnostic accuracy. Interpretable decision tree models were chosen for their transparent, rule-based logic, which is well suited for clinical translation, and bootstrap resampling was incorporated to enhance robustness. As demonstrated in prior applications to diabetic kidney disease and other non-genomic biomarker datasets (Gao *et al.*, 2019; Kreepala *et al.*, 2019; Liu *et al.*, 2023; Suthat Na Ayutaya *et al.*, 2024), incorporating signal-derived features into supervised learning pipelines can improve diagnostic performance while preserving interpretability.

Accordingly, the objective of this study is to develop and validate an explainable VOC-based AI model for prostate cancer detection, with the goal of producing clinically meaningful and reproducible diagnostic rules.

Materials and Methods

Clinical Data and Sample Collection

This study performed a secondary analysis of urine VOC data previously collected from male participants by using n-type metal oxide semiconductor sensors. Eligible participants included histopathology-confirmed cases of prostate adenocarcinoma, patients with BPH, and healthy male controls. All participants had provided written informed consent at the time of initial enrollment. Details of the collection protocol and ethical approval have been described in our earlier report (Suthat Na Ayutaya *et al.*, 2024), and the present analysis was conducted on de-identified data collected under that protocol.

VOC Signal Acquisition and Feature Engineering

VOC analysis was performed by using a custom platform, comprising five metal oxide semiconductor sensors, each operated under six thermal cycles per measurement session. Resistance values were recorded every 0.15 seconds, yielding approximately 12,000 data points per subject. From these time-series signals, four characteristic parameters were derived: (1) minimum resistance (min), (2) resistance change (gap), (3) time to minimum resistance (time), and (4) slope of decline. With five sensors across six heating cycles, a total of 120 structured features per participant were generated (Supplementary Figure 1) (Suthat Na Ayutaya *et al.*, 2024; Kreepala *et al.*, 2025).

Data Splitting and Robustness Assessment

The data set was randomly divided into training (80%) and testing (20%) subsets by using stratified partitioning to preserve class proportions. Model robustness was further examined through stratified cross-validation and bootstrap resampling.

Feature Selection

To reduce dimensionality and identify discriminatory features, a combined filter–model–based approach was applied. All feature selection procedures were performed exclusively on the training set to prevent information leakage and ensure unbiased model evaluation. First, Mutual Information (MI) was calculated to quantify statistical dependency between each VOC feature

and the class label. In parallel, Random Forest Feature Importance (RFI) was derived to measure the contribution of each feature to impurity reduction within an ensemble of decision trees. Features were then ranked independently by MI and RFI, and a consensus rank was computed by averaging both scores. The top 15 features with the lowest consensus ranks were selected for model construction, balancing statistical relevance with model-based influence to enhance reproducibility and minimize overfitting (Table 1).

Data Preprocessing and Class Imbalance Handling

The dataset exhibited class imbalance, with prostate cancer cases underrepresented compared with benign and control groups. To address this, the Synthetic Minority Oversampling Technique (SMOTE) was applied, yielding a balanced dataset across classes. All features were standardized by using Standard Scaler (mean = 0, SD = 1) fitted only on the training set to prevent data leakage and then applied to both training and test sets.

Model Development

Five machine learning classifiers were implemented to differentiate prostate cancer (PCa) from non-PCa cases. For model training, BPH and healthy controls were combined into a single non-PCa class to increase statistical power and to reflect the clinical objective of distinguishing malignant from non-malignant conditions. Logistic Regression (LR), Decision Tree (DT), Random Forest (RF),

Table 1. Top 15 VOC signal-derived features selected for prostate cancer classification, ranked by MI, RFI, and consensus rank. The consensus rank was calculated as the arithmetic mean of the MI rank and the RFI rank for each feature (Consensus Rank = (MI Rank + RFI Rank) / 2)

Feature*	MI	RFI	MI Rank	RFI Rank	Consensus Rank
Gap_S3_i5	0.51	0.04	2	2	2.0
Min_S3_i5	0.59	0.03	1	4	2.5
Gap_S2_i6	0.50	0.03	3	3	3.0
Slope_S2_i6	0.48	0.04	6	1	3.5
Min_S2_i6	0.50	0.03	4	6	5.0
Min_S2_i1	0.46	0.02	7	10	8.5
Gap_S4_i4	0.49	0.02	5	13	9.0
Gap_S3_i6	0.35	0.03	14	5	9.5
Slope_S3_i5	0.40	0.03	12	8	10.0
Gap_S2_i1	0.43	0.02	10	11	10.5
Min_S4_i4	0.44	0.02	9	12	10.5
Time_S4_i4	0.35	0.03	15	7	11.0
Slope_S5_i3	0.40	0.03	13	9	11.0
Slope_S2_i1	0.44	0.02	8	14	11.0
Min_S5_i3	0.40	0.02	11	15	13.0

*Note: Feature names correspond to signal-derived parameters (min, gap, time, slope) across different sensors and heating cycles. Detailed definitions and extraction methods are described in our earlier work (Suthat Na Ayutaya *et al.*, 2024).

Abbreviations: MI, Mutual Information; RFI, Random Forest Feature Importance

Naïve Bayes (NB), and an Ensemble Voting (EV) classifier were evaluated. LR was used as a linear baseline. DT and RF were included to capture non-linear interactions. NB was chosen due to its computational efficiency and suitability for high-dimensional biomedical datasets. Hyperparameter optimization was conducted by using GridSearchCV with 5-fold stratified cross-validation on the training set to ensure fair and unbiased parameter selection.

For the ensemble strategy, a hard voting classifier was constructed by combining LR, DT, RF, and NB. The final class label was assigned by majority rule across the base classifiers, a strategy adopted to integrate complementary decision boundaries and reduce the variance of individual models (Supplementary Figure 2).

The overall analytical workflow is summarized in Figure 1. The process began with data preparation, including feature engineering, followed by feature selection that used Mutual Information and Random Forest importance, class balancing with SMOTE, and normalization of numeric features by using standard scaling. The dataset was subsequently partitioned into independent training and test sets, with all preprocessing steps performed exclusively on the training set to prevent information leakage. In the model development stage, multiple machine learning classifiers were trained on the stratified training set, with hyperparameters optimized by using GridSearchCV and stratified 5-fold cross-validation. The optimized models were subsequently applied to the independent test set to generate predictions. Performance evaluation was conducted by comparing discriminative ability across models that used standard classification metrics and receiver operating characteristic (ROC) analysis.

The process began with data preparation, including data cleaning and feature engineering. The prepared dataset was then split into training and test sets. For the training set, feature selection was performed by using mutual information (MI) and random forest importance (RFI), followed by class imbalance handling with the SMOTE technique and feature scaling by using a standard scaler. Subsequently, multiple machine learning models were trained, and their hyperparameters were optimized by using the GridSearchCV method. The optimized models were subsequently evaluated on the independent held-out test set, while stratified 5-fold cross-validation was performed on the training set during hyperparameter optimization.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical data. Continuous variables were expressed as means with standard deviations, while categorical variables were reported as counts and percentages. A p-value < 0.05 was considered statistically significant. For model evaluation, ROC-AUC, accuracy, precision, recall, and F1-score were reported. Machine learning analyses were performed by using Python version 3.10 (scikit-learn library), while preliminary statistical summaries were computed with SPSS version 18.0.

Results and Discussion

Results

Study Cohort

As the previously study reported (Suthat Na Ayutaya *et al.*, 2024), the study cohort comprised 123 male participants, including healthy controls (n = 27), patients with benign prostatic hyperplasia (BPH; n = 67), and those with histologically

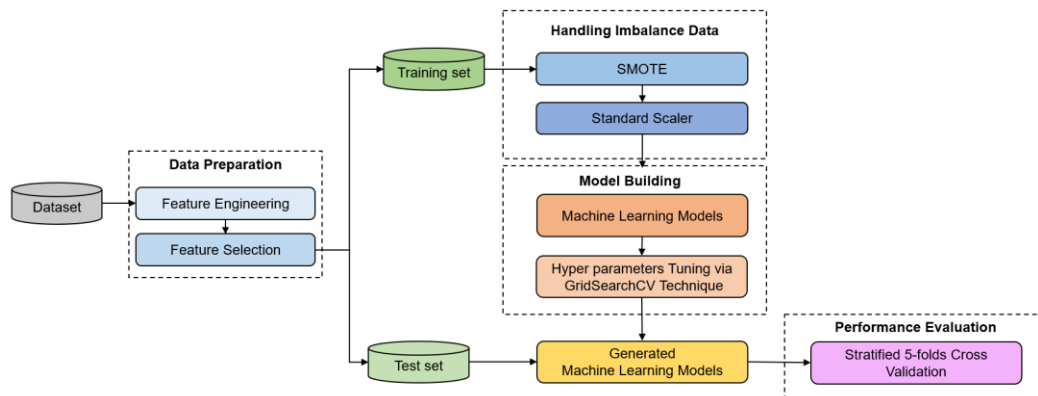


Figure 1. Flowchart of the machine learning pipeline from feature engineering to model evaluation

confirmed prostate cancer ($n = 29$). Baseline characteristics revealed group-level differences in several clinical variables. The prostate cancer subgroup was notable for a high proportion of advanced-stage disease, with more than 60% of patients presenting with Gleason grade group 4 or 5 histology. Over half also exhibited radiologic evidence of bone metastasis at the time of diagnosis, underscoring the systemic nature of disease in this population.

Although group-level differences in clinical variables, such as age, PSA, and prostate volume, were observed, these parameters were not incorporated as predictors in the present analysis. Instead, the study capitalized on the richness of VOC signal data. Each participant contributed 120 structured features ($5 \text{ sensors} \times 6 \text{ cycles} \times 4 \text{ parameters}$), yielding a high-dimensional feature matrix across 123 participants. While this feature richness enabled the extraction of informative signal patterns, we acknowledged that statistical power and generalizability have been primarily determined by the number of independent samples rather than feature dimensionality. To mitigate the risk of overfitting in this high-dimensional, low-sample setting, a consensus feature selection strategy, was applied, resulting in the identification of the 15 most informative features (Table 1), which were subsequently used for downstream classification of PCa versus non-PCa cases.

Model Performance Evaluation

To evaluate predictive performance for PCa classification, five machine learning models were

trained and assessed: LR, NB, DT, RF, and an EV classifier. Model performance was evaluated by using accuracy, precision, recall, F1-score, and the area under the receiver operating characteristic curve (ROC-AUC). Detailed results are shown in Figure 2 (independent test set performance) and Table 2 (cross-validated performance on the training set).

Final model discrimination performance that has been evaluated on the independent test dataset is illustrated in Figure 2. The ROC curves were generated exclusively from the held-out test set that was not used during model training or cross-validation. NB achieved the highest discriminative performance with an ROC-AUC of 0.90, followed by LR (0.81). RF (0.76) and the ensemble voting (EV) classifier (0.77) demonstrated moderate discrimination ability, while DT yielded the lowest ROC-AUC (0.67).

In contrast, Table 2 summarizes model performance during the training phase, where stratified 5-fold cross-validation was conducted exclusively within the training dataset. The reported values represent mean $\pm$ standard deviation across folds. During cross-validation, NB achieved the highest mean ROC-AUC; however, its accuracy, precision, recall, and F1-score were comparable to those of LR and RF, indicating balanced but not uniformly superior performance across all metrics. RF exhibited strong overall performance with high accuracy and F1-score. EV demonstrated moderate performance with relatively stable variability across folds, whereas DT consistently underperformed across most evaluation metrics.

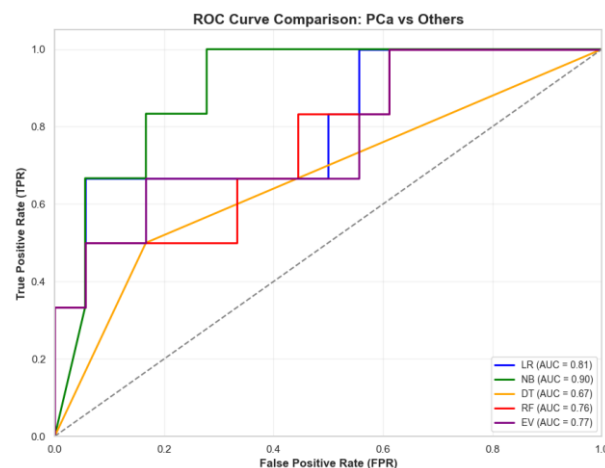


Figure 2. Receiver Operating Characteristic (ROC) Curves of Five Machine Learning Classifiers Evaluated on the Independent Test Dataset (Not Used During Training)

Note: ROC curves were generated from the independent held-out test dataset, which was not used during model training or cross-validation. Shaded areas represent 95% confidence intervals.

Table 2. Training-Phase Performance of Machine Learning Classifiers Using Stratified 5-Fold Cross-Validation Within the Training Dataset (Mean $\pm$ SD)

Model	Accuracy	Precision	Recall	F1-score	ROC-AUC
LR	0.76 $\pm$ 0.07	0.71 $\pm$ 0.15	0.76 $\pm$ 0.07	0.71 $\pm$ 0.10	0.81 $\pm$ 0.02
NB	0.76 $\pm$ 0.04	0.74 $\pm$ 0.05	0.76 $\pm$ 0.04	0.74 $\pm$ 0.04	0.90 $\pm$ 0.02
RF	0.82 $\pm$ 0.04	0.84 $\pm$ 0.04	0.82 $\pm$ 0.04	0.81 $\pm$ 0.05	0.76 $\pm$ 0.03
DT	0.74 $\pm$ 0.04	0.77 $\pm$ 0.03	0.74 $\pm$ 0.04	0.74 $\pm$ 0.03	0.67 $\pm$ 0.03
EV	0.74 $\pm$ 0.04	0.77 $\pm$ 0.03	0.74 $\pm$ 0.04	0.74 $\pm$ 0.03	0.77 $\pm$ 0.02

*Note: Performance metrics were calculated exclusively within the training dataset by using stratified 5-fold cross-validation.

Probabilistic Output Analysis of Naïve Bayes

To further characterize the predictive behavior of the NB classifier, we examined the distribution of predicted probabilities for the PCa class (Figure 3). The probability density plot demonstrated a bimodal pattern, with non-PCa cases concentrated near 0 and PCa cases clustered near 1. This clear separation between the two groups created distinct probability areas, making the output easy to interpret. Such well-delineated probability regions highlighted the strength of the AI model, confirming that NB not only achieved the highest AUC but also provided straightforward, clinically interpretable risk stratification.

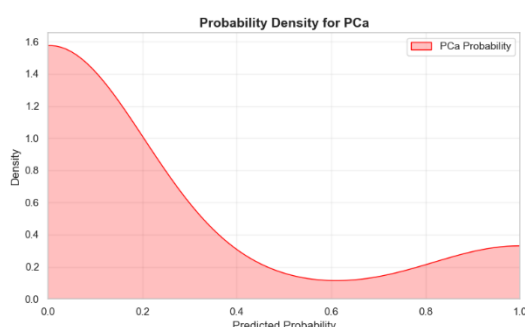


Figure 3. Probability density distribution of predicted probabilities for the PCa class generated by the NB classifier

The distribution exhibits a polarized pattern, with a substantial proportion of predictions concentrated near the lower and upper bounds of the probability range. This tendency toward high-confidence predictions is consistent with the strong discriminative performance of the NB model (ROC-AUC = 0.90).

Discussion

Principal Findings

This study demonstrated that urinary VOC signal-derived features, when analyzed using machine learning, effectively distinguished PCa from non-PCa cases. All five classifiers achieved reasonable discriminative ability, confirming that

VOC-based models were broadly feasible for this diagnostic task. Among them, the NB classifier achieved the highest performance with an ROC-AUC of 0.90, together with balanced accuracy, precision, recall, and F1-score. Importantly, the probabilistic output of NB showed clear separation between PCa and non-PCa, supporting its potential role as an interpretable risk stratification tool.

Comparison with Previous Studies

Our earlier exploratory work (Suthat Na Ayutaya *et al.*, 2024) identified candidate VOC parameters by using univariate statistics and descriptive comparisons. That approach was appropriate for hypothesis generation, but it did not extend to predictive modeling. In contrast, the present analysis employed a consensus feature selection strategy (MI + RFI) to reduce dimensionality and enable unbiased model construction. This transition from candidate panels to data-driven feature selection represented a methodological shift rather than a contradiction of earlier work; both approaches addressed different stages of biomarker discovery.

Previous reports, such as Gao *et al.* (2019) and Liu *et al.* (2023), evaluated urinary VOCs for PCa detection by using GC-MS platforms. While those methods demonstrated promising accuracy, their reliance on compound-level profiling limited scalability in real-world screening. By contrast, our use of semiconductor-based sensors generated structured VOC signals at low cost and with high practicality. This distinction is critical because prostate cancer screening is intended to identify candidates for biopsy, not to replace biopsy itself. A low-cost, portable, and reproducible sensor platform is more compatible with population-level deployment than expensive laboratory-based assays.

Interpretation and Clinical Relevance

The comparative performance of the classifiers indicated that all selected algorithms were viable, with ROC-AUC values ranging from 0.67 to 0.90. The superior performance of NB suggested that its

probabilistic framework aligned well with the distribution of VOC features in this dataset. The bimodal probability distribution produced by NB further highlighted its ability to generate clinically interpretable risk scores. Such outputs could be tailored to clinical context: sensitivity thresholds emphasized for screening, or specificity prioritized for confirmatory decisions.

The relatively lower performance of DT and RF models might reflect sample size constraints and high feature dimensionality, which increased variance. In contrast, linear (LR) and probabilistic (NB) approaches generalized more effectively, highlighting that simpler models could sometimes outperform more complex tree-based methods in small biomedical datasets.

Strengths and Innovations

This study extended our prior cohort analysis by introducing an AI-driven framework that advanced beyond descriptive comparisons. The consensus feature selection method enhanced reproducibility by combining statistical dependency with model-based importance. Using engineered VOC features rather than predefined panels allowed the AI to recognize complex signal interactions that might not be captured in candidate-based approaches. In addition, employing semiconductor sensors, instead of GC-MS, provided a cost-effective and portable strategy that was practical for screening purposes. Finally, the probabilistic outputs of NB added interpretability, enabling clinicians to view results not only as binary predictions but as probability-based risk estimates.

Limitations

Several limitations of this study should be acknowledged. The cohort size was modest ($n = 123$, including 29 PCa cases), and although SMOTE was applied to mitigate class imbalance, synthetic oversampling could not fully substitute for additional real-world data. External validation in larger, independent cohorts is therefore an essential next step to confirm generalizability.

However, the potential impact of the limited sample size was partly offset by the richness of the feature space. Each participant contributed 120 structured VOC parameters across multiple sensors and heating cycles, yielding more than 14,000 signal-derived features in total. This high-dimensional dataset, combined with a rigorous feature selection process, provided sufficient variance for robust model training despite the modest cohort size.

Another limitation is that semiconductor sensors, while cost-effective and highly reproducible, do not identify specific chemical compounds in the way that GC-MS profiling can. This constrains direct biochemical interpretation of the signals. Nevertheless, the trade-off favors practical application: sensor-based platforms are more portable, affordable, and scalable, making them particularly suited for screening workflows where the goal is to triage patients for confirmatory biopsy rather than replace histopathological diagnosis.

Future Directions

Future research should aim to expand the cohort size and include multi-center validation to test reproducibility across populations. Comparative evaluations against PSA, MRI, and biopsy outcomes will clarify the clinical role of VOC-AI tools as adjunctive diagnostics. Importantly, integration into decision support systems and prospective clinical trials will be necessary for real-world adoption. Given the robust and interpretable performance of the NB model in this study, it represents a promising candidate for further development and clinical translation.

Conclusion

This study demonstrates that urinary VOC signal-derived features, captured by low-cost semiconductor sensors, can be effectively leveraged through machine learning to distinguish prostate cancer from non-cancer cases. By applying a consensus feature selection strategy and evaluating multiple classifiers, all models achieved reasonable diagnostic performance, with the NB classifier showing the most robust and interpretable results (ROC-AUC = 0.90). These findings highlight the potential of combining semiconductor-based VOC profiling with AI as a practical, non-invasive screening tool to complement existing strategies and guide biopsy decisions. With further validation in larger, multi-center cohorts, this approach could be advanced toward clinical application for prostate cancer risk stratification.

Funding

This study received no financial support for the conduct of the research. Article publication expenses were supported by the Institute of Research and Development, Suranaree University of Technology.

Author Contributions

SC and AP were the primary contributors to data analysis, AI model design, and interpretation of machine learning outcomes. AP supervised the overall project design, secured administrative approvals, and led manuscript preparation. SA and WA were responsible for developing the computational framework and producing visualizations. CP and SC participated in clinical data extraction and project logistics. AP provided additional technical consultation. All authors contributed to the manuscript and approved its final version.

Data Availability Statement

Data generated and analyzed during this study are available from the corresponding author upon reasonable request.

Ethical Approval

This study was conducted as part of a broader research protocol previously reviewed and approved by the Human Research Ethics Committee under reference number EC-67-136. All procedures adhered to the principles of the Declaration of Helsinki.

Declaration of Generative AI

The authors declare that no generative artificial intelligence tools were used in the preparation of this manuscript.

Acknowledgements

The authors extend their heartfelt appreciation to Dr. Chaianan Tantisatirapoon, formerly of the School of Surgery, Institute of Medicine, Suranaree University of Technology, for his pioneering input and valuable guidance that laid the groundwork for this research. We also wish to acknowledge Dr. Rungrueang Pattanakul of the Synchrotron Light Research Institute, Thailand, whose expert advice greatly shaped the design and strategic direction of the AI learning framework applied in this study. Our sincere thanks go to all patients and staff of the urology clinic at Suranaree University of Technology Hospital for their kind cooperation, particularly in granting access to pathological data and urine samples used for volatile organic

compound (VOC) analyses. This study was financially supported by the Institute of Research and Development, Suranaree University of Technology, which provided funding for article publication.

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