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Review Article

Cross-population validation of PESI-MS and machine learning models for pancreatic cancer diagnosis: Insights from an independent Japanese cohort

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A B S T R A C T

Pancreatic cancer remains a major challenge in oncology due to its poor prognosis as it is symptomatically dormant and is found in later intractable stages. This study aims to validate the robustness and versatility of a diagnostic framework combining Probe Electrospray Ionization Mass Spectrometry (PESI-MS) and machine learning models for early PDAC detection across different ethnicities. Building on our previous study that demonstrated high sensitivity and specificity in a Taiwanese PDAC high-risk and PDAC patient cohort, we used those prebuilt models on an independent cohort of 38 Japanese patients diagnosed with pancreatic cancer. The model assessed sustained its performance on the Japanese cohort, correctly identifying 97% of all cancer cases, indicating robustness to demographic differences. Moreover, enhancing the original model with dimensionality reduction achieved 100% sensitivity, correctly detecting every cancer case. These findings underscore the potential of PESI-MS and machine learning as universal diagnostic tools for PDAC, with significant implications for early detection that improves patient outcomes. The findings advocate for further validation in larger, multi-ethnic studies to confirm the clinical implementation of this approach and its integration into global screening strategies for high-risk populations.

1. Introduction

Pancreatic cancer incidence has been rising globally in recent years and is projected to become the second leading cause of cancer-related deaths in the U.S. by 2030 (Gordon-Dseagu et al., 2017). Pancreatic ductal adenocarcinoma (PDAC) constitutes a representative subclass of pancreatic cancer (Park et al., 2021). It remains one of the most challenging malignancies to detect and treat, with five-year survival rates persistently around 10%. The lack of reliable diagnostic methods for early-stage detection brings about these dismal outcomes. For example, early-stage detection at stages 0 and 1 was only 3.7% in a Japanese cohort (Kanno et al., 2018), the figure urging us to develop a novel strategy for early diagnosis. Therefore, early diagnosis, especially in high-risk populations, has the potential to improve survival rates by enabling timely therapeutic interventions. Existing biomarkers, such as carbohydrate antigen 19-9 (CA19-9), suffer from limitations including false positives and are insufficient to detect early-stage disease (Conroy et al., 2023), highlighting the urgent need for innovative diagnostic solutions. Furthermore, recent upsurge of mucin-producing carcinoma developed from intraductal papillary mucinous carcinoma (IPMC) is also an important target of surveillance by a sensitive diagnosis (Ohtsuka et al, 2024).

Recent advances in mass spectrometry-based technologies have opened new avenues for biomarker discovery and early cancer detection. These techniques enable the high-resolution analysis of molecular profiles, offering insights into complex disease signatures that were previously inaccessible. By leveraging these advancements, researchers are working toward diagnostic platforms that not only improve sensitivity and specificity but also provide robust, reproducible results across diverse patient cohorts.

Probe Electrospray Ionization Mass Spectrometry (PESI-MS) is a simple analytical technique capable of capturing enumerative molecular profiles with minimal sample preparation (Takeda et al., 2020). Coupled with machine learning algorithms, PESI-MS demonstrated remarkable

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potential in distinguishing PDAC cases from high-risk controls based on spectral patterns without annotating each molecular profile. In the previous study (Chung et al., 2020), we validated this approach in a large Taiwanese cohort (n = 587 patients), achieving high sensitivity and specificity for PDAC detection, surpassing 90% in each parameter. However, the potential of those models to generalize across diverse ethnicity remains to be established, a critical step for their clinical implementation globally.

The aim of our previous study was to develop and validate a high-performance, non-invasive method for the early detection of pancreatic cancer using PESI-MS combined with machine learning. The goal was to discriminate PDAC sera from those with high-risk cohort, especially at early-stages of PDAC, with a method that is rapid, cost-effective, and easily implemented in clinical settings.

In contrast, the primary objective of the current study is to validate the robustness of the previously developed PESI-MS and machine learning diagnostic framework in detecting pancreatic cancer within a different ethnic population. To achieve this, we applied the previously built support vector machines (SVM) model to an independent cohort of 38 Japanese patients, comprising only of pancreatic cancer cases covering all cancer stages. This validation cohort provides an opportunity to evaluate the model under different demographic and biological conditions. Achieving high classification accuracy in this cohort could demonstrate the approach's versatility and reliability, paving the way for larger international validation studies and eventual clinical implementation. By confirming that the PESI-MS combined with machine learning model sustained its performance on the Japanese cohort, this study underscores the potential of this technology as a universal diagnostic tool for pancreatic cancer. The findings hold promise for the integration of this methodology into global screening strategies, targeting high-risk populations and advancing the fight against pancreatic malignancies.

2. Methods

2.1. Study design

This study was designed to validate the diagnostic framework combining PESI-MS and machine learning models for pancreatic cancer detection across different populations. The study used the Taiwanese cohort as a database (Chung et al., 2020) and a Japanese cohort for validation.

2.2. Modelling dataset: Taiwanese cohort

The original study population included serum samples from two distinct groups. The primary group comprised 322 patients with confirmed pancreatic cancer, while the second group consisted of 265 high-risk controls with a family history of pancreatic cancer, all originally collected at the National Taiwan University Hospital. Details of Taiwanese cohort are as described previously (Chung et al., 2020).

2.3. Validation dataset: Japanese cohort

To validate the models built on the above-mentioned Taiwanese cohort, we incorporated a validation cohort of 40 samples from Japan (from 38 patients, out of which 2 patients provided their sera twice), consisting of 31pancreatic ductal adenocarcinoma (PDAC), 3 intraductal papillary mucinous carcinoma (IPMC), 2 neuroendocrine neoplasm, 1 acinar carcinoma and 1 squamous cell carcinoma patients. The Japanese cohort was specifically selected to evaluate the robustness of the previously developed models in an independent sample set. This cohort included 38 pancreatic cancer patients with pathologically confirmed histotypes, ensuring alignment with the inclusion criteria of the original study. The samples were collected from the National Center for Global Health and Medicine (NCGM), Tokyo between 2013 and 2020. As in the Taiwanese cohort, the Japanese samples were processed and analyzed using the same PESI-MS methodology described previously (Takeda et al., 2020; Chung et al., 2020).Table 1 shows the demographics of the38Japanese patients included in this study.

This validation cohort served as a key component of this study's objective. Notably, two patients provided serum samples both prior to and following chemotherapy, yielding a total of 40 samples. To ensure consistency with the other patients, we excluded the post-chemotherapy measurements and retained only 38pre-chemotherapy samples. By applying the established diagnostic framework to these new samples, we aimed to assess whether the models, trained exclusively on the Taiwanese cohort, would maintain their high performance when evaluated on a distinct population, potentially differing in metabolic profiles and disease characteristics. This study is approved by the Ethical Committee of University of Yamanashi.

2.4. The PESI-MS serum sample analysis

PESI-MS analysis was performed using a PESI-MS system installed on a single quadrupole mass spectrometerLCMS-2020 (Shimadzu, Kyoto, Japan). In this process, 5 µl of serum was mixed with 95 µl of 50% ethanol in a 1.5 ml tube and vortexed for 2 min to facilitate protein precipitation and sample preparation. The samples were then centrifuged at 150,000×g for 1 min to separate the supernatant from the precipitated material, which was collected for subsequent analysis.

Sample analysis using PESI-MS was conducted as described previously (Takeda et al., 2020). Each specimen was analyzed in both positive and negative ion modes, ensuring a comprehensive profiling of the serum's molecular components. The mass spectra for each sample were generated using the LabSolutions software (Ver. 5.82 SP1; Shimadzu).

The ionization measurement was conducted for a duration of 2 min, using a time window of 10 s to capture the maximal ion intensity, which typically reached around 50,000 counts. This 10-s window was divided into 10 consecutive sets of spectral data, which were then analyzed to ensure the stability and reliability of the ionization process throughout the analysis. The *m/z* range of the analysis spanned from 10 to 2000 Da, and the data were divided into 1990 distinct bins. Each bin corresponds to a unitary mass, and the spectral accuracy of the Shimadzu PESI-MS 2020 was considered to ensure precise *m/z* measurements. Each of these bins contains detailed information on the mass-to-charge ratio (*m/z*) as well as the peak intensity, which are then utilized to construct a comprehensive database of spectral profiles for further analysis and comparison.Fig. 1 illustrates the workflow of sample collection, PESI sample analysis, model building and model validation processes used in this study.

2.5. Data processing and machine learning models

Previously trained models, including SVM and random forest (RF), utilized PESI-MS spectra as well as patients age, sex, carcinoembryonic

Table 1
Demographics of the 38 Japanese patients with pancreatic cancer used for cross-ethnicity model validation.

	mean (standard deviation) or (%)
Age	71.8 (9.31)
Sex	
Female	n = 18(47%) mean age 75.5(8.9)
Male	n = 20(53%) mean age 68.7(8.4)
PDAC stage	
0	n = 1
1	n = 1
2	n = 13
3	n = 2
4	n = 21
CA-19-9	988.6 (1701)
CEA	6.1 (7.8)

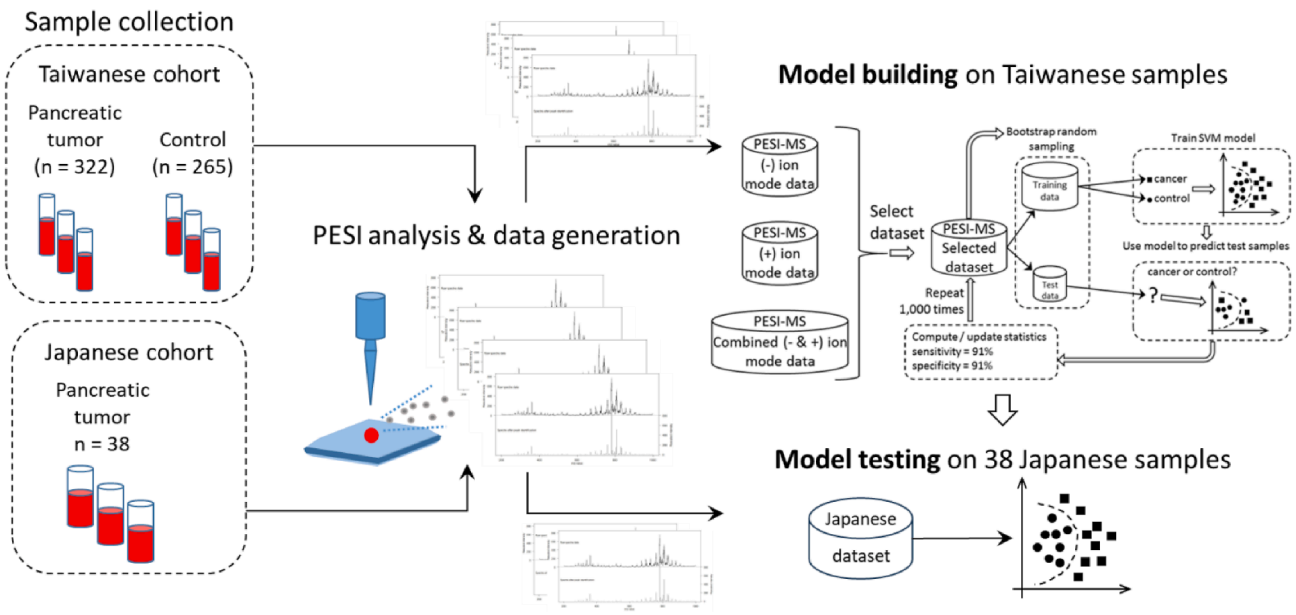

Fig. 1. Workflow of data collection, sample analysis and data analysis processes.

antigen (CEA) and CA19-9 levels as predictors. The original SVM model build on the Taiwanese samples were applied directly to the new Japanese cohort without further retraining. On this paper we focus only on the results produced by SVM, the best overall performing model (Chung et al., 2020).

As further (and independent) enhancement to the original approach, dimensionality reduction using linear discriminant analysis (LDA) was introduced as a new and additional step in data preparation. The models were then retrained (exclusively on the Taiwanese samples) identically to the original SVM model using the reduced feature set. These results, derived from the LDA-enhanced + SVM model, are distinct from those reported for the original models. The results obtained for the original (SVM only) and enhanced model (LDA-enhanced + SVM) are presented in the Results section. The primary goals of applying LDA were to reduce dimensionality, minimize noise, and emphasize the most relevant predictors. By projecting the data onto a lower-dimensional space while preserving class separability, LDA streamlines the analysis, enhancing model efficiency and its ability to identify key features associated with the outcome.

3. Results

3.1. Clustering of Japanese patients by cancer stage

Fig. 2 illustrates the clustering of patients in the Japanese cohort by cancer stage using Linear Discriminant Analysis. The plot shows that patients are distinctly grouped by cancer stage along the two linear discriminants (LD1 and LD2), which explain 81% and 22% of the variance, respectively. The separation between stages, particularly between Stage 1, Stage 2, and Stage 4, suggests clear discriminative potential for the classification model based on the features used.

3.2. Predictive models applied to the Japanese cohort

Classification performance metrics (accuracy, sensitivity and F1 score) were calculated on the original SVM only model. Applying the original model (SVM without retraining) to the 38 Japanese samples resulted in only one misclassification (37 correct out of 38), with the model achieving 97% accuracy and sensitivity and an F1 score of 0.98.

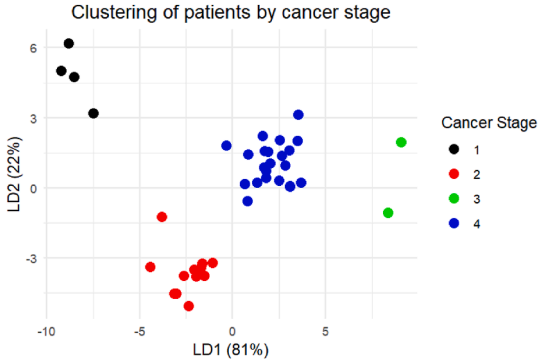

Fig. 2. Linear discriminant analysis clustering of the 38 Japanese patients by stage of cancer.

3.3. Misclassified sample and mass spectra

Out of 38 samples, only one produced a false negative in positive ion mode. In this case, the spectral pattern closely resembled the average spectra from the other samples (Fig. 3). However, a closer examination reveals slight deviations in both intensity and pattern from the average, suggesting that a combination of subtle differences in the mass spectra may contribute to accurate diagnosis.

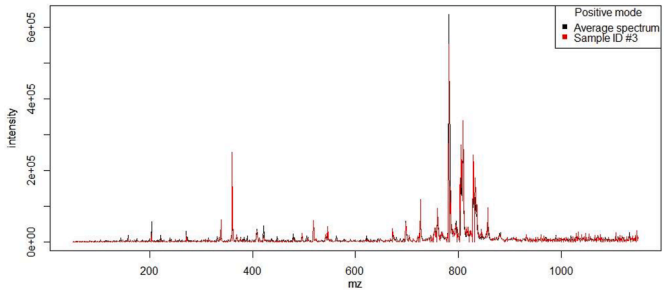

Fig. 3. Mass spectral pattern of misclassified case almost takes after that of average spectrum from 37 samples.

To minimize noise and highlight the most relevant predictors, the model was retrained exclusively on the Taiwanese samples. As a first step, LDA was applied for dimensionality reduction. The SVM model was then retrained identically to the original version but using the reduced feature set. When this newly trained machine learning model was applied to the Japanese cohort, it achieved outstanding performance with 100% accuracy and sensitivity and an F1 score of 1. These results demonstrate the approach's ability to accurately distinguish pancreatic cancer cases from high-risk individuals, without any misclassifications, regardless of histological subtype. The perfect concordance between predicted and actual classifications underscores the reliability of the PESI-MS and machine learning based diagnostic approach across different populations and tumor histotypes. Fig. 4 presents the confusion matrices generated by the SVM classification model.

4. Discussion

4.1. Interpretation of results

This study evaluated the performance of previously developed diagnostic models for the pancreatic cancer on an independent cohort of 38Japanese samples. The findings demonstrate exceptional robustness and versatility, as the models achieved 100% classification accuracy across all subsets of the data comprising various histotypes. Below, the results are detailed by cohort, cancer stage and histological diagnosis.

Classification performance across all cancer stages: when applied to the entire cohort of 38 Japanese pancreatic cancer samples, the model correctly classified all cases as "cancer," yielding near 100% sensitivity**.** This result confirms the model's ability to reliably detect pancreatic cancer, even when evaluated on a geographically distinct population, underscoring its potential utility in broader clinical applications. Of note, samples from early-stages such as 0 and 1 were correctly classified as cancer, implying its applicability to the screening of early-stage cancer in high-risk cohort.

Early-Stage Cancer Detection (stages0+1 + 2): The cohort of early-stage PDAC samples (15cases) also achieved 100% sensitivity**,** with all samples correctly classified as "cancer." Early detection of pancreatic cancer is a critical challenge in clinical settings, as early-stage disease is often asymptomatic and difficult to identify. The ability of the models to achieve strong classification accuracy for these stages highlights their potential as an early detection tool, which could significantly improve patient outcomes by enabling timely intervention.

Advanced-Stage Cancer Detection (stages 3 + 4): The models demonstrated unwavering effectiveness in classifying advanced-stage pancreatic cancer cases (23samples), achieving again 100% sensitivity with no misclassifications. While advanced-stage disease typically presents with more distinct clinical and molecular features, maintaining high accuracy in this group demonstrates the robustness of the models across varying disease presentations.

Diagnostic performance on the non-PDAC neoplasms: The cohort included histological subtypes beyond PDAC, such as mucin-producing tumors and neuroendocrine tumors. As all cases were accurately classified as cancer, this system demonstrates applicability across all pancreatic cancer types, regardless of histotype. Given the poor prognosis of neuroendocrine tumors, the approach presented here holds significant potential for improving patient outcomes. Additionally, mucin-producing tumors, such as intraductal papillary mucinous neoplasms (IPMN), often progress to malignancy, further underscoring the system's value as a powerful tool in the early detection and management of pancreatic cancer.

4.2. Generalizability and robustness

Reliable detection capabilitiesreaching100%across all cohorts, including early-stage and advanced-stage cancers, underscores the robustness and generalizability of the diagnostic models. These findings suggest that the models are not only sensitive to the molecular signatures of pancreatic cancer but also transferable across independent datasets and populations suggesting cross-ethnicity robustness and reliability.

4.3. Clinical implications

Performance in this independent cohort supports the reproducibility of the models' diagnostic classifications across cancer stages and histotypes. The ability to detect pancreatic cancer at an early stage is particularly promising, as early diagnosis offers the greatest opportunity to improve survival rates. By achieving high accuracy in early-stage samples, these models demonstrate significant potential to assist clinicians in identifying pancreatic cancer during its most treatable phase. Furthermore, their consistently high accuracy in advanced stages reinforces their clinical reliability across the full disease spectrum.

Looking ahead, these results lay the foundation for future validation in larger and more diverse cohorts, including both cancer and control samples. Such additional validation is essential for assessing specificity and confirming the models' suitability for widespread clinical application.

This study also affirms the generalizability of the PESI-MS and machine learning diagnostic framework. The remarkable classification performance in the Japanese cohort underscores the method's robustness across populations, addressing a key limitation of previous research. External validation is a critical step toward clinical implementation, and these results suggest that the models are well-positioned for larger, prospective trials.

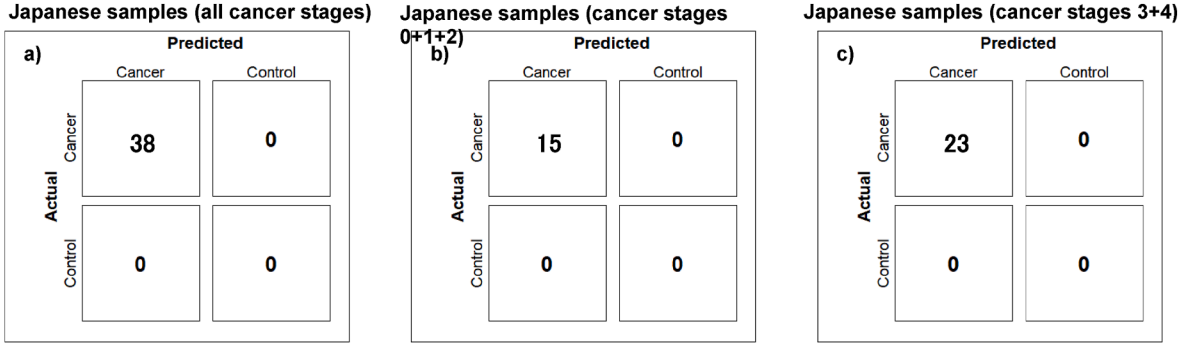

Fig. 4. Confusion matrices generated by the LDA-enhanced + SVM model to evaluate effectiveness of the predictive model applied to the Japanese validation cohort. a) all cancer stages; b) stages 0 + 1 + 2 cases and c) stages 3 + 4.

4.4. Implications for early detection

Although this study is limited by its small sample size and the absence of control cases, its findings highlight a significant advancement in pancreatic cancer detection. The ability to accurately identify PDAC at early-stages across different populations underscores the potential of this methodology for high-risk groups, including individuals with familial pancreatic cancer syndromes or new-onset diabetes.

Moreover, considering the rising prevalence of intraductal papillary mucinous neoplasm (IPMN) (Kiritani et al., 2023) and the necessity of regular monitoring to detect malignant transformation, this system holds great promise. Its ability to detect pathological conversion instantaneously could provide a valuable tool for early intervention, further enhancing its clinical utility in pancreatic cancer screening and surveillance.

4.5. Limitations and future directions

While this study successfully validates the models in a smaller cohort, its exceptional accuracy across multiple cancer stages and a distinct ethnic population highlights its strong potential for broader clinical application. To further enhance its impact, larger-scale studies incorporating multi-center international datasets will be essential. Additionally, prospective studies assessing the integration of PESI-MS into routine clinical workflows would provide valuable insights, paving the way for its seamless adoption in real-world healthcare settings. Despite the current limitations, these findings represent a critical step forward in advancing non-invasive, highly accurate diagnostic tools for pancreatic cancer.

5. Conclusion

This study highlights the remarkable robustness and broad applicability of a diagnostic framework that integrates Probe Electrospray Ionization Mass Spectrometry (PESI) with machine learning for pancreatic cancer detection. By achieving exceptional classification accuracy and sensitivity in an independent cohort, the results provide further evidence of the framework's versatility across different populations, addressing a critical limitation of previous diagnostic studies.

The implications of these findings are significant. Early detection of pancreatic cancer, particularly in asymptomatic or high-risk individuals, is essential for improving survival rates. These findings suggest that the PESI-MS and machine learning approach may serve as a promising adjunct to current diagnostic strategies, especially for early-stage PDAC detection. This is particularly significant given the limitations of existing biomarkers such as CA19-9, which lack the sensitivity and specificity needed for early detection and are often affected by benign conditions like chronic pancreatitis and cystic lesions. Furthermore, the framework's consistent performance across all disease stages reinforces its reliability as a diagnostic method throughout the cancer progression spectrum.

From a broader perspective, this study exemplifies the power of combining innovative analytical techniques like PESI-MS with machine learning to tackle complex challenges in oncology. The results confirm the feasibility of developing non-invasive, rapid, and highly accurate diagnostic tools that can be applied across diverse clinical and demographic settings (Hakoda et al., 2022; Giordano et al., 2022; Iwano et al., 2021). These technologies have the potential to revolutionize cancer screening, facilitating earlier intervention and significantly improving patient outcomes.

While these findings are highly promising, they also emphasize the need for further research to ensure the widespread clinical adoption of this approach. The study's small validation cohort, while sufficient to demonstrate feasibility, highlights the necessity of larger-scale studies to confirm these results. Multi-center, international trials incorporating both control and disease samples will be critical to establishing the framework's specificity and real-world applicability. Additionally, prospective studies evaluating the integration of PESI-MS into routine diagnostic workflows and its cost-effectiveness compared to traditional methods will further support its clinical translation. These limitations are inherent to the scope and design of the present study and are beyond its control.

Future research should also focus on refining the machine learning algorithms to account for variations in biomarker profiles influenced by ethnicity, dietary habits, and environmental factors. Investigating the framework's role in high-risk populations, such as individuals with familial pancreatic cancer syndromes or new-onset diabetes, will further validate its application in targeted screening programs. Moreover, integrating additional biomarkers and metabolic profiles from routine blood tests could enhance the algorithm's predictive power. Expanding research to assess its potential in monitoring disease progression and treatment response may also open new avenues for its clinical application.

In conclusion, this study provides compelling evidence that PESI-MS combined with machine learning is a powerful, dependable, and universally applicable diagnostic tool for pancreatic cancer. The outstanding classification performance achieved in an independent cohort not only reinforces its cross-population generalizability but also lays the foundation for its integration into global cancer screening strategies. While further research is needed to refine and validate the approach on a larger scale, these findings mark a crucial step toward transforming pancreatic cancer diagnostics. Ongoing refinements to this methodology are poised to enhance early detection rates and therapeutic decision-making, potentially transforming clinical management paradigms for this aggressive malignancy.

CRediT authorship contribution statement

Elon Correa: Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Wen Yuan Chung:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Nobuyuki Takemura:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Norihiro Kokudo:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Sen Takeda:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of interests

This work was sponsored by Shimadzu Corporation for their financial and technical support. The author Wen Yuan Chung is an Associate editor for this journal, and Executive editor for special issue " Surgery Oncology in the Age of AI" and was not involved in the editorial review or the decision to publish this article.

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