A Comprehensive Survey on AI-Driven Methods for Pancreatic Cancer Grading using High-Resolution Pathological Images

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Abstract
Pancreatic cancer is one of the most aggressive and lethal forms of cancer, with early detection and accurate grading being crucial for effective treatment planning and improving patient outcomes. Recent advancements in artificial intelligence (AI) have shown promise in enhancing the diagnostic accuracy of medical imaging for pancreatic cancer detection and classification. However, most of the existing AI models focus on imaging modalities such as MRI, CT, and PET scans, leaving a significant gap in utilizing pathological images for cancer grading. This survey provides a comprehensive review of the current state-of-the-art AI models developed for pancreatic cancer detection, highlighting the use of deep learning and ensemble learning approaches on MGG (May-Grünwald-Giemsa) and H&E (Haematoxylin and Eosin) stained pathological images. It discusses the effectiveness of binary and multiclass classification models, the application of transfer learning for feature extraction, and the integration of nature-inspired optimization techniques for feature engineering. The survey identifies key research gaps, including the lack of focus on pancreatic cancer grading using pathological images, and suggests future directions for developing AI-based grading systems that leverage high-resolution pathological images. The proposed methodologies aim to bridge the gap by developing robust, accurate, and clinically applicable AI models, which could significantly enhance the diagnostic and prognostic capabilities in clinical oncology.

Keywords: pancreatic cancer, artificial intelligence, deep learning, ensemble learning, transfer learning, pathological images, MGG stained images, H&E-stained images, cancer grading, feature extraction.
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1. Introduction

Pancreatic cancer is a highly lethal malignancy with a poor prognosis and is currently the fourth leading cause of cancer-related deaths worldwide. According to the American Cancer Society, in 2024, an estimated 64,050 new cases of pancreatic cancer will be diagnosed in the United States alone, and approximately 50,550 individuals are expected to die from the disease. Globally, the incidence rate varies significantly by region, with the highest rates observed in developed countries. The age-standardized incidence rate (ASR), Aspartate Aminotransferase to Alanine Aminotransferase Ratio (AAR) for pancreatic cancer is around 5.5 per 100,000 people worldwide as shown in Figure 1. This rate tends to increase with age, with most cases occurring in individuals over 65 years. The rising incidence of pancreatic cancer has been

attributed to several factors, including increased life expectancy, lifestyle changes, and a higher prevalence of risk factors such as obesity, smoking, and diabetes.Medical imaging techniques are becoming increasingly important for PCs [1,2], as they provide tissue information and could be used for diagnosis, treatment determination, and prognosis monitoring [3,4]. Current advanced medical imaging tools primarily include computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), positron emission tomography (PET), and pathological images [5,6]. Improvements based on these imaging tools include EUS-guided fine-needle aspiration (FNA) and biopsy (FNB), contrast-enhanced EUS (CE-EUS), contrast-enhanced computed tomography (CE-CT), contrast-enhanced magnetic resonance imaging (CE-MRI), and positron emission tomography (PET/CT).

The above-mentioned imaging tools have advantages and disadvantages. CT is the most commonly used tool that acquires tomographic images of the body through X-rays [7]. At the same time, its resolution for small and variable organs like the pancreas is limited. EUS has a higher resolution but is complicated to operate and the field of view is narrow. MRI generates soft-tissue imaging and can better distinguish between tumor and normal tissues but has a longer time and higher cost. PET reflects tumor metabolism that assesses PC metastasis but has lower resolution and is usually combined with CT. Pathological imaging is an invasive way of slicing and staining tissue samples. Although there are now multiple medical imaging modalities available, some early PCs will not be detected by CT, MRI, or EUS [8]. Manual diagnosis based on currently available imaging techniques is insufficient. The accurate diagnosis of PC still relies highly on invasive biopsies after the imaging step, which is complex and time-consuming. This delay may result in patients missing critical treatment opportunities.

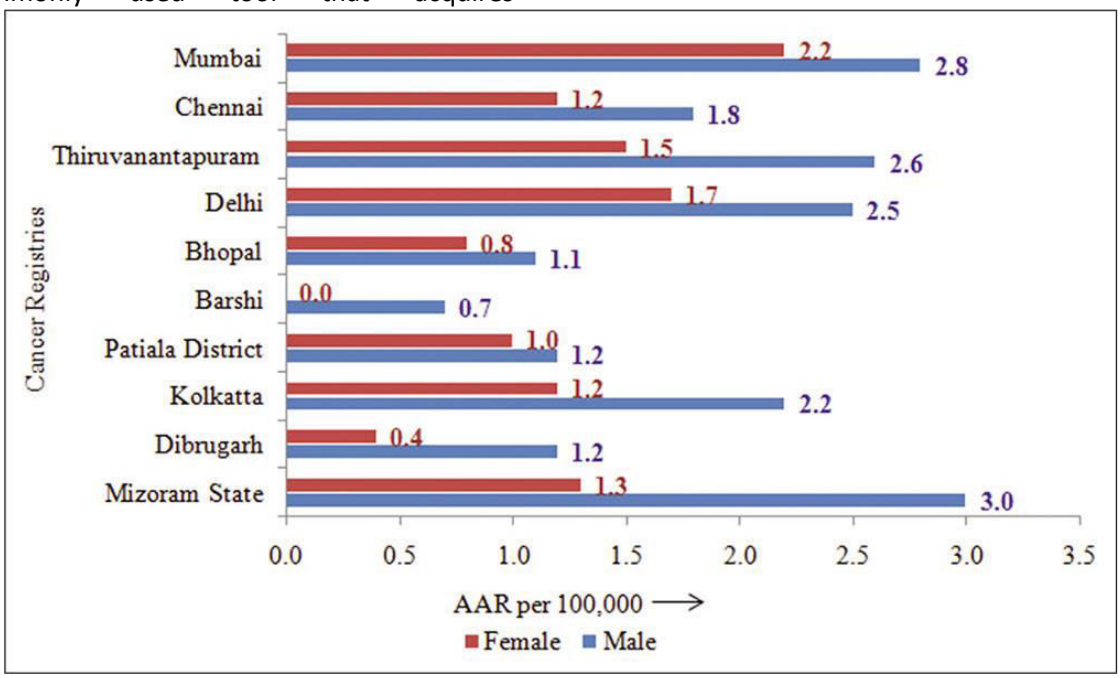

Figure 1. Statistics on pancreatic cancer.

In recent years, the AI-powered image process has been applied to the diagnosis of PC in the experimental stage with reasonable results, marking the beginning of a shift from the traditional diagnosis dependent on biopsy. AI is a computer technology that can simulate specific human behaviors, such as learning, reasoning, problem-solving, and decision-making. Deep learning is a milestone of AI and utilizes propagation algorithms, which have made significant breakthroughs in automated image analysis with high Accuracy, Specificity, and Recall in diagnosing PC and differentiating it from chronic pancreatitis [9,10]. Well-

trained AI models can process input medical images and output analytical results within seconds, minimizing the trauma to the patient. Studies have shown that AI models report comparable results with medical experts in PC detection and even better results in some cases [11,12,13,14]. Their significant cost and speed advantages also improve clinical diagnosis, treatment, and prognosis of PC, reducing the workload of doctors and the financial burden of patients.

For the diagnosis stage, the low prevalence of PC leads to a lack of early screening. Fast, low-cost AI models facilitate the scaling up of medical image-based early screening. Small and subtle lesions or precursors that might be missed by traditional diagnostic methods could be detected. As a result, more potential PC patients could notice their health condition in time and be operated on as soon as possible. The PC metastasis rate and mortality will be reduced. For the treatment stage, AI models could predict PC metastasis and the survival time of patients after surgery using image information [14,15]. Since the tissue structure of PC is complex and targeted therapies are insufficient for high costs, AI could help doctors make appropriate treatment decisions and reduce overall costs. Rational and timely treatment strategies in turn improve the prognostic outcome of PCs. Studies have shown that, in clinical trials, AI can reduce the burden of routine tasks in the medical workflow, allowing doctors to spend more time tackling other challenges [16]. Therefore, the automated analysis of pancreatic images by AI is an efficient and convenient aid to doctors.

2. Research Motivation

Patients diagnosed with pancreatic cancer face numerous challenges, primarily due to the aggressive nature of the disease and its often late-stage diagnosis. One of the most significant problems is the lack of early symptoms, which means that the disease is typically detected only after it has progressed to an advanced stage. This delay in diagnosis significantly limits treatment options and reduces the chances of survival. Furthermore, the symptoms that do manifest, such as abdominal pain, jaundice, and weight loss, are often non-specific and can be mistaken for other less severe conditions. This ambiguity can lead to further delays in seeking medical help. Additionally, pancreatic cancer patients frequently experience a high symptom burden and a poor quality of life due to severe pain, digestive issues, and fatigue. The psychological impact of a pancreatic cancer diagnosis, compounded by the low survival rates, can lead to depression and anxiety, which are often exacerbated by the physical toll of the disease and its treatments.

For healthcare professionals, managing pancreatic cancer presents a complex set of challenges. One of the primary difficulties is the lack of effective screening methods for early detection. Unlike other cancers, such as breast or colorectal cancer, there are no standardized screening tests for pancreatic cancer in the general population, largely because the pancreas is located deep within the abdomen and is difficult to examine using conventional imaging techniques. Moreover, the symptoms are vague and non-specific, making early diagnosis rare. Even when pancreatic cancer is detected, treatment options are limited and often have severe side effects. Surgical resection is only viable for a small percentage of patients and is often followed by aggressive chemotherapy or radiation, which can further compromise the patient's quality of life. Oncologists also face challenges in managing the disease's rapid progression and the frequent development of resistance to available treatments, necessitating the need for ongoing research into more effective therapies and the development of precision medicine approaches tailored to individual patient profiles.

3. Literature Survey

Some reviews have discussed the potential and effectiveness of combining AI techniques and pancreatic images. Cazacu et al. [17] surveyed deep learning models, mainly CNNs, to differentiate PC and chronic pancreatitis (CP) on EUS images and validated their high performance in diagnosis. Pereira et al. [18] examined AI in CT and MRI images for PDAC

early detection and prognosis evaluation. Kenner et al. [19] discussed the early detection of PDAC, the application of AI models to PDAC, the organizational structure to screen for PDAC, and the reflections of government, industry and advocacy. Yang et al. [20] outlined early PC screening and diagnosis approaches, such as imaging, pathological examination, serological examination, and liquid biopsy, with AI recognized as an innovative potential strategy.

Huang et al. [16] summarized AI applications in medical image analysis, pathological examination, and biomarkers in PC diagnosis; survival time, risk of recurrence, metastasis, and response to therapy in PC prognosis. Both limitations and significant potential of AI were identified in their work. Hameed and Krishnan [21] explored the AI-enabled PC diagnosis on four imaging modalities (EUS, MRI, CT, and PET), cytopathology, and serological markers. Ethical concerns about AI tools were also noted. Schlanger et al. [22] discussed AI and machine learning models for three PC surgery stages: preoperative diagnosis, intraoperative complication prediction, and prognostic evaluation. Their findings suggested that, while AI demonstrated great potential in diagnosis and prognosis, its research on intraoperative applications was still limited. Mikdadi et al. [23] detailed the advancements of AI in PDAC diagnosis and prognosis from CT images.

Jan et al. [24] synthesized AI techniques in PC prediction and early diagnosis, including AI tasks, models, medical data types, programming languages, and validation approaches. They noted that future PDAC detection could rely on a suite of models for whole-body regions rather than specific organs. Katta et al. [25] reviewed AI in PC biomarkers detection, diagnosis, and prognosis. They also identified shortcomings of AI applications in knowledge, data processing, ethics, and clinical implementation. Zhao et al. [26] summarized AI in early screening, diagnosis, surgical treatment, and prognostic prediction. They also identified potential dividends in the future despite current limitations of AI in terms of interpretability, generalizability, sample size, and ethical concerns. Daher et al. [27] delved into machine learning and deep learning approaches in PC detection based on CT, EUS, MRI, and PET images and their ethical concerns.

In [28], authors proposed using AI and ML to enhance pancreatic cancer immunotherapy. Their work focuses on utilizing these technologies to predict patient responses to various immunotherapy treatments, thereby optimizing therapeutic strategies [29]. This involves the integration of large-scale datasets and the development of predictive models to identify biomarkers associated with effective immune responses.In [30], authors conducted a multi-atlas labeling challenge that extends beyond the cranial vault to evaluate automated segmentation algorithms. The proposed methodology involves using a combination of multiple atlases to improve segmentation accuracy for various organs, including the pancreas, in medical imaging dataset [31]. This approach leverages the anatomical variability captured in different atlases to enhance the robustness of segmentation outcomes.

The Pancreas AI Platform (PAIP) 2023 challenge focuses on the development of advanced AI algorithms for pancreatic cancer diagnosis and treatment planning [32]. The proposed work includes designing models capable of high-accuracy segmentation and classification of pancreatic tissue in histopathological images, aiming to facilitate more effective clinical decision-making.In [33], authors introduced the M3bunet architecture, a lightweight neural network model optimized for mobile platforms, specifically designed for pancreas segmentation in CT scans. The model employs a mean max pooling technique and incorporates U-Net architecture to achieve high accuracy in segmentation with reduced computational costs, making it suitable for deployment on resource-limited devices.In [34], authors developed the Medical Image Segmentation Transformer (MIST), which integrates a Convolutional Attention Mixing (CAM) decoder for enhanced segmentation of

medical images. This approach leverages the strengths of both transformers and convolutional networks to achieve precise segmentation of pancreatic tumors, aiming to improve diagnostic accuracy and treatment planning.In [35], authors explored the application of the Segment Anything Model (SAM) to medical images, specifically for the segmentation of pancreatic tumors. The proposed methodology involves fine-tuning SAM for medical image analysis by incorporating domain-specific data, resulting in improved segmentation performance for pancreatic cancer detection and monitoring.

In [36], authors proposed a universal and extensible language-vision model tailored for organ segmentation and tumor detection in abdominal CT scans. This model integrates natural language processing and computer vision techniques to enhance the interpretability and accuracy of segmentation tasks, particularly for detecting pancreatic tumors and delineating surrounding anatomical structures.In [37], authors presented a semi-supervised 3D segmentation method for pancreatic tumors using PET/CT images. The proposed approach incorporates a mutual information minimization and cross-fusion strategy to improve segmentation accuracy, particularly in cases with limited labeled data.In [38], authors proposed methodology utilizes a deep learning model with channel and spatial long-range dependencies to improve pancreatic cancer pathology image segmentation. The model leverages multi-scale feature extraction and attention mechanisms to accurately segment pathological features in pancreatic tissue, aiding in more precise diagnosis and treatment planning.

In [39], authors reviewed various imaging modalities and the role of AI in enhancing the diagnostic accuracy of pancreatic adenocarcinoma. Their work focuses on integrating AI with imaging techniques such as CT, MRI, and PET to improve tumor detection, characterization, and treatment response evaluation, ultimately aiming to enhance patient outcomes.In [40], study reviewed recent advancements in Pancreatic Ductal Adenocarcinoma (PDAC) research enabled by AI. The authors discuss various AI-driven methodologies for early detection, treatment planning, and prognosis prediction, highlighting the potential of machine learning models in improving the management of PDAC.In [41],authors proposed a method using Fourier Transform Infrared (FT-IR) imaging combined with machine learning for detecting pancreatic intraepithelial neoplasia and grading duct pathology. This approach leverages spectral data to differentiate between normal and cancerous tissues, offering a non-invasive diagnostic tool for early-stage pancreatic cancer detection.

In [42], proposed methodology involves a fully automated AI model based on CT imaging to predict extrapancreatic perineural invasion in pancreatic ductal adenocarcinoma. The model utilizes deep learning techniques to analyze radiological features, providing a non-invasive predictive tool for assessing tumor aggressiveness and guiding surgical decision-making.In [43], authors developed a radiomics-based interpretable model to predict the pathological grade of pancreatic neuroendocrine tumors. This model integrates image-based features extracted from radiological scans with machine learning algorithms to provide a non-invasive method for tumor grading, facilitating personalized treatment strategies.In [44], focused on the role of biomarkers in the early detection of pancreatic cancer. The author discusses various biomarker candidates and their potential integration with AI-based screening tools to improve early diagnosis rates, thereby enhancing patient survival outcomes.

In [45], authors explored the role of AI in advancing pancreatic cancer research, particularly in areas such as early detection, personalized treatment planning, and prognostic assessments. Their work emphasizes the integration of AI technologies with clinical workflows to enhance decision-making processes and improve patient care.In [46], authors examined the prognostic significance of tumor budding in pancreatic carcinoma using a digitalized image approach enhanced by AI. The methodology involves

using AI algorithms to quantify tumor budding in histopathological images, providing an objective and reproducible measure of tumor aggressiveness that can inform prognosis and treatment strategies.In [47], authors employed machine learning techniques to predict the recurrence of resected pancreatic ductal adenocarcinoma based on histopathological images. The proposed methodology integrates image analysis with clinical data to develop predictive models that can identify patients at high risk of recurrence, guiding post-surgical treatment decisions.

In [48], authors conducted a systematic review of AI applications in pancreas endoscopic ultrasound imaging. The review highlights various AI methodologies used to enhance image quality, automate diagnostic processes, and improve the accuracy of pancreatic cancer detection, ultimately aiming to refine endoscopic imaging techniques.In [49], the proposed work involves developing AI-based models for the early detection of pancreatic cancer in the era of precision medicine. The authors focus on integrating multi-omic data with imaging modalities to create comprehensive diagnostic tools that improve early detection and patient stratification in pancreatic cancer management.In [50], authors introduced the Molecular Twin AI platform, which integrates multi-omic data to predict outcomes for pancreatic adenocarcinoma patients. This platform combines genomic, proteomic, and clinical data to create personalized predictive models, aiming to tailor treatment strategies and improve patient outcomes based on individual molecular profiles.

4. Research Gaps

Most of the existing literature on AI models for pancreatic cancer detection has focused on the use of imaging modalities such as MRI, CT, and PET. These imaging techniques have been extensively utilized because they are non-invasive and provide valuable anatomical and functional information, aiding in the detection and staging of pancreatic cancer. AI models, particularly those leveraging deep learning algorithms, have shown promising results in enhancing image interpretation, increasing diagnostic accuracy, and reducing the time required for radiological assessments. However, despite these advancements, the primary focus on MRI, CT, and PET images has certain limitations, especially in the early detection and precise characterization of pancreatic lesions, which are often challenging to identify in these imaging modalities.

The reliance on MRI, CT, and PET imaging for AI models in pancreatic cancer detection also presents challenges related to accessibility and cost. These imaging techniques are expensive and not universally available, particularly in low-resource settings, which limits their applicability in routine clinical practice. Moreover, while AI models have enhanced the detection of pancreatic masses and metastases, they often struggle with differentiating between benign and malignant lesions with high accuracy. This limitation is partly due to the inherent variability in the appearance of pancreatic lesions across different imaging modalities and the dependence on the quality of the imaging data. Additionally, the AI models developed to date are primarily focused on binary classification tasks, such as detecting the presence or absence of cancer, rather than providing a more nuanced analysis that could assist in clinical decision-making, such as predicting tumor aggressiveness or response to treatment.

Another significant research gap is the limited exploration of AI models for pancreatic cancer grading using pathological images. While MRI, CT, and PET imaging are valuable for initial detection and staging, pathological images obtained from biopsy or surgical resection provide a more definitive diagnosis by revealing the cellular morphology and tissue architecture. Grading pancreatic cancer based on pathological images can offer crucial insights into tumor aggressiveness, guide treatment planning, and predict patient outcomes more accurately. However, there has been a noticeable lack of studies developing AI models specifically for this purpose. Pathological images are rich in detail and present unique challenges for AI, such as

the need for high-resolution image analysis and robust algorithms capable of handling heterogeneous tissue patterns. Despite these challenges, developing AI models for pancreatic cancer grading in pathological images could significantly enhance diagnostic accuracy and treatment personalization. No existing research has thoroughly investigated or developed AI models focused on grading pancreatic cancer using pathological images, highlighting a critical gap in the literature.

5. Advantages of Histopathology Images

MGG (May-Grünwald-Giemsa) and H&E (Hematoxylin and Eosin) stained slides are crucial tools in histopathology for diagnosing pancreatic cancer. The MGG stain is primarily used to highlight cytoplasmic components and cellular details, particularly in fine-needle aspiration cytology, where it aids in the identification of malignancies by differentiating between types of cells, such as inflammatory cells and neoplastic cells. This stain is effective in diagnosing pancreatic cancer because it can highlight subtle morphological changes and provide clear differentiation of cellular components, aiding pathologists in distinguishing between benign and malignant cells. On the other hand, H&E staining is the gold standard in histology and is widely used in pancreatic tissue biopsies. It allows for the visualization of tissue architecture and cellular morphology by staining nuclei blue and the extracellular matrix and cytoplasm pink. This contrast helps pathologists evaluate the tumor margins, determine the degree of differentiation, and identify characteristic features of pancreatic cancer, such as glandular patterns and necrosis.

Compared to imaging modalities like MRI and CT scans, MGG and H&E-stained slides offer several advantages in the diagnosis and assessment of pancreatic cancer. Figure 2 shows the sample MGG and H-E Stain images with different grades of pancreatic cancer.Firstly, these staining techniques provide a microscopic view that reveals cellular and tissue-level details that imaging modalities cannot capture. While MRI and CT scans are excellent for detecting tumor size, location, and metastatic spread, they often lack the resolution to differentiate between tumor types or provide definitive diagnostic information about the nature of the lesions. MGG and H&E stains, however, allow for a more precise histopathological examination, which is critical for determining the exact type and grade of the cancer, guiding appropriate treatment strategies. Secondly, these staining techniques can be more cost-effective and quicker, offering immediate insights from biopsies without the need for extensive imaging sessions. This can be particularly advantageous in settings where rapid diagnosis is necessary, and where access to advanced imaging technology may be limited. Additionally, histopathological examination using these stains can reveal genetic and molecular features of the cancer that imaging cannot, which is increasingly important for targeted therapies and personalized medicine approaches.

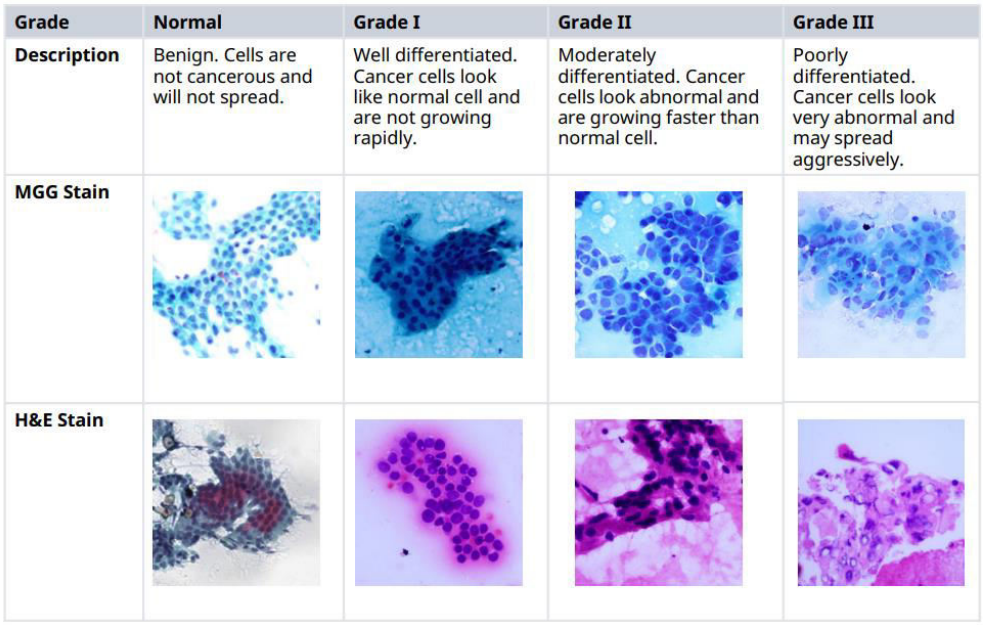

Figure 2. Sample MGG and H-E Stain images with different grades of pancreatic cancer.

6. Future Directions

The novel future directions to overcome above research gaps are defined as follows

- To develop a binary classification model using MGG and H-E datasets utilizing deep learning approaches to accurately differentiate between pancreatic cancer and non-cancerous tissues.
- To develop a multiclass classification model using MGG, H-E datasets, and a combined dataset, employing transfer learning for feature analysis and ensemble learning techniques to classify multiple types of pancreatic tissue abnormalities.
- To develop a multiclass classification model using MGG and H-E datasets, along with a combined dataset, incorporating nature-inspired optimized feature engineering techniques with transfer learning and ensemble learning to enhance classification accuracy and robustness in identifying various pancreatic tissue types.

7. Conclusion

In conclusion, this survey highlights the advancements and limitations in the current use of AI models for pancreatic cancer detection and grading, particularly focusing on the application of deep learning and ensemble learning techniques to MGG and H&E stained pathological images. While significant progress has been made in developing binary and multiclass classification models, the survey reveals a critical research gap in the lack of AI-based grading systems specifically designed for pancreatic cancer using high-resolution pathological images. Addressing this gap could lead to more accurate diagnostic tools and personalized treatment strategies, improving patient outcomes. Future research should focus on developing innovative AI models that integrate transfer learning and nature-inspired optimization techniques for feature extraction and engineering. These models should aim to enhance the robustness and accuracy of cancer grading, leveraging the detailed information available in pathological images to provide better clinical decision support. Additionally, expanding the dataset with more diverse and high-resolution images and exploring multimodal approaches combining imaging modalities with pathological data could further advance the field and pave the way for more effective and precise pancreatic cancer diagnosis and treatment strategies.

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