Artificial intelligence and imaging for risk prediction of pancreatic cancer: a narrative review

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Objective: To emphasize the importance of pancreatic imaging and the application of artificial intelligence (AI) for enhanced risk prediction of pancreatic ductal adenocarcinoma (PDAC).

Background: Detecting PDAC at the early stage is challenging as the disease either remains asymptomatic or presents nonspecific symptoms. Risk prediction of PDAC is an efficient strategy as subsequent targeted screening can assist in diagnosing cancer at the early stage even before the symptoms appear. However, the lack of specific clinical and epidemiological predictors of PDAC makes prediction a highly challenging task. Detecting precursor changes in the pancreas can potentially assist in the risk prediction of PDAC as the precancerous pancreas evolves through biological adaptations-presented as morphological and textural changes on abdominal imaging. However, such microlevel "clues" usually remain unnoticed or unappreciated, partly due to the unavailability of tools to detect and interpret such complex measurements, making the risk prediction of PDAC an unresolved problem.

Methods: This review study highlights the limitations of the current risk prediction models of PDAC and the importance of abdominal imaging for predicting PDAC. A suggestive narrative is made as to how recent AI tools can assist in extracting precise measurements of biomarkers, detecting early signs and precancerous abnormalities, quantifying tissue characteristics, and revealing complex features potentially indicative of future incidence of pancreatic cancer (PC) using abdominal imaging. With the help of peer examples of other cancers, a case is built about the application of AI in utilizing image features of the pancreas to enhance risk prediction of PDAC. Furthermore, the challenges of AI applications including insufficient data for model training, risk of data privacy violation, inconsistent data labeling, and limited computational resources, and their potential solutions are also discussed.

Conclusions: The recent advancement in the domain of AI is a potential opportunity to utilize automated tools for the identification of imaging-based indicators of PDAC and perform enhanced risk prediction of cancer. With this awareness and motivation, better management of PDAC has expected.

Keywords: Risk prediction; pancreatic cancer (PC); abdominal imaging

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal cancer accounting for over 90% of pancreatic cancer (PC) cases (1-3). PDAC is sporadic cancer that aggressively develops metastases. Although having a relatively low incidence rate, it is currently the 4th leading cause of all cancer deaths in both males and females (1,4,5), with expectations to become the 2nd most by 2030 (4,6,7). About 60,430 new cases and 48,220 deaths are expected to be PDAC-related in 2021 in the United States (8). Over 80% of PDAC diagnosis occurs at an advanced stage when complete surgical resection of tumor is complicated due to extensive vascular involvement and metastasis (9-12). This leaves a small portion of patients (<15%) having surgically resectable disease. As a result, the overall five-year survival rate (5YSR) of PDAC barely exceeds ~10%, though recent studies consistently suggest that early diagnosis of PDAC can improve treatment outcome and elevate the current 5YSR up to 50% (1,13,14). However, early-stage diagnosis is challenging as PDAC remains asymptomatic or presents nonspecific symptoms until cancer reaches advanced stage (3,11,15).

Predicting risk of PDAC allows subsequent targeted screening of high-risk individuals through longitudinal surveillance programs and consequently enhances cancer diagnosis at an early stage. Efficient risk prediction also enables treating certain precancerous conditions to decelerate or even prevent the development of PDAC. Unfortunately, risk prediction of PDAC is currently unresolved partially due to the absence of sensitive and specific biomarkers, lack of a viable prediction system, and low prevalence. Various approaches (16-18) have been proposed to identify individuals at high risk for PDAC or with early-stage disease by considering several clinical and epidemiologic characteristics including blood tumor markers, genetic biomarkers (e.g., familial PC), demographic characteristics, imaging findings (e.g., detectable lesions), pre-existing health conditions (e.g., pancreatitis, abdominal pain, recent onset diabetes), and lifestyle (e.g., weight loss, smoking, drinking alcohol) as risk indicators of PDAC. However, these indicators are nonspecific to PDAC and show association to a broad range of other diseases too. Thus, screening of a large population presenting these general indications is impractical, costly, and prone to result in false positives with the potential for leading to adverse outcomes considering risks of interventions to make the diagnosis and the anxiety in patients.

Studies show that the precancerous pancreas evolves through biological adaptations–expressed as morphological and textural variations on pancreatic imaging. Extensive analysis of such changes during or prior to development of PDAC via noninvasive abdominal imaging (e.g., MRI, CT, etc.) can provide insight to unique tissue characteristics and basis for precise prediction of PDAC. Systematic integration of these features with other indicators (e.g., clinical, genetic) can significantly improve estimating cancer risk and reduce prediction errors (e.g., false-positive rates), and unnecessary intensive examinations. However, such microlevel changes are imperceivable due to the complex location of pancreas, limited tissue contrast, and subjective bias, or neglected due to absence of connection to PDAC.

Artificial Intelligence (AI) offers enormous techniques for fast and extensive analysis of medical images for (I) accurate detection and classification of precancerous lesions, (II) discovering predictors through detailed examination of complex features, and (III) integration of multiple predicators to perform comprehensive risk assessment. AI models (19) for image analysis for risk prediction of several cancers have shown tremendous performance that surpasses traditional procedures in terms of accuracy and time efficiency. Unfortunately, the AI has not been yet fully utilized to address the challenges withholding efficient risk prediction of PDAC.

In this review article, the current risk prediction mechanisms for PDAC and their limitations are discussed. Supported by several peer examples of other cancers including breast cancer (BC), prostate cancer (PCa), and lung cancer (LC), a case is built as to how AI can efficiently assist in discovering highly specific predictors of PDAC through extensive assessment of pancreatic morphology and texture and precancerous lesions using abdominal imaging; followed by performing improved risk prediction by integrating the discovered predictors with conventional indicators of PDAC. The recent AI strategies to aid developing robust prediction models are also discussed. The purpose of this review is to emphasize the importance of abdominal imaging and AI application to resolve issues withholding efficient risk prediction of PDAC and provide readers with motivation and hope to expect improved management of PDAC in near future. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-117/rc).

Risk indicators of PDAC

A variety of complications and measurements are associated with the future incidence of PDAC. This includes clinical, hereditary, pre-existing health conditions, lifestyle, and demographic characteristics.

Elevations of certain blood compositions including carbohydrate antigen (CA)19-9 (20) and carcinoembryonic antigen (CEA) (21,22) are considered early indicators of PDAC. A recent study (23) claimed that CEMIP (cell migration-inducing hyaluronan binding protein), a newly identified protein, also called KIAA1199, can be a complementary marker to CA19-9 for enhanced prediction. However, the elevation could be due to other causes.

Also, genetic factors have been consistently linked with increased risk of developing PDAC. The familial pancreatic cancer (FPC) (24) describes that kindreds containing at least two first-degree relatives with PC have at ~10% higher risk to develop PDAC (24) than the general population. Genetic testing is usually the first assessment performed for FPC individuals to seek specific germline genetic mutations (25,26) including BRCA1, BRCA2, PALB2, hereditary pancreatitis, and Peutz-Jeghers syndrome.

Moreover, subjects with certain pre-existing health conditions are usually at high risk for PDAC. This includes pancreatic disorders such as pancreatitis that increases risk of PDAC by 2 to 3 times that of general population (27). Also, the new onset diabetes mellitus (NOD) has a bidirectional relationship with PDAC (28,29). Although its unknown when exactly NOD contributes to PDAC, there is established evidence that diabetes associated with ~25% of PDAC patients is diagnosed between 6 to 24 months before cancer diagnosis (30), suggesting that diabetes can both herald PDAC and act as a potential risk factor for PDAC. other studies have shown that subjects (>50 years) with NOD are at 6–8 times higher risk of developing PDAC within 3 years compared to non-diabetic population (28,29). Also, about 3–10% prevalence of PDAC is observed in NOD patients of age above 50 (31,32).

Furthermore, factors like smoking, alcohol (33), obesity (34), and poor diet (35) increases risk of PDAC. The risk in the FPC setting is observed even higher in smokers than in nonsmokers (36). The American Cancer Society has reported that chain cigarette smoking, and obesity increases the risk of PDAC by 25% and 20% respectively (37,38).

None of these factors is perfectly sufficient for predicting or confirming of PDAC as these factors are mostly general and are associated to a broad range of other diseases. Most of these do not even justify performing PDAC targeted screening. However, a combine assessment of all these factors may provide significant 'clues' to proceed with further screening or a good indication of future incidence of PDAC.

Image indicators

Pancreatic imaging plays a vital role in managing PDAC through prediction, diagnosis, staging, and prognosis. With several modalities including (e.g., CT, MRI) each with high versatility, pancreatic imaging provides a safe noninvasive means to look for specific potential predictors of PDAC. Several pancreatic complications occurred prior to or during the development of PDAC manifest unique morphological and textural changes on pancreas imaging. Such changes merit attention and can be regarded as credentialed predictors of PDAC. The distal parenchymal atrophy (39), intraductal papillary mucinous cancer of the pancreas (IPMNs) (40), and intraductal calculi (pancreatolithiasis) (41) are some of the disorders that cause progressive increase in tissue heterogeneity of the pancreas and are frequently considered as risk factors. In addition, pancreatic inflammation (42) and ductal dilatation (43) are consistently regarded as precancerous conditions that cause shape and size deformation of the pancreas and its components. Moreover, the signal intensity of the pancreatic region, where the tumor will likely develop, starts varying from peripheral regions during tumor development. For example, healthy cells turning into cancer start appearing darker on a CT scan. Furthermore, certain locations in the pancreas have relatively higher chances of developing tumor. For example, in 75–80% of the PDAC cases, the tumor develops in the head of the pancreas, while 20–25% chance for both body and tail (11,44). A consensus is that local changes in pancreatic subregions can provide concise measures to quantify risk. However, all these micro-level variations are difficult to determine by visual assessment, and therefore usually ignored or misperceived as normal, missing the opportunity to efficiently predict the risk of PDAC.

Risk prediction models of PDAC

Since clinical and genetic risk factors of PDAC lack sensitivity and specificity, imaging can be potential means to explore and appreciate adaptive features to cancer that can be integrated with existing indicators to achieve enhanced prediction. However, humans have limitations identifying, measuring, or interpreting such microlevel indicative features. Fortunately, the enormously advanced AI techniques for image processing and analysis together with conventional statistical methods offer insight into complex imaging data and reveal hidden patterns of information that assists in forecasting disease incidents.

Recently, conventional methods for risk prediction of several common cancers have been replaced by AI models that work by integrating multi-source risk factors (e.g., imaging, clinical) and perform enhanced risk prediction. For example, despite there are several risk prediction models (45-47) for BC including BCRAT (48), BCSC (49), BRCAPRO (50), BOADICEA (51), the Myriad model (52), the Rosner-Colditz model (53), the Tyrer-Cuzick (IBIS) model (54), and the Claus model (55), each utilizing variety of risk factors including hormonal and genetic indicators, radiation exposure, breast density, and lifestyle, the American Cancer Society guidelines urge to perform annual mammographic screening for women over 40 to have an enhanced risk prediction of BC. Since there is strong consensus that AI models could strengthen mammography analysis, several automated prediction models were recently proposed using imaging data alone that had surpassed the prediction accuracies of many of the existing non-image-based prediction models. Examples include a deep neural network (56,57), proposed in a multi-institutional study for assessment of breast density and beyond using mammograms, outperformed many existing risk prediction models. Also, a hybrid model (58) combining logistic regression and deep learning (DL) network, was trained on mammograms and outperformed Tyrer-Cuzick model and many others.

PCa is another example where AI has assisted to improve risk prediction. Recently, a hybrid model to stratify risk of PCa (59) was proposed that combined both machine learning (ML) and radiomic analysis of multiparametric MR images of the prostate and had achieved higher sensitivity and predictive value than conventional approaches. Also, a multi-institutional study (60) observed that ML techniques offer improved prostate specific antigen (PSA)-based risk stratification of PCa.

For LC, recently, promoting and implementing LC screening programs using low-dose CT imaging have resulted in improved diagnosis of LC at early-stage. To support such programs, a largescale study developed a deep ML model [referred to as DeepLR (61)] to predict LC risk using low-dose CT. The model is capable of accurately predicting which lesions will likely develop LC within a specific timeframe. The model showed excellent performance with a 1-, 2- and 3-year time-dependent AUC values for LC diagnosis of 0.968±0.013, 0.946±0.013, and 0.899±0.017.

AI for risk prediction of PDAC

Although AI applications remarkably improved risk prediction of many cancers, predicting PDAC using AI analysis of pancreatic imaging has remained forsaken, partially due to insufficient data to discover specific predictors in the precancerous pancreas, and perform model development and validation. Another possible reason is that imaging performed at the precancerous or early stage of PDAC usually comprises of CT examination which offers limited tissue discrimination to appreciate microlevel indicators of PDAC by naked eyes.

The peer examples indicate that AI can efficiently assist performing an in-depth examination of such images to discover and quantify predictors and systematically integrate such features with clinical and genetic indicators to perform enhanced prediction. To the best of our knowledge, only two research groups performed risk stratification of PDAC using CT images and AI.

A team at Kaiser Permanente Southern California (62) performed a retrospective study and developed a model that integrates known imaging (measured using CT images) and clinical risk factors to perform risk stratification of PDAC. They considered pancreas-related morphologic features from CT/MR images of individuals with their pancreas indicating ductal dilation (a potential PDAC predictor) at a precancerous stage. Some of the morphological and clinical features include atrophy, calcification, pancreatic cyst, and pancreatic ductal irregularity, and age, sex, race/ethnicity, tobacco, and alcohol use, respectively. Using a multi-state prediction model, they achieved reasonable discrimination (c-index 0.825–0.833) between those who developed PDAC and those who did not.

A team of imaging scientists and abdominal surgeons at Biomedical Imaging Research Institute of Cedars Sinai Medical Center (CSMC) Los Angeles extensively analyzed morphological and textural features of the pancreas in pre-diagnostic CT scans of PDAC patients (63). Their hypothesis was that the pre-diagnostic scans show unique features which are indicative of development of PDAC. They discovered several radiomic features which were significantly different than the normal and cancerous pancreas, and potentially predictive of PDAC. These scans were originally obtained for patients with non-PDAC reasons (e.g., other abdominal disorders due to vehicle accident or slip, etc.), who later (between 6 months to 3 years) developed PDAC. The discovered predictors were then used in a ML model to automatically perform risk stratification by classifying CT scans into control (healthy pancreas) and pre-diagnostic (high risk) classes. In the external validation process, their system achieved an average prediction accuracy of 86%. Deploying such a model in radiology room can significantly assist in identifying high risk individuals of PDAC. For example, it is reported that abdominal pain is the single most common reason for over 7 million patients visiting emergency room (ER) in the US; of which some subjects eventually develop PDAC in the next few years though remain undiagnosed until late stage. Since, CT examination is included in the current protocol of care for those having abdominal pain, a potential application to this proposed model would be to target such a group.

Both models perform reasonably well and justify the proposed design concept for risk prediction. However, the efficacy of these systems is still inadequate on account of insufficient data and model overfitting issues and thus require extensive external validation.

Discussion

Early diagnosis of PDAC is the call for immediate attention as the cases of PDAC are on the rise (10,64). The United States Prevention and Screening Task Force (USPSTF) has recommended a grade of "D" for screening for PDAC (65) in the general population suggesting that (I) imaging-based biomarkers for early detection are not yet established, and (II) the average risk population (~12 per 100,000) reduces the pre-test possibility of a laboratory test being truly positive. It is therefore the right time to take advantage of the emerging paradigm of AI and extensively explore the imaging features of pancreas to quantify the degree of elevated risk. With the support of AI, imaging of pancreas can be a vital source for classifying precancerous lesions, obtaining accurate measurements, discovering reliable predictors, and developing integrated systems to assist risk stratification of PDAC. The risk stratification of the PDAC will encourage follow-up targeted screening that could utilize AI-based techniques (66,67) to assist detecting PDAC in the early stage.

AI modelling for PDAC prediction (the opportunity)

In the recent years, the AI has addressed several potential challenges, related to deploying AI-based models, by offering alternate solutions.

Pretrained networks (68) offer a unique opportunity to train algorithms for tasks like lesion detection and classification, and pancreas segmentation even with a small amount of data. These AI networks are trained on thousands-to-millions of examples to perform similar tasks and can be adjusted to provide comparable performance for the current model.

Data privacy can be ensured when multicenter collaborative studies are performed to meet data requirements, maintain patients' data privacy, and obtain multidisciplinary support during model development. The concept of federated learning (FL) (69) has made it possible to run AI algorithms for model training and validation without exposing or physically transferring the data to other sites. The FL schemes ensure the similar performance of the model as if all the data is residing on a single site without violating HIPPA and local institutional guidelines for data privacy.

Reference data labeling is a requirement for rigorous training and unbiased validation. Manual outlining of structures like pancreas, tumors, and lesions can be highly subjective, time-consuming, and prone to errors. The AI-based platforms provide mechanisms for radiologists from different sites to collaborate and ensure labeling consensus and produce highly reliable labels using commercial labeling software.

Computational efficiency is no longer a challenge as several institutes and commercial companies have started offering access to their hardware resources to run AI models with high-speed performance.

PDAC management—a future prospective

With the recent improvement in pre-operative, radiation, and chemotherapy regimens (by exploring new drugs and drug combinations), surgical innovations (such as irreversible electroporation (70,71), and strategies to enhance the immune response against PDAC, along with the current efforts to develop AI-imaging-based models for risk prediction, one can foresee significant improvement for PDAC management. Also, choosing the best imaging modality for PDAC screening within the multitude of options and when and how often imaging should be used in surveillance are still debatable issues.

In a nutshell, the fusion of AI and imaging can adequately address major issues complicating risk prediction of PDAC to a significant extent and offer better alternatives to current manual systems in terms of accuracy, time efficiency, and consistency. Undoubtedly, it is a potential research opportunity for scientists to further investigate and take advantage of state-of-the-art AI technologies to upgrade current prediction systems. Recently, the National Institute of Health at United States has started a large multicenter study at BIRI-CSMC to further enhance and validate their proposed risk prediction model on large datasets. With this strong mutual benefit for both the public and the health industry, a far superior PDAC management system is expected in near future.

Conclusions

This brief review emphasizes the importance of risk prediction of PDAC, and the role of AI and imaging to address issues related to risk prediction of PDAC. The application of AI-based imaging for risk prediction of three common cancers including BC, PCa, and LC was discussed. Moreover, the current challenges and recent AI advancement to overcome such complications were also discussed. A fair concern has been observed in health institutes and research supporting departments about early diagnosis of PDAC and the scope of risk prediction of PDAC. Efforts have been started to make progress and it can be expected that a better management of PDAC would be a reality soon.

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