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Review: Role of Current Pancreatic Ductal Adenocarcinoma Biomarkers: CA19-9 and CEA. Limitations and future perspectives

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Abbreviations:

Pancreatic duct adenocarcinoma (PDAC), Carcinoembryonic antigen (CEA) Carbohydrate antigen 19-9 (CA 19-9), Cancer antigen 125 (CA 125), Endoscopic Ultrasound (EUS), Fine Needle Aspiration (FNA), Computed tomography (CT), and Magnetic resonance imaging/Magnetic resonance cholangiopancreatography (MRI), Karnofsky performance status (KPS), Eastern Cooperative Oncology Group performance status (ECOG PS), gemcitabine plus nab-paclitaxel (GN), Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs), glycosylphosphatidylinositol (GPI) intercellular adhesion molecule 1 (ICAM-1), osteoprotegerin (OPG) Pancreatic Intraepithelial Neoplasia (PanIN) MicroRNAs (miRNAs), open reading frames (ORF), Argonaute-2 (hAgo2), Circulating tumor cells (CTCs), Quantitative real-time reverse-transcription PCR (qRT-PCR),

1. Summary

Pancreatic ductal adenocarcinoma (PDAC) accounts for over 90% of pancreatic cancers, hence the reason the terms have been used interchangeably over the years. It is one of the most aggressive and brutal cancers known, due to its initial silent asymptomatic presentation which later grows into a mass that produces symptoms. As pancreatic cancer incidence grows in developed countries, it is estimated to overthrow colorectal cancer by the year 2030. With a five-year survival rate of less than 12%, early diagnosis and screening have been the focus point of studies concerning the disease with biomarkers Carbohydrate Antigen 19-9 (CA 19-9) and Carcinoembryonic Antigen (CEA) leading the way. These biomarkers have shown promise and are routinely used to detect pancreatic cancer, but there are major limitations to their use. The specificity and sensitivity of both Carbohydrate Antigen 19-9 and Carcinoembryonic Antigen are still suboptimal in asymptomatic individuals. Scientists have tackled this problem by adding and combining the findings of several promising biomarkers instead of reviewing them individually. The goal of this review was to update our understanding of CA 19-9 and CEA regarding pancreatic cancer and to find out any future implementations of the biomarkers. Another goal was to highlight where the biomarkers might fall short and emphasize what future studies should pay attention to.

2. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a poor prognosis, limited screening methods, and poor treatment options. As of 2023, it is the third leading cause of cancer deaths in the United States (US) and the seventh leading cause of cancer deaths in the world in 2023. (1) For European Union (EU) 27 countries it is estimated that pancreatic cancer in 2020 accounted for 3.5% of all new cancer diagnoses (excluding non-melanoma skin cancers) and 7.1% of all deaths due to cancer. That made it the seventh most frequently occurring cancer, and the fourth leading cause of cancer death after lung, colorectal, and breast cancer. (2) In Europe, PDAC death rates are steadily rising while rates for all other cancers continue to fall. (3) Due to the aggressive nature of the cancer, researchers have dedicated time and effort to come up with potential tumor markers to help screen asymptomatic people. Despite advances in the past decades, the 5-year survival rate is only approximately 12%. (1) Factors that contribute to the poor survival rate include the anatomical location of the pancreas in the abdomen, late clinical manifestations, and early metastasis of the disease. However, the poor prognosis mainly stems from inadequate screening and detection of the disease at an early stage.

Biomarkers play an important role in the diagnosis, evaluation of treatment response, and prognosis of the disease. (4)Over the years various biomarkers have been introduced and studied, but among them, Carcinoembryonic antigen (CEA) and Carbohydrate antigen 19-9 (CA 19-9) have emerged as the key players in the management and diagnosis of PDAC. (5)

CA 19-9, also called cancer antigen 19-9 or sialylated Lewis a antigen, is the most used and best-validated serum tumor marker for pancreatic cancer diagnosis in symptomatic patients and for monitoring therapy in patients with PDAC. It has a high sensitivity with reports ranging from 70-90% and specificity in the range of 90%, however, these values only correspond to symptomatic and advanced-stage cancer patients. When it comes to asymptomatic patients, the positive predictive value drops significantly indicating it not being suitable to be used for screening. (6)

Carcinoembryonic antigen (CEA), a glycoprotein with a molecular weight of 180–200 kDa, was initially isolated from fetal colon and colon cancer tissue in 1965. (7) CEA is increased not only in colorectal cancer but also in various other types of cancer, including breast cancer, lung cancer, and thyroid cancer. Moreover, the serum level of CEA is increased in 30%–60%

of pancreatic cancer patients. Currently, CEA is not approved as a diagnostic serum marker due to its low specificity. (8)(9)

Diagnosis of PDAC is mainly done by imaging. Abdominal ultrasound is usually the first imaging modality used, however, contrast-enhanced computed tomography (CT) scanning is recommended as the main modality and abdominal magnetic resonance imaging (MRI) is used when CT is inconclusive or unavailable. (10)

For small non-resectable tumors, Endoscopic ultrasound (EUS) guided fine needle aspiration (FNA) is used for precise diagnosis and staging of lesions. It is also used in the differential diagnosis of benign chronic pancreatitis and as a histological diagnosis for those initiating chemotherapy.

Surgical resection is the only potentially curative treatment for PDAC. Following radiological evaluation, only patients with a high probability of surgical resection with no tumor at the margin (R0; defined as no cancer cells within 1 mm of all resection margins) are good candidates for upfront surgery [Figure 1]. For patients with borderline resectable disease , there is now a stronger recommendation for neoadjuvant therapy before surgery. Borderline resectable disease is defined by 3 factors: A) anatomical, B) biological and C) conditional. A) tumor contact to major vessels, B) suspicion of metastasis and (CA) 19-9 level more than 500 units/ml C) A and/or B and Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or more. (ECOG is a scale of morbidity 0-5, with 0 meaning there is no effect on daily activities and 5 being deceased.) [Figure 1.] (10) Locally advanced PDAC patients are treated with chemotherapy. Serum CA 19-9 levels, clinical improvement, and tumor downstaging according to the effect. The next step depends on the effect of the chemotherapy (surgery or continuation of chemotherapy).

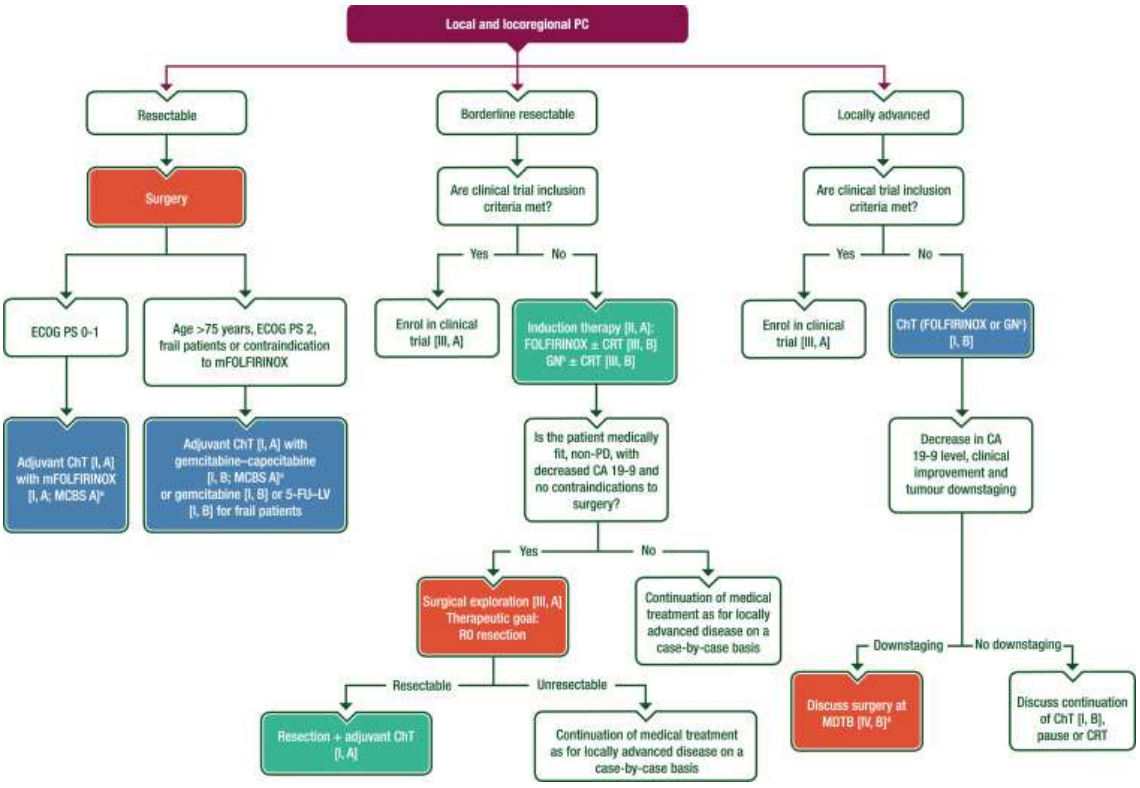


Figure 1. Treatment algorithm for early disease, European Society for Medical Oncology (ESMO) Clinical Practice Guidelines. (10)

Advanced PDAC is treated differently depending on the Karnofsky (KPS) and ECOG PS and bilirubin level. When ECOG PS is 0-1, bilirubin is less than 1.5x upper limit of normal (ULN) and the patient has no major comorbidities, FOLFIRINOX (a combination chemotherapeutic drug) or gemcitabine plus nab-paclitaxel (GN) is the first line therapy. For ECOG PS 2 with KPS $\geq$ 70 and bilirubin less than 1.5x ULN, GN is indicated. If KPS $\geq$ 70 and/or bilirubin is more than 1.5x ULN, Gemcitabine is the treatment of choice. For end-stage disease, ECOG PS 3-4, the treatment is symptom-directed care. [Figure 2.]

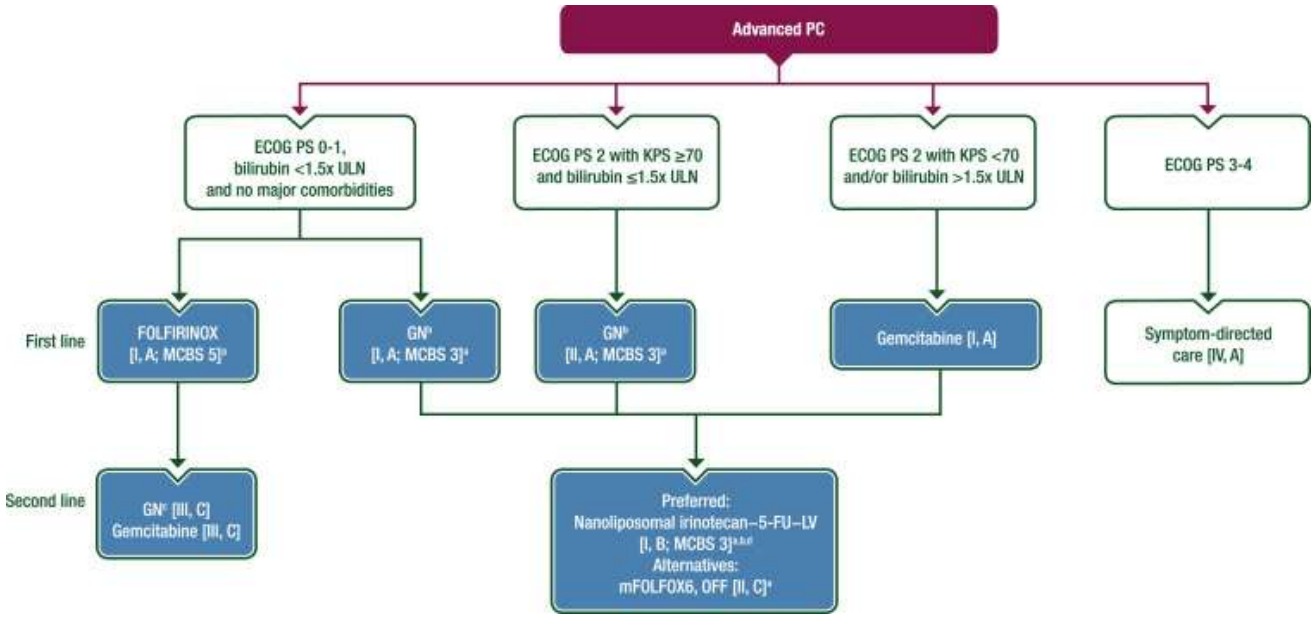


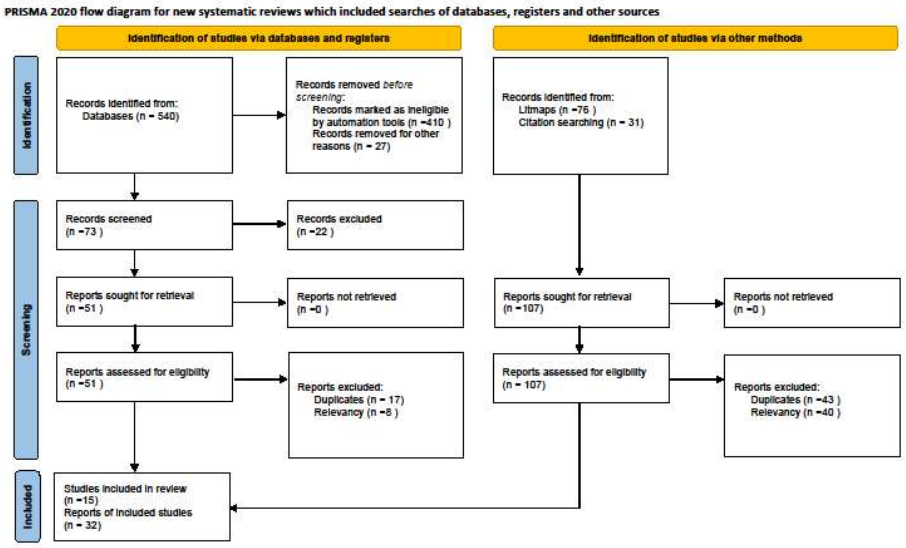
Figure 2. Treatment algorithm for advanced disease, European Society for Medical Oncology (ESMO) Clinical Practice Guidelines. (10)

Keywords: PDAC, CA 19-9, CEA, Biomarkers, Limitations, Future perspectives.

3. Selection Strategy

The objective of this literature review was to collect and analyze relevant research articles related to Pancreatic duct adenocarcinoma and its most studied biomarkers CA 19-9 and CEA. In addition, the aim was to highlight potential limitations and future perspectives pertaining to these biomarkers. A Pubmed search using the aforementioned keywords was conducted with Boolean operators (AND, OR,) to combine them. The initial search produced 540 articles. All non-English articles were excluded. Articles (Meta-analysis, Systematic Reviews, Clinical Trials, Randomized Controlled trials, Books and Documents) that were published between 2014 – 2024 were included, resulting in 51 articles. After this, the most relevant articles were picked and a comprehensive search using Litmaps was performed. Litmaps is a tool that helps visualize connections between different research papers. It

provides a family tree of articles, showing the chronological order of them including outliers that may have relevant information regarding the topic. No time frame was included in the Litmaps search. A total of 127 articles were produced in total from both databases (Pubmed, Litmaps). Additional articles were added from the references of the initial search. A total of 47 articles were included in this review.



4. CA19-9 as a PDAC Biomarker

CA 19-9 is the only routinely used and recommended marker for pancreatic cancer. (11) It was first described by Koprowski et al. in 1979, in colorectal carcinoma cell line using the mouse monoclonal antibody 1116-NS-19-9, this molecule was then discovered in the serum of patients with colon and pancreatic cancer in 1981 and was later found also to be a component of glycoproteins and mucins. (12) It belongs to the large family of mucinous markers: glycoproteins with a transmembrane protein skeleton and the extracellular side consisting of oligosaccharide chains extensively glycosylated, which are a normal component of the glandular secretions of mucous type. In particular, CA 19-9 is synthesized by normal

human pancreatic and biliary ductal cells and by gastric, colon, endometrial, and salivary epithelia. (12,13)

Normally present in small amounts in serum, in which it exists as mucin, CA 19-9 is over-expressed in certain inflammatory conditions such as pancreatitis and other benign gastrointestinal diseases. It exhibits an increase in its plasmatic levels in the course of neoplastic disease, during which several processes regulating both the passage of these molecules in the bloodstream and their metabolization appear altered. CA 19-9 is not found at high levels in normal tissues, whereas it is found at elevated levels in patients with pancreatic, hepatobiliary, gastric, hepatocellular, colorectal, and breast cancer. (14)

A major shortfall for CA 19-9 is the fact that approximately 5-10% of the population, Lewis antigen-negative individuals, have no or scarce secretion of the biomarker. (14) Lewis-negative individuals lack the enzyme α1-3,4 fucosyltransferase, which is required for CA 19-9 biosynthesis. This dysfunction of the Lewis gene is associated with deficient protein fucosylation, which has been involved in cancer development. (15) Considering the importance of CA 19–9 in pancreatic cancer, the development of biomarkers to assist CA 19–9 in the screening, management, and prognosis of Lewis-negative pancreatic cancer is a major focus point of future clinical studies. For example, Hamidov et al. investigated 15 biomarkers in PDAC and correlated the results with clinicopathological parameters. The objective of the study was to compare and test whether cell adhesion molecules such as desmocollins, cytokeratins, and other biomarkers are distinct at the protein level in PDAC patients and if they correlate to patient survival. Tissue microarrays containing samples from 115 consecutive patients were constructed. Tissue samples originated from surgical specimens, of patients who underwent surgical therapy of PDAC with curative intent between 1995 and 2009 at the surgical department of the Friedrich-Schiller University in Jena. Results showed that a reduced expression of Desmocollin 2 is independently correlated with shorter patient survival, higher tumor grading, and positive lymph node status in PDAC and could serve as a prognostic marker. (16)

Threshold levels for elevated CA 19-9, specifically for its diagnostic value in PDAC, are largely standardized at > 37-40 U/ml. (17)

The effectiveness of CA 19-9 in evaluating the suitability for surgery of pancreatic cancer relies on its association with tumor stage. Previous research has demonstrated that as the levels of CA 19-9 increase before surgery, the likelihood of successful resection decreases. (10,18)

Recommendations suggest that patients with radiographically operable pancreatic cancer, but elevated CA 19-9 levels should undergo staging laparoscopy or receive neoadjuvant therapy. (10) Although elevated CA 19-9 levels are indicative of increased risk for unresectability, a precise threshold defining "high" CA 19-9 levels remains undetermined. The International Association of Pancreatology suggests that cases with CA 19-9 levels exceeding 500 U/ml be classified as borderline resectable tumors. (19)

In addition to the relationship between CA 19-9 levels and tumor burden, sequential monitoring of CA 19-9 levels could serve as a means to assess the effectiveness of neoadjuvant therapy. Boone et al. demonstrated that in patients with borderline resectable pancreatic cancer, a reduction of more than 50% in CA19-9 levels was significantly associated with achieving R0 resection (OR = 4.2; P = 0.05), whereas none of the patients who experienced an increase in CA 19-9 levels achieved R0 resection. (20)

5. CEA as a PDAC Biomarker

In addition to CA 19-9, CEA is one of the most studied biomarkers for establishing both diagnosis and prognosis in PDAC patients. (8,21) The main reason why CEA is useful as a serum tumor marker is probably because CEA is a stable molecule, has a fairly restricted expression in normal adult tissue and is expressed at high levels in positive tumors. The bulk of the CEA in a healthy individual is produced in the colon. There, it is released from the apical surface of mature columnar cells into the gut lumen and disappears with the feces. Thus, only very low levels are normally seen in the blood of healthy individuals. (22)

Not long after the discovery of CEA in 1965, further studies revealed 28 other genes/pseudogenes related to the CEA gene family. (23) Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) belong to the glycosylphosphatidylinositol (GPI)-linked immunoglobulin (Ig) superfamily. This family encompasses more than 17 genes, whose products are primarily incorporated into the cell membrane. Among the CEACAM family, the CEACAM subtypes exhibit structural similarity and are typically expressed on the apical surface of various cell types, such as endothelial and hematopoietic cells, as well as epithelial cells across different organs. Upon binding with specific partners, the effects transmitted vary depending on the cell type and CEACAM subtype. These effects include the

regulation of cell adhesion, tumor suppression, angiogenesis, activation of leukocytes and other immune-reactive cells, and modulation of the cell cycle. (24,25) Several studies have proved CEACAM 1, 5, and 6 to have great potential as novel PDAC biomarkers.

Gebauer et al analyzed the effects of CEACAM 1, 5, and 6 in vitro and established a xenograft mouse model to investigate the functional role of CEACAM expression in PDAC. They concluded that approximately 70% of the examined PDAC tumor locations exhibited expression of either CEACAM 1, 5, or 6, or a combination of all of them. Univariate analysis demonstrated a correlation between the expression of CEACAM 5 and 6 and lymph node metastasis. Survival analysis indicated a decreased overall and disease-free survival among patients with high expression levels of CEACAM 5 or 6. (24)

Kurlinkus et al aimed to find a novel PDAC marker by comparing serum levels and expression of CEACAM 6 with conventional biomarkers CEA and CA 19-9. The study concluded that CEACAM 6 lacks diagnostic properties, however, the survival analysis revealed that it has significant prognostic potential and can help to predict chemoresistance. (25)

Van Manen et al. conducted a study aiming to assess serum levels of CEA and CA 19-9 in PDAC patients and to observe their association with advanced PDAC. The study identified optimal cut-off values of 7.0 ng/ml for CEA and 305.0 U/ml for CA19-9 to predict advanced PDAC, resulting in positive predictive values of 83.3%, 73.6%, and 91.4% for elevated CEA, CA19-9, and their combination, respectively. Both tumor markers emerged as independent predictors of advanced PDAC; however, the numerical contrast between CEA (OR: 4.18) and CA19-9 (OR: 2.66) suggests that CEA may exhibit greater robustness as a prognostic factor. (26)

A study by Zhou et al showed that the combination of 100 U/ml of preoperative serum CA19-9 and 10 μg/ml of CEA could be identified as ideal thresholds for anticipating the results of resectable PDAC, potentially serving as criteria for assessing its resectability. (27)

7. Limitations of CA 19-9 and CEA as PDAC Biomarkers

The effectiveness of CA 19-9 in diagnosing early PDAC is constrained by its relatively low sensitivity and specificity, hindering its clinical utility. (11,28,29) While maintaining a sensitivity ranging from 79% to 81% and a specificity between 82% and 90% in symptomatic patients, elevated CA 19-9 levels typically indicate advanced disease and a bleak prognosis.

However, since PDAC often presents no symptoms in its early stages, the positive predictive value of CA 19-9 in this context is merely 0.9%. (11)

Several studies have explored the limitations of CA 19-9 and CEA alone as biomarkers for PDAC. Brand et al. in 2011 utilized a Metropolis algorithm with Monte Carlo simulation to identify discriminatory biomarker panels, finding that the CA 19-9, intercellular adhesion molecule 1 (ICAM-1), osteoprotegerin (OPG) panel is selective for PDAC. This suggests that relying solely on CA 19-9 and CEA may not be sufficient for accurate detection of PDAC. (30) Furthermore, given the limitations of CA 19-9, CA125 could serve as an adjunctive tool in predicting resectability. Abnormal CA125 levels have been found to indicate the presence of peritoneal metastases in pancreatic cancer. (31)(32)

In addition, Hogendorf et al. found that Growth Differentiation Factor 15(GDF-15) concentration combined with CA125 levels in serum is superior to CA 19-9, CEA, and other commonly used biomarkers in differentiating pancreatic masses, further highlighting the limitations of CA 19-9 and CEA alone. (33)

Meng et al. also showed that a CEA-based panel is better at diagnosing pancreatic cancer than CA125 or CA 19-9 alone. Results concluded that high levels of serum CEA are significantly related to poor prognosis. Thus, the measurement of serum CEA, as a vital supplement to CA 19-9, is inexpensive, convenient, and necessary for monitoring this disease. (8) These studies reveal the limitations of CA 19-9 and CEA, but they also highlight the potential of combining several biomarkers to create a more accurate diagnostic tool.

a. Limited Utility in Surveillance

While both CA 19-9 and CEA can be useful for monitoring disease progression in patients with known PDAC, they may not be ideal for surveillance in high-risk populations due to their limited sensitivity to early-stage disease. Kruger et al. investigated the use of inflammatory cytokines and angiogenic factors in multivariate logistic models to facilitate earlier diagnosis of PDAC, with results suggesting that combined biomarker panels improve diagnostic accuracy in PDAC. (34) The first PDAC-specific blood test to be offered commercially was the IMMray PanCan-d test. This test combined an 8-plex biomarker signature with CA19-9, with initial data showing a specificity of 99% and sensitivity of 92% for PDAC detection. (34,35)

In 2020 Kim et al. identified a combination of 6 biomarkers (ApoA1, CA125, CA 19-9, CEA, ApoA2, and TTR) through a Random Forest classification algorithm method that increased the diagnostic accuracy of PDAC to 95%. They used blood samples from 180 PDAC patients and 573 healthy controls. (36) While this can be seen as a breakthrough, several limitations need to be addressed in future research. 29.5% of the patient group had stage 3 or 4 pancreatic cancer, which is not ideal when testing a biomarker panel to detect early disease. In addition, all the patients were treated in a single center. A larger study with multiple centers will provide more reliable data.

In general, extensive research is still needed to combat the surveillance limitations of CA 19-9 and CEA, however, studies indicate that correct steps are being taken to combat this issue. Better surveillance markers would positively impact the management of PDAC.

8. Future perspectives

While the research and exploration of CA 19-9 and CEA as PDAC biomarkers continues, other potential diagnostic and prognostic markers have been presented and studied. As technology progresses, the identification of biomarkers from various bodily fluids including serum, plasma, pancreatic fluid, urine, and feces emerges as a reliable, stable, and safe alternative to traditional tissue biopsies and surgical specimens. [Figure 3] These biomarkers encompass pancreatic-specific proteins, genetic and epigenetic markers, metabolites, and tumor stem cells, exhibiting significant diagnostic potential in accurately discerning pancreatic cancer from other ailments. (37–41) Additionally, pertinent markers hold promise in prognostication and guiding therapeutic interventions with appropriate medications. Liquid biopsies are gaining traction in the precise diagnosis and treatment of tumors due to their non-invasive nature and repeatability across different stages of disease management. Nonetheless, the efficacy of certain biomarkers in pancreatic cancer remains contentious, necessitating further research to ascertain the optimal combination of diverse marker panels.

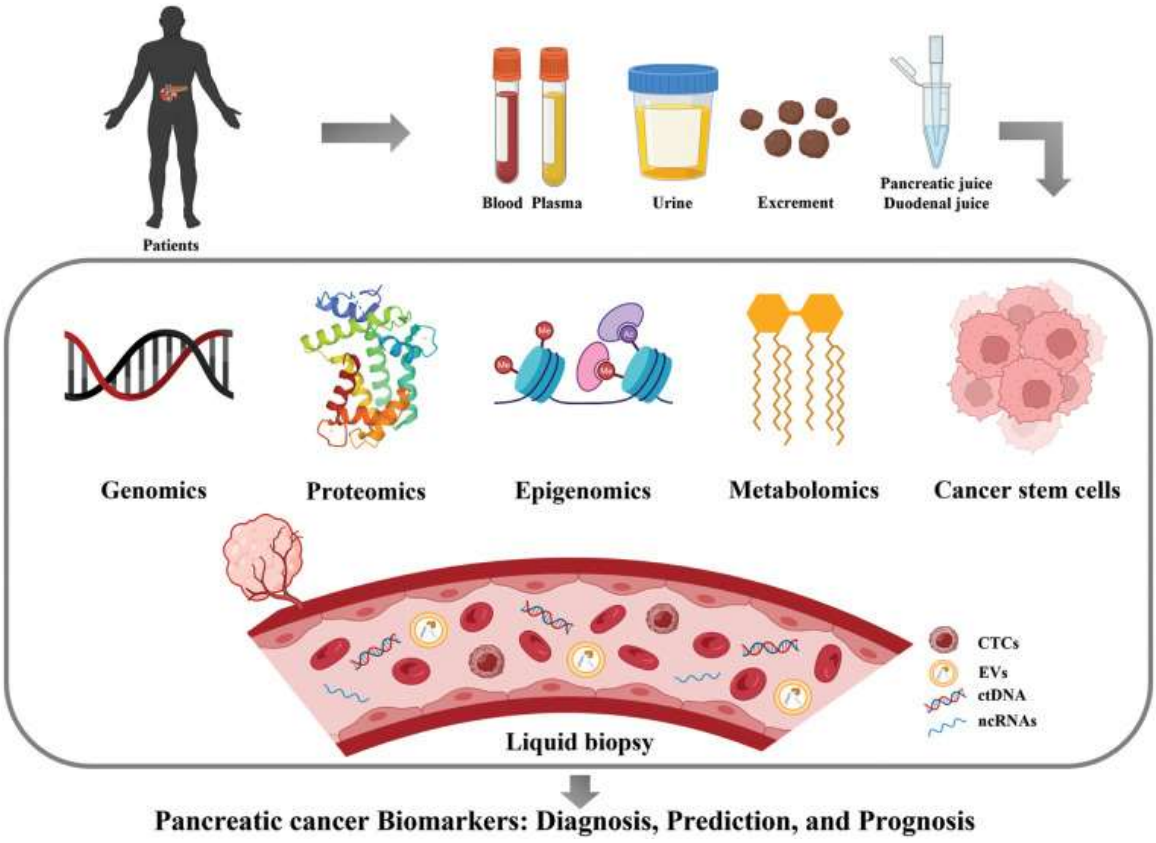


Figure 3. Pancreatic cancer future biomarkers (42)

a. Genetic Markers

The genetic alterations in PDAC have been extensively studied over the years. Dominant mutations including KRAS, TP53, SMAD4, and CDKN2A have been identified, each occurring in 65.8% of PDAC patients. (41,43) The frequencies of mutations in these four genes varied across different stages of Pancreatic Intraepithelial Neoplasia (PanIN), indicating that detecting gene mutations could serve as a valuable method for accurately distinguishing early invasive carcinoma from low or high-grade dysplasia. (44)

b. MicroRNAs

MicroRNAs (miRNAs) are tiny, non-coding RNA strands that influence gene expression by inhibiting translation or promoting the breakdown of corresponding mRNAs. These molecules do not contain open reading frames (ORF) and their stability is increased either through integration into nanoparticles or attachment to the human Argonaute-2 (hAgo2) protein, which protects them from RNase destruction. Certain miRNAs such as miR-10, miR-21, miR-155, and miR-196 are notably overexpressed in PDAC and other diseases. Specific

miRNAs in the bloodstream, including miR-486-5p, miR-1290, and miR-100a, have demonstrated superior diagnostic performance compared to the traditional marker CA19-9. MiRNAs have also been detected in stool and urine samples for diagnostic purposes; for example, miR-223 and miR-204 in urine can distinguish early-stage cancer from chronic pancreatitis, while higher levels of miR-21 and miR-155 have been found in the stools of PDAC patients versus healthy controls. (45) Furthermore, research by Lai et al. pinpointed a distinct exosomal miRNA profile in PDAC patients, which effectively differentiates them from individuals with chronic pancreatitis, highlighting the diagnostic utility of miRNA panels. (37)

c. Circulating tumor cells (CTCs)

Circulating tumor cells refer to cancer cells found in the bloodstream of patients, playing a key role in the spread of solid tumors to remote body areas. Research indicates that both the variety and overall number of CTCs in patients with PDAC are increased compared to healthy individuals. Identifying tumor markers on CTC surfaces or analyzing internal components like epithelial markers, mRNA, and DNA mutations facilitates a real-time cancer biopsy. Mataki and colleagues utilized Quantitative real-time reverse-transcription PCR (qRT-PCR) to assess CEA mRNA in CTCs, achieving diagnostic sensitivity and specificity rates ranging from 33.3% to 75% and 94.6% to 96% respectively, surpassing the diagnostic accuracy of traditional markers CEA and CA 19-9. (46) Additionally, Ankeny et al compared KRAS mutations in CTCs with those in primary tumors of five PDAC patients, noting a 100% match in the findings from both sources. (47)

9. Conclusions

The growing burden of late diagnosis of PDAC has been noted in the past few years with researchers and clinicians showing increased interest in finding new ways to detect pancreatic cancer early. Projected to overthrow colorectal cancer by the year 2030 and incidence growing by the year in developing countries, screening for PDAC using conventional biomarkers CA 19-9 and CEA has proved to be a challenge. The review showed that over recent years promising results have been noted, including comprehensive biomarker panels that enhance the diagnostic properties of the conventional biomarkers. Larger trials across the developing world need to be performed to standardize these panels and use them routinely.

In addition, genetic, epigenetic, and tumor mutation markers show promise in detecting early disease. Future studies need to implement more comprehensive categorization in terms of tumor size and stage, clinical symptoms, and population.

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