Inflammatory Biomarkers in the Pathogenesis of Pancreatic Cancer: A Literature Review

Manuscript NO: 109385

Dear Editor

The reviewers raised the following queries which are explained below.

A point-by-point response to the reviewers' reports

We would like to express our gratitude to the reviewers for dedicating their time to thoroughly evaluate the manuscript and providing us with insightful and constructive feedback.

Reviewers report

Reviewer #1:

This comprehensive review examines the role of inflammatory biomarkers—including erythrocyte sedimentation rate, plasma viscosity, procalcitonin, calprotectin, haptoglobin, serum amyloid A (SAA), ferritin, and fibrinogen—in the pathogenesis of pancreatic ductal adenocarcinoma (PDAC). The authors synthesize evidence from clinical and molecular studies to highlight how chronic inflammation contributes to tumor initiation, progression, and metastasis. Strengths include the systematic evaluation of diverse biomarkers, integration of recent clinical data (e.g., prognostic scores combining CRP and CA19-9), and emphasis on translational implications, such as biomarker-guided therapy. The inclusion of figures summarizing biomarker mechanisms adds visual clarity. A notable innovation lies in exploring understudied markers like calprotectin and fibrinogen, offering fresh insights into their diagnostic and prognostic utility in PDAC. However, some potential issues need to be addressed before accept for publish.

Comments: While the introduction details pancreatic cancer mortality in the United States, it lacks global and Asian-specific data. Pancreatic cancer incidence and mortality vary significantly across regions, with rising rates in Asia due to lifestyle and genetic factors. Incorporating updated global statistics (e.g., GLOBOCAN 2022) and regional disparities would strengthen the epidemiological relevance.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

'The global incidence of pancreatic cancer is projected to increase; however, the rate of this rise varies across countries, with some nations exhibiting a decelerating or declining trend in incidence [Shou et al.]. In several Asia-Pacific countries, including Armenia, Japan, Kazakhstan, New Zealand, Australia, and South Korea, pancreatic cancer is associated with notably high mortality rates. Conversely, in other nations such as China, mortality due to pancreatic cancer is on an upward trajectory, suggesting that peak death rates may be observed in the coming years [Pourhoseingholi et al.]. The incidence of pancreatic cancer is increasing globally, necessitating a thorough understanding of its epidemiological trends to inform effective public health policies and interventions. Countries with a high human development index (HDI) consistently report higher incidence, prevalence, and mortality rates associated with pancreatic cancer. This pattern is similarly observed across the Asia-Pacific region, where nations with elevated HDI levels demonstrate a greater burden of disease. The rising incidence in the Asia-Pacific population is attributed in part to increased life expectancy and ongoing socioeconomic development. However, in many low- and middle-income countries within the region, limited cancer registry infrastructure contributes to significant underreporting of pancreatic cancer cases [Ranganath et al.]. By 2040, the global prevalence of pancreatic cancer is expected to rise, with projections indicating a higher susceptibility among women. When accounting for percentage changes, regions characterized by lower socioeconomic status are predicted to bear a disproportionately greater burden of pancreatic cancer compared to more affluent areas [Hesami et al.]. The estimates, encompassing 36 cancer types by sex and age across 185 countries and territories, are derived from the most reliable local data sources available—primarily population-based cancer registries for incidence data and national vital statistics for mortality. As reported in the most recent GLOBOCAN estimates, pancreatic cancer is associated with one of the lowest survival rates among all malignancies and currently ranks as the sixth leading cause of cancer-related mortality worldwide [Bray et al., Filho et al.]. Between 2009 and 2018, the incidence of pancreatic cancer has risen across all ethnic groups and in both sexes. The disease disproportionately affects minority populations, males, and individuals residing in rural areas. Furthermore, the incidence is notably higher among older adults, indicating an elevated risk within this demographic group [Moshayedi et al.]. A marked disparity in pancreatic cancer survival rates exists between rural and urban areas, which may be attributed to variations in healthcare infrastructure, differences in stage at diagnosis, and underlying socioeconomic and lifestyle-related factors[Chandar et al.].'

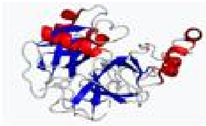
Structural and Logical Flow: The manuscript suffers from dense, monolithic paragraphs, particularly in the introduction and main text. Subdividing sections with descriptive subheadings (e.g., "Inflammatory Microenvironment and Stromal Interactions" or "Clinical Translation of Biomarkers") would enhance readability.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

In pancreatic cancer, inflammation is characterized by complex interactions among immune cells, inflammatory cells, cytokines, and chemokines. Both cancer cells and the surrounding stromal and inflammatory components contribute to the development of an inflammatory tumor microenvironment (TME). Inflammation is intricately linked to immune function, with immune cells playing dual roles in mediating both inflammatory processes and immune responses. TME is defined by two predominant features: tumor-promoting inflammation and tumor-suppressive immunity in pancreatic cancer [Li et al.]. The tumor microenvironment in pancreatic cancer comprises a diverse array of cell types and intricate signaling pathways that collectively facilitate tumor progression. A central component of this unique microenvironment is the symbiotic interaction between pancreatic cancer cells and pancreatic stellate cells (PSCs), which plays a pivotal role in shaping the TME. PSCs contribute to several malignancy-associated processes, including resistance to apoptosis, enhanced invasion and metastasis, angiogenesis, and the establishment of an immunosuppressive milieu. Current therapeutic strategies predominantly target cancer cells, despite these cells constituting only a small fraction of the tumor mass. Increasing evidence underscores the importance of focusing research efforts on the cellular interactions within the TME, particularly during the early stages of tumorigenesis, to enable the development of more effective and comprehensive treatment approaches [Tod et al.]. Pancreatic ductal adenocarcinoma represents the most aggressive subtype of pancreatic cancer, characterized by extensive inflammation and desmoplasia. These features contribute to a hypoxic microenvironment, metabolic reprogramming, and immune suppression, all of which facilitate tumor progression and metastasis. A major barrier to effective treatment is the limited ability of current therapies to penetrate the dense and fibrotic stromal microenvironment. This stroma comprises a heterogeneous assembly of cancer cells, immune cells, cancer-associated fibroblasts, vascular endothelial cells, and neuronal elements. Emerging evidence highlights that the dynamic interactions among these cellular components can exert both tumor-promoting and tumor-suppressive effects. The role of inflamed stroma in immune evasion, disease progression, metastasis, and resistance to therapy is likely influenced by the stage of tumor development and the biophysical characteristics of distinct tumor micro-niches. A deeper understanding of the stromal mechanisms driving tumorigenesis may reveal critical therapeutic windows, paving the way for the development of effective multimodal treatment strategies for pancreatic cancer [Boyle et al.]. The clinical translation of biomarkers in pancreatic cancer focuses on moving promising biomarkers from research labs to real-world clinical applications, such as early detection, diagnosis, prognosis, and treatment response prediction.

Figure Optimization: Figures 2–4 contain excessive text, diminishing their interpretability. Key pathways or mechanisms should be visualized through simplified diagrams (e.g., flowcharts, heatmaps) with minimal annotations. For example, Figure 2 (haptoglobin) could use arrows to depict fucosylation’s role in tumor-stroma crosstalk, supplemented by brief legends rather than verbose descriptions.

Author’s response: We have revised these points by adding possible main pathways or mechanisms in the revised manuscript with yellow highlighted.



Molecular structure of Haptoglobin
(A liver-derived acute phase protein)

Possible main pathways and mechanisms of haptoglobin's role in pancreatic cancer
Hp might bind to CD163 on macrophages → promotes M2 macrophage polarization, M2 macrophages support angiogenesis, fibrosis, and immune evasion.

Hp might enhance tumor cell migration and invasion

May facilitate epithelial-mesenchymal transition by upregulating mesenchymal markers.

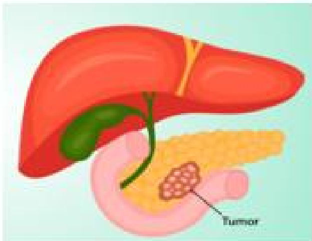
Elevated Hp reflects chronic inflammation, a hallmark of pancreatic cancer.

Serum fucosylated haptoglobin levels were considerably elevated for Hpt2–1 and Hpt2–2.

Alpha 1-3/alpha 1-4/alpha 1-6 fucosylation of haptoglobin was shown to be elevated in PC.

Haptoglobin secretion was significantly elevated when the conditioned medium from PC cells was used to cultivate the Hep3B hepatoma cell line.

Fucosylated haptoglobin may be a new pancreatic cancer marker.



Haptoglobin plays an active role in PC pathogenesis, not merely as a marker of inflammation but as a functional player in

- Immune suppression,
- Angiogenesis,
- Tumor growth,
- Oxidative stress regulation.

Immune cells, particularly macrophages, within the pancreatic tissue microenvironment are a source of fucosylated haptoglobin and its precursor form, proHpt.

These fucosylated variants are specifically recognized by the 10-7G monoclonal antibody (mAb), suggesting their potential utility as biomarkers for the detection of pancreatic cancer.

Molecular structure of Fibrinogen

With an advanced tumor stage, plasma fibrinogen levels were elevated.

the percentage of positive hyperfibrinogenemia cases increased as the tumor stage progressed.

The pancreatic cancer tumor stage was positively correlated with plasma fibrinogen levels.

Higher preoperative levels of plasma fibrinogen may be a good indicator of distant metastases in PC.

Fibrinogen to prognostic nutritional index (Fbg/PNI) ratio was still significant in multivariate analysis for

- Tumor differentiation,
- Nodal involvement,
- Overall survival.

Causes pathogenesis in Pancreatic Cancer

Invasiveness and lymphatic etastasis may be linked to the higher fibrinogen expression.

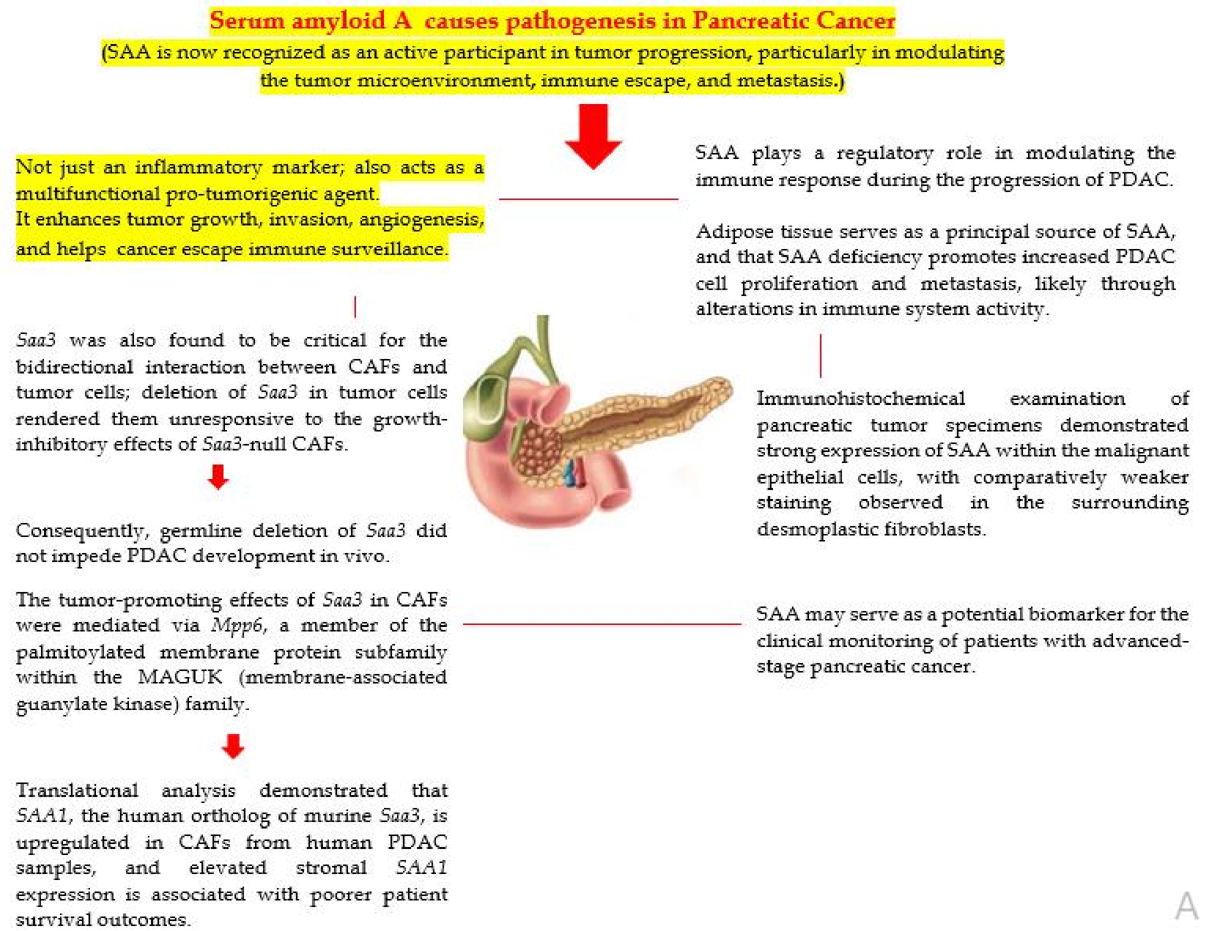
Fibrinogen is not just a marker but a functional mediator in PC pathogenesis, influencing multiple hallmarks of cancer including

- Growth,
- Metastasis,
- Immune escape,
- Angiogenesis.

Fibrinogen γ, a protein linked to the hypercoagulable condition of PC,

Fibrinogen may serve as a tumor marker.

Elevated levels of circulating fibrinogen and the fibrin degradation product D-dimer in plasma, with increased correlation in patients with distant metastasis.



Updated References: The global cancer burden discussion cites GLOBOCAN 2020; updating to GLOBOCAN 2022 (Filho et al., 2025) enhances timeliness and aligns with current trends. While the introduction addresses U.S. pancreatic cancer mortality, it lacks global/Asian data. As Asian-based authors, incorporating pancreatic cancer incidence, survival rates, and biomarker profiles (e.g., SAA/ferritin level disparities vs. Western cohorts) contextualizes findings broadly. Regional incidence/mortality disparities—including Asia's rising rates (lifestyle/genetic links)—warrant inclusion to strengthen epidemiological relevance.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

'The global incidence of pancreatic cancer is projected to increase; however, the rate of this rise varies across countries, with some nations exhibiting a decelerating or declining trend in incidence [Shou et al.]. In several Asia-Pacific countries, including Armenia, Japan, Kazakhstan, New Zealand, Australia, and South Korea, pancreatic cancer is associated with notably high mortality rates. Conversely, in other nations such as China, mortality due to pancreatic cancer is on an upward trajectory, suggesting that peak death rates may be observed in the coming years [Pourhoseingholi et al.]. The incidence of pancreatic cancer is increasing globally, necessitating a thorough understanding of its epidemiological trends to inform effective public health policies and interventions. Countries with a high human development index (HDI) consistently report higher incidence, prevalence, and mortality rates associated with pancreatic cancer. This pattern is similarly observed across the Asia-Pacific region, where nations with elevated HDI levels demonstrate a greater burden of disease. The rising incidence in the Asia-Pacific population is attributed in part to increased life expectancy and ongoing socioeconomic development. However, in many low- and middle-income countries within the region, limited cancer registry infrastructure contributes to significant underreporting of pancreatic cancer cases [Ranganath et al.]. By 2040, the global prevalence of pancreatic cancer is expected to rise, with projections indicating a higher susceptibility among women. When accounting for percentage changes, regions characterized by lower socioeconomic status are predicted to bear a disproportionately greater burden of pancreatic cancer compared to more affluent areas [Hesami et al.]. The estimates, encompassing 36 cancer types by sex and age across 185 countries and territories, are derived from the most reliable local data sources available—primarily population-based cancer registries for incidence data and national vital statistics for mortality. As reported in the most recent GLOBOCAN estimates, pancreatic cancer is associated with one of the lowest survival rates among all malignancies and currently ranks as the sixth leading cause of cancer-related mortality worldwide [Bray et al., Filho et al.]. Between 2009 and 2018, the incidence of pancreatic cancer has risen across all ethnic groups and in both sexes. The disease disproportionately affects minority populations, males, and individuals residing in rural areas. Furthermore, the incidence is notably higher among older adults, indicating an elevated risk within this demographic group [Moshayedi et al.]. A marked disparity in pancreatic cancer survival rates exists between rural and urban areas, which may be attributed to variations in healthcare infrastructure, differences in stage at diagnosis, and underlying socioeconomic and lifestyle-related factors[Chandar et al.].'

Language and Syntax: Some sections feature repetitive phrasing and convoluted sentences. Streamlining language and avoiding redundancy—particularly in biomarker-specific subsections—would improve clarity.

Author's response: We have revised this point in revised manuscript with yellow highlighted.

Conclusion Depth: The conclusion briefly reiterates findings but lacks a forward-looking perspective. Expanding on unresolved questions (e.g., biomarker validation in multiethnic cohorts, therapeutic targeting of SAA or fibrinogen) or clinical challenges (e.g., biomarker specificity in early-stage PDAC) would add critical depth.

Author's response: We have revised this point in revised manuscript with yellow highlighted.

'Pancreatic cancer cells, stromal cells, and cytokines collectively contribute to the establishment of an inflammatory and immunosuppressive tumor microenvironment. Emerging evidence underscores the importance of the intricate crosstalk between inflammatory processes and stromal elements within the pancreatic TME. Tumor-associated inflammation encompasses complex interactions among diverse immune cell populations, inflammatory cells, cancer cells, chemokines, and cytokines. Inflammation plays a critical role in the initiation, progression, and metastasis of pancreatic cancer. Inflammatory infiltration within the tumor microenvironment of pancreatic ductal adenocarcinoma plays a significant role in tumor growth and metastasis. Both systemic and localized chronic inflammation have been implicated as risk factors for PDAC development. However, this article concluded that the erythrocyte sedimentation rate, plasma viscosity, procalcitonin, calprotectin, haptoglobin, serum amyloid A, ferritin and fibrinogen play significant roles in the pathogenesis of pancreatic cancer as explained in figure 1 to 4. This inflammatory milieu plays a pivotal role in the initiation, progression, malignant transformation, metastasis, and therapeutic resistance—including resistance to chemotherapy, radiotherapy, and immunotherapy—of pancreatic cancer. A deeper understanding of the interplay between inflammatory processes and stromal components within the tumor microenvironment is essential for unraveling the mechanisms underlying immune tolerance in pancreatic cancer. Furthermore, a deeper understanding of the molecular mechanisms underlying pancreatic cancer development and progression is essential for the identification of novel targets and the development of more effective, personalized treatment approaches. Inflammatory biomarkers hold significant clinical value in enhancing diagnostic accuracy, predicting outcomes, guiding treatment decisions, and developing personalized therapeutic approaches in pancreatic cancer.’

Reviewer # 2:

This manuscript presents a mini-review exploring the role of various inflammatory biomarkers in the pathogenesis and clinical management of pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC). The authors aim to summarize the involvement of biomarkers such as CRP, IL-6, haptoglobin, serum amyloid A, calprotectin, ferritin, and others, drawing from a broad literature base. While the topic is of high clinical relevance and the review includes an extensive collection of cited studies, the manuscript requires significant revision in the areas of focus, clarity, structure, scientific depth, and linguistic accuracy.

1.The manuscript reads more like an exhaustive list of inflammatory markers with brief summaries of associated studies than a critically synthesized mini-review. The review would benefit from clearly structured sections that group biomarkers by biological pathways (e.g., cytokine signaling, acute-phase proteins, immune-modulatory functions), or by clinical utility (e.g., diagnostic, prognostic, predictive biomarkers), instead of treating each marker in isolation.

Author's response: We have revised this point in revised manuscript with yellow highlighted.

Biomarkers by biological pathways (e.g., cytokine signaling, acute-phase proteins, immune-modulatory functions) 'Changes in blood composition, especially the presence of acute-phase reactants, are reflected in the ESR, which is an indirect indicator of systemic inflammation. Cytokine signaling, particularly that of IL-6, TNF-α, and IL-1, is the main cause of its rise. Hepatocytes are stimulated to create acute-phase proteins such as fibrinogen, CRP, and serum amyloid A. By encouraging the production of rouleaux and changing the surface charge and aggregation characteristics of erythrocytes, these proteins hasten the sedimentation of red blood cells. In the context of inflammatory conditions, elevated levels of positively charged plasma proteins such as fibrinogen, other coagulation factors, and alpha globulins contribute to an increased erythrocyte sedimentation rate. Typically, ESR begins to rise within 24 to 48 hours following the onset of acute inflammation and declines gradually as the inflammatory process resolves, often requiring several weeks to months to return to baseline values. Notably, an ESR exceeding 100 mm/hour is associated with a high diagnostic yield, with studies indicating that over 90% of such cases are linked to an identifiable underlying pathology upon thorough evaluation [Bray et al.]. Immunomodulatory processes also affect ESR because persistent infection or inflammation increases immune cell activation and inflammatory mediator production, maintaining the acute-phase response. ESR is a helpful, although generic, indicator of continuing inflammatory or immunological processes because it captures the physiologic interaction between immune activation and hepatic protein synthesis, despite its lack of specificity.

Systemic inflammation causes an increase in plasma viscosity, a measure of the fluid's resistance to flow that reflects changes in the concentration and make-up of plasma proteins, especially acute-phase reactants. IL-6, IL-1, and TNF-α are examples of inflammatory cytokines that cause the liver to create more fibrinogen, immunoglobulins, and other acute-phase proteins, which thicken and make plasma stickier. In addition to directly influencing viscosity, these proteins also have an impact on immunological and vascular reactions. Elevated plasma viscosity is therefore a result of cytokine-driven hepatic protein synthesis and reflects the body's immune-modulatory response to inflammation, infection, or malignancy. While less commonly used than other inflammatory markers like CRP or ESR, plasma viscosity provides a sensitive and stable indicator of chronic inflammatory states [Thompson et al.].

Similar processes create acute phase proteins such as CRP and PCT. One of the main sources of PCT production seems to be the liver. PCT might therefore be regarded as an acute phase protein. PCT's apparent diagnostic capacity to distinguish bacterial infection from other sources of inflammation may be explained by its distinct kinetics rather than a radically different afferent route [Nijsten et al.].

As dietary practices became more Westernized globally, the prevalence of inflammatory bowel disorders (IBD) increased. Both Crohn's disease and ulcerative colitis are long-term, crippling illnesses that affect people with significant morbidity and pose problems for healthcare systems worldwide. Since calprotectin (CP) was discovered and described in the 1980s, fecal CP has become a very reliable, non-invasive biomarker for assessing intestinal inflammation. Faecal CP depicts the progression of human IBD and distinguishes between inflammatory and non-inflammatory gut disorders. The biological roles of the CP subunits S100A8 and S100A9 during the coordination of an inflammatory response at mucosal surfaces throughout organ systems have been clarified by recent research [Jukic et al.].

IL-6-type cytokines and other inflammatory mediators greatly stimulate the hepatic production of HP, a member of the evolutionarily conserved group of acute phase plasma proteins (APPs), which raises the plasma concentration from as low as <50 µg/ml to ~ 2.5 mg/ml in within 24 hours. Whether in connection with infections or a disease state like cancer, the function of inflammatory mediators in guiding host immune activity is increasingly being researched. It is unclear how these mediators' downstream targets, the APPs, contribute to this tightly controlled immune response. The idea that Hp may have a regulatory role in immune function stems from the close relationship between inflammation and the cytokine-induced increase of Hp expression, which is known to be essential for immune system regulation. Consistent with plasma Hp's suggested anti-inflammatory properties during an acute phase reaction [Wang Y et al.].

Serum amyloid A (SAA), an acute-phase reactant, plays a significant role in both acute and chronic inflammatory processes and is widely utilized in clinical laboratories as a biomarker of inflammation. Although both SAA and CRP are commonly used acute-phase proteins, SAA demonstrates superior diagnostic sensitivity in specific clinical scenarios, including viral infections, severe acute pancreatitis, and renal transplant rejection. Its utility is particularly notable in immunocompromised patients, individuals with cystic fibrosis receiving corticosteroid therapy, and preterm neonates with late-onset sepsis. However, for broader inflammatory and infectious conditions, particularly bacterial infections, the combined use of SAA with other APPs such as CRP and procalcitonin enhances diagnostic sensitivity and provides a more comprehensive assessment of the inflammatory status. This integrative approach can better inform clinical decisions, particularly regarding antibiotic management. Despite its promise, the diagnostic implications of various SAA isotypes remain incompletely understood due to the limited availability of clinically validated data, as current knowledge is largely based on experimental studies. Moreover, existing SAA assays, which utilize polyclonal antibodies, lack isotype specificity and may cross-react with multiple inflammatory conditions. Consequently, in clinical practice, SAA measurement is often interpreted alongside other biomarkers to improve diagnostic accuracy and clinical utility[56].

SAA is a major acute-phase protein produced predominantly by the liver in response to pro-inflammatory cytokines, particularly IL-6, interleukin-1β (IL-1β), and TNF-α. Persistently elevated SAA levels, especially in chronic inflammatory diseases, can lead to secondary amyloidosis, where misfolded SAA fragments deposit as amyloid fibrils in organs, disrupting normal function. Thus, SAA is both a marker and mediator of inflammation, linking cytokine signaling, acute-phase protein synthesis, and immune system activation [57]. SAA is an excellent indicator of inflammation in the body and has been shown to rise quickly by up to 1000 times in response to acute inflammation [58]. Several cytokines, such as IL-1, IL-6, and tumor necrosis factor-α, promote the development of serum amyloid A, an acute-phase hepatic protein released during acute infections and tissue damage [59]. A higher level of SAA protein is seen in cancer patients at an early stage in a variety of common cancers, including melanoma, lung, ovarian, renal, uterine, and nasopharyngeal cancer [60].
Ferritin is primarily known as an intracellular iron storage protein, but it also functions as an acute-phase reactant that is upregulated during inflammation. Its expression is strongly induced by pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α as part of the cytokine-mediated acute-phase response [Tran et al.]. During systemic inflammation or infection, ferritin synthesis increases in hepatocytes and macrophages, leading to elevated serum levels. This response serves a dual purpose: it sequesters iron away from pathogens (limiting microbial

growth) and reflects immune-modulatory activity, as ferritin itself can influence immune responses by modulating T-cell activity and suppressing pro-inflammatory cytokine production in some contexts. Elevated ferritin levels are commonly observed in inflammatory conditions, infections, malignancies, and autoimmune diseases, and in severe cases—such as macrophage activation syndrome or cytokine storms—it can signal hyperinflammation. Therefore, ferritin serves both as a marker of inflammation and an active participant in immune regulation and iron homeostasis [Wang et al.].

Fibrinogen is a soluble plasma glycoprotein produced by the liver and functions as a key acute-phase protein, with its synthesis markedly increased in response to pro-inflammatory cytokines, especially IL-6, IL-1β and TNF-α. As part of the cytokine-driven acute-phase response, fibrinogen plays a dual role in hemostasis and immune modulation. In the coagulation cascade, it is converted to fibrin by thrombin to form blood clots, aiding in tissue repair and limiting pathogen spread. Elevated fibrinogen levels during inflammation increase plasma viscosity and promote erythrocyte aggregation, contributing to a raised erythrocyte sedimentation rate. Beyond its coagulative role, fibrinogen interacts with immune cells via integrin receptors, facilitating leukocyte adhesion, migration, and cytokine release, thereby enhancing the inflammatory response. It also participates in wound healing and modulates vascular permeability. Thus, fibrinogen is a central mediator linking cytokine signaling, acute-phase protein production, and immune system activation in both inflammatory and thrombotic pathways. Fibrinogen caused the creation of the proinflammatory cytokines TNF-alpha and IL-6 in PBMC in a dose-dependent manner and markedly raised mRNA levels. Both fibrin and fibrinogen were equally successful in encouraging PBMC to produce cytokines. The findings provide evidence that fibrin and fibrinogen may actively regulate inflammation by causing PBMC to produce proinflammatory cytokines [Jensen et al.].'

Clinical utility of fibrinogen (e.g., diagnostic, prognostic, predictive biomarkers) in pancreatic cancer: 'The erythrocyte sedimentation rate, a non-specific marker of systemic inflammation, has limited diagnostic specificity in pancreatic cancer but may offer clinical utility as a prognostic and potentially predictive biomarker.

Elevated ESR levels have been associated with more advanced disease, increased tumor burden, and worse overall survival, reflecting the pro-inflammatory tumor microenvironment that supports cancer progression. While ESR alone is insufficient for diagnosis due to its elevation in numerous benign and malignant conditions, it can contribute to risk stratification when used alongside other markers such as CA19-9 or C-reactive protein. Additionally, persistently high ESR may indicate a poorer response to therapy and an increased likelihood of recurrence, suggesting a possible predictive role. Overall, ESR is a simple, cost-effective test that, while non-specific, may provide valuable prognostic insights in the management of pancreatic cancer.

Plasma viscosity, a measure of blood flow resistance influenced by plasma proteins and inflammation, has potential clinical utility in pancreatic cancer primarily as a prognostic biomarker. While not specific enough for diagnostic use on its own, elevated plasma viscosity levels have been linked to systemic inflammation and hypercoagulability commonly seen in cancer patients, including those with pancreatic malignancies. Higher plasma viscosity may correlate with advanced disease stage, greater tumor burden, and poorer overall prognosis. Some studies suggest it could also serve as a predictive marker, with elevated levels potentially indicating reduced responsiveness to treatment or increased risk of postoperative complications. When combined with other inflammatory or tumor-specific markers, plasma viscosity may enhance risk stratification and guide therapeutic decision-making, offering a low-cost, non-invasive adjunct in the clinical management of pancreatic cancer.

Procalcitonin, a biomarker typically elevated in bacterial infections, has emerging clinical relevance in pancreatic cancer, particularly in distinguishing infection-related complications from cancer-related inflammation. While its diagnostic utility for pancreatic cancer itself is limited, elevated procalcitonin levels can aid in identifying infectious complications such as cholangitis or pancreatic abscesses, which are common in advanced disease or post-interventional settings. Prognostically, higher procalcitonin levels have been associated with worse clinical outcomes, reflecting a heightened systemic inflammatory response or occult infection that may complicate cancer progression. As a predictive biomarker, procalcitonin may help guide antibiotic stewardship and monitor treatment response in infected patients, but its role in predicting chemotherapy response or long-term survival remains unclear. Overall, procalcitonin is a valuable adjunctive biomarker in the supportive care of pancreatic cancer patients, especially for managing infectious complications and tailoring clinical interventions.

Calprotectin, a calcium-binding protein released predominantly by activated neutrophils, has shown potential clinical utility in pancreatic cancer, particularly as a marker of inflammation associated with tumor progression. Although its diagnostic specificity is limited, elevated serum or fecal calprotectin levels have been observed in patients with pancreatic cancer and may help differentiate malignant from benign pancreatic conditions when used in conjunction with established markers like CA19-9. As a prognostic biomarker, higher calprotectin levels correlate with more aggressive disease, systemic inflammation, and poorer overall survival, reflecting the tumor-promoting role of chronic inflammation. Emerging evidence also suggests a potential predictive role, as elevated calprotectin may indicate resistance to treatment or a higher likelihood of disease recurrence. Overall, while not yet widely adopted in clinical practice, calprotectin holds promise as a non-invasive adjunctive biomarker for risk assessment and monitoring in pancreatic cancer.

Haptoglobin, an acute-phase glycoprotein involved in binding free hemoglobin and modulating inflammation, has demonstrated potential clinical utility in pancreatic cancer, particularly as a prognostic and possibly diagnostic biomarker. Elevated serum haptoglobin levels have been observed in pancreatic cancer patients and are associated with tumor progression, systemic inflammation, and poorer overall survival, supporting its role as a prognostic indicator. While haptoglobin alone lacks the specificity required for reliable diagnosis, when combined with established markers like CA19-9, it may enhance diagnostic accuracy, especially in distinguishing malignant from benign pancreatic conditions. Additionally, changes in haptoglobin levels during treatment may offer predictive insight into therapeutic response and disease monitoring. Overall, haptoglobin reflects the inflammatory and metabolic alterations associated with pancreatic cancer and holds promise as part of a multi-marker panel for improving clinical assessment and management.

SAA is an acute-phase reactant produced predominantly by the liver in response to inflammation, has demonstrated promising clinical utility in pancreatic cancer, particularly as a prognostic and potential diagnostic biomarker. Elevated SAA levels have been consistently associated with advanced disease stage, increased tumor burden, systemic inflammation, and reduced overall survival, underscoring its value in prognostication. While not specific enough for standalone diagnosis, SAA, when used in combination with conventional markers like CA19-9, may enhance diagnostic sensitivity, especially in early or ambiguous cases. Additionally, dynamic changes in SAA levels during therapy may reflect treatment response or disease progression, suggesting a possible predictive role. Given its close relationship with tumor-associated inflammation, SAA represents a valuable, non-invasive biomarker that can aid in risk stratification, monitoring, and potentially guiding therapeutic decisions in pancreatic cancer.

Ferritin, an intracellular iron-storage protein and acute-phase reactant, has shown clinical relevance in pancreatic cancer, primarily as a prognostic biomarker with potential diagnostic and predictive implications. Elevated serum ferritin levels are frequently observed in pancreatic cancer patients and are associated with systemic inflammation, greater tumor burden, and poorer overall survival, making it a useful indicator of disease severity and prognosis. Although ferritin lacks specificity for diagnostic use, when combined with other markers such as CA19-9, it may improve diagnostic accuracy in differentiating malignant from benign pancreatic conditions. Additionally, rising ferritin levels during treatment may reflect disease progression or therapeutic resistance, indicating a possible predictive role. Overall, ferritin serves as a cost-effective, non-specific marker that reflects the inflammatory and metabolic alterations in pancreatic cancer, with potential utility in comprehensive biomarker panels for risk assessment and clinical monitoring. Ferritin serves as a clinically important biomarker for the assessment of various iron-related disorders. It is routinely employed in the diagnostic evaluation of common conditions such as iron-deficiency anemia, as well as hereditary and acquired iron-overload syndromes, including hereditary hemochromatosis and iron accumulation secondary to chronic transfusion therapy. Serum ferritin is typically included as part of a broader panel of laboratory tests used to diagnose and monitor these conditions and is often considered the most informative single marker in many clinical contexts. However, its interpretation must be approached with caution due to potential confounding factors. Additionally, markedly elevated serum ferritin levels may serve as an important diagnostic indicator of rare but severe autoimmune or systemic inflammatory diseases [Wang et al.].

Fibrinogen, a key coagulation factor and acute-phase protein, has demonstrated significant clinical utility as a biomarker in pancreatic cancer, primarily in prognostic and emerging predictive contexts. Although its diagnostic specificity is limited when used alone, elevated plasma fibrinogen levels, especially when combined with CA19-9, may enhance diagnostic accuracy. More robustly, fibrinogen serves as a prognostic biomarker, with higher pre-treatment levels correlating with advanced disease stage, greater tumor burden, metastasis, and poorer overall and progression-free survival. Additionally, elevated fibrinogen may predict reduced responsiveness to chemotherapy and higher recurrence rates post-surgery, suggesting a potential predictive role. Mechanistically, fibrinogen promotes tumor progression through angiogenesis, immune evasion, and a pro-thrombotic tumor microenvironment. Thus, while not suitable as a standalone diagnostic tool, fibrinogen is a valuable marker for risk stratification and treatment planning in pancreatic cancer'.

2. The review often presents data uncritically. For example, conflicting results from studies on the same marker (e.g., CRP, IL-6) are presented without analysis of potential causes (e.g., differences in study design, stage of disease, assay methodology). There is minimal discussion of limitations, heterogeneity of findings, or gaps in the literature.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

'Tumor cells and associated stromal cells (e.g., cancer-associated fibroblasts, macrophages) secrete pro-inflammatory cytokines, including IL-6, which stimulate the hepatic synthesis of acute-phase proteins like CRP. Tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) within the tumor microenvironment produce IL-6. IL-6, in turn, drives the systemic acute-phase response, elevating CRP levels and promoting tumor-associated inflammation. Inflammation is recognized as a key contributor to carcinogenesis, mediated in part by pro-inflammatory markers such as IL-6 and CRP. Additionally, K-ras mutation represents a critical genetic event in the development of pancreatic cancer. This study aimed to evaluate and compare serum levels of IL-6 and CRP among patients with PDAC, chronic pancreatitis (CP), and healthy controls (HCs), and to investigate potential associations between these inflammatory markers and disease status, overall survival, and K-ras mutation status in PDAC patients. The study cohort comprised 135 PDAC patients, 25 individuals with CP, and 25 HCs. Serum IL-6 and CRP levels were quantified using enzyme-linked immunosorbent assay, while K-ras mutations were detected through polymerase chain reaction–restriction fragment length polymorphism analysis. Serum levels of both IL-6 and CRP were significantly elevated in PDAC patients compared to healthy controls. Elevated IL-6 and CRP levels were associated with more advanced disease features, including locally advanced tumors, lymphatic invasion, distant metastasis, and higher tumor stage. Among patients with unresectable PDAC, increased IL-6 levels correlated with the presence of K-ras mutations. These findings suggest that IL-6 and CRP may play key roles in PDAC progression, with elevated levels reflecting more aggressive tumor behavior. Moreover, the observed association between IL-6 and K-ras mutations implies potential molecular cross-talk contributing to the pathogenesis and advancement of PDAC. In pancreatic cancer, elevated CRP and IL-6 levels are driven by tumor-derived and immune cell–mediated inflammation, activation of oncogenic signaling pathways, tissue necrosis, and systemic metabolic alterations. These biomarkers not only reflect disease burden but may also actively contribute to cancer progression and poor clinical outcomes. The primary limitation of this study is that it focused on a limited subset of cytokines, whereas multiple cytokines are known to play roles in inflammation and tumorigenesis. A broader cytokine profile analysis is necessary to achieve a more comprehensive understanding of their involvement in disease progression. Nevertheless, the findings indicate that elevated serum IL-6 levels are associated with more aggressive disease phenotypes and the presence of K-ras mutations in patients with unresectable PDAC.'

3. The manuscript inadequately contextualizes how these biomarkers relate to current diagnostic or therapeutic standards in PDAC. How do they compare with CA19-9? Are any approved for clinical use? Are they integrated in current treatment algorithms or trials?

Author's response: we have revised this point in revised manuscript with yellow highlighted.

'As of now, there are no inflammation-specific biomarkers that are approved for routine clinical use in the diagnosis, prognosis, or monitoring of pancreatic cancer. While markers such as IL-6 and CRP have been extensively studied and are often elevated in patients with pancreatic ductal adenocarcinoma, they lack the specificity and validation required for clinical approval. These inflammatory markers are influenced by a variety of non-malignant conditions, including infections and systemic inflammatory responses, which limits their diagnostic accuracy. In contrast, CA 19-9 remains the only FDA-approved serum biomarker currently used in clinical practice for pancreatic cancer, primarily for monitoring disease progression, treatment response, and recurrence, rather than for early diagnosis. Although inflammatory biomarkers show promise as prognostic indicators and may help stratify disease severity or predict outcomes when used alongside established markers, their use remains largely confined to research settings. Ongoing studies are investigating whether combining inflammatory markers with genetic or tumor-specific biomarkers could enhance diagnostic and prognostic precision, but more evidence and regulatory validation are needed before they can be integrated into standard clinical protocols. Inflammation biomarkers are not yet formally integrated into standard treatment algorithms for pancreatic cancer; however, they are increasingly being explored in clinical trials and research studies as potential tools for prognostic stratification and treatment response prediction. Biomarkers such as

IL-6, CRP, and systemic inflammatory indices like the neutrophil-to-lymphocyte ratio and glasgow prognostic score (GPS) have shown associations with disease stage, aggressiveness, and overall survival in pancreatic ductal adenocarcinoma. Some clinical trials and retrospective studies incorporate these markers to identify high-risk patients, guide neoadjuvant therapy decisions, or assess immunotherapy responses, particularly in the context of the tumor microenvironment and cancer-associated inflammation. Despite promising findings, these markers are not yet part of evidence-based guidelines from bodies, due to the lack of large-scale prospective validation. As research progresses, particularly in the era of precision medicine and immuno-oncology, inflammation biomarkers may become part of integrated biomarker panels used to personalize treatment approaches for pancreatic cancer'.

4. The manuscript contains numerous grammatical issues, awkward phrasings, and repetition. For example, the abstract includes "However, this review article summarized...", which should be rephrased for clarity.

Author's response: We have revised this point in revised manuscript with yellow highlighted.

'This review article provided a comprehensive summary of the roles of erythrocyte sedimentation rate, plasma viscosity, procalcitonin, calprotectin, haptoglobin, serum amyloid A, ferritin, and fibrinogen in the pathophysiological mechanisms underlying pancreatic cancer.'

5. Several references appear inconsistently formatted and should follow the World Journal of Clinical Oncology style precisely.

Author's response: We have revised this point in revised manuscript with yellow highlighted.

6. The treatment for pancreatic cancer should be introduced (PMID: 34078087). TGF-beta is also an important biomarker (PMID: 33812073).

Author's response: we have added require data in revised manuscript with yellow highlighted.

'Pancreatic cancer remains a highly aggressive malignancy with a poor prognosis. Although gemcitabine is the standard chemotherapeutic agent used in its management, its clinical utility is hindered by considerable systemic toxicity. Previous clinical trials investigating the combination of gemcitabine with erlotinib have yielded limited therapeutic benefit and raised concerns regarding adverse effects. To address these limitations, the encapsulation of chemotherapeutic agents within polylactic-co-glycolic acid (PLGA) nanoparticles (NPs) has emerged as a promising strategy, offering controlled drug release and targeted delivery to minimize off-target toxicity. Moreover, surface modification of these NPs with macrophage-derived membranes enhances immune evasion and tumor-targeting capabilities. In this context, a novel nanoplatform was developed comprising gemcitabine-loaded PLGA nanoparticles cloaked with macrophage membranes (MPGNPs), aiming to enhance tumor-specific accumulation and reduce systemic toxicity. The co-administration of MPGNPs with erlotinib demonstrated a synergistic inhibitory effect on pancreatic cancer cell proliferation both in vitro and in vivo. Mechanistically, this combinatorial approach exerted its anti-tumor effects through simultaneous modulation of the PI3K/AKT/mTOR and Ras/Raf/MEK/ERK signaling cascades. Additionally, the macrophage membrane coating facilitated immune evasion and passive tumor targeting by circumventing phagocytic clearance. The findings by Cai et al. provide compelling preclinical evidence supporting the therapeutic potential of combining MPGNPs with erlotinib for the treatment of pancreatic cancer [Cai et al.].'

'Another study reported the design and synthesis of hollow-structured copper sulfide nanoparticles (CuS NPs) loaded with an ataxia telangiectasia mutated (ATM) kinase inhibitor and functionalized with an anti-TGF-β antibody on their surface (CuS-ATMi@TGF-β NPs). These engineered nanoparticles exhibited excellent photostability, efficient drug release, and the capacity to elevate local temperature under near-infrared (NIR) irradiation, enabling controlled, NIR-responsive activation. The CuS-ATMi@TGF-β NPs demonstrated selective tumor targeting, resulting in marked inhibition of tumor growth through a synergistic therapeutic approach combining low-temperature photothermal therapy (PTT) and chemotherapy. This nanoplatform not only facilitated effective tumor ablation at sub-lethal thermal levels—minimizing collateral damage to surrounding healthy tissues—but also enhanced therapeutic specificity and immune modulation via surface conjugation with the anti-TGF-β antibody. This modification contributed to improved tumor selectivity and promoted anti-tumor immune responses, highlighting the multifunctional therapeutic potential of CuS-ATMi@TGF-β NPs in precision cancer therapy [Cai et al.].'

7. "Approved immune checkpoint inhibitors include antibodies that block Programmed Cell Death 1 (PD-1), Programmed Cell Death ligand 1 (PD-L1), and Cytotoxic T lymphocyte-associated protein 4 (CTLA-4)." lacks reference such as doi.org/10.1016/j.cej.2024.152175.

Author's response: we have revised this point in the revised manuscript with yellow highlighted.

'DNA methyltransferase (DNMT) inhibitors represent a pivotal advancement in targeting aberrant epigenetic regulation in cancer. Agents such as decitabine can reverse hypermethylation-mediated silencing of tumor suppressor genes (TSGs), thereby reinstating their expression and contributing to anti-tumor effects. In this study, decitabine, a DNMT1 inhibitor, was encapsulated within polylactic-co-glycolic acid (PLGA) nanoparticles to form Dec@PLGA. These nanoparticles were subsequently coated with a hybrid vesicle composed of an anti-PD-L1 (aPD-L1) antibody and macrophage membrane (aMM), resulting in the formulation of Dec@PLGA@aMM. The Dec@PLGA@aMM nanoparticles exhibited a uniform spherical morphology with an average hydrodynamic diameter of 95.7 ± 9.1 nm and a surface zeta potential of −15.1 ± 3.3 mV. This targeted nanoplatform significantly suppressed tumor growth by restoring TSG activity and modulating the tumor immune microenvironment. In vivo, studies demonstrated that Dec@PLGA@aMM achieved a statistically significant reduction in tumor volume compared to control groups including PBS, PLGA@MM, aPD-L1, PLGA@aMM, free decitabine, Dec + aPD-L1, and Dec@PLGA@MM. These findings underscore the synergistic potential of combining epigenetic reprogramming via decitabine with immune checkpoint blockade through PD-L1 inhibition. The development of Dec@PLGA@aMM offers a promising strategy for HCC treatment by integrating DNA demethylation and immune modulation, paving the way for more effective epigenetically driven cancer therapies [Cai et al.].'

8. The manuscript oscillates between general "pancreatic cancer" and specific "pancreatic ductal adenocarcinoma" without clarification.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

'Pancreatic cancer (PC) is one of the most lethal malignancies with a poor 5-year survival rate of around 5%–9% that has remained almost stagnant since the 1960s [Hidalgo et al., Rawla et al.]. The vast majority of cases—over 85%—are attributed to pancreatic ductal adenocarcinoma (PDAC), which arises from the ductal epithelial cells, predominantly located in the head region of the pancreas [Rawla et al.]. PC is a general term that encompasses all malignant tumors originating in the pancreas, including both exocrine and endocrine types. Among these, PDAC is the most prevalent, accounting for approximately 90–95% of all pancreatic cancer cases. PDAC specifically arises from the epithelial cells lining the pancreatic ducts, making it a subtype of exocrine pancreatic cancer. In contrast, other forms of pancreatic cancer include acinar cell carcinoma, mucinous cystic neoplasms, and pancreatic neuroendocrine tumors (PNETs), each differing in cellular origin, biological behavior, and clinical course. PDAC is particularly aggressive, characterized by rapid progression, late diagnosis, and a poor prognosis, with a five-year survival rate of less than 10%. While pancreatic cancer as a whole includes tumors with varying degrees of malignancy and outcomes, PDAC is generally the most lethal and commonly referred to in clinical discussions and research due to its overwhelming predominance and clinical significance.'

9. It is suggested to condense and streamline the main text, eliminating overly detailed study descriptions that do not add value.

Author's response: We have revised this point in the revised manuscript with yellow highlighted.

10. Emphasize how this review differs from previous literature or systematic reviews in the field.

Author's response: This review article offers a detailed overview of the involvement of erythrocyte sedimentation rate, plasma viscosity, procalcitonin, calprotectin, haptoglobin, serum amyloid A, ferritin, and fibrinogen in the pathophysiological processes associated with pancreatic cancer. Notably, it also presents novel clinical insights and implications that have not been previously addressed in earlier literature or systematic reviews within this domain.

Revision reviewer 1

Comment: I AGREE THE PUBLICATION

Reply: Thanks for your comments.

Revision reviewer 2

The reviewers raised the following queries, which are explained below.

Reviewers report

I sincerely thank the authors for their diligent revisions in response to the previous review comments. The majority of concerns have been adequately addressed in the revised manuscript. However, upon reviewing the updated figures provided within the answering-reviewers file, I remain concerned that the textual elements within the figures appear overly dense and could impede visual clarity. I strongly recommend further optimization to reduce text redundancy, simplify labeling, or utilize graphical cues where possible to enhance readability without compromising essential information. Additionally, please ensure the finalized figures are embedded directly within the main manuscript file or supplementary materials, as appropriate, rather than solely within the "109385-answering-reviewers", to facilitate proper evaluation by readers and the editorial team. With these minor adjustments, the manuscript would be significantly strengthened.

Author's response: We have revised the figures, which increased visual clarity and reduced text redundancy, and figures are embedded directly in the revised manuscript with yellow highlighted.

'**Figure legends**

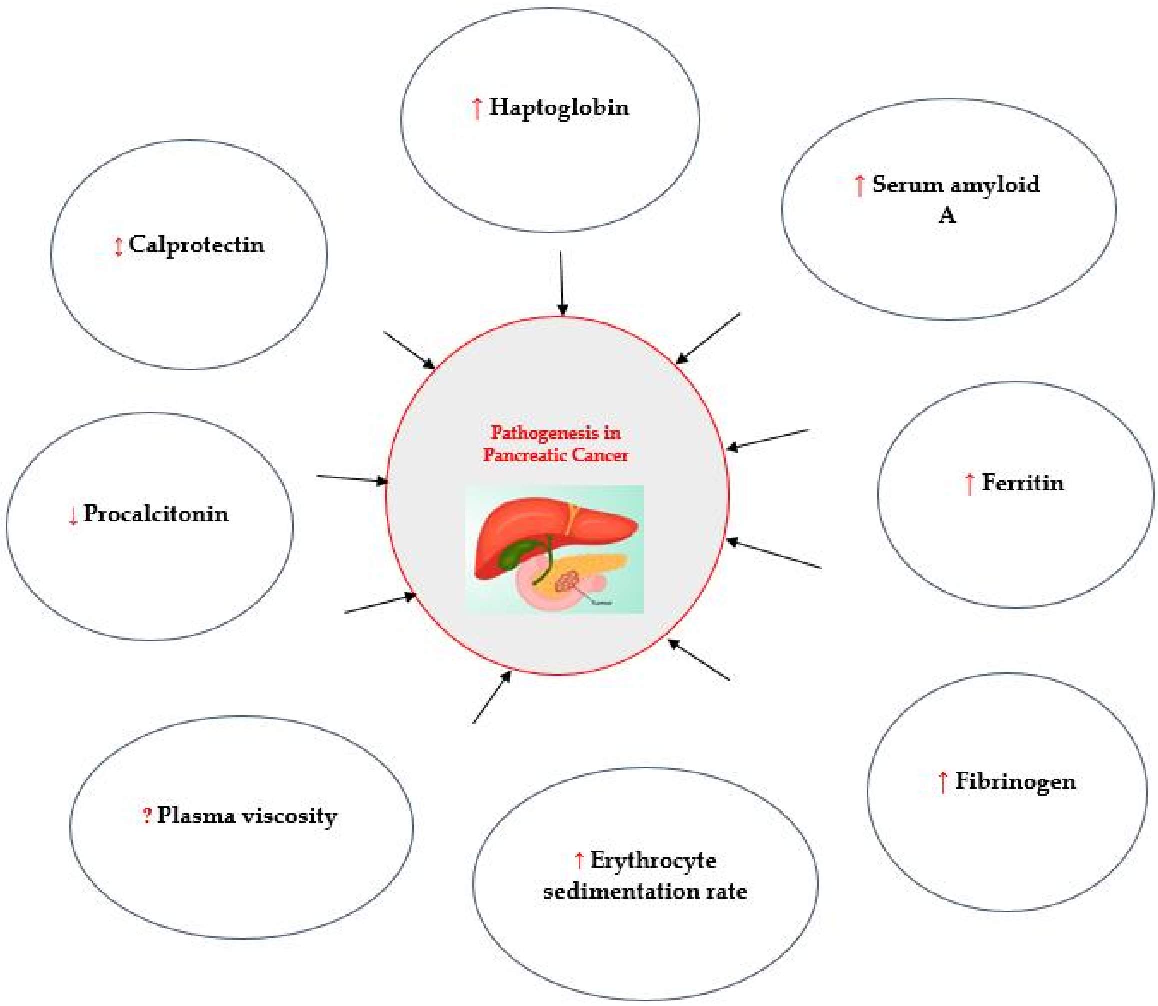


Figure 1: Circulating levels of inflammatory biomarkers in the pathogenesis of pancreatic cancer.

Source: Designed by the authors with the help of articles which are already cited in the references, (↑) increased levels (↓) decreased levels, (↕ not sure), (?) Not determined yet

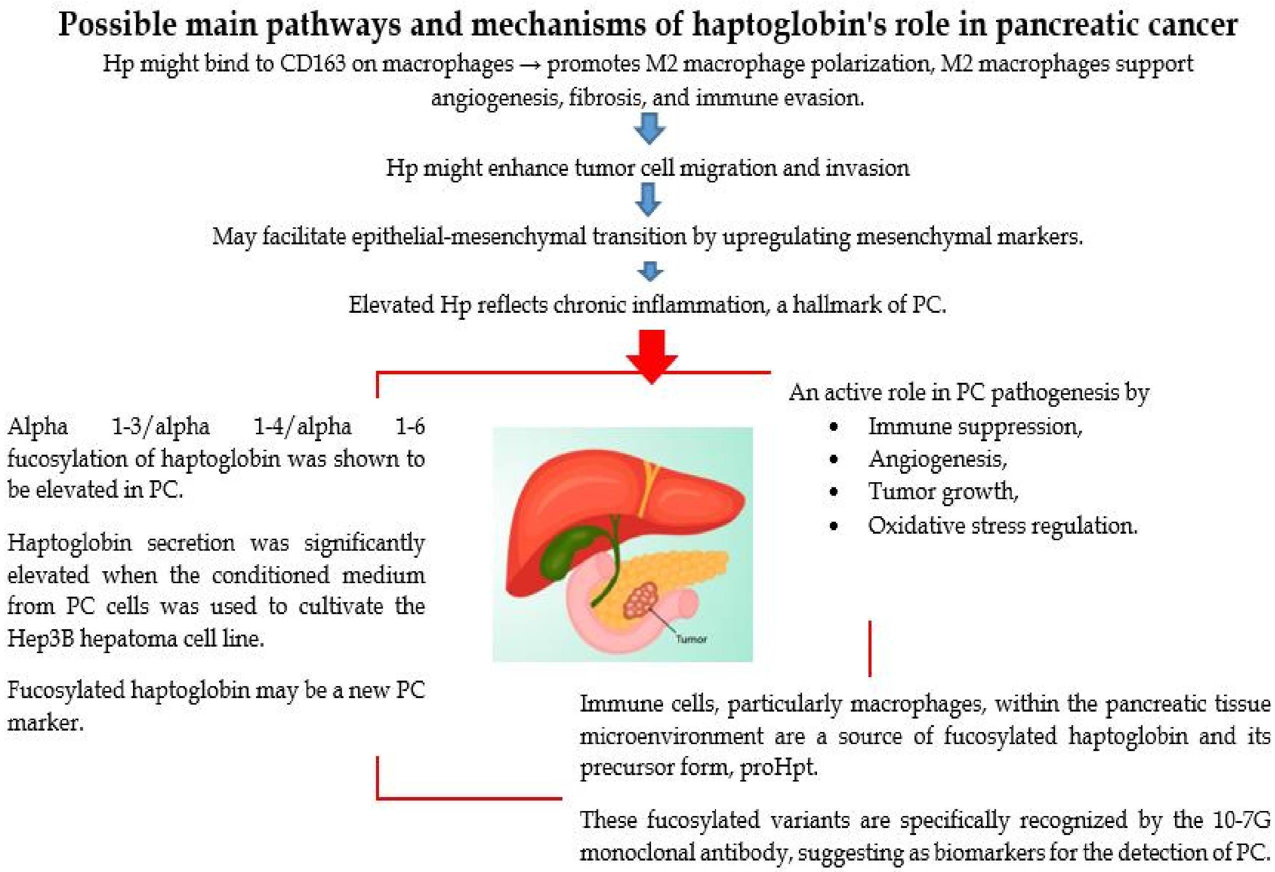


Figure 2: Haptoglobin causes pathogenesis in pancreatic cancer

Source: Designed by the authors with the help of articles which are already cited in the references, pancreatic cancer (PC)

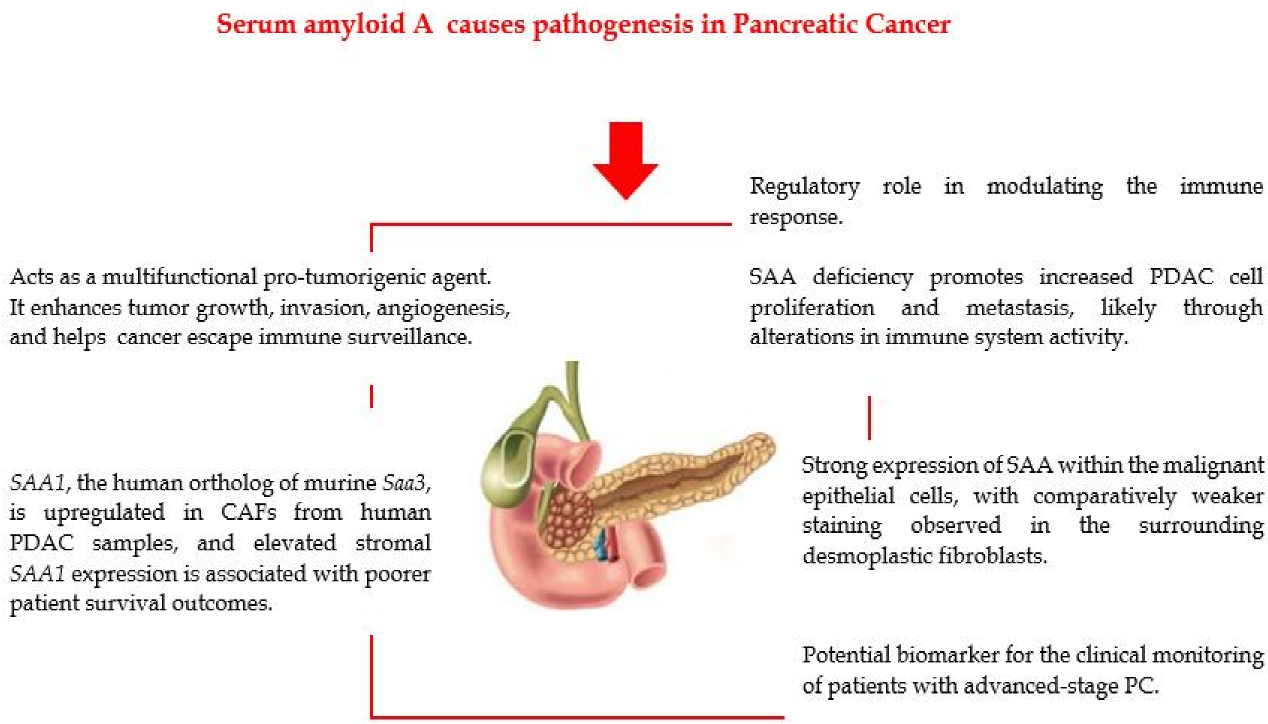


Figure 3: Serum amyloid A causes pathogenesis in pancreatic cancer

Source: Designed by the authors with the help of articles which are already cited in the references.

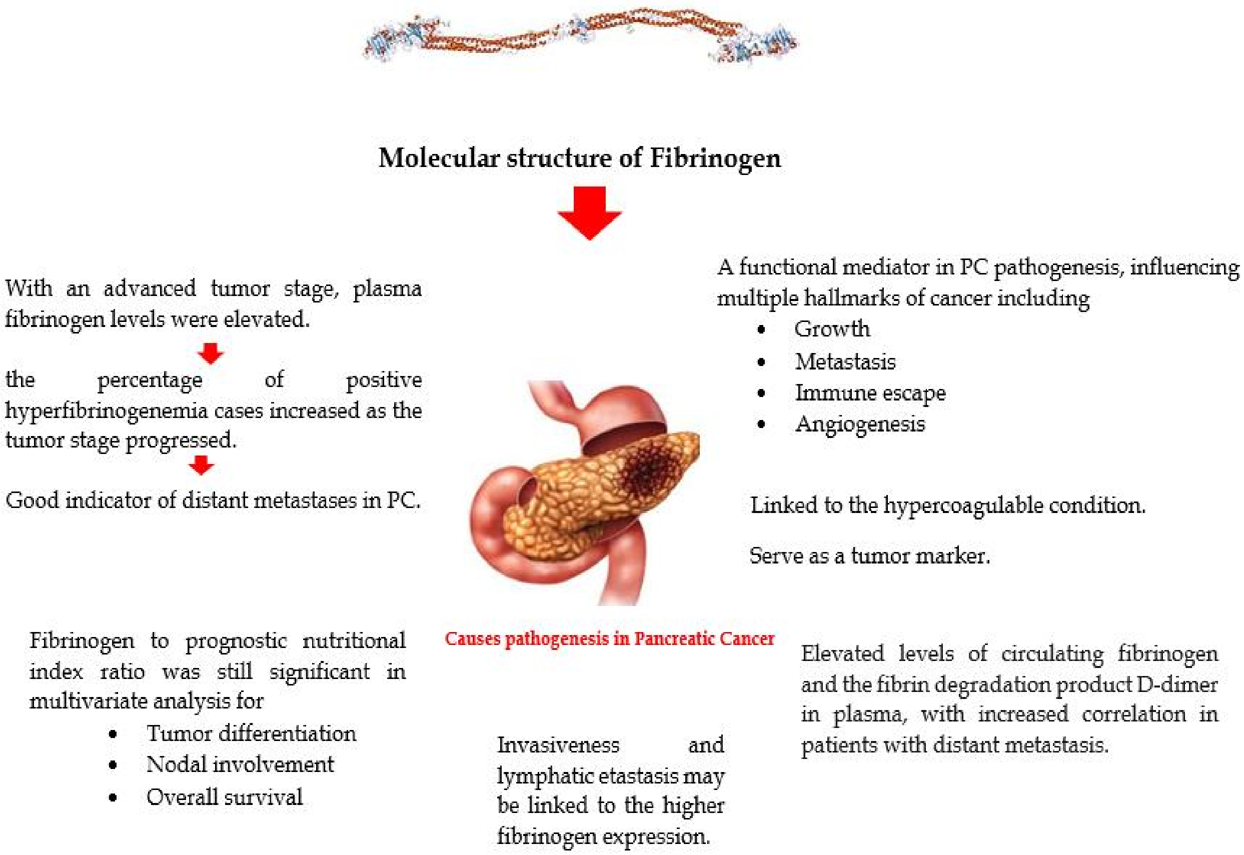


Figure 4: Fibrinogen causes pathogenesis in pancreatic cancer

Source: Designed by the authors with the help of articles which are already cited in the references, pancreatic cancer (PC)'.