OncoTargets and Therapy Dovepress

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Plasma COL10A1 Level, a Potential Diagnostic and Prognostic Biomarker for Pancreatic Ductal Adenocarcinoma

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Background: COL10A1 expression was up-regulated and could promote tumor development in pancreatic cancer. As a secreted protein, plasma COL10A1 level was proven to have certain diagnostic efficacy in gastric cancer, breast cancer, and colorectal cancer. It is still unknown whether it has a biomarker role for pancreatic cancer.

Aim: To explore and analyze the diagnostic and prognostic value of plasma COL10A1 level in pancreatic ductal adenocarcinoma (PDAC).

Method: The RNA-seq dataset of PDAC from The Cancer Genome Atlas (TCGA) and six expression profiling microarray datasets from Gene Expression Omnibus (GEO) were downloaded to analyze the expression of COL10A1 in tissues. Thirty-six patients with PDAC and eighteen healthy volunteers were enrolled to measure COL10A1 levels in tissues and plasmas, and the relationship between clinical characteristics and the COL10A1 levels was analyzed. The diagnostic and prognostic efficacy of plasma COL10A1 levels were calculated.

Results: Aspects of COL10A1 expression level in tissues, COL10A1 expression was significantly higher in PDAC tissue than adjacent normal tissue. The expression of COL10A1 was correlated with T, M, and AJCC stages. Patients with high COL10A1 expression had worse recurrence-free survival (RFS) and overall survival (OS) than those with low expression. Aspects of COL10A1 expression levels in plasma, its diagnostic area under the curve (AUC) for PDAC was 0.926 (95% CI 0.853–0.999), diagnostic sensitivity was 81% (95% CI 64–92%), and specificity was 100% (95% CI 81–100%). The time-dependent AUCs at 1-year and 3-year were 0.71 (95% CI 0.51–0.90) and 0.74 (95% CI 0.48–1.00), respectively.

Conclusion: In PDAC, plasma COL10A1 levels showed certain diagnostic and prognostic efficacy. COL10A1 may be a diagnostic and prognostic biomarker for PDAC and play a role in liquid biopsy of this disease.

Keywords: COL10A1, pancreatic ductal adenocarcinoma, biomarkers, diagnosis, prognosis

Background

Worldwide, there are nearly half a million new cases and deaths from pancreatic cancer each year, and the disease is the third leading cause of cancer death in both men and women. Especially in economically developed regions, such as Europe and North America, the incidence and mortality of pancreatic cancer are showing a steady upward trend.[1] Pancreatic ductal adenocarcinoma (PDAC) originates from the epithelial cells of the pancreatic duct and is the main pathological type of pancreatic cancer. It accounts for 80–90% of pancreatic cancer. In the process of PDAC, specific clinical symptoms are not easy to develop in the early stage because of the special anatomical location of the disease, which makes early diagnosis of the disease very difficult. When the disease develops into advanced or metastatic PDAC, patients completely lose the opportunity for radical treatment, coupled with the highly malignant biological characteristics of the disease, resulting in poor prognosis of patients. Early diagnosis and accurate assessment of the prognosis are

Received: 19 April 2024
Accepted: 1 November 2024
Published: 6 November 2024

important to improve the therapeutic effect of patients with PDAC, and the exploration of better screening and prediction tools is an important direction for future research in this field.

Currently, the diagnostic methods of pancreatic cancer mainly include ultrasound, CT, MRI, endoscopic ultrasonography, endoscopic retrograde cholangiopancreatography (ERCP), laparoscopic exploration, PET-CT, and CA19-9 level. The gold standard for diagnosis remains through histopathological examination. To explore new methods for screening pancreatic cancer, most scholars believed that the most promising direction was liquid biopsy technology. Previously, several studies have explored the early diagnosis of pancreatic cancer by using plasma proteins, DNA methylation, circulating tumor cells, MicroRNAs, and extracellular vesicles.[2–5] Some studies have shown good results, but the FDA has not yet approved any new method for early screening of pancreatic cancer based on liquid biopsy. The mining of new biomarkers and the construction of optimization models are important work in this field in the future.

The COL10A1 is located at 6q22.1 and encodes a protein consisting of three 680-amino acid type X collagen α1 chains, which belong to the collagen family and were found to be a secreted protein.[6,7] The expression of COL10A1 is increased in pancreatic cancer, breast cancer, gastric cancer, esophageal cancer, colorectal cancer, and laryngeal cancer, and is related to the prognosis of breast cancer, esophageal cancer, colorectal cancer, and bladder cancer.[8–14] Marta and Xavier found that plasma COL10A1 levels could also be used as a diagnostic marker for breast cancer and colorectal cancer, respectively.[15,16] Meanwhile, a similar study also found that it had a potential diagnostic marker role in gastric cancer, especially that it had potential value for early diagnosis of gastric cancer.[17] In pancreatic cancer, researchers found that COL10A1 could promote tumor development by regulating the MEK-ERK signaling pathway.[8] However, as a secreted protein, it is still unknown whether it has the biomarker role for PDAC. This study aims to explore the clinical significance of plasma COL10A1, to demonstrate whether it has clinical significance as a diagnostic marker and prognostic marker for PDAC, and to provide new evidence for the future development of liquid biopsy technology.

Methods

Patient and Clinical Sample Selection

A total of thirty-six patients with pathologically diagnosed PDAC who were hospitalized in the First Affiliated Hospital of Chengdu Medical College between January 2017 and June 2020 were enrolled in this study. The clinical data of patients were collected, including age, gender, tumor differentiation, T stage, N stage, M stage, survival status, and survival time. Tissue samples were collected from operation or puncture. Plasma samples were collected from patients before and after initial treatment.

This study follows the principles of the Declaration of Helsinki to ensure that the rights and safety of all participants are fully protected, and it was approved by the Ethics Committee of the First Affiliated Hospital of Chengdu Medical College (2020CYFYIRB-BA-88). All patients or their duly authorized representatives who participated in the study were adequately informed, and they received comprehensive information and provided written consent. In certain instances, patients may be incapable of providing informed consent independently due to their health status. Consequently, informed consent is obtained from duly authorized representatives of the patients following pertinent ethical guidelines. All consent procedures are reviewed and approved by the Ethics Committee to ensure the ethics of the study and the protection of patients' rights.

Bioinformatics Analysis of COL10A1 Expression and Clinical Features

The RNA-seq data and clinical information of PDAC were downloaded from The Cancer Genome Atlas (TCGA). GSE71989, GSE62165, GSE60979, GSE32676, GSE28735, and GSE91035 were downloaded from Gene Expression Omnibus (GEO). The clinical information collected included age, gender, tumor differentiation, T stage, N stage, M stage, survival status, and survival time.

RNA Extraction, Quantitative Real-Time PCR (qRT-PCR)

Tissues were ground into powder; RNA was isolated by TRIzol, chloroform, and isopropanol. Then washed with 75% ethanol, and dissolved in enzyme-free water. RNA samples were added according to the reaction system of the reverse

transcription kit (KR116-02, TIANGEN), and the reaction condition was: 25 ° C for 5 minutes, 42 ° C for 1 hour, 70 ° C for 15 minutes, and 4 ° C for 10 minutes. Then we dilute the concentration of cDNA to about 1000ng/μL. 8μL reaction system was prepared by using SYBR kit (1725272, Bio-rad), and a 2μL cDNA sample was added to test. The reaction condition was followed by the qRT-PCR three-step method, and the dissolution curve was plotted. GAPDH was used as a control, and the 5'-3' sequence of primers was GGAGTCAACGGATTTGGT and GTGATGGGATTTCCATTGAT.

Immunohistochemistry

Fresh tumor tissues and adjacent tissues were immediately fixed in 4% neutral paraformaldehyde, embedded in paraffin, sectioned at 4um, baked, deparaffinized, hydrated, permeated, blocked, and incubated with rabbit polyclonal COL10A1 antibody in the COL10A1 Ready-to-use IHC kit (KHC0743, Proteintech) at 4°C overnight. Then incubated with polymer-HRP-goat anti-rabbit secondary antibody at normal temperature for 1 hour, and then stained with diaminobenzidine, and photographed for recording. Results were quantitatively analyzed by using the H-score method. For the calculation of the H-score, 10 fields were randomly selected from each section, and the average staining intensity and number of tumor cells were recorded. The cell proportion of weak intensity was rated 1 point, moderate intensity was 2, and strong intensity was 3, and the H score was the sum of the above cell scores.

Plasma COL10A1 and CA19-9 Levels Were Measured

5mL fresh peripheral whole blood was collected from the subject by using an Ethylene Diamine Tetraacetic Acid (EDTA) routine blood tube and centrifuged at 2–8°C for 15 minutes at 900×g/ min within 30 minutes. The plasma was separated and stored at −80°C. COL10A1 protein was detected by a human COL10A1 ELISA kit (EH1637, FineTest). CA19-9 protein was detected by a human CA19-9 detection kit (RX105123H, Ruixin Biotech). The above ELISA experiments were performed according to the protocol of the kits.

Statistical Analysis

The data were analyzed and illustrated by GraphPad Prism 8 and R software v4.0. In comparison, two independent samples t-tests and paired t-tests were used for the parameter tests, while the Wilcox test was used for the non-parameter test. Kaplan-Meier curves analysis and Log rank test were performed by using the survival package of R software. The receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) were used to calculate the diagnostic efficacy of COL10A1 and CA199. Time-dependent survival prediction was performed using the survivalROC package. Youden's index was used to set the cut-off value of ROC. In this study, $p<0.05$ was considered to indicate statistical significance.

Results

Basic Information on the Public Datasets and Cohorts Included in the Study

To analyze the relationship between COL10A1 expression and clinical characteristics of patients with PDAC, we downloaded the RNA-seq data and clinical parameters of 177 patients in TCGA database. Meanwhile, 36 tissue samples and matched plasma samples of patients with PDAC, and 18 plasma samples of healthy volunteers were collected in our center. In our cohort of PDAC patients, the mean age was 55.94±10.92 years old, the patients with stage III–IV accounted for 44.4%, and the median survival time was 12 months. The basic information of patients with PDAC extracted from TCGA database and our cohort were shown in Table 1.

The Expression of COL10A1 Was Increased in PDAC Tissues and Was Associated with Poor Clinical Features

In the six expression arrays of PDAC downloaded from GEO, it was found that COL10A1 had higher expression in tumor tissues than in adjacent normal tissues (Figure 1A). The diagnostic AUC of COL10A1 expression in tissue was 0.882 (Figure 1B). In the validation, the total RNA of 36 pairs of tumor tissues and adjacent normal tissues were extracted. Through qRT-PCR, there was a significant difference in the expression of COL10A1 between the two types of

Table 1 Clinical Information of the Study Population

	TCGA	Our Cohort
Sample size	177	36
Age (%)		
>60	119 (67.2%)	13 (36.1%)
≤60	58 (32.8%)	23 (63.9%)
Gender (%)		
Female	80 (45.2%)	16 (44.4%)
Male	97 (54.8%)	20 (55.6%)
Grade (%)		
G1	31 (17.5%)	21 (58.3%)
G2+G3+G4	144 (81.4%)	15 (41.7%)
NA	2 (1.1%)	–
T Stage (%)		
T1+T2	31 (17.5%)	11 (30.6%)
T3+T4	144 (81.4%)	25 (69.4%)
NA	2 (1.1%)	–
N Stage (%)		
N0	49 (27.7%)	18 (50.0%)
N+	123 (69.5%)	18 (50.0%)
NA	5 (2.8%)	–
M Stage (%)		
M0	79 (44.6%)	26 (72.2%)
M1	4 (2.3%)	10 (27.8%)
Mx	89 (50.3%)	–
NA	5 (2.8%)	–
TNM Stage_AJCC(%)		
I	21 (11.9%)	6 (16.7%)
II	146 (82.5%)	14 (38.9%)
III	3 (1.7%)	6 (16.7%)
IV	4 (2.2%)	10 (27.8%)
NA	3 (1.7%)	–
Event (%)		
Alive	85 (48.0%)	9 (25.0%)
Dead	92 (52.0%)	27 (75.0%)
Median OS (month)	15.48	12.00

tissues, and the expression level of COL10A1 in tumor tissues was 4.365 times higher than that in normal tissues (Figure 1C). The result of immunohistochemistry also showed that the expression of COL10A1 in tumor tissues was significantly higher than that in adjacent normal tissues (Figure 1D–F).

In association analysis of RNA-seq data and clinical information of PDAC in TCGA database, the increased expression of COL10A1 in tumor tissues was found to be associated with tumor differentiation, T stage, and AJCC stage. The expression of COL10A1 was significantly higher in tumor tissues with G2-4 differentiation level than with G1 differentiation level. The expression of COL10A1 was significantly higher in T3/T4 patients than T1/T2 patients and in stage II–IV patients than in stage I patients. However, no significant difference was found between COL10A1 expression and age, sex, race, history of alcohol drinking, family history of cancer, history of chronic pancreatitis, history of diabetes, primary tumor site, N stage, or M stage (Figure 2A). In our cohort, COL10A1 expression was found to be correlated with T stage, AJCC stage, and M stage (Figure 2B). In the prediction of the efficacy and prognosis, RFS and OS were worse in high COL10A1 expression patients in TCGA database. Our cohort also showed that patients with high COL10A1 expression had worse OS (Figure 2C).

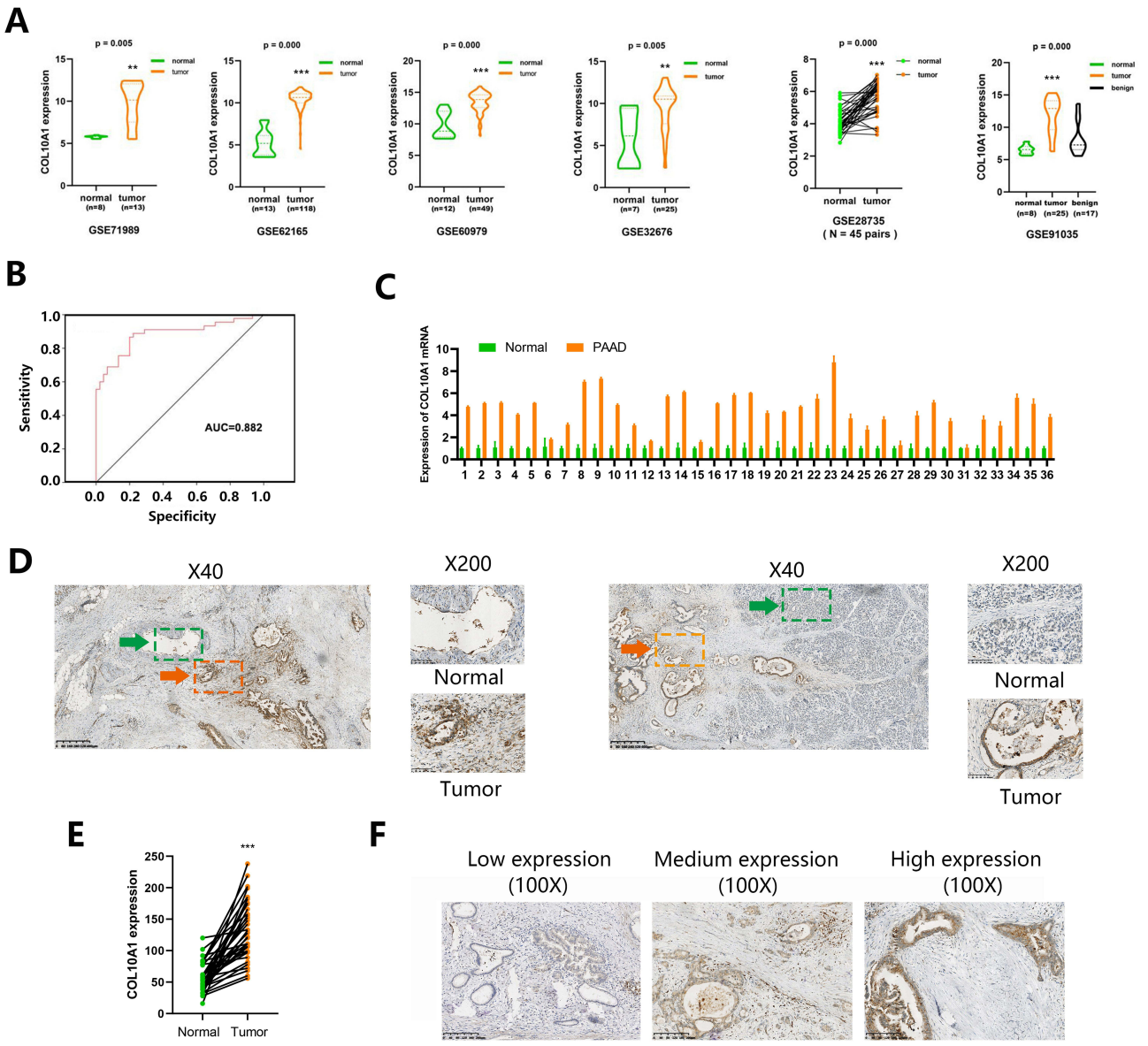

Figure 1 Expression of COL10A1 in PDAC and adjacent normal tissues. (**A**) mRNA Expression of COL10A1 in tissues in six GEO datasets. (**B**) Diagnostic efficacy of COL10A1 mRNA expression for PDAC in TCGA-PDAC dataset. (**C**) mRNA Expression of COL10A1 in tissues of 36 PDAC patients. (**D**) Detection of COL10A1 protein expression in tumor tissue and adjacent normal tissue of PDAC. (**E**) Difference of COL10A1 protein expression between tumor tissue and adjacent normal tissue. (**F**) Low, medium, and high expression levels of COL10A1 protein in PDAC tumor tissue.

Plasma COL10A1 Level Was Increased in Patients with PDAC and Was Associated with OS

The plasma COL10A1 level of 36 patients with PDAC was significantly higher than that of 18 healthy volunteers (Figure 3A). Based on the above result, we analyzed the diagnostic efficacy of plasma COL10A1 and found that its diagnostic AUC=0.926 (0.853,0.999), and the best diagnostic cut-off value was: 164.7ng/mL. Its diagnostic specificity was 99%, and the diagnostic sensitivity was 81%. As a control, the diagnostic AUC of CA19-9 was 0.891 (0.808,0.975), and the best cut-off value was 21.35U/mL. Its diagnostic sensitivity was 63% and the specificity was 99%. The combined diagnostic AUC of plasma COL10A1 and CA19-9 was 0.949 (0.897,1.000) (Figure 3B). The diagnostic AUC of COL10A1 for patients with stage I and II was 0.881 (0.757,1), and the diagnostic sensitivity was 0.75 (0.51–0.91). As a control, the diagnostic AUC of CA19-9 was 0.829 (0.699,0.959). The combined diagnosis AUC of plasma COL10A1 and CA19-9 was 0.922 (0.840,1.000) (Table 2 and Figure 3C).

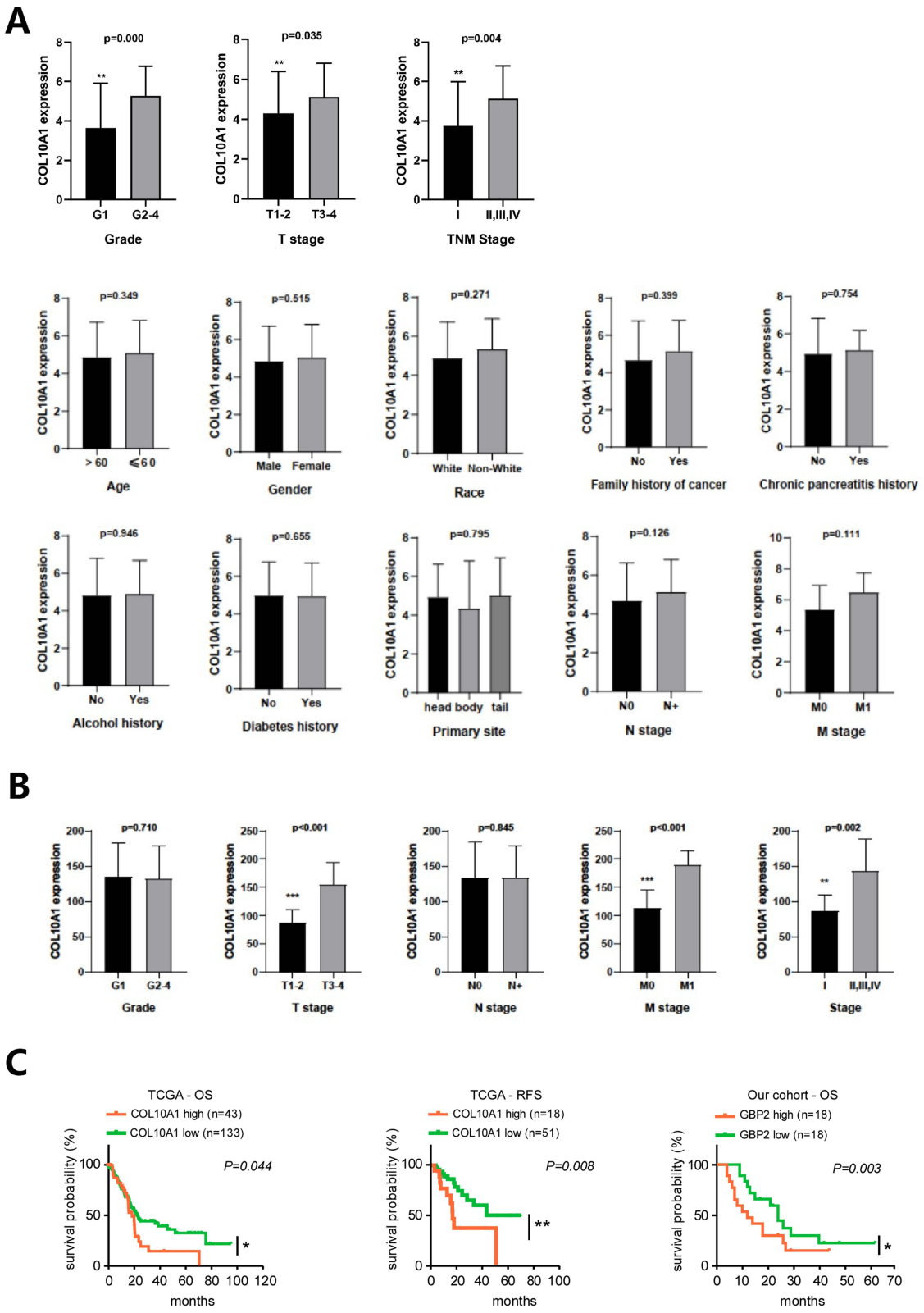

Figure 2 COL10A1 expression level in PDAC patients with different clinical phenotypes and the relationship between COL10A1 expression and prognosis of patients. (**A**) Expression level of COL10A1 in PDAC patients with different clinical phenotypes in TCGA database. (**B**) Expression levels of COL10A1 In PDAC patients with different clinical phenotypes in our cohort. (**C**) The relationship between COL10A1 expression and RFS and OS in TCGA-PDAC cohort and our cohort.

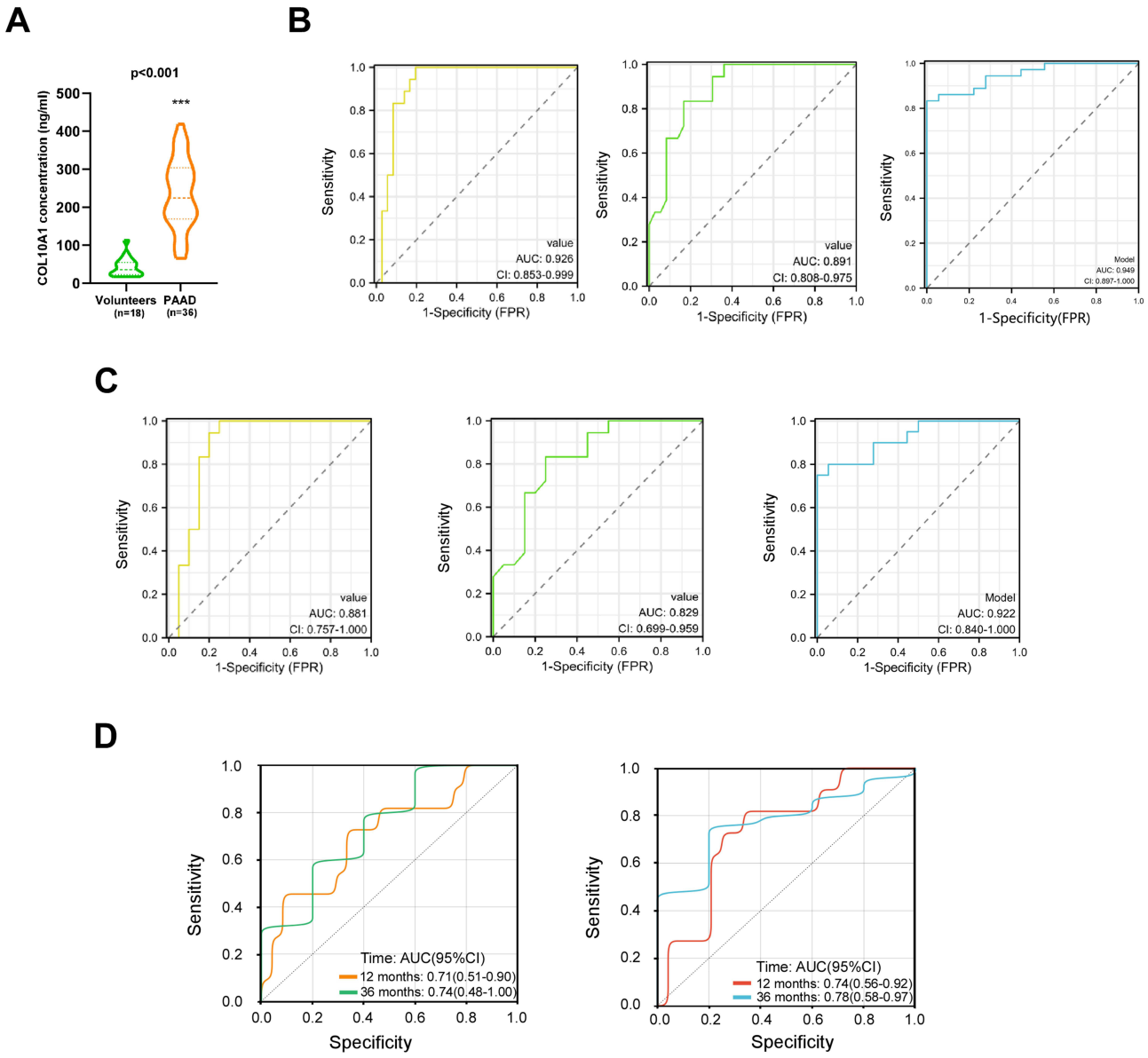

Figure 3 Detection of the diagnostic and prognostic efficacy of plasma COL10A1 for PDAC. (**A**) Differences in plasma COL10A1 levels between PDAC patients and healthy volunteers (**B**) Diagnostic ROC curves of plasma COL10A1, CA19-9 and their combination for overall PDAC patients. (**C**) Diagnostic ROC curves of plasma COL10A1, CA19-9 and their combination in PDAC patients with stage I/II. (**D**) Calculation of 1-year and 3-year time-dependent AUC in patients with PDAC by plasma COL10A1 and CA19-9.

When the analysis of the plasma COL10A1 level and the survival data was performed, it was found that the plasma COL10A1 level was correlated with the patients' OS, with 1-year and 3-year time-dependent AUC 0.71 (0.51,0.90) and 0.74 (0.48,1.00), respectively. For control, the 1-year and 3-year time-dependent AUC for CA19-9 was 0.74 (0.56,0.92) and 0.78 (0.58,0.97), respectively. In comparison, plasma COL10A1 showed better diagnostic sensitivity, and had similar 1-year and 3-year survival predictive power to CA19-9 (Figure 3D).

Discussion

Recently, liquid biopsy technology has developed rapidly in the field of diagnosis and treatment of cancers. It promoted the development of precise and individualized medicine in cancers by its use in early disease diagnosis, treatment efficacy evaluation, and prognosis prediction. Due to its special anatomical location, tissue biopsy of pancreatic cancer was relatively difficult. Liquid biopsy technology can provide effective and important information for clinical strategy.

Table 2 Diagnostic Efficacy of Plasma COL10A1 and Serum CA19-9 in Whole PDAC Patients and Stage I/II PDAC Patients

	Disease	AUC	p value	Sensitivity	Specificity
COL10A1	PDAC	0.926(0.853,0.999)	0.001	0.81(0.64–0.92)	1.00(0.81–1.00)
CA19-9	PDAC	0.891(0.808,0.975)	0.003	0.83(0.67–0.94)	0.83(0.59–0.96)
COL10A1	Stage I/II PDAC	0.881(0.757,1.000)	0.006	0.75(0.51–0.91)	1.00(0.81–1.00)
CA19-9	Stage I/II PDAC	0.829(0.699,0.959)	0.012	0.75(0.51–0.91)	0.83(0.59–0.96)

Biomarker selection is considered to be one of the most important contents in the development of liquid biopsy technology. At present, only serum CA19-9 was approved by US Food and Drug Administration (US FDA) as a diagnostic and prognostic marker, but this marker was still unable to meet the clinical needs. The diagnostic sensitivity and specificity of serum CA19-9 were only 70–92% and 68%-92%, respectively. Additionally, it also had some limitations of clinical application, such as unstable detection value and no expression in Lewis blood-group negative patients.[18–21] In 2021, Immunovia launched IMMray PanCan-d diagnostic kit used for pancreatic cancer diagnosis, which was an 8-plex biomarker signature with CA19-9 to detect serum samples for early screening of pancreatic cancer. It has a sensitivity of 85% and a specificity of 99% for the diagnosis of stage I–II PDAC, which has a good market application prospect.[22] In recent years, different types of blood biomarkers have been found to possess potential diagnostic and predictive capabilities, such as DNA methylation, MicroRNA, and extracellular vesicles.[2,4,5] Some studies have found that the combination of serum CA19-9, TIMP1, and 9-loci cfDNA methylation had higher diagnostic efficiency than serum CA19-9 alone for early pancreatic cancer, with an AUC of 0.86, while serum CA19-9 alone was 0.82.[2] In terms of MicroRNA, Shi reported that the diagnostic panel composed of hsa-miR-1246, hsa-miR-205-5p, and hsa-miR-191-5p had an accuracy value of 83.5% for pancreatic cancer.[4] miR-196a, miR-22-3p, miR-642b-3p, and miR-196a in serum or plasma have also been found to have certain diagnostic and prognostic value for pancreatic cancer in some other studies.[23–25] A study using extracellular vesicle proteins as biomarkers for early screening of pancreatic cancer found that a diagnostic panel composed of 9 extracellular vesicle proteins could achieve a sensitivity of 90% and a specificity of 92.8% in stage I/II patients. However, the validation cohort only included 30 patients, and the sample size still needs to be expanded to further test.[5] Currently, some studies using plasma proteins, circulating tumor cell (CTC), and circRNA as tumor markers have also achieved good results.[3,26] However, by reviewing most of the previous studies, it can be found that the identified biomarkers always show unstable performance in large sample cohorts in the real world, so it is necessary to continue the work to explore more accurate diagnostic or predictive biomarkers.

A recent study found that COL10A1 and its receptor DDR2 can activate the protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway to promote EMT and cell proliferation in PDAC cells.[8] In addition, some studies have also reported that COL10A1 can promote tumor development by regulating the expression of CD276 in PDAC.[27] It was found that pancreatic stellate cells and fibroblasts were the main producers of collagen in the pancreas. In the TCGA database, COL1A1, COL3A1, COL5A1, and COL6A1 were expressed in all cancer-associated fibroblasts (CAF) subtypes. COL8A1, COL10A1, COL11A1, and COL12A1 were specifically expressed in myoblast CAF (myCAF). Myofibroblast CAF (myCAF) collagen COL10A1 and COL11A1 are elevated in a variety of solid tumor types, and multiple associations have been found between high expression and poorer survival.[28] As a secreted protein, plasma COL10A1 has been confirmed to be a potential biomarker for the diagnosis and prognosis prediction of gastric cancer. For early gastric cancer, the AUC of plasma COL10A1 was as high as 0.8789.[17] Besides, COL10A1 is a potential diagnostic biomarker associated with deficient mismatch repair and immune infiltration in colon cancer.[29] Based on these findings, this study aims to test the diagnostic and prognostic value of plasma COL10A1 in PDAC. Firstly, the expression of COL10A1 in PDAC tissues was found to be correlated with T stage, M stage, and AJCC stage, which was consistent with the biological function of COL10A1 in promoting proliferation and metastasis. At the same time, the expression level of COL10A1 was also found to be related to the prognosis of patients. Secondly, plasma COL10A1 was found to have a certain diagnostic and prognostic ability for PDAC, and it still has a good diagnostic ability for stage I and II patients. Compared with the traditional serum CA19-9, plasma COL10A1 has better diagnostic sensitivity, and similar

ability to predict 1-year and 3-year survival. These results suggest that plasma COL10A1 may be a biomarker with potential diagnostic and prognostic value.

This study was a clinical application exploration based on the results of previous basic experiments and bioinformatics analysis. The sample size of subjects included in our center was a bit narrow, especially the patients with stage I/II. Due to the limited cases, it was also not possible to construct the diagnostic or prognostic model with other biomarkers to improve and optimize its clinical application value. We will expand the sample size in the follow-up study to further enhance the reliability of the conclusion. Additionally, if plasma COL10A1 level can play a role in the differential diagnosis of pancreatic cancer, it needs further detection in pancreatitis, pancreatic benign tumors, and other diseases.

Conclusion

The expression of COL10A1 was up-regulated in PDAC, and was significantly correlated with T stage, M stage, and AJCC stage. High COL10A1 expression levels are associated with poorer RFS and OS in PDAC patients, suggesting that it may serve as a biomarker for PDAC prognosis. In addition, we found that plasma COL10A1 levels were significantly elevated in PDAC patients and demonstrated good diagnostic potential with higher diagnostic sensitivity compared to CA19-9. These findings support the possibility of plasma COL10A1 as a diagnostic and prognostic biomarker for PDAC.

Abbreviations

PDAC, pancreatic ductal adenocarcinoma; TCGA, The Cancer Genome Atlas; GEO, Gene Expression Omnibus; RFS, recurrence-free survival; OS, Overall Survival; AUC, area under the curve; ERCP, endoscopic retrograde cholangiopancreatography; qRT-PCR, Quantitative real-time PCR; FR, Folate Receptor; ROC, Receiver operating characteristic; US FDA, US Food and Drug Administration; CTC, circulating tumor cell.

Data Sharing Statement

The RNA-seq data and clinical information of PDAC were downloaded from TCGA database (https://tcga-data.nci.nih.gov/tcga/). GSE71989, GSE62165, GSE60979, GSE32676, GSE28735, and GSE91035 were downloaded from GEO database (https://www.ncbi.nlm.nih.gov/geo/).

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Chengdu Medical College (2020CYFYIRB-BA-88).

Author Contributions

Tianlei Wang and Xinrui Bao contributed equally to this work and should be considered co-first authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The project was funded by the Natural Science Foundation of Sichuan Province (Grant No. 2023NSFSC0729), Chengdu Medical College Elite Peak Program (Grant No. 2024qnGzn04), Key Clinical Specialty of Sichuan Province (Grant No. YS00109), and Sichuan Provincial Health Commission Clinical Research Project (Grant No. 23LCYJ049). We are grateful to these funding organizations for their support of this study. The funders had no role in study design, data collection, and analysis, the decision to publish, or the preparation of the manuscript.

Disclosure

The authors declare no potential conflicts of interest.

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. *Ca-A Cancer J Clinicians*. 2023;73(1):17–48. doi:10.3322/caac.21763
2.. Ben-Ami R, Wang QL, Zhang J, et al. Protein biomarkers and alternatively methylated cell-free DNA detect early stage pancreatic cancer. *GUT*. 2023:gutjnl–2023–331074. doi:10.1136/gutjnl-2023-331074.
3. Stoecklein NH, Fluegen G, Guglielmi R, et al. Ultra-sensitive CTC-based liquid biopsy for pancreatic cancer enabled by large blood volume analysis. *Mol Cancer*. 2023;22(1):181. doi:10.1186/s12943-023-01880-1
4. Shi W, Wartmann T, Accuffi S, et al. Integrating a microRNA signature as a liquid biopsy-based tool for the early diagnosis and prediction of potential therapeutic targets in pancreatic cancer. *Br J Cancer*. 2023;130:125–134. doi:10.1038/s41416-023-02488-4
5. Hinestrosa JP, Sears RC, Dhani H, et al. Development of a blood-based extracellular vesicle classifier for detection of early-stage pancreatic ductal adenocarcinoma. *Commun Med*. 2023;3(1):146. doi:10.1038/s43856-023-00351-4
6. He Y, Siebuhr AS, Brandt-Hansen NU, et al. Type X collagen levels are elevated in serum from human osteoarthritis patients and associated with biomarkers of cartilage degradation and inflammation. *BMC Musculoskelet Disord*. 2014;15:309. doi:10.1186/1471-2474-15-309
7. Makitie O, Susic M, Ward L, et al. Schmid type of metaphyseal chondrodysplasia and COL10A1 mutations—findings in 10 patients. *Am J Med Genet A*. 2005;137A:241–248. doi:10.1002/ajmg.a.30855
8. Wen Z, Sun J, Luo J, et al. COL10A1-DDR2 axis promotes the progression of pancreatic cancer by regulating MEK/ERK signal transduction. *Front Oncol*. 2022;12:1049345. doi:10.3389/fonc.2022.1049345
9. Zhang M, Chen H, Wang M, et al. Bioinformatics analysis of prognostic significance of COL10A1 in breast cancer. *Biosci Rep*. 2020;40: BSR20193286.
10. Li T, Huang H, Shi G, et al. TGF-beta1-SOX9 axis-inducible COL10A1 promotes invasion and metastasis in gastric cancer via epithelial-to-mesenchymal transition. *Cell Death Dis*. 2018;9:849. doi:10.1038/s41419-018-0877-2
11. Li J, Wang X, Zheng K, et al. The clinical significance of collagen family gene expression in esophageal squamous cell carcinoma. *Peer J*. 2019;7: e7705. doi:10.7717/peerj.7705
12. Huang H, Li T, Ye G, et al. High expression of COL10A1 is associated with poor prognosis in colorectal cancer. *Onco Targets Ther*. 2018;11:1571–1581. doi:10.2147/OTT.S160196
13. Lapa RML, Barros-Filho MC, Marchi FA, et al. Integrated miRNA and mRNA expression analysis uncovers drug targets in laryngeal squamous cell carcinoma patients. *Oral Oncol*. 2019;93:76–84. doi:10.1016/j.oraloncology.2019.04.018
14. Liu Q, Diao R, Feng G, et al. Risk score based on three mRNA expression predicts the survival of bladder cancer. *Oncotarget*. 2017;8:61583–61591. doi:10.18632/oncotarget.18642
15. Giussani M, Landoni E, Merlino G, et al. Extracellular matrix proteins as diagnostic markers of breast carcinoma. *J Cell Physiol*. 2018;233:6280–6290. doi:10.1002/jcp.26513
16. Sole X, Crous-Bou M, Cordero D, et al. Discovery and validation of new potential biomarkers for early detection of colon cancer. *PLoS One*. 2014;9:e106748. doi:10.1371/journal.pone.0106748
17. Necula L, Matei L, Dragu D, et al. High plasma levels of COL10A1 are associated with advanced tumor stage in gastric cancer patients. *World J Gastroenterol*. 2020;26:3024–3033. doi:10.3748/wjg.v26.i22.3024
18. Goonetilleke KS, Siriwardena AK. Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer. *Eur J Surg Oncol*. 2007;33:266–270. doi:10.1016/j.ejso.2006.10.004
19. Singh S, Tang SJ, Sreenarasimhaiah J, et al. The clinical utility and limitations of serum carbohydrate antigen (CA19-9) as a diagnostic tool for pancreatic cancer and cholangiocarcinoma. *Dig Dis Sci*. 2011;56:2491–2496. doi:10.1007/s10620-011-1709-8
20. Zhang S, Wang YM, Sun CD, et al. Clinical value of serum CA19-9 levels in evaluating resectability of pancreatic carcinoma. *World J Gastroenterol*. 2008;14:3750–3753. doi:10.3748/wjg.14.3750
21. He Y, Lin J, Kong D, et al. Current state of circulating MicroRNAs as cancer biomarkers. *Clin Chem*. 2015;61:1138–1155. doi:10.1373/clinchem.2015.241190
22. Brand RE, Persson J, Bratlie SO, et al. Detection of early-stage pancreatic ductal adenocarcinoma from blood samples: results of a multiplex biomarker signature validation study. *Clin Transl Gastroenterol*. 2022;13(3):e00468. doi:10.14309/ctg.0000000000000468
23. Szafranska AE, Doleshal M, Edmunds HS, et al. Analysis of microRNAs in pancreatic fine-needle aspirates can classify benign and malignant tissues. *Clin Chem*. 2008;54:1716–1724. doi:10.1373/clinchem.2008.109603
24. Hussein NA, Kholy ZA, Anwar MM, et al. Plasma miR-22-3p, miR-642b-3p and miR-885-5p as diagnostic biomarkers for pancreatic cancer. *J Cancer Res Clin Oncol*. 2017;143:83–93. doi:10.1007/s00432-016-2248-7
25. Slater EP, Strauch K, Rospleszcz S, et al. MicroRNA-196a and −196b as potential biomarkers for the early detection of familial pancreatic cancer. *Transl Oncol*. 2014;7:464–471. doi:10.1016/j.tranon.2014.05.007
26. Xu C, Jun E, Okugawa Y, et al. A circulating panel of circRNA biomarkers for the noninvasive and early detection of pancreatic ductal adenocarcinoma. *Gastroenterology*. 2023;166(1):178–190.e16. doi:10.1053/j.gastro.2023.09.050
27. Xu Q, Zheng J, Su Z, et al. COL10A1 promotes tumorigenesis by modulating CD276 in pancreatic adenocarcinoma. *BMC Gastroenterol*. 2023;23 (1):397. doi:10.1186/s12876-023-03045-2
28. Thorlacius-Ussing J, Jensen C, Nissen NI, et al. The collagen landscape in cancer: profiling collagens in tumors and in circulation reveals novel markers of cancer-associated fibroblast subtypes. *J PATHOL*. 2024;262:22–36. doi:10.1002/path.6207
29. Cai S, Sun Z, Yan Y, et al. COL10A1 is a potential immunotherapy biomarker associated with immune infiltration and deficient mismatch repair in colon cancer. *Immunotherapy-Uk*. 2023;15. doi:10.2217/imt-2023-0096