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Original article

Micro-RNA-21 as a Potential Biomarker for Diagnosis of Pancreatic Cancer

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Abstract:

Background: Pancreatic cancer ranks fourth in terms of mortality caused by cancer. Pancreatic cancer is known to be aggressive and metastatic at the time of diagnosis. The accumulated evidence confirms that Micro Ribonucleic acid 21 (Micro-RNA-21) may play the main role in the pathogenesis of pancreatic cancer. Aim of the study: To assess plasma Micro-RNA-21 as a potential biomarker for diagnosis of pancreatic cancer and to correlate Micro-RNA-21 with tumor size, resectability, and prognosis. **Patients and methods:** This study was conducted on 110 subjects. Group I: (cases group) consisted of 55 patients who were diagnosed with pancreatic adenocarcinoma by histopathology through Endoscopic ultrasound-guided fine needle aspiration- biopsy (EUS-guided FNA-FNB) and monitored for 6 months. Group II: (control group) consisted of 55 healthy subjects without pancreatic cancer. All patients will be subjected to Abdominal ultrasound, Computed tomography (CT) Abdomen, EUS-guided FNA-FNB, and Micro-RNA isolation. **Results:** The current study showed in comparison to controls, Micro-RNA-21 was highly significant with p-value>0.01. The ROC curve analysis for miRNA demonstrated an area under the curve (AUC) of 0.73, indicating strong discriminatory power between pancreatic cancer cases and healthy controls. TNM staging of the tumor and the histopathological grade were statistically significant in correlation to Micro-RNA-21. The correlation between Micro-RNA-21 and resectability by EUS was highly significant. **Conclusion:** Plasma Micro-RNA-21 may be used as a potential biomarker for diagnosing pancreatic cancer in daily practice. Micro-RNA-21 showed a significant correlation with resectability by EUS. In addition, low detected Micro-RNA-21 significantly correlated with high overall survival.

Keywords: pancreatic cancer, Micro-RNA 21, EUS, FNA/FNB

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Introduction

Pancreatic cancer (PC) ranks fourth in terms of cancer-related mortality for both men and women, and it causes 3% of newly diagnosed cancer cases each year. Pancreatic cancer is known to be aggressive with severe symptoms (pain, jaundice, etc.), and most of the time it is metastatic at the time of diagnosis [(1)]. The majority (~ 95%) of pancreatic tumors are adenocarcinomas, originating from the exocrine part of the pancreas [(2)]. Though approximately 10-15% of newly diagnosed patients have surgically resectable disease at presentation, surgery is still the only treatment available for pancreatic cancer. After a margin-negative (R0) pancreaticoduodenectomy, the five-year survival rate for node-negative illness is around 30%, whereas for node-positive disease it is 10% [(3)].

The application of Endoscopic ultrasound (EUS), which is thought to be extremely accurate in diagnosing a pancreatic lesion, has recently resulted in a marked improvement in prognosis. The advantageous characteristics of both endoscopy and ultrasonography are combined in endoscopic ultrasound. Compared to other competing techniques like Computed tomography (CT) and Magnetic Resonance Imaging (MRI), which both offer a lower image resolution - and therefore detection rate - of small lesions, EUS provides a much higher image resolution. The ultrasound transducer is situated at the distal end of the endoscope, allowing for close placing of the transducer at the region of interest [(4)]. The diagnosis and staging of different lesions within and around the GI tract are made possible by the high picture quality. Typically, EUS examinations follow the standard endoscopy whenever additional, more detailed information about tissue characteristics, blood flow dynamics, or tumor invasion depths is required. Especially to determine the depth of the tumor and its staging playing a great role in treatment for such patients, avoiding under- and over-staging, which inevitably leads to suboptimal or wrong patient treatment [(5)]**.** EUS-guided fine needle aspiration (EUS-FNA) is the technique that involves puncturing a lesion with an EUS-guided tool and then aspirating cells or fluid for cytology, histology, or fluid analysis (such as tumor markers, fluid chemistries, or molecular markers). An EUS-guided core biopsy of a lesion is performed to acquire tissue for histology. EUS-guided fine needle biopsy is the term used for this procedure (EUS-FNB) [(6)].

Because Micro-RNAs' complementary sequences with messenger RNA sequences cause either transcriptional degradation or translation inhibition, they work by controlling the translation of messenger RNA and, consequently, the synthesis of proteins [(7)]. Many Micro-RNAs could control a single mRNA, or a single Micro-RNA could control multiple mRNAs [(8)].

Micro-RNAs are thought to be biomarkers for a wide range of illnesses and play a crucial role in the regulation of cell activity [(9)]. The accumulated evidence confirms that Micro-RNAs play a key role in the pathogenesis of pancreatic cancer, influencing genetic changes such as KRAS, Tp53, and TGFβ/SMAD, and supporting the unfavorable tumor microenvironment [(10)].

Aim of the work

To assess plasma Micro-RNA-21 as a potential biomarker for diagnosis of pancreatic cancer and to correlate Micro-RNA-21 with tumor size, resectability and prognosis.

Patients and Methods

This cohort study was conducted on 110 subjects. Patients were selected from the Hepatology and Gastroenterology Department, Benha University, and the Endemic Diseases Department, the gastrointestinal endoscopy and liver unit, Cairo University with the inclusion and exclusion criteria assigned for study with matched healthy control from January 2022 to June 2023.

Inclusion Criteria:

- Adult patients of both sexes.
- Group I: Sporadic pancreatic cancer, proved by endoscopic ultrasound and histopathology.
- Group II: control group with apparently healthy subjects with no history of pancreatic diseases.

Exclusion Criteria:

- Patients refusing the written medical consent.
- Acute pancreatitis.
- Chronic pancreatitis.
- Patients undergoing chemotherapy or radiotherapy.
- Benign pancreatic cysts.

Methods:

All individuals included in this study were informed about the study design and consent was obtained. Ethical committee approval was obtained under Code No: MD 14-10-2021.

All patients will be subjected to the following:

A. An informed written medical consent.
B. Full history taking focusing on family history of pancreatic cancer, history of chronic abdominal pain, jaundice, significant weight loss, and anemia.
C. Thorough clinical examination:
   - General examination focusing on cachexia, jaundice, pallor, and lymphadenopathy.
   - Local abdominal examination focusing on palpable abdominal masses.
D. Laboratory investigations, including: Complete blood count (CBC), alanine transaminase (ALT), aspartate aminotransferase (AST), Bilirubin, albumin, International normalized ratio (INR), Creatinine, Carbohydrate antigen 19-9 (CA19-9), and Carcinoembryonic antigen (CEA).
E. Imaging:

- Abdominal ultrasound using LOGIQ P6 PRO device: Prior to the procedure the patients were asked to fast for eight hours except for water intake and medication.
- CT Abdomen using Toshiba Aquilion 64 CT Scanner: Before the procedure, the patients were asked to fast for six hours except for water intake and medication.

F. Endoscopy: Endoscopic Ultrasound with fine needle aspiration or biopsy (FNA/ FNB) was done for diagnosis and staging of pancreatic cancer using Pentax EUS scope 5870 device. Patients were instructed for the procedure preparation as follows:

- Fasting starts at midnight the day before the procedure, including all medications except antihypertensive and antiepileptic medications, which will be taken at 6 AM the day of the procedure.
- Antidiabetic, anticoagulant, and antiplatelet medications are adjusted according to the patient's condition.

G. The Qiagen miRNeasy Serum/plasma kit was used to isolate Micro-RNAs, following the manufacturer's instructions.

The data was statistically examined and shown in useful tables and figures. The data were analyzed using Statistical Package for Social Sciences (IBM SPSS) advanced statistics version 27 (SPSS Inc., Chicago, IL).

Results

This study was conducted on 110 subjects of them 55 patients with pancreatic cancer (case group) and 55 controls. Cases ages ranged from 35 to 80 with a mean of 57.0±11.6 years and Controls ages from 40 to 80 with a mean of 53±8.4 years.

As regards the clinical presentation of the cases Abdominal pain was the main presenting symptom (74.5 %) and jaundice was the main presenting sign (60%) in the studied cases. In the studied cases smoking percentage was 45%.

Regarding staging and resectability of the tumor by EUS, about Forty-one percent of

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the studied cases (23 cases) were T2, 47.3% (26 cases) were T4, and 9.1% (5 cases) were T3. N2 was seen in 41 cases (74.5%), while the rest were N1 (25.5%). M0 was found in 48 cases (87.3%), while the rest were M1. Moreover, 40% of the detected lesions were borderline, 36.4% were non-resectable, and 23.6% were resectable. The detected lesions included 76.4% pancreatic adenocarcinoma grade II and 23.6% pancreatic adenocarcinoma grade III. In comparison to controls, miR-21 was highly significant as shown in Table (1) and Fig (1).

In this study, TNM staging of the tumor, and the histopathological grade were statistically significant in correlation to miRNA-21 as Table (2) provides and as shown in Fig (2). Table (3) presents the correlation between miRNA-21 and resectability by EUS which was highly significant. MiR-21 was significantly correlated with the overall survival of the studied cases as presented in Table (4).

Table (1): Significance of miR-21 in patients and controls.

	Cases Median (Range)	**Controls Median (Range)**	**P value**
miR-21	5.18(0.03-59.6)	1.0(0.93-1.09)	**<0.001**

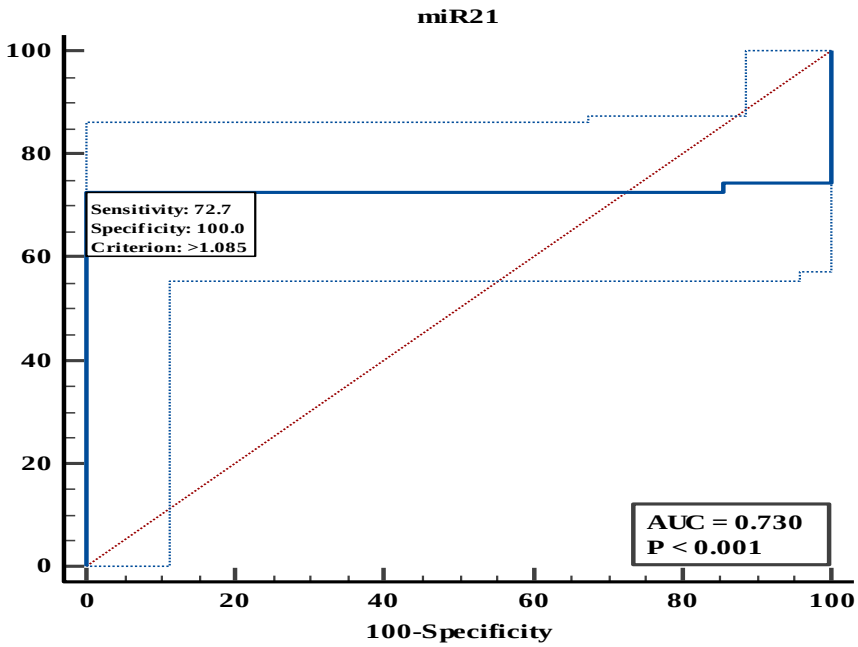

Figure (1): ROC curve of miRNA with 95%CI for discrimination between pancreatic cancer cases and controls.

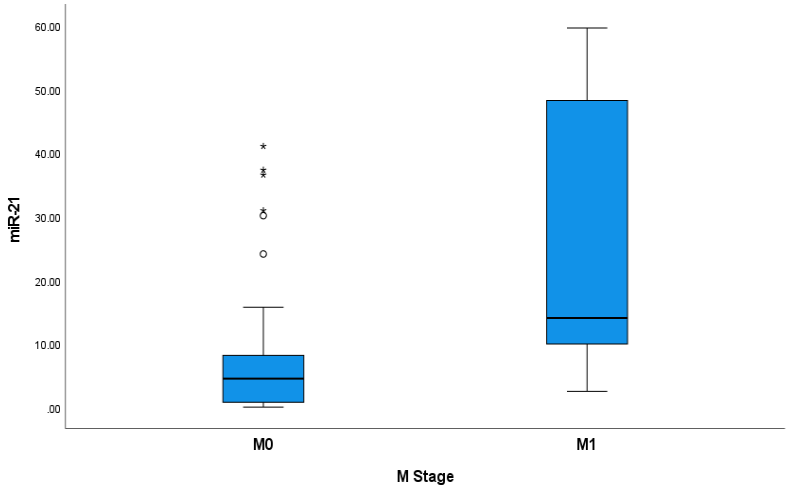

Figure (2): correlation between miRNA-21 and M tumor stage detected by EUS.

Table (2): correlation between miRNA-21 and each of tumor staging and pathological grading.

			miR-21			
			n	Median	Minimum	Maximum	P value
T stage	T1		1	5.34	5.34	5.34	NA
	T2	23		1.32	0.03	30.91	
	T3	5		12.34	1.69	36.5	
	T4	26		6.31	0.34	59.57	
T stage	Early(T1-2)	24		1.95	0.03	30.91	0.002
	Late(T3-4)	31		6.96	0.34	59.57	
N stage	N1	14		1.32	0.03	9.99	0.018
	N2	41		5.93	0.12	59.57	
M Stage	M0	48.0		4.51	0.03	41.0	0.003
	M1	7.0		14.03	2.51	59.57	
Grade	II	42.0		3.89	0.03	37.27	0.001
	III	13.0		12.34	2.58	59.57	

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Table (3): Correlation between miRNA-21 and resectability by EUS.

Respectability		miR-21				
		Count	**Median**	**Minimum**	**Maximum**	**P Value**
EUS	**Resectable**	13	0.95	0.03	9.99	**0.010**
	Non-resectable-borderline	42	6.20	0.12	59.57	

Table (4): Correlation between miR-21, and overall survival.

Factors	**n**	**Overall survival %**			
		3 months	**6 months**	**Median (95%CI)**	**P value**
All	55	79.0	46.8	6	NA
miR_21_groups					
≤5.1	28	89.3	85.3	NA	0.049
>5.1	27	68.4	36.2	5.0(3.4-6.6)	

Discussion

Pancreatic cancer ranks fourth in terms of cancer-related mortality for both men and women, and it causes 3% of newly diagnosed cancer cases each year **(11)**. Pancreatic cancer is mostly a very aggressive cancer with a poor prognosis (12). The diagnosis of pancreatic cancer is still a troubling issue. Patients often present with non-specific symptoms, which delay correct diagnosis **(13)**.

Several research have been carried out to find specific markers that may aid in the early detection of pancreatic lesions. However, none of them have a high sensitivity and specificity for diagnosing pancreatic cancer (14).

Micro-RNAs are short non-coding RNAs (19-25 nucleotides) that control gene expression interacting with mRNA targets. Micro-RNAs are endogenously expressed RNAs that suppress protein translation by binding with target mRNAs and have been described as an influence on cell proliferation, multiplication, and apoptosis (15). In pancreatic ductal adenocarcinoma (PDAC) patients, numerous Micro-RNAs including Micro-RNA-21, have been detected in the plasma/serum and have been suggested to be useful biomarkers for the diagnosis (16).

Therefore, the current study aimed to assess plasma Micro-RNA-21 as a potential biomarker for diagnosis of pancreatic cancer and to correlate Micro-RNA-21 with tumor size, resectability, and tumor progression.

This study was conducted on 110 subjects of them 55 patients with pancreatic cancer (case group) and 55 controls. Cases ages ranged from 35 to 80 with a mean of 57.0 ±11.6 years and Controls ages from 40 to 80 with a mean of 53±8.4 years.

In this study, there was a male majority of 58.2% in the pancreatic adenocarcinoma group; this finding was also corroborated by the Bray et al study, which reported that it develops more frequently in males (5.5 per 100,000) than in females (4.0 per 100,000) (17).

In our study, 27.3% of the patients had DM. Numerous studies have shown an association between DM and a higher risk of pancreatic cancer (18-20). However, since pancreatic cancer originates in the pancreas, it is certain that when cancer progresses, eventually disease-related diabetes will develop (21-23).

Regarding risk factors and clinical presentation in the studied cases, 45.5% were smokers and 5% reported positive family history. Abdominal pain was the main presenting symptom (74.5%)

followed by weight loss (60%) and jaundice was the main presenting sign (60%) followed by cachexia (12.7%) in the studied cases.

However, the American Cancer Society, 2024[24] states that cigarette smoking is believed to cause around 25% of pancreatic cancers. NCCN guidelines, 2024[25] state that pancreatic cancer is considered to have a familial component in roughly 10% of cases, and having a family history of pancreatic cancer increases the risk.

The tumor node metastasis system (TNM), which is outlined in the Cancer Staging Manual developed by the American Joint Committee on Cancer (JCC), is most frequently used to assess the extent and size of pancreatic cancer. In our study, about 47.3% (26 cases) were T4, 41% of the studied cases (23 cases) were T2, and 9.1% of them (5 cases) were T3. N2 was seen in 41 cases (74.5%) while the rest were N1 (25.5%). M0 was found in 48 cases (87.3%) while the rest were M1. We determined TNM by EUS which provides better visualization of vascular invasion and LN (LN) metastasis.

Moreover, 40% percent of the detected lesions by EUS were borderline, 36.4% were non-resectable, and 23.6% were resectable.

Regarding, the histopathological grade of the detected lesion, 76.4% were pancreatic adenocarcinoma grade II, while 23.6% were pancreatic adenocarcinoma grade III.

In this study, in comparison to controls, Micro-RNA-21 was highly significant with a P-value<0.001 in the cases group, median (range) of Micro-RNA-21 was 5.18 (0.03-59.6) in the cases group, while it was 1.0 (0.93-1.09) in the control group.

In agreement with this work, two studies [26-27] stated that the Micro-RNA expression profiles in PDACs compared to controls were statistically significant with a p-value<0.001. similarly**,** Alemar et al., 2016[28] analyzed the expression levels of 6 Micro-RNAs, including Micro-RNA-21 in serum and salivary samples to assess their potential role as circulating diagnostics biomarkers in PDAC tumorigenesis and noted that there was a significant difference between PDAC and healthy groups was observed for the expression of Micro-RNA-21 serum samples, and concluded that serum Micro-RNA-21 is potentially useful diagnostic biomarkers of PDAC.

Also, Pu et al., 2020[29] examined Micro-RNA-21 expression in patients with pancreatic cancer and healthy individuals, the expression level of Micro-RNA-21 was significantly greater in patients with pancreatic cancer compared with the control group.

For correlation between Micro-RNA-21 and TNM staging and pathological grading TNM staging of the tumor, and the histopathological grade were statistically significant in correlation to Micro-RNA-21.

Similarly, Jamieson and his colleagues [27] reported that Micro-RNA-21 was differentially expressed in association with tumor grade, stage, and LN status. In agreement, Hu et al., 2016[30] reported that 4 studies showed a significant correlation between Micro-RNA-21 expression and each LN metastasis and vascular invasion.

Kadera et al., 2013[31] found similar results regarding LNs but different results regarding tumor grade, they reported that Micro-RNA-21 in PDAC stroma did not correlate with tumor grade. They found that PDAC was strongly correlated with LN positivity (P=0.004). Regarding metastasis, Abue et al., 2015[16] reported that the plasma Micro-RNA-21 expression level was associated with advanced stage (P=0.023), metastasis to LN (P=0.007), and liver (P<0.001).

On the other hand, Hwang et al., 2010[32] disagree with this result and found that stage and LN were not associated with Micro-RNA-21 expression.

On the other hand, Negoi et al., 2017[33] a meta-analysis reported that the association between Micro-RNA-21 expression level and LN metastasis was statistically

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significant (OR = 1.45, 95 % CI 1.02–2.06, P = 0.038). However, no significant correlation between Micro-RNA-21 expression level and sex or vascular invasion.

The correlation between Micro-RNA-21 and resectability by EUS was highly significant (P-value=0.010), 13 cases (median=0.95) had resectable and 42 had non-resectable-borderline (median=6.20) mass.

In agreement with this, Abue et al., 2015[16] reported that the plasma Micro-RNA-21 level was not increased in operable patients.

In the current study, we monitored our patients over a 6-month interval to see if the studied Micro-RNA could be used as prognostic markers in pancreatic adenocarcinoma. The results showed that Micro-RNA-21 could be associated with patient survival at 3 and 6 months (p= 0.049). The overall survival for patients with Micro-RNA-21 less than and equal to 5.1 at 3 months was 89.3 % and 85.3% at 6 months (total 28 cases). On the other hand, the overall survival for Micro-RNA more than 5.1 was 68.4 % at 3 months and 36.2 % at 6 months (a total of 27 cases).

This finding was supported by Zhou et al., 2014[34] who found that elevated Micro-RNA-21 predicted poor survival. In agreement, several studies [16,27,30-31] reported also that elevated micro-RNA-21 expression significantly predicted poor Overall Survival.

In coherence with these results, a previous meta-analysis by Negoi et al., 2017[33] found that a total of 17 studies involving 1471 patients met the inclusion criteria for the quantitative synthesis. The micro-RNA-21 upregulation was significantly associated with poorer overall survival.

In line with these results, a previous meta-analysis by Guraya, 2018[35] quantitatively determines the prognostic significance of circulating Micro-RNA-21 in PDAC, this study found a significant prognostic value of Micro-RNA-21 in predicting worse overall survival in PDAC.

Similarly, Hwang et al., 2010[32] found that patients with high Micro-RNA-21 expression had significantly shorter overall survival. Thus, they concluded that low Micro-RNA-21 expression was associated with increased survival of PDAC cases.

There were some limitations in this study. First, our study is single-centered and observational, so there may be selection bias. Second, the number of patients is not large enough which limits the generalization of our findings. Finally, we did not relate to other inflammatory pancreatic conditions like acute and chronic pancreatitis and pancreatic cysts. So, we recommend More studies on larger scales and different Micro-RNAs.

Recommendations

- We recommend using plasma Micro-RNA-21 as a potential biomarker for diagnosis of pancreatic cancer.
- We recommend increasing the sample size in future studies to increase significance.
- Comparing different Micro-RNAs in pancreatic cancer.
- Assessing the diagnostic performance of Micro-RNA-21 in combination with other established and standard methods.

Conclusion

To sum up, our study Micro-RNA-21 may be a useful diagnostic and prognostic biomarker and a component of precision medicine in patients with pancreatic cancer in daily practice. Micro-RNA-21 showed a significant correlation with resectability by EUS. In addition, low detected Micro-RNA-21 significantly correlated with high overall survival.

Conflict of interest

None of the contributors declared any conflict of interest

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