ORIGINAL RESEARCH

DOI: 10.37047/jos.2022-93441

Ischemia-Modified Albumin and Thiol-Disulfide Homeostasis in Metastatic Pancreatic Cancer

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ABSTRACT Objective: This study aimed to assess two oxidative stress (OxS) markers, thiol-disulfide (TD) homeostasis and ischemia-modified albumin (IMA), in newly diagnosed metastatic pancreatic cancer (PC) patients. **Material and Methods:** This was a prospective case-control study including two groups: 30 cases each of histopathologically confirmed metastatic PC patients and healthy controls. Serum TD and IMA levels were measured and compared in both groups. Moreover, the association between TD and IMA levels, as well as overall survival (OS) in the patient group, were investigated. **Results:** Both native thiol (NT) and total thiol (TT) levels significantly decreased in the patient group than in the control group (p=0.016 and p=0.009, respectively). However, disulfide (D) and IMA levels were similar between the two groups (p=0.056 and p=0.068, respectively). Both the D/NT and D/TT ratios were significantly higher in the patient group (p=0.005 and p=0.004, respectively) than in the control group. Additionally, no association was observed between IMA, TD homeostasis, and OS. **Conclusion:** Our results showed that increased OxS levels affected PC progression. With the development of newer targeted therapeutics for OxS, the progression of PC in individuals with higher genetic risk may be prevented.

Keywords: Ischemia-modified albumin; oxidative stress; pancreatic cancer; thiol-disulfide homeostasis; overall survival

Pancreatic cancer (PC) is a highly aggressive, chemotherapy-resistant malignancy having an extremely poor survival rate. However, as the majority of patients are detected either in the metastatic or inoperable stage, newer treatment methods other than chemotherapy are being searched to improve the prognosis of such patients. The association between dysregulated inflammatory processes and oxidative stress (OxS) plays an important role in the development of PC.[1] A strong antioxidant defense system protects cells against mutations and genomic instability as well as strengthens DNA damage repair mechanisms. Dysregulated antioxidant systems cause oxidative DNA damage and lead to the development of new DNA mutations as well as tumor initiation.[2] OxS is associated with the development of several types of cancer. Because of the relationship between OxS and oncogenic transformation in PC, therapeutic interventions targeting OxS levels remain a subject of intense research. PC has the highest prevalence of KRAS mutation in all cancers.[3] KRAS mutations increase the production of reactive oxygen species (ROS), thus, initiating pancreatic tumor growth.[4,5] Additionally, oncogenic KRAS protein also increases ROS levels during the development and progression of PC.[6] The tumor suppressor gene, p53 is frequently mutated in PC and shows several antitumor effects like antioxidant ability.[7]

Thiol-disulfide (TD) homeostasis and ischemia-modified albumin (IMA) are important markers revealing the association of OxS and tumor progression. Thiol groups of amino acids are the pri-

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Peer review under responsibility of Journal of Oncological Sciences.

Received: 18 Sep 2022 ***Received in revised form:*** 22 Oct 2022 ***Accepted:*** 25 Oct 2022 ***Available online:*** 09 Nov 2022

mary targets of reactive oxygen derivatives; plasma thiols mainly contain albumin and other proteins.[8,9] Although they constitute an important portion of the total antioxidant system, they also have an important role in the antioxidant defense mechanism as they form disulfide (D) bonds by undergoing oxidation.[10] Increased OxS levels lead to a reduction in oxidized protein thiols and an increase in D bonds. It has been suggested that TD homeostasis is impaired in cases of malignancy.[11]

ROS overproduction alters the N-terminal domain of albumin and forms IMA by oxidative modification of serum albumin.[12] IMA was identified in the 1990s as an important OxS biomarker resulting from tissue hypoxia.[13] Certain conditions like liver and kidney failures, acute infections, and carcinomas cause increased IMA levels, and IMA levels increase in many cancers associated with OxS imbalance.[14]

This study aimed to determine TD homeostasis and IMA levels, indicators of increased OxS levels, in newly diagnosed metastatic PC patients and to compare the obtained data with healthy controls.

MATERIAL AND METHODS

This prospective study involved 30 cases each of histopathologically confirmed metastatic (Stage-4) pancreatic ductal adenocarcinoma patients and healthy controls. The patient and the control groups were assigned to the medical oncology and the internal medicine clinics of our hospital for general health screenings. The study was approved by the Ankara City Hospital Ethics Committee with decision number E1/536/2020 (date: May 7, 2020) according to good clinical practice and applicable laws, and the Declaration of Helsinki, and all participants submitted written informed consent.

Exclusion criteria were: history of a second primary cancer; history of rheumatic disease; an active infection; use of immunosuppressive or anti-inflammatory drugs; history of cardiovascular disease, diabetes mellitus, or liver, kidney, or thyroid dysfunction; and inability to feed orally. Smoking was considered an exclusion criterion for both groups. The age, gender, patients' complaints, Eastern Cooperative Oncology Group Performance Score (ECOG PS), size of the pancreatic primary mass, and metastatic sites were recorded. The patient survival information was obtained from the national population registry and follow-up system database.

Progression-free survival (PFS) was defined as the time interval from initiation of the treatment with first-line chemotherapy to progression or death from any cause.

Overall survival (OS) was defined as the time interval from the time of onset of metastatic disease to death due to any reason or last follow-up.

BLOOD LABORATORY INVESTIGATIONS

Blood samples for analyzing carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, lactate dehydrogenase (LDH), TD, and IMA were obtained from PC patients at the time of hospital admission before starting any treatment. Blood samples for TD and IMA measurements were also obtained from the healthy volunteers.

After 8 h of fasting, blood samples (5 mL) were collected, kept for 20 min, and centrifuged at 1,500 rpm for 10 min. After the separation of plasma and serum, the plasma TD homeostasis test was conducted according to the method described by Erel and Neselioglu in which these dynamic D bonds are reduced to functional thiol groups (sulfhydryl group) with sodium borohydride ($NaBH_4$).[15] The unused $NaBH_4$ was removed by formaldehyde, while the total thiol (TT) level was calculated by measuring the obtained chromogen compound with a modified Elmann reagent spectrophotometrically at 415 nm wavelength. The D value was acquired by subtracting the native thiol (NT) value from the TT value and dividing the result by 2. Disulfide/TT (D/TT), disulfide/NT (D/NT), and NT/TT ratios were duly calculated as percentages.

Serum IMA levels were measured as follows: 0.1% cobalt chloride (50 µL) was added into the plasma samples (200 µL).[16] The mixed solution was incubated for 10 min, and 1.5 mg/mL dithiothreitol (50 µL) was added as a coloring agent. The binding reaction was stopped after 2 min by adding 0.9% NaCl (1.0 mL), and sample absorbances were measured at 470 nm with a spectrophotometer. Furthermore, the color of the sam-

ples containing dithiothreitol was compared with the color of colorimetric control tubes.

In patients who initially presented with jaundice and reported extrahepatic bile duct dilatation, blood samples were collected after ensuring biliary drainage and normal values of bilirubin values.

STATISTICAL ANALYSIS

Data were analyzed with SPSS 22.0 software (IBM, Armonk, NY, USA). Compliance with normal distribution was evaluated by the Kolmogorov-Smirnov test. Continuous and categorical variables were expressed as medians (minimum-maximum ranges) and percentages, respectively. Differences in continuous variables between groups were evaluated with the Mann-Whitney U test, while categorical variables were assessed by the chi-square test. Spearman's or Pearson's correlation coefficient was calculated to determine the relationship between two continuous variables. Moreover, survival analysis was performed using the Kaplan-Meier method and $p<0.05$ values were considered statistically significant.

RESULTS

Thirty patients diagnosed with metastatic PC and 30 healthy volunteers were included in our study. Thirteen (43.3%) and 17 (56.7%) participants in the patient group were females and males, while 14 (46.7%) and 16 (53.3%) participants in the healthy control group were females and males ($p=0.795$), respectively. The median age was 61 and 59 years in the patient and the control groups ($p=0.131$), respectively.

Additionally, five patients (16.7%) could not receive chemotherapy; two patients had refused chemotherapy, while in the other 3 patients, treatment was discontinued due to poor general conditions and worsening of the ECOG PS after the first chemotherapy cycle. Twenty-five patients (83.3%), seven (23.3%), and four (13.3%) patients received 1 line, 2 lines, and 3 lines of chemotherapy, respectively. The patients' comorbidity, presenting symptoms, ECOG PS, tumor characteristics, treatment received, and treatment responses are summarized in Table 1.

The median PFS in the patient group was 4.9 (2.5-7.4) months (Figure 1), whereas the subgroup analysis revealed that the median PFS of 25 patients who received first-line chemotherapy was 5.8 (2.4-8.3) months. Furthermore, the median PFS of 11 patients who received only mFOLFIRINOX as primary therapy was 5.8 (1.5-8.2) months. The median OS in the patient group was 7.1 (2.5-11.6) months (Figure 2), whereas the subgroup analysis revealed that the median OS of 25 and 11 patients who received first-line chemotherapy and mFOLFIRINOX as primary care was 10 (7.8-11.6) months and 12.1 (9.3-11.6) months, respectively.

NT was 384.6 µmol/L and 437.9 µmol/L in the patient and the control groups ($p=0.016$), while TT was 405.9 µmol/L and 473.6 µmol/L in the patient and the control groups ($p=0.009$), respectively. The D/NT ratios were 4 and 3.1 in the patient and the control groups ($p=0.005$), while the D/TT ratio was 3.8 and 2.9 in the patient and the control groups ($p=0.004$), respectively (Table 2).

No significant difference was observed between the TD and IMA levels of the patients who received either one-line or ≥2 steps of chemotherapy (Table 3).

While a positive correlation was established between NT and both TT (r=0.998, $p=0.000$) and NT/TT (r=0.757, $p=0.000$), a negative correlation was observed between NT and the D/NT ratio (r=-0.672, $p=0.000$), D/TT ratio (r=-0.644, $p=0.000$), and IMA levels (r=-0.715, $p=0.000$). There were negative associations between NT/TT and IMA (r=-0.541, $p=0.002$) as well as OS with both LDH (r=-0.387, $p=0.034$) and CA 19-9 (r=-0.448, $p=0.013$, Table 4).

DISCUSSION

OxS induces tissue damage by the subsequent deterioration of the antioxidant activity due to increased antioxidants and an insufficient antioxidant defense mechanism.[17] Proteins, lipids, and DNA are the target molecules for OxS activities. Increased ROS levels cause cell membrane damage, DNA impairment, protein dysfunction, and lipid denaturation. Additionally, ROS formation increases IMA and downregulates

TABLE 1: Study characteristics of the patient and control groups.

		Patient group		Control group		
		n (%)	Median (minimum-maximum)	n (%)	Median (minimum-maximum)	p value
Gender	Female	13 (43.3)		14 (46.7)		0.795
	Male	17 (56.7)		16 (53.3)		
Age (years)			61 (33-8)		59 (41-76)	0.131
Comorbidity	Yes	18 (60)				
	No	12 (40)				
Symptoms	Abdominal pain	20 (66.7)				
	Abdominal pain+jaundice	5 (16.7)				
	Jaundice	1 (3.3)				
	Weight loss+jaundice	1 (3.3)				
	Weight loss	2 (6.7)				
	Back pain	1 (3.3)				
ECOG PS	1	21 (70)				
	2	6 (20)				
	3	3 (10)				
Tumor size (cm)			4.2 (1-9)			
CEA (ng/mL)			4 (0.6-4093)			
CA 19-9 (U/mL)			1497.7 (4.3-280000)			
LDH (U/L)			208 (34-596)			
Tumor site	Pancreatic head	19 (63.3)				
	Pancreatic neck	2 (6.7)				
	Pancreatic body	6 (20)				
	Pancreatic tail	3 (10)				
Metastasis site	Lymph node	9 (30)				
	Liver	5 (16.7)				
	Lymph node+liver	12 (40)				
	Liver+bone	1 (3.3)				
	Liver+lung	2 (6.7)				
	Bone+peritoneum	1 (3.3)				
Number of chemotherapy lines	0	5 (16.7)				
	1	25 (83.3)				
	2	7 (23.3)				
	3	4 (13.3)				
First line chemotherapy	mFOLFIRINOX	11 (44)				
	Gemcitabine+nab-paclitaxel	4 (16)				
	Gemcitabine	5 (20)				
	mFOLFOX	2 (8)				
	Gemcitabine+cisplatin	3 (12)				
Treatment response	PD	14 (56)				
	SD	7 (28)				
	PR	4 (16)				

ECOG PS: Eastern Cooperative Oncology Group Performance Score; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; LDH: Lactate dehydrogenase; PD: Progressive disease; SD: Stable disease; PR: Partial response.

NT levels, as well as forms D bonds due to the coupling of the sulfur atoms and thiol group. The resultant D bonds are precise indicators of the OxS levels.[18] Since PC is a malignancy with a high metastatic propensity and a very low survival rate, new targeted therapies for PC are still under investigation. Hence, our study aimed to examine the association between TD homeostasis, IMA levels, and the progression of PC. The resultant findings might shed some light on the discovery of new treatment targets in this field.

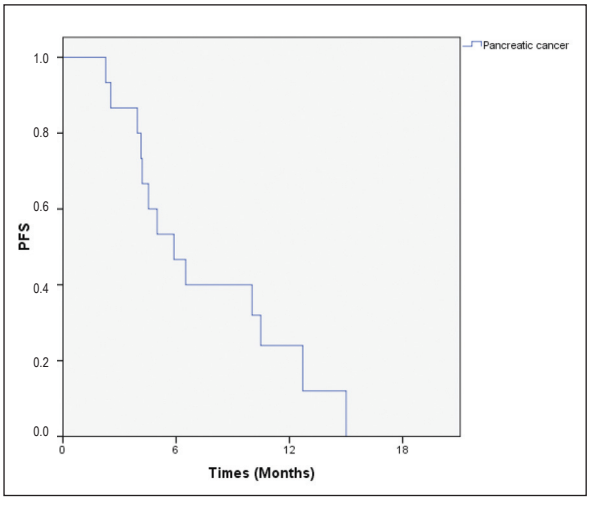

FIGURE 1: PFS analysis of pancreatic cancer patients.
PFS: Progression-free survival.

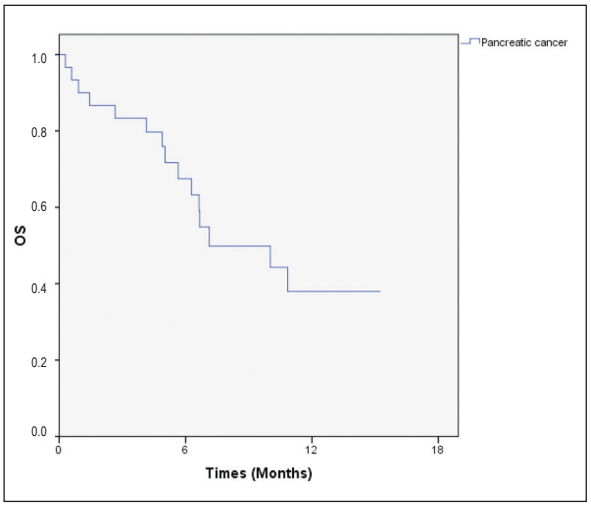

FIGURE 2: OS analysis of pancreatic cancer patients.
OS: Overall survival.

Several studies have investigated the role of IMA and TD homeostasis in different types of cancers. In a previous study, ROS were integral components required for the occurrence of KRAS mutations and tumor growth in PC.[4] It has been found that the oncogenic KRAS gene causes mitochondrial dysfunction and increases ROS levels by altering the NADPH oxidase activity.[19] Since p53 has antioxidant and tumor-protective properties. The subsequent mutations may lead to a loss of antioxidant properties and the triggering of tumorigenesis.

In our study, NT and TT values were low, whereas the DD/NT and DD/TT values were high in the patient group; DD levels were significantly higher in the patient group. This suggests that OxS plays a crucial role in pancreatic tumorigenesis and disease progression.

In a lung cancer study, 98% of stage 3 or 4 patients displayed lower NT and TT levels in the patient group, although D levels were similar in all the groups; there was no correlation between D, TT, or NT levels and OxS. These findings are similar to the results obtained in our study. In another study investigating TD homeostasis in non-small cell lung cancer patients, apart from the NT and TT levels, D, D/TT, D/NT, and NT/TT ratios also decreased in the patient group.[20] In the same study, while reduced OxS was observed in patients with low D levels, no relationship was found between NT or TT levels and OxS. A study examining TD homeostasis in prostate cancer patients who underwent radical prostatectomy revealed that the pre-and postoperative NT, TT, and D levels were significantly lower in the patient group.[21] In another study comparing TD ratios in basal cell carcinoma patients and a control group, the NT level was higher while the D level, as well as D/TT and D/NT ratios, were lower in the patient group.[22] Another study investigating the TD balance in patients with low-grade glioma showed significantly higher levels of TT, NT, and D.[23] The varying results suggest that TD homeostasis functions differently in diverse malignancies. It may also differ according to tumor stage and aggressiveness concerning different tumor biology. Although some studies support our hypothesis, few studies investigating OxS and tumor aggression disclosed a negative correlation between ROS and disease prognosis.[24,25] Furthermore, the OxS index increased with the progression of cancer.[26]

In this study, IMA levels were similar between the two groups; however, they increased in the opposite direction with NT and TT levels as well as in parallel with D/NT and D/TT ratios. This indicates that in the presence of OxS in PC, a decrease in serum thiol and an increase in D and IMA levels are observed. In a study comparing colon and breast cancer patients with a control group, IMA levels were upregulated in both patient groups. Another study conducted on patients with soft tissue sarcoma and

TABLE 2: Comparison of thiol-disulfide and ischemia-modified albumin levels between the patient and control groups.

	Control group Median (minimum-maximum)	Patient group Median (minimum-maximum)	p value
Native thiol (µmol/L)	437.9 (341.7-644.4)	384.6 (170.7-611.4)	**0.016***
Total thiol (µmol/L)	473.6 (369.3-699.1)	405.9 (200.5-633)	**0.009***
Disulfide (µmol/L)	14.4 (7.6-20.3)	17 (9.2-27.3)	0.056
Disulfide/native thiol	3.1 (1.3-59.4)	4 (2.8-10.4)	**0.005***
Disulfide/total thiol	2.9 (1.3-54.9)	3.8 (2.6-8.9)	**0.004***
Native thiol/total thiol	92.9 (90.1-96.6)	93.2 (85.1-96.5)	0.900
Ischemia-modified albumin (absorbance units)	0.8 (0.7-0.9)	0.8 (0.7-1.1)	0.068

*<0,05

TABLE 3: Comparison of thiol-disulfide and ischemia-modified albumin levels in the patients receiving one-line and ≥2 lines of chemotherapy.

	1 line of chemotherapy Median (minimum-maximum)	≥2 lines of chemotherapy Median (minimum-maximum)	p value
Native thiol (µmol/L)	415 (205.4-611.4)	361.3 (170-579.6)	0183
Total thiol (µmol/L)	449.7 (233.1-633)	376.6 (200.5-615.8)	0183
Disulfide (µmol/L)	16.7 (12.8-21.7)	17.8 (12.3-22.3)	0.25
Disulfide/native thiol	3.9 (2.9-6.6)	5 (3-10.4)	0.101
Disulfide/total thiol	3.6 (2.7-5.8)	4.5 (2.8-8.9)	0.112
Ischemia-modified albumin (absorbance units)	0.8 (0.7-1.1)	0.8 (0.7-1.1)	0.913

TABLE 4: Correlation analysis of laboratory values and OS in pancreatic cancer patients.

		1	2	3	4	5	6	7	8	9	10	11	12
1. Age	r	1	-0.075	0.183	0.075	0.079	0.316	0.030	0.056	0.097	-0.147	-0.007	-0.097
2. CEA	r	-0.075	1	**0.464****	-0.272	-0.272	0.198	**0.409***	**0.413***	-0.213	0.111	0.194	-0.255
3. CA 19-9	r	0.183	**0.464****	1	-0.210	-0.206	**0.411***	**0.377***	**0.392***	-0.153	0.060	**0.585****	**-0.448***
4. Native thiol	r	0.075	-0.272	-0.210	1	**0.998****	0.240	**-0.672****	**-0.644****	**0.757****	**-0.715****	-0.296	0.277
5. Total thiol	r	0.079	-0.272	-0.206	**0.998****	1	0.232	**-0.673****	**-0.648****	**0.716****	**-0.722****	-0.308	0.291
6. Disulfide	r	0.316	0.198	**0.411***	0.240	0.232	1	**0.482****	**0.532****	0.196	-0.199	0.326	-0.132
7. Disulfide/native thiol	r	0.030	**0.409***	**0.377***	**-0.672****	**-0.673****	**0.482****	1	**0.996****	**-0.595****	**0.546****	**0.406***	-0.287
8. Disulfide/total thiol	r	0.056	**0.413***	**0.392***	**-0.644****	**-0.648****	**0.532****	**0.996****	1	**-0.531****	**0.520****	**0.428***	-0.305
9. Native thiol/total thiol	r	0.097	-0.213	-0.153	**0.757****	**0.716****	0.196	**-0.595****	**-0.531****	1	**-0.541****	-0.076	0.035
10. Ischemia-modified albumin	r	-0.147	0.111	0.060	**-0.715****	**-0.722****	-0.199	**0.546****	**0.520****	**-0.541****	1	0.279	-0.322
11. LDH	r	-0.007	0.194	**0.585****	-0.296	-0.308	0.326	**0.406***	**0.428***	-0.076	0.279	1	-0.387*
12. OS	r	-0.097	-0.255	**-0.448***	0.277	0.291	-0.132	-0.287	-0.305	0.035	-0.322	**-0.387***	1

**p<0.01; *p<0.05; CEA: Carcinoembryonic antigen; CA: Carbohydrate antigen; LDH: Lactate dehydrogenase; OS: Overall survival.

neuroblastoma revealed significantly higher IMA levels in the patient groups.[27] In a study on prostate cancer patients, the patient group, showed increased IMA levels, whereas, in a different study conducted with benign prostatic hyperplasia and prostate cancer patients, IMA levels decreased from benign prostatic hyperplasia to prostate cancer and were the least in the control group.[28] In another study investigating IMA levels in gastric cancer patients, upregulated IMA levels were observed in the patient group, while the IMA levels in stage 4 patients were lower than those in stage 2-3 patient group.[29] Subsequently, increased IMA levels in benign prostatic hyperplasia compared to prostate cancer patients and increased IMA levels in stage 4 gastric cancer patients compared to stage 2-3 gastric cancer patients suggest that IMA levels may decrease with an increase in the cancer stage. Additionally, the differing results of OxS markers in different cancer phenotypes may be due to underlying differences in the individual tumor bi-

ology and different mutation subtypes. Another reason might be the different characteristics (healthy control groups, control groups with comorbidities, etc.) of their control groups.

In PC patients, clinical reduction of OxS may exert influence in preventing tumor formation, progression, and recurrence, as well as in the reduction of chemotherapy's toxic effects.[25] It was determined that vitamins E and C exert antitumoral effects by inhibiting RAS mutations via MAPK, PIK3/Akt, and ERK1/2 pathways; thus, affecting OxS.[25] ROS-related pathway agents, longikaurin E, and nexrutine, block the ROS-induced pathways, and induce apoptosis in PC.[30] In our study, neither TD nor IMA levels were associated with OS. This lack of a correlation between IMA or TD levels and OS in metastatic PC patients, along with the differences in NT, TT, DD/NT, and DD/TT levels in the patient group, may suggest that OxS plays an important role in pancreatic tumorigenesis and disease progression rather than contributing to the patient's survival. In genetically susceptible patients, therapeutic agents that can block ROS pathways and reduce OxS to prevent disease formation and progression might get promising results in PC patients.

In this study, negative correlations were found between LDH, CA 19-9 levels, and OxS. In another PC study, it was found that OxS levels deteriorated in patients with higher LDH levels.[31] Similar to our study, the NAPOLEON study showed that increased LDH and CA 19-9 levels adversely affected OxS.[32] In our study, although LDH and CA 19-9 levels had a positive correlation with D/NT and D/TT ratios, an increase in OxS, LDH, and CA 19-9 levels might negatively affect the chances of survival.

In our study, TD and IMA levels before chemotherapy were examined in Stage-4 PC patients, and their association with OxS was investigated; however, the TD and IMA levels of these patients after chemotherapy were not evaluated. Since some antineoplastic drugs may increase OxS levels, patients show signs of ROS-induced lipid peroxidation, decreased vitamin E, vitamin C, and β-carotene, as well as tissue glutathione levels.[33-35] Taxanes, vinca alkaloids, and antimetabolites release cytochrome c from mitochondria and induce apoptosis.[36] Moreover, platinum group drugs and anthracyclines increase ROS levels.[33] Chemotherapy administered to patients may also increase ROS production and accelerate tumor apoptosis. In our study, an intravenous steroid (dexamethasone) was used as premedication in patients receiving chemotherapy. It has been shown that steroids can increase OxS by affecting the ROS activity. Hence, steroids used in the study may also have contributed to OxS.[37]

There were a few limitations of this study. Few patients reported comorbidities such as asthma and hypertension. The control group consisted of healthy individuals of similar age and gender distributions, but the patient group had some comorbidities. However, patients with comorbidities that could affect the TD levels (such as diabetes, hypo-or hyperthyroidism, and benign prostatic hyperplasia) were not included. The influence of OxS on the KRAS mutation initiation and the effects of this mutation on pancreatic tumorigenesis are known. However, this mutation's effects could not be evaluated in our study.

CONCLUSION

Despite advanced cancer treatment options, PC mortality rates are high. This necessitates the discovery of new and effective treatment modalities in tumor biology. Our study results showed that OxS levels regulate the pathophysiology of PC. Hence, with the development of advanced therapeutic agents to target ROS, the progression of PC in genetically susceptible individuals can be prevented along with the reduction in treatment toxicity. There is an impending need for studies with larger patient populations, precise analysis of KRAS mutations, and the inclusion of PC patients at different disease stages for mitigating ROS effects in tumorigenesis.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or mem-

bers of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Selin Aktürk Esen, Esra Fırat Oğuz, Doğan Uncu, Özcan Erel;* ***Design:*** *Selin Aktürk Esen, Denizcan Hastürk;* ***Control/Supervision:*** *Gökhan Uçar, Yakup Ergün, Mehmet Ali Nahit Şendur, İhsan Ateş;* ***Data Collection and/or Processing:*** *Selin Aktürk Esen, Esra Fırat Oğuz, Murat Bardakçı, Denizcan Hastürk;* ***Analysis and/or Interpretation:*** *Selin Aktürk, Yakup Ergün, Mehmet Ali Nahir Şendur;* ***Literature Review:*** *Selin Aktürk Esen, Doğan Uncu;* ***Writing the Article:*** *Selin Aktürk Esen;* ***Critical Review:*** *Doğan Uncu, Özcan Erel, Gökhan Uçar;* ***References and Fundings:*** *Selin Aktürk Esen;* ***Materials:*** *Selin Aktürk Esen.*

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