

## RESEARCH ARTICLE

# Pancreatic Carcinoma, Thrombosis and Mean Platelet Volume: Single Center Experience from the Southeast Region of Turkey

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### Abstract

**Background:** The aim of this study was to investigate the general characteristics of patients with deep vein thrombosis (DVT) and pancreatic cancer as well as evaluate the relationship between mean platelet volume (MPV), DVT and survival. **Materials and Methods:** Seventy-seven patients with pancreatic cancer, who were admitted to Cukurova University Medical Faculty, Department of Medical Oncology, were enrolled in the study **Results:** The mean age was 59±20. Forty-nine (63.6%) were men and 28 women (36.4%). Sixty-eight (88.3%) patients had adenocarcinoma and 9 (11.7%) had a malignant epithelial tumor. Thirty-six (46.7%) had liver metastasis at diagnosis. Twenty-six (33.8%) patients were alive, 20 (26%) were dead and in 31 (40.2%) the status was unknown. Only 14 (18.1%) patients had DVT. In 42 (54.5%) patients MPV values were normal, in 28 (36.4%) patients they were above normal, and in 7 (9.1%) patients they were below normal. There was no statistically significant difference between gender, tumour localization, chemotherapy and survival rates (p:0.56, p:0.11, p:0.21). There was no significant difference between DVT, gender, localisation, histological subtype, the presence of metastasis, stage and if the patient had been treated with chemotherapy (p:0.5, p:0.6, p:0.2, p:0.32, p:0.1, p:0.84). There was also no significant difference between MPV and DVT (p:0.57) but there was a significant difference between liver metastasis and DVT (p:0.02). Age, stage, the presence of metastasis and DVT were prognostic in pancreatic cancer patients. **Conclusions:** Cases of pancreatic cancer with liver metastasis should be studied more carefully as thrombosis is more common in these patients.

**Keywords:** Pancreatic carcinoma - MPV - thrombosis - survival.

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### Introduction

Cancer of the exocrine pancreas is a highly lethal malignancy. It is the fourth leading cause of cancer-related death in the United States among both men and women and second only to colorectal cancer as a cause of digestive cancer-related death (Siegel et al., 2013). The majority of these tumours (85%) are adenocarcinomas arising from the ductal epithelium. Surgery is the only potentially curative treatment. Because of late presentation, only 15 to 20% of patients are candidates for pancreatectomy. Prognosis is poor, even after a complete resection. The five-year survival rate after pancreaticoduodenectomy is about 25 to 30% for node-negative and 10% for node-positive cases (Trede et al., 1990; Geer and Brennan, 1993).

The most common presenting symptoms in patients with exocrine pancreatic cancer are pain, jaundice, and weight loss. But the initial presentation of pancreatic

cancer varies according to tumour location. Approximately 60-70% of exocrine pancreatic cancers are localized to the head of the pancreas, while 20-25% are in the body/tail and the remainder involve the whole organ (Porta et al., 2005). Age and operation status were found to be independent prognostic factors for overall survival (OS) and perineural invasion was an independent and poor prognostic factor (Canyilmaz et al., 2013; Zhang et al., 2013). Racial and socioeconomic factors were associated with about 2% difference in absolute cause specific survival (Cheung, 2013). Median survival time was 3.4 months in Malaysia (Norsa'adah et al., 2012).

Systemic chemotherapy, radiotherapy (RT) or a combination of chemotherapy and RT has been used following surgery in an effort to improve the outcome in patients undergoing potentially curative resection. Chemotherapeutic agents like gemcitabine have resulted in modest survival benefits in pancreatic cancer patients

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compared to 5-FU (Burriss et al., 1997). A phase III trial showed the superiority of treatments with FOLFIRINOX (5-FU, leucovorin, irinotecan and oxaliplatin) over gemcitabine alone (Becouarn et al., 2007).

Pancreatic cancer is known to be associated with thromboembolism. Shaib et al. reported incidence of thromboembolism in up to 28.9% of pancreatic cancer patients (Shaib et al., 2010). In another study, it was found that, venous thromboembolism (VTE) affects up to 17% to 57% of pancreatic cancer patients (Habib and Saif, 2013). In a systematic analysis a thromboembolic event in pancreatic cancer patients showed a rise in premature (3 months) mortality (Sgouros and Maraveyas, 2008). Chemotherapy increased the risk of thromboembolism by 5 times (Chew et al., 2006). This higher incidence of thromboembolism is compounded further with the use of erythropoietin based therapies (Al Diab, 2010). MTHFR (methylenetetrahydrofolate reductase) gene polymorphisms have been reported to be associated with pancreatic cancer, but the published studies showed different results (Liu et al., 2012).

The MPV is a laboratory marker associated with platelet function and activity. Increased MPV in thromboembolic disease is considered an important risk factor.

Our objective was to define the patient characteristics of 77 pancreatic cancer patients who lived in the southeast

region of Turkey and the relationship between MPV and DVT in these patients.

## Materials and Methods

Patients who were treated at Cukurova University, Faculty of Medicine, Department of Medical Oncology between 2007 and 2012 were investigated retrospectively. By using imaging techniques, stages were determined for seventy-seven patients with histopathologically diagnosed pancreatic cancer. Doppler ultrasonography was conducted by the same radiologist for all patients. Complete blood count and MPV values were measured at the beginning and during follow-up visits. These measurements were done at the same laboratory and by the same machine. Patients' files were reviewed retrospectively and data were recorded. The statistical analysis of the data was performed using the Statistical Package for Social Sciences for Windows (SPSS) Version 18.0 software and overall survival was analyzed using the Kaplan-Meier method. Log rank test was used to compare the survival distributions of samples. Cox model is used for exploring the relationship between the survival and several explanatory variables. It provided us to estimate the hazard (or risk) of death for an individual, given their prognostic variables.

## Results

Seventy-seven patients with pancreatic cancer were involved in the study. The mean age of the patients was 59±20. Forty-nine (63.6%) of the patients were male, 28 (36.4%) were female. Localisation of the tumour was at the head of the pancreas in 51 (66.2%) patients, in the body in 21 (27.3%) patients, and in the tail of the pancreas in 5 patients (6.5%). Histopathologically 68 (88.3%) of them were adenocarcinoma and 9 (11.7%) were malignant epithelial carcinoma. Fifty-five (71.4%) patients were in stage 4, 8 (10.4%) in stage 3, 2 (2.6%) in stage 2. The remaining were unknown (Table 1). Thirty-six (41.4%) patients had liver metastasis at diagnosis. Twenty-six (33.8%) patients were alive, 20 (26%) were dead, the states of the others were unknown (Table 2). Fifty-one (66.2%) patients were treated with chemotherapy and 3 (2.9%) did not receive chemotherapy treatment. Twenty-three (28.6%) patients discontinued follow-up care (Table 1). Fourteen patients (18.1%) had DVT, 63 (81.9%) patients did not have thrombosis. After examining the MPV values of patients; 42 (54.5%) were normal, 28 (36.4%) above normal and 7 (9.1%) were under normal values (Table 4). The mean survival rate was 8.9 months in the adenocarcinoma group and 10.5 months in the epithelial tumour group (Table 2).

There was no statistical significance (p: 0.71) between the groups. There was also no statistical significance based on gender, chemotherapy and survival (Table 3).

**Table 1. Main Characteristics of Patients with Pancreatic Carcinoma**

Gender	Number (N)	Percent (%)
Male	49	63.6
Female	28	36.4
Tumor Localisation	Number (N)	Percent (%)
Head Of Pancreas	51	66.2
Trunk Of Pancreas	21	27/3
Tail Of Pancreas	5	6/5
Histological Subtype		
Adenocarcinoma	68	88.3
Malignant Epithelial Tumour	9	11/7
Stage		
Stage 4	55	71.4
Stage 3	8	10/4
Stage 2	2	2/6
Chemotherapy	Number(N)	Percent (%)
Yes	51	66.2
No	3	3/8
Unknown	23	30.0

**Table 2. Survival Status of Patients.**

Survival	Number (N)	Percent (%)
Alive	26	33.7
Not Alive	20	26
Unknown	31	40.3
Histological subtype (p:0.715)	Mean survival (months)	
Adenocarcinoma	8/9	
Malignant epithelial type	10/5	

**Table 3. Relationship between DVT, Survival and other Parameters (CT: Chemotherapy, Met: Metastasis)**

(p)	Age	Gender	Stage	Met (liver)	MPV	DVT	CT	Met (+)
DVT		0.503	0.109	0.029	0.574		0.846	0.326
Survival	0.02	0.563	0.037			0.02	0.217	0.006

**Table 4. Deep Vein Thrombosis and MPV Relationship.**

		DVT		Total
		No	Yes	
MPV	Low	6	1	7
	Normal	35	7	42
	High	22	6	28
Total		63	14	77

There was no significance between gender, stage, MPV, metastasis, chemotherapy application and DVT (Table 3). There was no statistically important difference between MPV values and the presence of DVT (p: 0.57) (Table 4). There was a significant difference between the localisation of metastasis (liver) and DVT (p: 0.02) (Table 3). The survival rate was associated with age, stage, the presence of metastasis and DVT (Table 3).

## Discussion

Patients with malignancy are in a hypercoagulable state. The risk of VTE is 4 to 6 times higher in patients with cancer (Heit et al., 2000; Streiff, 2011). Previous DVT, type of cancer, stage of cancer (localized vs. distant metastasis), time of diagnosis (greatest within the first 3 months), surgery, RT (pelvic radiation relative risk 2.0), and chemotherapy/biological therapy/anti-angiogenesis/other agents are factors that affect the risk of VTE development (Adess et al., 2006). Treatment of VTE with anticoagulants in cancer patients is associated with benefits as well as a high rate of complications (Hutten et al., 2000; Lip et al., 2002). Increased MPV in thromboembolic disease is considered an important risk factor, however it is unclear whether increased platelet size is a cause or a consequence of thrombosis. Previous studies have shown that increased MPV was associated with both arterial and venous disease such as myocardial infarction, stroke and VTE (Braekkan et al., 2012; Chu et al., 2012). Another study suggests that, MPV, measured at the time of diagnosis, is higher in patients presenting with acute DVT (Canan et al., 2012). However, another study failed to show MPV elevation in cases of thrombosis developed in patients with cancer. It was significantly low as compared to the MPV values at the time of cancer diagnosis (Mutlu et al., 2012).

A study done by Lee et al., touches on an important aspect of cancer epidemiology and diversity, especially with respect to racial and geographical differences (Lee et al., 2013). They reported incidence of VTE among Asians, which had not been described in detail in previous studies. Medical literature lacks studies comparing the incidence of thromboembolism in different ethnicities and the impact on survival (Lee et al., 2013).

Our study was done in the southeast region of Turkey and the incidence of VTE was 18,1% which was similar to a new study (Habib and Saif, 2013).

In an Italian epidemiological study of a genetic isolate in the general population several well known risk factors for thrombosis were confirmed, but failed to identify any predictive capacity of MPV for both arterial and VTE (Biino et al., 2012).

There are few reports examining the relationship

between MPV and pancreatic cancer. One addresses the predictive value of MPV in the diagnosis of non-functional pancreatic neuroendocrine tumors (PNETs) from pancreatic adenocarcinomas. MPV levels were significantly lower in patients with PNET, particularly in non-functional PNETs, than in patients with pancreatic adenocarcinoma (Karaman et al., 2011).

In another study; MPV was not found to be a prognostic parameter in pancreatic carcinoma (Aliustaoglu et al., 2010). In a study evaluating the role of MPV in the diagnosis of hepatocellular carcinoma (HCC) in patients with chronic liver disease, it was shown that MPV may be a potential or adjunctive marker of HCC (Kurt et al., 2012).

Our study showed no link between MPV values and thrombosis but there was a link between liver metastasis and thrombosis. There are only a few case reports analysing the relationship between DVT and liver metastasis. There is one case report of pancreatic endocrine tumour with neoplastic venous thrombus and bilobar liver metastasis (Barbier et al., 2010). The liver is the major organ that synthesizes procoagulants and anticoagulants. Pancreatic carcinomas frequently invade or metastasize the liver. In a study done by Alkim H et al, it was shown that abnormalities of coagulation and fibrinolysis systems have some role in provoking thrombosis of portal veins in HCC (Alkim et al., 2012). There is no study suggesting this finding regarding pancreatic cancer.

Especially in patients with liver metastasis, detailed studies should be performed to investigate the hypercoagulable state. It would give light to other researchers about the relationship between pancreatic cancer, thrombosis, and liver metastasis. Further studies to investigate the potential relationship

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