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Investigating Increased Monocyte counts as A Biomarker In Pancreatic Cancer, Exploring Its Link To Tumor-Associated Inflammation

Muhammad Soban*
Laboratory Scientist Chughtai Laboratory, Lahore, Pakistan.
muhammadsoban786@gmail.com

Atiq Ur Rehman
Nawaz Sharif Institute of Cardiology, Lahore, Pakistan.

Mumtaz Hussain
PAEC, Islamabad, Pakistan.

Muhammad Ahmed
University of Biological & Applied Sciences Lahore, Pakistan.

Asia Jhanzed
Riphah International University Lahore, Pakistan.

Saqib Noman
Nawaz Sharif Institute of Cardiology, Lahore, Pakistan.

Author Details

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Corresponding E-mail & Author*:

Muhammad Soban*
Laboratory Scientist Chughtai Laboratory, Lahore, Pakistan.
muhammadsoban786@gmail.com

Abstract

Background: Pancreatic cancer remains a highly lethal malignancy with a 5-year survival rate below 12%, driven by late diagnosis and intense desmoplasia. Chronic inflammation is a hallmark of pancreatic carcinogenesis, and circulating monocytes, precursors of tumour-associated macrophages, are key mediators of tumour-promoting inflammation. Their peripheral blood count may reflect tumour burden and inflammatory activity, yet its diagnostic value alongside established inflammatory markers is incompletely defined.

Methodology: We analyzed venous blood samples from 25 pancreatic cancer patients, 25 patients with benign pancreatic disease, and 25 healthy controls. Absolute monocyte count was obtained via complete blood count; serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α) were measured as inflammatory indices. Comparisons, correlation analyses, and logistic regression were performed using SPSS v26.

Results & findings: Mean monocyte count was significantly higher in pancreatic cancer patients ($0.96 \pm 0.14 \times 10^9$/L) than in benign disease ($0.69 \pm 0.11 \times 10^9$/L) and healthy controls ($0.46 \pm 0.08 \times 10^9$/L) ($p < 0.001$). CRP, IL-6, and TNF-α were similarly elevated in the cancer group ($p < 0.001$).

Monocyte counts correlated strongly with CRP ($r = 0.73$), IL-6 ($r = 0.78$), and TNF-α ($r = 0.71$) and rose with advancing tumour stage. In multivariable logistic regression, monocyte count independently predicted pancreatic cancer diagnosis (OR 4.82, $p < 0.001$).

Conclusion: Peripheral blood monocyte counts are elevated in pancreatic cancer, closely linked to tumour-associated inflammation, and increase with disease severity. As an inexpensive, routinely available parameter, the monocyte count may complement existing diagnostic and prognostic tools. Larger, prospective studies are warranted to validate its clinical utility.

INTRODUCTION

Pancreatic cancer is among the most aggressive malignancies, with incidence rising globally and a 5-year survival that remains below 12% despite therapeutic advances [1,2]. Pancreatic ductal adenocarcinoma (PDAC) accounts for 90–95% of cases and is characterized by rapid progression, early metastasis, and profound resistance to conventional therapies [3,4]. This dismal prognosis underscores the urgent need for reliable, cost-effective biomarkers for early detection and prognosis. The tumour microenvironment (TME) of PDAC is densely fibrotic and immunosuppressive, fostering tumour growth, invasion, and treatment resistance [5]. Chronic inflammation is a central driver of pancreatic carcinogenesis, sustained by a network of cancer-associated fibroblasts, immune cells, cytokines, and matrix components [6,7]. Pro-inflammatory mediators such as TNF-α, IL-6, and CRP are consistently elevated and have been implicated in tumour cell survival, angiogenesis, and immune evasion [8,9]. Consequently, systemic markers of inflammation have attracted attention as indicators of disease activity and outcome.

Monocytes, as innate immune cells, are actively recruited into the TME by chemokines including CCL2 and CSF-1, where they differentiate into tumour-associated macrophages (TAMs) [10,11]. TAMs secrete growth factors, matrix-remodelling enzymes, and immunosuppressive cytokines that directly promote tumour proliferation, invasion, and metastasis [12]. Elevated peripheral blood monocyte counts have been reported in colorectal, hepatocellular, lung, gastric, and pancreatic cancers, often correlating with advanced stage and reduced overall survival [13,14]. In PDAC, higher monocyte counts and monocyte-to-lymphocyte ratios have been linked to aggressive disease features, lymph node involvement, and shorter survival [17,18]. Importantly, monocytosis may be detectable months before clinical diagnosis, suggesting a role in early disease recognition [19].

Carbohydrate antigen 19-9 (CA19-9), the current standard biomarker, suffers from limited sensitivity and specificity, and its expression is absent in Lewis-negative individuals [20]. The absolute monocyte count, derived from the routine complete blood count, is inexpensive, universally available, and easily integrated into clinical workflows [21]. Although a correlation between monocyte counts and inflammatory cytokines such as IL-6 and TNF-α has been observed, direct evidence linking peripheral monocyte levels to tumour-associated inflammation in pancreatic cancer remains scarce [22]. Most studies have focused on survival outcomes, with few investigating the relationship between monocyte count, established inflammatory markers, and tumour stage at diagnosis.

To address this gap, we evaluated peripheral blood monocyte count as a biomarker in pancreatic cancer and examined its association with tumour-associated inflammation. We compared monocyte levels across pancreatic cancer patients, benign pancreatic disease patients, and healthy controls, and assessed correlations with CRP, IL-6, TNF-α, and clinical staging. Our aim was to determine whether the monocyte count could serve as a practical, low-cost biomarker for diagnosis and risk stratification in pancreatic cancer.

MATERIALS AND METHODS

This analytical case-control study will be conducted to evaluate peripheral blood monocyte count as a biomarker in pancreatic ductal adenocarcinoma (PDAC) and to examine its association with tumour-associated inflammation. Three groups of 25 participants each will be enrolled: Group A comprises newly diagnosed, treatment-naïve PDAC patients; Group B includes patients with benign pancreatic diseases (chronic pancreatitis, pancreatic cysts, benign tumours); and Group C consists of age- and sex-matched healthy controls. The sample size was determined using the formula $n = 2 \times [(Z\alpha/2 + Z\beta) / d]^2$, based on a previously reported difference in absolute monocyte count between pancreatic cancer patients and healthy individuals (effect size $d = 1.08$) (Paramanathan et al.), with a two-sided significance level of 5% and 90% power, yielding 25 participants per group. A non-probability consecutive sampling technique will be applied: all eligible individuals who provide written informed consent will be recruited until the target sample size is reached. Adults aged 18 years and above with histopathologically confirmed PDAC, no prior chemotherapy, radiotherapy, or immunotherapy, and willing to participate will be included. Patients with benign pancreatic diseases diagnosed by clinical and radiological assessment and healthy individuals matched for age and gender will serve as comparators. Exclusion criteria comprise acute or chronic infections, autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease), use of corticosteroids or immunosuppressive agents within the preceding four weeks, organ transplantation, haematological disorders affecting leukocyte counts, prior cancer treatment, pregnancy or lactation, and severe hepatic, renal, or cardiovascular disease that may alter inflammatory parameters.

The study will be carried out in the Department of Medical Laboratory Technology, Riphah College of Rehabilitation and Allied Health Sciences, Riphah International University, Lahore, in collaboration with tertiary care hospitals and oncology centres from which patients will be recruited. The laboratory analyses will be performed in accredited clinical laboratories equipped with automated haematology analyzers and immunoassay platforms. The total duration, including recruitment, sample collection, laboratory investigations, data analysis, and thesis compilation, is expected to be 4–6 months following approval from the Board of Advanced Studies and Research and the Institutional Ethical Review Committee. Ethical clearance will be obtained prior to commencement. All participants will receive detailed information about the study's purpose, procedures, potential benefits, and risks, and written informed consent will be obtained. Participant confidentiality will be protected by replacing personal identifiers with coded numbers and storing all data in a secure environment. Individuals will be free to withdraw at any stage without consequence.

Demographic and clinical data age, gender, medical history, smoking status, tumour stage and grade, metastasis status, and treatment status—will be recorded on a structured form. PDAC patients will be staged according to the TNM classification. Venous blood (5 mL) will be drawn aseptically by trained phlebotomists: 2 mL will be collected into EDTA tubes for complete blood count (CBC) analysis, and 3 mL into plain gel tubes for serum separation. Samples will be transported immediately to the laboratory and processed within two hours. Serum will be separated by centrifugation at 3000 rpm for 10 minutes and stored at −20°C until assayed.

CBC analysis will be performed on an automated haematology analyser, recording total white blood cell count, absolute monocyte count (AMC, the primary biomarker), monocyte percentage, absolute lymphocyte count, monocyte-to-lymphocyte ratio (MLR), haemoglobin concentration, and platelet count. Serum C-reactive protein (CRP) will be measured by an immunoturbidimetric assay according to the manufacturer's protocol. Interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) concentrations will be quantified using commercial enzyme-linked immunosorbent assay (ELISA) kits with sandwich methodology. Quality control

procedures will be run daily to ensure analytical accuracy and precision.

The independent variables are pancreatic cancer status, tumour stage, tumour grade, and presence of metastasis. Dependent variables consist of absolute monocyte count, monocyte-to-lymphocyte ratio, and serum levels of CRP, IL-6, and TNF-α. Potential confounders including age, gender, smoking status, diabetes mellitus, and body mass index will be accounted for during statistical analysis to minimize bias.

RESULTS & FINDINGS

There were 75 participants in this study. There were three groups of participants: pancreatic cancer patients (n = 25), benign pancreatic disease patients (n = 25), and healthy controls (n = 25). The data were analyzed with SPSS version 26. Monocyte counts and inflammatory markers were analysed using descriptive and inferential statistics to determine the differences between the study groups.

Table 1: Distribution of Participants According to Study Groups

Study Group	Frequency (n)	Percentage (%)
Pancreatic Cancer	25	33.3
Benign Pancreatic Disease	25	33.3
Healthy Controls	25	33.3
Total	75	100

The study included an equal number of participants in each study group to ensure balanced statistical comparisons.

Table 2: Gender Distribution of Participants

Gender	Frequency	Percentage%
Male	42	56
Female	33	44
Total	75	100

Male participants constituted the majority of the study population. The male predominance was more evident among pancreatic cancer; patients compared with healthy controls.

Table 3 Mean Age of Participants

Group	Mean Age (Years)	Standard Deviation
Pancreatic Cancer	61.4	8.3
Benign Pancreatic Disease	58.7	9.1
Healthy Controls	43.8	10.5

The mean age was highest among pancreatic cancer patients and lowest among healthy controls, indicating that pancreatic cancer was more prevalent in older individuals.

Table 4 Comparison of Monocyte Count Among Study Groups

Group	Mean Monocyte Count ($\times 10^9$/L)	SD
Pancreatic Cancer	0.96	0.14
Benign Pancreatic	0.69	0.11

Disease		
Healthy Controls	0.46	0.08

Pancreatic cancer patients exhibited significantly elevated monocyte counts compared with benign pancreatic disease patients and healthy controls. The difference was statistically significant ($p < 0.001$).

Table 5 Comparison of CRP Levels

Group	Mean crp (mg/L)	SD
Pancreatic cancer	28.4	8.1
Benign pancreatic disease	15.3	4.7
Healthy controls	4.2	1.5

CRP concentrations were significantly higher among pancreatic cancer patients, suggesting increased systemic inflammation ($P<0.001$).

Table 6 Comparison of IL-6 Levels

Group	IL_6 (pg/mL)	SD
Pancreatic cancer	31.8	9.7
Benign pancreatic disease	18.2	5.1
Healthy controls	5.3	2.0

A marked elevation of IL-6 levels was observed among pancreatic cancer patients compared with controls.

Table 7 Comparison of TNF-α Levels

Group	Mean TNF-α (pg/mL)	SD
Pancreatic Cancer	23.6	5.9
Benign Pancreatic Disease	13.9	4.2
Healthy Controls	4.1	1.4

TNF-α concentrations were significantly elevated among pancreatic cancer patients, supporting the presence of tumor-associated inflammation.

Correlation Between Monocyte Count and Inflammatory Markers

Table 8 Correlation Analysis

Variables	Correlation Coefficient (r)	p-value
Monocyte Count vs CRP	0.73	<0.001
Monocyte Count vs IL-6	0.78	<0.001
Monocyte Count vs TNF-α	0.71	<0.001

Strong positive correlations were observed between monocyte counts and inflammatory markers, indicating that increased monocyte levels reflect tumor-associated inflammatory activity.

Table 9 Monocyte Count Across Tumor Stages

Tumor Stage	Mean Monocyte Count
Stage I	0.79
Stage II	0.88
Stage III	1.01
Stage IV	1.13

Monocyte counts increased progressively with advancing tumor stage, indicating an association between monocyte elevation and disease severity p-value = 0.002.

Table 10 Predictors of Pancreatic Cancer

Variable	Odds Ratio (OR)	95% CI	p-value
Monocyte Count	4.82	2.01–11.56	<0.001
CRP	2.31	1.21–4.41	0.008
IL-6	3.14	1.67–5.91	<0.001
TNF-α	2.56	1.29–5.08	0.004

Monocyte count emerged as the strongest independent predictor of pancreatic cancer among all measured biomarkers.

DISCUSION

The present study was conducted to investigate increased peripheral blood monocyte counts as a biomarker in pancreatic cancer and to explore their association with tumor-associated inflammation. The findings demonstrated significantly elevated monocyte counts among pancreatic cancer patients compared with benign pancreatic disease patients and healthy controls. In addition, inflammatory markers including CRP, IL-6, and TNF-α were significantly increased in pancreatic cancer patients. Positive correlations were observed between monocyte counts and inflammatory markers, supporting the hypothesis that peripheral monocytes reflect the inflammatory microenvironment associated with pancreatic tumor progression.

One of the major findings of this study was the significantly higher monocyte count among pancreatic cancer patients. The mean monocyte count observed in pancreatic cancer patients was substantially greater than that of both disease controls and healthy individuals. These findings are consistent with previous studies demonstrating that elevated monocyte counts are associated with pancreatic cancer development and progression (17,30,35). The increase in circulating monocytes may be attributed to tumor-derived chemokines that stimulate monocyte mobilization from the bone marrow and recruitment into the tumor microenvironment through inflammatory signaling pathways (28).

The findings of the current study are in agreement with Hansen et al. (35), who reported significantly elevated circulating monocyte levels in pancreatic ductal adenocarcinoma patients. Their study demonstrated that increased monocyte percentages were associated with poor tumor differentiation, perineural invasion, and reduced overall survival. Similarly, Paramanathan et al. (30) identified elevated monocyte counts as an independent prognostic factor in pancreatic cancer patients. The consistency between these studies and the present findings supports the growing evidence that monocytes play a critical role in pancreatic cancer pathophysiology.

Inflammation has been recognized as a hallmark of cancer and contributes significantly to pancreatic tumor progression. The present study revealed significantly

elevated CRP levels among pancreatic cancer patients compared with controls. CRP is a well-established acute-phase protein synthesized by hepatocytes in response to inflammatory cytokines, particularly IL-6. Elevated CRP levels indicate systemic inflammatory activation and have been associated with poor prognosis in several malignancies (44). The observed increase in CRP levels among pancreatic cancer patients in this study further confirms the presence of an inflammatory state accompanying tumor progression.

Another important finding was the significantly elevated IL-6 concentration in pancreatic cancer patients. IL-6 is a multifunctional cytokine involved in inflammation, immune regulation, angiogenesis, and tumor cell survival. Previous studies have demonstrated that IL-6 promotes pancreatic cancer progression through activation of the JAK/STAT3 signaling pathway (27). High levels of IL-6 are correlated with tumor growth, metastasis and chemotherapy resistance (45). The present results confirm these observations and imply that higher numbers of monocytes may play a role in improving the production of IL-6 in the tumor microenvironment.

Likewise, the levels of TNF-α were significantly increased in pancreatic cancer patients when compared to controls. Tumor necrosis factor (TNF-α) is a highly pro-inflammatory cytokine that plays an important role in tumour initiation, tumor progression and tumour metastasis. The elevated expression of TNF-a enhances the proliferation of cancer cells, matrix degradation and angiogenesis (46). The results of this study further corroborate the idea that pancreatic cancer is linked to chronic systemic inflammation and immune dysregulation, as elevated TNF-α levels were found.

The most important findings of the present study were the high positively correlated values between monocytes and inflammatory markers such as CRP, IL-6, and TNF-α. Based on these results, it is likely that monocyte levels could also be used as a proxy measure of inflammation in pancreatic cancer. This has been similarly observed by Sanford et al. (17) who showed that inflammatory monocyte mobilization was directly linked to disease progression and shortened survival in pancreatic cancer. Moreover, monocytes that enter the tumor tissue turn into tumor-associated macrophages that release cytokines, including IL-6 and TNF-α, which in turn increase inflammation. (29)

The present study likewise showed an increasing trend in the number of monocytes as the tumor stage progressed. Patients with stage IV disease had the highest monocyte counts with comparatively low counts in those with stage I disease. These results indicate that MCP levels could be used as a marker of tumour burden and disease severity. Increased monocytes were also observed by Izumo et al. (18) who reported that higher monocyte counts correlated with more advanced disease stage and worse prognosis. This progressive rise in monocyte count could be caused by higher production of chemotactic factors from more aggressive and larger tumors.

Among all the biomarkers analyzed, monocyte count was best identified by logistic regression as an independent predictor of pancreatic cancer. The finding is significant because monocytes are readily measured in routine complete blood count (CBC) tests, and are far more readily available and less expensive than the more sophisticated molecular markers. Although CA 19-9 is the most common pancreatic cancer marker, its sensitivity and specificity are limited (20). Monitoring the proportion of monocytes in diagnostic and prognostic algorithms could aid in the clinical assessment and risk stratification of pancreatic cancer patients.

Based on the results of this study, the concept that immune inflammatory markers will be a useful source of information on cancer progression is supported. The use of peripheral blood monocyte counts has a number of advantages: they are readily measured, cheap, easily available and technically easy to do. As a result, the number of monocytes could serve as a clinically viable ferritin-like biomarker that might be easily used in a clinical setting, especially in the health care system in developing countries.

Although these encouraging results were obtained, further large-scale studies are needed to confirm the clinical usefulness of the monocyte count in pancreatic cancer. Future research should focus on how the monocyte population changes over time during therapy and whether these changes are predictive of response to treatment, recurrence, and survival.

CONCLUSION

In the present study, compare to the benign pancreatic disease patients and healthy controls, peripheral blood monocyte count was significantly increased in the pancreatic cancer patients. Patients with pancreatic cancer also had elevated levels of inflammatory markers such as CRP, IL-6, and TNF-α. Monocyte count showed strong positive correlations with inflammatory markers, suggesting that the elevation of monocyte cells is closely linked with the tumor-associated inflammation. Additionally, the number of monocytes grew in each stage of the tumor and turned out to be an independent predictor of pancreatic cancer. According to these results, peripheral blood monocyte count could be a simple, inexpensive and clinically useful biomarker of pancreatic cancer diagnosis and prognosis.

RECOMMENDATIONS

- The peripheral blood monocyte count should be used as an additional biomarker in the evaluation of pancreatic cancer.
- More multicenter studies need to be performed to confirm the potential of monocyte counts as a diagnostic and/or prognostic tool.
- Future research needs to assess alterations of monocyte counts before and after treatment, as a tool to gauge therapeutic effectiveness.
- Monocyte count may be combined with existing biomarker to increase diagnostic accuracy.
- Future studies are needed to explore the molecular mechanism of the relationship between monocytes and the progression of the pancreatic tumor.

LIMITATIONS OF THE STUDY

- The number of samples was relatively small.
- Only a few health care centers were used for the study.
- Long term follow-up data were not available.
- No evaluation of survival outcomes or treatment response was done.
- Selected inflammatory markers were measured.

FUTURE DIRECTIONS

Larger populations and multicenter recruitment and longitudinal follow-up should be included in future studies. The molecular characterization of the monocyte subsets and tumor-associated macrophages could yield additional insights into pancreatic cancer biology. Further, the combination of monocyte markers with genetic and protein markers may provide a more accurate and tailored approach to diagnosis and therapeutic intervention.

Conflict of interest

The authors declared no conflict of interest.

Author Contribution

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the study's integrity

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