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Article

The Relationship between Monocytic CD66b+ Levels and Disease Stage in Gastrointestinal System Cancers

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Abstract

Background and Objectives: TNM staging is one of the most important prognostic factors in gastrointestinal system cancers. It has been demonstrated that an inflammatory condition develops due to the tumor's microenvironment in gastrointestinal system cancers. Myeloid-derived cells play a key role in this inflammation. Some of these myeloid derived cells are monocytic cells that express CD66b+ on their surfaces. CD66b+ monocytes were defined as a novel cell subpopulation that is isolated from the peripheral blood of cancer patients. The aim of this study was to investigate the relationship between monocytic CD66b+ levels and disease stage in gastrointestinal system cancers. *Materials and Methods:* Monocyte CD66b+ levels were measured by collecting peripheral venous blood samples in EDTA tubes from 50 gastric, colorectal, and pancreatic adenocarcinoma patients. The normality of the distributions of numeric variables was analyzed using "Shapiro-Wilk" test, and "Mann-Whitney U" test was used to analyze difference in median and min-max values, and "Spearman's correlation" test was used for the correlation analyses. *Results:* A strong positive correlation was found between monocytic CD66b+ levels and disease stage in gastrointestinal system cancers ($p<.001$). As the disease stage advanced, monocytic CD66b+ levels were found to increase at a statistically significant rate. *Conclusion:* While whether elevated monocytic CD66b+ levels are a cause or effect in advanced-stage disease is unknown, increased monocytic CD66b+ levels are in parallel with the progression of disease stage. In light of these results, future studies should investigate whether monocytic CD66b+ levels are associated with prognosis and survival in gastrointestinal system cancers.

Keywords: gastrointestinal system cancers; CD66b+; monocytic cells

1. Introduction

Cancers of the gastrointestinal system have an incidence of 26% among all cancer cases, and they are responsible for 35% of cancer-related mortalities.[1] Colorectal cancers are the most frequently diagnosed types of cancer among cancers of the gastrointestinal system at a rate of 37%, and they have a mortality rate of 48%.[2] The prevalence of gastric cancer among cancers of the gastrointestinal system is 20%, and it has a mortality rate of 77%.[2] The prevalence of pancreatic cancer among these cancers is 10%, and its mortality rate of over 90%.[1] Because they are frequently encountered diseases with high mortality rates, in gastrointestinal system cancers, studies on immune markers that could support early diagnosis and treatment are highly important, and their numbers are increasing constantly. Monocytes are cells of the innate immune system. They originate from hematopoietic stem cells found in the bone marrow. They are produced in the bone marrow and enter circulation

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after the completion of their maturation. In homeostatic conditions, 10-15% of monocytes settle in tissues and differentiate into macrophages and dendritic cells, whereas those remaining in circulation die as a result of apoptosis when their cycle is complete.[3]

The rate of monocytes that migrate to tissues and differentiate increases in cases such as inflammation and cancer where homeostasis is disrupted and as a result of cytokines secreted from the microenvironment of a tumor. Monocytes that migrate to tissues differentiate into antigen-presenting dendritic cells or macrophages. With their powerful antigen presentation capacity, dendritic cells are critically important cells in the formation of adaptive immune system responses. Dendritic are professional antigen-presenting cells that achieve the effective stimulation of T cells by presenting both intracellular and extracellular antigens they collect to T cells with the assistance of the activation molecules on their surfaces.[4]

Macrophages found in tissues are divided into two main groups based on their origins. The first group includes macrophages that are colonized in tissues in the embryonic period (osteoclasts in bones, alveolar macrophages in the lungs, Kupffer cells in the liver, histiocytes in connective tissue), while the second group includes those that are created by monocytes that migrate from blood to tissues and differentiate. Macrophages play an important role in the formation of the first immune response against pathogens and the preservation of homeostasis. They also have antigen-presenting capacities and are effective in the removal of pathogenic agents from tissue and renewal of the damaged tissue.

When monocytes, which differentiate into two significant cell populations of the innate immune system (macrophages and dendritic cells) after migrating to tissues, leave the bone marrow under homeostatic conditions, they are divided into three main groups based on the expression of the CD14 and CD16 surface molecules. Cells that are $CD14^{++}$ $CD16^{-}$ are known as “classical” monocytes, those that are $CD14^{++}$ $CD16^{+}$ are “intermediate” monocytes, and those that are $CD14^{+}$ $CD16^{++}$ are “non-classical” monocytes.[5] In addition to the 3 main groups of monocytes mentioned above, there are also other subgroups defined in cases such as chronic infections and cancer where the homeostatic balance is disrupted. These groups of cells that are known to proliferate in cases of inflammation and cancer are constantly under stimulation via cytokines secreted due to chronic inflammation or by tumor microenvironments. Under this constant stimulation, these cells cannot complete their development and differentiation, these cells that are not sufficiently differentiated usually have suppressive effects on the immune system, and they are called “myeloid-derived suppressor cells” (MDSCs).[6, 7]

MDSCs have a regulating effect on many immune cells, while they mostly limit the antigen recognition capacity of T cells and antigen-presenting capacity of dendritic cells. Moreover, with the cytokines they secrete such as IL-10 and TGF-Beta, these cells facilitate modulatory T cell and M2 macrophage transition. With M2 macrophage-like behaviors, tumor-associated macrophages trigger tumor development by activating helper T cells (Th2)[8] With all these properties, MDSCs limit anti-tumor response and lead the immune system to be desensitized against cancer cells.[9, 10]

These cells have been found to contain $CD33^{+}$ and low concentrations of HLA-DR as surface markers. Additionally, based on the markers they carry such as CD14, CD15, and CD66b, they are divided into polymorphonuclear MDSCs (PMN-MDSC), monocytic MDSCs (M-MDSC), and early-stage MDSCs (e-MDSC). Immunosuppressive properties associated with cancer-related inflammation and factors secreted from the tumor microenvironment have been demonstrated in all these myeloid cell subtypes.[11] It is known that PMN-MDSCs, which can be recognized by $CD66b^{+}$ surface expression, show immunosuppressive properties by inhibiting T cell proliferation.[12] In cancer patients, increased $CD66b^{+}$ PMN-MDSC levels compared to healthy individuals were shown.[13]

In cells that have been isolated from the blood of cancer patients, studies have encountered a monocyte subtype that had not been studied before, and this $CD66b^{+}$ monocytic cell subtype differs from MDSCs in terms of its functional properties and surface markers.[14, 15] With the demonstration of the surface expression of CD66b which had been defined for PMN-MDSC and shown to have immunosuppressive properties on monocytes in the cancer subpopulation, monocytic CD66b+ cells were defined as a new myeloid cell type. As opposed to the MDSCs previously identified in cancer

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patients, the CD66b$^+$ monocyte cell subtype shows proinflammatory properties with a better capacity for phagocytosis, migration, and adhesion and supports T cell proliferation.[14] CD66b$^+$ monocytic cells show immunostimulatory properties that could support survival in contrast to immunosuppression. Although it has been shown that CD66b$^+$ monocytic cell counts increase in cancer patients, a study demonstrating the relationship of these cells to types or stages of cancer was not encountered in the literature review that was conducted in this study. The purpose of this study is to investigate the relationship between monocytic CD66b+ levels and disease stage in cancers of the gastrointestinal system.

2. Materials and Methods

2.1. Design and Ethics

This prospective study was performed with the approval of the Noninterventional Clinical Research Ethics Committee of Hacettepe University with the decision coded GO 21/1245 and numbered 2021/20-37. All stages of the study complied with the principles of the Declaration of Helsinki and the Guideline for Good Clinical Practice. Informed consent was obtained from the patients who were included in the study. In this study, the relationship between monocytic CD66b+ levels and disease stage in gastrointestinal cancer cases was investigated. For this purpose, the sample of the study included gastric, colon, rectal, and pancreatic cancer patients who presented to the Department of General Surgery and the Medical Oncology division of the Department of Internal Medicine at the Faculty of Medicine at Hacettepe University between October 2021 and March 2022 and voluntarily agreed to participate in the study. Besides, 10 healthy individuals also participated in the study as a control group. Peripheral venous blood samples were collected from all 50 newly diagnosed participants and from 10 healthy individuals into EDTA tubes at a volume of 10 ml for each participant. The blood samples were collected at the Department of General Surgery and the Medical Oncology branch of the Department of Internal Medicine at the Faculty of Medicine at Hacettepe University. The parameters in cells that were isolated from the collected peripheral blood samples were examined at the Laboratory of the Department of Basic Oncology. Ex vivo and in vitro experiments were carried out, and the participants were not subjected to any procedure other than peripheral blood sample collection. All data were obtained as a result of routine analyses or research laboratory analyses.

2.2. Data Collection and Definitions

The study included peripheral blood samples that were collected pre-treatment from gastric cancer (adenocarcinoma), colorectal cancer (adenocarcinoma), and pancreatic cancer (adenocarcinoma) patients who were recently diagnosed and had not yet received treatment. The inclusion criteria were determined as being newly diagnosed and not having received treatment yet. The exclusion criteria were having a chronic disease that could affect the immunological parameters of the patient and being in an acute/chronic inflammatory process. Cancer staging was performed based on the 8th edition of the guidelines of the American Joint Committee on Cancer (AJCC 8th). In the staging process, the postoperative pathology results of all patients, except for Stage 4 patients whose metastatic disease was radiologically or pathologically documented, were taken as a basis. The study included a total of 60 patients including 24 colon, 9 rectal, 10 gastric, 7 pancreatic adenocarcinoma patients and 10 healthy individuals. A data template was created by checking the flow-cytometric analysis results of the monocytic CD66b+ cells isolated from the peripheral blood sample of each patient.

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2.3. Cell Sorting / Isolation of Peripheral Blood Mononuclear Cells (PBMC)

Peripheral blood samples from patients were collected into EDTA vacutainer tubes (BD Biosciences, USA) to prevent coagulation until isolation of the cells. The anticoagulant EDTA chelates calcium and magnesium ions, which are essential cofactors for the coagulation cascade, thereby preserving the cellular integrity and viability of blood components for downstream analysis. A diluted blood sample (1:1 ratio with phosphate-buffered saline, PBS) was prepared to reduce the overall density and viscosity of the sample, facilitating better separation during density gradient centrifugation. The PBS served as an isotonic medium that maintained osmotic balance and prevented cell lysis or crenation during the dilution process. The diluted blood sample was then carefully and gently layered over Histopaque-1077 (Sigma Aldrich, USA), a proprietary solution composed of sodium diatrizoate and polysucrose. Histopaque-1077 is critical for isolating Peripheral Blood Mononuclear Cells (PBMCs) due to its precisely calibrated density of approximately 1.077 g/mL at 20°C. This specific density is optimized to match the buoyant density of mononuclear cells, including lymphocytes (T cells, B cells, and natural killer cells) and monocytes, which are the target cell populations for most immunological studies. When the diluted blood sample was carefully layered over Histopaque-1077 without mixing, and the sample was subsequently centrifuged at standard gravitational forces (typically 400–600 × g for 20–30 minutes at room temperature low increase and decrease speed break), the blood components separated based on their differential densities. The buffy coat layer was subsequently collected using a sterile pipette, carefully aspirating from the interface zone without disturbing the red blood cell pellet at the bottom or the plasma layer above. The collected cells were then typically washed with PBS in order to remove residual Histopaque solution and prepare the cells for downstream applications.

2.4. Flow Cytometry

Immunophenotyping was performed with the monoclonal antibodies anti-human CD45 (HI30), CD66b (G10F5), HLA-DR (L243), and CD14 (M5E2) (BioLegend, USA). The percentage of positive cells was determined according to isotype-matched antibodies. Acquiring fully stained multi-color samples, the compensation matrix was applied in realtime or during post-acquisition analysis. This subtracted the calculated spillover from each channel, revealing the "true" fluorescence signal for each marker. The samples were run on Canto II (BD Biosciences, USA), and data were analyzed by FlowJo software (v.10). 2.4.

2.5. Statistical Analysis

The statistical analyses of the data were carried out using the IBM SPSS software (version 20.0). Descriptive statistics are given in frequencies and percentages for the categorical variables and mean ± standard deviation, minimum-maximum, and median values for the numeric variables. According to the results of the "Shapiro-Wilk" test that was conducted on the numeric data to test normality, the numeric data were not normally distributed, and non-parametric methods were used in the analyses of these data. The "Mann-Whitney U" test was used to test the significance of the difference in median values between two independent groups. "Spearman's correlation" analysis was used to analyze the correlations between the numeric variables. The results were evaluated in a 95% confidence interval, and $p<.05$ was accepted statistically significant.

3. Results

3.1. Descriptive Statistics

To investigate whether CD66b+ monocytic cell levels differed significantly based on disease stages, the 24 colon, 10 gastric, 9 rectal, and 7 pancreatic adenocarcinoma patients were examined in 4 groups based on staging according to the *AJCC 8th* guidelines: Stage 1 [n=13 (6 female, 7 male), mean age: 62], Stage 2 [n=11 (6 female, 5 male), mean age: 59], Stage 3 [n=11 (3 female, 8 male), mean

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age: 66], and Stage 4 [n=15 (6 female, 9 male), mean age: 61]. The descriptive statistics of the groups are shown in Table 1.

Table 1. Descriptive statistics.

	Stage 1	Stage 2	Stage 3	Stage 4
Frequency	13	11	11	15
Mean Age	65	59	66	61
Mean CD66b+	2.81	4.19	8.05	11.34
SD	1.07	1.72	2.65	3.01

SD: Standard deviation.

3.2. Correlation Analysis

A positive, strong and statistically significant correlation was found between the gastrointestinal system cancer stages of the patients and their monocytic CD66b+ levels (p<.001). The results of the correlation analysis between disease stage and monocytic CD66b+ levels are presented in Table 2.

Table 2. Correlation between stage and monocytic CD66b+ levels.

Stage – Monocyte Correlation		
Spearman test	Correlation coefficient	.885
	Sig. (2-tailed)	.000
	n	50

Sig: Significance, n:Number.

3.3. Comparison of Monocytic CD66b+ Levels Based on Disease Stages

In all binary comparisons of the median monocytic CD66b+ levels of the patients based on their disease stages, the differences were statistically significant. The mean, standard deviation, median, and minimum-maximum values of the monocytic CD66b+ levels of the patients based on their disease stages are presented in Table 3, while the comparison of the median values and correlation p-values of these levels based on stages is given in Table 4.

Table 3. Comparison of monocytic CD66b+ levels based on stages.

	Frequency	Mean	SD	Median	Minimum	Maximum
Stage 1	13	2.815	1.0730	2.5	1.0	4.8
Stage 2	11	4.191	1.7213	4.5	1.0	7.1
Stage 3	11	8.055	2.6497	8.0	5.1	14.0
Stage 4	15	11.340	3.0104	11.0	7.9	18.0

SD: Standard deviation.

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Table 4. Comparison of monocytic CD66b+ levels based on stage.

	p (Median)	Correlation Coefficient	p (Correlation)
1 vs 2	.023	.474	.019
1 vs 3	<.001	.867	<.001
1 vs 4	<.001	.868	<.001
2 vs 3	<.001	.762	<.001
2 vs 4	<.001	.859	<.001
3 vs 4	.004	.569	.002

3.4. Stages 1-2 vs. Stages 3-4 Comparison

The monocytic CD66b+ levels of the patients were compared between two groups as Stages 1-2 and Stages 3-4. Based on the p-value of <.001 for the median difference, the correlation coefficient of .846, and the significance of the correlation coefficient at p<.001, the two groups were found to have significantly different monocyte CD66+ levels. The results of the comparisons of these two groups are given in Table 5.

Table 5. Comparison of monocytic CD66b+ levels between Stages 1-2 and Stages 3-4.

	Frequency	Mean	SD	Median	Minimum	Maximum
Stages 1-2	24	3.446	1.5424	3.5	1.0	7.1
Stages 3-4	26	9.950	3.2594	9.0	5.1	18.0

p<.001.

3.5. Stages 1-2-3 vs. Stage 4 Comparison

The monocytic CD66b+ levels of the patients were compared between two groups as Stages 1-2-3 and Stage 4. Based on the p-value of <.001 for the median difference, the correlation coefficient of .710, and the significance of the correlation coefficient at p<.001, the two groups were found to have significantly different monocyte CD66+ levels. The results of the comparisons of these two groups are given in Table 6.

Table 6. Comparison of monocytic CD66b+ levels between Stages 1-2-3 and Stage 4.

	Frequency	X	SD	Median	Minimum	Maximum
Stages 1-2-3	35	4.894	2.8959	4.5	1.0	14.0
Stage 4	15	11.340	3.0104	11.0	7.9	18.0

p<.001.

4. Discussion

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In cancers of the gastrointestinal system, one of the most significant factors determining the prognosis is TNM staging. As the stage progresses, the prognosis worsens, and survival rates decrease. Treatment modalities for gastrointestinal system cancers consist of different components depending on the stage of the disease and require a multidisciplinary approach. The diagnosis, treatment, and follow-up methods of these diseases have an important role in the development, progression, and metastasis of the disease. Making an effort to increase survival rates by developing these methods is one of the most important fields of research on this issue.

Monocyte CD66b+ cells constitute one of the myeloid-derived cell groups in the tumor microenvironment. With the detection of CD66b surface expression, which had previously been defined for granulocytic cell groups, in monocytes, they have been defined as a new myeloid cell group found in the tumor microenvironment.[14] It was seen that these monocytic cells with the $CD14^+$ $CD33^+$ $CD16^-$ HLA-DR^+ phenotype typically have $CD66b^+$ expression. This $CD66b^+$ monocytic cell subtype that is detected in cancer patients is distinguished from myeloid cells that have immunosuppressive properties with its capacity for higher phagocytosis, adhesion, and migration and immunoregulatory and pro-inflammatory effects such as the stimulation of T cell proliferation.[14] Research continues on the relationship between this newly defined monocyte cell subtype and cancer diagnosis and staging.

As in several other types of cancer, tumor immunology has a significant role in the development, progression, and metastasis stages of cancer in cases of gastrointestinal system cancers. While it is not completely known whether the inflammation in the tumor microenvironment causes or is caused by carcinogenesis, it is known that the microenvironment of a gastrointestinal tumor is infiltrated by a group of myeloid cells.[16] This group of myeloid cells includes neutrophils, MDSCs, monocytes, macrophages, and dendritic cells. The main mechanism of the immunosuppression in the tumor microenvironment caused by myeloid cells is the inhibition of T cell activity.[15, 17] In examinations of myeloid-derived cell groups in the tumor microenvironment, it has been shown that granulocytic cell groups are more prominent in this inhibition than monocytes.[15, 18] Considering the surface expressions of these myeloid cell groups, it was shown that cells with CD66b+ expression were more involved in T cell activity inhibition in comparison to other expressions, and these cells were associated with lower survival rates.[19] Horzum et al. showed CD66b+ surface expression, which had previously been defined for granulocytic cell groups, in monocytes and reported that as opposed to other myeloid cell groups, monocytic CD66b+ cells showed immunostimulatory properties.[14] Yamada et al. reported a correlation between elevated granulocytic CD66b+ levels and disease stage in some types of cancer.[20] Nevertheless, the literature review in this study did not reveal any previous study showing the relationship between monocytic CD66b+ cells, which differ from these cell groups with their immunostimulatory properties, and the progression and prognosis of the disease. In this study, a strong positive correlation was found between monocytic CD66b+ levels and disease stage in patients with cancers of the gastrointestinal system. In the patient group consisting of 50 patients, including those with gastric, colon, rectal, and pancreatic cancer (adenocarcinoma), significant relationships were identified between monocytic CD66b+ levels and disease stage in the comparisons among Stages 1, 2, 3, and 4; between Stages 1-2 and Stages 3-4 as earlier and later stages; between Stages 1, 2, 3 and Stage 4 as non-metastatic and metastatic stages. Accordingly, as the stage of the disease progressed, monocytic CD66b+ levels also increased in correlation. In light of this information, in this study, the hypothesis that “there is a relationship between disease stage and monocytic CD66b+ levels in cancers of the gastrointestinal system” was confirmed. Hence, a clear relationship was demonstrated between elevated monocytic CD66b+ levels and advanced disease stage. It is important in terms of supporting these results to conduct studies with larger samples where the prognoses of patients are also followed up.

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Limitations

The small sample size, the heterogeneity of the cohort, and limited previous studies on this novel "monocyte CD66b^{+}" topic in the literature were limitations of this study.

Institutional Review Board Statement: This study was performed with the approval of the Noninterventional Clinical Research Ethics Committee of Hacettepe University with the decision coded GO 21/1245 and numbered 2021/20-37. All stages of the study complied with the principles of the Declaration of Helsinki and the Guideline for Good Clinical Practice.

Informed Consent Statement: Informed consent was obtained from the patients who were included in the study.

Conflicts of Interest: The authors have no related conflicts of interest or financial interest to declare. The study was partially supported by Hacettepe University Scientific Research and Coordination Unit. None of the authors has any financial interest in the unit supporting the study.

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