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A novel indicator predicts 2019 novel coronavirus infection in subjects with diabetes

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ABSTRACT

Aims: Diabetes mellitus (DM) is associated with significant morbidity and mortality. The disease severity in 2019 novel coronavirus (Covid 19) infection has varied from mild self-limiting flu-like illness to fulminant pneumonia, respiratory failure and death. Since DM and Covid 19 infection are closely associated with inflammatory status, mean platelet volume (MPV) was suggested to be useful in predicting Covid infection onset. This study aimed to evaluate the diagnostic role of MPV in Covid patients with diabetes.

Methods: A total of 640 subjects (160 Covid patients with type 2 diabetes, 160 healthy controls, 160 patients with non-spesific infections and 160 Covid patients without type 2 diabetes) enrolled in the study.

Results: MPV was significantly higher (11.21 ± 0.61 fL) as compared to the results from the last routine visits of the the same individuals with diabetes (10.59 ± 0.96 fL) (p = 0.000).

Conclusions: MPV could be used as a simple and cost-effective tool to predict the Covid infection in subjects with diabetes in primary care.

1. Introduction

Diabetes mellitus (DM) is a prevalent metabolic disorder characterized by hyperglycemia resulting from absolute or relative deficiencies in insulin secretion and/or insulin action [1].

DM has been considered as a prothrombotic condition with increased platelet reactivity [2], morphological changes of platelets and the increased platelet activity have been reported in DM and mean platelet volume (MPV) was found to be significantly higher in diabetic patients [3,4]. MPV and an accurate measure of the platelet size are considered markers and determinants of platelet function. Larger platelets with higher MPV are hemostatically more reactive and produce higher amounts of the prothrombotic factor thromboxane. The increase in thromboxane generation causes a thrombotic susceptibility and therefore, results in thrombotic complications [5,6].

In December 2019, pneumonia cases of unknown origins was recognized and reported in China where most of the earlier patients having pneumonia had worked or visited a seafood market selling live animals in Wuhan. This newly identified illness termed COVID-19 by the World Health Organization (WHO) has spread rapidly through China and the rest of the world. On 11 March 2020, WHO declared the outbreak a global pandemic. A novel beta-coronavirus, was identified as the COVID-19 pathogen, which triggered severe pneumonia and acute, even lethal, lung failure. There were confirmed cases of COVID-19 worldwide nearly approaching 1.8 million

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with a mortality rate of 6.3% according to the situation report of World Health Organisation on April 13, 2020 [7].

Individuals with diabetes have a higher overall risk of infection that results from multiple disturbances of inherent immunity, Not only this, patients with diabetes have a severe disease when infected with respiratory viruses, especially influenza and pneumonia.

Indeed, diabetes was seen as an important risk factor for mortality in patients infected with Pandemic Influenza A 2009 (H1N1), Severe Acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome-related coronavirus (MERSCoV) [8]. Data about COVID-19 in patients with diabetes is limited at present. Diabetes was present in 42.3% of 26 fatalities due to COVID-19 in Wuhan, China [9]. In a study in 140 patients with COVID-19 inWuhan, China, diabetes was not a risk factor for severe disease course [10]. However, another study in 150 patients (68 deaths and 82 recovered patients) in Wuhan showed that the number of co-morbidities to be a significant predictor of mortality [11]. Analysis of 11 studies regarding laboratory abnormalities in patients with COVID-19 did not mention raised blood glucose or diabetes as predictor of severe disease [12]. Notwithstanding these small series, a report of 72,314 cases of COVID-19 published by Chinese Centre for Disease Control and Prevention showed increased mortality in people with diabetes (2.3%, overall and 7.3%, patients with diabetes) [13].

However, MPV of COVID-19 patients with diabetes were not fully reported, which may have diagnostic and prognostic value. In this study, we aimed to compare levels of MPV in diabetics before and after the Covid infection whether it could be used as an diagnostic indicator in diabetics.

2. Materials and Methods

2.1. Study population

This study was conducted at the Bezmialem Vakif University Hospital at the largest city of the Turkey, namely Istanbul, between February 2020 and April 2020. Our population is represented by consecutive 160 patients who were laboratory confirmed Covid cases with Type 2 DM (T2DM) admitting to Covid out-patient clinic and age- and sex-matched 160 non-diabetic laboratory confirmed non-Covid adults admitting to Family Medicine out-patient clinic. A control group of sex and age matched individuals with non-specific upper respiratory and other infections (patients with urinary tract infection, patients with soft tissue infection) was enrolled in the study. We have retrospectively analyzed the MPV values of age- and sex-matched 160 laboratory confirmed Covid patients without diabetes admitted to the Covid out-patient clinic. Previous results of complete blood count of the enrolled same non-diabetic individuals with Covid infection which were studied during their last visit to any out-patient clinic at the hospital before onset of Covid infection were yielded from the archive records via patient information management system of the hospital. A group of age- and sex-matched 160 laboratory confirmed Covid patients without diabetes admitted to the Covid out-patient clinic were also enrolled in the study.

2.2. Anthropometric and biochemical measurements

All the diabetic and non-diabetic subjects underwent a complete clinical evaluation as well as any drugs taken. Height in centimeters (rounded to the nearest 0.5 cm) and weight in kilogrammes (rounded to the nearest 0.1 kg) of all the subjects were recorded. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters.

The diagnosis of DM was based on previous history of diabetes treated with or without drug therapies, fasting glycaemia > 126 mg/dL, random glycaemia > 200 mg/dL or HbA1c > 6.5% according to the ADA criteria in two samplings. Adults whose fasting glucose values < 100 mg/dL were accepted as normal sujects and included in the non-diabetic group.

We excluded patients with iron deficiency anemia, hypo-hyperthyroidism, congestive heart failure, recent infection. For the sake of minimizing confounding factors, we did not include patients with leukocytosis, anemia or thrombocytopenia as they may effect platelet and erythrocyte size. Patients with known inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus, were excluded. Non-diabetic subjects with coronary artery disease and diabetics on antiplatelet drugs such as aspirin and clopidogrel were also excluded. Subjects with any diagnosed malignancy were also excluded [14]. Written informed consent was taken from each subject before study inclusion.

Blood withdrawal was done following an overnight fasted state (≥8 h) by the clinic nurse and physician on duty. Fasting blood samples were collected and transferred immediately to appropriate tubes described below for centrifugation. Collected serum was then transferred to pre-labeled plain tubes and delivered to the bio-chemistry laboratory in Bezmialem Vakif University Hospital.

To identify SARS-CoV-2 infection, throat swab samples were obtained from all participants at admission and tested using real-time reverse transcriptase–polymerase chain reaction assays.

Past results of complete blood count of enrolled the same diabetic individuals with Covid infection which were studied during the last routine out-patient clinic visit (the newest visit was a month ago and the oldest visit was three months ago) before start of Covid infection in the participant were yielded from the archive records via patient information management system of the hospital.

We measured the MPV and platelet using an automated hematology analyzer (Sysmex 1800 t, USA). Venous blood samples were collected in dipotassium EDTA and tested within 1 h of collection to minimize variations due to sample aging. Samples were maintained at room temperature. Samples for plasma glucose estimation and HbA1c were collected in sodium fluoride and dipotassium EDTA, respectively. The estimation of fasting plasma glucose and HbA1c levels carried out by the glucose oxidase method in the chemical auto-analyzer (Cobas 8000, Roche, Germany) and that of HbA1c by the high-performance liquid chromatography method. It should be noted that the Quality Assurance (QA) standards are maintained by TS EN ISO 15189, whereas the QA department audits the laboratory at regular intervals.

2.3. Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences version 16.0 (SPSS, Chicago, IL, USA). Normal continuous variables were presented as mean ± standard deviation. Test of significance was calculated by unpaired student's t test between cases and controls. Correlation of MPV with other parameters was performed by two-tailed Pearson's.

3. Results

A total of 640 subjects (160 Covid patients with type 2 diabetes, 160 healthy controls, 160 patients with non-spesific infections and 160 Covid patients without type 2 diabetes) enrolled in the study. General characteristics and laboratory data of groups enrolled in the study are shown in Table 1. There were 93 (58.1%) male diabetics and 67 (41.9%) female diabetics in the study. There were 88 (55.0%) non-diabetic males and 72 (45.0%) non-diabetic females in the study. Gender was not statistically significant different between groups (p = 0.994). The mean age of the diabetic population was 57.00 ± 11.03 years whereas that of non-diabetic population was 58.02 ± 12.16 years. Age of the groups were not statistically significant different (p = 0.215). The mean duration of diabetes was 7.83 ± 4.58 years. The mean BMI in the diabetic group was 29.35 ± 4.67 kg/m^2 and it was 24.54 ± 2.46 kg/m^2 in non-diabetic subjects (p = 0.000). The mean fasting blood glucose level in the diabetic population was 172.88 ± 43.06 m g/dL while that of the non-diabetic group was 89.08 ± 10.30 mg/gL (p = 0.000). The mean HbA1c level in the diabetic group was 8.60 ± 1.62 as compared to 5.41 ± 0.24 of the non-diabetic group (p = 0.000). The mean platelet count in the diabetic group was 257.22 ± 71.13 × 10^9/L and it was 267.27 ± 64.64 × 10^9/L in non-diabetic group (p = 0.356). In the Covid patients with diabetes, MPV was significantly higher (11.21 ± 0.61) as compared to the last routine visit results of the same diabetic individuals (10.59 ± 0.96 fL) (p = 0.000). The mean LDL cholesterol level was 146.28 ± 32.39 mg/dL in the diabetic group while it was 114.38 ± 14.08 mg/dL in normal subjects. Level of LDL cholesterol was statistically significant different between groups (p = 0.004) (see Table 2).

The mean MPV values of the enrolled Covid patients after their laboratory confirmed recovery were yielded. The data showed that mean MPV decreased to 10.61 ± 0.88 after patients recovered, to original level (p > 0.05). We looked at the MPV values of the enrolled subjects classifying as patients with asymptomatic Covid, moderately severe Covid and severe Covid. We detected there were no statisticaly significant differences among the groups, 11.12 ± 0.51, 11.35 ± 0.16 and 11.54 ± 0.91, respectively (p > 0.05). The mean MPV values of the control group of individuals with non-specific upper respiratory and other infections (patients with urinary tract infection, patients with soft tissue infection) was found to be 10.60 ± 1.10 (p < 0.001). We have made some correlation analysis between MPV and COVID-19, however there were no statistically significant differences.

The MPV values of age- and sex-matched 160 laboratory confirmed Covid patients without diabetes admitted to the Covid out-patient clinic were detected as 10.49 ± 0.96 and 10.66 ± 0.94 before and after Covid infection in these individuals, respectively (p = 0.37).

Comparison of MPV in person with diabetes before Covid infection and in healthy person were 10.59 ± 0.96 and 10.02 ± 1.01, respectively. (p < 0.05) We thought that increase in MPV caused both by infection and diabetes. When we analyzed, there was no statistically significant difference in person with other infections.

We have analyzed the MPV values of the participants and detected the MPV in the same subjects with diabetes before Covid infection was 10.59 ± 0.96, however the MPV in the same subjects with diabetes during Covid infection was 11.21 ± 0.61 (p = 0.000). The mean MPV in the same subjects with diabetes with Covid infection after recovery was found

Table 1 – Comparison of various parameters between the groups enrolled in the study.

Characteristic	T2DM	Non-diabetic	p
Number	160	160	–
Age	57.00 ± 11.03	58.02 ± 12.16	0.215
Female	67 (41.9%)	72 (45.0%)	0.994
Male	93 (58.1%)	88 (55.0%)	0.994
Mean duration of DM (years)	7.83 ± 4.58	–	–
Body Mass Index (kg/m2)	29.35 ± 4.67	24.54 ± 2.46	0.000
Fasting blood glucose (mg/dL)	172.88 ± 43.06	89.08 ± 10.30	0.000
HbA1c (%)	8.60 ± 1.62	5.41 ± 0.24	0.000
Haemoglobin (gr%)	13.32 ± 1.51	13.90 ± 1.62	0.174
Platelets (×10^9/L)	257.22 ± 71.13	267.27 ± 64.64	0.366
Mean platelet volume (fL)	11.21 ± 0.61	10.02 ± 1.01	0.000
LDL Cholesterol (mg/dL)	146.28 ± 32.39	114.38 ± 14.08	0.004

Table 2 – Comparison of MPV in diabetics before and after Covid infection.

Characteristic	before Covid	after Covid	p
Mean platelet volume (fL)	10.59 ± 0.96	11.21 ± 0.61	0.000

to be 10.61 ± 0.88 when compared to the levels before onset of the Covid infection ($p > 0.05$). Comparison of MPV in person with diabetes before Covid infection and in healthy person were 10.59 ± 0.96 and 10.02 ± 1.01, respectively ($p < 0.05$). When we analyzed, there was no statistically significant difference in person with other infections.

4. Discussion

To the best of our knowledge, there are no studies that have examined the association between MPV and Covid patients with diabetes mellitus in primary health care in Turkey.

DM is a complex syndrome characterized by chronic hyperglycemia responsible for well-known sensitivity against infections that results from multiple disturbances of inherent immunity. Diabetes affects more than 300 million individuals in the world with significant morbidity and mortality worldwide [15]. It was detected that prevalence of diabetes in Turkish population was reached to 13.7% according to TURDEP II study [16]. It was reported that MPV might be used as a simple and cost-effective laboratory test in the follow-up of DM. It was shown that in diabetes mellitus, platelets become more reactive and their MPV is increased. Therefore, MPV would be a useful prognostic marker of widespread complications in diabetes [17]. MPV might be used as a simple and cost-effective laboratory test in the follow-up of DM and thereby help hold the morbidity and mortality.

COVID-19 is an acute infectious disease caused by a new coronavirus (SARS-CoV-2), the usual clinical characteristics involve fever, dry cough, fatigue, sore throat, rhinorrhea, conjunctivitis, headache, myalgia, dyspnea, nausea, vomiting and diarrhea. Patients may gradually develop dyspnea. In severe cases, the disease progresses rapidly. MODS, septic shock, difficult to correct metabolic acidosis, and coagulation dysfunction may ocur within a few days. Some patients have severe inflammatory storms leading to death [18]. Therefore, judging the development trend and diagnosis of the disease at an early stage, and taking active and effective treatment for patients who may develop into severe illness can effectively reduce the mortality rate.

Platelets are important immune cells in the human body, which play an important role in hemostasis, coagulation, vascular integrity maintenance, angiogenesis, innate immunity, inflammatory response, tumor biology and so on. Recent research has revealed platelets as more active components of the immune system besides the previously considered passive immune-modulatory role. Through a cross-talk with the immune system, platelets have emerged as both critical modulators of atherothrombosis and vascular inflammation and as effector cells in the combat of microbial infection [19]. Changes in its number and activity are closely related to a variety of diseases [20,21]. In addition to their well-established function in thrombus formation, platelets are also rapidly emplaced to sites of inflammation. Recent studies reveal that modulation of inflammatory processes by platelets can occur via interaction with neutrophils, internalization of pathogens and secretion of cytokines, platelet microbicidal proteins (PMPs) and other inflammatory regulators [22]. Platelets are produced by mature megakaryocytes in the bone marrow, and current studies have shown that a variety of cytokines, including TPO, IL-3, IL-6, IL-9, IL-11, and stem cell factor (SCF), can promote the production of megakaryocytes [23]. The absolute value of lymphocytes and platelet levels can be used as sensitive indicators to reflect the body's infection and inflammation control. But can MPV as an indicator has the same clinical value for COVID-19 patients with diabetes?

Therefore, we analyzed the changes in peripheral blood of the COVID-19 patients with diabetes, and the association between the changes before and after the Covid infection. Through the observation of patients included, we found that the mean platelet volume level of patients were positively correlated with the Covid infection. The reason may be that the possible platelet changes in COVID-19 patients. In addition, it may be also related to the limited number of patients enrolled in this study.

We thought that the statistically significant difference in MPV between diabetic patients before onset of Covid infection and healthy individuals was caused by hyperglycemia in diabetes.

In previous studies, the possible causes of platelet changes in COVID-19 patients were analyzed and it was shown that the lung may be one of the organs in which mature megakaryocytes release platelets and that thrombocytopenia in patients with SARS-CoV infection may be associated with lung damage [24]. Injury of lung tissue and pulmonary endothelial cells can lead to activation, aggregation, and retention of platelets in the lung, and the formation of thrombus at the injured site, which may lead to the depletion of platelets and megakaryocytes, resulting in decreased platelet production and increased consumption [25].

As a new type of inflammation index, MPV mainly reflects the level of systemic inflammation. Previous studies have confirmed that MPV is closely related to tumors, diabetes, coronary heart disease, and connective tissue diseases, and the increase of MPV is related to tumor size, lymph node infiltration, distant metastasis and prognosis, and can be used as a potential inflammatory indicator for the clinical diagnosis of community-acquired pneumonia [3,26,27]. As an indicator of inflammation, MPV is mainly caused by megakaryocytes in bone marrow hematopoietic tissue and is a major participant in thrombosis. It plays a crucial role in the inflammatory response to recruit neutrophils and other inflammatory cells to the site of injury. PLT exists in an inactive form and can be activated quickly at the site of vascular injury, and can be rapidly activated in response to proinflammatory cytokine or infectious factors. The activation of platelets by this mechanism, even without any vascular damage, opens up new functions of platelets, namely inflammation and immune regulation, and the proinflammatory cytokine activity of PLT is mediated by its interaction with other leukocytes in the circulation, followed by the release of cytokines and chemokine to promote inflammation [28].

This study has some limitations. This study was conducted at a single-center hospital with limited sample size. Larger cohort studies of diabetic patients with COVID-19 pneumonia would help to further define the clinical characteristics and exploration of new indicators for the disease.

In conclusion, in the presence of this rapidly emerging, novel infection faced in recent months, identification of biomarkers that could predict disease presence are essential to guiding clinical care. As such, biomarkers are needed to identify disease among patients. Our data revealed from 160 diabetic patients with laboratory confirmed COVID-19, presumed that the MPV is getting increased with Covid infection and may be indicative of a useful diagnostic marker of an emerging Covid infection in diabetics. In consideration of our findings, we propose that MPV can be used as a simple, economic, rapid, commonly available and cost-effective tool to monitor the onset of Covid infection in primary care.

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Declaration of Competing Interest

The author declares no conflict of interest.

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