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Frailty in Diabetic Subjects during COVID-19 and Its Association with HbA1c, Mean Platelet Volume and Monocyte/ /Lymphocyte Ratio

ABSTRACT

Background: Frailty is associated with increased risk of hospitalization in diabetic patients. Both SARS-CoV-2 pandemic and type 2 diabetes mellitus contribute to the frailty. In this study we aimed to observe clinical and laboratory indices of the diabetic subjects during COVID-19 pandemic who were either frail or not according to Edmonton frail score.

Material and methods: During the pandemic era, 100 consecutive patients with type 2 diabetes mellitus divided into two groups either as frail or non-frail according to the Edmonton Frail Scale scores. Laboratory and clinical features of the frail and non-frail subjects were compared.

Results: Frail patients were older than the non-frail diabetics. Blood urea, serum creatinine, eGFR, plasma albumin, total cholesterol, triglyceride, HbA1c, mean platelet volume (MPV), and monocyte lymphocyte ratio (MLR) levels of the frail and non-frail groups were significantly different. Moreover, Edmonton frail score was significantly and positively correlated with blood urea, serum creatinine, MLR, MPV, HbA1c and inversely correlated with eGFR and plasma albumin levels.

Conclusions: We think that HbA1c, MPV and MLR could be surrogate markers of frailty in diabetic elderly during COVID-19 outbreak. Strategies to keep them in normal range do not only improve diabetes control but also reduce the risk of frailty in this population. (Clin Diabetol 2022, 11; 2: 119–126)

Keywords: type 2 diabetes mellitus, COVID-19, frailty, mean platelet volume, HbA1c, monocyte to lymphocyte ratio

Introduction

Frailty is a geriatric state of reduced functional reserve and vulnerability that represent a major public health problem because of its relationship with systemic diseases, increased risk of hospitalization, institutionalization, and mortality [1]. On the other hand, respectively the SARS-CoV-2 pandemic has affected almost 27 million people and the prevalence of type 2 diabetes mellitus (T2DM) has reached epidemic proportions and is estimated to afflict over 400 million people worldwide [1, 2]. Therefore, many individuals with frailty get exposed to COVID-19. Some reports argued that frail individuals may develop more severe COVID-19 [3, 4]. However, data is inconsistent as it has also been suggested that there may be a sort of resilience by which certain frail subjects remain asymptomatic [5].

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Moreover, the incidence of diabetes is expected to continue to rise [6]. These projections suggest that there is an urgent need for the development and implementation of novel preventative and treatment strategies to combat the rise in T2DM prevalence. T2DM manifests through the development of fasting and postprandial hyperglycemia, which is the primary contributor to the induction of numerous life-threatening complications and co-morbidities [7]. There is good evidence that a combination of healthful behavioral habits and pharmacotherapy can generally help to slow the evolution of T2DM. Guidelines are aligned in emphasizing the importance of personalizing therapy [8–11], in particular in older individuals, given their diverse comorbidities, functional capacities and social circumstances. Indeed, recent analyses using information from the databases of the United States Centers for Medicare and Medicaid Services, National Health and Nutrition Examination Survey and Veterans Health Administration suggest that older adults with T2DM may be over-treated and, accordingly, subjected to higher risks of hypoglycemia and its associated morbidities [12, 13]. Severe treatment can be avoided by calculating pre-treatment fragility in elderly patients with T2DM.

Frailty was evaluated by the use of the Edmonton frail score, a validated field instrument which consists of 11 items including cognition, general health status, functional independence, social support, medication use, nutrition, mood, incontinence, and balance/motility [14]. Edmonton frail score is a scale that classifies elderly patients whether they are frail or not. It is ranged between 0 and 19 points and it grades subjects as not frail, vulnerable, mild frailty, moderate frailty or severe frailty [14].

In this study we aimed to observe clinical and laboratory indices (e.g., mean platelet volume and monocyte/lymphocyte ratio) of the diabetic subjects during COVID-19 pandemic who were frail or not according to Edmonton frail score. We also aimed to study whether Edmonton frail score was correlated with metabolic and hematologic parameters of the diabetic subjects.

Material and methods

Ethics, study design and participants

After approval from local ethics committee (approval number: 2020/247), 100 consecutive patients with type 2 diabetes mellitus who showed up to outpatient internal medicine clinics of our institution between May and August 2020 were enrolled in the present study. Exclusion criteria included recent infectious disease history, chronic inflammatory conditions such as rheumatoid arthritis, malignancy and women with pregnancy. Data of the patients, such as age, sex, height, weight, waist circumference, smoking and drinking history, systolic and diastolic blood pressures, duration of type 2 diabetes mellitus, comorbidities, medications used and diabetic complications (if present), were obtained from the institutional database and patients' files and recorded. Body mass index (BMI) was calculated by dividing body weight in kilograms by height in meters squared.

Laboratory analyses

Laboratory data, including, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), blood urea, serum creatinine, estimated glomerular filtration rate (eGFR), aspartate and alanine transaminases (AST and ALT, respectively), plasma sodium (Na) and potassium (K), serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride), C-reactive protein (CRP), plasma albumin, hemogram parameters, such as white blood cell count (WBC), neutrophil count (neu), lymphocyte count (lym), monocyte count (mono), hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), red cell distribution width (RDW), platelet count (PLT), platelet distribution width (PDW) and mean platelet volume (MPV), were also recorded. Neutrophil-lymphocyte-ratio (NLR), platelet-lymphocyte-ratio (PLR) and monocyte lymphocyte ratio (MLR) were calculated dividing neu, PLT and mono by lym, respectively.

Study population was divided into two groups, frail or non-frail, according to the Edmonton Frail Scale score. Patients were defined as not frail (0–5 points), vulnerable (6–7 points), mildly frail (8–9 points), moderately frail (10–11 points) or severely frail (12–17 points) by this scale. Patients with an Edmonton score of 7 or less were assigned to the not frail group (vulnerable and not frail patients according to the Edmonton frail score) while 8 or more were classified as frail (mildly, moderately and severely frail patients according to the Edmonton frail score). Data of frail and not frail diabetic subjects were compared.

Statistical Analysis

Statistical analyses were held with SPSS software (SPSS 15.0 for Windows, IBM, Chicago, IL, USA). Kolmogorov-Smirnov test was used to determine whether the study variables were conformed to the normal distribution among the groups. Continuous variables with normal distribution were presented as mean ± standard deviation and compared with independent samples t test, while variables without normal distribution were expressed as median (min.-max.) and compared with Mann Whitney U test. Categorical variables were compared with chi-square test and presented as numbers (n) and percentage (%). Pearson's

correlation analyses were performed to determine the correlation between study variables. Receiver operative characteristics (ROC) analysis was used for determination of sensitivity and specificity of the study variables in selecting frail subjects. $P < 0.05$ was considered to be statistically significant.

Results

A total of 100 consecutive patients with type 2 diabetes mellitus were enrolled in the study. Of those, 40 (40%) were in frail group and 60 (60%) were in non-frail group. There were 20 (50%) men and 20 (50%) women in frail group while 37 (62%) men and 23 (38%) women in non-frail group ($p = 0.25$). Mean ages of the frail and non-frail groups were 73 ± 8 years and 66 ± 8 years, respectively ($p < 0.001$). Weight ($p = 0.54$), height ($p = 0.13$), waist circumference ($p = 0.13$), BMI ($p = 0.54$), duration of type 2 diabetes mellitus ($p = 0.37$), SBP ($p = 0.08$), DBP ($p = 0.07$), the rates of good diabetic control ($p = 0.84$), smoking ($p = 0.34$), alcohol drinking ($p = 0.62$), comorbidities ($p = 0.30$), diet compliance ($p = 0.08$), diabetic retinopathy ($p = 0.22$), diabetic neuropathy ($p = 0.25$), diabetic nephropathy ($p = 0.64$), cerebrovascular diseases ($p = 0.17$), coronary heart disease ($p = 0.29$) and peripheral arterial disease ($p = 0.55$) were not significantly different among frail and non-frail groups. However, the rate of the compliance with exercise treatment was higher in non-frail group compared to frail diabetics ($p = 0.02$). Table 1 shows the general characteristics and clinical data of the frail and non-frail groups.

There were no significant difference between frail and non-frail groups according to the WBC ($p = 0.60$), neu ($p = 0.85$), lym ($p = 0.21$), mono ($p = 0.37$), Hb ($p = 0.10$), Htc ($p = 0.47$), MCV ($p = 0.08$), RDW ($p = 0.50$), PLT ($p = 0.15$), PDW ($p = 0.85$), NLR ($p = 0.48$), PLR ($p = 0.55$), FPG ($p = 0.99$), AST ($p = 0.62$), ALT ($p = 0.27$), Na ($p = 0.20$) K ($p = 0.53$), LDL cholesterol ($p = 0.18$), HDL cholesterol ($p = 0.10$) and CRP ($p = 0.31$), NLR ($p = 0.48$), PLR ($p = 0.55$) levels.

Blood urea ($p = 0.01$), serum creatinine ($p = 0.047$), eGFR ($p < 0.001$), plasma albumin ($p = 0.045$), total cholesterol ($p = 0.01$), triglyceride ($p < 0.001$), and expectedly, the Edmonton frail score ($p < 0.001$) levels of the frail and non-frail groups were significantly different. Table 2 shows the laboratory parameters of the frail and non-frail groups.

Mean HbA1c levels of the frail and non-frail groups were 9.9 ± 2.6% and 7.9 ± 1%, respectively ($p < 0.001$). Mean MPV levels of the frail and non-frail groups were 10.9 ± 1.1 fL and 10.3 ± 1.3fL, respectively ($p = 0.02$). Median MLR levels of the frail and non-frail groups were 0.40 (0.13–1.63)% and 0.28 (0.08–0.92)%, respectively ($p = 0.04$).

Edmonton frail score was significantly and positively correlated with blood urea ($r = 0.40$, $p < 0.001$), serum creatinine ($r = 0.22$, $p = 0.03$), MLR ($r = 0.39$, $p < 0.001$), MPV ($r = 0.250$, $p = 0.01$) and HbA1c ($r = 0.40$, $p < 0.001$) levels. On the other hand, Edmonton frail score was significantly and negatively correlated with eGFR ($r = –0.41$, $p < 0.001$) and plasma albumin ($r = –0.27$, $p = 0.01$) levels.

In ROC analysis, a HbA1c value greater than 9.1% had 70% sensitivity and 90% specificity in selecting frail diabetic subjects (AUC: 0.76, $p < 0.001$, 95% CI: 0.64–0.87). The sensitivity and specificity of MPV greater than 10.5 FL in selecting frail diabetic subjects were 70% and 57%, respectively (AUC: 0.63, $p = 0.03$, 95% CI: 0.52–0.74). The sensitivity and specificity of blood urea greater than 38 mg/dL in selecting frail diabetic subjects were 65% and 62%, respectively (AUC: 0.65, $p = 0.01$, 95% CI: 0.54–0.77). The sensitivity and specificity of MPV greater than 0.89 mg/dL in selecting frail diabetic subjects were 63% and 52%, respectively (AUC: 0.62, $p = 0.047$, 95% CI: 0.50–0.73). The sensitivity and specificity of MPV greater than 0.32% in selecting frail diabetic subjects were 58% and 62%, respectively (AUC: 0.62, $p = 0.037$, 95% CI: 0.50–0.74). Figure 1 shows the ROC curves of the study parameters.

Discussion

The main findings of the present study are: (I) HbA1c, MPV, MLR, blood urea and serum creatinine values of the frail subjects were significantly higher than those of the non-frail diabetics while total cholesterol, triglyceride, eGFR and plasma albumin values of the frail subjects were significantly lower than those of the non-frail diabetic patients; (II) Edmonton frail scores of the participants were positively correlated with blood urea, serum creatinine, MPV, MLR and HbA1c levels, and inversely correlated with eGFR and plasma albumin levels; (III) HbA1c level greater than 9.1% has the greater sensitivity and specificity than any other study variables in selecting frail diabetic patients.

We studied Edmonton frail score in patients with type 2 DM before COVID-19 and enrolled 101 consecutive subjects in the study who presented to outpatient internal medicine clinics of our institution and found that 41 (40.5%) of the 101 subjects were frail [15]. In the present study, 40% of the study population was frail. We shall speculate that COVID-19 had no significant impact on the frailty rate of type 2 diabetic subjects treated in our institution.

The HbA1c is the most commonly used predictor of diabetic control level. Elevated levels of HbA1c have

Table 1. General Characteristics of the Frail and Non-Frail Subjects

	Frail group	Non-Frail Group	P
Gender			
Men (n, %)	20 (50%)	37 (62%)	0.25
Women (n, %)	20 (50%)	23 (38%)	
Diabetic regulation			
Well (n, %)	8 (20%)	11 (18.3%)	0.84
Poor (n, %)	32 (80%)	49 (81.7%)	
Smoking			
Present (n, %)	11 (27.5%)	22 (37%)	0.34
Absent (n, %)	29 (72.5%)	38 (63%)	
Alcohol			
Present (n, %)	4 (10%)	8 (13%)	0.62
Absent (n, %)	36 (90%)	52 (87%)	
Comorbidity			
Present (n, %)	24 (60%)	42 (70%)	0.30
Absent (n, %)	16 (40%)	18 (30%)	
Compliance with diet			
Present (n, %)	8 (20%)	22 (37%)	0.08
Absent (n, %)	32 (80%)	38 (63%)	
Compliance with exercise			
Present (n, %)	5 (12.5%)	20 (33%)	**0.02**
Absent (n, %)	35 (87.5%)	40 (67%)	
Diabetic retinopathy			
Present (n, %)	16 (40%)	17 (28%)	0.22
Absent (n, %)	24 (60%)	43 (72%)	
Diabetic neuropathy			
Present (n, %)	26 (65%)	32 (53%)	0.25
Absent (n, %)	14 (35%)	28 (47%)	
Diabetic nephropathy			
Present (n, %)	9 (22.5%)	16 (27%)	0.64
Absent (n, %)	31 (77.5%)	44 (73%)	
Cerebrovascular diseases			
Present (n, %)	4 (10%)	2 (3%)	0.17
Absent (n, %)	36 (90%)	58 (97%)	
Coronary heart disease			
Present (n, %)	25 (62.5%)	31 (52%)	0.29
Absent (n, %)	15 (37.5%)	29 (48%)	
Peripheral arterial disease			
Present (n, %)	4 (10%)	4 (7%)	0.55
Absent (n, %)	36 (90%)	56 (93%)	
	Mean ± SD		
Age (years)	73 ± 8	66 ± 8	**< 0.001**
	Median (min–max)		
Height [m]	1.64 (1.48–1.80)	1.70 (1.45–1.82)	0.13
Weight [kg]	80 (58–115)	83 (57–125)	0.54
Waist circumference [cm]	102 (72–131)	105 (88–149)	0.13
BMI [kg/m^2]	30.7 (20.5–43.4)	29.4 (22.5–55.6)	0.54
SBP [mmHg]	130 (100–170)	130 (100–180)	0.08
DBP [mmHg]	73 (50–100)	80 (70–100)	0.07

BMI — body mass index; DBP — diastolic blood pressure; SBP — systolic blood pressure

Table 2. Laboratory Data of the Frail and Non-Frail Groups

	Frail group	Non-frail group	P
	Mean ± SD		
HbA1c (%)	9.9 ± 2.6	7.9 ± 1	**< 0.001**
Hb [g/dL]	12.2 ± 2	12.9 ± 2.1	0.10
PLT [k/mm^3]	235 ± 38	268 ± 86	0.15
MPV [fL]	10.9 ± 1.1	10.3 ± 1.3	**0.02**
LDL cholesterol [mg/dL]	96 ± 41	107 ± 33	0.18
	Median (min–max)		
WBC [k/mm^3]	7.8 (1.8–26.4)	7.3 (1.1–13.8)	0.60
neu [k/mm^3]	4.5 (1–17.7)	4.5 (0.1–9.7)	0.85
lym [k/mm^3]	1.6 (0.4–7.6)	2.1 (0.1–4.1)	0.21
mono [k/mm^3]	0.62 (0.23–12.3)	0.59 (0.03–1.63)	0.37
Htc [%]	36.1 (22.1–49.4)	39.6 (26–51)	0.47
MCV [fL]	87 (73–110)	86 (66–98)	0.08
RDW [%]	13.5 (11.9–22.5)	13.8 (11.7–22.5)	0.50
PDW [%]	12.6 (8.4–22.5)	12.4 (8.8–19.1)	0.85
NLR [%]	2.03 (0.55–36.8)	2.12 (0.1–7.02)	0.48
PLR [%]	118 (11–627)	127 (63–282)	0.55
MLR [%]	0.40 (0.13–1.63)	0.28 (0.08–0.92)	**0.04**
FPG [mg/dL]	153 (50–800)	166 (65–518)	0.99
AST [U/L]	17 (9–112)	17 (9–84)	0.62
ALT [U/L]	15 (7–62)	21 (6–95)	0.27
Na [meq/L]	138 (126–147)	139 (129–144)	0.20
K [meq/L]	4.4 (3.1–6.1)	4.5 (3.2–6)	0.53
Total cholesterol [mg/dL]	168 (83–284)	190 (94–308)	**0.01**
HDL cholesterol [mg/dL]	50 (25–86)	46 (24–114)	0.10
Triglyceride [mg/dL]	125 (39–302)	189 (66–540)	**< 0.001**
Blood urea [mg/dL]	46 (13–334)	34 (15–92)	**0.01**
Serum creatinine [mg/dL]	1.03 (0.4–6.2)	0.88 (0.6–5.5)	**0.047**
eGFR [%]	61 (8.2–100)	78 (9.6–102)	**< 0.001**
Plasma albumin [g/dL]	3.7 (2.3–4.8)	4.1 (2.4–5.7)	**0.045**
CRP [U/L]	11.4 (0.3–140)	11.9 (0.1–146)	0.31
Edmonton Frail Score	8 (6–14)	4 (1–5)	**< 0.001**

ALT — alanine transaminase; AST — aspartate transaminase; CRP — C-reactive protein; eGFR — estimated glomerular filtration rate; FPG — fasting plasma glucose; Hb — hemoglobin; HbA1c — glycated hemoglobin; HDL — high-density lipoprotein; Htc — hematocrit; K — potassium; LDL — low-density lipoprotein; lym — lymphocyte; MCV — mean corpuscular volume; MLR — monocyte lymphocyte ratio; mono — monocyte; MPV — mean platelet volume; Na — sodium; neu — neutrophil; NLR — neutrophil-lymphocyte-ratio; PDW — platelet distribution width; PLR — platelet-lymphocyte-ratio; PLT — platelet; RDW — red cell distribution width; WBC — white blood cell count,

been reported in frail diabetic subjects compared to the non-frail diabetics [15–18]. Moreover, HbA1c was considered as an independent risk factor for frailty in diabetic subjects [19]. In accordance with literature knowledge, HbA1c levels of the frail subjects were higher than the non-frail subjects in the present study.

Mean platelet volume has been studied in recent reports. It has been linked to inflammatory and metabolic conditions, and elevated MPV levels have been notified in various diseases. For instance, increased MPV levels have been noted in patients with type 2 diabetes mellitus and obesity [20, 21]. Moreover, MPV has been associated with ulcerative colitis [22], rheumatoid arthritis [23], irritable bowel syndrome [24], and nasal polyposis [25], which are all associated with some degree of inflammatory burden. In addition, proportion of MPV and lymphocyte count has been reported to be related with frailty in elderly population [26]. A possible mechanism of increased MPV in frail subjects could be increased platelet activity [27]. Since MPV is a surrogate marker of platelet activation [28], elevated MPV should be an expected laboratory finding in frail

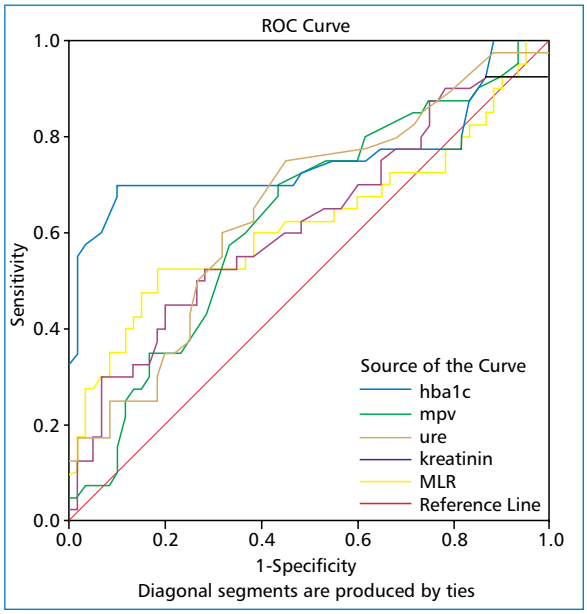

Figure 1. ROC Curves of the HbA1c, MPV, Blood Urea, Serum Creatinine, and MLR in Selected Frail Diabetic Subjects. MLR — monocyte lymphocyte ratio; MPV — mean platelet volume; ROC — receiver operative characteristics

diabetic patients. Elevated MPV in frail diabetic subjects compared to the non-frail diabetics is consistent with the literature data.

Recent articles in medical literature pointed out the association between MLR and several clinical conditions. These include non-alcoholic fatty liver disease [29], gastrointestinal stromal tumor [30], preeclampsia [31], type 2 diabetes mellitus [32], irritable bowel disease [33], osteoporosis [34], diabetic kidney injury [35], and hyperglycemia during pregnancy [36]. All of these conditions are associated with various amount of inflammation. Frailty is also associated with increased blood levels of inflammatory molecules [37, 38]. Hence, elevated MLR level in frail subjects in the present study is in accordance with the knowledge in literature.

Increased blood urea and serum creatinine, and consequently, decreased eGFR levels might contribute to the frailty in elderly population. Our findings suggest this hypothesis. However, there are conflicting results in literature. Authors reported similar creatinine and GFR levels in frail and robust subjects with Alzheimer's disease [39]. Moreover, Hammami et al. reported that serum creatinine levels of the non-frail, frail and severely frail subjects were not significantly different [40]. Study population was limited to the diabetic subjects in the present study and type 2 DM is one of the leading causes of the chronic kidney disease. Therefore, serum creatinine, blood urea and thus EGFR levels were significantly different between frail and non-frail subjects in the present study.

Increased frailty risk is associated with decreased total cholesterol levels [41]. Similarly, decreased triglyceride levels could be related with decreased metabolic capacity in frail subjects. In contrast, authors reported increased triglyceride levels in frail individuals [42]. Nevertheless, we believe that decreased triglyceride in frail subjects may reflect the exhaustion of the metabolic resources. Similarly, albumin is a marker of general well-being. Serum albumin levels have been suggested to be correlated with muscle mass [43]. Since sarcopenia is a significant contributor of frailty, decreased level of albumin in frail subjects in the present study is not an unexpected finding.

Limitations

Limitations of this study are relatively small study population and defining frailty by only one scale. However, the results of the present study which pointed out the frailty score's correlation with HbA1c, MLR and MPV may contribute to the literature significantly.

Conclusions

We think that HbA1c, MPV and MLR could be surrogate markers of frailty in diabetic elderly. Strategies to keep them in normal range do not only improve diabetic control but also reduce the risk of frailty in this population.

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Conflict of interest

None declared.

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