Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2023;48(2):336-343
DOI: 10.17826/cumj.1222031

RESEARCH

Comparison of eGFR formulas (CKD-EPI and MDRD) in patients with multiple myeloma

Multipl miyelom hastalarında eGFR formüllerinin (CKD-EPI ve MDRD) karşılaştırılması

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Abstract

Purpose: Modification of Diet in Renal Disease' (MDRD) and 'Chronic Kidney Disease Epidemiology Collaboration' (CKD-EPI) formulas are generally accepted and widely utilized tools to assess renal function. In this study, we aimed to investigate the power of the MDRD and CKD-EPI formulas, which are the two most used formulas in the measurement of eGFR in patients with multiple myeloma (MM).

Materials and Methods: A total of 40 patients, newly diagnosis with MM, were consecutively enrolled to the study and their records were analyzed in terms of demographic features and laboratory parameters of the patients, type of paraproteinemia and stage of disease. MDRD and CKD-EPI formulas were used to evaluate renal function.

Results: The difference found between basal and third-month estimated Glomerular Filtration Rate (eGFR) using MDRD (61±15.4 mL/min/1.73 m², third month 75±18.2 mL/min/1.73 m²) and CKD-EPI formulas (62±15.7 mL/min/1.73 m², third month 76±18.4 mL/min/1.73 m²) were significant. There was no significant difference between two formulas regarding basal and third month eGFR mean values. According to CKD staging, 12.5% of all subjects changed and 80% of them moved to better stage.

Conclusion: CKD-EPI tends to produce higher eGFR values with compared to MDRD, especially when they are used to evaluate mildly impaired renal function. Hence, prevalence of renal disease was determined lower when assessed with CKD-EPI. Therefore, we recommend that it is important to use the same eGFR estimation formula for a consistent outcomes analysis.

Keywords:. multiple myeloma, renal function, renal failure, CKD-EPI, MDRD.

Öz

Amaç: Renal Hastalıkta Diyet Modifikasyonu (MDRD) ve Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formülleri renal fonksiyonları değerlendirmede genel kabul gören ve geniş kullanım alanı olan formüllerdir. Çalışmada, Multipl miyelomalı (MM) hastalarda eGFR ölçümünde en sık kullanılan iki formül olan MDRD ve CKD-EPI formüllerinin gücünü araştırmayı amaçladık.

Gereç ve Yöntem: Toplam 40 yeni tanı alan MM hastaları çalışmaya alınıp dosyaları demografik özellikler, myelom tipleri, evreleri, laboratuvar verileri açısından retrospektif olarak incelendi. Renal fonksiyonları, MDRD ve CKD-EPI formülleri ile değerlendirildi.

Bulgular: Bazal ve 3.ay glomerül filtrasyon hızı değerleri arasında MDRD (61±15.4 mL/dk/1.73 m², 3. ay 75±18.2 mL/min/1.73 m²) ve CKD-EPI(62±15.7 mL/dk/1.73 m², 3 ay 76±18.4 mL/min/1.73 m²) formülleriyle anlamlı fark saptandı. MDRD ve CKD-EPI formülleri arasında bazal ve 3.ay GFH ortalamaları bakımından ise anlamlı fark saptanmadı. KBH evrelemesine göre, tüm katılımcıların %12.5'i evre değiştirirken, bunların %80'inin daha iyi bir evreye geçiş yaptığı saptandı.

Sonuç: Böbrek fonksiyon bozukluğu hafif olan hastalarda MDRD ve CKD-EPI formülleri karşılaştırıldığında, CKD-EPI eGFR değerlerini daha yüksek hesaplama eğilimindedir. Böylece CKD-EPI formülü kullanıldığında böbrek hastalığı prevalansı daha düşük saptanmaktadır. Bu sebeple, hasta takibinde tutarlı bir sonuç analizi için aynı GFR tahmin formülünü kullanmanın önemli olduğunu öneriyoruz.

Anahtar kelimeler: multipl myelom, renal fonksiyon, böbrek yetmezliği, CKD-EPI, MDRD.

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Received: 20.12.2022 Accepted: 02.04.2023

INTRODUCTION

Multiple myeloma (MM) is a monoclonal plasma cell neoplasia that makes up to 1% of all malign tumors and one-tenth of all hematological malignancies[1]. MM is characterized by any of end-organ injury findings such as bone pain, anemia, hyperviscosity, recurrent bacterial infections, renal failure (RF), amyloidosis or hypercalcemia with the presence of monoclonal plasma cells in the bone marrow or identification of monoclonal proteins (MP) in serum or urine[2-3].

Renal failure is a common complication of MM and is among the essential causes of mortality and morbidity. While it is seen in approximately 30% of patients at diagnosis this rate can be as high as 50% during the disease course[4-5]. Although it is generally moderate, approximately 10% of patients require renal replacement therapy[6]. RF is an essential risk factor shortening the life expectancy of patients with MM. In addition, it is very important to detect it as early as possible because it independently increases mortality[7].

The occurrence of RF in MM is related to various factors such as age, the severity of the illness and the structural properties of the monoclonal component. Its etiology is multifactorial and although it is not known exactly, immunoglobulin light chains are postulated to have an important role. However, most patients can synthesize large amounts of light chains and secrete these compounds without renal impairment. Light chain storage disease, amyloidosis, light chain glomerulopathy and Fanconi syndrome are other types of kidney disease. Dehydration, hyperuricemia, use of contrast agents and nephrotoxic drugs are other effective factors in the development of RF and their role in the pathogenesis is to increase the nephrotoxic effects of light chains[8-9].

The formula known as Modification of Diet in Renal Disease (MDRD) was the first and most common formula using a known calibration method. The equation named by the 'Chronic Kidney Disease Epidemiology Collaboration' (CKD-EPI) was launched in 2009 to eliminate the bias caused by the MDRD approach, especially in those with a estimated glomerular filtration rate (eGFR) above 60 mL / min / 1.73 m^2 [10].

Comparative studies were conducted regarding the utilization of MDRD with CKD-EPI formulas in RF staging in different clinical situations. Schwandt et al. compared the performance of these two equations and concluded that MDRD formula had a higher accuracy for diabetic patients than CKD-EPI formula[11]. Furthermore, accurately assessing kidney function is critical for the safe administration of medicines which have renal elimination. A study conducted by Palacio et al. indicated that CKD-EPI equation has a better correlation with ganciclovir clearance than the MDRD equation[12]. Another prospective cohort analysis discovered that CKD-EPI and MDRD formulas had similar CKD staging with small changes in lenalidomide dose adjustment. In another study which designed as prospective cohort found that with CKD-EPI and MDRD formulas had similar CKD staging with minor differences in lenalidomide dosage administration and recommended utilizing the CKD-EPI equation to standardize eGFR calculation in myeloma patients[13].

The most accurate assessment of the eGFR value and the stage of renal failure in patients with MM is crucial for the management of the selected treatment as well as for the staging and prognosis of the disease. With this scope, we aimed to investigate the power of the MDRD and CKD-EPI formulas, which are the two most used formulas in the measurement of eGFR in patients with MM.

MATERIALS AND METHODS

Participants

A total of 40 patients who were admitted to the Department of Hematology at Istanbul University Istanbul Faculty of Medicine were retrospectively enrolled in this study. A priori power analysis was performed for determination of the sample size and calculated as 40 by taking impact size 0.8, $\alpha = 0.05$, and statistical power of 0.90. The basal and 3rd-month renal functions of patients with MM were evaluated to compare the most common eGFR formulas such as MDRD and CKD-EPI. Only adult patients have been enrolled in the present study, patients with MM who were identified with other plasma cell diseases such as Monoclonal gammopathy of undetermined significance, Waldenstrom Macroglobulinemia and admitted into the department after diagnosis and treatment in another institution and whose examinations were not

fully obtained were excluded from the study. Determination of participants was summarized in Figure 1. In addition to, demographic characteristics of the patients, stages of their disease, MM types, presence of lytic lesions and/or plasmacytoma were investigated. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and we received. Ethical approval of the present study was received from The Clinical Research Ethics Committee of Istanbul University Istanbul Faculty of Medicine [Approval no: 1448/17]. The data acquired during this investigation were kept secret in terms of the dependability of the records, as well as the confidentiality and privacy of the patients participated in the study, and were never disclosed.

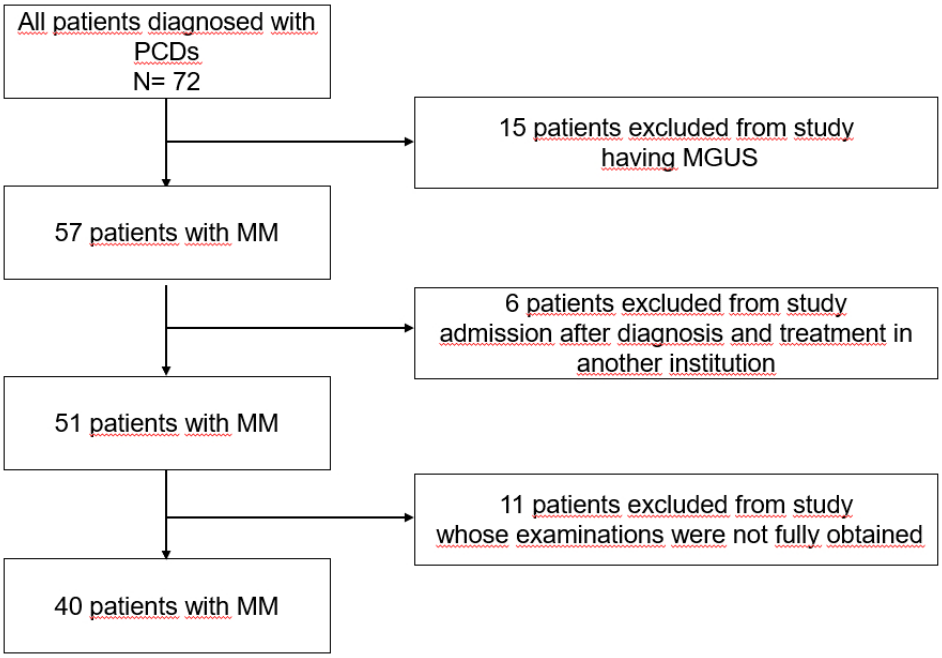

Figure 1. Determination of participants.

Assessment of renal function

The beta (β)-2 microglobulin, creatinine, albumin, calcium (Ca) and hemoglobin (Hb) levels of all patients were recorded. The eGFR values of patients were calculated with both MDRD and CKD-EPI following formulas:

MDRD: eGFR in mL/min per 1.73 m^2 = 175 x $SCr^{-1.154}$ x $age^{-0.203}$ x 1.212 (if black) x 0.742 (if female)[14].

CKD-EPI: eGFR in mL/min per 1.73 m^2= 141 x min $(Scr/\varkappa, 1)^{\alpha}$ x max $(Scr/\varkappa, 1)^{-1.209}$ x 0.993^{Age} x 1.018 (if female) x 1.159 (if black)[15].

Scr is standardized creatinine. $\varkappa$ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/$\varkappa$or 1, and max indicates the maximum of Scr/$\varkappa$ or 1.

All subjects were categorized according to stage of CKD. Patients were assigned to 5 categories in line with measured eGFR values; eGFR ≥120 ml/min/1.73 m^2 Stage 1, 90-120 ml/min/1.73 m^2 Stage 2, 60-89 ml/min/1.73 m^2 Stage 3, between 30-59 ml/min/1.73 m^2 as Stage 4 and those with <30 ml/min/1.73 m^2 in Stage 5[16].

Statistical analysis

SPSS Version 17.0 program was utilized for data analysis. The Kolmogorov-Smirnov test was used to analysis normality of variables. The parametric variables were indicated as mean ± standard deviation (SD) and categorical variables as percentages (%). The relationship between parametric continuous variables was analyzed with the paired t-test. Additionally categorical variables were compared via The Pearson Chi-square and the Fisher's Exact tests. P values below 0.05 were deemed significant in all analyzes.

RESULTS

The demographic features of all participants were indicated in Table 1. Female patients comprised most of the patients recruited in the study (n=22, 55%). Mean age was found as 58 ±13 years. Also, the clinical characteristics including presence of Diabetes Mellitus and Hypertension, types of MM, Durie-Salmon (DS), and International Staging System (ISS) were summarized in Table1.

Table 2 summarizes the results of all subjects' biochemical parameters at the baseline and third mount follow-up. As expected, it was achieved recovery of renal impairment of renal function including creatinin, eGFR values, hemoglobin, and β-2 microglobulin levels.

Measurements of creatinine value of 1.3 mg/dl and above was accepted as the threshold of kidney damage (KD). There were no significant differences in terms of gender and age between KD and non-KD groups (p=0.457). Additionally, the characteristics of β-2 microglobulin, calcium, Hb, MM type, ISS and DS stages in patients with and without kidney damage are shown in Table 3. There was no significant statistical difference between MDRD and CKD-EPI formulas in terms of basal and 3rd month eGFR means (p=0.607 and 0.089, respectively).

Table 1. The overview of patients with MM's clinical and demographic features.

Variable	
Gender	
Female %	22 (55%)
Male %	18 (45%)
Age, year	58 ±13
Diabetes Mellitus %	14 (35%)
Hypertension %	14 (35%)
MM types	
IgG kappa	9 (22.5%)
Ig G lambda	9 (22.5%)
Ig A kappa	7 (17.5%)
kappa light chain	7 (17.5%)
lambda light chain	4 (10 %)
Ig A lambda	2 (5 %)
Ig M kappa	2 (5 %)
lytic lesions/ plasmacytoma %	23 (57%)
Durie-Salmon	
I A	6 (15%)
I B	2 (5%)
II A	7 (17.5 %)
II B	1 (2.5 %)
III A	15 (37.5%)
III B	9 (22%)
International Staging System	
I	10 (25 %)
II	10 (25 %)
III	20 (50 %)

MM: Multiple Myeloma, Ig: Immunoglobulin,

Table 2. Biochemical laboratory parameters of patients at basal and 3th mount follow up.

	Basal assessment	3th mount follow up	*p* value
Creatinine mg/dL	1.7± 0.2	1.2±0.3	<0.001
eGFR with MDRD ml/min/1.73 m²	61±15.4	75±18.2	0.004
eGFR with CKD-EPI ml/min/1.73 m²	62±15.7	76±18.4	0.003
Hemoglobin mg/dL	9.8± 2	12.3±4.1	0.023
Calcium mg/dL	10±1.3	10.5±0.8	0.869
β-2 microglobulin	9.9±1.5	5.1±1.3	0.012
Albumin mg/dL	3.5±0.7	3.7±0.5	0.752

eGFR: estimated Glomerular Filtration Rate, MDRD: Modification of Diet in Renal Disease, CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration

Table 3. The characteristics of β-2 microglobulin, calcium, Hb, MM type, ISS and DS stages in patients with and without kidney damage.

	Patients with KD n=18	**Patients with non-KD n=22**	***p* value**
Gender Female % Male %	 9 (50%) 9 (50%)	 12 (54.5 %) 10 (45.5 %)	0.457
Age, year	57±17	59±9	0.314
Creatinine mg/dL	3.99±1.71	0.9±0.2	**<0.001**
Hemoglobin g/dL	9.1±1.6	10.5±2	**0.032**
Calcium mg/dL	10.3±1.6	9.8±1	0.320
β-2 microglobulin	17.4±3.4	3.8±1.5	**0.002**
Monoclonal IgG type IgG IgA IgM	 3 (16.7) 4 (22.3) 2 (11.1)	 15 (68.2) 5 (23.7) 0 (0)	0.107
Light Chain types Kappa Lambda	 12 (66.7) 6 (33.4)	 13 (59.1) 9 (40.8)	0.695
International Staging System I II III	 0 (0) 2 (11.2) 16 (88.8)	 10 (45) 8 (37) 4 (18)	**<0.001**
Durie-Salmon I II III	 4 (22) 2 (12) 12 (66)	 4 (18) 8 (36) 10 (46)	0.495

Ig: Immunoglobulin, KD: Kidney damage

At the time of diagnosis, when we use MDRD formula, 2 patients (%5) were at Stage 1, 11 patients (27.5%) were at Stage 2, 8 (20%) were at Stage 3, 9 (22.5%) were at Stage 4 and 10 (25%) were at Stage 5. When we use CKD-EPI formula for eGFR staging; 1 patient (2.5%) was at Stage 1, 15 patients (37.5%) were at Stage 2, 6 (15%) were at Stage 3, 8 patients (20%) were at Stage 4 and 10 (25%) were at Stage 5.

It was noted that 5 patients (12.5%) whose eGFR values were calculated with the MDRD formula changed category when their eGFR value was recalculated with the CKD-EPI formula. It was found that 80% of the patients who changed category (4 patients) switched to a higher eGFR category, while one patient was assigned to a lower eGFR category. The category change was mostly seen in Stage 3 patients with eGFR in the range of 60-89 ml /min/1.73 m^2.

DISCUSSION

In the present study, the files of 40 consecutive adult patients diagnosed with MM were analyzed in a retrospective design. The mean age of the patient group with RF was 57 ± 17 years, and the male/female ratio was equal. When all patients were examined, mean age was 58 years, and the number of female patients was found to be higher than men (22 and 18, respectively). With these results, it was observed that the gender distribution was slightly different from some studies[17-18-19]. The frequency of RF in those with MM changes between 20-50% depending on the description of RF [4,5]. In this study, we accepted the KD limit of 1.3 mg / dl and above and percentage of KD in MM patents was 45%.

In our study, the relationship between MM type and RF was investigated. Consistent with previous studies, the frequency of kappa and lambda light chain types (33% -16.7%, respectively) is remarkable in the patient group with RF. There was no difference between Ig and light chain types in terms of RF development. However, the frequency of Ig D reported in patients with RF was not found in our study. It is known that approximately 2% of all MM patients are Ig D type and among the 40 patients participating in our study, there is no Ig D type MM patient[5].

In our study, the ISS stage based on β-2 microglobulin level, which is an indicator of tumor burden, was found to be higher in patients with RF. While 88.8% of patients with RF had ISS Stage 3 disease, this rate was 18% ($p < 0.001$) in patients without RF. However, when the DS staging system was used, stage 3 disease was detected in 55% of all patients, 66.7% of those with RF, and 45.5% of those without RF ($p=0.495$). This difference between the two staging systems was thought to be due to β-2 microglobulin. β-2 microglobulin is a molecule that reflects the tumor burden, determines the ISS stage, and is known to increase serum levels in RF, due to its metabolism with the kidneys. Therefore, the level of β-2 microglobulin was found to be higher in patients with KD than in those without KD in our study. Naturally, ISS stage 3 was found in the group with KD. The rate of patients is thought to be statistically significantly higher.

When patients with and without KD were compared with regard to Ca and Hb, it was observed that the Hb level was statistically significantly lower in the group with KD, similar with previous studies. In terms of Ca levels, the mean Ca in the group with KD was higher, but unlike other studies, no significant difference was found [20-21]. With these results, the fact that KD in MM does not originate from a single factor comes to mind and it is note that the effect of Ca as a factor was not detected in this study. When considered in the same context, based on the conclusion that the Hb level is associated with KD, it can be concluded that outcome factors interact with each other in MM, and one prognostic factor can influence another one through nested mechanisms.

Recent years witnessed studies on the comparison of MDRD and CKD-EPI equations take their place in the literature. In a study conducted by Willems et al. in 2013 in a healthy population, examining the differences between Cockcroft-Gault, MDRD and CKD-EPI equations in eGFR measurement, it was reported that in the sixth decade, the mean eGFR was calculated higher than the MDRD equation with the CKD-EPI formula (78 and 75±18.2 ml/ min/1.73 m^2, respectively), and lower after the age of 60, especially after the age of 70 (65, respectively. and 69 ml / min / 1.73 m^2)[22]. With regard to the classical epidemiological knowledge that the mean age of occurrence of MM is around 70, it can be thought that the CKD-EPI formula measures the eGFR value lower in the MM group. In this study, mean levels of eGFR was found higher than the MDRD formula with the CKD-EPI formula. It was thought that the result of this study might be related to the fact that the mean age of the patients was 58 years old and 19% of patients were over 70 years old.

In another study conducted by Moazzeni et al. in 2021 comparing the MDRD and CKD-EPI formulas in the diabetic population, the incidence of CKD was found to be lower with the CKD-EPI formula than the MDRD formula (95%CI, 4.3% and 5.5%, respectively)[23]. Zhou et al. have reported that compare several creatinine-based equations to estimate eGFR in patients with atrial fibrillation, the eGFR median value was found to be significantly higher when calculated with the CKD-EPI approach than the MDRD equation (67.61 and 66.44 ml/min/1.73 m2, respectively)[24]. Stevens A. et al. found that eGFR median value was higher than the MDRD formula with CKD-EPI (85 and 79 ml / min / 1.73m^2, respectively)[25]. As in our present study, when the participants were categorized with the MDRD formula according to their eGFR value and then recategorized with CKD-EPI, it was observed that a total of 20% of them changed the category and 17.5% was categorized in a better eGFR category. The study of Willems et al. was reported that the CKD-EPI formula measured eGFR lower in elderly patients[22]. Parallel with mentioned studies above, our results showed that the basal eGFR mean value was 61±15.4 ml/min/1.73 m^2 with the MDRD formula and 62±15.7 ml/min/1.73 m^2 with the CKD-EPI formula, and the 3rd month eGFR mean value was 75±18.2 ml/min/1 with the MDRD and 76±18.4 m^2 ml/min/1.73 m^2 with the CKD-EPI formula. Additionally, the patients were assigned to 5 categories in accord with eGFR values with the MDRD formula and then categorized with the CKD-EPI formula, it was observed that 12.5% of them changed the category. It was determined that 80% of those who changed the category moved to a better category. Those who changed the category were seen in Stage 3 patients with an eGFR range of 60-90 ml/min/1.73 m^2, as in the study of Stevens A. et al[25].

It can be postulated that calculating the eGFR values and determining the relevant CKD stages of the patients using different equations could affect both the risk assessments and outcomes of the patients and the choice of appropriate treatments and accordingly, drug dose modifications. Determination of renal function in patients with MM is important in terms of staging and determining prognosis, as well as regulation of chemotherapy to be chosen.

When eGFR values at the time of diagnosis were compared with those after treatment, a statistically significant improvement was observed in renal functions with both MDRD and CKD-EPI formulas. Initiation of MM treatment as soon as possible after diagnosis is of great importance in the recovery of renal functions. Considering that MM is a common hematological malignancy and approximately half of MM patients have at least 'kidney problem', it is of great importance to define the renal functions with which formula. Basal and 3rd month eGFR mean values were determined higher than the MDRD formula with the CKD-EPI formula. MDRD and CKD-EPI formulas were not significantly different in regard to basal and 3rd month eGFR mean. It was observed that when CKD-EPI formula was used instead of MDRD formula, especially in high eGFR values, eGFR value was measured higher and therefore the prevalence of the kidney disease stage was found to be low. The fact that the mean age of the patients was found to be lower than classical epidemiological data in our study and that the CKD-EPI formula was shown to measure eGFR lower than the MDRD formula in older ages in large-scale studies, especially after the age of 70, suggests that it would be more appropriate to use the MDRD formula in our patient population. However, it is clear that there is a need for larger-scale studies approaching the subject from this perspective.

This study has some limitations. The sample size of our study was limited due to the low prevalence of MM disease in our population. In addition, another limited part of our study could be lack of evaluation with gold standard of glomerular filtration by urinary inulin clearance to compare two common eGFR formulas.

In conclusion**,** CKD-EPI tends to produce higher eGFR values with compared to MDRD, especially when they are used to evaluate mildly impaired renal function. The classification of patients according to the stages of CKD was significantly different between MDRD and CKD-EPI formulas at baseline and the 3rd month of follow-up. The differences in estimated eGFR values at baseline and the 3rd month of follow-up of MM patients could pose a significant skewing effect when predicting the prognosis and treatment outcomes. Based on this fact, prevalence of renal disease can be underestimated when assessed with CKD-EPI. Therefore, we recommend that it is important to use the same eGFR estimation formula for a consistent outcomes analysis. Further research with a larger sample size will be required to corroborate our results.

Author Contributions: Concept/Design : OE, MN; Data acquisition: OE; Data analysis and interpretation: OE, MN; Drafting manuscript: OE; Critical revision of manuscript: SY, MN; Final approval and accountability: OE, SY, MN; Technical or material support: OE; Supervision: MN; Securing funding (if available): n/a.
Ethical Approval: Ethical approval was obtained for this study by the decision of the Clinical Research Ethics Committee of Istanbul University İstanbul Faculty of Medicine dated 04.09.2013 and numbered 1448/17.
Peer-review: Externally peer-reviewed.
Conflict of Interest: Authors declared no conflict of interest.
Financial Disclosure: The authors declared that they did not receive financial support

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