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The relationship between magnesium levels and mortality in the respiratory intensive care unit

Mustafa Özgür Cırık, MD[a], Mukaddes Kılınç, MD[a], Güler Eraslan Doğanay, MD[a], Meriç Ünver, MD[a], Murat Yıldız, MD[b], Sema Avcı, MD[c,*]

Abstract

Magnesium deficiency is defined as a pathophysiologic factor in numerous illnesses. This study aims to define the effects of magnesium levels on patients in the intensive care unit (ICU) regarding length of stay in the ICU, length of mechanical ventilation (MV), and 28-day mortality.

The following data were collected during initial assessment of patients admitted to the ICU with acute respiratory failure (ARF). Demographic data, magnesium and potassium levels, Charlson's Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, length of MV, length of hospital stay in the ICU, 28-day mortality, and ICU discharge status.

In the initial serum analysis prior to treatment of patients in the ICU, the mortality rate of the patient group with hypermagnesemia was found to be statistically significant when compared with other magnesium levels ($P = .018$). Apart from renal failure, ICU mortality is higher in the hypermagnesemia group than other groups.

Hypermagnesemia is an electrolyte abnormality that is generally seen in older individuals and those with serious comorbidity and it can be used in mortality prediction.

Abbreviations: ICU = intensive care unit, MV = mechanical ventilation, ARF = acute respiratory failure, CCI = Charlson's Comorbidity Index, APACHE II = Acute Physiology and Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, COPD = Chronic obstructive pulmonary disease.

Keywords: acute respiratory failure, hypermagnesemia, intensive care unit, magnesium level, mortality

Learning points

- Hypomagnesemia has been associated with ICU mortality in numerous studies.
- However, hypermagnesemia, an electrolyte abnormality generally seen in older patients and those with serious comorbidity, is also associated with mortality.
- Hypermagnesemia is a result of the cell lysis process and can be used as a parameter in predicting mortality.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Anesthesiology and Intensive Care, [b] Department of Chest Diseases, Health Sciences University Ankara Atatürk Chest Diseases and Chest Surgery Education and Research Hospital, Ankara, [c] Department of Emergency Medicine, Usak University Medical Faculty, Usak, Turkey.

[*] Correspondence: Dr. Sema Avcı, Department of Emergency Medicine, Usak University Medical Faculty, Usak, Turkey (e-mail: dnzlsema@gmail.com).

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1. Introduction

Magnesium is the fourth most common electrolyte in the human body and has a role as a cofactor in nucleic acid synthase, particularly in adenosine triphosphate as well as in enabling nerve conduction, insulin metabolism, protein synthesis, cardiac muscle contraction, bronchodilatation, the functioning of the autonomic nerve system, and more than 300 biochemical reactions in the body.[1,2] Magnesium deficiency has been found to cause an increase in systemic inflammatory response which is one of the agents in the pathophysiology of numerous illnesses.[1] Although magnesium levels play an important role in the process of illnesses it has not been routinely monitored in clinical practice. This lack of attention is defined as "the Forgotten Electrolyte" by some authors.[3,4]

Numerous research studies have been conducted on the negative impact of high hypomagnesemia incidence rates in patients treated in the ICU, such as increased mortality, need for prolonged mechanical ventilation (MV) and increased stay in the ICU. Even with these negative effects of hypomagnesemia, there is not sufficient evidence on the beneficial effects of magnesium replacement for patients with hypomagnesemia.[2,5]

This study aims to evaluate the effect of magnesium levels, measured initially on admission of patients to the ICU due to ARF, on the length of MV, length of stay in the ICU, and mortality. Moreover, since the majority of the participants were diagnosed with COPD (chronic obstructive pulmonary disease), the relationship between the existence of COPD and magnesium levels was also evaluated.

2. Methods

Ethical approval for this cross-sectional study was obtained (05.30.2019/630) from Health Sciences University Ankara

Atatürk Education and Research Hospital, and 351 patients, who were 18 years and older and admitted to the ICU in 2018 with a diagnosis of COPD, were evaluated. The magnesium and potassium values of 20 patients could not be obtained and 2 patients died within 24 hours after hospitalization. These patients were excluded from the study. Therefore, the data of 329 patients were analyzed (Flowchart, http://links.lww.com/MD/F323).

The data were obtained from the hospital registration system and consisted of information regarding age, gender, existence of COPD, length of hospital stay and time in the ICU, magnesium and potassium levels, Charlson's Comorbidity Index (CCI), Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score, length of MV, 28-day mortality, and ICU discharge status. Additionally, the patients were categorized in the following groups according to their serum magnesium levels: hypomagnesemia (below 1.8 mg/dl), normomagnesemia (1.8–2.6 mg/dl), and hypermagnesemia (over 2.6 mg/dl). Patients were additionally categorized according to the existence of COPD. The serum electrolyte analyses were carried out in the biochemistry laboratory of the hospital in which this study was conducted using the Beckman Coulter AU 5800 (Beckman Coulter, Inc. CA, US).

2.1. Statistical analysis

Data were analyzed using the SPSS 21.0 software package. Continuous variables were defined as mean ± standard deviation, and the categorical variables as number and percentage. The differences between categorical variables were analyzed with the Chi-Squared analysis. The distribution of the variables were measured with the Kolmogorov Smirnow test. The Mann–Whitney *U* and Kruskal–Wallis tests were used in the analysis of quantitative independent data. The prediction success of the mortality prediction scores were evaluated using the ROC analysis. In the analyses, $P < .05$ was accepted as statistically significant.

Table 1

Patient age, gender, existence of COPD, and magnesium levels.

	Mean ± sd	Percentage (%)
Age	70.27 ± 13.3	–
Gender (F/M)	126/203	38.3/61.7
COPD (+/−)	222/107	67.5/32.5
Magnesium level (mg/dL)		
Hypomagnesemia	85	25.8
Normomagnesemia	219	66.6
Hypermagnesemia	25	7.6

COPD = Chronic Obstructive Pulmonary Disease, F = female, M = male, age mean ± standard deviation, gender, existence of COPD, and magnesium levels were defined as number and percentage.

3. Results

Of the participants, 203 were male (61.7%) and 126 were female (38.3%) The mean age was found to be 70.27 ± 13.33 years. Since this study was conducted in a pulmonology hospital, the

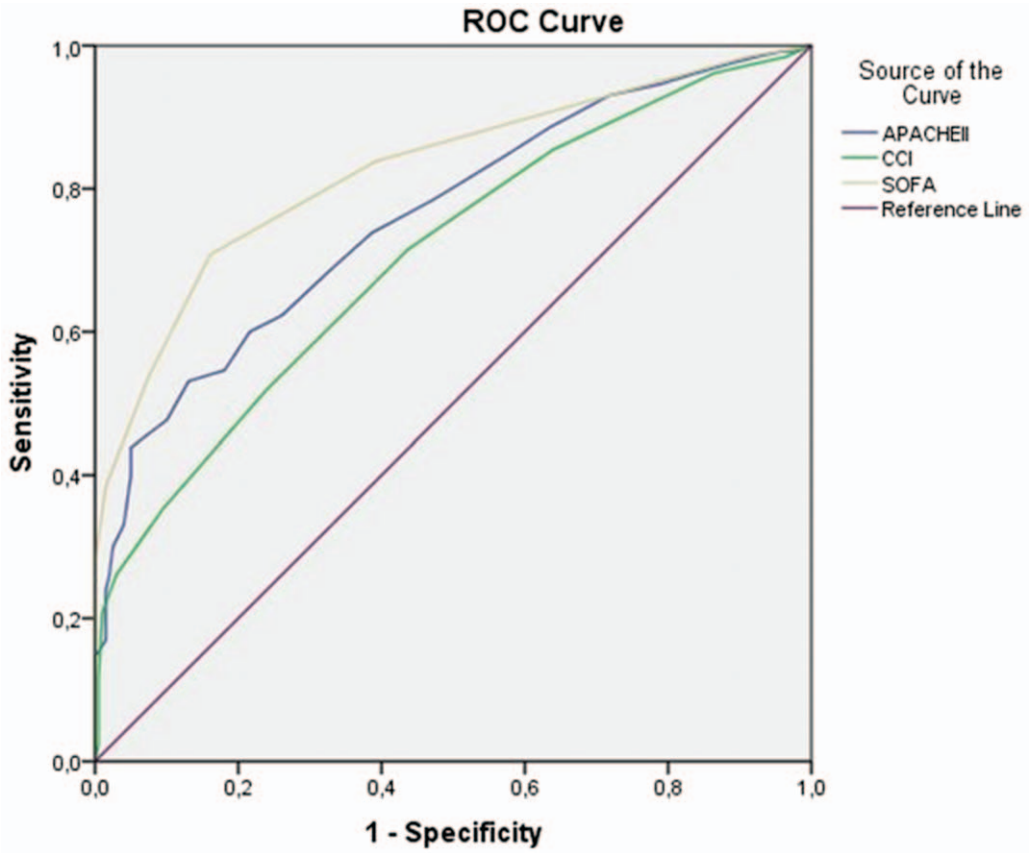

Figure 1. Cut-off values of mortality prediction scores (APACHE II, CCI, SOFA). APACHE AUC (0.761), CCI AUC (0.706), SOFA AUC (0.826).

Table 2

APACHE II and SOFA scores, CCI, length of hospital stay, length of stay in the ICU, length of MV follow-up, and magnesium and potassium levels.

	Mean ± sd
APACHE II	22.31 ± 7.1
SOFA	6.6 ± 2.3
CCI	5.98 ± 2.2
Length of hospital stay (days)	18.94 ± 15.7
Length of MV follow-up (n = 149)* (days)	6.98 ± 8.7
Length of stay in the ICU (days)	5.72 ± 6.6
Magnesium (mg/dl)	1.9 ± 0.48
Potassium (mEq/L)	4.3 ± 0.86

APACHE II = Chronic Health Evaluation II, CCI = Charlson's Comorbidity Index, ICU = Intensive Care Unit, MV = Mechanical Ventilation, SOFA = Sequential Organ Failure Assessment. Data were given as mean ± standard deviation.

* Patients with MV follow-up.

majority of the patients had a COPD diagnosis (n = 222, 67.5%). Table 1 shows patient information including age, gender, existence of COPD and magnesium levels. (Figure 1)

Table 2 shows patient groups APACHE II and SOFA scores, CCI, length of hospital stay, length of stay in the IC, length of MV, and serum magnesium and potassium values. Moreover, the efficiency of APACHE II and SOFA scores and CCI regarding the prediction of 28-days mortality were found to be statistically significant (Figure 2 and Table 3).

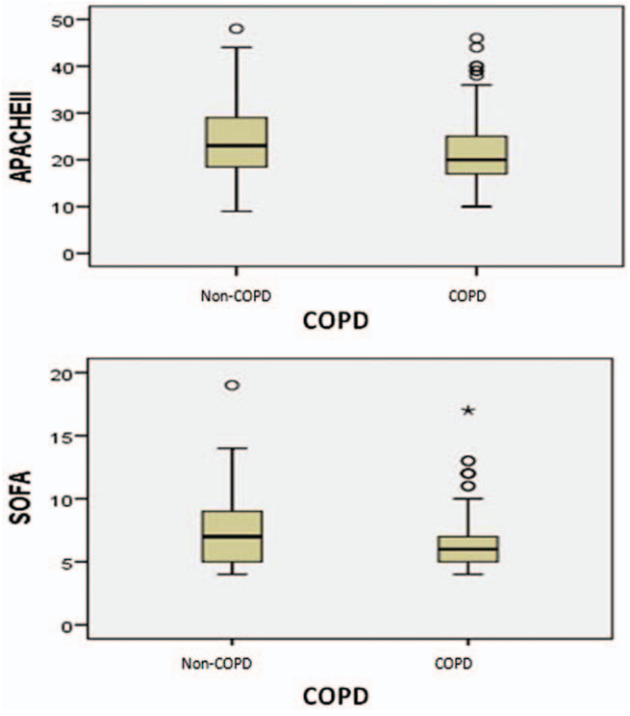

Figure 2. The APACHE II and SOFA scores were statistically significant in the group without COPD diagnosis when compared to the group with COPD (APACHE II $P = .001$; SOFA $P = .003$). The APACHE II and SOFA scores of the group without COPD were higher. The figure shows the median values and the interquartile range-IQR values of APACHE II and SOFA scores of patients with and without COPD.

Table 3

Mortality prediction scores (APACHE II, CCI, SOFA).

	AUC	Standard Deviation	*P* value	95% CI for AUC
APACHE II	0.761	0.027	$P < .01$	0.707–0.815
CCI	0.706	0.029	$P < .01$	0.648–0.764
SOFA	0.826	0.025	$P < .01$	0.778–0.874

APACHE II = Chronic Health Evaluation II, AUC = area under the curve, CCI = Charlson's Comorbidity Index, SOFA = Sequential Organ Failure Assessment.

Discharge rates from ICU to inpatient service were higher in the group with COPD than the other group, and were statistically significant ($P < .01$). The 28-day mortality was significantly higher in the group without COPD when compared to the group with COPD ($P < .01$).

The groups with and without COPD were evaluated based on potassium and magnesium levels, and no statistically significant relationship was found between these groups (Mg^{+2}, $P = .718$; K^{+}, $P = .147$). There was no statistically significant relationship between the group with and without COPD in terms of length of hospital stay, length of stay in the ICU, and length of MV (Table 4).

In the evaluation of 28-mortality according to the Mann–Whitney *U* test, there was no statistically significant difference between hypomagnesemia, normomagnesemia, and hypermagnesemia ($P = .198$).

The patients were categorized according to their magnesium levels as hypomagnesemia, normomagnesemia, and hypermagnesemia; no statistically significant difference was found between these groups in terms of COPD and 28-day mortality (Table 5). ICU mortality was found to be significantly higher in the hypermagnesemia group than the other groups ($P = .018$).

No statistical significance was found between magnesium levels and the length of hospital stay, length of stay in the ICU, length of MV, and potassium values (Table 6). In the comparison of APACHE II, SOFA, and CCI scores in terms of magnesium levels, SOFA and CCI scores were found to be significantly higher in the hypermagnesemia group (SOFA; CCI $P < .01$). All mean mortality prediction scores of the hypermagnesemia group (APACHE II, SOFA, CCI) were above the cut-off values according to the ROC curve analysis (Table 7).

Magnesium levels of the seven patients who received continuous renal replacement therapy (CRRT) were evaluated and it was found that six of those patients were normomagnesemic and only 1 of them was hypomagnesemic. None of the patients with hypermagnesemia needed CRRT.

In the comparison of the magnesium levels of the patients who received MV, it was found that the majority of those patients were normomagnesemic (n = 101, 67.3%); and no statistical significant relationship was found between the need for MV and magnesium levels ($P = .082$).

4. Discussion

This study, which evaluated the effect of magnesium levels of patients in the ICU due to ARF on 28-day mortality, length of hospital stay and stay in the ICU, and length of MV, showed that hypomagnesemia and normomagnesemia did not have an impact on these results. Additionally, patients diagnosed with hypermagnesemia had higher mortality rates during the ICU follow-up process than the other groups. In this study, which mostly

Table 4

The relationship between the existence of COPD and length of hospital stay, length of stay in the ICU, and length of MV.

	COPD (+)		COPD (-)		
	mean ± sd	median	mean ± sd	median	*P* value[m]
Age	70.62 ± 11.4	70	69.54 ± 16.5	73	.616
APACHE II	21.39 ± 6.60	20	24.21 ± 7.60	23	.001
SOFA	6.28 ± 1.94	6	7.30 ± 2.80	7	.003
CCI	5.73 ± 1.9	6	6.51 ± 2.6	6	.012
Length of hospital stay (days)	19.35 ± 15.9	15	18.07 ± 15.3	14	.271
Length of stay in the ICU (days)	5.58 ± 6.50	3	6.02 ± 6.82	4	.706
Length of MV follow-up* (n = 149) (days)	7.57 ± 9.5 (n = 84)	3	6.22 ± 7.48 (n = 65)	3	.291
Magnesium (mg/dL)	1.9 ± 0.49	1.9	2.01 ± 0.47	1.9	.718
Potassium (mEq/L)	4.40 ± 0.80	4.4	4.20 ± 0.90	4.3	.147

APACHE II = Chronic Health Evaluation II, COPD = Chronic Obstructive Pulmonary Disease, ICU = Intensive Care Unit, MV = Mechanical Ventilation, SOFA = Sequential Organ Failure Assessment.
* Patients with MV follow.

Table 5

The relationship of magnesium levels with COPD, 28-day mortality, and discharge from ICU.

	Hypomagnesemia		Normomagnesemia		Hypermagnesemia		
	n	%	n	%	n	%	*P* (x^2)
COPD (+/−)	59/26	69.4/30.6	149/70	68/32	14/11	56/44	.432
28-day mortality (Yes/No)	25/60	29.4/70.6	89/130	40.6/59.4	16/9	64/36	.07
Discharge (Transfer to inpatient service / ICU death	63/22	74.1/25.9	163/56	74.4/25.6	12/13	48/52	.018

COPD = Chronic Obstructive Pulmonary Disease, ICU = Intensive Care Unit. x^2 = Chi-Squared test.

Table 6

Relationship of hypomagnesemia, normomagnesemia, and hypermagnesemia with APACHE II, SOFA scores, CCI, length of hospital stay, length of stay in the ICU, length of MV, and potassium values.

	Hypomagnesemia		Normomagnesemia		Hypermagnesemia			
	Number	Mean Rank	Number	Mean Rank	Number	Mean Rank	x^{2*}	P^{**}
Age (Years)	85	145.42	219	174.17	25	151.28	6.1	.46
APACHE II	85	154.65	219	164.13	25	207.76	6.0	.48
SOFA	85	155.22	219	160.84	25	234.68	15.6	.000
CCI	85	149.55	219	164.39	25	222.84	11.7	.003
Length of MV follow-up (days) (n = 149)	33	68.7	100	77.48	16	72.53	1,113	.573
Length of stay in the ICU (days)	85	162.62	219	167.53	25	150.90	0.7	.679
Length of hospital stay (days)	85	153.25	219	169.76	25	163.24	1.8	.395
Potassium (mEq/L)	85	152.05	219	168.59	25	150.90	2.3	.312

APACHE II = Chronic Health Evaluation II, CCI = Charlson's Comorbidity Index, ICU = Intensive Care Unit, MV = Mechanical Ventilation, SOFA = Sequential Organ Failure Assessment.
* Chi-Squared.
** Kruskal–Wallis-H test.

included COPD patients, the analysis of the COPD subgroup showed there was no difference in terms of 28-day mortality, length of stay in the ICU, and length of MV in this subgroup. Moreover, APACHE II and SOFA scores and CCI were found to be effective in predicting mortality.

There are numerous studies showing that lower magnesium levels in serum can be associated with chronic inflammatory stress and have an impact on mortality.[6–9] However, there are also studies that show that hypermagnesemia is associated with mortality but lower magnesium levels are not.[5,10]

Table 7

Mean mortality prediction scores according to magnesium levels.

	Hypomagnesemia	Normomagnesemia	Hypermagnesemia
APACHE II	21.42	22.16	26.64
SOFA	6.32	6.49	8.64
CCI	5.58	5.94	7.72

APACHE II = Chronic Health Evaluation II, CCI = Charlson's Comorbidity Index, SOFA = Sequential Organ Failure Assessment.

The relationship between coronary failure and magnesium levels are a popular subject among researchers. Teeranan et al have conducted a metanalysis which included studies evaluating the relationship between magnesium levels and mortality of patients diagnosed with coronary failure.[11] They found that a hypermagnesemic (Mg ≥1.05 mmol/L (2.5 mg/dl)) patient group who presented with coronary failure was found to have higher rates of cardiovascular mortality. This result shows that the relationship between cardiac function disorder, which is commonly observed in critical patients group, and magnesium is significant. Guerin et al have investigated the relationship between hypermagnesemia and mortality in their study which included different illness groups in the general ICU.[5] Although in this study the number of patients in the hypermagnesemia

groups are less than that of the normo-hypomagnesemia group, ICU mortality was found to be significantly higher in the former ($P = .018$). Additionally, these patients were in the group which did not have a COPD diagnosis and their APACHE II, SOFA, and CCI scores were higher.

Hypermagnesemia is an uncommon electrolyte disorder and its etiology is based on reduced renal excretion or increased magnesium intake in patients with acute or chronic renal failure. Increased magnesium absorption due to reduced gastrointestinal motility may be induced by inflammatory bowel diseases or the use of laxative treatments including anticholinergics, opioids, and magnesium. Moreover, hypermagnesemia can also develop due to a magnesium shift to serum from erythrocytes such as acidosis, rhabdomyolysis, and tumor lysis syndrome.[12] This study included only seven patients who received CRRT due to renal failure, and none of these patients had hypermagnesemia. Therefore, this study did not include a hypothesis on hypermagnesemia induced by renal excretion failure. The data regarding patients anamnesis of bowel diseases and motility disorders could not be obtained; however, frequently encountered bowel dysfunction in the patient group at high risk can be a determinant of hypermagnesemia. The effect of early enteral nutrition administration for patients in the ICU on outcomes is a well-known concept. Enteral nutrition given during routine care in the ICU can reduce magnesium abnormalities. Although this study found lower hypermagnesemia rates in the group which consisted mainly of COPD patients or those with other chronic hypoxic respiratory diseases, a magnesium shift from erythrocyte to serum and the related development of hypermagnesemia is possible in this group in which acidosis and hypoxia is commonly encountered. ARF is a clinical case that develops suddenly; however, besides newly diagnosed illnesses such as pneumonia and acute respiratory distress syndrome (ARDS), the underlying cause of ARF is associated with chronic respiratory or vascular disorder. COPD has continued to be one of the most common respiratory diseases that cause acute inflammation, infection related respiratory failure, and long and frequent hospital and ICU stays.[13] It has been shown that COPD is a systemic inflammatory illness that not only affects the respiratory system but also other organ systems, and has a significant effect on health care expenditures.[14,15] This study, which mostly included COPD patients, was designed based on the hypothesis that chronic systemic inflammatory stress is associated with low magnesium levels and affects the prognosis. However, contrary to this hypothesis, it was found that the patient group followed in the ICU was predominantly normomagnesemic, and the effect of magnesium levels of patients with COPD on mortality could not be confirmed. In line with this result, magnesium support and accepted magnesium cut-off values should be reevaluated for COPD patients whose stay in the hospital and ICU are frequent and long. However, when analyzing all patients without separating them according to the existence of COPD, it was found that a magnesium level higher than normal was significantly correlated with mortality. This can be associated with the extracellular increase of magnesium, one of the important intracellular cations in enzymatic reactions, during the catabolic process of the cells related to acute severe hypoxia. Similarly with this study, the fact that the mortality rate is higher in patients who have a diagnosis other than COPD and have higher CCI supports this hypothesis.

There are numerous studies on the effectivity of parameters such as APACHE II, SOFA, and CCI in predicting mortality of patients in the ICU, and these parameters continue to be up-to-date. In their study on patients with sepsis, Li et al[16] have found that particularly APACHE II and SOFA scores are effective in predicting 28-day mortality ($P = .000$ for each. AUC degrees for ROC analysis: APACHE II (0.893), SOFA (0.871)). Moreover, CCI is a commonly used test in the prediction of mortality. Yıldız et al[17] have found that the relationship between CCI and mortality was statistically significant. This study also found that the APACHE II, SOFA, and CCI was effective in predicting the 28-day mortality of patients in the ICU with ARF diagnosis. There are certain limitations in this study. This study is a mono-center and retrospective study. During this study, the magnesium levels were only measured during admission to the hospital and were not monitored during the follow-up process. Additionally, only the total serum magnesium level was measured and it was not separated into complex and ionized forms based on proteins and anions. However, repeated measures were not analyzed, since the aim of this study was to measure magnesium levels during admission to the ICU and evaluate the effect of the spot values on the mortality. Moreover, patients who were diagnosed with hypomagnesemia during the measurements were routinely given magnesium replacement. Patients renal clearance values and urine magnesium levels could not be obtained. More complex and well-designed studies which include a broader sample size, and technically separate different forms of magnesium should be carried out to confirm that hypermagnesemia is induced by cell lysis mechanism.

Author contributions

Conceptualization: Mustafa Özgür Cırık, Güler Eraslan Doğanay.
Data curation: Mustafa Özgür Cırık, Mukaddes Kılınç, Güler Eraslan Doğanay.
Formal analysis: Mustafa Özgür Cırık, Mukaddes Kılınç.
Investigation: Mukaddes Kılınç.
Methodology: Güler Eraslan Doğanay, Meriç Ünver.
Project administration: Mustafa Özgür Cırık.
Resources: Güler Eraslan Doğanay, Meriç Ünver.
Supervision: Murat Yıldız, Sema Avcı.
Visualization: Mukaddes Kılınç, Murat Yıldız.
Writing – original draft: Meriç Ünver, Murat Yıldız.
Writing – review & editing: Sema Avcı.

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