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VITAMIN D LEVELS AND DISEASE SEVERITY IN COVID-19

COVID-19'DA D VİTAMİNİ DURUMU VE HASTALIK ŞIDDETİ

Pinar ALARSLAN[1] Esin CELIKER[2] Zeliha ARSLAN[2]
Gokcen UNAL KOCABAS[3] Oguzhan OZYURTKAN[4]

[1]Department of Endocrine And Metabolic Diseases, Medicana International Istanbul Hospital, Istanbul, Turkey
[2]Department of Chest Diseases, Medicana International Istanbul Hospital, Istanbul, Turkey
[3]Department of Endocrine And Metabolic Diseases, Izmir Baskent University Hospital, Izmir, Turkey
[4]Department of Thoracic Surgery, Medicana International Istanbul Hospital, Istanbul, Turkey

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SUMMARY

Introduction: *to evaluate the clinical and biochemical characteristics of patients with Covid-19 with regard to disease severity, and to assess vitamin D levels.*

Material and methods: *A total of 153 patients diagnosed with Covid-19 were enrolled in this retrospective cohort study. Patients were divided into following three groups in terms of clinical severity: those managed as outpatients (n=75), those managed in wards (n=61) and those requiring intensive care unit (ICU) (n=17).*

Results: *The levels of WBC, neutrophil, BUN, CRP, AST, ALT, D-dimer, ferritin, procalcitonin and BNP were significantly higher in the intensive care group compared to ward patients and outpatients. Albumin levels, hemoglobin values and lymphocyte percentages were lower in the severe disease group compared to the other two groups. Estimated marginal means of the adjusted vitamin D levels were 14.32 ± 1.26 ng/mL for the inpatients (ward and ICU) and 18.30±1.28 ng/mL for the outpatients (p=0.032).*

Conclusion: *Vitamin D deficiency may have been effective on the aggravation or prognosis of the disease, possibly with its anti-inflammatory, anti-fibrotic, anti-oxidant and immunomodulatory effects. In this respect, the role of vitamin D supplementation on treatment should be examined in further studies by monitoring vitamin D levels in patients.*

ÖZ

Giriş: *Covid-19'lu hastaların klinik ve biyokimyasal özelliklerini hastalık şiddetine göre değerlendirmek ve D vitamini düzeylerini değerlendirmek.*

Gereç ve Yöntem: *Bu retrospektif kohort çalışmasına Covid-19 tanısı konan toplam 153 hasta dahil edildi. Hastalar klinik şiddet açısından şu şekilde üç gruba ayrıldı: ayakta tedavi gören hastalar (n = 75), servislerde tedavi edilenler (n = 61) ve yoğun bakım ünitesi (YBÜ) gerektirenler (n = 17).*

Bulgular: *Yoğun bakım grubunda WBC, nötrofil, BUN, CRP, AST, ALT, D-dimer, ferritin, prokalsitonin ve BNP düzeyleri serviste ve ayakta tedavi gören hastalara göre anlamlı olarak yüksekti. Şiddetli hastalık grubunda albümin düzey, hemoglobin değeri ve lenfosit yüzdesi diğer iki gruba göre daha düşüktü. Düzeltilmiş D vitamini*

düzeylerinin tahmini marjinal ortalamaları yatan hastalar (servis ve YBÜ) için 14.32 ± 1.26 ng / mL ve ayakta tedavi gören hastalar için 18.30 ± 1.28 ng / mL idi (p = 0.032).

***Sonuç:** D vitamini eksikliği, muhtemelen anti-enflamatuar, anti-fibrotik, anti-oksidan ve immünomodülatör etkileriyle hastalığın şiddetlenmesi ya prognozu üzerinde etkin olmuş olabilir. Bu açıdan hastalarda D vit düzeyi takibi yapılarak ileri çalışmalarda D vit takviyesinin tedavi üzerindeki rolü incelenmelidir.*

INTRODUCTION

The World Health Organization announced on 11 March 2020 that the outbreak of novel coronavirus disease (Covid-19) was a global pandemic. As of 9 June, more than 7,000,000 confirmed individuals and about 400,000 deaths have been reported globally (1). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an enveloped, single stranded RNA virus characterized with its spike proteins, is the identified pathogen of Covid-19 and causes clinical outcomes ranging from very mild flu-like symptoms to severe pneumonia that may lead to death. The major cause of death in patients infected with SARS-CoV-2, as the name suggests, is severe acute respiratory syndrome as a result of increased inflammatory response and cytokine storm syndrome, particularly in the lung, leading to impaired pulmonary oxygenation, severe pneumonia and also multiple organ damage (2). To date, there is no effective and definitive treatment of this condition which has caused and will continue to cause huge economic and health burdens. The disease is of particular concern in the elderly population and those with comorbidities, who constitute the main risk group.

Vitamin D has been known to play an important supportive role in both the adaptive and innate immune systems through cytokine and cell signaling pathways, in addition to its well-described roles, such as its immunomodulatory, anti-oxidant, anti-fibrotic, anti-infective and anti-inflammatory effects (3). Immunomodulation may help to alleviate disease progression and severity and could improve outcomes. Recently, some articles have reported a possible association between vitamin D and reduced risk for respiratory tract infections, particularly influenza and Covid-19 (4). However, studies that have investigated the levels of vitamin D in the varying ranges of clinical courses of Covid-19 have not reported conclusive results and their findings require confirmation.

The aim of the study was to determine biochemical characteristics of patients with different degrees of Covid-19 disease and to evaluate the effects of biochemical parameters including vitamin D levels on mortality and clinical outcomes.

MATERIAL AND METHODS

The study was designed as a retrospective single center study and was carried out by including patients admitted from March 2020 to May 2020 in the Chest Disease Department at Medicana International Hospital, Istanbul, Turkey. A total of 153 patients diagnosed with Covid-19 according to the WHO interim guidance report (5) were enrolled in this study. Each patient's diagnosis was confirmed with real-time reverse transcription polymerase chain reaction using specimens derived from nasopharyngeal swabs or sputum, prior to, or during hospitalization. The patients were divided into the following three groups in terms of clinical severity: outpatients, ward patients and intensive care patients. Seventy-five patients were outpatients who had mild clinical symptoms including cough and fatigue without imaging findings of pneumonia (mild disease). Sixty-one patients had moderate clinical symptoms including fever >39ºC and respiratory symptoms, and were followed as inpatients in wards (moderate disease). Seventeen patients were severe Covid-19 patients admitted to the intensive care unit, with respiratory distress and decreased resting oxygen saturation in addition to any other symptoms (severe disease). Patients that were younger than 12 years old, those with history of malignancy, severe kidney, liver diseases, leukemia or other serious blood conditions, pregnant patients, individuals that were identified to have other infectious diseases, and recipients of treatment before their initial visit to our center were excluded from the study. All research procedures were evaluated and accepted by the Research Ethics Committee of Medicana International Hospital and Ministry of Health, Turkey and were conducted in agreement with the ethical standards specified in the most recent amendments of the Declaration of Helsinki. All

research procedures were evaluated and accepted by the Research Ethics Committee of Medicana International Hospital and Ministry of Health (Approval No: 11.05.2020). Written informed consent was obtained from patients prior to their participation in this study.

The records of patients were reviewed and recorded. The previous vitamin D use or the drugs and supplementations which could have an effect on vitamin D levels were recorded. There were no such a drug or supplementation use before the six months till the study period. Demographic characteristics including age, gender and comorbidities, and laboratory findings were retrospectively obtained from patient files. Complete blood cell counts including white blood cell (WBC) count, neutrophil percentage (NEU), lymphocyte percentage (LYM), monocyte percentage (MONO), hemoglobin value (HB) and platelet count (PLT) were measured with a CELL-DYN 4000 System device (Abbott Laboratories, IL, USA). Blood biochemistry parameters including C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate amiotransferase (AST), creatinine, blood urea nitrogen (BUN), albumin, Ferritin, Brain type natriuretic peptide (BNP), procalcitonin and vitamin D were determined using a Cobas 6000 series autoanalyzer (Roche Diagnostics, Mannheim, Germany). D-dimer measurements were performed using a coagulation analyzer (Sysmex CA 1500, Siemens, Germany). All blood samples were examined within less than one hour after sampling. All biochemical analyses, which were routinely repeated every day, were performed with the same analyzers and same kits in the central laboratory of our hospital.

Statistical Analyses

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). For the normality check, the Kolmogorov-Smirnov test was used. Data are given as mean ± standard deviation or median (minimum-maximum) for continuous variables according to normality of distribution for quantitative variables, and frequency (percentage) for qualitative variables. Normally distributed variables were analyzed with one-way analysis of variances (ANOVA). Non-normally distributed variables were analyzed with the Kruskal Wallis test. Pairwise comparisons of the variables were performed with the Tukey test or Bonferroni correction method depending on normality of distribution. Categorical variables were analyzed with the Chi-square test or Fisher's exact test. Analysis of covariance (ANCOVA) was performed to analyze vitamin D levels adjusted with age. Analyses with *p* values of < 0.05 were accepted as statistically significant results.

RESULTS

One hundred and fifty-three patients infected by SARS Cov-2 were included in the study. Clinical and biochemical characteristics were shown in (Table 1). The mean age of patients was 38.4 ± 9.9 years in the outpatient group, 43.9 ± 14.3 years in the ward group, and 58.1 ± 14.5 years in the intensive care group ($p<0.001$). There were no significant differences between groups in terms of gender ($p=0.431$). The most important comorbidities were diabetes mellitus and hypertension that were present in 70% of the intensive care patients. The WBC counts, neutrophil percentage, and levels of BUN, CRP, AST, ALT, D-dimer, ferritin, procalcitonin and BNP were significantly higher in those with severe disease compared to the moderate and mild disease groups (all, $p<0.05$). Albumin levels, hemoglobin values and lymphocyte percentages were lower in the severe group compared to the other two groups (all, $p<0.05$). Vitamin D levels were 14.1 ng/mL in the mild disease group, 11 ng/mL in the moderate disease group, and 16.3 ng/mL in severe patients ($p=0.446$). The outcome in 150 patients was discharge after complete remission, while 3 patients died because of respiratory failure.

There was significant correlation between age and vitamin D levels ($r=0.250$, $p=0.002$). Since we found significant differences between the in-patient (severe and moderate disease) and out-patient groups ($p<0.001$), we performed analysis of covariance (ANCOVA) with vitamin D levels as a dependent variable and age as a covariate. We found age to be a significant covariate ($F=7.076$, $p=0.009$). Estimated marginal means of the adjusted vitamin D levels were 14.32 ± 1.26 ng/mL for inpatients and 18.30 ± 1.28 ng/mL for outpatients (Figure 1). There was a significant difference between groups with regard to vitamin D levels adjusted for age ($F=4.663$, $p=0.032$).

Table 1. Summary of patient characteristics with regard to groups

	Outpatients (n=75)	Ward (n=61)	Intensive Care (n=17)	*p* value
Age	38.36 ± 9.94 [a]	43.89 ± 14.28 [b]	58.06 ± 14.50 [c]	<0.001
Gender				
Male (n, %)	39 (52.00%)	28 (45.90%)	6 (35.29%)	0.431
Female (n, %)	36 (48.00%)	33 (54.10%)	11 (64.71%)	
Diabetes Mellitus (n, %)	8 (10.67 %)	15 (24.59%)	12 (70.59%)	<0.001
Hypertension (n, %)	11 (14.67 %)	25 (40.98%)	12 (70.59%)	<0.001
WBC (x10^9/L)	6.51 (1,83 - 16,6)	5.71 (2,56 - 12,5)	7.15 (2,1 - 42.3)	0.021
% Neutrophil	57.8 (3.41 - 81.8)	66.3 (23.2 - 91)	82.4 (35.7 - 96.1)	<0.001
% Lymphocyte	30.1 (1.93 - 64.4)	24.5 (1.64 - 64.9)	13.6 (0.51 - 42.4)	<0.001
% Monocyte	7.1 (0.76 - 23.1)	7.86 (1.36 - 14.5)	5.03 (0.72 - 18.8)	0.064
Hemoglobin (g/dL)	13.73 ± 1.37	12.98 ± 1.67	12.80 ± 1.45	0.005
Platelet (x10^9/L)	212 (111 - 572)	213 (97.6 - 586)	190 (37.9 - 334)	0.263
CRP (mg/L)	0.2 (0.1 - 11.89)	1.18 (0.1 - 16.38)	1.79 (0.1 - 31.21)	<0.001
AST (U/L)	19 (11 - 73)	24 (13 - 222)	27 (15 - 1378)	<0.001
ALT (U/L)	18 (7 - 99)	24 (10 - 629)	38 (11 - 994)	0.003
Urea (mg/dL)	21 (11 - 47)	19 (13 - 71)	26 (9 - 107)	0.032
Creatinine (mg/dL)	0.74 (0.52 - 2.4)	0.72 (0.56 - 1.77)	0.77 (0.48 - 3.24)	0.282
D-Dimer (µg/L)	278 (41 - 1660)	642 (157 - 23900)	570 (215 - 53200)	<0.001
Ferritin (ng/mL)	96.7 (1 - 527.18)	113.31 (1 - 2000)	500 (26.83 - 2000)	<0.001
BNP (pg/mL)				
≤ 70 (n, %)	66 (88.00%)	42 (68.85%)	6 (35.29%)	<0.001
> 70 (n, %)	9 (12.00%)	19 (31.15%)	11 (64.71%)	
Procalcitonin (ng/mL)				
≤ 0.12 (n, %)	74 (98.67%)	51 (83.61%)	11 (64.71%)	<0.001
> 0.12 (n, %)	1 (1.33%)	10 (16.39%)	6 (35.29%	
Albumin (mg/dL)	4.4 (3.3 - 5.2)	4.2 (2.5 - 4.8)	3.7 (2.6 - 4.9)	0.002
Vitamin D (ng/mL)	14.1 (4.4 - 77.5)	11 (4.2 - 46.4)	16.3 (4.5 - 34.2)	0.446
Exitus (n, %)	0 (0.00%)	0 (0.00%)	3 (17.65%)	<0.001

WBC: White blood cell counts, CRP: C-reactive protein, BNP: Brain-type natriuretic peptide. Data are given as mean ± standard deviation or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables.

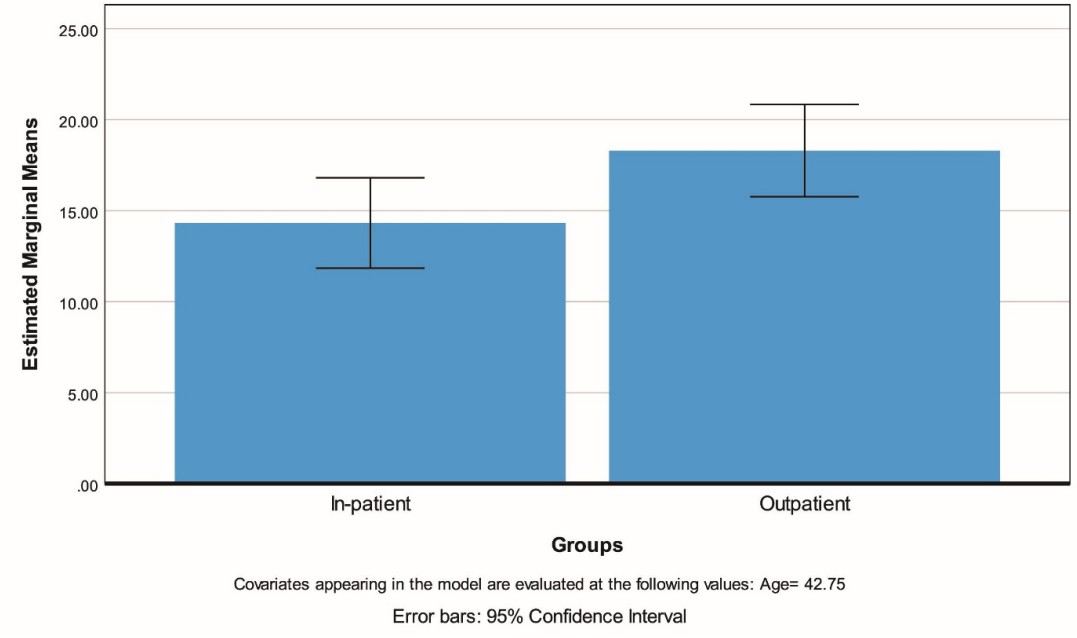

Figure 1. Estimated marginal means of the adjusted vitamin D levels in the patient groups

DISCUSSION

This study was aimed at comparing various biochemical parameters including vitamin D in Covid-19 patients with regard to disease severity. We found increased levels of WBC, CRP, ALT, AST, D-dimer, ferritin, procalcitonin and BNP in Covid-19 patients admitted to the intensive care unit when compared with patients treated in wards and outpatients. We have shown that age-adjusted vitamin D levels alter significantly between the different degrees of the disease. In relation, we also found lower vitamin D levels among inpatients with Covid-19 (who had moderate or severe disease) compared to outpatients (mild disease).

Covid-19 is an infectious condition caused by the virus named SARS-CoV-2, and has resulted in a dramatic pandemic with severe consequences. The most common symptoms in patients infected with COVID-19 were fever and mild-to-moderate respiratory symptoms, including cough and shortness of breath. Some patients developed severe disease with various complications, including acute respiratory distress syndrome and multiple organ failure, and these patients required intensive care and utilization of mechanical ventilation. To observe the relationship between Covid-19 severity and biochemical parameters, we included three different clinical stages of Covid-19. In a previous study, Zhang et al. found increased CRP, decreased albumin and lymphopenia in a meta-analysis of 4663 Covid-19 patients (6). In another meta-analysis including 5912 patients with Covid-19, Bao et al. showed that severe cases had higher leukocyte (1.2 fold) and neutrophil (1.33 fold) counts, and increased CRP (3.04 fold), procalcitonin (2.0 fold), AST (1.40-fold), ALT (1.34-fold), urea (1.28-fold), creatinine (1.09-fold), and D-dimer (2.74-fold) levels, in addition to lower lymphocyte count (1.44-fold), and hemoglobin (1.53-fold) and albumin (1.15-fold) levels (7). Taneri and colleagues found increased ferritin levels and decreased hemoglobin values in severe cases compared to moderate cases in a meta-analysis of 14044 Covid-19 patients (8). Consistent with these studies, we found that those with severe disease had increased WBC count, neutrophil percentage, and BUN, CRP, ALT, AST, D-dimer, ferritin, procalcitonin and BNP levels; whereas, albumin, hemoglobin and lymphocyte percentages were decreased, in comparison to non-severe cases. These laboratory biomarkers can be used as clinical indicators of worsening prognosis and poor outcome in COVID-19. Appropriate close-monitoring and meticulous management is required for patients that demonstrate these alterations, and they should be transferred to the intensive care unit if necessary.

Vitamin D is an essential vitamin and was considered to be mostly associated with the bone and musculoskeletal system functions until a flurry of studies demonstrated its contributions to a great number of physiological mechanisms and disease conditions –possibly due to the advances in quantification methods that greatly increased accuracy of measurements (9). More recently, studies have focused on the crucial role of vitamin D in immunity and immunomodulation. For instance, Martineau et al. showed in a meta-analysis of 11321 patients from 25 randomized controlled trials that vitamin D supplementation protected against acute respiratory tract infection. They reported that patients who were severely vitamin D deficient (<25 nmol/L) received the most benefit from supplementation (4). Vitamin D modulates adaptive immunity through promoting induction of T regulatory cells and by reducing the production of Th1 cells, and consequently suppressing the progression of inflammation by decreasing the formation of inflammatory cytokines such as Interleukin (IL)-6, IL-8, IL-12 and IL-17 (10, 11). Furthermore, it has been established that Vitamin D reduces the formation of nuclear factor-KB and tumor necrosis factor-α, and directly inhibits gamma interferon and IL-2 (11, 12). Covid-19 has been associated with cytokine storm syndrome that may aggravate the clinical severity; taking into consideration the aforementioned effects of vitamin D, it is plausible to suggest that it may decrease the possibility of cytokine storm and could prevent multiple organ failure. It was shown that the inactive vitamin D form can be transformed into the active form by the respiratory epithelial cells during infection (13). Increased active vitamin D induces expression of cathelicidins and defensins, which decrease the survival and replication of enveloped respiratory viruses and have protective effects against lung damage due to hypoxia (14). Vitamin D also reduces the levels of renin, angiotensin II and angiotensin

converting enzyme (ACE), and increases the levels of ACE2 (10). Angiotensin II catalyzed by ACE2 increases blood pressure through inducing aldosterone; thus, causing a systemic vasoconstructive effect (15). COVID-19 infection is thought to downregulate ACE2 function and may lead to excessive accumulation of toxic Angiotensin II that causes ARDS, myocarditis and hypertension (15, 16). ACE2 receptors are the host functional receptors for SARS-COV2 that enable entry into host cells including alveolar and intestinal cells (17). Hanff and colleagues suggested that renin-angiotensin system blockade drugs might increase ACE2 levels and can be used as an available substrate for SARS-Cov2 infection (16). Vitamin D promotes expression of the ACE2 gene. Kuba et al. demonstrated that higher levels of ACE2 were related with better outcomes for coronavirus diseases (18). Thus, vitamin D supplementation may reduce the risk of worse Covid-19 prognosis through its effects on the renin-angiotensin system.

Covid-19 appeared and began its spread in the Northern hemisphere during the winter of 2019, a period in which vitamin D levels are suggested to be minimal across the population (19, 20). It has been shown that reduced sunlight, low temperatures and less humidity appear suitable for Covid-19 (21). Laird et al. showed in a cross-sectional study across Europe that Covid-19 mortality was related with vitamin D status in different populations, and Nordic countries had higher vitamin D levels and lower infection and mortality rates of Covid-19, possibly owing to the routine fortification of foods with vitamin D (22). They also surprisingly demonstrated that sunny and lower-latitude countries such as Spain and Italy had lower vitamin D levels. It is well known that these countries have also been experiencing the highest infection and mortality rates for Covid-19 in Europe (5), albeit the age groups and various other factors may also be associated with this difference.

Since it is one of the first studies in the period of the study, besides being an important study, it is necessary to mention its various limitations. First of all, it can be considered that the classification method used in the study is not compatible with international standards. The general functioning of the hospital can be shown as the reason for this situation, but this classification (outpatient treatment, hospitalization and intensive care treatment) can be considered appropriate since it is a classification that has been used in clinics for a long time. Second, the retrospective nature of the study and the relatively small number of patients studied. In the relevant period, the number of patients was not as high as today and it was not easy to do with the study. Finally, since vitamin D level measurements are instantaneous measurements and the prognosis of the patients after the disease has not been followed for a long time, it has been impossible to report the vitamin D level as a real risk factor.

Epidemiological studies have shown that elderly patients infected with Covid-19 have higher mortality rates, this may also be associated with the presence of severe vitamin D deficiency in this age group (23). Aging causes a decline in immunity and also endogenous vitamin D production. Serum vitamin D levels tend to reduce with ageing, which may be important for Covid-19 because mortality rates increase with age. We found decreased age-adjusted vitamin D levels in all patient groups, but inpatients were found to have significantly lower levels. Therefore, it is possible to argue that vitamin D may have a protective role against Covid-19 infection and its severity.

In conclusion, we found a relationship between age-adjusted vitamin D levels and the severity of Covid-19. Vitamin D deficiency may have been effective on the aggravation or prognosis of the disease, possibly with its anti-inflammatory, anti-fibrotic, anti-oxidant and immunomodulatory effects. In this respect, the role of vitamin D supplementation on treatment should be examined in further studies by monitoring vitamin D levels in patients.

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Corresponding Author

Pinar ALARSLAN (MD)
Department of Endocrine
And Metabolic Diseases,
Medicana International Istanbul Hospital,
Beylikduzu Cd. No: 3, 34520
Beylikduzu/Istanbul, Turkey
Phone: +905052714605
E-mail: pinaralarslan@hotmail.com,
ORCID: 0000-0003-1790-0796

Pinar ALARSLAN (MD) ORCID: 0000-0003-1790-0796
Esin CELIKER (MD) ORCID: 0000-0001-7530-0647
Zeliha ARSLAN (Assoc. Prof.) ORCID: 0000-0002-1022-3406
Gokcen UNAL KOCABAS (MD) ORCID: 0000-0002-1849-3179
Oguzhan OZYURTKAN (Prof. Dr.) ORCID: 0000-0003-2754-2080S