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## Original Articles



## Case Reports

# Comparison of the Effectiveness of Computed Tomography and Magnetic Resonance Imaging Techniques in Patient Groups Aged under and over 65 Years and Diagnosed with Ischemic Stroke in the Emergency Department

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## ABSTRACT

**Objectives:** Stroke is a condition with high morbidity and mortality. This study aims to investigate whether the effectiveness of Computed Tomography (CT) and diffusion-weighted Magnetic Resonance Imaging (MRI), the techniques that have a significant place in the diagnosis of ischemic stroke, the most common form of stroke, are affected by the physiological changes of advanced age.

**Methods:** A total of 436 patients were included in the study. The study population was divided into two groups depending on age: those above 65 and those under 65 years of age. Medical files, both the emergency department and clinical ward files, of the patients who were admitted to the emergency department in nine months and admitted to the neurology clinic with the diagnosis of ischemic stroke were retrospectively analyzed. The time from admission to imaging was determined depending on patient files and the Hospital Management Information System (HBYS). The CT and MRI reports interpreted by radiologists were also reviewed. While recording the data, the presence of a lesion, its direction, and localization were also noted.

**Results:** CT positivity was 21.3%, and the positivity of diffusion-weighted imaging was 82.1% in the study population. The time was shorter in the group of patients with positive CT results than in the group with negative CT results. In subjects under 65, the time between onset and imaging was shorter in the group with positive CT results than in the group with negative CT results. In subjects over 65, the time with positive CT results was not different from the group with negative CT results. It was determined that the mean time was shorter in the group with positive MRI results than in the group with negative results. In both the groups under the age of 65 and over the age of 65, the time interval was shorter in the patients with positive MRI results compared to those with negative MRI results.

**Conclusions:** Regardless of the positivity or negativity of CT and MRI results, the mean time from symptom onset to imaging was shorter in the group under 65 years of age compared to the group over 65 years. Aging prolongs the time to admission and the neuroradiological response of geriatric patients.

**Keywords:** Emergency department, stroke, geriatrics, penumbra

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## INTRODUCTION

According to the definition recommended by the World Health Organization (WHO) in 1970, "Stroke is a condition characterized by rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin"[1]. According to the WHO, stroke is the second leading cause of mortality worldwide and the third leading cause of death in developing countries. Stroke is the major cause of disability worldwide. The prevalence of stroke in the United States increases with advancing age in both men and women. It was reported that an estimated 7.6 million Americans over the age of twenty had a stroke, and the overall prevalence of stroke was estimated to be 2.7% based on data from 2018 [2,3]. In the US, the annual incidence of new or recurrent stroke is approximately 795,000. Of those, 610,000 are first-time strokes, and 185,000 are recurrent strokes. Of all stroke cases, 87% are ischemic, 10% are intracerebral hemorrhage, and 3% are subarachnoid hemorrhage [3].

Early and effective treatment can reduce mortality and morbidity in strokes. Neuroimaging is the most helpful test for physicians after a comprehensive neurological examination in determining the strategy for treating strokes. Computed Tomography (CT) and diffusion-weighted Magnetic Resonance Imaging (MRI) are emergency neuro-imaging techniques used in ischemic stroke, which is more common and in which medical or invasive intervention is more valuable due to the race against the clock in this condition. For this reason, diffusion-weighted MRI has a significant place. A gold standard neuroimaging method has not been determined yet for acute ischemic stroke [4]. Computed tomography and MR angiography of the brain are used to detect vascular anatomy and intravascular thrombus. CT perfusion and MR perfusion help detect the penumbra. Diffusion-weighted MR imaging (DW-MRI) is used to measure the volume of the infarct area called the 'core' in ischemic stroke patients. In contrast, CT Perfusion and MR Perfusion sequences are used to measure the penumbra area that can be salvaged with reperfusion therapy [5]. Because advanced age is an independent risk factor for stroke, whether the success of CT and MRI is also affected by the physiological changes brought by advancing age can be a question that needs to be answered. We aimed to contribute to the diagnosis stage of ischemic stroke with this study, in which we tried to compare the effectiveness of CT and diffusion-weighted MRI in patient groups with ischemic stroke who were younger than and older than 65 years.

## METHODS

The present study was conducted retrospectively on patients who presented to the emergency department of Bursa Yüksek İhtisas Training and Research Hospital and who were diagnosed with ischemic stroke. Medical files, both the emergency department and clinical ward files, of the patients who presented to the emergency department in nine months and were admitted to the neurology clinic with the diagnosis of ischemic stroke were reviewed. The time from admission to imaging was determined depending on the patient file and the Hospital Management Information System (HBYS). The CT and MRI reports interpreted by radiologists were examined. Obtained data were recorded in the study form. While recording the data, the presence of a lesion, its direction, and localization were also noted.

Patients aged over 18 years of age who underwent CT and MRI and were diagnosed with non-traumatic ischemic stroke were included in the study. Patients who were diagnosed with ischemic stroke but had contraindications for MRI (e.g., pacemaker, incompatible orthoses and prosthesis, permanent teeth) were excluded from the study. Moreover, patients detected to have artifacts or additional pathologies, such as mass or encephalitis, on imaging were excluded from the study. Ultimately, a total of 436 patients were included in the study. The local ethics committee approved the study (2011-KAEK-25 2015/18-08).

### Statistical Analysis

We used the mean, standard deviation, median, minimum, maximum, frequency, and ratio values for descriptive statistics. The Kolmogorov-Smirnov test was used to measure the distribution of the variables. Quantitative data were analyzed using the Mann-Whitney U test. Qualitative data were analyzed using the Chi-square test. The Kappa Compatibility test was used for compatibility analysis. The SPSS 22.0 program was used for analysis.

## RESULTS

Of the 436 patients included in the study, 48.6%

were female and 51.4% were male. Considering age distribution, 35.3% were under 65, while 64.7% were 65 and older. In general, the time from the onset of symptoms to imaging was 2.2 hours on average. In the CT imaging performed for 436 patients who presented to ED, 21.3% were positive (Table 1). In the MRI evaluation of 436 patients included in the study, 82.1% were positive (Table 2).

**Table 1.** Computerized Tomography (CT) findings of the patients admitted to the Emergency Department

| | | n | % |
|---|---|---|---|
| **CT Findings** | (+) | 93 | 21.3 |
| | (-) | 343 | 78.7 |
| **CT-Cerebrum** | (+) | 55 | 12.6 |
| | (-) | 381 | 87.4 |
| **CT-Diencephalon** | (+) | 22 | 5.0 |
| | (-) | 414 | 95.0 |
| **CT-Brainstem** | (+) | 6 | 1.4 |
| | (-) | 430 | 98.6 |
| **CT-Cerebellum** | (+) | 19 | 4.4 |
| | (-) | 417 | 95.6 |

**Table 2.** Magnetic Resonance Imaging (MRI) findings of the patients admitted to the Emergency Department

| | | n | % |
|---|---|---|---|
| **MR Finding** | (+) | 358 | 82.1 |
| | (-) | 78 | 17.9 |
| **MR-Cerebrum** | (+) | 219 | 50.2 |
| | (-) | 217 | 49.8 |
| **MR-Diencephalon** | (+) | 147 | 33.7 |
| | (-) | 289 | 66.3 |
| **MR-Brainstem** | (+) | 30 | 6.9 |
| | (-) | 406 | 93.1 |
| **MR-Cerebellum** | (+) | 49 | 11.2 |
| | (-) | 387 | 88.8 |
| **MR-Supratentorial** | (+) | 301 | 69.0 |
| | (-) | 135 | 31.0 |
| **MR-İnfratentorial** | (+) | 77 | 17.7 |
| | (+) | 359 | 82.3 |
| **Lesion Side** | Bilateral | 45 | 10.3 |
| | Right | 152 | 34.9 |
| | Left | 165 | 37.8 |
| | Absent | 74 | 17.0 |

There was no significant difference between the groups with positive CT results and negative CT results in terms of mean age and gender distribution, respectively [(p>0.05), (p>0.05)]. Nevertheless, the time was significantly shorter in patients with positive CT results than in the group with negative CT results (Table 3).

There was no significant difference between the groups with positive MRI results and negative MRI results in terms of mean age and gender distribution, respectively [(p>0.05), (p>0.05)]. On the other hand, in patients with positive MRI results, the time was significantly shorter compared to the group with negative MRI results (Table 4).

In the group under 65, the time was significantly shorter in patients with positive CT results than in those with negative CT results. In the group over the age of 65 years, however, the time was not significantly (p>0.05) different between patients with positive CT results compared to those with negative CT results (Table 5).

In the group under age 65, the time interval was significantly shorter in patients with positive MRI results compared to those with negative MRI results (p<0.05). In the group over the age of 65, the time was significantly (p>0.05) shorter in patients with positive CT results than in patients with negative CT results (Table 6).

There was significant (36.9%) consistency between MRI and CT. There was a significant (59.2%) consistency between MRI and CT regarding cerebrum localization. There was a significant (68.6%) consistency between MRI and CT regarding the localization of the Diencephalon. There was a significant (68.6%) consistency between MRI and CT regarding the localization of the brain stem. There was a significant (68.6%) (p<0.05) consistency between MRI and CT in terms of the localization of the cerebellum (Table 7).

## DISCUSSION

Previous studies on strokes of ischemic origin, which constitute the majority of stroke cases, investigated the importance of gender differences between subjects. Petty et al. reported that large vessel occlusions and related stroke cases were more common in men than in women [6]. Similarly, in a study conducted by İnal et al., stroke was more common in the male population compared to women [7]. In our study, the number of male subjects was higher, and our results were consistent with the literature.

Kıyan et al. stated in the study they conducted with 124 patients with acute ischemic stroke and published in 2009 that the complaints of patients who applied to the emergency department started at 13±18.5 hours before admission [8]. In Schroeder et al., the mean time from the onset of symptoms to admission to the hospital was reported as 2.85 hours in stroke patients

**Table 3.** Evaluation of the demographics between positive and negative Computerized Tomography (CT) findings groups

| | | CT Finding (+) | | CT Finding (-) | | |
|---|---|---|---|---|---|---|
| | | Mean±SD n (%) | Median (Min-Max) | Mean±SD n (%) | Median (Min-Max) | p |
| **Age** | | 67.6±13.2 | 70 (42-95) | 70.0±12.2 | 72 (29-95) | 0.078 |
| **Age** | **< 65** | 40 (43.0) | | 114 (33.2) | | 0.080 |
| | **≥ 65** | 53 (57.0] | | 229 (66.8) | | |
| **Gender** | **Female** | 39 (41.9) | | 173 (50.4) | | 0.146 |
| | **Male** | 54 (58.1) | | 170 (49.6) | | |
| **Time (hour)** | | 1.8±1.5 | 1 (1-9) | 2.3±1.9 | 2(1-12) | ***0.005*** |

**Table 4.** Evaluation of the demographics between positive and negative Magnetic Resonance Imaging (MRI) findings groups

| | | MRI Finding (+) | | MRI Finding (-) | | |
|---|---|---|---|---|---|---|
| | | Mean±SD n (%) | Median (Min-Max) | Mean±SD n (%) | Median (Min-Max) | p |
| **Age** | | 69.7±12.2 | 71 (30-95) | 68.4±13.7 | 71 (29-93) | 0.547 |
| **Age** | **< 65** | 123 (34.4) | | 31 (39.7) | | 0.367 |
| | **≥ 65** | 235 (65.6) | | 47 (60.3) | | |
| **Gender** | **Female** | 177 (49.4) | | 35 (44.9) | | 0.464 |
| | **Male** | 181 (50.6) | | 43 (55.1) | | |
| **Time (hour)** | | 2.1±1.7 | 2(1-12) | 2.6±1.9 | 2 (1-10) | ***0.000*** |

**Table 5.** Comparison of the time between positive and negative Computerized Tomography (CT) findings

| | CT Finding (+) | | CT Finding (-) | | |
|---|---|---|---|---|---|
| | Mean±SD n (%) | Median (Min-Max) | Mean±SD n (%) | Median (Min-Max) | p |
| ***Age< 65*** | | | | | |
| Time (Hours) | 1.2±0.5 | 1(1-4) | 1.5±1.6 | 1(1-12) | ***0.042*** |
| ***Age ≥ 65*** | | | | | |
| Time (Hours) | 2.4±1.8 | 2(1-9) | 2.7±1.8 | 2(1-12) | 0.129 |

**Table 6.** Comparison of the time between positive and negative Magnetic Resonance Imaging (MRI) findings

| | MR Finding (+) | | MR Finding (-) | | |
|---|---|---|---|---|---|
| | Mean±SD n (%) | Median (Min-Max) | Mean±SD n (%) | Median (Min-Max) | p |
| ***Age < 65*** | | | | | |
| **Time (hour)** | 1.4±1.5 | 1 (1-12) | 1.5±0.8 | 1 (1-4) | ***0.034*** |
| ***Age≥ 65*** | | | | | |
| **Time(hour)** | 2.5±1.7 | 2 (1-12) | 3.4±2.1 | 3 (1-10) | ***0.000*** |

**Table 7.** The evaluation of the consistency between Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI) findings

| | | MRI (+) | MRI (-) | Consistency | Non-consistence | Kappa | p |
|---|---|---|---|---|---|---|---|
| CT ***Findings*** | (+) | 88 | 5 | 36.9% | 63.1% | 0.078 | ***0.000*** |
| | (-) | 270 | 73 | | | | |
| CT ***Cerebrum*** | (+) | 48 | 7 | 59.2% | 40.8% | 0.186 | 0.000 |
| | (-) | 171 | 210 | | | | |
| CT ***Diencephalon*** | (+) | 16 | 6 | 68.6% | 31.4% | 0.111 | ***0.000*** |
| | (-) | 131 | 283 | | | | |
| CT ***Brainstem*** | (+) | 3 | 3 | 93.1% | 6.9% | 0.147 | ***0.000*** |
| | (-) | 27 | 403 | | | | |
| CT ***Cerebellum*** | (+) | 17 | 2 | 92.2% | 7.8% | 0.466 | ***0.000*** |
| | (-) | 32 | 385 | | | | |

included in the study [9]. In our study, the interval from the onset of symptoms to imaging was 2.2±1.8 hours on average.

Imaging methods developed in the last 30 years guide not only the diagnosis process but also the medical attention and intervention to be applied in acute ischemic stroke. Brain CT continues to be the primary screening method at the first post-stroke admission as it is faster, cheaper, non-invasive, and easily accessible for all patients. In a study conducted by Taşdemir et al. based on 64 patients, 44% negative and 56% positive were found in CT results obtained within the first 8 to 12 hours [10]. The longer the time passes after the onset of ischemic stroke, the greater the possibility of seeing a lesion in CT. Decreased contrast between cerebral gray matter and white matter, in other words, the anatomical boundaries between gray matter and white matter becoming invisible, is the first sign of ischemia on CT and can be detected in the first 3 hours after stroke onset. It was stated in another reference that signs gradually emerge in ischemic stroke, and no pathology was detected in 60% of cases in the first few hours [11]. In general, our CT results are consistent with the literature.

Considering the time from symptom onset to imaging, the mean time interval in the group with positive CT results was 1.8±1.5 hours. The mean time interval was 2.3±1.9 hours in the group with negative CT results. In short, the mean time from symptom onset to imaging was statistically significantly shorter in the group with positive CT results than in negative CT results. Considering these facts, it can be concluded that patients with a more severe clinical course and more obvious symptoms seek medical attention earlier. In other words, it can be said that the prognosis is worse in patients who show positive CT results early. Taşdemir et al. [10] compared various demographic, clinical, and examination results between patients who showed CT findings in the early period (within the first 8-12 hours) and those who did not and demonstrated that there was no variable causing a significant difference between the groups. In our study, however, we identified that the patients with positive CT results had presented to the hospital earlier than those with negative CT results.

The positivity of diffusion-weighted imaging was 82.1% of our study population. The most significant and common use of diffusion-weighted MRI is ischemic stroke imaging. It is reported that the sensitivity of DW-MRI is close to 100% 2 hours after the onset of ischemia. In human studies, diffusion-weighted MRI is defined as a technique that has nearly 100% sensitivity and specificity and does not require invasive procedures [12]. Simonsen et al. [13] reported that diffusion-weighted MRI combined with perfusion-weighted imaging had a sensitivity of 97.5% in acute ischemic stroke. Considering the data in the literature, the sensitivity of DW-MRI was found to be a bit lower in our study.

When evaluated in terms of time, the mean time was 2.1±1.7 in patients with positive results and 2.6±1.9 in those with negative results. The time was statistically significantly shorter in the group with positive MRI results than those with negative MRI results. We believe that this might be because, as the patient's clinical conditions and initial symptoms were more severe, they presented to the hospital earlier. In other words, patients' clinical symptoms with early positive MRI findings are more apparent. The localizations with the highest involvement in patients with positive MRI findings were the cerebrum, diencephalon, cerebellum, and brain stem.

In the group under age 65, the mean time was 1.2±0.5 hours in the CT-positive group and 1.5±1.6 hours in the CT-negative group. In the group under the age of 65, the time was statistically significantly ($p<0.05$) shorter in patients with positive CT results compared to those with negative CT results. In the group over 65, the mean time was 2.4±1.8 hours in the CT-positive group and 2.7±1.8 hours in the CT-negative group. However, in the group over the age of 65, the time was not significantly ($p>0.05$) different between patients with positive and negative CT results. If we need to address the reasons underlying the difference here, the clinical course and symptoms of CT-positive patients under the age of 65 are more obvious than the group with negative symptoms. Also, small changes in an individual with full physical and cognitive capacities can be noticed early. This shortens the time it takes for patients to present. In patients aged 65 years or older, on the other hand, pathologies cannot be noticed unless there is a significant change in the physical and cognitive functions of the patients due to age-related limitations or co-morbidities. Due to these facts, there was no statistically significant difference between the groups with negative and positive results regarding the time interval.

In the group aged under 65 years, the mean time was 1.4±1.5 hours in the group with positive MRI results and 1.5±0.8 hours in the group with negative MRI results. In the group under age 65, the time was significantly shorter in patients with positive MRI

results compared to those with negative MRI results ($p<0.05$). In the group aged over 65 years, the mean time was 2.5±1.7 hours in the group with positive MRI results and 3.4±2.1 hours in the group with negative MRI results. In the group aged over 65 years of age, the time was significantly ($p>0.05$) shorter in patients with positive MRI results than in patients with negative MRI results. In both the group under the age of 65 years and the group over the age of 65, the time from symptom onset to imaging was shorter in the patients with positive MRI results than in the group with negative MRI results.

The mean time of CT-positive patients under 65 years of age is similar to that of MRI-positive patients under 65. Additionally, the mean time of CT-positive patients over the age of 65 is similar to the meantime of MRI-positive patients over the age of 65. Nevertheless, when we compare the groups under 65 years of age and over 65 years of age, it will be seen that there is a serious difference between the groups regarding the mean time from symptom onset to imaging. It is necessary to address the reasons leading to this difference. Neurological deficits are noticed later in the patient group over 65 due to physical and cognitive limitations in this age group. This may be the primary reason for the difference. Compensation for edema occurring in the ischemic region due to atrophy in the brain resulting from aging may cause a late onset of the obvious clinical course in patients with limited cognitive and physical capacity. On the other hand, there will inevitably be a decrease in blood flow to the brain due to the contribution of both advanced age and diseases such as hypertension, diabetes mellitus, and hyperlipidemia to atherosclerosis. The clinical reaction and neuroradiological manifestation time will differ in ischemic stroke developing after a decrease in chronic cerebral flow and ischemic stroke developing in individuals with the ideal cerebral flow. As a different hypothesis, when we look at stroke at the cellular level, it is predicted that the need for cells for oxygen and glucose will decrease due to the reduction in neuronal activity resulting from aging. Even if an ischemic stroke develops, the cell can live on the remaining blood in the region for a while, so the activation of cellular destruction mechanisms may be delayed.

Today, CT remains in first place in the treatment and management of acute ischemic stroke in the emergency setting. However, based on strong evidence from some guidelines, MRI has an equivalent success rate to CT in detecting intraparenchymal hemorrhages in the first 6 hours [14]. Diffusion-weighted MRI is more specific and sensitive than non-contrast CT in ischemic stroke in both patients under 65 years of age and patients above 65 years of age [15].

The incidence of stroke and ischemic stroke, the most common subtype, will increase in the future due to the increased life expectancy. Furthermore, with the increase in unhealthy eating habits and the effect of genetic factors, stroke will be seen in younger populations, leading to a significant increase in disability and health expenditures in society. Early diagnosis is essential for the effective treatment of ischemic stroke. Most of these patients present to the hospital using 112 emergency health services or hastily by their means. Emergency medicine physicians have a crucial role at this point. The sooner they make a diagnosis and guide the treatment process, the higher they contribute to reducing the mortality and morbidity rates. The first step of the diagnosis is a good anamnesis and physical examination, which are essential in medicine. Especially in patient groups over 65 years, a physical examination may be insufficient. Therefore, the information that the physician receives from the patient's relatives in the anamnesis is valuable. Deterioration in the patient's nutrition, sleep, or mood may be a precursor of a stroke. Currently, CT is the easiest imaging method to access in most places for a physician diagnosing ischemic stroke. The clinician manages the ischemic stroke treatment process in the absence of hemorrhage on CT. With the advancements of the day, clinicians have found the opportunity to evaluate the patient group without CT results with diffusion-weighted MRI. Its higher sensitivity and specificity in ischemic stroke make diffusion-weighted MRI superior to CT. Therefore, the clinician should be able to interpret and evaluate the examinations ordered effectively. In this study, we tried to compare and examine the effectiveness of CT and diffusion-weighted MRI in ischemic stroke in the patient groups over and under 65. We want to present our achievements respectively.

## CONCLUSION

First, as stated in the literature, our study also proved that diffusion-weighted MRI is superior to CT in imaging ischemic stroke. Our achievements are the outcomes we've identified that, based on our literature review, have not been previously documented. The time from symptom onset to imaging was significantly shorter in the patient group with positive CT results

than in the group with negative CT results. In the group under 65, the time was significantly shorter in those with positive CT results than in those with negative CT results. In the group over 65 years of age, the time with positive CT results was not significantly ($p>0.05$) different from the group with negative CT results. There was no statistically significant difference between the groups with positive and negative MRI results regarding mean age and gender distribution. It was determined that the mean time was significantly shorter in the patient group with positive diffusion-weighted MRI results than in the group with negative DW-MRI results. In both the groups under the age of 65 and over the age of 65, the time from symptom onset to imaging was shorter in the patients with positive MRI results compared to the group with negative MRI results. Regardless of the positivity or negativity of CT and MRI results, the mean time from symptom onset to imaging was shorter in the group under 65 years of age compared to the group over 65 years. In the present study, we tried to explain what may cause this situation based on the factors related to pathophysiology and aging. However, to provide a better explanation of the issue, there is a need for additional studies examining other various factors, such as the potential effect of comorbidities and whether the quality of the imaging devices affects results or not. There is a need for further studies to indicate the factors that affect the results more precisely.

*Conflict of Interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Ethical Approval*

The protocol of the study was approved by the Medical Ethics Committee of Bursa Yüksek Ihtisas Training & Research Hospital, Bursa, Türkiye. (Decision number: 2011-KAEK-25 2015/18-08).

*Authors' Contribution*

Study Conception: KÇ; Study Design: KÇ, EU; Literature Review: KÇ, EU; Critical Review: KÇ, FE; Data Collection and/or Processing: KÇ, FE,; Analysis and/or Data Interpretation: KÇ; Manuscript preparing: KÇ.

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# Comparison of the effectiveness of the quick COVID-19 severity index and the COVID-19 gram critical illness risk score in identifying critical patients with COVID-19

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## ABSTRACT

**Objectives:** This study aimed to compare the effectiveness of the Quick COVID-19 Severity Index (qCSI) and the COVID-GRAM Critical Illness Risk Score (CGCIRS) in identifying critically ill patients with COVID-19 admitted to the emergency department of a tertiary hospital.

**Methods:** Patients over 18 years of age with a positive PCR test who presented to the Emergency Department of Bursa Yüksek İhtisas Training and Research Hospital between 15.03.2020 and 15.03.2021 with COVID-19 findings were retrospectively included in the study. Mortality, qCSI (respiratory rate per minute, oxygen saturation, oxygen demand per minute), and CGCIRS (x-ray abnormality, age, hemoptysis, dyspnea, impaired consciousness, comorbid disease, presence of cancer, neutrophil/lymphocyte ratio, lactate dehydrogenase (LDH) value, direct bilirubin value) were investigated within 1, 7 and 28 days.

**Results:** A total of 1499 patients with a positive COVID-19 PCR test were included in the study. Invasive mechanical ventilation was performed in 44 (2.9%) and non-invasive mechanical ventilation in 63 (4.2%) patients. 57 (3.8%) patients were hospitalized in the intensive care unit (ICU). Mortality occurred in the first 24 hours in 1 (0.1%) and 28 days in 41 (2.7%) patients. Having comorbidities, use of 10 lt/min oxygen, use of high flow oxygen, need for non-invasive and invasive mechanical ventilation, and need for ICU were found to increase 28-day mortality significantly. The qCSI and CGCIRS were found to be significantly different in patients who developed 28-day mortality with qCSI and CGCIRS, respectively ($p<0.001$), ($p<0.001$). In the ROC analysis for 28-day mortality, the area under the curve (AUC) value of qCSI was 0.966 [(95% CI: 0.934-0.998), ($p<0.001$)] and the AUC value of CGCIRS was 0.971 [(95% CI: 0.959-0.983), ($p<0.001$)]. qCSI had a sensitivity of 97.6% and specificity of 84% with a cut-off value of 4.5 for 28-day mortality; CGCIRS had a sensitivity of 95.1% and specificity of 91.2% with a cut-off value of 116.5 for 28-day mortality.

**Conclusions:** This study demonstrated that both qCSI and CGCIRS have significant predictive capabilities in identifying critical Covid-19 patients over a 28-day period. These scores are valuable for early identification and appropriate management of critically ill patients in the emergency department.

**Keywords:** COVID-19, prognosis, pandemic, qCSI, CGCIRS, mortality.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has recently emerged and rapidly spread globally. The emerging coronavirus disease 2019 (COVID-19) has been declared a pandemic by the World Health Organization (WHO) [1]. In adults, COVID-19 has been found to cause clinical manifestations ranging from asymptomatic infection to respiratory failure and death. The disease is easily transmitted from person to person, causing it to become active worldwide [2]. To date, despite the existence of various prognostic scales in COVID-19, none have been as universally accepted and used in routine clinical practice as the CURB-65 (confusion, blood urea nitrogen, respiratory rate, blood pressure, and age 65 or older) or the Pneumonia Severity Index scales [3].

Due to the rapidly increasing number of people infected with the virus, new disease-related scoring systems were needed to predict morbidity and mortality. For the qCSI score, vital signs, oxygen requirement, and high oxygen / invasive / non-invasive ventilation requirement within 24 hours were examined in patients hospitalized due to Covid-19 disease in the United States. With the qCSI scoring system, it was aimed to determine the respiratory prognosis of the patients within 24 hours [4].

CGCIRS was developed to ensure early detection of patients exposed to COVID-19. This score aims to help in the early recognition of those who will progress to critical illness, to provide appropriate treatment, and to use the existing facilities most efficiently [5,6].

In our study, we aimed to compare qCSI with CGCIRS in identifying critically ill patients with COVID-19 admitted to the emergency department of our hospital and to investigate their effectiveness in predicting morbidity and mortality.

## METHODS

Before the start of the study, the study information was registered with the Ministry of Health, General Directorate of Health Services, and Scientific Research Studies Platform, and approval was obtained. The study was conducted using the 2011-KAEK-25 2021/02-07 protocol approved by the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee.

Patients who presented to the Adult Emergency Department of the University of Health Sciences Bursa Yüksek İhtisas Training and Research Hospital between 15.03.2020 and 15.03.2021 with COVID-19 symptoms, who were diagnosed with COVID-19 pneumonia, who had positive RT-PCR test, who were 18 years of age or older, of both sexes and whose complete study data could be accessed were retrospectively included in the study. Patients whose complete study data were unavailable, under 18 years of age, who had a negative RT-PCR test, and who did not have COVID-19 pneumonia were excluded from the study.

Since our study was retrospective, written or verbal informed consent was not obtained from the patients included in the study. A standardized study data entry form was created. The patients' data included in the study were obtained from the hospital information management system and emergency patient files. Demographic data (age, gender), date of presentation to the emergency department, vital signs (respiratory rate, Glasgow Coma Score (GCS), systolic blood pressure (SBP), diastolic blood pressure (DBP), fingertip oxygen saturation (SPO2), presence/absence of confusion, complaints at presentation, Data such as chronic diseases, thoracic computed tomography imaging findings, laboratory values (BUN, d-dimer, lymphocyte count), RT-PCR results, patient's outcome from the emergency department (discharge, ward admission, intensive care unit admission, death) were obtained. In addition, the mortality of the patients within 28 days was followed.

### Statistical Analysis

IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp. Armonk, NY, USA, 2012) software package was used for the study. In statistical analyses, descriptive statistics of numerical variables were expressed as mean ± standard deviation (minimum-maximum), while descriptive statistics of categorical variables were reported as a number of cases and percentage (%).

In order to use parametric test statistics for continuous numerical variables between groups, assumptions must be met. When these assumptions were met, the significance of the difference was tested using the student's t-test. When the assumptions of parametric test statistics were not met, the significance of the difference in continuous numerical variables was evaluated by Mann-Whitney U test.

Pearson correlation analysis was used to evaluate the relationships between variables for variables with

parametric distribution, and Spearman correlation analysis was preferred for variables with non-parametric distribution.

ROC curve plotting was performed to investigate the diagnostic values of variables and 28-day mortality of qCSI and CGCIRS. Results were presented at 95% confidence intervals and p<0.05 was considered statistically significant.

## RESULTS

5216 patients were included in the study. 1923 patients with negative COVID-19 PCR test, 1022 patients under 18 years of age and 772 patients with incomplete data were excluded from the study. The study included 1499 patients with positive COVID-19 PCR test and complete data. The median age of the patients included in the study was 43 years (IQR 25-75: 32-59). 763 (50.9%) of the patients were male and 1283 (85.6%) were Turkish citizens. The most common symptoms were fatigue (n= 787, 52.5%) and cough (n= 738, 49.2%). 433 (28.9%) of the patients had a history of comorbidity and the most common comorbidities were hypertension (HT) (n= 308, 20.5%) and diabetes mellitus (DM) (n=152, 10.1%). Invasive mechanical ventilation was performed in 44 (2.9%) and non-invasive mechanical ventilation in 63 (4.2%) patients. Of these patients, 1099 (73.3%) were treated with hydroxychloroquine and 679 (45.3%) with favipiravir. 655 (43.7%) of the patients were hospitalized in the ward, while 57 (3.8%) were hospitalized in the intensive care unit (ICU). Mortality occurred in the first 24 hours in 1 (0.1%) and in 28 days in 41 (2.7%) of these patients (Table 1).

The mean body temperature was 36.92 ± 0.58 °C, median systolic blood pressure (SBP) was 130 (IQR 25-75: 120-150) mm/Hg, median respiratory rate was 17/min (IQR 25-75: 15-20), median qCSI value 0 (IQR 25-75: 0-0), median CGCIRS 63 (IQR 25-75: 37-90), mean CRP level 34.83 ± 63.52 mg/dL and mean troponin level 9.71 ± 39.71 ng/L (Table 2).

Mann Whitney U test was performed to investigate whether there was a difference between the laboratory values of the patients and 28-day mortality. At 28 days, LDH (p<0.001), D-dimer (p<0.001), Troponin (p<0.001), CRP (p<0.001), ferritin (p<0.001), WBC (p<0.001), Neutrophil count (p<0, 001), lymphocyte count (p<0.001), NLO (p<0.001), hemoglobin (p=0.005), platelet count (p=0.001) and bilirubin (p=0.006) values were significantly different.

**Table 1. Demographic and clinical information of the patients**

| | | |
|---|---|---|
| **Gender** | Male | 763 (50.9) |
| | Woman | 736 (41.9) |
| **Nationality** | Republic of Turkey | 1283 (85.6) |
| | Foreign Nationals | 216 (14.4) |
| **Symptoms** | Fatigue | 787 (52.5) |
| | Cough | 738 (49.2) |
| | Muscle/Joint Pain | 736 (49.1) |
| | Fire | 556 (37.1) |
| | Shortness of breath | 384 (25.6) |
| | Sore Throat | 343 (22.9) |
| | Headache | 327 (21.8) |
| | Loss of taste/odor | 284 (18.9) |
| | Diarrhea | 197 (13.1) |
| | Chest Pain | 57 (3.8) |
| | Loss of Speech / Movement | 6 (0.4) |
| | Hemoptysis | 3 (0.2) |
| | Other | 13 (0.9) |
| **Additional Diseases** | Hypertension | 308 (20.5) |
| | Diabetes Mellitus | 152 (10.1) |
| | Coronary Artery Disease | 118 (7.9) |
| | Chronic Renal Failure | 28 (1.9) |
| | Chronic Obstructive Pulmonary Disease/Asthma | 69 (4.6) |
| | Cerebrovascular Disease | 24 (1.6) |
| | Malignancy | 16 (1.1) |
| | More than 10 lt/min oxygen demand | 104 (6.9) |
| **Additional Diseases** | Non-invasive Mechanical Ventilation | 63 (4.2) |
| | Invasive Mechanical Ventilation | 44 (2.9) |
| | High Flow Oxygen | 61 (4.1) |
| | Hydroxychloroquine | 1099 (73.3) |
| | Favipiravir | 679 (45.3) |
| | Other Antibiotics | 562 (37.5) |
| | Anticoagulant | 437 (29.2) |
| | Steroid | 50 (3.3) |
| | Discharged | 817 (54.5) |
| **Emergency Room Treatment#** | Service Hospitalization | 655 (43.7) |
| | Intensive Care Unit Admission | 57 (3.8) |
| | Dispatch | 5 (0.3) |
| | Treatment Rejection | 3 (0.2) |
| | Low | 683 (45.6) |
| | Middle | 747 (49.8) |
| | High | 69 (4.6) |
| **Intensive care needs in the first 24 hours#** | | 24 (1.6) |
| **Mortality in the first 24 hours** | | 1 (0.1) |
| **Mortality in the first 7 days#** | | 10 (0.7) |
| **Mortality in the first 28 days** | | 41 (2.7) |

# n (%). & Median (IQR 25-75)

**Table 2. Clinical and Laboratory Data of the Patients**

| Variables | Value |
|---|---|
| Quick COVID-19 Severity Index Median IQR (25-75) | 0 (0-0) |
| COVID-GRAM Critical Illness Risk Score Median IQR (25-75) | 63(37-90) |
| Fever Mean ± SD | 36.92 ± 0.58 |
| Heart Rate Median IQR (25-75) | 90 (80-98) |
| SBP mm/Hg Median IQR (25-75) | 130 (120-150) |
| DBP mm/Hg Median IQR (25-75) | 80 (75-90) |
| Oxygen Saturation Median IQR (25-75) | 96 (94-98) |
| Respiratory Count Median IQR (25-75) | 17 (15-20) |
| Length of Hospitalization Mean ± SD | 3.77 ± 5.39 |
| LDH Mean ± SD | 254.73 ± 118.87 |
| D-dimer Mean ± SD | 1.16 ± 10.99 |
| Troponin Mean ± SD | 9.71 ± 39. 71 |
| CRP Mean ± SD | 34.83 ± 63.51 |
| Ferritin Mean ± SD | 203.91 ± 321.52 |
| Leukocyte Count Mean ± SD | 6526.2 ± 2.61 |
| Neutrophil count Mean ± SD | 4134.2 ± 2.19 |
| Lymphocyte count Mean ± SD | 1666.1 ± 0.78 |
| NLR Mean ± SD | 3.30 ± 4.10 |
| Hemoglobin Mean ± SD | 13.75±1.76 |
| Platelets Mean ± SD | 240556±7960 |
| Bilirubin Mean ± SD | 0.40±0.30 |

SBP: Systolic Blood Pressure. DBP: Diastolic Blood Pressure. LDH; Lactate dehydrogenase. CRP; *C-reactive protein*. NLR: Neutrophil/Lymphocyte Ratio

Chi-square/Fisher's exact analysis performed to determine the relationship between comorbidities and 28-day mortality showed a significant relationship between age (p<0.001), comorbidity (p<0.001), HT (p<0.001), DM (p<0.001), CAD (p<0.001), CRF

**Table 3. Relationship between the Presence of Comorbidities and 28-Day Mortality**

| Variables | | | 28-Day Mortality | | Ki-kare/Fisher's exact test |
|---|---|---|---|---|---|
| | | | No | YES | |
| Age | | | 42 (32-58) | 70 (64-81) | **p<0.001**# |
| Gender | Woman | n (%) | 746 (97.8) | 17 (2.2) | p>0.05& |
| | Male | n (%) | 712 (96.7 ) | 24 (3.3) | |
| Comorbidity | No | n (%) | 1064 (99.8) | 2(0.2) | **p<0.001&** |
| | Yes | n (%) | 394 (91.0) | 39 (9.0) | |
| HT | No | n (%) | 1183 (99.3) | 8 (0.7) | **p<0.001&** |
| | Yes | n (%) | 275 (89.3) | 33 (10.7) | |
| DM | No | n (%) | 1330 (98.7) | 17 (1.3) | **p<0.001&** |
| | Yes | n (%) | 128 (84.2) | 24 (15.8) | |
| CAD | No | n (%) | 1358 (98.3) | 23 (1.7) | **p<0.001&** |
| | Yes | n (%) | 100 (84.7) | 18 (15.3) | |
| CKF | No | n (%) | 1436 (97.6) | 35 (2.4) | **p<0.001&** |
| | Yes | n (%) | 22 (78.6) | 6 (21.4) | |
| COPD/Asthma | No | n (%) | 1391 (97.3) | 39 (2.7) | p>0.05& |
| | Yes | n (%) | 67 (97.1) | 2 (2.9) | |
| malignancy | No | n (%) | 1443 (97.3) | 40 (2.7) | p>0.05& |
| | Yes | n (%) | 15 (93.8) | 1 (6.3) | |
| CVH | No | n (%) | 1440 (97.6) | 35 (2.4) | **p<0.001&** |
| | Yes | n (%) | 18 (75.0) | 6 (25.0) | |
| Total | | n (%) | 1458 (97.3) | 41 (2.7) | |

&; Fisher's exact test. HT; Hypertension. DM; Diabetes Mellitus. CAD: Coronary Artery Disease. CKD; Chronic Kidney Failure. COPD; Chronic Obstructive Pulmonary Disease. CVH; Cerebrovascular Disease # Mann Whitney U Test

(p<0.001) and other comorbidities and 28-day mortality, respectively (Table 3).

The Mann Whitney U test performed to investigate whether there was a difference between qCSI and CGCIRS and 28-day mortality showed that qCSI (p<0.001) and CGCIRS (p<0.001) were significantly different in patients with mortality at 28 days, respectively (Table 4).

**Table 4. Relationship between qCSI and CCGIRS and 28-Day Mortality**

| | 28-day mortality | n | Value | p value # |
|---|---|---|---|---|
| Quick COVID-19 Severity Index | No | 1458 | 0 (0-0) | **<0.001** |
| | Yes | 41 | 12 (9.5-12) | |
| | Total | 1499 | 0 (0-0) | |
| COVID-GRAM Critical Illness Risk Skoru | No | 1458 | 61 (37-87) | **<0.001** |
| | Yes | 41 | 149 (131-171) | |
| | Total | 1499 | 63 (37-90) | |

# Mann Whitney U Test

In the ROC analysis of qCSI and CGCIRS for 28-day mortality, the area under the curve (AUC) value of qCSI was 0.966 [(95% CI: 0.934-0.998), (p<0.001)] and the AUC value of CGCIRS was 0.971 [(95% CI: 0.959-0.983), (p<0.001)] (Figure 1)

qCSI has a sensitivity of 97.6% and specificity of 84.0% for 28-day mortality with a cut-off value of 4.5, and a sensitivity of 92.7% and specificity of 84.0% with a cut-off value of 5.5. 91.5%. In 28-day mortality, CGCIRS had a sensitivity of 95.1% and specificity of 91.2% with a cut-off value of 116.5 and a sensitivity of 92.7% and specificity of 91.5% with a cut-off value of 117.5 (Table 5).

In the Spearman correlation analysis performed to investigate whether there was a relationship

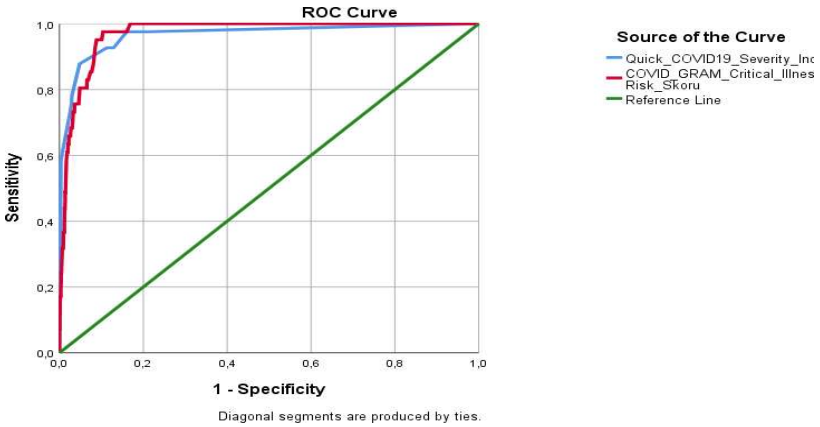


**Figure 1.** ROC Analysis Curve Showing the Effect of Variables on 28-Day Mortality

between qCSI, CGCIRS, LDH, D-dimer, Troponin, CRP, ferritin, and NLO levels of the patients, qCSI was correlated with CGCIRS (p<0.001, r= 0.613), LDH (p<0.001, r= 0.613), LDH (p<0, 001, r= 0.3711), D-dimer (p<0.001, r= 0.296), Troponin (p<0.001, r= 0.393), CRP (p<0.001, r= 0.322), ferritin (p<0.001, r= 0.249) and NLO (p<0.001, r= 0.169) levels (Table 6).

**Table 5. 28-Day Mortality Rate of Variables According to ROC Analysis**

| AUC (% 95 CI) | p | Risk Factor | Cut-off value | Sensitivity % | Specified % |
|---|---|---|---|---|---|
| 0.966 (0.934-0.998) | <0.001 | Quick COVID-19 Severity Index | 4.5 | 97.6 | 84 |
| | | | 5.5 | 92.7 | 91.5 |
| | | | 6.5 | 87.8 | 91.9 |
| 0.971 (0.959-0.983) | <0.001 | COVID-GRAM Critical Illness Risk Score | 116.5 | 95.1 | 91.2 |
| | | | 117.5 | 92.7 | 91.5 |
| | | | 118.5 | 87.8 | 91.9 |

AUC: Area Under the Curve; CI: Confidence Interval

## DISCUSSION

It is known that rapid and reliable biomarkers and scoring systems are critical for prognosis prediction in patients admitted to the emergency department and diagnosed with Covid-19 pneumonia. Prognosis prediction plays an important role in making decisions such as whether the patient should be treated as an outpatient or hospitalized and followed up. Our study found that qCSI has a high sensitivity (97.6%) and a slightly lower specificity (84.0%) and may be less successful in accurately ruling out true negative results. On the other hand, we found that CGCIRS had lower sensitivity (95.1%) and higher specificity (91.2%) than qCSI, meaning that it may be more successful in ruling out true negative results. However, in terms of implementation, we found that qCSI was faster and more practical and could more quickly predict a patient's ICU admission decision without waiting for laboratory results.

**Table 6. Spearman Correlation Analysis of Variables**

| Variables | | qCSI | CGCIRS | LDH | D-dimer | Troponin | CRP | Ferritin | NLR |
|---|---|---|---|---|---|---|---|---|---|
| **qCSI** | r | 1 | *.613*** | *.371*** | *.296*** | *.393*** | *.322*** | *.249*** | *.169*** |
| | p | | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* |
| **CGCIRS** | r | *.613*** | 1 | *.585*** | *.419*** | *.557*** | *.440*** | *.344*** | *.304*** |
| | p | *<0.001* | | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* |
| **LDH** | r | *.371*** | *.585*** | 1 | *.281*** | *.337*** | *.344*** | *.365*** | *.194*** |
| | p | *<0.001* | *<0.001* | | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* |
| **D-dimer** | r | *.296*** | *.419*** | *.281*** | 1 | *.336*** | *.319*** | *.103*** | *.204*** |
| | p | *<0.001* | *<0.001* | *<0.001* | | *<0.001* | *<0.001* | *<0.001* | *<0.001* |
| **Troponin** | r | *.393*** | *.557*** | *.337*** | *.336*** | 1 | *.312*** | *.281*** | *.206*** |
| | p | *<0.001* | *<0.001* | *<0.001* | *<0.001* | | *<0.001* | *<0.001* | *<0.001* |
| **CRP** | r | *.322*** | *.440*** | *.344*** | *.319*** | *.312*** | 1 | *.281*** | *.310*** |
| | p | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | | *<0.001* | *<0.001* |
| **Ferritin** | r | *.249*** | *.344*** | *.365*** | *.103*** | *.281*** | *.281*** | 1 | *.134*** |
| | p | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | | *<0.001* |
| **NLR** | r | *.169*** | *.304*** | *.194*** | *.204*** | *.206*** | *.310*** | *.134*** | 1 |
| | p | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | *<0.001* | |

qCSI; Quick COVID- 19 Severity Index. CGCIRS; COVID-GRAM Critical Illness Risk Score LDH: Lactate dehydrogenase. CRP; *C-reactive protein*. NLR: Neutrophil/Lymphocyte Ratio

There are many reports that COVID-19 is more severe in men. One meta-analysis analyzed 39 studies and 77,932 patients. In this analysis, it was found that men were significantly more at risk for a severe course of the disease (OR=1.63; 95% CI=1.28-2.06), men had a higher mortality rate than women (OR=1.71; 95% CI=1.51-1.93), and the mortality rate increased in the subgroup analysis over the age of 50 (OR=1.94; 95% CI=1.16-3.26) [7]. In a study by Fang et al., it was shown that men were at higher risk for the development of acute respiratory distress syndrome, the need for intensive care, the need for invasive ventilation, cardiac abnormalities, and death [8]. In a study conducted by Sezgin et al. with 248 patients, no significant difference was found between genders [9]. In our study, although the disease was more common in men, no significant difference was found between genders. In the literature, it has been shown in many studies that disease severity and mortality increase with advancing age. In a study of 548 patients in

China, advanced age was associated with the severity of COVID-19. In addition, it was found that 56.9% of patients aged 65 years and older and 26.9% of patients younger than 65 years had severe disease [10]. In a review of patients with SARS-CoV-2 pneumonia by Sagnelli et al., it was reported that advanced age was considered an important risk factor [11]. In a study of 191 patients, age was an independent risk factor for mortality (OR=1.10, 95% CI=1.03-1.17 increase per year; p=0.0043) [12]. The median age of the patients in our study was 43 years (IQR,25-75: 32-59). The mortality rate increased with age, and there was a correlation between 28-day mortality and increasing age. Our results show a statistically significant relationship between age and mortality, parallel to other studies.

One of the risk factors of COVID-19 is the presence of comorbid diseases. In a systemic analysis, a relationship was found between the presence of comorbid diseases and the severity of COVID-19 [8]. In a meta-analysis by Wang et al., it was found that COVID-19 was more severe, and the mortality rate was higher in the patient group with comorbid diseases [13]. A meta-analysis by Khan et al. analyzed 27,670 cases from 40 studies and found that the most common comorbidities in COVID-19 patients were hypertension (39.5%), cardiovascular disease (12.4%), and diabetes (25.2%). In this meta-analysis, COVID-19 patients with pre-existing comorbidities were proven to have a higher risk of death [14]. One or more comorbid diseases were identified in 433 (28.9%) of the patients included in our study. The most common diseases were hypertension (n=308, 20.5%) and diabetes mellitus (n=152, 10.1%), respectively. The need for intensive care and mortality were found to be higher in patients with comorbid diseases.

In a systematic meta-analysis by Rodriguez-Morales et al., the most common complaints were fever (88.7%), cough (57.6%), and dyspnea (45.6%) [15]. In a study by Satıcı et al., 681 patients were analyzed, and the most common presenting complaints were cough (71.2%), fever (32.5%), and dyspnea (27.3%) [16]. Similarly, the most common symptoms and findings in the patient population included in our study were fatigue (n=787, 52.5%), cough (n=739, 48.2%), muscle/joint pain (n=736, 49.1%) and fever (n=556, 37.1%).

Elevated D-dimer levels are a reliable coagulation parameter in predicting poor prognosis and mortality. A retrospective study of 343 patients reported that in-hospital mortality could be predicted with a sensitivity of 92.3% and specificity of 83.0% when the D-dimer cut-off value was 2.0 µg/ml [17]. In a study conducted in China, D-dimer levels were statistically significantly higher in patients who needed intensive care than patients who did not need intensive care (p=0.0042) [18]. In a systemic review of prognostic factors in COVID-19 patients, D-dimer elevation was found to be associated with both severe disease and mortality [19]. Our study found a significant correlation between D-dimer level and 28-day mortality (p<0.001). The relationship between mortality and D-dimer level is consistent with the literature.

The qCSI score developed by Haimovich et al. [4] effectively predicts the risk of critical respiratory illness in COVID-19 patients and can help predict the need for ICU. In a study by Shi et al., 257 patients were included. It was reported that CURB-65 was better in predicting death in hospitals than CGCIRS, and the negative predictive value of CURB-65 was found to be 97.2% for death in hospitals and 88.1% for critical illness [20]. According to Arminanzas et al. [21], CGCIRS was more successful than CURB-65 in predicting the severity of COVID-19 disease, but both scores could be used for risk stratification. Another study found that CURB 65 was superior to qCSI in predicting mortality [22].

Rodriguez-Nava et al. [23] found that qCSI successfully predicted intensive care unit admission in COVID-19 patients. In our study, qCSI had a higher sensitivity for 28-day mortality than CGCIRS, while CGCIRS had a higher specificity for 28-day mortality than qCSI.

## CONCLUSION

qCSI is a scale used to assess the risk of 28-day mortality. With a low cut-off value, qCSI has a high sensitivity and ability to detect true positive results accurately. However, it has a slightly lower specificity and may be less successful in accurately ruling out true negative results.

CGCIRS is also a score used to assess 28-day mortality risk. CGCIRS again has a high sensitivity and ability to detect true positive results accurately. Its specificity is also slightly higher than qCSI, so it may be more successful in ruling out true negative results. However, it is important to note that qCSI is faster and more practical in application and can predict the patient's ICU admission decision faster without waiting for laboratory results.

Regarding ease of use, qCSI is superior in

identifying critically ill patients with COVID-19 in the Emergency Department. However, the use of CGCIRS is also useful.

## Limitations

In this study, one of the most important limiting factors was the study's retrospective nature and the fact that data searches were performed through files and the Hospital Information Management System. In addition, the single-center nature of the study and the fact that some patients had to be excluded due to missing data are other limitations of our study. In this study, one of the most important limiting factors was the study's retrospective nature and the fact that data searches were performed through files and the Hospital Information Management System. In addition, the single-center nature of the study and the fact that some patients had to be excluded due to missing data are other limitations of our study.

*Conflict of Interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Ethical Approval*

The protocol of the study was approved by the Medical Ethics Committee of Bursa Yüksek Ihtisas Training & Research Hospital, Bursa, Türkiye. (Decision number: 2011-KAEK-25 2021/02-07).

*Authors' Contribution*

Study Conception: BN, MOA; Study Design: MY, HK; Literature Review: BN, YI, MY; Critical Review: HK, MY; Data Collection and/or Processing: YI, MY, HK,; Analysis and/or Data Interpretation: YI, HK; Manuscript preparing: BN, YI, MOA.

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# The efficacy of levonorgestrel intrauterine device, medroxyprogesterone acetate, and norethisterone acetate in the treatment of endometrial hyperplasia without atypia

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## ABSTRACT

**Objectives:** Pregestational treatments, which trigger apoptosis and suppress endometrium, are the gold standard therapy for endometrial hyperplasia without atypia. The levonorgestrel-intrauterine device is the first choice in current guidelines due to its low dose. Still, oral progestins have no clear evidence due to their lower regression rates and side effects. Here, we aimed to compare the regression rates, hysterectomy requirement, and the occurrence of side effects in the sixth month between the levonorgestrel-intrauterine device, norethisterone acetate, and medroxyprogesterone acetate treatment.

**Methods:** A total of 60 patients were included. The study group was divided into three groups: levonorgestrel-intrauterine device group (n=20), norethisterone acetate group (n=20), and medroxyprogesterone acetate group (n=20). Demographic findings, body mass index, gravida, parity, comorbid diseases, regression, hysterectomy requirement, patient desire to continue treatment, and side effects such as amenorrhea, headache, weight gain, intermenstrual spotting, nausea, and breast tenderness were compared between three groups.

**Results:** There was no statistically significant difference between the three groups regarding headache, weight gain, intermenstrual spotting, and breast tenderness. Regression rates were significantly higher in the levonorgestrel intrauterine device group compared to medroxyprogesterone acetate (p=0.044) and norethisterone acetate group (p=0.020). Similarly, hysterectomy rates were significantly lower in the levonorgestrel intrauterine device group compared to medroxyprogesterone acetate (p=0.031) and norethisterone acetate group (p=0.028). Amenorrhea was significantly more common in the levonorgestrel intrauterine device group than in other groups (p=0.020 for both), whereas nausea was rarer in the levonorgestrel intrauterine device group (p=0.047 for both). According to the patient's satisfaction, the levonorgestrel intrauterine device was the most satisfactory treatment compared to medroxyprogesterone acetate and norethisterone acetate (p=0.028 and p=0.031). No significant difference was found between the medroxyprogesterone acetate and norethisterone acetate groups in terms of regression rates, hysterectomy requirements, amenorrhea, nausea, and patient satisfaction.

**Conclusion:** Considering low hysterectomy requirement, high regression rates, and patient satisfaction, the levonorgestrel intrauterine device should be the first choice for endometrial hyperplasia without atypia as compared to oral progestins. Thus, patients must be informed about side effects and offered levonorgestrel intrauterine devices before oral progestins for endometrial hyperplasia without atypia.

**Keywords:** medroxyprogesterone acetate, endometrial hyperplasia, levonorgestrel-intrauterine device, norethisterone acetate, oral progestins

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## INTRODUCTION

Endometrial hyperplasia, the increment of the endometrial gland to stroma ratio, is a precursor for genital malignancies, especially endometrioid endometrial carcinoma [1]. The most significant risk factor for progression to malignancy is atypia [2]. Hyperplasia without atypia progresses to endometrial cancer with a 1-3% chance. It has nearly 72% rates of regression with expectant management and 89-96% rates of regression with progesterone treatment [3]. Contrary to this, hyperplasia with atypia has 8-30% malignancy and a 54% regression chance [4].

Appropriate treatment is crucial in endometrial hyperplasia, not developing a malignancy. Treating endometrial hyperplasia without atypia involves expectant management, progesterone, and surgery [5]. Considering the regression rates, hysterectomy could be a too-invasive way for endometrial hyperplasia without atypia, and they have generally been treated with progestins [6].

Progesterone treatment decreases glandular cellularity, inactivates endometrium, and results in pseudo-decidualization [7]. However, progestins are very effective in endometrial hyperplasia; side effects such as weight gain, headache, amenorrhea, nausea, mood changes, and thromboembolic events limit the usage of these agents [2]. Although initial treatment regimens had high doses and long duration, current practice focused on using fewer doses, shorter duration, and lesser side effects [8].

Levonorgestrel intrauterine device (LNG-IUD) contains 52 mg of levonorgestrel and releases 20 µg daily to the endometrial cavity, resulting in high endometrial and low blood concentration [9]. A systematic review reported higher regression rates for LNG-IUD than oral progestins for endometrial hyperplasia without atypia [10]. There is no clear evidence of oral progestin being the first choice. It is known that oral progestins do not always provide regression, and they also have systemic side effects [11].

Here, we aimed to compare the regression rates, hysterectomy requirement, and the occurrence of side effects in the sixth month between LNG-IUD, norethisterone acetate (NETA), and medroxyprogesterone acetate (MPA) treatment.

## METHODS

This retrospective study was conducted at a university-affiliated research and training hospital between January 2019 and January 2024. The present study was approved by the local ethics committee (decision number 2024-TBEK 2024/07-08), and it complies with the declaration of Helsinki. Written informed consent was obtained from all patients when using medical records.

### Study Population

A total of 168 patients who attended the University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital, Obstetrics and Gynecology Department outpatient clinic and were diagnosed with endometrial hyperplasia without atypia were initially searched for the study.

Inclusion criteria were composed of being 18-65 years old, having a detailed history, clinical examination, pap-smear, and endometrial biopsy results. Patients who have any contraindications for endometrial sampling and progesterone treatment, whose pathology results are other than hyperplasia without atypia, who have any pathology causing abnormal uterine bleeding or uterine anomaly, who have using hormonal therapy in the last six months, having liver disease, thromboembolic events, mammary cancer and who have unavailable data were excluded.

After selecting according to the inclusion and exclusion criteria, 60 patients were included in the study. The study group was divided into three groups the LNG-IUD group (n=20), the NETA group (n=20), and the MPA group (n=20).

A levonorgestrel-intrauterine device was inserted in the uterine cavity after menstruation. Norethisterone acetate was routinely prescribed as 15 mg/day for ten days, while MPA was prescribed 10 mg/day. Oral progestins were used for 10 days in a month (from the 16th day to the 25th day). All treatments were performed during six months.

Pipelle endometrial suction curette was used for endometrial sampling for each group in our clinic. Pipelle is a sterile, plastic, disposable curette used for sample extraction of the uterus. It has the advantage of needing no cervical dilatation. Biopsy results after treatment were evaluated as regression if no hyperplasia was detected at six months.

Demographic findings, body mass index, gravida, parity, comorbid diseases, pathology results before and after treatment, hysterectomy requirement, and side effects such as amenorrhea, headache, weight gain,

intermenstrual spotting, nausea, and breast tenderness were noted and compared between three groups. Also, patient satisfaction (willingness to continue treatment) was recorded.

The study's primary outcome was the regression of hyperplasia in the sixth month. The secondary outcome was the occurrence of side effects of treatment and hysterectomy requirement.

### Statistical Analysis

Shapiro Wilk test was used to analyze the distribution characteristics of variables. Variables were presented as mean (±standard deviation), median (minimum-maximum) values for continuous variables, and frequency (percentages) for categorical variables. The one-way ANOVA test was used to compare continuous nonparametric variables, while the Kruskal-Wallis test was used for non-normally distributed ones. Qualitative variables were compared with Chi-square or Fisher Freeman Halton test. Analyzes were carried out by using SPSS version 22.0 software. A p-value ≤0.05 was accepted as statistically significant.

## RESULTS

The demographic findings of the study participants are demonstrated in Table 1. The three groups had no significant difference regarding age, body mass index, gravida, parity, presence, and distribution of comorbid diseases.

**Table 1.** Demographic findings of the study participants

| | LNG-IUD (n=20) | MPA (n=20) | NETA (n=20) | p |
|---|---|---|---|---|
| **Age (years)** | 43.1 ± 6.02 | 42.75 ± 6.52 | 43.7 ± 5.36 | 0.879 |
| **Body mass index (kg/m²)** | 31.8 (27.2-36.7) | 29.9 (23.5-37.1) | 32.3 (23.5-37.1) | 0.340 |
| **Gravida (n)** | 3 (1-6) | 3 (1-6) | 3 (1-5) | 0.918 |
| **Parity (n)** | 3 (1-4) | 3 (1-4) | 2.5 (1-4) | 0.876 |
| **Presence of comorbid disease (n, %)** | 4 (20%) | 3 (15%) | 4 (20%) | 1.000 |
| **Comorbid disease (n, %)** | | | | 1.000 |
| - **Hypertension** | 2 (10%) | 2 (10%) | 2 (10%) | |
| - **Diabetes mellitus** | 2 (10%) | 1 (5%) | 2 (10%) | |

Regression rates, hysterectomy requirement, and side effects of treatment groups are shown in Table 2. The three groups had no statistically significant difference according to headache, weight gain, intermenstrual spotting, and breast tenderness. Regression rates, hysterectomy requirement, patient satisfaction, the incidence of amenorrhea, and nausea were significantly different in at least one group.

**Table 2.** Regression rates, hysterectomy requirement, and side effects of treatment groups

| | LNG-IUD (n=20) | MPA (n=20) | NETA (n=20) | p |
|---|---|---|---|---|
| **Regression (n, %)** | 19 (95%) | 13 (65%) | 12 (60%) | **0.031** |
| **Hysterectomy (n, %)** | 2 (10%) | 9 (45%) | 8 (40%) | **0.045** |
| **Amenorrhea (n, %)** | 6 (30%) | 0 (0%) | 0 (0%) | **0.002** |
| **Headache (n, %)** | 8 (40%) | 7 (35%) | 7 (35%) | 1.000 |
| **Weight gain (n, %)** | 3 (15%) | 3 (15%) | 3 (15%) | 1.000 |
| **Intermenstrual spotting (n, %)** | 5 (25%) | 3 (15%) | 3 (15%) | 0.766 |
| **Nausea (n, %)** | 0 (0%) | 5 (25%) | 5 (25%) | **0.036** |
| **Breast tenderness (n, %)** | 1 (5%) | 2 (10%) | 3 (15%) | 0.863 |
| **Patient satisfaction (n, %)** | 18 (90%) | 12 (60%) | 11 (55%) | **0.036** |

A pairwise comparison of significant variables was presented in Table 3. Regression rates and hysterectomy requirements were significantly higher in the LNG-IUD group as compared to MPA (p=0.044) and NETA (p=0.020). Similarly, hysterectomy rates were significantly higher in the LNG-IUD group than in MPA (p=0.031) and NETA (p=0.028). Amenorrhea was significantly more common in the LNG-IUD group than in other groups (p=0.020 for both), whereas nausea was rarer in the LNG-IUD group (p=0.047 for both). According to the patients' satisfaction, LNG-IUD was the most satisfactory treatment compared to MPA and NETA (p=0.028 and p=0.031). No significant difference was found between the MPA and NETA groups in terms of regression rates, hysterectomy requirement, amenorrhea, nausea, and patient satisfaction.

**Table 3.** Pairwise comparison of significant variables

| | p LNG-IUD and MPA | p LNG-IUD and NETA | p MPA and NETA |
|---|---|---|---|
| **Regression (n, %)** | **0.044** | **0.020** | 0.744 |
| **Hysterectomy (n, %)** | **0.031** | **0.028** | 0.749 |
| **Amenorrhea (n, %)** | **0.020** | **0.020** | 1.000 |
| **Nausea (n, %)** | **0.047** | **0.047** | 1.000 |
| **Patient satisfaction (n, %)** | **0.028** | **0.031** | 1.000 |

## DISCUSSION

Endometrial hyperplasia, defined as the excessive growth of epithelial cells in the endometrium, can be classified into two subtypes: endometrial hyperplasia without atypia and atypical hyperplasia. Although expectant management is a treatment option for endometrial hyperplasia without atypia in cases with risk factors but no clinical symptoms, it is unclear how often these patients would be observed [5]. Thus, progesterone is the most used treatment option in endometrial hyperplasia without atypia, with higher remission rates than expectant management [10,12,13].

Current literature suggests that LNG-IUD is the preferred regimen because of its fewer side effects and higher remission rates [10,14,15]. However, the oral progestin regimen is still the first choice for patients who opt against LNG-IUD. Oral progesterone treatment could be performed continuously or cyclically, and the

remission rates are similar [16]. Medroxyprogesterone acetate, megestrol acetate, dydrogesterone, and norethisterone are the most commonly used oral progestins in endometrial hyperplasia [3,17,18].

A meta-analysis including 7 randomized controlled trials and searching the efficacy of LNG-IUD in endometrial hyperplasia without atypia reported higher regression rates than oral progestins [19]. A Cochrane study with 11 randomized controlled trials showed that the regression rates were 85-92% for LNG-IUD and 72% for oral progestins [15]. In a study by Shen et al., LNG-IUD and oral progestins were compared, and LNG-IUD showed a 93% regression rate, whereas oral progestins showed a 66% regression rate [11]. The same study concluded that LNG-IUD is seven times more effective than oral progestins for the regression of endometrial hyperplasia. Also, the time to regression was longer in the oral progestin group than in the LNG-IUD group [11]. A study by Orbo et al. claimed that cyclic oral progestins are less effective than LNG-IUD [20]. In a systematic review of Gallos et al., hyperplasia was grouped as complex and simple. LNG-IUD had a higher regression rate as compared to oral progestins in complex endometrial hyperplasia, while it had similar regression rates in simple hyperplasia [15].

Current studies are focused on comparing LNG-IUD and oral progestin forms separately. In a study by El Behery et al., LNG-IUD and dydrogesterone were compared. After six months, LNG-IUD had a higher regression rate of 96%, and dydrogesterone was 80% [3]. In a meta-analysis searching 12 studies reported 96.7% regression rates for LNG-IUD and 71.7% for MPA which was statistically significant [21]. Vereide et al compared LNG-IUD and cyclic MPA for 3 months in all types of endometrial hyperplasia in their study and showed higher regression rates for LNG-IUD [22]. Another study searching the effects of LNG-IUD and MPA for six months in all endometrial hyperplasia types was performed by Orbo et al. and obtained 100% effectiveness with LNG-IUD, which was significantly higher than MPA [23]. Ismail et al. compared the role of LNG-IUD, MPA, and NETA in premenopausal women. This study demonstrated the highest resolution rate without obvious side effects with LNG-IUD compared to MPA and NETA [24]. A meta-analysis including 4 randomized controlled trials showed 86.5% regression rates for LNG-IUD and 64.2% regression rates for NETA [21]. Many studies compared different oral progestogens in the treatment of endometrial hyperplasia. Reed et al. demonstrated that no difference between oral progestogens was present [25]. Girbash et al. compared dienogest and NETA in managing endometrial hyperplasia without atypia. Dienogest showed a better regression rate than NETA [2]. Four randomized controlled trials comparing MPA and NETA reported similar regression rates [21].

In Turkey, there are a few studies about the treatment options of endometrial hyperplasia without atypia. In a study by Gezer et al., the efficiency of vaginal micronized progesterone was compared with LNG-IUD, and vaginal micronized progesterone was found as effective as LNG-IUD [26]. Uysal et al. compared dienogest, depo MPA, and micronized progesterone, and the complete resolution rate was found to be 93.5% in micronized progesterone, 88.5% in MPA and 96.9% in the dienogest group [27]. In another study, lynestrenol and micronized progesterone were compared in simple endometrial hyperplasia without atypia in perimenopausal women. The study found that lynestrenol had better endometrial control than micronized progesterone [28]. Ozdegirmenci et al. compared MPA, lynestrenol, and NETA in endometrial hyperplasia without atypia and reported no difference between the three agents [29]. Our study compared LNG-IUD, MPA, and NETA for the regression rates in endometrial hyperplasia without atypia. We found a 95% regression rate for LNG-IUD, 65% for MPA, and 60% for NETA. While no difference was present between MPA and NETA, LNG-IUD was superior to the two treatments for regression. Our results were in accordance with the literature.

Hysterectomy is an important issue for female well-being. So, the selection of patients for hysterectomy has a crucial role. Karimi-Zarchi et al. reported lower hysterectomy rates in LNG-IUD than in MPA [30]. Girbash et al. compared dienogest and NETA in managing endometrial hyperplasia without atypia and showed lower hysterectomy rates than NETA [2]. The present study showed lower hysterectomy rates in LNG-IUD than in MPA and NETA groups.

Another issue about progesterone treatment is its side effects. Girbash et al. reported similar irregular bleeding, nausea, and mastalgia with NETA as compared to dienogest [2]. Likewise, Uysal et al. found similar side effects between dienogest, MPA, and micronized progesterone [27]. In contrast, other research showed an increased tendency for thromboembolism for dienogest [31,32]. In a study by El Behery et al., intermenstrual spotting and amenorrhea were more common in the LNG-IUD

group than in the dienogest group [3]. We found higher rates of amenorrhea in LNG-IUD as compared to MPA and NETA. Nausea was more common in both MPA and NETA groups than in LNG-IUD.

Regression, hysterectomy rates, and side effects are the representatives of patient satisfaction. Only limited data on patient satisfaction with progesterone is present in the literature. Karimi-Zarich reported higher satisfaction in LNG-IUD than in MPA [30]. Similar to this study, Rezk et al. found higher satisfaction rates for LNG-IUD than MPA and NETA [33]. Our study found higher satisfaction rates for LNG-IUD than for MPA and NETA. No significant difference was present between MPA and NETA.

This study has some limitations. It has a small sample size and retrospective design. It lacks long-term follow-up data and other commonly used oral progesterone agents. The menopausal status was not considered. Lastly, no continuous and cyclic therapy for oral progestins was compared.

## CONCLUSION

Considering low hysterectomy requirement, high regression rates and patient satisfaction, levonorgestrel intrauterine device should be the first choice for endometrial hyperplasia without atypia compared to oral progestins. Thus, patients must be informed about side effects and offered levonorgestrel intrauterine devices before oral progestins for endometrial hyperplasia without atypia.

*Conflict of Interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Ethical Approval*

The protocol of the study was approved by the Medical Ethics Committee of Bursa Yuksek Ihtisas training & research hospital, Bursa, Türkiye. (Decision number: 2024-TBEK 2024/07-08).

*Authors' Contribution*

Study Conception: BD, GO, LO; Study Design: BD; Literature Review: LO; Critical Review: GO; Data Collection and/or Processing: LO; Analysis and/or Data Interpretation: BD; Manuscript preparing: BD, GO.

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# What should be the anatomical target in deep brain stimulation in an essential tremor plus rest tremor case? Technical case report of deep brain stimulation

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## ABSTRACT

While Deep Brain Stimulation (DBS) of Subthalamic Nucleus (STN) is effective on resting tremors, but its effectiveness on postural and kinetic tremors is limited. DBS of the Ventral Intermediate Nucleus (VIM) is effective on many types of tremors, especially postural and kinetic tremors, but its effect is weak on motor symptoms in Parkinson's disease (PD). Although there is a consensus in the literature about where the anatomical target should be in essential tremor (ET) and PD, there are only case reports about where the anatomical target should be in Essential Tremor Plus Rest Tremor (ET+RT) cases. In this article, we aimed to reveal the effectiveness of STN DBS in a case-diagnosed with ET+RT. The patient had action tremors in both upper extremities for 21 years and developed rest tremors in both upper and lower extremities for the last six years. Rest tremor was effectively controlled with bilateral STN DBS. Postural tremor in the right upper extremity was continued, although it decreased.STN may be an appropriate choice when choosing an anatomical target in DBS in cases of resting, postural, and kinetic tremor.

***Keywords:*** Essential tremor plus rest tremor, deep brain stimulation, subthalamic nucleus

Tremor is defined as rhythmic, involuntary movements seen in body parts. We can categorize tremors under two headings: physiological and pathological tremors. While physiological tremor occurs with excitement and anxiety, pathological tremors can almost always be seen [1].

Essential tremor (ET) is defined as action tremor in the upper extremities that has persisted for at least 3 years. It is one of the most common types of tremors. While the incidence rate in all age groups is 0.4-0.9%, the incidence rate in individuals over 65 years of age is between 4.6-6.3%. ET is considered to be a risk factor for the development of Parkinson's disease (PD) in the future. In some studies, this risk increases up to 4 times [2]. In our country, its prevalence in the group aged 18-60 was calculated at 226,454 per hundred thousand [3]. The International Parkinson and Movement Disorder Society published a new 2-axis

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classification of tremors in 2018. According to this classification, tremor was divided into two isolated tremor syndrome and combined tremor syndrome according to their clinical features in Axis-1.

ET was included in isolated tremor syndromes. In Axis 2, classification was made according to etiology. When resting tremor, dystonic posture, cognitive impairment, or tandem walking difficulty are added to ET, the term ET-plus is used [4]. ET may change over the years and turn into ET-plus. The most common group among ET-plus cases is Essential Tremor Plus Rest Tremor (ET+RT) [5].

While Deep Brain Stimulation (DBS) of Subthalamic Nucleus (STN) is effective on resting tremor its effectiveness on postural and kinetic tremor is limited. DBS of the Ventral Intermediate Nucleus (VIM) is effective on many types of tremors, especially postural and kinetic tremors, but its effect is weak on motor symptoms in PD [6]. Although there is a consensus in the literature about where the anatomical target should be in DBS in ET and PD there are only case-based studies where the anatomical target should be in DBS in ET+RT cases or in cases where ET and Parkinsonism findings overlap [7-12]. STN may be an appropriate choice when choosing an anatomical target in DBS in cases of resting, postural, and kinetic tremor.

## CASE REPORT

40-year-old male patient complaints started with slim tremors in both hands at the age of 19. During this period, his complaints were mild; he was able to carry out his daily activities without any problems despite the tremors. He enlisted in the military at the age of 20 and was able to use a gun. His complaints increased over the years that tremors appeared in his head and feet as well as in his hands and that he could not do his daily activities in recent years. He used drugs such as propranolol, primidone, gabapentin, L-dopa, and dopamine agonists in his medical history and did not benefit from them. He could not use the drug at the recommended doses due to the development of involuntary movements approximately 1-2 years after starting levodopa+benserazide. He partially benefited from trihexyphenidyl 8 mg/day among the medications given. Routine blood tests were unremarkable. No pathology was detected in Magnetic Resonance Imaging (MRI). There was no family history of tremor. He had never drunk alcohol in his life, so his response to alcohol was unknown. In his neurological examination, resting, postural and action tremors were observed in both upper extremities. Due to severe tremors, bradykinesia could not be evaluated properly in the finger-tapping test. Upper extremity tremor was accompanied by lower extremity and head tremor. Tremor continued intensely during the walk. There was +2 rigidity in the right upper extremity. L-dopa response was examined, but the response could not be evaluated clearly due to the development of severe dyskinesia after L-dopa. ET+RT was considered in the foreground because the patient's complaints had been present for 21 years, The tremor initially started as a bilateral slim tremor and got worse over the years, and while it was only an action tremor at first, rest tremor was also added over the years.

We applied STN DBS to the patient to suppress resting, postural, and kinetic tremors and to control Parkinsonism findings that are likely to become evident in the future. The most effective response was


**Figure-1.** After DBS a significant improvement was observed in the straight line drawing test and spiral drawing test.

obtained at Contact 3. Right STN: amp:5.45 mA, pulse width 60 seconds, frequency 120 Hz. Left STN: amp:6.00 mA, pulse width 60 seconds, frequency 120 Hz. After effective stimulation, we were able to completely control resting tremors in both the upper and lower extremities. İn the right upper extremity, postural and kinetic tremor marked reduced but continued. After DBS, a significant improvement was observed in the straight line drawing test and spiral drawing test (Figure 1). According to the Fahn-Tolosa-Marin tremor rating scale, the score he received after stimulation decreased from 60 to 15.

## DISCUSSION

High-flow nasal cannula (HFNC) oxygen therapRetrospective studies have shown that ET-plus cases constitute 53-84% of ET cases and are more common than ET [13-14]. The most common group among ET-plus cases is ET+RT (5). ET+RT has a heterogeneous structure. There are different opinions about how it emerged. First rest tremor may be a late feature in cases of ET that persists for many years. Secondly, ET+RT may represent a separate disease from ET that develops with different pathophysiological mechanisms. Third, the development of rest tremor in ET may define superimposed PD. Fourth, these cases may have been misdiagnosed as ET and have a different disease, such as dystonic tremor [15]. Considering the change in tremor over the past 21 years of disease we thought that our case was ET+RT.

When the literature was examined, it was seen that different points were targeted in DBS in cases where rest tremor and severe kinetic tremor coexisted. These are:

1. Ventral-intermediate nucleus (VIM) [7]
2. Subthalamic nucleus (STN) [8]
3. STN and VIM with two separate electrodes [9]
4. STN and VIM with a single electrode [10,11]
5. STN and Zona incerta (ZI) with a single electrode [12]

In a retrospective study of 44 patients who underwent VIM DBS, no change was observed in Fahn-Tolosa-Marin Tremor scores between ET and ET-plus cases, and VIM DBS was shown to be as effective as ET in ET-plus cases. It was observed that in ET-plus cases, higher stimulation parameters were needed, and the active electrodes were located more dorsally. This study showed that VIM DBS can be used safely to control tremors in ET-plus cases [7]. Symptom control was achieved with left VIM DBS and right STN DBS in the patient who had ET for 30 years and PD for the last 10 years with resting, postural, and kinetic tremors. In this case, motor symptoms of Parkinson's disease were controlled with STN DBS. ET was able to be controlled due to the effect of STN DBS on the cerebellothalamic pathway [8]. In a 79-year-old treatment-resistant tremor-dominant Parkinson's case there was no adequate response with bilateral VIM-DBS. Dual stimulation was later applied by additionally applying STN-DBS to the left side, and tremor control was achieved by simultaneous stimulation of STN and VIM. In this case, simultaneous stimulation of two separate targets and stimulation of the posterior subthalamic area, where ZI is located, by both electrodes were thought to be effective in tremor control [9].

In some studies, two separate electrodes were used to target the STN and VIM, but due to the risk of bleeding, infection, and increase in cost, stimulation of two points with a single electrode was later brought to the agenda. Targeting VIM and STN with a single electrode was found effective and reliable in controlling the symptoms of a tremor-dominant Parkinsonian patient resistant to L-dopa [10]. VIM and STN were targeted with a single electrode in a tremor-dominant case who was followed up with the diagnosis of PD for eight years. Initially, postural tremor was controlled by stimulating VIM, and it was planned to stimulate the STN to control Parkinson's motor symptoms, which are likely to become more pronounced in the future [11]. In the case of a patient who had ET for many years and PD for the last seven years, symptom control was achieved by stimulating STN and ZI with a single electrode. In the first application using 'Monopolar Directional Montage, ' akinesia, rigidity, and rest tremor were taken under control, but kinetic tremor could not be effectively suppressed. Using "Bipolar Directional Montage," STN and the adjacent ZI were activated simultaneously, and thus, kinetic tremor could be controlled [12].

In our case, we were able to control the rest of the tremors in the left upper extremity and both lower extremities after the bilateral STN DBS application. Although we were able to almost completely control

the rest tremor in the right upper extremity, postural tremor and kinetic tremor continued, albeit partially. In this case, STN+VIM could be targeted with a single electrode on the left side to control the right upper extremity rest and postural tremor. By using the "Bipolar Directional Montage" on the left STN, the adjacent ZI can be activated simultaneously. Or after bilateral STN DBS, left VIM DBS could be applied. However, these were not applied because the patient's clinical condition was good, and he was able to perform all daily life activities comfortably.

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*Conflict of Interest*

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

*Authors' Contribution*

Study Conception: NBP, DY; Study Design: NBP, DY; Literature Review: NBP, DY; Critical Review: NBP, DY; Data Collection and/or Processing: NBP, DY; Analysis and/or Data Interpretation: NBP, DY; Manuscript preparing: NBP, DY.

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