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Original Article

Gilteritinib (XOSPATA®) in Turkey: Early Access Program Results

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Abstract. ***Background And Objectives*: Gilteritinib (XOSPATA ®, Astellas) is a type I oral FLT3 inhibitor, a tyrosine kinase AXL inhibitor, involved in both c-Kit and FMS-like tyrosine kinase 3 (FLT3) resistance. In the phase 3 ADMIRAL trial, gilteritinib was compared with the standard of care in (R/R) acute myeloid leukemia (AML) patients who harbored any FLT3 mutation and showed superior efficacy with regard to response and survival.**
***Objectives*: This research aimed to investigate the real-life efficacy and safety of gilteritinib in FLT3-positive R/R AML patients who were treated as a part of an early access program held in Turkey in April 2020 (NCT03409081).**
***Results*: The research included 17 R/R AML patients who had received gilteritinib from seven centers. The overall response rate was 100%. The most common adverse events were anemia and hypokalemia (7 patients, 41.2%). Grade 4 thrombocytopenia was observed in one patient only (5.9%), leading to permanent treatment discontinuation. Patients with peripheral edema had a 10.47 (95% CI: 1.64-66.82) times higher risk of death than those without peripheral edema ($p<0.05$).**
***Conclusion*: This research showed that patients with febrile neutropenia and peripheral edema were at a high risk of death when compared to patients without febrile neutropenia and peripheral edema.**

Keywords: Gilteritinib; Acute myeloid leukemia (AML); Early access; Real-life data; Response; Prognosis.

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Introduction. Prognosis is relatively poor in relapsed or refractory (R/R) acute myeloid leukemia (AML) that

does not respond to standard induction chemotherapy.[1-3] FMS-like tyrosine kinase 3 (FLT3) is expressed in hematopoietic stem cells as a cytokine receptor tyrosine kinase and plays a role in proliferation and differentiation.[4,5] Approximately 25% of adult AML patients have FLT3-internal tandem duplication (FLT3-ITD) mutations, while 10% have point mutations or deletions of the FLT3 tyrosine kinase domain (FLT3-TKD).[4-6] FLT3-mutated AML patients are more susceptible to relapse than other AML patients.[4-6]

FLT3 tyrosine kinase inhibitors are used in the treatment of AML with different clinical activities.[7-9] As a first-generation FLT3 inhibitor, midostaurin was given combined with standard anthracycline-cytarabine therapy.[10] In contrast to midostaurin and lestaurtinib, which are ineffective as single agents, quizartinib and gilteritinib have proved to exert overt clinical activity as monotherapies.[11,12]

Gilteritinib (XOSPATA®, Astellas) is a type I oral FLT3 inhibitor, a tyrosine kinase AXL inhibitor involved in both c-Kit and FLT3 resistance, as well as FLT3-ITD and T.K.D. mutations.[13,14] The phase 1/2 study of gilteritinib monotherapy confirmed potent inhibition of FLT3-provided receptor autophosphorylation at an 80 mg/day dose with an overall response rate (ORR) of 52%.[14] In the phase 3 ADMIRAL trial,[11] gilteritinib was compared with the standard of care in (R/R) AML patients who harbored any FLT3 mutation and showed superior efficacy with regard to ORR and survival.

This research aimed to investigate the real-life efficacy and safety of gilteritinib in FLT3-positive R/R AML patients who were treated as a part of an early access program held in Turkey in April 2020 (NCT03409081).

Materials and Methods. The research included 17 R/R AML patients who had received gilteritinib as a part of the early access program from seven centers, allowing the use of their data across Turkey between April 2020 and October 2021. In addition to patient demographic and clinical characteristics, their genetic risk classifications for AML, diagnostic information, response to induction therapy, salvage therapy, exposure to FLT3 inhibitors before gilteritinib (midostaurin or sorafenib), clinical course following gilteritinib, adverse event profiles, and survival data (overall survival (OS) and progression-free survival (PFS)) were recorded.

The genetic classification was based on the 2022 ELN risk classification by genetics at initial diagnosis.[4] The patients were required to have either FLT3-ITD or TKD (D835/I836) mutations and all were ITD mutants. Responses to gilteritinib were assessed on day 1 of cycle 2. The ORR was defined as complete remission (CR), CR with incomplete platelet counts (CRp), CR with incomplete hematologic recovery (CRi), and partial remission (PR). The preferred dose of gilteritinib was the same in all patients, with a daily dose of 120 mg, which remained consistent throughout the follow-up period without any necessary adjustments. Any drug-related adverse events of any grade associated with gilteritinib were also noted.

While the primary endpoints of the research were PFS and OS, other endpoints included the factors affecting the adverse event profile and survival. The research was reviewed and approved by the Ethics Committee of Istanbul Training and Research Hospital (Date: 23.12.2022; approval number: 402). It was conducted according to the principles of the Declaration of Helsinki.

Statistical Methods. The central limit theorem is parametric without using a normality test based on fitness tests.[15] However, nonparametric tests were used because the number of previous treatment steps was an ordinal variable, and the deviation from the mean of the time to progression and exitus was too high. The mean, standard deviation, and minimum and maximum values were used in the data analysis to generate the statistics in the continuous structure. The frequency and percentage values were used to define categorical variables. Student's t-test and Mann–Whitney U test were used to comparing the means of two independent groups. Chi-square/exact test statistics were used to evaluate the relationship between categorical variables. The Kaplan–Meier method was used to estimate overall survival curves. The log-rank test was used to determine differences according to risk factors, and the hazard ratio was given with a 95% confidence interval. The statistical significance of the data was taken as $p<0.05$. Data analysis was performed using IBM SPSS version 25 and the MedCalc statistical software.

Results.

Patients. The initial clinical characteristics, follow-up, and survival times of the patients are shown in **Table 1**. The research included 17 patients who were diagnosed with AML The mean age of the patients at diagnosis was 49.8±13.8 years, and the median age was 55 years (range: 27-73). At the time of diagnosis, four patients (23.5%) harbored any cytogenetic feature that placed them in the adverse risk category, according to ELN 2022. The number of patients who received allogeneic transplantation before gilteritinib use was 2 (11.8%). Six patients were exposed to midostaurin before gilteritinib, and only one had received both gilteritinib and sorafenib simultaneously.

Efficacy. The median duration of gilteritinib use was 8.5 (range: 1-21) months. After using gilteritinib, seven patients (41.2%) received allogeneic transplantation and two patients (11.8%) received maintenance therapy after transplantation. All patients had at least PR with gilteritinib. The ORR was 100% (nCR=11, 64.7%;

Table 1. Sociodemographic and clinical characteristics with gilteritinib response status.

Gilteritinib response (Presence of progression)		**Total (n=17)**	**No (n=11)**	**Yes (n=6)**	
		x±≥SD Median (min-max)	**x±≥SD Median (min-max)**	**x±≥SD Median (min-max)**	p value
Age		49.8±13.8 55 (27-73)	50.8±14.8 55 (27-73)	48±12.9 48 (27-61)	0.7
		n (%)	**n (%)**	**n (%)**	
Gender	Female	13 (76.5)	7 (63.6)	6 (100)	0.24
	Male	4 (23.5)	4 (36.4)	-	
Risk Classification by genetics at initial diagnosis	Intermediate	13 (76.5)	8 (72.5)	5 (83.5)	0.99
	Adverse	4 (23.5)	3 (27.3)	1 (16.7)	
Presence of mutations other than FLT3	No	10 (58.8)	7 (63.6)	3 (50)	0.64
	Yes	7 (41.2)	4 (36.4)	3 (50)	
Allogeneic transplantation in previous treatment	No	15 (88.2)	9 (81.8)	6 (100)	0.52
	Yes	2 (11.8)	2 (18.2)	-	
Induction therapy response	No	9 (52.9)	5 (45.5)	4 (66.7)	0.62
	Yes	8 (47.1)	6 (54.5)	2 (33.3)	
Salvage therapy	No	7 (41.2)	4 (36.4)	3 (50)	0.64
	Yes	10 (58.8)	7 (63.6)	3 (50)	
Pre-gilteritinib FLT3 exposure	No	10 (58.8)	6 (54.5)	3 (60)	0.99
	Yes	7 (41.2)	5 (45.5)	2 (40)	
		x±≥SD Median (min-max)	**x±≥SD Median (min-max)**	**x±≥SD Median (min-max)**	
Number of previous treatment steps		2 (1.3) 1 (1-5)	2.3±1.3 2 (1-5)	1.5±1.2 1 (1-4)	0.18

SD: Standard deviation, **FLT3:** FMS-like tyrosine kinase 3. (p<0.05 significance) Student's t|Mann–Whitney U test, Chi-Square|Exact test.

nCRp=3, 17.6%; nCRi=1, 5.9%; nPR=2, 11.8%) (**Table 2**).

Survival Analyses. The median PFS was 300.5 (15-813) days, and the OS was 355.5 (21-905) days with gilteritinib. The statistical analyses were conducted according to the progression status during treatment and there was no significant difference in the mean ages of the two groups (p>0.05). Similarly, there was no significant difference between them in terms of time to relapse, duration of gilteritinib use (months), time to progression (days), or overall survival (days) (p>0.05) (**Table 2**, **Figures 1** and **2**).

Adverse Events and Possible Effects on Survival. The most common adverse events were anemia and hypokalemia (n=7, 41.2%). Grade 4 thrombocytopenia was observed in only one patient (5.9%), which led to permanent treatment discontinuation; no other patient experienced any dose reduction or curtailment (**Supp. Table 1**, **Figure 3**). The median PFS of the patients with febrile neutropenia was 88 (95% CI: 31-88) days, while the median PFS of the patients without febrile neutropenia was 762 (95% CI: 457-762) days (p=0.19). The median PFS of patients with peripheral edema during gilteritinib treatment was 88 (95% CI: 31-88) days, while it was 762 (95% CI: 457-762) days in patients without peripheral edema, with no significant difference (p=0.19). Neither was there a significant PFS difference in terms of adverse events (p>0.05) (**Supp. Table 2**, **Figure 3**).

The mean OS of patients with febrile neutropenia was 96.25 (95% CI: 47.1-145.4) days, while it was longer in patients without febrile neutropenia and 530.5 (95% CI: 310.8-750.2) days (p=0.03). Febrile neutropenia was found to shorten OS significantly. The

Table 2. Efficacy and survival with gilteritinib response status.

Gilteritinib response (Presence of progression)		Total (n=17)	No (n=11)	Yes (n=6)	
		n (%)	n (%)	n (%)	p-value
Gilteritinib usage	Monotherapy	11 (64.7)	8 (72.7)	3 (50)	0.6
	Combination	6 (35.3)	3 (27.3)	3 (50)	
Allogeneic transplantation after gilteritinib	No	9 (52.9)	3 (27.3)	6 (100)	**0.009**
	Yes	8 (47.1)	8 (72.7)	-	
Post-transplant gilteritinib maintenance	No	15 (88.2)	9 (81.8)	6 (100)	0.51
	Yes	2 (11.8)	2 (18.2)	-	
		x±≥SD Median (min-max)	**x±≥SD Median (min-max)**	**x±≥SD Median (min-max)**	
Total gilteritinib usage time (months)		8.62±7.2 8.5 (1-21)	9±7.45 8.5 (1-21)	7.5±7.2 7.5 (1-14)	0.54
Progression-free survival (days)		292.23±285.48	325.18±281.56	231.83±308.99	
		300.5 (15-813)	426 (106-813)	247.5 (15-762)	0.15
Overall survival (days)		310.47±303.61	434±343.63	283.5±367.52	0.18
		355.5 (21-905)	426 (106-813)	328 (21-905)	

SD: Standard deviation. (p<0.05 significance) Student's t|Mann–Whitney U test, Chi-Square|Exact test.

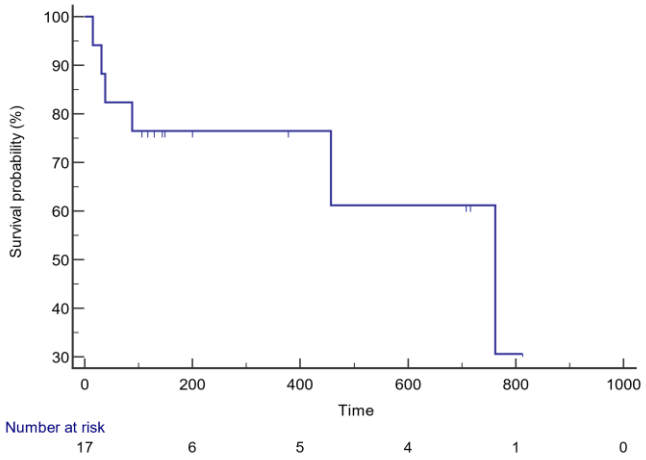

Figure 1. Progression-free survival (PFS) probabilities (%).

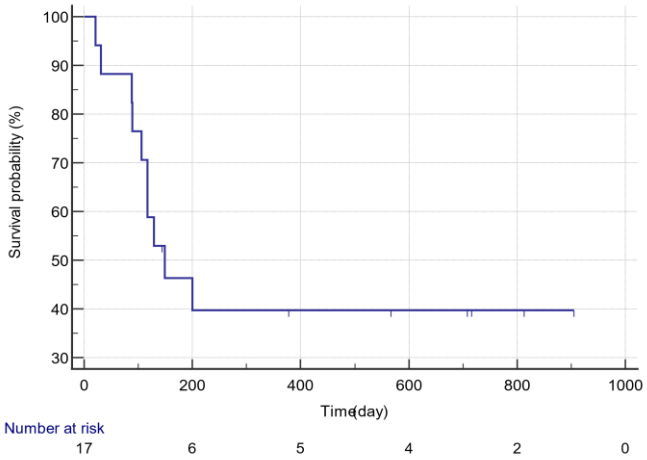

Figure 2. Overall survival (OS) probabilities (%).

risk of death in patients with febrile neutropenia was 7.36 (95% CI: 1.26-43.05) times higher than that in patients without febrile neutropenia (p<0.05). While the mean OS was 93.5 (95% CI: 45.6-141.4) days in patients with peripheral edema during gilteritinib treatment, it was longer with 531.3 (95% CI: 312.1-750.5) days in those without peripheral edema (p=0.01). Patients with peripheral edema had a 10.47 (95% CI: 1.64-66.82) times higher risk of death than those without peripheral edema (p<0.05) (**Supp. Table 3**, **Figure 3**).

*Mortality***.** Six patients experienced progression during the follow-up period (35.3%), and 10 (58.8%) died eventually due to disease progression. No fatal adverse event that could be possibly related to gilteritinib was observed. **Table 3** shows the mortality rates of the patients according to their time intervals. The 30- and 60-day, 6-month, and 1-year mortality rates were 5.9% (n=1), 11.8% (n=2), 58.8% (n=10), and 64.7% (n=11), respectively.

Discussion. In R/R AML patients, gilteritinib is considered a differentiating agent and highly effective molecule. The present study, including Turkey's early access patient group, with similar features, superiorities and differences, demonstrates the efficacy and treatment

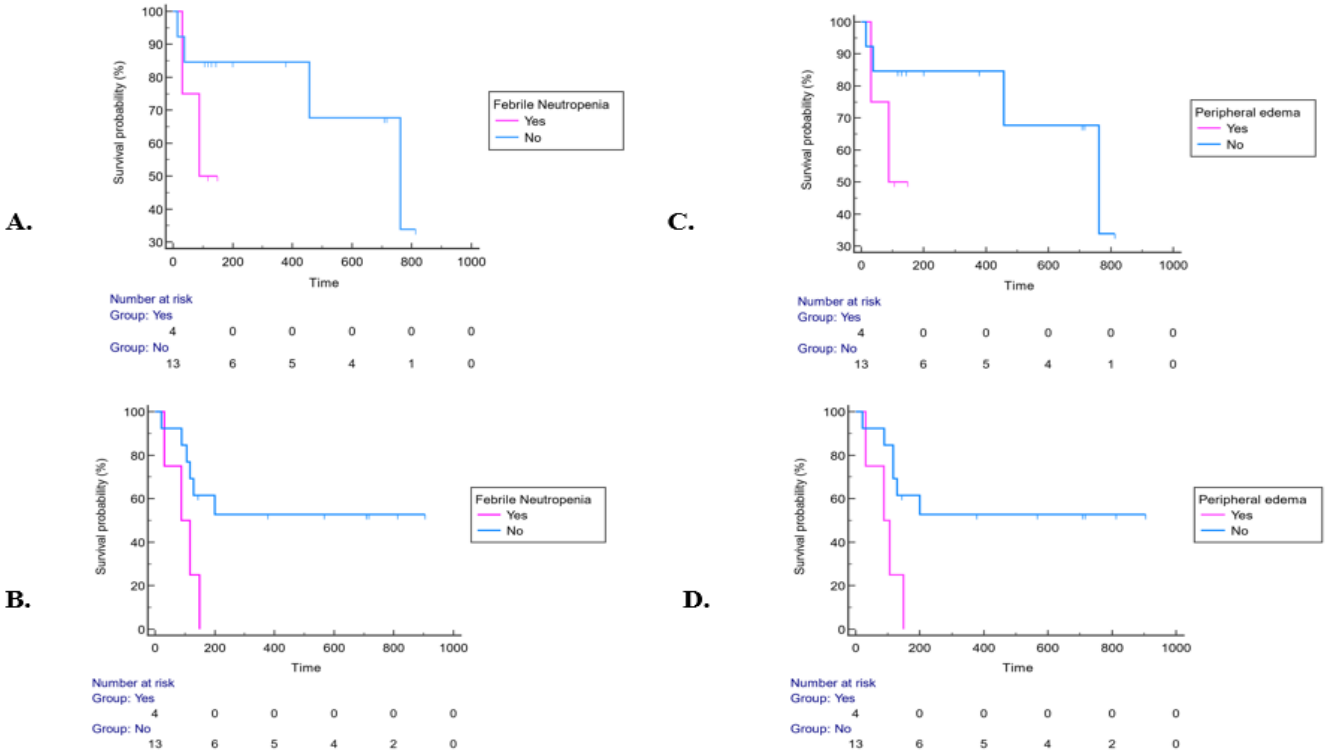

Figure 3. Adverse event-survival analyses: A. Febrile neutropenia - progression-free survival (PFS), B. Febrile neutropenia - overall survival (OS), C. Peripheral edema - PFS, D. Peripheral edema - OS

Table 3. Mortality course: 30 days, 60 days, 6 months and 1 year.

(n=17)	**EX n (%)**	**Mortality Rate (95% CI)**
30-Day mortality	1 (5.9)	0.05-0.17
60-Day mortality	2 (11.8)	0.04-0.24
6-Month mortality	10 (58.8)	0.35-0.85
1-Year mortality	11 (64.7)	0.42-0.87

success of gilteritinib in R/R AML patients with FLT3.

In the phase 1/2 trial of gilteritinib,[14] the ORR in FLT3-mutated patient group was 49% at all doses (CR=9%, CRp=5%, CRi=22%, PR=12%; n=191), while it was 52% (CR=11%, CRp=6%, CRi=24%, PR=11%) in patients receiving ≥80 mg/day. In the ADMIRAL trial,[11] the ORR was reported as 67.6%. The ORR was 100%_(nCR =11, 64.7%; nCRp =3, 17.6%; nCRi = 1, 5.9%; nPR =2, 11.8%) in our research group, which was quite higher compared to the literature counterparts.

In the phase 1/2 trial, the median PFS was 20 (95% CI: 14-33) and the median OS was 30 weeks (23-33).[14] In the phase 3 ADMIRAL trial, the median PFS was 2.8 (1.4-3.7), and the median OS was 9.3 (7.7-10.7) months in the gilteritinib group.[11] In our research group, the median PFS was 300.5 (range: 15-813), and the OS was 355.5 (range: 21-905) days under the treatment of gilteritinib. Compared to phase 1/2 and phase 3 ADMIRAL studies, the survival times in our research group were significantly longer, with more prominent PFS.

In the phase 1/2 trial, the most common grade 3/4 adverse events were reported to be febrile neutropenia (n=97/252, 38%), anemia (n=61/252, 24%), thrombocytopenia (n=33/252, 13%), sepsis (n=28/252, 11%) and pneumonia (n=27/252, 11%). Serious adverse events in ≥5% of patients were febrile neutropenia (n=78/252, 31%), progressive disease (n=43/252, 17%), sepsis (n=36/252, 14%), pneumonia (n=27/252, 11%), acute renal failure (n=25/252, 10%), pyrexia (n=21/252, 8%), bacteremia (n=14/252, 6%) and respiratory failure (n=14/252, 6%). The most common reasons for treatment discontinuation were disease progression (n=15/252, 6%) and sepsis (n=7/252, 3%). The most common adverse event that led to treatment discontinuation was elevated blood creatinine kinase (n=3/252, 1.2%).[14] In the ADMIRAL trial, the most common grade 3 or higher adverse events were febrile neutropenia (n=113, 45.9%), anemia (n=100, 40.7%), and thrombocytopenia (n=56, 22.8%). The most

common reasons for the discontinuation of treatment with gilteritinib were relapse, progression, lack of efficacy (50.2%), death (14.6%), and adverse events (11.3%). Drug-related adverse events leading to the discontinuation of gilteritinib occurred in 27 patients (11.0%). The most common events were elevated aspartate aminotransferase levels (n=4, 1.6%), elevated alanine aminotransferase levels (n=3, 1.2%), and pneumonia (n=3, 1.2%).[11] In our patient group, the most common adverse events were anemia and hypokalemia (n=7, 41.2%), and the only adverse event with grade 3 or higher was thrombocytopenia in one patient (5.9%). The only adverse event that led to treatment discontinuation was thrombocytopenia (n=1, 5.9%).

Another important finding of the research was the effect of adverse events on survival. Patients with febrile neutropenia had a 7.36 (95% CI: 1.26-43.05) times higher risk of death than those without febrile neutropenia. Patients with peripheral edema were found to have a 10.47 (95% CI: 1.64-66.82) times higher risk of death than patients without peripheral edema. The OS of patients with febrile neutropenia is expected to be significantly shorter. Considering that sepsis and infections are some of the most common adverse events associated with gilteritinib, the shortening of OS may be considered a natural outcome. Peripheral edema has been associated with differentiation syndrome.[16-18] Although there is no clear evidence, the literature has associated patients without gilteritinib-related differentiation syndrome and findings with improved OS and complete morphologic remission.[18] However, not all FLT3 inhibitors are the same, and quizartinib without differentiation is characterized by hypocellular bone marrow and incomplete peripheral blood cell recovery.[19] Peripheral edema and fluid retention may be a subclinical manifestation of the differentiation syndrome that occurs independently of the differentiation syndrome and may be associated with longer overall survival. Gilteritinib-related cardiotoxicity has rarely been reported. Although the definite effect is unknown,[20] gilteritinib-related cardiotoxicity was not observed in our cases, so peripheral edema was not associated with cardiotoxicity.

In the phase 1/2 trial, a total of seven deaths were observed, which were considered to be possibly related to treatment. Mortality was attributed to pulmonary embolism, respiratory failure, hemoptysis, intracranial hemorrhage, ventricular fibrillation, septic shock, and neutropenia.[14] In the ADMIRAL trial, there were 170 deaths among 246 patients (69.1%). In the intention-to-treat population, mortality at 30 and 60 days in the gilteritinib group was 2.0% and 7.7%, respectively. Common fatal adverse events in the gilteritinib group were disease progression (n=30, 12.2%) and infections (n=28, 11.4%). The most common fatal adverse events considered possibly related to gilteritinib were pneumonia (n=3, 1.2%), large intestine perforation (n=2, 0.8%), and septic shock (n=2, 0.8%).[11] In our research group, the 30- and 60-day mortality rates were 5.9% (n=1) and 11.8% (n=2), with no fatal adverse event possibly related to gilteritinib.

The main limitation of the research was the limited number of patients, as it consisted of patients in the early access program only.

Conclusions. The ORR was 100%, the median PFS under gilteritinib was 300.5 (range: 15-813), and the OS was 355.5 (range: 21-905) days. Compared to phase 1/2 and phase 3 studies, the survival times were significantly longer, with more prominent PFS. The most common adverse events were anemia and hypokalemia. Grade 4 thrombocytopenia was observed in only one patient, which led to permanent treatment discontinuation, and no other patient experienced any dose reduction or curtailment. Patients with febrile neutropenia and peripheral edema were at a high risk of death when compared to patients without febrile neutropenia and peripheral edema. No fatal adverse event possibly related to gilteritinib was observed.

Availability of Data and Materials. The data that support the findings of this research are openly available: SERIN, Istemi (2022), "Gilteritinib Turkey", Mendeley Data, V1, https://doi.org/10.17632/95n3n246ct.1

Ethics Approval and Consent to Participate. Ethical committee approval was received from the Istanbul Training and Research Hospital Ethics Committee (Date: 23.12.2022; approval number: 402). The experimental procedures were based on the Declaration of Helsinki and relevant institutional regulations.

Authors' Contributions. M.H.D.: Conceptualization, Methodology, Software. I.S.: Data curation, Writing-Original draft preparation. B.D., G.K., M.C., O.G.S., O.Y., and M.H.D.: Software, Validation, Writing-Reviewing and Editing.

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