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Research Article

HER2-low expression in patients with hormone receptor positive and HER2 negative advanced breast cancer treated with ribociclib or palbociclib in combination with endocrine therapy

Hormon reseptörü pozitif, HER2 negatif metastatik meme kanseri tanısıyla ribosiklib veya palbosiklib ile letrozol kombinasyon tedavisi verilen hastalarda HER2-düşük ekspresyonunun önemi

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Abstract

Aim: Hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer which represents the most common subgroup of metastatic breast cancer (MBC). Recently, further subclassification for HER2-negative tumors has emerged as HER2-low. There is limited knowledge regarding the effect of HER2-low expression on outcomes of patients with HR-positive and HER2-negative MBC treated with CDK 4/6 inhibitors plus hormonal therapy. Therefore, we evaluated survival parameters according to HER2-low status for this patient group in this study.

Material and Methods: As the Turkish Oncology Group (TOG) Project, retrospectively collected data from 423 patients with HR-positive/HER2-negative MBC treated with ribociclib and palbociclib plus letrozole therapy was assessed. Included patients had metastatic first-line therapy and endocrine-sensitive disease. Survival outcomes were compared between HER2-negative and HER2-low patient groups.

Conclusion: HER2-low status had no statistically significant impact on survival in patients treated with palbociclib or ribociclib plus letrozole.

Keywords: Cyclin-dependent kinase 4/6 inhibitors, palbociclib, ribociclib, hormone receptor positive and HER2 negative advanced breast cancer, HER2-low

Öz

Amaç: Metastatik meme kanserinin (MMK) en yaygın alt grubunu temsil eden hormon reseptörü (HR) pozitif, insan epidermal büyüme faktörü 2 (HER2) negatif meme kanseridir. Yakın dönemde HER2 negatif tümörler için daha ileri bir alt sınıflandırma olarak HER2-düşük terimi ortaya çıkmıştır. HER2-düşük ekspresyonunun, CDK 4/6 inhibitörleri ve hormonal tedavi kombinasyonuyla tedavi edilen HR-pozitif/HER2-negatif MMK'li hastaların sonuçları üzerindeki etkisine ilişkin sınırlı bilgi bulunmaktadır. Bu nedenle çalışmamızda bu hasta grubu için HER2-düşük durumuna göre sağkalım parametrelerini değerlendirdik.

Gereç ve Yöntemler: Türk Onkoloji Grubu (TOG) Projesi olarak Türkiye genelindeki 43 farklı tıbbi onkoloji merkezinden retrospektif olarak veri toplandı. Haziran 2016 ile Ağustos 2022 arasındaki dönemde Ribosiklib veya Palbosiklib ile letrozol kombinasyon tedavisi verilmiş HR-pozitif/HER2-negatif MMK'li 423 hastadan retrospektif olarak toplanan veriler değerlendirildi. Dahil edilen hastalar metastatik birinci basamak olarak tedaviye başlanan ve endokrin duyarlı hastalığa sahipti. Hastaların sağkalım sonuçları, HER2-negatif ve HER2- düşük hasta grubu arasında kıyaslandı.

Sonuç: HER2-düşük durumu, palbosiklib veya ribosiklib ile letrozol tedavisi alan hastalarda sağkalım üzerinde istatistiksel olarak anlamlı bir etki göstermedi.

Anahtar kelimeler: CDK4/6 inhibitörleri, metastatik meme kanseri, HER2-düşük ekpresyon

Introduction

Breast cancer (BC) is the most common cancer in women worldwide and the leading cause of cancer deaths among women [1]. In regard to treatment of metastatic hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer which represents the most common subgroup of metastatic breast cancer (MBC), cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with traditional endocrine therapy (ET) (an aromatase inhibitor or fulvestrant) has become the standard-of-care strategy [2-8]. Recently, further subclassification for HER2-negative tumors has emerged as HER2-low, which is defined as a score of 1+ on immunohistochemical (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization (ISH) due to its potantial prognostic significance and treatment options [9-11]. Novel anti-HER2 antibody–drug conjugates have demonstrated substatial clinical activity in patients with

HER2-low MBC [12,13]. There is currently limited knowledge regarding the effect of HER2-low expression on outcomes of patients with advanced HR-positive and HER2-negative BC and treated with CDK 4/6 inhibitors plus hormonal therapy. Based on the current data, molecular profile of HR-positive and HER2-low BC may differ from that of HER2-zero disease [10]. Furthermore, the data regarding the prognostic significance of HER2-low expression in the advanced setting are conflicting [14-16]. The current study was therefore conducted to evaluate the survival parameters of the patients with metastatic HR-positive and HER2-negative BC treated with CDK 4/6 inhibitors plus letrozole according to HER2-low status.

Material and Methods

We retrospectively collected data from 43 different medical oncology centers in Turkey. 423 patients with HR-positive/ HER2-negative advanced breast cancer treated with ribociclib and palbociclib plus letrozole therapy between June 2016 and August 2022 were included. Due to reimbursement conditions in Turkey, all patients were ER-positive which was defined as at least 10% of cells staining positive, and CDK 4/6 inhibitors were limited to ribociclib and palbociclib. Included patients had either de-novo metastatic disease or endocrine-sensitive recurrent disease which relapsed >12 months after the completion of (neo) adjuvant ET. The outcome of the patients with HER2-0 (IHC score 0) and HER2-low (HER2 IHC score1+ or 2+ and ISH negative) tumors were compared. HER2 scored from both primary and metastatic tissue if present. For the patient with two pathology samples (primary and metastatic tissue), those with HER2-low levels in two samples were included.

Progression free survival (PFS) was calculated as the time from CDK 4/6 inhibitor treatment initiation to disease progression or death, whichever was earlier. Overall survival (OS) was defined as the time interval in months between the date of initiation of CDK 4/6 inhibitor treatment and death from any cause. Kaplan–Meier method were used to analyse survival data. Log-rank test was used to compare PFS and OS across groups. We conducted this study according to the Declaration of Helsinki. Ankara Bilkent City Hospital Ethics Committee approved the study protocol (2021, E2-21-1167). as a multicenter retrospective observational study.

Statistical Analysis

Progression free survival (PFS) was calculated as the time from CDK 4/6 inhibitor treatment initiation to disease progression or death, whichever was earlier. Overall survival (OS) was defined as the time interval in months between the date of initiation of CDK 4/6 inhibitor treatment and death from any cause. Median PFS (mPFS) and median OS (mOS) of the patients were calculated with the Kaplan-Meier method. Various clinical features were tested in a univariate analysis using Kaplan-Meier method and evaluated by Log-rank analysis. The p values <0.05 was considered statistically significant. SPSS Statistics version 26.0 was utilized for data analysis.

Results

In this study, 418 of the patients were female (98.8%). 75.7% of female patients were postmenopausal. Median age was 58 (25-90). While the HER2 IHC score was 0 in 285 of the patients (67.4%), the HER2 IHC score was 1+ and 2+ (HER2-low) in 138 patients (32.6%). Progesterone receptor expression was negative in 38 patients (9.1%). 196 patients had bone-only metastatic disease (46.3%). 9 patients had Central nervous system (CNS) metastases (2.1%) and 74 patients had liver metastases (17.5%). Table 1 shows patient characteristics.

The median follow up was 10.5 (95% CI, 9.7-11.4) months. Median OS could not be calculated at follow-up, with an estimated 81% of patients alive at 24 months. The median PFS was 29.4 months (95 CI, 16.2-42.7) for the entire cohort. In patients treated with ribociclib/palbociclib plus letrozole in the first-line and endocrine sensitive disease setting, there were no statistically significant difference in terms of mPFS between HER2-0 and HER2-low patients (36.2 and 29.4 months, p = 0.12) (Figure1). Compared with its HER2-0 counterpart, HER2-low expression seemed to have a better course in the mOS curves but there was no statistically significance (p = 0.49) (Figure2).

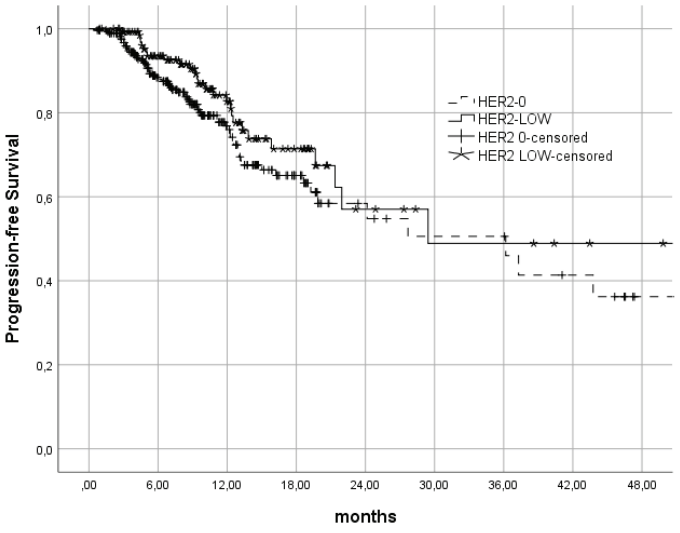

Figure 1. mPFS for HER2-0 and HER2-low patients in the entire cohort.

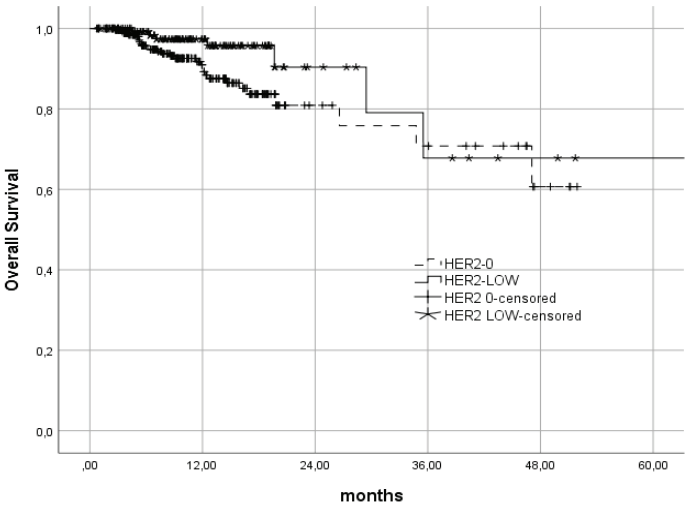

Figure 2. mOS for HER2-0 and HER2-low patients in the entire cohort.

In HER2-low patient group, no significant differences were observed regarding mPFS (95 CI, 21.35, (18.3-24.4) and 29.4, (NE-NE) months) and mOS between patients receiving palbociclib letrozole or ribociclib letrozole in the follow-up period (p = 0.98 for mPFS, and p = 0.53 for mOS) (Figures 3,4).

"In the patient receiving palbociclib plus letrozole, no statistically significant differences in mPFS (Figure 5) and mOS were found between HER2-0 and HER2-low patients (p = 0.75 and p = 0.27, respectively).

Although mPFS curves showed a divergence from the first months in favor of HER2- low, no statistically significant differences in mPFS (Figure 6) and mOS were observed between HER2-0 and HER2-low patients who received ribociclib plus letrozole (p = 0.11 and p = 0.13, respectively)

In HER2-zero patient group, there was a numerically difference in favor of palbociclib plus letrozole in terms of mPFS, although it did not reach statistical significance (36.2 (8.3-64.0) and 24.1 (9.0-39.0), p = 0.1) (Figure 7).

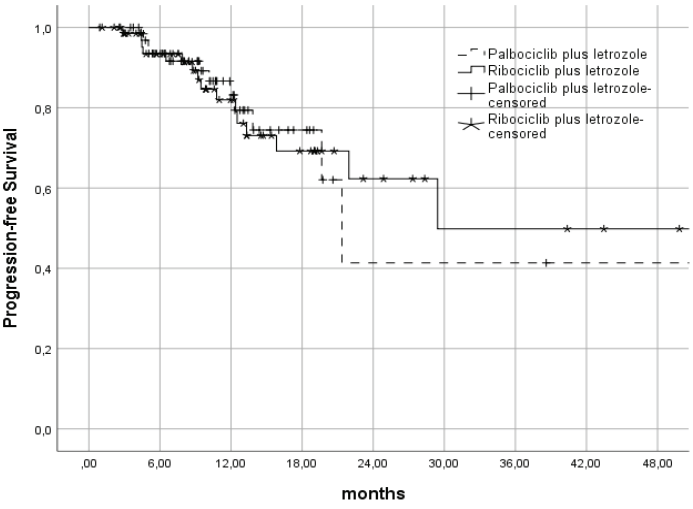

Figure 3. mPFS with palbociclib plus letrozole and ribociclib plus letrozole in HER2-low patients.

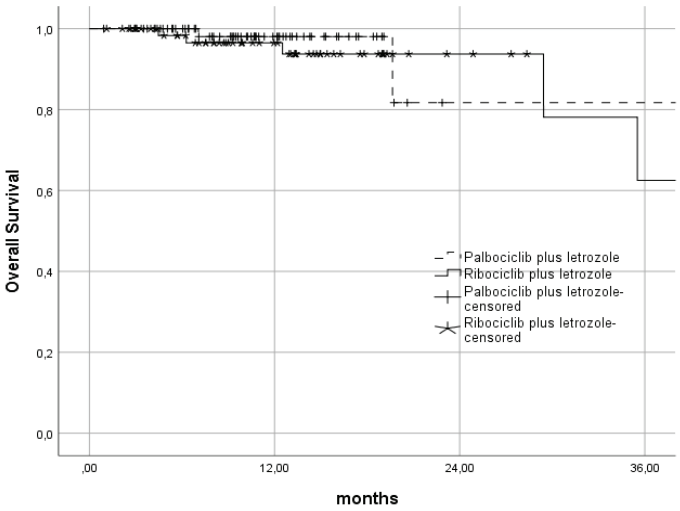

Figure 4. mOS with palbociclib plus letrozole and ribociclib plus letrozole in HER2-low patients.

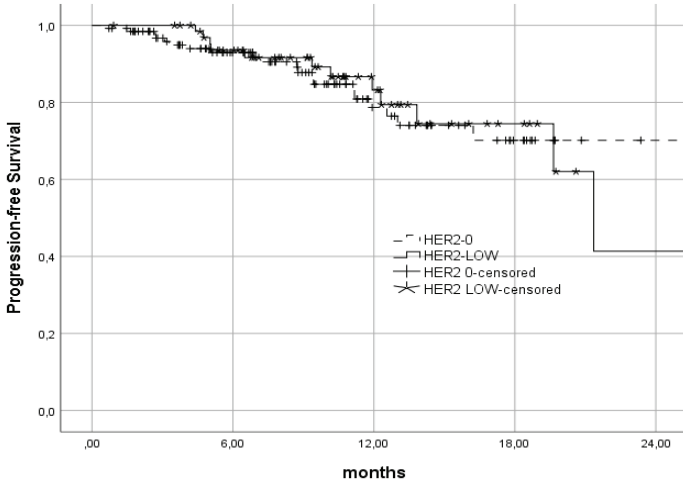

Figure 5. mPFS for HER2-0 and HER2-low in patients receiving palbociclib plus letrozole.

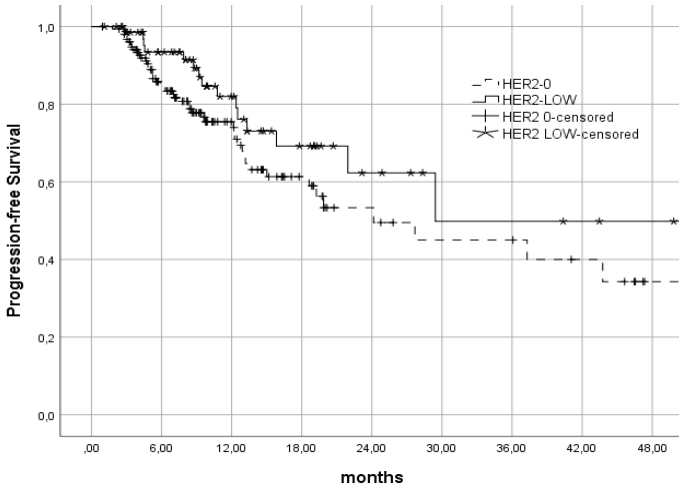

Figure 6. mPFS for HER2-0 and HER2-low in patients receiving ribociclib plus letrozole.

Table 1. Clinicopatological characteristics of the patients			
Characteristic	HER2-zero (n = 285) N (%)	HER2-low (n = 138) N (%)	p
Age (years, median)	58 (25-90)	58 (27-86)	
ECOG PS 0-1 2	 248 (88.6%) 32 (11.4%)	 126 (94.7%) 7 (5.3%)	 <0.045
Menopausal status Premenopausal Postmenopausal Men	 68 (23.9%) 215 (75.7%) 1 (0.4%)	 33 (21.5%) 116 (75%) 4 (3.5%)	0.70
Disease status De-novo Endocrine naive recurrent	 195 (68.4%) 90 (31.6%)	 67 (48.6%) 71 (51.4%)	 <0.001
Metastatic sites type Visceral +/- bone Bone-only	 161 (56.5%) 124 (43.5%)	 66 (47.8%) 72 (52.2%)	 0.94
Vissceral metastasis sites Liver CNS Lung	 48 (16.8%) 6 (2.1%) 92(32.4%)	 26 (18.8%) 3 (2.2%) 43(31.7%)	 0.61 0.60 0.80
Progesteron receptor negative	27 (9.5%)	11 (8.1%)	0.63
Treatment type Palbociclib-Letrozole Ribociclib-Letrozole	 129 (45.3%) 156 (54.7 %)	 67 (48.6%) 71 (51.4%)	0.52
ECOG PS: The Eastern Cooperative Oncology Group performance status CNS: central nervous system			

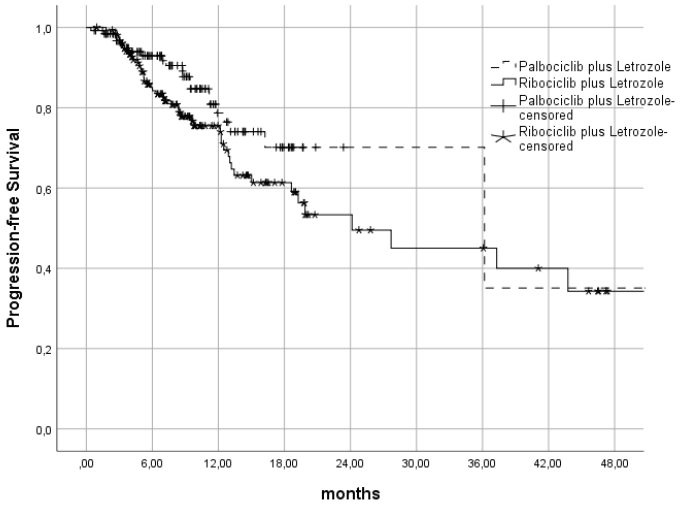

Figure 7. mPFS with palbociclib plus letrozole and ribociclib plus letrozole in HER2-zero patients.

Discussion

According to guidelines, BC is classically subdivided into three main groups as HR-positive and HER2-negative, HER2-positive, and triple-negative breast cancer (TNBC). As a relatively new entity, HER2-low-expressing tumors which are present in HER2-negative breast cancer represent approximately half of the cases in the entire breast cancer group. Recent data suggested that HER2-low rate was higher among HR-positive BC than HR-negative BC [17, 18]. More specifically, regarding advanced HR-positive HER2-low tumors, in DESTINY-Breast04 trial trastuzumab deruxtecan showed clinical benefit in patients who had received at least one line of therapy. Currently CDK 4/6 inhibitors plus ET are still accepted as the SoC therapy in the first line for this group of tumors.

Regarding data on CDK 4/6 inhibitors, only ribociclib among 3 agents in combination with ET demonstrated OS benefit in advanced HR-positive HER2-negative BC in the first-line treatment setting. After the release of OS data for MONALEESA-2, PALOMA-2, and MONARCH-3 [19-21], decisions regarding treatment selection in clinical practice continue to evolve. Before the completion of these data, ribociclib and palbociclib which provided reimbursement conditions in our country have been used since June 2016.

Our study cohort included patients with denovo metastatic or recurrent endocrine-sensitive disease diagnosed with HR-positive, HER2-negative MBC and treated with ribociclib or palbociclib plus letrozole as first-line therapy. Since providing reimbursement was relatively late in Turkey, the rate of the patients in our country pretreated with chemotherapy for metastatic disease before CDK4/6 inhibitor treatments were comperatively high. Therefore, the rate of patients who started CDK4/6 inhibitor treatment with a diagnosis of de novo disease was comparatively high in our cohorts [22]. In this study, we retrospectively evaluated whether HER2-low expression status has prognostic implication.

In our study, we found that there was no significant difference between HER2-low and HER2-0 in terms of treatment effectiveness. The efficacy of palbociclib or ribociclib and letrozole also did not differ significantly in the HER2-low patient group. A numerical inferior efficacy results of ribociclib were observed in the HER2-0 patient group that did not reflect statistical significance. In terms of patient characteristics, there was a statistically significant predominance of denovo disease in the HER2-0 group. However, mPFS or mOS were similar for the patients with denovo or endocrine sensitive relapsed disease ($p = 0.70$ and $p = 0.15$, respectively). Therefore, the numerical difference between both agents in the HER2-0 group can be more clearly demonstrated in terms of HER2 biology or the difference between the two agents with long-term follow-up.

There is controversy and limited data on the efficacy of CDK 4/6 inhibitors in patients with HR-positive and HER2-low tumors. One of the first analysis of Bao et al., in 106 patients with HR+/ERBB2– MBC treated with CDK4/6 inhibitors, they reported that HER2-low expression was associated with an inferior PFS (8.9 months; 95%CI, 6.49-11.30 months vs 18.8 months; 95%CI, 9.44-28.16 months; $p = 0.01$) [23]. This study included a heterogeneous patient group that received CDK 4/6 inhibitor treatment as a second or third line.

A Greek real-life data published later, evaluated the impact of low HER2 expression in metastatic HR-positive HER2-negative breast cancer treated with first-line CDK4/6 inhibitors and reported that despite numerical differences, treatment efficacy of CDK4/6 inhibitors was equal and independent of HER2 expression level [24].

In a cohort of 45 patients treated with palbociclib and either AI or fulvestrant according to treatment line, authors reported no significant differences in ORR (41.7% and 28.6%, respectively, $p = 0.360$) and mPFS (16.2 and 14.1 months, respectively, $p = 0.263$) between HER-2-zero and HER-2-low patients [25].

Based on the retrospective study of Lapuchesky LS et al., HER2-low expression did not show a statistically significant impact on patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors in the first-line setting [26]. In this study 70.4% of 186 patients received CDK4/6 inhibitors and endocrine therapy in the first-line treatment setting. They reported no statistically significant differences in PFS and OS between HER2-0 and HER2-low patients treated with CDK4/6 in the first-line setting.

An observational study also found that there were no association between HER2 status and clinical outcomes in 919 HR + /HER2- advanced BC patients treated with first-line ET plus CDK4/6 inhibitors [27]. Two other current studies investigating the role of HER2-low status, one from a single center showed a clearly numerically favorable PFS in the HER2-zero group, while the other multicenter study reported that HER2-low status was not associated with survival [28,29].

In our study, we could not show any difference in survival and prognosis between HER2-0 and HER2-low in the patient group with metastatic HR+/HER2- BC who received palbociclib or ribociclib combined with letrozole as first-line therapy. We believe that our study contributes to the literature with favorable number of patients and real-life data. However, the results should be evaluated considering the short follow-up period and the retrospective nature of the study. As interpreted in the systematic review, the predictive rather than the prognostic significance may be emphasized for HER2-low metastatic BC based on current level of evidence [30].

To sum up, based on our current knowledge, CDK 4/6 inhibitors in combination with ET is the standard treatment for HR-positive, HER2-low MBC. For the patients who progressed after SOC treatment, the optimal sequencing of ADCs in this setting and efficacy of combinations of ADCs with endocrine therapies or immunotherapies remain unclear. The search for an optimal HER2- low MBC treatment continues. In our study, HER2-low status did not show a statistically significant impact on treatment efficacy for patients treated with palbociclib or ribociclib plus letrozole. Results of prospective studies for this group of patients are awaited.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics Approval

The study protocol was approved by Ankara City Hospital Ethics Committee as a multicenter retrospective observational study in 22 December 2021 (E2-21-1167).

Author Contributions

Conception and design: MANS, SK, development of methodology, analysis and interpretation of data, and writing of the article: SK,MH,MANS, data acquisition: All authors, manuscript co-writing: All authors, final approval of manuscript: All authors. All authors revised the manuscript critically for important intellectual content and approved the version to be published.

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