Clinicopathological Features and Survival Outcomes of Colorectal Cancer Patients Under 40 Years: A 20-Years Single-Center Experience

Ali Kaan GUREN[1], Nazim Can DEMIRCAN[1], Sedef Seyma OZGUR[2], Tugce BULUN AKYOL[2], Nargiz MAJIDOVA[3], Erkam KOCAASLAN[1], Yesim AGYOL[1], Pinar EREL[1], Burak PACACI[1], Mustafa Alperen TUNC[1], Nadiye SEVER[1], Abdussamet CELEBI[1], Rukiye ARIKAN[1], Selver ISIK[1], Murat SARI[1], Osman KOSTEK[1], Ibrahim Vedat BAYOGLU[1]

[1] Marmara University Faculty of Medicine, Department of Medical Oncology, Division of Internal Medicine
[2] Marmara University Faculty of Medicine, Department of Internal Medicine
[3] VM Medical Park Maltepe Hospital, Department of Medical Oncology

ABSTRACT

In recent years, there has been a significant increase in the number of patients diagnosed with colorectal cancer (CRC) under the age of 40. Patients in this age group are diagnosed at more advanced stages, and their disease prognosis is more aggressive. We aim to present the clinicopathologic features, treatment options, and survival outcomes of patients diagnosed with CRC under 40 in our clinic and compare our data with the literature. Our study, designed with a retrospective approach, focused on patients younger than 40 with CRC diagnosed by histopathologic examination between 2004 and 2024. At diagnosis, 5% of patients were Stage 1, 25% Stage 2, 37% Stage 3, and 31% Stage 4. 41.9% of the tumors were located in the rectum, and 26.3% in the sigmoid colon. 24.8% of patients had a family history of colorectal cancer, 23.7% of patients had mucinous subtype, 12.1% had MSH/I features and 55.6% were KRAS/NRAS mutant. Among metastatic patients, oxaliplatin-based and irinotecan-based first-line therapies showed no significant difference in PFS (8.9 vs. 9.7 months, p= 0.627) and OS (34.5 vs. 32.2 months, p= 0.690). Patients are usually diagnosed at an advanced stage, which leads to an aggressive course of the disease and makes clinical management difficult. Screening programs should not be interrupted in terms of early diagnosis, especially in individuals with a family history. Furthermore, in the future, defining the molecular profile underlying the early development of sporadic CRC will help to plan individualized screening recommendations and improve management.

Keywords: Colorectal cancer, Young-onset colorectal cancer, Oxaliplatin, Irinotecan

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer among all cancers worldwide and ranks second in cancer-related deaths.[1] Although it is frequently seen in the older age group, the incidence of CRC has decreased in individuals over 65 years of age in recent years, while the significant increase in the incidence of CRC in individuals under 50 is noteworthy.[2] Since the 1990s, the incidence of CRC in individuals under 50 has increased by 1-2% annually. While 11% of cases were in this age group in 1995, this rate increased to 20% in 2019.[3] Increasing incidence rates are associated with multifactorial factors such as lifestyle changes, changes in dietary habits, environmental exposures, genetic predispositions, and adaptation of early diagnosis and screening methods to the young population.[4] Especially syndromes such as Lynch syndrome (hereditary non-polyposis colorectal cancer) and familial adenomatous polyposis (FAP) are known to increase the risk of CRC.[5] CRC cases, whose incidence increases in the young age group, generally exhibit more aggressive biological features and are diagnosed in advanced stages.[6-7]

The American Cancer Association has lowered the screening age to 45 due to the increase in CRC patients seen at a young age.[8] With the increase in cases seen at a young age, current studies have started to examine patients under 40 in more detail.[9-10] CRC developing at an early age should be considered a different subtype, the underlying molecular profiles should be better defined and treatment options should be reviewed. Studies on early-onset CRC often encompasses individuals below the age of 50. Further delineation of the age groups is necessary to more accurately characterize patient attributes.

In this study, we aim to present the clinicopathologic features, treatment options, and survival outcomes of CRC patients diagnosed under 40 in our clinic and compare our data with the literature.

PATIENTS AND METHODS

Study Population

The study was designed as a retrospective, single-center study. It included patients who were treated in the Medical Oncology Clinic between 01.06.2004 and 01.06.2024 and diagnosed with colorectal carcinoma by histopathologic examination. Patients excluded from the study were those who discontinued follow-up, were diagnosed outside the 18-40 age range, missed available pathology results at diagnosis, had unavailable treatment information, and deliberately discontinued therapy at the metastatic stage.

Data Collection and Study Design

The patients' data were analyzed using patient files and the hospital's electronic information system. Patients' ages, genders, histopathologic features, sites of involvement, diagnostic stages, conventional chemotherapies, dates of diagnosis, treatment start and end dates, mortality dates, or last outpatient clinic dates were recorded. Patients with a first-degree relative diagnosed with CRC were considered to have a family history. Patients with a more than 50% mucinous component were considered as mucinous histology subtype. Performance scores were calculated using the Eastern Cooperative Oncology Group Performance Status (ECOG PS). Treatment responses of the patients were evaluated according to Response Evaluation Criteria in Solid Tumours (RESIST) version 1.1. Diagnostic staging was performed according to the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) classification and staging system 8th Edition.

The patients were divided into 4 groups according to the stages, an overall survival (OS) analysis was performed according to the stage of each patient. Patients who received oxaliplatin-based treatment (FOLFOX (fluorouracil+folinic acid+oxaliplatin) or XELOX (capecitabine+oxaliplatin) ± bevacizumab or anti-VEGF) and patients who received irinotecan-based treatment (FOLFIRI (fluorouracil+folinic acid+irınotecan) ± bevacizumab or anti-VEGF) in the first series treatment of metastatic-stage patients were grouped into 2 separate groups. Finally, the progression-free survival (PFS) and OS of these two groups were compared.

Ethical Approval was granted by Marmara University School of Medicine Ethic Committee, number: 09.2024.1528.

Statistical Analysis

SPSS version 22.0 (IBM Corp.) was used for all statistics. PFS was calculated as the time in months from the patient's first dose of treatment to disease progression or to the day of the last visit if the patient was still receiving treatment. If the patient died while on treatment, the last date was considered as the date of death. OS was calculated as the time in months from the first treatment dose until the date of death or until the date of the last visit if the patient was still alive. The parameters' conformity to normal distribution was evaluated during the study data evaluation using the Shapiro-Wilks test. Brookmeyer and Crowley's method was used to calculate 95% confidence intervals (CI). Categorical variables between the two groups were compared using the Independent Samples t-test and Mann-Whitney U Test. Kaplan-Meier survival analysis was used, and survival differences between the groups were compared using a log-rank test. Hazard ratio (HR) was calculated by Cox regression analysis. Significance was evaluated at $p< 0.05$ level.

Table 1. Baseline Characteristics of the patients and tumors

	Total Patients (n= 177)
Age (range)	33.9 (18-40)
Gender (%)	
Male	82 (46.3)
Female	95 (53.6)
Family history of colorectal cancer (%)	44 (24.8)
ECOG PS (%)	
0-1	169 (95.5)
2 and more	8 (4.5)
Tumor location (%)	
Cecum and ascending colon	31 (18.5)
Transverse colon	13 (7.7)
Descending colon	9 (5.3)
Sigmoid colon	44 (26.3)
Rectum	70 (41.9)
Unknown	10
Mucinous histology (%)	42 (23.7)
Microsatellite status (%)	
MSS	72 (87.8)
MSI/H	10 (12.1)
Unknown	95
Mutation status (%)	
Wild type	32 (40.5)
KRAS/NRAS mutant	44 (55.6)
BRAF-V600E mutant	2 (2.5)
HER-2 amplification	1 (1.2)
Unknown	98
Stage at diagnosis (%)	
Stage 1	9 (5)
Stage 2	45 (25.4)
Stage 3	67 (37.8)
Stage 4	56 (31.6)

ECOG PS: Eastern Cooperative Oncology Group Performance Status, MSS: Microsatellite Stable, MSI/H: Microsatellite instability/high, KRAS/NRAS: Kirsten Rat Sarcoma/Neuroblastoma Rat Sarcoma, BRAF: v-raf murine sarcoma viral oncogene homolog B (BRAF), HER-2 Human Epidermal Growth Factor Receptor 2.

Table 2. Histopathological features and adjuvant therapies of stage 1-2-3 patients who underwent surgery

	Total Patients (n= 121)
pT (%)	
1	4 (3.3)
2	11 (9)
3	84 (69.4)
4	22 (18.1)
pN (%)	
0	51 (42.1)
1	43 (35.5)
2	27 (22.3)
Grade (%)	
1	8 (8.1)
2	74 (74.7)
3	17 (17.2)
Missing	22
Removed Lymph Node (%)	
≥ 12	95 (78.5)
< 12	26 (21.4)
Lymphovascular invasion (%)	
Positive	74 (61.1)
Negative	47 (38.9)
Perineural invasion (%)	
Positive	62 (51.2)
Negative	59 (48.7)
Obstruction (%)	27 (22.3)
Perforation (%)	18 (14.8)
Adjuvant chemotherapy (n=91) (%)	
XELOX	32 (35.1)
FOLFOX	19 (20.8)
Capecitabine	16 (17.5)
FUFA	24 (26.3)

FOLFOX: Fluorouracil+Folinic acid+Oxaliplatin, FUFA: Flourouracil+Folinic acid, XELOX: Capecitabine+Oxaliplatin

RESULTS

The study included 177 patients diagnosed with CRC by histopathologic examination. 82 of the patients were male, and 95 were female. The median age of the patients was 33.9 years, and the age range was 18 to 40 years. 24.8 percent of the patients had a family history of colorectal cancer. The tumors were located in the rectum 41.9%, sigmoid colon 26.3%, descending colon 5.3%, transverse colon 7.7%, cecum and ascending colon 18.5%. 23.7% of the patients had a mucinous pattern. Microsatellite instability/high (MSI/H) was detected in 10 (12.1%) of 82 patients with microsatellite status (MS). Seventy nine patients had Kirsten Rat Sarcoma/Neuroblastoma Rat Sarcoma (KRAS/NRAS), v-raf murine sarcoma viral oncogene ho-

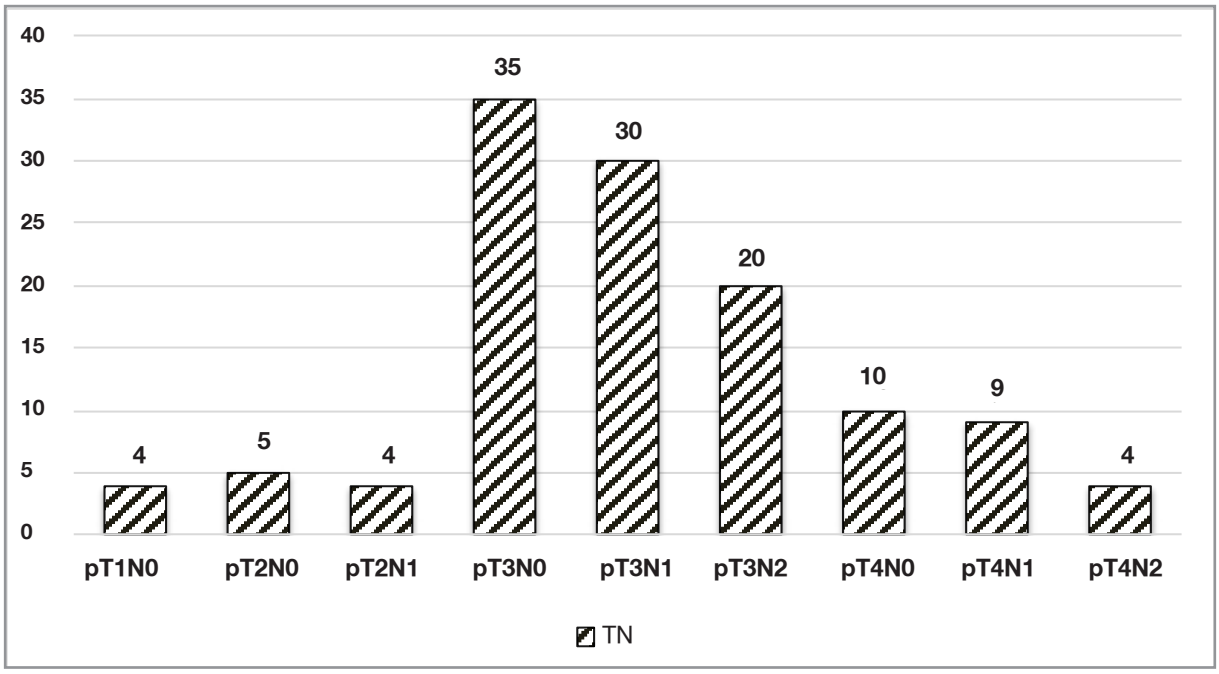

Figure 1. T and N stages of patients who underwent surgery

molog B (BRAF), and Human Epidermal Growth Factor Receptor 2 (HER-2) analysis was performed, and 40.5% of patients had a wild type; 44 patients were KRAS/NRAS, 2 were BRAF mutant, and 1 had HER-2 amplification. These findings are summarized in Table 1.

One hundred and twenty-one patients with stage 1-2-3 disease underwent surgery. Of these patients, 4 had pT1, 11 had pT2, 84 had pT3, and 22 had pT4 tumors. 51 patients had no nodal involvement (pN0), 43 had pN1, and 27 had pN2 tumors. The combination of the patients' T and N stages is shown in Figure 1.

Tumor grade was calculated in 99 patients; 8 were grade 1, 74 were grade 2, and 17 were grade 3. In 95 patients (78.5%), 12 or more lymph nodes were dissected, while 26 patients (21.4%) had less than 12 lymph nodes dissected. Lymphovascular invasion was positive in 61.1%, and perineural invasion was positive in 51.2%. Twenty seven patients were diagnosed with obstruction, and 18 patients with perforation after hospital admission. These findings are summarized in Table 2.

In stage 1 and stage 2 patients, the 1-year survival rate was 100%, the 5-year survival rate was 88% and 86%, and the 10-year survival rate was 88% and 84%, respectively, while the median survival time was not yet reached. In stage 3 patients, these rates were 89% for 1 year, 64% for 5 years, and 43% for 10 years, with a median survival of 88.2 months (95% CI: 35.87-140.12). In stage 4 patients, the 1-year survival rate was 73%, the 5-year survival rate was 32%, and the 10-year survival rate was 14%, with a median survival of 23.72 months (95% CI: 4.33-41.66). The survival rates for all stages were 87% for 1 year, 60% for 5 years, and 51% for 10 years, and the median survival time was 89.20 months (95% CI: 25.13-152.86). The findings are summarized in Table 3. OS between stages was calculated by the Log-rank test, $p< 0.001$, which is statistically significant ($p< 0.05$). Inter-stage HR was calculated based on Stage 1. For Stage 2 HR was 0.09 (95% CI: 0.012-0.653), for Stage 3 HR was 0.121 (95% CI: 0.054-0.270), and for Stage 4 HR was 0.316 (95% CI: 0.190-0.526) with p-values of 0.017, < 0.001, and < 0.001, respectively. Kaplan-Meier curves are shown in Figure 2.

Systemic treatment agents of 75 patients who were metastatic at the time of diagnosis or developed recurrence or distant metastasis afterward are summarized in Table 4. Fifty seven patients received 2

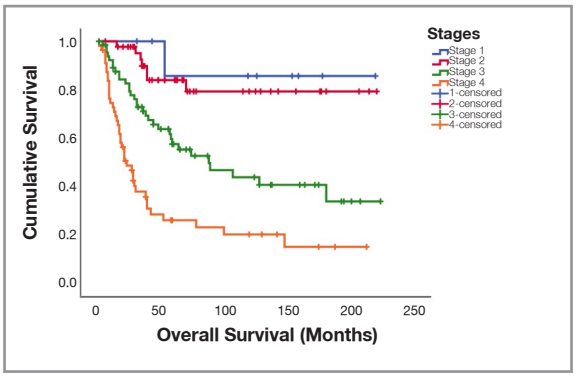

Figure 2. Survival analysis with Kaplan-Meier curves according to stages

Table 3. Survival rates of patients according to stage

	1.-5.-10. years OS	Median OS (%95 CI)
Stage-1	100%-88%-88%	NR (NR-NR)
Stage-2	100%-86%-84%	NR (NR-NR)
Stage-3	89%-64%-43%	88.20 (35.87-140.12)
Stage-4	73%-32%-14%	23.72 (4.33-41.66)
Overall	87%-60%-51%	89.81 (25.13-152.86)

series, 38 patients received 3 series, and 22 patients received 4 or more series of treatment. Comparing patients who received oxaliplatin-based therapy (n= 37) and irinotecan-based therapy (n= 25) in the first series, the median PFS was 8.9 months (95% CI: 6.36-9.63) for oxaliplatin-based therapy and 9.7 months (95% CI: 7.22-10.78) for irinotecan-based therapy. Log-rank p= 0.627. The series 1 PFS for all patients was 8.7 months (95% CI: 6.33-9.66). Median OS was 34.5 months (95% CI: 21.12-47.90) for those receiving oxaliplatin-based therapy and 32.2 months (95% CI: 21.16-43.26) for those receiving irinotecan-based therapy. Log-rank p= 0.690. The OS for all patients in the first series was 33.9 months (95% CI: 25.11-42.86). There was no statistical difference between age and gender when the two groups were compared (p= 0.425 for age, p= 0.874 for gender; p> 0.05).

Table 4. Systemic therapies in metastatic stage

	Patients (n)
First line chemotherapy (n= 75) (%)	
FOLFOX	15 (20)
FOLFOX + Bevacizumab	8 (10.6)
FOLFOX + anti-EGFR	4 (5.3)
FOLFIRI	5 (6.6)
FOLFIRI + Bevacizumab	16 (21.3)
FOLFIRI + anti-EGFR	4 (5.3)
XELOX	2 (2.6)
XELOX + Bevacizumab	8 (10.6)
FOLFOXIRI	5 (6.6)
FOLFOXIRI+ Bevacizumab	2 (2.6)
FUFA or Capacitabine	4 (5.3)
FUFA or Capacitabine + Bevacizumab	2 (2.6)
Second line chemotherapy (n= 57) (%)	
FOLFOX	5 (8.7)
FOLFOX + Bevacizumab	9 (15.7)
FOLFOX + anti-EGFR	6 (10.5)
FOLFIRI + Aflibercept	8 (14)
FOLFIRI + Bevacizumab	16 (28.1)
FOLFIRI + anti-EGFR	9 (15.7)
XELOX + Bevacizumab	4 (7)
Third line chemotherapy (n= 38) (%)	
FOLFOX	6 (16.2)
FOLFOX + Bevacizumab	4 (10.8)
FOLFIRI	2 (5.2)
FOLFIRI + Bevacizumab	3 (7.8)
Irinotecan + anti-EGFR	10 (26.3)
XELOX + Bevacizumab	2 (5.2)
Regorafenib	11 (28.9)

FOLFOX: Fluorouracil+Folinic acid+Oxaliplatin, FOLFIRI: Fluorouracil+Folinic acid+Irinotecan, FOLFOXIRI: Fluorouracil+Folinic acid+Oxaliplatin+Irinotecan, FUFA: Flourouracil+Folinic acid, XELOX: Capecitabine+Oxaliplatin

DISCUSSION

In our study, CRC patients diagnosed under the age of forty years had later stages at the time of diagnosis, and patients diagnosed in the metastatic stage showed a more aggressive course compared to other stages. In addition, the incidence of KRAS/NRAS and BRAF mutations and the incidence of tumors located in the distal colon or rectum were higher compared to the general population. There was no statistical difference between the survival

rates obtained with conventional chemotherapy agents based on oxaliplatin or irinotecan in the first-line metastatic stage.

According to American Cancer Society data, 32.8% of all patients had local disease, 38.7% had regional disease, and 22.1% had metastatic disease at the time of diagnosis.[8] In the study by O'Connell et al., patients aged 20-40 years were diagnosed at a later stage than patients aged 60-80 years (56 vs 40 for stage 3-4).[10] In our study, 37% had stage 3, and 31% had stage 4 disease. Most of our patients were diagnosed at an advanced stage, and our data are compatible with the literature.

It is known that colorectal cancers diagnosed at an early age have a more aggressive course.[5-7,10] However, when the 1st, 5th, and 10th-year survivals according to the stages were analyzed, our study was similar to the CRC survivals, including all patients in the literature. However, since the number of stage 4 patients was higher, the mean survival of the whole patient group was shorter than in the literature. Based on this, our opinion that the most important reason for the more aggressive course of young CRC patients is that they are diagnosed at late stages.

In one study, KRAS mutation was found in 54% and NRAS mutation in 7% of patients diagnosed under the age of 40.[11] However, a large meta-analysis, including patients under 50, found that KRAS/NRAS BRAF mutations were less common in this patient group than in the whole population.[12] In our data, the rate of KRAS/NRAS was 55%, higher than the normal population, and BRAF mutation was 2.5%, lower than the normal population. MSI/H status is observed between 10-20% in all colorectal cancers, varying from population to population.[13] In one study, it was shown to be more frequent in the young population.[14] In our study, 12.1% of the patients with microsatellite status were MSI/H, and this rate was similar to that of the general population. Mucinous histology is seen in 5-15% of all colorectal cancers.[15] A study showed that the 40-year-old group contained more mucinous components than the group over 60 years of age.[16] In our study, the rate of a mucinous component was 23.7%, which was above the average for the whole population.

In studies conducted in previous years, approximately 10% of all CRC patients had a history of CRC in first-degree family members.[17-18] In the study by Chen et al., approximately 25% of patients diagnosed with CRC under 50 had a family history.[19] In another study, mutations causing hereditary cancer predisposition syndromes were found in 30% of patients diagnosed under the age of 50, and 20% had a familial history of CRC.[20] In our study, 24.8 percent of the patients had a familial history of colorectal cancer. In all studies, patients without a family history are more common than patients with a family history. Although screening methods were recommended more frequently in previous years, especially in patients with a family history, effective screening methods are required for all cases considering the increase in the number of sporadic cases and the rate among all cases.

Treatment of metastatic CRC includes conventional chemotherapies (FOLFOX, FOLFIRI, FOLFOXIRI) and targeted therapies (bevacizumab, cetuximab/panitumumab).[21] While bevacizumab is utilized in the presence of KRAS, NRAS or BRAF mutations, anti-EGFRs are utilized in patients with negative mutations. In addition, sotarasib and adagrasib are utilized in the presence of KRAS 12c mutation, encorafenib in the presence of BRAF mutation and trastuzumab-based therapies in the presence of HER-2 amplification.[22] Immunotherapies are seen as a breakthrough approach in microsatellite instability (MSI-H) positive patients.[23] In studies comparing FOLFOX and FOLFIRI in primary care, no significant difference was found between the two treatments.[24] In our study, similar to the literature, no statistically significant PFS and OS difference was found between the two treatment modalities. On the other hand, it is known that FOLFOXIRI provides a survival benefit over FOLFOX or FOLFIRI.[25-26] Based on this, our opinion that FOLFOXIRI may be preferred in the MSS group in young patients with good performance, especially in patients with a chance of definitive treatment afterward. At the same time, immunotherapy agents should be chosen primarily in the MSI/H group after considering the MSI/H status of the patients.

The limitations of our study are the need for detailed molecular characteristics of the tumors; pa-

tients lost to follow-up due to long follow-up periods, and the heterogeneity of the treatment options applied.

In conclusion, the reasons for the increasing incidence of CRC in younger age groups, screening methods, and treatment modalities must be better examined. The fact that this patient group is usually diagnosed at an advanced stage and the aggressive course of the disease makes clinical management difficult. Screening programs should continue with attention to individuals with a family history as well as the entire population for early diagnosis. However, the development and elaboration of molecular investigations provide guidance for the evaluation of treatment options and future developments. Furthermore, in the future, defining the molecular profile underlying the early development of sporadic CRC will help to plan individualized screening recommendations and improve management; this will increase the number of patients diagnosed at an early stage and improve their prognosis.

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Correspondence:

Dr. Ali Kaan GUREN

Marmara Universitesi Tip Fakultesi

Pendik Egitim ve Arastirma Hastanesi

Ic Hastaliklari Anabilim Dali

Tibbi Onkoloji Bolumu

Pendik

ISTANBUL / TURKIYE

Tel: (+90-530) 725 00 18

e-mail: alikaanguren@gmail.com

ORCIDs:

Ali Kaan Guren	0000-0002-3562-5006
Nazim Can Demircan	0000-0001-6630-5278
Sedef Seyma Ozgur	0009-0006-7294-5478
Tugce Bulun Akyol	0009-0009-9307-6701
Nargiz Majidova	0000-0002-2575-5819
Erkam Kocaaslan	0000-0002-8994-2904
Yesim Agyol	0000-0002-4409-6003
Pinar Erel	0000-0002-2797-2075
Burak Pacaci	0000-0002-9543-9053
Mustafa Alperen Tunc	0000-0002-1537-3032
Nadiye Sever	0000-0001-7312-3827
Abdussamet Celebi	0000-0002-6922-1018
Rukiye Arikan	0000-0003-2688-1515
Selver Isik	0000 0002 2726 1740
Murat Sari	0000-0003-0596-1559
Osman Kostek	0000-0002-1901-5603
Ibrahim Vedat Bayoglu	0000-0002-0481-1084