

# Changing trends in the corneal transplantation and the impact of the COVID-19 pandemic on corneal transplant recipient selection

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## Abstract:

**PURPOSE:** The aim of this study was to analyze the trends in the major indications and types of keratoplasty over a 15-year period and to determine the effect of the coronavirus disease-2019 (COVID-19) pandemic on the selection of corneal transplant recipients at a tertiary referral center in Turkey.

**METHODS:** We retrospectively reviewed the data of patients who underwent keratoplasty at the center from January 2006 to March 2021. The keratoplasty indications and types of surgery were evaluated after classification into three groups (period I – January 2006–December 2012; period II – January 2013–March 2020; COVID-19 period – April 2020–March 2021).

**RESULTS:** A total of 5016 corneal transplants were performed in 3862 patients. Lamellar keratoplasty (LK) techniques were found to demonstrate a statistically significantly increasing trend compared to penetrating keratoplasty in the period between 2006 and 2021 ( $\chi^2 = 240.55$ ,  $P < 0.001$ ). The top 4 indications over the 15-year period were aphakic/pseudophakic bullous keratopathy (BK) (1105, 22%), keratoconus (1085, 21.6%), regraft (1084, 21.6%), and keratitis (645, 12.8%). The most common keratoplasty indication during the COVID-19 period was regraft (27, 54.0%), followed by BK (13, 26.0%) and corneal perforation (5, 10%).

**CONCLUSION:** BK was the most common keratoplasty indication at our clinic during the 15-year period. LK rates have been found to increase in recent years, although still not reaching the rates of developed countries. There was a marked decrease in the number of keratoplasties during the COVID-19 pandemic and patients requiring urgent keratoplasty or those who suffered from a painful eye were prioritized.

## Keywords:

Changing trends, corneal transplantation, lamellar keratoplasty

## INTRODUCTION

Corneal transplantation is the most common and successful form of tissue transplantation worldwide.<sup>[1]</sup> Eduard Zirm performed the first successful full-thickness corneal transplantation (now known as penetrating keratoplasty [PK]) in humans in 1906.<sup>[2]</sup> Since then, the indications and techniques of keratoplasty and the instrumentation used have been constantly evolving.<sup>[3]</sup>

The development of lamellar keratoplasty (LK) techniques has made it possible to replace

only the corneal layer involved by the corneal disorder.<sup>[4]</sup> Deep anterior LK (DALK), one of the LK techniques, is used in stromal corneal disorders such as keratoconus where the recipient endothelium is not involved.<sup>[5]</sup> An advantage of anterior LK is the possibility of preserving the healthy endothelium. This significantly decreases the potential for endothelial cell loss and graft rejection in the postoperative period.<sup>[6]</sup> Endothelial keratoplasty (EK) techniques such as descemet stripping automated endothelial keratoplasty (DSAEK) or descemet membrane endothelial keratoplasty (DMEK) are used for pathologies where only the corneal endothelium is involved such as bullous keratopathy (BK) and

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Fuchs' endothelial dystrophy.<sup>[7]</sup> The posterior LK techniques provide various benefits over PK such as minimal invasiveness, quick visual improvement, faster wound healing, preservation of the ocular surface and globe integrity, minimal refractive shift, and significantly lower risk of immune rejection.<sup>[8]</sup> These advantages of the LK techniques have resulted in an increase in the use of lamellar surgery, especially since the 1990s.<sup>[9,10]</sup>

There are various factors that determine the main corneal transplantation indications and surgical techniques for any given region. Pseudophakic BK (PBK) and re-graft have been reported as the main keratoplasty indications in studies from the USA and Canada.<sup>[11,12]</sup> In contrast, the most frequent corneal transplantation indication is reported as keratoconus in studies from Europe, Turkey, Iran, and Israel, and as infectious keratitis in studies from Asia.<sup>[13-17]</sup>

Various factors such as social, geographic, financial, and political determinants in addition to the etiology of the corneal disorder determine whether the patient actually has access to transplantation.<sup>[18]</sup> The recent coronavirus disease-2019 (COVID-19) pandemic has been reported to significantly limit the availability of corneal donors.<sup>[19]</sup> The lockdowns during this period have resulted in delays in many types of ophthalmic surgery around the world and in our country. The fact that the COVID-19 agent has been demonstrated in the tear fluid and conjunctival surfaces has highlighted the risk of potential transmission from the corneal donors to the recipients.<sup>[20]</sup> Tissue-dependent corneal transplantation has been one of the ocular surgical procedures that were the most significantly affected due to the limited number of donors during the pandemic.

The aim of the current study was to analyze the trends in the major indications and types of keratoplasty and evaluate the effect of the COVID period on the selection of corneal transplant recipients at the Eye Bank of Istanbul Dr. Lutfi Kirdar Kartal Education and Research Hospital, a tertiary referral center in Turkey.

## METHODS

We retrospectively analyzed the data of 3862 patients registered at the University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital's Eye Bank who had undergone corneal transplantation between January 2006 and March 2021. The study protocol was approved by the Ethics Committee of the Dr. Lutfi Kirdar Kartal Education and Research Hospital, and the study was conducted in accordance with the Declaration of Helsinki. The

Institutional Review Board and Ethics Committee approved the study (IRB No: 2021/514/200/4). The demographic data, keratoplasty indications, and the keratoplasty technique used (PK, DALK, DMEK) were recorded. The study was divided into the three periods of January 2006–December 2012 (period I), January 2013–March 2020 (period II), and April 2020–March 2021 (the COVID-19 period for Turkey) so as to evaluate the changes in the corneal transplantation trends and the effect of the COVID-19 pandemic on the corneal transplantation indications.

## Statistical analysis

The SPSS software, Version 21.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analyses. The Kolmogorov–Smirnov test was initially used to determine whether the data were distributed normally. We compared continuous variables between the groups with the Kruskal–Wallis test. The Tamhane T2 test was used for pairwise comparison. The results are presented as arithmetic mean  $\pm$  standard deviation. The Chi-square test was used to evaluate the differences between the groups regarding categorical variables. Chi-square trend tests were used to determine the statistical significance of keratoplasty types by year. A  $P < 0.05$  was considered statistically significant.

## RESULTS

A total of 3862 patients underwent 5016 keratoplasties between January 2006 and March 2021 at our clinic. There were 2268 males (58.7%) and 1594 females (41.3%). The mean age was  $50.33 \pm 20.79$  years (range, 1–111 years). The distribution of eye laterality was almost equal with 2460 (49.0%) right eyes and 2556 (51.0%) left eyes. The mean age of the patients during period I (2006–2012), period II (2013–2020), and the COVID period was  $46.39 \pm 20.56$ ,  $52.76 \pm 20.51$ , and  $57.28 \pm 22.67$ , respectively ( $P = 0.0001$ ). The mean age of the period I patients was statistically significantly lower than those in the other groups while there was no statistically significant difference between the patients in period II and the COVID period (period I vs. period II,  $P = 0.0001$ ; period II vs. COVID period,  $P = 0.0001$ ; period II vs. COVID period,  $P = 0.262$ ). A statistically significant was not found between the periods regarding the gender distribution ( $P = 0.063$ ). The distribution of the patients' demographic data by period is shown in Table 1.

The 5016 keratoplasties consisted of 4201 (83.8%) PK and 815 (16.2%) LK procedures. The LK cases included 448 (8.9%) DALK and 367 (7.3%) DMEK procedures. Figure 1 presents the distribution of the corneal transplantation

**Table 1: The patient's demographic characteristics**

Characteristics	2006-2012 Period I (n=1492)	2013-March 2020 Period II (n=2320)	April 2020-March 2021 COVID-19 period (n=50)	Overall (n=3862)
Age (years), mean $\pm$ SD, (range)	46.39 $\pm$ 20.56 (1-89)	52.76 $\pm$ 20.51 (1-111)	57.28 $\pm$ 22.67 (1-84)	50.33 $\pm$ 20.79 (1-111)
Male, n (%)	907 (60.8)	1332 (57.4)	29 (58.0)	2268 (58.7)
Female, n (%)	585 (39.2)	988 (42.6)	21 (42.0)	1594 (41.3)

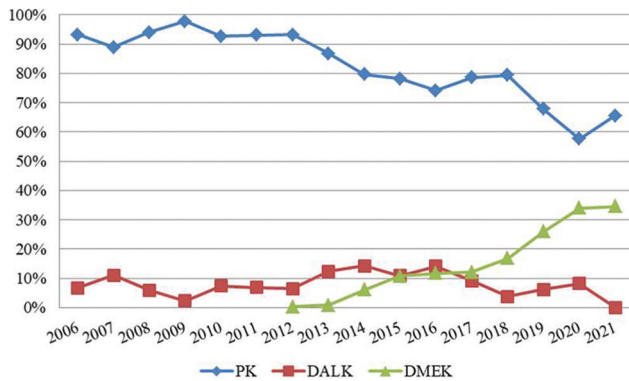
SD: Standard deviation, COVID-19: Coronavirus disease-2019

types by year. The number of lamellar keratoplasties showed a statistically significant increase compared to PK between the years of 2006 and 2021 ( $\chi^2 = 240.55, P < 0.001$ ). Evaluation of the number of PK cases after dividing the total time into three periods revealed that the PK percentage decreased in time with a marked dip during the COVID period, while the DALK percentage was generally around 10%. The DMEK percentage showed an increasing trend over the years. Figure 2 presents the rates of the surgical procedures by period.

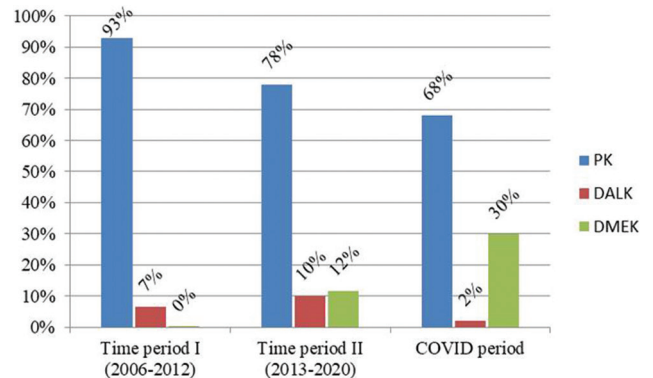
The first place among all the transplantation indications between 2006 and 2021 at our clinic belonged to aphakic/PBK (1105, 22%), followed by keratoconus (1085, 21.6%), regrant (1084, 21.6%), keratitis (645, 12.8%), and stromal dystrophy (392, 7.8%). The first three transplantation indications during period I (2006–2012) were keratoconus

(474, 24.3%), BK (392, 20.1%), and regrant (382, 19.6%), in order of frequency. The frequency order for period II (2013–2020) was BK (700, 23.2%), regrant (675, 20.2%), and keratoconus (609, 22.4%). The same order for the COVID period was regrant (27, 54.0%), BK (13, 26.0%), and corneal perforations (5, 10.0%). Table 2 presents the distribution of the transplantation indication percentages by period. Comparison of the keratoplasty indications in the three periods indicated an increase in the regrant indication, especially in the COVID period, while the keratoconus indication showed a significant decrease in the same period. The corneal perforation indication rate was found to have increased in the COVID period.

Comparison of the three most common keratoplasty indications according to type of surgery revealed that the percentages of PK and DMEK for the indication of bullous keratoplasty showed a gradually increasing trend from 2012 to 2020 [Figure 3].



**Figure 1:** The percentage distribution of the penetrating keratoplasty, deep anterior lamellar keratoplasty, and Descemet membrane endothelial keratoplasty cases by year



**Figure 2:** The percentage distribution of the type of corneal transplantation by period

**Table 2: Indications for corneal transplantation from January 2006 to March 2021 at a Tertiary Referral Center in Turkey**

Diagnosis	2006-2012Period I (n=1948), n (%)	2013-2020Period II (n=3018), n (%)	COVID period (n=50), n (%)	Overall (n=5016), n (%)
Aphakic/pseudophakic BK*	392 (20.1)	700 (23.2)	13 (26.0)	1105 (22.0)
Keratoconus	474 (24.3)	609 (20.2)	2 (4.0)	1085 (21.6)
Regrant	382 (19.6)	675 (22.4)	27 (54.0)	1084 (21.6)
Keratitis	298 (15.3)	346 (11.5)	1 (2.0)	645 (12.8)
Non-herpetic microbial keratitis	168 (8.6)	196 (6.5)	1 (2.0)	368 (7.3)
Herpetic keratitis	130 (6.7)	147 (4.9)	-	277 (5.5)
Stromal dystrophy	127 (6.5)	265 (8.8)	-	392 (7.8)
Macular dystrophy	63 (3.2)	158 (5.3)	-	221 (4.4)
Granular dystrophy	40 (2.1)	70 (2.3)	-	110 (2.2)
Lattice dystrophy	8 (0.4)	33 (1.1)	-	41 (0.8)
Other stromal dystrophy	16 (0.8)	4 (0.1)	-	20 (0.4)
Traumatic corneal scar	139 (7.1)	214 (7.1)	-	353 (7.0)
Endothelial dystrophy	60 (3.1)	74 (2.5)	2 (4.0)	136 (2.7)
Fuchs' endothelial dystrophy	59 (3.0)	70 (2.3)	2 (4.0)	131 (2.6)
CHED	1 (0.1)	4 (0.2)	-	5 (0.1)
Corneal perforations	24 (1.1)	80 (2.7)	5 (10.0)	109 (2.2)
Chemical injuries	30 (1.5)	20 (0.7)	-	50 (1.0)
Other causes	15 (0.8)	15 (0.5)	-	30 (0.6)
Congenital opacities	7 (0.4)	20 (0.7)	-	27 (0.5)

\*Includes aphakic BK, pseudophakic BK with anterior intraocular lens, and pseudophakic BK with posterior intraocular lens. BK: Bullous keratopathy, CHED: Corneal hereditary endothelial dystrophy, COVID-19: Coronavirus disease-2019

PK/DALK percentage evaluation by period according to the keratoconus indication showed a gradually increasing trend in the DALK percentage [Figure 4]. The PK percentage by period for the regrant indication showed a gradual decrease, while the DMEK rates showed a significant increase in the COVID period [Figure 5]. The comparative distribution of the four keratoplasty indications used most commonly by all the years revealed a decrease in recent years in the keratoplasty indications of keratoconus and keratitis, in contrast to an increase in the indications due to BK [Figure 6].

## DISCUSSION

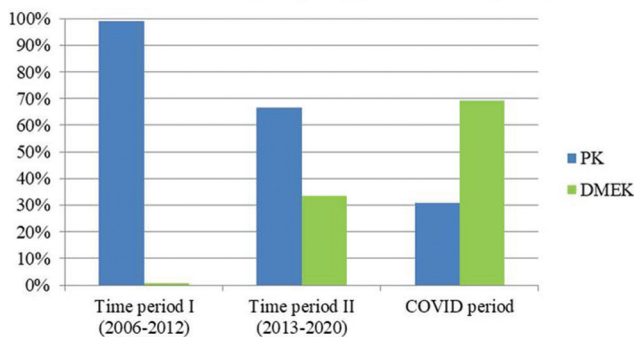
This study has reported the changing trends in the corneal transplantation indications and keratoplasty types at a tertiary referral center in Turkey during a 15-year period. Other points of focus included how the COVID-19 pandemic affected the corneal transplantation process at our clinic and the changes in the types and indications of keratoplasty over the years.

A total of 5016 keratoplasties were performed at our clinic during a 15-year period. The mean age was  $50.33 \pm 20.79$  years. There was a statistically significant difference between the periods as regards the mean age ( $P = 0.0001$ ). The mean age was lower in the period I patients than those in the period II or the COVID period. Keratoconus took first place among

the corneal transplantation indications in period I. The lower mean age of the patients in period I could be explained by the keratoplasty indications by period as keratoconus patients undergo keratoplasty at a younger age than for other indications. The mean age of keratoplasty patients as reported by other studies has been  $63.3 \pm 18.9$  years in Canada,  $50.4 \pm 20.2$  in Italy, and  $40.59 \pm 19.03$  in another study from our country. The mean age shows regional variance but this could also be directly related to the keratoplasty indications.<sup>[13,21,22]</sup> A study from Canada has reported high rates of keratoplasty indications of Fuchs dystrophy and BK while keratoconus was reported to be frequent in studies from our country and Italy.<sup>[13,21,22]</sup>

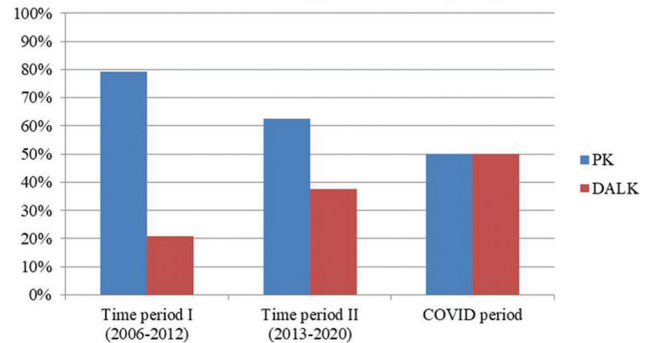
The 5016 keratoplasties in this study included 4201 (83.8%) PK and 815 (16.2%) LK cases. The LK group comprised 448 (8.9%) DALK and 367 (7.3%) DMEK procedures. DALK has been in use for a long time in our clinic while DMEK has only been used since 2012. We have no experience with DSAEK. We found LK techniques to shown an increasing trend when compared with PK between 2006 and 2021 ( $\chi^2 = 240.55, P < 0.001$ ). Data from the Eye Bank Association of America (EBAA) reveal that the number of PKs and EKs performed in the United States were approximately equal in 2011 but EK has become the most frequently performed type of corneal transplantation since then.<sup>[18]</sup> Figure 1 presents the distribution of the keratoplasty types at our clinic by year

**Bullous Keratopathy: Type of Keratoplasty**



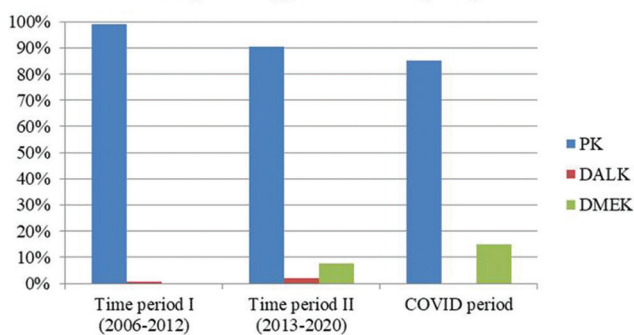
**Figure 3:** The percentage distribution of the type of keratoplasty for an indication of bullous keratopathy by period

**Keratoconus: Type of Keratoplasty**



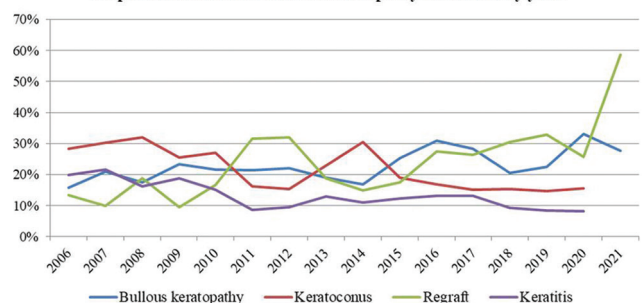
**Figure 4:** The percentage distribution of the type of keratoplasty for an indication of keratoconus by period

**Regrant: Type of Keratoplasty**



**Figure 5:** The percentage distribution of the type of keratoplasty for an indication of regrant by period

**Proportions of the most common keratoplasty indications by years**



**Figure 6:** The percentage distribution of the four most common keratoplasty indications by year

and reveals that the percentage of DMEK, a type of EK, has now approached that of PK. A 2015 study has reported that developed countries such as Sweden, the United States, and the United Kingdom had higher EK rates, with such surgery constituting about half (41%–52%) of all graft procedures. Singapore similarly had a high rate of EK adoption at 44%. The EK rate was much lower in less developed countries such as Thailand, Philippines, India, and China (1%–4%).<sup>[23]</sup> The EK rate at our own clinic was 15% in 2016 but increased to 34% in 2020. EK has become increasingly popular in developing countries, such as our own country, in recent years. It is not at the level seen in developed countries yet, but there is an increasing trend. The rates of DALK surgery, another LK technique, have not shown a significant increase in developing or developed countries, unlike that seen for EK. EBAA data reveal that there is no significant change in the rate of DALK surgery between 1996 and 2016 in the United States.<sup>[18]</sup> Although we detected a minimum increase in the DALK surgery rate at our clinic between 2013 and 2016, the rate remained below 10% in both the previous years and at recent times. We believe that this decrease is due to the change in the surgical indication criteria for keratoconus, the most common indication for DALK surgery, especially in the recent period.<sup>[24]</sup> Successful results have been obtained as regards visual rehabilitation in keratoconus with the scleral contact lens and intrastromal corneal ring segment procedures.<sup>[25,26]</sup> It has now become possible to make an earlier diagnosis with the development of corneal tomographic devices and to prevent progression of the disorder with earlier application of cross-linking treatment.<sup>[27]</sup> This has decreased the indication for keratoplasty in keratoconus cases. We similarly found a marked decrease in the keratoconus indication at our center after 2015 [Figure 6].

Many factors have been reported to influence the access of patients with a corneal pathology to corneal transplantation. These include social, geographic, economic, and political factors; the etiology of the corneal disorder; the expected postoperative graft prognosis; patient age and physical fitness; and other ocular and medical factors present in the patient.<sup>[18]</sup> The order of frequency for all transplantation indications at our clinic between 2006 and 2021 was aphakic/PBK (1105, 22%), keratoconus (1085, 21.6%), regrant (1084, 21.6%), and keratitis (645, 12.8%). There has been an increase in recent years in the transplantation rates for BK and regrant while a decreasing trend was noted in the keratoconus and keratitis indications. A study from Germany has reported the most common indication for corneal transplantation as endothelial cell failure due to Fuchs endothelial corneal dystrophy (FECD) or BK, and this was followed by regrant, keratoconus, and corneal scarring.<sup>[28]</sup> EBAA data indicate that endothelial cell failure secondary to FECD or cataract surgery (e.g., BK) is again the most common transplantation indication, followed by regrant, keratoconus, and corneal scarring.<sup>[29]</sup> The 2019 EBAA data show a significant increasing trend for keratoplasty performed for an FECD diagnosis while

BK-related keratoplasty had a decreasing trend. There was also a significant decrease in the number of keratoplasties for a diagnosis of keratoconus. No marked change was observed in the regrant rates by year.<sup>[29]</sup> The number of FECD diagnoses in our clinic was much lower than in other studies and that reported by the EBAA.<sup>[29-31]</sup> It is of course also possible that a large proportion of BK patients is actually previously undiagnosed FECD cases. This could be the reason for the large increase in the keratoplasties due to BK in our clinic in recent years. There has also been a large increase in the regrant rates in recent years. Our clinic is a referral center where complicated patients make up the majority of the patients and the fact that surgery is performed at our center on the regrant indications from other clinics could be the reason for the large increase in the relevant rate.

Asia is the region with the highest keratoplasty rates due to keratitis (32.3%). The areas with the lowest rates for this complication are Australia (5.2%), South America (8.7%), and the Middle East (3.6%). The keratitis-related keratoplasty rate at our clinic was 12.8%. This rate is similar to that from Europe (13.2%).<sup>[17]</sup>

The current COVID-19 pandemic has become a major global problem. The first COVID-19 case from Turkey was reported on March 10, 2020.<sup>[32,33]</sup> This was followed by a rapid increase in the number of Turkish cases despite the efforts made to prevent the disease at both the individual and public levels starting on mid-January 2020 and the consecutive efforts to increase such measures. Turkey became one of the ten countries with the highest number COVID-19 cases in the world within 30 days of the beginning of the disease in the country.<sup>[32]</sup> Many elective cases have had to be canceled during this period. Corneal transplantation has been one of the most significantly affected among all ophthalmic surgeries.<sup>[34]</sup> Studies from India have reported a decrease to one-fourth of the previous numbers during the pandemic. Taking the April 2020–March 2021 period as the COVID period, the total number of transplantations at our clinic was 50. The total number during the 1-year period of 2019 was 320. This means that the numbers at our clinic decreased to one-seventh of the previous total. There have been significant changes in the corneal transplant indications during this process due to the difficulties in corneal procurement. The rate of regrant as an indication has increased from 20% to 43.3% during this period. There has also been an increase in BK as an indication, and it is the second most common indication. The rate of corneal perforation as an indication has shown a significant increase compared to the previous period (from 2.7% in period II to 10% in the COVID period). The keratoconus indication, a common indication for corneal transplantation, has decreased from 20% to 4% in the COVID period. The global health-care problem of COVID-19 has therefore had a negative effect on the patients waiting for corneal transplantation. The waiting time for corneal transplantation has not been evaluated in our study but the number of patients waiting for a corneal transplantation at

our eye bank increased and the cornea transplantation waiting time became longer during this time.

Evaluation of the most common keratoplasty indications by period showed a marked increase in the number of patients undergoing DMEK for BK in period II (2013–2020) compared to period I (2006–2012). Approximately 70% of the patients with a BK diagnosis had undergone DMEK during the COVID period. Despite the marked decrease in keratoconus as an indication for keratoplasty, there was an increasing trend in the use of anterior LK for this indication. An increasing trend has also been observed in the re-graft indication in patients who have undergone DMEK in recent years. The increase in the re-graft indication (54%), followed by the BK (26%) and perforation (10%) indications, during the COVID period is an indication of the prioritization of painful eyes and urgent cases at this time. There was no corneal transplantation surgery from April 2020, the time of the first closure, to July 2020 in our country. Once the restrictions were gradually lifted, keratoplasty surgery was started again in August 2020. However, the lack of corneal procurement in adequate numbers has resulted in a constant increase in the number of waiting patients.

## CONCLUSION

The corneal transplantation indications and the type of keratoplasty used show regional variations according to the socioeconomic status of the country and its demographic features. BK has been the most common keratoplasty indication in our clinic. Although LK techniques have not reached the rates seen in developed countries, there has been a trend to use them increasingly more frequently in recent years. The COVID-19 pandemic has resulted in a significant decrease in the number of keratoplasties globally and in our own clinic, a tertiary referral center. The number of corneal transplantations performed has decreased to one-seventh of the previous year.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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