Trends in Corneal Transplant Indications and Techniques in Coimbra, Portugal: 2011 -2016

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ABSTRACT

Objective: The aim of this study is to determine the recent trends in corneal transplant indications and corneal tissue use in Coimbra.

Methods: data concerning all corneal transplantation procedures performed at Centro Hospitalar e Universitário de Coimbra (CHUC) between 2011 and 2016 were collected and stored at the CHUC Eye Bank. We retrospectively analysed recipient age, gender, primary diagnosis and transplantation technique.

Results: 710 corneal transplants were reviewed for analysis. Regraft accounted for 207 (29.2%) of all procedures, followed by bullous keratopathy, with 125 cases (17.6%) and keratoconus, with 118 cases (16.6%). No statistically significant shift in indications for grafting was identified over the 6-year period ($p = 0.70$). Penetrating keratoplasty (PK) accounted for 506 procedures (71.3%), Descemet's stripping automated endothelial keratoplasty (DSAEK) for 129 (18.2%), and deep anterior lamellar keratoplasty (DALK) for 64 (9.0%). Over the 6 years, we observed a statistically significant decline in the numbers of PK, accompanied by an increase in DSAEK and DALK.

Conclusions: Eye bank registries provide an effective means to evaluate corneal transplantation evolution. Transplant indications have remained stable across the time frame considered. Compared with other series, we report more repeat grafts, less keratoconus and similar percentages of bullous keratopathy and corneal dystrophies. In terms of surgical technique, this study provides further evidence of the increasing popularity of lamellar keratoplasties, in opposition to PK. In conclusion, the indications and techniques for corneal transplantation continue to evolve rapidly, and merit continued investigation to optimize the activities of eye banks and transplant centres.

Keywords: Corneal grafting, Eye Bank, Penetrating keratoplasty, Descemet Stripping Endothelial Keratoplasty, Deep anterior lamellar keratoplasty

INTRODUCTION

Corneal diseases are the fourth cause of blindness worldwide (surpassed only by cataract, glaucoma, and age-related macular degeneration), accounting for 4% of the more than 39 million cases of blindness worldwide.[1] Etiology of corneal blindness ranges from scarring, infectious and nutritional corneal disorders, most common in developing countries, to inherited, degenerative or iatrogenic causes in the developed world.[2]

Corneal transplantation, the partial or total replacement of a diseased cornea with a healthy donor cornea, has been an invaluable weapon against many otherwise untreatable corneal diseases since its inception, more than a century ago.[3] It remains to this day the most common transplant procedure in the world.[2]

The limited availability of donor tissue remains one of the main obstacles to solving corneal blindness. Recent studies estimate the worldwide shortage of corneal grafts to be in the magnitude of 1 cornea available for every 70 corneas needed.[4] Establishing a successful corneal transplantation program, one that adequately meets demand and supply, relies on a series of separate steps along a complex chain: from identifying potential donors to ultimately supplying each patient with the appropriate corneal graft. One of those steps is to thoroughly analyse both the indications for which transplants are needed and the techniques used to deliver corneal transplants. Both indications and techniques are constantly evolving and knowledge on such trends is essential to guide local and global strategies on corneal transplantation and eye banking.

In the past decade, keratoconus, pseudophakic bullous keropathy (PBK), regraft and Fuchs dystrophy were described as the main indications for transplant in developed countries.[5,6] However, increased prevention of PBK and the development of alternative treatments for keratoconus are rapidly changing the traditional patterns of corneal transplant indications, prompting the need for new data.[7]

Additionally, transplantation surgical techniques have also evolved dramatically, and recent studies have reported a marked shift from penetrating keratoplasty (PK) to newer procedures such as deep anterior lamellar keratoplasty (DALK) and Descemet's stripping automated endothelial keratoplasty (DSAEK).[8,9]

A precise knowledge on changes in indications and applications for corneal transplants is fundamental to help plan the activity of health systems. Moreover, it provides the opportunity to compare data from different countries and establish parallels and discrepancies. Papers have been published reporting on transplant databases from all over the world, comprising tens of thousands of procedures.[5-14] However, there are, to this date, no data from Portugal.

The aim of this study is to determine the current and recent trends in corneal transplant indications and techniques in Portugal, using data from 2011 to 2016 provided by the Eye Bank from the Coimbra University Hospital (CHUC), Portugal.

METHODS

Centro Hospitalar e Universitário de Coimbra (CHUC) is a government funded teaching hospital and a tertiary care referral centre for the whole of Portugal. It offers a formal residency training program and also higher specialist training in cornea as well as in other subspecialty areas of expertise. The CHUC Eye Bank collects the eyes of all potential eligible donors within the CHUC hospital and across other affiliated hospitals in the centre of Portugal. Eyes are then processed and stored in the Eye Bank and supplied to corneal surgeons for transplants or other surgeries. Importantly, the Portuguese health system is based on a state funded single payer system, meaning all patients are fully covered for all corneal transplant surgeries. This means that both surgeon and patient do not need to prioritise financial factors when choosing a specific surgical method.

The Eye Bank at CHUC was originally funded in 1977 and has been supplying donor corneas for transplants inside and outside of CHUC ever since. Since 2011 the CHUC Eye Bank is certified to comply with the ISO 9001:2008 quality management system. This certification process was undertaken to ensure that the CHUC Eye Bank consistently meets both costumer and patient's expectations as well as the applicable regulatory requirements. The standard of quality management adopted since 2011 has a strong focus on process approach and end customer satisfaction but also on continual improvement. As the 5-year hallmark as a certified eye bank has been reached, it felt essential to establish a broad overview of the work developed during the last years. This

prompted the necessity of this work and will hopefully serve as a stepping stone on our efforts for future improvement.

Transplant recipient demographic and clinical data were collected and stored in the Eye Bank database for all corneal transplantation procedures performed at CHUC only from 1st January 2011 to 31st December 2016, totalling 711 procedures. Retrospectively analysed data in this study included recipient age, gender, primary diagnosis, transplantation technique used and date of the surgery. Primary diagnoses were grouped into the following categories: keratoconus, bullous keratopathy, active keratitis, post-infectious scar, corneal perforation, Fuchs dystrophy, non-Fuchs corneal dystrophies, repeat graft and other indications. For cases in which a regraft was performed, regraft was considered the indication for the transplant regardless of the original diagnosis. Techniques used were labelled as penetrating keratoplasty (PK), deep anterior lamellar keratoplasty (DALK), Descemet's stripping automated endothelial keratoplasty (DSAEK), or keratoprosthesis (KPRO).

Tables and charts were created using Microsoft Office Excel 365®. IBM SPSS 24® was used for statistical analysis. All categorical data are presented as "number of cases (percentage of total)", whereas quantitative data are presented as "mean (standard deviation)", if they follow a normal distribution, and as "median (25th percentile; 75th percentile)" if otherwise. Association between two categorical variables, such as gender, primary diagnosis, surgical techniques, or calendar year of transplantation, was evaluated using chi-squared test. Recipient age (the only quantitative variable in this study) was compared between groups using non-parametric tests, Mann-Whitney for comparison between two groups, Kruskal-Wallis for three or more. For every statistical test used, a 2-tailed P value inferior to 0.05 will be considered statistically significant to reject the null hypothesis.

This study was designed and conducted according to the tenets of the Declaration of Helsinki for medical research involving human subjects.

RESULTS

Between 1st January 2011 and 31st December 2016, 710 corneal transplants – 345 right eye (48.6%) and 365 (51.4%) left eye grafts - were performed at Coimbra University Hospital on a total of 587 patients, 305 (52.0%) males and 282 (48.0%) females. The number of transplants performed in the different calendar years are presented in Figure 1. Recipients' age ranged from 5 to 94 years old, with a median of 61 (41; 75). The mean age of transplantation was 57.4. No significant shift in patient age was observed over the course of the study (p = 0.08). Patient demographics across the different diagnosis and surgical techniques are summarized in Table 1.

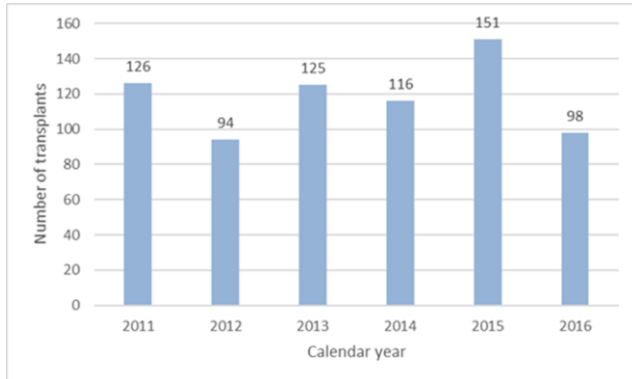

Figure 1 – Number of transplants performed per calendar year

Table 1

Indication	Total	Female	Male	Age distribution
Post-infectious scar	81	35	46	60 (46; 75)
Corneal Distrophies (excluding Fuchs)	6	1	5	60.5 (44; 77)
Fuchs Distrophy	59	40	19	69 (60; 76)
Others	32	15	17	53.5 (39; 65)
Corneal Perforation	32	15	17	62 (29; 69)
Active Keratitis	50	18	32	67 (47; 78)
Keratoconus	118	48	70	34.5 (26; 45)
Bullous Keratopathy	125	77	48	74 (60; 81)
Repeat graft	207	100	107	61 (33; 75)
Technique	**Total**	**Female**	**Male**	**Age distribution**
KPRO	11	5	6	64 (56; 79)
PKP	506	226	280	61 (42; 75)
DSAEK	129	91	38	69 (56; 79)
DALK	64	27	37	33 (26; 48)
Total	**710**	**349**	**361**	**61 (41; 75)**

Indication

Throughout the five-year period, the most frequent indication for corneal transplantation was regraft, which accounted for 207 (29.2%) of all procedures, followed by bullous keratopathy, with 125 cases (17.6%) and keratoconus, with 118 cases (16.6%). Post-infectious corneal scarring and active keratitis accounted for 81 (11.4%) and 50 (7.0%) procedures respectively. Corneal perforation was the cause for 32 (4.5%) transplants. Fuchs dystrophy – 59 (8.3%) cases - largely surpassed other corneal dystrophies – 6 (0.8%) - as transplant indication. Other causes totalled 32 (4.5%) cases. No significant shift in indications for grafting was identified during this study, as the distribution of primary diagnosis was similar across the five years ($p = 0.70$).

A statistically significant difference was found regarding indications for transplant when comparing different genders ($p<0.01$) and age groups ($p<0.01$) as well as when comparing techniques used between gender ($p<0.01$) and age groups ($p<0.01$). Table 1 illustrates these differences: the data show that keratoconus is a common indication for transplant, especially among young male adults, whereas bullous keratopathy is more frequent in elderly females.

Surgical technique

Of the 710 procedures, penetrating keratoplasty (PK) accounted for 506 (71.3%), Descemet's stripping automated endothelial keratoplasty (DSAEK) for 129 (18.2%), deep anterior lamellar keratoplasty (DALK) for 64 (9.0%), and keratoprosthesis for 11 cases (1.5%). The data appear to show a gradual increase in partial transplantation techniques: DALK was the technique used for 5.6% of all transplants in 2011, and 12.2% in 2016. DSAEK represented 13.5% of all graft procedures in 2011 and 27.6% in 2016. This was accompanied by a decrease in the incidence of PK (from 74.6% in 2011 to 60.2% in 2016). These trends were shown to be statistically significant ($p<0.01$) and are illustrated in Figure 2.

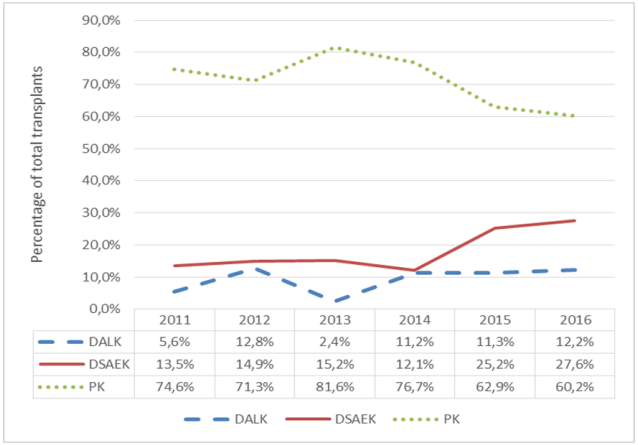

Figure 2 –Trends in transplantation techniques

There were some associations observed regarding procedure choice and demographic profile. For example, DSAEK was more commonly performed on females, and DALK in younger adults of both sexes, as can be seen in Table 1. However, these results are very likely explained by the fact that the choice of technique was shown to be strongly associated with the indication for transplant. Figure 3 breaks down the surgical technique used for every one of the diagnosis considered. For example, DALK was primarily used in patients with keratoconus ($p<0.01$), throughout the 6 years of study ($p=0.30$). Lamellar endothelial keratoplasty techniques – in this case DSAEK – were, as expected, used in patients with endothelial dysfunction, namely in those with bullous keratopathy or Fuchs dystrophy ($p<0.01$). This finding was increasingly noticeable in more recent years ($p<0.01$ and p0.02 respectively), as shown in Figures 4 and 5.

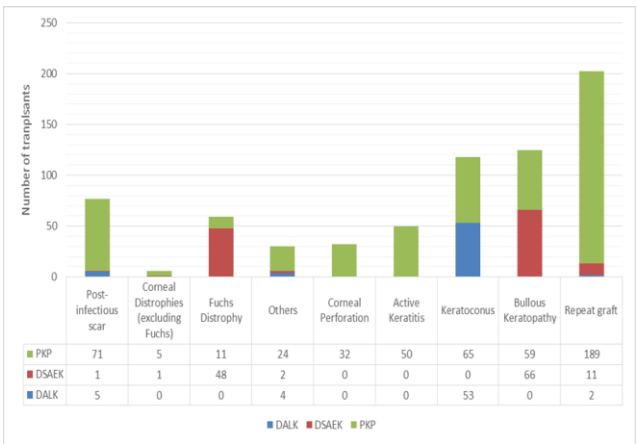

Figure 3 – transplant technique used by indication.

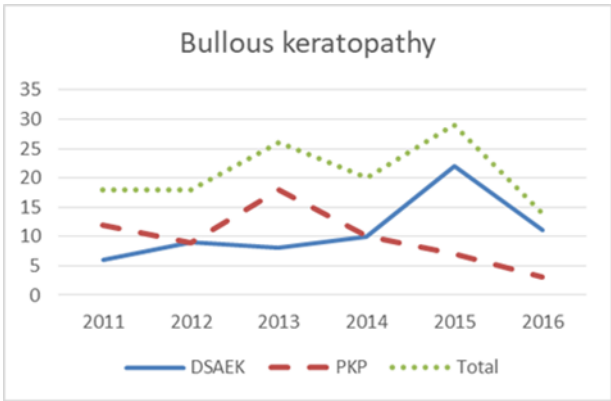

Figure 4 – growth of DSAEK for bullous keratopathy

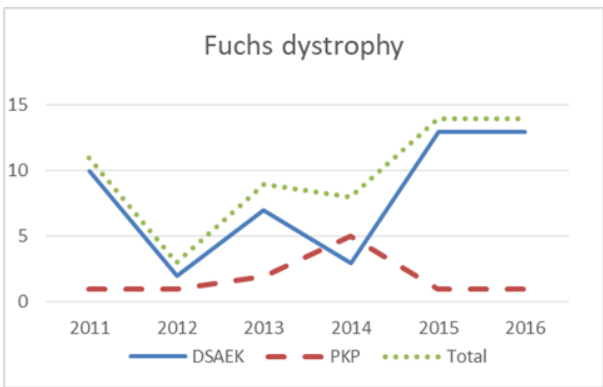

Figure 5 – growth of DSAEK for Fuchs dystrophy

DISCUSSION

This study provides a first insight on corneal tissue usage in one of the main reference centres of Portugal for corneal transplantation. The results obtained from the 710 procedures provide ample opportunity for comparison with those already published in other transplantation centres worldwide. The time frame of six years, albeit smaller than that of other studies, also gives us a broader insight into the ongoing changing trends in transplantation technique.

Patient Demographics

Patient age median, although constant throughout the 6-year period, is higher than that of older studies[5,8-10,12,13] by about 10 years, but similar to that of a study conducted during the current decade.[11] This may be explained by the changing trends in transplant indications, namely the emergence of non-surgical treatments for diseases affecting younger patients such as keratoconus. However, the bimodal distribution of age reported in the past[5,6,8] is still observable in this study, with a short peak in the 28 to 36-year-old age group and a much higher one between 75 and 83 years of age.

Indication

Across the last 6 years, our results presented no evident changes regarding indications for corneal transplant. Despite some remarkable advances in the treatments made available to our patients with common diagnoses – corneal crosslinking for progressing keratoconus or topography guided PRK for irregular astigmatism after PKP, for example - this doesn't necessarily come as a surprise, as 6 years may be an insufficient period to reflect the impact of those changes. For example, corneal collagen cross-linking (CXL) was introduced in our department during the year 2014, in the second half of the time frame considered for this study. One expects that the ability of CXL of halting keratoconus progression in more early stages and ultimately preventing advanced ectasia will eventually lead to a decrease in corneal transplant for this indication. In fact, that effect was noted on two studies[15,16] that compared earlier periods – 2005 to 2007 and 2005 to 2006, respectively – with numbers after the introduction of CXL. Since keratoconus often takes years to progress, the impact of the use of this new technique on the relative composition of our transplant patients is likely to be felt in the following years. Our present series provides us with a good descriptive analysis of our "pre-CXL" era. It will be interesting to compare it with future series.

However, comparison of indications for transplant between different studies from different countries yielded some compelling results, summarized in Table 2. Compared to other studies, this study reported a higher rate of repeat grafts (29.2%), which was the main indication for corneal transplantation in CHUC across the 6 years. Some different reasons may be behind this result. Firstly, it is important to notice that, for coding reasons, all repeated transplants performed were included under the designation "repeat graft", regardless of the primary indication or the technique used for both the first or second transplant. This encompasses multiple possible situations – from primary failures, to rejections, to regrafting for refractive correction – which might explain its relative importance. Another important cue is the relative importance of the other indications. Compared with some of the other series considered, our series has a much larger representation of active keratitis (18.5% against 4.2%[5] or

7.9%[8,11]) while keratoconus is remarkably underrepresented (16.6% against 41.3%[5] or 41.1%[8]). This is likely due to the nature of our centre (a public end-point tertiary referral centre) and understandably impacts on the overall number of regrafts on our pool – active keratitis for example has a much worse graft survival than keratoconus. Interestingly, there have been significant increases in the frequency of regrafts in many series,[5,17] in some cases more than doubling its frequency from previous series.[17] This is probably linked with a global increase in transplant procedures. Overall, differences in regraft incidences among countries are difficult to interpret as they are more likely to reflect the total number of grafts performed that accumulate in the short- and long-term follow-up than any actual difference in patient representation.

Keratoconus accounted for 16.6% of all indications, a result very close to that of the recent Canadian[11] and Colombian[12] studies, and a much lower percentage than seen in Italy[5] and New Zealand[8] in the last decade. Despite the influence of geographical and ethnical factors that may contribute to decreased keratoconus prevalence and progression in Portugal, especially when compared to New Zealand,[8] a worldwide trend of reduction of keratoconus treatment through corneal transplant can be observed in the past decade,[18] a probable consequence of the introduction of new treatments such as collagen cross-linking.[19]

Bullous keratopathy (17.6% of all transplants in this study) remains a significant cause of transplantation worldwide. This may be explained by the very high number of cataract surgeries performed around the world, despite advances in phacoemulsification and intraocular lens placement.[20] Corneal dystrophies were the indication for 9.2% of transplants, similarly to most other studies.

Infectious causes were a more prevalent indication in this study than in most others, at 18.5% of all causes. Lastly, corneal perforation represented 4.5% of all transplant causes, and other causes 4.5%.

Table 2

Country	**Italy[5]**	**New Zealand[8]**	**Canada[11]**	**Colombia[12]**	**USA[17]**	**Portugal**
First author	Frigo	Cunningham	Ryan Le	Galvis	Gosheh	Current study
Years studied	2002/2008	2000/2009	2012/2013	2004/2011	2001/2005	2011/2016
Number of transplants	13173	2205	229	450	1162	710
Indication	**Italy[5]**	**New Zealand[8]**	**Canada[11]**	**Colombia[12]**	**USA[17]**	**Portugal**
Corneal Perforation	6,3%	3,7%	7,4%	15,7%	-	4,5%
Active Keratitis and post-infectious scar	4,2%	7,9%	7,9%	14,4%	11.2%	18,5%
Corneal Distrophies (including Fuchs)	6,3%	10,7%	28,0%	7,5%	11.8%	9,2%
Keratoconus	41,3%	41,1%	12,2%	12,7%	16.0%	16,6%
Bullous Keratopathy	16,3%	13,9%	20,9%	34,6%	30.6%	17,6%
Repeat graft	17,4%	17,0%	17,4%	7,7%	22.0%	29,2%
Others	8,2%	5,7%	6,2%	7,4%	8.4%	4,5%
Technique	**Italy[5]**	**New Zealand[8]**	**Canada[11]**	**Colombia[12]**	**USA[17]**	**Portugal**
PK	81,5%	90,7%	39,0%	89,5%	98.5%	71,3%
DALK	12,5%	6,2%	10,0%	0,0%	0.6%	9,0%
DSAEK	6,0%	2,8%	41,0%	10,5%	0.1%	18,2%
Other	0,0%	0,3%	10,0%	0,0%	0.8%	1,5%

Technique

During the 6-year period of this study, lamellar keratoplasties, namely DALK and DSAEK, grew in importance in this reference centre: in 2011, they represented 19.1% of all transplants, a number that grew gradually, reaching 39.8% in 2016. This was logically accompanied by a decrease in penetrating keratoplasties. This is a trend that has been reported all over the world since the turn of the century,[5-12,14] and is a result of accumulating scientific evidence on the advantages of lamellar techniques.[2] The paradigm has changed from a “one size fits all” approach to a selective and minimally invasive approach, as our data confirms. As equipment and technique improve, our expectation is that even more refined lamellar techniques will emerge and this trend becomes even more meaningful.

Despite that, in the foreseeable future, PKP remains an invaluable surgical technique for many important indications and is not likely to become irrelevant.

When comparing the different data in table 2, the variations in transplant technique choice can be explained by several factors: firstly, the years portrayed: older studies have a higher rate of PKP and lower rate of lamellar techniques, especially DSAEK – for example, comparing the Italian[5] and New Zealander[8] data with that of Canada[11] and Portugal. Secondly, the relative importance of different indications for transplant in different series, as lamellar techniques are indicated for specific diagnosis, e.g., we see a higher percentage of DALK in Italy, where keratoconus is the most prevalent indication. Lastly, the actual difference in technique choice by the different centres, dependant on factors such as graft availability and surgical expertise.

At CHUC, during the 6 years of this study, PK appears to have been the technique of choice for corneal perforations, active keratitis, non-Fuchs corneal dystrophies, and for most regrafts (91.3%) and post-infectious scars (87,7%). DALK was an alternative technique for patients with keratoconus (44.9%). DSAEK was most used in cases of bullous keratopathy (52.8%) and Fuchs dystrophy (81.4%). These technical choices appear to be in accordance with the latest scientific evidence.[2]

As all studies, ours is not without limitations, although attempts were made throughout to minimize these limitations. Firstly, the accuracy of all the data used relies on the proper completion of all record forms. It is not impossible that some data was lost due to incompleteness of the data set or because some forms were lost. Also, record filling and data coding inevitably lead to some loss of information as we were forced to compile individual cases into broad categories. Not only this may lead to some bias and loss of useful information, but also it is not always straightforward that the same coding procedures were undertaken in different centres, leading to some possible misinterpretation when comparing results from different centres. Diagnosis were provided in the surgical reports but, for the most part, were not confirmed by histopathological examination. Finally, differences in social and economic organization amongst countries, demographic patterns, referral procedures in between hospitals and overall changes in health settings greatly hamper our ability to extract information from comparing different case series.

In conclusion, to our knowledge, this is the first comprehensive study of recent trends in corneal transplantation performed in Portugal, including analyses by the type of graft and the surgical indication. This type of study has become especially relevant since the advent of lamellar keratoplasty, as changes in the techniques used impact on the way tissues are distributed: tissues with low endothelial cell counts can still be used for DALK, while tissues with stromal scars but good endothelial cell density are useful for endothelial keratoplasties. Our data shows that lamellar keratoplasties have steadily taken the centre stage for many indications and are now almost universally used in some of those (EK for Fuchs dystrophy for example). The use of a centralized, certified Eye Bank allowed us to collect and analyse large amounts of strictly coded data that can be used to produce reproducible, consistent reports across time. Changes in population demographics and ophthalmological practice are inevitable and will continue to drive the need for further similar studies in the future.

Our goal as clinicians and researchers is always to provide our patients with the best possible care. Good clinical care and sound health policies are both impossible without reliable data. We hope that the data provided in this report can be meaningful and relevant to clinicians devoted to corneal surgery. We also hope that it can provide health decision makers with a useful tool to diagnose current necessities, optimize patient and resources allocation, and plan the activities for the future ahead of us.

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