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## Ophthalmological instruments of Al-Halabi fill in a gap in the biomedical engineering history

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### Abstract

Al-Halabi is an intriguing ophthalmologist who invented numerous surgical instruments for treating various eye diseases. The illustrations of such instruments in his invaluable book "*Kitab Al-Kafi fi Al-Kuhl*" reflect his willingness to teach. Moreover, he included in his book a magnificent illustration of the anatomical structure of the eye. The book reflects Al-Halabi's medical practice and teaching and shows several advanced medical techniques and tools. His invaluable comments reflect his deep experimental observations in the field of ophthalmology. The current article provides proof that Al-Halabi is one of our early biomedical engineers from more than 800 years ago. Al-Halabi represents a ring in the chain of biomedical engineering history. His surgical instruments represent the biomechanics field. Al-Halabi should be acknowledged among the biomedical engineering students for his various contributions in the field of surgical instruments.

**Key Words:** Al-Halabi; Biomedical engineering education; Biomedical engineering history; Ophthalmological instruments

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**Core Tip:** Medieval Islamic ophthalmological instruments are a rich, complex, and understudied subject. This topic is interesting and deserves more attention than it has had. The book of Al-Halabi is indeed one of the interesting books on ophthalmology written in Arabic. The ophthalmological instruments included in Al-Halabi's table represent an untold story about the contributions of Muslim and Arab scholars in the field of ophthalmology. The aim of the present article is to fill in one of the gaps to some extent in biomedical engineering history. The ophthalmological instruments represent the biomechanics field.



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## INTRODUCTION

Studying the biomedical engineering history has greatly influenced the creative and inventive sense of biomedical engineering students[1]. Biomedical technologies have a very long history, among which are the ancient surgical instruments[2]. Bronze age epilation forceps were found in Ur, Iraq. The forceps, used in the treatment of trachoma, date back to ca. 2600 BC[3]. Other epilation forceps were discovered in tombs of the New Kingdom of Egypt (1570-1070 BC). Moreover, pots containing copper, zinc oxide, lead, and antimony sulphates were uncovered at the same tombs. These pigments were utilized for treating conjunctivitis[4]. It is argued that the first “book” on medicine in the world which is a medical papyrus (1553-1550 BC) was discovered in Luxor (Thebes), Egypt, in 1872 by the German archeologist Georg Ebers (1837-1898). In the eye treatment section, the only surgical procedure mentioned in the papyrus that has survived was applying to the eyelid onions, myrrh, gazelle excrement, and blood from lizards or bats after epilation through the use of feathers of a vulture[3].

Furthermore, in Egypt, several surgical needles could be seen carved in stone from the relief on the internal facade of the second wall in Kom Ombo Temple, constructed during the Ptolemaic dynasty (180-47 BC). Moreover, W.M. Flinders Petrie (1853-1942) (English Egyptologist) has discovered a series of ancient cooper needles with no hooks or apertures in King Khasekhemwy’s tomb (ca. 2690 BC) in the Royal Necropolis at Abydos, Upper Egypt, in 1900. These needles represent the earliest known ancient surgical instruments for dislodging the cataract away from the pupil[5]. These needles could be found in the National Museums in Liverpool, England[6].

Hippocrates (Greek physician d. 370 BC) recommended using wool rounded around a wooden rod soaked in a caustic solution for scraping the eyelids when treating trachoma. Celsus (Roman encyclopaedist d. 50 AD) included in the medical work of his encyclopedia the recommendation of using a hook, a threaded needle, and a scalpel in the treatment of pterygium. Galen (Greek physician d. 210 AD) utilized a cuttlefish bone for roughness in treating trachoma and as an agent to dissolve pterygium. Aëtius of Amida (Byzantine Greek physician, mid-5<sup>th</sup> century to mid-6<sup>th</sup> century) applied a blunt hook, a tiny hook, a horse-hair and linen thread through a needle, and a knife in the treatment of pterygium[7]. Numerous gaps exist in the biomedical engineering history, one of which the present article aims to fill in through providing an overview of Al-Halabi’s contributions.

## AL-HALABI’S BIOGRAPHY

Al-Halabi (middle of the 13<sup>th</sup> century)[8,9] - whose full name was Khalifah ibn Abi Al-Mahasin Al-Halabi[10] and who was known as Khalifa Ben Abi Al-Mahassin[11], Khalifa ibn Abi Al-Mahasin Al-Halabi[12], Halifa B Abi L-Mahasin[13], and Halifa[14] for short - was named after Aleppo (Arabic: Halab), a city in the northern part of Syria, known for its thriving trades and wealth in the middle ages before the Mongol onslaught (in 1260 AD)[11]. It was mostly where he was born and died[15,16]. He mentioned two incidents that happened to him in Aleppo in 1252 and 1254 AD (650 and 652 AH)[11,15]. Aleppo was, as it has been for centuries, an important city and the capital of a principality[17]. It appears that Al-Halabi must have had a wide spectrum of knowledge about medical sciences as can be derived from the list of references that he cited. He was considered the first ophthalmologist to use a magnet in order to remove metallic foreign body from the eye by Wafai and Kalaji as well as Hirschberg, as he extracted a couching needle that was broken in a patient’s eye during the surgery [14-16,18]. He realized that an instrument may be substituted by another because of unavailability[15].

## AL-HALABI'S BOOK

*The Sufficient Knowledge in Ophthalmology* (Arabic: Kitab Al-Kafi fi Al-Kuhl), expected to be written within the period from 1256 to 1275 AD, is the only known book by Al-Halabi[11,13,14]. It is one of the masterpieces of Islamic ophthalmological medicine and surgery. The book's scientific value is incomparable to European manuscripts till the beginning of the nineteenth century[14]. The book describes in a separate chapter the measurements, weights, and sizes used at that time by physicians. It quotes 73 authors and 41 books before its time[9,18]. He referenced famous Arabian or Muslim authors such as Al-Razi, Ibn Sina (Avicenna), Al-Tabari, Hunayn ibn Ishaq, Al-Ghafiqi, Ibn Zuhri (Avenzoar), and Al-Zahrawi; Greeks such as Galen, Hippocrates, and Oribasius; and Indians[15,16].

The two copies of the book are to be found in the Bibliothèque Nationale in Paris, France (under the number 1043d. Arabe), and the Süleymaniye Kütüphanesi in Istanbul, Turkey (under the number Yeni Jami 924). The Paris manuscript was written by the Christian copyist Abd Al-Aziz ibn Abi Saeed Al-Masihi Al-Mawsili Al-Mutatabbeeb in 1277 AD, meaning that it is very close to the time of the author. The Istanbul manuscript was written by the Muslim copyist Ahmad Al-Wali in 1560 AD, meaning that the manuscript was written around 300 years after the death of the author[15].

The book was disappointingly ignored until the French medical historian Lucien Leclerc (1816-1893) had described it briefly for the first time in 1876 in his book “*Histoire de la Médecine Arabe*”[19]. In 1905, the German ophthalmologist and historian Julius Hirschberg (1843-1925) with the orientalist J. Lippert (1839-1909) and E. Mittwoch (1876-1942) wrote a book entitled “*Arabian Ophthalmologists*” in which they studied the book with great detail[15,16,20].

The present article depends basically on the reproduction of Al-Halabi's book edited by M. Z. Wafai and M. R. Kalaji. They produced Al-Halabi's book within the combined series “*The Islamic Heritage in Ophthalmology*” in which they unearthed the Islamic glorious heritage and its valuable knowledge that served humanity for over thirteen centuries. They compared the two copies of the book (in Paris and Istanbul) and put in the text the most accurate words. They explained in the footnotes some words that could contain more than one meaning. They gave the modern names of the diseases that Al-Halabi described. The book was published by the Islamic Educational, Scientific and Cultural Organization, Rabat, Morocco in 1990[15].

## THE INSTRUMENTS TABLE

Al-Halabi's book is the first book to place thirty-six surgical instruments in a very elegant table[9,21]. This table is considered to be well organized as each surgical instrument was placed in a special frame with the name of the instrument on the top and the way to use it underneath it, as shown in Figure 1[16,22]. This was the first time that an author put a table for the surgical instruments, unlike his predecessors who used to put the drawing of the instrument within the text[15].

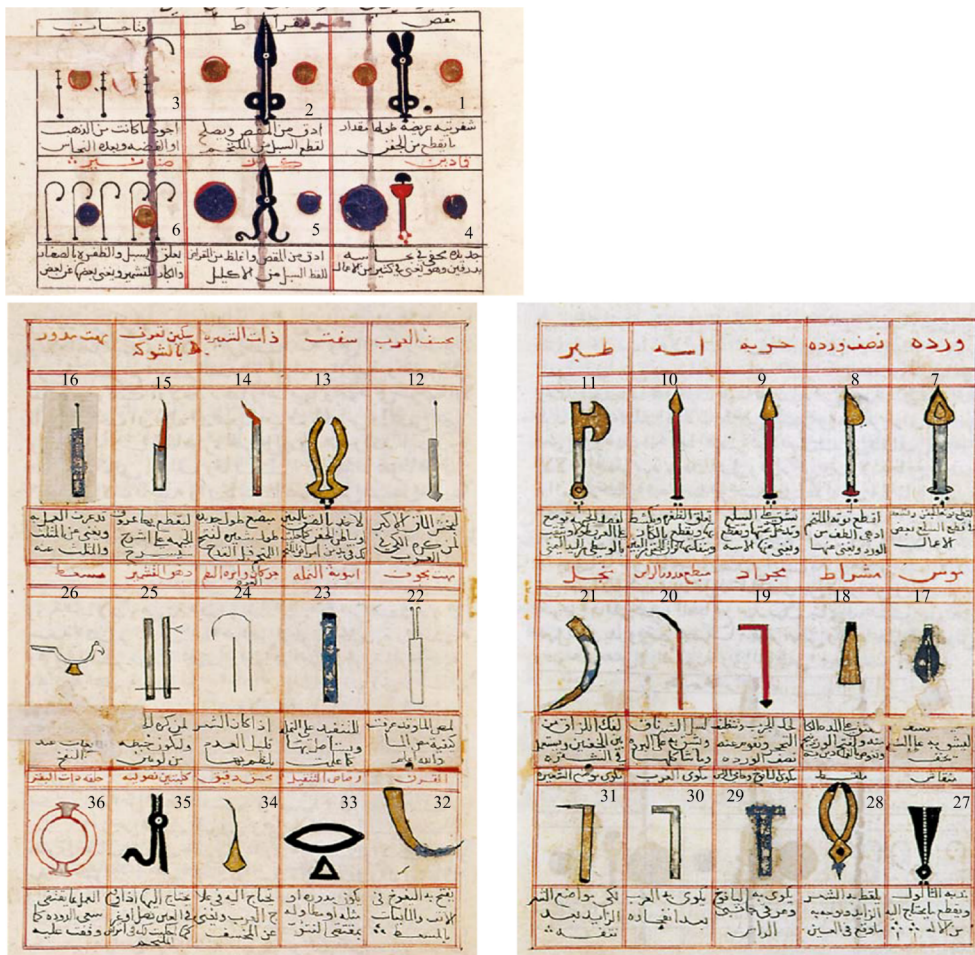
Some of these instruments were known and used by earlier Arabic ophthalmologists, and a few authors also included illustrations of the instruments, but none was as comprehensively or as systematically as Al-Halabi[18]. For example, Al-Razi (d. 925 AD) recommended the rose leaf needle (No. 7 in Figure 1) for scraping off the chronic trachoma. Moreover, Al-Razi used hooks (No. 6 in Figure 1) to lift thick pannus, which was then excised with scissors[23]. Al-Zahrawi (d. 1013 AD) used spear (No. 9 in Figure 1) to treat symblepharon[24]. Al-Ghafiqi (d. 1165 AD) used drill (No. 12 in Figure 1) and small drill (No. 34 in Figure 1) in dacryocystorhinostomy[25]. Ammar ibn Ali Al-Mawsili (d. 1010 AD) invented a hollowed aspirating needle (No. 22 in Figure 1) for cataract surgery[26]. Ibn Al-Nafis (d. 1288 AD)[27] used the scalpel (No. 4 in Figure 1) or the rose leaf needle for scraping the eyelid in trachoma surgery. Besides, Ibn Al-Nafis used speculums (No. 3 in Figure 1), scissors (No. 2 in Figure 1), and hooks in the treatment of pannus. Furthermore, Ibn Al-Nafis applied the rounded couching needle (No. 16 in Figure 1) to penetrate pterygium and strip it away from the conjunctiva and cornea[28].

It is worth mentioning that Al-Halabi used the instruments with other diseases other than what he mentioned in the instruments table. So, for all the instruments discussed in the current article, the statements of use on the table itself were given first and then supplemented with other uses given elsewhere in his treatise (with page numbers given for those), as could be seen in Table 1. These instruments were as

**Table 1 The descriptions of the uses of the instruments[15]**

<b>Instrument name</b>	<b>No. in Figure 1</b>	<b>Uses in his table</b>	<b>Other uses in his book with page numbers in reference[15] given</b>
Scissors	1	Distichiasis	
Scissors	2	Pannus	Concretions (p.121, p.276); Ectropion (p.278); Styne (p.279); Distichiasis (p.282); Hordeolum (p.287); Hemangioma at the eyelid (p.287); Wart (p.289); Lacrimal caruncle swelling (p.291); Pterygium (p.293); Hemangioma at the conjunctiva (p.297); Iris prolapse (p.299); Superficial temporal artery (p.300)
Speculums	3	Only description	Pannus (p.295)
Scissors	5	Pannus, pterygium (a note with the myrtle leaf needle)	Granuloma at the conjunctiva (p.297)
Hooks	6	Pannus, pterygium, distichiasis	Symblepharon (p.277); Ectropion (p.278); Distichiasis (p.281); Hemangioma at the eyelid (p.287); Sebaceous cyst (p.290); Lacrimal caruncle swelling (p.291); Hemangioma at the conjunctiva (p.297); Granuloma at the conjunctiva (p.297); Superficial temporal artery (p.300)
Rose leaf needle	7	Hemangioma at the eyelid, sebaceous cyst, hemangioma at the conjunctiva (a note with the half rose leaf needle)	Trachoma (p.275); Symblepharon (p.277); Lagophthalmos (p.123, p.278); Ectropion (p.278); Wart (p.289)
Half rose leaf needle	8	Hemangioma at the conjunctiva, (Trachoma, concretions) (a note with the scraper)	Adhesions between the two eyelids (p.277)
Spear	9	Sebaceous cyst	Symblepharon (p.277); Ectropion (p.278)
Myrtle leaf needle	10	Pterygium, symblepharon, sebaceous cyst (a note with the spear)	
Axe	11	Bloodletting the supraorbital vein	
Drill	12	Dacryocystitis	
Raven's beak	13	Removing whatever sticks to the eye or the inner side of the eyelid	Conjunctival wound (p.213)
Lancet	14	Cataract	
Rounded couching needle	16	Could be substituted by the triangular needle	Pannus (p.295); Hemangioma at the conjunctiva (p.297); Cataract (p.305)
Scalpel	18	Hypopyon, chemosis	Adhesions between the two eyelids (p.277); Allergic dermatitis (p.288)
Scraper	19	Trachoma, concretions	
Lancet	20	Lipoma, chalazion	Concretions (p.276); Chemosis (p.285); Blepharitis (p.289); Hypopyon (p.298); Superficial temporal artery (p.300); Cataract (p.307)
Sickle	21	Adhesions between the two eyelids, ectropion	
Hollowed aspirating needle	22	Cataract	
Gooseneck speculum and tailor's needle	24	Distichiasis	
Gatherer	27	Wart	'Foreign body' fallen into the eye (p.215), Styne (p.279), Hordeolum (p.287),
Gatherer	28	Distichiasis, 'foreign body' fallen into the eye	
Cautery	29	Supraorbital vein, superficial temporal veins	Superficial temporal artery (pp.300-301)
Cautery	30	Dacryocystitis	
Cautery	31	Distichiasis	
Small drill	34	Dacryocystitis	
Awn-tongs	35	'Foreign body' fallen into the eye	

functional as the seventy-six instruments invented by the Austrian ophthalmic surgeon Wilhelm Czermak (1856-1906) as considered by Hirschberg[14].



**Figure 1** Ophthalmological instruments from Al-Halabi's book, the Istanbul manuscript of the Süleymaniye Kütüphanesi, Yeni Cami 924. Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 6. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) (Supplementary Material).

## CONTRIBUTIONS IN EYELID DISEASES

Al-Halabi utilized a needle in the treatment of trachoma (called granular conjunctivitis or Egyptian ophthalmia, which is a contagious, chronic inflammation of the mucous membranes of the eyes, caused by *Chlamydia trachomatis*; it is characterized by swelling of the eyelids, sensitivity to light, and eventual scarring of the conjunctivae and corneas of the eyes). The patient was lied down and Al-Halabi stayed beside the diseased eye. A nurse stayed beside Al-Halabi for handing him the required surgical instrument. The shape of the tip of the needle resembled the rose leaf with a small, short, pointed end, as illustrated in Figure 2[22]. He started stripping the scabies by the needle from the medial canthus to the lateral canthus. He noted that the ophthalmologist should preserve mildness and tranquility to prevent eye damage. As an alternative to the needle, a scraper can be used. It looks like a right-angled bolt extractor, as seen in Figure 3[22]. It is utilized for scratching scabies[15].

Moreover, Al-Halabi used the rose leaf needle when treating lagophthalmos (a condition in which a complete closure of the eyelids over the eyeball is difficult or impossible). If lagophthalmos was a result of a healed ulcer or a strained suture of a wound leading to eyelid attraction, the rose leaf needle was used to incise the place of the healed ulcer or the strained suture. Then, a piece of cotton was inserted at the place of the incision[15].

He used a lancet in order to remove chalazion (a cyst that appears on the eyelid because of a blocked meibomian gland)[8]. If medications did not heal chalazion, an incision should be applied to it. If the chalazion was at the upper eyelid, it should be extended downwards. If the chalazion was at the lower eyelid, it should be extended upwards. At this point, a horizontal incision was applied to the chalazion through the





**Figure 2 Rose leaf needle (instrument number 7 in Figure 1) used in treatment of trachoma, lagophthalmos, symblepharon, hemangioma at the eyelid, and sebaceous cyst.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 45. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 3 Scraper (instrument number 19 in Figure 1) for scratching scabies and for digging out concretions.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 49. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).

use of a lancet with a rounded tip ([Figure 4](#)) in order to cleave the chalazion[22]. If the chalazion was inclined to the outer side of the eyelid, the incision should be applied on the outer side of the eyelid, and vice versa. Finally, the chalazion should be removed using a spoon[15,29].

The lancet as well could be used in the treatment of chemosis (abnormal edematous swelling of the mucous membrane covering the eyeball and lining the eyelids) and lipoma (benign fatty tumor occurring at the inner side of the upper eyelid between its layers). In case of lipoma, Al-Halabi warned the ophthalmologists that they should be cautious of the penetration of the eyelid leading to the puncture of the tarsal cartilage of the eyelid, and a perforated cornea and iris. Furthermore, the lancet could be used in the incision of blepharitis (inflammation of the eye glands and eyelash follicles along the margin of the eyelids).

The same lancet was applied for removing the concretions (small, separated tumors at the inner side of the eyelid). A horizontal deep incision was conducted through the use of the lancet for digging out the stone formations. Besides, the scraper could be used as a substitution for the lancet. Al-Halabi mentioned that the ophthalmologist should be careful while using either the lancet or the scraper to prevent the penetration of the eyelid. Scissors may be used after the eradication of the concretions to cut off the incision slits. This procedure slows the healing of the incision in order to prevent the reappearance of the concretions. The scissors (Arabic: Miqrada) have a flattened, sharp, and straight shape, with the pivot tempered, as shown in [Figure 5](#)[15, 22].

Al-Halabi used a tool that resembles to some extent an extremely small sickle (see [Figure 6](#)) in the treatment of the adhesions between the two eyelids[22]. If the two eyelids were closely adhered, a small incision should be performed using a fine scalpel (instrument number 18 in [Figure 1](#)) or a needle at the origins of the eyelashes to let the tip of the sickle be introduced between the two eyelids. The shape of the tip of the needle resembles half the rose leaf (instrument number 8 in [Figure 1](#)). He started opening the incision from the direction of the medial canthus towards the lateral canthus[15].





**Figure 4 Lancet with rounded tip (instrument number 20 in Figure 1) used in treatment of chalazion, chemosis, lipoma, blepharitis, concretions, hypopyon, headache, and cataract.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 49. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 5 Scissors (Miqrad) (instrument number 2 in Figure 1) used in treatment of concretions, ectropion, sty, hordeolum, lacrimal caruncle swelling, pannus, pterygium, hemangioma, iris prolapse, and headache.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 48. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).

If the adhesions were between the eyelid and the conjunctiva or the cornea (symblepharon), two hooks were utilized for holding up the eyelid. If the adhesions were at the upper eyelid, it should be extended upwards. If the adhesions were at the lower eyelid, it should be extended downwards. Al-Halabi used the rose leaf needle to separate the adhesions. He stated that the ophthalmologist should use delicacy when the adhesions were between the eyelid and the conjunctiva. A tremendous delicacy should be applied when the adhesions were between the eyelid and the cornea in order to prevent making punctures in the corneal layers. These punctures could cause iris prolapse (protrusion of the iris or part of the iris through an injury in the cornea).

When the adhesions are closer to the bones of the eyebrow, it is harder to separate them, and a longer tool should be used like the needle or the spear. The shape of the tip of the needle resembles the myrtle leaf with a small, long pointed end appropriate for cleaving the adhesions, as presented in [Figure 7](#)[22]. The spear has a big long pointed end, as shown in [Figure 8](#), and could replace the myrtle leaf needle[15,22].

Al-Halabi used hooks (instrument number 6 in [Figure 1](#)), the spear, and the scissors (Miqrad) in the treatment of ectropion (eversion or turning outward of the margin of the eyelid). If the ectropion was due to the growth of a superfluous fleshy tissue on the inner side of the eyelid, two or three hooks were inserted in the fleshy tissue for holding up the eyelid. Then, the tip of the spear was inserted under the fleshy tissue to



**Figure 6 Sickle (instrument number 21 in Figure 1) for splitting adhesions between the two eyelids.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 52. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 7 Myrtle leaf needle (instrument number 10 in Figure 1) used in treatment of symblepharon, and pterygium.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 47. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 8 Spear (instrument number 9 in Figure 1) used in treatment of symblepharon, ectropion, and sebaceous cyst.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 45. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).

warn it off the eyelid skin. Finally, the scissors were utilized for dissecting the fleshy tissue. Al-Halabi pointed out that the ophthalmologist should use tremendous delicacy in order to prevent the laceration of the eyelid skin and its dissection with the fleshy tissue[15].

He used the scissors (Miqrād) and a gatherer for treating sty (inflammation of the sebaceous gland of an eyelash) or wart (small, benign growth caused by a viral infection of the skin). The gatherer which has two broad heads (instrument number 27 in Figure 1) was utilized for holding sty or wart from its middle and extending it away from the eyelid. Then, the scissors were used for cutting it out of its roots. In the case of the wart, the scissors could be replaced by a horse-tail hair. In order to saw off the wart, the horse-tail hair was placed under the gatherer[16]. Actually, a recent study indicated that the horse-tail hair is about 0.2 mm thick, and it recommended using it in ophthalmic surgeries[30].

In addition, the scissors and gatherer were utilized for eradicating hordeolum (suppurative inflammation of a gland of the eyelid). Furthermore, the scissors were used for uprooting the hemangioma at the eyelid (benign tumor found on the eyelid, composed of dilated blood vessels, and often encapsulated within a fibrous shell) with the aid of a hook. The rose leaf needle could substitute the scissors.

The rose leaf needle was used in sebaceous cyst removal. The function of the needle was to make a horizontal incision at the liquefied tissue. Then, a hook and the rose leaf needle were utilized for removing the pus. The spear was applied for a deeper, T-shaped incision when the inflamed area was bigger and deeper. The myrtle leaf needle could substitute the spear. Al-Halabi elucidated that the liquefied tissue should be completely removed in order to avoid the reappearance of the sebaceous cyst[15].

## CONTRIBUTIONS IN DISTICHIASIS TREATMENT

Al-Halabi used annexation technique in the treatment of distichiasis (congenital, abnormal, accessory row of eyelashes, often causing severe discomfort from contact with the eye). If the eyelashes number was from one to five, a very thin tailor's needle could be used. A thread was twisted through the needle hole and around itself to make a buttonhole. Another thread was entered in the buttonhole to make it ready for annexation. The needle was applied at the margin of the eyelid from its inner side to the center of the distichiasis. The abnormal eyelashes were entered in the buttonhole with the aid of a tip of a gooseneck speculum (instrument number 24 in Figure 1). Then, the needle was pulled slowly and carefully to tighten the buttonhole on the eyelashes. Finally, the needle was extended quickly away of the eyelid, and the eyelashes were epilated at the middle of the buttonhole[15].

Another technique for treating distichiasis was the use of glue. If the abnormal eyelashes were long enough and their number was from one to five, they were pasted to the nearest normal eyelashes. The components of the glue are listed in Table 2[31, 32]. First, the glue was placed on a plate made of bronze. Second, the glue was melted on a soft flame. He noted that the flame should be near the ophthalmologist and ready to be used in order to prevent the glue from cooling down while being used. Third, an eye stick or a tip of a hook was utilized for applying the glue on the misdirected eyelashes. Finally, these eyelashes were extended to allow them to paste to the normal eyelashes for preventing the irritation of the eyeball. If the glue reached undesired normal eyelashes, it was removed by rubbing[15].

Moreover, distichiasis could be treated by cauterization. If the aberrant eyelashes number was from one to five despite being long or short, they should be plucked out first through the use of the gatherer. It could also be used in pulling out any "foreign body" that has fallen into the eye, as shown in Figure 9[22]. Then, a cautery was applied to the position of the pulled-out eyelashes. The cautery was pointed to be appropriate for the narrow places, as seen in Figure 10[22]. Al-Halabi preferred gold as a material of the cautery as the disease was cleared quickly and blisters did not appear at the cauterized position. When the eyelash was plucked out, the cautery was heated till its color turned red. Then, it was directed to the position of the pulled-out eyelashes. It should be slightly deeper to destroy the lash follicle[15].

In case of abnormal eyelashes number being more than five, their place on the eyelid should be cut using scissors. First, the eyelid was rolled up and incised at the location of the abnormal eyelashes from the medial canthus to the lateral canthus. A tailor's needle and a thread were used to sew the incision. Then, Al-Halabi placed the amount of the eyelid's skin between the two blades of the scissors. The scissors (Arabic: Miqass) (see Figure 11) should have two broad blades with their length equal to or more than the amount of the eyelid's skin that should be removed[22]. He distinguished the Miqass scissors from the Miqrad scissors that the first type has thicker and longer blades than the second being appropriate for removing the amount of the eyelid's skin in one cut[15].

## CONTRIBUTIONS IN MEDIAL CANTHUS DISEASES

Al-Halabi used a hook and scissors (Miqrad) in treating lacrimal caruncle swelling. The hook was utilized for hanging up the swelling. Then, the swelling was excised by the scissors. Finally, he warned the ophthalmologists that they should be cautious of the excision of a normal part of the lacrimal caruncle causing epiphora[15].

In case of dacryocystitis (congenital displacement of lacrimal tissue results in subconjunctival cysts), he placed a cautery that looks like a right-angled screwdriver, as shown in Figure 12[22]. Its shape is appropriate for the target with a smooth rounded tip contact. This cautery was used to cauterize the lacrimal gland fistula after its rupture until the vessels stop bleeding. He preferred gold as a material of the cautery. The cautery was heated till its color turns red. Then, it was directed to the

**Table 2 Medicinal natural products used in distichiasis treatment[15,31,32]**

Common name	Scientific name	Arabic name	Effects
Mastic	<i>Pistacia lentiscus</i>	Mustaqy	Antiseptic, anti-inflammatory, analgesic, sedative
Sarcocolla	<i>Astragalus Sarcocolla L</i>	Aanzarout	Anthelmintic, emollient
Aloe	<i>Aloe vera</i>	Sabr	Wound healing, antimicrobial



**Figure 9 Gatherer (instrument number 28 in Figure 1) used in treatment of distichiasis.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 53. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 10 Pointed cautery (instrument number 31 in Figure 1) for cauterizing the places of superfluous eyelashes after they have been pulled out.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 51. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).

position of the fistula till boiling. The cauterized position was wiped with a rag. Next, cauterization was repeated several times till the crust on the lacrimal bone was peeled. Finally, the cauterized position was cleaned from rot[15].

A drill was utilized in case the patient refused the cauterization solution. It consists of a handle and a long shaft with a small sharp pointed end, as seen in [Figure 13](#)[22]. It was used to clean the entire corner of the eye. In addition, a perforation was made at the tear-producing gland fistula in the nasal direction. A high strength should be applied until the blood flows from the nose and the mouth. Al-Halabi discussed that the perforation should not be directed upward as this would be the incorrect direction. Moreover, he noted that the ophthalmologist's working hand should be inclined to the nose (not to the eye) in order to avoid damage to the eye layers. Through this, a smaller drill (instrument number 34 in [Figure 1](#)) was wrapped in cotton which should be dry or soaked in ox fat or in verdigris ointment (corrosive, anti-inflammatory effects). He pointed that the verdigris became less effective if used after a year of its manufacture date. This would then be exchanged every day until the cotton was extracted clean in order to reach the bone pureness. With some details, the opening of



**Figure 11 Scissors (Miqass) (instrument number 1 in Figure 1) used in treatment of distichiasis.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 46. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 12 Cautery (instrument number 30 in Figure 1) used in treatment of dacryocystitis.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 43. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 13 Drill (instrument number 12 in Figure 1) for cleaning the entire corner of the eye.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 43. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).

the wound should be widened through the use of the smaller drill, and the cotton should be exchanged as it is expected that the cotton would be extracted from the wound with small dirty fractures of the bone[15].



## CONTRIBUTIONS IN PANNUS TREATMENT

Al-Halabi used eye speculums, hooks, scissors (Miqrada), couching needle with a rounded tip, dove's feather, and eye stick in the treatment of pannus (membrane of fine blood vessels and fibrous tissue that spreads down over the peripheral cornea in trachoma and other inflammatory corneal disorders causing loss of vision)[34]. The patient was lied down, and he stayed behind the patient. A sessile pillow was put under the patient's head to make it slightly declined[15].

A tool, which looks somewhat like the eye speculum nowadays (instrument number 3 in Figure 1), was used to keep the patient's diseased eye open. Al-Halabi expressed his preference of using two thumbs of a skilled nurse instead of two eye speculums. The disadvantage of using the eye speculums from Al-Halabi's viewpoint was the obstruction of the eye speculums to the movement of the scissors (Miqrada) while cutting off the pannus. Three hooks were applied to hang up the pannus, one from the medial canthus, one from the center of the conjunctiva, and one from the lateral canthus. The hooks were applied near the upper eyelid[15].

A tip of the scissors (Miqrada) was utilized for cutting off a part of the membrane from the lateral canthus. Then, the couching needle was introduced to saw off the pannus. Al-Halabi recommended that the couching needle should be made of red bronze (instrument number 16 in Figure 1). A dove's feather might substitute the couching needle. The Miqrada scissors were used again to pick out the membrane until reaching the medial canthus. At this part, the three hooks were applied near the lower eyelid, and the same procedure was repeated till the pannus was completely removed. He noted that the ophthalmologist should watch out the cornea while performing this procedure[15].

A tiny eye stick was wrapped in cotton which should be soaked in egg yolk and rose oil (calms painful sores and constricts and cools wounds). He recommended that the rose oil should not be used after two years of its manufacture date as it got expired. The eye stick should be applied at the middle of the eye and extended in the directions of the two eyelids in order to prevent any adhesions that might occur[15].

Al-Halabi described another way to get rid of the pannus. One hook was applied to hang up the pannus. The scissors (Arabic: Kaz) were used to make a cut in the membrane. The Kaz scissors were thinner than the Miqrada scissors and thicker than the Miqrada scissors, as shown in Figure 14[23]. Consequently, the hook was raised up while connected to the membrane, another hook was inserted, and the Kaz scissors were applied again. This procedure was repeated many times until the membrane was gathered by the Kaz scissors as one piece[15].

A third technique was elucidated by Al-Halabi for removing the pannus. Several hooks were used to hang up the pannus. The number of hooks ranged from six to twelve depending on the size of the eye. The insertion of the hooks started from the medial canthus near the upper eyelid and ended near the lower eyelid in a circular shape. A tip of the Miqrada scissors was used for cutting off a part of the membrane from the lateral canthus near the upper eyelid, and then near the lower eyelid. Then, the couching needle was introduced to saw off the pannus. At this point, the Kaz scissors were applied to make a circular incision in the membrane. The pannus would be extracted in a shape that looks like a signet ring[15].

## CONTRIBUTIONS IN CONJUNCTIVA DISEASES

Al-Halabi used a hook, a smooth dove's feather, myrtle leaf needle, Miqrada scissors, and Kaz scissors in treating pterygium (a pink, fleshy tissue that grows on the conjunctiva)[33]. The hook was utilized for raising the pterygium from its center. If the pterygium loosely adhered to the conjunctiva, a smooth dove's feather was inserted under the hook to saw off the pterygium. If the pterygium hardly adhered to the conjunctiva, two or three hooks could be added to the sides of the pterygium. Then, the myrtle leaf needle was used for sawing off the tissue. Finally, the Miqrada scissors or the Kaz scissors were used for cutting off the pterygium[15].

Al-Zahrawi used a horse-tail hair to saw off the pterygium. The dove's feather and the horse-tail hair were utilized due to the inability of the technology of that era to manufacture a man-made instrument with the required thickness and sharpness[24]. Al-Halabi stated that the ophthalmologist should use extreme delicacy in order to avoid penetrating the cornea or the medial canthus. He asked the ophthalmologist to beware of the total removal of the pterygium to avoid its reappearance. Furthermore, he asked the ophthalmologist to take care of the adhesiveness of the pterygium with



**Figure 14 Scissors (Kaz) (instrument number 5 in Figure 1) used in treatment of pannus, pterygium, and granuloma at the conjunctiva.**

Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 48. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) (Supplementary Material).

the conjunctiva. If the pterygium extremely adhered to the conjunctiva, the surgical instruments should not be applied at all in order to avoid eye damage[15].

Al-Halabi used a hook, a couching needle, the half of the rose leaf needle, and the Miqrad scissors in treating hemangioma at the conjunctiva. The hook was applied to raise up the hemangioma. He stated that the ophthalmologist should use tremendous delicacy while raising up the hemangioma because it has a spongy consistency, and the hook might turn up during the treatment. The couching needle was inserted under the blood vessels, and he started sawing off the hemangioma. The half of the rose leaf needle could replace the couching needle in sawing off the hemangioma. Finally, the scissors were utilized for uprooting the hemangioma[15].

Al-Halabi used a hook and the scissors (Kaz) in the treatment of granuloma at the conjunctiva (growth appearing like a nodule, consisting essentially of granulation tissue, and occurring as a result of localized inflammation). The hook was utilized for holding up the granuloma. If the size of the granuloma was large, two or three hooks should be applied. The Kaz scissors were applied to eradicate the granuloma[15].

He used a Raven's beak in the treatment of conjunctival wound (presence of wound or laceration of the conjunctiva with swelling and edema of the wound edges). The Raven's beak is a slim gatherer with two heads, as displayed in Figure 15[22]. The Raven's beak was used to extract an extremely small piece of wood that penetrated the eyeball and was fallen between the sclera and the eye bones. In addition, the Raven's beak could be used for removing whatever sticks to the eye or the inner side of the eyelid. The awn-tongs (see Figure 16) were utilized when an awn (either a hair- or bristle-like appendage) or a similar object fell down into the eye[15,22].

## CONTRIBUTIONS IN CORNEA AND IRIS DISEASES

Al-Halabi used a scalpel and a lancet in treating hypopyon (inflammatory cells in the anterior chamber of the eye). The scalpel was applied between the cornea and the conjunctiva to make an incision. He noted that the ophthalmologist should be cautious of the penetration of the iris. The lancet was applied at the position of the incision for the expulsion of the inflammatory cells. He used a needle, a thread, and scissors (Miqrad) in the treatment of the iris prolapse. A needle with a thread was inserted beneath the protrusion from the medial canthus and extracted from the lateral canthus. The two ends of the thread were drawn out of the eye. Then, the scissors were used to cleave the protrusion[15].



**Figure 15 Raven's beak (instrument number 13 in Figure 1) for removing whatever sticks to the eye or the inner side of the eyelid.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 52. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) (Supplementary Material).



**Figure 16 Awn tongs (instrument number 35 in Figure 1) used when an awn or something of that kind falls into the eye.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 53. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) (Supplementary Material).

## CONTRIBUTIONS IN HEADACHE AND MIGRAINE TREATMENT

In case of pain in the temporal muscles, headache, and migraine due to eye diseases, Al-Halabi used scissors (Miqrada), a hook, a lancet, and a cautery in the bloodletting and cutting the superficial temporal arteries and the posterior auricular veins[13]. A cord was tightened around the patient's throat with great mildness. Then, the patient was asked to throttle himself/herself with leniency. This procedure was conducted to make the arteries and the veins of the head visible and to target them. In case of the superficial temporal artery, he suggested shaving the temple, and spotting the artery with ink – this made the artery visible. After targeting the artery, the patient was asked to stop throttling himself/herself, and the cord was released to reduce the amount of the seepage blood while working[15].

Then, he attracted the skin over the artery using two fingers of his left hand. At this point, an incision was performed in the skin through the use of scissors (Miqrada). Consequently, the artery was extracted from its position and eradicated through the

use of a hook's tip. In case the artery was slim, a lancet was inserted under it to cut it off. Equally, the artery might be cut off using the scissors (Miqrad) instead of the lancet. In case the artery was thick, Al-Halabi used a needle and a thread made of silk or linen so that the artery would be tied in two places. Then, the lancet was utilized for opening an aperture between the two ligatures so that the desired amount of blood would flow out. After bloodletting, the artery was ligated and the blood flow was controlled[15].

Al-Halabi provided the cauterization by a flathead cautery instead of the eradication of the artery through the use of the lancet or the scissors. The same procedures were conducted for the posterior auricular vein except that the cautery was smaller than that for the superficial temporal artery. His usage of smaller cautery for the posterior auricular vein is in line with modern knowledge, as the thickness of the outer walls and the layers of muscle and elastic fibers of the veins is less than that of the arteries. As a disinfection procedure, he recommended the use of medical packs made of cotton after cauterization[15].

In case the previous procedures were unfruitful in treating migraine and headache, the supraorbital vein and the superficial temporal veins should be cauterized. First, the head was shaved from the middle of the scalp towards the forehead. Al-Halabi described how to know the position of the supraorbital vein in the forehead. The patient was asked to put the nail of his/her thumb of the right hand on the apex of the nose. Then, his/her forefinger was extended on the nasal septum towards the forehead. The maximum point the forefinger could reach was the position of the supraorbital vein. Next, this position was massaged using rough linen pack until it became red. At this point, a cautery was applied on the position longitudinally and horizontally in order to make a cross-shaped cauterization. The cautery looks like a fleshy olive and was made of iron, as shown in Figure 17[22]. The same procedures were performed on the superficial temporal veins. A knife that resembles to some extent an extremely small axe (see Figure 18) might replace the cautery for the supraorbital vein[22]. The knife was utilized for bloodletting the supraorbital vein. It was placed lengthwise on the vein, and the severing was conducted with the middle finger of the right hand[15].

## THE ANATOMICAL STRUCTURE OF THE EYE

Al-Halabi's book was the first book to give a remarkable illustration of the anatomy of the brain, the eyes, and the visual pathway among them, as displayed in Figure 19[9, 22]. The illustration presented the eyes, the optic chiasm, the cerebral ventricles, the pericranium, the dura mater, the pia mater, the olfactory nerves, and the petrosal bone [34]. The illustration showed that the left eye is controlled by the right part of the brain, and vice versa. All the ocular coats (cornea, sclera, choroid, zonules, and the retina) and the three humidities (vitreous, crystalline lens, and aqueous) are clearly illustrated and labelled. In this drawing, the conjunctiva seemed to originate from the pericranium and the sclera from the dura mater[16].

He drew the optic nerves as hollow, parallel lines, stemming from the back of the sclera to meet the optic chiasm and continue their course posteriorly through the brain tissue until finally reaching the occipital lobe[35]. Two parallel lines extended from the back of the lens to the sclera and optic nerve, almost nearing the description of Cloquet's canal. Although Al-Halabi drew a small circle in the middle of the triangle behind the chiasm, he did not mention or give the pituitary gland a name.

The American neuroanatomist and neurologist Stephen Lucian Polyak (1889-1955) considered all the European diagrams of the eye until the end of the 16<sup>th</sup> century, including those by Leonardo da Vinci (1452-1519)[36], to be dependent on Arabic models[37]. Al-Halabi's drawing is more detailed and informative than Leonardo da Vinci's one (Codex Atlanticus: Biblioteca Ambrosiana, Milan, vol. 3, fol. 628). Al-Halabi's drawing remained a reference to all the books dealing with the anatomy of the eye until the German physician D. W. Soemmerring (1793-1871) drew a cross section of the eye in 1827. The American Academy of Ophthalmology used a modified version of Al-Halabi's drawing as the emblem for the 1987 annual meeting without giving credit to him[11,15,16].

J. Hirschberg stated that *"First of all one must appreciate that the Arab ophthalmologists since Hunain had made real efforts to exploit the anatomy, the physiology and the pathology of the brain for their patients. Therefore we do not wish to criticize them for having dragged the optic nerve crossing unnaturally to the front in this imaginary stylized representation of the brain in order to be able to illustrate it at all; we also do that in our diagrams"* and *"In any*



**Figure 17 Olivary-shaped cautery (instrument number 29 in Figure 1) used for headache, and migraine.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 50. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).



**Figure 18 Axe (instrument number 11 in Figure 1) for bloodletting the supraorbital vein.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 50. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) ([Supplementary Material](#)).

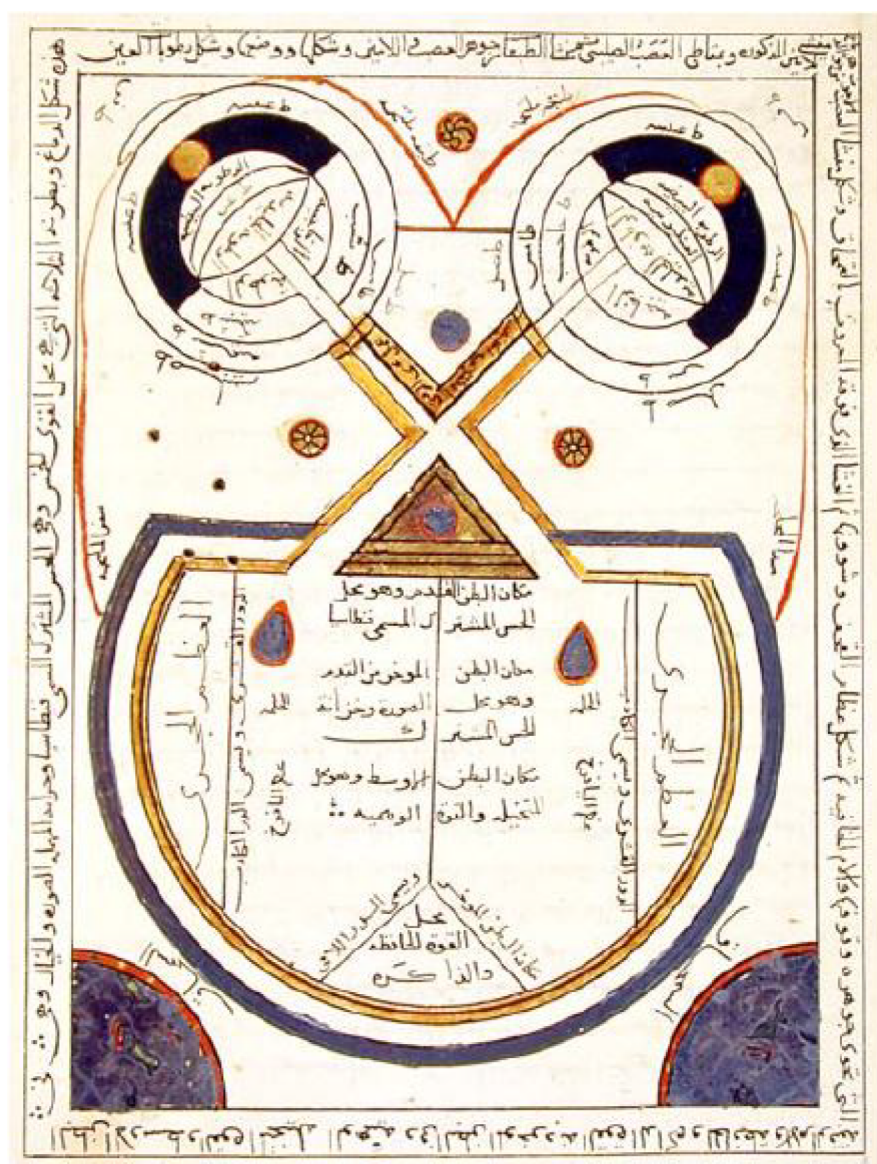
*case we see in this venerable picture, which probably goes back to models at least from the time around 1000 A.D., a cautious attempt to represent what D. W. Soemmerring insightfully arranged in his classic illustration in 1827” commenting on Al-Halabi’s illustration[22].*

## CONTRIBUTIONS IN CATARACT SURGERY

Al-Halabi detailed cataract operation representing twelve sorts of cataract in a table [14]. He dedicated a chapter of his book to the surgeries for removing the cataract. He described cataract operations, the required instruments, and the steps to be taken after the operation. He included his own experience which was described in good detail. He is so confident in his own talents that he had the courage to operate the cataract surgery on a one-eyed man for forty days[11,13]. Moreover, he surprisingly reported that he performed a successful cataract surgery for a predatory bird that was owned by his servant. However, the bird’s head movement after the surgery allowed the reappearance of the cataract[15].

He preferred the use of the hollowed cataract needle for aspiration[33], on the solid three-edged couching needle or the rounded couching needle for its safety in the operation. First, a lancet with a rounded tip (instrument number 14 in [Figure 1](#)) was utilized for puncturing the outer coats. Then, the hollowed needle (instrument number 22 in [Figure 1](#)) was applied to the iris without perforating the cornea. Extracting the lens by suction, using the hollowed needle that resembles to some extent the aspirating syringe nowadays as what could be understood from Al-Halabi’s description has the benefit of excluding the possibility of the lens falling back into the eye[8,15].





**Figure 19 Optic nerve crossing together with that of the eye and the brain from Al-Halabi's book, the Istanbul manuscript of the Süleymaniye Kütüphanesi, Yeni Cami 924.** Citation: Sezgin F, Neubauer E. Volume IV: Catalogue of the collection of instruments of the institute for the history of Arabic and Islamic sciences. In: Sezgin F. Science and technology in Islam. Frankfurt am Main, Germany: Institute for the History of Arabic-Islamic Science, 2010: 27. Copyright ©The Author(s) 2010. Published by Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften). The author has obtained the permission for figure using from the Institute for the History of Arabic-Islamic Science (Institut für Geschichte der Arabisch-Islamischen Wissenschaften) (Supplementary Material).

## CONCLUSION

Al-Halabi is an early biomedical engineer who invented various ophthalmological instruments. He is the first ophthalmologist to use a magnet for removing metallic foreign body from the eye. He utilized his instruments in the treatment of different eye diseases such as trachoma, lagophthalmos, chalazion, chemosis, symblepharon, ectropion, hordeolum, distichiasis, pannus, pterygium, and cataract. Al-Halabi's book was the first to give a remarkable illustration of the anatomy of the brain, the eyes, and the visual pathway among them. Al-Halabi detailed cataract operation representing twelve sorts of cataract in a table.

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## Severe acute respiratory syndrome coronavirus 2 pandemic related morbidity and mortality in patients with pediatric surgical diseases: A concerning challenge

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### Abstract

The global spread of the novel severe acute respiratory syndrome coronavirus 2 has had serious consequences in terms of patient morbidity and mortality and overburdened health care systems as well as the socioeconomic implications. In the absence of effective therapies and vaccinations during the viral outbreak, the major and most concise means to control viral spread is spread prevention. Although information concerning the impact of severe acute respiratory syndrome coronavirus 2 on pediatric surgical patients has greatly expanded, relevant comprehensive studies are scarce. However, pandemic related morbidity has increased, while under normal circumstances mortality could have been minimized.

**Key Words:** SARS-CoV-2; COVID-19; Pandemic, Pediatric surgery; Children; Morbidity; Mortality

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**Core Tip:** Severe acute respiratory syndrome coronavirus 2 pandemic related morbidity and mortality have been increased in children. Moreover, pandemic may manifest additional clinical problems. Pediatric surgeons must be aware of the different forms and symptoms in children affected by coronavirus disease 2019 infection.

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## INTRODUCTION

It has been approximately 1 year since the outbreak of novel pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in the city of Wuhan in China. The disease was subsequently named coronavirus disease 2019 (COVID-19)[1]. The global spread of this new virus forced the World Health Organization to declare it a pandemic on March 11, 2020[2]. It is estimated that up to June 23, 2021, about 180079074 people worldwide have already been infected, and the number of confirmed deaths had reached 3900967[3].

In an attempt to restrict the accelerated transmission of the disease, governments and health organizations across the world adopted various measures[4]. The pediatric surgical community responded accordingly, both globally and locally. The American College of Surgeons and the American Pediatric Surgical Association proposed certain criteria for the management and prioritization of pediatric surgical procedures, taking into account elective procedures that could be postponed and balancing the risk between disease progression and viral vulnerability[5,6]. Similarly, the European Association of Urology issued a statement of recommendations for pediatric urological cases during the SARS-CoV-2 era[7]. In the same spirit, the Spanish Association of Pediatric Surgery published and announced elective surgery restrictions, with the exception of emergencies and oncological cases[8]. Several organizations in the United Kingdom also provided evidence-based guidelines for elective pediatric surgical services[9]. In addition to these measures, many hospitals at the local level established extensive protocols for the security, protection, and proper management of sick children and their parents[10].

Apart from the resultant drop in elective surgeries amid SARS-CoV-2 cases[11,12], many pediatric surgical centers also noted a decline in emergency cases[11]. Moreover, the pandemic has seen the emergence of a new clinical entity, defined as multisystem inflammatory syndrome in children (MIS-C), which is considered by many to be a complication of SARS-CoV-2[13].

This study aims to identify the influence of the SARS-CoV-2 pandemic on morbidity and mortality among children with surgical diseases.

## METHODS

We selected all related articles regarding the morbidity and mortality of surgical pediatric patients during the SARS-CoV-2 pandemic by searching PubMed, Google Scholar, and Mendeley search network ([www.mendeley.com](http://www.mendeley.com)) from January 1, 2020 to June 23, 2021. The search terms "COVID-19 and pediatric surgery" or "SARS-CoV-2 and pediatric surgery" or "COVID-19 and pediatric surgery and morbidity" or "SARS-CoV-2 and pediatric surgery and morbidity" or "COVID-19 and pediatric surgery and mortality" or "SARS-CoV-2 and pediatric surgery and mortality" were used. Articles in full texts including reviews, original articles, case reports, case series, and letters to the Editor were screened without language restrictions. Abstracts, recommendations, strategies, and opinions were excluded.

## RESULTS

A data-based search retrieved 939 articles from the period January 1, 2020 to June 23, 2021. After subtracting duplicates, out of the 809 articles that emerged, we assessed 118 manuscripts in full text and finally reviewed 46 studies (Figure 1). The details of these studies are described below and summarized in Table 1.

The literature search revealed 24 articles[14-35] concerning the influence of SARS-CoV-2 in children with acute appendicitis (AA). More specifically, we found 14 retrospective studies[14-27], one letter to the editor[28], two case series[29,30], one brief communication[31], and four case reports[32-35]. In many series[17,20,24], the diagnosis of AA was delayed for various reasons, such as fear of contact with SARS-



**Table 1 Morbidity and mortality in pediatric surgical patients in the pandemic era**

Ref.	Journal	Patient number	SARS-CoV-2 test	Disease	Treatment	Outcome	Study details
Place R <i>et al</i> [14]	JAMA Network Open 2020; 3: e2027948	90	N/A	CAA: 35CAA + abscess: 8	OT: 35; Abscess drainage with IA: 8	Successful	<i>Retrospective study.</i> The authors noted increased number of CAA compared with the same period in 2019
Kvasnovsky CL <i>et al</i> [15]	J Pediatr Surg 2020(Epub head of print)	55	Positive: 3 (without symptoms)	NOT: 25 (2 with CAA); OT: 30 (CAA: 13, Simple AA:17)	NOT: 25 pts (3 CAA); OT: 30 (13 CAA); 1 patient SARS-CoV-2+: OT; 2 patients SARS-CoV-2+: NOT	Successful	<i>Retrospective study.</i> 45.5% of all patients: NOT protocol to minimize operative resources; The majority of children (78.2%) did not meet previous criteria for non-admissions comparable to pre- SARS-CoV-2 era
Gerall CD <i>et al</i> [16]	J Pediatr Surg 2020 (Epub head of print)	89 (41: pre SARS-CoV-2 era, 48: SARS-CoV-2)	Positive: 4 (excluded from the study)	UAA and CAA	NOT: Antibiotics 3 in the pre- SARS-CoV-2 era <i>vs</i> 7 during pandemic; OT: 33 in the pre- SARS-CoV-2 era <i>vs</i> 23 during pandemic	Successful	<i>Retrospective study.</i> It compares children's' symptoms and complications in pro- <i>vs</i> SARS-CoV-2 era. Patients in SARS-CoV-2 era: -Duration of symptoms: longer; -Increased number of imaging findings for perforation, increased LOS, increased time until resolution of symptoms.
Snapiri O <i>et al</i> [17]	Acta Pediatr 2020; 109: 1672-1676	7	N/A	CAA (perforated, abscess)	OT: 4; NOT: 4 (abscess drainage)	Successful	<i>Retrospective study.</i> Delayed diagnosis: Insufficient initial evaluation, telemedicine: 3, parental concerns)
Fisher JC <i>et al</i> [18]	Ann Surg 2020 (Epub head of print)	57 patients SARS-CoV-2 era <i>vs</i> control: 1292	Positive: 11/28	CAA in the SARS-CoV-2 era: 45% <i>vs</i> 27% in the control group	OT: UAA: 30; CAA: 20; NOT: 7	Successful	<i>Retrospective study.</i> Comparison of clinical characteristics of children <i>vs</i> pre- SARS-CoV-2 era. Main findings: Higher duration of symptoms and perforation rates in the SARS-CoV-2 era. No differences between perforation rates and LOS among positive or negative SARS-CoV-2 children.
La Pergola F <i>et al</i> [19]	Front Pediatr 2020; 8: 600320	86 <i>vs</i> 309 in the pre-SARS-CoV-2 era	Positive: 3	UAA: 59; CAA: 27	N/A	Successful	<i>Retrospective study.</i> COVID-19 era <i>vs</i> previously (2017-2019); - No differences: in the prevalence of the AA, duration of symptoms and CAA
Raffaele A <i>et al</i> [20]	Br J Surg 2020; 107: e529-e530	14	Positive: None	UCC: 7; CAA: 71	OT: 13/14; NOT: 1 (abscess drainage)	Successful	<i>Retrospective study.</i> -Delayed presentation in the ED <i>vs</i> previous years, delayed admission to OT due to COVID-19 test preoperatively
Montalva L <i>et al</i> [21]	Pediatr Surg Int 2020; 36: 1397-1406	108 (69 during lockdown)	Positive: 3	UAA: 24; CAA: 84	OT: UAA and CAA with peritonitis:94; CAA with abscess: 14 (drainage or medical treated)	Successful	<i>Retrospective cohort study.</i> The authors found increased cases of AA during the period of lockdown compared to pre-lockdown era. LOS, complication rates, re-admissions and peritoneal abscesses similar
Bellini T <i>et al</i> [22]	Acta Pediatr 2021 (Epub head of print)	27 in the SARS-CoV-2-era <i>vs</i> 75 control group	Positive: None	UAA: 14; CAA: 13 <i>vs</i> UAA: 50; CAA: 25	N/A	Successful	<i>Retrospective study.</i> CAA cases significantly more when compared with previous 3 yr due to delayed admissions ( $P = 0.004$ )
Zampieri N <i>et al</i> [23]	Minerva Pediatr 2020;	N/A	N/A	N/A	N/A	N/A	<i>Retrospective study.</i> The authors found decreased number cases of AA during lockdown <i>vs</i> post-lockdown period ( $P < 0.05$ ) possibly due to the less exposure to co-factors
Velayos M <i>et al</i> [24]	Ann Pediatr (Barc) 2020; 93:	Pre- SARS-CoV-2-era: 41; Post- SARS-CoV-2:	Positive: 1	CAA: -pre- SARS-CoV-2: 3; - post- SARS-CoV-2: 8	OT: All patients	Successful	<i>Retrospective study.</i> Increased number of CAA in SARS-CoV-2 era compared to pre- SARS-CoV-2 era due to delayed

	118-122	25					diagnosis ( $P = 0.019$ ), LOS increased in the CAA SARS-CoV-2 group
Malhotra A <i>et al</i> [25]	Pediatr Inf Dis J 2021; 40: e49-e55	10	Positive: 10	CAA+MIS-C: 5; UAA: 5	OT: 8; NOT: 2	Successful	Retrospective study. CAA associated with MIS-C
Cai <i>et al</i> [26]	Front Pediatr 2020;8: 1-9	5	Positive: 5	1 patient: CAA + MIS-C	OT	Successful	Retrospective study. CAA associated with MIS-C
Schäfer FM <i>et al</i> [27]	Front Pediatr 2021; 9: 683607	514	N/A	CAA			
Zvizdic Z <i>et al</i> [28]	J Pediatr Surg 2021; 56: 196-200	6	Positive: None	AA	OT	Successful	Letter to the Editor. Decreased admissions of AA compared to pre- SARS-CoV-2 era. Hypothesis: Correlation with decreased exposure to microbes due to lockdown
Lishman J <i>et al</i> [29]	J Pediatr Infect Dis 2020; 39: e472-e473	4	Positive: 4	UAA: 4; CAA: 2; MIS-C: 3	OT: 3	Successful	Case series. AA with MIS-C
Meyer JS <i>et al</i> [30]	J Pediatr Surg Case Rep 2021; 64: 101734	4	Positive: All	UAA: 2; CAA: 2	OT: 4	Successful	Case series. Possible association of SARS-CoV-2 with AA
Lee-Archer P <i>et al</i> [31]	J Pediatr Child Health 2020; 56: 1313-1314	48	N/A	UAA: 25; CAA: 23	OT	Successful	Brief communication. Increased number of CAA compared to previous years (2014-2019), parental concerns
Wang H <i>et al</i> [32]	Chin J Pediatr Surg 2020; 41: 299-302	1	Positive	UAA +; pneumonia	OT		Case report. UUA associated with pneumonia of the right lung
Harwood R [33]	J Surg Case Rep 2020; 9: 1-3	2	Positive: 1	CAA + MIS-C	OT	Successful	Case report. CAA associated with MIS-C
Shahbaznejad L [34]	BMC Pediatrics 2020; 513	10	Positive: 10	1 patient: UAA with MIS-C	OT	Successful	Case report. UAA associated with MIS-C
Alsuwallem AB <i>et al</i> [35]	Cureus 2020; 12: e8677	1	Positive	CAA	OT	Successful	Case report. CAA associated with COVID-19 Infection
Mehl SC <i>et al</i> [36]	Pediatr Infect Dis J 2021	1	Positive	NEC	NOT	Successful	Case report. Full term neonate with NEC secondary to SARS-CoV-2 infection
Rohani P <i>et al</i> [37]	J Pediatr Surg Case Rep 2021; 61: 101667	1	Positive	NEC	NOT	Successful	Case report. Gastrointestinal SARS-CoV-2 manifestation
Moazzam Z <i>et al</i> [38]	J Pediatr Surg Case Reports 2020; 59:101533	1	Positive	Intussusception	Pneumatic reduction	Successful	Case report. Gastrointestinal manifestation of SARS-CoV-2
Rajalakshmi L <i>et</i>	Indian J Pract	1	Positive	Intussusception	Pneumatic reduction	Successful	Case report. Gastrointestinal manifestation of SARS-CoV-2

al[39]	Pediatr 2020; 22:236							
Martinez-Castañoi[40]	Pediatr Emerg Care 2020;36: e368	1	Positive	Intussusception	Hydrostatic reduction	Successful	Case report.	Gastrointestinal manifestation of COVID-19
Makrinioti H <i>et al</i> [41]	J Pediatric Infect Dis Soc 2020; 9: 504-506	2	Positive: 2	Intussusception; Intussusception + malrotation	Pneumatic reduction; Surgical reduction + ladd procedure	Death; Successful	Case reports.	Fatal gastrointestinal manifestation of SARS-CoV-2; Gastrointestinal manifestation of SARS-CoV-2
Bazuaye-Ekhuyasi EA <i>et al</i> [42]	Emerg Radiol 2020; 27: 761-764	1	Positive	Intussusception	Hydrostatic reduction	Successful	Case report.	Gastrointestinal manifestation of SARS-CoV-2
Guerrón N <i>et al</i> [43]	Global Pediatr Health 2021; 8: 1-3	1	Positive	Intussusception	Hydrostatic reduction	Successful	Case report.	Gastrointestinal manifestation of COVID-19
Osorno JF <i>et al</i> [44]	Global Pediatr Health 2021; 8: 1-3	1	Positive	Intussusception (delayed presentation)	Laparotomy	Successful	Case report.	Gastrointestinal manifestation of COVID-19
Kawalec AM[45]	Burns 2020; 46: 1713-1714	Increased admissions in ED compared to previous year	N/A	Increased TBSA burns, house fire burns and PICU admissions <i>vs</i> previous year	Outpatient care, hospitalization, PICU	N/A	Retrospective study.	Need for a family plan during pandemic
Demircan M[46]	Burns 2020 (Epub ahead of print)	Increased admissions and hospitalizations compared to previous year	N/A	Increased TBSA burns, increased all kinds of burns	Outpatient care, hospitalization	N/A	Retrospective study.	Burn care material must be ready
Sethuraman U [47]	Burns 2020 (Epub head of print)	Increased admissions in ED <i>vs</i> all visits	N/A	Increased TBSA	Outpatient care, hospitalization, PICU	1 death	Retrospective study.	Parents should keep children away from hot liquids and surfaces
Pelizzo G <i>et al</i> [48]	Healthcare 2021; 9: 551	84 (pandemic era: 52; previous pre-pandemic period: 32)	Positive: 1	TBSA < 10%: 32; 10%-15%: 11; > 15% >: 9	34/52: Discharge; 18/52: Burn Service Area; (10/18: Ward; 8/18: PICU)	Successful	Retrospective study.	A higher number of admissions during pandemic was noticed compared to the same period in the previous year. An appropriate planned service and care ensure a safe and feasible hospitalization without risks of infections and major complications
Marino-Mateo L <i>et al</i> [49]	Actas UrolEsp 2020; 44: 659-654	45	Positive: 0	Pelviureteric junction obstruction, spina bifida, lithiasis, hypospadias	49 interventions	Successful	Retrospective study.	A stratification of the urological based on the different phases of pandemic and EAU was conducted
Cesaro S <i>et al</i> [50]	Pediatr Blood Cancer 2020; 67: e8466	247	Positives: 10	Solid tumors, leukemia	Ceased chemotherapy and radiation for 12-26 d	Successful	Retrospective study.	Mild or asymptomatic patients with positive tests may continue therapy
Hrusak O <i>et al</i> [51]	Eur J Cancer 2020;132: 11-16	200	Positives: 9	Hepatoblastoma: 2; Wilms tumor: 1; Ewing's sarcoma: 1; osteosarcoma: 1; cervical rhabdoid: 1; ALL: 1	Antibiotics and/or hydroxychoquine, lopinavir, ritonavir	Successful	Retrospective study.	Children on anticancer therapy may have mild or asymptomatic course of infection with SARS-CoV-2. In this case anticancer treatment should not be delayed or postponed

Madhusiidhan PP <i>et al</i> [52]	Pediatr Blood Cancer 2020; e28843	578	Positive: 98; No symptoms: 73	Neuroblastoma: 5; Solid tumor: 16; Others: 77	Mechanical; ventilation: 7; Supplemental oxygen: 25; SARS-CoV- 2 direct treatment: 98	Successful: 94; Death: 4	<i>Multi-institutional cohort study.</i> Low morbidity and mortality among oncologic patients but higher than in general pediatrics. Significant impact of pandemic: Delay in therapy in 67% of positive patients; Overall delays: Chemotherapy 54%, surgery 46%, transplant 30%
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CAA: Complicated acute appendicitis; OT: Operative treatment; IA: Interval appendectomy; NOT: Non-operative treatment; AA: Acute appendicitis; UAA: Uncomplicated acute appendicitis; LOS: Length of hospital stay; MIS-C: Multisystem inflammatory syndrome in children; ED: Emergency department; NEC: Necrotizing enterocolitis; TBSA: Total body surface area; ALL: Acute lymphoblastic leukemia; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; PICU: Pediatric intensive care unit.

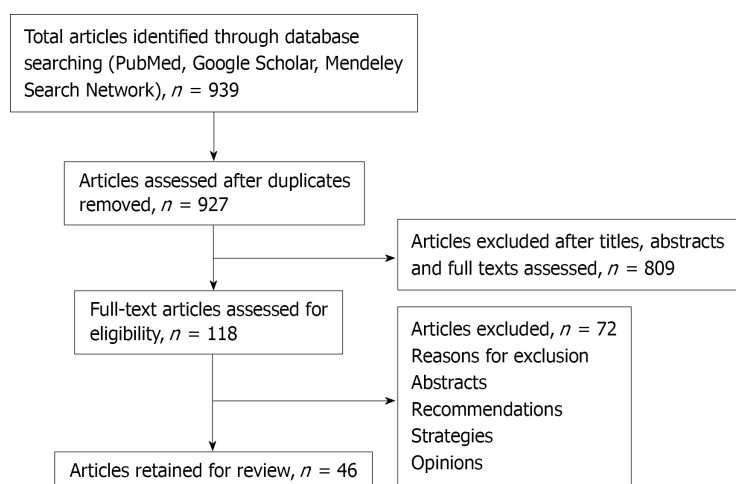
CoV-2 patients, telemedicine, fear of traveling, and disruption of the local health system; this led to an increase in the number of cases with complicated AA (CAA). While an association between AA and SARS-CoV-2 has been speculated[26], other studies have also reported 13 children with CAA diagnosed in the context of MIS-C [29,33,34]. It is worth noting that one case reported the coexistence of AA and pneumonia[32].

Two children aged 7 wk and 6 years respectively, both positive for SARS-CoV-2 infection, presented with clinical signs of acute abdomen. The clinical and diagnostic investigation showed necrotizing enterocolitis (NEC), which was successfully treated with antibiotics. The authors considered infection to be responsible for this emergency clinical manifestation[36,37].

Seven articles[38-44] referred to cases of ileocolic intussusception. Eight infants, aged 4-10 mo, presented with clinical symptoms related to intussusception (abdominal cramps, bilious vomiting, currant jelly stools) and were confirmed by ultrasound. On admission, seven infants were found to be positive for SARS-CoV-2, and one was found to be positive on the third postoperative day; four[38,40-42] had relatives with suspected or confirmed SARS-CoV-2 infection. Reduction (pneumatic or hydrostatic) was attempted in seven patients, six of whom had a successful outcome. Only two cases were treated surgically. Notably, in one case, at laparotomy, malrotation was found in addition to intussusception, and a Ladd's procedure was performed[41]. In the other case, intestinal resection with consequent ileostomy and mucous fistula was performed due to intestinal ischemia and peritonitis[44]. Moreover, following successful pneumatic reduction of intussusception, one female infant with documented SARS-CoV-2 infection went on to develop acute respiratory infection and multiorgan complications during hospitalization, including abdominal ascites and intestinal failure, which subsequently led to her death[41].

A total of four articles was extracted for SARS-CoV-2 in children with burns[45-48]. All of them disclosed useful information. Specifically, they recorded an increase in admissions of children with moderate and severe fire-related burns in comparison to earlier years, while the greater difference in burned total body surface area was statistically significant[46-48].





**Figure 1** Flow chart of articles selection.

One article from Spain was included[49] that reported clinical and surgical data, complications, and readmissions of all children who underwent procedures for various urological conditions. The authors developed an escalation program based on the different phases of the pandemic and the European Association of Urology recommendations. They concluded that this strategy allowed them to manage successfully urological diseases.

Three studies[50-52] that screened pediatric oncology/hematology patients for SARS-CoV-2 infection were evaluated. In the first study, 334 nasopharyngeal swabs were taken from 247 patients, only 10 (4%) of whom tested positive for SARS-CoV-2 infection (eight patients were asymptomatic and two had a mild fever). In nine patients, chemotherapy was postponed until they had tested negative (time period ranges from 12-26 d), while only one patient on chemotherapy and radiation was positive after 30 d[50]. In a multicenter survey performed in 25 countries involving 200 suspected patients, only nine tested positive for SARS-CoV-2 infection[51]. Notably, none required admission to pediatric intensive care or mechanical ventilation. Finally, a retrospective, multicenter study among 13 institutions including 578 patients examined test-positive SARS-CoV-2 patients aged  $\leq 21$  years receiving active anticancer treatment[52]. Among those 578 patients, 98 (16.95%) were positive, 78 (79.6%) of whom were symptomatic, and four died (4%). Delay of anticancer therapy occurred in 67% of these patients. Overall, these studies raised the question concerning the benefits of discontinuing or delaying chemotherapy in mild or asymptomatic SARS-CoV-2 positive patients.

## DISCUSSION

This study provides descriptive data on pediatric surgical patients infected with the novel coronavirus SARS-CoV-2. The data show that the impact of SARS-CoV-2 seems to be multifactorial as it interferes directly with human health due to the vulnerability of the virus and indirectly with the resources to access care, thereby increasing morbidity and mortality[12].

SARS-CoV-2 infection can affect all ages of children with median age of infection of 6.7 years (1 d to 15 years)[53], with no gender predominance[54]. The angiotensin-converting enzyme 2 is the main host receptor of SARS-CoV-2 and is frequently expressed in ciliated epithelial cells in human lungs. The second most common site of angiotensin-converting enzyme 2 receptors is the gastrointestinal cells[53]. Notwithstanding, gastrointestinal symptoms attributed to SARS-CoV-2 infection are more prevalent in children, while respiratory involvement is more common in adults[55,56]. In line with this finding, Meyer *et al*[30] speculated a conceivable association of SARS-CoV-2 and AA based on the assumption of the predominant association of gastrointestinal infection and SARS-CoV-2. However, in the era of SARS-CoV-2, other factors such as the fear of contact with persons positive for SARS-CoV-2, difficulty in visiting health centers, and insufficient evaluation *via* telemedicine may constitute strong reasons for delayed diagnosis of CAA[17,20,24].

The predominant association of gastrointestinal infection and SARS-CoV-2 might also explain the cases of intussusception[38-44] and the two cases of NEC[36,37]. Intussusception is the most common cause of intestinal obstruction in infancy[57]. Although in most cases it is thought to be idiopathic, a preceding viral infection due to adenovirus and rotavirus has been reported in approximately 30% of cases[58]. Notably, all cases described here were positive for SARS-CoV-2 infection, while a previous history of upper respiratory tract infection was diagnosed in three cases[38-40]. In the two cases of NEC, the association of SARS-CoV-2 test positivity with coexistence of pneumatosis intestinalis and bloody stools suggests ischemic necrosis in both cases and hence NEC[36,37].

The increase in the number of children presenting with burns during the outbreak could be ascribed to the fact that the lockdown obliged children to stay home where they may have had less surveillance, since parents were constrained to work from home and were thus unable to keep a close watch on children. Educational programs are needed to increase parents' knowledge concerning safety behaviors during a prolonged stay at home[45-48].

The impact of SARS-CoV-2 outbreak on children with urological problems is not known. An escalation program based on different phases of the pandemic has been proposed by Merino-Mateo *et al*[49] for the management of urological problems. However, the lengthy postponement of certain crucial surgical procedures, such as cryptorchidism, or obstructive uropathies including ureteropelvic junction obstruction, ureterovesical junction obstruction, or neurogenic bladder may lead to loss of a testicle function or loss of renal function. Three articles referred to testicular torsion[59-61]. The conclusions were contradictory, as increased rate of orchidectomies was noticed in the two articles due to delayed presentation[59,60], while in the remaining one article the authors found early presentation in testicular torsion and no differences in rates of orchidectomies between SARS-CoV-2 period and preceding era[61].

Children with cancer face significant health problems in view of the rapid changes in the health system and restrictions in accessing medical support. Compromised immunity due to malignancy and the unknown behavior of SARS-CoV-2 lead to further insecurity. Although the studies mentioned above[54-56] did not show significant consequences from the virus itself, it was clear that postponement of therapies owing to the heavily burdened health system could result in insufficient medical support.

In May 2020, the Centers for Disease Control in the United States expressed concern for a new entity termed MIS-C associated with SARS-CoV-2[34,62]. MIS-C is defined by clinically severe illness requiring hospitalization that presents with fever, elevated inflammatory markers, and multisystem organ dysfunction in the setting of recent proven or probable SARS-CoV-2 infection and the absence of a plausible alternative explanation[34]. However, there are no data available as to whether the mechanism that can lead to severe respiratory failure resembles that of MIS-C. Current data raise the suspicion for a distinct entity related to severe SARS-CoV-2 infection[62]. MIS-C-related AA was suspected in three studies[25,33,34] in which the coexistence of CAA and positive was tested.

This study is not without its limitations inasmuch as it is based on all types of articles, most of which included retrospective studies, letters to the Editor, case reports, and case series, all of which were written during the pandemic within a short period of time in an effort to share experiences and divulge information that could help the scientific community. Furthermore, in order to achieve a better understanding, a substantial number of studies compared their results with those to pre- SARS-CoV-2 era, which can lead to a significant bias. Another limitation is that most data were collected within 204 mo. Consequently, there is a lack of acceptable follow-up that would have helped us gain precise knowledge as concerns post-operative outcomes and readmissions of patients treated during the pandemic.

## CONCLUSION

Pediatric surgical practice during the SARS-CoV-2 pandemic is challenging. Summarizing the information and results of studies, we conclude that SARS-CoV-2 infection could have a negative influence on virtually the entire pediatric surgical spectrum. Morbidity has increased for various reasons in children with burns, urological problems, and cancer including fear of contracting the virus in health centers, lockdown, telemedicine, postponement of medical consultation and elective surgeries, or unknown manifestations of SARS-CoV-2. Under normal circumstances,

mortality could have been minimized. The delay in presentation and consequent management of AA has resulted in an increased number of CAA. The impact of SARS-CoV-2 on the gastrointestinal system has further exacerbated the manifestation of common pediatric surgical conditions such as AA, intussusception, and NEC. Further studies and research are needed to overcome the demands of this period.

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## Liver transplant allocation policies and outcomes in United States: A comprehensive review

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### Abstract

Liver transplant allocation policies in the United States has evolved over 3 decades. The donor liver organs are matched, allocated and procured by the Organ Procurement and Transplantation Network which is administered by the United Network of Organ Sharing (UNOS), a not-for-profit organization governed by the United States human health services. We reviewed the evolution of liver transplant allocation policies. Prior to 2002, UNOS used Child-Turcotte-Pugh score to list and stratify patients for liver transplantation (LT). After 2002, UNOS changed its allocation policy based on model for end-stage liver disease (MELD) score. The serum sodium is the independent indicator of mortality risk in patients with chronic liver disease. The priority assignment of MELD-sodium score resulted in LT and prevented mortality on waitlist. MELD-Sodium score was implemented for liver allocation policy in 2016. Prior to the current and most recent policy, livers from adult donors were matched first to the status 1A/1B patients located within the boundaries of the UNOS regions and donor-service areas (DSA). We reviewed the disadvantages of the DSA-based allocation policies and the advantages of the newest acuity circle allocation model. We then reviewed the standard and non-standard indications for MELD exceptions and the decision-making process of the National Review Liver Review Board. Finally, we reviewed the liver transplant waitlist, donation and survival outcomes in the United States.

**Key Words:** Liver transplant; Allocation; Distribution; Waiting list; Policies; Acuity circles; Transplant exceptions; National Review Liver Review Board

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**Core Tip:** The liver transplant donor allocation and distribution policies have evolved over three decades. The liver donor distribution policy has recently changed from donor-service area-based policy to the acuity circle model. The new policy is believed to work more efficiently and equitably for waitlist candidates across the United States.

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## INTRODUCTION

In the United States, organ transplantation is regulated by the United Network Of Organ Sharing (UNOS). UNOS is a not-for-profit and scientific organization which manages the Organ Procurement and Transplantation Network (OPTN), the sole network which is responsible for procuring, matching and allocating donated human organs in the United States by maintaining the national organ transplant database (UNet)[1,2]. UNOS was first established by the United States Congress *via* the National Organ Transplant Act in 1984. OPTN began its operations in 1986. In 2000, "the Final Rule" was published by the United States Department of Health and Human Services establishing federal regulations on OPTN policies including listing requirements, organ procurement, identification of organ recipient, allocation of donated organs, designated transplant program requirements, reviews, evaluation and enforcement of transplant programs[3]. Similar to UNOS, National Health Service Blood and Transplant is responsible for the matching, procurement and allocation of organ transplantation in the United Kingdom[4]. In Europe, the Eurotransplant network is responsible for organ procurement and allocation[5].

The two primary goals of OPTN/UNOS are (1) The equitable distribution of donated organs; and (2) The appropriate care of minority candidates. It is crucial not to discriminate transplantation on age, gender, ethnicity and socioeconomic backgrounds. The National Organ Transplant Act published in 1984 indicates UNOS to establish medical criteria when organs are being allocated. The medical criteria were put in place to ensure justice and reinforce equity. The Final Rule which was later published in 1999 elaborated the national framework for matching, allocation and distribution of the donated organs. The OPTN must institute equitable allocation policies which are based on medical judgement in order to achieve the best outcomes of donated organs and to promote the access to transplantation. Policy 3.6 requires the OPTN to standardize medical criteria for determining suitable transplant candidates and set priority rankings based on objective and measurable medical criteria. The rankings must be sequenced from the most medically urgent to the least and the geographic area must be feasible for organ distribution in order of decreasing medical urgency[6].

## CHILD-PUGH SCORE

Prior to 2002, UNOS used Child-Turcotte-Pugh (CTP) score to list and stratify patients for liver transplantation (LT). CTP score was first developed in 1973 to risk stratify patients undergoing portosystemic shunt surgery. CTP score includes blood tests such as serum total bilirubin, serum albumin, international normalized ratio (INR) as well as the severity of symptoms such as ascites and hepatic encephalopathy[7]. One of the disadvantages of using symptoms in CTP scoring was the lack of standardization of perceived symptom severity. Different transplant physicians might interpret the severity of ascites and hepatic encephalopathy in different manners. Moreover, CTP score was not able to predict which patients were in greater need of an orthotopic LT (OLT).



## MODEL FOR END-STAGE LIVER DISEASE SCORE

In 2001, Kamath *et al*[8] from Mayo Clinic developed the model for end-stage liver disease (MELD), a mathematical model using all objective tests such as serum bilirubin, INR, serum creatinine, to predict poor survival among cirrhotic patients undergoing transjugular intrahepatic portosystemic shunts[8]. MELD score was also shown to accurately predict disease severity and survival outcome in patients with chronic liver disease[9]. Brown *et al*[10] demonstrated that the MELD score is superior to CTP score in estimating pre-OLT disease severity and optimize the timing of OLT [10]. The OPTN/UNOS committees developed the LT allocation policy based on MELD score. This allocation policy was approved by the OPTN/UNOS Board of Directors in November 2001 and went into effect in February 2002[11].

## MELD-SODIUM SCORE

Hyponatremia is the independent risk factor which negatively impacts the survival in patients with cirrhosis. The degree of hyponatremia correlates with the severity of chronic liver disease. In 2005, Biggins *et al*[12] from University of California San Francisco demonstrated that serum sodium level < 126 mEq/L at liver transplant listing or while listed for OLT is a strong independent predictor of mortality. The researchers concluded that addition of serum sodium to MELD score can increase the accuracy to predict 3- and 6-mo mortality in patients with cirrhosis[12]. In their 2008 study, Kim *et al*[13] studied OPTN data of 1781 participants who underwent OLT and 422 who died within 90 d after registration on the waiting list. The MELD and serum sodium combined score was significantly higher than the MELD score alone in patients who died on the waiting list. This data indicated that the priority assignment of MELD-sodium score might have resulted in OLT and prevented mortality[13].

The MELD-sodium score Policy 9.1 was approved by the OPTN/UNOS Board of Directors in June 2014 and implemented in January 2016[14].

## PEDIATRIC END-STAGE LIVER DISEASE SCORE

The pediatric end-stage liver disease (PELD) score calculates the pediatric version of the MELD score for liver cirrhosis severity. In addition to serum bilirubin and INR, patient's age, growth failure and serum albumin are included in the mathematical formula of PELD score, contrast to MELD score[15].

### ***Evolution of liver transplant organ allocation systems***

Liver transplant organ allocation systems have evolved tremendously over two decades to reduce disparity, increase equity and access to liver transplant based on new evidence-based data with the primary goal of increased "best use" of donated livers.

### ***Allocation priorities based on UNOS status***

Patients who are listed as status 1A on UNOS waiting list have acute onset liver failure and are deemed not likely to survive more than a few days without an OLT. Status 1B is reserved for extremely sick, chronically ill pediatric patients with cirrhosis who are younger than 18 years of age-pediatric population. Status 1A and 1B patients are usually less than 1% of overall waitlisted patients at any given time.

### ***Historical background of liver distribution–donor-service areas-based policy***

Prior to the current and most recent policy, livers from adult donors were matched first to the status 1A adult patients, then to status 1B pediatric patients located within the boundaries of the same region as the donor hospital but could be outside of donor-service area (DSA). There are 11 UNOS regions and 58 DSAs catered by various organ-procurement organizations (OPO) in the United States. "Share-35 rule", implemented in June 2013, mandated that the waitlisted patients with MELD-sodium score of 35 or above would be offered donated livers outside of the OPO and within the same region. While "Share-35" policy increased the number of OLT by 6% and the number of regional sharing by 11%, there was no impact on the overall waitlist mortality, the post-transplant survival and the overall liver discard rate. The UNOS/OPTN leadership considered a concept of restructuring 11 UNOS regions to 8 districts to

lower geographic disparity, waitlist mortality and the high variability of MELD-sodium at the time of transplant among various liver transplant centers across the regions. The statistical model for “Region Redistricting” was limited by the minimum number of transplant centers *per* district which was set to be 6 centers and maximum of 3 h allotted travel time between the DSAs in the same district.

### ***New liver distribution policy-acuity circles***

Due to the disadvantages of DSA-based liver distribution policy and geographic inequities in access to OLT, the OPTN Board of Directors mandated a thorough review process for system improvement since 2014. The new liver policy was proposed by transplant experts, reviewed, and debated by organ recipients, donor families with thousands of public comments on UNOS website. The priority of the new distribution policy is to ensure that the organ distribution is equal for waitlisted candidates where they live or wish to seek a transplant. DSA-based donation boundaries had led waitlisted patients to get more than one wait list (*i.e.*; dual listing practice) or travel to different regions in the country to get access to transplant. The new process is simple with a measure of distance from donor hospital to the transplant hospital in nautical miles, eliminating DSAs. The sole benefit of the December 2018 policy is that it is projected to save more lives by lowering waitlist mortality by 100 lives annually[16].

According to UNOS data, organ donation from deceased donors set an all-time high record in 2020 despite the global COVID-19 pandemic. 36548 organs from deceased donors were transplanted resulting in 33309 people receiving life-saving transplants [17]. The implementation of the December 2018 acuity circles (AC) policy is projected to reduce the impact of where waitlist candidates live, or what hospital they choose for their care. The new policy is believed to work more efficiently and equitably for waitlist candidates across the United States.

### ***AC-status 1A/1B***

Under the new policy, livers from all deceased donors are offered for status 1A and 1B candidates listed at transplant hospitals within a radius of 500 nautical miles from the donor hospital.

### ***AC-non-donating upon cardiorespiratory death donors younger than age 70***

For the deceased liver donors which are not donating upon cardiorespiratory death (DCD) and under age 70, waitlist candidates with MELD or PELD score of 37 or higher are prioritized after status 1A/1B candidates. The initial offers will go out to the candidates at transplant hospitals within a radius of 150 nautical miles from the donor hospital. The next sequence offers will go out to the candidates within a radius of 250 nautical miles from the donor hospital. Then, the offers will go out to the candidates within a radius of 500 nautical miles from the donor hospital. The MELD/PELD score ranges will progressively continue from 33 to 36, from 29 to 32 and from 15 to 28.

### ***AC-DCD donors and/or adult donors older than 70***

For the deceased liver donors who are donating DCD and/or adult donors older than 70 years of age, the new liver distribution policy prioritizes the candidates more local to the donor hospital with earlier access to transplant. The candidates with MELD or PELD of 15 or higher are offered these donated livers after status 1A/1B candidates. The sequence of distribution is for candidates within a radius < 150 nautical miles, then 150-500 nautical miles and lastly > 500 nautical miles from the donor hospital[17].

### ***Challenges of the new liver distribution policy***

The new liver distribution policy with AC allocation was approved in December 2018 after a lawsuit was filed in New York by patients who stated that their wait time was longer than other patients with lower MELD score in other parts of the country. The new AC policy went into effect on May 14, 2019. However, a United States federal judge in Atlanta, Georgia temporarily blocked the new policy on May 17, 2019, citing that waitlist candidates and hospitals in less-populated areas would suffer if the AC distribution model rules remained in effect. The liver allocation policy was reverted to DSA-based distribution on May 23, 2019. On February 4, 2020, the OPTN/UNOS re-instated the new AC model distribution policy. This model was supported by the Scientific Registry of Transplant Recipients’ (SRTR) 2018 analysis which projected that the AC model would decrease the variability of MELD score at the time of transplant (MMaT) across DSAs. The model predicted a substantial decrease from 9.97 to 4.33 based on historical statistics[17].

Chyou *et al*[18] compared the center- and DSA-level changes in the 6-mo period pre-AC model era (August 8, 2019 to February 3, 2020) and post-AC era (March 5, 2020 to August 31, 2020) using OPTN/UNOS data. The focus was on non-status 1A adult deceased donors on following metrics: Transplant volume, MMaT, procurements requiring flights and termed “flight-consistent distance” procurements. The volume of adult non-status 1A deceased liver donors decreased by 2.7% during this post-AC era. The DSA-level MMaT ranged from 18.5 to 32 in the pre-AC era while it ranged from 18 to 33 in the post-AC era. The median change in MMaT was +1 MELD point. The DSA-level variance in MMaT was unchanged: 12.2 pre-AC era *vs* 12.1 post-AC era. The number of “flight-consistent distance” procurements increased: 42.5 % pre-AC era *vs* 60.5% post-AC era. The post-AC era has coincided with the coronavirus disease 2019 (COVID-19) global pandemic and the transplant volumes could be affected by the COVID-19 restrictions and hospital constraints. However, these early data have raised the concern that the AC model projection based on mathematical simulations may not match the real-world transplant metrics. Longer-term data are needed to evaluate the benefits of the AC distribution model[18].

## NATIONAL LIVER REVIEW BOARD

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee has established regulation/guidance for both hepatocellular carcinoma (HCC) and non-HCC adult MELD exceptions and extensions requests. MELD exception policies allow opportunity to have a diseased donor liver transplant for the patient whose natural MELD score does not reflect the true liver related mortality risk. These MELD-exceptions could be standardized or non-standardized. All standardized MELD-exceptions requests do not need to be approved by the National Liver Review Board (NLRB) but all non-standardized MELD exceptions must be submitted to the NLRB.

In January 2017, the OPTN/UNOS liver and Intestinal Organ Transplantation Committee proposed NRRB and on May 14, 2019, NLRB replaced the Regional Review Boards (RRB) for each individual 11 OPTN regions for MELD exception scores approval. According to the briefing paper from OPTN/UNOS, the need for this change was warranted secondary to wide range (75.8% to 93.5%) of MELD exception requests being approved among different regions[19]. The NLRB is a nationwide peer review system that provides fair and increase consistency in providing MELD exception scores candidates of all liver transplant programs in United States and has eliminated the regional differences for granting MELD exception points. NLRB reviewers are assigned from a pool of nationwide liver transplant physicians and surgeons. NLRB has three boards, one for HCC exception requests, 2<sup>nd</sup> for non-HCC exception request and 3<sup>rd</sup> for pediatrics. NLRB is responsible for approval or denying exception points for patients who do not qualify for standardized MELD exception points. The liver transplant program may request MELD exception points to NLRB, if the calculated MELD score does not accurately reflect the severity of the candidate's disease. The candidate's respective transplant center must submit a request to NLRB with specific MELD score and justification why candidate's current status does not accurately reflect urgency for LT. The initially all cases are reviewed by five randomly assigned reviewers and four out five has to approve the request. According to the current OPTN policy[20]: (1) The NLRB is responsible to review MELD exceptions/extensions requests within 3 wk after the request has been submitted to the OPTN. If the NLRB is unable to complete the decision within 3 wk, candidate will be assigned the requested MELD score; (2) The candidate's transplant program as a right to appeal within 2 wk to the NLRB if the MELD exceptions/extension request has been denied. The appeal must be reviewed by the NLRB within 3 wk after submission to the OPTN, if the decision could not be reached within 3 wk, the candidate will be assigned the requested MELD score; (3) Upon denial of appeal by the NLRB, the candidate's transplant program has a right to further appeal to the appeals review team (ART) within 1 wk after denial notification. Each ART team has 9 members but 5 needs to be present at given time to review the case and must review the request within 2 wk after submission to OPTN. If ART unable to make the final decision within assigned 2 wk' period, candidate will be assigned requested MELD exceptions/extension points; and (4) Upon denial the MELD exception/extension request by ART, the candidate's respective liver transplant program has a right to appeal within 1 wk after denial notification to Liver and Intestinal Organ Transplantation Committee.

### **MELD-exception for HCC**

HCC is the 5<sup>th</sup> most common cancer and 3<sup>rd</sup> most common cancer related death in both sexes and in all ages[21]. Incidence of HCC in United States is rapidly rising secondary to chronic hepatitis C related cirrhosis. LT is an effective and curative treatment for non-resectable HCC since removal of both tumor and cirrhotic liver will maximize recurrence-free patient survival. MELD score predicts 3 mo' mortality for majority of the patient with cirrhosis but unfortunately underestimates mortality in the patients with HCC and hence high probability of weight list mortality and weight list dropout secondary to tumor progression while waiting for OLT[22].

Since HCC patients historically have low MELD score, without MELD exception points, realistically will not be able to get diseased donor LT. The liver transplant allocation system designates MELD exception points to patients with HCC if they meet MILAN criteria, which is defined as one lesion to 5 cm or up to 3 lesions each  $\leq$  3 cm without radiologic evidence of macrovascular invasion or metastatic disease[23]. The MELD exception points for patients with HCC, decreases wait-list mortality and increases priority for LT. By for the commonest indication of MELD exception point is HCC in united states.

The 1st HCC exception points policy was implemented on February 27, 2002. Since then, significantly high number of patients with HCC have been transplanted. Secondary to donor organ shortage and high number of patients being transplanted for HCC, needing multiple revisions of UNOS MELD-exception allocation policy for HCC over the last 2 decades (Table 1). In comparison to policy change in October 2015 which focused on timing of exception and incremental increase in tumor MELD exception points with maximum points of 34, the most recent organ allocation policy change in May 2019 does not allow incremental increase in MELD exception points. The current organ allocation policy mandates to list the patient with actual Na-MELD of the patient and after 3 mo, request a MELD extension. Once 6 mo' observation period is finished and the patient is still in with in MILAN criteria, the patient will be granted HCC-MELD exception points. The maximum points are median MELD at transplant (MMaT) 2. The MMaT remains fixed score and does not increase every 3 mo. By using previous 12 mo' data, the median MELD is recalculated every 6 mo and subsequently MMaT is readjusted. The purpose of this change was to promote more balanced allocation of donor organs between HCC and non-HCC patients on liver transplant wait list. 6 mo wait list observation period for HCC patients also will provide better understanding to assess the tumor biology.

The OPTN/UNOS Liver and Intestinal Organ Transplantation Committee has established regulation for adult MELD exceptions for HCC. The following is the summary of summary of current UNOS Policy for HCC exception points[20].

Documentation of number and sizes by multiphasic CT or MRI of all OPTN class 5 lesions (5A or 5B), ruling out metastatic disease, AFP and candidate being not eligible for resection (Tables 2 and 3).

Wait listed patient within MILAN criteria (T2 lesion) and AFP  $\leq$  1000 ng/mL will be eligible for standardized MELD exception points. If AFP > 1000 ng/mL with T2 lesion, candidates may be treated with local-regional therapy (LRT): (1) After treatment if AFP < 500 ng/mL, eligible for standardized MELD exception points; and (2) After treatment if AFP > 500 ng/mL, candidate would need to be referred to and NLRB for MELD exception points.

Standardized MELD exception points if the lesions meet the down staging protocols (Tables 2 and 3) and after LRT the lesion meets the definition of T2 lesion, demonstrated on CT or MRI. If candidates do not meet initially the downstaging protocol and subsequently down staged to T2 lesions must go through NLRB for MELD exception points.

After initial automatic approval of MELD exception points, extensions of HCC exception points would need to be requested every 3 mo. Automatic MELD exception points will be granted as long as lesions do not progress beyond T2 criteria, AFP < 500 ng/mL.

The candidates who meet the standardized MELD score exception, will be granted calculated MELD score on initial and first extension request. After 6 mo (second extension request), the candidate will be granted 3 points below MMaT.

### **Non-HCC standard MELD-exceptions**

In February 2002, non-HCC MELD exception points policy was implemented which allowed exception points for hepatopulmonary syndrome (HPS), familial amyloidosis and primary oxaluria. Subsequently familial amyloidosis and primary oxaluria were removed in 2009 from UNOS/OPTN policy as standard MELD exceptions. According



**Table 1 Model for end-stage liver disease exception points granted**

Year of policy implementation	MELD exception points granted	
	T2 lesion (A single nodule with diameter $\geq 2$ cm and $\leq 5$ cm or 2-3 lesions each between 1-3 cm)	T1 lesion (A single nodule $\geq 1$ cm and $< 2$ cm)
February 2002	29 points	24 points
February 2003	24 points	20 points
April 2004	24 points	No exception points
March 2005	22 points	No exception points
October 2015	Natural MELD score at the time of listing	No exception points
	28 points after 6 mo with maximum 34 exception points	
May 2019	MMaT-3	No exception points

MELD: Model for end-stage liver disease; MMaT-3: Median MELD at transplant-3.

**Table 2 Lesions eligible for downstaging protocols**

Number of lesions	Size	Description
1	$> 5$ cm and $\leq 8$ cm	
2-3	At least one lesion $> 3$ cm and all $\leq 5$ cm	Total diameter of all lesions $\leq 8$ cm
4-5	Each $< 3$ cm	Total diameter of all lesions $\leq 8$ cm

**Table 3 Organ procurement and transplantation network imaging classification for class 5 lesions in patients with cirrhosis**

OPTN class	Description	Comments
0	Incomplete are technically in adequate study	No MELD exception points
5A	Lesion size $\geq 1$ cm and $\leq 2$ cm	Increased contrast enhancement in the late hepatic arterial phase along with either: (1) Wash out during late contrast phases and peripheral rim enhancement (capsule or pseudocapsule); and (2) Biopsy consistent with HCC
5A-g	Lesion size $\geq 1$ cm and $\leq 2$ cm	Increased contrast enhancement in the late hepatic arterial phase along with growth $\geq 50\%$ documented on serial CT or MR obtained $\leq 6$ mo apart
5B	Lesion size $\geq 2$ cm and $\leq 5$ cm	Increased contrast enhancement in the late hepatic arterial phase along with either: (1) Wash out during late contrast phases; (2) Peripheral rim enhancement (capsule or pseudocapsule); (3) Growth $\geq 50\%$ documented on serial CT or MR obtained $\leq 6$ mo apart in the absence of ablative therapy; and (4) Biopsy consistent with HCC
5T	Prior local regional therapy for HCC	Any residual lesion or perfusion defect at the site of prior class 5A, 5A-g, 5B lesion

OPTN: Organ procurement and transplantation network; MELD: Model for end-stage liver disease; HCC: Hepatocellular carcinoma.

to the OPTN policy change from November 2009 several non-HCC conditions were granted standardized MELD-exceptions, without the need to go through the evaluation process by RRB and now RRB has been replaced by NLRB. This OPTN/UNOS policy change was the results of recommendations made by the MELD exception study group and conference (MESSAGE) in 2006[24,25].

Following is the summary of all non-HCC conditions eligible for standardized MELD exception points according to the current OPTN/UNOS policy and MELD extension request are valid for 90 d after submission[26] (Table 4).

### **Cholangiocarcinoma**

In order to be eligible for MELD exception points of MMaT-3, the candidate must meet all the criteria. The center needs to have written protocol including selection criteria,

**Table 4 Conditions eligible for non-hepatocellular carcinoma standard model for end-stage liver disease-exceptions**

Condition	Requirements for exception points	MELD score assigned
CCA	Un-resectable hilar CCA with biopsy/cytology consistent with malignancy or CA19-9 > 100 U/mL or aneuploidy  Center must have written protocol regarding selection of criteria, neoadjuvant therapy, operative staging for metastatic disease  Imaging to exclude metastatic disease	MMaT-3
HPS	Evidence of portal hypertension without any evidence of underlying significant pulmonary disease  PaO <sub>2</sub> < 60 mmHg on room air  ECHO or lung scan confirming intra-pulmonary shunt	MMaT-3
POPH	Evidence of portal hypertension along with MPAP > 35 mmHg and PVR > 3 woods unit  MPAP < 35 mmHg and PVR < 5.1 woods unit post treatment of pulmonary hypertension	MMaT-3
FAP	Biopsy proven amyloid along with TTR gene mutation and able to walk independently  Must be on heart transplant wait list or EF > 40% on ECHO within 30 d	MMaT-3
Cystic fibrosis	Genetic analysis confirmation needed  FEV1 below 40% of predicted FEV1 with 30 d prior to initial request	MMaT-3
HAT	HAT within 2 wk of OLT	40
Primary hyperoxaluria	AGT deficiency proven on liver biopsy/genetic analysis  On kidney transplant list with eGFR ≤ 25 mL/min on two instances 42 d apart	MMaT

CA19-9: Carbohydrate antigen 19-9; FEV1: Forced expiratory volume at one second; TTR: Transthyretin; AGT: Alanine glyoxylate aminotransferase; MELD: Model for end-stage liver disease; CCA: Cholangiocarcinoma; HPS: Hepatopulmonary syndrome; MPAP: Mean pulmonary artery pressure; FAP: Familial amyloid polyneuropathy; HAT: Hepatic artery thrombosis; PVR: Pulmonary vascular resistance; POPH: Portopulmonary hypertension.

neoadjuvant therapy prior to transplant and operative staging to exclude metastatic disease. Needs to be unresectable hilar cholangiocarcinoma (CCA) and meeting the diagnostic criteria for CCA with malignant appearing stricture on cholangiography with either biopsy/cytology consistent with malignancy or aneuploidy or carbohydrate antigen 19-9 > 100 U/mL without cholangitis. Imaging studies showing one lesion < 3 cm without metastatic disease. After completion of neoadjuvant therapy, operative staging to assess involvement of regional nodes and peritoneal metastases prior to considering for transplant. The biopsy of the original lesion must be avoided secondary to high risk of tumor seeding.

### **Cystic fibrosis**

The candidate will be eligible for MELD exception points of MMaT-3 if has genetic analysis confirmation for cystic fibrosis (CF) and the forced expiratory volume at one second (FEV1) is < 40% of predicted FEV1 within one month prior to initial exception request. After 90 d' extension request needed to be submitted.

### **HPS**

The candidate will be eligible for MELD exception points of MMaT-3 if the candidate has evidence of portal hypertension (ascites, varices, splenomegaly, or thrombocytopenia) in the presence of intrapulmonary shunt confirmed with contrast echocardiogram (ECHO) or lung scan. Also, the partial pressure of oxygen (PaO<sub>2</sub>) < 60 mmHg on room air within one month prior to submission of initial MELD exception request along with no underlying significant primary lung disease. To be eligible for MELD extension, the candidate must have PaO<sub>2</sub> < 60 mmHg within last 1 mo.

### **Portopulmonary hypertension**

To be eligible for MELD exception points of MMaT-3, the candidate must have evidence of portal hypertension along with mean pulmonary artery pressure (MPAP)

> 35 mmHg and pulmonary vascular resistance (PVR) > 3 woods unit or  $\geq 240$  dynes/sec/cm<sup>5</sup>. The candidates must have documentation of treatment for pulmonary hypertension with improvement in MPAP < 35 mmHg along with post treatment PVR < 5.1 woods unit or 400 dynes sec/cm<sup>5</sup>. For MELD extension request cardiac catheterization needs to be repeated every 3 mo with confirmation of MPAP < 35 mmHg.

### **Familial amyloid polyneuropathy**

The candidate will be eligible for MELD exception points of MMaT-3 if the candidate has biopsy-proven Amyloid along with confirmation of transthyretin (TTR) gene mutation with good functional status (able to ambulate without assistance). The candidate must be on liver transplant list or has ejection fraction (EF) > 40% on ECHO been performed within last 1 mo. To be eligible for extension, the candidate must be on active heart transplant list and ECHO showing EF > 40% within last 4 mo.

### **Primary hyperoxaluria**

MELD exception points of MMaT will be granted if the candidates have alanine glyoxylate aminotransferase (AGT) deficiency on liver biopsy sample analysis or genetic mutation analysis and on active kidney transplant list with estimated the glomerular filtration rate (eGFR)  $\leq 25$  mL/min on two instances at least 42 d apart.

### **Hepatic artery thrombosis**

The candidate will be eligible for MELD exception points of 40 if hepatic artery thrombosis (HAT) is within 2 wk after LT and does not meet the criteria of status 1A which includes HAT within 7 d of liver transplant along with aspartate aminotransferase  $\geq 3000$  and at least 1 of the following (INR  $\geq 2.5$  or arterial pH  $\leq 7.3$  or venous pH  $\leq 7.2$  or lactate  $\leq$  for mmol/L).

### **Liver transplant outcomes in the United States**

The OPTN/SRTR publishes annual liver transplant outcomes report in the United States every year. The most recent reported liver transplant outcomes in the United States were from the year 2018 and they were published in January 2020[27].

### **Waiting list outcomes**

The deceased donor OLT rate had increased to 54.5 *per* 100 waitlist-years in 2018 regardless of the recipients' geographic location (metropolitan and rural), gender and age. This trend has been rising since 2012. Historically, minorities such as Asian and Latino liver transplant candidates were not favored to received OLT, compared to their Caucasian and African American counterparts. This gap has narrowed to 10%, 44 and 48 *per* 100 waitlist-years for Asians and Latinos, compared to 56 and 62.5 for Caucasians and African Americans. The OLT rate was 66% higher for HCC candidates than for non-HCC candidates. This gap has been steadily narrowing since 2006. The overall median time from UNOS listing to transplant was 10.8 mo. The overall pre-OLT mortality rate was 13.2 *per* 100 waitlist-years in 2018. Age 65 or older candidates, candidates listed with acute liver failure, candidate listed with status 1A and MELD  $\geq 35$  had higher waitlist mortality. However, pre-OLT waitlist mortality of candidates listed at status 1A or MELD  $\geq 35$  had decreased since the regional "Share 35" rule implemented in 2013. Pre-OLT waitlist mortality also varied significantly by candidates' DSA regions geographically, ranging from 6.5 to 37.4 *per* 100 waitlist-years. That was one of the chief reasons for the UNOS/OPTN to change the liver distribution policy from DSA-based allocation model to the AC model.

### **Liver donation outcomes**

The number of deceased liver donations continued to increase in 2018. There were total of 7766 deceased liver donations. The use of hepatitis C virus (HCV) exposed donor livers has increased steadily since 2013. Approximately 8% of deceased donor OLTs in 2018 were from HCV donors. This trend has increased due to the effective HCV direct-acting antiviral (DAA) therapies and increased anoxic brain deaths from drug overdose secondary to national opioid epidemic. The liver donor organ discard rate has been trending down since 2012. The liver donor organ discard rate in 2018 was 8.4%. HCV-exposed donor livers were more likely to be utilized.

### **Liver transplant outcomes**

In 2018, the annual volume of OLTs was the highest in the United States history, recording 8250 transplants in a single year. In comparison, this number was a huge 31% increase from 2008 when only 6319 OLTs were performed. The percentage of

DCD donations also increased to 6.9% in 2018, compared to 4.8% in 2008. Although the majority of OLT recipients were Caucasian males between 50 to 64 years of age, the number of Asian and Latino transplant recipients increased by 15% and 11% respectively. The two most common diagnoses were alcohol-associated liver disease and cryptogenic disease, which are, in many cases, undiagnosed burnt-out non-alcohol steatohepatitis in etiology. The third most common diagnosis for OLT was HCC. The number of OLT recipients with HCV continued to decline in 2018. Only 10% of OLT recipients had the primary diagnosis of HCV-related chronic liver disease.

Overall and graft survival of OLTs continued to rise in 2018. 1-year and 3-year liver graft failure rates of deceased donor liver transplant were 8.8% and 16% respectively. 1-year and 3-year graft failure rates of living donor liver transplant were 7.8% and 14.6% respectively. 5-year overall and graft survival outcomes for the recipients with HCV diagnosis were comparable to the recipients with other etiologies. This trend was due to the effective DAA therapies for recurrent HCV infection after OLT. While the OLT recipients with HCC had better 1-year graft survival rate than the recipients with non-HCC diagnosis (90% *vs* 88%), they both had a similar 5-year graft survival rate (77% *vs* 76%)[27].

## CONCLUSION

In summary, we reviewed the evolution of liver transplant allocation policies in the United States over 3 decades; from CPT score system to MELD score to MELD-sodium score. We reviewed the liver transplant distribution policies; from older DSA-based distribution to the newer AC model and its potential advantages and drawbacks. We also reviewed the indications for both standard and non-standard MELD exceptions granted by the National Liver Review Board. Finally, we reviewed the liver transplant waitlist, donation and survival outcomes in the United States.

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## Interrogating the interplay of angiogenesis and immunity in metastatic colorectal cancer

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### Abstract

Colon cancer is the third most common malignancy and the fifth most frequent cause of death from neoplastic disease worldwide. At the time of diagnosis, more than 20% of patients already have metastatic disease. In the last 20 years, the natural course of the disease has changed due to major changes in the management of metastatic disease such as the advent of novel surgical and local therapy approaches as well as the introduction of novel chemotherapy drugs and targeted agents such as anti-epidermal growth factor receptor, anti-BRAF and antiangiogenics. Angiogenesis is a complex biological process of new vessel formation from existing ones and is an integral component of tumor progression supporting cancer cells to grow, proliferate and metastasize. Many molecules are involved in this proangiogenic process, such as vascular endothelial growth factor and its receptors on endothelial cells. A well-standardized methodology that is applied to assess angiogenesis in the tumor microenvironment is microvascular density by using immunohistochemistry with antibodies against endothelial CD31, CD34 and CD105 antigens. Even smaller molecules, such as the micro-RNAs, which are small non-coding RNAs, are being studied for their usefulness as surrogate biomarkers of angiogenesis and prognosis. In this review, we will discuss recent advances regarding the investigation of angiogenesis, the crosstalk between elements of the immune microenvironment and angiogenesis and how a disorganized tumor vessel network affects the trafficking of CD8<sup>+</sup> T cells in the tumor bed. Furthermore, we will present recent data from clinical trials that combine antiangiogenic therapies with immune checkpoint inhibitors in colorectal

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**Core Tip:** Colon cancer is one of the most common malignancies with a poor prognosis in patients with metastatic disease. Because of the need to find more effective treatments, researchers are focusing on deciphering the mechanisms used by the cancer cell for survival, food and metastasis. The main events in this process are neo-angiogenesis and immune escape through the interplay of growth factors involved in both pathways. This review presents the events involved in these pathways with a focus on their prognostic and predictive value.

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## INTRODUCTION

Colorectal cancer (CRC), the third most common cancer in both genders, accounts for 9% of new cancer diagnoses in men and 8% in women and is the third leading cause of cancer death in both sexes. Although it is more common in those over the age of 70, a significant proportion of patients are of middle age. The 5-year survival rate of patients with localized disease CRC is 90%. However, this rate is significantly lower in patients with metastatic disease, reaching 14% and 15% in those with colon and rectal cancer, respectively[1].

Due to the poor prognosis of metastatic CRC (mCRC), the need for novel therapeutic approaches in these patients is urgently needed. A step towards this direction was made possible by the introduction of antiangiogenic agents, but there are several unmet needs to better define patient profiles benefiting from such an approach. Moreover, despite this and other new treatments, the prognosis of patients with mCRC is still poor, and research is focusing on biomarkers with predictive and prognostic value (Table 1). Despite extensive research, in everyday practice only mutations in *RAS*, *BRAF*, *NTRK* and *HER2* genes as well as the level of microsatellite instability have found application in the targeted therapy of mCRC[2,3]. As the complex process of carcinogenesis and metastasis is continuously defined, this knowledge is expected to lead to the discovery of new therapies.

In this review, we will discuss recent advances in CRC regarding the investigation of angiogenesis, the crosstalk between the immune microenvironment and angiogenesis and the ways through which cancer cells escape the host immune system. Furthermore, we will present recent data from clinical trials that combine antiangiogenic agents with immune checkpoint inhibitors.

## ANGIOGENESIS

### Vascular endothelial growth factor

Angiogenesis is a complex mechanism of new vessel production that the cancer cell uses to ensure the supply of oxygen and nutrients and thus to multiply and generate evolving solid tumors with distant metastases[4].

There are two main regulators of angiogenesis that are essential for the development of CRC, hypoxia factor-1 $\alpha$  and vascular endothelial growth factor (VEGF). Hypoxia factor-1 $\alpha$  is a proangiogenic factor and is found in the tumor microenvironment. It is secreted by the cancer cell under hypoxic conditions and affects a wide

**Table 1 Factors related to angiogenesis and immunity and studied as biomarkers in colorectal cancer**

Factor	Biologic material	Pathway	Significance	Ref.
VEGF	Tissue, blood	Angiogenesis	Prognostic & predictive	Bendardaf <i>et al</i> [63] 2017, Des Guetz <i>et al</i> [7] 2006, Ferroni <i>et al</i> [64] 2006, Pascual <i>et al</i> [65] 2018, Tsai <i>et al</i> [66] 2013, Tsai <i>et al</i> [67] 2015, Boussios <i>et al</i> [68] 2019, Zygoń <i>et al</i> [23] 2017, Mohamed <i>et al</i> [69] 2019
VEGF polymorphism	Tissue, blood	Angiogenesis	Prognostic & predictive	Mousa <i>et al</i> [9] 2015
HIF-1 $\alpha$	Tissue	Angiogenesis	Prognostic	Baba <i>et al</i> [5] 2010
CTCs	Blood	Angiogenesis	Prognostic & predictive	Arrazubi <i>et al</i> [34] 2019, Burz <i>et al</i> [25] 2018, Cabel <i>et al</i> [28] 2017, Tan <i>et al</i> [33] 2018, Wang <i>et al</i> [35] 2019, Zhang <i>et al</i> [70] 2017
CTCs	Blood	Angiogenesis	Predictive	Nakamura <i>et al</i> [3] 2018
MicroRNA	Tissue, blood, stools	Angiogenesis	Prognostic & predictive	Balacescu <i>et al</i> [40] 2018, Boussios <i>et al</i> [68] 2019, Peng <i>et al</i> [41] 2017, To <i>et al</i> [38] 2018
MVD	Tissue	Immunity	Prognostic	den Uil <i>et al</i> [71] 2019, Des Guetz <i>et al</i> [7] 2006, Mohammed <i>et al</i> [72] 2020, Zhu <i>et al</i> [19] 2017, Zygoń <i>et al</i> [23] 2017

VEGF: Vascular endothelial growth factor; HIF-1 $\alpha$ : Hypoxia-inducible factor 1-alpha; CTCs: Circulating tumor cells; MVD: Microvascular density.

variety of signaling pathways, including the upregulation of the VEGF cascade[4-6]. VEGF has several important functions, the most important one being the increase of vascular permeability and the induction of new blood vessels through its binding to endothelial cells and by promoting their proliferation[7,8].

VEGF comprises a group of glycoproteins that, together with placental growth factor, interact with three VEGF receptors (VEGFR1, VEGFR2, VEGFR3) and two neuropilin co-receptors (NRP1, NRP2). VEGFRs are tyrosine kinase receptors found in endothelial vascular cells. The binding of the glycoprotein to its receptor results in the initiation of a sequence of events that ultimately result in the formation of new vessels [3].The ligation of VEGF-A with VEGFR-2 is the most important step in the activation of angiogenesis in CRC[9].

Bevacizumab is a monoclonal antibody targeting VEGF-A and the first antiangiogenic agent to be used against metastatic cancer. Bevacizumab was approved in 2004 in the United States and in 2005 in Europe for use in patients with mCRC. Its mechanism of action is mediated through the inhibition of the interaction of VEGF-A with VEGFR, and thus bevacizumab inhibits the signaling pathway that promotes neovascularization[10]. Finding biomarkers that could predict the response to antiangiogenic therapy so that it could be used only in patients who would benefit from its administration is a currently unmet need.

Due to the dominant role of VEGF in angiogenesis, researchers investigated whether the expression of this factor could be a predictive biomarker for patients receiving antiangiogenic therapy. One study indicated that high VEGF baseline levels associated with worse response to bevacizumab treatment and progression-free survival[11]. In 2013 Hegde *et al*[12] showed that there is no statistically significant relationship between plasma VEGF-A levels and the clinical response to bevacizumab. Therefore, it has no predictive value in metastatic colon cancer. Another exploratory analysis investigating epithelial and stromal VEGF expression, assessed by in situ hybridization and immunohistochemistry on tissue microarrays and whole tumor tissue sections, suggested that in patients with mCRC the addition of bevacizumab to chemotherapy improves survival regardless of the level of VEGF expression[13]. Mavericc was the first prospective mCRC study using gene expression data from blood (plasma VEGF-A protein levels) to evaluate the efficacy of mCRC chemotherapy regimens indicating that high plasma VEGF levels were associated with shorter treatment duration of response and progression-free survival[14]. More interesting, VEGF polymorphisms have also been studied, and it appears that they could possibly be used as predictive agents in mCRC in patients treated with irinotecan and bevacizumab[15]. In another study, VEGF-A (c.\*237C>T) was associated with a significantly better time to treatment failure[16]. Another study investigating the predictive role of VEGF-A indicated a significant association of rs833061 single nucleotide polymorphism with the overall response rate in advanced CRC patients treated with cytotoxic chemotherapy plus bevacizumab[17].

### Microvascular density

An important indicator used in translational studies to assess the degree of neovascularization of the tumor is the microvascular density (MVD). MVD appears to increase as it progresses from normal mucosa to adenoma and from adenoma to cancer, and this is explained by the intense angiogenesis that aims to meet the neoplastic cells need for oxygen[18]. MVD was found to be higher in primary tumors than in metastases[5, 18], while its levels within the tumor were associated with an increased risk of distant metastases[19]. The assessment of MVD includes pan-endothelial cell markers, also expressed in normal tissues, such as CD31 and CD34, as well as endothelial markers expressed on the surface of proliferating endothelial cells, such as CD105[18,20]. Endoglin is expressed mainly in vascular endothelial cells during active angiogenesis, while it is only weakly expressed or absent in pre-existing vascular endothelial cells, making this marker an important indicator of neoangiogenesis[18].

A systematic review and meta-analysis have indicated that increased VEGF and MVD expression markers are associated with an increased incidence of metastasis in CRC patients treated with surgery and chemotherapy[21]. An attempt was also made to correlate MVD with clinicopathologic features, such as sex, age, location, grade of differentiation, infiltrated lymph nodes and distant metastases, but with contradictory results. A negative correlation was found in two studies that investigated MVD in relation to the above variables[22,23], but in two other studies MVD staining was positively associated with tumor invasion, lymph node metastases[18] and distant metastases[19].

Since MVD is a biomarker for the quantification of angiogenesis, the question arises whether it can be used as a predictor of the treatment outcome with the antiangiogenic agent bevacizumab.

In 2006, Jubb *et al*[13], reported a clinical study of 813 patients with mCRC and found no association between elevated MVD or VEGF expression and the clinical outcome in relation to bevacizumab treatment. Although the predictive value of MVD in relation to bevacizumab response has been recognized in other cancers such as advanced ovarian cancer[24], in mCRC this has not yet been demonstrated.

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## CIRCULATING TUMOR CELLS

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It has been postulated that cancer cells circulate in the peripheral blood of patients with metastatic disease[25,26]. It is reasonable to expect that the isolation and study of these cells can provide information about the metastatic potential of primary disease and an assessment of their value as prognostic and predictive biomarkers[25].

The mechanism by which cancer cells enter the circulation and acquire the ability to metastasize is not fully understood. However, this process appears to be activated by tumor hypoxia, which also activates angiogenesis[27].

It has been estimated that the frequency of circulating tumor cells (CTC) is about 1 per 1 mL of peripheral blood[28] or otherwise 1 g of tumor releases 10<sup>6</sup> cells into the bloodstream[25]. Despite the large number of cells released into the bloodstream daily, a small number can be detected and isolated. This is partly due to the fact that these cells are covered by platelets and coagulation factors[29]. However, with the advent of new methods, it is now more feasible to isolate circulating cancer cells and study them [30]. Liquid biopsy, the isolation of CTCs or tumor cell-free DNA from peripheral blood is only minimally invasive compared to tumor biopsy and can be repeated many times for the monitoring of genomic changes that contribute to cancer progression and/or resistance to chemotherapy[31].

Although CTCs have been isolated in the blood of patients with polyps of the colon, the number of CTCs measured in the blood of patients with colon cancer is statistically significantly higher[28]. Furthermore, a smaller number of CTCs is detected in well-differentiated tumors compared to the less differentiated counterparts. The number of CTCs does not seem to be related to the tumoral histologic subtype, whereas it seems to be related to the anatomical location, being higher in cancer of the rectum and sigmoid colon compared to other sites[32]. Circulating cancer cells is an independent prognostic factor for the survival of patients with CRC[33]. In patients with mCRC and liver secondaries treated with complete resection of the primary tumor site and liver metastases, the presence of two or more CTCs/7.5 mL of blood preoperatively was an indicator of poor disease outcome and low survival[34]. Furthermore, according to another recent study, the CTC-positivity rate was an independent predictive factor of progression-free survival and overall survival in patients with advanced disease treated with chemotherapy. In addition, the CTC concentration was related to the



pathological stage of the disease, the presence of metastatic disease, the depth of tumor invasion, the presence of lymphatic invasion and high serum carcinoembryonic antigen levels[35].

### MicroRNAs

In recent years microRNAs, have been studied as biomarkers for diagnosis, prognosis and treatment resistance in patients with CRC. MicroRNAs are small non-coding molecules consisting of 18 to 25 nucleotides that control the expression of many target genes, either by inhibiting their expression or by stimulating it. Thus, by affecting the expression of oncogenes it is possible to either inhibit or promote oncogenesis[36]. These molecules can be detected not only in tissues but also in the serum and feces of cancer patients. They are found extracellularly either as a result of cancer cell death or due to extracellular secretion by cancer cells[37]. MicroRNAs target the 3' untranslated region of target genes, thereby degrading and controlling their expression[36]. MicroRNA interaction with target genes and their mRNA is affected by single nucleotide polymorphisms in the 3' untranslated region of these target genes, which also affect their expression. These polymorphisms have been studied to predict treatment outcomes, such as resistance to chemotherapy[38].

MicroRNAs are extremely stable molecules because they are stored in extracellular structures or bound to lipoproteins[38]. This feature and the fact that they do not require invasive methods for their detection make them potential ideal diagnostic and prognostic biomarkers.

The association of microRNAs with CRC was first described by Michael *et al*[39] in 2003. In this study, the authors showed that microRNA-143 and microRNA-145 levels were reduced in precancerous adenomatous lesions and CRC compared with normal mucosa. Since then, several research studies and meta-analyses have been published, emphasizing the importance of microRNAs in cancer[40].

In addition to oncogenesis, there are microRNAs that target regulatory molecules that lead to angiogenesis. These molecules, known as "angiomiRs," either promote or suppress angiogenesis, thereby indirectly affecting tumor formation and metastasis.

MicroRNA-21 is the most representative of neoangiogenesis as it has been studied in many types of cancer and by several researchers. In a meta-analysis published in 2017, Peng *et al*[41] analyzed data from 57 studies and concluded that microRNA-21 has a diagnostic sensitivity of 64% and a specificity of 85%, making it a potential prognostic indicator for patient survival. According to this study, peripheral blood microRNA-21 levels can be used as an indicator of CRC detection, and tissue levels can be an indicator to predict patient survival.

In addition to microRNA-21, there are many other microRNAs that target regulatory molecules leading to angiogenesis. Such molecules are microRNA-126, microRNA-30, microRNA-182, microRNA-194, microRNA-23b, microRNA-27a, microRNA-27b, microRNA-29b, microRNA-143, microRNA-145 and the complexes microRNA17-92, microRNA15a/16-1, microRNA-885-3p and microRNA885-3p[42].

MicroRNAs in the stool are the least studied but have been proven stable enough to correlate with the stage of the disease and have a high sensitivity and specificity in distinguishing patients from healthy individuals[38].

Long non-coding RNAs are made up of about 200 nucleotides and have also been studied as prognostic biomarkers. Although not translated into proteins, they act competitively by binding to common microRNA binding sequences and trapping them to alter the expression of their target genes. Available data suggest that long non-coding RNAs play a role not only in CRC development but also in metastasis[43].

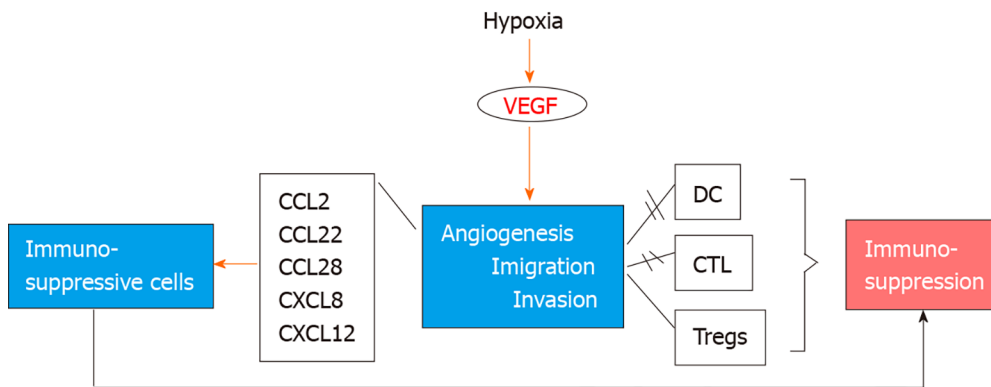
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## THE CROSSTALK BETWEEN ANGIOGENESIS AND IMMUNITY

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Tumor development and progression are highly dependent on the vascular network that penetrates the tumor bed and supplies proliferating malignant cells with oxygen and nutrients[44]. Although several mechanisms contribute to the constant development of the new vascular network, *i.e.*, neoangiogenesis, most new vessels are considered to be formed by the sprouting from parental ones[45]. The process of neoangiogenesis is triggered by hypoxia and deprivation of nutrients and is regulated by many proangiogenic and antiangiogenic factors such as VEGF-A, fibroblast growth factor, platelet-derived growth factor, transforming growth factor and others[45-47]. Compared to normal tissue vasculature, tumor neoangiogenesis is characterized by abnormalities in structure and function, driven by the imbalance between pro-angiogenic, mainly VEGF, and antiangiogenic factors in the tumor microenvironment





**Figure 1** The sequence of events following hypoxia and vascular endothelial growth factor secretion leading to immune system escape and carcinogenesis. VEGF: Vascular endothelial growth factor; CCL: C-C motif chemokine ligand; CXCL12: C-X-C motif chemokine ligand 12; DC: Dendritic cells; CTL: Cytotoxic T lymphocytes; Tregs: Regulatory T cells.

[48]. The abnormal structure and function of the tumor vasculature significantly affect the anti-tumor immunity, facilitating immune evasion in many different aspects (Figure 1). Overexpression of VEGF, produced by tumor cells, platelets and inflammatory cells such as neutrophils and monocytes, promotes the formation of an immature vascular network with increased leakiness, which in combination with the increased physical compression in the tumor bed leads to impaired blood perfusion and reduction of delivering oxygen and cytotoxic T cells in the tumor area[8,49]. Moreover, hypoxia/acidosis induced growth factors and cytokines such as transforming growth factor- $\beta$  and VEGF suppress the activity of cytotoxic T cells, suppress the antigen presenting capacity of dendritic cells, reprogram macrophages into a protumorigenic phenotype and upregulate the expression of programmed cell death-ligand 1 by tumor cells, myeloid-derived suppressor cells and dendritic cells and macrophages, further increasing immune evasion in the tumor microenvironment [8,50-52]. Of note, hypoxia-induced chemokines such as C-C motif chemokine ligand 2, C-C motif chemokine ligand 22, C-C motif chemokine ligand 28, C-X-C motif chemokine ligand 8 and C-X-C motif chemokine ligand 12 recruit immunosuppressive cells in the tumor microenvironment such as myeloid-derived suppressor cells, regulatory T cells and M2 macrophages[53] (Figure 1). In addition, tumor endothelial cells, in contrast to normal vasculature, express FasL and acquire the ability to kill effector CD8<sup>+</sup> T cells but not regulatory T cells[54,55].

Immunotherapy is now a key therapeutic weapon in the treatment of many cancers, such as melanoma, lung and urothelial cancer and has significantly improved patients' prognosis. Immunotherapies target immune checkpoints that are abnormally expressed in many patients and aim to kill the tumor indirectly by boosting the anti-tumor immune responses. Cytotoxic T-lymphocyte-associated protein 4 and programmed cell death protein 1 with its ligand programmed cell death-ligand 1 are primarily involved in inhibitory immune signaling and are essential regulators of cancer immune evasion. Current clinical practice includes mainly two types of immune checkpoint inhibitors such as anti-cytotoxic T-lymphocyte-associated protein 4 (ipilimumab and tremelimumab) and anti-programmed cell death protein 1/programmed cell death-ligand 1 (nivolumab, atezolizumab, pembrolizumab) monoclonal antibodies[56]. However, in CRC these therapies have not proved to mediate similar effects, except in tumors with microsatellite instability[57].

As the immunosuppressive tumor microenvironment is additionally induced in part by the dysfunctional vascular network, a window for therapeutic application opens for the combination of immunotherapies and antiangiogenics. This strategy has been exploited in several clinical trials for different tumor types[51], such as non-small cell lung cancer (atezolizumab and bevacizumab)[58], renal cell carcinoma (axitinib and pembrolizumab or cabozantinib and nivolumab)[59,60], endometrial cancer (lenvatinib and pembrolizumab)[61] and hepatocellular carcinoma (atezolizumab and bevacizumab)[62].

Regarding CRC, ongoing clinical studies (Table 2) are investigating the effectiveness of combinations of antiangiogenic agents and immune checkpoint inhibitors. It is possible that such combinations could be applied in the future treatment of mCRC.

**Table 2 Clinical trials related to antiangiogenic agent therapy and immunotherapy in colorectal cancer**

Status	Study title	Drugs	Country
Recruiting	A study evaluating the efficacy and safety of multiple immunotherapy-based treatment combinations in patients with metastatic colorectal cancer (Morpheus-CRC)	Regorafenib, atezolizumab	United States
Recruiting	Study of chemotherapy combination with autologous cell	Bevacizumab, oxaliplatin, capecitabine; Biological component: PD1-T cells	China
Recruiting	Treatment of colorectal liver metastases with immunotherapy and bevacizumab	Atezolizumab, bevacizumab, oxaliplatin	Korea
Recruiting	Neoadjuvant treatment in rectal cancer with radiotherapy followed by atezolizumab and bevacizumab (TARZAN)	Atezolizumab, bevacizumab	Netherlands
Not yet recruiting	Chemotherapy and immunotherapy as treatment for MSS metastatic	Capecitabine, oxaliplatin, bevacizumab, pembrolizumab	France
Not yet recruiting	QL1101 in combination with JS001 in patients with pMMR/MSS refractory metastatic	Bevacizumab, tripleitriumab	China
Not yet recruiting	Comparison of sintilimab to XELOX	Sintilimab vs XELOX + bevacizumab	China

CRC: Colorectal cancer; PD-1: Programmed cell death protein 1.

## CONCLUSION

Due to the poor prognosis of patients with mCRC, research has focused not only on finding prognostic and predictive factors but also on new therapeutic combinations. Immunohistochemistry methods have been instrumental in finding molecules that could be used as predictors, but molecular biology and immunology have been most informative in dissecting the mechanisms by which the cancer cell survives and spreads. Understanding how the immune and vascular microenvironments interact has opened new horizons in cancer treatment. Although such combination therapies for CRC have not yet been approved, the results of clinical trials are eagerly awaited.

Finding new molecular targets for different approaches including immunotherapy may enrich treatment options for CRC in the future.

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## Retrospective Study

# Phenomenology of obsessive-compulsive disorder in children and adolescents: Sample from a tertiary care center in Istanbul, Turkey

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**Author contributions:** Cifter A and Erdogan AB designed the project and created data collection tools; Cifter A examined the patient files; Cifter A and Erdogan AB did the analysis, interpreted the data and wrote the paper for publication; Erdogan AB critically revised the paper.

### Institutional review board

**statement:** The study protocol was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Protocol No: 09.2019.360, date: April 5, 2019).

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Written informed consent was obtained from parents or legal guardians of the patients.

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## Abstract

### BACKGROUND

Obsessive-compulsive disorder (OCD) is a heterogeneous disease in many respects and exhibits this diversity in terms of phenomenology. It also displays several different characteristics in children compared to adults.

### AIM

To describe the socio-demographic and phenomenological features of children with OCD and to investigate the impact of these features on response to pharmacotherapy.

### METHODS

This retrospective study was carried out with 150 children and adolescents who had been diagnosed with OCD between 2014 and 2018. Data was collected by examining the files of the patients with diagnosis of OCD and similar disorders from the hospital database. Yale-Brown Obsessive-Compulsive Scale for Children was used for the assessment of obsession-compulsion subtypes. The Clinical Global Impression (CGI) scale was used to evaluate the severity of the disease (CGI-S) and global improvement (CGI-I). The predictors of treatment response were evaluated using linear regression analysis. The level of significance for all statistic tests was set as  $P < 0.05$ .

### RESULTS

The sample was divided into prepubertal (44%) and adolescent (56%) age groups. The most prevalent obsessions were contamination and aggression obsessions, and the most frequent compulsions were washing and checking. While contamination was observed more commonly in the prepubertal age group, the religious obsession was seen more frequently in adolescents. Patients with aggression obsession presented a higher frequency of comorbid anxiety ( $P = 0.022$ ) and mood

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( $P = 0.047$ ) disorder. CGI-I scores did not differ according to phenomenological subgroups ( $P > 0.05$ ). A lower CGI-I score was linked to a lower CGI-S score (95% confidence interval 0.21-0.39,  $P < 0.001$ ) and the prepubertal age of admission (95% confidence interval 0.03-0.87,  $P = 0.020$ ).

## CONCLUSION

The phenomenology of OCD shows differences depending on the age group and the comorbid psychiatric disorders. Earlier identification and treatment of OCD may help to prevent the impairment of the mental health of children and adolescents.

**Key Words:** Obsessive-compulsive disorder; Phenomenology; Comorbidity; Treatment response; Serotonin reuptake inhibitors

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**Core Tip:** We aimed to analyze the socio-demographic and phenomenological features of children and adolescents with obsessive-compulsive disorder and to investigate the impact of these features on the pharmacotherapy response. Contamination was the commonest obsession, and washing-cleaning was the most common compulsion. The type of obsession varied with the age group: Contamination was seen more frequent in prepubertal age group, whereas the religious obsessions in adolescents. Aggression obsession was associated with the comorbid anxiety disorders and depression. The treatment response deteriorated with the increase in severity of disease and the age of admission. No difference was observed between the phenomenological subgroups in case of treatment response.

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## INTRODUCTION

Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by recurrent, unwanted thoughts (obsessions) and rituals to reduce anxiety (compulsions), which may lead to significant distress in a person's life[1]. The age of onset varies between the ages of 2 and 46, and symptoms usually begin around the age of 10 [2].

In contemporary psychiatric terminology, the term *phenomenology* is used to describe the symptoms and signs of diseases[3]. As a disorder with heterogeneous features in many respects, OCD also shows its variability and diversity in terms of phenomenological features, which are affected by many structural and environmental factors, and shows several different characteristics in children compared to adults. Rosario-Campos *et al*[4] stated that aggression, sexual and religious obsessions are more common in adults, whereas symmetry-ordering obsession/compulsions are more common in the pediatric age group. In addition, comorbid psychiatric disorders have been associated with some phenomenological subgroups. While mood and anxiety disorders accompany aggression obsession more frequently, it is reported that symmetry-ordering obsession and compulsions are more common in patients with tic disorders[5].

Whilst phenomenology is affected by multifactorial components, it also plays an essential role in the treatment response of OCD. However, there are contradictory results in the literature about which subgroup responds better to treatment[6]. In clinical practice, some subgroups benefit from selective serotonin reuptake inhibitors (SSRI) and clomipramine, whereas some groups need an antipsychotic augmentation in treatment[7].

In this study, we aimed to analyze the socio-demographic and phenomenological features of children and adolescents with OCD and to investigate the influence of these features on the pharmacotherapy response.

## MATERIALS AND METHODS

### *Procedures and study group*

This research was conducted in the Marmara University School of Medicine, which houses the largest child and adolescent psychiatry clinic on the Asian side of Istanbul, Turkey. The study was carried out retrospectively by examining the files of the emergency and outpatient clinics of the Child and Adolescent Psychiatry Department.

For our research, files of patients with International Classification of Diseases-10 diagnostic code F42 and refractions (OCD and similar disorders) were collected from the hospital database from a total of 88710 outpatient and 3896 emergency /consultation admissions between 2014 and 2018. There was totally 1516 applications belonging to 642 patients, and the patient files were overviewed systematically according to date of admission to the clinic. Out of the files overviewed, 153 could not be accessed due to problems in file archiving, and 101 patients were excluded since the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition for OCD were not fully met[1]. Also, the information in another 238 patient files was not taken into consideration due to lack of data. Finally, a total of 150 children and adolescents fully meeting the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition criteria were included in the study.

At least one drug treatment (SSRI, clomipramine, second generation antipsychotics) had been given to 118 (78.7%) children who had applied for at least two follow-up interviews, and seven of the children who started drug treatment discontinued the follow-up. One hundred and eleven children under medication continued their follow-up for an average of 5.5 mo. Children who had not used any psychotropic drugs received supportive psychotherapy.

### *Data collection tool*

The data were collected through Patient Follow-Up Form from patient records. Obsession and compulsion subgroups were established based on the Yale-Brown Obsessive-Compulsive Scale for Children[8]. Obsessions such as the need to know or remember, fear of saying certain things, fear of not saying just the right thing, intrusive images and sounds were evaluated under the heading of “miscellaneous obsessions” in Yale-Brown Obsessive-Compulsive Scale for Children. Also, compulsions such as mental rituals, the need to tell, ask or confess, the need to take precautions to prevent damage to himself/herself and others, and the need to touch, tap or rub were evaluated as “miscellaneous compulsions.”

Clinical Global Impression (CGI), one of the most commonly used clinician rated tools in psychiatry, measures the severity of the disease with CGI-S and the global improvement with CGI-I. The CGI-S score ranges from 1 (normal, not at all ill) to 7 (among the most extremely ill patients), and the CGI-I assesses the improvement from 1 (much improved) to 7 (much worse), which was recorded at the last interview following the treatment[9].

### *Statistical analysis*

SPSS 20.0 for Windows (IBM, 2011, Armonk, NY, United States) was used during the statistical analyses. The Shapiro-Wilk test was used to evaluate the normality of data distribution. Parametric variables were analyzed with Pearson's  $\chi^2$  or Fisher's exact test, independent samples *t* test, one-way analysis of variance, and for the non-parametric variables Kruskal-Wallis and Mann-Whitney *U* tests were used. The predictors of treatment response were evaluated using linear regression analysis. The level of all significance for all statistical tests was set as  $P < 0.05$ .

### *Ethics*

The study protocol was conducted in keeping with the code of ethics of the Declaration of Helsinki and was approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Protocol No: 09.2019.360, date: April 5, 2019). Written informed consent was obtained from parents or legal guardians of the patients.

## RESULTS

A total of 150 children, with a mean age of admission to the clinic of  $11.90 \pm 3.02$  (min: 4, max: 17) and a mean age of onset of symptoms of  $11.01 \pm 3.36$  (min: 3, max: 17), participated in our study. As the age of onset of the symptoms was in congruence with the age of admission and was prone to recall bias, we divided the study group into prepubertal/childhood (44.0%) and postpubertal/adolescent (56.0%) age groups based on the age at admission and accepted the onset of puberty as 12 years of age. The socio-demographic and clinical characteristics of the children are shown in Table 1. The socio-demographic features such as parental educational and employment status were similar in terms of sex ( $P > 0.05$ ).

In the year prior to the admission, 35.3% of the children had experienced a stressful life event, which included the death of one of the nuclear or extended family members (10.7%), material loss (8.0%), serious illness of themselves or family members (8.0%), moving to another place (7.3%), an accident (3.3%) and parental divorce (0.7%). Before admission to our clinic, 22.0% of the children had been admitted to a mental health professional due to OCD, and 20.0% had shown psychiatric symptoms other than OCD. Out of all participants, 35.3% of the first-degree relatives had a history of psychiatric disorder, the most prominent of these being major depressive disorder (19.3%), which was followed by OCD and panic disorder (both 7.5%).

While 96.6% of the children had an obsession and 88.0% had a compulsion, 55.3% had more than one obsession, and 47.3% had more than one compulsion. The patterns of obsessions are shown in Figure 1 and compulsions are shown in Figure 2. There was no difference in the phenomenological subgroups between females and males ( $P > 0.05$ ). Contamination obsessions were observed more commonly in the prepubertal age group ( $\chi^2 = 4.658$ ,  $P = 0.031$ ), whereas religious obsessions were more common in adolescents ( $\chi^2 = 7.013$ ,  $P = 0.008$ ). There was no variance in compulsions and other obsessions according to age group ( $P > 0.05$ ). In terms of stressful life events, aggression obsession was observed more frequently in children who had recently lost one of their family members ( $\chi^2 = 3.684$ ,  $P = 0.05$ ), and superstitious obsession was more common in children who had recently been in or witnessed an accident ( $\chi^2 = 12.312$ ,  $P = 0.023$ ). Ordering-arranging compulsion was found to be more common in children who had moved in the last year ( $\chi^2 = 4.718$ ,  $P = 0.03$ ).

In respect of comorbid psychiatric disorders, patients with aggression obsession presented a higher frequency of comorbid anxiety disorders ( $\chi^2 = 5.239$ ,  $P = 0.022$ ) and major depressive disorder ( $P = 0.047$ , Fisher's exact test). Ordering-arranging compulsion was seen less frequently in children with comorbid disruptive behavior disorders ( $\chi^2 = 6.042$ ,  $P = 0.014$ ).

The baseline CGI-S and post-treatment CGI-I scores are shown in Table 2. A positive, moderately strong and statistically significant correlation was found between CGI-S and CGI-I scores ( $r = 0.443$ ,  $P < 0.001$ ). The CGI-I scores of the adolescents were higher than children ( $t = -2.231$ ,  $P = 0.027$ ), but there was no significant difference between CGI-S scores of age groups ( $t = -0.894$ ,  $P = 0.373$ ). While CGI-S scores were higher ( $t = 2.342$ ,  $P = 0.021$ ) in children with superstitious behaviors (mean:  $4.42 \pm 0.53$ ) compared to those without (mean:  $3.20 \pm 1.37$ ), CGI-I scores did not differ according to phenomenological subgroups ( $P > 0.05$ ).

In the linear regression analysis, the CGI-S score and the age of admission were found to be the parameters that predicted the CGI-I score (Table 3).

## DISCUSSION

To the best of our knowledge, this study is the largest from Turkey concerning the phenomenology of pediatric OCD. Also, the study data was derived from a child and adolescent psychiatry clinic in a tertiary university hospital rather than a specialized clinic for OCD and therefore should be more representative of all pediatric OCD patients. So, ranging from mild to moderate, all severity levels of OCD, including treatment-resistant patients, were represented in the sample, suggesting that the findings could be broadly applied to OCD.

In the present study, the most common obsession was contamination, followed by miscellaneous, aggression and religious obsessions, and the most common compulsions were washing/cleaning, control, the miscellaneous category and ordering-arranging. Many studies worldwide also indicated contamination as the commonest obsession and cleaning as the commonest compulsion [10-12]. However, some researchers revealed symmetry-ordering as the most prevalent phenomeno-



**Table 1 Socio-demographic and clinical characteristics of children according to age group**

Socio-demographic characteristics	Prepubertal	Postpubertal	Overall	Statistical analysis
	n (%)	n (%)	n (%)	
Sex (male)	40 (60.6)	43 (51.2)	83 (55.3)	$\chi^2 = 1.326, P = 0.250$
<b>Educational level of mother</b>				
Secondary school and lower	24 (32.9)	40 (54.1)	73 (49.7)	$\chi^2 = 6.704, P = 0.010^1$
High school and above	49 (67.1)	34 (45.9)	74 (50.3)	
Employment status of mother	16 (24.6)	13 (15.5)	29 (19.5)	$\chi^2 = 1.953, P = 0.162$
<b>Educational level of father</b>				
Secondary school and lower	20 (35.1)	44 (51.2)	57 (39.9)	$\chi^2 = 3.583, P = 0.058$
High school and above	37 (64.9)	42 (48.8)	86 (60.1)	
Employment status of father	63 (96.9)	67 (82.7)	130 (89.0)	$\chi^2 = 7.459, P = 0.006^1$
Parents live together	62 (93.9)	73 (86.9)	135 (90.0)	$\chi^2 = 2.032, P = 0.154$
Consanguinity	13 (19.7)	21 (25.0)	34 (22.7)	$\chi^2 = 0.593, P = 0.441$
Mental disorder in 1 <sup>st</sup> degree relatives	24 (36.4)	29 (34.5)	53 (35.3)	$\chi^2 = 0.055, P = 0.815$
<b>Comorbid psychopathology</b>				
Anxiety disorders <sup>a</sup>	22 (33.3)	29 (34.5)	51 (34.0)	$\chi^2 = 0.023, P = 0.879$
Disruptive behavioral disorders <sup>b</sup>	23 (34.8)	18 (21.4)	41 (27.3)	$\chi^2 = 3.351, P = 0.067$
Neurodevelopmental disorders <sup>c</sup>	20 (30.3)	16 (19.0)	36 (24.0)	$\chi^2 = 2.567, P = 0.109$
Mood disorders (major depressive disorder)	1 (1.5)	6 (7.1)	7 (4.7)	$\chi^2 = 2.631, P = 0.105$
<b>mean <math>\pm</math> SD</b>				
Age gap between mother and father	3.34 $\pm$ 2.75	4.54 $\pm$ 4.18	4.00 $\pm$ 3.26	$t = -1.736, P = 0.085$
Birth order	1.69 $\pm$ 0.86	2.17 $\pm$ 1.37	1.95 $\pm$ 1.19	$t = -2.444, P = 0.016^1$

<sup>1</sup>Indicates emphasis of significance.<sup>a</sup>Generalized anxiety disorder, separation anxiety disorder, social anxiety disorder, specific phobias and panic disorder.<sup>b</sup>Attention deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder.<sup>c</sup>Articulation/phonation disorders, mental retardation, autism spectrum disorders, dyslexia and tic disorder.

SD: Standard deviation.

**Table 2 Clinical Global Impression-Severity and Clinical Global Impression-Improvement scores of the children**

CGI-S <sup>1</sup>			CGI-I <sup>2</sup>		
Score	Remark	%	Score	Remark	%
2	Borderline mentally ill	5.0	1	Very much improved	39.1
3	Mildly ill	19.3	2	Much improved	24.3
4	Moderately ill	54.3	3	Minimally improved	25.2
5	Markedly ill	19.3	4	No change	6.1
6	Severely ill	2.1	5	Minimally worsened	5.2

<sup>1</sup>Evaluated in the first session (baseline).<sup>2</sup>Evaluated in the last session (post-treatment).

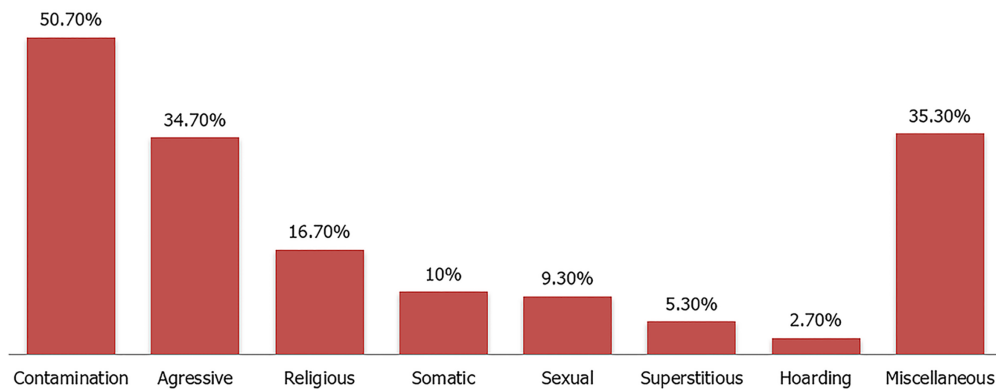
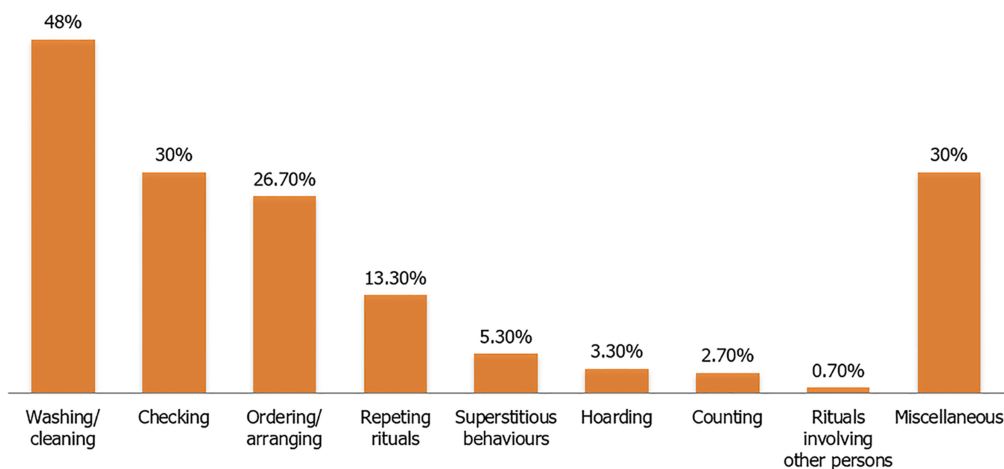
CGI-S: Clinical Global Impression-severity score; CGI-I: Clinical Global Impression-global improvement score.

logical subgroup[4,13], whereas Bryńska and Wolańczyk[14] described aggression as the most frequent obsession in adolescents. There was no sex difference between phenomenological subgroups in our study. Despite that, Tanidir *et al*[15] reported more contamination and somatic obsessions in males by using another diagnostic tool

**Table 3 Regression model indicating variables affecting response to treatment in children with obsessive-compulsive disorder**

Independent variables	Non-standardized coefficients		Standardized coefficients	P	Confidence interval 95%	t
	$\beta$	Standard error	$\beta$			
CGI-S	0.259	0.070	0.289	< 0.001	(0.121)-(0.397)	3.719
Age of admission <sup>1</sup>	0.507	0.238	0.165	0.035	(0.036)-(0.878)	2.127
R = 0.336; F = 9.347; P < 0.001; Durbin-Watson = 1.925						

<sup>1</sup>Age of admission was divided into two groups as prepubertal and postpubertal and categorically included in the analysis. CGI-S: Clinical Global Impression-severity score.

**Figure 1 Pattern of obsessive symptoms among participants.****Figure 2 Pattern of compulsive symptoms among children.**

(K-SADS-PL) on 110 children and adolescents in Istanbul. Mataix-Cols *et al*[16] found in their study in the United States that hoarding was common in girls, while sexual obsessions were more common in boys. The variance in results of such studies may be due to the wide range of age and methodologies and the cultural differences.

Regarding age group, contamination obsessions were related to prepubertal age group, whereas religious obsessions to adolescent age group. Consistent with our findings, studies conducted with children and adults asserted that contamination obsessions were seen in earlier ages[17], and religious obsessions were more apparent in older ages[15,18-19]. Exceptionally, Albert *et al*[20] related religious obsessions in adult OCD patients with the disease onset before the age of ten. Considering that the concepts of abstract thought and religion in children become more elaborated during adolescence, it is expected that religious obsessions would be seen more frequently in this period.

During our follow-up, approximately two-thirds of the children were diagnosed with a psychiatric disorder other than OCD, and the most common comorbid disorder was anxiety disorders (34.0%). Similar pediatric OCD studies also reported high rates of comorbidity, and the commonest comorbid mental disorders were defined as anxiety disorders, attention deficit/hyperactivity disorder, and tic disorder[14,16,21]. Among the phenomenological subgroups, variations in terms of comorbidities were observed, and the aggressive obsession was more frequently seen in children with anxiety and mood disorders. Studies conducted in Western and Asian countries have related anxiety disorder with aggressive symptomatology of OCD[5,22-23]. Also, Storch *et al*[24] observed daily functional impairment in the presence of either comorbid anxiety disorder or aggressive obsessions in children with OCD. Additionally, we observed nearly one-third of the children had a history of psychiatric disorder in their first-degree relatives. In other studies, the rate of psychiatric family history in childhood-onset OCD cases varied from 35%-45%[13,25], and the earlier age of onset of symptoms has been strongly associated with the familiarity of the disorder [26].

In the light of our results, the treatment response deteriorated with the increase in severity of disease and the age of admission. Congruent with our results, Masi *et al*[27] highlighted that a better response to SSRIs is related to less severe illness in pediatric OCD. In a systematic review, early pharmacotherapeutic intervention was found to be the most remarkable indicator of treatment response in pediatric OCD[28]. Notwithstanding, some researchers did not find a significant relationship between age of onset/admission and response to pharmacotherapy in children with OCD[29,30]. Furthermore, in our study group maternal educational level and paternal employment level were found significantly higher in the prepubertal age group, which are supposed to be critical protective factors for a child's mental health and might be associated with better therapy outcomes.

Between the phenomenological subgroups, no difference was observed in case of treatment response. Results of the studies concerning which single subgroup responds better to SSRIs are controversial[29,31], and this may be due to the heterogeneous nature of the disorder. Therefore, in future studies, response to pharmacotherapy of OCD symptoms in children and adolescents should be examined in homogeneous subgroups with a dimensional approach rather than in single phenomenological groups.

There are also some limitations to the study. First, some of the children were excluded from the study due to lack of data, failure to meet the diagnostic criteria and problems in file archiving, all of which limited the number of participants. Second, retrospective data collection from the files might cause reporting bias. Third, due to its nature, the sample might have some ascertainment biases such as medication discontinuation due to fear of stigmatization, type of responders to SSRIs in terms of OCD phenomenology, family characteristics, and underlying neuropathology, *etc.* Lastly, data concerning the children who dropped-out would provide a comparison of the results with the follow-up group and could strengthen our results.

## CONCLUSION

In the present study, it has been shown that obsessive-compulsive disorder in children and adolescents show their heterogeneity in terms of phenomenology. There are variations in the phenomenology of obsessions depending on the age group and comorbid mental disorders. During the follow-up of pediatric OCD patients, comorbid psychiatric disorders associated with certain phenomenological subgroups should be considered. The response to pharmacotherapy was associated with a younger age of admission and lower severity of disorder, which emphasizes the value of therapeutic interventions in the early stages of the disease in order to limit the impairment of social functioning and prevent the development of secondary mental disorders in adulthood.

## ARTICLE HIGHLIGHTS

### Research background

As a disease with heterogeneous features in many respects, obsessive-compulsive disorder (OCD) shows variability in terms of phenomenology.

**Research motivation**

Phenomenology of obsessions and compulsions are affected by many structural and environmental factors and shows several different characteristics in children compared to adults.

**Research objectives**

To identify the most common phenomenological subgroups of pediatric OCD and to determine the relationship of these subgroups with familial and clinical characteristics of children and the treatment response.

**Research methods**

Data of 150 children and adolescents, who had been diagnosed with OCD between 2014 and 2018, were examined retrospectively.

**Research results**

Contamination obsession was observed more frequently in the prepubertal age group, whereas religious obsessions were more frequent in adolescents. The treatment response deteriorated with the increase in severity of disease and the age of admission.

**Research conclusions**

Variations in phenomenology of obsessions are found in terms of age groups. The response to pharmacotherapy was found to be better in patients in the prepubertal age group and with lower severity of disease.

**Research perspectives**

Earlier diagnosis and therapeutic interventions in OCD may limit the impairment of mental health of children and adolescents.

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