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Clinical Application of Confocal Microscope in Diagnosis and Treatment of Fungal Keratitis

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Abstract: To explore the clinical application of confocal microscopy combined with corneal scraping in fungal keratitis. In this paper, 50 patients with clinical diagnosis of fungal keratitis were examined by hybrid microscope and keratotomy, postoperative microscope and fungal culture, and drug or combined surgical treatment, and drug or combined surgical treatment was performed, and the positive rate of diagnosis was counted. The positive rate of confocal microscopy diagnosis at admission was 70%, and the positive rate of corneal scraping pathogen diagnosis was 80%. It is mainly because they have received different degrees of treatment before this, which has an impact on this initial clinical diagnosis. After treatment, 35 eyes (79%) received clinical care through simple medication, while 15 eyes (21%) required surgery to treat infections that could not be controlled by simple medication. Confocal microscopy has the characteristics of non-invasive, rapid, and good repeatability. Combined with laboratory examination of corneal scraping can improve the diagnostic positive rate of fungal keratitis and better guide the treatment.

1. Research Background

If fungal keratitis is not diagnosed and treated in time, it will cause serious consequences, such as corneal perforation and endophthalmitis [1]. Accurate, fast and definite diagnosis helps accurate treatment. Common laboratory pathogenic examinations of fungal keratitis include examination of the cornea and darkening under microscope and fungal culture [2]. The mixture is simple and fast, and pathogens can be detected on the screen [3]. Culture is the gold standard, but there is less corneal damage. The positive rate is usually not high, and the hybrid microscope can observe the cornea at the cellular level non-invasively, dynamically and in real time. In recent years, some research results have been obtained by studying the etiology, depth of disease, stage of disease

development and treatment effect of fungal keratitis. The purpose of this study was to compare the positive rate of confocal microscopy and laboratory examination of corneal fragments in the diagnosis of fungal keratitis and the clinical application of two auxiliary methods [4-5]. There are many pathogenic bacteria in fungal keratitis. To date, more than 105 fungi that have caused corneal infections have been found. Therefore, many pathogenic bacteria have different toxicity to the cornea and spread to the cornea through different bacteria [6]. The clinical manifestations of inflammation are diverse, complex, and variable, and the response of antifungal drugs is also different, resulting in great difficulties in evaluating clinical diagnosis and treatment [7]. Due to the lack of reliable and effective screening methods and techniques, in the early stages of the disease, outpatients only rely on clinical manifestations, disease characteristics, and treatment experience. Accurate diagnosis and treatment are often difficult, often leading to misdiagnosis or delayed treatment, and even blindness. Therefore, early diagnosis is one of the keys to successful treatment.

At present, fungal keratitis can only be confirmed by fungal culture. But it also has its limitations: fungal culture usually lasts from a few days to two weeks, the time spent is the longest of all examinations, so the result is that the last treatment is also the least efficient, and statistically speaking, the sensitivity is low, only Half of the studies have positive corneal fragments [8-9]. The results of corneal scraping microscope and fungal culture are negative, but the clinical manifestations are debatable, and corneal tissue biopsy may be considered [10]. Early diagnosis and treatment are particularly important in the treatment of this disease, so patients cannot wait for the culture results of pathogen detection, and then select specific antifungal drugs for targeted therapy [11]. It is particularly important to eliminate the possibility of delaying the healing of ulcers or corneal toxicity caused by pathogens due to the lack of timely and effective treatment.

Ophthalmic confocal microscopy as a real-time, non-invasive imaging tool provides an effective method for the early diagnosis of fungal keratitis, making the diagnosis of fungal keratitis visible and significantly improving fungal keratitis [12]. The accuracy of early diagnosis. In recent reports, in most cases, the clinical diagnostic accuracy of clinical confocal microscopy has reached 96%. The possibility of serious complications is important to prevent the risk of blindness. Confocal microscopy is to observe the physiological and pathological changes of ocular surface tissue and cell structure through live corneal tissue. As a non-invasive screening method, it can directly detect fungal pathogens in early disease of the disease, so it has been widely used in clinical diagnosis, diagnosis, treatment and prognosis of superficial corneal diseases, improving the early diagnosis of corneal diseases accuracy.

2. Diagnosis and Treatment of Fungal Keratitis

2.1. Preliminary Diagnosis Method

IVCM examination: use 0.4% hydrochloric acid three times on the eye, drop eye drops on the conical objective lens of the laser microscope, open the objective lens with a sterile corneal contact cover with the eyelid opening, and place the mandible on the inspection frame. And keep your forehead close to the inspection frame. The patient should look at the light spot facing forward, and then gradually move the objective lens so that the tape contacts the cornea to keep the objective patient still. SAPI adjusts slowly, moves the lens to the surface of the cornea, and then obtains scanned images of each layer of the cornea. Carefully scan the corneal ulcer lesion area and environment, select clear and valuable images for protection, and use a computer analysis program for measurement and analysis. Before the examination, each patient must be covered with a sterile cap, and all operations are performed on the same machine by the same experienced doctor.

Corneal scrape examination: apply 0.4% hydrochloric acid to the eye 3 times to destroy the necrotic corneal tissue of the ulcer infiltration site, slide the blood clot, stain mycelium with Gram's

or look for spores.

2.2. Treatment

(1) All patients receive systematic and local empirical antimicrobial management immediately after admission, and select drugs with higher sensitivity based on drug resistance. Iodine burn was used to burn debris intermittently during treatment. Each patient chooses different types of drugs, uses and dosages according to your severity and stage progress, evaluates the effectiveness of the drugs, and adjusts the drugs according to the situation of each follow-up.

(2) Surgical treatment If you cannot use drugs to control infection, you can use drug combination therapy, and choose various surgical techniques such as conjunctival flap coverage, corneal transplantation, and balloon removal. During the operation of the eye, the infected corneal tissue is sent to the laboratory for pathogen examination.

(3) IVCM examination is performed after 2 weeks of treatment and 1 month of treatment to evaluate the clinical efficacy. The treatment plan and prognosis mentioned: clinical care of simple drug treatment and clinical care of combined drug surgery. For combined drug surgery, if it is an eye surgery, please specify the specific surgical method and pay attention to the management of postoperative infection.

2.3. Common Focus Detection Method

(1) Install the camera and cornea module, connect the computer, open the software, and the image acquisition window will appear on the computer screen.

(2) To ensure that there are no bubbles in the gel, drop a drop of ophthalmic gel on the conical lens of the confocal microscope object and cover it with a disposable sterile corneal contact pad.

(3) Manually rotate the objective lens of the Rostock corneal microscope to move the cornea to contact the focal plane on the outer surface of the lid until a bright reflected image appears on the computer screen.

(4) The patient's ocular surface has 0.4% hydrochloride eye drops. Using an eyelid opener to open the eyelid, the patient places the lower jaw on the examination frame and fixes the forehead tightly on the examination frame.

(5) Instruct the patient to look at the fixed point in front, adjust the position of the camera so that the optical axis is perpendicular to the optical axis of the lens, and slowly move the lens forward, ensure that the objective lens contacts the cornea through the gel, and tell the patient not to move.

(6) Use the movable adjustment handle to slowly move the lens to the surface of the cornea. You can view the scanned images of each layer of the cornea on a computer monitor in real time, and fully control the corneal ulcers and surrounding areas of the corneal lesions.

(7) Select and save valuable clear images, and analyze and statistical data after exporting the images.

At the end of the operation, instruct the patient not to rub their eyes until the local anesthetic effect disappears. Ofloxacin eye drops can be applied to the tested eye once every 15 minutes for a total of four times.

2.4. Fungal Culture

The fungal culture of corneal scraping explained the purpose of the examination to the patient, obtained the patient's consent and guided the patient's cooperation. Procaine hydrochloride 0.5% eye drops 3 times, open the eyelids, and instruct the patient to check the location. Under the slit lamp, use a sterile surgical blade to scrape the tissue at and around the lesion. 15 Inoculate blood

agar plate medium and send it to the fungal culture laboratory. According to statistical data, the mushroom culture is returned to the laboratory.

The diagnosis of fungal keratitis can be confirmed by any laboratory examination: corneal smear microscopy found spores or fungal hyphae; corneal culture results were positive. When the clinical manifestations and signs are consistent with fungal keratitis disease and antifungal drug treatment is effective, the diagnosis of fungal keratitis can also be considered correct.

Statistical analysis: Use the statistical calculator V1.70 of the chi-square test calculator, and use the chi-square test of four pairs of grid data to compare the positive frequency difference between the two inspection methods. $P<0.05$ indicates that the difference is statistically significant.

3. Research Objects and Experimental Setup

3.1. Experimental Subjects

50 eyes of 50 patients with fungal keratitis who were hospitalized from 2019-05-2019-10 were selected, including 25 males and 25 females, aged between 20 and 71 years (average 55.0±10.9. Course of illness before hospitalization) for 2-45 days (average 19.9±11.7) days, 15 eyes had a history of vegetative trauma, 20 eyes had a history of trauma, 5 had exposure keratitis, and 10 had no disease There is an obvious induction method. Before admission, 24 eyes were treated with antifungal treatment, 14 eyes were treated with anti-infective treatment, no antifungal treatment was performed, and 12 eyes were treated with unknown treatment. Slit lamp and corneal confocal microscopy the eyes of all patients, and the cornea was scraped for fungal culture. Inclusion criteria (1) history of traumatic foreign bodies such as nutritive cornea and soil, history of ophthalmic surgery, history of long-term use of hormones and antibiotics. (2) corneal lesion surface is relatively dry, It has the characteristics of hyphae, prosthetic feet, accessory lesions, immune loops, endothelial plaques, and empyema with a thick anterior chamber. (3) Corneal scraping, confocal microscopy, fungal culture, corneal tissue biopsy, etc. They confirmed the bacteria the presence of filaments or spores. (4) Antifungal treatment is effective. (5) The patient has received anti-infection or anti-fungal or other treatment outside the hospital before hospitalization (5 is a necessary condition, of which 1-4 can meet one of them Conditions). Exclusion criteria: patients with missing confocal microscope and fungal culture.

3.2. Experimental Design and Implementation

All patients were counted from the first day of hospitalization to the day before discharge, the length of hospitalization. Since most patients come from different regions and cities in the province, different levels of medical conditions and levels of medical units are different, so the treatment received by patients is not systematic and uniform. It is not included in the calculation and statistics of hospital stay. The duration of this study varied from 4 days to 36 days. Through confocal microscopy and etiology testing corneal curettage laboratory, using various methods such as drugs and surgical treatment.

3.3. Judgment of Efficacy

If there is no eye bandage, please try to check the slit lamp every day to observe the corneal ulcer: whether the corneal edema is reduced, whether the penetration is absorbed, whether the corneal epithelium has been cured, and the size and depth of the ulcer are reduced. Check the results of the corneal confocal microscope every other week. Contrast observation and analysis of fungal invasion depth, local mycelium quantity and epithelial healing in ulcer center and surrounding area.

According to the patient's disease status at the time of discharge, according to the cure, improvement and exacerbation, the treatment effect is divided into three A / B / C grades:

(A) Healing: The patient's clinical symptoms are significantly relieved, the scars on the surface of the ulcer are repaired, healed, infiltrated and absorbed, corneal epithelial edema is reduced and healed, and pan and pannus;

(B) Improvement: The patient's clinical symptoms are reduced, ulcers are reduced, and the infiltration is absorbed more than before, and confocal examination shows that the mycelium of the lesion is reduced; after conservative antifungal treatment, clinical care or improvement can be considered effective.

(C) Aggravation: If the patient's clinical symptoms are not significantly relieved, the corneal ulcer does not show significant improvement or the scope is further enlarged, the depth is deepened and the anterior chamber sepsis is increased, leading to any risk of corneal perforation or perforation, including the eye Enditis is considered invalid.

4. Experimental Results

4.1. The effect of Mycelium Depth and Anterior Chamber Accumulation

As can be seen from Figure 1, in patients with mild disease, the average depth of mycelium infiltration is 62um. In moderate disease, the average infiltration depth of mycelium is 137um. In severe diseases, the average infiltration depth of mycelium is 134um; from Table 1, the average silk infiltration depth of patients with anterior chamber empyema in group C is 136.1 μm, and 128.2um for patients without anterior chamber empyema. After analyzing the relationship between the severity of the patient's condition and the depth of mycelium infiltration in the confocal test, it was found that the statistical significance of the three groups A, B and C was P <0.05. It was analyzed whether there was no correlation between the anterior chamber empyema and the depth of mycelial infiltration, and it was found that P> 0.05 was not statistically significant.

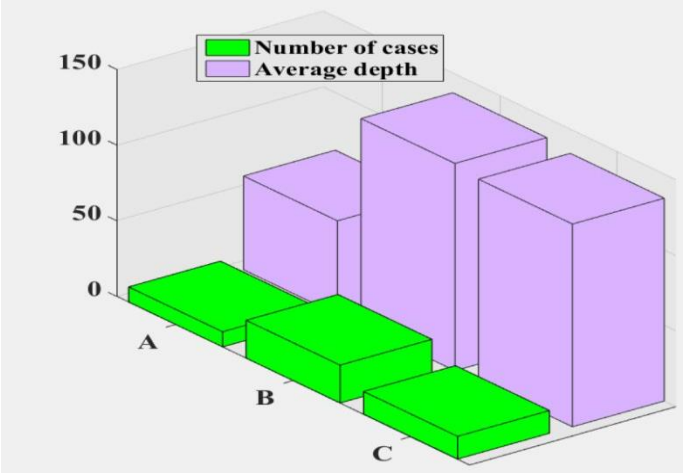

Figure 1. Relationship between the depth of fungal hyphae and the severity of the disease

Table 1. Relationship between the depth of fungal hyphae and empyema

Condition grade	Number of cases	Average depth(um)	Standard deviation	P value
Empyema	11	136.1	136.1±30.1	P>0.05
No anterior chamber empyema	4	128.2	128.2±20.3	P>0.05

4.2. Treatment Effect

Of all patients, 35 eyes (79%) received clinical care through simple medication, while 15 eyes (21%) required surgery to treat infections that could not be controlled by simple medication, including 6 eyes (13%) who experienced conjunctival flaps Occlusion. Five eyes (10%) underwent corneal transplantation, and all patients with conjunctival flap occlusion or corneal transplantation met the standard of clinical care; another 4 eyes (10%) underwent severe eyeball removal due to infection, and all patients underwent infection control, as show in Figure 2.

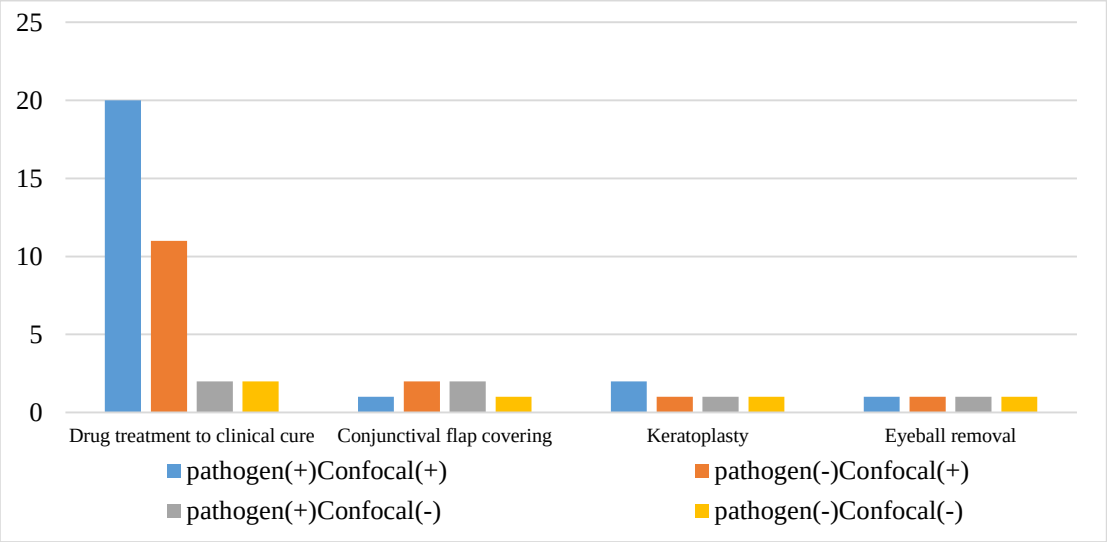

Figure 2. Patient's treatment effect

4.3. Impact of Hospital Stay

It can be seen from Figure 3 that 10 patients with milder disease (A) have an average hospitalization of 13.5. 25 patients with moderate illness (B) were hospitalized on average 14 days. 15 cases were severely ill (C). The average hospital stay was 16.5 days. The analysis of the relationship between the severity of the disease course and the length of hospitalization revealed that the statistical significance of the three groups A, B and C was P <0.05.

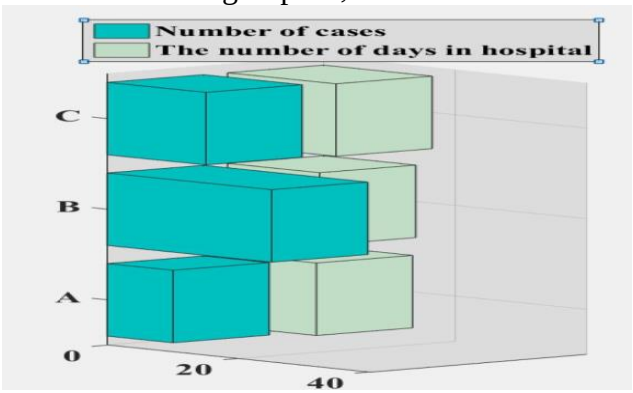

Figure 3. The relationship between the severity of the disease course and the length of hospitalization

4.4. Pre-Hospital Diagnosis

It can be seen from figure. 4 that among 22 patients who received antifungal treatment outside

the hospital, 19 eyes were positive for fungal culture, with a positive rate of 86.3%, and 18 eyes were positive under a corneal confocal microscope, with a positive rate of 81.8%. Among the 16 patients who received anti-infection treatment before admission, 14 eyes were positive for fungal culture, with a positive rate of 87.5%, and 12 eyes were positive for corneal confocal microscopy, with a positive rate of 75%. Twelve cases of fungal culture were treated positively in 7 eyes with an unknown rate before admission, the positive rate was 58.3%, and 5 eyes were positive under a corneal confocal microscope, the positive rate was 41.7%.

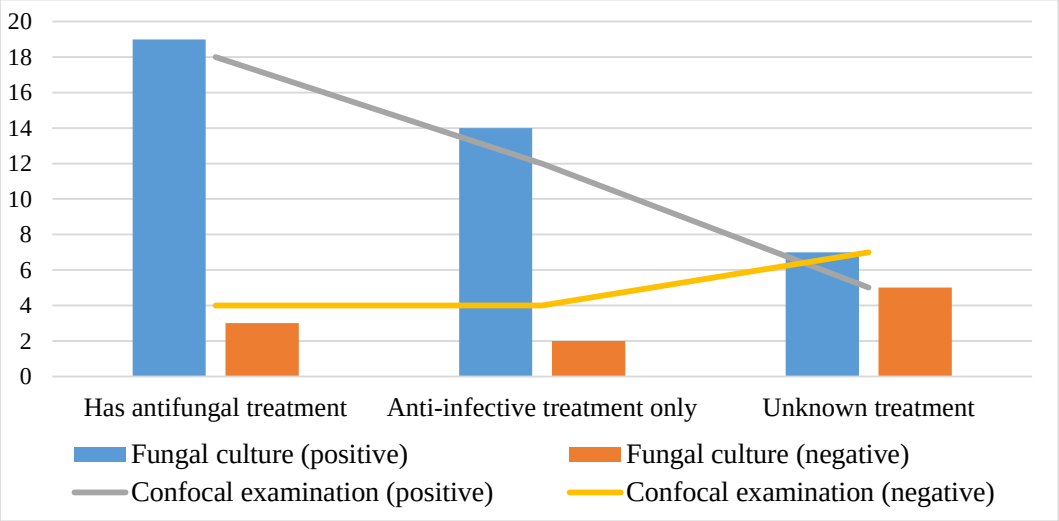

Figure 4. Pre-hospital diagnosis results

5. Analysis and Discussion

5.1. Analysis of Experimental Results

The positive diagnosis rate of the focused microscope is greater than the cause of corneal fragmentation. The combination of the two screening methods can further improve the positive diagnosis rate. After making a preliminary diagnosis, some patients may use antifungal drugs in other hospitals or perform corneal fragment examination in other hospitals. Confocal microscopy and pathogen screening will affect the positive rate. These patients are often transferred to several hospitals due to their serious condition and forced to be transferred to other hospitals due to poor treatment. In addition, various drug poisoning and other factors are mixed together, resulting in atypical clinical manifestations under the slit lamp at the initial diagnosis. The positive rate of auxiliary examination is not high.

In this study, patients who were initially diagnosed as positive for corneal fragments and negative for confocal microscopy had corneal edema, excessive necrotic tissue on the surface of the ulcer, cornea and anterior chamber endothelium, the generation of microscopic lesions was restricted, and turbo Unable to enter necrotic tissue. In the cornea and deep endothelial cells. In addition, when the corneal fracture does not show spores of sterile silk, it can cause spore morphology, which can cause yeast infection. If it is not typical, the number is very small and the number of inflammatory cells is very large. In addition, it is more difficult to diagnose yeast through a hybrid microscope, which requires extensive experience based on testing.

The research in this paper shows that the size of spores is about 1-2um, and the confocal microscope is not easy to distinguish, so the rate of missed diagnosis is very high. There were 2 patients with "pathogen (-) confocal (-)", but the antifungal drugs were effective and the clinical diagnosis was fungal keratitis. One of them is corneal injury in other hospitals. Confocal

microscopy can cause corneal fragments to destroy and destroy mycelium, resulting in atypical morphology and affecting the morphology of pathogens. Confocal microscopy should be performed before corneal rupture to avoid pathogens being observed through the observation microscope. The second is the history of plant trauma and the history of small corneal penetration. Although the wound was closed at the visit, the fungus also had corneal infections, and corneal ulcers entered the anterior chamber and caused endophthalmitis. The lesions are mainly concentrated in the deep stroma of the cornea and the endothelial surface of the cornea, and there are no superficial fragments of the corneal stroma. Pathogenesis, corneal stromal edema and the detection of necrotic tissue around the wound also affect the penetration of the confocal microscope.

In this study, surgery was performed on patients who could not effectively control drug infection. Surgical methods included obstetrics, gynecology and obstetrics, amniotic membrane transplantation, corneal transplantation, and eyelid removal. All patients were monitored postoperatively, and there was no spread of fungal infections. Two patients underwent destructive eye removal, and one of the patients had used hormones in the clinic after the first diagnosis. During the first diagnosis, we initially checked the "confocal (+) pathogen (+)" situation. Because the fungus penetrates directly into the eye through the cornea, it leads to severe complete keratitis infection. When the initial diagnosis was made, the other eye was "mixed (-) pathogen (-)".

5.2. Discussion

The laboratory examination of corneal scraping pathogens is a traditional inspection method, which can accurately identify pathogens and eliminate some pathogens and tissue necrosis. Examining smears under a microscope is a fast and convenient method, and is a standard cultivation method, but due to limited materials, it is not suitable for timely diagnosis and treatment of invasive examination methods, nor for re-examination for monitoring disease changes . Confocal microscopy can quickly and non-invasively identify fungal pathogens at a living level, and start antifungal treatment based on early diagnosis. In addition, it can accurately determine the depth of the lesion, objectively assess the prognosis and help non-invasively dynamically monitor changes in the disease, thereby monitoring changes in the number, density and depth of mycelia in the cornea.

In this study, confocal microscopy is a fast, non-invasive and repetitive procedure used to assess the severity of disease and the development trend of the disease. For the treatment plan, the type and frequency of drug use, the effective selection of the time, duration and duration of the medication provides an objective and favorable basis. However, hybrid microscopes also have their limitations. For example, the confocal microscope depends to a large extent on the skill level of the inspector, it is difficult to popularize the hospital, the cooperation of the inspector is very high, and it is difficult to find an area that is not conducive to accurately comparing the subtle changes in different areas. The transparency of the cornea will affect the laser's ability to penetrate. Misunderstanding of certain atypical graphical features will lead to certain false negative and false positive rates.

In nature, there are many types of fungi. Among such large populations, only 300 species are threatening and pathogenic to humans. But in infectious eye diseases, the power of fungal keratitis cannot be underestimated, which makes it an important factor in blindness of corneal diseases. In recent years, the incidence of fungal keratitis has gradually increased, but there are few relevant studies and epidemiological reports. Most bacteria are common pathogens in soil, plants and animals, and usually cause humus in the soil, causing plants and animals to rot. In tropical and subtropical regions, the prevalence of fungal keratitis is high. According to the pathogenic role of different pathogenic fungi in eye infections, they are divided into two categories: filamentous fungi, one is branched mycelium with special length, the colonies grow into feathers or cotton, and the

other is yeast (Most are Candida). Representatively, it is distributed on the buttons and is intrusive. Pseudohyphae formed, opaque colonies appeared, emulsified in the middle. The pathogenic bacteria causing fungal keratitis have obvious regional differences. Candida albicans dominates in cold climates, and Fusarium and Aspergillus mainly occur in hot or hot areas, such as India, Indonesia and South Florida. Fusarium is the first pathogen in these areas, followed by Aspergillus.

China is a large agricultural country. During the harvest season, plant damage is more common and this disease is more common. In this study, there were more than 50 patient farmers and workers, most of whom did not understand medical knowledge. Most of them were diagnosed in local clinics. Due to medical and medical device limitations, most patients do not receive standard antifungal treatment. When his condition deteriorated or could not be controlled, he was transferred to a superior hospital to postpone treatment. In order to correctly diagnose and treat these patients, it is very important to control the disease, shorten the disease process and reduce the patient's material burden.

6. Conclusion

The research in this paper found that confocal microscope and corneal scraping laboratory have their own advantages and disadvantages, but the combination of the two can complement each other. Two methods should be used in the joint examination to improve the positive rate of pathogen examination, improve the accuracy of diagnosis, and better guide treatment. During follow-up, confocal microscopy can be used to monitor disease progression. Although the hybrid microscope cannot replace the fungal culture as the gold standard for diagnosis, its high sensitivity, non-invasiveness, recurrence and rapidity provide a useful tool for clinical diagnosis and treatment of fungal keratitis, and have broad application prospects.

This study still has many defects, mainly due to the following reasons (1) some time before admission, the patient may have received treatment outside the hospital, thereby reducing the positive rate of the confocal microscope. (2) At different stages of the disease, the detection rates of mycelium and fungal spores are different, and the progress of the disease also affects the detection results. (3) Different mycelium and fungal spores have different detection rates under confocal microscope. (4) Different confocal microscopy instruments have different image qualities. Bad images will affect the positive rate of the test. (5) The contact medium between the head and the cornea can have a certain effect on the image quality.

In summary, fungal culture is an important auxiliary examination method for the diagnosis of non-first diagnosis of fungal keratitis and clarification of fungal species. The positive rate is higher than that of confocal microscopy. Its disadvantage is that it takes longer (3 to 7 days) Suitable for rapid diagnosis. Fungal culture is an important auxiliary method for diagnosing fungal keratitis and fungal species, and its positive rate is higher than that of confocal microscopy. Due to the characteristics of rapid, non-invasive and proliferative diagnosis and clinical treatment, hybrid microscopy should be the first choice for suspicious auxiliary examination, and positive examination can guide early and correct treatment. This possibility cannot be easily ruled out, and doctors who provide empirical treatment based on clinical experience and medical knowledge are invaluable. Although there are many unsolvable problems, the important role and significant advantages of confocal effect in the early diagnosis and treatment of fungal keratitis are not considered, and it is worth our doctors to conduct in-depth research and further discussion.

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Data Availability

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Conflict of Interest

The author states that this article has no conflict of interest.

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