Evaluation of the Clinical Characteristics of Dry Eye Secondary to Different Types of Liver Diseases

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Research Article

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Abstract

Purpose

Comparing the clinical characteristics of dry eye secondary to primary biliary cholangitis (PBC), drug-induced liver injury (DILI) and viral hepatitis B(HBV) to evaluate the ocular surface damage caused by different types of liver diseases.

Methods

32 patients with secondary dry eye, included 10 cases of PBC, 10 cases of DILI and 12 cases of HBV. All patients were evaluated by SPEED questionnaire, corneal fluorescein staining(CFS), non-invasive tear breakup time(NIBUT), Schirmer I test(SIt), tear meniscus height test(TMH), the area of meibomian glands dropout(MG dropout) , partial blinking rate(PBR) and lipid layer thickness(LLT).

Results

Compared with DILI and HBV groups, PBC group had a lower SPEED questionnaire score, but the difference was not statistically significant (F=0.83, P=0.45); the CFS score was higher (c^2=7.16,P=0.03), the PBR was higher (F=14.34, P=0.00), the SIt was lower (F=4.30,P=0.02), and the differences were statistically significant. The TMH of PBC and DILI groups was significantly lower than HBV group, and the difference was statistically significant (F=4.15, P=0.02). Compared with PBC group, the LLT of DILI group decreased, the difference was statistically significant (P=0.03). The NIBUT of three groups was lower than normal, but there was no statistical difference between groups (Ff=1.35,Pf=0.27;Fa=2.03,Pa=0.14).The area of meibomian glands dropout of three groups had mild to moderate defects, but there was no significant statistical difference between groups (F=0.32, P=0.73).

Conclusions

The PBC group was more prone to aqueous-deficient dry eye. The DILI group was more prone to obstructive meibomian gland dysfunction (MGD).The HBV group was more prone to non-obstructive MGD. The symptoms of dry eye in the PBC group are mild to moderate discomfort, but the degree of corneal damage is higher, indicating that the corneal sensitivity is reduced, which may be related to the high rate of partial blinking.

1. Introduction

Dry eye is a disease caused by multiple factors. It not only causes itching, foreign body sensation, burning sensation, but also affects vision and psychology, and reduces the quality of life of patients. Previous studies have shown that dry eye is related to many systemic diseases, including autoimmune diseases, endocrine diseases, liver diseases and mental diseases[1–3]. Liver diseases affect millions of people worldwide. More than one fifth of people in China have liver diseases, including primary biliary cholangitis (PBC), drug-induced liver injury (DILI), hepatitis B (HBV), HCV, non-alcoholic fatty liver disease

and alcoholic liver disease, among others. PBC is the most common type of autoimmune liver disease in clinical practice. According to the literature, 47-73% of the patients with PBC had dry eyes. Objective examinations showed that 30%-50% of the patients' tear secretion test decreased[4]. The main manifestation of drug-induced liver injury is immune liver injury caused by drugs, such as non-suppurative cholangitis, which has many similarities with PBC in clinical manifestations[5]. HBV has the highest prevalence rate among patients with liver disease. Compared with the normal population, the risk of dry eye secondary to HBV is much higher[5].

Therefore, this project selects the types of liver diseases that are most prone to secondary dry eye and the most common types of liver diseases for ocular surface analysis. In order to clarify the clinical characteristics of dry eye caused by different types of liver diseases and provide a more valuable help for the treatment of dry eye secondary to liver disease.

2. Materials And Methods

2.1. Patients

Case-control retrospective analysis was used in this study. The study was approved by the Ethics Committee of Beijing Youan hospital and followed the guidelines of the Declaration of Helsinki. All the patients were from March to December 2019 in the Department of Hepatology and Immunology, Beijing Youan hospital affiliated to Capital University of Medical Sciences. After ophthalmic consultation, 32 patients with dry eye secondary to different types of liver diseases were diagnosed.

There were 10 patients (20 eyes) with primary biliary cirrhosis, including 2 males and 8 females. The mean age was 56.00±6.54 years old. There were 10 patients (20 eyes) with drug-induced liver injury, including 1 males and 9 females. The mean age was 49.00±4.20 years old. There were 12 patients (24 eyes) with hepatitis B, including 5 male and 7 females, mean age 56.17±9.49 years old.

Patients with primary biliary cholangitis receive long-term oral administration of ursodeoxycholic acid 13-15 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$ on the basis of hepatoprotective therapy, and chronic hepatitis B patients receive long-term oral administration of entecavir 0.5$mg{\cdot}d^{-1}$,/tenofovir 300$mg{\cdot}d^{-1}$ antiviral therapy, patients with drug-induced liver injury stop liver injury drugs and give liver protection treatment.Three groups of patients were in mild abnormal liver function after treatment[6] ,there was no significant difference among the three groups(Table 1).

Table 1
Basic data and ocular surface evaluation of three groups

	PBC(n=10)	DILI(n=10)	HBV(n=12)
Sex(male: female)	2: 8	1: 9	5: 7
age(years)	56.00±6.54	49.00±4.20	56.17±9.49
AST(U/L)	46.62±33.91	47.92±33.39	48.04±42.19
ALT(U/L)	54.84±27.88	54.98±50.21	53.70±48.37
SPEED score	5.40±2.63	7.00±4.92	7.75±4.47
First NITBUT (s)	3.65±1.18	3.41±0.84	4.31±2.17
Average NITBUT (s)	5.36±2.74	5.10±1.17	7.19±4.25
TMH(mm)	0.21±0.05	0.20±0.04	0.26±0.06
MG dropout of upper eyelid (%)	30.30±12.54	24.29±5.36	23.19±10.56
MG dropout of lower eyelid (%)	22.06±11.91	28.26±12.34	21.32±11.27
MG dropout score	2.81±0.75	3.00±0.77	2.77±0.73
CFS (score)	1.90±1.85	0.60±1.35	0.42±1.00
Schirmer I test(mm)	4.11±5.14	10.00±8.71	10.27±6.82
LLT(nm)	84.36±15.41	69.00±19.51	83.30±13.53
PBR(%)	92.5±14.1%	60.2±11.1%	80.1±16.3%
NIKBUT, non-invasive breakup time. TMH, tear meniscus height. MG, Meibomian gland. CFS, corneal fluorescein staining. LLT, lipid layer thickness. PBR, partial blinking rate.			

According to the guidelines of Tear Film and Ocular Surface Society Dry Eye Workshop II[7] and Expert consensus on clinical diagnosis and treatment of dry eye in China[8]. Dry eye was diagnosed when a patients had at least one of the following subjective symptoms including tiredness, discomfort, sandiness, dryness, burning and blurred vision, with Schirmer I (no anesthesia)≤5mm/5min or BUT ≤5s; one of the subjective symptoms, with 5mm/5min < Schirmer I (no anesthesia)≤10mm/5min or 5s < BUT ≤10s, accompanied by positive corneal and conjunctiva fluorescence staining fluctuation[7, 8].

2.2. Clinical Observation Index Assessment

SPEED Questionnaire score

The symptoms included dryness or grittiness or scratchiness, soreness or irritation, burning or watering and eye fatigue. On a scale of the frequency of occurrence: 0 none at all; 1 sometimes; 2 often ; 3 all the time. On a severity scale : 0 no effect; 1 temporarily tolerable; 2 uncomfortable, none daily life interfering;

3 bothersome, daily life interfering; 4 intolerable, unable to normal life. The four symptom scores add up to a highest total score of 28. The criterion of SPEED score was as follows: 0~5(no symptoms), 6~14(mild to moderate), 15~28(severe)[9].

Corneal fluorescein staining score (CFS)

Using aseptic fluorescein test strip, moistening with normal saline and pasting the conjunctiva of the lower eyelid of the outer canthus gently, the patients were observed with cobalt blue light under slit lamp after blink of eye. According to the Oxford scoring standard revised by Sjögren's International Collaborative Clinical Alliance (SICCA), The Punctate epithelial erosions (PEEs) were counted and scored: 0 =absent, 1= 1 to 5 PEEs, 2 = 6 to 30 PEEs, and 3 = more than 30 PEEs. An additional point is added if PEEs occur in the central 4mm diameter of the cornea, if any filaments are seen on the cornea, or if any patches of confluent staining including linear stains are found anywhere on the cornea. The maximum total score is 6[10].

Non-invasive tear breakup time (NITBUT)

Non-invasive tear breakup time, tear meniscus height and meibomian gland photos were measured by Keratograph5M ocular surface comprehensive analyzer (Oculus,Wetzlar, Germany). Ask the patient to blink normally twice and keep his eyes open until he had to close them. The instrument automatically recorded the time of first NIKBUT (fNIKBUT) and average NIKBUT (avNIKBUT) when the Placido ring was projected onto the cornea. NITBUT < 5s is abnormal, ≥10s is normal[11].

Schirmer I test

No topical anesthetic was applied before examination. The patient was seated and a 5mm×35mm tear test strip was used. The first segment of the eyelid is retracted 5mm and placed in the middle and outer 1/3 of the fornix of the lower eyelid with the long end hanging outside the eyelid. Asked the patient to close his eyes and took out the filter paper 5 minutes later, measure the length of infiltration. The wet length of the test paper< 5 s was abnormal, ≥10s was normal[12].

Tear meniscus height (TMH)

Asked the patient to blink and measure the height of the tear meniscus at 6 o'clock directly below the cornea. Repeated 3 times and took an average. The normal tear meniscus height was 0.2 ~ 0.3 mm[13].

Assessment of meibomian gland dropout area

The missing rate of meibomian gland of upper and lower eyelid was calculated by ImageJ software. Meibomian gland loss was quantified by 4 points method, 0 ~ 3 points respectively corresponding to different meibomian loss rates, 0%, < 25%, 25% ~ 75%, > 75%[14]. The scores of the upper and lower eyelid meibomian gland were 0-6 points in each eye[15].

Examination of lipid layer thickness and partial blinking rate

Using Lipiview TearScience(USA) to capture the interference images and videos of the eyes'tear film for 20-seconds. the color unit of the interference images are converted to the lipid layer thickness of the tear film, and the partial blinking and total blinking times are obtained. Lipid layer thickness (LLT), partial blinking (PB) which is the ratio of partial blinking to total blinking, were recorded[16].

2.3. Statistical analysis

All the data were analyzed by SPSS21.0 statistical software, and the data were expressed in the form of mean±standard deviation. SPEED questionnaire score, non-invasive tear film breakup time, Schirmer I test, tear meniscus height, the meibomian gland dropout score, lipid layer thickness and incomplete blink rate, were compared among three groups using one-way analysis of variance, and LSD test was used between two groups. Rank sum test was used for corneal fluorescein staining score among three groups. All the statistics were regarded as statistically different when $P<0.05$.

3. Results

3.1. SPEED Questionnaire score

The primary biliary cirrhosis group was 5.40±2.63, the drug-induced liver injury group was 7.00±4.92, and the hepatitis B group was 7.75±4.47. There was no significant statistical difference in SPEED among the three groups (F= 0.83, P= 0.45) (Fig. 1A) .

3.2. Corneal fluorescein staining score (CFS)

The primary biliary cirrhosis group was 1.90±1.85, the drug-induced liver injury group was 0.60±1.35, and the hepatitis B group was 0.42±1.00. The corneal staining score of the primary biliary cirrhosis group was significantly higher than that of the other two groups(c^2=7.16, P=0.03)(Fig. 1B) Representative images are shown in (Fig. 2).(Fig. 1B)

3.3. Non-invasive tear film breakup time

The first tear film breakup time: 3.65±1.18s in the primary biliary cirrhosis group, 3.41±0.84s in the drug-induced liver injury group and 4.31±2.17s in the hepatitis B group. There was no significant statistical difference in fNITBUT among the three groups(F_f=1.35, P_f=0.27). The average tear film breakup time: 5.36±2.74s in primary biliary cirrhosis group, 5.10±1.17s in drug-induced liver injury group and 7.19±4.25s in hepatitis B group. There was no significant statistical difference in avNITBUT among the three groups (Fa=2.03, Pa=0.14)(Fig. 1C&D).

3.4. Schirmer I test

4.11±5.14mm in primary biliary cirrhosis group, 10.00±8.71mm in drug-induced liver injury group and 10.27±6.82mm in viral hepatitis B group. The basal tear secretion in the primary biliary cirrhosis group was significantly lower than that in the other two groups, and the difference was statistically significant(F=4.30, P=0.02)(Fig. 1E).

3.5. Tear meniscus height (TMH)

0.21±0.05mm in primary biliary cirrhosis group, 0.20±0.04mm in drug-induced liver injury group and 0.26±0.06mm in hepatitis B group. The tear meniscus height in the primary biliary cirrhosis and drug-induced liver injury group were significantly lower than that in the hepatitis B group, and the difference was statistically significant (F=4.15, P=0.02)(Fig. 1F) .Representative images are shown in (Fig. 2).

3.6. Assessment of meibomian gland dropout area

In the primary biliary cirrhosis group, the upper eyelid was 30.30±12.54%, the lower eyelid was 22.06±11.91%, and the total score was 2.81±0.75. In drug-induced liver injury group, the upper eyelid was 24.29±5.36%, the lower eyelid was 28.26±12.34%, and the total score was 3.00±0.77. In the hepatitis B group, the upper eyelid was 23.19±10.56%, and the lower eyelid was 21.32±11.27%, so the total score was 2.77±0.73.There was no significant statistical difference among the three group(F=0.32, P=0.73) (Fig. 1G).Representative images are shown in (Fig. 3).

3.7. Lipid layer thickness

The primary biliary cirrhosis group was 84.36±15.41nm; the drug-induced liver injury group was 69.00±19.51nm, and the hepatitis B group was 83.30±13.53nm. The lipid layer thickness of tear film in the drug-induced liver injury group was significantly lower than that in the primary biliary cirrhosis group, and the difference were significant in statistics (p = 0.03). But there was no significant statistical difference between the drug-induced liver injury group and the hepatitis B group(P=0.06) (Fig. 1H).Representative images are shown in (Fig. 4).

3.8. Partial blinking rate

The primary biliary cirrhosis group was 92.5±14.1%. The drug-induced liver injury group was 60.2±11.1%.The hepatitis B group was 80.1±16.3. There was significant statistical difference in the comparison of partial blinking rate among the three groups(F=14.34, P=0.00).

4. Discussion

In this retrospective study, we reported for the first time the ocular surface damage of PBC, DILI and HBV. Hepatitis B virus (HBV) infection is very common in the population. Of the 350 million people infected with HBV worldwide, 33% live in China[17]. Virus infection can activate the autoimmune response, and induce neoantigen expression due to molecular mimicry between viral and host antigens resulting in the production of autoantibodies, cytotoxic T-cell or both directed to different host tissue[18]. It has been

established that human T-cell lymphotropic virus (HTLV), human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), and hepatitis C virus (HCV) infections are related to the occurrence of dry eye[19]. And we reported for the first time that hepatitis B virus infection is related to the occurrence of dry eye in the mainland of China. As we all know, the tear film is divided into three layers: lipid layer, aqueous layer and mucin layer. The Schirmer I test of patients with hepatitis B virus is 10.27±6.82 mm, and the TMH is normal, indicating that the aqueous layer is normal. The meibomian glands have mild to moderate deletions, with an LLT of 83.30±13.53nm, which is mainly manifested as non-obstructive meibomian gland dysfunction. HBV infection is different from HCV infection. Since 1992, more than 400 cases of HCV infection accompanied by Sjogren's syndrome have been reported, resulting in aqueous tear-deficient dry eye. The prevalence of HBV in Sjogren's syndrome is only 0.83%, which is very close to the prevalence of HBV in the general population in Spain (0.7%). This suggests that chronic HBV infection may not be associated with Sjogren's syndrome in this region. Another study proposed that HBV infection may provide some protection against autoimmune diseases. It can be seen that dry eye caused by HBV infection, which may not be related to the immune response caused by the virus, is mainly caused by meibomian gland dysfunction. Another study suggested that HBV infection may provide some protection against autoimmune diseases. It can be seen that dry eyes caused by HBV infection may not be caused by immune response, but by meibomian gland dysfunction.

DILI is a common liver disease which generally occurs between several days and a few months after drug ingestion. There are no reports about the ocular complications of drug-induced liver injury. We discovered for the first time that DILI can be combined with dry eye. In the DILI group, the Schirmer I test decreased only slightly, but the LLT was significantly decreased, accompanied by atrophy of the meibomian glands. One study reported that an LLT of less than or equal to 75 nm could be used for the detection of obstructive MGD (sensitivity of 65.8% and specificity of 63.4%)[16]. While the LLT value of hyposecretory MGD in Hwang h et al.'s study was lower at 45.2 ± 11.6 nm[20]. In obstructive MGD, the value of LLT is negatively correlated with the loss of upper and lower meibomian glands[21]. In addition, LLT is also related to gender and age. The LLT of the elderly and women may be higher[22]. Considering the sex and age factors of patients in the DILI group, the type of dry eye was more consistent with obstructive MGD. Long-term, excessive and irregular application of systemic drugs can not only cause liver cell damage, but also cause meibomian gland atrophy, which can lead to changes in lipid secretion, tear osmotic and tear film stability. Examples include anticholinergics, including antidepressants, antipsychotics, antiparkinsons, antihistamines, and antispastics. Functional cholinergic receptors have been found in human meibomian gland epithelial cells. These drugs may inhibit the secretion of meibomian glands by binding to cholinergic receptors[23].

Dry eye patients in the PBC group were characterized by a significant decrease in tear secretion. Although the meibomian glands were also slightly to moderately missing, the thickness of the lipid layer did not change significantly. It may be that the remaining meibomian glands compensatory secrete more lipids, thereby maintaining the thickness of the ocular surface lipid layer[24]. The most common extrahepatic manifestation of PBC is Sjogren's syndrome[25], which mainly causes aqueous tear-deficient dry eye. This is consistent with our research results. The main pathogenesis may be that autoimmune-mediated

local lymphocyte infiltration destroys the function of the lacrimal glands, and finally leads to insufficient water secretion[26]. In addition, our study show that the SPEED scores of the PBC, DILI, and HBV groups all showed mild to moderate dry eye symptom, but the corneal fluorescence staining scores of the PBC group were significantly higher than those of the other two groups. It appears as a Punctate epithelial staining or even fusion into a small patch(Fig. 2). The PBC group had severe ocular surface damage but reduced corneal sensitivity. Adatia FA[27] also found that a negative correlation between corneal staining and corneal sensitivity, suggesting reduced symptoms but worsened corneal epithelial damage. This is consistent with our findings, which suggest that dry eye may impair corneal sensation as the disease progresses. This decrease in corneal sensitivity may be related to the decrease in the density of corneal subepithelial nerve fibers[28]. On the other hand, Rahman EZ[29] also found that the reduced sensitivity of the cornea is not only related to tear film instability and ocular surface damage, but also closely related to the blink rate. The blinking rate is positively correlated with the staining of the ocular surface, which means that the faster the blinking speed, the worse the stability of the tear film, and the more severe the ocular surface damage. Our study found that partial blinking rate of the PBC group was significantly higher than that of the other two groups, and the tear film rupture time of the three groups was significantly lower than the normal value. The previous study of our research group also confirmed that partial blinking is closely related to the shortening of tear film breakup time and the instability of the ocular surface[30]. Kim AD[31] also demonstrated that the improvement in blinking patterns will help relieve dry eye symptoms, and moderately change the objective indicators of tear film quality.Therefore, partial blinking may be strongly associated with increased ocular surface damage and decreased corneal sensitivity.

Of course, our research also has shortcomings. PBC and DILI patients still belong to a small group, so the number of people included in this study for observation is limited. A larger sample size, more comprehensive, and more detailed observation will be more convincing.

In short, our research results show that the types of dry eye disease are different in different types of liver diseases. The dry eye secondary to PBC showed aqueous tear-deficient dry eye, secondary to drug-induced liver injury and viral hepatitis B showed evaporative dry eye, the former is more prone to obstructive MGD, and the latter is more prone to non-obstructive MGD. This provides a new understanding of dry eye caused by different types of liver diseases.

Declarations

Acknowledgements

Not applicable for this study.

Authors' contributions

SL,AL,FR and YJ conceived and designed the experiments. SL,FR,WZ,JC,CH and YJ performed the experiments. SL,AL and YJ analyzed the data. SL, AL and YJ wrote the paper. All authors have read and

approved the manuscript, and ensure that this is the case.

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Beijing Youan hospital and followed the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Consent for publication

Not applicable for this study.

Competing interests

The authors declare that they have no competing interest.

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Figures

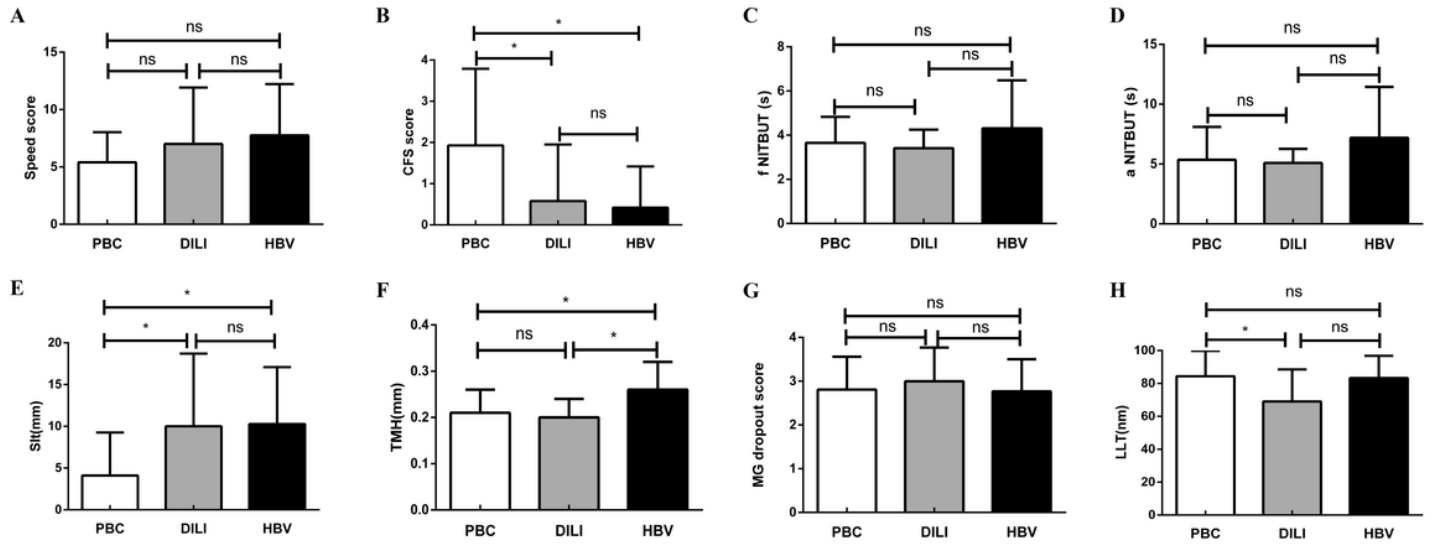

Figure 1

Comparison of clinical characteristics of dry eye among PBC, DILI and HBV groups. PBC,primary biliary cirrhosis; DILI,drug-induced liver injury; HBV,hepatitis B; (A) Speed score; (B) corneal fluorescein staining (CFS) score; (C) first NITBUT (f NIBUT); (D) average NITBUT (a NIBUT); (E) Schirmer I test (SIt); (F) tear meniscus height (TMH); (G) meibomian gland dropout (MG dropout) score; (H) lipid layer thickness (LLT) *P < 0 05,**P < 0 01, ns=not significant P0 05).

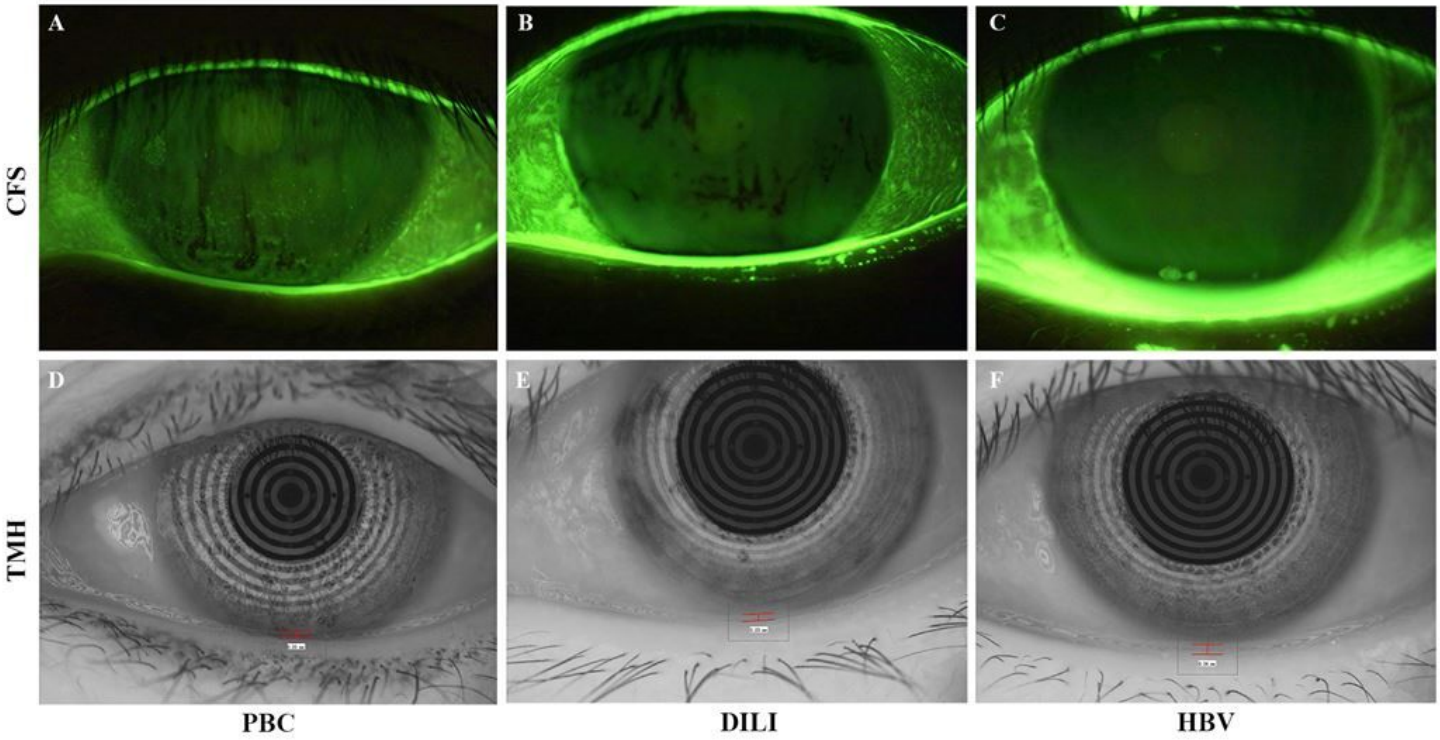

Figure 2

Corneal fluorescein staining (CFS) and Tear river height (TMH) The representative images of the three patients are (A&D), (B&E) and (C&F).PBC group (A) showed Punctate epithelial staining, or even fusion into a small patch, no obvious corneal staining in DILI (B) and HBV (C) groups. TMH was 0.20mm, 0.23mm and 0.34mm respectively in PBC (D) , DILI (E) and HBV (F) groups.

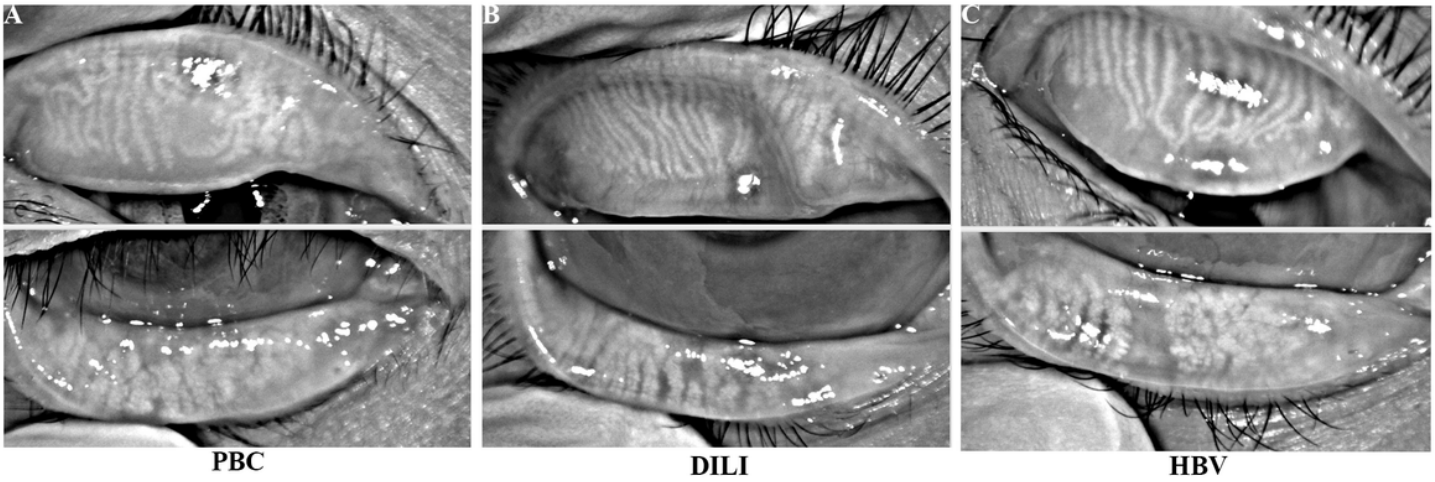

Figure 3

Assessment of meibomian gland dropout area Representative images of meibomian gland dropout area in three groups.(A)PBC group , the upper eyelid was 25.10 %, the lower eyelid was 20.37% .(B) DILI group , the upper eyelid was 23.27% , the lower eyelid was 24.27%. (C) HBV group, the upper eyelid was 24.96% , and the lower eyelid was 27.45% .

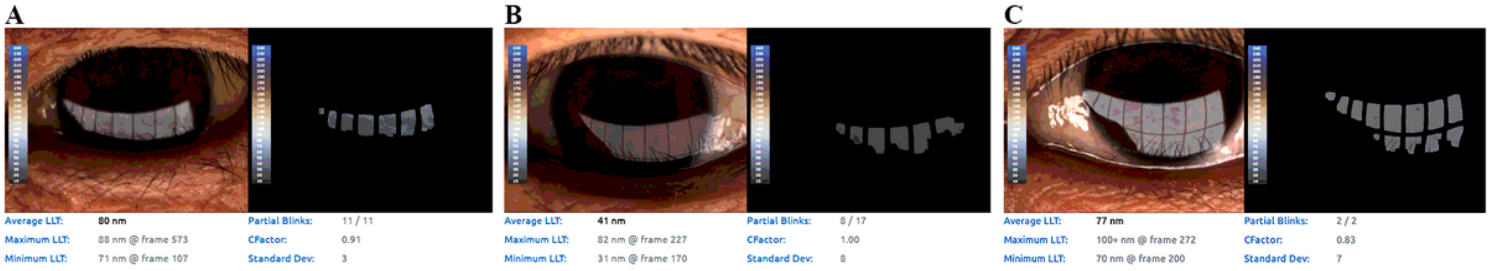

Figure 4

Lipid layer thickness（LLT） According to the color and structure of lipid layer, the value in (nm) was generated for evaluation. Representative images of LLT in three groups: The average LTT in PBC group(A) was 80nm; the DILI(B) group was 41nm, and the HBV group(C) was 77nm.