Ophthalmol Ther (2023) 12:2493–2503
https://doi.org/10.1007/s40123-023-00747-4

ORIGINAL RESEARCH

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

Shang Li · Ao Li · Fang Ruan · Wei Zhang · Jie Chen · Chunyang Huang · Ying Jie

Received: January 2, 2023 / Accepted: May 30, 2023 / Published online: June 23, 2023

ABSTRACT

Introduction: This study compares 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: Thirty healthy people were included as control group. Sixty patients with dry eye secondary to different types of liver disease were included, including 19 cases of PBC, 18 cases of DILI, and 23 cases of HBV. All patients were evaluated by the SPEED questionnaire, corneal fluorescein staining (CFS), noninvasive 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), lipid layer thickness (LLT), meibum expressibility, and meibum quality.

Results: There are statistical differences in ophthalmic examination results between different types of liver diseases and normal people ($P < 0.05$). Compared with DILI and HBV groups, the CFS score of PBC group score was higher ($P < 0.05$), the PBR was higher ($P < 0.05$), and the SIt was lower ($P < 0.01$). The TMH of PBC and DILI groups were significantly lower than the HBV group, and the difference was statistically significant ($P < 0.05$). Compared with the PBC group, the LLT of the DILI group decreased ($P < 0.01$). The area of meibomian glands dropout of the three groups had mild-to-moderate defects, but there was no significant statistical difference between groups ($P > 0.05$).The Meibum quality score in the DILI group was significantly higher than the HBV group ($P < 0.05$).

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 nonobstructive 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.

Keywords: Dry eye; Ocular surface damage; Meibomian gland dysfunction; Primary biliary cirrhosis; Drug-induced liver injury; Hepatitis B

S. Li · A. Li · Y. Jie (✉)
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Ophthalmology and Visual Sciences Key Lab, Beijing Tongren Hospital, Capital Medical University, No. 1 Dong Jiao Min Xiang, Dong Cheng District, Beijing 100730, China
e-mail: jie_yingcn@aliyun.com

S. Li · F. Ruan · W. Zhang · J. Chen · C. Huang
Department of Ophthalmology, Beijing YouAn Hospital, Capital Medical University, Beijing, China

Key Summary Points

Why carry out this study?

Dry eye has attracted increasing attention worldwide, in which liver disease was found to be associated with the pathogenesis of dry eye. Currently, more than one-fifth of the population in China has liver disease.

This clinical study evaluated the clinical characteristics of dry eye secondary to different types of liver diseases.

What was learned from the study?

This study found that dry eye secondary to primary biliary cholangitis was more prone to aqueous-deficient dry eye, whereas dry eye secondary to drug-induced liver injury and hepatitis B were more prone to meibomian gland dysfunction.

The types of dry eye secondary to different types of liver disease are not the same, which is important to guide the clinical treatment of liver disease combined with dry eye.

INTRODUCTION

Dry eye is a disease caused by multiple factors. It not only causes itching, foreign body sensation, and 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, endocrine, liver, and mental diseases [1–3]. Liver diseases affect millions of people worldwide. More than one-fifth of people in China have a liver disease, including primary biliary cholangitis (PBC), drug-induced liver injury (DILI), hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic 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 patients with PBC had dry eyes. Objective examinations showed that 30–50% of patient had decreased tear secretion [4]. The main manifestation of drug-induced liver injury is immune liver injury caused by drugs, such as nonsuppurative cholangitis, which has many similarities to 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 [6].

Therefore, this study has selected 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, 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.

METHODS

Patients

A 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 enrolled 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, 94 patients with dry eye secondary to different types of liver diseases were diagnosed. Exclusion criteria are shown in Fig. 1. Eventually 60 patients were included. There were 19 patients (38 eyes) with primary biliary cirrhosis, including 4 males and 15 females. The mean age was 56.00 ± 6.47 years. There were 18 patients (36 eyes) with drug-induced liver injury, including 2 males and 16 females. The mean age was 51.83 ± 3.68 years. There were 23 patients (46 eyes) with hepatitis B, including 10 males and 13 females, mean age 53.7 ± 5.09 years. Thirty healthy people (60 eyes) were included as

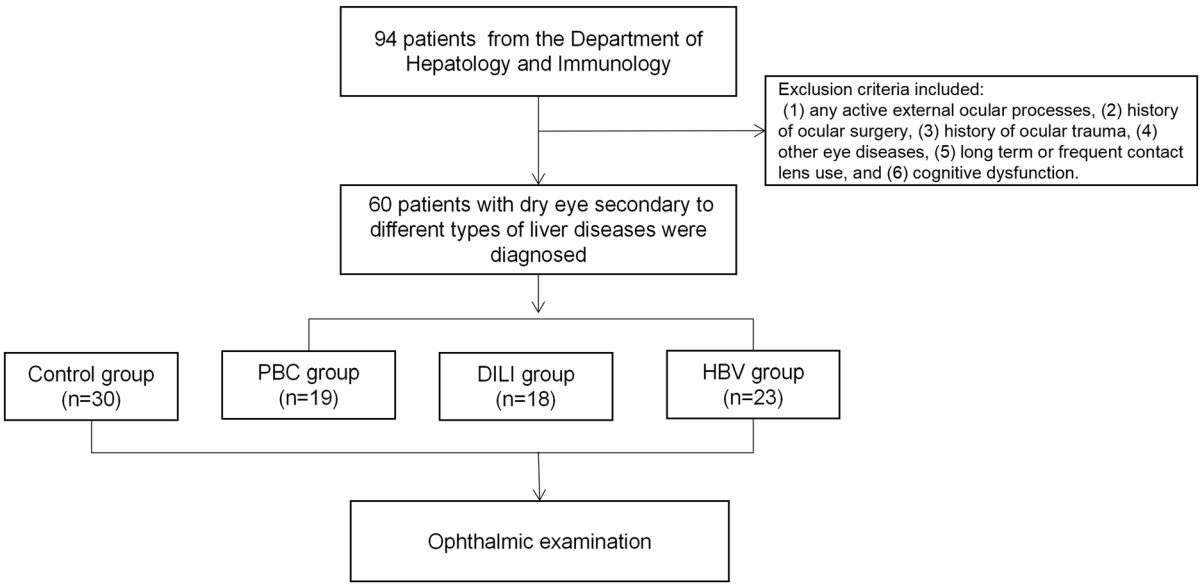

Fig. 1 Flowchart for inclusion of study participants

control group, including 12 male and 18 females, mean age 52.77 ± 7.84 years. Patients with primary biliary cholangitis receive long-term oral administration of ursodeoxycholic acid 13–15 mg kg^{-1} d^{-1} on the basis of hepatoprotective therapy; chronic hepatitis B patients receive long-term oral administration of entecavir 0.5 mg d^{-1}/tenofovir 300 mg d^{-1} antiviral therapy; and patients with drug-induced liver injury stop liver injury drugs and are given liver protection treatment.

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

Clinical Observation Index Assessment

SPEED Questionnaire Score

The symptoms included dryness or grittiness or scratchiness, soreness or irritation, burning or watering and eye fatigue, with the following scale of the frequency of occurrence: 0 none at all; 1 sometimes; 2 often; 3 all the time; and the severity scale: 0 no effect; 1 temporarily tolerable; 2 uncomfortable, none daily life interfering; 3 bothersome, daily life interfering; 4 intolerable, unable to live a 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 an aseptic fluorescein test strip, moistened with normal saline and by pasting the conjunctiva of the lower eyelid of the outer canthus gently, the patients were observed with cobalt blue light under a slit lamp after eye blinking. 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 = 1–5 PEEs, 2 = 6–30 PEEs, and 3 = more than 30 PEEs. An

additional point is added if PEEs occur in the central 4 mm 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].

Noninvasive Tear Breakup Time (NITBUT)

Noninvasive tear breakup time, tear meniscus height and meibomian gland photos were measured by a Keratograph5M ocular surface comprehensive analyzer (Oculus, Wetzlar, Germany). The patient was asked to blink normally twice and keep their eyes open until they 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 < 5 s is abnormal, ≥ 10 s is normal [11].

Schirmer I Test

No topical anesthetic was applied before examination. The patient was seated and a 5×35 mm tear test strip was used. The first segment of the eyelid was retracted 5 mm and placed in the middle and outer one-third of the fornix of the lower eyelid with the long end hanging outside the eyelid. The patient was asked to close their eyes and the filter paper was removed 5 min later, and the length of infiltration was measured. A wet length of test paper < 5 s is abnormal, ≥ 10 s is normal [12].

Tear Meniscus Height (TMH)

The patient was asked to blink, and the height of the tear meniscus at 6 o'clock directly below the cornea was measured. This was repeated three times to obtain the average time. The normal tear meniscus height was $0.2 \sim 0.3$ 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 a 4 point method, $0 \sim 3$ points respectively corresponding to different meibomian loss rates of 0%, $< 25\%$, $25 \sim 75\%$, and $> 75\%$ [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

Lipiview TearScience (USA) was used to capture the interference images and videos of the tear film for 20 s. 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) and partial blinking (PB), which is the ratio of partial blinking to total blinking, were recorded [16].

Meibum Expressibility and Meibum Quality

After applying stable finger pressure, the meibomian secretion ability of five MGs in the central area of the lower eyelid were tested and the following criteria applied: 0 = all glands can express; 1 = 3–4 glands can be expressed; 2 = 1–2 glands can be expressed; 3 = no glandular expression [17]. The quality of expressed meibum was scored from 0 to 3; 0 = clear fluid; 1 = cloudy fluid; 2 = cloudy; particulate fluid; 3 = opaque, toothpaste-like meibum. The final meibum quality score was a sum of all eight central MGs in the lower eyelid [18].

Statistical Analysis

All the data were analyzed by SPSS 21.0 statistical software, and the data were expressed as mean ± standard deviation. SPEED questionnaire scores, noninvasive tear film breakup time, Schirmer I test, tear meniscus height, the meibomian gland dropout score, lipid layer thickness, meibum expressibility score, meibum quality score, and incomplete blink rate were compared among the three groups using a one-way analysis of variance, and the least significant difference (LSD) test was used between two groups. The rank sum test was used for corneal fluorescein staining score among the three groups. All the statistics were regarded as statistically different when $P < 0.05$ (Table 1).

Table 1 Basic data and ocular surface evaluation of three groups

	PBC (n = 19)	DILI (n = 18)	HBV (n = 23)	Control (n = 30)	F	P
Sex (male: female)	4: 15	2: 16	10: 13	12: 18	–	–
Age (years)	56.00 ± 6.47	51.83 ± 3.68	53.7 ± 5.09	52.77 ± 7.84	1.600	0.20
SPEED score	5.37 ± 2.61	7.00 ± 4.51	7.74 ± 3.35	1.33 ± 1.24	24.544	0.00
First NITBUT (s)	3.65 ± 1.18	3.41 ± 0.74	4.33 ± 1.89	8.83 ± 3.02	38.496	0.00
Average NITBUT (s)	5.36 ± 2.74	5.10 ± 1.15	7.19 ± 3.56	10.92 ± 2.76	23.650	0.00
TMH (mm)	0.21 ± 0.05	0.20 ± 0.04	0.26 ± 0.05	0.25 ± 0.04	10.341	0.00
MG dropout of upper eyelid (%)	30.3 ± 11.45	24.28 ± 5.38	23.19 ± 8.83	17.95 ± 4.89	9.843	0.00
MG dropout of lower eyelid (%)	22.06 ± 10.9	28.25 ± 10.58	21.32 ± 9.12	16.80 ± 4.76	6.536	0.00
MG dropout score	2.79 ± 0.79	3.00 ± 0.69	2.78 ± 0.67	2.10 ± 0.31	10.673	0.00
CFS (score)	1.95 ± 1.65	0.56 ± 1.2	0.43 ± 0.95	0 ± 0.00	14.128	0.00
Schirmer I test (mm)	4.11 ± 5.00	11.33 ± 7.12	10.61 ± 6.75	15.15 ± 10.18	7.673	0.00
LLT (nm)	87.05 ± 8.26	67.44 ± 14.83	83.3 ± 12.55	84.53 ± 14.06	9.086	0.00
Meibum expressibility score	0.05 ± 0.23	1.94 ± 0.54	2.09 ± 0.73	0.07 ± 0.25	126.229	0.00
Meibum quality score	0.37 ± 1.12	6.67 ± 2.57	4.87 ± 2.42	0.03 ± 0.18	76.880	0.00
Total blinking, n	8.79 ± 3.51	10.44 ± 2.85	8.96 ± 3.17	7.53 ± 2.06	3.954	0.01
PBR (%)	92.69 ± 22.85	60.08 ± 10.47	80.33 ± 12.82	53.31 ± 21.75	22.419	0.00

NIKBUT, noninvasive breakup time; TMH, tear meniscus height; MG, meibomian gland; CFS, corneal fluorescein staining; LLT, lipid layer thickness; PBR, partial blinking rate

RESULTS

SPEED Questionnaire Score

The PBC group had a SPEED questionnaire score of 5.37 ± 2.61, the DILI group was 7.00 ± 4.51, the HBV was 7.74 ± 3.35, and the control group was 1.33 ± 1.24. There was a significant difference in SPEED scores among the four groups (F = 24.544, P = 0.00). There were no statistically differences among the three groups of different types of liver disease (Fig. 2A).

Corneal Fluorescein Staining Score (CFS)

The PBC group had a CFS score of 1.95 ± 1.65, the DILI group was 0.56 ± 1.2, the HBV group was 0.43 ± 0.95, and the control group was 0 ± 0. The corneal staining score of the PBC group was significantly higher than that of the other three groups ($P < 0.05$) (Fig. 2B).

Noninvasive Tear Film Breakup Time

The first tear film breakup time was 3.65 ± 1.18 s in the PBC group, 3.41 ± 0.74 s in the DILI group, 4.33 ± 1.89 s in the HBV group, and 8.83 ± 3.02 in the control group. There was significant difference in fNITBUT among the four groups (F = 38.496, P = 0.00). There was no significant statistical difference in fNITBUT among the three groups of different types of liver disease ($P > 0.05$). The average tear film breakup time was 5.36 ± 2.74 s in the PBC group, 5.10 ± 1.15 s in the DILI group, 7.19 ± 3.56 s in the HBV group, and

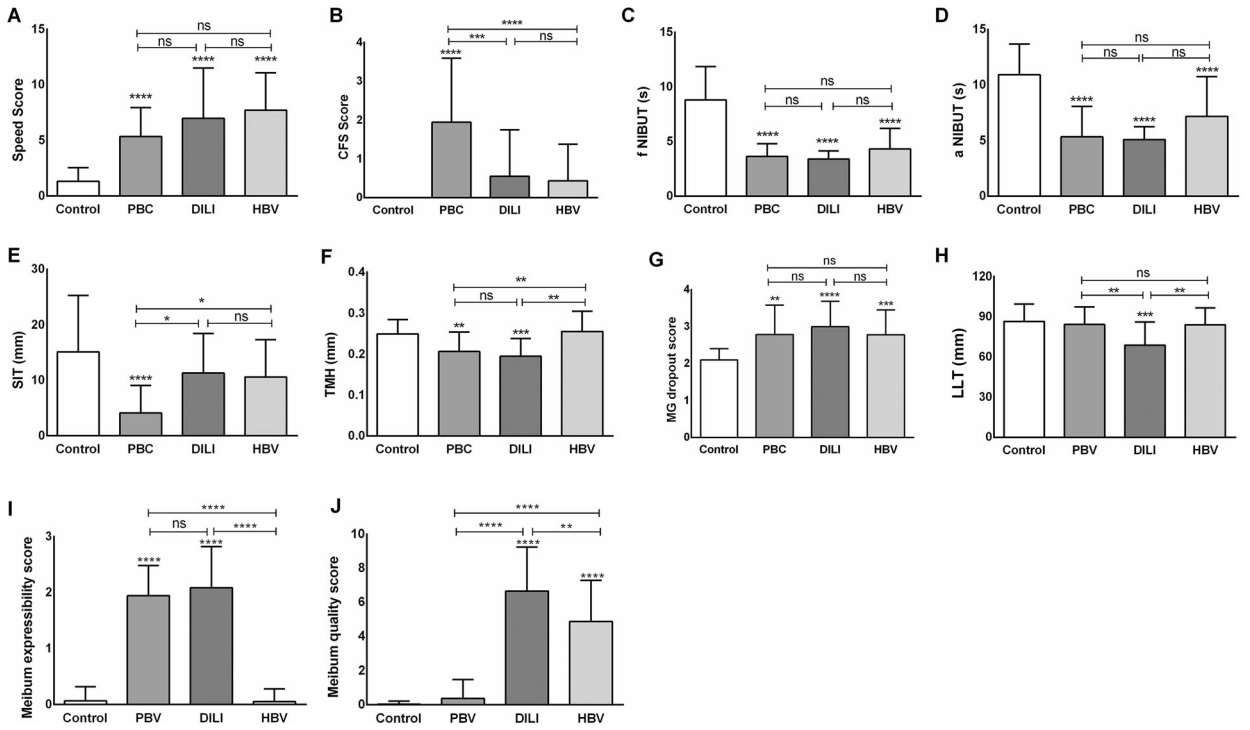

Fig. 2 Comparison of clinical characteristics of dry eye among PBC, DILI, and HBV groups. PBC, primary biliary cirrhosis; DILI, drug-induced liver injury; HBV, hepatitis B virus. **A** Speed score; **B** corneal fluorescein staining (CFS) score; **C** first NITBUT (f NIBUT); **D** average NITBUT (a NIBUT); **E** Schirmer I test (SIt); **F** tear meniscus height (TMH); **G** meibomian gland dropout (MG dropout) score; **H** lipid layer thickness (LLT); **I** meibum expressibility score; **J** meibum quality score; (*$P < 0.05$, **$P < 0.01$, ns, not significant $P > 0.05$)

8.83 ± 3.02 in the control group.There was a significant difference in aNITBUT among the four groups ($F = 23.65$, $P = 0.00$) but no significant difference in aNITBUT among the three groups of different types of liver disease ($P > 0.05$) (Fig. 2C, D).

Schirmer I Test

The SIT scores were 4.11 ± 5.00 mm in the PBC group, 11.33 ± 7.12 mm in the DILI group, 10.61 ± 6.75 mm in the HBV group, and 15.15 ± 10.18 mm in the control group. There was a significant difference in SIT among the four groups ($F = 7.673$, $P = 0.00$). The basal tear secretion in the primary biliary cirrhosis group was significantly lower than those in the DILI and HBV groups, and the difference was statistically significant ($P < 0.05$) (Fig. 2E).

Tear Meniscus Height (TMH)

The TMH was 0.21 ± 0.05 mm in the PBC group, 0.20 ± 0.04 mm in the DILI group, 0.26 ± 0.05 mm in the HBV group, and 0.25 ± 0.04 in the control group. The tear meniscus height in the PBC and DILI group were significantly lower than in the HBV group, and the difference was statistically significant ($P < 0.0$) (Fig. 2F).

Assessment of Meibomian Gland Dropout

In the PBC group, the upper eyelid was 30.3 ± 11.45%, the lower eyelid was 22.06 ± 10.9%, and the MG dropout score was 2.79 ± 0.79. In the DILI group, the upper eyelid was 24.28 ± 5.38%, the lower eyelid was 28.25 ± 10.58%, and the MG dropout score was

3.00 ± 0.69. In the HBV group, the upper eyelid was 23.19 ± 8.83%, and the lower eyelid was 21.32 ± 9.12%, so the MG dropout score was 2.78 ± 0.67. In the control group, the upper eyelid was 17.95 ± 4.89%, and the lower eyelid was 16.80 ± 4.76%, so the MG dropout score was 2.10 ± 0.31. There was a significant difference in the MG dropout score among the four groups ($F = 10.673$, $P = 0.00$). There was no significant difference in the MG dropout score among the three groups of different types of liver disease ($P > 0.05$) ($F = 0.32$, $P = 0.73$) (Fig. 2G).

Lipid Layer Thickness

The LLT in the PBC group was 87.05 ± 8.26 nm, in the DILI group it was 67.44 ± 14.83 nm, in the HBV group it was 83.3 ± 12.55 nm, and in the control group it was 84.53 ± 14.06 nm. The LLT in the DILI group was significantly lower than in the PBC and HBV groups, and the difference were significant ($P < 0.05$), but there was no significant statistical difference between the PBV and the HBV groups ($P = 0.06$) (Fig. 2H).

Partial Blinking Rate

The PRB in the PBC group was 92.69 ± 22.85%, in the DILI group it was 60.08 ± 10.47%, in the HBV group it was 80.33 ± 12.82%, and in the control group it was 53.31 ± 21.75%. There was a significant difference in the PRB among the four groups ($F = 22.419$, $P = 0.00$).

Meibum Expressibility

The meibum expressibility score of the PBC group was 0.05 ± 0.23, the DILI group score was 1.94 ± 0.54, the HBV group score was 2.09 ± 0.73, and the control group score was 0.07 ± 0.25. The meibum expressibility score in the PBC group was significantly lower than those of the DILI and HBV groups ($P < 0.05$), but there was no significant difference between the DILI and the HBV groups ($P = 0.35$) (Fig. 2I).

Meibum Quality

The meibum quality score of the PBC group was 0.37 ± 1.12, the DILI group score was 6.67 ± 2.57, the HBV group score was 4.87 ± 2.42, and the control group score was 0.03 ± 0.18. There was a significant difference in meibum quality scores among the four groups ($P = 0.00$), and the meibum quality score in the DILI group was significantly higher than the HBV group ($P = 0.00$) (Fig. 2J).

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. Of the 350 million people infected with HBV worldwide, 33% live in China [19]. Viral 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 cells, or both, directed to different host tissue [20]. 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 [21]. We have reported for the first time that hepatitis B virus infection is related to the occurrence of dry eye in mainland China. The tear film is divided into three layers: the lipid layer, the aqueous layer, and the mucin layer. The Schirmer I test of patients with hepatitis B virus was 10.61 ± 6.75 mm, and the TMH was normal, indicating that the aqueous layer is normal. Although the meibum expressibility score was greater than 1, the meibomian glands have mild-to-moderate deletions with an LLT of 83.3 ± 12.55 nm, and the quality of expressed meibum was mostly clear fluid, which is more prone to nonobstructive 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 an immune response, but by meibomian gland dysfunction.

DILI is a common liver disease that 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. The meibum expressibility score was greater than 1, and meibum quality score was greater than 5, which is mainly manifested as obstructive meibomian gland dysfunction [22]. 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 the study by Hwang et al. was lower, at 45.2 ± 11.6 nm [23]. In obstructive MGD, the value of LLT is negatively correlated with the loss of upper and lower meibomian glands [24]. In addition, LLT is also related to gender and age. The LLT of the elderly and of women may be higher [25]. Considering the sex and age factors of the patients in the DILI group, the type of dry eye was more consistent with obstructive MGD. The long-term, excessive, and irregular application of systemic drugs can not only cause liver cell damage, but also meibomian gland atrophy, which can lead to changes in lipid secretion and tear osmotic and film stability. Examples include anticholinergics, including antidepressant, antipsychotic, anti-Parkinson, antihistamine, and antispastic drugs. 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 [26].

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 [27]. The most common extrahepatic manifestation of PBC is Sjogren's syndrome [28], which mainly causes aqueous tear-deficient dry eye. This is consistent with our 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 [29]. In addition, our study show that the SPEED scores of the PBC, DILI, and HBV groups all had mild-to-moderate dry eye symptoms, but the corneal fluorescence staining scores of the PBC group were significantly higher than those of the other two groups. This 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 [30] also found 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 the corneal subepithelial nerve fibers [31]. Rahman [32] also ound 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 the 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 [33]. Kim [34] also demonstrated that an 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.

This 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, with a more comprehensive and more detailed observation will be more convincing.

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

ACKNOWLEDGEMENTS

Funding. No funds, grants, or other support were received. The journal's Rapid Service fee was funded by the authors.

Author Contributions. Shang Li, Ao Li, Fang Ruan, and Ying Jie conceived and designed the experiments. Shang Li, Fang Ruan, Wei Zhang, Jie Chen, Chunyang Huang, and Ying Jie performed the experiments. Shang Li, Ao Li, and Ying Jie analyzed the data. Shang Li, Ao Li, and Ying Jie wrote the paper. All authors have read and approved the manuscript and ensure that this is the case.

Disclosures. Shang Li, Ao Li, Fang Ruan, Wei Zhang, Jie Chen, Chunyang Huang, and Ying Jie confirm that they have no conflicts of interest to declare.

Prior Presentation. A preprint has previously been published on Research Square on December 14, 2021 [35].

Compliance with Ethics Guidelines. The study was approved by the Ethics Committee of Beijing Youan hospital and followed the guidelines of the Declaration of Helsinki. As a retrospective study patient consent for inclusion in this study was not required.

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

REFERENCES

1. Lemp MA. Advances in understanding and managing dry eye disease. Am J Ophthalmol. 2008;146:350–6.

2. Schaumberg DA, Sullivan DA, Dana MR. Epidemiology of dry eye syndrome. Adv Exp Med Biol. 2002;506(Pt B):989–98.

3. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. Cornea. 2000;19:644–9.

4. Selmi C, Meroni PL, Gershwin ME. Primary biliary cirrhosis and Sjögren's syndrome: autoimmune epithelitis. J Autoimmun. 2012;39:34–42.

5. Wang T-J, Wang I-J, Hu C-C, Lin H-C. Comorbidities of dry eye disease: a nationwide population-based study. Acta Ophthalmol. 2012;90:663–8.

6. Green RM, Flamm S. AGA technical review on the evaluation of liver chemistry tests. Gastroenterology. 2002;123:1367–84.

7. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II diagnostic methodology report. Ocul Surf. 2017;15:539–74.

8. Liu ZG, Liu J, Yang WZ. Emphasizing clinical investigation on anti-inflammatory therapy of dry eye. Zhonghua Shiyan Yanke Zazhi/Chin J Exp Ophthalmol. 2013;31:417–20.

9. Finis D, Pischel N, Knig C, Hayajneh J, Geerling G. Comparison of the OSDI and SPEED questionnaires for the evaluation of dry eye disease in clinical routine. Ophthalmologe. 2014;111:1050–6.

10. Whitcher JP, Shiboski CH, Shiboski SC, Heidenreich AM, Kitagawa K, Zhang S, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol. 2010;149:405–15.

11. Ichihashi Y, Ide T, Kaido M, Ishida R, Hatou S, Tsubota K. Short break-up time type dry eye has potential ocular surface abnormalities. Taiwan J Ophthalmol. 2015;5:68–71.

12. Labbé A, Brignole-Baudouin F, Baudouin C. Ocular surface investigations in dry eye. J Francais Ophtalmol. 2007;30:76–97.

13. Baek J, Doh SH, Chung SK. Comparison of tear meniscus height measurements obtained with the keratograph and fourier domain optical coherence tomography in dry eye. Cornea. 2015;34:1209–13.

14. Nichols JJ, Berntsen DA, Mitchell GL, Nichols KK. An assessment of grading scales for meibography images. Cornea. 2005;24:382–8.

15. Arita R, Itoh K, Inoue K, Amano S. Noncontact infrared meibography to document age-related changes of the meibomian glands in a normal population. Ophthalmology. 2008;115:911–5.

16. Finis D, Pischel N, Schrader S, Geerling G. Evaluation of lipid layer thickness measurement of the tear film as a diagnostic tool for Meibomian gland dysfunction. Cornea. 2013;32:1549–53.

17. Pflugfelder SC, Tseng SC, Sanabria O, Kell H, Garcia CG, Felix C, et al. Evaluation of subjective assessments and objective diagnostic tests for diagnosing tear-film disorders known to cause ocular irritation. Cornea. 1998;17:38–56.

18 Bron AJ, Benjamin L, Snibson GR. Meibomian gland disease. Classification and grading of lid changes. Eye (Lond). 1991;5(Pt 4):395–411.

19. Wright TL. Introduction to chronic hepatitis B infection. Am J Gastroenterol. 2006;101(Suppl 1):S1-6.

20. Moutsopoulos HM, Papadopoulos GK. Possible viral implication in the pathogenesis of Sjögren's syndrome. Eur J Med. 1992;1:219–23.

21. Alves M, Angerami RN, Rocha EM. Dry eye disease caused by viral infection: review. Arq Bras Oftalmol. 2013;76:129–32.

22. Arita R, Itoh K, Maeda S, Maeda K, Furuta A, Fukuoka S, et al. Proposed diagnostic criteria for obstructive meibomian gland dysfunction. Ophthalmology. 2009;116:2058-2063.e1.

23. Image-based quantitative analysis of tear film lipid layer thickness for meibomian gland evaluation—PubMed. https://pubmed.ncbi.nlm.nih.gov/29169367/. Accessed 16 Apr 2023.

24. Eom Y, Lee J-S, Kang S-Y, Kim HM, Song J-S. Correlation between quantitative measurements of tear film lipid layer thickness and meibomian gland loss in patients with obstructive meibomian gland dysfunction and normal controls. Am J Ophthalmol. 2013;155:1104-1110.e2.

25. Jung JW, Park SY, Kim JS, Kim EK, Seo KY, Kim T-I. Analysis of factors associated with the tear film lipid layer thickness in normal eyes and patients with dry eye syndrome. Invest Ophthalmol Vis Sci. 2016;57:4076–83.

26. Kam WR, Sullivan DA. Neurotransmitter influence on human meibomian gland epithelial cells. Invest Ophthalmol Vis Sci. 2011;52:8543–8.

27. Zang S, Cui Y, Cui Y, Fei W. Meibomian gland dropout in Sjögren's syndrome and non-Sjögren's dry eye patients. Eye (Lond). 2018;32:1681–7.

28. Floreani A, Cazzagon N. PBC and related extrahepatic diseases. Best Pract Res Clin Gastroenterol. 2018;34–35:49–54.

29. Selmi C, Gershwin ME. Chronic autoimmune epithelitis in Sjögren's syndrome and primary biliary cholangitis: a comprehensive review. Rheumatol Ther. 2017;4:263–79.

30. Adatia FA, Michaeli-Cohen A, Naor J, Caffery B, Bookman A, Slomovic A. Correlation between corneal sensitivity, subjective dry eye symptoms and corneal staining in Sjögren's syndrome. Can J Ophthalmol. 2004;39:767–71.

31. Effects of corneal nerve density on the response to treatment in dry eye disease—PubMed. https://pubmed.ncbi.nlm.nih.gov/25542519/. Accessed 16 Apr 2023.

32. Rahman EZ, Lam PK, Chu C-K, Moore Q, Pflugfelder SC. Corneal sensitivity in tear dysfunction and its correlation with clinical parameters and blink rate. Am J Ophthalmol. 2015;160:858-866.e5.

33. Jie Y, Sella R, Feng J, Gomez ML, Afshari NA. Evaluation of incomplete blinking as a measurement of dry eye disease. Ocul Surf. 2019;17:440–6.

34. Kim AD, Muntz A, Lee J, Wang MTM, Craig JP. Therapeutic benefits of blinking exercises in dry eye disease. Cont Lens Anterior Eye. 2021;44: 101329.

35. Shang Li, Ao Li, Fang Ruan, Wei Zhang, Jie Chen, Chunyang Huang, Ying Jie. Evaluation of the clinical characteristics of dry eye secondary to different types of liver diseases. Research Square. [Preprint]. December 14, 2021, Available from: https://www.researchsquare.com/article/rs-1097557/v1.