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# Clinical Characteristics of *K. pneumoniae* Related Endogenous Endophthalmitis in China

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**Purpose:** To investigate the clinical characteristics and systemic risk factors of *K. pneumoniae* related endogenous endophthalmitis (KPREE) in China and explore the possible pathophysiological mechanisms.

**Methods:** This was a retrospective comparative study. All enrolled KPREE patients were followed up for at least 1 month to observe their clinical characteristics, unfavorable prognosis, and risk factors, and were compared with intraocular surgery-related postoperative endophthalmitis (ISRPE).

**Results:** Finally, a total of 15 eyes (3 both eyes) from 12 patients were enrolled in KPREE group, and 11 eyes (none both eyes) from 11 patients were enrolled in ISRPE group. Compared to the ISRPE group, the KPREE group had a higher percentage of fever (100% vs 9.09%, P = 0.000), liver abscess (91.67% vs 0%, P = 0.000), lung involvement (50.00% vs 0%, P = 0.024), and lower plasma albumin levels (24.1 [17.8, 31.7] vs 44.0 [37.7, 48.4], P = 0.001). Furthermore, Pearson's partial correlation analysis showed that fever (adjusted r = 0.592, adjusted P = 0.026) and plasma albumin (adjusted r = −0.658, adjusted P = 0.011) were independent factors associated with KPREE. In the KPREE group, ten eyes received 1–3 intravitreal antibiotic injections within one month. In the ten eyes that underwent injections, due to poor treatment reaction, four eyes experienced evisceration, and two eyes underwent vitrectomy with silicone oil tamponade at 1-month follow-up. And one eye developed sympathetic ophthalmia at 8-month visit.

**Conclusions:** Patients with *K. pneumoniae* infection with hypoproteinemia or fever should be highly vigilant about the occurrence of KPREE, and more attention should be paid to the contralateral risk of KPREE or sympathetic ophthalmia.

**Keywords:** *K. pneumoniae*, endogenous endophthalmitis, postoperative endophthalmitis, sympathetic ophthalmia, no light perception

## Introduction

*K. pneumoniae* bacteremia often causes metastatic infections in multiple areas, especially in the liver, lungs, brain, urinary tract, eyeballs, and orbits.[1–3] Among them, endogenous endophthalmitis is one of the rare but devastating complications of *K. pneumoniae* bacteremia in East Asia, Southeast Asia, and even globally, and it is increasing day by day.[2,4,5] *K. pneumoniae* related endogenous endophthalmitis (KPREE) often leads to unfavorable ocular outcomes such as no light perception (NLP), hypotony, and evisceration, and up to 25% of patients are affected bilaterally.[1,6]

KPREE is induced by *K. pneumoniae*, a type of gram-negative bacteria that is commonly found in the human gut and respiratory tract, often affecting patients with low immunity, diabetes, or liver abscess.[3,4,7–10] Intraocular surgery-related postoperative endophthalmitis (ISRPE), which is mainly caused by gram-positive bacteria, also easily occurs in immunosuppressed patients or patients with diabetes.[11,12]

However, although there are many options to treat KPREE, including intravitreal antibiotic injections, systematic treatment with appropriate antibiotics, and vitrectomy with or without silicone oil tamponade, the results are often unsatisfactory.[1,3] Furthermore, the differences in clinical characteristics and systemic risk factors between these two types

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of endophthalmitis are rarely reported in the literature. Therefore, we conducted a comparative study among Chinese populations.

# Methods

## Participants and Baseline Assessments

KPREE occurred in 12 patients evaluated at the Weihai Central Hospital Affiliated to Qingdao University between February 2019 and February 2023. The clinical characteristics and systemic risk factors of KPREE were retrospectively reviewed and compared with those of ISRPE in 11 other cases without any intraoperative complications during the same period. Institutional Review Board approval was obtained from Weihai Central Hospital Affiliated to Qingdao University, and this study adhered to the tenets of the Declaration of Helsinki (approval No. LL-2024-034). The Board waived the requirement for written consent because of the retrospective nature of the study. All analyzed data were anonymized and de-identified.

Demographic data (age, sex, and laterality) and medical history (arterial hypertension, diabetes, and other severe systemic diseases) were collected from the inpatient or outpatient electronic medical record system. Systemic parameters (such as the presence of fever, routine blood tests, plasma albumin, and procalcitonin) and important complications (such as liver, lung, and brain abscesses) were collected during enrollment. Inclusion criteria: All patients with KPREE were included in the KPREE group, regardless of whether the first affected organ was the eye; all patients with ISRPE were included in the ISRPE group; and the types of intraocular surgeries included cataract phacoemulsification combined with intraocular lens implantation and intravitreal injection. The exclusion criteria for this study were as follows: (1) fungal endophthalmitis and aseptic endophthalmitis, (2) endophthalmitis following open eye trauma, and (3) follow-up period of <1 month.

All enrolled subjects were subjected to a series of ocular examinations as follows: (1) best-corrected visual acuity (BCVA), (2) intraocular pressure (IOP) through non-contact tonometer, (3) slit-lamp microscopy, and (4) ocular B-ultrasound scan. For patients with a predisposition to orbital involvement, magnetic resonance imaging or computed tomography was performed for further evaluation. All enrolled patients were followed up for at least 1 month and up to 12 months. The baseline was defined as the first ocular assessment at enrollment conducted by the same ophthalmologist (SS). Hypoproteinemia was defined as a plasma albumin level <35 g/L. Lung involvement was defined as a pulmonary abscess, pyothorax, or pneumonia. Ocular hypertension (OHT) was defined as IOP >21 mmHg.

## Definitions of Terms and Representative Images in This Study

*KPREE* was defined as typical clinical manifestations of endophthalmitis (such as hypopyon [Figure 1A, white arrow], severe fibrinous exudates [Figure 1A, blue arrow], liver abscess [Figure 1B, red asterisk], yellow-white infectious lesion [Figure 1C, yellow arrow] on fundus, and abnormalities on optical coherence tomography (Figure 1D)) in combination with positive *K. pneumoniae* culture of vitreous aspirates or positive *K. pneumoniae* high-throughput gene detection with metagenomic next-generation sequencing technology (mNGS) of intraocular fluid, accompanied by evidence of *K. pneumoniae* bacteremia (such as positive culture or positive *K. pneumoniae* high-throughput gene detection of blood or liver puncture drainage fluid).

*ISRPE* was defined as typical clinical manifestations of postoperative endophthalmitis following intraocular surgery (such as hypopyon [Figure 1E, white arrow] et al), with either bacterial smear of gram-positive/-negative bacterium or positive bacterial culture of intraocular fluid, without any evidence of *K. pneumoniae* bacteria in the intraocular fluid (neither positive culture nor positive mNGS). With aggressive and standardized treatment, ISRPE usually has a favorable prognosis (Figure 1F).

*Unfavorable ocular outcomes* were defined as NLP, hypotony (Figure 1G and H), evisceration and (or) sympathetic ophthalmia (SO).

## Bacterial Culture and mNGS Analysis

Vitreous aspirates were placed in 1 mL phosphate buffer saline as a sterile transport medium and sent to the microbiology laboratory. The sterile pipette was used to transfer the sample onto a chocolate agar plate (approximately 0.1 mL). The

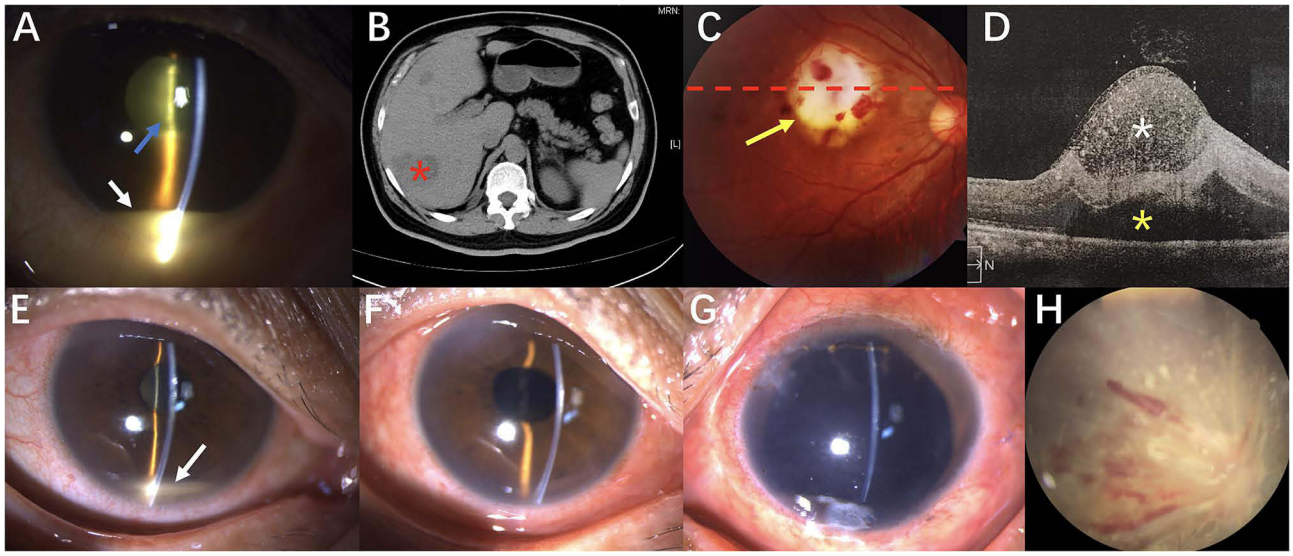


**Figure 1** Representative clinical features of *K. pneumoniae* related endogenous endophthalmitis (KPREE) and intraocular surgery related postoperative endophthalmitis (ISRPE). A 61-year-old female (case 3) was diagnosed with KPREE due to 1-day left blurred vision, 3-day eye pain and 10-day fever, at the post-operative 4-month visit of hilar cholangiocarcinoma. (**A**) The slit-lamp photography showing 2-mm hypopyon (white arrow), cloudy aqueous humor, and severe fibrinous exudates on the surface of the lens (blue arrow). (**B**) A computed tomography on the abdomen showing a liver abscess with the size of 4 cm in diameter (red asterisk). A 40-year-old male (case 4) was diagnosed with KPREE due to 6-hour right central scotoma following a 2-day fever history, without any past medical history. (**C**) The color fundus photography showing a yellow-white infectious lesion (yellow arrow) located superior the fovea with a 2-disc diameter size, leaving several bleeding spots around the lesion margin. (**D**) Optical coherence tomography scanning of the infectious lesion along the red dotted line in C showing a highly reflective signal (white asterisk) and subretinal fluid (yellow asterisk). A 64-year-old female was diagnosed with ISRPE due to 1-day right sudden vision loss, following a prior 3-day history of cataract phacoemulsification combined with intraocular lens implantation, without previous diabetes. (**E**) The slit-lamp photography showing congested conjunctiva, 1-mm hypopyon (white arrow), and cloudy aqueous humor. (**F**) Slit-lamp photography at the 2-week visit after intravitreal injection (1 mg of vancomycin) showed absence of hypopyon. A 48-year-old male (case 5) was diagnosed with KPREE due to 5-day left decreased vision with eye redness and pain, following 4-day fever, with a 1-year uncontrolled diabetes history (with plasma hemoglobin A1C of up to 9.4% and maximum IOP of 35 mmHg). (**G**) Slit-lamp photography at the 1-month follow-up showing severe iridocolobom, aphakia, and intraocular silicone oil tamponade. (**H**) Color fundus photography taken on the same day as shown in G showing a pale retina, superficial flame-like hemorrhage, and complete retinal vascular whitening.

plate was incubated in a $CO_2$ incubator at 37 °C, 5% $CO_2$, and checked daily for bacterial growth for a week. Bacterial identification was determined by an automated identification system (VITEK 2 XL) and mass spectrometry microbial identification (VITEK MS, France).

High-throughput gene detection with mNGS of intraocular fluid was performed as follows: Bacterial DNA was extracted using the QIAamp DNA Microbiome Kit (QIAGEN, Germany) and subjected to 16S metagenomic sequencing library preparation. 16S rRNA gene was amplified using 341F and 805R primers. Subsequently, 16S amplicons were purified using sparQ Puremag Beads (Quantabio, USA), followed by 10 cycles of amplification. The raw sequences were categorized into groups based on the 5' barcode sequences.

## Statistical Analysis

All calculations were performed using SPSS Statistics for Windows (version 25.0; IBM Corp). Continuous variables were recorded as median (range), and categorical variables as counts and percentages. BCVA was converted to the logarithm of the minimum angle of resolution (log MAR) units for analysis. For BCVA of counting fingers or worse, the following conversion was used: counting fingers, 2.0 log MAR; hand movements, 2.3 log MAR; light perception, 2.6 log MAR; and NLP, 2.9 log MAR.[13]

First, the Mann–Whitney *U*-test was used to compare continuous variables, and the chi-square test was used to compare categorical variables between the two groups (KPREE and ISRPE groups). Pearson's correlation analysis was used to screen the risk factors most associated with KPREE occurrence, with variables ($P < 0.05$) from Table 1 (fever duration, liver abscess, lung involvement, plasma albumin) as candidate parameters. The Pearson's correlation coefficients were calculated. Pearson's partial correlation analysis was used to screen independent risk factors associated with KPREE occurrence. Third, Spearman rank-based correlation analysis was performed between the final NLP and the

**Table 1** Demographic and Clinical Features of All Enrolled Patients

| Parameters | All patients (n=23) | KPREE (n=12) | ISRPE (n=11) | *p* value |
|---|---|---|---|---|
| Demographic | | | | |
| Sex (male/female) | 10/13 | 7/5 | 3/8 | 0.280 |
| Age (years) | 64(36,86) | 62(40,76) | 69(36,86) | 0.147 |
| Laterality (right/left/bilateral) | 9/11/3 | 4/5/3 | 5/6/0 | 0.206 |
| Systemic features | | | | |
| Fever | 13(56.52) | 12(100) | 1(9.09) | 0.000 |
| Liver abscess | 11(47.83) | 11(91.67) | 0(0.00) | 0.000 |
| Lung involvement | 6(26.09) | 6(50.00) | 0(0.00) | 0.024 |
| Brain abscess | 4(17.39) | 2(16.67) | 2(18.18) | 1.000 |
| Arterial hypertension | 11(47.83) | 4(33.33) | 7(63.64) | 0.146 |
| Diabetes | 13(56.52) | 7(58.33) | 6(54.55) | 1.000 |
| Plasma albumin levels (g/L) | 28.2(17.8,48.4) | 24.1(17.8,31.7) | 44.0(37.7,48.4) | 0.001 |
| | **All eyes (n=26)** | **KPREE (n=15)** | **ISRPE (n=11)** | |
| Ocular features | | | | |
| Interval from initial eye presentation to baseline (days) | 1(1,13) | 1(1,13) | 2(1,7) | 0.524 |
| BCVA at baseline (log MAR) | 2.3(0.7,2.9) | 2.6(0.7,2.9) | 2.3(1.4,2.6) | 0.017 |
| NLP at baseline | 5(19.23) | 5(33.33) | 0 (0) | 0.104 |
| OHTwithin 1 week after initial eye presentation onset | 11(42.31) | 11(73.33) | 1(9.09) | 0.001 |
| NLP at final visit | 10(38.46) | 10(66.67) | 0(0) | 0.002 |
| Evisceration at final visit | 4(15.38) | 4(26.67) | 0(0) | 0.190 |

**Notes**: Lung involvement was defined as pulmonary abscess, pyothorax, or pneumonia. Data were presented as n. (%) or median (range). Mann–Whitney *U*-test was used to compare continuous variables, and the chi-squared test was used to compare categorical variables.
**Abbreviations**: BCVA, best-corrected visual acuity; ISRPE, intraocular surgery related postoperative endophthalmitis; KPREE, *K. pneumoniae* related endogenous endophthalmitis; log MAR, logarithm of the minimum angle of resolution; NLP, no light perception; OHT, ocular hypertension.

potential risk factors (P < 0.05) from Table 1 (BCVA at baseline, fever duration, liver abscess, lung involvement, plasma albumin, plasma procalcitonin, and post-baseline 1-week OHT). Spearman's rank-based correlation coefficients were calculated. Statistical significance was defined as a 2-sided P value <0.05. A strong correlation was defined as a correlation coefficient greater than 0.8.

# Results

## Demographic and Clinical Characteristics of All Enrolled Cases

Finally, a total of 15 eyes (4 right eyes vs 5 left eyes vs 3 both eyes) from 12 patients (7 males vs 5 females) were enrolled in KPREE group, and 11 eyes (5 right eyes vs 6 left eyes) from 11 patients (3 males vs 8 females) were enrolled in ISRPE group, without statistically significance in the sex distribution (P = 0.280), age (62 [40, 76] vs 69 [36, 86], P = 0.147), laterality distribution (P = 0.206), brain abscess (16.67% vs 18.18%, P = 1.000), arterial hypertension (33.33% vs 63.64%, P = 0.146), diabetes (58.33% vs 54.55%, P = 1.000), interval from initial eye presentation to baseline (1 [1, 13] vs 2 [1, 7], P = 0.524), NLP at baseline (33.33% vs 0%, P = 0.104) and evisceration at final visit (26.67% vs 0%, P = 0.190). In the ISRPE group, 10 eyes experienced post-operative endophthalmitis following cataract phacoemulsification combined with intraocular lens implantation, and 1 eye developed post-operative endophthalmitis induced by intravitreal anti-vascular endothelial growth factor injection due to wet age-related macular degeneration.

Compared with the ISRPE group, more patients in the KPREE group had fever (100% vs 9.09%, P = 0.000), liver abscess (91.67% vs 0%, P = 0.000), lung involvement (50.00% vs 0%, P = 0.024), and more eyes experienced OHT within 1 week after the initial eye presentation onset (73.33% vs 9.09%, P = 0.001), and NLP at the final visit (66.67% vs 0%, P = 0.002). In addition, there was lower plasma albumin (24.1 [17.8,31.7] vs 44.0 [37.7, 48.4], P = 0.001) and worse BCVA at baseline (2.6

[0.7, 2.9] vs 2.3 [1.4, 2.6], P = 0.017) in the KPREE group than in the ISRPE groups. The demographic and clinical characteristics of the 23 patients enrolled in both groups are listed in Table 1 and depicted in Figure 2.

## Possible Causes and Pearson's Correlation Analysis for KPREE

To screen for the most possible causes associated with KPREE, we considered the above parameters with statistical differences (P < 0.05) between the two groups as candidate parameters. Pearson's correlation analysis showed a statistically strong correlation between KPREE and the presence of fever (r = 0.916, P = 0.000), liver abscess (r = 0.917, P = 0.000), and plasma albumin (r = −0.929, P = 0.000), with the exception of lung involvement (r = 0.423, P = 0.103). Further partial correlation analysis showed that the presence of fever (adjusted r = 0.592, adjusted P = 0.026) and plasma albumin (adjusted r = −0.658, adjusted P = 0.011) were independent factors associated with KPREE. The possible causes and Pearson's correlation analysis for KPREE are shown in Table 2.

## Potential Risk Factors for Final NLP in the KPREE Group

Of the 15 eyes in the KPREE group, 10 (66.67%) eventually developed NLP. To screen the most valuable risk factors that led to the final NLP, we considered the above parameters with statistical differences (P < 0.05) between the two groups as potential risk factors. Simultaneously, fever duration and plasma procalcitonin level were also added as potential risk factors. Further Spearman rank-based correlation analysis for final NLP showed that BCVA at baseline was the only statistically significant risk factor (β = 0.664, P = 0.007), without statistical significance for fever duration, liver abscess, lung involvement, plasma albumin, plasma procalcitonin, and post-baseline 1-week OHT (P = 0.473, 0.500, 0.884, 0.559, 0.375, and 0.115, respectively). The potential risk factors and Spearman rank-based correlation analysis for the final NLP are shown in Table 3.

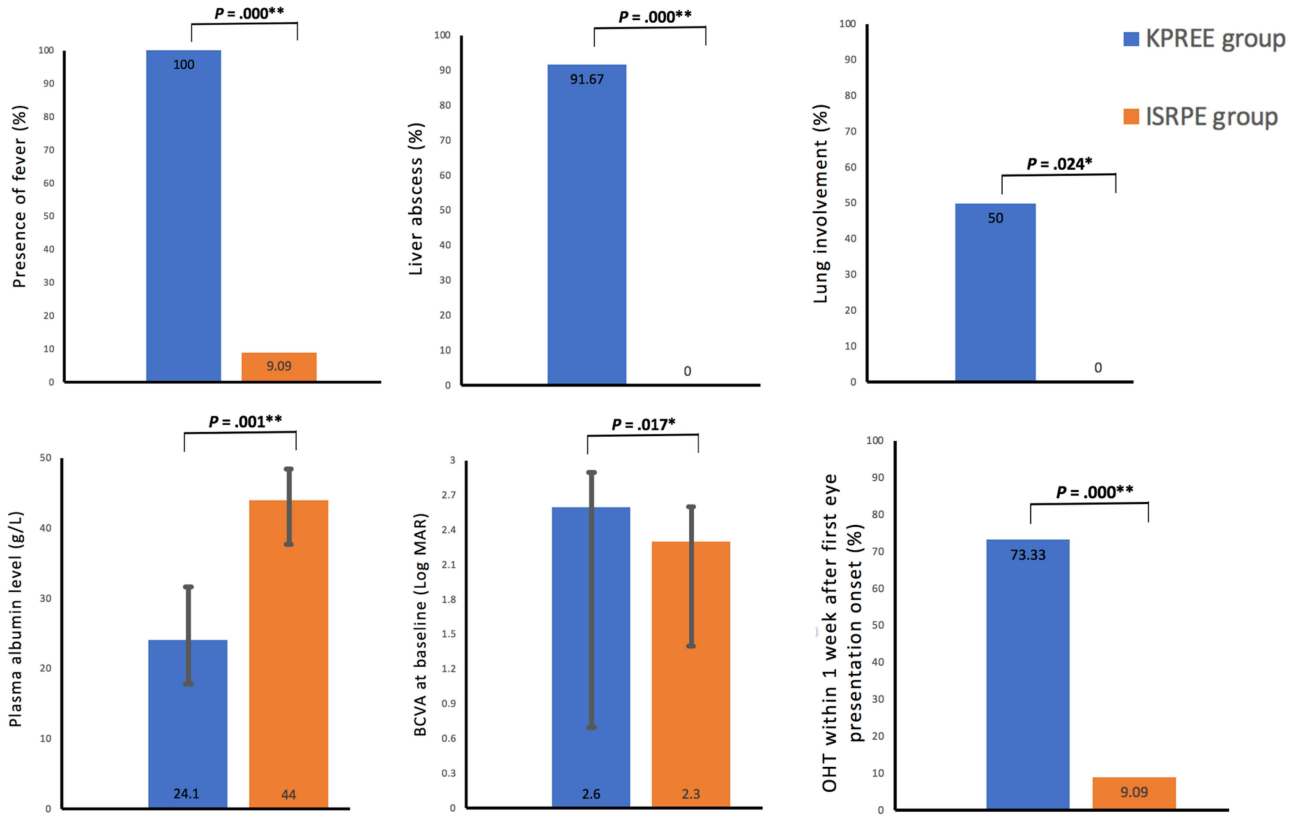


**Figure 2** Clinical characteristics with statistical differences between the two groups. * *P* < 0.05; ** *P* < 0.01.
**Abbreviations**: BCVA, best-corrected visual acuity; ISRPE, intraocular surgery related postoperative endophthalmitis; KPREE, *K. pneumoniae* related endogenous endophthalmitis; log MAR, logarithm of the minimum angle of resolution; OHT, ocular hypertension.

**Table 2** Possible Causes and Pearson's Correlation Analysis for KPREE

| Possible Causes (N=23) | | Pearson's Correlation for KPREE | | | |
|---|---|---|---|---|---|
| | | *r* | *P** | *Adjusted r* | *Adjusted P*** |
| Fever, N=13, (n, %) | 12 (92.3) | 0.916 | 0.000 | 0.592 | 0.026 |
| Liver abscess, N=11, (n, %) | 11 (100) | 0.917 | 0.000 | 0.335 | 0.242 |
| Lung involvement, # N=6, (n, %) | 6 (100) | 0.423 | 0.103 | – | – |
| Plasma albumin, (median [range], g/L) | 24.1 (17.8, 31.7) | −0.929 | 0.000 | −0.658 | 0.011 |

**Notes**: #Lung involvement was defined as pulmonary abscess, pyothorax, or pneumonia. n indicating patients with KPREE. Strong correlation was defined as a correlation coefficient greater than 0.8. *Pearson's correlation analysis. **Pearson's partial correlation analysis.
**Abbreviation**: KPREE, *K. pneumoniae* related endogenous endophthalmitis.

**Table 3** Potential Risk Factors and Spearman Rank-Based Correlation Analysis for Final NLP

| Potential Risk Factors (N=15) | | Spearman Rank-Based Correlation for Final NLP | |
|---|---|---|---|
| | | *β* | *P** |
| BCVA at baseline, (median [range], log MAR) | 2.6 (0.7, 2.9) | 0.664 | **0.007** |
| Fever duration, (median [range], days) | 9 (2, 10) | 0.209 | 0.473 |
| Liver abscess, N=14, (n, %) | 9 (64.29%) | −0.189 | 0.500 |
| Lung involvement, # N=8, (n, %) | 5 (62.50%) | −0.043 | 0.884 |
| Plasma albumin, (median [range], g/L) | 25.3 (17.8, 31.7) | 0.179 | 0.559 |
| Plasma procalcitonin, (median [range], ng/mL) | 6.92 (0.08, 100) | −0.268 | 0.375 |
| Post-baseline 1-week OHT, N=11, (n, %) | 9 (81.82%) | 0.440 | 0.115 |

**Notes**: #Lung involvement was defined as pulmonary abscess, pyothorax, or pneumonia.; n indicating patients with final NLP. *Spearman rank-based correlation analysis. Significant *P* values ($P < 0.05$) are in bold font.
**Abbreviations**: BCVA, best-corrected visual acuity; log MAR, logarithm of the minimum angle of resolution; NLP, no light perception; OHT, ocular hypertension.

## Unfavorable Ocular Outcomes in the KPREE Group

Among the 15 eyes from 12 patients in the KPREE group, only two eyes (cases 4 and 5) were followed up for more than 1 month. Within the first month, ten eyes (10/15) received 1–3 intravitreal antibiotic injections. In the ten eyes that underwent injections, due to poor treatment reaction, four eyes (4/15) experienced evisceration, and two eyes (2/15) underwent vitrectomy with silicone oil tamponade at 1-month follow-up. And one eye (1/15) developed sympathetic ophthalmia at 8-month visit. Of the 12 patients with KPREE, the first organ to be affected was most often the liver (6/12), followed by the eye(s) (3/12), and then the lungs (3/12). Most of the pathogenic evidence (10/12) was obtained through bacterial culture of vitreous aspirates, with one patient (case 6) receiving mNGS of intraocular fluid and one patient (case 5) receiving both bacterial culture and mNGS. Fever occurred in 11 patients, with a median fever duration of (8 [2,10]) days and a median serum procalcitonin concentration of (6.92 [0.08, 100]) ng/mL. Liver abscesses occurred in 91.7% of patients (11 cases), yet only 36.4% of liver abscesses (4 cases) were secondary to prior liver disease (one cirrhosis with hepatitis B virus carrier, one hilar cholangiocarcinoma, one decompensated phase of liver cirrhosis, and one hepatitis B virus carrier).

It is important to note that 25% of the patients (3 cases) in the KPREE group had binocular involvement, while none in the ISRPE group had binocular involvement. A 63-year-old man with binocular KPREE (case 8), with an extremely high serum procalcitonin level of 100 ng/mL, died of acute myocardial infarction secondary to sepsis. The other two patients (cases 4 and 5) who were followed up for more than 1 month both developed hypotony at the 12-month follow-up. Among them, case 5 developed SO in both eyes at the 8-month follow-up visit. The demographic and detailed clinical characteristics of the 12 patients enrolled in the KPREE group are shown in Table 4.

**Table 4** The Demographic and Detailed Clinical Characteristics of All 12 Cases Enrolled in the KPREE Group

| Case No. | Follow-Up (Months) | Initial Involved Organ | Sex/ Age | Laterality | Pathogenic Evidence | Fever Duration (days) | Procalcitonin (ng/mL) | Unfavorable Outcomes | Combined Liver Disease |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | Liver | M/41 | OS | Bacterial culture | 10 | – | NLP, Evisceration | – |
| 2 | 1 | Eye | M/55 | OD | Bacterial culture | 8 | 0.08 | NLP, Evisceration | Cirrhosis, HBV carrier |
| 3 | 1 | Liver | F/61 | OS | Bacterial culture | 10 | 36.41 | NLP, Lost | Hilar cholangiocarcinoma |
| 4 | 12 | Eye | M/40 | OD | Bacterial culture | 2 | – | Hypotony | – |
| 5 | 24 | Eye | M/48 | OS | Bacterial culture mNGS | 4 | 4.33 | NLP, Hypotony, SO | – |
| 6 | 1 | Lung | F/68 | OS | mNGS | 10 | 1.01 | NLP, Evisceration | – |
| 7 | 1 | Liver | F/65 | OD | Bacterial culture | – | 0.291 | NLP, Evisceration | Decompensated phase of liver cirrhosis |
| 8 | 1 | Liver | M/63 | OU | Bacterial culture | 5 | 100 | NLP (OU), death | – |
| 9 | 1 | Liver | F/65 | OS | Bacterial culture | 3 | 10.66 | Lost | – |
| 10 | 1 | Liver | F/75 | OD | Bacterial culture | 5 | 23.35 | Lost | – |
| 11 | 1 | Lung | M/49 | OU | Bacterial culture | 10 | 6.92 | Lost | HBV carrier |
| 12 | 1 | Lung | M/76 | OU | Bacterial culture | 9 | 0.321 | NLP (OU) | – |

**Abbreviations**: F, female; HBV, hepatitis B virus; *KPREE*, *K. pneumoniae* related endogenous endophthalmitis; M, male; mNGS, metagenomic next-generation sequencing; NLP, no light perception; OD, right eye; OS, left eye; OU, both eyes; SO, sympathetic ophthalmia.



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## Discussion

According to previous reports,[10,14] the average age at KPREE onset was 55.9 years old, and 62.9–76.5% of the patients were males. These demographic characteristics were similar to our results, with a median age of (62 [40,76]) years and a male distribution of 58.3%. Lee et al and Tiecco et al found that systemic risk factors associated with KPREE included diabetes (23.5–55.0%) and liver abscesses (54.5–70.6%).[10,14] In particular, liver abscesses larger than 5 cm were more likely to be associated with KPREE.[8] Similarly, in the 12 patients with KPREE we observed, diabetes and liver abscess were highly prevalent, accounting for 58.3% and 91.7%, respectively. However, diabetes appeared to be a common risk factor for infectious endophthalmitis in both the KPREE and ISRPE groups and not just a risk factor for KPREE.

Compared to the ISRPE group, KPREE had a higher proportion of NLP at the final visit (66.7%) and a greater likelihood of evisceration (26.7%), which were higher than the proportion (55.2%) reported by Zhang et al[15] and were greater than the likelihood (11.1–14.3%) in the previous three studies.[10,14,16] Final NLP was significantly correlated with BCVA at baseline ($\beta = 0.664$, $P = 0.007$). Similarly, Lee et al pointed out that poor initial visual acuity, worse than counting fingers, was significantly associated with poor final visual outcome.[10] In addition, KPREE was more likely to be associated with OHT (73.3% vs 9.09%, $P = 0.001$). Therefore, when infectious endophthalmitis is complicated with OHT, KPREE should be considered. In summary, the short-term poor ocular prognosis of KPREE includes NLP, OHT, and evisceration. Lin et al reported a case of a 51-year-old male diabetes patient who developed KPREE combined with liver abscess after 20 days of fever; despite aggressive treatment, his left eye eventually developed NLP and OHT, and finally underwent evisceration.[17]

Our study showed that KPREE had several common systemic clinical features, including fever (100%), with a median fever duration of (8 [2,10]) days, liver abscess (91.7%), and hypoproteinemia (24.1 [17.8,31.7] g/L). We hypothesized that the relationship between the three is as follows: hypoproteinemia makes patients more likely to develop liver abscesses, especially in patients with diabetes or pre-existing liver disease. When a liver abscess progresses to sepsis, it presents with fever and metastatic infections. Therefore, when hypoproteinemia, liver abscess, and fever are present simultaneously, the risk of developing KPREE is very high. Li et al reported a case of a female patient with liver abscess who developed KPREE after 7 days of fever,[18] which was completely consistent with our hypothesis. Unfortunately, the patient eventually died of severe pneumonia. Of the 12 KPREE patients enrolled, one male patient died of acute myocardial infarction secondary to sepsis. His serum procalcitonin level was up to 100 ng/mL, far exceeding the median serum procalcitonin level of other patients (4.33 [0.08,36.41] ng/mL). Similarly, Hamide et al introduced a young patient with uncontrolled diabetes who died of infective endocarditis secondary to liver abscess.[19] Therefore, we recommend intensive care for KPREE patients with high serum procalcitonin levels to prevent life-threatening complications.

We also concluded that approximately 25% of KPREE eyes were bilaterally involved, which is slightly higher than the 12.1% reported in the literature.[20] Pathogen evidence was mainly obtained through bacterial culture and mNGS, which is increasingly being used because of its higher positive rate (88.9%) and faster detection speed.[21,22] In contrast, the positive rate of bacterial cultures was only 27.8%.[22] In our cases, the bacterial culture in case 6 showed negative results, which had no guiding value for the patient's treatment. mNGS suggested *K. pneumoniae*, which was more conducive to our choice of sensitive antibiotics and timely control of infection. Similarly, in case 5, although *K. pneumoniae* was detected by both methods, the mNGS results were obtained two days earlier than the bacterial culture. Therefore, we believe that mNGS testing is necessary for extremely severe infections such as KPREE.

This study is the first to show that hypoproteinemia is independently associated with KPREE occurrence (adjusted $r = -0.658$, adjusted $P = 0.011$). Li et al reported that hypoproteinemia is an independent risk factor for 30-day mortality in hospital-acquired *K. pneumoniae* related pneumonia.[23] Zhang et al and Xiao et al also found that hypoproteinemia was closely related to pulmonary infection in patients with traumatic brain injury and carbapenem-resistant *K. pneumoniae* bacteremia.[24,25] However, the exact association between hypoproteinemia and KPREE remains unclear. Several studies have reported that hypoproteinemia can lead to choroidal thickening and detachment.[26–28] We suspected that hypoproteinemia led to choroidal edema and thickening, which made it easier for more *K. pneumoniae* to accumulate in the thickened choroid and ultimately induced KPREE. Another highlight of this paper is that it is the first report of SO secondary to KPREE. Of the 12 patients with KPREE, case 5 eventually underwent vitrectomy with silicone oil tamponade due to a severe ocular infection.

However, SO developed in this case at the postoperative 8-month follow-up. We believe that severe endophthalmitis may lead to exposure to intraocular antigens that trigger SO. Chen et al reported 12 cases of *K. pneumoniae* related endogenous panophthalmitis with scleral abscess; however, no SO was observed in the fellow eyes of all patients.[29] Similarly, several other studies have reported SO after vitrectomy for infective endophthalmitis, whereas no *K. pneumoniae* have been identified.[30–32] Furthermore, the single pathogenic bacterium (*K. pneumoniae*) was detected in the 11 patients who received only one pathogenic test, either bacterial culture of vitreous aspirates or mNGS of intraocular fluid. However, in the only patient (case 5) who received both microbial detection tests, the mNGS detected a high abundance of two types of bacteria, *K. pneumoniae* and *Escherichia vulneris*. It was reported that *Escherichia vulneris* is a new species usually in human wounds and an opportunistic gram-negative bacterium.[33] Combined with the ocular manifestations of the patient and the positive *K. pneumoniae* culture of vitreous aspirates, we believed that *K. pneumoniae* was the most likely pathogenic bacterium. Therefore, we are still unable to confirm whether it is *K. pneumoniae, Escherichia vulneris*, or vitrectomy itself, which is more commonly associated with SO.

Of course, there are still some limitations that deserve attention in this study. First, due to the rare nature of such catastrophic infections, only 23 cases (including the KPREE and ISRPE groups) were included, even after 4 years of enrollment. In addition, this was a retrospective study, and most patients were lost after 1 month, so we lacked data on unfavorable long-term outcomes (eg, how many patients had hypotony or phthisis bulbi at the 1-year follow-up). Due to the very small sample size in enrolled cases, and unknown strains in the 11 ISPRE eyes, whether hypoproteinemia and fever are independent risk factors for KPREE cannot be fully determined. Even so, we still believe that the hypoproteinemia found in this study is worthy of further study as an important risk factor for KPREE, and the exact association between KPREE and SO requires further elucidation.

## Conclusions

Patients with *K. pneumoniae* infection and hypoproteinemia or fever should be highly vigilant about the occurrence of KPREE, and more attention should be paid to the contralateral risk of KPREE or sympathetic ophthalmia.

## Abbreviations

BCVA, best-corrected visual acuity; IOP, intraocular pressure; ISRPE, intraocular surgery-related postoperative endophthalmitis; KPREE, *K. pneumoniae* related endogenous endophthalmitis; log MAR, logarithm of the minimum angle of resolution; NLP, no light perception; OHT, ocular hypertension; SO, sympathetic ophthalmia.

## Data Sharing Statement

The data that support the findings of this study are available upon request from the corresponding author [SS].

## Ethics Approval

Institutional Review Board approval was obtained from Weihai Central Hospital Affiliated to Qingdao University, and this study adhered to the tenets of the Declaration of Helsinki (approval No. LL-2024-034). The Board waived the requirement for written consent because of the retrospective nature of the study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

All authors declare that they have no competing interests.

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