


BMJ Open Relationship between renal function and prognosis of Chinese proliferative diabetic retinopathy patients undergoing the first vitrectomy: protocol for a prospective cohort study

Chunyan Lei,^{1,2} Keren Zhang,^{1,2} Tiancong Chang,^{1,2} Qibo Ran,^{1,2} Meixia Zhang ^{1,2}

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¹Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, Sichuan, China

²Research Laboratory of Macular Disease, West China Hospital, Sichuan University, Chengdu, Sichuan, China

Correspondence to

Professor Meixia Zhang; zhangmeixia@scu.edu.cn

ABSTRACT

Introduction China has the largest number of adults with diabetes aged 20–79 years (116.4 million) in 2019. Due to the socioeconomic condition or a lack of awareness of diabetic complications, many adults with diabetes have proliferative diabetic retinopathy (PDR) or renal function impairment at their first visit to the clinic for a sudden loss of vision, and pars plana vitrectomy (PPV) is required for their treatment. Risk factors for the outcomes and complications of PPV surgery in PDR patients have been widely explored in many epidemiological studies and clinical trials. However, few prospective studies have analysed the association between renal function and surgical outcomes in PDR.

Methods and analysis This is a single-centre, prospective cohort study of PDR patients with type 2 diabetes mellitus who have definite indications for PPV surgery with or without renal function impairment. We will consecutively enrol PDR patients who meet the inclusion and exclusion criteria from November 2020 to December 2023. Each participant will be followed up for at least 6 months after surgery. Clinical data from medical records and vitreous fluid will be collected.

Demographic characteristics and study outcomes will be summarised using descriptive statistics. The variation will be described and evaluated using the χ^2 test or Kruskal-Wallis test. Generalise additive mixed models will be used to explore the association between the renal profile and surgical outcomes including BCVA, and retinal and choroidal microvasculature/microstructure. Multivariate ordinal regression analysis will be used to detect the independent association between renal profile and BCVA changes, and smooth curve fitting will be employed to briefly present the tendency.

Ethics and dissemination The trial has received ethical approval from the West China Hospital of Sichuan University. Results of this trial will be disseminated through publication in peer-reviewed journals and presentations at local and international meetings.

Trial registration number ChiCTR2000039698.

INTRODUCTION

China has the largest number of adults with diabetes aged 20–79 years (116.4 million)

Strengths and limitations of this study

- The present study will identify the association between renal profile and prognosis of proliferative diabetic retinopathy patients undergoing the first pars plana vitrectomy surgery in the Chinese population; therefore, it might provide a reference for clinical decision making in real-world clinical practice.
- Our research provides the possibility to find out the factors affecting prognosis after vitrectomy and to explore the underlying mechanism.
- It is currently the largest prospective cohort study, and we will use strict statistical adjustment to minimise the effect of residual confounders.
- The study population is restricted to the Chinese with type 2 diabetes mellitus; therefore, the generalisation of the results may be limited.
- Due to an observational design, it is impossible to infer causality in the association between renal function and surgical prognosis; therefore, the findings in our study need to be corroborated by randomised controlled trials.

in 2019, and the number is anticipated to increase to 140.5 million in 2030 and 147.2 million in 2045.¹ It is estimated that the prevalence of diabetes is up to 12.8% among adults living in the mainland Chinese population.² The prevalence of diabetes varies by ethnicity and region. Han ethnicity has the highest prevalence of diabetes (12.8%) with merely 33.2% of diabetes awareness in South-west China.² With the increasing prevalence of diabetes, diabetes-related complications including diabetic retinopathy (DR) and diabetic kidney disease (DKD) are becoming more common.

DR is the primary cause of visual impairment and blindness among working-age individuals in developed countries.³ Proliferative DR (PDR), the most advanced stage of DR,

is characterised by neovascularisation and proliferative membrane formation, which may cause vitreous haemorrhage and tractional retinal detachment (TRD), resulting in progressive vision loss.⁴⁻⁷ Among Chinese patients with diabetes, the prevalence of any DR, non-PDR and PDR are 18.45%, 15.06% and 0.99%, respectively.⁸ Due to the socioeconomic condition or a lack of awareness of diabetic complications, many adolescents with diabetes have PDR and renal function impairment at their first visit to the clinic for a sudden loss of vision, and pars plana vitrectomy (PPV) is required frequently for their treatment.

PPV treatment for PDR aims at improving visual acuity, removing vitreoretinal traction and vitreous haemorrhage (VH), reattaching detached neuroretina, maintaining media transparency and improving ocular circulation.⁷⁻⁹ With the improvement of surgical techniques and instruments, anatomical success rates have become relatively high, even in cases of TRD, though functional results are less favourable.¹⁰⁻¹² Benefiting from the improvement of living and medical conditions, the 5-year survival rate of PDR patients undergoing PPV varies from 68% to 95%.¹³ However, how to improve the visual acuity and quality of life of those patients remains a problem that needs to be solved urgently.

Previous studies¹⁴⁻²¹ have proved that renal function impairment, especially low estimated glomerular filtration rate (eGFR), is involved in the development of DR. Other studies²¹⁻²⁶ have suggested that renal function is associated with retinal and choroidal microvasculature/microstructure in DR with type 2 diabetes. Also, a clinical study reported that renal transplantation could normalise serum urea and creatinine early and stabilise the retinopathy status in the majority of patients.²⁷ Furthermore, renal function is positively correlated with the DR stages and diabetic macular oedema in Southern China.²¹ These studies indicated that renal malfunction may affect retinal function and structure. Katagiri *et al*²⁸ found that the vitreous soluble receptor for advanced glycation end products may be a potential biomarker for renal dysfunction associated with DR. Except for the high blood glucose, these findings lead to speculation regarding vitreous as the potential target intermediary media between renal function and retinal function in type 2 diabetes.

An epidemiological study²⁹ of diabetes has shown the high consistency between DR and renal insufficiency. DR and DKD are related to each other through a common pathophysiological mechanism. However, there are other studies³⁰⁻³¹ suggesting that the relationship between DR and diabetic nephropathy (DN) is not always consistent. Evidence from the Chinese Han population study indicates that DR and DN may be independent diseases.³⁰ Another study found that the association between the microvascular complications of the eye and kidney may vary depending on race, obesity and the use of renin-angiotensin-aldosterone antagonists.³²

At present, few relevant studies have investigated the association between systemic comorbidities and the outcomes of PDR surgery. Previous studies³³⁻³⁵ targeting the association between renal function and prognosis of PDR patients undergoing the first vitrectomy failed to draw any positive conclusion. Song *et al*³⁶ found that severe renal dysfunction may be a risk factor in PDR requiring bilateral vitrectomy in Japanese, which indicated the association between severe unilateral PDR and severe renal dysfunction. However, all of these clinical findings are from retrospective studies and are limited to small samples. Furthermore, there is no relevant evidence from the Chinese patients. Therefore, our study aims to conduct a prospective cohort study to explore the association between renal function and prognosis in the Chinese population with PDR.

Aim and objectives

Aim

1. To investigate the association between renal function and the outcomes of Chinese PDR patients with type 2 diabetes undergoing the first PPV surgery in real-world clinical practice.
2. To investigate the prevalence of complications associated with PPV surgery and reoperation rates in the short term.
3. Keep the vitreous fluid to further expound possible cytokines and pathways in the prognosis of PDR and to further study the relationship between renal malfunction and PDR.

Specific objectives

To describe the clinical outcomes of hospitalised PDR patients undergoing primary PPV surgery in China, including trends in these outcomes over time.

Significance

This study is designed to understand the prognosis of PDR patients undergoing the first vitrectomy and to further understand whether renal function is related to the prognosis of PPV surgery and provide a reference for clinical decision-making.

METHODS AND ANALYSIS

Study design

This clinical study is a prospective, single-centre, cohort study. The clinical trial began in November 2020, and participants enrolment will be completed in December 2023. Each participant will be followed up for at least 6 months after surgery. We will consecutively collect the patients who meet the criteria for inclusion and exclusion.

Eligibility criteria of the study population

Inclusion criteria

Patients with PDR who meet the following criteria will be enrolled in the trial:

1. PDR that has definite indications for surgery and no absolute contraindications to surgery in general condition.
2. Fasting blood glucose is less than 8mmol/L, and blood glucose 2 hours after three meals is less than 11 mmol/L. Besides, this blood glucose level lasts at least 7 days.
3. Vitrectomy for the target eye is performed for the first time.
4. Agree to join after full understanding of the informed consent of the clinical research.

Exclusion criteria

Patients meeting any of the following criteria will be excluded from the study:

1. AIDS, syphilis, leukaemia, etc.
2. Type 1 diabetes.
3. Rubeosis iris or neovascular glaucoma (NVG), uveitis, branch retinal vein occlusion, age-related macular degeneration, ocular trauma, endophthalmitis, etc.

Participant discontinuation/withdrawal from the study

Patients can leave the study at any time for any reason if they wish to do so without any consequences. In this case, the data and samples already used for the study cannot be destroyed.

Informed consent

Before the study, the general study process and the responsibilities of the participants and researchers will be explained to potential participants or their guardians. Participants or their guardians will be informed that their entry into the trial is entirely voluntary and that they could withdraw at any time. In the event of their withdrawal, data collected on the participant will not be erased and will be used in the final analyses. Written informed consent should be obtained from each participant before he or she undergoes any interventions related to the study.

Participants

Study setting

Eligible PDR patients hospitalised in the Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, China, during the period from November 2020 to December 2023 will be considered for enrolment. Those who enter the trial will be centrally managed via social application (WeChat) and have the privilege of priority in follow-up and medical consulting, as a strategy for achieving adequate participant enrolment to reach the target sample size.

Sample size

According to the previous literature report,³⁷ it is estimated that the occurrence rates of poor vision at 6 months in the DKD group (glomerular filtration rate lower than 60 mL/(min 1.73m²)) and the non-DKD group are 0.077 and 0.206, respectively. PASS V.15 software (PASS 15.0.5 NCSS, LLC, USA) was adopted to calculate the experimental size of the DKD group and the non-DKD group: $N1=N2=149$

cases. Assuming that the loss to follow-up rate of the study subjects is 20%, the sample size is $N1=N2=149\div0.8=186$ cases. Therefore, the minimum sample size included in this study will be 372 cases. In real-world clinical practice, a total of 400 cases will be included.

Surgical procedure

All surgeries will be performed by one skilled retinal surgeon (Meixia Zhang) under retrobulbar anaesthesia using a standard three-port 25G vitrectomy. Phacoemulsification will be performed in patients with severe cataracts at the beginning of vitrectomy. Then we will collect the vitreous sample with a 5 mL sterile tube. The harvested vitreous samples will be immediately kept on ice and transferred to the laboratory within 4 hours for centrifugation at 4°C, 4000 rpm for 15–30 min. Supernatant sample aliquots will then be stored at –80°C until further analysis. Then triamcinolone acetonide (TA) will be applied for offering a better identification to eliminate vitreous cortex and proliferative membranes. Indocyanine green will be only used in patients with epiretinal membranes. Remarkably, we will observe the degrees of posterior vitreous detachment (PVD) in the surgical eyes, including partial PVD and complete PVD. Panretinal laser photocoagulation will be done or supplemented during surgery, and at the end of the surgery, silicone oil or perfluoropropane (C3F8) or balanced salt solution will be used in cases according to the retinal condition. Surgical records and surgical videos will be kept well to check the procedure.

Outcomes

Primary outcomes

The primary outcome is the association between renal profile and visual outcome (best-corrected visual acuity (BCVA)).

Secondary outcomes

1. Associations between renal function and retinal and choroidal microvasculature/microstructure in PDR inpatients.
 1. Retinal and choroidal microvasculatures include foveal avascular zone (FAZ), vessel density of superficial capillary plexus (SCP), deep capillary plexus (DCP) and vessel density of the choriocapillaris, respectively.
 2. Retinal and choroidal microstructures include the central macular thickness (CMT) and subfoveal choroidal thickness (SFCT), respectively.
2. The rates of postoperative complications (posterior capsular opacification, progressed cataract, high intraocular pressure (IOP), early VH (before 4 weeks after surgery), late VH (occurred later than 4 weeks after surgery), epiretinal membrane, macular hole, macular oedema, retinal/macular redetachment and NVG) will be explored.
3. We will explore the vitreous-related cytokines and pathways in the prognosis of PDR patients undergoing the first PPV surgery in the Chinese population.

Data and sample collection

Relevant baseline characteristics that are important in the management of hospitalised PDR patients will be collected. Demographic information includes age, sex, ethnicity, education level, occupation, living region, etc. Relevant medical history includes diabetes duration, hypertension history, DKD history, chronic kidney disease history, history of cardiovascular diseases including coronary heart disease, stroke, heart failure, etc. Systemic medication history includes oral diabetes medication, insulin treatment, oral antihypertensive drugs, anticoagulant/antiplatelet agent administration and kidney protection drugs. General characteristics at initial presentation including smoking/drinking status, height, weight, waist circumference and systolic and diastolic blood pressure will be extracted.

All relevant laboratory tests will be completed on admission. Laboratory values include preoperative glycosylated haemoglobin, renal profile (eg, serum blood urea nitrogen, serum creatinine, eGFR, uric acid, serum cystatin C, etc), hepatic function, blood lipids, C reactive protein, erythrocyte sedimentation rate, serum homocysteine, etc.

Moreover, the ophthalmological findings will be categorised into three sections: preoperative, intraoperative and postoperative. The preoperative ophthalmological history contains the history of intraocular lens implantation, the history of intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents and anti-inflammatory treatment (TA, Orudex, etc), the history of panretinal photocoagulation, duration from visual loss awareness to the primary vitreous surgery, etc.

The intraoperative ophthalmological findings will be listed as follows: duration of operation, cataract surgery, intraoperative retinal photocoagulation, C3F8 tamponade, silicone oil tamponade, intraoperative complications (iatrogenic retinal break, etc), macular hole, PVD, fibrovascular membrane, retinal detachment, macular detachment, etc.

Finally, the postoperative complications will be collected including posterior capsular opacification, progressed cataract, high IOP, early VH, late VH, epiretinal membrane, macular hole, macular oedema, retinal/macular redetachment and NVG. Patients with macular oedema will be given treatment options to select among anti-VEGF agents or anti-inflammatory drugs by intravitreal injection.

When we use vitreous fluid to investigate the relationship between renal function and the prognosis after the first PPV surgery for PDR patients, we will exclude the patients with anti-VEGF treatment or anti-inflammatory treatment (TA, Orudex, etc) as the adjuvant pretreatment before vitrectomy at least 6 months.

Examination data

All participants will undergo complete ocular examination, including BCVA, IOP, axial length, slit lamp examination, anterior segment photography focused on the cortical, nuclear and posterior subcapsular of the lens, optical coherence tomography (OCT), optical coherence tomography angiography (OCTA) and electroretinogram (ERG). Each type of examination will be completed by the same appointed

operator. The OCT, OCTA and ERG examinations will be conducted after pupillary dilation with Compound Tropicamide Eye Drops (Mydrin-P; Santen, Osaka, Japan). The Lens Opacities Classification System III (LOCS III) system is used for cataract grading using anterior segment photography. In addition to the first 6 months, participants will be followed up every 6 months until the end of follow-up if no new complications occur; otherwise, the duration and treatment will be adjusted according to clinical needs.

Best-corrected visual acuity (BCVA)

For visual acuity measurement, the decimal BCVA will be measured using the standard logarithmic visual acuity scale placed 5m away from the patient. Decimal BCVA will be measured preoperatively and at every follow-up time after the primary PPV surgery. The decimal BCVA will be converted into the logarithmic minimum angle of resolution (logMAR) to detect visual acuity change. BCVA will be recorded using the logMAR scale, and count-fingers will be assigned a logMAR value of 1.6, hand motion 2.0, light perception 2.5 and no light perception 3.0.³⁸ The scheme we adopt has been described previously.³⁷ BCVA changes in comparison with the preoperative value at each follow-up visit will be recorded and divided into three categories. An increase of > 0.3 logMAR unit, a change of < 0.3 logMAR unit and a decrease of > 0.3 logMAR unit will be defined as 'improvement', 'invariant' and 'worsening', respectively.

OCT imaging

All OCT scans will be obtained using spectral-domain OCT (Spectralis OCT, Heidelberg Engineering; Heidelberg, Germany). OCT measurements will be performed according to the Early Treatment Diabetic Retinopathy Study protocol. A standardised imaging protocol with enhanced depth imaging will be performed: a six-line radial scan centred on the fovea. Quantitative assessments included CMT and SFCT will be measured manually using digital callipers provided by Heidelberg Eye Explorer software (Heidelberg Engineering) at baseline if applicable and at all follow-up visits. CMT is defined as the distance in the macula from the inner limiting membrane (ILM) to the retinal pigment epithelium (RPE). SFCT is defined as the distance in the macula from the outer border of the hyper-reflective line corresponding to the RPE perpendicular to the choriocleral interface.

We also will collect the presence and changes of OCT morphological features including subretinal fluid, the presence of intraretinal cystoid changes, hyperreflective dots, continuity of the ellipsoid zone/interdigitation zone layer (continuous and disrupted) and the presence of an epiretinal membrane.

OCT images of poor quality that are difficult to analyse will be excluded from the study. Two experienced physicians, who are blinded to patients' clinical data, will perform measurements independently.

OCTA imaging

OCTA examinations will be conducted with the AngioVue OCTA system (RTVue-XR Avanti; Optovue, Fremont,

Table 1 Schedule

Examination parameter	Baseline visit (Preoperative)	Intraoperative	Follow-up visit (postoperative first day)	Follow-up visit (postoperative 1 week)	Follow-up visit (postoperative 5 weeks)	Follow-up visit (postoperative 13 weeks)	Follow-up visit (postoperative 6 months)	Follow-up visit (as-needed (PRN))
Patient ID	x	x	x	x	x	x	x	x
Date of visit	x	x	x	x	x	x	x	x
Patient informed consent	x							
Time to diagnose diabetes	x							
Time of sudden vision loss	x							
Eligibility assessment	x							
Demographic data	x							
Questionnaires	x							
Medical history	x							
Systemic medication history	x							
General characteristics	x							
Laboratory data	x							
Intraoperative findings		x						
Examination								
BCVA	x		x	x	x	x	x	x
OCT	x (if applicable)		x	x	x	x	x	x
OCTA	x (if applicable)		x	x	x	x	x	x
ERG				x	x	x	x	x
Postoperative complications			x	x	x	x	x	x

BCVA, best-corrected visual acuity; ERG, electroretinogram; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography.

California, USA) using a standard protocol as specified by the manufacturer. The macula-centred 3×3 mm and optic disc-centred 4.5×4.5 mm OCTA images will be acquired for each study eye at baseline if applicable and all follow-up time. The vessel density of the SCP and DCP, FAZ and the vessel density of the radial peripapillary capillaries and RNFL thickness will be generated based on the automated layer segmentation by the in-built RTVue XR Avanti AngioVue software. The vessel density will be quantified as a percentage.

The FAZ is considered present if a distinct avascular zone is present without any vessel crossing the centre. The FAZ will be quantified both automatically by the machine using the flow measure software module and manually by an independent investigator if the automatic recognition is inaccurate. The SCP is defined as extending from the ILM to 15 µm above the inner plexiform layer (IPL), and the DCP is defined as extending from 15 µm to 75 µm above the IPL. The choriocapillary layer is defined as extending from 30 µm to 60 µm beneath RPE. The parafoveal area is defined as an annulus centred on the fovea, with an inner diameter of 1 mm and an outer diameter of 3 mm. The total and parafoveal vessel densities of SCP and DCP and the total vessel density of the choriocapillaris are automatically calculated by the AngioVue OCTA software.

Only OCTA images with signal quality >5/10 and no obvious segmentation error or artefacts are used. Patients whose images have poor quality with motion artefacts, inadequate signal strength <5/10, poorly focused scans or segmentation failure will be excluded.

ERG recordings

Full-field dark-adapted and light-adapted ERGs will be recorded with a visual electrophysiology diagnosis system (RETI-Port/Scan21; Roland, Germany) as per ISCEV standard.³⁹ Before recording, the subjects will be dark adapted for 30 min. Pupils will be dilated to 8 mm after pupillary dilation with Compound Tropicamide Eye Drops (Mydrin-P; Santen, Osaka, Japan). Topical anaesthesia will be achieved by applying 0.4% of oxybuprocaine (Santen, Osaka, Japan). Under dim red light, a gold wire loop electrode will be placed on the cornea, a reference electrode will be attached to the ear, and a ground electrode will be placed on the wrist of the right hand.

Dark-adapted 3.0 and light-adapted 3.0 responses will be recorded. The interstimulus interval for dark-adapted 3.0 is 30 s, and the interstimulus interval for light-adapted 3.0 is 1.0 s. Five individual responses are averaged. The light adaptation is 20 min after the dark-adapted 3.0 recordings. The ERG will only be conducted at all follow-up visits after the first week postoperatively.

Data storage and management

We will adopt the electronic, secure web-based platform (empowerstats dataweb) to acquire and store data with well-designed case report forms (CRFs). Data will either be entered directly into the empowerstats dataweb or will be collected using paper CRFs by the investigators and then enter into empowerstats dataweb. All the investigating

physicians are trained in using the web-based application, and the data on the host server is protected by an individual user ID and password. The patient ID remains with a patient even if he or she moves or changes practitioner. This method of assigned patient ID ensures that patients can be followed up through a long period in case of transition. The study protocols specify the examination parameters required at baseline and follow-up visits (table 1). Investigating physicians are encouraged to record data as soon as clinic visits end. Regular data quality checks include reviewing missing data and checking for outliers and discrepancies. For data safety and security, the electronic data will be maintained under secure, password-protected conditions, while hard copy records will be kept in a locked office.

Proposed statistical methods

Demographic characteristics and study outcomes will be summarised using descriptive statistics. Continuous variables will be summarised with means, medians and IQRs and the categorical variables with frequencies and percentages. The variation will be described and evaluated using the χ^2 test or Kruskal-Wallis test. Generalised additive mixed models will be used to explore the association between the renal profile and surgical outcomes including BCVA, and retinal and choroidal microvasculature/microstructure. Multivariate ordinal regression analysis will be used to detect the independent association between renal profile and BCVA changes, and smooth curve fitting will be employed to briefly present the tendency. A two-sided $p < 0.05$ is considered to be statistically significant. Statistical analyses will be performed using Empower Stats (<http://www.empowerstats.com>; X&Y Solutions Inc, Boston, Massachusetts, USA) and R software, V.3.4.3 (<http://www.R-project.org/>; The R Foundation).

Patient and public involvement

This research will be done without patient involvement. Patients will be not invited to comment on the study design and not consulted to develop patient-relevant outcomes or interpret the results. Patients will be not invited to contribute to the writing or editing of this document for readability or accuracy.

ETHICS AND DISSEMINATION

Ethics approval

The trial has received ethical approval from the West China Hospital of Sichuan University. The protocol to be used adhere to the principles of the Declaration of Helsinki and has been registered in the Chinese Clinical Trial Registry (registered 6 November 2020). Written informed consent will be obtained from each participant before enrolling in the study.

Dissemination and data sharing

The study will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies. The first author will be responsible for the data and analysis.

Study results will be distributed using a broad dissemination strategy, including presentations at national and international meetings, and publications in high-impact open access journals.

Contributors CL conceived and designed the study, drafted the first version of the manuscript and revised subsequent versions of the manuscript. MZ conceived and designed the study and revised the manuscript. KZ, TC and QR participated in the design of the study and manuscript revisions. All authors have read and given final approval of the submitted manuscript.

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ORCID iD

Meixia Zhang <http://orcid.org/0000-0002-2633-6819>

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