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# BMJ Open

## The relationship between renal function and prognosis after vitrectomy in Chinese proliferative diabetic retinopathy patients with type 2 diabetes mellitus: protocol for a prospective cohort study

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**The relationship between renal function and prognosis after vitrectomy in Chinese proliferative diabetic retinopathy patients with type 2 diabetes mellitus: protocol for a prospective cohort study**

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**Introduction:**

China has the largest number of adults with diabetes aged 20-79 years (116.4 million) in 2019. Due to a lack of knowledge about diabetic complications or some socioeconomic factors, many diabetics have developed into proliferative diabetic retinopathy (PDR) and renal function impairment when they first visited the ophthalmology department for a sudden loss of vision, those patients often require pars plana vitrectomy (PPV) treatment. The risk factors for the outcomes and complications of PPV surgery in PDR patients have been widely explored. However, few prospective studies have analyzed the influence of renal function on surgical outcomes in PDR.

**Methods and analysis:**

This is a single-center, 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 enroll PDR patients who meet the inclusion and exclusion criteria from November 2020 to December 2023. Each participant will follow 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 summarized using descriptive statistics. The variation will be described and evaluated using the  $\chi^2$  test or Kruskal-Wallis test.

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Generalize additive mixed models (GAMM) 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:** ChiCTR2000039698, registered November 6, 2020.

**Strengths and limitations of this study**

1. The study will be the first prospective cohort study that aims at the association between renal function and outcomes of PDR after PPV treatment in the Chinese population with type 2 diabetes mellitus.
2. We 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.
3. The complication rates associated with PPV surgery and reoperation rates will be explored in the short term.
4. As an observational design, this study is impossible to infer causality in the association between renal function and surgical prognosis and has unmeasured confounders in nature.

**Introduction**

China has the largest number of adults with diabetes aged 20-79 years (116.4 million) in 2019, and the number is anticipated to increase to 140.5 million in 2030 and 147.2 million in 2045.<sup>1</sup> It is estimated that the prevalence of diabetes is up to 12.8% among adults living in the mainland Chinese population.<sup>2</sup> The prevalence of diabetes varies in ethnicity and region. Han ethnicity has the highest prevalence of diabetes and only 33% of patients with diabetes awareness in Southwest China. With the increasing prevalence of diabetes, diabetes-related complications are becoming more common, including diabetic retinopathy DR and diabetic kidney disease (DKD), etc.

DR is the primary cause of visual impairment and blindness among working-age individuals in developed countries.<sup>3</sup> Proliferative DR (PDR), the most advanced stage of DR, is characterized by neovascularization and proliferative membrane formation, which may cause vitreous hemorrhage and tractional retinal detachment (TRD), resulting in progressive vision loss.<sup>4-7</sup> In Chinese patients with diabetes, the prevalence of any DR, non-PDR, and PDR are 18.45%, 15.06%, and 0.99%, respectively.<sup>8</sup> Due to a lack of knowledge about diabetes and diabetic complications or some socioeconomic factors, many patients have developed PDR and renal function impairment when they first visited the department of Ophthalmology for a sudden loss of vision, they often require pars plana vitrectomy (PPV) treatment and emergency management to prevent further vision loss.

PPV treatment for PDR aims at improving visual acuity, removing vitreoretinal traction and vitreous hemorrhage, reattaching detached neuroretina, maintaining media transparency, and improving ocular circulation.<sup>7-9</sup> With the improvement of surgical techniques and instruments, anatomical success rates have become relatively high, even in cases of TRD, although functional results are less favorable.<sup>10-12</sup> Benefit from the improvement of living conditions and medical conditions, the 5-year survival rate of PDR patients undergoing PPV is between 68% and 95%.<sup>13</sup> How to make those patients with advanced PDR preserve their vision and improve their quality of life is a problem that needs to be solved urgently.

Amounting studies<sup>14-21</sup> have proved that renal function impairment, especially low estimated glomerular filtration rate (eGFR), is involved in the development of DR. Besides, numerous studies<sup>21-26</sup> have shown that the 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 normalize serum urea and creatinine early and stabilize the retinopathy status in the majority of patients.<sup>27</sup> Furthermore, renal function is positively correlated with the DR stages and diabetic macular edema in southern China.<sup>21</sup> Those studies indicated that renal malfunction may affect retinal function and structure. Besides, a study<sup>28</sup> evidenced that vitreous soluble receptor for advanced glycation end products (sRAGE) may be a potential biomarker for renal dysfunction associated with DR. Except for high blood glucose, these data led to speculation regarding vitreous as the potential target intermediary media between renal function and retinal function in type 2 diabetes.

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Epidemiological studies<sup>29</sup> of diabetes have shown the high consistency between DR and renal insufficiency. DR and DKD are related to each other through a common pathophysiological mechanism, but there are also studies<sup>30 31</sup> showing that the relationship between DR and diabetic nephropathy (DN) is sometimes inconsistent. In the Chinese Han population study, DR and DN may be independent diseases.<sup>30</sup> The relationship between the microvascular complications of the eye and kidney may vary depending on race, obesity, and the use of renin-angiotensin-aldosterone antagonists.<sup>32</sup>

At present, few relevant studies have analyzed the influence of systemic comorbidities on the outcome of PDR surgery. Previous studies<sup>33-35</sup> targeted renal function and prognosis after the first vitrectomy in PDR patients failed to find any relationship between both. Song et. al<sup>36</sup> found that severe renal dysfunction may be a risk factor in PDR requiring bilateral vitrectomy in Japanese, which indicated that the association between severe unilateral PDR and severe renal dysfunction. However, these clinical findings are all from retrospective studies and are restricted to small samples. Furthermore, there is no related evidence from the Chinese patients. That is why we conduct this prospective cohort study to explain the relationship between both in the Chinese population.

**Aim and objectives**

**Aim**

1. To investigate the renal function on the outcomes of PPV for Chinese PDR patients with type 2 diabetes in the 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 hospitalized PDR patients after primary PPV surgery in China, including trends in these outcomes over time.

**Significance**

This study is designed to understand the prognosis of PDR patients after 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-center, cohort study. The clinical trial began in November 2020 and will be completed in December 2023. Each participant will follow up for at least 6 months after surgery. We will consecutively collect 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 which has definite indications for surgery and no absolute contraindications to surgery in general condition;
- (2) Vitrectomy for the target eye is performed for the first time;
- (3) Agree to join after fully understanding the informed consent of the clinical research.

#### **Exclusion criteria**

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

- (1) Acquired Immune Deficiency Syndrome, syphilis, leukemia, 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;
- (4) <6 months follow-up after primary vitrectomy.

### **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.



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**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 hospitalized 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 enrollment. Those who enter the trial will be centrally managed by social application (Wechat) and have the privilege of priority in follow-up and medical consulting, as a strategy for achieving adequate participant enrollment to reach the target sample size.

**Sample size**

According to the previous literature report,<sup>37</sup> it is estimated that the occurrence rates of poor vision at 6-month in DKD group and non-DKD group are 0.077 and 0.206, perspective. PASS 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  $N1=N2=149 \div 0.8=186$  cases. Therefore, the minimum sample size included in this study is 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 anesthesia using a standard three-port 25G vitrectomy. Phacoemulsification will be

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performed in patients with severe cataracts at the beginning of vitrectomy. Then we will collect the vitreous sample with a 5-ml sterile tube. Harvested vitreous will be immediately kept on ice and transferred to the laboratory within four hours for centrifugation at 4°C, 4000 rpm for 15-30 minutes. Supernatant sample aliquots will be then stored at -80°C until further analysis. Then triamcinolone acetonide will be applied for offering a better identification to eliminating vitreous cortex and proliferative membranes, indocyanine green will be used in patients with epiretinal membranes. Remarkably, we will observe degrees of posterior vitreous detachment (PVD) in the surgical eyes, including partial PVD and complete PVD. Pan-retinal laser photocoagulation will be done or supplemented during surgery, and at the end of surgery, silicone oil or perfluoropropane (C3F8) or balanced salt solution (BSS) will be used in cases according to the retinal condition. Surgical records and surgical videos will keep well to check the procedure.

## Outcomes

### Primary outcomes

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

### Secondary outcomes

1. Associations between retinal and choroidal microvasculature/microstructure and renal function in PDR inpatients.

① Retinal and choroidal microvasculature 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 microstructure includes 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, early VH (before 4 weeks after surgery), late VH (occurred later than 4 weeks after surgery), epiretinal membrane, macular hole, macular edema, retinal/macular re-detachment, and NVG will be explored.

3. We will explore the vitreous related cytokines and pathways in the prognosis after the first

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1 PPV surgery for PDR in Chinese.  
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3 **Data and sample collection**  
4 The relevant baseline characteristics will be collected, which are important in the management  
5 of hospitalized PDR patients. Demographic information includes age, sex, ethnicity, education level,  
6 occupation, living region, etc. Relevant medical history includes diabetes duration, hypertension  
7 history, DKD history, chronic kidney disease history, history of cardiovascular diseases including  
8 coronary heart disease, stroke, heart failure, etc. Systemic medication history includes oral diabetes  
9 medication, insulin treatment, oral antihypertensive drugs, anticoagulant/antiplatelet agent  
10 administration, kidney protection drugs. General characteristics at initial presentation including  
11 smoking/drinking status, height, weight, waist circumference, systolic and diastolic blood pressure  
12 will be extracted.  
13 All relevant laboratory tests will be completed on admission. Laboratory values include  
14 preoperative glycosylated hemoglobin (HbA1c), renal profile (e.g., serum blood urea nitrogen  
15 (BUN), serum creatinine, eGFR, uric acid, serum cystatin C, etc), hepatic function, blood lipids, C  
16 reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum homocysteine, etc.  
17 Moreover, the ophthalmologic findings will be categorized into three sections: preoperative,  
18 intraoperative, and postoperative. The preoperative ophthalmologic history will be as follows: the  
19 history of intraocular lens implantation, the history of intravitreal injection of anti-vascular  
20 endothelial growth factor (VEGF) agents and anti-inflammatory treatment (TA, Orudex, etc), the  
21 history of pan-retinal photocoagulation, duration from visual loss awareness to the primary vitreous  
22 surgery, etc.  
23 The intraoperative ophthalmologic findings will be listed as the following: duration of  
24 operation, cataract surgery, intraoperative retinal photocoagulation, C3F8 tamponade, silicone oil  
25 tamponade, intraoperative complications (iatrogenic retinal break, etc), macular hole, PVD,  
26 fibrovascular membrane, retinal detachment, and macular detachment, etc.  
27 Lastly, the postoperative complications will be collected including posterior capsular  
28 opacification, progressed cataract, high intraocular pressure, early VH, late VH, epiretinal  
29 membrane, macular hole, macular edema, retinal/macular re-detachment, and NVG. Macular edema  
30 will give the treatment option to select anti-VEGF agents or anti-inflammatory drugs by intravitreal

injection.

### Examination data

All participants will undergo complete ocular examination, including BCVA, intraocular pressure (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. 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. All follow-up time except for the essential first 6 months, every 6 months thereafter until the final follow-up if no new complications occur, otherwise follow-up and taking treatment both according to clinical need.

### BCVA

For visual acuity measurement, the decimal BCVA will be measured using the standard logarithmic visual acuity scale placed 5 m away from the patient. We will measure decimal BCVA preoperatively and all follow-up time after the primary PPV surgery. The decimal BCVA will be converted into the logarithmic minimum angle of resolution (logMAR) to examine 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.<sup>38</sup> We will adopt the scheme described previously.<sup>37</sup> The BCVA changes in comparison with the preoperative value will be 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 (SD)-OCT (Spectralis OCT, Heidelberg Engineering; Heidelberg, Germany). OCT measurements will be performed according to the Early

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1 Treatment Diabetic Retinopathy Study (ETDRS) protocol. A standardized imaging protocol with  
2 enhanced depth imaging (EDI) will be performed: a 6-line radial scan centered on the fovea.  
3 Quantitative assessments included CMT and SFCT will be measured manually using digital calipers  
4 provided by Heidelberg Eye Explorer software (Heidelberg Engineering, Heidelberg, Germany) at  
5 baseline and all follow-up time. CMT is defined as the distance in the macula from the inner limiting  
6 membrane (ILM) to the retinal pigment epithelium (RPE). SFCT is defined as the distance in the  
7 macula from the outer border of the hyperreflective line corresponding to the RPE perpendicular to  
8 the choriocleral interface.

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

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

17 **OCTA imaging**

18 OCTA examinations will be conducted with the AngioVue OCTA system (RTVue-XR Avanti;  
19 Optovue, Fremont, CA, USA) using a standard protocol as specified by the manufacturer. The  
20 macula-centered 3×3 mm and optic disc-centered 4.5×4.5 mm OCTA images will be acquired for  
21 each study eye at baseline and all follow-up time. The vessel density of the SCP and DCP, foveal  
22 avascular zone (FAZ), and the vessel density of the radial peripapillary capillaries (RPC) and RNFL  
23 thickness will be generated on the basis of automated layer segmentation by the in-built RTVue XR  
24 Avanti AngioVue software. The vessel density will be quantified as a percentage.

25 The FAZ is considered present if a distinct avascular zone is present without any vessel  
26 crossing the center. The FAZ will be quantified both automatically by the machine using the flow  
27 measure software module and manually by an independent investigator if the automatic recognition  
28 is inaccurate. The SCP is defined as extending from the ILM to 15 μm above the inner plexiform  
29 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  $\mu\text{m}$  to 60  $\mu\text{m}$  beneath RPE. The parafoveal area is defined as an annulus centered 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 artifacts are used. Patients whose images have poor quality with motion artifacts, inadequate signal strength  $< 5/10$ , poorly focused scans, or segmentation failure will be excluded.

### ERG recordings

Full-field dark- and light-adapted ERGs will be recorded with a visual electrophysiology diagnosis system (RETI-Port/Scan21; Roland, Germany) as per ISCEV standard.<sup>39</sup> 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 anesthesia 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 inter-stimulus 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 times after the first week postoperatively.

### Data storage and management

We 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 physician investigators 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 long term and through the transition. The

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1 study protocols specify the examination parameters required at baseline and follow-up visits (**Table**  
2 **1**). Physician investigators are encouraged to enter data as soon as possible after clinic visits.  
3 Regular data quality checks will review missing data and check for outliers and discrepancies. For  
4 data safety and security, the electronic data will be maintained under secure, password-protected  
5 conditions while hard copy records will be kept in a locked office.  
6

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**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		X	X	X	X	X	X
	OCTA	X		X	X	X	X	X	X
	ERG				X	X	X	X	X
Postoperative complications				X	X	X	X	X	X



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1           **Proposed statistical methods**

2           Demographic characteristics and study outcomes will be summarized using descriptive  
3           statistics. Continuous variables will be summarized with means, medians, and interquartile ranges  
4           (IQRs) and categorical variables with frequencies and percentages. The variation will be described  
5           and evaluated using the  $\chi^2$  test or Kruskal-Wallis test. Generalize additive mixed models (GAMM)  
6           will be used to explore the association between the renal profile and surgical outcomes including  
7           BCVA, and retinal and choroidal microvasculature/microstructure. Multivariate ordinal regression  
8           analysis will be used to detect the independent association between renal profile and BCVA  
9           changes, and smooth curve fitting will be employed to briefly present the tendency. A two-sided P  
10          < 0.05 is considered to be statistically significant. Statistical analyses will be performed using  
11          Empower Stats (<http://www.empowerstats.com>; X&Y Solutions Inc., Boston, MA) and R  
12          software, version 3.4.3 (<http://www.R-project.org/>, The R Foundation).

14           **Strengths and limitations**

15           **Strengths**

- 16          1. The current study will be the first prospective cohort study that aims at the association between  
17           the renal function and outcomes of PDR after PPV treatment in the Chinese population with  
18           type 2 diabetes mellitus. Prior studies on the association between renal function and the  
19           outcomes after vitrectomy of PDR have been retrospective. A prospective design would  
20           facilitate more complete documentation, particularly clinical data.  
21          2. We keep the vitreous fluid to further expound possible cytokines and pathways in the prognosis  
22           of PDR and to further study the relationship between renal malfunction and PDR.  
23          3. The rates of complications associated with PPV surgery and reoperation rates will be explored  
24           in the short term.

26           **Limitations**

27          This study has several limitations. First, as an observational study, it is impossible to infer  
28          causality in the association between renal function and surgical prognosis. Second, unlike a  
29          randomized controlled trial, an observational study has unmeasured confounders in nature. Even  
30          though we used statistical models to adjust for potential bias, some unforeseen confounders may

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1 still potentially have an effect on our conclusions. Third, due to the limitation of the research  
2 population, our research results are not applicable to people from other countries.

### 4 **Patient and public involvement**

5 This research was done without patient involvement. Patients were not invited to comment on  
6 the study design and were not consulted to develop patient relevant outcomes or interpret the results.  
7 Patients were not invited to contribute to the writing or editing of this document for readability or  
8 accuracy.

## 9 **Ethics and dissemination**

### 10 **Ethics approval**

11 The protocols to be used adhere to the principles of the Declaration of Helsinki and have been  
12 approved by the Chinese Clinical Trial Registry (ChiCTR2000039698, registered November 6,  
13 2020). Written informed consent will be obtained from each participant before enrolled in the study.

### 15 **Dissemination and data sharing**

16 The study will be reported according to the Strengthening the Reporting of Observational  
17 Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies. The first  
18 author will be responsible for the data and analysis. Study results will be distributed using a broad  
19 dissemination strategy, including presentations at national and international meetings, and  
20 publications in high-impact open access journals.

### 22 **Acknowledgements**

23 None.

### 25 **Authors' contributions**

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

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**Funding statement**

This work was supported by the Sichuan Provincial Science and Technology Support Project ( no.2018FZ0031) and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z2018B22).

**Competing interest statement**

The authors declare that they have no competing interests.

**Patient consent for publication**

Not required.

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**Word Count: 3507.**

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## SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	The relationship between renal function and prognosis after vitrectomy in Chinese proliferative diabetic retinopathy patients with type 2 diabetes mellitus: protocol for a prospective cohort study
Trial registration	2a	ChiCTR2000039698, registered November 6, 2020.
	2b	Not applicable
Protocol version	3	V0.0 (2021/4/16)
Funding	4	the Sichuan Provincial Science and Technology Support Project (no.2018FZ0031) and National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University (Z2018B22).
Roles and responsibilities	5a	Chunyan Lei <sup>1,2</sup> ; Keren Zhang <sup>1,2</sup> ; Tiancong Chang <sup>1,2</sup> ; Qibo Ran <sup>1,2</sup> ; Meixia Zhang <sup>1,2,3</sup> 1 Department of Ophthalmology, West China Hospital, Sichuan University, Chengdu, 610041, China 2 Research Laboratory of Macular Disease, West China Hospital, Sichuan University, Chengdu, 610041, China 3 National Clinical Research Center for Geriatrics, West China Hospital, Sichuan University, Chengdu, 610041, China
	5b	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.
	5c	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.
	5d	

## Introduction



1			
2	Background and	6a	China has the largest number of adults with diabetes aged 20-79
3	rationale		years (116.4 million) in 2019. Due to a lack of knowledge about
4			diabetic complications or some socioeconomic factors, many diabetics
5			have developed into proliferative diabetic retinopathy (PDR) and renal
6			function impairment when they first visited the ophthalmology
7			department for a sudden loss of vision, those patients often require
8			pars plana vitrectomy (PPV) treatment. The risk factors for the
9			outcomes and complications of PPV surgery in PDR patients have
10			been widely explored. However, few prospective studies have
11			analyzed the influence of renal function on surgical outcomes in PDR.
12			
13			
14			
15		6b	Explanation for choice of comparators
16			
17	Objectives	7	To investigate the renal function on the outcomes of PPV for Chinese
18			PDR patients with type 2 diabetes in the real-world clinical practice.
19			
20	Trial design	8	Eligible PDR patients hospitalized in the Department of
21			Ophthalmology, West China Hospital, Sichuan University, Chengdu,
22			China during the period from November 2020 to December 2023 will
23			be considered for enrollment. Those who enter the trial will have the
24			privilege of priority in follow-up and medical consulting, as a strategy
25			for achieving adequate participant enrollment to reach the target
26			sample size.
27			
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29			

30 **Methods: Participants, interventions, and outcomes**

31			
32	Study setting	9	Eligible PDR patients hospitalized in the Department of
33			Ophthalmology, West China Hospital, Sichuan University, Chengdu,
34			China
35			
36	Eligibility criteria	10	Inclusion criteria
37			Patients with PDR who meet the following criteria will be enrolled in
38			the trial:
39			(1) PDR which has definite indications for surgery and no absolute
40			contraindications to surgery in general condition;
41			(2) Vitrectomy for the target eye is performed for the first time;
42			(3) Agree to join after fully understanding the informed consent of the
43			clinical research.
44			
45			
46			
47			Exclusion criteria
48			Patients meeting any of the following criteria will be excluded from the
49			study:
50			(1) Acquired Immune Deficiency Syndrome, syphilis, leukemia, etc;
51			(2) Type 1 diabetes;
52			(3) Rubeosis iris or neovascular glaucoma (NVG), uveitis, branch
53			retinal vein occlusion, age-related macular degeneration, ocular
54			trauma, endophthalmitis, etc;
55			(4) <6 months follow-up after primary vitrectomy.
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- Interventions
- 11a All surgeries will be performed by one skilled retinal surgeon (Meixia Zhang) under retrobulbar anesthesia 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. Harvested vitreous will be immediately kept on ice and transferred to the laboratory within four hours for centrifugation at 4°C, 4000 rpm for 15-30 minutes. Supernatant sample aliquots will be then stored at -80°C until further analysis. Then triamcinolone acetonide will be applied for offering a better identification to eliminating vitreous cortex and proliferative membranes, indocyanine green will be used in patients with epiretinal membranes. Remarkably, we will observe degrees of posterior vitreous detachment (PVD) in the surgical eyes, including partial PVD and complete PVD. Pan-retinal laser photocoagulation will be done or supplemented during surgery, and at the end of surgery, silicone oil or perfluoropropane (C3F8) or balanced salt solution (BSS) will be used in cases according to the retinal condition. Surgical records and surgical videos will keep well to check the procedure.
- 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)
- 11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
- 11d Relevant concomitant care and interventions that are permitted or prohibited during the trial



1			
2	Outcomes	12	Primary outcomes
3			The primary outcome is the association between visual outcome
4			(best-corrected visual acuity (BCVA) and renal profile.
5			
6			Secondary outcomes
7			1. Associations between retinal and choroidal
8			microvasculature/microstructure and renal function in PDR inpatients.
9			① Retinal and choroidal microvasculature include foveal avascular
10			zone (FAZ), vessel density of superficial capillary plexus (SCP), deep
11			capillary plexus (DCP), and vessel density of the choriocapillaris,
12			respectively.
13			② Retinal and choroidal microstructure includes the central macular
14			thickness (CMT) and subfoveal choroidal thickness (SFCT)
15			respectively.
16			2. The rates of postoperative complications (posterior capsular
17			opacification, progressed cataract, high intraocular pressure, early VH
18			(before 4 weeks after surgery), late VH (occurred later than 4 weeks
19			after surgery), epiretinal membrane, macular hole, macular edema,
20			retinal/macular re-detachment, and NVG will be explored.
21			3. We will explore the vitreous related cytokines and pathways in the
22			prognosis after the first PPV surgery for PDR in Chinese.
23			
24	Participant	13	A schematic diagram is highly recommended (see Table 1)
25	timeline		
26			
27	Sample size	14	According to the previous literature report, <sup>37</sup> it is estimated that the
28			occurrence rates of poor vision at 6-month in DKD group and non-
29			DKD group are 0.077 and 0.206, respectively. PASS 15 software
30			(PASS 15.0.5 NCSS, LLC USA) was adopted to calculate the
31			experimental size of the DKD group and the non-DKD group
32			N1=N2=149 cases. Assuming that the loss to follow-up rate of the
33			study subjects is 20%, the sample size is $N1=N2=149\div0.8=186$ cases.
34			Therefore, the minimum sample size included in this study is 372
35			cases. In real-world clinical practice, a total of 400 cases will be
36			included.
37			
38	Recruitment	15	Those who enter the trial will have the privilege of priority in follow-up
39			and medical consulting, as a strategy for achieving adequate
40			participant enrollment to reach the target sample size.
41			
42	<b>Methods: Data collection, management, and analysis</b>		
43			
44	Data collection	18a	Page8-11
45	methods		
46		18b	
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48	Data	19	Page 11-12
49	management		
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Statistical methods 20a Page 14

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## Methods: Monitoring

Data monitoring 21a Page 11

21b

Harms 22 Page 5-6

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

## Ethics and dissemination

Research ethics approval 24 Page 15

Protocol amendments 25 Not applicable

Consent or assent 26a Page 6

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27 Page 15

Declaration of interests 28 Page 16

Access to data 29 All the authors in our team have access to the final trial dataset, and disclosure of contractual agreements

Ancillary and post-trial care 30

Dissemination policy 31a Page 15

31b Authorship eligibility guidelines and any intended use of professional writers

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code

## Appendices

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Informed consent materials	32	We have related document in Chinese, not in English.
Biological specimens	33	Page 6-7

\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

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# BMJ Open

## The relationship between renal function and prognosis of Chinese proliferative diabetic retinopathy patients undergoing the first vitrectomy: protocol for a prospective cohort study

Journal:	BMJ Open
Manuscript ID	bmjopen-2021-052417.R1
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# **The relationship between renal function and prognosis of Chinese proliferative diabetic retinopathy patients undergoing the first vitrectomy: protocol for a prospective cohort study**

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## **Introduction:**

China has the largest number of adults with diabetes aged 20-79 years (116.4 million) in 2019. Due to some socioeconomic factors or a lack of awareness of diabetic complications, diabetics may be found to have proliferative diabetic retinopathy (PDR) or renal function impairment at their first visit to the clinic for a sudden loss of vision, when pars plana vitrectomy (PPV) needs to be involved in their treatment. Risk factors for the outcomes and complications of PPV surgery in PDR patients have been widely explored in many epidemiologic studies and clinical trials. However, few prospective studies have analyzed the association between renal function and surgical outcomes in PDR.

## **Methods and analysis:**

This is a single-center, 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 enroll 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 summarized using descriptive statistics. The variation will be described and evaluated using the  $\chi^2$  test or Kruskal-Wallis test. Generalize additive mixed models (GAMM) will be used to explore the association between the renal profile and surgical outcomes including BCVA, and retinal and choroidal

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1 microvasculature/microstructure. Multivariate ordinal regression analysis will be used to detect  
2 the independent association between renal profile and BCVA changes, and smooth curve fitting  
3 will be employed to briefly present the tendency.

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

7       **Trial registration:** ChiCTR2000039698, registered November 6, 2020.

8

9       **Strengths and limitations of this study**

10 1. The present study will identify the association between renal profile and prognosis of proliferative  
11 diabetic retinopathy patients undergoing the first PPV surgery in the Chinese population, therefore,  
12 it might provide a reference for clinical decision-making in real-world clinical practice.

13 2. Our research provides the possibility to find out the factors affecting prognosis after vitrectomy,  
14 and to explore the underlying mechanism.

15 3. It is currently the largest prospective cohort study and we will use strict statistical adjustment to  
16 minimize the effect of residual confounders.

17 4. The study population is restricted to the Chinese with type 2 diabetes mellitus, therefore, the  
18 generalization of the results may be limited.

19 5. As an observational design, this study is impossible to infer causality in the association between  
20 renal function and surgical prognosis, therefore, the findings in our study need to be corroborated  
21 by randomized controlled trials.

22       **Introduction**

23       China has the largest number of adults with diabetes aged 20-79 years (116.4 million) in 2019,  
24 and the number is anticipated to increase to 140.5 million in 2030 and 147.2 million in 2045.<sup>1</sup> It is  
25 estimated that the prevalence of diabetes is up to 12.8% among adults living in the mainland Chinese  
26 population.<sup>2</sup> The prevalence of diabetes varies by ethnicity and region. Han ethnicity has the highest  
27 prevalence of diabetes (12.8%) with merely 33.2% of diabetes awareness in Southwest China.<sup>2</sup> With  
28 the increasing prevalence of diabetes, diabetes-related complications including diabetic retinopathy  
29 (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.<sup>3</sup> Proliferative DR (PDR), the most advanced stage of DR, is characterized by neovascularization and proliferative membrane formation, which may cause vitreous hemorrhage and tractional retinal detachment (TRD), resulting in progressive vision loss.<sup>4-7</sup> Among Chinese patients with diabetes, the prevalence of any DR, non-PDR, and PDR are 18.45%, 15.06%, and 0.99%, respectively.<sup>8</sup> Due to some socioeconomic factors or a lack of awareness of diabetes and diabetic complications, diabetics may be found to have PDR and renal function impairment at their first visit to the clinic for a sudden loss of vision, when pars plana vitrectomy (PPV) needs to be involved in their treatment.

PPV treatment for PDR aims at improving visual acuity, removing vitreoretinal traction and vitreous hemorrhage, reattaching detached neuroretina, maintaining media transparency, and improving ocular circulation.<sup>7-9</sup> 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 favorable.<sup>10-12</sup> Benefiting from the improvement of living and medical conditions, the 5-year survival rate of PDR patients undergoing PPV varies from 68% to 95%.<sup>13</sup> Even though, how to improve the visual acuity and quality of life of those patients remains a problem that needs to be solved urgently.

Previous studies<sup>14-21</sup> have proved that renal function impairment, especially low estimated glomerular filtration rate (eGFR), is involved in the development of DR. Other studies<sup>21-26</sup> 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 normalize serum urea and creatinine early and stabilize the retinopathy status in the majority of patients.<sup>27</sup> Furthermore, renal function is positively correlated with the DR stages and diabetic macular edema in southern China.<sup>21</sup> These studies indicated that renal malfunction may affect retinal function and structure. Katagiri M et al.<sup>28</sup> found that vitreous soluble receptor for advanced glycation end products (sRAGE) may be a potential biomarker for renal dysfunction associated with DR. Except for 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.

Epidemiological study<sup>29</sup> of diabetes have 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 studies<sup>30 31</sup> suggesting that the relationship between DR and diabetic nephropathy (DN) is not always consistent. Evidence from the Chinese Han population study indicating that DR and DN may be independent diseases.<sup>30</sup> Another study found that the associations between the microvascular complications of the eye and kidney may vary depending on race, obesity, and the use of renin-angiotensin-aldosterone antagonists.<sup>32</sup>

Presently, few relevant studies have investigated the association between systemic comorbidities and the outcomes of PDR surgery. Previous studies<sup>33-35</sup> targeting at the association between renal function and prognosis of PDR patients undergoing the first vitrectomy failed to draw any positive conclusions. Song et. al<sup>36</sup> 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, these clinical findings are all from retrospective studies and are restricted to small samples. Furthermore, there is no relevant evidence from the Chinese patients. That is why we conduct this prospective cohort study to explore the association between the both in the Chinese population.

**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 hospitalized 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-center, cohort study. The clinical trial began in November 2020 and participants enrollment will be completed in December 2023. Each participant will follow up for at least 6 months after surgery. We will consecutively collect 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 which has definite indications for surgery and no absolute contraindications to surgery in general condition;
- (2) Fasting blood glucose is less than 8 mmol/L, and blood glucose two 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) Acquired Immune Deficiency Syndrome, syphilis, leukemia, 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

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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 hospitalized 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 enrollment. 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 enrollment to reach the target sample size.

**Sample size**

According to the previous literature report,<sup>37</sup> it is estimated that the occurrence rates of poor vision at 6-month in DKD group (glomerular filtration rate lower than 60 ml/(min 1.73 m<sup>2</sup>)) and non-DKD group are 0.077 and 0.206, respectively. PASS 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÷0.8=186 cases. Therefore, the minimum sample size included in this study is 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

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retrobulbar anesthesia 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. Harvested vitreous will be immediately kept on ice and transferred to the laboratory within four hours for centrifugation at 4°C, 4000 rpm for 15-30 minutes. Supernatant sample aliquots will be then stored at -80°C until further analysis. Then triamcinolone acetonide will be applied for offering a better identification to eliminating vitreous cortex and proliferative membranes, indocyanine green will be only used in patients with epiretinal membranes. Remarkably, we will observe degrees of posterior vitreous detachment (PVD) in the surgical eyes, including partial PVD and complete PVD. Pan-retinal 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 (BSS) 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, early VH (before 4 weeks after surgery), late VH (occurred later than 4 weeks after surgery), epiretinal membrane, macular hole, macular edema, retinal/macular re-

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1 detachment, and NVG) will be explored.

2 3. We will explore the vitreous-related cytokines and pathways in the prognosis of PDR

3 patients undergoing the first PPV surgery in the Chinese population.

4

5 **Data and sample collection**

6 Relevant baseline characteristics which are important in the management of hospitalized PDR

7 patients will be collected. Demographic information includes age, sex, ethnicity, education level,

8 occupation, living region, etc. Relevant medical history includes diabetes duration, hypertension

9 history, DKD history, chronic kidney disease history, history of cardiovascular diseases including

10 coronary heart disease, stroke, heart failure, etc. Systemic medication history includes oral diabetes

11 medication, insulin treatment, oral antihypertensive drugs, anticoagulant/antiplatelet agent

12 administration, kidney protection drugs. General characteristics at initial presentation including

13 smoking/drinking status, height, weight, waist circumference, systolic and diastolic blood pressure

14 will be extracted.

15 All relevant laboratory tests will be completed on admission. Laboratory values include

16 preoperative glycosylated hemoglobin (HbA1c), renal profile (e.g., serum blood urea nitrogen,

17 serum creatinine, eGFR, uric acid, serum cystatin C, etc), hepatic function, blood lipids, C reactive

18 protein, erythrocyte sedimentation rate, serum homocysteine, etc.

19 Moreover, the ophthalmologic findings will be categorized into three sections: preoperative,

20 intraoperative, and postoperative. The preoperative ophthalmologic history contains the history of

21 intraocular lens implantation, the history of intravitreal injection of anti-vascular endothelial growth

22 factor (VEGF) agents and anti-inflammatory treatment (TA, Orudex, etc), the history of pan-retinal

23 photocoagulation, duration from visual loss awareness to the primary vitreous surgery, etc.

24 The intraoperative ophthalmologic findings will be listed as follows: duration of operation,

25 cataract surgery, intraoperative retinal photocoagulation, C3F8 tamponade, silicone oil tamponade,

26 intraoperative complications (iatrogenic retinal break, etc), macular hole, PVD, fibrovascular

27 membrane, retinal detachment, and macular detachment, etc.

28 Finally, the postoperative complications will be collected including posterior capsular

29 opacification, progressed cataract, high intraocular pressure, early VH, late VH, epiretinal

30 membrane, macular hole, macular edema, retinal/macular re-detachment, and NVG. Patients with

macular edema 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, intraocular pressure (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. 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.

### BCVA

For visual acuity measurement, the decimal BCVA will be measured using the standard logarithmic visual acuity scale placed 5 m 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.<sup>38</sup> The scheme we adopt has been described previously.<sup>37</sup> 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 (SD)-OCT (Spectralis OCT, Heidelberg Engineering; Heidelberg, Germany). OCT measurements will be performed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. A standardized imaging protocol with enhanced depth imaging (EDI) will be performed: a 6-line radial scan centered on the fovea. Quantitative assessments included CMT and SFCT will be measured manually using digital calipers provided by Heidelberg Eye Explorer software (Heidelberg Engineering, Heidelberg, Germany) at baseline if applicable and at all follow-up time. 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 hyperreflective line corresponding to the RPE perpendicular to the choriocleral interface.

We also will collect the presence and changes of OCT morphologic 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 analyze 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, CA, USA) using a standard protocol as specified by the manufacturer. The macula-centered 3×3 mm and optic disc-centered 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 (RPC) and RNFL thickness will be generated on the basis of 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 center. 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  $\mu\text{m}$  above the inner plexiform layer (IPL), and the DCP is defined as extending from 15  $\mu\text{m}$  to 75  $\mu\text{m}$  above the IPL. The choriocapillary layer is defined as extending from 30  $\mu\text{m}$  to 60  $\mu\text{m}$  beneath RPE. The parafoveal area is defined as an annulus centered 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 artifacts are used. Patients whose images have poor quality with motion artifacts, inadequate signal strength  $< 5/10$ , poorly focused scans, or segmentation failure will be excluded.

### **ERG recordings**

Full-field dark- and light-adapted ERGs will be recorded with a visual electrophysiology diagnosis system (RETI-Port/Scan21; Roland, Germany) as per ISCEV standard.<sup>39</sup> 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 anesthesia 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 inter-stimulus 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 times after the first week postoperatively.

### **Data storage and management**

We 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



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1 empowerstats dataweb or will be collected using paper CRFs by the investigators and then enter  
2 into empowerstats dataweb. All the physician investigators are trained in using the web-based  
3 application, and the data on the host server is protected by an individual user ID and password. The  
4 patient ID remains with a patient even if he or she moves or changes practitioner. This method of  
5 assigned patient ID ensures that patients can be followed up through a long period in case of  
6 transition. The study protocols specify the examination parameters required at baseline and follow-  
7 up visits (**Table 1**). Physician investigators are encouraged to record data as soon as clinic visits  
8 end. Regular data quality checks include reviewing missing data and checking for outliers and  
9 discrepancies. For data safety and security, the electronic data will be maintained under secure,  
10 password-protected conditions while hard copy records will be kept in a locked office.

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**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
	OCT	X (If applicable)		X	X	X	X	X
	OCTA	X (If applicable)		X	X	X	X	X
	ERG				X	X	X	X
Postoperative complications			X	X	X	X	X	X

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1           **Proposed statistical methods**

2           Demographic characteristics and study outcomes will be summarized using descriptive  
3           statistics. Continuous variables will be summarized with means, medians, and interquartile ranges  
4           (IQRs), and categorical variables with frequencies and percentages. The variation will be  
5           described and evaluated using the  $\chi^2$  test or Kruskal-Wallis test. Generalize additive mixed models  
6           (GAMM) will be used to explore the association between the renal profile and surgical outcomes  
7           including BCVA, and retinal and choroidal microvasculature/microstructure. Multivariate ordinal  
8           regression analysis will be used to detect the independent association between renal profile and  
9           BCVA changes, and smooth curve fitting will be employed to briefly present the tendency. A two-  
10          sided  $P < 0.05$  is considered to be statistically significant. Statistical analyses will be performed  
11          using Empower Stats (<http://www.empowerstats.com>; X&Y Solutions Inc., Boston, MA) and R  
12          software, version 3.4.3 (<http://www.R-project.org/>, The R Foundation).

15          **Patient and public involvement**

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

20          **Ethics and dissemination**

21          **Ethics approval**

22          The protocols to be used adhere to the principles of the Declaration of Helsinki and have been  
23          approved by the Chinese Clinical Trial Registry (ChiCTR2000039698, registered November 6,  
24          2020). Written informed consent will be obtained from each participant before enrolled in the study.

26          **Dissemination and data sharing**

27          The study will be reported according to the Strengthening the Reporting of Observational  
28          Studies in Epidemiology Statement: Guidelines for Reporting Observational Studies. The first  
29          author will be responsible for the data and analysis. Study results will be distributed using a broad

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dissemination strategy, including presentations at national and international meetings, and publications in high-impact open access journals.

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None.

#### **Authors' contributions**

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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#### **Competing interest statement**

The authors declare that they have no competing interests.

#### **Patient consent for publication**

Not required.

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# BMJ Open

## The relationship between renal function and prognosis of Chinese proliferative diabetic retinopathy patients undergoing the first vitrectomy: protocol for a prospective cohort study

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# **The relationship between renal function and prognosis of Chinese proliferative diabetic retinopathy patients undergoing the first vitrectomy: protocol for a prospective cohort study**

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## **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 diabetics 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 epidemiologic studies and clinical trials. However, few prospective studies have analyzed the association between renal function and surgical outcomes in PDR.

## **Methods and analysis:**

This is a single-center, 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 enroll 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 summarized using descriptive statistics. The variation will be described and evaluated using the  $\chi^2$  test or Kruskal-Wallis test. Generalize additive mixed models (GAMM) 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

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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:** ChiCTR2000039698, registered November 6, 2020.

**Strengths and limitations of this study**

1. The present study will identify the association between renal profile and prognosis of proliferative diabetic retinopathy patients undergoing the first PPV surgery in the Chinese population, therefore, it might provide a reference for clinical decision-making in real-world clinical practice.
2. Our research provides the possibility to find out the factors affecting prognosis after vitrectomy, and to explore the underlying mechanism.
3. It is currently the largest prospective cohort study and we will use strict statistical adjustment to minimize the effect of residual confounders.
4. The study population is restricted to the Chinese with type 2 diabetes mellitus, therefore, the generalization of the results may be limited.
5. 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 randomized controlled trials.

**Introduction**

China has the largest number of adults with diabetes aged 20-79 years (116.4 million) in 2019, and the number is anticipated to increase to 140.5 million in 2030 and 147.2 million in 2045.<sup>1</sup> It is estimated that the prevalence of diabetes is up to 12.8% among adults living in the mainland Chinese population.<sup>2</sup> 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 Southwest China.<sup>2</sup> 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.<sup>3</sup> Proliferative DR (PDR), the most advanced stage of DR, is characterized by neovascularization and proliferative membrane formation, which may cause vitreous hemorrhage and tractional retinal detachment (TRD), resulting in progressive vision loss.<sup>4-7</sup> Among Chinese patients with diabetes, the prevalence of any DR, non-PDR, and PDR are 18.45%, 15.06%, and 0.99%, respectively.<sup>8</sup> Due to the socioeconomic condition or a lack of awareness of diabetic complications, many diabetics 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 hemorrhage, reattaching detached neuroretina, maintaining media transparency, and improving ocular circulation.<sup>7-9</sup> 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 favorable.<sup>10-12</sup> Benefiting from the improvement of living and medical conditions, the 5-year survival rate of PDR patients undergoing PPV varies from 68% to 95%.<sup>13</sup> But how to improve the visual acuity and quality of life of those patients remains a problem that needs to be solved urgently.

Previous studies<sup>14-21</sup> have proved that renal function impairment, especially low estimated glomerular filtration rate (eGFR), is involved in the development of DR. Other studies<sup>21-26</sup> 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 normalize serum urea and creatinine early and stabilize the retinopathy status in the majority of patients.<sup>27</sup> Furthermore, renal function is positively correlated with the DR stages and diabetic macular edema in southern China.<sup>21</sup> These studies indicated that renal malfunction may affect retinal function and structure. Katagiri et al.<sup>28</sup> found that the vitreous soluble receptor for advanced glycation end products (sRAGE) 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 study<sup>29</sup> of diabetes has shown the high consistency between DR and renal

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insufficiency. DR and DKD are related to each other through a common pathophysiological mechanism. However, there are other studies<sup>30 31</sup> 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.<sup>30</sup> 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.<sup>32</sup>

At present, few relevant studies have investigated the association between systemic comorbidities and the outcomes of PDR surgery. Previous studies<sup>33-35</sup> targeting the association between renal function and prognosis of PDR patients undergoing the first vitrectomy failed to draw any positive conclusion. Song et. al<sup>36</sup> 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 hospitalized PDR patients undergoing primary PPV surgery in China, including trends in these outcomes over time.

**Significance**

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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-center, cohort study. The clinical trial began in November 2020 and participants enrollment 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 which has definite indications for surgery and no absolute contraindications to surgery in general condition;
- (2) Fasting blood glucose is less than 8 mmol/L, and blood glucose two 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) Acquired Immune Deficiency Syndrome, syphilis, leukemia, 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

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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 hospitalized 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 enrollment. 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 enrollment to reach the target sample size.

**Sample size**

According to the previous literature report,<sup>37</sup> it is estimated that the occurrence rates of poor vision at 6-month in the DKD group (glomerular filtration rate lower than 60 ml/(min 1.73 m<sup>2</sup>)) and the non-DKD group are 0.077 and 0.206, respectively. PASS 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÷0.8=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 anesthesia 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 four hours for centrifugation at 4°C, 4000 rpm for 15-30 minutes. Supernatant sample aliquots will then be stored at -80°C until further analysis. Then triamcinolone acetonide 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. Pan-retinal 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 (BSS) 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, early VH (before 4 weeks after surgery), late VH (occurred later than 4 weeks after surgery), epiretinal membrane, macular hole, macular edema, retinal/macular re-

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detachment, 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 which are important in the management of hospitalized 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, kidney protection drugs. General characteristics at initial presentation including smoking/drinking status, height, weight, waist circumference, systolic and diastolic blood pressure will be extracted.

All relevant laboratory tests will be completed on admission. Laboratory values include preoperative glycosylated hemoglobin (HbA1c), renal profile (e.g., 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 ophthalmologic findings will be categorized into three sections: preoperative, intraoperative, and postoperative. The preoperative ophthalmologic history contains the history of intraocular lens implantation, the history of intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents and anti-inflammatory treatment (TA, Orudex, etc), the history of pan-retinal photocoagulation, duration from visual loss awareness to the primary vitreous surgery, etc.

The intraoperative ophthalmologic 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, and macular detachment, etc.

Finally, the postoperative complications will be collected including posterior capsular opacification, progressed cataract, high intraocular pressure, early VH, late VH, epiretinal membrane, macular hole, macular edema, retinal/macular re-detachment, and NVG. Patients with

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macular edema 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, intraocular pressure (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.

### 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.<sup>38</sup> The scheme we adopt has been described previously.<sup>37</sup> BCVA changes in comparison with the preoperative value at each follow-up visit will be recorded and divided into three categories. An

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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 (SD)-OCT (Spectralis OCT, Heidelberg Engineering; Heidelberg, Germany). OCT measurements will be performed according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol. A standardized imaging protocol with enhanced depth imaging (EDI) will be performed: a 6-line radial scan centered on the fovea. Quantitative assessments included CMT and SFCT will be measured manually using digital calipers provided by Heidelberg Eye Explorer software (Heidelberg Engineering, Heidelberg, Germany) 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 hyperreflective line corresponding to the RPE perpendicular to the choriocleral interface.

We also will collect the presence and changes of OCT morphologic 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 analyze 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, CA, USA) using a standard protocol as specified by the manufacturer. The macula-centered 3×3 mm and optic disc-centered 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 (RPC) and RNFL thickness will be generated based on the automated layer segmentation by the in-built RTVue XR Avanti

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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 center. 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  $\mu\text{m}$  above the inner plexiform layer (IPL), and the DCP is defined as extending from 15  $\mu\text{m}$  to 75  $\mu\text{m}$  above the IPL. The choriocapillary layer is defined as extending from 30  $\mu\text{m}$  to 60  $\mu\text{m}$  beneath RPE. The parafoveal area is defined as an annulus centered 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 artifacts are used. Patients whose images have poor quality with motion artifacts, inadequate signal strength  $< 5/10$ , poorly focused scans, or segmentation failure will be excluded.

### ERG recordings

Full-field dark- and light-adapted ERGs will be recorded with a visual electrophysiology diagnosis system (RETI-Port/Scan21; Roland, Germany) as per ISCEV standard.<sup>39</sup> 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 anesthesia 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 inter-stimulus 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

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1 and store data with well-designed case report forms (CRFs). Data will either be entered directly into  
2 the empowerstats dataweb or will be collected using paper CRFs by the investigators and then enter  
3 into empowerstats dataweb. All the investigating physicians are trained in using the web-based  
4 application, and the data on the host server is protected by an individual user ID and password. The  
5 patient ID remains with a patient even if he or she moves or changes practitioner. This method of  
6 assigned patient ID ensures that patients can be followed up through a long period in case of  
7 transition. The study protocols specify the examination parameters required at baseline and follow-  
8 up visits (**Table 1**). Investigating physicians are encouraged to record data as soon as clinic visits  
9 end. Regular data quality checks include reviewing missing data and checking for outliers and  
10 discrepancies. For data safety and security, the electronic data will be maintained under secure,  
11 password-protected conditions while hard copy records will be kept in a locked office.

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**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
	OCT	X (If applicable)		X	X	X	X	X
	OCTA	X (If applicable)		X	X	X	X	X
	ERG				X	X	X	X
Postoperative complications			X	X	X	X	X	X



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**Proposed statistical methods**

Demographic characteristics and study outcomes will be summarized using descriptive statistics. Continuous variables will be summarized with means, medians, and interquartile ranges (IQRs) and the categorical variables with frequencies and percentages. The variation will be described and evaluated using the  $\chi^2$  test or Kruskal-Wallis test. Generalized additive mixed models (GAMM) 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, MA) and R software, version 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 (ChiCTR2000039698, registered November 6, 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

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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.

### **Acknowledgments**

None.

### **Authors' contributions**

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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### **Competing interest statement**

The authors declare that they have no competing interests.

### **Patient consent for publication**

Not required.

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**Word Count: 3436.**

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