Clinical and Histopathological Features of Diffuse Infiltrating Retinoblastoma in Chinese Children

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Research Article

Keywords: Retinoblastoma, Diffuse infiltrating retinoblastoma, Histopathology, Histopathologic risk factors

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Clinical and Histopathological Features of Diffuse Infiltrating Retinoblastoma in Chinese Children

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Abstract

Purpose: To describe the clinical and histopathological characteristics of diffuse infiltrating retinoblastoma underwent primary enucleation from Chinese children.

Methods: It was a hospital-based retrospective study that included all eyes with retinoblastomas consecutively enucleated in the Beijing Tongren Hospital between October 2005 and October 2019. Further studies were carried out in patients diagnosed by clinicians and pathologists as diffuse infiltrating retinoblastoma.

Results: Out of 1,911 patients, 37 eyes of 37 patients (2%) were classified as diffuse infiltrating type and treated with primary enucleation. The tumors were detected at a mean age of 47 months (range: 6–108 months). There were two (5%) patients with binocular tumors and one (3%) patient with a positive family history. Anterior chamber fine needle aspiration biopsy was obtained in 5 cases for diagnostic purpose. In 11 patients (30%), the retinoblastoma had not initially been diagnosed as a tumor. The most common symptoms found on ophthalmic examination were conjunctiva injection (n=17;46%) of anterior segment and vitreous seeds (n=23; 62%) of posterior segment. 12 of 37 tumors measured by imaging examination and cross-section showed the average height was 7mm and average width was 10mm. The minimum tumor diameter was just 3mm. Histopathology revealed tumor invasion into optic

nerve (n=26; 70%), iris (n=14; 38%), ciliary body (n=12; 32%), massive choroid (n=2;5%) and iris neovascularization (n=24; 65%). Histopathologic risk factors (HRF) were detected in 26 eyes. Anterior chamber fine needle aspiration biopsy (FNAB), cornea endothelium with tumor seeds, anterior chamber free-floating tumor seeds, or pseudohypopyon might contribute to a higher rate of histopathological risk factors. **Conclusions:** Diffuse infiltrating retinoblastoma was usually masqueraded as endophthalmitis. Therefore, it should always be considered as a differential diagnosis in intraocular inflammation. Considering the so small diameter of the tumor, it should be examined carefully. Anterior chamber fine needle aspiration biopsy should be used with caution.

Key words: Retinoblastoma, Diffuse infiltrating retinoblastoma, Histopathology, Histopathologic risk factors

Introduction

Retinoblastoma is the most common primary intraocular malignancy usually occurring in childhood[1]. Based on tumor growth pattern, four groups of retinoblastoma have been distinguished, that is exophytic, endophytic, mixed endophytic-exophytic, and diffuse infiltrating type. Diffuse infiltrating retinoblastoma, where the tumor tissues grow along the retina and develop a flat neoplastic lesions, is a rare growth pattern, and it may then present with atypical features, posing a diagnostic challenge and potentially leading to a masquerade syndrome[2]. Fundus lesions of diffuse infiltrating type are usually neglected by the ophthalmologic examination, and almost all of those patients need enucleation because of the late diagnosis and high-risk factors.

Studying eyes of children enucleated for diffuse infiltrating retinoblastoma may therefore improve the diagnosis of tumors in eyes with a masquerade syndrome and facilitate better personalization treatment. Those were the reasons for conducting this study, in which we retrospectively reviewed a large series of eyes enucleated for retinoblastoma in a major Chinese eye hospital with the aim of investigating the clinical manifestations and histopathological characteristics of eyes with diffuse infiltrating retinoblastoma.

Material and Method

This retrospective hospital-based study included all eyes which had been primary enucleated in the study period from October 2005 to October 2019, for which the histological examination at the ophthalmic oncological center of the Beijing Tongren Hospital had revealed a retinoblastoma with diffuse infiltrating type. Patients who received chemotherapy, radiotherapy or laser therapy prior to surgery were excluded. The study was approved by the Ethics Committee of the Beijing Tongren Hospital and followed the tenets of the Declaration of Helsinki. Due to the retrospective design of the study, the ethics committee waived the necessity for an informed written consent signed by the patients.

Clinical date such as the age at the time when the symptom onset, gender, tumor laterality, hereditary pattern, primary diagnosis, chief complaint, ophthalmic examination features were collected. The hematoxylin-eosin–stained slides contain the central pupil–optic nerve section and the optic nerve cut margin section were reviewed to assess parameters include tumor growth pattern, tumor differentiation, calcification, tumor invasion into the surrounding structures, and histopathologic risk features. According to the International Retinoblastoma Staging Working Group (IRSWG)[3], the tumor invasion into the optic nerve was categorized as 'prelaminar', 'laminar', 'retrolaminar', or 'tumor at surgical margin'. Choroidal involvement was differentiated into 'none', 'focal', or 'massive' (defined as ≥ 3 mm in diameter) [3]. We additionally assessed high-risk features such as tumor invasion into the anterior chamber, iris, ciliary body, choroid (massive), optic nerve (retrolaminar with or without tumor cells at the resected optic nerve margin), sclera, and extrascleral soft tissue. The date were tabulated and statistically analyzed using SPSS for Windows (version 21.0; IBM-SPSS, Chicago, Ill., USA).

Result

Of the totally 1,911 patients who were consecutively undergoing primary enucleation in the study period, 37 eyes of 37 patients (2%) with a diffuse infiltrating retinoblastoma were enrolled. 35 (95%) patients occurred unilaterally while 2 (5%) cases had binocular tumors. The mean age at the time when symptoms were first

noted was 45 months (range: 6-108 months). Among these children, 23 (62%) were boys and 14 (38%) were girls, and 20 (54%) were right eyes and 17 (46%) were left eyes. Diffuse infiltrating retinoblastoma occurrence was not significantly associated with sex ($p = 0.27$) or right or left eye ($p = 0.17$). A history of blunt trauma was positive in 3 of these eyes (8%). Only one (3%) patient had a positive family history of ocular tumor. Anterior chamber fine needle aspiration biopsy (FNAB) was obtained for diagnostic purpose, and 4 of 5 revealed to be retinoblastoma by cytology, while the other one only showed inflammatory cells.

The main complaints expressed by the children or indirectly by their parents at the time of presenting were 'white pupil' in 14 cases (38%), 'red eye' in 7 cases (19%), 'decreased vision' in 7 cases (19%), 'strabismus' in 5 cases (14%), 'anterior chamber with white sediment' in 3 cases (8%), 'pupil dilated and ocular pain' in 1 case (2.5%) separately. 11 of 37 patients (30%) had a wrong initial diagnosis or a wrong referral diagnosis. Among them, 3 (28%) children presented with uveitis, 2 (18%) with conjunctivitis, 2 (18%) with vitreous hemorrhage, 1 (9%) with hyphema, 1 (9%) with endophthalmitis, 1 (9%) with Coats disease, and 1 (9%) with retinal detachment.

Ophthalmic examination revealed that most patients had a reduced vision (18/19, 95%), and elevated intraocular pressure (13/19, 68%). The commonest symptom of anterior segment was conjunctiva injection (17/37, 46%), secondly is corneal stromal edema (14/37, 38%), followed by pseudohypopyon (12/37, 32%), and iris tumor nodules (12/37, 32%) (Fig. 1). Ocular fundus examination under general anesthesia revealed that, 23 eyes (62%) with vitreous opacity, 15 eyes (41%) with subretinal tumor, 9 eyes (24%) with retinal detachment, almost all of them had the total retinal detachment or retinal thickening with retinal detachment (Fig. 1). Ophthalmic examination findings and the relationship between clinical features and histopathologic risk features were listed in Table 1. It was obvious that anterior chamber FNAB had relation to histopathologic risk features ($p < 0.05$). Ophthalmic examination disclosing cornea endothelium with tumor seeds, anterior chamber

free-floating tumor seeds, or pseudohypopyon were an indicator for a higher ratio of histopathologic risk features ($p<0.05$).

Computed tomography (CT) was considered the most valuable method to reveal the calcification in solid tumors. CT was available in 31 cases in our cases, and disclosed calcification in 16 (52%) cases. Magnetic resonance imaging (MRI) was the most useful for diffuse infiltrating retinoblastoma diagnosis for retina thickened. The most frequently observed changes were vitreous opacity through B-scan ultrasonography. Ultrasonography performed in 28 eyes showed vitreous opacification (16/28, 57%), retinal detachment (6/28, 21%), calcification (4/28, 14%), and retina thickened (2/28,7%) (Fig. 2). 12 of 37 tumors were measured by imaging examination and cross-section showing the average height was 7mm and average width was 10mm. The minimum tumor diameter was just 3mm.

Histopathologic examination of the enucleated globes revealed that the differentiated types were detected in histologic sections in 32 of 37 (86%) eyes, calcifications were observed in 3 (8%), and necrosis in 2 (5%). Tumor cells infiltrated into the optic disc (26/37, 70%), lamina (16/37, 43%), and iris (14/37, 38%). Iris neovascularization were found in 24 eyes (65%). Tumor cells involvement of massive choroid were found in 2 (5%). And all tumor cells were not detected on the cross section of the optic nerve. Histopathologic high-risk factors were detected in 26 eyes (70%), among them, 24 eyes (65%) with one factor and 2 eyes (5%) with two factors. Histopathologic feature findings were listed in Table 2 and Fig. 3. The correlation between histopathological features and the time to diagnosis was analyzed and listed in Fig. 4. There is no correlation between the time to diagnosis and histopathological features($p>0.05$). Histopathological features were not affected by the time interval between onset of symptoms and diagnosis. In addition, the relationship between the time to diagnosis and histopathologic risk factors was showed in Fig. 5. Most of patients had 1-50 days interval between onset of symptoms and diagnosis. The patients whose time interval was longer than 150 days had the histopathologic risk factors.

Discussion

It is generally accepted that the diffuse infiltrating retinoblastoma is different from the exophytic tumor, which initiates in the external retinal layers and develops beneath the retina in the subretinal space with subretinal fluid, and the endophytic tumor, which presents a retinal mass growth towards the vitreous cavity with vitreous seeds. It is a rare subtype and only accounted for about 1-2% of retinoblastoma[4]. Our single-center study confirmed this again, only 37(2%) of the 1,911 patients with eyes consecutively enucleated for the diffuse infiltrating retinoblastoma.

In our cohort, all diffuse infiltrating retinoblastoma patients were detected at an age ranging between 6 months and 9 years and the mean age was 45 months. 2 of 37 patients (5%) had a bilateral diffuse infiltrating retinoblastoma and the ages were 6 months and 2 years respectively. Previous studies indicated that typical retinoblastoma cases were diagnosed at a very early stage, two-thirds before 2 years of age[5]. And the children with bilateral retinoblastoma tended to present at a younger age (usually before 1 year of age) than patients with unilateral disease (often in the second or third year of age) [6]. The growth speed of diffuse infiltrating retinoblastoma was supposed to be slower [7], which could explain the later age at presentation.

In our study, only one child (3%) with unilateral retinoblastoma (diffuse infiltrating type in one eye) had positive family history. His father and uncle had a history of eye tumor, but more details were unknown. The family history of traditional retinoblastoma was positive in 10-15%[8], while diffuse infiltrating subtype had mostly been described to occur sporadically, and was believed to be non-hereditary in previous reports[4, 9]. However, there were also several case reports holding a hypothesis about hereditary component[10-12]. KAO[12] et al. first reported two unilateral cases of retinoblastoma in a family: the diffuse infiltrating subtype in the mother while a typical retinal mass in her daughter. Crosby[13] et al. described a child with anterior diffuse retinoblastoma who presented with the pseudohypopyon. Genetic analysis showed a germline mutation of the *RB1* allele that is potentially heritable. Schedler[10] et al. reported on a family with three children affected by retinoblastoma, among them one girl with diffuse infiltrating subtype. Genetic

analysis of the family showed that all three children and the clinically unremarkable father were carriers of the same oncogenic mutation in the *RB1* gene.

Clinical appearance showed a different pattern between diffuse infiltrating retinoblastoma and typical retinoblastoma. The most common clinical manifestation for diffuse infiltrating subtype was vitreous opacity (23/37, 62%) in our cases, whereas leukocoria for typical retinoblastoma. Moreover, the diffuse infiltrating subtype possessed a lot of special clinical signs, such as cornea edema, iris tumor nodules and pseudohypopyon. Besides this, fundus examination showed vitreous cells and no definite retinal mass. Due to lack of typical characteristics, most patients were initially misdiagnosed as endophthalmitis. To clarify the diagnosis, anterior chamber fine-needle aspiration biopsy (FNAB) often was performed. Notably, it was not normally recommended. The utilization of FNAB for retinoblastoma was a controversial matter among ophthalmologists. Some researchers[14] had argued against FNAB because of the possibility that the tumor cells could be seeded into the subconjunctival or outside of the globe. Other investigators considered that the FNAB could be applied when the parents of retinoblastoma children demand histopathologic verification before enucleation. Our study revealed that anterior chamber FNAB might contribute to a higher rate of histopathological risk factors. Karcioglu[15] clearly suggested that the preoperative diagnosis of retinoblastoma could be established with noninvasive differential techniques. However, some reviewed studies[4, 7] argued that the clinical findings obtained by technical devices such as ultrasonography, CT or MRI were not helpful. Because of the calcification, the major sign of retinoblastoma on imaging studies was always absent from the majority diffuse infiltrating subtype cases. In our cohort, only one case was first diagnosed with diffuse infiltrating retinoblastoma by MRI. Most patients were diagnosed as global occupying lesions by ultrasonography or CT.

All patients were treated with enucleation in this study. Histological examination of the eyes showed that, the anterior segment invasion was observed more often in the diffuse infiltrating retinoblastoma compared with typical retinoblastoma. Our study identified that 24 patients (64.9%) had iris neovascularization**,** which was more

evident in the diffuse infiltrating retinoblastoma (62%) than typical RB(44%)[16]. Massive choroid-involvement was presented in 2 patients, retrolaminar optic nerve involvement (4-5mm) also been observed in these 2 patients, which implied that they need a more intensive adjuvant chemotherapy [17]. Furthermore, 26 of 37 eyes with histopathological risk factors, suggested a poor prognosis of patients. Calcification was more frequent in typical retinoblastoma (84.9%)[18] compared with diffuse infiltrating retinoblastoma (2/37, 8%). We speculated that the nourishing blood vessels of the tumor were abundant to meet the need for oxygen and nutrients of the slowly growing tumor. Previous reports[19] had shown that tortuous and dilated retinal vessels with complex and multiple branches within the areas of tumor involvement were the most obvious feature of the retinovascular changes of diffuse infiltrating retinoblastoma in fluorescein angiography. The correlation between clinical signs and histopathological risk factors of 37 diffuse infiltrating retinoblastoma samples was statistically analyzed. Cornea endothelium with tumor seeds, anterior chamber free-floating tumor seeds, or pseudohypopyon revealed by ophthalmic examination suggested that patient had a higher probability for tumor recurrence and metastasis after enucleation. Adjuvant chemotherapy was necessary for those patients.

Currently, there is no clearly established criteria for the diagnosis of diffuse infiltrating retinoblastoma, such as the width and height of the tumor, the layer of the retina of tumor cells infiltration, and the delimitation of the tumor margins. Christina Stathopoulos [20] reported that, the diffuse infiltrating lesion appeared as an homogenous hyper-reflective thickening of the ganglion cell layer at an early stage. In this study, the height and width of the tumor were measured by imaging examination on the maximum cross section. Almost all the tumors thickness in our series were below 10mm, and the smallest diameter was only 3mm. This result was agreed with the character of diffuse infiltrating retinoblastoma, tumor cells along the retina with little vertical growth. There was no clear explanation for the reason for the special growth pattern so far. Some investigators held their hypotheses about the reason for the special growth pattern, mutation of a heterotopic precursor cell in the anterior chamber[21], or variation in the immune response to tumor antigens[12]. Additionally,

Schedler KJ[10] included a theory of certain mutation of the tumoral adhesive molecules that provoked the diffuse infiltrating growth type.

Conclusion

Diffuse infiltrating retinoblastoma often presents at an older age than typical retinoblastoma. Based on our study and previous literature reviews, we found that diffuse infiltrating retinoblastoma has a hereditary susceptibility, and the offspring of patients should be judged carefully. This variant of retinoblastoma is extremely rare, the absence of an obvious retinal mass and atypical clinical signs easily leads to misdiagnosis. Clinically, it should be paid more attention to the cornea endothelium with tumor seeds, anterior chamber free-floating tumor seeds, and pseudohypopyon. MRI is a very useful imaging modality for diagnosis. The imaging modality revealed retinoblastoma infiltrating the retina for a mean basal diameter of 10 mm and thickness of 7mm. Needle biopsy of anterior chamber generally is not recommended because of the possible risk of tumor occurrence and metastasis. Histopathological examination results show rare calcification and high rate of histopathologic risk factors in diffuse infiltrating retinoblastoma.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Beijing Tongren Hospital and followed the tenets of the Declaration of Helsinki. Due to the retrospective design of the study, the ethics committee waived the necessity for an informed written consent signed by the patients.

Consent for publication

Not available.

Availability of data and materials

All relevant data and materials are within the paper.

Competing interests

The authors have declared that no competing interests exist.

Authors' Contributions

LB contributed to the study concept and supervised the study. CY contributed to the study design and revised the manuscript. ZYN conducted statistical analysis and drafted the manuscript. LB and XXL provided pathological analysis. ZX made contributions to analysis and interpretation of data. All authors read and approved the final manuscript. The contributions of YaNan Zhang and Ying Chang were equally important, so they were Co-first author.

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Table 1. The correlation between clinical signs and histopathologic risk factors

Clinical Features	Cases (37)	HRF (26)	P value
Eyelid edema	1	1	1.000
Conjunctiva injection	17	9	0.069
Cornea endothelium with tumor seeds	6	1	0.005
Cornea stromal edema	14	10	1.000
Cornea band keratopathy	1	1	1.000
Anterior chamber free-floating tumor seeds	8	1	0.000
Pseudohypopyon	12	4	0.001
Anterior chamber hyphema	2	2	1.000
Iris atrophy	1	0	0.279
Iris tumor seeds	12	6	0.122
Iris neovascularization	10	6	0.442
Lens cataract	6	2	0.051
Retinal detachment	9	8	0.229
Subretinal tumor seeds	15	12	0.466
Retinal telangiectasia	5	4	1.000
Subretinal fluid	1	1	1.000
Vitreous hemorrhage	8	8	0.076
Vitreous haze	23	18	0.268
Fine needle aspiration FNAB	5	0	0.001

Table2. Histopathologic invasion with diffuse infiltrating retinoblastoma

Histopathologic invasion	**Cases（%）**	**Histopathologic invasion**	**Cases（%）**
Anterior segment		Choroid	
Cornea	6（16）	≥3mm	2（5）
Anterior chamber	6（16）	<3mm	0（0）
Anterior chamber angle	9（24）	Optic nerve	
Ciliary body	12（32）	Prelaminar	26（70）
Iris	14（38）	Laminar	16（43）
Vitreous	3（11）	Retrolaminar	10（27）
Retinal pigment epithelium	5（14）	Schlemm’s canal	1（3）

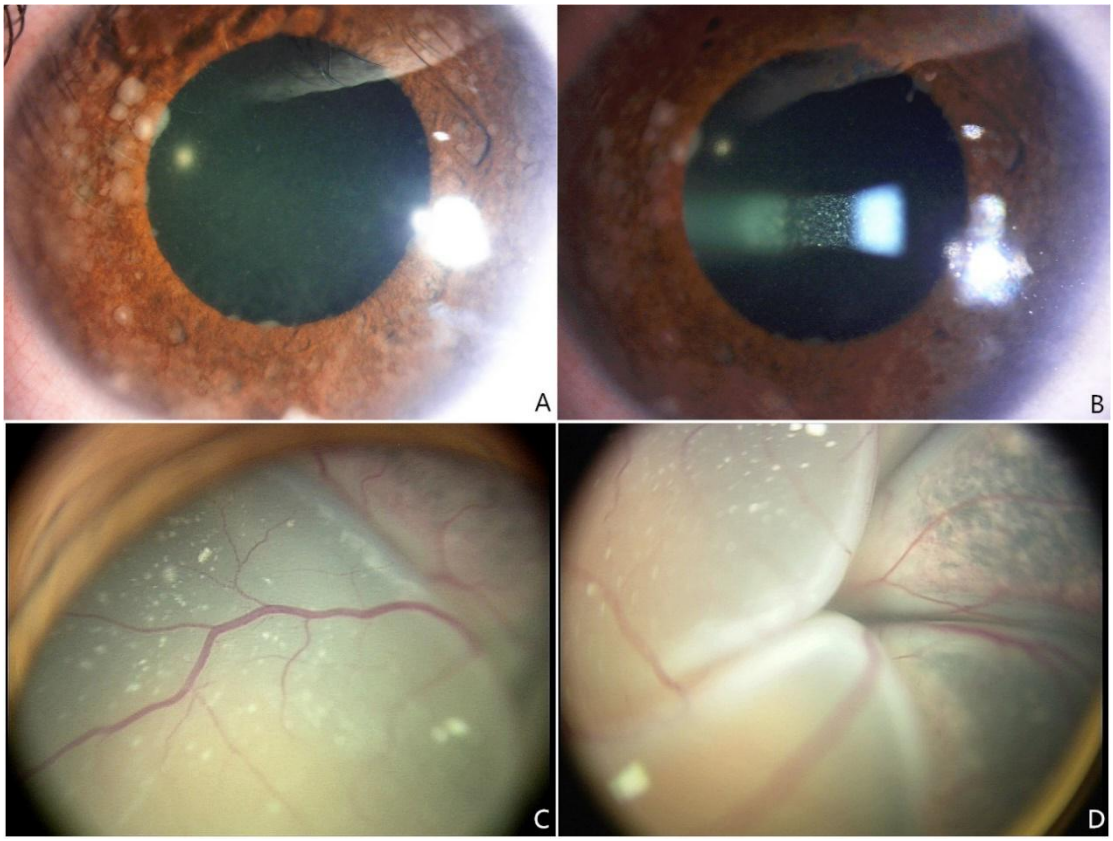

Figure 1. Clinical features of diffuse infiltrating retinoblastoma. Iris nodules (A) and anterior chamber floating cells (B) in an 8-year-old girl revealed by slit lamp examination; Fundus examination revealed retinal detachment, retinal telangiectasia and subretinal tumor in an 8-year-old boy (C, D).

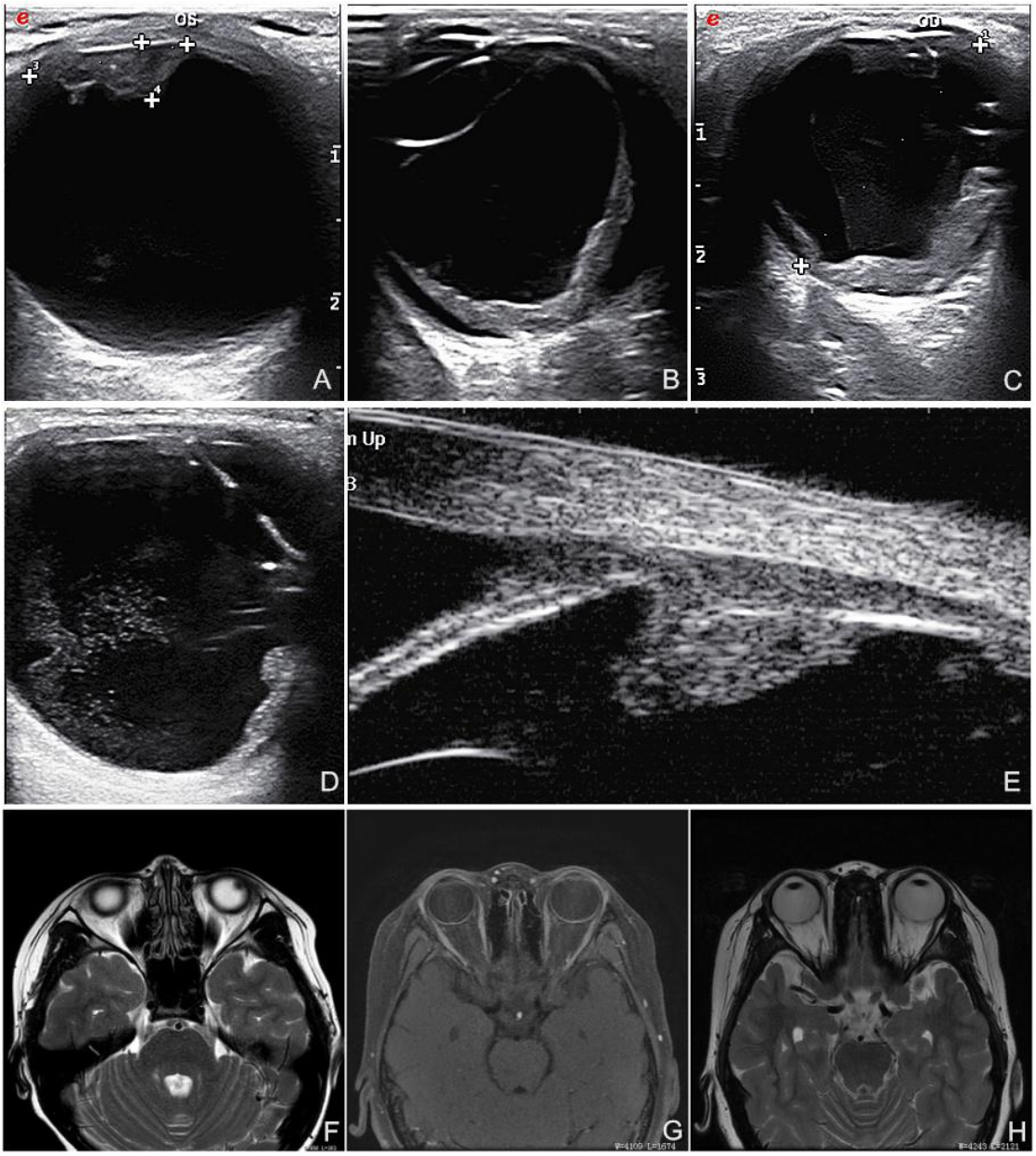

Figure 2. Imaging examination of diffuse infiltrating retinoblastoma.

Ultrasonography showed small tumor in the anterior segment (A), “V” shape retinal detachment and retinal thicken (B, C) and vitreous haze (D)； UBM revealed tumor located at the anterior chamber (E); MRI showed small tumor in the temporal peripheral global (F), abnormal signal of ciliary body (G, H) (A and F were a 8-year-old boy; D, E, G and H were a 8-year-old girl)

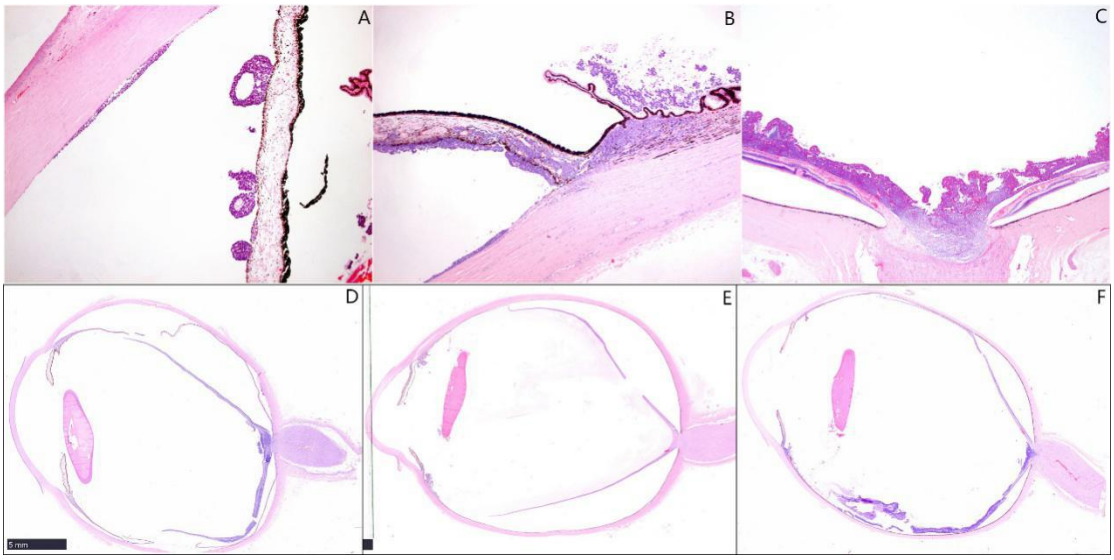

Figure 3 Histopathology findings of diffuse infiltrating retinoblastoma.

Histopathology revealed tumor invading anterior segment(A, B, E) and growing along the retina in a flat shape (C, D, F) (A, B HE×50; C HE×20).

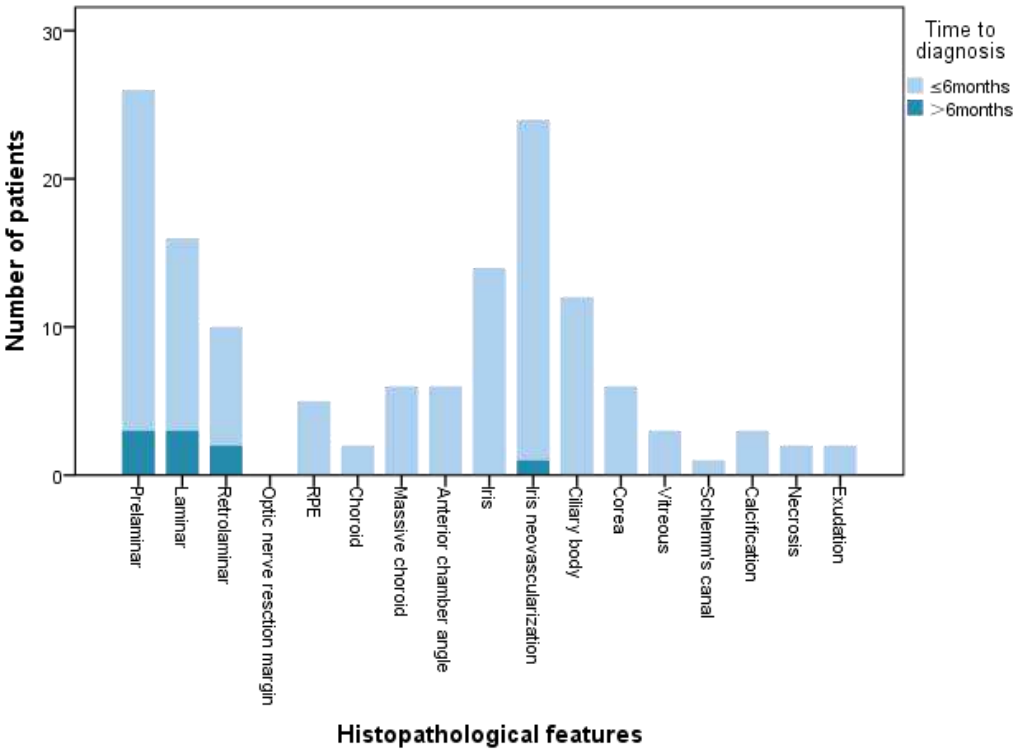

Figure 4. Histogram showing the distribution of histopathological features at the time to diagnose diffuse infiltrating retinoblastoma.

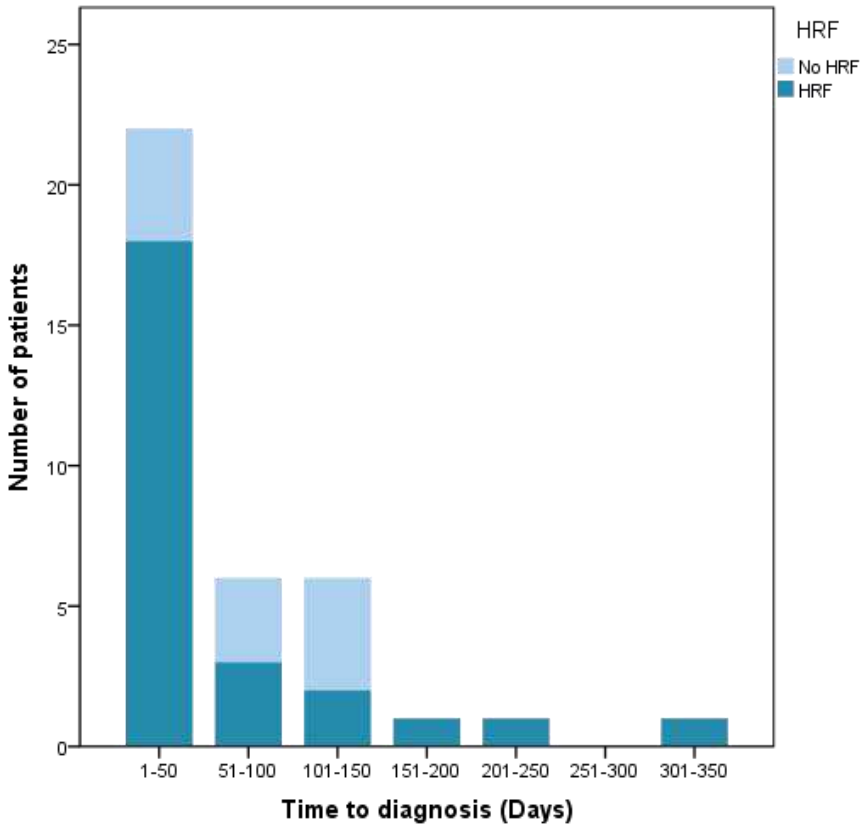

Figure 5. Histogram showing the time to diagnosis of the diffuse infiltrating retinoblastoma and histopathologic risk factors (HRF) of diffuse infiltrating retinoblastoma at the Beijing Tongren Hospital

Figures

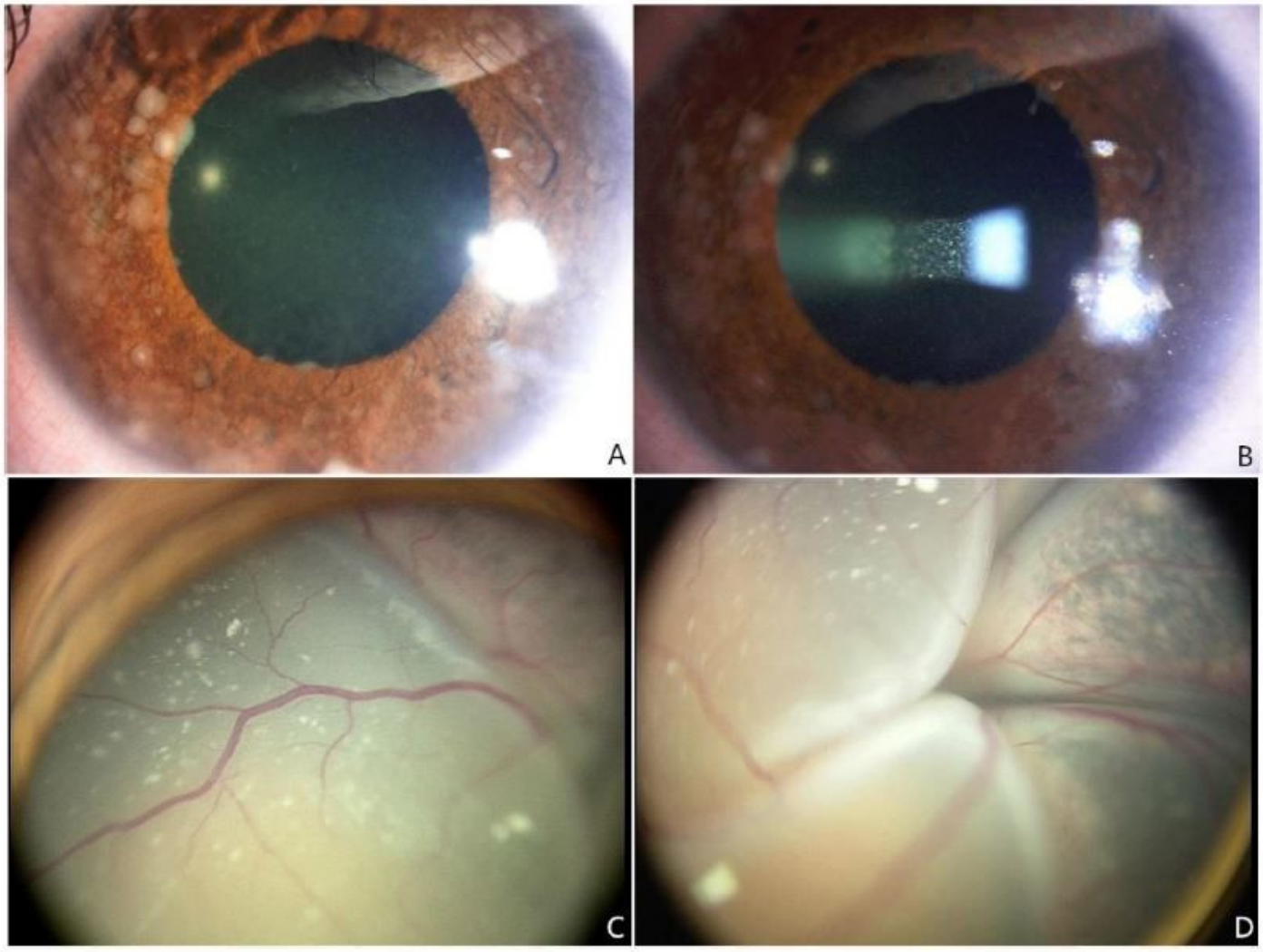

Figure 1

Clinical features of diffuse infiltrating retinoblastoma. Iris nodules (A) and anterior chamber floating cells (B) in an 8-year-old girl revealed by slit lamp examination; Fundus examination revealed retinal detachment, retinal telangiectasia and subretinal tumor in an 8-year-old boy (C, D).

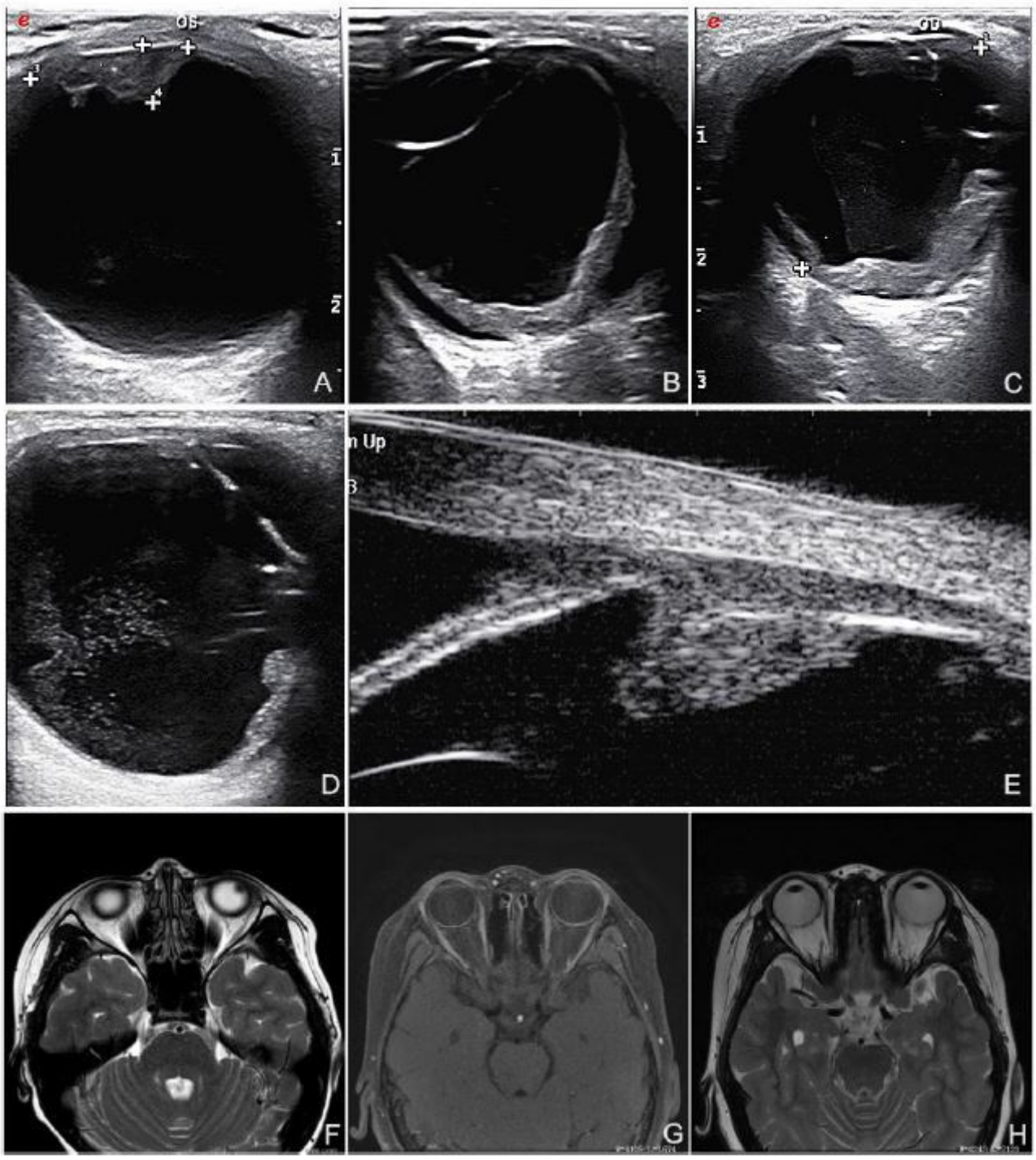

Figure 2

Imaging examination of diffuse infiltrating retinoblastoma. Ultrasonography showed small tumor in the anterior segment (A), “V” shape retinal detachment and retinal thicken (B, C) and vitreous haze (D)，UBM revealed tumor located at the anterior chamber (E); MRI showed small tumor in the temporal peripheral global (F), abnormal signal of ciliary body (G, H) (A and F were a 8-year-old boy; D, E, G and H were a 8-year-old girl)

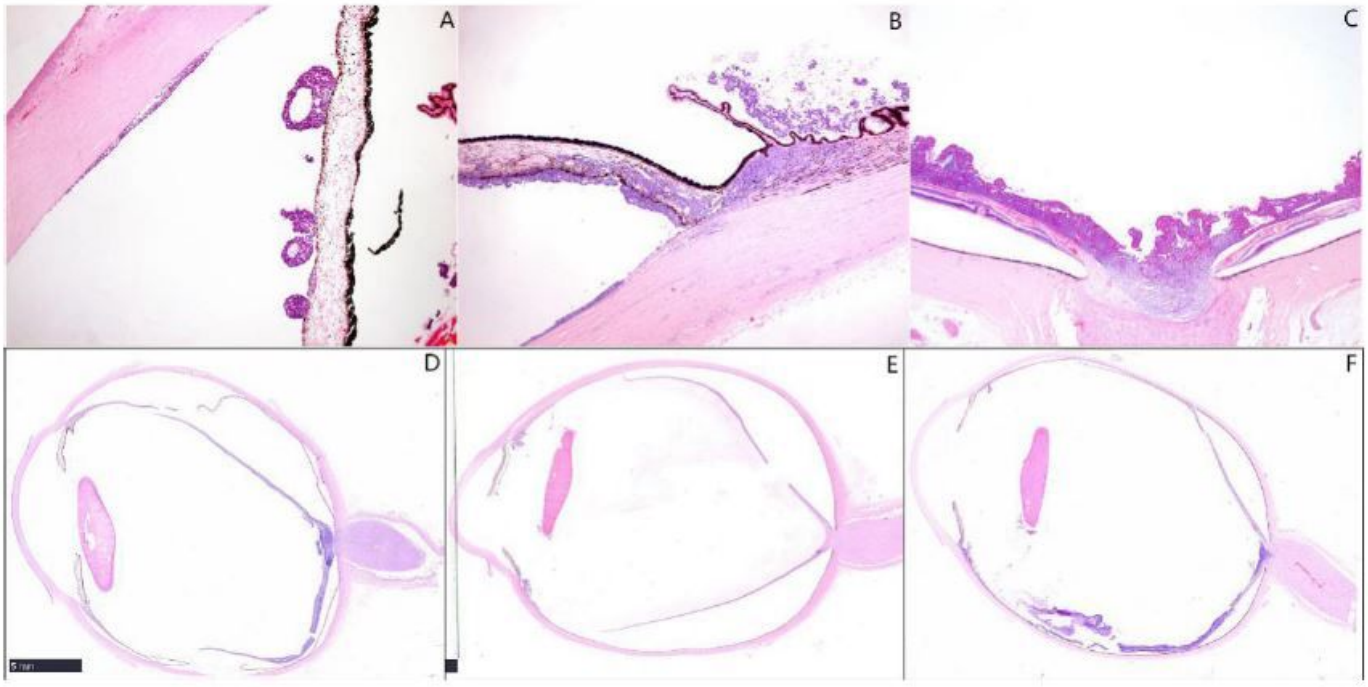

Figure 3

Histopathology findings of diffuse infiltrating retinoblastoma. Histopathology revealed tumor invading anterior segment(A, B, E) and growing along the retina in a flat shape (C, D, F) (A, B HE×50; C HE×20).

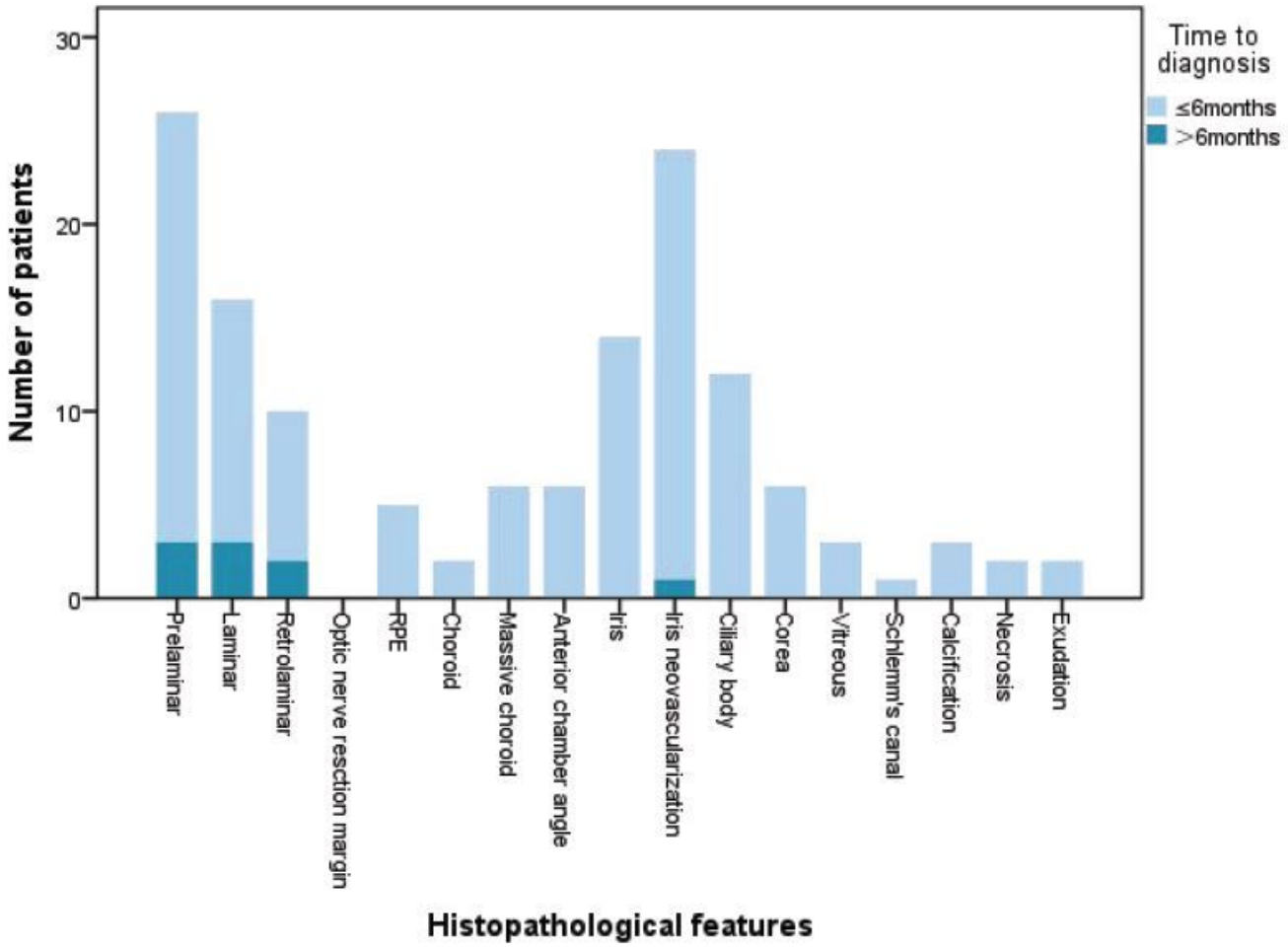

Figure 4

Histogram showing the distribution of histopathological features at the time to diagnose diffuse infiltrating retinoblastoma.

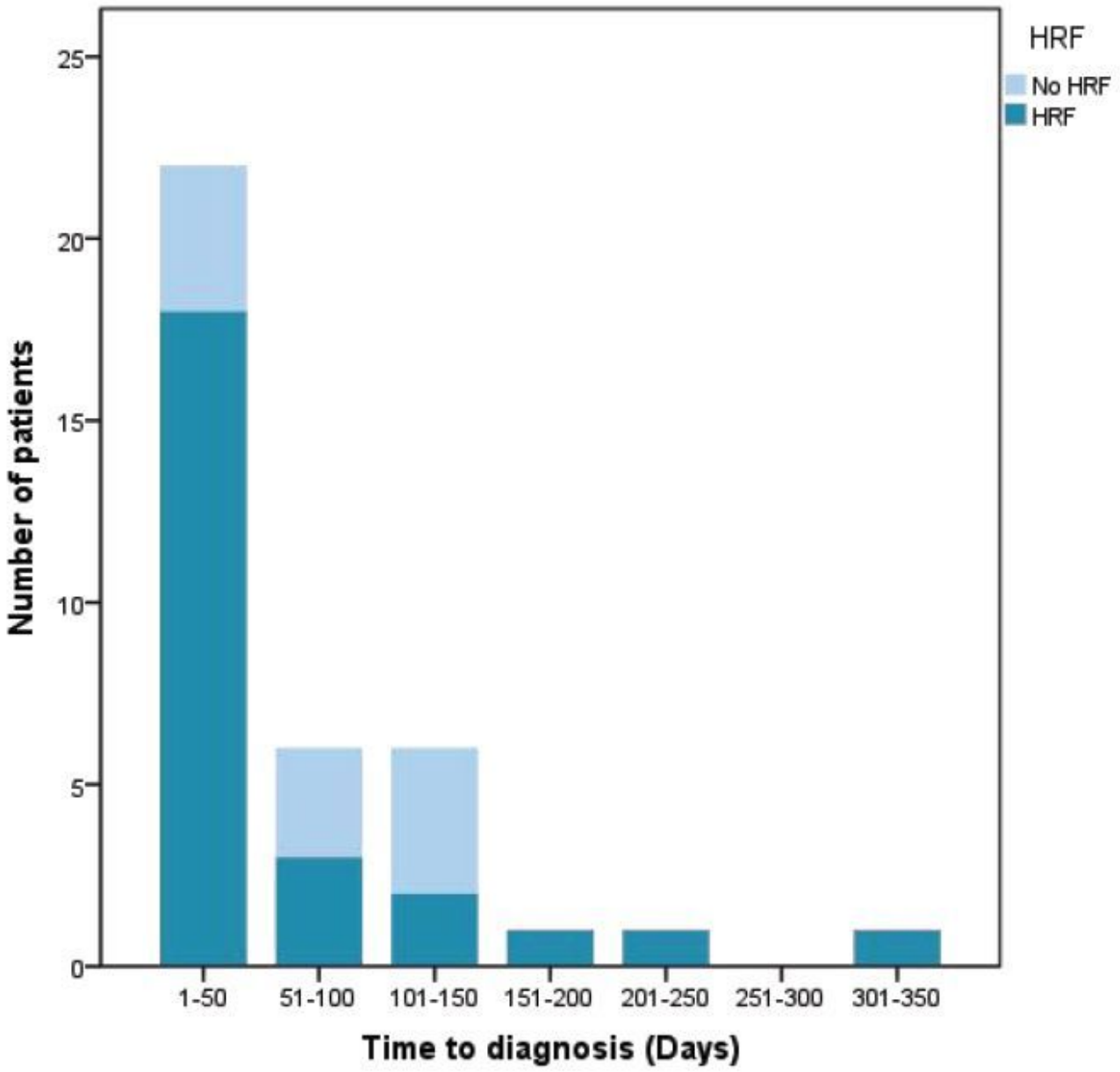

Figure 5

Histogram showing the time to diagnosis of the diffuse infiltrating retinoblastoma and histopathologic risk factors (HRF) of diffuse infiltrating retinoblastoma at the Beijing Tongren Hospital