PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

| TITLE (PROVISIONAL) | Prevalence and associated relating factors in patients with hereditary retinal dystrophy—a nationwide population-based study in Taiwan |
|---------------------|--------------------------------------------------------------------------------------------------------------------------|
| AUTHORS             | Woon, Peng Yeong; Chien, Jia-Ying; Wang, Jen-Hung; Chou, Yu-Yau; Lin, Mei-Chen; Huang, Shun-Ping |

VERSION 1 – REVIEW

| REVIEWER            | Shih-Jen Chen |
|---------------------|---------------|
|                     | Taipei Veterans General Hospital |
| REVIEW RETURNED     | 21-Sep-2021   |

| GENERAL COMMENTS    | The authors analyzed the prevalence of HRD and its associated risk factors in claim data from the Taiwan national health institute. From 2000 to 2013, the authors identified 403 patients and found the patients had higher associated features of cataract, CME when comparing to age-matched controls of 2015 subjects. They also found that in patients who were younger than 55 y/o, they had higher comorbidity of hypertension, DM and chronic kidney disease. Although the data of this nation wide survey was valuable, the authors did not use the wordings appropriately and the methods were flaw. The so-called “risk factors” were actually clinical features or ophthalmic characteristics that happened in many patients with HRD. One cannot say that these features were “risk factors ” for acquiring HRD. This cannot be applied when comparing to those age-matched controls who did not have any HRD unless the authors choose a groups of control patients with eye diseases except HRD and stratified with visual acuity level for comparison. However, the comparison with their controls is OK in studying systemic comorbidity. A recent article by Chen TC, et al (Genomic Medicine 2021;6:16 ; https://doi.org/10.1038/s41525-021-00180-1) should be referenced to provide in-depth discussion. The last sentence of the conclusion “...Regular screening and monitor of HRD patients with…” was not supported by their data. |

| REVIEWER            | Hortensia Sanchez-Tocino |
|---------------------|--------------------------|
|                     | University of Valladolid, Ophthalmology |
| REVIEW RETURNED     | 20-Oct-2021   |

| GENERAL COMMENTS    | To the editor: This study is interesting, because it is important that a country has a national registry of genetic retinal diseases. However, the authors explain very little about how the diagnosis was made and if there has been a follow-up of these patients. The study does not provide relevant information. Most of the findings are already widely known and those other more novel are not |

1
METHODS
The authors must explain why they have used the CIE-9 classification and not the most current CIE-10
In Methods. Should the authors explain how the diagnosis of retinal dystrophy is made, by the clinic, by electrophysiology? A genetic analysis has been carried out to confirm the diagnosis
How the prevalence of ocular complications has been studied. The diagnosis of macular or epiretinal membrane is clinic or by optical coherence tomography

RESULTS
Patient histories have only been read once, their follow-up has not been reviewed, this could explain the low incidences of cataract or epiretinal membrane found
While the authors describe a cataract percentage of 8.2, other studies have reported percentages between 15.4-20.4%. Very similar occurs with macular edema, with percentages reported between the 20-50%
Nor do they define or clarify in relation to the variables that represent comorbidity. Diabetes, type of diabetes, what type of kidney disease. It would be interesting to know if in patients under 55 years chronic kidney disease it was related to a syndromic retinitis pigmentosa.

DISCUSSIONS
The authors do not indicate when cataract surgery is indicated, how many patients are operated and because they have a less impact with regard to other series
It is possible that patients with HRD are better studied for diabetes and hyperlipidemia than their corresponding controls, then we would be with a selection bias.
The authors do not compare their results with other similar series, nor do they explain the physiopathogenic mechanism for the presence of these comorbidities.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1) Although the data of this nationwide survey was valuable, the authors did not use the wordings appropriately and the methods were flaw. The so-called “risk factors” were actually clinical features or ophthalmic characteristics that happened in many patients with HRD. One cannot say that these features were “risk factors” for acquiring HRD. This cannot be applied when comparing to those age-matched controls who did not have any HRD unless the authors choose a groups of control patients with eye diseases except HRD and stratified with visual acuity level for comparison. However, the comparison with their controls is OK in studying systemic comorbidity.

Amendment: apologies for the confusion created, as mention earlier in the Abstract (Page 2, line 10), the so-called “risk factors” have all been amended to "relating factors"
Comment 2) A recent article by Chen TC, et al (Genomic Medicine 2021;6:16; https://doi.org/10.1038/s41525-021-00180-1) should be referenced to provide in-depth discussion.

Amendment: an entire new in-depth discussion has been added as suggested (Page 10, line 24-38 & Page 11, line 1-4), this recent publication by Chen TC, et al focused mainly on gene mutations identified by capture-based target enrichment followed by NGS, of Inherited Retinal Degenerations (IRDs) in Taiwan, where 69.5% of the IRD with a mean age-onset between 31-40 (71+146/total 312), and 14.4% are age-onset below 10-year-old (11+34/total312). Of which ABCA4 gene mutations was the single most common disease-causing gene in their cohort (15.2%), echoed the data published from the US cohort (17.3%).

Comment 3) The last sentence of the conclusion “...Regular screening and monitor of HRD patients with...” was not supported by their data.

Clarification: We recommended that regular screening and monitoring of HRD patients with optical coherence tomography (OCT), blood pressure, levels of electrolytes and serum glucose levels may beneficial for early intervention of patients with HRD and may help to maintain central vision and may prevent vascular, metabolic and renal comorbidities (Page 3, line 1-5 and Page 12, line 1-5).

Reviewer: 2

Comment 1) the authors explain very little about how the diagnosis was made and if there has been a follow-up of these patients

Clarification: We retrieved the data from National Health Insurance Database, diagnosis was made at ophthalmologists at respective hospitals or clinics. The NHI Administration performs the review of medical claims by random audit of medical records. No claim will be paid to healthcare providers if any drug or medical services are deemed ‘unnecessary’ or ‘inappropriate’ by the peer review committee. Furthermore, a penalty of 10–100 times of the total claims is charged to the healthcare providers according to the regulations of the NHI Administration. Thus, it is reliable to identify patients with HRD or other comorbidities via diagnosis.

Comment 2) The study does not provide relevant information. Most of the findings are already widely known....
Clarification: Perhaps this is not novel but our study is unique to East-Asia region. Our study indicating that 74% of the diagnosed HRD are retinitis pigmentosa. Population-based data suggested an increased risk of cataract in younger patients, whereas older HRD patients are more susceptible to develop CME (Page 3, line 33-37).

Comment 3) The authors must explain why they have used the CIE-9 classification and not the most current CIE-10

Clarification: Thanks for your kindly reminding. In our study, we analyzed the NHIRD claim data from 2000 to 2013. In Taiwan, the NHI administration requested all hospital to transform to ICD-10-CM Code from 2016. Thus, it is appropriate to consider ICD-9-CM Code in current study. In future the NHID may update its system to CIE-10 classification.

Comment 4) Should the authors explain how the diagnosis of retinal dystrophy is made, by the clinic, by electrophysiology? A genetic analysis has been carried out to confirm the diagnosis

Clarification: The diagnosis of hereditary retinal dystrophies (HRD) (ICD-9-CM Code 362.7x) were confirmed mostly by clinical examination because only medical centers (there are 23 medical centers in Taiwan) have ERG for electrophysiology. The analysis included the age of symptoms onset and the type of visual symptoms including rod-cone dystrophy, cone-rod dystrophy, achromatopsia, congenital stationary night blindness and Leber’s congenital amaurosis. There isn't yet a genetic analysis provided or causative gene mutation is unknown.

Comment 5) How the prevalence of ocular complications has been studied. The diagnosis of macular or epiretinal membrane is clinic or by optical coherence tomography

Clarification: The prevalence of ocular complications is not well study in this country, this is why this study is so important. The diagnosis of macular or epiretinal membrane in this country is mainly clinic since the first OCT was imported in Taiwan at 2007 and clinical data retrieved from NHID does not provide optical coherence tomography data. However, some specialist center may provide optical coherence tomography as evidence-based diagnosis.

Comment 6) While the authors describe a cataract percentage of 8.2, other studies have reported percentages between 15.4-20.4%. Very similar occurs with macular edema, with percentages reported between the 20-50%
Clarification: Our findings here perhaps are unique to Taiwan as Taiwan’s population is made up of many different ethnic groups and is not as homogeneous as Caucasian population. According to the official released, “Taiwanese ethnic groups are generally divided into Taiwanese indigenous groups and the Hans. The former is classified into 16 ethnic groups, Amis, Atayal, Puyuma, Bunun, Paiwan, Yami (Tao), Rukai, Tsou, Saisiyat, Thao, Kavalan, Taroko, Sakizaya, Seediq, Kanakanavu and Saaroa. The latter is classified into Holo Taiwanese, Hakka Taiwanese and mainlanders.”, and the mainlanders are recent immigrants from mainland China beginning in the mid-1940s (https://ogme.edu.tw/lc/culturalGroups). As for macula edema, we did discuss the big difference in the prevalence of CME in the discussion paragraph 2 “The reported prevalence of CME in patient with HRD especially RP ranges from 14% to 23% as evaluated by fluorescein angiography (FA)6-8, 7.5% to 49% as evaluated by time domain OCT (TD-OCT)9-12 and 12.5% to 58.6%13-18 as evaluated by spectral domain OCT (SD-OCT). However, these reports mostly were single-hospital study and were non-population-based data which cannot be used to calculate the exact prevalence rate of CME. Our prevalence for CME (6.5%) is relatively lower than the previous reports but similar to the studies by Oishi et al11., detected CME in 49 eyes (7.5%) out of 652 eyes of 326 patients and Hagiwara et al19., reported CME was detected in 26 (8%) out of 323 patients with RP using TD-OCT. The big discrepancy in CME prevalence rate among the studies may associated with different definition of CME, different detection methods and equipment or different populations.”

Comment 7) Nor do they define or clarify in relation to the variables that represent comorbidity. Diabetes, type of diabetes, what type of kidney disease.

Clarification: NHID provided no further information regarding this matter.

Comment 8) The authors do not indicate when cataract surgery is indicated, how many patients are operated and because they have a less impact with regard to other series

Clarification: Because of the tight cost and volume control of “case payment”, preoperative peer review required for patients younger than 55 years old with cataract according to the Taiwan NHI regulations. Our results suggest that cataract occurred at younger age (≦55 y/o) in HRD patients. When cataract surgery is indicated and pass the preoperative peer review, surgery will be arranged within month.

Comment 9) It is possible that patients with HRD are better studied for diabetes and hyperlipidemia than their corresponding controls, then we would be with a selection bias.

Clarification: NHID have no clear indication that this is the case and thus a selection bias unlikely. Our study was a retrospective case control study, we identified patients with HRD as
case group and selected 1:6 age-sex matched subjects without HRD as control group. The index date was the date on which those HRD patients were firstly diagnosed. Then, we retrospectively analyzed whether they were exposed in those related factors. Thus, it was of less possibility for these HRD patients to be better studied for diabetes and hyperlipidemia than their corresponding controls.

Comment 10) The authors do not compare their results with other similar series,

Clarification: As suggested by Reviewer 1, we have added a new paragraph regarding this matter (Page 10, line 24-38 & Page 11, line 1-4),

Comment 11) nor do they explain the physiopathogenic mechanism for the presence of these comorbidities.

Amended: As suggested, we have added sentences in Discussion (Page 11,line 11-16).

"On the other hand, visual blood vessel endothelium cells are most sensitive to osmotic changes due to high serum glucose levels. An increase in serum glucose level endorses oxidative stress and the production of excessive free radicals which subsequently damage the visual blood vessels. In addition, an increase in blood pressure will further worsen the visual disease progression".

VERSION 2 – REVIEW

| REVIEWER         | Shih-Jen Chen          | Taipei Veterans General Hospital |
|------------------|------------------------|----------------------------------|
| REVIEW RETURNED  | 06-Jan-2022            |

| GENERAL COMMENTS | 1. Table 5 legend was confusing without mentioning that it was comparing to those non-HRD with stratification of gender and age. Since the result is obvious in table 4 and had been described in the text, table 5 can be deleted.  
2. The most interesting and novel findings of this report is the higher comorbidity of HTN, DM and kidney disease in the HRD cohort. The authors attributed this difference to those rare systemic disease such as BBS, AS and others. However, 70% of the HRD were diagnosed as RP alone. The speculated reasons and impact as well as future measures for this higher comorbidity rate in these low vision patients should be discussed. For example, any life style factors can explain the higher incidence of comorbidity due to their low vision? Is there higher incidence of obesity? Are these patients with comorbidity being taken good care of (e.g., types of medication and intervention of HTN, DM or kidney disease)? |

| REVIEWER         | Hortensia Sanchez-Tocino | University of Valladolid, Ophthalmology |
|------------------|--------------------------|----------------------------------------|
| REVIEW RETURNED  | 19-Dec-2021              |
In relation with the discussion and the studying systemic comorbidity and the physiopathogenic mechanism for the presence of these comorbidities.

Authors argue that vision in patients with HRD may be compromised not only by the process itself but by complications arising from systemic comorbidity, in particular hyperglycemic.

Retinopathy pigmentosa (RP) and diabetes are two pathologies that can be associated by chance or as part of genetic diseases. However, there is a negative correlation between the incidence of diabetic retinopathy and that of pigmentary retinopathy relative hyperoxia induced by apoptosis of photoreceptor cells in RP compensating for diabetes-induced tissue hypoxia. (P Sternberg JR 1994) (Arden JB 2001) (Chen YF 2012). Rarely clinical signs of diabetic retinopathy are presented in a patient with retinal dystrophy. (Pasquale Mucciolo D, 2017)

When RP occurs, the gradual disappearance of photoreceptors restricts retinal oxygen requirements, resulting in decreased retinal blood flow in the form of diffuse arteriolar narrowing. In case of added diabetes, the amount of VEGF and free radicals produced as a result of hyperglycemia and the usual tissue hypoxia, is reduced due to the improved availability of oxygen in the retinal tissue following the disappearance of a large number of photoreceptors. These facts could explain, in part, the lower frequency of diabetic retinopathy and diabetic macular edema in this field. (Arden GB 2012) (De Gooyer TE 2006) (Lahdenranta J 2001)

Al Adsani A and Gader FA, reported two cases with diabetes and retinitis pigmentosa in the form of Bardet-Biedl syndrome and Alström syndrome.

Authors must modify this paragraph of the discussion.