

Hypertension affects the treatment of wet age-related macular degeneration

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ABSTRACT.

Purpose: Due to population ageing as well as the high prevalence of hypertension and age-related macular degeneration (AMD) in elderly individuals, and the relationship between hypertension and AMD is unclear. Our research aimed to investigate the association between hypertension, wet AMD (wAMD) and the treatment strategy of wAMD patients affected by hypertension.

Methods: Data of wAMD patients at Zhongshan Ophthalmic Center, Sun Yat-sen University, between 1 January 2002 and 30 June 2019, were extracted from the electronic healthcare information system. wAMD patients were divided into subgroups by hypertension status, age, sex, the need for vitrectomy surgery and the number of anti-VEGF drug intravitreal injections that these were divided in 1–3 vs. >3 (available time from 1 January 2012 to 30 June 2019).

Results: A total of 3096 wAMD patients (41.7% female, 58.3% male) with an age range of 50–96 years (68.7 (SD 9.42) years) were included. wAMD was significantly associated with hypertension ($p < 0.001$). After adjustment for sex and age, Cox regression model showed a significant association between hypertension in wAMD patients and the number of injections (RR = 1.31, 95% CI: 1.13–1.50, $p < 0.001$). There was no significant association between hypertension and the need for vitrectomy ($p = 0.82$).

Conclusions: wet AMD was associated with hypertension status, and after the regular series of three injections, wAMD patients with hypertension were more likely to receive anti-VEGF drug intravitreal injections than those without hypertension. These results may facilitate prospective research on the prevention of wAMD and contribute to the management of wAMD patients.

Key words: wet age-related macular degeneration – hypertension – anti-VEGF treatment – vitrectomy

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Introduction

Age-related macular degeneration (AMD) and hypertension are two prevalent diseases among the elderly. Age-related macular degeneration (AMD) is a progressive neurodegenerative disease that often occurs in those aged 60 years or older (Klaver et al. 2001; Wong et al. 2014). It is one of the most common reasons for severe visual impairment and, following cataract and uncorrected refractive error, accounts for 5–9% of blindness globally (Bourne et al. 2013). Previous studies have suggested that AMD is a multifactorial disease associated with genetic factors, environmental factors and inflammatory immune response factors (Cascella et al. 2014; Cheung & Wong 2014).

Hypertension, defined as increased systolic pressure above 140 mmHg and/or diastolic pressure above 90 mmHg, is a systemic disease that can have harmful effects on multiple organs including the heart, kidneys, brain and eyes (Whelton et al. 2018). Hypertension is also considered as a risk factor for retinal vascular occlusion (RVO), retinal microaneurysm (RAMA) and ischaemic optic neuropathy (Wong & Mitchell 2004; Wong & Mitchell 2007).

A previous study reported that uncontrolled hypertension was significantly correlated with AMD after adjusting for age, sex and cigarette

smoking status (Klein et al. 2013). Consistently, a study of 2764 participants in the Beaver Dam Eye Study showed that AMD was associated with hypertension (Klein et al. 2003). Moreover, in a prospective study, van Leeuwen et al. (2003) demonstrated that increased systolic blood pressure or pulse pressure was associated with an increased risk for AMD. However, a study involving 14,067 participants in Korea did not find a significant relationship between hypertension and AMD (Park et al. 2014). There were no benefits of antihypertension medication in preventing the progression of AMD (Tomany et al. 2004).

Choroidal neovascularization (CNV) is one of the most important characters of wAMD, and the development of CNV results from retinal endothelial cell apoptosis and VEGFR-2 upregulation induced by excessive activation of the renin-angiotensin-aldosterone system (RAAS) (Metelitsina et al. 2006; Li et al. 2019). Renin-angiotensin-aldosterone system (RAAS) hyperactivation also contributes to the development of hypertension (Drummond et al. 2019). Therefore, wAMD patients with hypertension may have a greater possibility to trigger CNV in their fundi than those without hypertension, and it may also affect the treatment of wAMD. The current treatment strategies for AMD are intravitreal anti-VEGF drug and vitrectomy (Treumer et al. 2017; Kitagawa Y et al. 2016). The use of anti-VEGF drug slows the progress of wAMD. Vitrectomy is an important way to manage vitreous haemorrhages caused by CNV. Our research aimed to investigate the association between hypertension, wAMD and the treatment strategy of wAMD patients affected by hypertension, including the number of anti-VEGF drug intravitreal injections and the need for vitrectomy.

Methods

This retrospective study identified individuals with wAMD in Zhongshan Ophthalmic Center's (ZOC's) electronic records. Zhongshan Ophthalmic Center (ZOC) is a tertiary and public ophthalmology hospital in China. The electronic healthcare information system (HIS), maintained by ZOC, contains data on real-world practice patterns. For each patient

identification (ID), we documented age, sex, hypertension status, wAMD status, whether vitrectomy surgery was performed, and the presence of other diseases from 1 January 2002 to 30 June 2019. For hypertension status, the patients' history were inquired, and if patients were on hypertensive therapy, they were defined as hypertensive. If patients were not on hypertensive therapy, they were asked to rest for fifteen minutes, and then, their blood pressure was measured. If the systolic pressure was above 140 mmHg, and/or diastolic pressure was above 90 mmHg, the status of these patients was defined as hypertensive. In order to assist the arrangement of treatment, nurses would measure the pressure for patients who were considered as hypertension and it was also a way to check the hypertension status for patients. To minimize variation, records of patients younger than 50 years old were excluded from the statistical analysis, and duplicate IDs were merged.

There are several different kinds of anti-VEGF drugs, with different effects on wAMD. Ranibizumab was the first anti-VEGF drug used to treat wAMD in our hospital and was used by the largest number of wAMD patients in our hospital. Thus, only patients receiving treatment with intravitreal ranibizumab injections were included. Patients who had received other intravitreal therapies were excluded. Anti-VEGF drugs were not officially used to treat wAMD in China until 2012, so the records of the number of intravitreal injections range from 1 January 2012 to 30 June 2019. According to the Preferred Practice Patterns (PPPs) of the American Academy of Ophthalmology (American Academy of Ophthalmology, 2015), the regular anti-VEGF treatment for wAMD patients should be implemented once a month for the first three months and then as needed. Due to the large imbalance in the number of patients receiving injections, we divided the number of injections into two categories: one group with more than three injections and another with one to three injections. The follow-up times were defined as observed months from the first time wAMD patients received injection to June 2019.

For vitrectomy surgery, the specific indications are retinal and vitreous haemorrhage in clinic. Patients who

underwent vitrectomy surgeries were included only when the main diagnoses for these patients were wAMD from 1 January 2012 to 30 June 2019. The general procedures of this surgery include removal of turbid vitreous and blocking the CNV using lasers or freezing it with liquid nitrogen. Data from the HIS registry were de-identified; hence, this study did not require patient consent.

Considering the characteristics of the data and the purpose of the research, we used various methods to analyse the data using SPSS 26.0 statistical software (SPSS Inc. Chicago, IL, USA). Chi-squared tests were used to compare the ratio of male and female wAMD patients with hypertension and in the number of intravitreal injections. Logistic regression was employed to analyse the association between hypertension and wAMD, as well as the relationship between the need for vitrectomy surgery and hypertension. Cox regression was used to analyse the association between hypertension and the number of intravitreal injections. In addition, the regression models were adjusted by age and sex. Values are presented as the mean (SD). Statistical tests were two-sided, with a p value less than 0.05 considered statistically significant.

Results

A total of 224334 (67.45 (SD 9.66) years) unique patients were identified in the HIS dataset of ZOC from 1 January 2002 to 30 June 2019. Of these patients, 3096 (1.4%) were diagnosed with wAMD. The age range of wAMD patients was 50–96 years (68.72 (SD 9.42) years, interquartile range 61–76 years), and the ratio of male patients (58.3%) to female patients (41.7%) was 1.4:1. Of the wAMD patients, 380 (12.3%) had diagnosed hypertension. The age range of patients with both wAMD and hypertension was 50–94 years (68.73 (SD 9.43) years, interquartile range 61–76 years). In the ZOC dataset, wAMD and wAMD plus hypertension were most common among patients aged 70–79 years (1062 patients and 156 patients, respectively). The detailed age distributions are shown in Fig. 1. Among the wAMD patients, there were more male patients with hypertension than female patients ($\chi^2 = 6.14$, $p = 0.013$). There

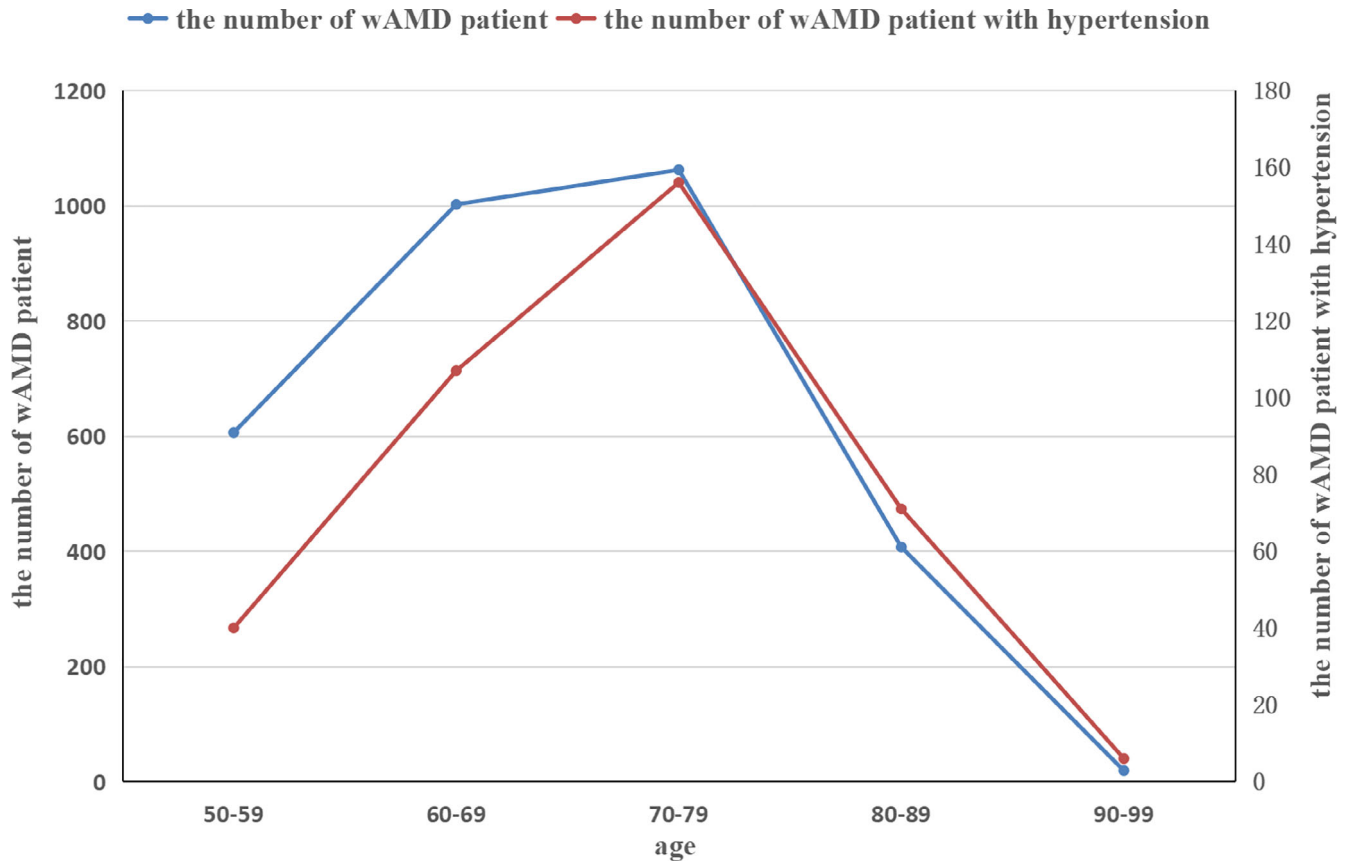


Fig. 1. The distribution of wAMD patients and wAMD patients with hypertension. In the ZOC dataset, wAMD and wAMD plus hypertension were most prevalent among patients aged 70–80 years (1164 patients and 154 patients, respectively). [Colour figure can be viewed at wileyonlinelibrary.com]

was a significant association between wAMD and hypertension (Table 1), suggesting that patients with hypertension had a higher chance of developing wAMD than patients without hypertension.

We investigated the influence of hypertension on the treatment of wAMD patients, including the number of anti-VEGF drug intravitreal injections and the need for vitrectomy surgery. In the ZOC dataset, 1386 wAMD patients who used anti-VEGF drugs were included. The detailed number of injections is shown in Fig. 2. The follow-up times for these patients ranged one month to ninety months

(38.85 (SD 26.45)) months, interquartile range 15.75–63.00 months). Group A comprised 84.4% of the total patients who received anti-VEGF injections, of which 201 (17.2%) patients had hypertension. Group B comprised 15.6% of the total patients, of which 29.2% had hypertension. The detailed information on the two groups is provided in Table 2. Male wAMD patients received more injections ($p = 0.006$) than female wAMD patients. Cox regression model showed a statistically significant association between hypertension in wAMD patients and the number of injections (RR = 1.28, 95% CI: 1.11–1.47, $p = 0.001$). After

adjustment for age and sex, the value of relative risk (RR) was 1.30 (95% CI: 1.13–1.50, $p < 0.001$) in the regression model.

Vitrectomy is an essential treatment for severe wAMD. A total of 650 wAMD patients (ages, 64.09 (SD 8.28) years) underwent vitrectomy surgery. Of these patients, 73 had hypertension. The distribution of patients who underwent vitrectomy surgery is shown in Table 3. It seemed that hypertension would decrease the risk of undergoing vitrectomy surgery (OR = 0.63, 95% CI: 0.45–0.89, $p = 0.008$); however, after adjusting the age and sex, whether wAMD patients underwent vitrectomy

Table 1. The relationship between hypertension status and wAMD

		wAMD	No wAMD	β	χ^2	p^*	OR (95%CI)
Univariate	Hypertension	380	22774	0.20	12.89	<0.001	1.22 (1.10–1.36)
	No hypertension	2716	198464				
Multivariate	Hypertension			0.18	10.77	<0.001	1.20 (1.08–1.34)
	Sex			−0.57	244.43	<0.001	0.56 (0.52–0.61)
	Age			−0.015	61.10	<0.001	0.99 (0.99–1.00)

* Logistic regression; wAMD = wet age-related macular degeneration, β = regression coefficients, OR = odds ratios.

The distribution of the number of intravitreal injections

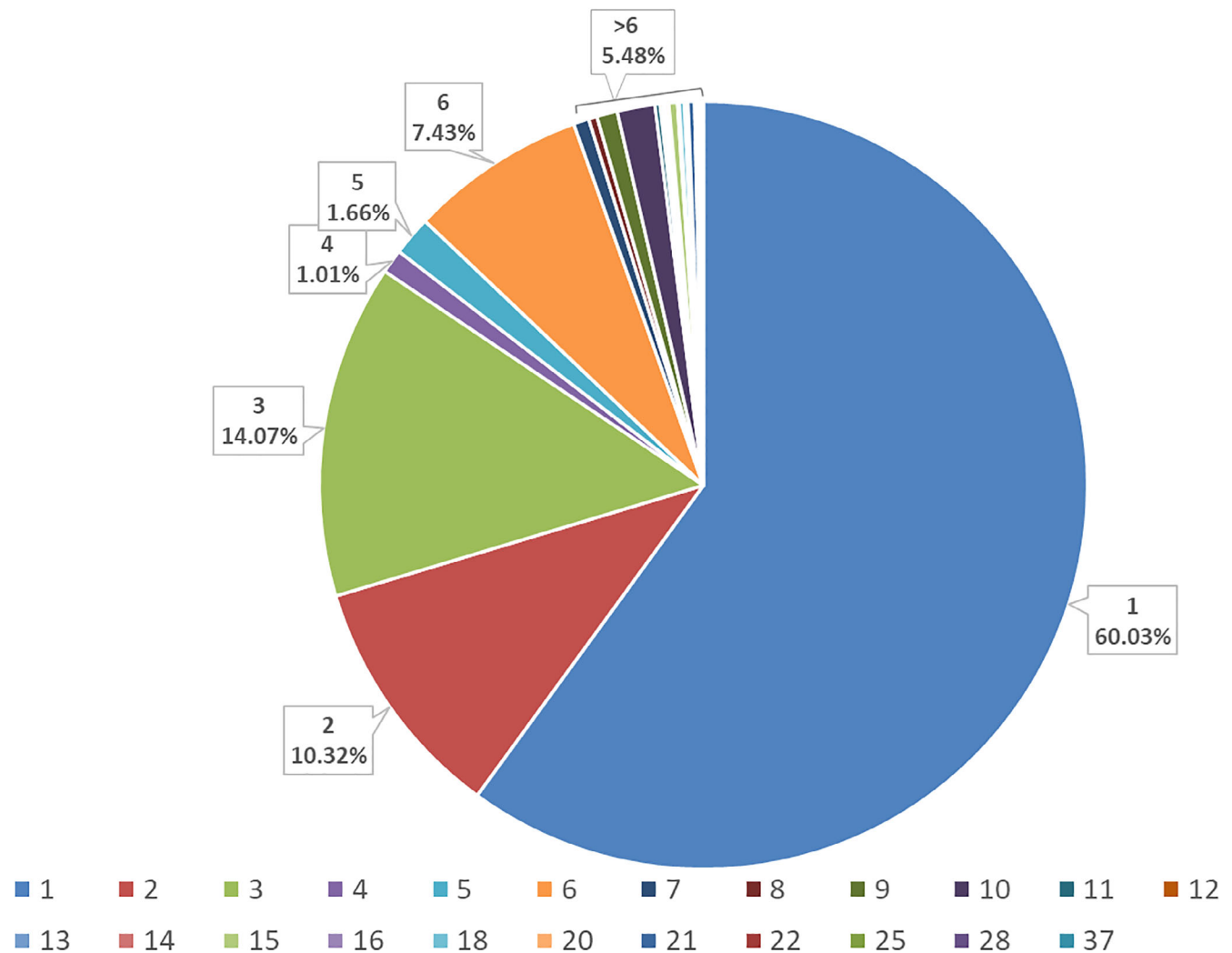


Fig. 2. The distribution of the number of intravitreal injections. [Colour figure can be viewed at wileyonlinelibrary.com]

surgery was not associated with hypertension ($p = 0.82$).

Discussion

Our research investigated 3096 wAMD patients in the ZOC HIS registry and analysed the association between wAMD and hypertension. After the regular series of three injections, wAMD patients with hypertension were more likely to receive anti-VEGF drug intravitreal injections than those without hypertension. To our knowledge, our study investigated, for the first time, the association between hypertension and the treatment of wAMD. Considering the growing ageing population, and the high prevalence of hypertension and wAMD, our results may facilitate prospective

research on the prevention of wAMD and contribute to the clinical management of wAMD and hypertension.

Our findings regarding the relationship between wAMD and hypertension were consistent with those of other studies (Klein et al. 2013, van Leeuwen et al. 2003); however, a meta-analysis including 9523 adults from Australia, Europe and North America showed that there was no significant association between AMD and hypertension (Tomany et al. 2004). The discrepancy may be due to the type of AMD and differences in population characteristics. Unlike Tomany’s study which included wAMD and dry AMD, our study only focused on wAMD and investigated Asian patients from 50 to 96 years old. In addition, a four-year prospective follow-up study revealed that neither

pulse pressure nor hypertension was associated with the progression of AMD (Choudhury et al. 2011). In our study, we collected data from 1 January 2002 to 30 June 2019, approximately nineteen years, and the prevalence of hypertension among wAMD patients was significantly higher than the incidence of hypertension in those with other diseases such as keratitis, tumour, uveitis, cataract and retinal detachment.

The PPPs of AAO suggest that anti-VEGF treatment for wAMD should be implemented once a month for the first three months, and then as needed. Therefore, we classified those with one to three anti-VEGF treatments (inclusive) as group A, and those with over three treatments as group B. Many of the patients in our study were not local residents. If a wAMD patient from

Table 2. The relationship between hypertension status and numbers of anti-VEGF drug intravitreal injections.

		Group A	Group B	β	χ^2	p*	RR (95% CI)
Univariate	Hypertension	201	63	0.24	11.85	0.001	1.27 (1.11–1.467)
	No hypertension	969	153				
Multivariate	Hypertension			0.27	13.68	<0.001	1.30 (1.13–1.50)
	Sex			0.04	0.57	0.45	1.04 (0.93–1.16)
	Age			-0.005	2.75	0.10	1.0 (0.99–1.01)

* COX regression; group A: patients received 1–3 injections; group B: patients received more than three injections; β : regression coefficients; RR: relative risk.

Table 3. The relationship between hypertension status and the need for vitrectomy

		Vitrectomy	No vitrectomy	β	χ^2	p*	OR
Univariate	Hypertension	73	307	-0.46	7.45	0.008	0.63 (0.45–0.89)
	No hypertension	577	2139				
Multivariate	Hypertension			-0.40	0.05	0.82	0.96 (0.66–1.38)
	Sex			-0.31	5.08	0.02	0.73 (0.56–0.96)
	Age			-0.09	139.50	<0.001	1.10 (1.08–1.12)

* Logistic regression; wAMD = wet age-related macular degeneration, β = regression coefficients, OR = odds ratio.

another city needs regular anti-VEGF treatment, the attending physician may advise local follow-up injections. This phenomenon can help patients save time and money in the process of seeing doctors and may explain why the number of patients in group B (216) was less than that in group A (1170). In spite of that, the number of patients with hypertension in group B (29.17%) was greater than in group A (17.18%), implying that wAMD patients with hypertension are more likely to need more anti-VEGF treatment than those without hypertension.

The reason why wAMD patients with hypertension need more anti-VEGF treatment than those without hypertension may be that RAAS not only affects critical components of the heart and cardiovascular system, but also influences blood vessels in the retina. Ang II caused apoptosis in retinal endothelial cells, which can cross the blood–retina barrier and support the development of CNV (Kulkarni et al. 1999; Metelitsina et al. 2006). Additionally, Ang II can reduce the blood flow to the choroid by decreasing the diameter of retinal arterioles and capillaries (Metelitsina et al. 2008). Moreover, Ang II upregulates VEGFR-2, which contributes to the development of CNV by destroying the balance of antiangiogenic and angiogenic factors (Otani et al. 2001; Li et al. 2019). Renin–angiotensin–aldosterone system (RAAS) hyperactivity promotes

an inflammatory condition as well, and inflammation causes macrophage infiltration that induces ocular CNV (Pons et al. 2011; Kim et al. 2015). Thus, RAAS may aggravate the progression of wAMD, which requires wAMD patients with hypertension to need more anti-VEGF treatments than those without hypertension.

Some limitations existed in our study. First, the data records came from a single eye hospital. Even though ZOC is a leading eye hospital in China, and many patients, especially the serious ill patients, from all over the country are seen there, the single-centre analysis influenced the credibility of the conclusions. Our results showed that male AMD patients were more than female AMD patients only mean men were more likely to see doctors at ZOC. There need more researches for the prevalence of AMD in different sex in Asian counties. And no wAMD people we included to analyse the relationship between hypertension and wAMD were not absolutely health. Due to be over 50 years old, some of them may have another age-related disease. It may create bias, and explain why the age appears to decrease risk of AMD (OR = 0.99) in Table 1. What's more, as some wAMD patients had only the first injection at ZOC and the follow-up injections at a local hospital, the recorded number of injections of some patients was less than the actual number. This may be one reason that the

number of patients in group B was much lower than group A. Moreover, the specific hypertension conditions and the aetiology of patients could not be obtained from the HIS registry; therefore, we knew only whether patients had hypertension or not. Socio-economic factors may be a potential confounder for analysing the relationship between hypertension and the number of injections. However, because of the limitation of data, we did not take socio-economic status into account for patients in our analysis.

In conclusion, our results demonstrated that patients with hypertension had a significant correlation with wAMD, and after the regular three injections, wAMD patients with hypertension were more likely to receive anti-VEGF drug intravitreal injections than were those without hypertension. These results may facilitate prospective research on the prevention and treatment of wAMD.

Data Availability Statement

The concise dataset was uploaded in Zenodo. (<https://zenodo.org/record/4090407#.X4gUUG5uIhc>).

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