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Original Article – Clinical Science

Clinical and social characteristics associated with reduced visual acuity at presentation in Australian patients with neovascular age-related macular degeneration: a prospective study from a long term observational dataset. The Fight Retinal Blindness Project

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ABSTRACT

Importance: Identifying variables that influence presenting visual acuity (VA) in patients with neovascular age-related macular degeneration (nAMD) is important because it is a strong predictor of long-term outcomes.

Background: To assess the clinical and social characteristics associated with low presenting VA in nAMD patients.

Design: Cross-sectional analysis from a prospective, observational database.

Participants: We identified 3242 treatment-naïve patients from 54 Australian practices in the Fight Retinal Blindness! registry.

Methods: Age, gender, ethnicity and VA were recorded at the baseline visit. Socio-economic status was determined using the Australian Bureau of Statistics socio-economic indexes for areas.

Main Outcome Measures: Association between clinical and socio-economic characteristics with presenting VA.

Results: Poor VA (≤35 letters) in the presenting eye was associated with older age (adjusted odds ratio [AOR] 1.33 for patients ≥80 years vs. <80 years [95%CI 1.04-1.71]), treatment at a public practice (AOR 1.91 for public vs. private practices [95%CI 1.46-2.50]) and intermediate (36-69 letters) VA in the fellow eye (AOR 0.67 [95%CI 0.47-0.95] and 0.64 [95%CI 0.48-0.85] for poor [≤35 letters] and good [≥70 letters] VA vs. intermediate VA in fellow eye). Gender, ethnicity and socio-economic status were not independently associated with VA at presentation.

Conclusions and Relevance: Poor presenting vision is detrimental to the long-term outcomes of nAMD. Poor presentation of nAMD in Australia may not be related to socio-economic circumstances, but due to systems of care. Further research is warranted to determine why patients at public practices present with worse vision compared with private practices in Australia.

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Key Words: neovascular age-related macular degeneration, socioeconomic factors, visual acuity

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INTRODUCTION

Large variations in the long term outcomes of anti-vascular endothelial growth factor (anti-VEGF) therapy for neovascular age-related macular degeneration (nAMD) were reported by the Comparison of Age-related Macular Degeneration Treatments Trials (CATT),[1] the Seven-Up study[2] and the Fight Retinal Blindness (FRB!) study.[3] This may be related to differences in a variety of clinical characteristics such as baseline features and treatment protocols.[4]

The visual acuity (VA) at first presentation has a strong influence on outcomes of anti-VEGF therapy.[5-9] Patients with poorer VA at presentation achieve larger gains in vision compared with those with good VA, possibly due to a ceiling effect.[3, 5] Conversely, better VA at presentation is associated with smaller gains; despite this, long-term vision is still considerably better than patients presenting with poor VA.[3, 5] Early detection and intervention of nAMD should therefore be a health-care priority to improve long-term outcomes and delay the loss of independence often associated with vision loss.[10, 11]

We have previously reported an improvement in presenting VA over time from 54.2 Logarithm of minimum angle of resolution [LogMAR] letters in 2008 to 58.7 letters in 2014 [approximately 20/80 to 20/60]).[12] However, poor VA at presentation is still common, with 12-13% of patients between 2013 and 2015 presenting with VA < 20/200 (35 letters).[13] This may be related to many factors including the severity of the neovascular lesion, older age, and delayed presentation. A lower socio-economic status (SES) has been associated with low VA at presentation of nAMD, but this has not been a consistent finding.[14, 15]

The Australian health system currently provides anti-VEGF therapy for free under the Pharmaceutical Benefits Scheme in both public and private practices. However, private practices carry additional out-of-pocket expenses (e.g. doctor's fees) which may vary. Moreover, there is no reimbursement for spectral domain optical

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coherence tomography (SD-OCT). Ophthalmologists are unevenly distributed, potentially creating an access barrier for patients in rural and remote areas.[16] Availability of public hospital services are also limited: only 45/1250 (3.6%) of patients were receiving treatment from a public hospital despite significant demand in a 2015 nationwide survey conducted by the Macular Disease Foundation, Australia.[17]

The present study aimed to assess the clinical and socio-economic characteristics associated with presenting VA in a large registry of practices in Australia. Our secondary objective was to evaluate the variation of presenting VA and other patient characteristics over a 7-year period.

METHODS

This paper followed the STROBE guidelines for reporting outcomes in observational studies.[18]

Design and Setting

This was a cross-sectional analysis comparing baseline VA of patients with various demographic and clinical characteristics.

Data were obtained from the FRB! database which prospectively tracks real-world outcomes of treatments for nAMD during routine clinical practice as described previously.[19] FRB! is compliant with the International Consortium for Health Outcomes Measurement's macular degeneration minimum set of outcomes.[20] Institutional ethics approval was obtained from the Human Research Ethics Committees of the University of Sydney, the Royal Victorian Eye and Ear Hospital and the Royal Australian and New Zealand College of Ophthalmologists. Ethics committees in Australia approved the use of "opt out" patient consent. The research described adhered to the tenets of the Declaration of Helsinki.

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Study Measurements

Patient age (years), gender, ethnicity, VA in LogMAR letters, lesion size and type were recorded at the baseline visit. While there are several ethnicities present in the FRB! database, we only distinguished between Caucasian and non-Caucasian as individual ethnic groups were not well represented. Lesion size was defined as the greatest linear dimension of the neovascular lesion in micrometres as identified by fundus fluorescein angiography and determined by the treating physician during consultation.

Study participants at presentation of nAMD were classified into visual impairment categories as described by the World Health Organisation based on their best seeing eye: mild or no visual impairment (≥58 letters), moderate visual impairment (35-57 letters), severe visual impairment (20-34 letters) and blindness (<20 letters).[21]

SES was assessed using the Australian Bureau of Statistics (ABS) socio-economic indexes for areas (SEIFA).[22] Briefly, the SEIFA is a composite index that takes into account income, education, unemployment rates, occupation, housing circumstances, and other indicators of social and economic advantage/disadvantage. Indexes are assigned to areas (postcodes) and divided into deciles for ease of interpretation.[22] After linking SEIFA with the postcode of the patients, the SES of patients was categorised into 3 groups: poor (deciles 1-3), average (deciles 4-7) and wealthy (deciles 8-10).

Practice characteristics included: private vs. public and rural vs. urban. Urban and rural were classified using the definitions provided by the ABS in the Australian Statistical Geography Standard. [23]

Study Outcomes

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The primary objective was to determine which variables were associated with presenting VA. We assessed the relationship between the presenting VA in the eye with nAMD and:

- Demographic characteristics: age, gender, ethnicity, patient SES, clinical practice type and location, year of study entry.
- Clinical characteristics: presence of ocular conditions other than nAMD and VA of the fellow eye irrespective of the presence of nAMD.

The secondary objective was to assess the change in demographic and clinical characteristics at presentation over 7 years for nAMD patients.

Participants

The study included only Australian practices because SES was not available for other countries participating in the FRB! registry. Only treatment-naïve patients beginning treatment for nAMD from 1st January 2006 to 1st September 2016 were considered. Secondary analyses of clinical and demographic variations over time considered only practices that had actively contributed to FRB! from 2009-2016 to avoid any "practice effect" related to practices joining or dropping out of FRB.

When nAMD was present in both eyes, we defined the "first eye" as the eye that was diagnosed first or, if diagnosed simultaneously, the eye presenting with worse VA. Primary analyses were conducted on the first eye. VA of the fellow eye was used as a covariate and taken at the baseline visit of the first eye.

Statistical Analysis

Descriptive statistics included the mean (SD), median (interquartile range, IQR), and percentages. Chi-square tests were used to assess categorical variables.

Unconditional associations between patient- and practice-level characteristics were assessed using univariate analysis. Variables significant at the 0.2 significance level were included in a multivariate model adjusted for the year of study entry.

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Presenting VA was analysed as a continuous variable. Multicollinearity in the multivariate model was measured using the variance inflation factor (VIF), and was considered to be an issue when the VIF exceeded 3.[24] Univariate and multivariate (adjusted for year of study entry) odds ratios (OR) were calculated treating presenting VA as a categorical variable (VA ≤35 letters and >35 letters) using logistic regression. Age and VA of the fellow eye were analysed as both continuous and categorical variables (age <80 years and ≥80 years; fellow eye VA ≤35 letters, 36-69 letters, and ≥70 letters); for brevity, ORs are only presented when these variables were categorical. Categorical variables such as SES were analysed as ordered variables where appropriate. Additional sensitivity analyses were conducted removing bilateral cases where patients were diagnosed for both eyes simultaneously which may affect first vs. second eye relationships and using multiple imputations when missing data were present.

A p-value <0.05 was considered to be statistically significant for the multivariate analysis. All analyses were performed using R version 3.2.4, with the *mice* package (version 2.25) for multiple imputations.[25, 26]

RESULTS

Study participants and practices

We identified 3242 treatment-naïve patients from 54 practices commencing treatment for nAMD. At presentation of nAMD, 84.2% presented with mild or no visual impairment, 13.5% presented with moderate visual impairment, 1.3% presented with severe visual impairment and 1.1% were classified as blind according to the World Health Organisation definitions for visual impairment. [21]

Practices were mostly private and located in urban areas (Table 1**)**. There was a strong association between SES of the patient and practice type and location. A higher proportion of patients treated in private clinics were from a poor SES (32.8%)

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compared with public clinics (18.2%, P<0.001). Similarly, patients treated in rural clinics were more likely to be from a poor SES (50.0%) compared with urban clinics (28.9%, P<0.001).

Table 1: Association between practices characteristics and the socio-economic status of their patients. Percentages for the distribution of patient SES sum to 100% across rows.

Practice Characteristic	Practices	Patients	SES of Patient, n (%)			P-value
			Poor	Average	Wealthy	
Total	54	3242	278 (8.6%)	294 (9.1%)	371 (11.4%)	
Type						
Private	50	2802	239 (32.8%)	209 (28.7%)	281 (38.5%)	**<0.001**
Public	4	440	39 (18.2%)	85 (39.7%)	90 (42.1%)	
Location						
Urban	48	3156	265 (28.9%)	281 (30.6%)	371 (40.5%)	**<0.001**
Rural	6	86	13 (50.0%)	13 (50.0%)	0 (0%)	

Visual acuity at presentation for various demographic and clinical subgroups

The overall mean (SD) presenting VA for first eyes was 54.2 letters (19.62; Table 2). The VA of the fellow eye was on average 8.4 (95% CI: 6.9, 9.9; P<0.001) letters better than the first eye at presentation (P<0.001). Higher VA in the fellow eye was still observed after removing bilateral nAMD presenting simultaneously (7.1 letters, 95% CI: 5.4, 8.7, P<0.001). VA of the presenting eye and its fellow eye were significantly associated when the VA of the fellow eye was treated as a categorical variable (categorical, P<0.001 and continuous, P=0.101), suggesting a non-linear relationship (Figure 1). Mean (SD) VA in the presenting eye was better when VA of the fellow eye was ≤35 letters (51.1 [19.3] letters) or ≥70 letters (54.2 [19.5]) compared with intermediate vision (47.1 [19.3] letters, P=0.728, P=0.002 and P<0.001 for ≤35 vs. ≥70 letters, ≤35 vs. 36-69 letters and ≥70 vs. 36-69 letters respectively following adjustment for multiple comparisons).

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Table 2: Comparison of baseline visual acuity (VA) for each demographic and clinical group. Percentages for presenting VA (categorical) sum to 100% across rows. Odds ratios (OR) show the risk of presenting with vision ≤35 letters.

	Presenting VA (Continuous)				Presenting VA (Categorical)			
	Patients	**Mean Baseline VA (SD)**	**Univariate P-value**	**Multivariate P-value**	**VA ≤35 Letters, n (%)**	**VA >35 Letters, n (%)**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**
Overall	3242	54.2 (19.6)	-	-	577 (17.8%)	2665 (82.2%)	-	-
Age								
<80 Years	1376	56.7 (19.2)	**<0.001**†	**<0.001**†	211 (15.3%)	1165 (84.7%)	1	1
≥80 Years	1863	52.4 (19.7)	**<0.001**‡	**<0.001**‡	365 (19.6%)	1498 (80.4%)	1.35 (1.12, 1.62)	1.33 (1.04, 1.71)
Gender								
Females	1939	54.4 (19.0)	0.353		331 (17.1%)	1608 (82.9%)	1	
Males	1301	53.8 (20.5)			246 (18.9%)	1055 (81.1%)	1.13 (0.94, 1.36)	
Ethnicity								
Caucasian	3087	54.1 (19.6)	0.293		549 (17.8%)	2538 (82.2%)	1	
Non-Caucasian	155	55.8 (19.8)			28 (18.1%)	127 (81.9%)	1.02 (0.66, 1.53)	
SES								
Poor	278	54.4 (21.0)	0.434		50 (18.0%)	228 (82.0%)	1	
Average	294	52.7 (20.3)			59 (20.1%)	235 (79.9%)	0.87 (0.65, 1.18)	
Wealthy	371	54.5 (18.0)			57 (15.4%)	314 (84.6%)	0.83 (0.62, 1.11)	
Ocular Condition								
nAMD Only	2782	54.0 (19.8)	0.599		505 (18.2%)	2277 (81.8%)	1	
*Other**	460	55.1 (19.0)			72 (15.7%)	388 (84.3%)	0.84 (0.63, 1.11)	
Fellow Eye VA								
≤35 Letters	342	51.1 (19.3)	**<0.001**†	0.101†	70 (20.5%)	272 (79.5%)	0.71 (0.50, 1.00)	0.67 (0.47, 0.95).
36-69 Letters	392	47.1 (19.3)	**<0.001**‡	**<0.001**‡	104 (26.5%)	288 (73.5%)	1	1
>70 Letters	1004	54.2 (19.5)			176 (17.5%)	828 (82.5%)	0.59 (0.45, 0.78)	0.64 (0.48, 0.85)

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Practice Type								
Private	2802	55.3 (19.3)	**<0.001**	**<0.001**‡	453 (16.2%)	2349 (83.8%)	1	1
Public	440	47.3 (20.3)			124 (28.2%)	316 (71.8%)	2.03 (1.61, 2.56)	1.91 (1.46, 2.50)
Practice Location								
Urban	3156	54.2 (19.6)	0.895		562 (17.8%)	2594 (82.2%)	1	
Rural	86	53.9 (22.3)			15 (17.4%)	71 (82.6%)	0.98 (0.53, 1.67)	

Abbreviations: VA=Visual Acuity, SD=Standard Deviation, CI=Confidence Interval, SES=Socio-economic Status, OR=Odds ratio

* Other ocular conditions included: amblyopia, axial myopia, clinically significant media opacity, diabetic retinopathy, glaucoma, posterior uveitis, geographic atrophy, pseudophakia and vitreomacular traction.

† Demographic/clinical variable analysed as continuous

‡ Demographic/clinical variable analysed as categorical

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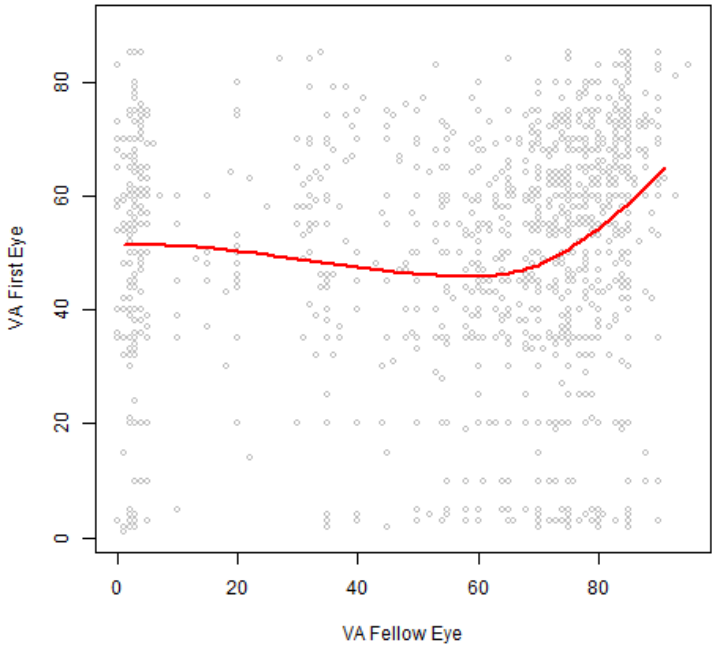

Figure 1: Relationship between visual acuity of the first eye at presentation compared to the fellow eye. Each circle represents observed VA for both eyes for each patient while the red line is the LOESS regression line fitted to the data. When the baseline visual acuity of the fellow eye was over 60 LogMAR letters, the baseline VA of the first eye tends to be better.

Univariate and multivariate odds ratios when presenting vision was analysed as a categorical variable (VA ≤35 letters vs. VA > 35 letters) are presented in Table 2. Presenting with VA ≤35 letters was associated (AOR [95%CI]) with older age (1.33 [1.04, 1.71] for patients <80 years vs. ≥80 years) and treatment at public practices (1.91 [1.46, 2.50] for private vs. public practices), after multivariate adjustment (Table 2). Patients with poor (≤35 letters) or good (≥70 letters) vision in the fellow eye were less likely to present with VA ≤35 letters in the first eye (AOR [95%CI] 0.67 [0.47, 0.95] and 0.64 [0.48, 0.85] for VA ≤35 letters and ≥70 letters vs. VA between 36 and 69 letters in the fellow eye respectively). Gender, ethnicity and SES

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were not independently associated with VA at presentation (P=0.353, P=0.293 and P=0.434, respectively; Table 2). Sensitivity analyses using multiple imputations for missing data gave similar results in both the univariate or multivariate models.

Evolution of patient characteristics over time

Demographic characteristics of patients from 14 practices that contributed data for at least 7 years are shown in Figure 2. Mean age at first presentation remained constant over time (overall mean [SD] 79.6 [8.6] years; P=0.608). Patients in the poor SES group increased in representation over time and represented the majority of patients treated in 2013 (56%) and 2014 (63%). Non-Caucasian made up less than 5% of patients treated from 2009 to 2014, but increased to 17% in 2015 and 26% as of September 2016. However, this increase in representation was driven primarily by a single practice. Across all 54 practices, the mean (SD) VA for first eyes increased from 50.7 (19.3) letters in 2009 to 60.3 (17.4) letters in 2016.

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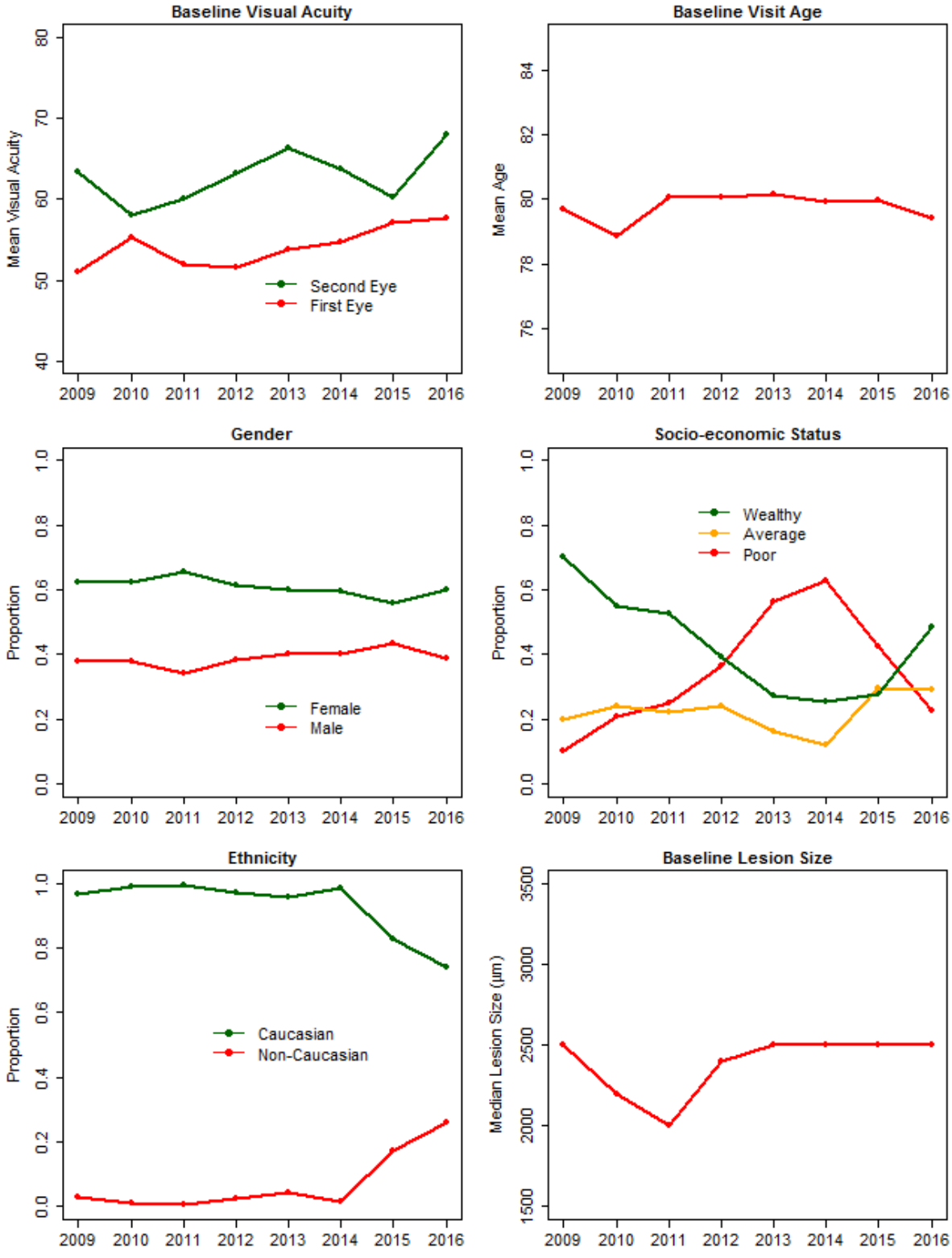

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Figure 2: Evolution of demographic and clinical characteristics at presentation over time for neovascular age-related macular degeneration patients.

DISCUSSION

The prospectively designed observational FRB! registry allowed us to assess the characteristics associated with VA at presentation of 3242 Australian patients with nAMD. Contrary to expectations, we found that SES was not significantly associated with poor vision at presentation of nAMD in Australia. Poorer VA at presentation was significantly associated with older age and treatment at a public practice highlighting a possible disparity between private and public clinics in their capacity to provide timely treatment for nAMD patients. VA of the fellow eye was better on average than the presenting eye. Better vision in the presenting eye was associated with good or poor vision in the fellow eye suggesting a non-linear relationship.

Acharya et al. reported that lower levels of vision at presentation of nAMD were associated with older patients.[14] However, they found no relationship between the fellow eye and the eye presenting with nAMD. We observed a higher mean VA in the eye presenting with nAMD when the fellow eye had either a low (≤ 35 letters) or a high (≥ 70 letters) VA. The reasons this non-linear relationship are speculative. Patients with poor vision in one eye may be more sensitive to changes in their other eye but it is not clear why people with very good vision in their fellow eye present early. The presence of co-morbid conditions in the second eye may have played a role, however we found presenting with ocular conditions other than nAMD had no impact on VA of the presenting eye.

Patients attending public practices were twice as likely to present with VA ≤35 letters compared with private practices. Non-means tested access to free public care is available to all Australians. We found patients from a higher SES made up the majority of those treated in public facilities. Therefore, lower presenting VA in public

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practices is possibly influenced by other factors such as longer waiting times rather than SES factors. Delays between diagnosis and treatment of nAMD lead to a deterioration in vision [5] and may be more likely in public hospital settings.[27, 28] It is unknown whether poor SES patients attending public practices were underrepresented in the present study. Indeed, poor SES patients may be competing for limited access to treatment at public hospitals. Public provision of treatment for nAMD is in significant demand,[17] and lack of availability of public services may hinder their capacity to treat patients early. Further research is warranted to determine the factors leading to poorer presenting VA in patients treated at public hospitals.

The association between SES and visual impairment is well known.[29, 30] Social deprivation has been linked to a variety of eye conditions such as glaucoma, retinal detachment and cataract surgery.[31-33] Data concerning the relationship between SES and VA at presentation of nAMD are scarce. Patients from lower socio-economic backgrounds had worse VA at first presentation in a study conducted in Birmingham (UK) on 120 patients suggesting this vulnerable group may have encountered barriers in accessing treatment in nAMD.[15] A study on 240 patients in Scotland presenting between July 2004 and June 2005 found SES was not associated with VA at presentation of nAMD.[14] The present study consisting of 3242 patients found no association between SES, gender or ethnicity and poor VA at presentation of nAMD. Such differences between studies may be related to variation in access and reimbursement to treatment for nAMD between countries. At first glance, our results suggest the Australian health care system provides good access to nAMD treatments without discrimination between gender, ethnicity and SES.

We are aware, however, that the FRB! registry may not be a representative sample of the entire Australian population with nAMD. There are an estimated 7316 cases of nAMD per year in Australia not receiving treatment and thus not captured by the registry; such patients are more likely to be non-English speakers at home, live in rural areas, or have a low SES.[16] Patients were similarly distributed across the 3

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socio-economic grades and low socio-economic patients increased in representation over time in the present study. Thus, patients from all socio-economic backgrounds seem equally at risk of presenting with poor vision. The increase in representation of low SES patients observed here is encouraging, however, lack of access to ophthalmologists and public hospital services may still act as barriers to the initial diagnosis and treatment for lower socio-economic groups. Non-Caucasian ethnic groups and rural patients may be under-represented in our sample which could also account for a subset of untreated individuals. Accessing treatment in rural areas may be particularly problematic as there tend to be few ophthalmologists in these areas in Australia.[16] It is also possible that these patients represent a sample being treated by ophthalmologists not currently registered in FRB.

Increase in VA at presentation over the past several years reported in the FRB! registry are encouraging.[12] We can only speculate the reasons for this result, though it is likely to be multifactorial. Increased awareness amongst patients at-risk to nAMD may have been a contributing factor. Polls and Medicare surveys found awareness of AMD in Australians aged 50 years or older increased from 58% in 2007 to 92% in 2011 following media campaigns by the Macular Disease Foundation.[34]

The strengths of the present study include high-quality data collected prospectively with both clinical and social indicators over several years. This is the largest study to assess the relationship between social variables and VA at presentation for nAMD with a primary analysis conducted on 3242 patients from 54 different practices including public and private, metropolitan and rural. Limitations include a possible selection bias of patients and ophthalmologists in the FRB! cohort as discussed above. The SEIFA indexes used to assign SES are externally validated to establish their credibility for socio-economic analyses, although caution should be used as the postal area code may not reflect the SES of the individuals resulting in some misclassification.[22, 35] The registry currently does not record the duration of

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symptoms before presentation for nAMD, which could be a key performance indicator.

Previous research has highlighted the relationship between early presentation and treatment of nAMD and better long-term visual outcomes. This study provides an important step towards improving visual outcomes for Australian patients with nAMD by identifying factors associated with poor presenting VA. Poor vision at presentation was highly associated with treatment at a public practice, regardless of SES. Indeed, we found no association between presenting VA and SES, suggesting patients may be at risk independent of their socio-economic circumstances. Clinical audits into public practices are warranted to determine why patients are presenting with worse VA than private counterparts.

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