Analysis of 12 years of anti-VEGF therapy for neovascular age-related macular degeneration (AMD)

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ABSTRACT
This analysis piece looks at AMD patients recieving anti-VEGF therapy, and evaluates the patients characterists in order to identify the statistically significant covariates.

1 Introduction

In the UK, age-related macular degeneration (AMD) continues to be the leading cause of visual impairment certification. Without treatment, AMD causes irreversible vision deterioration, trouble with many elements of everyday life, and loss of independence. A meta-analysis of untreated eyes in clinical trials indicated that almost 50% had a “significant” decline (≥ 15 EDTRS letters) in vision after 12 months, with a comparable proportion categorised as legally blind (≤35 ETDRS letters).

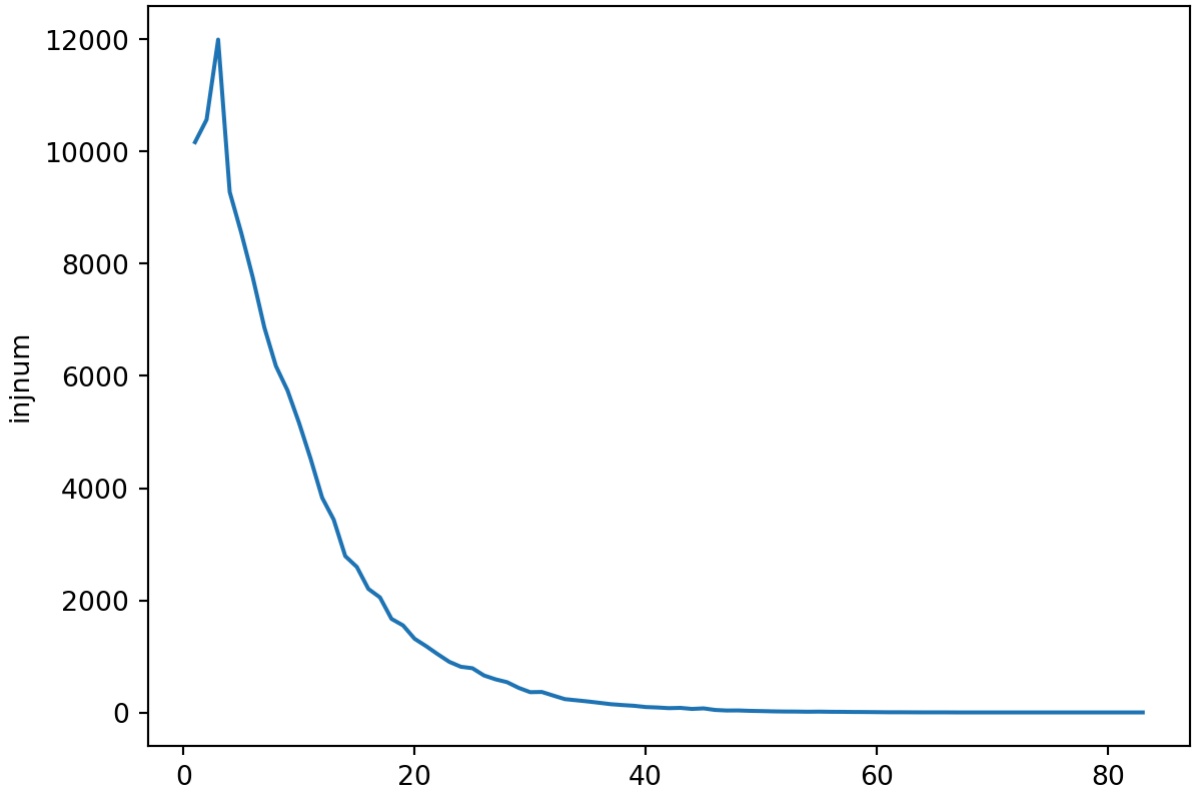
In order to study at this issue, we refer to a publicly available dataset: https://doi.org/10.5061/dryad.nvx0k6dqg , that was published as part of the scientific article named “Insights from survival analyses during 12 years of anti-VEGF therapy for neovascular age-related macular degeneration”. The researchers of that article focused on a survival analyses for retrospective clinical practice visual outcomes.

We decided to look at this dataset from a different angle, looking at the main factors that cause poor visual acuity. This was done based on the definitions of The Second Report of Age-related Macular Degeneration Audit (AMD) of the National Ophthalmology Database Audit report, where defined the proportion of eyes with “good” visual acuity (≥ 70 ETDRS letters) after one year of treatment and the proportion of eyes with “poor” visual acuity change (≥10 ETDRS letter loss) after one year of treatment.

2 Load Data & Description

```
The total number of subjects in this dataset is:  7802
```

Regarding the number of injections received by patients, we see the following count:



Where the peak was at the 3 dose count, and then it decreases from there. This is likely due to a data error, as to have 3 doses at least you must have 1 and 2 be the same.

We proceeded to transform the event-based data to a patient-centric dataset, where the first and last measurements were compared in order to label the data, as mentioned in the introduction.

2.1 Proportion

After classifying beteween “good” and “bad” va, and removing those that didn’t fit either criteria, the propotion of the classes are:

	va outcome
good	60.81
bad	39.19

and in absolute numbers:

	va outcome
good	2588
bad	1668

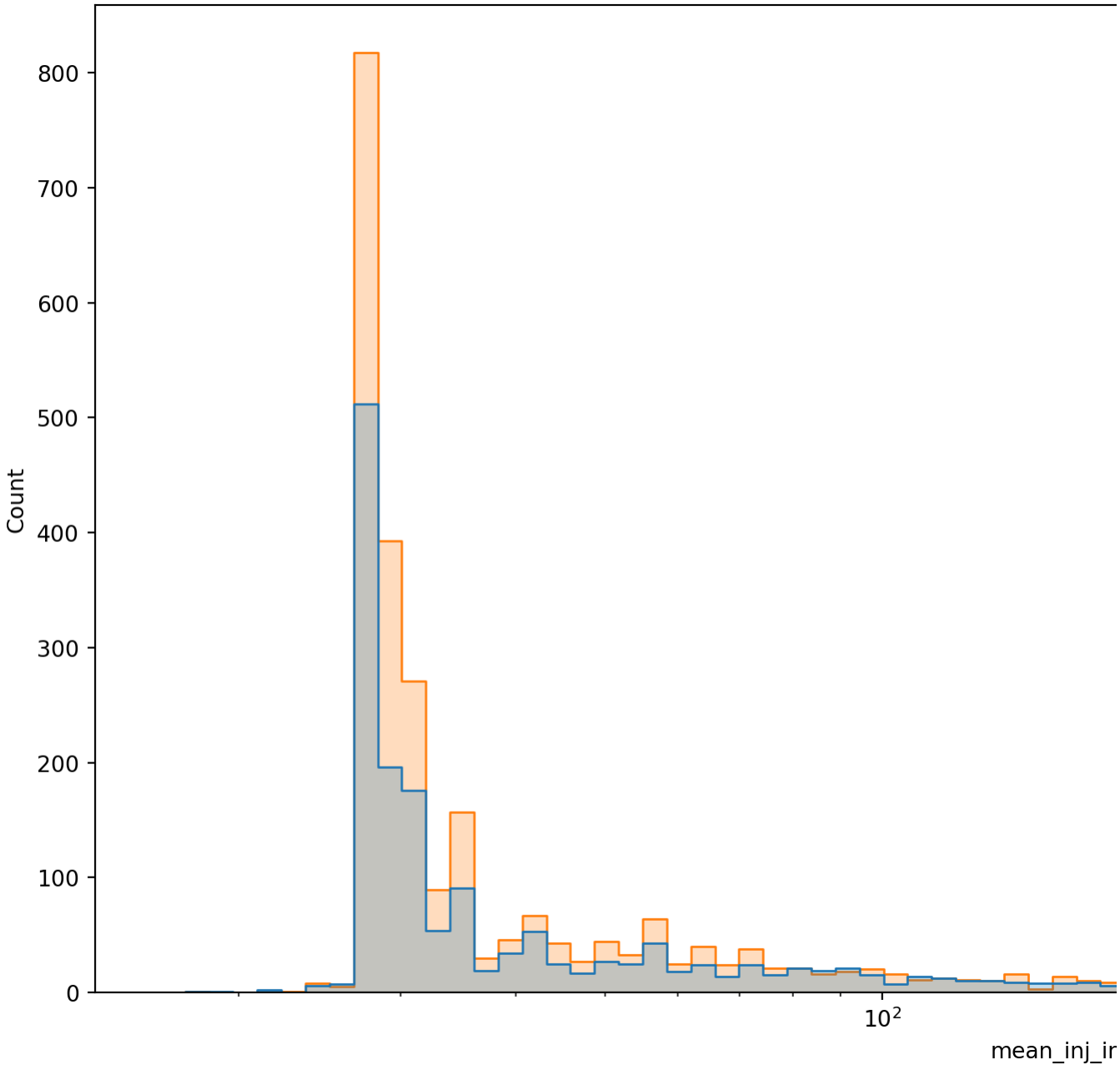
2.2 Continous Variables

In this section we visualise and describe the continous variables:

2.2.1 Mean injection interval (mean_inj_interval)

Mean interval between injections in induction phase in days.

Normalised plot:



The mode, minimum and maximum mean_inj_interval per group are:

	mode	min	max
va outcome			
bad	28.00	17.50	1,600.00
good	28.00	17.50	888.00

It is a time-based feature, where both classes share the mode and minimum spacing, with the bad class having a higher max spacing.

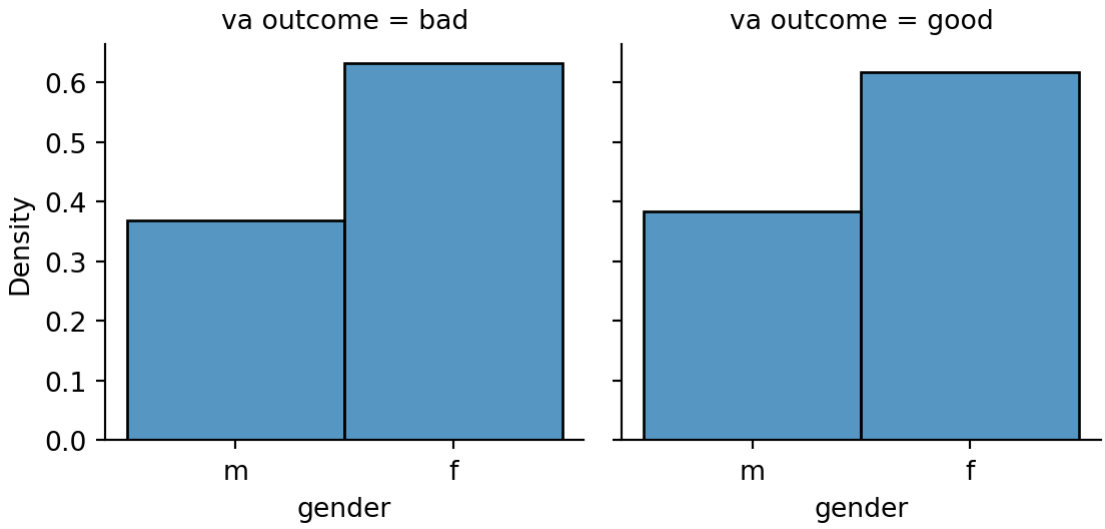
2.3 Categorical Variables

In this section we visualise and describe the categorical/binary variables:

2.3.1 Gender

Gender of patient (m = male, f = female).

Normalised plot:



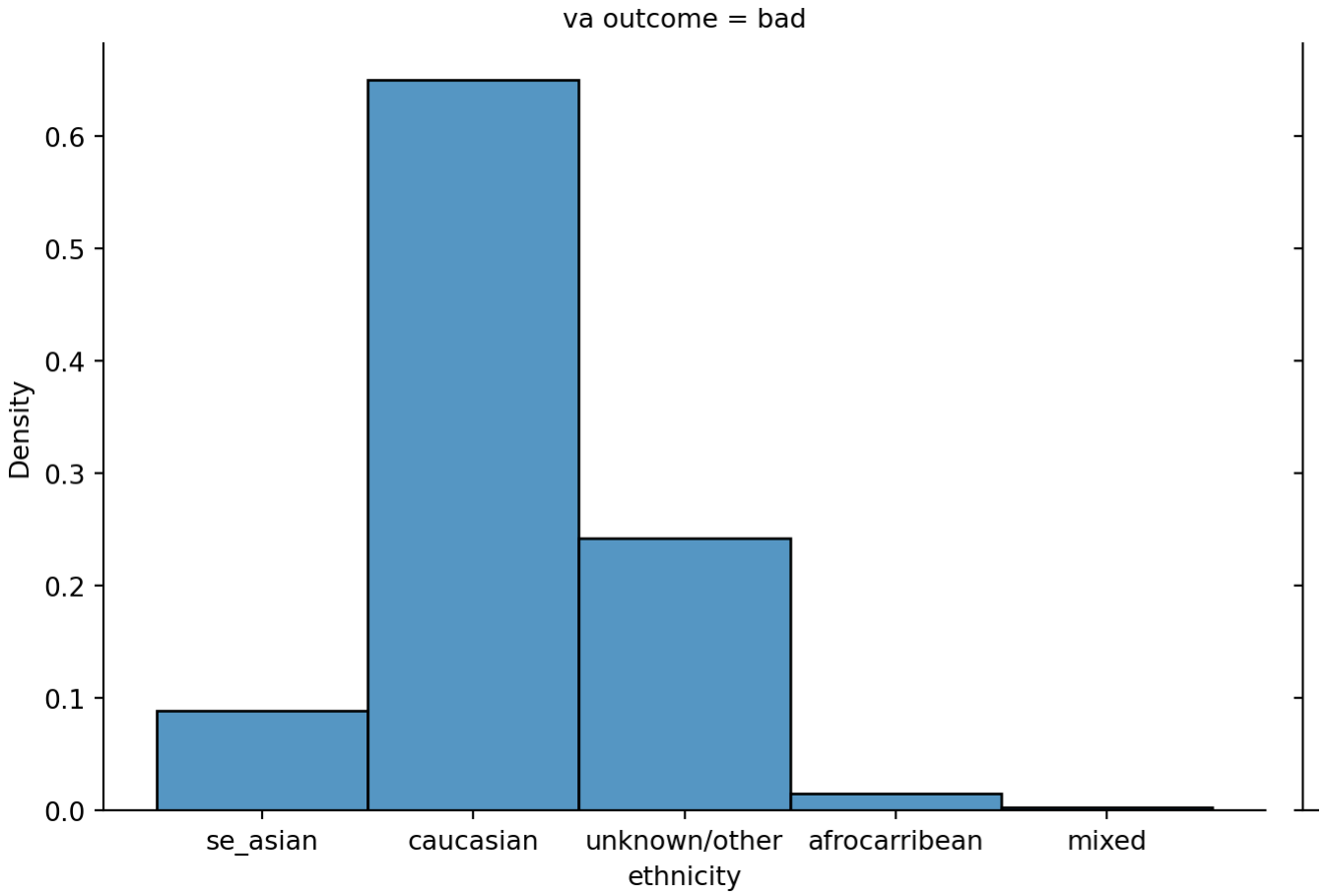
The proportions of gender per group are:

		gender
va outcome	**gender**	
bad	f	63.19
	m	36.81
good	f	61.71
	m	38.29

Where the female to male ratio is closely to 62/38% in both.

2.3.2 Ethnicity

Normalised plot:



The proportions of Ethnicity per group are:

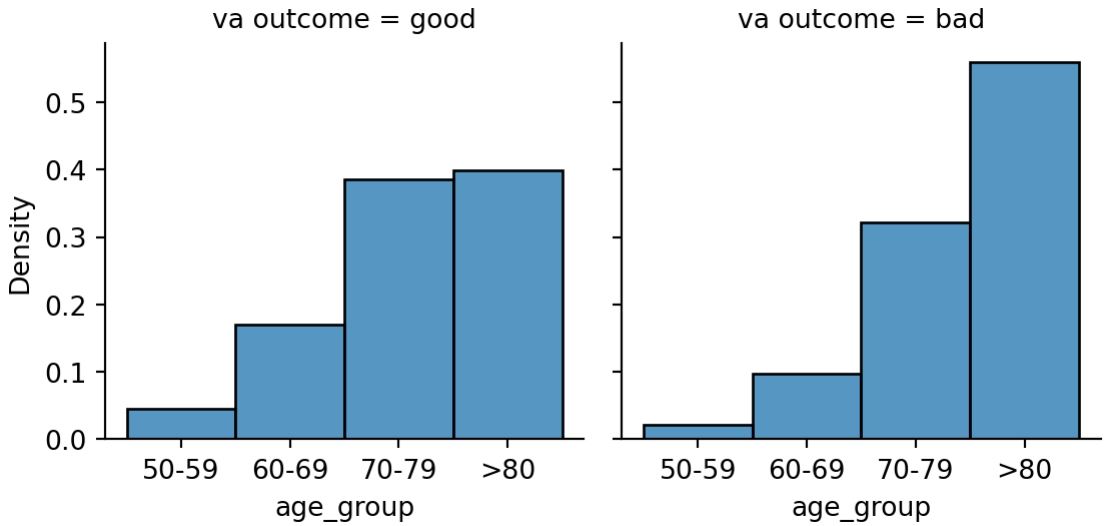
		ethnicity
va outcome	**ethnicity**	
bad	caucasian	65.05
	unknown/other	24.22
	se_asian	8.93
	afrocarribean	1.50
	mixed	0.30
good	caucasian	61.63
	unknown/other	27.63
	se_asian	7.50
	afrocarribean	2.94
	mixed	0.31

Where in the bad outcome we find 3% more caucasian, 3% less other, 1% more south east asian, half of the afrocarribean and 0.1% more mixed.

2.3.3 Age group (age_group)

Age at initiation of anti-VEGF therapy (50-59 years, 60-69 years, 70-79 years, 80 years and above).

Normalised plot:



The proportions of Age group per group are:

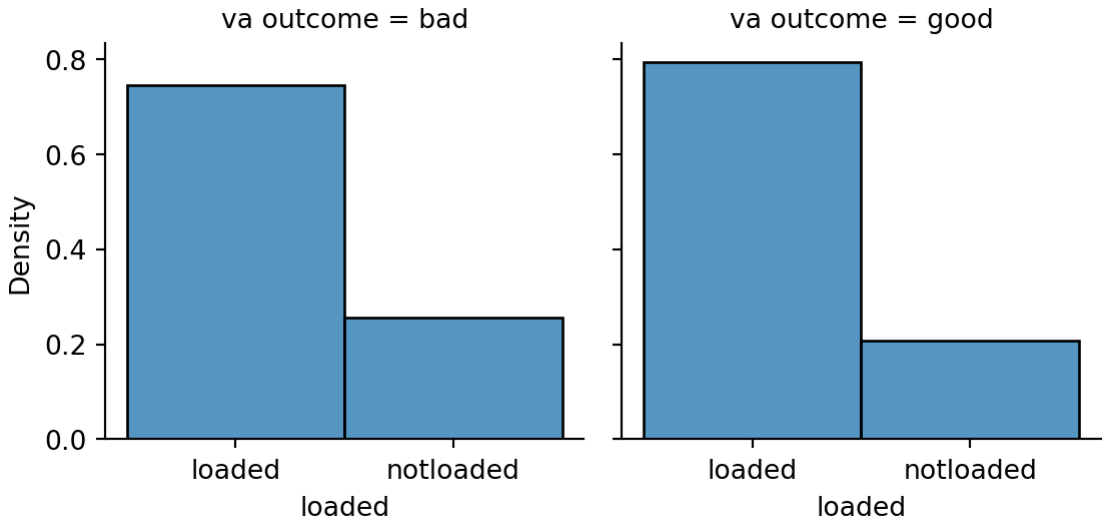
		age_group
va outcome	**age_group**	
bad	>80	55.94
	70-79	32.19
	60-69	9.77
	50-59	2.10
good	>80	39.91
	70-79	38.64
	60-69	16.96
	50-59	4.48

Where we see an increase of counts from younger to older bins in both groups, however the bad category has a significant (10% more) over 80 than the good category.

2.3.4 Loaded (loaded)

If the induction phase was appropriately completed within 90 days (loaded) or not (nonleaded).

Normalised plot:



The proportions of loaded per group are:

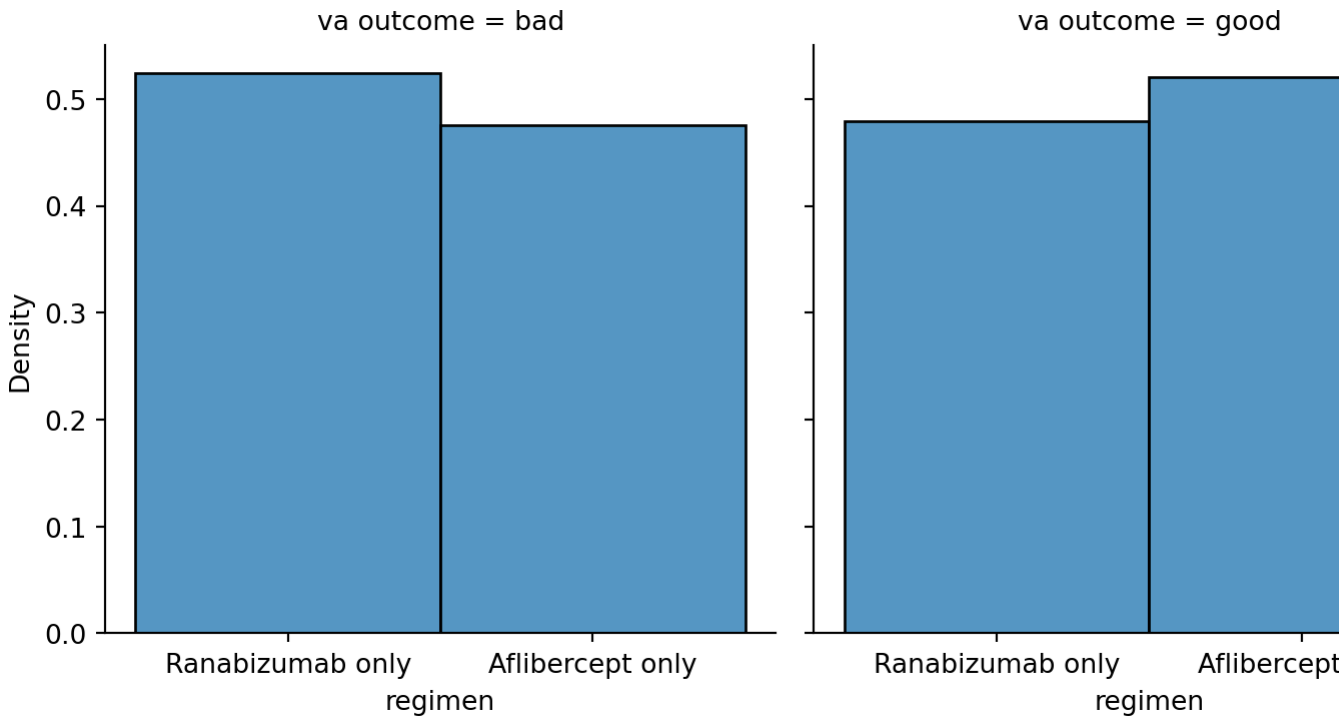
		loaded
va outcome	**loaded**	
bad	loaded	74.46
	notloaded	25.54
good	loaded	79.29
	notloaded	20.71

Where we see a slight increase of non loaded (5%) in the bad category compared to the good category.

2.3.5 Regimen

If the anti-VEGF drug given is ranibizumab (Ranabizumab only) or aflibercept (Aflibercept only).

Normalised plot



The proportions of regimen per group are:

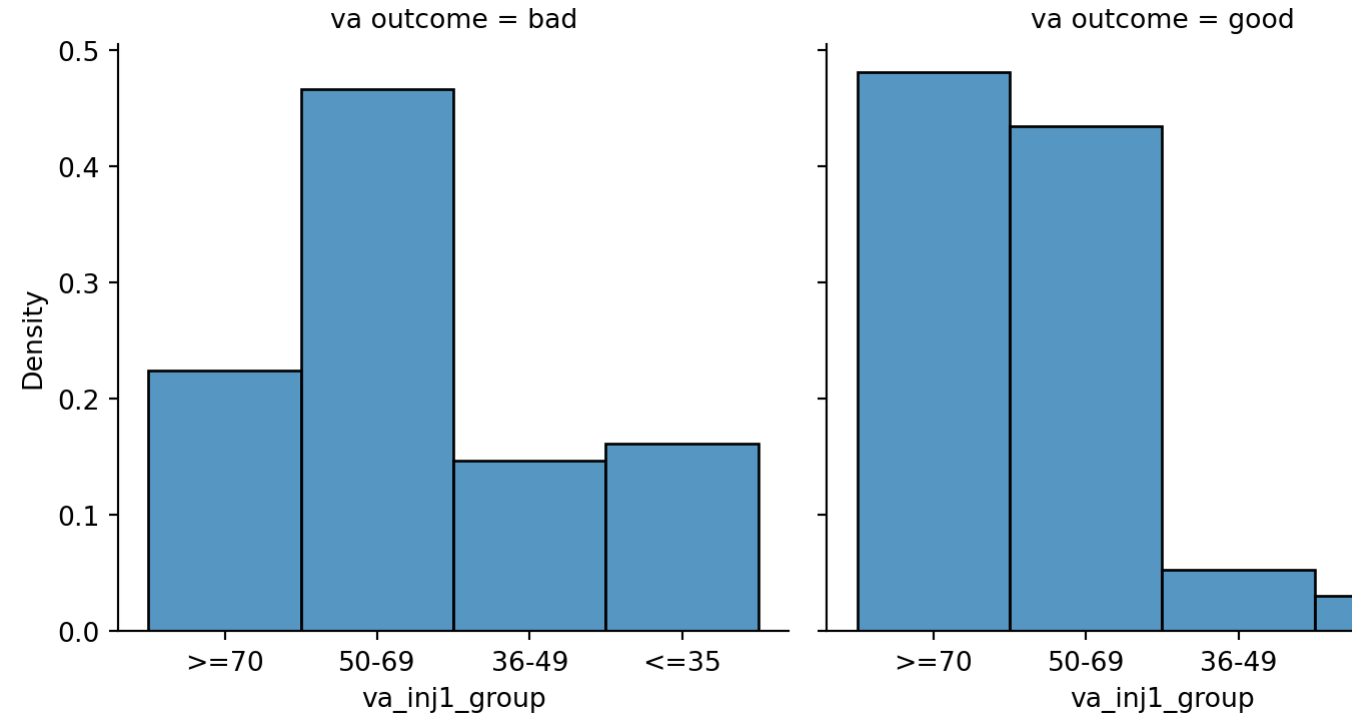
		regimen
va outcome	**regimen**	
bad	Ranabizumab only	52.40
	Aflibercept only	47.60
good	Aflibercept only	52.09
	Ranabizumab only	47.91

Where we see a very simlar proportion in both groups.

2.3.6 Visual Acuity at first injection group (va_inj1_group)

Visual acuity at baseline (initiation of anti-VEGF therapy) in early treatment diabetic retinopathy study letter score.

Normalised plot



The proportions of va_inj1_group per group are:

		va_inj1_group
va outcome	**va_inj1_group**	
bad	50-69	46.64
	>=70	22.48
	<=35	16.19
	36-49	14.69
good	>=70	48.15
	50-69	43.47
	36-49	5.33
	<=35	3.05

Where we seea change in the mode from >=70 in good to 50-69 in bad.

3 Univariate Analysis

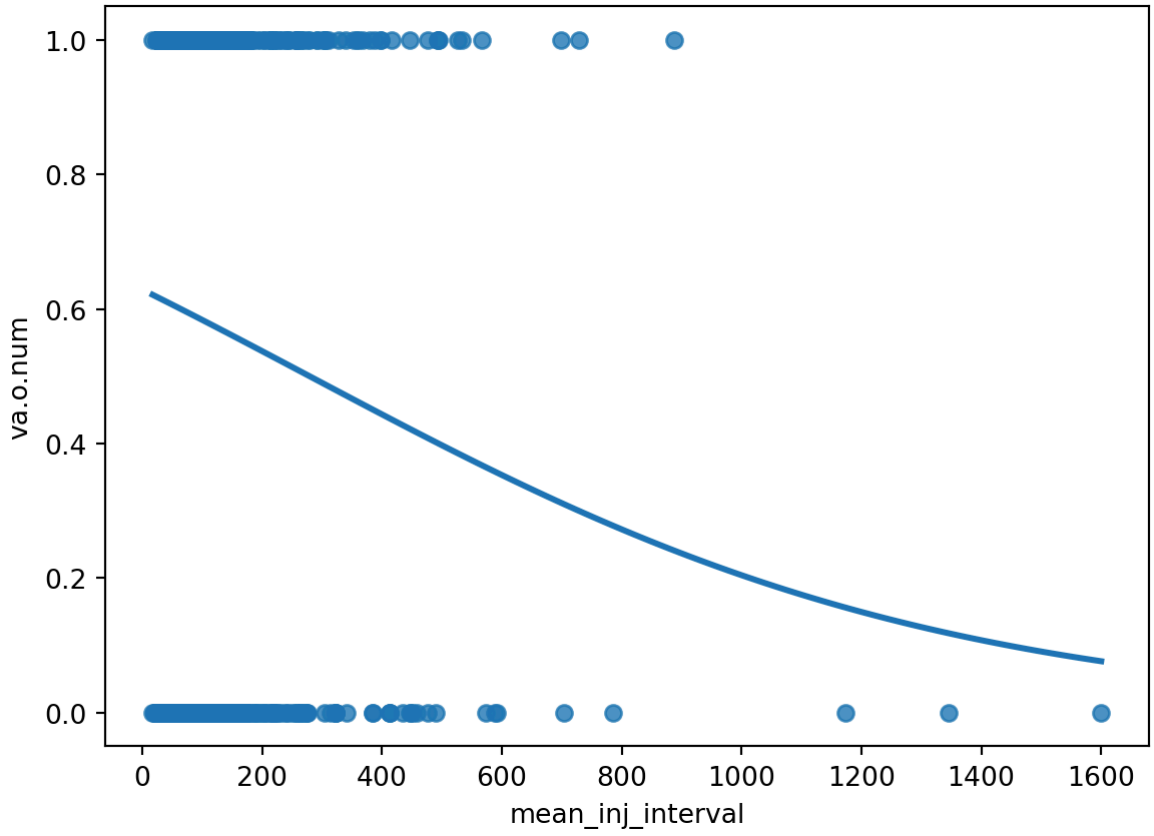
Variables considered statistically significant from univariate testing at the 10% level were considered in the multivariate model

3.1 Continuous Covariates

For continuous covariates, univariate logistic regression was used to evaluate if they are statistically significant to add to the multivariate model.

3.1.1 Mean injection interval (mean_inj_interval)

```
Optimization terminated successfully.
         Current function value: 0.689463
         Iterations 4
                           Logit Regression Results
==============================================================================
Dep. Variable:                 va.o.num   No. Observations:                 4256
Model:                           Logit   Df Residuals:                     4255
Method:                            MLE   Df Model:                            0
Date:                Mon, 06 May 2024   Pseudo R-squ.:                -0.02967
Time:                        10:09:08   Log-Likelihood:                -2934.4
converged:                       True   LL-Null:                       -2849.8
Covariance Type:            nonrobust   LLR p-value:                       nan
==============================================================================
                 coef    std err          z      P>|z|      [0.025      0.975]
------------------------------------------------------------------------------
mean_inj_interval     0.0022      0.000      5.254      0.000       0.001       0.003
==============================================================================
```



Where a coefficient near 0 indicates it is not a good predictor.

3.2 Binary and Categorical Covariates

For binary and categorical covariates, univariate analysis was made using Chi- square tests.

	covariate	statistic	p value	significant
0	gender	0.886	0.347	no

	covariate	statistic	p value	significant
1	ethnicity	17.795	0.001	yes
2	age_group	121.345	0.000	yes
3	loaded	13.243	0.000	yes
4	regimen	7.982	0.005	yes
5	va_inj1_group	489.715	0.000	yes

Where we identify as statistically significant covariates: va_inj1_group, ethnicity,age_group, loaded and regimen.

4 Conclusion

Both the initial VA and the ethnicity are factors of a patients can’t be addressed, but in order to prevent lowering the VA of the patient: the treatment should aim to start the younger the patient is, the induction phase should be aimed to be completed within 90 days, and the regimen should be Aflibercept only. Lastly, the gender did not play a role in the VA progression, and neither did the Mean injection interval.