Neutrophil to Lymphocyte Ratio as a Predictor of Diabetic Retinopathy Incidence in a Scottish population

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Introduction

Diabetic retinopathy (DR) is hypothesized to be a result of inflammatory reaction due to diabetes. The neutrophil-lymphocyte ratio (NLR) is a cost-effective marker of inflammation which is routinely available as a part of clinical investigations.

Previous studies have reported an association of NLR with a variety of pathological conditions including cancers, mortality, and diabetes.

Methods

Diabetes retinal screening data from Tayside and Fife region in Scotland was used. Complete case analysis (n=24,433) with a 10 years follow up period was performed to predict Diabetic Retinopathy (DR) incidence. DR was defined by the time to first diagnosis of R1 or above grade under the Scottish diabetic retinopathy grading scheme.

Study duration includes time from diagnosis date of diabetes (T0) to the last follow-up visit or censoring point (T1) within the ten-year follow-up. Censoring includes date of DR, death or end of follow-up. All participants who already had retinopathy at diagnosis were excluded from the analysis. NLR and other clinical covariates closest to the time of diagnosis of diabetes were included in the analysis. NLR readings were not considered if measured after diagnosis of cancer or NLR readings <=31 days for an admission with infectious disease.

Death prevents observation of retinopathy and hence it is considered a competing risk for the analysis of DR. Association between NLR and time to DR was investigated by competing risks analysis using both cause-specific and Fine and Gray model approaches, adjusted for age, sex, blood pressure, HbA_{1c}, Non-HDL, BMI and anti-diabetic drugs at diagnosis. NLR and non-HDL-c were log-transformed Calibration plot was used to assess the goodness of fit for both the models.

Results

There was no correlation between Neutrophils and Lymphocytes (r = 0.05, p=<0.001). Neutrophil count and NLR was closely related in hierarchical cluster (Figure1). Kruskal–Wallis Test showed a significant difference in NLR distributions among the three outcome groups (those that develop DR, those that died and those with no DR and still alive at the end of follow-up) in (Figure2).

Figure 1.Correlation heatmap of NLR with other covariates

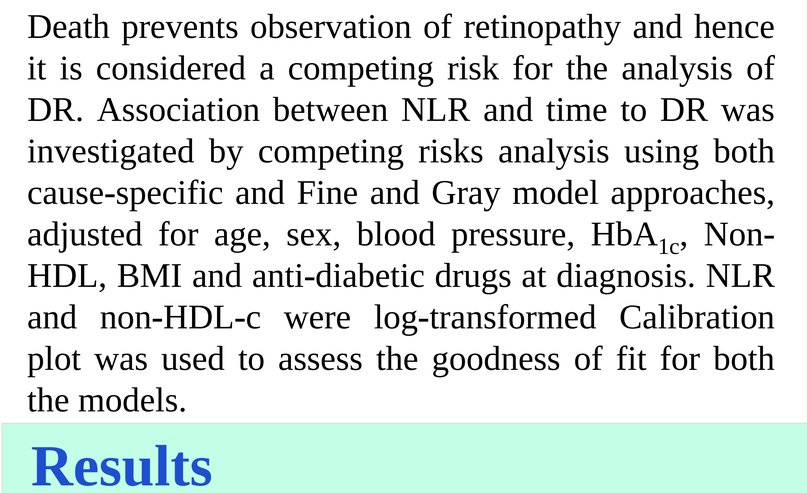


Figure 2. Pairwise comparison of NLR with different events at 10 years

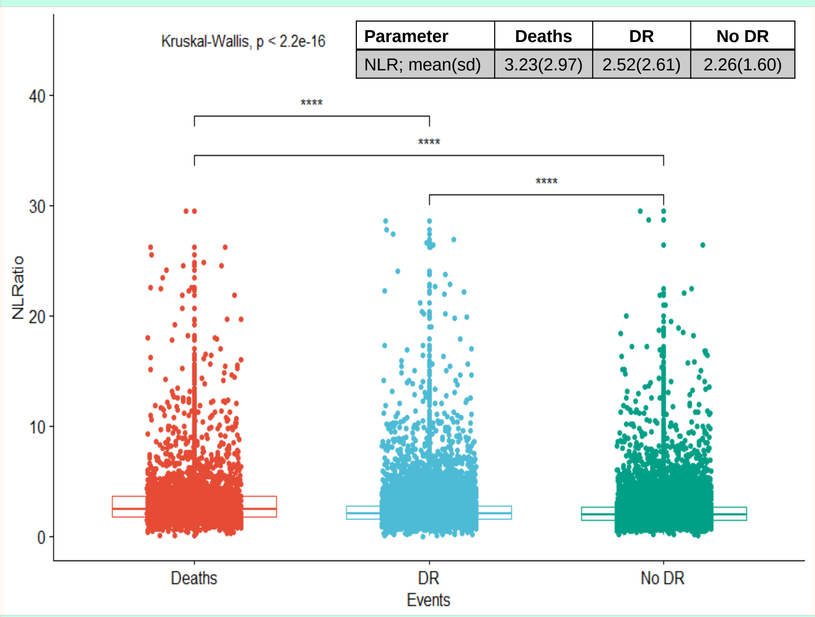
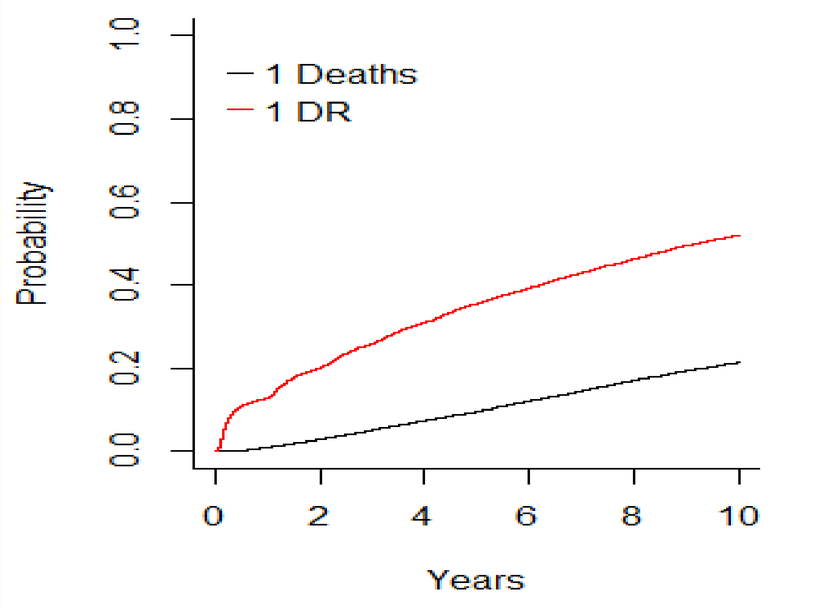


Figure 3. Predicted Cumulative curve for the probability of DR incidence in the study population



At the end of 10 years, there were 9018 DR events and 3013 deaths. Probability of DR incidence was 50% at the end of 10 years(Figure3).

NLR was associated with incident DR in both cause-specific (HR 1.32;1.08- 1.62) and Fine and Gray models (HR=1.44,1.14- 1.80) (Fig 4 and Table 1).

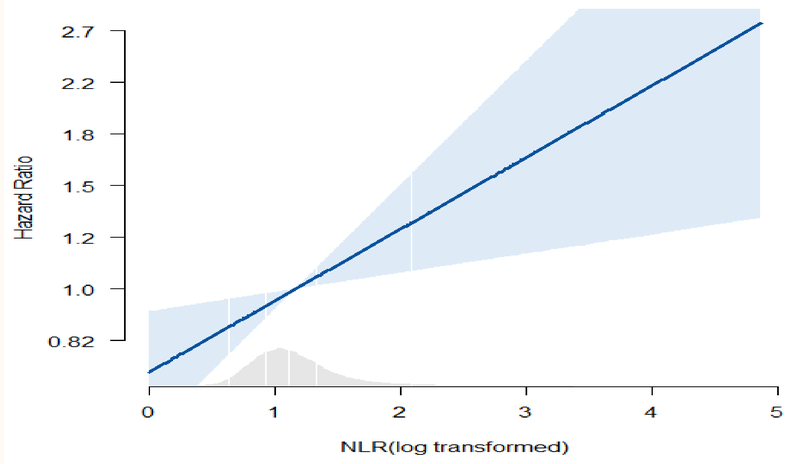
Interactions between HbA_{1c} and NLR was significant in the cause-specific model (HR=0.98, 0.95- 1.00) while in the Fine-Gray model both HbA_{1c} and NLR interaction and Age and NLR were significant (HR=0.97,0.95- 0.99 for HbA_{1c} and HR=0.99,0.99-0.99 for Age interaction respectively) .

Figure 4. Forest Plot of Cause-Specific Hazards Model for association of NLR with DR Incidence

Variable		N	Hazard ratio	p
Age		24433	1.00 (1.00, 1.00)	0.015
Diabetic_Drug	No	13228	Reference	
	Yes	11205	1.09 (1.04, 1.15)	<0.001
DBP		24433	1.00 (1.00, 1.00)	0.036
HbA1cxNLR		24433	0.98 (0.95, 1.00)	0.043
Sex	F	10901	Reference	
	M	13532	1.07 (1.03, 1.12)	0.002
Non_HDL		24433	0.86 (0.79, 0.94)	<0.001
HbA1c		24433	1.10 (1.07, 1.14)	<0.001
SBP		24433	1.00 (1.00, 1.01)	<0.001
BMI		24433	0.99 (0.99, 0.99)	<0.001
NLR		24433	1.32 (1.08, 1.62)	0.007

0.8 1 1.2 1.4 1.6

Figure 5. Adjusted effect plot for association of NLR with DR Incidence

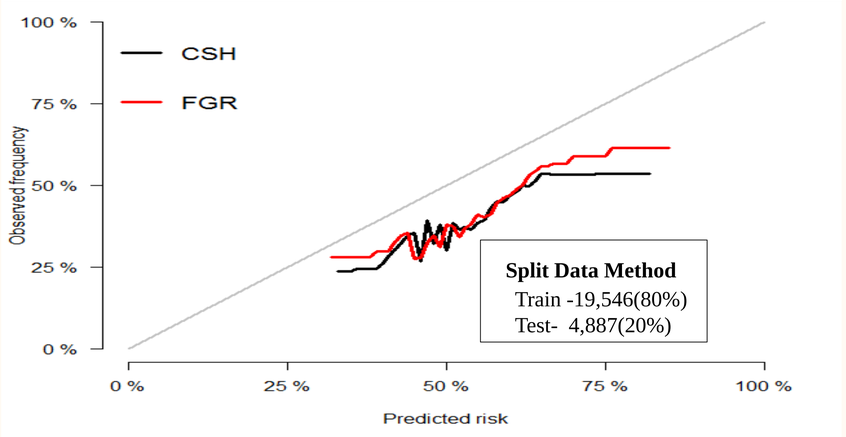


The Hazard of developing retinopathy almost tripled for participants with very high levels of Neutrophil-Lymphocyte Ratio.

Table 1. Fine and Gray Model for association of NLR with DR Incidence

Parameter	SHR	95% CI	P value
Age x NLR	0.99	0.99- 0.99	<0.01**
Diabetic drug	1.06	1.01- 1.11	<0.05**
DBP	1.00	1.00- 1.00	<0.05*
HbA_{1c} x NLR	0.97	0.95- 0.99	<0.05*
Sex(M)	1.05	1.01-1.10	<0.05*
Non-HDL	0.90	0.83- 0.98	<0.05*
HbA1c	1.10	1.06- 1.13	<0.001***
SBP	1.00	1.00- 1.00	<0.001***
BMI	0.99	0.98- 0.99	<0.001***
NLR (log)	1.44	1.14- 1.80	<0.01**

Figure 6. Calibration plot- goodness of fit



Conclusions

- NLR has a great potential to predict DR incidence in the Scottish population. HbA_{1c} and Age attenuated the effect of NLR for DR incidence at their higher values.
- Both main and interaction terms for NLR are significant in the model suggesting insights into pathological mechanisms involved in DR. Modelling Interaction of NLR with other covariates is helpful to understand the real-world relationship of variables.
- The calibration plot suggests that Fine and Gray model has more predictive accuracy than Cause specific Model in predicting incidence of DR and both models overestimate DR incidence.

Acknowledgements

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