The 'Newcastle Nomogram' – Statistical Modelling Predicts Malignant Transformation in Potentially Malignant Disorders

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Abstract

Background: Nomograms are graphical calculating devices used to predict risk of malignant transformation (MT) or response to treatment during cancer management. To date, a nomogram has not been used to predict clinical outcome during oral potentially malignant disorder (PMD) treatment. The aim of this study was to create a nomogram for use by clinicians to predict the probability of MT, thereby facilitating accurate assessment of risk and objective decision making during individual patient management.

Methods: Clinico-pathological data from a previously treated cohort of 590 newly presenting PMD patients were reviewed and clinical outcomes categorised as disease free, persistent PMD or MT. Multiple logistic regression was used to predict the probability of MT in the cohort using age, gender, lesion type, site, and incision biopsy histopathological diagnoses. Internal validation and calibration of the model was performed using the bootstrap method (n=1000), and bias-corrected indices of model performance were computed.

Results: PMDs were predominantly leukoplakias (79%), presenting most frequently at floor of mouth and lateral tongue sites (51%); 99 patients (17%) developed oral squamous cell carcinoma (SCC) during the study period. The nomogram performed well when MT predictions were compared with patient outcome data, demonstrating good bias-corrected discrimination and calibration (D_{xy} = 0.58; C = 0.790), with a sensitivity of 87% and specificity 63%, and a positive predictive value of 32% and negative predictive value 96%.

Conclusion: The 'Newcastle Nomogram' has been developed to predict the probability of MT in PMD, based on an internally validated statistical model. Based upon readily available and patient-specific clinico-pathological data, it provides clinicians with a pragmatic diagrammatic aid for clinical decision making during diagnosis and management of PMD.

Keywords: Potentially Malignant Disorders, Malignant Transformation, Prediction, Nomogram

1. Introduction

Potentially malignant disorders (PMD) comprise a group of distinct oral mucosal lesions such as leukoplakia, erythroleukoplakia and erythroplakia, or more widespread disorders such as proliferative verrucous leukoplakia (PVL), that precede squamous cell carcinoma (SCC) development. Despite advances in modern management, oral SCC remains a lethal and deforming disease of rising global significance. PMD often display histopathological change characteristic of epithelial disorganisation and dysmaturation, termed epithelial dysplasia and representative of an increased SCC risk, although other progressive lesions may only exhibit hyperkeratosis, lichenoid inflammation or chronic candidal infection on initial presentation[1]. A systematic review and meta-analysis of oral epithelial dysplasia estimated an overall risk of malignant transformation (MT) of 12%, over a mean period of 4.3 years[2].

Despite widespread recognition of risk factors, particularly long-term tobacco smoking and over-use of alcohol, and investigation of potential biomarkers for early SCC recognition, reliable prediction of MT for an individual patient remains elusive. Contemporaneous clinical practice is based upon lesion assessment and incision biopsy for provisional diagnosis, with patients deemed to be 'high risk' for SCC undergoing excision surgery for definitive diagnosis and management. It is recognized, however, that such decisions are subjective, based primarily upon observational studies and open to clinician preference and bias[3-6].

A number of clinically applicable tools have been trialed to aid diagnostic and predictive accuracy, including exfoliative cytology, chemical luminescence and tissue auto-fluorescence, but none are universally applicable and most exhibit limited sensitivity and specificity even when used in combination or in specialist clinical settings[7,8]. There is, therefore, a pressing need for innovation to improve clinical outcome prediction for patients presenting with PMD and, in particular, to identify those most at risk of developing SCC.

Evolution of predictive statistical tools offers new opportunities to refine preventive and interventional strategies[9]. Nomograms are graphical calculators that allow clinicians with limited statistical acumen to assess pre-prepared two-dimensional diagrammatical figures to calculate outcome predictions based upon risk factor analysis. Consisting of a set of scales, and usefully constructed with relevant clinico-pathological variables, the 'unknown' outcome variable can be determined by plotting the point of intersection of an index line drawn across the scales. Nomograms have been developed to aid outcome prediction for several cancers including prostate[10,11], breast[12],

bladder[13] and renal[14]. Whilst nomogram prediction following different treatment regimens have been used to study oral cancer and to predict the risk of post-operative complications following surgery[16-20], to the best of our knowledge there are no studies in the literature examining the use of nomograms to aid in the diagnosis and management of PMD.

The aim of this study, therefore, was to develop a nomogram, using clinico-pathological variables routinely available to clinicians in specialist care facilities, to predict to predict the probability of MT in patients presenting for PMD diagnosis and treatment.

2. Method

2.1 Study Population and Database

The study re-visited the database of a previously reported 590 PMD patient treatment cohort from Northern England[6]. Caldicott Approval from Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust facilitated anonymized, retrospective and prospective data collection from medical records, operating books and histopathology reports from newly presenting PMD patients managed via a coordinated interventional laser surgery protocol between August 1996 and December 2014. Demographic and clinico-pathological data reviewed for this study required patient age at initial presentation, gender, appearance and site of presenting PMD, histopathology diagnoses from pre-operative incision biopsies, and clinical outcome documented at the study census date (31 December 2014).

PMD management was coordinated by the third author (PJT) working to well-established guidelines[4-6]. Formalin-fixed specimens were assessed by histological examination by oral pathologists at the Royal Victoria Infirmary, using standardized diagnostic criteria and consensus grading. The World Health Organization (WHO) system classified lesions as mild, moderate and severe dysplasia or carcinoma-in-situ (CiS). In addition, diagnoses of hyperkeratosis, lichenoid inflammation, PVL and chronic hyperplastic candidosis were recorded.

2.2 Statistical Analyses

Statistical analyses were performed in the R Environment for Statistical Computing (version 3.5.3, www.r-project.org/). We used binary multiple logistic regression to model the probability of MT occurring within the patient cohort. Model predictors included age (continuous variable fitted as a

restricted cubic spline with 4 pre-specified knots) and the categorical variables: gender, lesion appearance, site, and incision biopsy histopathology (Table 1). To increase predictive performance, estimation of shrunken parameters was achieved using penalized maximum likelihood. Rigorous internal validation and calibration of the model were performed using the optimism bootstrap method (n=1000) and a number of bias-corrected indices of model performance were computed. For discrimination, Somers D_{xy}, Harrell's concordance index (C), and the g index were computed. For calibration, mean absolute error, mean squared error and 0.9 quantile of absolute error were calculated, and we produced a calibration plot using a lowess (locally weighted scatterplot smoothing) non-parametric smoother. As an overall index of model performance, the Brier score, a quadratic proper scoring rule combining both discrimination and calibration, was also computed[19,20].

3. Results

Data from 590 study patients (346 male and 244 female; mean age 60 years at time of presentation) were used to populate the model, with the categorical variables and their individual frequencies listed in Table 1. Clinically, the majority of lesions presented as leukoplakia (468) with erythroleukoplakia (99) and erythroplakia (23) less common, whilst the most frequently affected anatomical sites included floor of mouth (173) and lateral tongue (130). Review of histopathological diagnoses showed that 433 lesions (73%) exhibited epithelial dysplasia (of varying severity) or CiS on initial incision biopsy. Followed for a mean period of 7.3 years post-treatment, clinical outcome documented that 438 patients (74%) were disease free, 53 (9%) had persistent PMD, and 99 (17%) had undergone MT by the study census date.

Table 2 presents a comparison of the clinically documented MT outcome versus the statistical model prediction. Based upon a true prevalence of 0.17, the model demonstrated a sensitivity of 87% and specificity 63%, positive predictive value of 32% and negative predictive value 96%, with a positive likelihood ratio of 2.34. Table 3 summarizes the validation data for the model, demonstrating good bias-corrected discrimination and calibration (D_{xy} = 0.58; C = 0.79). Figure 1 illustrates the calibration plot confirming a good fit for both the apparent and bias-corrected model predictions with the observed data (perfect agreement is indicated by the diagonal 1:1 line).

In Figure 2, the importance of individual clinico-pathological variables in predicting outcome are ranked (using n=1000 bootstrap samples), demonstrating that the most reliable MT predictor was incision biopsy histopathology (ranked 5), whilst patient age (1) and gender (2) were least useful. Lesion appearance and anatomical site were of intermediate predictive value in the model (ranking 3 and 4, respectively). The resulting 'Newcastle Nomogram' is presented in Figure 3a. The score for each predictive variable is read in turn using the uppermost 'Points' scale, with the sum of predictor scores calculated by the 'Total Points' scale, thus determining overall MT probability via the bottom scale. Figure 3b is an illustrative example of the nomogram used to assess a 58-year old female presenting with severely dysplastic erythroleukoplakia on the lateral tongue who subsequently underwent MT; the nomogram estimates the probability of MT at 0.55.

4. Discussion

4.1 PMD Population Studies

Longitudinal patient cohort studies have provided substantive data to improve our understanding of PMD natural history[4-6]. Whilst we have learned much, our ability to predict clinical outcome, especially MT, remains limited[9]. Although based upon a Northern England population, the clinico-pathological data from 590 newly presenting patients in this study provided an invaluable resource to populate our statistical model; salient features of age, gender, lesion, site and histopathology are all consistent with those reported globally for PMD[6]. Our previous studies have emphasized that erythroleukoplakia, severe dysplasia and lesions presenting at ventro-lateral tongue and floor of mouth sites are at greatest risk of MT[4-6], but such generalized information can be difficult to communicate and apply effectively to individual patients in the clinical scenario. Although ranking of factors in the model supports these observations, it is also recognized that MT may arise in the absence of such predisposing features, rendering new and reliable predictive tools essential for clinical application[3].

4.2 The 'Newcastle Nomogram'

Construction and internal validation of the statistical model described in this paper led to the development of the 'Newcastle Nomogram'. This is a practical, diagrammatic tool to aid clinicians in predicting an individual PMD patient's SCC risk by systematically analyzing readily available clinico-pathological data. Additional investigations, attempts at biomarker analysis and long-term observational strategies are potentially rendered redundant; a significant advance in current practice. By calculating a numerical MT probability score for each patient, direct communication and personal

risk awareness are facilitated, leading to appropriate prevention and earlier intervention targeted precisely to the individual. These are essential features of personalized health care provision offering real prospects of minimizing disease progression and cancer prevention[24]. We have previously emphasized the significant prognostic benefit of identifying and treating SCC at its earliest stage during interventional PMD management[25].

4.3 Study Limitations

PMD studies are notoriously difficult to organize in terms of clinically relevant prospective, randomized trials. Based upon a 590 PMD patient cohort undergoing coordinated treatment and followed for a mean of 7.3 years, the clinico-pathological details and outcome data in this study provide one of the largest samples in contemporaneous literature. Nonetheless, as a single-site retrospective review of one specific geographic population, the data are limited and application of the statistical model and nomogram will require further testing and validation in a much larger sample. Increased patient numbers might also allow predictive analyses to determine the risk of persistent PMD development, which was not feasible by analyzing only 53 cases in this cohort. Risk factor behaviour, such as smoking and alcohol habits, were not assessed in this model owing to their variable influence during follow-up and a lack of precise data entry into the original database. We do know, however, that around 90% of Newcastle PMD patients are current or ex-smokers and 84% regularly consume alcohol, so it is less likely that these variables would prove discriminatory[6]. Nevertheless, introduction of reliable risk factor data may prove important in further refining the statistical model and nomogram, and it would also be interesting to attempt temporal assessment in future analyses. Finally, it is important to recognize that all patients in this study underwent laser surgery which, although beneficial in a treatment sense, inevitably influences disease progression and clinical outcome compared with non-intervention[26].

4.4 The Future

This nomogram was constructed on a patient population attending for specialist care in one dedicated interventional PMD management centre. It is clear that future studies will require greater validation in a wider, ideally international, arena to determine how nomogram predictions compare more broadly with ‘expert opinion’ during long-term clinical management and applied to differing patient cohorts. Such investigations may be complex and difficult to organize but it is hoped that clinicians involved in PMD management will consider trialing the nomogram. Whilst the authors do not believe that the ‘Newcastle Nomogram’ should in any sense replace ‘expert opinion’, especially during the assessment and management of complex ‘potentially malignant’ disease, it is interesting to note that

in prostate cancer care nomograms have now been shown to consistently outperformed human 'experts'[10].

5. Conclusions

An internally validated prediction model for PMD management, based upon patient-specific clinico-pathological data, was developed. Derived from the model, the 'Newcastle Nomogram' is a practical diagrammatic tool for clinicians to objectively predict the probability of MT during individual patient treatments and assist in clinical decision-making. Further investigations to test the nomogram in different populations, in which additional or alternative risk factor variables influencing MT may be included, are now encouraged in larger, international studies.

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Funding

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Competing Interests

None declared.

Ethical Approval

Newcastle University / Newcastle upon Tyne Hospitals NHS Foundation Trust Caldicott Guardian Approval for Anonymised Patient Data Collection & Retrospective Review of Hospital Records ID 4143 (2015)

Patient Consent

Not required.

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Figure Legends

Figure 1: Calibration plot showing the ideal model line (perfect agreement between modelled and observed probabilities), apparent curve (model calibrated with patient cohort data) and bias-corrected curve (model calibrated using the bootstrap method); mean absolute error=0.013, mean squared error=0.0002, 0.9 quantile of absolute error=0.027.

Figure 2: Rank of importance for each predictive variable with 1 the weakest and 5 the strongest (plus 95% bootstrap confidence intervals).

Figure 3: (A) The Newcastle Nomogram: the score for each predictor is read in turn using the uppermost 'Points' scale. The sum of predictor scores is then calculated from the 'Total Points' scale, determining overall MT probability via the bottom scale. (B) Illustrative assessment of a 58-year old female with severely dysplastic erythroleukoplakia on the lateral tongue that subsequently underwent MT; nomogram calculated probability of MT is 0.55.

Figure 1

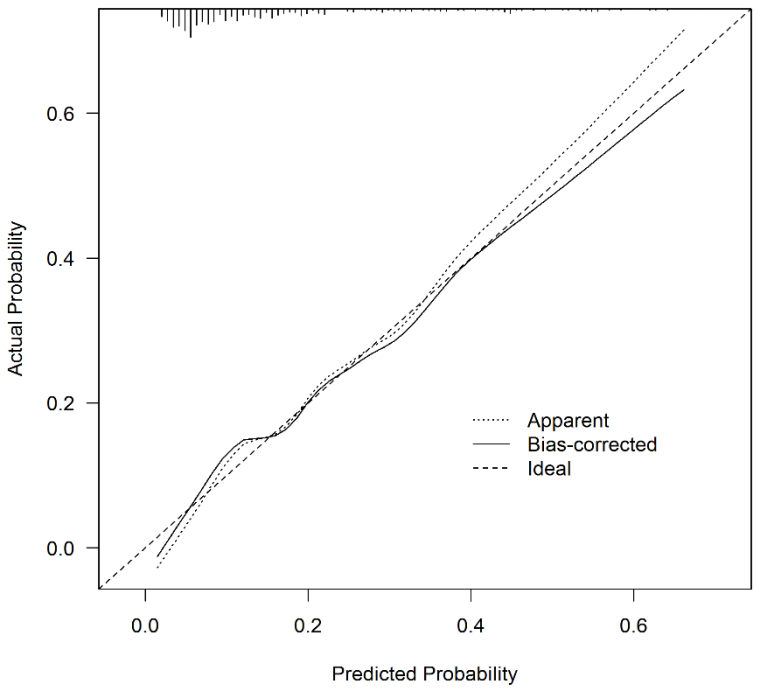

Figure 2

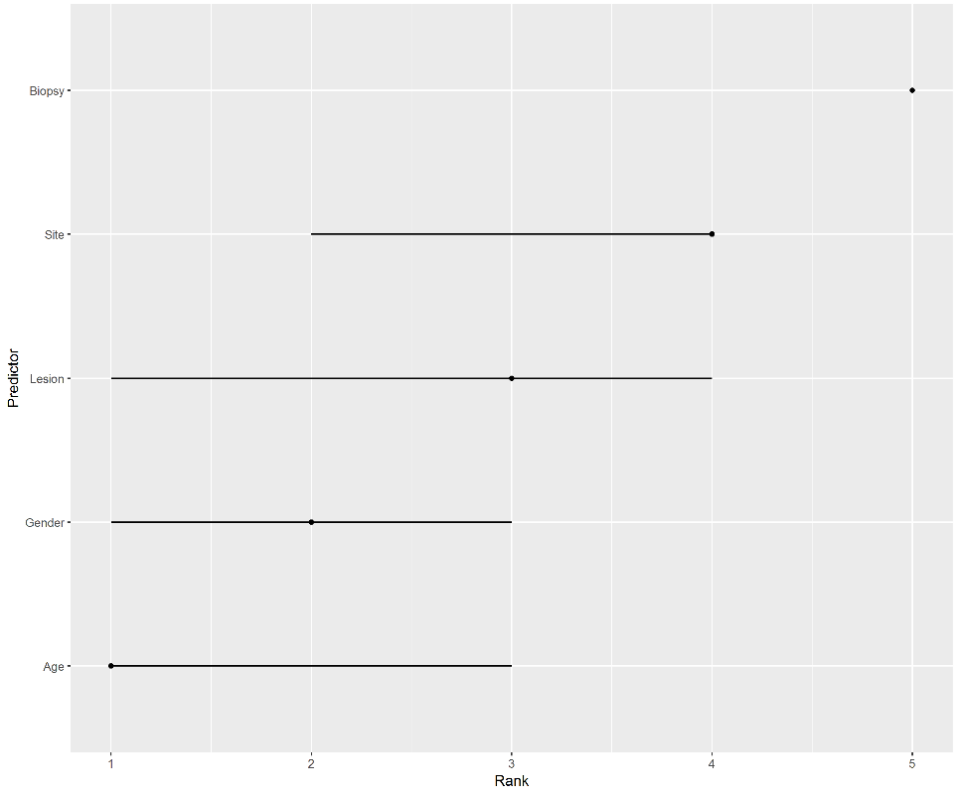

Figure 3(A)

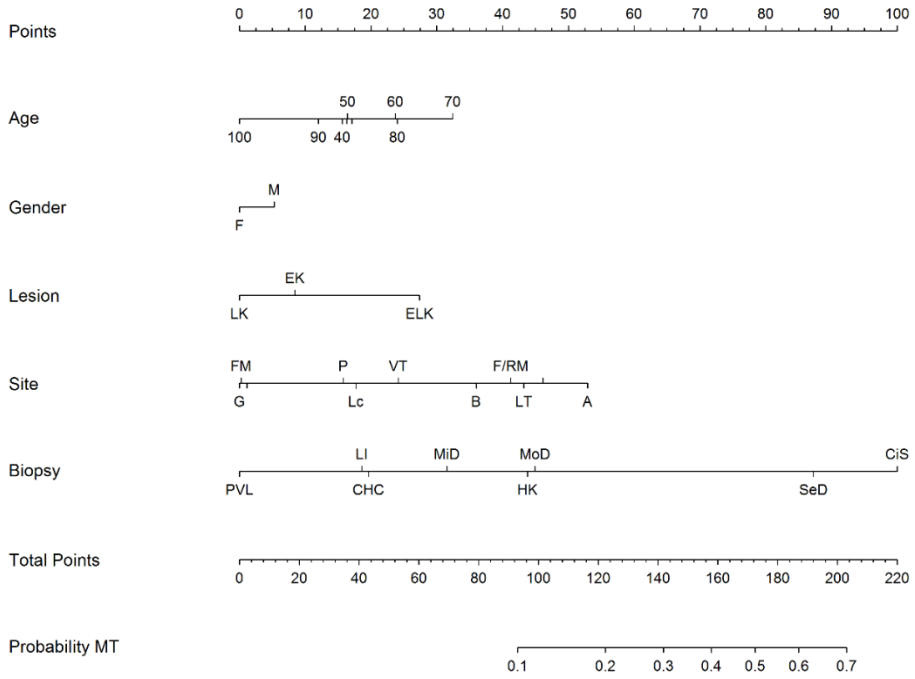

Figure 3(B)

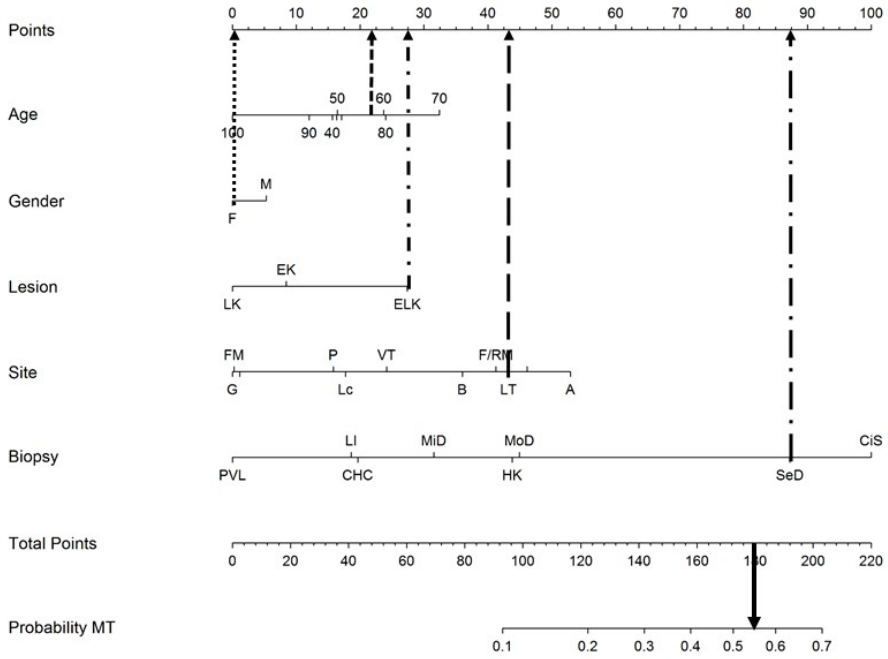

Table 1: Clinico-Pathological Variables Used in Constructing the Model.

Variable	Grouping	Number *(%)*
Gender	Male	346 *(59%)*
	Female	244 *(41%)*
Lesion	Leukoplakia	468 *(79%)*
	Erythroleukoplakia	99 *(17%)*
	Erythroplakia	23 *(4%)*
Site	Floor of Mouth	173 *(29%)*
	Lateral Tongue	130 *(22%)*
	Buccal Mucosa	58 *(10%)*
	Palate	57 *(10%)*
	Ventral Tongue	56 *(9%)*
	Labial Commissure	29 *(5%)*
	Fauces/Retromolar	26 *(4%)*
	Gingiva	21 *(4%)*
	Alveolus	18 *(3%)*
	Labial Mucosa	11 *(2%)*
	Dorsum of Tongue	11 *(2%)*
Incision Biopsy Histopathology	Mild Dysplasia	148 *(25%)*
	Moderate Dysplasia	*122 (21%)*
	Severe Dysplasia	89 *(15%)*
	Carcinoma in Situ	74 *(12%)*
	Lichenoid inflammation	62 *(10%)*
	Proliferative Verrucous Leukoplakia	59 *(10%)*
	Chronic Hyperplastic Candidosis	19 *(4%)*
	Hyperkeratosis	17 *(3%)*
Clinical Outcome	Disease Free	438 *(74%)*
	Malignant Transformation	99 *(17%)*
	Persistent PMD	53 *(9%)*

Table 2: Documented Clinical Outcome (Columns) versus Model Prediction (Rows)

	MT Cases	Disease Free/Persistent PMD Cases	Total Number
MT Predicted	86	182	268
No MT Predicted	13	309	322
Total	99	491	590

Point estimates + 95% Confidence Intervals

Apparent Prevalence	0.45 (0.41, 0.50)
True Prevalence	0.17 (0.14, 0.20)
Sensitivity	0.87 (0.79, 0.93)
Specificity	0.63 (0.58, 0.67)
Positive Predictive Value	0.32 (0.27, 0.38)
Negative Predictive Value	0.96 (0.93, 0.98)
Positive Likelihood Ratio	2.34 (2.04, 2.69)
Negative Likelihood Ratio	0.21 (0.13, 0.35)

Table 3: Original and Bias-Corrected Metrics of Model Accuracy

Metric	Original	Bias-Corrected
Somer's D	0.66	0.58
Harrell's C	0.83	0.79
G Index	1.30	1.28
Brier Score	0.11	0.12