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Stratifying Ischaemic Stroke Patients Across 3 Treatment Windows Using T_2 Relaxation Times, Ordinal Regression and Cumulative Probabilities

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Synopsis: *Unknown onset time is a common contraindication for anti-thrombolytic treatment of ischaemic stroke. T_2 relaxation-based signal changes within the lesion can identify patients within or beyond the 4.5-hour intravenous thrombolysis treatment-window. However, now that intra-arterial thrombolysis is recommended between 4.5 and 6 hours from symptom onset and mechanical thrombectomy is considered safe between 6 and 24 hours, there are three treatment-windows to consider. Here we show a cumulative ordinal regression model, incorporating the T_2 relaxation time, predicts the probabilities of a patient being within one of the three treatment-windows and is more accurate than signal intensity changes from T_2 weighted images.*

Introduction: Hyperacute ischaemic stroke patients with unknown onset time are ineligible for intravenous (IV) and intra-arterial (IA) thrombolytic therapies.[1] Previous studies identified patients within the 4.5-hour IV treatment-window[2–4] and 6-hour IA treatment-window[5] by quantifying changes in T_2-based image intensities caused by ischaemia. However, these studies approached unknown onset time as a binary classification problem, where a patient is within or beyond a specific treatment-window. Now that mechanical thrombectomy (MT) is considered safe between 6 and 24 in patients with large vessel occlusion[6] there are three time-windows to stratify patients within (IV < 4.5 hours, IA 4.5-6 hours, MT 6 – 24 hours). Ordinal regression may be a suitable solution as it is recommended for classification problems with three or more naturally ordered categories, where misclassification errors are unequal.[7] Here we, a) examined whether logistic ordinal regression[8] applied to image intensity ratios from ADC, DWI, T_2 weighted (T_2W), and T_2 relaxation time images can stratify patients into the three time-windows and b) compared the efficacy of these parameters on the task.

Methods: Thirty-five ischaemic stroke patients with onset time < 9 hours were scanned at 3T with a 32-channel head coil. MRI protocol included DWI for ADC maps and localisation of ischaemia, 3DT_1 weighted (T_1W) for anatomical reference and co-registration and multi-echo T_2 for T_2 relaxation time maps and echo-summed T_2W images. Image intensity ratios indicating a change in signal due to ischaemia were calculated (Figure 1).[2]

Image intensity ratios were standardised using the Agresti method[10] to account for the different magnitudes of change over time between the ratios,[2] and to make coefficients comparable across features.[10] Based on onset times patients were divided into classes corresponding to treatment-windows of < 4.5 hours for IV thrombolysis (n = 16), 4.5 – 6 hours for IA thrombolysis (n = 5) and 6 – 9 hours for MT (n = 14). Ordinal logistic regression models[8] were created for different combinations of image intensity ratios, including univariate models for ADC, DWI, T_2W and T_2 relaxation time ratios and multivariate models that combined diffusion and T_2-based ratios. For each combination of features, we created one multivariate model based on a simple linear combination of the features and an extended version that included an interaction term between input features.

For each patient, our ordinal regression models predict a probability distribution across the treatment-windows, which can be used to inform treatment decisions in two ways. The maximum likelihood approach predicts the treatment-window with the maximum probability. For example, given a probability distribution of IV=0.4, IA=0.3, and MT=0.3, we predict the patient is within the IV thrombolysis window. However, although in this example, IV has the maximum probability of 0.4, there is 0.6 probability that IV is not suitable. This problem is addressed by using the ordinal relationship between treatment-windows and the concept of cumulative probability below a treatment threshold; a patient is within the IV window if the probability of IV is greater than the probability of not being IV (P(IV) > P(IA) + P(MT)), or if a patient is not IV, then they are classified as in the IA window if there is more probability that they are IA or IV than that they are MT (P(IV) + P(IA) > P(MT)). Otherwise, they are in the MT window. We used leave one out cross-validation to evaluate the accuracy of our models using these decision criteria.

Results: The T_2 relaxation time ratio model was the most accurate for the maximum likelihood (Figure 2) and cumulative (Figure 3) approaches. Only the cumulative probability approach identified patients in the IA window.

Discussion: Acute ischaemic stroke patients scanned within one of three treatment-windows can be identified using T_2 relaxation times, ordinal regression, and cumulative probabilities. By accounting for the cumulative probabilities of a patient being within a certain time-window, ordinal regression enables patients in the middle IA treatment-window to be identified which previous binary approaches did not allow for. Admittedly the accuracy dropped using cumulative probability, but it was able to identify patients in the IA window (Figure 3), which the maximum likelihood model could not do. We believe this is an important observation because the IA window is the most difficult to identify both because clinically it is a transitional phase, and from a data perspective it was the minority class in the dataset.

Results also support and extend previous conclusions regarding the superior ability of T_2 relaxation times over other T_2-based weighted image intensities for onset time estimation[2,15,16,17] and that combining diffusion and T_2-based parameters does not improve accuracy.[2] Higher accuracy of the T_2 relaxation time is likely due to T_2 being a single quantitative parameter.[2,17] Fitting signal intensities to the T_2 decay curve, removes the influence of confounding factors that affect weighted images such as magnetic field inhomogeneities, proton density and T_1 relaxation.[2,17]

Conclusion: With further development, the methods presented here could support clinicians in treatment decisions for stroke patients with unknown onset time. Future work will involve a larger sample with balanced class sizes and application of a cost weighting function to each category, to account for different clinical costs associated with misclassifications and improve overall prediction accuracy.

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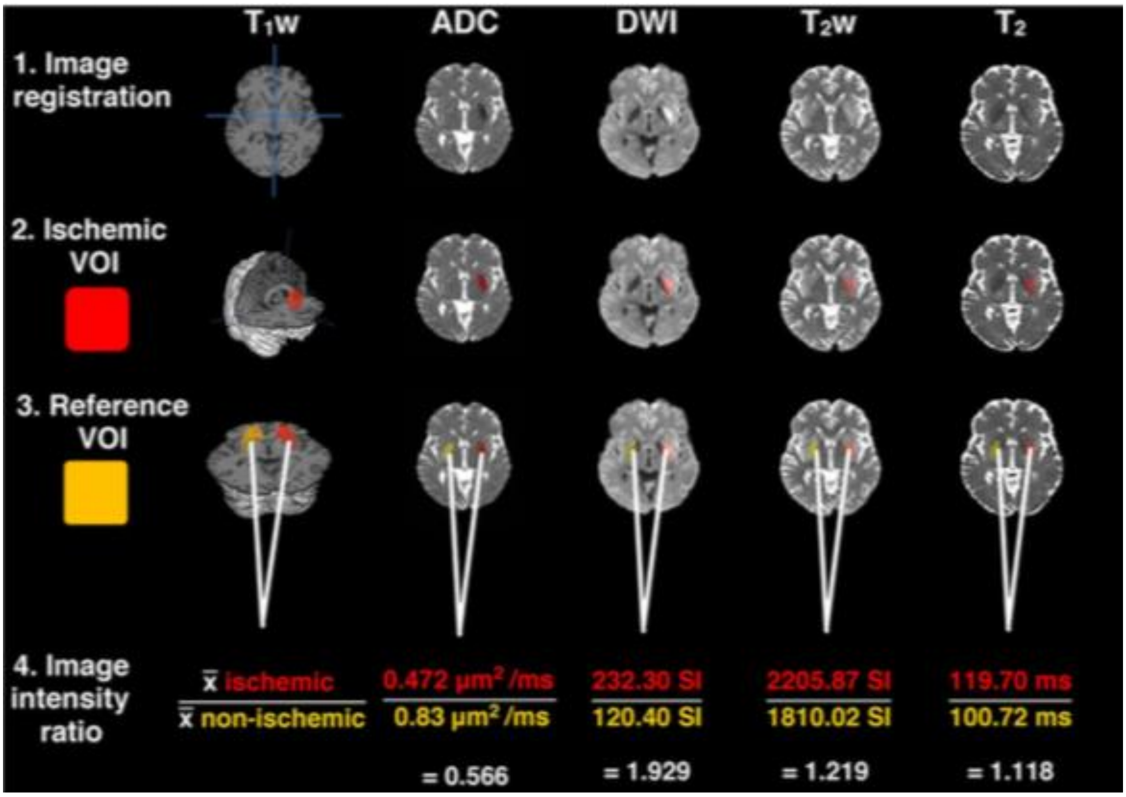

Figure 1: 1. All images were resampled to 1mm isotropic resolution and co-registered to the MNI registered T_1W image. 2. Ischaemic VOIs were created using previously defined ADC and T_2 limits to reduce CSF contribution.[2,9] 3. Non-ischaemic VOIs were created by reflecting the ischaemic VOI across the vertical axis and applying the ADC and T_2 limits. 4. Image intensity ratios were computed by dividing the mean values of ischaemic VOIs by mean non-ischaemic VOIs. SI = signal intensity.

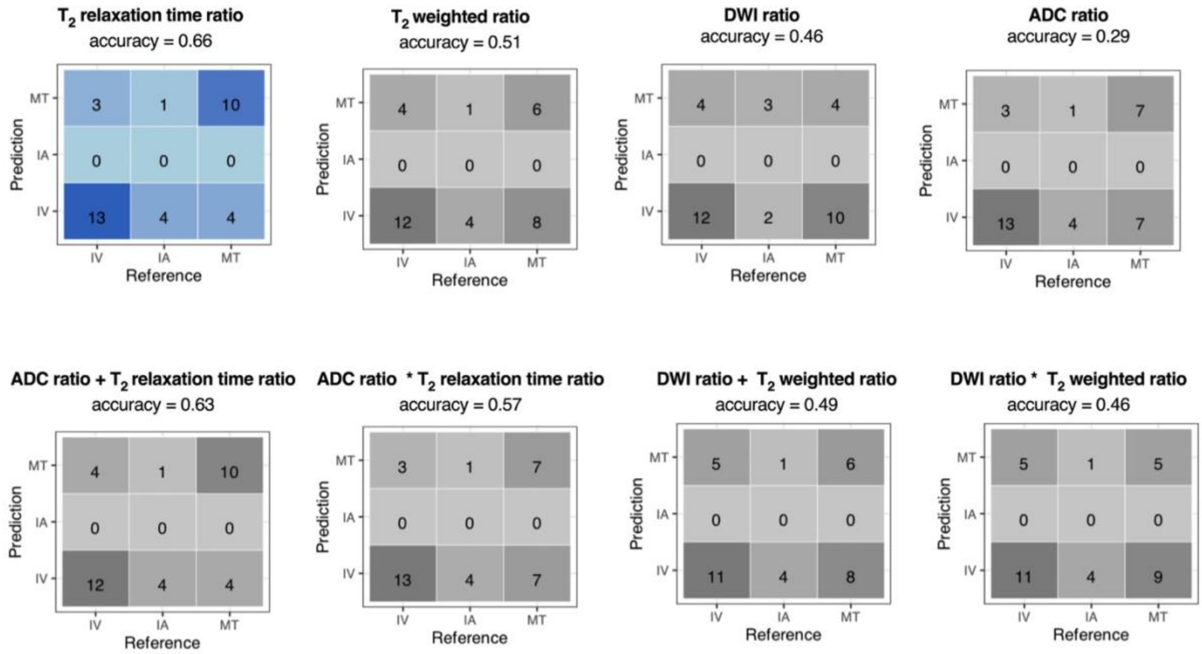

Figure 2: Accuracy and confusion matrices for maximum likelihood ordinal regression models. Darker shades indicate the higher number of correct predictions. The standardised T_2 relaxation time ratio was the most accurate at identifying patients within each treatment window, but none of the models identified patients within the middle IA treatment window. In this figure, a + indicates a linear combination of input features, and * indicates the inclusion of an interaction term.

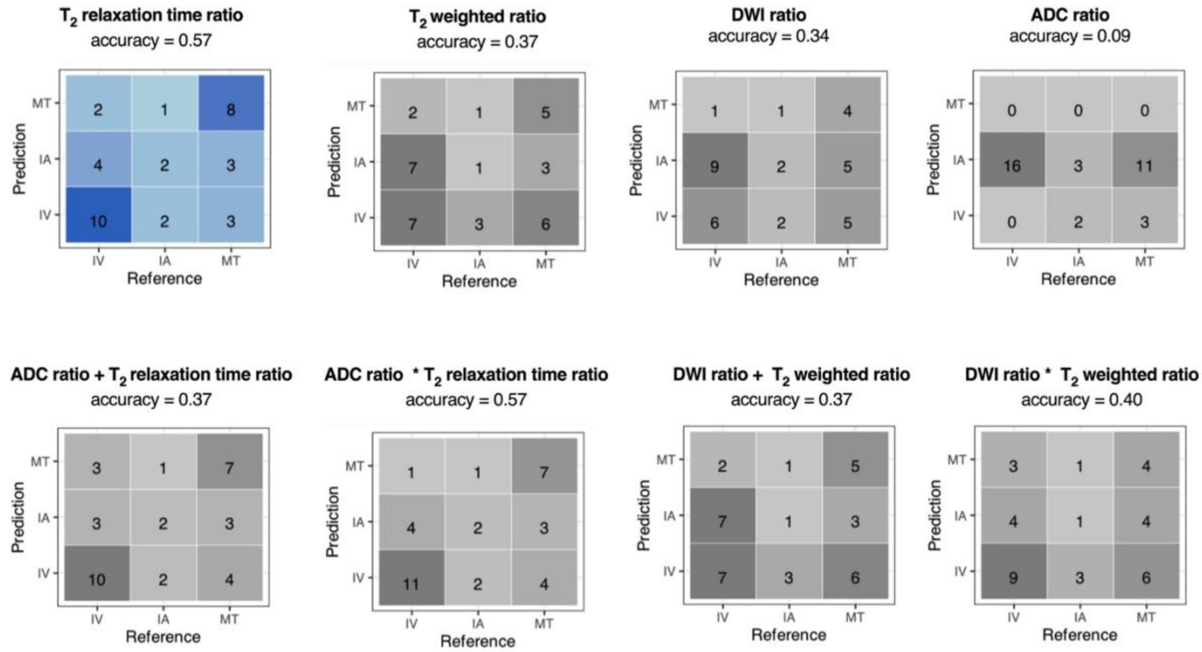

Figure 3: Accuracy and confusion matrices for cumulative ordinal regression models. Darker shades indicate the higher number of correct predictions. The standardised T_2 relaxation time ratio was the most accurate at identifying patients within each treatment window. All models identified patients within the middle IA treatment window. In this figure, a + indicates a linear combination of input features, and * indicates the inclusion of an interaction term.

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