Machine learning model to predict short duration HCV treatment response

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Background: Expanding HCV treatment among key populations with transmission risk is critical to achieve elimination. Standard direct acting antiviral (DAA) durations (8–12 weeks) can be a barrier to adherence among marginalised populations. This study aimed to develop a machine learning model using baseline clinical factors to predict short-duration (4–6 weeks) DAA treatment response with the potential to improve treatment uptake, cost-effectiveness, and health system efficiency.

Methods: Baseline data from several short-duration DAA clinical trials and treatment discontinuations from real-world cohort studies were used. Multiple machine learning models were evaluated. Nested cross-validation was employed to optimise hyperparameters and assess model performance. Clinical utility was evaluated using Area Under Receiver Operator Characteristics (AUROC), Area Under Precision Recall Curve (AUPRC) and Matthews Correlation Coefficient (MCC). Threshold optimisation strategies were applied to balance diagnostic accuracy and treatment costs. Statistical analyses were conducted to estimate HCV RNA cutoffs predictive of treatment failure.

Results: Of 264 individuals receiving short duration DAA therapies (median 42 days; IQR 28-42), 94 (36%) experienced treatment failure. Predictors of failure included shorter durations, higher HCV RNA, higher AST–ALT ratio, genotype 3, and DAA class. The Elastic Net (regularised logistic regression) model demonstrated strong performance (AUROC: 83%; AUPRC: 73%). The Youden Index threshold balanced sensitivity (81%) and specificity (76%) with MCC of 0.56. A cost-optimized threshold, prioritizing retreatment minimization by capturing treatment failures, achieved high sensitivity (98%) but reduced specificity (51%). HCV RNA cutoffs predictive of failure were higher for protease+NS5A inhibitors compared to NS5A+NS5B inhibitors (**Figure**).

Conclusion: Predictive models using readily available baseline clinical data can identify individuals likely to respond to short-duration DAA therapy, with tailored thresholds enhancing clinical utility. Such models, if validated in larger datasets could facilitate HCV elimination efforts by improving treatment uptake, particularly for people who inject drugs, are homeless or incarcerated.

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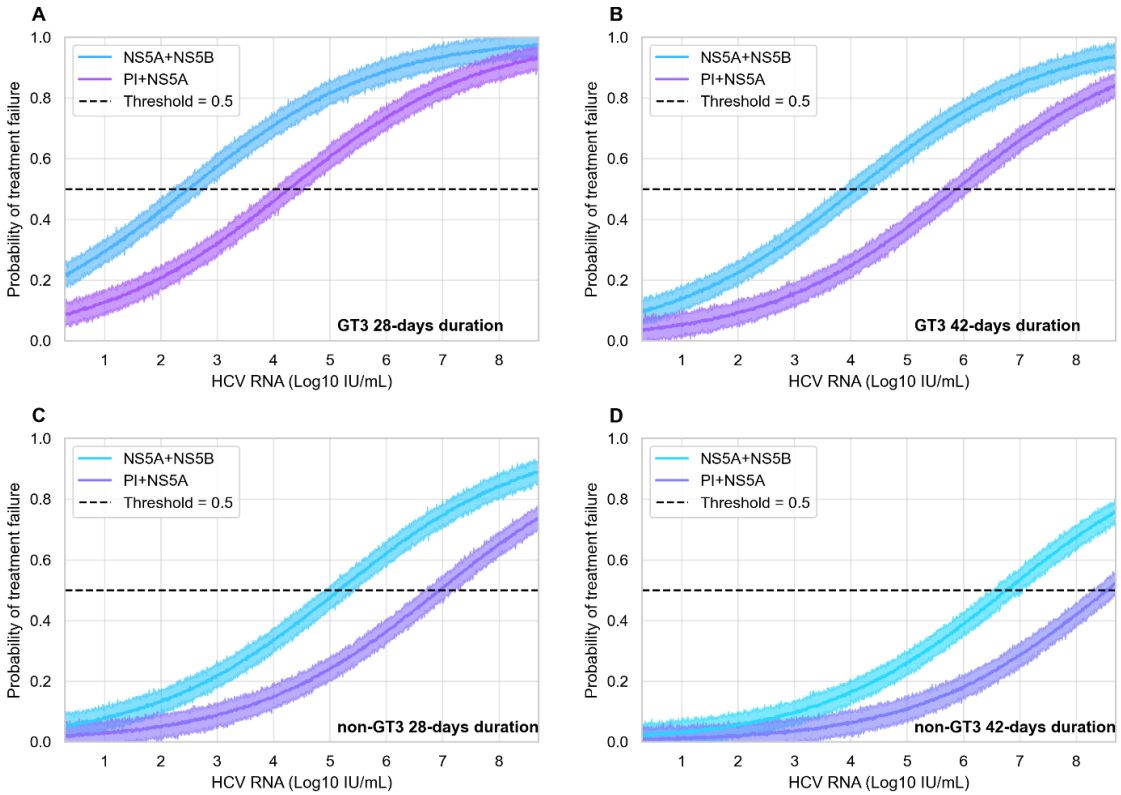

Figure 3. HCV RNA values predictive of treatment failure. Predicted probabilities of treatment failure are plotted against baseline HCV RNA levels, as estimated by the Elastic Net model, with bootstrapped 95% confidence intervals. The curves illustrate differences in HCV RNA cutoffs for predicting treatment response for NS5A+NS5B and PI+NS5A regimens, stratified by treatment duration and genotype. Results are shown for genotype 3 infections treated with **(A)** 28-day and **(B)** 42-day durations; and for non-genotype 3 infections treated **(C)** 28-day and **(D)** 42-day durations with. AST-ALT ratio was fixed at the mean value in all scenarios, and HCV RNA cutoff points correspond to probabilities crossing the default 0.5 threshold.

Abbreviations: HCV, hepatitis C virus; GT, genotype; PI, protease inhibitor.