PREDICTABLY POSITIVE?

AN EVALUATION ON GENOTYPE PREDICTOR CLINICAL TOOLS IN A SPECIALISED INHERITED CARDIAC CONDITION CENTRE

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Introduction

Genetic testing is increasingly utilised in the investigation and management of patients with inherited cardiac conditions (ICC). This study evaluates the efficacy of genotype predictor clinical tools for three ICCs; the Mayo score (MS) for hypertrophic cardiomyopathy (HCM), the Madrid DCM score for dilated cardiomyopathy (DCM), and the Schwartz score (SS) for long QT syndrome (LQTS).

Methods

A retrospective service evaluation was conducted on genetic tests from a single centre for ICC in 2022. The cohort included patients undergoing diagnostic genetic testing for HCM, DCM, and LQTS. Pathogenic/Likely Pathogenic Genetic Variations (G+), variations of uncertain significance (VUS) and no pathogenic genetic variations (G-) were identified. Predictive scoring tools were applied to each condition to assess the predictive efficacy of each tool.

Results

91 genetic tests were conducted on patients with suspected ICC, comprising of 46 HCM, 22 DCM, and 23 LQTS patients. Of these, 25 tests were G+, 9 were VUS and 57 were G-.

The application of the MS for HCM revealed a distinct pattern. For G- patients, mean MS was 1.75, with a median of 3 and mode of 0. These findings align with expected likelihood of obtaining a negative result based on MS. However, in G+ patients, mean MS increased to 2.46, with a median and mode of 3. Although the mean is marginally higher than the comparator, MS exhibited variability in the G+ group, and higher scores were not consistently observed in every G+ case.

Similarly for LQTS, the G- group had a mean SS of 1.18, a median of 1.14 and a mode of 1. These findings are consistent with the rationale that lower SS are less likely to be associated with a true genetic cause for LQTS. Conversely, the G+ group displayed a significantly higher mean SS of 3.28, with a median and mode of 4.

Finally, in DCM the Madrid scoring for G+ group displayed a mean of 43.34%, with median and mode of 36.55%. In contrast, the G- group had a marginally lower mean of 27.26%, a median of 36.34% and mode of 6.57%. This predictive score was less specific, and displayed wide variability between positive and negative results

Conclusion

The application of predictive scoring tools for each condition varied in their effectiveness. Firstly, the Schwartz score for long QT syndrome proved most accurate in predicting pathogenic and likely pathogenic genetic results, as well as also being useful for predicting no genetic variations. Based on this study ,the Schwartz score was the most useful in clinical practice for genetic predictability. Lower scores for the mayo criteria in hypertrophic cardiomyopathy cases, were consistent with no genetic variations identified on genetic testing, however exhibited variability in pathogenic and likely pathogenic results, giving it a more useful negative predictive value, but potentially limiting its utility in predicting pathogenic/likely pathogenic variants. Finally, the Madrid score demonstrated wide variation in scores for both pathogenic/likely pathogenic, and for no genetic variations, indicating limited usefulness in clinical practice for dilated cardiomyopathy.

This study reinforces the importance of clinical correlation on a case by case bases. Further studies are warranted to comprehensively evaluate the specificity and sensitivity of these clinical tools, to ultimately determine their utility in practice.

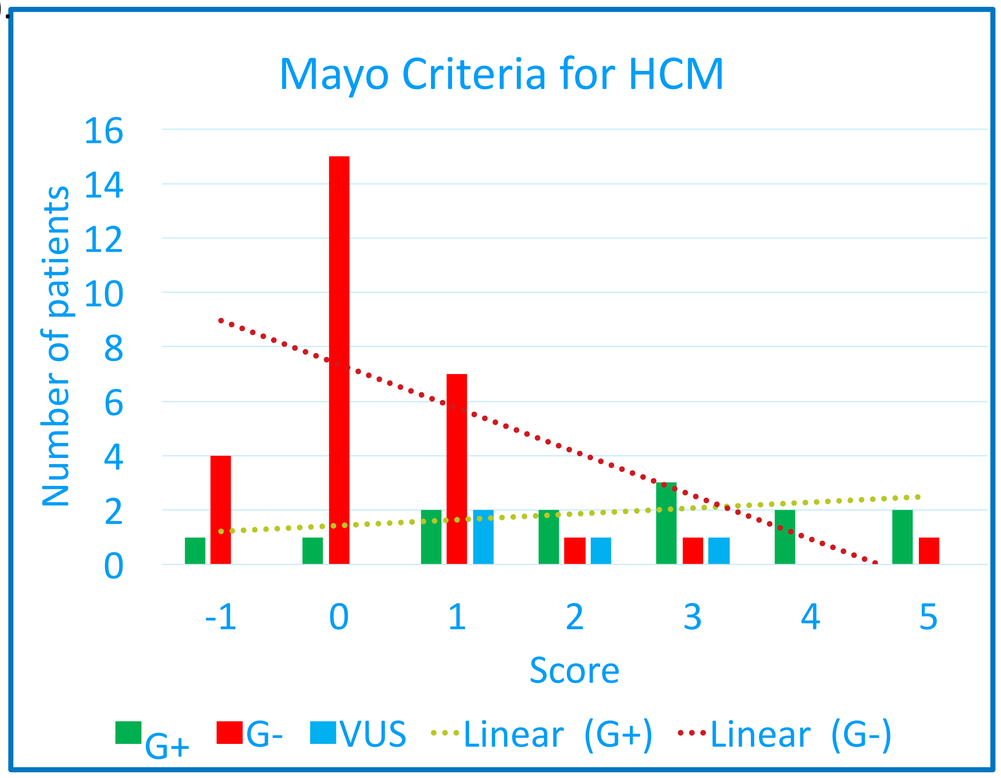

Figure 1 - Bar chart of results after applying the Mayo criteria to HCM patients. G+ (Pathogenic/Likely Pathogenic). G- (No genetic Variation). VUS (Variation of uncertain significance)

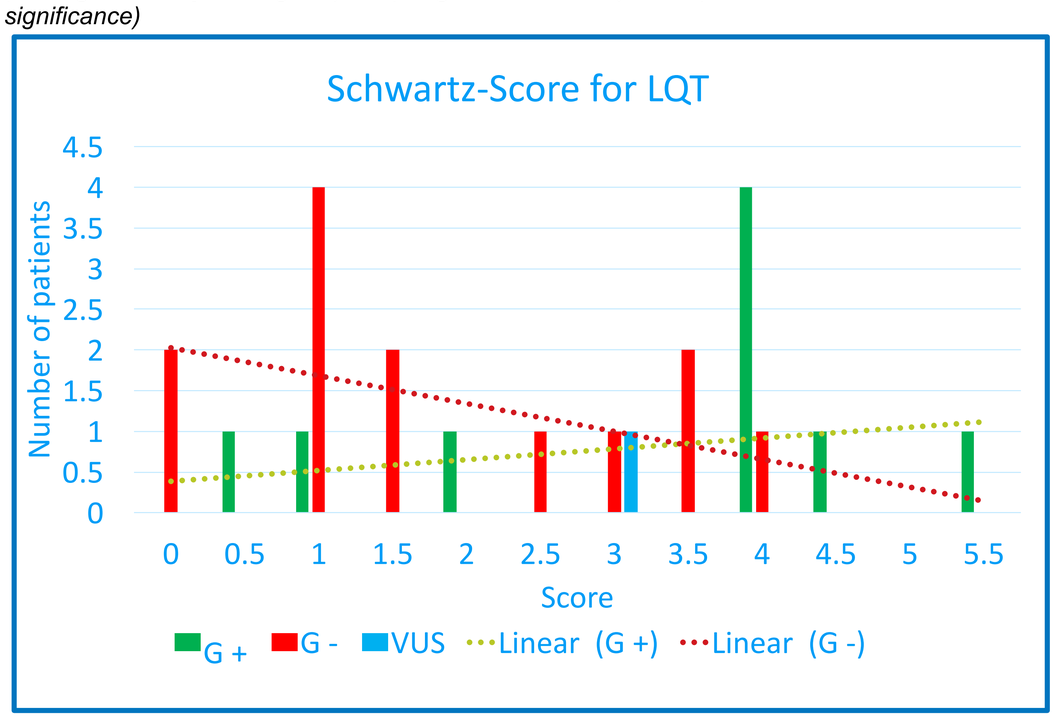

Figure 2 - Bar Chart of results after applying the Schwartz Score to the LQTS patients. G+ (Pathogenic/Likely Pathogenic). G- (No genetic variation). VUS (Variation of uncertain significance)

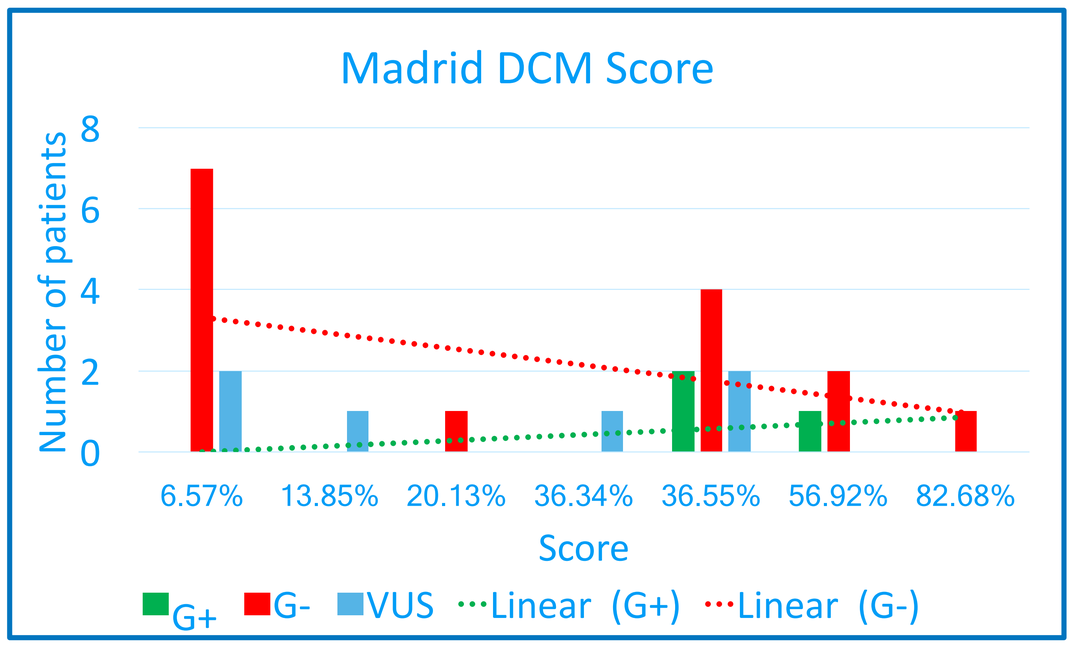

Figure 3. - Bar Chart of results after applying the Madrid DCM Calculation to the DCM patients. G+ (Pathogenic/Likely Pathogenic). G- (No genetic variation). VUS (Variation of uncertain significance)

References:

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3. Escobar-Lopez, L, Ochoa, J, Royuela, A. et al. Clinical Risk Score to Predict Pathogenic Genotypes in Patients With Dilated Cardiomyopathy. *J Am Coll Cardiol.* 2022 Sep, 80 (12) 1115–1126.

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