A Semi-Supervised Network Analysis on the Medical Records of Patients with Wild-Type Transthyretin Cardiomyopathy Provides Insights into Disease Sub-Structures and Associated Symptomologies

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Introduction: Wild-type transthyretin amyloid cardiomyopathy (wtATTR-CM), a rare but increasingly recognized cause of heart failure, is caused by the deposition of misfolded transthyretin protein aggregates in the myocardium resulting in transthyretin amyloid cardiomyopathy (ATTR-CM). Amyloidogenic plaques are known to deposit in organs and tissues systemically, resulting in varied signs and symptoms linked to multisystemic pathology. A semi-supervised network analysis provides an opportunity to evaluate 817 wtATTR-CM patients and evaluate a constellation of associated co-morbidities and reveal sub-structures within the clinical signs and symptoms (‘features’) of the disease.

Figure legend: 2D representation of the features of wtATTR CM delineated by the Fruchterman Reingold network visualization algorithm. Node size (circles) corresponds to the percentage of patients within the wtATTR CM population with the condition, edge width (connectors) represented the number of shared patients between the conditions.

- Pericarditis
- Paraproteinemia
- Abnormal serum Enzyme Levels
- Immune Disorders
- Carpal Tunnel

Methods: US ICD-10 codes from IQVIA (N >300 million patients with up to 10 years of medical history) were utilized. Two patient cohorts were created using ICD-10 codes: wtATTR-CM [N=817 with ICD-10 codes for both wtATTR CM (E85.82) and heart failure (I50.X)] and a heart failure control group [N=817 patients with ICD-10 codes for heart failure (I50.X) without wtATTR-CM]. Each patient in the wtATTR-CM cohort was matched to a randomly selected patient in the heart failure cohort using propensity score matching to reduce the effect of age, gender, and medical history related confounders. Complete history of all diagnoses for each patient in the two cohorts was extracted from the claims data and odds ratios (wtATTR-CM vs heart failure) were calculated for every diagnosis code present in the patient records. Diagnoses for conditions with statistically significant odds ratio in favor of wtATTR-CM (odds ratio > 4.0, $p < 10e^{-6}$) were selected for interrogation using the Fruchterman Reingold network analysis algorithm. Network metrics and associations between co-morbidities were calculated to reveal insights about disease sub-structures.

Results: Network visualization of features significantly over-represented in the wtATTR-CM population (vs heart failure) revealed 5 central nodes that connected to all major features of wtATTR-CM. These nodes and their corresponding connectivity coefficient were carpal tunnel (0.55), immune disorders (0.40), abnormal serum enzyme levels (0.27), monoclonal gammopathy (0.24), and pericardial effusion/pericarditis (0.08). These nodes, representing features with the highest connectivity overall, indicated high levels of co-occurrence with specific sets of features as illustrated in the network graph (figure 1). Carpal tunnel had the highest number of connections with other conditions overall, as it shared a large number of patients with other significant features: carpal tunnel +metabolic disorders (N=235, 29% overlap), +respiratory abnormalities (N=216, 26% overlap), +joint disorders (N=220, 27% overlap), +nonrheumatic aortic valve disorders (N=140, 17% overlap), +sleep disorders (N=132, 16% overlap).

Conclusion: Various constellations of symptoms centered around 5 dominant nodes were identified. These constellations may help inform the clinical presentation of wtATTR-CM. The centrality of these nodes across a diverse constellation of associated diagnoses and syndromes suggests important clinical sub-structures unique to patients with wtATTR-CM compared to heart failure controls. Additional research is needed to evaluate and confirm other disease sub-structures due to the systemic nature of the disease and how to better inform clinician understanding of this rare and fatal disease.

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