PO-01-188

A MULTI-OMIC COMPARISON OF SURGICAL MYECTOMY LEFT VENTRICULAR TISSUE REVEALS SEX-SPECIFIC DIFFERENCES IN OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

Ramin Garmany; Surendra Dasari; Johan M. Bos; Evelyn Kim; Katherine Martinez; David Tester; Cristobal dos Remedios; Joseph Maleszewski; Joseph A. Dearani; Steve Ommen; John R. Giudicessi and Michael J. Ackerman

Background: Hypertrophic cardiomyopathy (HCM) is a common genetic cause of sudden death in the young. Several cohort studies have shown sex-specific differences in HCM outcomes with females being diagnosed at an older age and having an increased risk of adverse cardiac events with higher symptom burden. We hypothesized there may be sex-based differences in the transcriptome and proteome of HCM.
Objective: To characterize sex-based differences in the transcriptome and proteome of surgical myectomy tissue derived from patients with obstructive HCM.
Methods: The cohort consisted of myectomy tissue from 97 patients with obstructive HCM and interventricular cardiac tissue from 23 cardiac donors for whom a suitable recipient was not found. RNA-sequencing and mass-spectroscopy based proteomics were performed on the cardiac tissue. Differential and pathway analyses were performed to identify sex-specific differences. For RNA-sequencing data a log2fc $\geq |1|$ and FDR$\leq$0.05 threshold was used. For proteomics log2fc $\geq |0.5|$ and FDR$\leq$0.05 threshold was used.
Results: There were 1983 differentially expressed genes (DEGs) between females with HCM compared with female controls and 1064 DEGs between males with HCM compared with male controls. The DEGs unique to females with HCM impacted 219 pathways including PI3K/AKT signaling and ERK/MAPK signaling while the DEGs specifically altered only in males impacted 101 pathways including ERK5 signaling. There were 119 differentially expressed proteins (DEPs) between females with HCM and controls and 27 DEPs between males with HCM compared with controls. The DEPs unique to females with HCM impacted 130 pathways including ERK/MAPK signaling, PI3K/AKT signaling, and collagen synthesis while the DEPs unique to males with HCM impacted 33 pathways including RHO GTPase signaling and contractility.
Conclusion: There are sex-specific differences in the transcriptome and proteome of HCM including significant changes in pathways relevant to the pathobiology of the disease such as hypertrophy and contractility pathways. Whether these multi-omic changes influence sex-specific differences in clinical presentation or responsivity to current therapies warrants further investigation.

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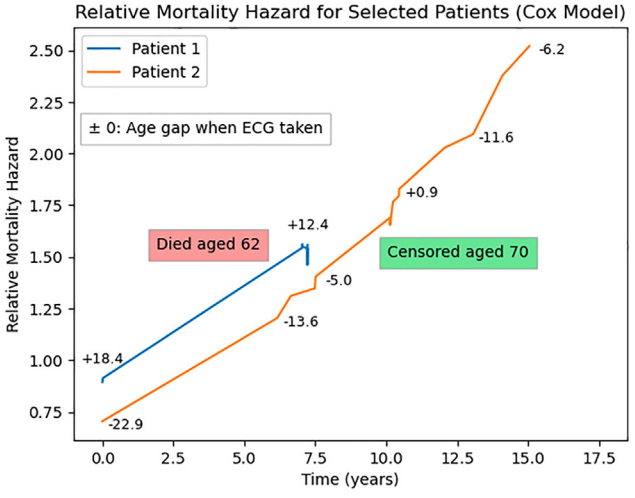
ARTIFICIAL INTELLIGENCE (AI) ECG-PREDICTED BIOLOGICAL AGE GAP AND MORTALITY: SUCCESSIVE ECGS OUTPERFORM SINGLE ECGS

Shaun Evans; Sarah Howson; Andrew E. Booth; Stephen Bacchi; Mohanaraj Jayakumar; SURAYA HANI Kamsani; John Fitzgerald; Anand Thiyagarajah; Melissa E. Middeldorp and Prashanthan Sanders

Background: AI-ECG predicted biological age gap has been linked to mortality rates. As a measure of biological aging, AI-ECG age is inexpensive and readily available compared with other markers of biological age, with potential use as a tool for lifestyle counselling. To date, the age gap between AI-ECG age and chronological age has been modelled as a fixed hazard. The effect of using multiple ECGs to estimate a time-varying hazard has not been explored.
Objective: To compare models using one vs multiple ECGs to estimate patient mortality hazards.
Methods: Using AI-ECG trained to predict age, biological age was estimated to calculate a biological age gap. Patients included were 20–90 years old and had at least two ECGs recorded in hospital. Two Cox models were compared: one using each patient's first ECG as a fixed hazard, and the other using all available ECGs as a time-varying hazard. Goodness-of-fit was then compared using the log-likelihood ratio test and the adjusted Akaike Information Criterion (AIC).
Results: 46,960 patients with 337,415 ECGs were included. The median follow-up was 4.5 years with 6622 patient deaths. The multiple-ECG model provided a superior fit for mortality hazard compared with a single ECG, as demonstrated by the higher log-likelihood ratio test of 6098 vs 5136 (higher indicates a better fit). Even when penalised for including repeated measurements of the age gap, the lower AIC 123,662 vs 124,676 indicated improved model performance. Both models estimated that every year increase in age gap increased the mortality hazard by 1% independently of age (coeff.$=$0.01, P$<$0.005). Figure 1 illustrates two example patients aged 60 at first ECG and the hazard evolution with time.
Conclusion: The AI ECG-derived age gap is a significant predictor of mortality, and this is further improved by using multiple ECGs as a time-varying hazard. These findings suggest that multiple ECGs can improve risk estimation to guide care in clinical settings.



Two patients aged 60 at first ECG. Relative hazards plotted over successive ECGs and annotated with the age gap

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META-ANALYSIS OF RNASEQ DATA FROM TWO LARGE ATRIAL TISSUE BANKS IDENTIFIES MORE THAN 8000 TRANSCRIPTS ASSOCIATED WITH AF AND SUGGESTS A PROMINENT ROLE FOR MITOCHONDRIAL PROCESSES AND ENERGY METABOLISM: THE CATCH ME AND RACE V CONSORTIA

Aaron Isaacs; Joris Winters; Stef Zeemering; Michal Kawczynski; Martijn D. Gilbers; Bart Maesen; Jos Maessen; Elham Bidar; Bas J. Boukens; Ben J. Hermans; Arne Van Hunnik; Barabara Casadei; Larissa Fabritz; Winnie Chua; Laura Sommerfeld; Eduard Guasch; Lluis Mont; Montserrat Batlle; Stephane Hatem; Paulus Kirchhof; Reza Wakili; Moritz F. Sinner; Stefan Kaab; Sander Verheule;