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Assessing the prognostic value of metabolites in patients with Heart Failure: a systematic review and meta-analysis

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Introduction: While the association of plasma lipids and the risk of poor cardiovascular (CV) outcomes are known, other plasma circulating metabolites might add value to the prognosis of CV-associated events. Metabolomics may help uncover metabolic dysregulations underlying such associations.

Aim: To compile risk associations between metabolites and poor CV outcomes in patients with Heart Failure (HF) through a systematic review and meta-analysis.

Methods: We performed a systematic review using the Medline and PubMed database (last searched on 31/12/2022). Studies that used blood (plasma or serum) metabolomics in HF patients to predict poor cardiovascular outcomes (death or hospitalization due to worsening of HF), irrespective of follow-up time were included. Time-to-event outcomes were collected for each metabolite through adjusted Hazard Ratio (HR) along with its uncertainty. Fixed and random effects models were used to compute statistical combined measures (HR) and 95% confidence intervals (CI) of individual metabolites.

Results: We identified 69 studies that used metabolomics in patients with HF. Of these, 5 articles, totalizing 2076 patients from 6 independent cohorts, computed and reported the HR of 129 metabolites (*log-transformed and standardized*). Forty-five metabolites were present in at least two studies/cohorts and assessed through meta-analysis. The mean (or median) follow-up period ranged from 1.0 to 6.3 years, and the rate of events ranged from 13-38% of the included sample (n varying from 136 and 516). We identified 8 metabolites with a significant pooled HR and low heterogeneity (I2< 50%) using fixed- and random-effect models. Higher histidine (HR: 0.74 95%CI [0.64-0.86]) and tryptophan (HR: 0.82 [0.71-0.96]) seem to be protective of CV events, while higher symmetric dimethylarginine (SDMA) (HR 1.58 [1.30-1.93]), N-methyl-1-histidine (HR: 1.56 [1.27-1.90]), SDMA/arginine (HR: 1.58 [1.14-1.68]), putrescine (HR: 1.31 [1.06-1.61]), methionine sulfoxide (HR: 1.26 [1.03-1.52]) and 5-hydroxylysine (HR: 1.25 [1.05-1.48]) were associated with a higher risk of events. Of these findings, tryptophan and histidine were reported in 3 studies/cohorts, while the remaining metabolites were reported in 2.

Conclusions: Despite the limited data available, we identified 8 metabolites associated with CV events in patients with HF, suggestive of derangement in inflammatory processes and in the nitric oxide synthesis pathways that need further exploration. The lack of standardization in metabolomic studies and data reporting hampers combining and comparing different studies. Taking metabolomics into a clinical scenario, in the long run, could greatly benefit from harmonizing analytical analysis procedures and adopting open data-sharing policies.

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Decoding The Genetic Architecture Behind Disease Heterogeneity: A Genome-Wide Association Study And Cluster Analysis In COPD

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Background: Pulmonary, as well as extrapulmonary features such as muscle weakness and reduced exercise capacity, contribute significantly to the morbidity and mortality as well as the individual, social and economic burden of chronic obstructive pulmonary disease (COPD). Aetiology is multifactorial, including extrinsic factors such as smoking, inactivity, malnutrition and corticosteroid use, as well as intrinsic factors such as hypoxia, hypercapnia, inflammation and oxidative/nitrosative stress. Evidence suggests single-nucleotide polymorphisms (SNPs) may be involved in muscle wasting and other pathophysiological processes. A known genetic predisposition to functional impairment could therefore be useful in optimising the treatment of this meaningful patient-centred health domain. Hence, we conducted a cluster analysis and genome-wide association study (GWAS), to identify genetic variants associated with functional impairment in individuals with COPD.

Methods: A cross-sectional study was conducted. Exercise capacity was assessed with the one-minute sit-to-stand test and the six-minute walk test. Peripheral muscle strength was measured by handgrip strength and quadriceps maximum voluntary contraction. Hierarchical cluster analysis (Ward method) based on principal component analysis (PCA)-transformed data was used to classify patients. A PCA was performed to reduce the correlation between the independent variables. GWAS was performed using multivariate logistic regression with cluster assignment as phenotype, adjusted for age, sex, body mass index, smoking status and FEV1 %predicted. An additive model was assumed with a significant SNP p-value threshold of 5x10-8 and a suggestive SNP p-value threshold of 5x10-5 to account for multiple testing. Functional annotation was performed using FUMAGWAS. All statistical analyses were performed with PLINK 1.9 and R statistical software.

Results: We included 208 patients with COPD (68±8 years old; 21% female; FEV1 53 [40, 67] %predicted), of whom a subset of 170 had genotyping data available. Cluster 1 (n=66) was characterised by younger, mostly male individuals with fewer symptoms and preserved exercise capacity and strength. Cluster 2 (n=96) was intermediate between the other two clusters in terms of patients' clinical and demographic characteristics, with preserved functional capacity but decreased strength. Cluster 3 (n=46) was characterised by older, symptomatic patients with a higher prevalence of women, reduced exercise capacity and muscle weakness. Six SNPs were found to be suggestive from GWAS and mapped to genes previously associated with inflammation and muscle wasting mechanisms.

Conclusion: These results suggest that functional impairment in COPD may be influenced by genetics, as individuals with polymorphisms in the mapped genes were at increased risk for functional impairment.