FAILURE OF THE HEART DETERMINATION PROTEOMIC PROFILING RELATED TO PATIENTS WHO ARE ELDERLY

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Abstract

Objective

These eighty proteins have been identified to be connected with cardiovascular pathology in the past, and the purpose of this study paper is employing proteomic profiling of these proteins in order to discover new risk factors for heart failure or heart failure in general.

Materials and Methods

Analyses of the proximity extension (Proteomic profiling) has been performed in two different communities with varying cohorts in the elderly at the baseline in the absence of cardiac failure. The prospective of the research were Prospective Investigation of the Vasculature (PIV) and Longitudinal Study of Adult Men (LSAM) having respective values (80 events, median age = 70.2 years, n = 901) and (90 events, median age = 77.8 years, n = 685). Incident of heart failure was associated with 29 proteins as observed in PIV with adjusted sex and age. Corrections were made after multiple tests. In LSAM there were 18 proteins associated with heart failure. High level of 9 proteins were related to the incident of heart failure among both the cohorts. There were additional modifications made to the established risk variables. There was a deficit in the left ventricular systolic function that was found to be associated with the presence of growth differentiation factor 15 (GDF-15), urokinase-type plasminogen activator surface receptor (U-PAR), matrix metalloproteinase-12 (MMP-12), tumour necrosis factor-related apoptosis-inducing ligand receptor 2 (TRAIL-R2), spondin-1 (SPON1), and follistatin (FS). This was discovered through echocardiographic monitoring. Each and every one of the P values was lower than 0.02.

Results

The final characteristics of PIV included median age of 70 years among a total of 901 participants. In LSAM the characteristic showed median age of 78 years among 685 participants. During follow-up among PIV the age range was 0.1-10.9 years with a median of 10 years, 80 hospitalizations due to heart failure with a heart failure rate of 0.96 among 100 persons. There were 90 hospitalisations for heart failure among LSAM, the age range was 0.2-10.9 years with a median of 8 years, and the heart failure rate was 1.83 per 100 people. False discovery rate among PIV was 5% with the association of 29 proteins after adjusted sex and age. Among LSAM the association of 18 proteins was nominal for the incident of heart failure.

Conclusion

Several novel associations for the involvement of proteins in fibrinolysis, apoptosis, inflammation, matrix remodeling and heart failure were identified through Proteomic profiling in the research study among elderly. The outcomes of this research also correspond to other investigations that studied underlying clinical utilities and mechanisms.

Keywords: Epidemiology, Heart failure, Left ventricular dysfunction, Risk prediction, Proteomics and Biomarkers.

НЕУДАЧА ОПРЕДЕЛЕНИЯ ПРОТЕОМНОГО ПРОФИЛИРОВАНИЯ СЕРДЦА

Резюме

В прошлом было установлено, что эти восемьдесят белков связаны с сердечно-сосудистой патологией, и целью данной исследовательской работы является использование протеомного профилирования этих белков с целью обнаружения новых факторов риска сердечной недостаточности или сердечной недостаточности в целом.

Материалы и методы

Анализ расширения близости (протеомное профилирование) проводился в двух разных сообществах с разными когортами пожилых людей на исходном уровне при отсутствии сердечной недостаточности. Перспективами исследования были «Проспективное исследование сосудистой сети» (PIV) и «Продольное исследование взрослых мужчин» (LSAM), имеющие соответствующие значения (80 событий, средний возраст = 70,2 года, n = 901) и (90 событий, средний возраст = 77,8 лет). , n = 685). Случаи сердечной недостаточности были связаны с 29 белками, наблюдаемыми при PIV с учетом пола и возраста. Исправления были внесены после многочисленных испытаний. В LSAM было 18 белков, связанных с сердечной недостаточностью. Высокий уровень 9 белков был связан с возникновением сердечной недостаточности в обеих когортах. Были внесены дополнительные изменения в установленные переменные риска. Выявлено нарушение систолической функции левого желудочка, что связано с наличием фактора дифференцировки роста 15 (GDF-15), поверхностного рецептора активатора плазминогена урокиназного типа (U-PAR), матриксной металлопротеиназы-12 (MMP- 12), лиганд-рецептор 2, индуцирующий апоптоз, связанный с фактором некроза опухоли (TRAIL-R2), спондин-1 (SPON1) и фоллистатин (FS). Это было обнаружено посредством эхокардиографического мониторинга. Каждое из значений P было ниже 0,02.

Полученные результаты

Окончательные характеристики PIV включали средний возраст 70 лет среди 901 участника. В LSAM средний возраст 685 участников составил 78 лет. За время наблюдения за PIV возрастной диапазон составил 0,1-10,9 года при медиане 10 лет, 80 госпитализаций по поводу сердечной недостаточности с частотой сердечной недостаточности 0,96 на 100 человек. Среди LSAM было 90 госпитализаций по поводу сердечной недостаточности, возрастной диапазон составлял 0,2-10,9 года при медиане 8 лет, а частота сердечной недостаточности составила 1,83 на 100 человек. Частота ложных обнаружений среди PIV составила 5% при ассоциации 29 белков после корректировки пола и возраста. Среди LSAM ассоциация 18 белков была номинальной для возникновения сердечной недостаточности.

Заключение

Несколько новых связей с участием белков в фибринолизе, апоптозе, воспалении, ремоделировании матрикса и сердечной недостаточности были выявлены с помощью протеомного профилирования в исследовании среди пожилых людей. Результаты этого исследования также соответствуют другим исследованиям, изучавшим основные клинические преимущества и механизмы.

Ключевые слова: эпидемиология, сердечная недостаточность, дисфункция левого желудочка, прогнозирование риска, протеомика и биомаркеры.

INTRODUCTION

Heart failure has gained serious attention globally as a major health issue which requires serious attention for the identification of associated risk factors among individuals along with the investigation of preventive and therapeutic strategies [1]. Insufficient attention has been paid to the most important guidelines for cardiovascular prevention, which are designed to assist in the prediction of heart failure and the processes that underlie it [2, 3]. Despite all efforts, the development of heart failure remains a mystery. The underlying pathophysiology requires innovative investigations via risk assessment of heart failure by identifying linked biomarkers. Few associated biomarkers highlighted in the last few decades include GDF-15 and U-PAR [4, 5]. These only indicate general risk beyond cardiovascular risk variables and NT-proBNP [6]. This study sought to confirm the link between heart failure and 80 cardiovascular disease-associated proteins. The research also assesses the association of proteins with the improved prediction of heart failure that is beyond established factors among elderly as study in two studies PIV and LSAM. The research also sought to link left ventricular systolic and diastolic echocardiographic indices to proteins.

MATERIALS AND METHODS

Proximity extension assay (Proteomic profiling) has been performed in two different communities with varying cohorts in the elderly at the baseline without heart failure. The potential outcomes of the research were the Prospective Investigation of the Vasculature (PIV) and the Longitudinal Study of Adult Men (LSAM), with respective values of (80 events, median age = 70.2 years, n = 901) and (90 events, median age = 77.8 years, n = 685 individuals). A total of 29 proteins were shown to be linked with the occurrence of heart failure in the PIV study, with age and gender being controlled for. After conducting a number of tests, adjustments were made. In LSAM there were Eighteen proteins that are linked to severe cardiac failure. High level of 9 proteins were related to the incident of heart failure among both the cohorts. Known risk variables were also altered. Growth differentiation factor The parameters 15 (GDF-15), U-PAR, MMP-12, TRAIL-R2, SPON1, and FS were shown to be linked with a decrease in the left ventricular systolic function on echocardiograms. The P-value for all was <0.02.

Clinical assessment was conducted for the participants of the PIV participants among which 50.2% were at the age of 70 years. We did not include all the participants who were missing for prevalent heart failure, missing plasma samples, missing protein data, low quality protein data and missing model covariates. Final research sample was limited to 685 for LSAM and 901 for PIV. Overnight fasting was observed before the clinical investigation conducted in the morning. The samples of venous blood were kept at a temperature of -70℃. Standard methods were utilized for anthropometry, blood pressure, lipid, glucose, biochemistry, echocardiography and electrocardiogram. Tabulated data was also prepared for medical history, medications and smoking habits. Both the cohorts were also assessed for the the presence of atrial fibrillation and left ventricular hypertrophy through electrocardiograph. Plasma samples were collected from PIV and serum from LSAM which were assessed with Proseek Multiplex CVD proximity extension assay [9]. The assay used specific antibodies to simultaneously measure 92 proteins by creating polymerase chain reaction which followed quantitative polymerase chain reaction [10]. Mean was

set to zero to level protein by normalizing the plate. Subsequent analysis of the relative values was also made for protein level deviation within storage time and each plate. Missing measurements in each cohort were not made the part of this study. Lower limit detected values were imputed to half of the lower detected limit. Supplementary material included the details about the excluded and imputed proteins. Study design was not influenced by the manufacturer of the protein assay even in the manuscript preparation and statistical analysis.

RESULTS

The baseline data was blinded for the physicians for the hospitalized cases of heart failure and discharged patients [11]. According to the European society the classified events of heart failure are questionable, definite and miscoded. The final characteristics of PIV included median age of 70 years among a total of 901 participants. In LSAM the characteristic showed median age of 78 years among 685 participants. During follow-up among PIV the age range was 0.1-10.9 years with a median of 10 years, 80 hospitalizations due to heart failure with a heart failure rate of 0.96 among 100 persons. Among LSAM there were 90 hospitalizations due to heart failure the age range was 0.2-10.9 years with a median of 8 years and the heart failure rate was 1.83 among 100 persons. False discovery rate among PIV was 5% with the association of 29 proteins after adjusted sex and age. Among LSAM the association of 18 proteins was nominal for the incident of heart failure. Major extent of most of the proteins has no association with the onset of heart failure risk factors and heart failure was also not influenced with proteins. NT-proBNP remained significant heart failure predictor when added to the adjusted nine proteins TIM-1. U-PAR, OPG and MMP-12. Follow-up outcomes showed that a total of 114 patients suffered non-ischaemic heart failure. There was an independent association of higher levels of ST2, MMP-12, TIM-1 and FS with the higher risk of non-ischaemic heart failure.

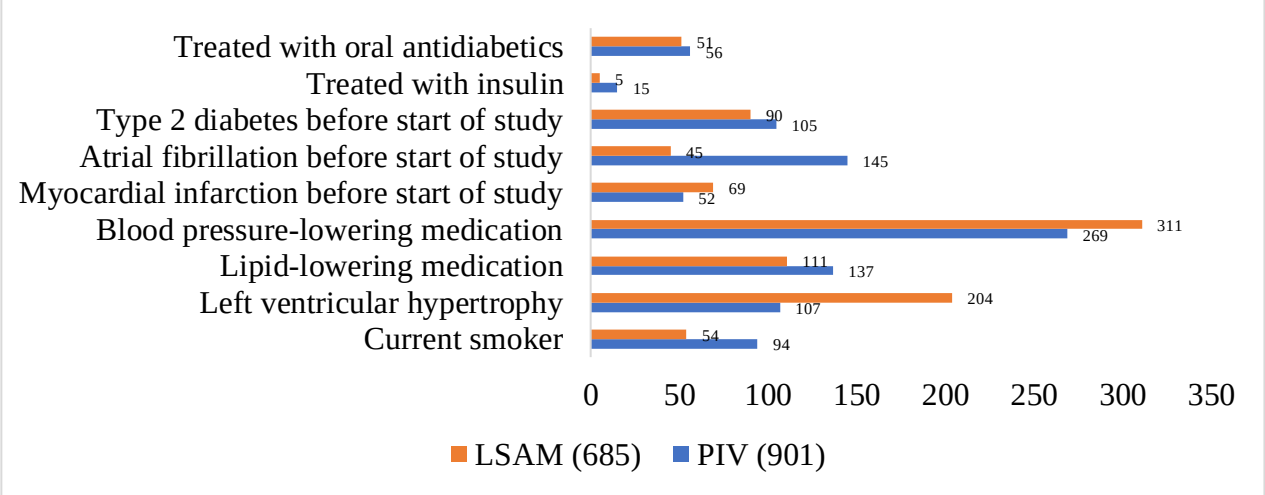
Table – I: Clinical Baseline Characteristics

Parameter	Unit	PIV (901)	LSAM (685)
Age, years	Years	70.2	77.8
Gender	Male	444	685
BMI	Kg/M^2	27	26.2
LDL-C	Mmol/L	3.4	3.5
HDL-C	Mmol/L	1.5	1.3
Fasting glucose	Mmol/L	5.9	5.8
Triglycerides	Mmol/L	1.1	1.2
Systolic blood pressure	Mmhg	150	151
Diastolic blood pressure	Mmhg	79	81
Glomerular filtration rate	$Ml/Min/1.73M^2$	93	74
NT-proBNPa	Mmol/L	109	N/A
Isovolumic relaxation time	Ms	121	N/A
Ejection fraction	%	67	N/A

Table – II: Baseline Parameters for Heart Failure

Parameter	PIV (901)	LSAM (685)
Current smoker	94	54

Left ventricular hypertrophy	107	204
Lipid-lowering medication	137	111
Blood pressure-lowering medication	269	311
Myocardial infarction before start of study	52	69
Atrial fibrillation before start of study	145	45
Type 2 diabetes before start of study	105	90
Treated with insulin	15	5
Treated with oral antidiabetics	56	51



DISCUSSION

Researchers also examined the cross-sectional link between nine proteins, diastolic baseline function, and left ventricular systolic echocardiographic parameters in PIV alone. When sex and age are adjusted, worsened systolic function is associated with greater levels of SPON1, TRAIL-R2, MMP-12, U-PAR, and GDF-15, while worsened diastolic function is associated with TIM-1. During random training part of the 915 persons through Lasso regression optimum addition of the risk factors was noted in 24 and 11 protein set with ARIC score included and excluded for NT-proBNP levels. Model excluded for NT-proBNP in the sample size of 457 individuals for validation there was a significant risk factors prediction improvement with the addition of protein data (C 0.751-0.852, 95% confidence interval 0.030-0.173, P-value <0.001). There was no significant improvement in the model which included NT-proBNP with the addition of protein markers (C 0.821-0.841, 95% P-value 0.06, Delta-C 0.020, confidence interval -0.027-0.068. Proteomic screening of two older cohorts found 18 proteins linked to heart failure. The independent association with the risk factors was observed among nine proteins which include ST2, OPG, U-Par, FS, MMP-12 and SPON1. The independent association of proteins with the onset of non-ischaemic heart failure was observed in ST2, MMP-12 and TIM-1. Worsened systolic function was associated with SPON1, TRAIL-R2, MMP-12, U-PAR and GDF-15. Worsened diastolic function was associated with TIM-1. This research model excluded NT-proBNP proteomics data that enhanced risk prediction on recognised parameters.

CONCLUSION

Several novel associations for the involvement of proteins in fibrinolysis, apoptosis, inflammation, matrix remodeling and heart failure were identified through Proteomic profiling in

the research study among elderly. The outcomes of this research also correspond to other investigations that studied underlying clinical utilities and mechanisms. More research on proteome profiling in clinical practice will boost heart failure reporting.

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