Growth Differentiation Factor-15 as candidate predictor for mortality in adults with pulmonary hypertension

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SUPPLEMENTARY MATERIAL

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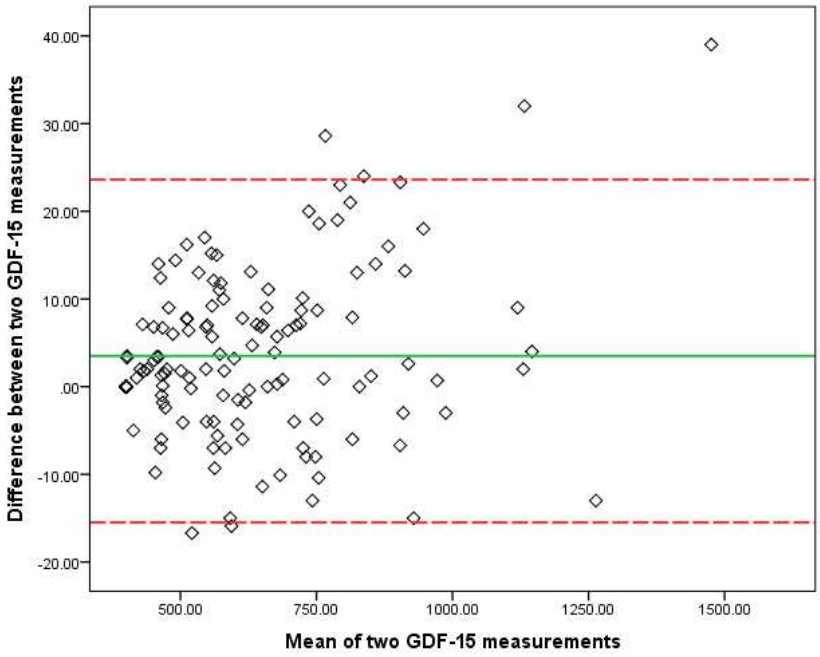
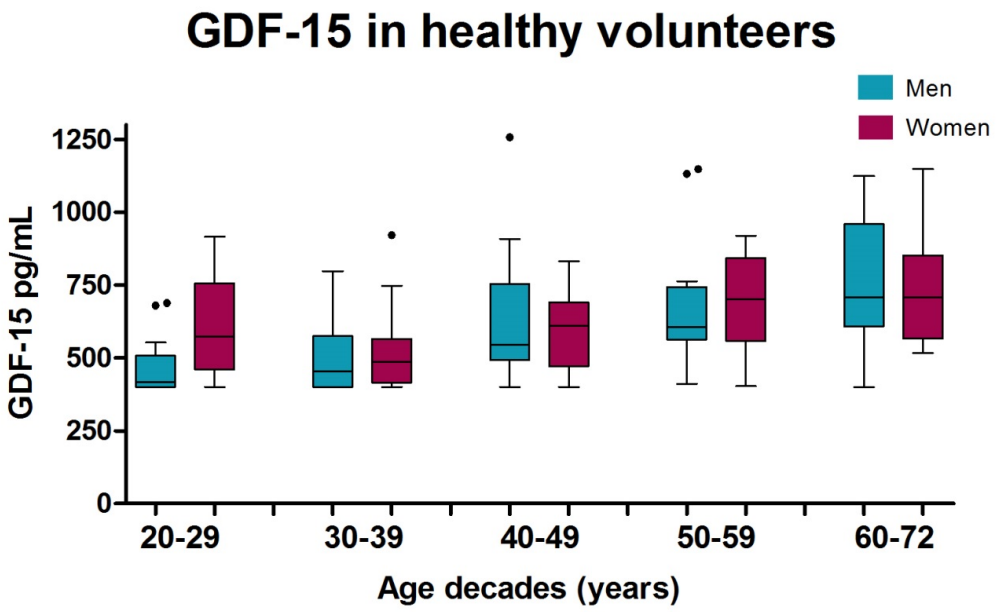


Supplementary File 1. Reproducibility of GDF-15 assay in healthy volunteers shown by a Bland-Altman plot.

Legend: The green line corresponds with the mean difference between two GDF-15 measurements.
The red dotted-lines correspond to the corresponding limits of agreement (+/- 1.96 SD)
The coefficient of variation was 0.68%.

Geenen LW, *et al. Heart* 2020; 106:467–473. doi: 10.1136/heartjnl-2019-315111



Supplementary File 2. Levels of GDF-15 in healthy volunteers stratified according to sex and age decades. Each age decade is approximately equally represented by the number of healthy volunteers.

Legend: boxplots showing the median and interquartile ranges. Spread of the data is shown by the whiskers (Turkey boxplot). Outliers are plotted with a dot. The lowest limit of detection of the GDF-15 assay was 400 pg/mL.

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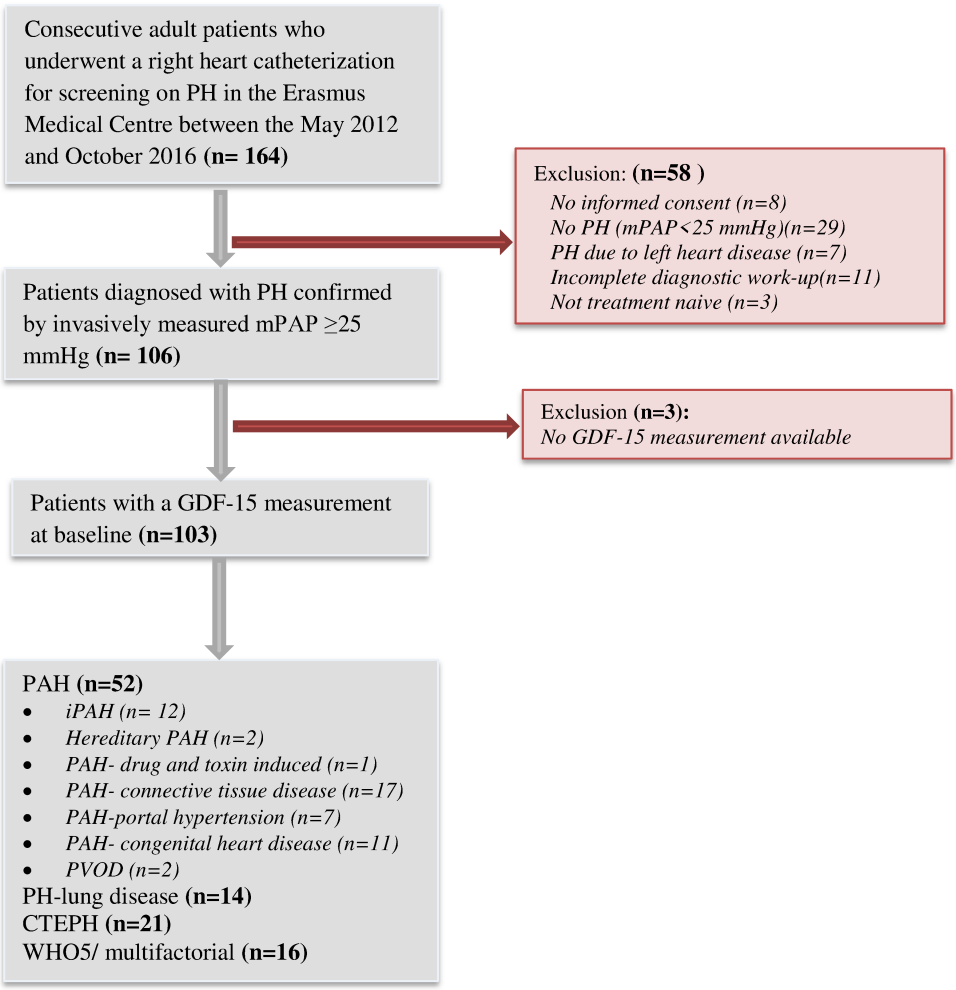

Supplementary File 3. Flowchart of the patient selection process of the study cohort.

Abbreviations: PH= pulmonary hypertension, mPAP= mean pulmonary arterial pressure, GDF-15= growth differentiation factor-15, PAH= pulmonary arterial hypertension, iPAH= idiopathic pulmonary arterial hypertension, PVOD= pulmonary veno-occlusive disease, CTEPH= chronic thromboembolic pulmonary hypertension, WHO5= World Health Organization group 5.

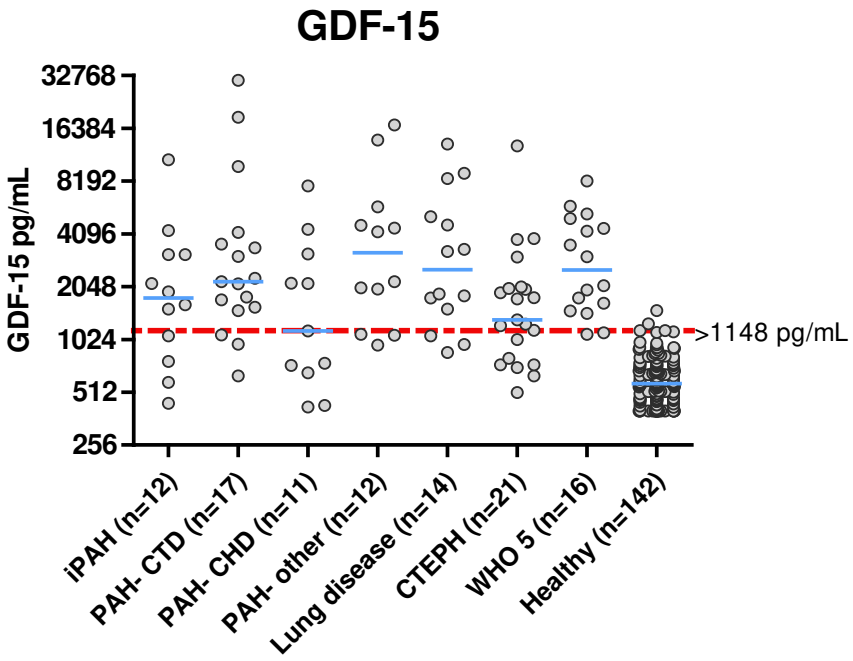

Figure 4. Measurements of GDF-15 in pg/mL according to subgroups in pulmonary hypertension patients and GDF-15 measurements performed in healthy volunteers.

Figure legend: Y-axis is on the 2-log scale. The red line indicates the 97th percentile level of GDF-15 based on measurements in healthy volunteers. The black line indicates the median GDF-15 level in each subgroup.
PAH-other consisted of; pulmonary veno-occlusive disease(n=2), PAH- associated with portal hypertension (n=7), hereditary PAH (n=2), drug and toxin induced PAH (n=1).
Abbreviations: iPAH= idiopathic pulmonary arterial hypertension, PAH-CTD = pulmonary arterial hypertension due to connective tissue disease, PAH-CHD= pulmonary arterial hypertension due to congenital heart disease,

Cause of death	Number of cases (%)
End-stage heart failure	9 (30.0)
Sudden death presumed cardiac	4 (13.3)
Euthanasia*	3 (10.0)
Multi-organ failure	3 (10.0)
Kidney/liver failure	2 (6.7)
Malignancy	1 (3.3)
Myocardial infarction	1 (3.3)
Hepatic encephalopathy	1 (3.3)
Progression of systemic sclerosis	1 (3.3)
Sudden death, presumed cerebral	1 (3.3)
End stage lung fibrosis and PH due to polymyositis	1 (3.3)
Occlusion of femoral artery	1 (3.3)
Post lung transplantation	1 (3.3)
Unknown	1 (3.3)

Supplementary File 5. Detailed list of death causes in 30 adults with pulmonary hypertension.
**In patients with end-stage cardiovascular and pulmonary disease.*

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	Pulmonary arterial hypertension(PAH)			
	Primary endpoint (n=16)		**Secondary endpoint (n=20)**	
	HR*(95%CI)	p-value	HR*(95%CI)	p-value
GDF-15 (univariable)	1.57 (1.14-2.15)	0.005	1.50 (1.13-1.97)	0.004
Adjusted for:				
Age	1.44 (1.02-2.02)	0.038	1.35 (1.00-1.82)	0.052
Sex	1.57 (1.15-2.15)	0.005	1.49 (1.13-1.97)	0.004
NYHA class 3/4	1.50 (1.10-2.06)	0.012	1.41 (1.08-1.86)	0.013
6-MWD	1.38 (1.01-1.90)	0.046	1.21 (0.91-1.61)	0.183
Right atrial area	1.48 (1.09-2.02)	0.012	1.49 (1.10-1.90)	0.008
Cardiac index	1.61 (1.16-2.25)	0.005	1.56 (1.34-1.81)	0.003
mRAP	1.71 (1.24-2.34)	<0.001	1.55 (1.17-2.05)	0.002
eGFR	1.37 (0.92-2.04)	0.117	1.27 (0.90-1.80)	0.178
NT-proBNP	1.55 (1.07-2.25)	0.020	1.43 (1.03-1.99)	0.031

Supplementary File 6. Association between GDF-15 and the primary and secondary endpoint restricted to only adults with pulmonary arterial hypertension

Legend: *HR per two-fold higher value of GDF-15.
Abbreviations: HR= hazard ratio, GDF-15= growth differentiation factor-15, NYHA= New York Heart Association, mPAP= mean pulmonary arterial pressure, mRAP= mean right atrial pressure, eGFR= estimated glomerular filtration rate, NT-proBNP= N-terminal pro B-type natriuretic peptide

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