Characterizing And Prognosticating Heart Failure With Improved Ejection Fraction Using NT-proBNP, Growth Differentiation Factor- 15 And Global Longitudinal Strain

Dr Ling Hwei Sung, HFRA2

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Background

- HF with improved EF (HFimpEF) is a new HF subgroup.[1,2]
- Improved EF is not a cure but a remission state. [1]
- Little is known about biomarkers and imaging parameters that prognosticate the clinical outcome in this subgroup.

Bozkurt B, Coats AJ, Tsutsui H, Abdelhamid M, Adamopoulos S, Albert N, Anker SD, Atherton J, Böhm M, Butler J, Drazner MH, Felker GM, Filippatos G, Fonarow GC, Fiuzat M, Gomez-Mesa JE, Heidenreich P, Imamura T, Januzzi J, Jankowska EA, Khazanie P, Kinugawa K, Lam CSP, Matsue Y, Metra M, Ohtani T, Francesco Piepoli M, Ponikowski P, Rosano GMC, Sakata Y, SeferoviĆ P, Starling RC, Teerlink JR, Vardeny O, Yamamoto K, Yancy C, Zhang J, Zieroth S. Universal Definition and Classification of Heart Failure: A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. J Card Fail. 2021 Mar 1:S1071-9164(21)00050-6. doi: 10.1016/j.cardfail.2021.01.022. Epub ahead of print. PMID: 33663906.

He Y, Ling Y, Guo W, Li Q, Yu S, Huang H, Zhang R, Gong Z, Liu J, Mo L, Yi S, Lai D, Yao Y, Liu J, Chen J, Liu Y and Chen S (2021) Prevalence and Prognosis of HFimpEF Developed From Patients With Heart Failure With Reduced Ejection Fraction: Systematic Review and Meta-Analysis. *Front. Cardiovasc. Med.* 8:757596. doi: 10.3389/fcvm.2021.757596

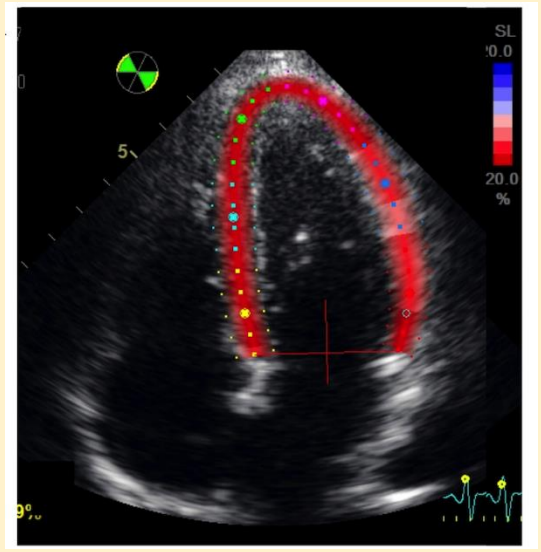
GDF-15 and GLS in Heart Failure

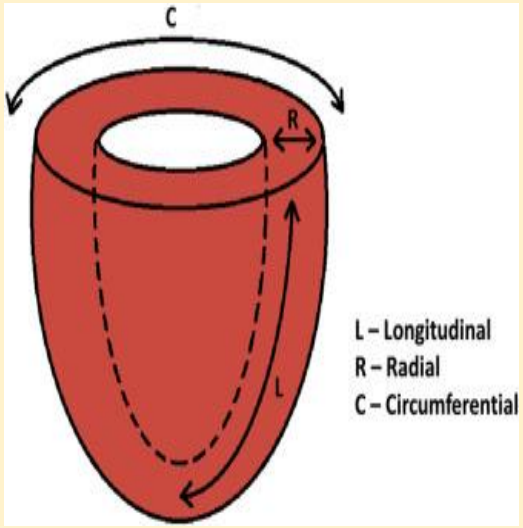
GDF-15

- Member of transforming growth factor-beta **cytokine**
- Expressed by cardiomyoctyes during stress, ie. **pressure/inflammation**
- Higher GDF-15 levels **predicts mortality** in chronic heart failure

Global Longitudinal Strain (GLS)

- **Speckle tracking** echo assessment





- GLS **more sensitive** than LVEF and **predicts mortality** in chronic heart failure

Tibor Kempf; Stephan von Haehling; Timo Peter; Tim Allhoff; Mariantonietta Cicoira; Wolfram Doehner; Piotr Ponikowski; Gerasimos S. Filippatos; Piotr Rozentryt; Helmut Drexler; Stefan D. Anker; Kai C. Wollert (2007). Prognostic Utility of Growth Differentiation Factor-15 in Patients With Chronic Heart Failure. , 50(11), 1054–1060. doi:10.1016/j.jacc.2007.04.091

Ashish, K., Faisaluddin, M., Bandyopadhyay, D., Hajra, A., & Herzog, E. (2018). Prognostic value of global longitudinal strain in heart failure subjects: A recent prototype. International journal of cardiology. Heart & vasculature, 22, 48–49. https://doi.org/10.1016/j.ijcha.2018.11.009

Objectives

To determine among **HFimpEF** patients the:

1. Level and correlation between **NT-proBNP, GDF-15 and GLS**
2. Association of NT-proBNP, GDF-15 and GLS with patient demographics, clinical parameters, and imaging parameters
3. Association of each parameter with the 1-year composite outcome
4. Association of each parameter with LVEF deterioration

Methodology

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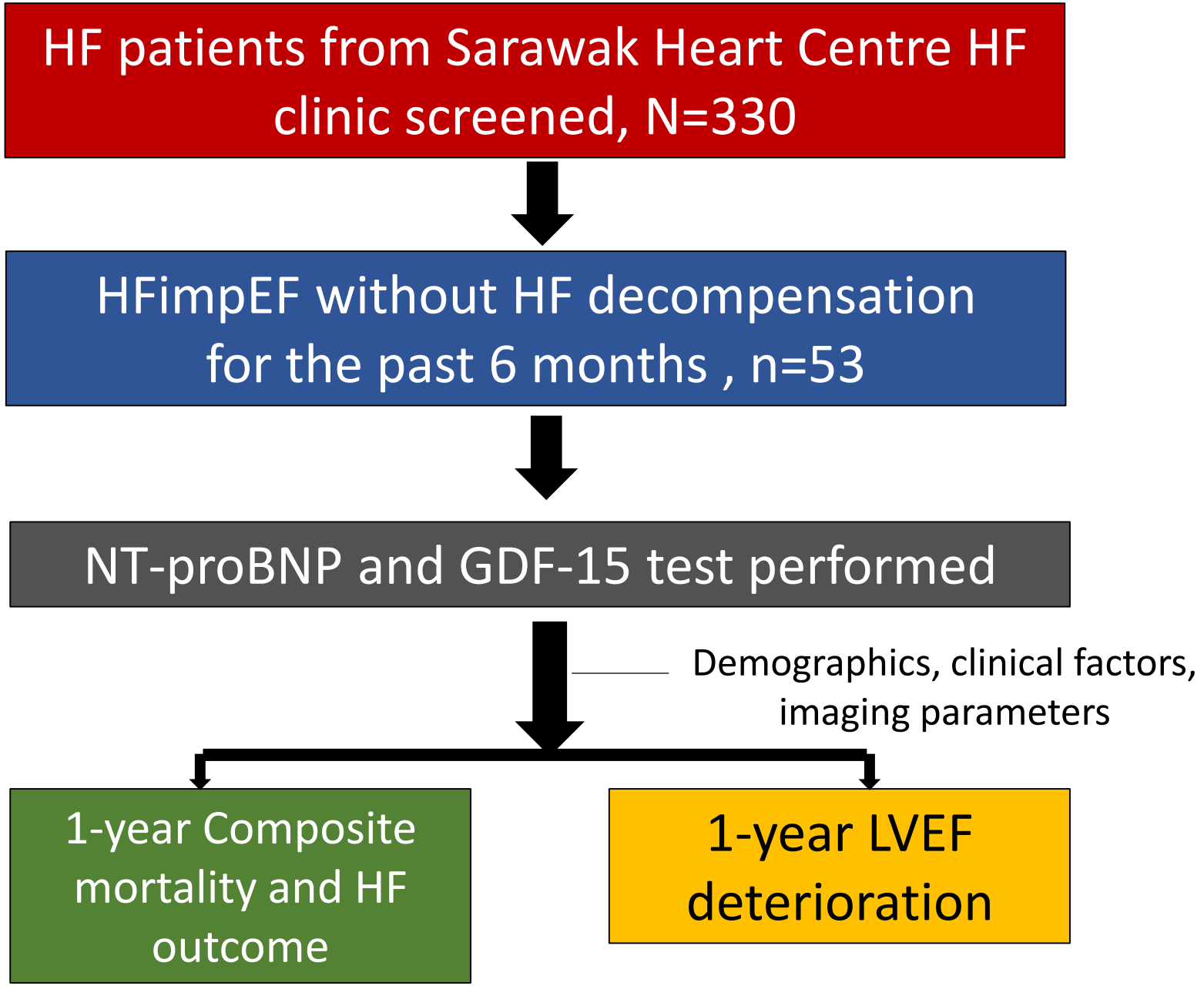

Study cohort

To determine among **HFimpEF** patients the:

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1. HF with improved EF (HFimpEF):

Universal definition of Heart Failure 2021

HF with baseline LVEF ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF >40%

2. No HF readmission, unscheduled visit, and/or increasing diuretics due to worsening HF symptoms for at least 6 months

3. Had GDF-15 and NT-proBNP performed

Clinical Factors

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Patient demographics and clinical parameters:

1. **Age**
2. **Gender**
3. **NYHA class**
4. **Blood pressure, heart rate**
5. **Hypertension, Diabetes, dyslipidemia**
6. **Ischemic and non-ischemic etiology**
7. **MAGGIC score**
8. **BMI**

Imaging parameters

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Echocardiographic imaging parameters assessed:

1. **LVEF when achieving HFimpEF**
2. **LVEDD**
3. **LA diameter**
4. **TR Vmax- TR maximum velocity**
5. **Average E/e'**
6. **LV Mass**

Outcomes

To determine among **HFimpEF** patients the:

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1-year composite outcome

All cause mortality, HF readmissions, unscheduled visit due to HF, and/or uptitration of diuretics due to worsening of HF signs and symptoms

Outcomes

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LVEF deterioration at 1-year

>5% absolute LVEF drop

and LVEF is below 40%

Baseline Characteristics (n=53)

Mean age	52±14.1
Male Gender	43 (81%)
NYHA class	
NYHA 1	46 (87%)
NYHA 2	7 (13%)
Vital signs	
Mean BP, mmHg	134/80
Mean Heart rate, bpm	69
Comorbidities	
Hypertension	40 (75%)
Type 2 DM	24 (45%)
Stage 3 CKD and above	5 (9%)
Etiology	
Ischemic	14 (26.4%)
Non Ischemic	39 (73.6%)

Baseline Characteristics (n=53)	
MAGGIC score	9.547 (1-year risk of death: 3.2%, 3-year risk of death 9.2%)
Mean BMI, kg/m²	31.6±8.6
Mean Creatinine, mmol/L	102±38.8
Mean LVEF when achieved HFimpEF status	53±9
Medications	
ACEi/ARB	38 (71.6%)
Beta blockers	51 (96.2%)
MRA	30 (56.6%)
ARNI	12 (22.6%)

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NT-proBNP

(mean, pg/ml)

357±575

[<125]

GDF-15

(mean, ng/L)

***1972*±1451**

[<1200]

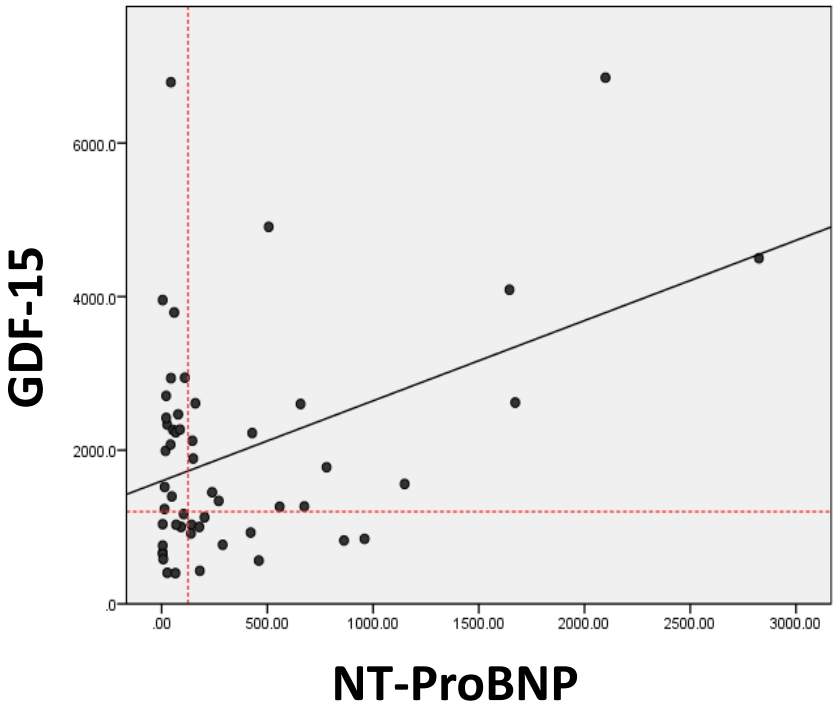
GLS

(mean, %)

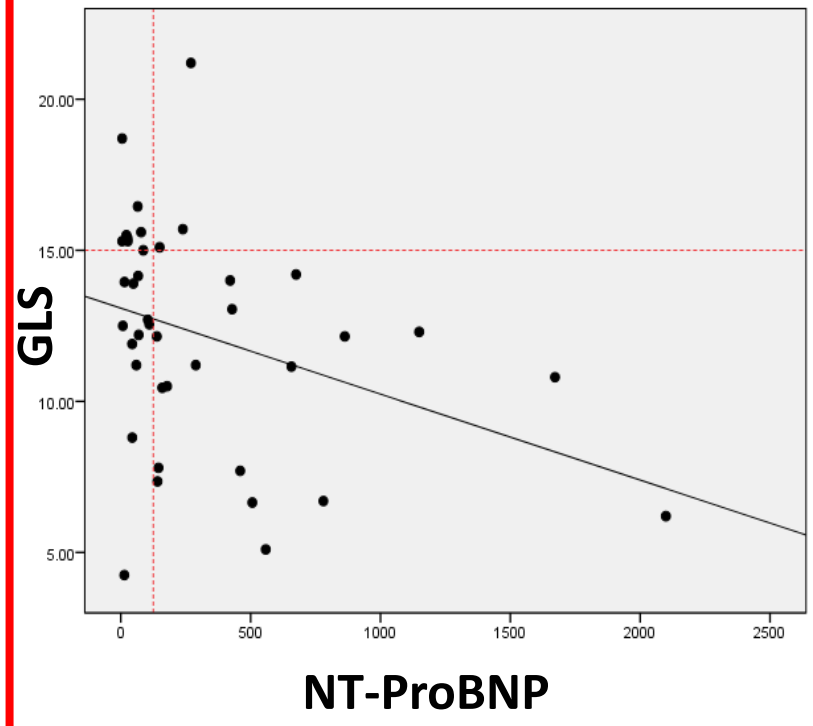
***-12.1*±-3.7**

[-15.9%- -22.1%]

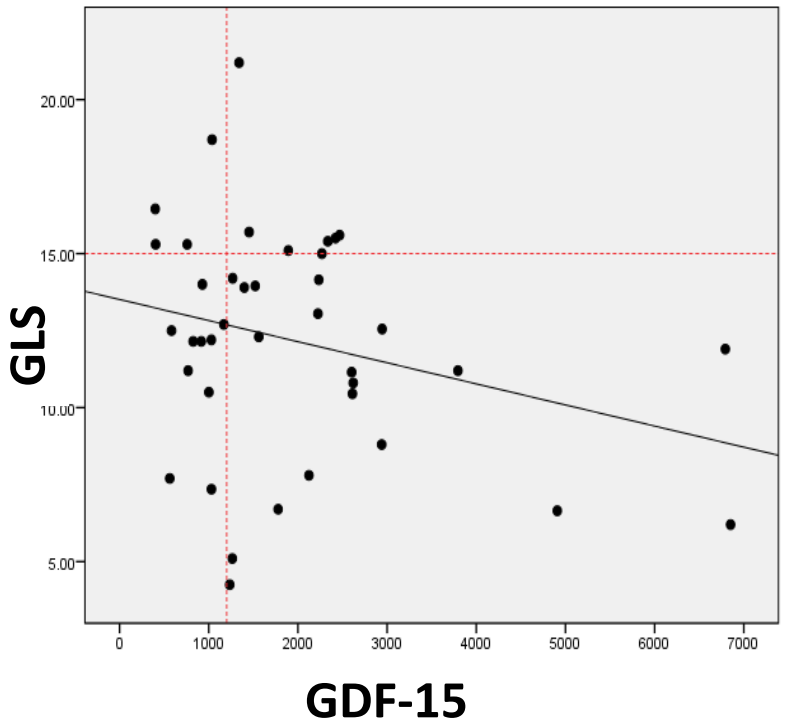
Relationship between GDF-15 and NT-proBNP levels



Relationship between GLS and NT-proBNP



Relationship between GLS and GDF-15



MODERATE CORRELATION: GDF-15 and NT-ProBNP, r= 0.41, *p*= 0.002*

WEAK CORRELATION: GLS and NT-ProBNP, r=-0.351, *p*= 0.026*

WEAK CORRELATION: GLS and GDF-15, r=-0.273, *p*= 0.044*

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Association of **NT-proBNP** level with demographic, clinical factors and imaging parameters

Variable	Correlation	P value

HFimpEF patients with higher NT-proBNP level are:

- older,
- lighter (kg),
- more symptomatic and
- higher MAGGIC score

HFimpEF patients with higher NT-proBNP level have more markers suggestive of diastolic dysfunction:

- Larger LA size
- More tricuspid regurgitation
- Higher tissue doppler (Average E/e')

Association of **GDF-15** level with demographic, clinical factors and imaging parameters

Variable	N, mean	P value

HFimpEF patients with higher GDF-15 level are:

- older
- higher MAGGIC score
- Systemic illness: DM, Hypertension
- More symptomatic (Higher NYHA)

HFimpEF patients with higher GDF-15 level have higher LV filling pressure:

- Higher tissue doppler (Average E/e’)

Association of **GLS** with demographic, clinical factors and imaging parameters

Variable		P value	Odds ration	CI 95%

No clinical characteristics or diastolic parameters are associated with GLS level in this cohort.

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All cause mortality

1.9%

(n=1)

HF events

3.8%

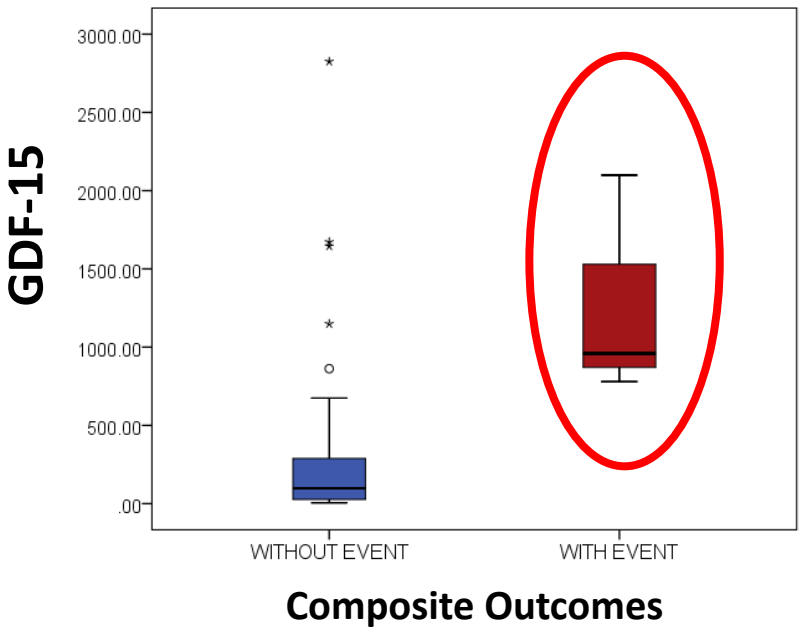
(n=2)

Composite outcomes

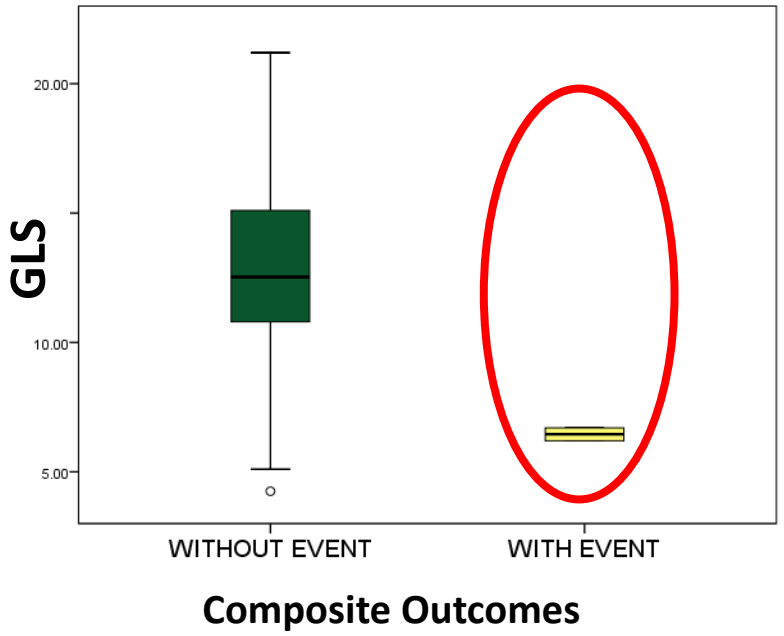
5.7%

(n=3)

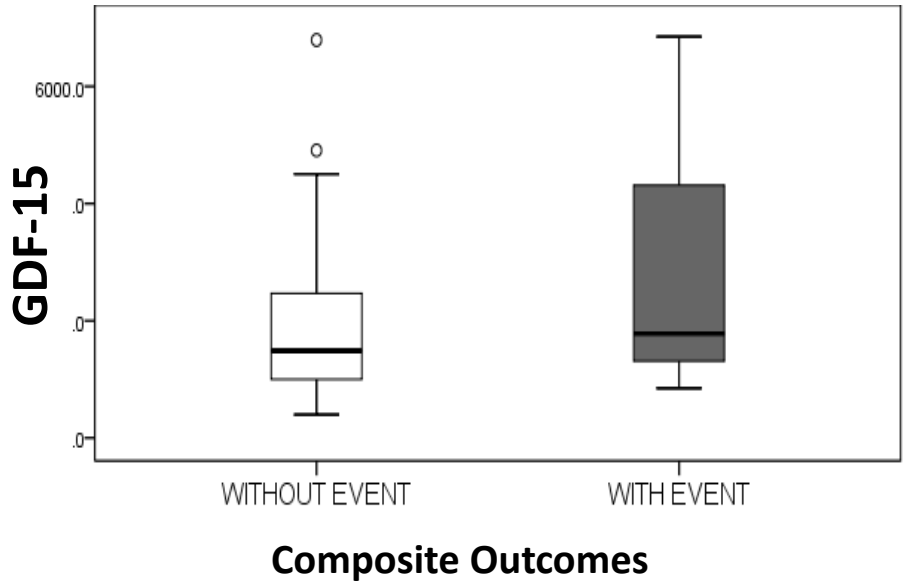
Association of NT-proBNP and composite outcomes



Association of GLS and composite outcomes



Association of GDF-15 and composite outcomes



NT-ProBNP and composite outcome, 301 vs 1279, p= 0.003*

GLS and composite outcome, -12.4 vs -6.4, p= 0.023*

GDF-15 and composite outcome, 1901 vs 3158, p= 0.571

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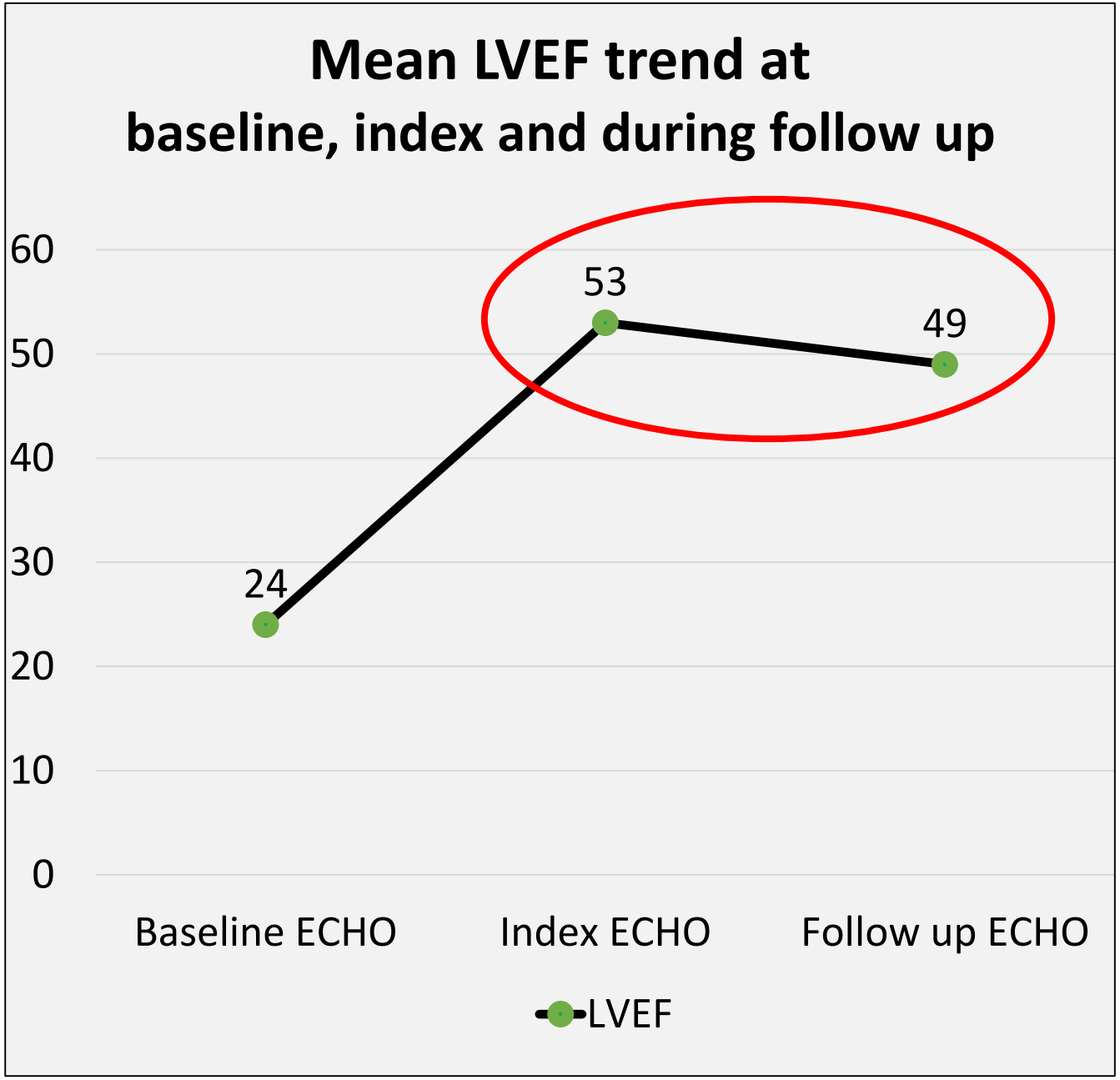


LVEF Deterioration

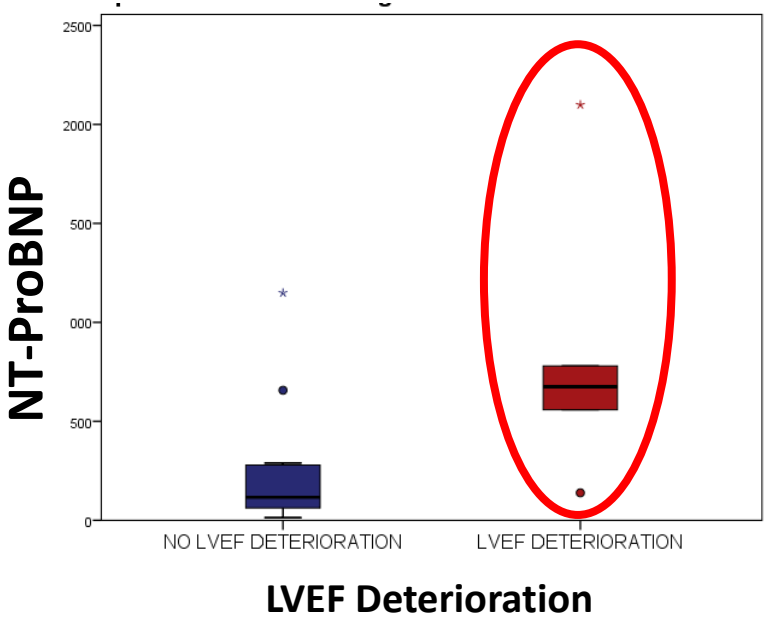
29%

(n=5)

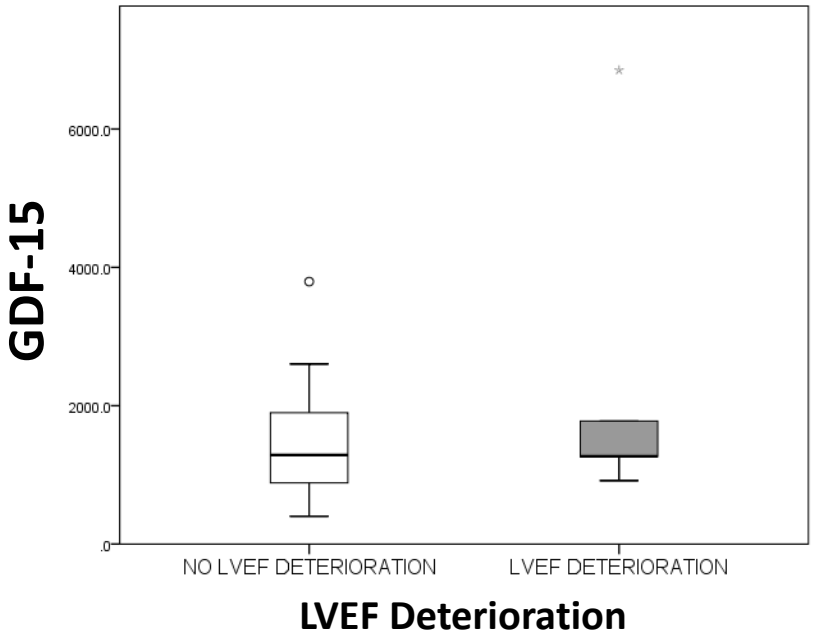
Follow up Echo

N=17

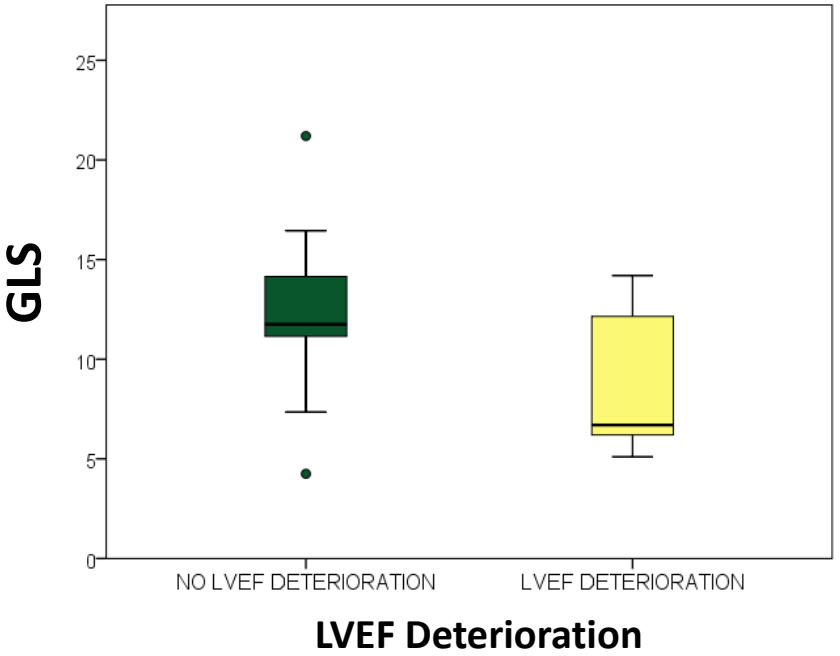
Association of NT-proBNP and LVEF deterioration



Association of GDF-15 and LVEF deterioration



Association of GLS and LVEF deterioration



NT-ProBNP and LVEF deterioration, 249 vs 850, *p*= 0.032*

GDF-15 and LVEF deterioration, 1493 vs 2415, *p*= 0.277

GLS and LVEF deterioration, -12.3 vs -8.87, *p*= 0.183

Conclusion

In our HFimpEF cohort:

1. NT-proBNP, GDF-15 levels and GLS can be abnormal.

2. Higher NT-proBNP and GDF-15 level are associated with more HF symptoms, presence of systemic illness and diastolic dysfunction.

3. Only NT-proBNP significantly predict adverse clinical outcomes at 1-year.

Limitations

1. Small sample size.

2. Single centre.

3. GLS performed using 2 views instead of 3.

Clinical relevance, application and insights

1. Beside Echo, NT-proBNP can be used to monitor patient in HF remission.

2. Appropriate cut-off levels of GDF-15 and GLS should be defined for risk stratification.

3. To investigate clinical relevance of paired GDF-15 samples and GLS level.

Thank You

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