Circulating growth differentiation factor-15 as a novel biomarker in heart transplant

Nithi Tokavanich¹, Supanee Sinphurmsukskul², Narisorn Kongruttanachok³, Kanokwan Thanmanatsakul², Supaporn Sritangsirikul², Aekarach Ariyachaipanich¹,², Pat Ongcharit⁴,⁵, Sarawut Siwamogsatham¹,⁶, Smonporn Boonyaratavej¹,⁴ and Sarinya Puwanant¹,²,⁴*

¹Division of Cardiovascular Medicine, Department of Medicine, Faculty of Medicine, Chulalongkorn University, 1873 Rama IV Rd, Pathumwan, Bangkok, 10330, Thailand; ²Excellent Center for Organ Transplantation, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand; ³Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; ⁴Cardiac Center, King Chulalongkorn Memorial Hospital, the Thai Red Cross Society, Bangkok, Thailand; ⁵Division of Cardiothoracic Surgery, Department of Surgery, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; ⁶Chula Clinical Research Center, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

Abstract

Aims This study aimed to examine (i) whether circulating growth differentiation factor-15 (GDF-15) is associated with acute cellular cardiac allograft rejection (ACR); (ii) a longitudinal trend of GDF-15 after heart transplantation; and (iii) the prognostic value of GDF-15 in predicting a composite outcome of severe primary graft dysfunction (PGD) and 30 day mortality post-transplant.

Methods and results Serum samples were collected before heart transplantation and at every endomyocardial biopsy (EMB) post-heart transplantation in de novo transplant patients. A total of 60 post-transplant serum samples were matched to the corresponding EMBs. Seven (12%) were considered International Society for Heart Lung Transplantation Grade 1R ACR, and one (2%) was identified as Grade 2R ACR. GDF-15 levels in patients with ACR were not different from those in the non-rejection group (6230 vs. 6125 pg/mL, P = 0.27). GDF-15 concentration gradually decreased from 8757 pg/mL pre-transplant to 5203 pg/mL at 4 weeks post-transplant. The composite adverse outcome of PGD and 30 day mortality was significantly associated with increased post-operative GDF-15 (odds ratio: 40; 95% confidence interval: 2.01–794.27; P = 0.005) and high inotrope score post-transplant (odds ratio: 18; 95% confidence interval: 1.22–250.35; P = 0.01).

Conclusions Circulating GDF-15 concentration was markedly elevated in patients with end-stage heart failure and decreased after heart transplantation. GDF-15 was significantly associated with post-transplant PGD and mortality. A lack of association between ACR and GDF-15 did not support routine use of GDF-15 as a biomarker to detect ACR. However, GDF-15 may be potentially useful to determine heart transplant recipients at high risk for adverse post-transplant outcomes. We suggest that GDF-15 levels in recipient serum can provide risk stratification for severe PGD including death during post-operative period. This novel biomarker may serve to inform and guide timely interventions against severe PGD and adverse outcomes during the first 4 weeks after transplantation. Further studies to support the utility of GDF-15 in heart transplantation are required.

Keywords Growth differentiation factor-15; Heart transplant; Primary graft dysfunction; Biomarker; Outcomes

Introduction

Growth differentiation factor-15 (GDF-15) is a novel biomarker responsible for tissue injury, inflammation, and cellular stress.¹⁻⁵ The expression of the GDF-15 is enhanced in inflammatory conditions, malignant tissue, chronic kidney disease, aging, organ dysfunction, and metabolic diseases including obesity and diabetes mellitus.⁶⁻¹² A growing body of evidence has demonstrated that GDF-15 is a promising prognostic biomarker in patients with heart failure and various cardiovascular diseases.⁴,¹³⁻¹⁶ Elevated GDF-15 levels have been found predictive of cardiovascular events in...
Women with atherosclerosis. Circulating levels of GDF-15 in patients with heart failure or ventricular dysfunction have been found to increase with heart failure severity. As myocardial inflammation is a hallmark feature of acute cellular cardiac allograft rejection (ACR), the use of a biomarker associated with tissue inflammation has been proposed. Previous studies failed to indicate the clinical use of biomarkers including natriuretic peptide, soluble ST2, procalcitonin, interferon-α, interleukin, and troponin, to detect ACR or to predict post-transplant outcomes. Whether GDF-15 is associated with ACR or clinical outcomes after heart transplantation has not yet been studied. This study aimed to fill this gap by examining three areas: (i) whether GDF-15 is associated with ACR, (ii) a longitudinal trend of the levels of GDF-15 after heart transplantation, and (iii) the prognostic value of GDF-15 in predicting a composite outcome composed of severe primary graft dysfunction (PGD) and 30 day mortality post-transplant.

Methods

Patients

The study population enrolled de novo transplant recipients undergoing heart transplantation from February 2019 to February 2020. The study protocol was approved by the Chulalongkorn University Institutional Review Board. All patients provided written informed consent.

Serum sample collection and growth differentiation factor-15 measurements

Serum samples were collected before heart transplantation and at every endomyocardial biopsy (EMB) at Weeks 1, 2, 3, and 4 post-transplant. Serum samples were taken from the vascular access prior to administration of anaesthesia in patients undergoing heart transplantation and prior to EMBs in transplant recipients. The samples were processed immediately and stored at −70°C. GDF-15 concentrations were analysed by electrochemiluminescence immunoassay using Elecsys® assay (Roche Diagnostics, Germany), measuring 400–50 000 pg/ml (ng/L). All analyses were conducted in once. The assay has an intra-assay coefficient of variation of 0.99% at 1410 pg/ml and an inter-assay coefficient of variation of 1.2% at 1410 pg/ml and 0.97% at 6800 pg/ml.

Endomyocardial biopsies

Using a standard protocol, EMBs were obtained at multiple times post-transplant (Weeks 1, 2, 3, and 4). Pathological analysis for ACR was performed in accordance with the International Society for Heart Lung Transplantation 2005 working formulation: (i) Grade 0R: no rejection; (ii) Grade 1R: an infiltrate without or with only one focus of myocyte damage; (iii) Grade 2R: an infiltrate with multifocal myocyte damage; and (iv) Grade 3R: diffuse myocyte damage with or without oedema, haemorrhage, or vasculitis. Post-transplant serum samples were matched with EMBs.

Clinical outcomes

Patients were clinically managed by the standard of post-heart transplant care. The primary endpoint included a composite outcome composed of severe PGD and 30 day mortality post-transplant. Severe PGD-left ventricle (LV) was defined as post-transplant LV ejection fraction (EF) ≤ 40% or haemodynamics with right atrial pressure (RAP) > 15 mmHg, pulmonary capillary wedge pressure (PCWP) > 20 mmHg, and cardiac index < 2.0 L/min/m² requiring mechanical circulatory support (MCS), excluding intra-aortic balloon pump, as previously described in the International Society for Heart Lung Transplantation report from a consensus conference on PGD after cardiac transplantation.

Statistical analyses

Continuous variables are presented as median and range or mean and standard deviation. Categorical variables are presented as frequency and percentage. Comparisons of continuous variables were tested using a Student’s t-test for normally distributed continuous data and a Wilcoxon rank-sum test for non-normally distributed continuous data. Comparisons of categorical variables between patients with and without ACR or adverse outcomes were tested using a χ² test or Fisher’s exact test, where appropriate. Univariate logistic regression was employed to identify the predictors of the composite events. Due to the small number of composite outcomes, a multivariate analysis was not performed. The original sample size was estimated based on the prevalence of ACR in our centre. P-values of <0.05 were considered significant.

Results

Characteristics of transplant patients and collection of samples

The baseline characteristics of the patients enrolled in this study are shown in Table 1. During the study period, serum samples were obtained and matched to their EMBs. A total of 60 serum samples for GDF-15 measurements were collected from 15 de novo transplant recipients who
underwent clinically indicated or routine EMBs during the study period. These serum samples were matched to the EMBs and included in the study.

**Post-transplant growth differentiation factor-15 and acute cellular cardiac allograft rejection**

Growth differentiation factor-15 was detected in all post-transplant samples at a mean concentration of 6218 pg/mL. Of 60 EMBs, seven (12%) were considered Grade 1R ACR, and one (2%) was identified as Grade 2R ACR. The GDF-15 concentration in the ACR group was not different from the non-ACR group (6230 vs. 6125 pg/mL, \( P = 0.27 \)).

**Longitudinal trends of growth differentiation factor-15 after explanting the failing hearts**

In pre-operative serum samples, the mean GDF-15 concentration prior to heart transplant was high at 8757 pg/mL. GDF-15 concentration gradually decreased over time with each subsequent biopsy. GDF-15 levels decreased from the first week (mean 7238 pg/mL) to the nadir (mean 5203 pg/mL) at 4 weeks post-transplant (Figure 1A).

**Prognostic power of growth differentiation factor-15 in post-transplant adverse outcomes**

At 30 days post-transplant, six of the 15 de novo heart transplant recipients (40%) met the composite of severe PGD (\( n = 5 \)) and 30 day mortality (\( n = 1 \)). Post-transplant GDF-15 concentrations were significantly higher in patients who had severe PGD or died at 30 days post-transplant than those without events (pre-transplant Week 0 (13 032 vs. 2344 pg/mL; \( P = 0.08 \)), post-transplant Week 1 (14 301 vs. 2530 pg/mL; \( P = 0.025 \)), Week 2 (15 538 vs. 1651 pg/mL; \( P = 0.034 \)), Week 3 (10 394 vs. 1778 pg/mL; \( P = 0.025 \)), Week 4 (9914 vs. 2062; \( P = 0.045 \)), and overall post-transplant (12 537 vs. 2025 pg/mL; \( P = 0.025 \)) (Figure 1B). The cut-off for post-transplant GDF-15 at 4208 pg/mL had a sensitivity of 83% and a specificity of 100% for predicting the composite adverse outcome. This equates to an area under the receiver operating characteristic curve of 0.85 [95% confidence interval (CI) 0.66–1.0]. Factors associated with a composite of severe PGD or death at 30 days post-transplant included post-transplant high inotrope score (odds ratio: 18; 95% CI: 1.22–250.35; \( P = 0.01 \)). Increased GDF-15 post-transplant was associated with an increase in a composite adverse outcome (odds ratio: 40; 95% CI: 2.01–794.27; \( P = 0.005 \)).

**Discussion**

This study examined changes in GDF-15 levels among patients with end-stage heart failure and post-heart transplantation. Key findings of our study are as follows: (i) GDF-15 concentration was not associated with ACR; (ii) GDF-15 levels decreased over time in the first month after heart transplantation; and (iii) high levels of post-transplant GDF-15 were significantly associated with adverse outcomes (severe PGD or 30 day mortality).

**Growth differentiation factor-15 and acute cellular cardiac allograft rejection**

Although GDF-15 is a biomarker of the inflammatory process, the association between GDF-15 and ACR remains speculative as the incidence of significant (≥2R) ACR was lower than anticipated rejection rates in this study. GDF-15 activation may involve other pathways of inflammation including myocyte wall stress, cell injury, or apoptosis. These results do not provide any support for the clinical use of GDF-15 as a biomarker to detect ACR. The results of previous studies examining the relationship of biomarkers and ACR have been conflicting. Patel et al. studied the role of high-sensitivity cardiac troponin I to screen for ACR in 98 heart transplant recipients. The authors found that using a cut-off 15 ng/L produced a sensitivity of 94% and a specificity of 60% in detecting Grade 2R ACR or higher. The authors concluded that a high-sensitivity troponin I may play an important role to rule out ACR, although additional studies are needed to validate this finding. Other studies have failed to demonstrate the usefulness of biomarkers, including high-sensitivity troponin T assay, B-type natriuretic peptide, soluble ST2, and troponin T and I in the clinical detection of ACR. Agbor-Enoh et al. recently demonstrated that a novel non-invasive genomic blood test or per cent donor-derived cell-free DNA can detect ACR with a high area under the curve of 0.92 and a negative predictive value of 99% in 171 cardiac transplant recipients. Their findings highlight the promising path for clinical utility of ACR detection and may minimize a need for EMB.

**Growth differentiation factor-15 after heart transplantation**

Cardiac transplant replaces the dysfunctional failing heart and restores normal haemodynamics. Findings from our study support cardiac haemodynamic restoration to be associated with a decrease in GDF-15 concentration. This association is compatible with the knowledge that surgical stress, myocardial injury, and the inflammatory response begin to decrease after transplant.
biomarkers, Kimball et al. have demonstrated that interleukin-6 decreased to a normal range within 3 weeks after heart transplantation. A recent study by Nykänen et al. showed that donor-derived cell-free DNA levels decayed after surgery by Day 28. Boilson et al. also found evidence that migration of recipient cells into donor myocardium resulted in decreased inflammatory responses, reduced oedema, and LV dysfunction over time after transplantation. These findings are consistent with our observation of a decrease in GDF-15 during the first 4 weeks after heart transplantation.

**Growth differentiation factor-15 and post-transplant adverse outcomes**

We observed that a much higher post-transplant GDF-15 concentration was found in patients with adverse post-transplant outcomes, including severe PGD and 30 day mortality. Our findings are in stark contrast with the study by Starling et al. that analysed immune biomarkers and heart transplant outcomes in a cohort of 200 primary heart transplant recipients at 12 US transplant centres. They concluded that there was no relationship between immune biomarkers and a composite index of death, graft loss, ACR, and cardiac allograft vasculopathy at 6–8 weeks after transplantation.

**Table 1 Baseline clinical and biochemical characteristics**

|                          | De novo transplant recipients (n = 15) | Patients with composite events (n = 6) | Patients with no composite events (n = 9) | P-valuea |
|--------------------------|--------------------------------------|----------------------------------------|------------------------------------------|----------|
| **Recipient characteristics** |                                       |                                        |                                          |          |
| Age (years)              | 39 ± 15                               | 38 ± 17                                | 41 ± 15                                  | 0.813    |
| Male, n (%)              | 14 (93)                               | 5 (83)                                 | 9 (100)                                  | 0.205    |
| Pre-transplant ischaemic aetiology, n (%) | 4 (27)                              | 2 (33)                                 | 2 (22)                                   | 0.634    |
| Diabetes, n (%)          | 1 (7)                                 | 0                                      | 1 (11)                                   | 0.398    |
| Stroke, n (%)            | 1 (7)                                 | 1 (11)                                 | 0                                        | 0.205    |
| Pre-transplant anaemia, n (%) | 6 (40)                              | 2 (33)                                 | 4 (44)                                   | 0.667    |
| Pre-transplant hepatopathy, n (%) | 8 (53)                              | 5 (83)                                 | 3 (33)                                   | 0.060    |
| Pre-transplant systolic blood pressure (mmHg) | 95 ± 12                              | 91 ± 8                                 | 100 ± 14                                 | 0.260    |
| **Pre-transplant haemodynamics** |                                       |                                        |                                          |          |
| PVR (WU)                 | 3.4 ± 1.8                             | 3.5 ± 2.5                              | 3.3 ± 1.4                                 | 0.723    |
| PASP (mmHg)              | 48 ± 14                               | 51 ± 12                                | 47 ± 15                                  | 0.516    |
| PADP (mmHg)              | 23 ± 9                                | 26 ± 10                                | 22 ± 8                                   | 0.409    |
| PCWP (mmHg)              | 23 ± 7                                | 26 ± 6                                 | 21 ± 7                                   | 0.133    |
| CVP (mmHg)               | 12 ± 6                                | 14 ± 3                                 | 11 ± 7                                   | 0.138    |
| Cardiac index (L/min/m²) | 2.28 ± 0.61                           | 2.16 ± 0.55                            | 2.34 ± 0.66                              | 0.463    |
| Pulmonary arterial oxygen saturation (%) | 66.1 ± 8.1                           | 62.8 ± 8.0                             | 68.0 ± 8.0                               | 0.205    |
| Pre-transplant BUN (mg/dL) | 30 ± 13                              | 39 ± 9                                 | 24 ± 12                                  | 0.034*   |
| Pre-transplant Cr (mg/dL) | 1.2 ± 0.4                             | 1.42 ± 0.53                            | 1.03 ± 0.28                              | 0.195    |
| Pre-transplant serum sodium (mEq/L) | 135 ± 5                              | 136 ± 6                                | 134 ± 4                                  | 0.592    |
| Pre-transplant LVEF (%)  | 22 ± 8                                | 25 ± 7                                 | 20 ± 9                                   | 0.110    |
| Pre-transplant mechanical circulatory support, n (%) | 2 (13)                              | 2 (33)                                 | 0                                        | 0.143    |
| Pre-transplant INTERMACS | 4.3 ± 1.2                             | 4.1 ± 1.5                              | 4.3 ± 1.0                                | 0.900    |
| Waiting time on waiting list (days) | 66 ± 87                             | 50 ± 63                                | 77 ± 101                                 | 0.593    |
| **Donor characteristics** |                                       |                                        |                                          |          |
| Age (years)              | 27 ± 10                               | 27 ± 10                                | 28 ± 10                                  | 0.859    |
| Male, n (%)              | 15 (100)                              | 6 (100)                                | 9 (100)                                  | N/A      |
| **Operative characteristics** |                                       |                                        |                                          |          |
| Ischaemic time (min)     | 235 ± 51                              | 251 ± 30                               | 224 ± 60                                 | 0.479    |
| **Post-operative conditions** |                                       |                                        |                                          |          |
| Maximal inotrope scoreb | 106 ± 68                              | 165 ± 62                               | 67 ± 37                                  | 0.009*   |
| Pre-transplant Cr (mg/dL) | 1.35 ± 0.93                           | 1.89 ± 1.21                            | 0.99 ± 0.49                              | 0.113    |
| Serum lactate (mmol/L)   | 2.4 ± 2.7                             | 3.6 ± 3.7                              | 1.7 ± 1.6                                | 0.342    |
| **Immunosuppressive therapy at hospital discharge** |                                       |                                        |                                          |          |
| FK 506                   | 12 (80)                               | 4 (67)                                 | 8 (89)                                   | 0.292    |
| Cyclosporin              | 3 (20)                                | 2 (33)                                 | 1 (11)                                   | 0.292    |
| MMF                      | 15 (100)                              | 6 (100)                                | 9 (100)                                  | N/A      |
| Everolimus               | 1 (6)                                 | 1 (17)                                 | 0                                        | 0.205    |
| Prednisolone             | 15 (100)                              | 6 (100)                                | 9 (100)                                  | N/A      |

**Notes:**
- BUN, blood urea nitrogen; Cr, creatinine; CVP, central venous pressure; FK 506, Tacrolimus; LVEF, left ventricular ejection fraction; MMF, mycophenolate mofetil; N/A, not applicable; PADP, pulmonary artery diastolic pressure; PASP, pulmonary artery systolic pressure; PCWP, pulmonary artery capillary wedge pressure; PVR, pulmonary vascular resistance.
- Data are presented as n (%) or mean ± standard deviation.
- P-value was comparing the data between patients with and without composite events.
- Inotrope score: dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) with each drug dosed in mcg/kg/min. Adapted from Iyer et al. *p* < 0.05
post-transplant. Their study did not include GDF-15. Elevated post-transplant GDF-15 in severe PGD may involve a similar pathophysiology as described in heart failure, including pressure overloading, oxidative stress, myocyte injury, and/or end-organ dysfunction. Donor characteristics, catecholamine associated with brain lesions, inotropic drugs, and cardiac preservation may also play important roles in the pathophysiology of PGD. Elevated tumour necrosis factor-α, interleukin-6, neutrophils, procalcitonin, troponin assay, and natriuretic peptides in cardiac donors have been described as potential predictors of PGD. However, little is known about the roles of these biomarkers obtained in cardiac transplant recipient serum samples in association with PGD. The predictive value of GDF-15 may be useful in determining transplant recipients at high risk of early cardiac allograft dysfunction and/or end-organ dysfunction. As GDF-15 levels gradually declined post-transplant, increases in GDF-15 levels occurred among recipients experiencing severe adverse outcomes. Repeated GDF-15 determinations during the first 4 weeks can play a potential role in rapidly identifying patients at risk. Those patients should have intensive peri-operative and post-operative monitoring and timely intervention, including initiation of MCS therapy for PGD when indicated. While the previous studies have shown that pre-operative classical biomarkers in donor serum can predict PGD, the advantage of GDF-15 is that GDF-15 levels in recipient serum can provide risk stratification for severe PGD including death during the post-operative Weeks 1 to 4 period. The risk stratification characteristics of this novel biomarker can serve to inform and guide timely therapeutic interventions against severe PGD and adverse clinical outcomes. Additionally, a combination of biomarkers may be more effective than individual biomarker in identifying heart transplant recipients at risk of developing severe PGD as different biomarkers are involved in different mechanisms that may develop into severe PGD. Further studies to establish the clinical utility of GDF-15 or the best set of biomarkers in heart transplantation are required.

Study limitations

The small sample in our study reduced the ability to identify additional factors at play especially moderate or small differences, which could be important. Adverse outcomes occurred in only six recipients, which is generally too small to draw firm conclusions, and follow-up was limited to 4 weeks post-transplant. Another limitation of our study was the lower than anticipated rate of Grade ≥2R ACR leading to reduced ability to find statistically significant differences between ACR and GDF-15. Our study also enrolled only one female, which may influence levels of GDF-15. Further studies with a broader gender recruitment, a larger number of serum samples in de novo recipients, and a longer follow-up period in post-heart transplant are required.

Conclusions

This paper presents findings from the first study to examine the role of GDF-15 in heart transplantation. Our results did not find an association between GDF-15 and ACR. GDF-15 levels declined precipitously during each of the 4 weeks post-transplant. Elevated post-transplant GDF-15
concentrations were found strongly associated with a 40 times odds increase in severe PGD including death. Although our findings do not support the clinical use of GDF-15 as a biomarker to detect ACR, GDF-15 may be potentially useful to identify heart transplant recipients at increased risk of adverse outcomes. We suggest that GDF-15 can provide risk stratification for severe PGD including death in recipients during post-operative period. This novel biomarker may serve to inform and guide timely interventions against severer PGD and adverse clinical outcomes during the first 4 weeks after transplantation. Our findings highlight the need for further studies to explore the value of GDF-15 in improving heart transplantation outcomes.

Acknowledgements

We thank Prof. Stephen Kerr, Ph.D., for his assistance with the statistical analysis and insightful advice. We also thank the research team of the Department of Medicine, Faculty of Medicine, Chulalongkorn University, for editing the final manuscript.

Conflict of interest

None declared (for all co-authors).

Funding

This research was supported by the Ratchadapisek Somphot Endowment Fund (2019), Chulalongkorn University (Grant No. RA 62/082).

References

1. Emmerson PJ, Duffin KL, Chimtharlapalli S, Wu X. GDF15 and growth control. Front Physiol 2018; 9: 1712.
2. Lindahl B. The story of growth differentiation factor 15: another piece of the puzzle. Clin Chem 2013; 59: 1500–1502.
3. Kempf T, Zarbock A, Widera C, Butz S, Stadtmann A, Rossaint J, Bolomini-Vittori M, Korf-Klingebiel M, Napp LC, Hansen B, Kanwischer A, Bavendiek U, Beutel G, Hapke M, Sauer MG, Laußanna C, Hogg N, Vestweber D, Wollert KC. GDF-15 is an inhibitor of leukocyte integrin activation required for survival after myocardial infarction in mice. Nat Med 2011; 17: 581–588.
4. Vocka M, Langer D, Fryba V, Petryl J, Hanus T, Kaloussova M, Zima T, Petruzelka L. Growth/differentiation factor 15 (GDF-15) as a potential serum marker in patients with metastatic colorectal cancer. Canc Biomarkers 2018; 21: 869–874.
5. Ratnam NM, Peterson JM, Talbert EE, Ladner KJ, Rajasekera PV, Schmidt CR, Dhilloff ME, Swanson BJ, Haverick E, Kladney RD, Williams TM, Leone GW, Wang DJ, Gudttridge DC. NF-kB regulates GDF-15 to suppress macrophage surveillance during early tumor development. J Clin Invest 2017; 127: 3796–3809.
6. Adela R, Banerjee SK. GDF-15 as a target and biomarker for diabetes and cardiovascular diseases: a translational prospective. J Diabetes Res 2015; 2015: 490842.
7. Nair V, Robinson-Cohen C, Smith MR, Bellovich KA, Bhat ZY, Bobadilla M, Brosius F, de Boer JH, Essioux L, Formentini I, Gadebeku CA, Gipsion D, Hawkins J, Himmelfarb J, Kestenbaum B, Kretzler M, Magnone MC, Perumal K, Steigerwalt S, Ju W, Bansal N. Growth differentiation factor-15 and risk of CKD progression. J Am Soc Nephrol 2017; 28: 2233–2240.
8. Benes J, Kotrc M, Wohlfarth P, Conrad S, Nair V, Robinson-Cohen C, Smith MR, Wu X. GDF15 and growth control. J Diabetes Res 2015: 2018; 2015: 93.
9. Schernthaner-Reiter MH, Kasses D, Heyl JM, Scherdel MA, Leppert J, Henriksen E. Growth differentiation factor-15 in a community-based sample: age-dependent reference limits and biomarker for diabetes and cardiovascular disease. Clin Chem Lab Med 2013; 51: 35–40.
10. Tran T, Yang J, Gardner J, Xiong Y. Utility of growth differentiation factor-15, a marker of oxidative stress and inflammation, for risk assessment in patients with atrial fibrillation: insights from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial. Circulation 2014; 130: 1847–1858.
11. George M, Jena A, Srivatsan V, Muthukumar R, Dhandapany VE. GDF-15—a novel biomarker in the offering for heart failure. Curr Cardiol Rev 2016; 12: 37–46.
12. Sharmar A, Stevens SR, Lucas J, Fiuza M, Adams K, Whellan DJ, Donahue MP, Kitzman DW, Piña Il, Zannad F, Kraus WE, O’Connor CM, Felker GM. Utility of growth differentiation factor-15, a marker of oxidative stress and inflammation, in chronic heart failure: insights from the HF-ACTION study. JACC Heart Fail 2017; 5: 724–734.
13. Rohatgi A, Patel P, Das SR, Ayers CR, Khera A, Martinez-Rumayor A, Berry JD, McGuire DK, de Lemos JA. Association of growth differentiation factor-15 with coronary atherosclerosis and mortality in a young, multiethnic population: observations from the Dallas Heart Study. Clin Chem 2012; 58: 172–182.
14. Gohar A, Gonzalves I, Vrijhoek J, Haitjema S, van Koeverden I, Nilsson J, de Borst G, de Vries J, Pasterkamp G, den Ruiter HM, Björkbacka H, de Jager SC. Circulating GDF-15 levels predict future secondary manifestations of cardiovascular disease explicitly in women.
but not men with atherosclerosis. *Int J Cardiol* 2017; 241: 430–436.
18. Rullman E, Melin M, Mandic M, Gonon A, Fernandez-Gonzalo R, Gustafsson T. Circulatory factors associated with function and prognosis in patients with severe heart failure. *Clin Res Cardiol* 2020; 109: 655–672.
19. Dengler TJ, Gleissner CA, Klingenberg R, Sack F-U, Schnabel PA, Katus HA. Biomarkers after heart transplantation: nongenomic. *Heart Fail Clin* 2007; 3: 69–81.
20. Starling RC, Stehlik J, Baran DA, Armstrong B, Stone JR, Ikle D, Morrison Y, Bridges ND, Putheti P, Strom TB, Bhasin M, Guleria I, Chandraker A, Sayegh M, Daly KP, Briscoe DM, Heeger PS, the CTOT-05 consortium. Multicenter analysis of immune biomarkers and heart transplant outcomes: results of the Clinical Trials in Organ Transplantation-05 study. *Am J Transplant* 2016; 16: 121–136.
21. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, Andersen CB, Angelini A, Berry GJ, Luu M, Mancini D, Patel J, Razi R, Macdonald P, Leprince P, Esmailian F, Armstrong B, Stone JR, Ikle D, Morrison PS, the CTOT-05 consortium. Multicenter analysis of immune biomarkers and heart transplant outcomes: results of the Clinical Trials in Organ Transplantation-05 study. *Am J Transplant* 2016; 16: 121–136.
22. Kobashigawa J, Zuckermann A, Macdonald P, Leprince P, Esmailian F, Lai M, Mancini D, Patel J, Razi R, Reichenspurner H, Russell S, Segovia J, Smedira N, Stehlik J, Wagner F, Consensus Conference participants. Report from a consensus conference on primary graft dysfunction after heart transplantation. *J Heart Lung Transplant* 2014; 33: 327–340.
23. Kittiipibul V, Tantrachoti P, Onghcharit P, Aryachapanich A, Siwanomsagatham S, Sritangsirikul S, Thammanatsakul K, Puwanasant S. Low-dose basiliximab induction therapy in heart transplantation. *Clin Transplant* 2017; 31: e13132.
24. Iyer A, Kumarasinghe G, Hicks M, Watson A, Gao L, Doyle A, Keogh A, Kotlyar E, Hayward C, Dhilat K, Granger E, Jansz P, Pye R, Spratt P, Macdonald PS. Primary graft failure after heart transplantation. *J Transplant* 2011; 2011: 175768.
25. BENZIMRA M, CALLIGARO GL, GLANVILLE AR. Acute rejection. *J Thorac Dis* 2017; 9: 5440–5457.
26. Subberwal S, Kobashigawa JA, Cogert G, Patel J, Espejo M, Oser B. Incidence of acute cellular rejection and non-cellular rejection in cardiac transplantation. *Transplant Proc* 2004; 36: 3171–3172.
27. Patel PC, Hill DA, Ayers CR, Lavingia B, Kaiser P, Dyer AK, Barnes AP, Thibodeau JT, Mishkind JD, Mammen PPA, Markham DW, Stastny P, Rin W, de Lemos JA, Drazner MH. High-sensitivity cardiac troponin I assay to screen for acute rejection in patients with heart transplant. *Circ Heart Fail* 2014; 7: 463–469.
28. Muñoz-Esparza C, Garrido IP, Blanco R, Casas T, González-Cánovas C, Pastor-Pérez F, Pena F, Minguela A, Valdés M, Pascual-Pigal DA. Usefulness of high sensitivity troponin I assay in detecting acute allograft rejection after heart transplantation. *Rev Esp Cardiol* 2011; 64: 1109–1113.
29. Bader PM, Rogers RK, Kfoury AG, Gilbert EM, Horne BD, Stehlik J, Renlund DG. Time-dependent changes in B-type natriuretic peptide after heart transplantation: correlation with allograft rejection and function. *Congest Heart Fail* 2009; 15: 63–67.
30. Lee GY, Choi JD, Ju ES, Lee YJ, Jeon ES. Role of soluble ST2 as a marker for rejection after heart transplantation. *J Heart Lung Transplant* 2016; 46: 811–820.
31. Mullen JC, Bentley MJ, Scherr KD, Chorney SG, Burton NJ, Tymchak WJ, Koshal A, Modry DL. Troponin T and I are not reliable markers of cardiac transplant rejection. *Eur J Cardiothorac Surg* 2002; 22: 233–237.
32. Agbor-Enoh S, Shah P, Tunc I, Hsu S, Russell S, Feller E, Shah K, Rodrigo ME, Najjar SS, Kong H, Pirooznia M, Fidelis U, Bikineyeva A, Marishta A, Bhatti K, Yang Y, Muteli C, Yu K, Ryoo Jang M, Marboe C, Berry GJ, Valantine HA, For the GRAFT Investigators. Cell-free DNA to detect heart allograft acute rejection. *Circulation* 2021; 143: 1184–1197.
33. Lok SI, Winkens B, Goldschmeding R, van Geffen AJP, Nous FMA, van Kuijk J, van der Weide P, Klöpping C, Kerkels JH, Lahpor JR, Doevendans PA, de Jonge N, de Weger RA. Circulating growth differentiation factor-15 correlates with myocardial fibrosis in patients with non-ischaemic dilated cardiomyopathy and decreases rapidly after left ventricular assist device support. *Eur J Heart Fail* 2012; 14: 1249–1256.
34. Kimball PM, Radovancic B, Isom T, Spickard A, Frazier OH. The paradox of cytokine monitoring-predictor of immunologic activity as well as immunologic silence following cardiac transplantation. *Transplantation* 1996; 61: 909–915.
35. Nykänen AJ, Holmström EJ, Tuuminen R, Krebs R, Dhaygude K, Kankainen M, Jokinen JJ, Lommi J, Helanterä I, Räisänen-Sokolowski A, Syrjälä SO, Lemström KB. Donor simvastatin treatment in heart transplantation. *Circulation* 2019; 140: 627–640.
36. Boilson BA, McGregor CGA, Kushwaha SS. Pathophysiological changes after cardiac transplantation: the role of chronic inflammation and rejection. *Heart (British Cardiac Soc)* 2011; 97: 1634–1635.
37. Boccheiame N, Audibert G, Rangeard O, Charpentier C, Perrier JF, Lalot JM, Voltz C, Strub P, Loos-Ayav C, Meistelman C, Mertes PM, Longoïs D. Serum troponin Ic values in organ donors are related to donor myocardial dysfunction but not to graft dysfunction or rejection in the recipients. *Int J Cardiol* 2009; 133: 80–86.
38. Potapov EV, Wagner PD, Loeb M, Ivanitskia EA, Müller C, Sodian R, Jonitz B, Hetzer R. Elevated donor cardiac troponin T and procalcitonin indicate two independent mechanisms of early graft failure after heart transplantation. *Int J Cardiol* 2003; 92: 163–167.
39. Ostovaneh MR, Moazzami K, Yoneyama K, Venkatesh B, Heckbert SR, Wu CO, Shea S, Post WS, Fitzpatrick AL, Burke GL, Bahrami H, Sanchez OA, Daniels LB, Michos ED, Bluemke DA, Lima JC. Change in NT-proBNP (N-terminal pro-B-type natriuretic peptide) level and risk of dementia in Multi-Ethnic Study of Atherosclerosis (MESA). *Hypertension* 2020; 75: 316–323.
40. Venkateswaran RV, Dronavalli V, Lambart PA, Steeds RP, Wilson IC, Thompson RD, Mascaro JG, Bonser RS. The proinflammatory environment in potential heart and lung donors: prevalence and impact of donor management and hormonal therapy. *Transplantation* 2009; 88: 582–588.