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Research Letter In-Press Preview **Clinical Research** **Vascular biology**

GDF15 is a Putative Biomarker for Distinguishing Pulmonary Veno-Occlusive Disease and Pulmonary Arterial Hypertension

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Therapeutics. M.A.S. is consulting with Merck, Janssen Pharmaceuticals, Aerovate Therapeutics, and Gossamer Bio. A.P., G.L., and A.H. filed related intellectual property.

To the Editor: Pulmonary veno-occlusive disease (PVOD) is a rare, severe Group 1 pulmonary arterial hypertension (PAH) subtype with poor survival (1). PAH-targeted vasodilators can cause life-threatening pulmonary edema in PVOD, underscoring the need for diagnostic tools to distinguish it from other PAH subtypes (1). In patients and mitomycin C (MMC)-induced model animals, aberrant activation of integrated stress response (ISR) via Protein Kinase R (PKR) drives cardiovascular phenotypes of PVOD (2-4). Inhibition of the PKR-ISR axis, using either the PKR inhibitor C16 or the ISR inhibitor ISRIB, reverses PVOD phenotypes (2-4). Because GDF15 is a cytokine induced by the ISR (5), we compared plasma GDF15 levels in rat models of PVOD and PAH to evaluate its potential as a biomarker. Upon MMC treatment, GDF15 mRNA and plasma protein levels increased (**Supplementary Figure 1A**), which was reversed with ISRIB treatment (6) (**Supplementary Figure 1B**). Plasma GDF15 levels were 2.2-fold higher in PVOD model rats compared to those in monocrotaline (MCT)-induced PAH model rats (**Supplementary Figure 1C**), suggesting a potential distinction in circulating GDF15 levels between PVOD and other PAH subtypes.

Plasma GDF15 concentrations in patients with PVOD, idiopathic PAH (IPAH), heritable PAH (HPAH), Group 2-4 PH (Other PH), chronic obstructive pulmonary disease without PH (COPD), and healthy controls (Ctrl) were quantified (**Figure 1A**). The median GDF15 level in PVOD was 12.4-, 3.0-, 2.4-, 2.1-, and 2.4-fold higher than in Ctrl, IPAH, HPAH, Other PH, and COPD, respectively (**Figure 1A**). No significant sex-dependent differences in GDF15 were observed (**Supplementary Figure 2A**). ROC analysis showed that PVOD had the highest AUC among all cohorts with both sensitivity

and specificity of 100% (**Figure 1B**), whereas specificity for IPAH, HPAH, Other PH, and COPD was lower at the same sensitivity (**Figure 1C**). It also showed that plasma GDF15 levels distinguished PVOD from other cohorts with AUC values of 94% or higher (**Figure 1D**). At 100% specificity for PVOD, GDF15 maintained a specificity greater than 58% when compared to other cohorts (**Figure 1D-F)**. GDF15 also distinguished PVOD from the combined IPAH+HPAH+Other PH and IPAH+HPAH cohorts with an optimal cutoff value of 1,658 pg/ml with 81% sensitivity and 98% specificity. GDF15 levels were significantly associated with PVOD compared to all reference cohorts (**Figure 1E**). An inverse correlation was observed between age-adjusted GDF15 and 6-minute walk distance (6MWD) in the PVOD+IPAH+HPAH cohort, indicating an association with disease severity (**Figure 1G**); however, no such correlation was observed in the PVOD cohort alone (**Supplementary Figure 2B**). Age-adjusted GDF15 (**Figure 1H**), but not other parameters (**Figure 1I–M**), differentiated PVOD from IPAH and HPAH. Higher levels of GDF15 were associated with poorer survival in the PVOD+IPAH+HPAH cohort (**Figure 1N**), with a similar trend observed in the PVOD cohort (**Supplementary Figure 2D**). Our findings suggest that GDF15 may serve as both a diagnostic biomarker to distinguish PVOD from other PAH subtypes and a prognostic biomarker for patients with PVOD, IPAH, and HPAH.

See Supplemental Data for study population characteristics, methods, additional data, author contributions, and acknowledgments.

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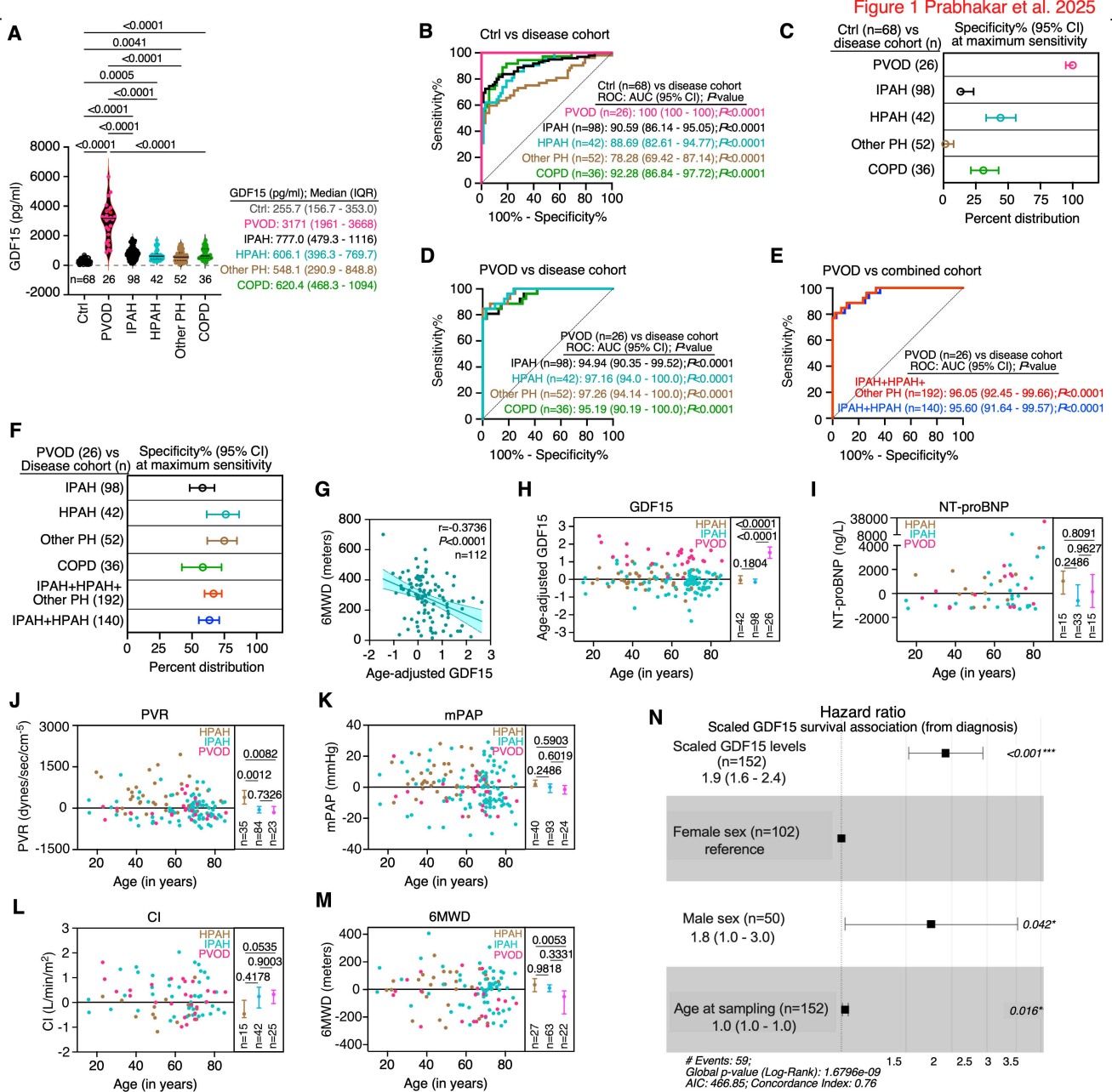
Figure legend

Figure 1 Plasma GDF15 as a diagnostic and prognostic biomarker for PVOD.

A. Violin plot of plasma GDF15 concentrations across different cohorts; $P<0.0001$ by one-way ANOVA with Turkey's post hoc test. **B.** ROC curves comparing GDF15 levels between healthy controls (Ctrl) and individual cohorts. **C.** Specificity% (95% CI) at 100% sensitivity for distinguishing Ctrl from individual cohorts. **D.** ROC curves for distinguishing PVOD from individual cohorts. **E.** ROC curves comparing PVOD with combined cohorts: IPAH+HPAH+Other PH or IPAH+HPAH. **F.** Specificity% (95% CI) at 100% sensitivity for distinguishing PVOD from individual or combined cohorts. **G.** Pearson correlation between age-adjusted GDF15 and 6MWD in the combined cohort: PVOD+IPAH+HPAH. **H-M.** Standardized distributions of diagnostic parameters: age-adjusted GDF15 (**H**), NT-proBNP (**I**), pulmonary vascular resistance (PVR) (**J**), mean

pulmonary arterial pressure (mPAP) (**K**), cardiac index (CI) (**L**), and 6MWD (**M**) in PVOD, IPAH, and HPAH. Left: individual values normalized to the median (y=0). Right: median values with 95% CI. **N.** Cox proportional hazards model showing the association between plasma GDF15 and transplant-free survival in the combined cohort: PVOD+IPAH+HPAH, adjusted for age and sex.


A
<0.0001
0.0041
<0.0001
0.0005
<0.0001
<0.0001
<0.0001
<0.0001
<0.0001
<0.0001
GDF15 (pg/ml)
n=68 26 98 42 52 36
Ctrl
PVOD
IPAH
HPAH
Other PH
COPD
GDF15 (pg/ml); Median (IQR)
Ctrl: 255.7 (156.7 - 353.0)
PVOD: 3171 (1961 - 3668)
IPAH: 777.0 (479.3 - 1116)
HPAH: 606.1 (396.3 - 769.7)
Other PH: 548.1 (290.9 - 848.8)
COPD: 620.4 (468.3 - 1094)
B
Ctrl vs disease cohort
Sensitivity%
100% - Specificity%
Ctrl (n=68) vs disease cohort
ROC: AUC (95% CI); P value
PVOD (n=26): 100 (100 - 100); P<0.0001
IPAH (n=98): 90.59 (86.14 - 95.05); P<0.0001
HPAH (n=42): 88.69 (82.61 - 94.77); P<0.0001
Other PH (n=52): 78.28 (69.42 - 87.14); P<0.0001
COPD (n=36): 92.28 (86.84 - 97.72); P<0.0001
C
Ctrl (n=68) vs disease cohort (n)
Specificity% (95% CI) at maximum sensitivity
PVOD (26)
IPAH (98)
HPAH (42)
Other PH (52)
COPD (36)
Percent distribution
D
PVOD vs disease cohort
Sensitivity%
100% - Specificity%
PVOD (n=26) vs disease cohort
ROC: AUC (95% CI); P value
IPAH (n=98): 94.94 (90.35 - 99.52); P<0.0001
HPAH (n=42): 97.16 (94.0 - 100.0); P<0.0001
Other PH (n=52): 97.26 (94.14 - 100.0); P<0.0001
COPD (n=36): 95.19 (90.19 - 100.0); P<0.0001
E
PVOD vs combined cohort
Sensitivity%
100% - Specificity%
PVOD (n=26) vs disease cohort
ROC: AUC (95% CI); P value
IPAH+HPAH+ Other PH (n=192): 96.05 (92.45 - 99.66); P<0.0001
IPAH+HPAH (n=140): 95.60 (91.64 - 99.57); P<0.0001
F
PVOD (26) vs Disease cohort (n)
Specificity% (95% CI) at maximum sensitivity
IPAH (98)
HPAH (42)
Other PH (52)
COPD (36)
IPAH+HPAH+ Other PH (192)
IPAH+HPAH (140)
Percent distribution
G
6MWD (meters)
r=-0.3736
P<0.0001
n=112
Age-adjusted GDF15
H
GDF15
Age-adjusted GDF15
HPAH
IPAH
PVOD
<0.0001
<0.0001
0.1804
n=42
n=98
n=26
Age (in years)
I
NT-proBNP
NT-proBNP (ng/L)
HPAH
IPAH
PVOD
0.8091
0.9627
0.2486
n=15
n=33
n=15
Age (in years)
J
PVR
PVR (dynes/sec/cm-5)
HPAH
IPAH
PVOD
0.0082
0.0012
0.7326
n=35
n=84
n=23
Age (in years)
K
mPAP
mPAP (mmHg)
HPAH
IPAH
PVOD
0.5903
0.6019
0.2486
n=40
n=93
n=24
Age (in years)
L
CI
CI (L/min/m2)
HPAH
IPAH
PVOD
0.0535
0.9003
0.4178
n=15
n=42
n=25
Age (in years)
M
6MWD
6MWD (meters)
HPAH
IPAH
PVOD
0.0053
0.3331
0.9818
n=27
n=63
n=22
Age (in years)
N
Hazard ratio
Scaled GDF15 survival association (from diagnosis)
Scaled GDF15 levels (n=152)
1.9 (1.6 - 2.4)
<0.001***
Female sex (n=102)
reference
Male sex (n=50)
1.8 (1.0 - 3.0)
0.042*
Age at sampling (n=152)
1.0 (1.0 - 1.0)
0.016*
Events: 59;
Global p-value (Log-Rank): 1.6796e-09
AIC: 466.85; Concordance Index: 0.76