

# Natriuretic Peptide Levels and Clinical Outcomes Among Patients Hospitalized With Coronavirus Disease 2019 Infection

**OBJECTIVES:** There is increasing evidence of cardiovascular morbidity associated with severe acute respiratory syndrome coronavirus 2 (coronavirus disease 2019). Pro-B-type natriuretic peptide is a biomarker of myocardial stress, associated with various respiratory and cardiac outcomes. We hypothesized that pro-B-type natriuretic peptide level would be associated with mortality and clinical outcomes in hospitalized coronavirus disease 2019 patients.

**DESIGN:** We performed a retrospective analysis using adjusted logistic and linear regression to assess the association of admission pro-B-type natriuretic peptide (analyzed by both cutoff  $> 125$  pg/mL and log transformed pro-B-type natriuretic peptide) with clinical outcomes. We additionally treated body mass index, a confounder of both pro-B-type natriuretic peptide levels and coronavirus disease 2019 outcomes, as an ordinal variable.

**SETTING:** We reviewed hospitalized patients with coronavirus disease 2019 who had a pro-B-type natriuretic peptide level measured within 48 hours of admission between March 1, and August 31, 2020, from a multihospital U.S. health system.

**PATIENTS:** Adult patients ( $\geq 18$  yr old;  $n = 1232$ ) with confirmed coronavirus disease 2019 admitted to the health system.

**INTERVENTIONS:** None.

**MEASUREMENTS AND MAIN RESULTS:** After adjustment for demographics, comorbidities, and troponin I level, higher pro-B-type natriuretic peptide level was significantly associated with death and secondary outcomes of new heart failure, length of stay, ICU duration, and need for ventilation among hospitalized coronavirus disease 2019 patients. This significance persisted after adjustment for body mass index as an ordinal variable. The adjusted hazard ratio of death for log transformed pro-B-type natriuretic peptide was 1.56 (95% CI, 1.23–1.97;  $p < 0.0001$ ).

**CONCLUSIONS:** Further investigation is warranted on the utility of pro-B-type natriuretic peptide for clinical prognostication in coronavirus disease 2019 as well as implications of abnormal pro-B-type natriuretic peptide in the underlying pathophysiology of coronavirus disease 2019–related myocardial injury.

**KEY WORDS:** biomarkers; coronavirus disease 2019; heart failure; natriuretic peptide; obesity; pandemic

Infection by severe acute respiratory syndrome coronavirus 2 has led to the coronavirus disease 2019 (COVID-19) global pandemic, with myocardial injury increasingly recognized as contributing to significant morbidity and mortality (1). To date, almost one fifth of patients have been reported to develop severe-critical COVID-19 infection, highlighting the importance of early risk stratification (2). Pro-B-type natriuretic peptide (proBNP or its biologically

M. Imran Aslam, MD<sup>1</sup>

Anum Minhas, MD<sup>1,2</sup>

Anahita Ghorbani, MD, MPH<sup>1</sup>

Julie K. Shade, BS<sup>3</sup>

Vivek Jani, BS, MS<sup>1</sup>

Steven Hsu, MD<sup>1</sup>

Kavita Sharma, MD<sup>1</sup>

Daniela Cihakova, MD, PhD<sup>4</sup>

Allison G. Hays, MD<sup>1</sup>

Nisha A. Gilotra, MD<sup>1</sup>

Copyright © 2021 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of the Society of Critical Care Medicine. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

DOI: 10.1097/CCE.000000000000498

inactive N-terminal segment [NT-proBNP]) is a well-established cardiac neurohormone that reflects ventricular wall stress from volume expansion and pressure overload (3). ProBNP can play a diagnostic and prognostic role in heart failure (HF), myocarditis, and acute respiratory distress syndrome, all of which have been described as clinical manifestations of COVID-19 (1, 2). However, proBNP levels can be affected by characteristics such as race, weight, renal function, and cardiovascular comorbidities (4). Notably, proBNP levels are lower in obesity, whereas obesity has been shown to independently increase mortality in COVID-19 (5). To date, studies of proBNP in COVID-19 are limited to short-term outcomes in relatively small, homogenous cohorts or do not adjust for relevant comorbidities, including obesity (6–10). Therefore, we sought to analyze the association of proBNP with clinical outcomes in a large, racially diverse multihospital U.S. health system cohort of patients hospitalized with COVID-19. We hypothesized that initial proBNP level obtained at admission for COVID-19 would be independently associated with cardiovascular and clinical outcomes. We further sought to investigate if these outcomes would be influenced by body mass index (BMI).

## MATERIALS AND METHODS

### Data Collection

Data were obtained from the Johns Hopkins COVID-19 Precision Medicine Analytic Platform Registry (JH-CROWN) on a racially and ethnically diverse cohort of adult patients ( $\geq 18$  yr old). JH-CROWN includes data from patients treated at five hospitals in the Johns Hopkins Health System. Patients included in this analysis had confirmed COVID-19 by reverse transcriptase polymerase chain reaction test, were admitted and died, or were discharged between March 1, and August 31, 2020 and had a proBNP level measured within 48 hours of admission. Comorbidities and clinical events were obtained using *International Classification of Diseases*, 10th Edition codes or key words; sex and race were self-identified. Laboratory data were first recorded values during hospitalization. COVID-19 severity was classified as severe (respiratory rate  $> 30$ /min, supplemental oxygen flow rate  $\geq 6$ L/min, oxygen saturation  $< 93\%$ ) or critical (with shock defined as hypotension requiring vasopressors and respiratory failure defined as need for mechanical ventilation), with the remainder as mild-moderate

(2). The study was approved by the Johns Hopkins University Institutional Review Board (IRB-3 approval, IRB00249548).

### Clinical Outcomes

The primary outcome was death, and secondary outcomes included new HF (defined as a new diagnosis during hospitalization for COVID-19 without a prior history of HF; without specified ejection fraction), need for mechanical ventilation, mechanical ventilator duration, and hospital and ICU lengths of stay (in days).

### Statistical Methods

Categorical variables are presented as frequencies and percentages and continuous variables as either mean and SD or median and interquartile range (IQR) depending on skewness of data. Between group comparisons were made using chi-square test for categorical and either independent-sample *t* tests or Mann-Whitney *U* test for continuous variables. Multiple groups comparisons were performed using one-way analysis of variance with the Bonferroni test for post hoc analysis. ProBNP was analyzed as a 1) binary variable: less than or equal to 125 pg/mL or greater than 125 pg/mL, based on reported normal values of proBNP at our institution and 2) continuous variable by log transformation given skewed distribution.

Univariate logistic or linear regression analyses were performed between dichotomized proBNP or log transformed proBNP for categorical or continuous outcome variables, respectively. Multivariate logistic or linear regression analyses were performed using forward-selection models with covariates known to effect proBNP and COVID-19 outcomes, and odds ratios (ORs) or regression coefficients of death and secondary outcomes were obtained. Logistic regression was performed for categorical outcomes (death, new HF, ventilator need), whereas linear regression was performed for continuous outcomes (length of stay, ICU duration, ventilator duration). Covariates included were age, sex, race, preexisting HF (for non-HF outcomes), BMI, hypertension, coronary artery disease, diabetes mellitus, smoking history, and stage of chronic kidney disease (race-adjusted estimated glomerular filtration rate of  $< 30$  cc/min, 30–60 cc/min or  $> 60$  cc/min). Multivariable regression models were designated Model 1 (including the aforementioned covariates), and Model 2,

adding serum cardiac troponin I to Model 1. Analysis of time-dependent outcome death was accomplished using nonparametric right-censored life table analysis with the Kaplan-Meier method. A multivariate Cox proportional hazard model incorporating log transformed proBNP and the specified covariates above were used to identify potential predictors of survival. Proportional hazards assumption was checked and met. The confounding effect of BMI on proBNP was additionally analyzed using adjusted logistic or linear regression Models 1 and 2. For this analysis, BMI was transformed into an ordinal variable (1: < 25%, 2: 25–75% or 3: > 75% percentile). All statistical analyses were performed using Stata/SE 15.1 (StataCorp LLC, College Station, TX). A *p* value of less than 0.05 was considered statistically significant.

## RESULTS

Patient characteristics (*n* = 1,232) are shown in **Table 1**. Median proBNP level was 238 pg/mL (60–1,275 pg/mL). 38.2% of patients had proBNP less than or equal to 125 pg/mL, and 61.8% had proBNP greater than 125 pg/mL. Patients with severe-critical COVID-19 disease profile more frequently had an abnormal (> 125 pg/mL) proBNP level at admission (*p* < 0.0001). In our patient cohort, over the designated time period, mortality was 16.2% (*n* = 198), new HF occurred in 7.6% (*n* = 94), and ventilator need was 22.8% (*n* = 281). Average length of admission was 13.3 ± 15.1 days, ICU length of stay 8.5 ± 10.8, and duration of mechanical ventilation 16.9 ± 18.0 (mean ± SD).

Higher proBNP (using 1: categorical cutoff > 125 pg/mL, and 2: continuous log transformed proBNP) had a significant association with death, new HF diagnosis, need for mechanical ventilation, length of stay, and ICU duration, but not with mechanical ventilation duration (**Table 2**). In adjusted logistic and linear regression analyses (Models 1 and 2), proBNP cutoff and log[proBNP] were significantly associated with the prespecified clinical outcomes (Table 2). The unadjusted hazard ratio for death for log[proBNP] was 1.66 (95% CI, 1.42–1.94; *p* < 0.0001). The adjusted hazard ratio of death from multivariate Cox regression for log[proBNP] was 1.56 (95% CI, 1.23–1.97; *p* < 0.0001) for Model 1 and 1.48 (95% CI, 1.03–2.12, *p* = 0.034) for Model 2.

Median BMI was 28.9 kg/m<sup>2</sup> (IQR, 24.8–34.2 kg/m<sup>2</sup>; 90th percentile 40.4 kg/m<sup>2</sup>; *n* = 1,083). Patients

with proBNP less than or equal to 125 pg/mL had a higher median BMI than those with a proBNP greater than 125 pg/mL (30.8 [27.0–35.8] vs 27.4 kg/m<sup>2</sup> [23.4–32.5 kg/m<sup>2</sup>]; *p* < 0.0001). Even after adjusting for BMI as either a continuous or ordinal variable, proBNP categorical cutoff and log[proBNP] were still significantly associated with all clinical outcomes, except for new HF events and ICU duration in Model 2 by categorical proBNP (**Supplemental Table 1**, <http://links.lww.com/CCX/A734>).

Among the 217 patients with serial proBNP measurements, percent increase in proBNP was significantly associated with death in unadjusted (OR, 1.13; 95% CI, 1.05–1.22; *p* = 0.002) and adjusted (Model 1: OR, 1.17; 95% CI, 1.05–1.30; *p* = 0.004 and Model 2: OR, 1.25; 95% CI, 1.09–1.43; *p* = 0.002) analyses.

## DISCUSSION

We report that among hospitalized patients, the majority of whom had severe-critical COVID-19, admission serum proBNP level was an independent risk factor for relevant clinical outcomes, including mortality, despite adjustment for confounders. There are currently only limited studies of natriuretic peptides in COVID-19. Another study has shown prognostic utility of proBNP in a small cohort (102 patients) of severe COVID-19 patients (11). A meta-analysis on cardiac biomarkers also demonstrated that NT-proBNP was significantly higher in severely ill COVID-19 patients compared with nonsevere cases (8). Only a few observational studies have not shown B-type natriuretic peptide (BNP) as a marker of clinical significance; although, comparatively, these studies were smaller, relatively racially homogenous, had limited follow-up time, and had significantly fewer days of mechanical ventilation (9, 10). However, to our knowledge, no prior study has specifically reported on BMI and proBNP in a diverse COVID-19 inpatient population. Obesity has been associated with higher COVID-19 severity (5), whereas BMI also has an inverse relationship with proBNP level, the latter finding demonstrated in our cohort as well (4). However, our findings suggest that proBNP has strong prognostic value in acute COVID-19, even after adjusting for BMI as both a continuous or ordinal variable.

Our data are consistent with prior non-COVID-19 studies demonstrating differences in proBNP based on

**TABLE 1.**  
**Baseline Characteristics of Hospitalized Patients With Coronavirus Disease 2019 Based on Initial Pro-B-Type Natriuretic Peptide Value**

Variables	Total (N = 1,232)	ProBNP ≤ 125 pg/mL (N = 470)	ProBNP > 125 pg/mL (N = 760)	p
Sex (male), n (%)	661 (53.8)	250 (53.2)	411 (54.1)	0.762
Age (yr), mean (± sd)	62.7 (± 17.6)	50.9 (± 14.1)	70.0 (± 15.5)	< 0.001
Race, n (%)				< 0.001
White	343 (27.8)	49 (10.4)	294 (38.7)	
Black	441 (35.8)	175 (37.2)	266 (35.0)	
Hispanic	324 (26.4)	193 (41.1)	131 (17.2)	
Other	122 (9.9)	53 (11.3)	69 (9.1)	
Body mass index, kg/m <sup>2</sup> , mean (± sd)	30.4 (± 10.0)	32.5 (± 12.0)	29.0 (± 8.3)	< 0.001
Hypertension, n (%)	702 (57.0)	189 (40.2)	513 (67.5)	< 0.001
Diabetes, n (%)	388 (31.5)	117 (24.9)	271 (35.7)	< 0.001
Coronary artery disease, n (%)	111 (9.0)	7 (1.5)	104 (13.7)	< 0.001
Preexisting heart failure, n (%)	130 (10.6)	12 (2.6)	118 (15.5)	< 0.001
ICU level of care, n (%)	1,115 (90.5)	434 (92.3)	681 (89.6)	0.109
Estimated glomerular filtration rate < 60 cc/min (race adjusted), n (%)	435 (36.0)	59 (12.6)	376 (49.4)	< 0.001
History of smoking, n (%)	222 (18.0)	54 (11.5%)	168 (22.1)	< 0.001
Medications, n (%)				< 0.001
Aspirin	143 (11.6)	26 (5.5%)	117 (15.4)	
Statin	223 (18.1)	50 (10.6%)	172 (22.6)	
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker	197 (16.0)	48 (10.2%)	149 (19.6)	
Troponin I (ng/mL, n = 748), median (interquartile range)	0.04 (0.02–0.04)	0.04 (0.02–0.04)	0.04 (0.02–0.08)	< 0.0001
C-reactive protein (mg/dL, n = 1,142), median (interquartile range)	10.7 (4.55–25)	7.1 (3.6–15.85)	13.95 (5.7–36.05)	< 0.0001
Ferritin (ng/mL, n = 1,134), median (interquartile range)	637.5 (292–1,208)	632 (264–1,102)	639 (324–1,298)	0.044
Fibrinogen (mg/dL, n = 730), median (interquartile range)	546.5 (437–652)	523 (434–636)	565.5 (438–673)	0.110
Coronavirus disease 2019 severity <sup>a</sup> , n (%)				< 0.0001
Mild-moderate	68 (7.3)	33 (9.9)	35 (5.9)	
Severe	558 (60.0)	234 (70.1)	324 (54.4)	
Critical	304 (32.7)	67 (20.1)	237 (39.8)	

ProBNP = pro-B-type natriuretic peptide.

<sup>a</sup>Available for 930 patients, 334 in proBNP ≤ 125 pg/mL group and 596 in proBNP > 125 pg/mL group.

**TABLE 2.**  
Unadjusted and Adjusted Clinical Outcome Analysis of Pro-B-Type Natriuretic Peptide

Outcome	ProBNP (>125 pg/mL)		Log Transformed ProBNP	
<b>Unadjusted</b>				
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Death ( <i>n</i> = 1,230) <sup>a</sup>	6.5 (4.1–10.4)	< 0.0001	2.4 (2.0–2.9)	< 0.0001
New HF ( <i>n</i> = 1,100)	3.3 (1.7–6.4)	< 0.0001	2.2 (1.7–2.0)	< 0.0001
Ventilator need ( <i>n</i> = 1,230)	2.4 (1.8–3.3)	< 0.0001	1.5 (1.3–1.7)	< 0.0001
	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>
Length of stay ( <i>n</i> = 1,230)	6.1 (4.4–7.9)	< 0.0001	3.4 (2.5–4.3)	< 0.0001
ICU duration ( <i>n</i> = 1,230)	2.8 (1.5–4.0)	< 0.0001	1.2 (0.5–1.8)	0.0003
Ventilator duration ( <i>n</i> = 280)	–1.2 (–6.2 to 3.8)	0.64	–0.4 (–2.9 to 2.2)	0.77
<b>Model 1 (Age, Sex, Race, Body Mass Index, Hypertension, Coronary Artery Disease, Diabetes Mellitus, Smoking, Chronic Kidney Disease)</b>				
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Death ( <i>n</i> = 1,059)	3.4 (1.6–4.8)	< 0.0001	2.1 (1.6–2.7)	< 0.0001
New HF ( <i>n</i> = 957)	1.7 (1.2–6.3)	0.013	3.0 (2.0–4.4)	< 0.0001
Ventilator need ( <i>n</i> = 1059)	3.4 (2.2–4.8)	< 0.0001	1.9 (1.5–2.4)	< 0.0001
	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>
Length of stay ( <i>n</i> = 1,059)	4.7 (2.6–6.7)	< 0.0001	2.6 (1.4–3.9)	< 0.0001
ICU duration ( <i>n</i> = 1,059)	2.4 (0.9–4.0)	0.002	1.4 (0.5–2.4)	0.003
Ventilator duration ( <i>n</i> = 219)	–1.3 (–6.7 to 4.0)	0.62	–2.3 (–5.4 to 0.7)	0.14
<b>Model 2 (Model 1 + Troponin I)</b>				
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Death ( <i>n</i> = 636)	3.4 (4.6–7.3)	0.002	2.0 (1.4–3.0)	< 0.0001
New HF ( <i>n</i> = 578)	1.7 (0.7–4.1)	< 0.0001	2.5 (1.5–4.0)	< 0.0001
Ventilator need ( <i>n</i> = 636)	3.4 (2.1–5.5)	< 0.0001	2.1 (1.6–2.8)	< 0.0001
	$\beta$ (95% CI)	<i>p</i>	$\beta$ (95% CI)	<i>p</i>
Length of stay ( <i>n</i> = 636)	4.4 (1.4–7.3)	0.004	3.2 (1.3–5.1)	0.001
ICU duration ( <i>n</i> = 636)	2.1 (0.1–4.3)	0.06	1.9 (0.5–3.3)	0.009
Ventilator duration ( <i>n</i> = 150)	–2.9 (–9.9 to 4.3)	0.44	–2.2 (–6.6 to 2.1)	0.31

HF = heart failure, OR = odds ratio, proBNP = pro-B-type natriuretic peptide.

<sup>a</sup>*n* indicates number of patients analyzed for specified outcome in each model based on available data. Logistic regression performed for categorical outcomes (death, new HF, and ventilator need), and regression coefficient is reported as an OR. Linear regression performed for continuous outcomes (length of stay, and ICU duration), and regression coefficient is reported as  $\beta$ .

demographics, for example, race (higher percentage of patients with elevated proBNP in Caucasians vs Hispanics) and smoking status (12). However, a notable difference in COVID-19 patients is that the cutoff values

of proBNP to predict worse clinical outcome (i.e., mortality) are lower than values in other conditions such as acute respiratory distress syndrome or even HF (3, 13). Another study demonstrated peak measured BNP

mean value in those requiring mechanical ventilation was only 116.4 pg/mL, although the study included only survivors (9). One hypothesis may be that proBNP elevation may occur independently of myocardial stress. A recent study posits that subclinical BNP elevation may indicate endothelial dysfunction leading to impaired microvascular compliance and subsequently impaired adaptation to hypoxia in COVID-19 (14). It is unknown whether this may be the underlying mechanism of seemingly stochastic lung injury in COVID-19 and is not addressed by our study. In addition, impact of proBNP levels during acute COVID-19 infection on postacute COVID-19 syndrome is unknown and warrants further investigation.

This study has a few limitations. The analysis was a retrospective, single health system study limited to patients hospitalized early during the pandemic who also had an admission proBNP level, possibly resulting in selection bias and missing data. Therefore, findings may not be generalizable to other populations. More so, as the study was performed in a cohort of primarily severely ill hospitalized COVID-19 patients, results should be extrapolated to the outpatient setting with caution. Further studies should be performed for other clinical settings.

## CONCLUSIONS

In a large and racially diverse hospitalized COVID-19 population, we find that proBNP is associated with adverse clinical outcomes, including mortality and new HF, despite adjustment for other clinical predictors. These data are hypothesis generating, and additional prospective investigation is needed to investigate use of proBNP as a prognostic marker in COVID-19.

1 Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD.

2 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.

3 Department of Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD.

4 Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (<http://journals.lww.com/ccejournal>).

The authors have disclosed that they do not have any conflicts of interest.

For information regarding this article, E-mail: [naggarw2@jhmi.edu](mailto:naggarw2@jhmi.edu)

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

## REFERENCES

1. Lala A, Johnson KW, Januzzi JL, et al; Mount Sinai COVID Informatics Center: Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol* 2020; 76:533–546
2. Wu Z, McGoogan JM: Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. *JAMA* 2020; 323:1239–1242
3. Levin ER, Gardner DG, Samson WK: Natriuretic peptides. *N Engl J Med* 1998; 339:321–328
4. Krauser DG, Lloyd-Jones DM, Chae CU, et al: Effect of body mass index on natriuretic peptide levels in patients with acute congestive heart failure: A ProBNP investigation of dyspnea in the emergency department (PRIDE) substudy. *Am Heart J* 2005; 149:744–750
5. Kass DA: COVID-19 and severe obesity: A big problem? *Ann Intern Med* 2020; 173:840–841
6. Wungu CDK, Khaerunnisa S, Putri EAC, et al: Meta-analysis of cardiac markers for predictive factors on severity and mortality of COVID-19. *Int J Infect Dis* 2021; 105:551–559
7. Izcovich A, Ragusa MA, Tortosa F, et al: Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *PLoS One* 2020; 15:e0241955
8. Walker C, Deb S, Ling H, et al: Assessing the elevation of cardiac biomarkers and the severity of COVID-19 infection: A meta-analysis. *J Pharm Pharm Sci* 2020; 23:396–405
9. Gavin W, Campbell E, Zaidi SA, et al: Clinical characteristics, outcomes and prognosticators in adult patients hospitalized with COVID-19. *Am J Infect Control* 2021; 49:158–165
10. Almeida Junior GLG, Braga F, Jorge JK, et al: Prognostic value of Troponin-T and B-type natriuretic peptide in patients hospitalized for COVID-19. *Arq Bras Cardiol* 2020; 115:660–666
11. Gao L, Jiang D, Wen XS, et al: Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res* 2020; 21:83
12. Patel N, Cushman M, Gutierrez OM et al: Racial differences in the association of NT-proBNP with risk of incident heart failure in REGARDS. *JCI Insight* 2019; 5:e129979.
13. Qin JJ, Cheng X, Zhou F, et al: Redefining cardiac biomarkers in predicting mortality of inpatients with COVID-19. *Hypertension* 2020; 76:1104–1112
14. Khatri R, Gupta RK, Vats P, et al: Subclinical elevated B-type Natriuretic Peptide (BNP) indicates endothelial dysfunction contributing to hypoxia susceptibility in healthy individuals. *Life Sci* 2020; 260:118408