High Levels of Pro B-Type Natriuretic Peptides Are Associated with Adverse Outcomes in COVID-19 Disease: A Single Center Experience

Kashif Bin Naeem, Najiba Abdulrazzaq

ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus-2, has caused widespread morbidity and mortality worldwide. Cardiac injury is reported to be common in hospitalized patients. We evaluated whether Pro B-type Natriuretic Peptide (proBNP) levels measured on admission in COVID-19 patients were associated with worse outcomes. A retrospective analysis of laboratory-confirmed COVID-19 patients who were admitted between February 2020 and July 2020 to Al Kuwait Hospital, Dubai, UAE. Patients were divided into two groups: normal proBNP (≤ 125 ng/L) and high proBNP (>125 ng/L) upon admission. Clinical characteristics and outcomes were compared between the two groups. A total of 389 patients were studied. Overall, mean age was 50.2 years (range 16-94 years), 77.3% were males, 35.7% diabetics, 35.2% hypertensives and 5.6% had history of cardiovascular disease. Compared to the group with normal proBNP; patients with high proBNP on admission were: older, more diabetics and hypertensives, with more history of cardiovascular disease; they presented with abnormal chest radiograph; and had lower lymphocytes, higher neutrophils, lower eGFR, higher D-dimers, higher CRP and higher procalcitonin on admission laboratory tests. These patients had more risk of developing critical illness during the hospitalization, undergoing mechanical ventilation and risk of death. Elevated pro B-type natriuretic peptide levels on admission in COVID-19 patients may predict subsequent risk of developing critical illness, undergoing mechanical ventilation, and significant high risk of death.

Keywords: COVID-19, pro B-type natriuretic peptide, outcomes.

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K. B. Naeem*

Al Kuwait Hospital, Dubai, UAE.

(e-mail: kbncardiology@yahoo.co.uk)

N. Abdulrazzaq

Al Kuwait Hospital, Dubai, UAE.

(e-mail:

najiba.abdulrazzaq@mohap.gov.ae)

**Corresponding Author*

I. INTRODUCTION

Since first reported in Wuhan, China, in December 2019 [1], COVID-19 disease, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2), has caused widespread morbidity and mortality. As of 7 August, 2020, the total number of confirmed cases worldwide are 19,111,123, with 715,163 confirmed deaths, whereas, United Arab Emirates (UAE) has 61,845 confirmed cases with 354 deaths (Johns Hopkins Coronavirus Resource Center). Cardiac injury is commonly reported in COVID-19. Huang et al [2] reported a 12% incidence of acute cardiac injury in patients with COVID-19, while another study of 138 hospitalized Covid-19 patients reported that 7.2% had acute myocardial injury and 16.7% had arrhythmias [3]. Although elevated cardiac troponin levels in COVID-19 has been reported to be associated with adverse outcomes including mortality [4], few have reported about the significance of pro B-type natriuretic peptide (proBNP) in these patients. Hence, we conducted this study to evaluate whether high proBNP

levels upon admission are associated with adverse events during hospitalization.

II. METHODS

We enrolled all consecutive COVID-19 patients who were admitted at Al Kuwait Hospital, Dubai, UAE between February 2020 and July 2020. We included all patients who had a positive Real Time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) test to diagnose COVID-19 and proBNP level measured on admission. The study was approved by the Ministry of Health and Prevention, Research Ethics Committee (approval reference no. MOHAP/DXB-REC/AAA/No. 39/2020), and informed consent was waived off. Patients were divided into two groups according to the admission proBNP levels: normal proBNP ≤ 125 ng/L and >125 ng/L. Data was extracted retrospectively from the hospital electronic medical records. This included basic demographics, comorbidities, admission laboratory parameters, chest radiography, disease severity, management

and mortality. All data was independently reviewed and entered into the computer excel sheet by two analysts.

Results are expressed as counts and percentages for categorical variables and mean (standard deviation) or median (interquartile range) for continuous data. The two groups were compared group were made by the independent-samples T-test (normally distributed continuous variables), Mann-Whitney U test (non-normally distributed continuous variables) and chi-square test (categorical variables). P-value less than 0.05 was considered statistically significant. Data was analyzed using Stat Plus: mac, Analyst Soft Inc. - statistical analysis program for macOS, Version v7.

III. RESULTS

A total of 389 patients were studied; 160/389 had normal proBNP levels and 229/389 had high proBNP levels.

Table 1 describes the clinical characteristics of the two groups. Overall, mean age was 50.2 years (range 16-94 years), 77.3% were males, 35.7% diabetics, 35.2% hypertensives and 5.6% had history of cardiovascular disease. Compared to the group with normal proBNP on admission, patients with high proBNP (>125 ng/l) were older (mean age 54.5 yrs vs 44 yrs, $p < 0.001$), more diabetics (47% vs 19%, $p < 0.001$) and hypertensives (41% vs 28%, $p < 0.001$), and more history of cardiovascular disease (9% vs 0.6%, $p < 0.001$). There was no difference in body mass index between the two groups ($p = 0.223$).

All patients had chest radiography on admission. Overall, 72.2% had bilateral airspace opacities on admission chest radiography. 82.5% in high proBNP group had abnormal chest radiograph with bilateral lung opacities compared to 57.5% in the normal proBNP group ($p < 0.001$).

Laboratory tests on admission showed that high proBNP group had lower mean lymphocytes ($1.1 \times 10^3/\text{mcL}$ vs $1.46 \times 10^3/\text{mcL}$, $p < 0.001$). Although neutrophils were higher in the high proBNP group ($p < 0.001$), there was no difference in the platelet count ($p = 0.060$). Mean estimated glomerular filtration rate (eGFR) was lower in the high proBNP group (74.8 vs $94.0 \text{ ml/min/1.73 m}^2$, $p < 0.001$). There was no difference in the liver enzymes between the two groups. Regarding the inflammatory markers, the high proBNP group had higher mean CRP (121 mg/L vs 65 mg/L , $p < 0.001$), procalcitonin (1.6 mcg/L vs 0.25 mcg/L , $p = 0.004$) and D-dimers (4.4 mg/dL vs 0.86 mg/dL , $p < 0.001$). There was no difference in mean ferritin ($p = 0.054$) or troponin levels ($p = 0.139$).

All patients were followed up during the hospitalization. Patients with high proBNP developed more critical illness during the hospitalization (54% vs 14%, $p < 0.001$), and underwent more mechanical ventilation (37.5% vs 3%, $p < 0.001$) compared to normal proBNP group. These patients were also more at risk of mortality compared to patients with normal proBNP levels (36% vs 3%, $p < 0.001$).

IV. DISCUSSION

The present study explores the association between the proBNP levels on admission in hospitalized COVID-19 patients and clinical outcomes and represents the rare data from the Middle East region.

B-type natriuretic peptide (BNP) was first discovered by de Bold and colleagues in 1981 [5]. Since then, interest in evaluating its physiology and clinical application has increased exponentially. BNP is initially released as a 134-amino acid precursor, pre-pro-BNP. This is cleaved into pro-BNP that is further broken down into the active 32-amino acid BNP and the inactive 76-amino acid N-terminal pro-BNP [6]. However, recent studies suggest the process is more complex. BNP is released from the ventricles in response to left ventricular wall stretch and volume overload and acts by decreasing plasma volume and blood pressure through vasodilatation and natriuresis [6]. The exact mechanism for BNP to rise in COVID-19 infection remains unclear. Postulated mechanisms include a BNP rise either as a result of virus-induced cardiac damage mediated by ACE2 receptor expression [7] or related to cytokine storm [8].

We studied 389 patients with laboratory-confirmed COVID-19 disease. The patient cohort was diverse as it comprised of cases from various ethnic backgrounds. Mean age was 50 years indicating a middle-aged population. This was a high cardiovascular risk cohort as 35% were diabetics and hypertensives. A cut-off proBNP value of 125 ng/L was taken as upper limit of normal as per the hospital laboratory values, to divide the sample into normal and high BNP groups. We found that more than 80% presented with high proBNP and bilateral airspace opacifications on chest radiography on admission. Also, the high proBNP group had higher CRP, procalcitonin and d-dimer levels. This indicates the association of high proBNP levels with severe disease. Interestingly, we found that although the other cardiac biomarker, troponin, had high mean values in the high proBNP group, the difference between the two groups was not statistically significant. Also, ferritin, considered a sensitive marker of inflammation, showed no statistically significant difference between the two groups.

High BNP levels have been reported in COVID-19 patients to be associated with adverse outcomes. We found that more than half (54%) patients in the high proBNP group developed more critical illness during the hospitalization. Also, more than one-thirds were mechanically ventilated due to severe respiratory distress. Guo and colleagues [9] also reported gradual rise in BNP levels along with cardiac troponins in patients who deteriorated clinically compared to low and stable BNP levels in successfully discharged patients. Our study showed mortality to be significantly high in the high proBNP group with 36% dying compared to only 3% in the normal proBNP group. This is consistent with what Shie et al [10] reported, a high mortality rate (51.2%) in patients with significantly raised BNP levels.

The study has some limitations. This is a retrospective analysis of a small sample size from a single center. Also, proBNP was tested on admission only. We believe that increased sample size with continuous measurements would provide additional information about the prognostic impact of proBNP levels.

TABLE 1: CLINICAL CHARACTERISTICS OF 389 COVID-19 PATIENTS ACCORDING TO ADMISSION PROBNP LEVELS

	All patients	Admission Pro-BNP ≤ 125 ng/L	Admission Pro-BNP > 125 ng/L	p-value (between two pro-BNP groups) Significant < 0.05
Characteristic	N= 389	n= 160/389	n= 229/389	
Age, mean (range)	50.2 (16-94)	44 (16-91)	54.5 (22-94)	< 0.001
Male sex, no. (%)	301 (77.3%)	117 (73.1%)	184 (80.3%)	0.029
BMI, mean (SD) median (IQR)	28.3 (5.65) 27 (25-30.95)	28.76 (5.96) 28 (25-31)	28.01 (5.39) 27 (25-30)	0.223
Diabetes, no. (%)	139 (35.7%)	31 (19.4%)	108 (47.16%)	< 0.001
Hypertension, no. (%)	137 (35.2%)	44 (27.5%)	93 (40.6%)	< 0.001
Cardiovascular disease, no. (%)	22 (5.6%)	1 (0.62%)	21 (9.2%)	< 0.001
Bilateral opacities on chest radiography, no. (%)	281 (72.2%)	92 (57.5%)	189 (82.5%)	< 0.001
Lymphocytes x10 ³ /mcL, mean (SD) median (IQR)	1.25 (0.71) 1.08 (0.76-1.59)	1.46 (0.73) 1.29 (0.92-1.88)	1.11 (0.66) 0.97 (0.67-1.3)	< 0.001
Neutrophils x10 ³ /mcL, mean (SD) median (IQR)	6.89 (4.0) 6.02 (4.06-8.56)	6.01 (3.28) 5.3 (3.58-7.53)	7.52 (4.38) 6.53 (4.48-9.2)	< 0.001
Platelets x10 ³ /mcL, mean (SD) median (IQR)	251.7 (105.4) 232 (181-301)	263.7 (117.1) 235.5 (191-305)	243.3 (95.9) 229 (167-301)	0.060
PT seconds, mean (SD) median (IQR)	12.37 (1.94) 12.1 (11.3-13.1)	11.9 (1.69) 11.8 (11.1-12.4)	12.69 (2.04) 12.5 (11.5-13.5)	< 0.001
eGFR ml/min/1.73 m ² , mean (SD) median (IQR)	82.7 (32.45) 86.5 (62.3-105.7)	94.04 (27.8) 98.5 (75.1-114.2)	74.8 (33.16) 76.7 (54.2-98.7)	< 0.001
ALT, IU/L, mean (SD) median (IQR)	74.3 (138.05) 45 (29-77.25)	92.07 (179.6) 53 (31-88)	62.0 (98.1) 42 (27-72)	0.034
AST, IU/L, mean (SD) median (IQR)	66.36 (133.34) 43 (29-69)	63.23 (87.3) 41 (25.5-71)	68.5 (157.7) 45 (31-65)	0.701
HS Troponin I ng/L, mean (SD) median (IQR)	151.9 (886.9) 9.9 (5.8-26.5)	21.8 (65.6) 6.4 (4.5-12.4)	240.7 (1141.9) 15.1 (7.8-36.6)	0.139
Pro-BNP ng/L, mean (SD) median (IQR)	1371.76 (4246.8) 199.5 (56-682.5)	49.5 (33.6) 43 (21-72.5)	2290 (5343) 544 (268-1657)	< 0.001
D-dimer mg/dL, mean (SD) median (IQR)	2.94 (6.45) 0.85 (0.46-1.90)	0.86 (1.17) 0.55 (0.28-0.95)	4.37 (8.02) 1.12 (0.65-3.56)	< 0.001
Ferritin >mcg/L, mean (SD) median (IQR)	1148.34 (1755.1) 647 (245.7-1574)	940.2 (1220.8) 475 (164-1466)	1288 (2027) 737 (339-1679)	0.054
CRP mg/L, mean (SD) median (IQR)	97.76 (102.5) 74.4 (20.9-148.8)	65 (108.1) 33.5 (5.78-88.7)	120.76 (91.8) 104.4 (47.75-172.5)	< 0.001
Procalcitonin mcg/L, mean (SD) median (IQR)	1.08 (4.69) 0.13 (0.05-0.37)	0.25 (0.77) 0.08 (0.03-0.17)	1.59 (5.88) 0.2 (0.08-0.62)	0.004
Critical illness, no. (%)	146 (37.5%)	22 (13.75%)	124 (54.1%)	< 0.001
Mechanical ventilation, no. (%)	94 (24.2%)	5 (3.1%)	86 (37.5%)	< 0.001
Death, no. (%)	87 (22.4%)	5 (3.1%)	82 (35.8%)	< 0.001

Data presented as counts (percentages) and mean (SD)/median (IQR).

BMI, body mass index; PT, prothrombin time; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; pro-BNP, pro-B-type natriuretic peptide; CRP, C-reactive protein.

V. CONCLUSION

Elevated pro B-type natriuretic peptide levels on admission in COVID-19 patients may predict subsequent risk of developing critical illness, undergoing mechanical ventilation, and significant high risk of death. Large

prospective studies with continuous measurements of proBNP levels will help further confirm the findings.

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Dr Kashif Bin Naeem is currently working as a Consultant Cardiologist at Al Kuwait Hospital, Dubai, Ministry of Health and Prevention, UAE. After completing MBBS from Pakistan, he moved to UK where he completed his Residency in Internal Medicine from London and achieved MRCP (UK) in 2007. He pursued his career in Non-invasive Cardiology and was awarded CESR, CCT equivalent, in Cardiology by the General Medical Council/Royal College of Physicians, UK in 2018. His work affiliation includes Guy's and St. Thomas' Hospitals; London Chest Hospital; Royal Free Hospital, London; and King Fahad Medical City, Riyadh. He specializes in Advanced Echocardiography and been awarded Diplomate American Board of Echocardiography. He is a member of British Cardiovascular Society, European Society of Cardiology (ESC), Emirates Cardiac Society, Acute Cardiovascular Care Association (ESCC) and European Association of Cardio Vascular Imaging. He is an active researcher; published several papers in peer-reviewed journals and presented abstracts in European Cardiology conferences. He has keen interest in voluntary work where he offers free consultation at medical camps, World Heart Day and World Hypertension Day events; and visits schools to educate students. He is affiliated with the University of Sharjah to teach year 5 medical students. His current interests include preventive cardiology and echocardiography and has delivered talks at different platforms.