

The prognostic effect of brain natriuretic peptide levels on outcomes of hospitalized patients with COVID-19

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Access this article online

Website: www.avicennajmed.com

DOI: 10.4103/ajm.ajm_169_20

Quick Response Code:



ABSTRACT

Natriuretic peptides are biomarkers of myocardial stress and are frequently elevated among patients with severe respiratory illnesses, typically in the absence of elevated cardiac-filling pressures or clinical heart failure. Elevation of brain natriuretic peptide (BNP) or NT-proBNP is associated with worse outcomes among patients with Acute Respiratory Distress Syndrome (ARDS). We conducted a retrospective cohort study based on a comprehensive review of Electronic Medical Records (EMRs) of patients with Coronavirus Disease 2019 (COVID-19) to evaluate whether BNP on admission has prognostic value on mortality and hospital length of stay (LOS) among patients admitted with confirmed COVID-19 along with the inclusion of additional prognostic variables. Overall, 146 patients were included after analyzing 230 patients' EMR and excluding potential confounding factors for abnormal BNP. Our statistical analysis did not show a statistically significant association between BNP level and mortality rate ($P = 0.722$) or ICU LOS ($P = 0.741$). A remarkable secondary outcome to our study was that impaired renal function (GFR<60) on admission was significantly associated with an increased mortality rate ($P = 0.026$) and an increased ICU LOS ($P = 0.022$). Although various studies have presented the predictive role of pro-BNP among patients with respiratory distress in the past years, our study did not find BNP to be an accurate predictive and prognostic factor among patients with COVID-19 in our study population. Renal impairment and high Acute Physiology and Chronic Health Evaluation (APACHE) II scores on admission, on the other hand, have demonstrated to be strong predictors for COVID-19 morbidity and mortality. This study could represent an introduction to more prominent multicenter studies to evaluate additional prognostic factors and minimize the ordering of nonspecific testing.

Key words: Brain natriuretic peptide, COVID-19, SARS-CoV-2

INTRODUCTION

COVID-19, a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that belongs to the Coronaviruses family, has been one of the most devastating outbreaks that led to the first Coronavirus pandemic in the 21st century.^[1] SARS-CoV-2 is a highly infectious virus that could result in significant morbidity and mortality, as reported by the Centers for Disease Control and Prevention

(CDC).^[2] SARS-CoV-2 mainly affects the respiratory system, resulting in a spectrum of illnesses ranging from Upper Respiratory Tract Infections to Severe Acute Respiratory Syndrome (SARS).^[1,3] Due to the devastating effects of

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Cite this article as: Abdeen Y, Kaako A, Alnabulsi M, Okeh A, Meng W, Miller R. The prognostic effect of brain natriuretic peptide levels on outcomes of hospitalized patients with COVID-19. *Avicenna J Med* 2021;11:20-6.

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COVID-19 on the health-care system, prognostication has become crucial for proper resource allocation and triaging patients with COVID-19 according to their risks. Therefore, more focus has been directed toward identifying COVID-19 infection, including patient factors and diagnostic tests, to identify patients with higher risk.^[4,5] Natriuretic peptides are biomarkers of myocardial stress and are frequently elevated among patients with severe respiratory illnesses, typically in the absence of elevated cardiac-filling pressures or clinical heart failure.^[6] Elevation of BNP or NT-proBNP is associated with worse outcomes among patients with ARDS.^[7] Therefore, this study was conducted to identify the prognostic value of BNP among hospitalized patients with SARS-CoV-2 infection.

METHODS

The study design and oversight

This study is a retrospective cohort study based on a comprehensive review of electronic medical records (EMRs). It was designed by the principal investigator. All of the authors reviewed the manuscript before submission for publication. The approval of the Institutional Review Board (IRB) (#16/20) was issued before data collection. The study variables were extracted from the EMR system (EPIC at Saint Michael's Medical Center) and were inserted directly into and stored in a password-protected EXCEL worksheet available only to the study investigators. No paper files were printed or stored. All the data were kept private and confidential per IRB and HIPAA policies. Based on the study's retrospective nature, the patients' informed consent requirement was waived by the IRB.

The study population

Saint Michael's Medical Center (SMMC) is an inner-city community hospital located in Newark, New Jersey, and affiliated with New York Medical College. It serves an area with a Latino and African American majority. The SMMC hosted a significantly number of patients with COVID-19 during the pandemic. The EMRs were screened for all the adult patients (age ≥ 18 years) and admitted to SMMC with respiratory distress and confirmed COVID-19 infection between 1 February 2020 and 30 April 2020.

Study outcomes

The primary outcomes were in-hospital mortality and admission to the intensive care unit (ICU) with mechanical ventilation and the hospital LOS. Our primary goal was to evaluate whether BNP on admission has prognostic value for the earlier-mentioned outcomes among patients admitted with confirmed COVID-19. Our secondary goal

was to evaluate any other potential prognostic variables that may predict outcomes associated with COVID-19 infection.

Definitions

A fatal case of COVID-19 was defined as any death that occurred during hospitalization with a confirmed diagnosis of COVID-19 made by PCR testing of nasopharyngeal swab samples. A non-fatal case was defined as a confirmed case of COVID-19 by PCR in a hospitalized patient who had not died (whether discharged or still hospitalized) as of 30 April 2020. Due to the limited intensive care unit (ICU) bed availability during the pandemic and the state of emergency declaration, almost all the ICU patients were on mechanical ventilation. Almost all the extubated patients were transferred out of the ICU on the same day, a few hours after extubation. Hence, the time of mechanical ventilation was used as a proxy estimate for the ICU length of stay (LOS), which was not measured directly in our study. The hospital LOS was calculated (in days) by subtracting the date of admission from the day of discharge.

Inclusion criteria

The main inclusion criteria were as follows:

1. Adult patients (age ≥ 18 years) presenting with active respiratory symptoms related to SARS-CoV-2 infection, including shortness of breath, cough along with oxygen saturation less than 92% on room air.
2. Confirmed case of COVID-19 by PCR.
3. Patients had blood BNP levels drawn and reported on the day of admission.

Clinically, some medical conditions may independently alter BNP levels in patients with normal heart function and no respiratory distress.^[6] To minimize confounding factors that may affect our evaluation of the dependent variable (BNP) effect on the primary outcomes, we excluded patients with a known history of End-Stage Renal Disease (ESRD), GFR ≤ 15 mL/min, or patients with morbid obesity (BMI ≥ 40 kg/m²) on presentation since these medical conditions may independently alter the BNP levels.^[6]

Methods

EMRs were reviewed to extract the study variables, which included demographics (age, sex, and race), BMI, Ejection Fraction, GFR on admission, and comorbidities, including Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), and ESRD. A total of 230 patients were identified to be admitted with respiratory distress and positive COVID-19 in the defined period. One hundred forty-six patients were included in the final analysis.

Cases excluded were as follows: 22 patients had no BNP drawn on admission, 13 patients had a history of ESRD, 10 patients presented with $\text{GFR} \leq 15 \text{ mL/min}$ on admission, 21 patients had $\text{BMI} \geq 40 \text{ kg/m}^2$ on admission, and eight patients had no EF available. APACHE II score; a known predictor of mortality,^[8] was calculated for all the included subjects by using the SFAR scoring website^[9] and number recorded on our datasheet.

The primary endpoints or outcomes were to determine the in-hospital mortality outcome as well as the duration of mechanical ventilation for patients admitted to the ICU (in days) and the hospital LOS (in days) for all subjects. To evaluate the effect of some continuous variables on the outcomes of interest, we classified the subjects into subgroups. We classified the patients based on the BNP value into two groups: one with normal BNP (defined as $\text{BNP} \leq 100 \text{ pg/mL}$) and the other with high BNP (defined as $\text{BNP} > 100 \text{ pg/mL}$). All the patients with available prior or current echocardiogram reports were classified into two subgroups based on the ejection fraction ($\text{EF} \geq 50\%$ vs. $< 50\%$). Further, all the patients were classified into two subgroups based on the GFR ($\text{GFR} \geq 60 \text{ mL/min}$ vs. $\text{GFR} < 60 \text{ mL/min}$).

Statistical analysis

We described the cohort characteristics by using frequency tables with proportions for binary and categorical variables and mean (with standard deviation) or median (with interquartile ranges) for the continuous variables based on the distribution. We reported the descriptive statistics for all the patients and then categorized them into two subgroups (patients with fatal cases and patients with non-fatal cases) based on the death outcome. We analyzed the binary, categorical, and continuous variables between the two subgroups and measured the association between the two, by using Pearson χ^2 -test for binary and categorical variables and *t*-test or nonparametric tests for continuous variables, as appropriate. We examined the association between the multiple variables and both hospital and ICU LOS by conducting univariate (unadjusted) and multivariate (adjusted) regression analyses. The highly correlated variables were removed from the regression analyses models to avoid collinearity. A *P*-value of < 0.05 is considered statistically significant. All calculations were made by using STATA version 14.2 (StataCorp, College Station, TX, USA).

RESULTS

A total of 230 patients were identified to be admitted with respiratory symptoms, including dyspnea, cough, and hypoxia related to a confirmed diagnosis of COVID-19.

One hundred forty-six patients were included in the final analysis.

Table 1 shows the demographic and clinical characteristics of the patients. Overall, 61.6% of patients were men, and the mean (\pm SD) age was 60.8 ± 15.1 years. More than half (56.2%) of the patients were Hispanic, and the remainder as outlined in Table 1. The mean (\pm SD) BMI was 28.7 ± 5.24 , and 44.5% of the patients had obesity. Almost one-quarter of the patients (24%) had $\text{GFR} < 60$ (keeping in mind that patients with ESRD and $\text{GFR} \leq 15$ were excluded). Almost one-third of the patients (30.1%) had a history of DM, and only a small fraction (6.2%) had a history of COPD. Most patients (93.1%) had no history of cardiomyopathy with documented $\text{EF} \geq 50\%$, and only 6.9% of the patients had a documented $\text{EF} < 50\%$. The average (\pm SD) hospital LOS for all the patients was 8.38 ± 6.33 days. The average (\pm SD) ICU LOS was 9.94 ± 6.7 days for the critical patients who required ventilation and ICU admission. The mean APACHE II score (\pm SD) on admission was 11.5 ± 5.6 . The differences between the two subgroups based on the mortality outcome are listed in Table 1.

Based on the lack of normal distribution for the BNP values, the median and interquartile range were reported, and the Wilcoxon rank-sum (Mann-Whitney) test was used to compare the two subgroups. Although the *P*-value was consistent with a statistically significant difference between the two subgroups, it was not clinically relevant as the statistical difference was accounted for by the significant variation in the normal values ($\text{BNP} < 100$) in the two subgroups. When the comparison was performed, using a value of $\text{BNP} > 100$, there was no statistically significant difference between the two subgroups. Patients in the group of $\text{GFR} < 60$ had significantly higher rates of death compared with the group of $\text{GFR} \geq 60$ ($P = 0.026$). APACHE II score on admission was a reliable prognostic indicator for the outcome of death, with a remarkably higher APACHE II score on admission in patients with fatal cases vs patients with nonfatal cases [15.5 ± 6.4 vs. 10.7 ± 5.1 respectively, with $P = 0.001$]. There was no statistically significant difference between the two subgroups (patients with and without in-hospital mortality) regarding age, gender, race, obesity, DM, COPD, EF subgroups, BMI, and hospital LOS.

We examined the association between hospital LOS as an outcome with each of the appropriate variables, as shown in Table 2. Age, BMI, and APACHE II score were added as continuous variables. Sex, race, GFR, COPD, DM, and EF subgroups were all added as binary variables with male, Hispanic race, normal GFR, no COPD, no DM, and normal EF

Table 1: Case status, demographic and clinical characteristics of patients with COVID-19, with and without associated in-hospital mortality

Variable	All patients	Patient with in-hospital mortality	Patient without in-hospital mortality	P-value
Mean age (SD)—year	60.79 (15.11)	64.08 (16.11)	60.147 (14.90)	0.27
Male	59.9 (14.68)	61.526 (15.689)	59.52 (14.48)	
Female	62.16 (15.824)	73.8 (15.32)	61.02 (15.55)	
Sex: no./total no. (%)				0.053
Male	90/146 (61.6%)	19/24 (79%)	71/122 (58%)	
Female	56/146 (38.36 %)	5/24 (21%)	51/122 (42%)	
Race: no./total no. (%)				0.896
Hispanic	82/146 (56.16%)	13/24(54%)	69/122 (57%)	
African American	20/146 (13.7 %)	4/24(17%)	16/122 (13%)	
Other	2/146 (1.37%)	0	2/122 (2%)	
Missing data	42/146 (28.77 %)	7/24(29%)	35/122 (29%)	
BMI—mean (SD)	28.7 (5.24)	29.6 (5.1)	28.5 (5.27)	0.35
Obesity BMI [30–40]	65/146 (44.5%)	10/24 (42%)	55/122 (45%)	0.758
Median BNP (IQ range)	22.5 (8–60)	50.5 (14.5–175.5)	21(6–48)	0.011
BNP >100	256(169.5–808)	374 (175.5–876)	241(159.5–808)	0.722
GFR group				0.026
≥60	111/146(76%)	14/24 (58%)	97/122 (80%)	
<60	35/146 (24%)	10/24 (42%)	25/122 (20%)	
DM	44/146 (30.14%)	6/24 (25%)	38/122 (31%)	0.549
COPD	9/146 (6.2%)	2/24 (8%)	7/122 (6%)	0.629
EF group				0.569
≥50	136/146(93.15%)	23/24 (96%)	113/122 (92%)	
<50	10/146 (6.85%)	1/24 (4%)	9/122 (7%)	
ICU LOS (if applicable)	9.94 (6.7)	7.54 (4.88)	12.45 (6.48)	0.01
Average hospital LOS (SD): day	8.38 (6.33)	9.4 (5.3)	8.2 (6.5)	0.32
Mean APACHE II score (SD)	11.5 (5.6)	15.5 (6.4)	10.7 (5.1)	0.0014

Table 2: Effect of demographic and clinical characteristics of patients with COVID-19 on the hospital LOS (Model Unadjusted and Model Adjusted Regression Analysis)

Variable	Univariate unadjusted model		Multivariate adjusted model*	
	Coef. (95% CI)	P-value	Coef. (95% CI)	P-value
Age (year)	-0.006 (-0.075–0.06)	0.861	-0.58 (-0.14–0.028)	0.184
Sex	-0.466 (-2.6–1.67)	0.667	-0.33 (-2.48–1.8)	0.758
Race	0.08 (-1.054–1.21)	0.892	.198 (-.98–1.37)	0.739
BMI	0.04(-0.16–0.24)	0.714	.0185523 (-0.19–0.23)	0.860
BNP	0.0008 (-0.001–0.003)	0.422	.0003 (-.002–0.002)	0.741
GFR group	-0.65 (-3.08–1.79)	0.600	-3.57(-6.62–0.52)	0.022
DM	-0.21 (-2.48–2.05)	0.852	-0.67 (-3.05–1.71)	0.579
COPD	-0.17 (-4.49–4.16)	0.940	-0.34 (-4.75–4.06)	0.878
EF group	0.5617647(-3.56–4.68)	0.788	1.07 (-03.29–5.42)	0.629
APACHE II score	0.2067085(.025–0.39)	0.026	0.46 (0.2–0.71)	0.001

*The model includes age, sex, race, BMI, BNP, GFR group, EF group, DM, COPD, and APACHE II score.

used as reference groups, respectively. The highly correlated variables were removed from the regression analysis models to avoid collinearity. The variable obesity was excluded, as BMI (as a continuous variable) was included as an independent variable. Adding obesity as a binary variable (BMI >30) after excluding the continuous BMI variable did not yield any statistically significant difference. The ICU LOS was removed from the model that predicts the hospital LOS (and vice versa) due to their potential collinearity.

In the univariate regression analyses, only the APACHE II score showed a strong association with the hospital LOS ($P = 0.026$). On adjustment with multivariate regression analysis to predict hospital LOS, APACHE II remained

a strong predictor of the hospital LOS after adjustment ($P = 0.001$). Further, the GFR group was also strongly associated with hospital LOS ($P = 0.22$). None of the other variables had any predictive value in estimating the hospital LOS based on the univariate and multivariate analyses.

Of the total of 146 patients included in our final cohort, 46 patients were admitted to the ICU. We performed both univariate and multivariate regression analyses to evaluate the association between the ICU LOS as an outcome with each of the appropriate variables in a similar way to the hospital LOS unadjusted and adjusted models. None of the variables was a reliable predictor of the ICU LOS with the small sample size of ICU patients.

DISCUSSION

Our study aimed at finding prognostic factors associated with more severe outcomes in patients who acquired COVID-19 infection to help providers determine patients at high risk. Identifying prognostic and predictive factors is crucial to assess various medical conditions and to help physicians anticipate clinical outcomes, especially for patients with critical conditions.^[4,10,11] Although the APACHE II scoring system is utilized mainly in critical care settings, the variety of physiologic and laboratory parameters needed for calculation may not be readily available.^[12,13] Hence, the search for other predictive and prognostic factors is rising, especially in the light of the SARS-COV-2 pandemic, which has generated vast numbers of critically ill patients in a short time.^[4,10,11] We applied the APACHE II among our subjects, and as expected, it was shown to be a valuable tool to predict mortality and LOS among patients with COVID-19 in our study. Two recent studies have illustrated a correlation between obesity, male sex, increasing age, and DM, with worse outcomes among hospitalized patients with COVID-19 infection.^[14,15]

Lang Wang *et al.* found that a high percentage of severe to critical cases and high mortality rates were observed in elderly patients with COVID-19.^[16] Patients' conditions on admission, such as dyspnea, lymphocytopenia, cardiovascular disease, COPD, and ARDS occurrence during hospitalization, predicted fatal outcomes.^[16] Another study by Tao Guo suggested that myocardial injury due to potential inflammation has a significant association with fatal outcomes of patients with COVID-19 due to impairment of cardiac function and ventricular tachyarrhythmias.^[17]

BNP level offers a promising value for patients presenting with acute dyspnea among patients with heart failure.^[18] Studies have demonstrated that plasma BNP level on admission helps differentiate between pulmonary and cardiogenic causes of dyspnea with high specificity and negative predictive value.^[18,19] NT-proBNP is usually released from the myocardial cell wall secondary to stress, in addition to the inflammatory molecules such as lipopolysaccharide, interleukin 1, C-reactive protein, and cardiotrophin, which are independent of ventricular function.^[10,20] Moreover, Nagaya *et al.* have suggested that there is likely a strong correlation between BNP levels and the mean pulmonary arterial pressure, as pressure load or right ventricular strain may be the underlying pathophysiologic mechanism.^[21,22]

Acknowledgment of the cardiac and noncardiac factors that affect the BNP plasma level is vital in identifying

underlying pathologies and excluding confounding factors on clinical encounters. BNP has a principal and robust effect on the kidneys by promoting tubular natriuresis and diuresis. Under normal physiologic circumstances, falls in cardiac output, adequate blood volume, and renal blood flow are accompanied by activation of the renin-angiotensin-aldosterone system to preserve the blood pressure and intravascular volume. The BNP effect is to oppose this effect by promoting natriuresis and increasing GFR.^[23] Renal dysfunction decreases this effect, as the kidney becomes less responsive to BNP, denoting BNP's oversecretion to compensate for the relative hypervolemia and cardiac wall stress from the overload. At the same time, heart failure reduces renal function effectiveness by reducing cardiac output and potentiating adverse effects. Thus, heart failure and renal dysfunction act synergistically in their ability to increase the secretion of BNP. This pathophysiological mechanism explains the elevation of BNP concentrations seen in renal failure patients^[24,25] and resonates with what was found in previous studies that BNP concentrations were progressively higher in patients with progressively advanced CKD and ESRD.^[26] Omitting confounding factors is likewise essential to yield vigorous results and increase the significance of a study.

Some reports from cardiologists in Chongqing, China, have suggested a correlation between NT-proBNP level and an increased risk of mortality in hospitalized patients with COVID-19.^[11]

One of our study's goals was to find whether there was a correlation between elevated BNP levels and a higher risk of death after SARS-CoV-2 infection. Our statistical analysis did not find a statistically significant association between BNP level and mortality rate ($P = 0.722$) or ICU LOS ($P = 0.741$). Our study findings were similar to the previous study, which showed no correlation between BNP levels and ICU LOS in patients with dyspnea.^[13]

Interestingly, a remarkable secondary outcome to our study was that impaired renal function ($GFR < 60$) on admission was significantly associated with an increased mortality rate ($P = 0.026$) and an increased ICU LOS ($P = 0.022$). In addition, patients with CKD were more likely to be admitted to the ICU and undergo mechanical ventilation. This observation suggests that kidney disease, whether acute or chronic, may represent a higher risk to faster deterioration and more significant adverse clinical outcomes. The putative receptor for SARS-CoV-2, the angiotensin-converting enzyme 2 (ACE2), is expressed in the human's kidneys, which may explain why the kidneys may be a direct target of the virus.^[27] Another plausible

mechanism is the superimposed pulmonary edema due to impaired fluid excretion. Another possibility is the limited COVID-19 pharmacological treatment options in patients with renal impairment due to the lack of safety data among these patient groups. These findings have corresponded to some of the previous studies that kidney injury was associated with an increased risk of death in patients with influenza A virus subtype H1N1 and SARS^[28,29] as well as recent studies in patients with COVID-19 infection.^[30] Further, recent studies showed that COVID-19 virus directly infects the human kidney tubules and induces acute tubular toxicity through different direct and indirect paths that result in tubular pathophysiology.^[31,32]

Our study population consisted of a high percentage of the Hispanic race, which is expected based on the Latino majority in the hospital area. There is only a small fraction of the Caucasian race in the surrounding area, which explains why it is included under “other” in Table 1.

Limitations

Our study included subjects from a single inner-city hospital. Our study population consists of a high percentage of Hispanic and African American races, which precludes generalization. Due to the strict inclusion criteria to minimize confounding factors, many subjects have been excluded from our analysis, which limited the number of our inclusion subjects. Further, all the patients who were screened and met the criteria were included in the study without a random selection process implemented, which may generate a selection bias. As echocardiograms (and other tests) were minimized during the pandemic to reduce unnecessary contact with patients with COVID-19, we used the patients’ previous echocardiogram reports as a proxy to determine their ejection fraction and congestive heart failure (CHF) status on admission. Previous echocardiograms may not reflect the current CHF and ejection fraction status for patients admitted with COVID-19, which could be considered another confounder. Finally, the retrospective design of the study has its own inherited limitations.

CONCLUSION

Ongoing research is being conducted to identify prognostic factors among patients with COVID-19. Although various studies have presented the predictive role of pro-BNP among patients with respiratory distress in the past years, our study did not find BNP an accurate predictive and prognostic factor among patients with COVID-19 in our study population. Renal impairment and high APACHE II scores on admission, on the other hand, have demonstrated to be strong predictors for COVID-19 morbidity and

mortality. This study could represent an introduction to more prominent multicenter studies to evaluate additional prognostic factors and minimize the ordering of nonspecific testing.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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