OPEN ACCESS

GAVIN PUBLISHERS

International Journal of Cerebrovascular Disease and Stroke

Ali S, et al. Int J Cerebrovasc Disease Stroke 4: 135.

DOI: 10.29011/2688-8734.000035

Research Article

Inpatient Utility of Pro-BNP in COVID-19: A Single Center Experience

Saif Ali[1*], Shuktika Nandkeolyar[1], Tanya Doctorian[1], Payush Chatta[2], Eunwoo Park[2], Sharon Fabbri[1], Shaunrick Stoll[3], Kristoff Foster[3], Reece Stutzman[3], Dmitry Abramov[1], Liset Stoletniy[1], Antoine Sakr[1]

[1]Division of Cardiology, Loma Linda University, California, USA

[2]Department of Internal Medicine, Loma Linda University, California, USA

[3]Loma Linda University School of Medicine, Loma Linda, California, USA

[*]**Corresponding author:** Saif Ali, MD, Division of Cardiology, 11234 Anderson Street, Room 4420, Loma Linda University, California, USA

Citation: Ali S, Nandkeolyar S, Doctorian T, Chatta P, Park, et al. (2021) Inpatient Utility of Pro-BNP in COVID-19: A Single Center Experience. Int J Cerebrovasc Dis Stroke 4: 135. DOI: 10.29011/2688-8734.000035

Received Date: 27 April, 2021; **Accepted Date:** 14 May, 2021; **Published Date:** 20 May, 2021

Abstract

Aims: The purpose of this study was to identify serologic and clinical factors in SARS-Coronavirus 2 (SARS-CoV-2) patients which may correlate and predict need for mechanical ventilation and mortality. Furthermore, we sought to determine if a diagnosis of heart failure and elevations in Pro B-Type Natriuretic Peptide (pro-BNP) predicted clinical endpoints.

Methods: 135 patients age 18 or older admitted to Loma Linda University Medical Center with SARS-Co-2 between March 16, 2020 and June 8, 2020 were categorized by demographic data (age, race, and gender), clinical parameters (temperature, heart rate, blood pressure, and peak Fraction of inspired Oxygen (FiO2)), and serologic markers pro-BNP. A regression analysis was done to correlate need for mechanical ventilation and mortality.

Results: In univariate analysis, elevated pro-BNP correlated with need for mechanical ventilation (p=0.006) and mortality (p=0.001). In multivariate analysis, elevated pro-BNP was significantly associated with requiring intubation (OR 4.5, p=0.03). Each year of age (OR 1.08, p=0.006) and unit of BMI (OR= 1.05, p=0.03) were significantly associated with increased mortality. In patients without a diagnosis of heart failure, average pro-BNP was elevated (1141.66 ng/dL) however it did not correlate with need for intubation or mortality.

Conclusions and clinical implications: Coronavirus disease-19 (COVID-19) is associated with increased mortality and worse clinical outcomes in patients with heart failure. Despite a lack of heart failure diagnosis, elevated markers such as NT-Pro-BNP have been associated with increased mortality in COVID-19 hospitalized patients. Although no clear 'cut-off' has been described, our study findings suggest elevated pro-BNP may be a useful marker for disease severity and respiratory complications of COVID-19 patients with possible cardiac involvement. Similar to other single center findings, our study demonstrates worsened clinical outcomes for patients with advanced age and elevated body-mass index.

Keywords: COVID-19; Pro-BNP; Heart Failure; Pneumonia

Key Points

- COVID-19 is a severe respiratory illness associated with increased mortality and risk for respiratory failure.
- Need for mechanical ventilation in COVID-19 patients increases with BMI and age.
- COVID-19 patients demonstrate an elevated pro-BNP even without a diagnosis of heart failure suggesting pro-BNP may be a marker for respiratory distress syndrome.

Introduction

Coronavirus disease-19 (COVID-19) is a global pandemic which originated in China and is propagated by SARS-CoV-2 which enters human epithelial cells via a transmembrane protein, Angiotensin Converting Enzyme 2 (ACE-2). ACE-2 is the shared target protein of ACEi and may be upregulated with use of Angiotensin Receptor Blockers (ARBs) [1]. The hallmark of COVID-19 is a severe respiratory distress syndrome [2]. Clinical characteristics reported in case series from China and New York include fevers, myalgias, cough, gastrointestinal symptoms, and a hyper-inflammatory response possibly related to a 'cytokine storm'[3,4].

In addition to acute respiratory distress syndrome, COVID-19 outcomes have close ties to cardiovascular disease and cardiovascular manifestations. There is an increased burden of myocardial injury in COVID-19 non-survivors compared to COVID-19 survivors [5]. Retrospective studies have found elevated Body-Mass-Index (BMI), lactic acidosis, and markers of cardiovascular injury correlate with increased mortality risk [6]. In the critically ill, older age, higher SOFA scores, and D-Dimer greater than 1 ug/mL are associated with increased mortality [7]. The severity of illness in COVID-19 has been found to correlate with viral load from respiratory secretions and inflammatory markers such as C-related peptide and Interleukin-6 [8].

The COVID-19 pandemic has re-sparked the interest in assessing the role ACEi or ARBs in viral pneumonias and Acute Respiratory Distress Syndromes (ARDS). Yet, retrospective studies of patients with ARDS have demonstrated ACEi or ARB may in fact have beneficial effects [9]. While other smaller studies have suggested ACEi/ARB may be therapeutic and possibly protective in COVID-19 [10]. Current society guidelines from the American College of Cardiology recommend continuing ACEi/ARB for COVID-19 patients with additional indications such as hypertension, diabetes, or heart failure [11].

To date, retrospective studies have found elevated pro-BNP correlates with disease severity or mortality outcomes in COVID patients [6]. We present an analysis of the COVID-19 cohort within a "blue zone", Loma Linda, California.

Methods

This is an observational study of 135 consecutive adult patients admitted to Loma Linda University Medical Center with COVID-19. Inclusion criteria was age ≥ 18 years old, and a documented positive COVID-19 testing by RT-PCR (Simplexa by DiaSorin Molecular) admitted between March 16, 2020 and June 8, 2020. Data was collected on basic characteristics such as age, gender race, admission vital signs, peak fraction of inspired oxygen (FiO_2), pro b-type natriuretic peptide (pro-BNP)(ng/dL), and prior to admission to medications. The clinical end points in this study were requiring intubation and mortality. The Loma Linda University Institutional Review Board approved the data collection protocol used in this study.

Statistical Analysis

Univariate analysis was performed with T-tests, Chi-Square or ANOVA as appropriate. Multivariate analysis was performed logistic regressions or cox proportional hazards as appropriate. There were two models the first with comorbidities on presentation: Age, gender, race, BMI, CAD, hypertension, Diabetes, COPD, OSA, heart failure, and hyperlipidemia; the second model included admission characteristics: elevated BNP, admission heart rate, admission systolic blood pressure, admission diastolic blood pressure, admission lactate, and admission QTc.

Baseline characteristics are described as mean ± standard deviation for continuous variables and number (proportion) for categorical variables. Age-corrected elevated pro-BNP was defined as pro-BNP > 450 ng/L in age<50, pro-BNP > 900 ng/L in age 50-75, and pro-BNP > 1800 ng/L in age >75 [12]. R version 4.0.2 was used for all statistical analysis (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Basic characteristics of the patients by age are summarized in Table 1. Overall, 133 patients were included, who had an average age of approximately 60 years, 48% were women, average BMI was 31.5 kg/m2. Of the 133 patients, 25.6% had heart failure diagnosed prior to admission. 13% of patients had CAD, 67% hypertension, 41% diabetes, 36% hyperlipidemia, and 9% COPD. On admission, average heart rate was 94 bpm, systolic blood pressure 124 mmHg, and diastolic blood pressure 70mmHg. Mean admission lactate was 2 mmol/L and proBNP was 3953 pg/mL. Average QTc of the cohort was 457ms. Of the 133 patients, 36% had an age-adjusted elevated proBNP [12]. During their hospitalization, all patients required supplemental oxygenation with average FiO2 37%, 21.8% required intubation, and had an average length of stay (days) of 9.5. The overall mortality rate was 15.8% (Table 1 and Supplementary Figure 1).

A. Baseline Characteristics	**Overall**	**<50 years old**	**50-75 years old**	**>75 years old**	**P-value**
Number of patients *(n)*	133	38	72	23	
Age (mean (SD))	59.83 (16.80)	39.66 (9.86)	62.76 (6.91)	84.00 (5.78)	**<0.001**
Women (n (%))	64 (48.1)	14 (36.8)	35 (48.6)	15 (65.2)	0.098
Race (n (%))					0.109
Caucasian	47 (35.3)	9 (23.7)	31 (43.1)	7 (30.4)	
Hispanic	42 (31.6)	13 (34.2)	19 (26.4)	10 (43.5)	

African American	13 (9.8)	5 (13.2)	4 (5.6)	4 (17.4)	
Other	31 (23.3)	11 (28.9)	18 (25.0)	2 (8.7)	
Body Mass Index (kg/m²) (mean (SD))	31.55 (10.24)	35.95 (9.94)	31.45 (10.56)	24.97 (5.21)	**<0.001**
Heart Failure (n (%))	34 (25.6)	3 (7.9)	21 (29.2)	10 (43.5)	**0.005**
Coronary Artery Disease (n (%))	17 (12.8)	1 (2.6)	9 (12.5)	7 (30.4)	**0.007**
Hypertension (n (%))	89 (66.9)	19 (50.0)	52 (72.2)	18 (78.3)	**0.028**
Diabetes (n (%))	55 (41.4)	6 (15.8)	37 (51.4)	12 (52.2)	**0.001**
Hyperlipidemia (n (%))	48 (36.1)	7 (18.4)	27 (37.5)	14 (60.9)	**0.003**
Chronic Obstructive Pulmonary Disease (n (%))	12 (9.0)	2 (5.3)	8 (11.1)	2 (8.7)	0.595
Obstructive Sleep Apnea (n (%))	14 (10.5)	5 (13.2)	8 (11.1)	1 (4.3)	0.539
ACEi / ARB/ ARNI (n (%))	101 (75.9)	32 (84.2)	53 (73.6)	16 (69.6)	0.342
Admission heart rate (mean (SD))	93.82 (24.02)	102.53 (21.70)	92.19 (22.66)	84.52 (27.99)	**0.011**
Admission systolic blood pressure (mean (SD))	123.74 (25.46)	124.32 (14.40)	123.42 (29.78)	123.83 (26.01)	0.985
Admission diastolic blood pressure (mean (SD))	70.29 (18.11)	75.16 (14.48)	69.92 (18.59)	63.39 (20.23)	0.046
Admission Lactate (mmol/L) (mean (SD))	2.03 (2.50)	1.98 (2.29)	2.11 (2.88)	1.85 (1.45)	0.922
Admission QTc (ms) (mean (SD))	457.13 (42.13)	449.00 (34.81)	460.25 (48.18)	460.65 (31.88)	0.395
Admission proBNP (ng/L) (mean (SD))	3953.96 (11451.74)	5732.60 (18936.93)	2593.83 (5226.51)	5042.05 (8012.09)	0.499
Elevated proBNP (n (%))	32 (36.8)	6 (23.1)	17 (37.0)	9 (60.0)	0.061
ACEi: Angiotensin Converting Enzyme inhibitor; **ARB:** Aldosterone Receptor Blocker; **ARNI**: Angiotensin Receptor Neprilysin Inhibitor					

Table 1: Baseline Characteristics and Outcomes of COVID-19 Patients.

In univariate analysis, patients requiring intubation were more likely to have heart failure (p=0.049), higher admission lactate (p<0.001), longer QTc (p=0.001), and more likely to have age-corrected elevated proBNP (p=0.006). Heart failure diagnosis (p=0.005), admission QTc (p=0.006) and age-corrected elevated proBNP (p=0.001) were significantly associated with mortality in univariate analysis, while a diagnosis of OSA (p=0.076) and admission SBP (p=0.059) trended towards significance. The results of the univariate analyses are summarized in Supplementary Table 1. Patients who had a known diagnosis of heart failure were more likely to have an age-adjusted elevated pro-BNP (p=0.001) (Supplementary Table 2). However, even those without a known diagnosis of heart failure had an overall elevated pro-BNP of 1141 ng/L (Supplementary Table 2).

In multivariate analysis, women were less likely to require intubation (OR = 0.22, p=0.04), whereas each 1% increase in BMI connoted an 8% increased risk of requiring intubation (OR 1.08, p=0.02). Additionally, patients who required intubation were more likely to have an elevated age-corrected proBNP (OR = 4.5, p=0.03), and each 1 mmol/L of lactate connoted a 60% increase in risk of requiring intubation (OR 1.6, p=0.047), and each 1 bpm increase in heart rate connoted a 3% increased risk of requiring intubation (OR 1.03, p=0.03). Age (OR 1.08, p=0.006) and BMI also correlated with mortality, with each 1 unit of BMI associated with a 5% increase in risk of mortality (OR 1.05, CI 1.02-1.14, p=0.03). The results of the multivariate analyses are summarized in Table 2A and 2B.

Variable	Require Intubation		Mortality	
	Odds Ratio	**P-value**	**Odds Ratio**	**P-value**
Age	1.11	0.2	1.08	**0.005**
Caucasian	1	-	1	-
Hispanic	1.58	0.44	1.17	0.8
African American	0.32	0.32	2.23	0.48
Other	1.98	0.32	1.12	0.87
Female	0.32	**0.04**	0.87	0.78
Body Mass Index	1.08	**0.02**	1.05	**0.03**
Coronary Artery Disease	2.41	0.24	1.66	0.49
Hypertension	1.11	0.86	0.44	0.23
Diabetes	0.77	0.63	1.48	0.5
Heart failure	1.52	0.55	2.14	0.22
Hyperlipidemia	0.34	0.08	1.05	0.94
Chronic Obstructive Pulmonary Disease	1.04	0.96	0.45	0.35
Obstructive Sleep Apnea	1.97	0.37	2.77	0.15
Admission Lactate	1.72	**0.048**	1.13	0.11

Table 2A: Multivariate Odds Ratios of Requiring Intubation and Mortality in COVID-19 Patients.

Variable	Require Intubation		Mortality	
	Odds Ratio	**P-value**	**Odds Ratio**	**P-value**
Admission Heart Rate	1.03	**0.03**	1.01	0.45
Admission Systolic Blood Pressure	1.03	0.06	1	0.7
Admission diastolic blood pressure	0.98	0.34	0.98	0.34
Admission QTc	1.01	0.13	1.01	0.32
Admission elevated proBNP	4.5	**0.03**	2.35	0.23

Table 2B: Multivariate Odds Ratios of Requiring Intubation and Mortality in COVID-19 Patients.

Discussion

Our single center experience echoes the results of the COVID-19 cohorts from China and New York. The diagnosis of heart failure, pro-BNP elevation, increased FiO2 requirements, and elevated lactate, predicted mortality in univariable analyses. Notably, patients who were older and had elevated BMI were at independently higher risk of mortality in multivariate analysis (Table 2). Higher elevations in pro-BNP were associated with increased mortality and need for intubation in univariate analysis in all COVID-19 patients. Our findings mirror those of a recent meta-analysis from Pranata et al regarding their COVID-19 cohort where pro-BNP was higher in non-survivors and was associated with a 6.4 magnitude increase in likelihood ratio for mortality [13]. The loss of significance of pro-BNP in multivariate analysis of mortality with a heart failure diagnosis signals that pro-BNP in this viral pandemic may indicate severity of illness related to pulmonary injury. In the critically ill, increase in pro-BNP is often clinically correlated to severity of heart failure, however its utility may be expanded to assess illness severity in ARDS necessitating mechanical ventilation [14].

In a recent single center study, elevated levels of NT-Pro-BNP above 156 ng/L were associated with increased mortality in patients without heart failure admitted for COVID-19 pneumonia [15]. The authors chose a cut-off for NT-Pro-BNP within the 'gray zone' where mild elevation may not necessarily reflect underlying heart failure. It is known that both NT-Pro-BNP and pro-BNP have gray zones and should always be interpreted contextually [16]. The significance of elevated pro-BNP in non-heart failure patients hints at a possible cardiac and pulmonary involvement of COVID-19. However, due to small sample size and predominantly single center experiences, results should be interpreted cautiously.

An adjunctive finding was the significant association between BMI and risk for intubation. These findings make BMI a useful clinical marker to predict need for increased ventilator support (OR: 1.1, CI: 1.05-1.15, p= 0.04). Notably, with each 1 unit increase in BMI, there is a 10% associated increase in need for intubation. Many studies have demonstrated increased risk for pneumonia with rising BMI. In fact, meta-analysis of patients with pneumonia have proposed a paradoxical 'U' or 'J' shaped curve for BMI and mortality [17]. These results expand the findings from prior studies demonstrating increased risk for pulmonary complications in patients with an elevated BMI in COVID-19 [18-20].

A limitation of our study is the relatively small cohort which may not have been sufficiently powered to detect differences in mortality amongst COVID-19 patients. Our population remained at increased risk for mortality with increasing age (Supplemental Figure 1). The majority of fatal cases occurred in patients at the second and third highest age groups (i.e. above age 50). These findings are consistent with the seminal reports from Wuhan, China in which median age of the fatal COVID-19 cases was 65 and higher, with majority of death associated with acute respiratory failure (81%) and ARDS (74%) [21]. Finally, our data is limited due to a lack of follow up beyond inpatient hospitalizations.

Despite these limitations, our study indicates that pro-BNP may be a useful marker of disease severity in COVID-19 patients who may or may not have heart failure or a marker suggestive of possible cardiac involvement.

Future Directions

As clinicians globally attempt to treat COVID-19 with alternative approaches, there is a need for prospective studies elucidating risk factors for increased morbidity, mortality, and comparative efficacy of different treatments. Large, multicenter studies are needed to better inform providers and address the current global pandemic.

Acknowledgment

Saif Ali, Shuktika Nandkeolyar and Tanya Doctorian were critical to the conception, data analysis, and editing of the manuscript. Payush Chatta, Eunwoo Park, Sharon Fabbri, Shaunrick Stoll, Kristoff Foster and Reece Stutzman assisted in data collection. Dmitry Abramov, Liset Stoletniy and Antoine Sakr provided intellectual concepts and were critical to the process of editing this manuscript. The authors have no financial or material support to disclose.

Conflict of Interest

Saif Ali, Shuktika Nandkeolyar, Tanya Doctorian, Payush Chatta, Eunwoo Park, Sharon Fabbri, Shaunrick Stoll, Kristoff Foster, Reece Stutzman, Dmitry Abramov, Liset Stoletniy, and Antoine Sakr declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Authors' Contributions

All work in this manuscript is original. All authors had access to the data and played a role in writing the manuscript, and each accepts responsibility for the content.

References

1. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, et al. (2003) Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 426: 450-454.
2. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, et al. (2020) COVID-19 and Cardiovascular Disease. Circulation. 141: 1648-1655.
3. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. (2020) Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 382: 1708-1720.
4. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, et al. (2020) Clinical Characteristics of Covid-19 in New York City. N Engl J Med. 382: 2372-2374.
5. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW (2020) Association of Coronavirus Disease 2019 (COVID-19) With Myocardial Injury and Mortality. JAMA Cardiol. 5: 751-753.
6. Chen T, Wu D, Chen H, Yan W, Yang D, et al. (2020) Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 368: m1091.
7. Zhou F, Yu T, Du R, Fan G, Liu Y, et al. (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 395: 1054-1062.
8. Liu Y, Yang Y, Zhang C, Huang F, Wang F, et al. (2020) Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 63: 364-374.
9. Kim J, Choi SM, Lee J, Park YS, Lee CH, et al. (2017) Effect of Renin-Angiotensin System Blockage in Patients with Acute Respiratory Distress Syndrome: A Retrospective Case Control Study. Korean J Crit Care Med. 32: 154-163.
10. Gurwitz D (2020) Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 81: 537-540.
11. Bavishi C, Maddox TM, Messerli FH (2020) Coronavirus Disease 2019 (COVID-19) Infection and Renin Angiotensin System Blockers. JAMA Cardiol. 5: 745-747.

12. Januzzi JL, van Kimmenade R, Lainchbury J, Bayes-Genis A, Ordonez-Llanos J, et al. (2006) NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: the International Collaborative of NT-proBNP Study. Eur Heart J. 27: 330-337.

13. Pranata R, Huang I, Lukito AA, Raharjo SB (2020) Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. Postgrad Med J. 96: 387-391.

14. Bajwa EK, Januzzi JL, Gong MN, Thompson BT, Christiani DC (2008) Prognostic value of plasma N-terminal probrain natriuretic peptide levels in the acute respiratory distress syndrome. Crit Care Med. 36: 2322-2327.

15. Yoo J, Papamanoli A, Grewal P, Nakamura J, Dhaliwal S, et al. (2020) N-Terminal Pro-B-Type Natriuretic Peptide and Mortality in Patients without Heart Failure Hospitalized with Severe Covid-19 Pneumonia. J Card Fail. 26: S73.

16. McCullough PA, Kluger AY (2018) Interpreting the Wide Range of NT-proBNP Concentrations in Clinical Decision Making. J Am Coll Cardiol. 71: 1201-1203.

17. Nie W, Zhang Y, Jee SH, Jung KJ, Li B, et al. (2014) Obesity survival paradox in pneumonia: a meta-analysis. BMC Med. 12: 61.

18. Hussain A, Mahawar K, Xia Z, Yang W, El-Hasani S (2020) Obesity and mortality of COVID-19. Meta-analysis. Obes Res Clin Pract. 14: 295-300.

19. Raisi-Estabragh Z, McCracken C, Ardissino M, Bethell MS, Cooper J, et al. (2020) Renin-Angiotensin-Aldosterone System Blockers Are Not Associated With Coronavirus Disease 2019 (COVID-19) Hospitalization: Study of 1,439 UK Biobank Cases. Front Cardiovasc Med. 7: 138.

20. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, et al. (2020) Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. N Engl J Med. 382: 1653-1659.

21. Du Y, Tu L, Zhu P, Mu M, Wang R, et al. (2020) Clinical Features of 85 Fatal Cases of COVID-19 from Wuhan. A Retrospective Observational Study. Am J Respir Crit Care Med. 201: 1372-1379.