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Elevated N-Terminal Pro-B-Type Natriuretic Peptide (Nt-Probnp) Levels in Critically Ill Patients with Normal Transthoracic Echocardiogram and Normal Renal Function Tests

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ABSTRACT

Objective: To determine frequency of critically ill patients who have elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels with normal transthoracic echocardiogram and normal renal function tests.

Study Design: Descriptive cross-sectional study.

Place and Duration of Study: Medical Intensive Care Unit (ICU) of Pak Emirates Military Hospital, Rawalpindi Pakistan, from Jan to Jul 2022

Methodology: All patients fulfilling inclusion criteria and admitted in ICU of PEMH over the duration of study were enrolled in the study through non-probability consecutive sampling. Data for 50 patients was collected and their NT-proBNP levels in pg/mL were measured at admission and compared with reference limit based on age, for excluding congestive heart failure (CHF) after which frequency and percentage of patients with elevated NT-proBNP levels was calculated.

Results: Majority of critically ill patients with normal transthoracic echocardiogram and normal renal function tests had elevated NT-proBNP levels. Out of 50 patients included in this study, 37(74 %) had elevated NT-proBNP levels.

Conclusion: At the time of admission in ICU, critically ill patients with normal transthoracic echocardiogram and normal renal function tests had markedly elevated NT-proBNP levels. Thus, NT-proBNP levels alone cannot be reliably used in critically ill patients to rule out heart failure.

Keywords: Amino-terminal probrain natriuretic peptide; Brain natriuretic peptide; B-type natriuretic peptides; natriuretic peptide.

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INTRODUCTION

Critically ill patients often need assessment to rule out Congestive Heart Failure (CHF) for which NT-proBNP appeared promising as a single test.[1] The human natriuretic peptides include atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), with primary synthesis occuring in cardiac ventricular muscle cells.[2] Cardiac ventricular wall stress leads to production of pre-pro-BNP in the ventricular myocytes.[3] In kidneys, BNP leads to increased sodium excretion and inhibition of secretion of aldosterone.[4] In cardiovascular system, BNP reduces preload and afterload by vasodilatation along with regulation of ventricular remodelling and suppressing sympathetic activity.[5] Renal clearance is the main mode for clearance of NT-proBNP, with a half-life of 120 minutes, with higher serum levels of NT-proBNP than BNP, in spite of both being produced equally,[6] due to which cut-off values of NT-proBNP should be adjusted for estimated glomerular filtration rate as interpretation of a specific abnormal result should be based upon the reference range reported for that result.[7] As low NT-proBNP is useful for excluding HF in the ICU, elevated levels in this setting require careful interpretation and may serve as an indicator of severity and prognosis in mainly non-cardiac diseases.[8] Patients with sepsis also have increased BNP levels, with sepsis being the main cause for the increase in BNP, independent of cardiac function.[9] Although a BNP level of 350 pg/mL was associated with a high negative predictive value (95%) for diagnosing cardiogenic shock, BNP levels are noted to be increased in majority of patients so could not differentiate between different forms of shock.[10] This study aims to investigate the frequency of critically ill patients who have elevated NT-proBNP levels with normal transthoracic echocardiogram and normal renal function tests, thus examining the reliability of NT-proBNP as a single test in ruling out CHF and fluid overload in critically ill patients.

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METHODOLOGY

This was a descriptive cross-sectional study carried out at the in the Medical Intensive Care Unit

(ICU) of Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, over a duration of six months, January to July 2022 after obtaining approval from Ethics Review Committee of PEMH, vide certificate number A/28/206/EC/470/1072. Non-randomized consecutive sampling techniques were used. Sample size was determined using previously available literature1 with confidence level of 95 %, anticipated population proportion of 66 %[1], population size was taken as 116, based on average number of new critically ill patients admitted in ICU during a 6-month-period, acceptable margin of error was 10% and sample size was calculated by Raosoft online calculator as 50.

Inclusion Criteria: Critically ill patients of either gender, with age ranging from 18 to 80 years, were included this study if they had a normal transthoracic echocardiogram and normal renal functions.

Exclusion Criteria: Patients who were transferred from other ICUs or who had been admitted multiple times previously in ICU were excluded.

Age and gender of all enrolled patients was noted. Primary diagnosis at the time of admission was recorded and their NT-proBNP level was sent within 4 hours of their admission in ICU. Data was analysed with Statistical Package for the Social Sciences (SPSS) version 26.0. Quantitative variables were calculated as Mean±SD. Qualitative variables were calculated as frequency and percentage.

RESULTS

Out of 50 patients, 28 were males (56%) and 22 were females (44%) with minimum age being 18 years and maximum being 76 years. Values of NT-proBNP were noted above limits for their age 37 patients (74%) and only 13(26%) patients had levels of NT-proBNP low enough to rule out heart failure for their age. Table-I shows the number and percentage of primary diagnosis of patients enrolled in the study. Table-II shows the values of NT-proBNP.

Table-I: Frequency of Primary Diagnoses Among ICU Patients, (n=50)

Diagnosis	n(%)
Sepsis	7(14%)
Acute bacterial meningitis	3(6%)
COPD	3(6%)
Community-acquired pneumonia	3(6%)
COVID-19	3(6%)
Haemorrhagic stroke	3(6%)
Tuberculous meningitis	2(4%)
Acute hepatic failure	2(4%)
Acute pancreatitis	2(4%)
Acute severe asthma	2(4%)
Dengue fever	2(4%)
Eclampsia	2(4%)
Influenza	2(4%)
Ischaemic stroke	2(4%)
Malaria	2(4%)
Rodenticide ingestion	2(4%)
Snakebite	2(4%)
Acute haemolytic anaemia	1(2%)
Acute respiratory distress syndrome	1(2%)
Alcohol withdrawal	1(2%)
Autoimmune encephalitis	1(2%)
Dural venous sinus thrombosis	1(2%)
Subarachnoid haemorrhage	1(2%)

Table-II: Quantitative Parameters Obtained In The Study (n=50)

NT-proBNP	Value (pg/mL)
Mean±SD	638.3±30.40
Range	756
Minimum	287
Maximum	1043

DISCUSSION

Regarding NT-proBNP levels, increased levels up to 35,000 pg/mL in patients with sepsis have been reported,[11] as patients with sepsis are as likely to have increased levels of NT-proBNP along with patients having acute decompensated HF, with NT-proBNP levels being similar in both groups.[12] In our study, all patients with sepsis had elevated levels of NT-proBNP, consistent with previous studies as sepsis leads to dilatation of both ventricles, interleukin-1 and cardiotrophin-1 with lipopolysaccharides upregulate the NT-pro BNP gene and hence increase secretion of NT-proBNP causing volume resuscitation to lead to increased natriuretic peptide levels.[13] Evidence suggest that APACHE II score was markedly raised higher with NT-proBNP and also independently predicted increased levels of NT-proBNP.[14] The frequency of interventions like volume resuscitation, vasopressor agents and mechanical ventilation are more in patients with higher levels of NT-proBNP and these interventions affect intravascular, intracardiac and intrathoracic pressures, leading to increased secretion of NT-proBNP.[15] One author reported that BNP and NT-proBNP levels were elevated in both patients with sepsis and HF at the time of ICU admission and despite haemodynamic differences, both did not have statistically different levels of NT-proBNP, similar to our study although median value of NT-proBNP in our study is much lower.[16] In another study, BNP levels were increased in majority

of patients and could not differentiatee between different types of shock on the basis of NT-proBNP,[17] also similar to our study where patients with normal cardiac function had values much higher than those which rule out heart failure. Another author reported elevated NT-proBNP values upto 35,000 pg/mL in patients with sepsis,[18] with NT-proBNP levels noted to increase with severity of disease and can be used to predictsmortality,[19,20] however the number and variety of factors reported to be associated with NT-proBNP is large,[21-24] rendering its specificity indeterminate.

LIMITATIONS OF STUDY

The present study has several limitations. The small number of patients in each diagnostic category limited assessment of the specific effect of individual diseases on NT-proBNP. Patients with conditions known to elevate NT-proBNP acutely, such as ischaemic or haemorrhagic stroke and acute COPD exacerbations, were not excluded or analyzed separately. Standardized severity scores (e.g., APACHE II) were not recorded, restricting evaluation of the relationship between illness severity and NT-proBNP. Moreover, important management variables, including fluid resuscitation, vasopressor support, and mechanical ventilation, were not systematically documented despite their potential influence on NT-proBNP levels.

CONCLUSION

NT-proBNP levels were elevated in 74 percent of ICU patients in this study. At the time of admission in ICU, critically ill patients with normal transthoracic echocardiogram and normal renal function tests had markedly elevated NT-proBNP levels. Thus NT-proBNP levels alone cannot be used in critically ill patients to rule out heart failure or volume overload.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

KMD & ZS: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

KH & AM: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

AZK: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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