PROGNOSTIC VALUE OF TRANSTHORACIC ECHOCARDIOGRAPHY AND BNP AS A BIOMARKER OF CARDIAC DYSFUNCTION IN PATIENTS WITH COMMUNITY ACQUIRED PNEUMONIA ADMITTED TO INTENSIVE CARE UNITS

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ABSTRACT

Background: Community acquired pneumonia (CAP) is a common and serious infection worldwide and severe CAP (SCAP) is usually defined as pneumonia that requires intensive care unit admission**.** Although 2 _20% of CAP patients require ICU admission, the mortality rates can be as high as 20-50%.

Aim and objectives: to determine the prognostic role of echocardiography and compare with admission N-terminal pro B-type natriuretic peptide (NT-proBNP) levels in adult patients with community-acquired pneumonia (CAP) who were admitted into intensive care units**.**

Subjects and methods: Our study was conducted on 90 consecutive adult patients admitted between May 2020 and February 2021 to intensive care, all patients were diagnosed to have CAP as primary diagnosis or as a part of diagnosis. We categorized the patients into 2 groups, group (A) non COVID19 CAP, and group (B) COVID -19 CAP.

Results: there was no statistically significant difference between the studied groups as regard (Demographic data, Severity scores at admission (except in CURB 65), ECHO findings of LV at admission, ECHO findings of RV at admission, ECHO findings of LV, ECHO findings of RV (except in FAC) and MV, ICU and hospital LOS) among non COVID-19 pneumonia patients and COVID-19 pneumonia patients with RV impairment.

Conclusion: RV dysfunction carried higher risk of mortality in community acquired pneumonia. However this was not statistically significant despite worsening of RV parameters and this might be type II error attributed to small sample size. ProBNP could predict mortality in CAP with reasonable accuracy.

Keywords: COVID-19, CAP, NT-proBNP, RV impairement

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INTRODUCTION

Community acquired pneumonia (CAP) refers to an infection of the lung parenchyma acquired in the community (outside a healthcare setting). Community-acquired pneumonia CAP forms a part of a larger group of diseases known as lower respiratory tract infections (LRTIs). The term "severe CAP (SCAP)" signifies a more serious form of pneumonia acquired in the community **(1)**.

According to the World Health Organization (WHO) estimates 2016, LRTIs accounted for around three million deaths worldwide. They ranked fourth globally and first among the low-income nations as the leading causes of death. In India, LRTI resulted in 63.1 deaths per 100,000 population and were the fourth biggest killer after ischemic heart disease, chronic obstructive pulmonary disease (COPD), and stroke **(2)**.

Community-acquired pneumonia is the third leading cause of hospital admissions **(3)**. About 20–40% cases of CAP require hospital admission and 5–10% of these need ICU admission. The 30-day mortality rates and re-admission rates among hospitalized patients with CAP are 10–12% and 18%, respectively **(4)**.

The role of echocardiography in adult patients with community acquired pneumonia has not been well tested in the clinical trials **(5)**.

Human BNP is a 32 amino acid polypeptide, this peptide is predominately released by left and right cardiac ventricles and regulates a wide array of physiological effects, including natriuresis, diuresis and vasodilatation. The main stimulus for secretion of BNP is cardiac stress, as reflected by myocardial stretch and pressure or volume overload **(6)**.

The aim of this study was to determine the presense of ventricular dysfunction in the setting of community acquired pneumonia in patients admitted to ICU and the prognostic role of transthoracic echocardiography combined with cardiac biomarker (Pro-BNP) in such patients.

PATIENTS AND METHODS

The study was a prospective observational cross-sectional study conducted on 90 adult patients

admitted between May 2021, and February 2022 to intensive care units in Imbaba General Hospital and El Sheikh Zayed Specialized Hospital. All patients had a diagnosis of Community acquired pneumonia either as a primary diagnosis or as a part of diagnosis. 45 patients suffered CAP non COVID -19 and 45 patients were diagnosed severe COVID-19 infection and were confirmed by a positive reverse-transcriptase polymerase chain reaction assay for coronavirus in a respiratory tract sample.

Inclusion criteria: Patients aged ≥ 18 years admitted to ICU with evidence of CAP as a primary diagnosis or a part of primary diagnosis, confirmed by chest radiography, whether patient need mechanical ventilation or judged to be unstable condition requiring intensive care.

Pneumonia was defined as new infiltrate on chest radiogram and two out of six clinical signs of pneumonia: cough, production of sputum, signs of consolidation on respiratory auscultation, temperature ≥ 38^{o} c or ≤ 35.8◦c, leukocytosis ≥ 10 $x10^{9}$/l, or leukopenia ≤ 4 $x10^{9}$/l, and more than 10 % rods.

The patients with severe COVID-19 enrolled in this study were diagnosed according to the guidelines for diagnosis and treatment of COVID-19 (trial sixth edition) published by the Chinese National Health Commission on 18 February 2020. The cases in this study included severe and critically ill disease, which was defined by the presence of any of the following: respiratory rate >30/min; oxygen saturation ≤ 93%;

PaO2/FiO2 ratio ≤ 300; patients with > 50 % lesions progression within 24- 48 hours in lung imaging ; respiratory failure requiring mechanical ventilation; shock; or respiratory failure combined with other organ failure requiring ICU treatment **(7)**.

Exclusion criteria: Patients aged > 18 years, Patients with chronic chest disease, Patients with poor echocardiographic window, Patients with known tricuspid valve lesion or right ventricular dysfunction and Patients with congestive heart failure.

Ethical Considerations: This study was done after approval of the Ethical committee of the Faculty of Medicine, Cairo University.Informed Written consent was taken from all participants or their legal representative if participant not able to give consent before recruitment in the study, and after explaining the purpose and procedures of the study.

Patients included in this study were subjected to the following: Detailed History, Physical examination, Laboratory findings, Pro-BNP was measured on admission to ICU in all CAP patients, X ray chest and Chest computed tomography score, The severity of CAP was evaluated with pneumonia severity index score, CURB -65 score, APACHE-II score, SOFA score, SMARTCOP score, A comprehensive transthoracic echocardiography done within 48 hours of admission using machine (GE Versana with probe 4C –RS) and (SonoScape M22 with probe 2P1) and A follow-up echocardiography was performed in our study on patients after one week.

Echocardiographic examination method: Echocardiography assessment with special emphasis on RV assessment.

Ultrasound device: (GE Versana active with probe 4C –RS) and (SonoScape M22 with probe 2P1 PHASED ARRAY transducer 1-6 MHZ).

Figure (1): (GE Versana active with probe 4C –RS).

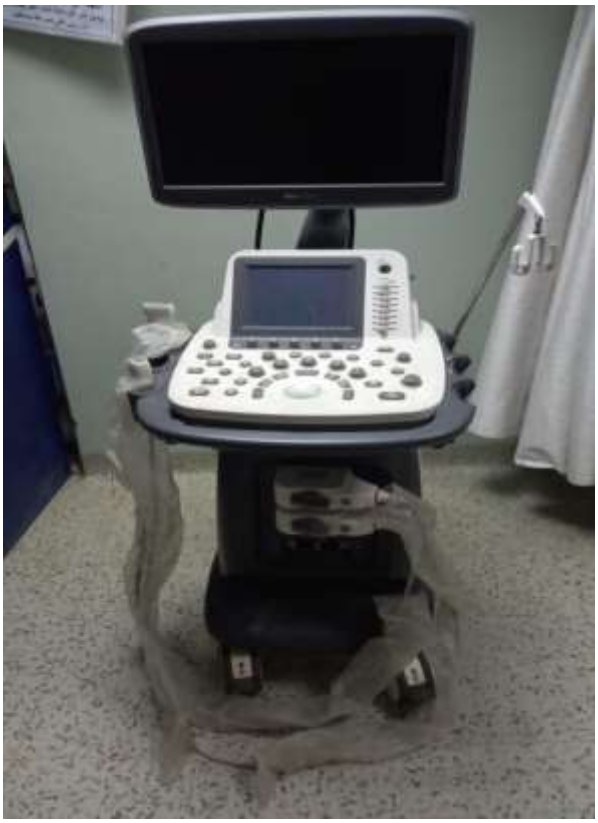

Figure (2): (SonoScape M22 with probe 2P1 PHASED ARRAY transeducer 1-6 MHZ)

Pro-BNP analysis methods: We used ELISA immunoassay technique that allows in vitro quantitative determination of human NT pro-BNP concentrations in serum, plasma and biological fluids.

Data Analysis and Statistical Methods

An Excel spreadsheet was established for the entry of data. We used validation checks on numerical variables and option-based data entry method for categorical variables to reduce potential errors. Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 24. Data was summarized using mean, standard deviation, median, minimum, maximum and interquartile range in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann-Whitney test. Correlations between quantitative variables were done using Spearman correlation coefficient. ROC curve was constructed with area under curve analysis performed to detect best cutoff value of NT proBNP for detection of outcomes. P-values less than 0.05 were considered as statistically significant.

RESULTS

Table (1): Shows Demographic among non COVID-19 pneumonia patients and COVID-19 pneumonia patients with RV impairment.

	Non COVID patients with RV impairment (TAPSE<1.7) (N=18)	**COVID patients with RV impairment (TAPSE >1.7) (N=13)**	**P value**
Age	65.4 ± 8.5	68.3 ± 10.4	0.4
Sex **Male** **Female**	 11 (61%) 7 (39%)	 8 (62%) 5 (38%)	0.98

Comorbidities None DM Cardiac diseases Cerebrovascular stroke Others	 0 (0%) 5 (28%) 13 (72%) 7 (39%) 8 (44%)	 0(0%) 4 (31%) 6 (46%) 2 (15%) 2 (15%)	0.25
Creatinine	1.5 ± 1.07	1.76 ±1.04	0.5

Data are represented as mean ± SD or number (%). Data are analyzed using independent student t test.

This table shows that there was no significant difference between COVID and non COVID patients with RV impairment regarding the demographic data.

Table (2): Severity scores at admission among non COVID-19 and COVID-19 patients with RV impairment.

	Non COVID 19 RV impairment Patients (n=18)	**COVID RV impairment patients (n=13)**	**P value**
CURB 65	3 ± 0.59	3.6 ± 0.63	0.006*
PSI	152 ±26	166 ± 27.2	0.13
APACHE II	19.9 ± 5.5	22.3 ± 9.3	0.88
SOFA D0	6.1 ± 6.01	5 ±1.77	0.52
SOFA D2	5.4 ± 2.4	6.6 ± 3.1	0.37
Smart COP	5.5 ± 2.4	6.3 ± 1.6	0.3

Data are represented as mean ± SD. Data are analyzed using Mann Whitney test.

This table showed that CURB 65 was higher in COVID-19 patients with RV impairment than non COVID-19 pneumonia patients with RV impairment while there was no significant difference regarding other severity scores.

Table (3): ECHO findings of LV at admission among non COVID 19 and COVID-19 patients with RV impairment.

	non COVID RV impairment Patients (n=18)	**COVID RV impairment patients (n=13)**	**P value**
LVEDD	5.4 ± 0.72	5.23 ± 0.66	0.51
LVESD	3.8 ± 0.77	3.38 ± 0.52	0.07
LVEF	60.2 ± 11.3	62.3 ± 7.5	0.56

Data are represented as mean ± SD or number (%). Data are analyzed using independent student t test

This table showed that there was no significant difference between non COVID-19 and COVID-19 patients with RV impairment regarding LVEDD, LVESD and LVEF at admission.

Table (4): ECHO findings of RV at admission among non COVID19 and COVID patients with RV impairment.

	Non COVID RV impairment Patients (n=18)	**COVID RV impairment patients (n=13)**	**P value**
RV (mid)	3.4± 0.51	3.3 ± 0.48	0.82
TAPSE	1.5 ± 0.11	1.57 ± 0.17	0.54
S'	8.9 ± 1.6	8.8 ± 1.22	0.83
TV max	2.8 ± 0.39	2.8 ± 0.32	0.87
RVSP	31.6 ± 6.2	32.2 ± 7.5	0.82
FAC	34.2 ± 7.5	32.08 ± 4.4	0.36

Data are represented as mean ± SD or number (%). Data are analyzed using independent student t test

This table showed that there was no significant difference between non COVID 19 and COVID-19 patients with RV impairment regarding RV, TAPSE, S', TV max, RVSP, FAC.

Table (5): ECHO findings of LV among non COVID 19 and COVID-19 patients with RV impairment at follow up.

	Non COVID 19 RV impairment Patients (n=14)	COVID RV impairment patients (n=8)	P value
LVEDD	5.6 ± 0.73	5.4 ± 0.66	0.43
LVESD	3.99 ± 0.83	3.6 ± 0.58	0.35
LVEF	54.9 ± 11.1	52.1 ± 6.2	0.52

Data are represented as mean ± SD or number (%). Data are analyzed using independent student t test

This table showed that there was no significant difference between non COVID 19 and COVID patients with RV impairment regarding LVEDD, LVESD and LVEF at follow up.

Table (6): ECHO findings of RV among non COVID 19 and COVID-19 patients with RV impairment at follow up.

	Non COVID RV impairment Patients (n=14)	COVID RV impairment patients (n=8)	P value
RV (mid)	3.3 ± 0.4	3.7 ± 0.52	0.07
TAPSE	1.6 ± 0.13	1.5 ± 0.39	0.41
S'	9.25 ± 1.17	8.8 ± 1.2	0.47
TV max	2.7 ± 0.4	3.02 ± 0.38	0.12
RVSP	31.5 ± 9.2	37.6 ± 9.5	0.15
FAC	37.7 ± 7.8	31.2 ± 4.4	0.04*

Data are represented as mean ± SD or number (%). Data are analyzed using independent student t test

This table showed that there was no significant difference between non COVID 19 and COVID-19 patients with RV impairment regarding RV (mid), TAPSE, S', TV max, RVSP at follow up while there was significant difference regarding FAC that was higher in non COVID-19 patients with RV impairment than COVID-19 patients with RV impairment.

Table (7): MV, ICU and hospital LOS among non COVID-19 and COVID-19 patients with RV impairment.

	Non COVID RV impairment Patients (n=18)	COVID RV impairment patients (n=13)	P value
MV	5 (28%)	2 (15%)	0.66
ICU LOS	9.9 ± 6.04	8 ± 4.8	0.35
Hospital LOS	11.6 ± 7.5	9.2 ± 6.6	0.36

Data are represented as mean ± SD or number (%). Data are analyzed using independent student t test or Fischer exact test.

This table showed that there was no significant difference between non COVID 19 and COVID-19 patients with RV impairment regarding MV, ICU LOS and hospital LOS.

DISCUSSION

Community-acquired pneumonia (CAP) is a leading cause for hospital admission and results in substantial morbidity, mortality, and significant healthcare expenditures **(8)**.

Our study showed no significant difference in severity scores apart from CURB 65 in COVID-19CAP patients and non COVID-19 CAP patients with RV dysfunction.

In agreement with our study, **van Blydenstein et al. (9)** demonstrated that there was no significant difference between the groups regarding severity scores. He also found that both groups had similar severity of ARDS scores which may be due to small sample size of both studies as he compared 48 patients with severe and critically ill COVID19 with 24 patients with non COVID-19CAP. This is in comparison to a Turkish study 268 which described exclusively critically ill patients and showed no difference between the SOFA scores of the COVID-19 ARDS group and the non-COVID-19 ARDS group were comparable (7 and 8 respectively), and the APACHE II was the same (21) **(10)**.

In disagreement with our study**, Evrard et al. (11)** reported that ARDS unrelated to SARS-CoV-2 patients had a higher SOFA score and required more frequently a vasopressor support than patients of ARDS related to SARS-CoV-2, presumably due to the low incidence of primary bacterial infection in his patients.

In our study, we found significant difference in NT-Pro BNP levels between COVID-19and non COVID-19 patients with RV impairment, as it was higher in COVID patients with p value of 0.001. Unlike our study, **Jirak et al. (12)** was comparing critically ill COVID-19 patients admitted to intensive care with CAP patients of other etiology other than COVID-19 and he found that non-COVID-19 presented higher levels of cardiac biomarkers (hs-Tn, creatine kinase myoglobin fraction, and Nterminal pro-BNP) with P value of 0.001 suggesting a higher burden of CI in non-COVID-19 and noted that Simultaneously, a higher frequency of myocardial injury in laboratory results and pulmonary congestion on radiography imaging in nonCOVID-19 was observed Therefore, he speculated that a high burden of myocardial injury is generally observed in critical pneumonic disease of various non-COVID-19 origin and not specifically a COVID-19-dependent finding.

In the current study, there was no significant difference between

COVID-19 and non COVID-19 patients with RV impairment regarding LVEDD, LVESD and LVEF at admission or follow up, in agreement with our study, **Evrard et al. (11)** demonstrated similar finding as he found indexed LVED volume (44 versus 43 ml/m2) indexed LVES volume (20 versus 20 ml/m2), LVEF (52 % versus 54.5%)

We showed that there was no significant difference between COVID-19 and non COVID-19 patients with RV impairment regarding RV, TAPSE, S', TV max, RVSP, FAC at admission or during follow up. In agreement with our study, **van Blydenstein et al. (9)** demonstrated that there were no significantly different echocardiography findings between the complicated and non-complicated COVID-19 patients.

We showed that there was no significant difference between COVID-19 and non COVID-19 patients with RV impairment regarding RV (mid diameter), TAPSE, S', TV max, RVSP on admission and follow up while there was significant difference regarding RVFAC that was lower COVID-19 patients with RV impairment than non COVID-19 patients with RV impairment.

In disagreement with our study, **Evrard et al. (11)** reported that RVFAC and TAPSE were statistically lower in ARDS not related to SARS-CoV-2 compared to ARDS related to SARS-CoV-2, whereas tricuspid S' maximal velocity was not. These parameters were preserved in patients with ARDS related to SARS-CoV-2, this could be related to that all his patients were mechanically ventilated, intrathoracic positive pressure have presumably altered RV hemodynamic, in increasing RV afterload and reducing venous return, hence RV preload, also the prevalence of acute cor-pulmonale (ACP) was higher in this group than that in other groups (SARS-COV-2 related ARDS and the control group). ACP develops in the presence of excessive RV afterload. This results in a prolonged RV contraction, RV-LV pressure imbalance, and subsequent paradoxical interventricular septal motion. It has previously been suggested than increased RV afterload induces a reduction of RV radial shortening. Interestingly, transverse wall motion (i.e., RV radial shortening), which is reflected by RVFAC, was a better marker of RVEF than the longitudinal wall motion assessed using TAPSE in patients with pulmonary hypertension. RV volume overload states have also been shown to influence the ventricular mechanical pattern. The interventricular septum is a major contributor to RV contraction, when the LV contracts, septal circumferential myocardial fibers shorten, leading to a RV shortening along both the radial and antero-posterior axes. In the case of a paradoxical septal motion, the septum is unable to efficiently contract, potentially leading to a reduction in RV radial and anteroposterior shortening.

We showed that there was no significant difference between COVID-19 and non COVID-19 patients with RV impairment regarding RRT while there was significant difference regarding vasopressors that was higher in COVID-19 than non COVID-19 patients with RV impairment. Unlike our study **Evrard et al. (11)** reported statistically significant difference regarding vasopressors where patients with ARDS unrelated to SARS-CoV-2 group required more frequently a vasopressor support than patients ARDS related to SARS-CoV-2 group as the Main causes of ARDS in group(ARDS unrelated to SARS-CoV-2) were septic shock (45%), community-acquired pneumonia (18%), and Influenza virus pneumonia (13%).

We showed that there was no significant difference between COVID-19 and non COVID-19 patients with RV impairment regarding MV, ICU LOS and hospital LOS, although these parameters were higher in non COVID-19 patients but we thought it was due to the higher mortality in COVID-19 patients in early days of admission.

In agreement with our study **Asar et al. (10)** reported that there was no significant difference regarding time of stay in the ICU, and duration of invasive mechanical ventilation of the COVID-19 and non COVID-19 pneumonia groups.

We showed that mortality rate was higher in COVID-19 patients with RV impairment than non COVID-19 patients with RV impairment (more than

twice, 62% versus 28%, p value 0.07) but it did not reach statistically significant difference.

In line with our study, **Jirak et al. (12)**, demonstrated that mortality was high in both groups critically ill (COVID-19 and non COVID-19 pneumonia patients) and tended to be even higher in nonCOVID-19 but not significantly different, thus reflecting a poor outcome in both COVID-19and non-COVID-19-related pneumonia.

CONCLUSION

We concluded in our results that RV dysfunction carried higher risk of mortality in community acquired pneumonia. However this was not statistically significant despite worsening of RV parameters and this might be type II error attributed to small sample size. ProBNP could predict mortality in CAP with reasonable accuracy.

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