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Original article

Prognostic value of transthoracic echocardiography and biomarkers of cardiac dysfunction in community-acquired pneumonia

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ABSTRACT

The aim of this study was to determine the prognostic role of echocardiography and compare with admission N-terminal proB-type natriuretic peptide (NT-proBNP) levels in adult patients with community-acquired pneumonia (CAP). Consecutive adult patients hospitalized with CAP were prospectively enrolled and followed-up until hospital discharge or death. Echocardiography was performed within the first 48 hours. Complicated hospitalization (CH) was defined as intensive care unit admission, need for mechanical ventilation or in-hospital mortality. This study was registered with ClinicalTrials.gov, number NCT02441855. A total of 15 CH (13.5%) occurred among 111 patients with CAP. CAP patients with a CH compared with those without CH had significantly higher NT-proBNP values (1267.4±1146.1 vs. 305.6±545.7 pg/mL, p <0.001) and troponin I (23.8±24.3 vs. 10.3±6.3 ng/mL, p 0.02) but had lower left ventricle ejection fraction (52.7±8.7 vs. 60.5±6.7%, p <0.001) and tricuspid annular plane systolic excursion (TAPSE), which is a measure of right ventricular systolic function (17.1±4.4 vs. 21.8±4 mm; p 0.001). Patients with elevation of NT-proBNP and decreased TAPSE at presentation had a significantly higher probability of CH (60%) than patients with either elevated NT-proBNP or decreased TAPSE (40%). Patients with neither elevated NT-proBNP nor decreased TAPSE had a 0% probability of CH. This is the first study to demonstrate that decreased right ventricular systolic function is associated with increased rates of adverse events in patients with CAP.
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Introduction

Community-acquired pneumonia (CAP) is a leading cause for hospital admission and results in substantial morbidity, mortality, and significant healthcare expenditures [1]. Risk stratification and prediction of prognosis are the key issues for management of CAP patients, allowing the selection of the most appropriate care setting, whether outpatient treatment, admission to a hospital ward or the intensive care unit. Several risk scores, such as the pneumonia severity index (PSI) and CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure, age ≥65 years), can be used to assess the severity of pneumonia and predict complicated hospitalizations (CH) and mortality [2–4]. Sepsis and septic shock are often associated with myocardial dysfunction that involves both ventricles [5,6]. Although recent studies showed that cardiac complications are common in patients with CAP and associated with more severe disease, the prevalence of myocardial dysfunction and its relation with outcome is unclear [7,8]. Brain natriuretic peptide (BNP) is a neurohumoral marker for left ventricular dysfunction secreted by the heart in response to myocardial stretch caused by volume overload [9]. It has been demonstrated to be a potent prognostic marker in CAP, which may reflect the comorbidity load and also provide further prognostic information in patients with CAP [10,11]. Elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) has also been shown to have good correlation with clinical scores and to be an important predictor of short- and long-term mortality and acute kidney injury in patients with CAP [12,13]. Although effects of pneumonia on cardiac structures are theoretically possible because of increased systemic inflammatory

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activity and altered myocardial metabolic balance during infections, the role of transthoracic echocardiography has not been adequately studied in patients with CAP.

We have very recently shown that patients with CAP had significantly higher NT-proBNP levels, lower tricuspid annular plane systolic excursion (TAPSE), which is an excellent measure of right ventricular systolic function, and reduced elasticity of aorta compared with a control group [14]. Current data show that a depressed TAPSE portends a poor prognosis in patients with heart failure [15], pulmonary hypertension [16], and acute pulmonary embolism [17]. However, the clinical and prognostic significance of TAPSE has not been tested in adult patients with CAP. Thus, we conducted a prospective observational study to determine whether TAPSE represents a simple noninvasive measure of right ventricle function and has prognostic value in patients with CAP.

Methods

Study design

The study was a prospective, observational, and single-centre study, conducted at the Muğla Sıtkı Koçman University Hospital, Muğla, Turkey, from March 2015 to May 2015. All patients included in this study were treated according to the Infectious Diseases Society of America/American Thoracic Society consensus guidelines for management of CAP in adults [18]. All patients were followed up during hospitalization or until death. This project was approved by the regional ethics committee and registered with ClinicalTrials.gov, number NCT02441855. All patients or their relatives gave informed written consent.

Selection of participants

All patients of at least 18 years of age with a diagnosis of CAP hospitalized through the emergency department were prospectively recruited. We excluded patients who met any of the following criteria: younger than 18 years, active pulmonary tuberculosis, hospital-acquired pneumonia, pregnancy, severely immunocompromised patients, patients undergoing chronic dialysis, and patients sent for ambulatory treatment. Pneumonia was defined by the presence of two or more of the following recently acquired symptoms or signs: temperature >38°C, dyspnoea, cough, sputum production, pleuritic chest pain, or bronchial sounds or crackles on chest auscultation, plus radiographical findings of pneumonia.

Chest radiographs used for the diagnosis of pneumonia were independently reviewed by two staff radiologists who had no patient-specific clinical information. Patients were excluded if the radiographic findings were considered to represent a pre-existing infiltrate or if they were consistent with an alternative diagnosis.

CAP was defined as pneumonia acquired outside a hospital or long-term care facility that occurred within 48 hours of hospital admission or in a patient presenting with pneumonia who did not have any of the characteristics of healthcare-associated pneumonia (i.e. hospitalized in an acute care hospital for 2 or more days within 90 days of infection; stayed in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or haemodialysis clinic).

Data collection

The following parameters were collected on admission to the emergency department: sociodemographic characteristics, vital signs including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature. Complete blood count, routine biochemical analyses, NT-proBNP and troponin I concentrations were measured within the first 24 hours. For all patients with CAP, severity of pneumonia was quantified by the PSI and CURB-65 (confusion, blood urea nitrogen >20 mg/dL, respiratory rate >30 breaths/min, blood pressure <90/60 mmHg, and age ≥65 years) scores, which were calculated on admission as previously described [19,20]. A PSI score ≥4 and a CURB-65 score ≥3 were considered to be associated with complicated hospitalization, as previously described [4].

Transthoracic echocardiography

Standard M-mode and two-dimensional colour Doppler echocardiography was performed in all patients using Philips System (Philips Epiq 7G, Andover, MA, USA) within 2 days of hospital admission. Physicians performing echocardiography were blinded to the history and physical examination as well as biomarker results. Standard views, including the left lateral decubitus and supine positions, were obtained. The M-mode traces were recorded at a speed of 50 mm/s and the Doppler signals were also recorded at a speed of 100 mm/s. M-mode echocardiographic measurements were obtained based on the standards of the American Society of Echocardiography [21]. Diameter of the ascending aorta was measured from the same view on the M-mode tracing at 3 cm above the aortic valve. The systolic diameter was measured at the maximal anterior motion of the aorta, whereas the diastolic diameter was measured at the peak of the QRS complex on the simultaneously recorded electrocardiogram. Five consecutive cardiac beats were measured routinely and averaged.

Blood pressure was measured with an external sphygmomanometer. The aortic stiffness index, aortic distensibility, and aortic strain were determined as aortic elasticity properties. The formula used in calculation of these parameters were as follows [22,23].

$$\text{Aortic strain (\%)} = (\text{aortic systolic diameter} - \text{diastolic diameter}) \times 100 \,/\, \text{diastolic diameter}$$

$$\text{Aortic distensibility (cm}^2\text{/dyn)} = (2 \times \text{aortic strain}) \,/\, (\text{systolic pressure} - \text{diastolic pressure})$$

Left ventricular ejection fraction was measured by transthoracic echocardiography using modified Simpson's rule. Tricuspid annular plane systolic excursion (TAPSE), which is an index of right ventricular systolic function, was estimated by two-dimensional echoguided M-mode recordings from the apical four-chamber view with the cursor placed at the free wall side of the tricuspid annulus (Fig. 1) [24]. Twelve random aortic strain, TAPSE, M-mode and Doppler recordings were analysed to determine the inter- and intraobserver variability. Intraobserver and interobserver variabilities were <5% for all echo parameters.

Study endpoints

The primary study endpoint was CH defined as at least one of the following: in-hospital mortality, intensive care unit admission, or need for mechanical ventilation. The secondary outcome of interest was length of stay in hospital. Univariate analyses were performed to assess the associations between initial prognostic indicators (PSI, CURB-65, biomarkers, and echo parameters) and outcome.

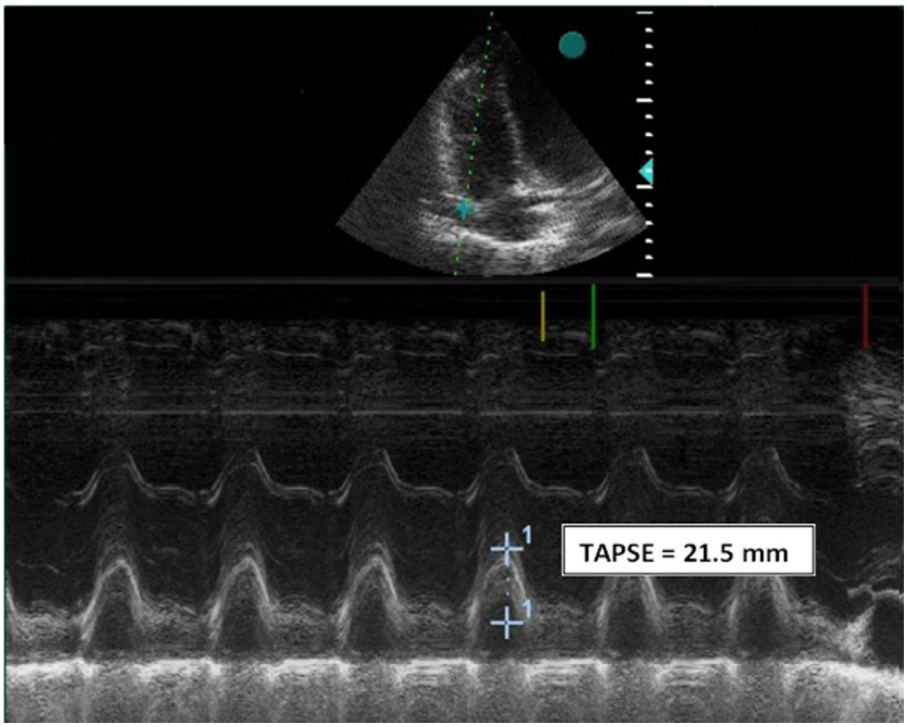

Fig. 1. Measurement of tricuspid annular plane systolic excursion (TAPSE) obtained using an M-mode cursor passed through the tricuspid lateral annulus in a four-chamber view and measuring the amount of longitudinal displacement of the annulus at peak-systole.

Statistical analysis

Data were analysed using SPSS for Windows (version 15; SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation and were compared between groups by two-tailed Student *t* test. Nonparametric tests were also used when necessary (Mann-Whitney *U* test). Statistical differences among groups were tested by one-way analysis of variance and Kruskal-Wallis tests for parametric and nonparametric variables, respectively. Fisher exact test or chi-square test was used for comparison of categorical variables. Univariate analyses were applied to determine OR and 95% CI of TAPSE, BNP, PSI, and CURB-65. ROC curve analyses were performed to determine sensitivity and specificity of BNP and TAPSE.

Correlation analyses were performed using the Pearson test. For all analyses, $p < 0.05$ was considered to be statistically significant.

Results

Baseline characteristics of study patients

A total of 111 patients with CAP (mean age 65.8±13.8 and 52% male) were enrolled. Hypertension was the most common comorbidity (51.4%), followed by coronary artery disease (25.2%), diabetes mellitus (19.8%), and chronic obstructive pulmonary disease (13.5%). The mean CURB-65 and PSI score values were 1.7±1.2 and 3.2±1.2, respectively. Respiratory rate was 24.1±4.4 breaths/min, heart rate was 77.2±14.2 bpm, and body temperature was 37.6±0.6°C on admission. Median length of stay was 6 days.

Antibiotic therapy

The decision for antibiotic treatment and the choice of the antibiotic agent was left to the discretion of the physicians. Combination therapy with ceftriaxone, cefotaxime, ertapenem, or ampicillin-sulbactam plus a macrolide or clarithromycin or clarithromycin XL was the preferred regimen. Monotherapy with a respiratory fluoroquinolone given either i.v. or orally was also used in 35 patients.

Complicated hospitalizations

Complicated hospitalization occurred in 24 episodes of 15 (13.5%) patients. Three patients (2.7%) died during follow-up, mechanical ventilation was required in eight patients (7.2%), and intensive care unit admission was required in 13 patients (11.7%).

Comparison of complicated and uncomplicated hospitalizations

The baseline characteristics of patients with complicated and uncomplicated CAP are presented in Table 1. There were no statistically significant differences between the groups in terms of gender, systolic and diastolic blood pressure, body temperature, history of hypertension, hyperlipidaemia, or smoking. Not surprisingly, patients who incurred a complicated course were older and more likely to have underlying comorbid diseases such as atrial fibrillation, diabetes, coronary artery disease, heart failure, cerebrovascular disease, or chronic obstructive pulmonary disease. Respiratory rate and heart rate on admission were higher in patients who had a complicated course of pneumonia. Comparison of laboratory parameters, echocardiography results, pneumonia severity scores, and length of stay in patients with and without CH are also shown in Table 1. CAP patients with a CH had significantly higher NT-proBNP (1267.4±1146.1 vs. 305.6±545.7 pg/mL, $p < 0.001$), troponin I (23.8±24.3 vs. 10.3±6.3 ng/mL, p 0.02), creatinine (1.1±0.44 vs. 0.88±0.29 mg/dL, p 0.013), and red blood cell distribution width values (17.9±4.4 vs. 15±2%, p 0.04) compared with patients without CH. However, albumin levels on admission

Table 1
Comparison of patients who had complicated and uncomplicated hospitalizations

	Uncomplicated hospitalizations (n=96)	Complicated hospitalizations (n=15)	p-Value
Male	48 (50)	10 (66.7)	0.23
Age, years	63.5±13.4	79.4±7.8	<0.001
Heart rate, bpm	74.9±12.5	92±15.7	<0.001
Body temperature, °C	37.6±0.6	37.7±0.5	0.42
Respiratory rate, bpm	23.3±3.9	29.2±4.3	<0.001
Systolic blood pressure, mmHg	126±15.4	124.4±14.8	0.85
Diastolic blood pressure, mmHg	78.1±8.4	78.4±7.9	0.70
Medical history			
Atrial fibrillation	5 (5.2)	3 (20)	0.040
Smoking	20 (20.8)	3 (20)	0.94
Diabetes mellitus	15 (15.6)	7 (46.7)	0.005
Hypertension	48 (50)	9 (60)	0.47
Hyperlipidaemia	31 (32.3)	3 (20)	0.34
Coronary artery disease	20 (20.8)	8 (53.3)	0.007
Cerebrovascular disease	7 (7.3)	4 (26.7)	0.020
Heart failure	5 (5.2)	3 (20)	0.040
Chronic obstructive pulmonary disease	10 (10.4)	5 (33.3)	0.016
Malignancy	9 (9.4)	2 (13.3)	0.63
Laboratory results			
NT-proBNP, pg/mL	305.6±545.7	1267.4±1146.1	<0.001
Troponin I, ng/mL	10.3±6.3	23.8±24.3	0.002
White blood count, $\times 10^3$ cells/mL	9.7±3.6	8.3±3.6	0.098
Haemoglobin, g/dL	12.6±1.9	11.8±1.7	0.12
Albumin, g/dL	3.9±0.5	3.6±0.4	0.036
Creatinine, mg/dL	0.88±0.29	1.1±0.44	0.013
Mean platelet volume, fL	8.5±1.1	8.1±1	0.17
Red cell distribution width, %	15±2	17.9±4.4	0.004
Echo parameters			
Aortic systolic diameter, cm	3.5±0.4	3.3±0.2	0.16
Aortic diastolic diameter, cm	3.3±0.4	3.2±0.1	0.59
Aortic strain, %	6.2±1.9	3.2±1	<0.001
Aortic distensibility, cm^2/dyn/10	2.7±1	1.8±0.7	<0.001
Left ventricle ejection fraction, %	60.5±6.7	52.7±8.7	<0.001
TAPSE, mm	21.8±4	17.1±4.4	0.001
Pneumonia severity index	3±1.2	4.4±0.6	<0.001
CURB-65	1.5±1	2.9±1.3	<0.001
Length of stay, days	6.0±3.2	18.9±11.2	<0.001

Values are given as mean ± standard deviation or number (percentage).

were lower in patients with CH compared with patients without CH (3.6±0.4 vs. 3.9±0.5 g/dL, p 0.036).

When echocardiographic parameters were evaluated, patients with CH had lower left ventricular ejection fraction (52.7±8.7 vs. 60.5±6.7%, p <0.001), TAPSE (17.1±4.4 vs. 21.8±4 mm, p 0.001), aortic distensibility (1.8±0.7 vs. 2.7 ±1 cm^2/dyn/10, p <0.001), and aortic strain (3.2±1 vs. 6.2±1.9%, p <0.001) compared with those without CH. The median lengths of stay were 5 and 19 days in uncomplicated and complicated patients, respectively (p <0.001). Patients with a CH of CAP had much higher CURB-65 (2.9±1.3 vs. 1.5±1, respectively, p <0.001) and PSI scores (4.4±0.6 vs. 3±1.2, respectively, p <0.001) compared with patients with uncomplicated course.

Performances of severity scoring systems, NT-proBNP and TAPSE

Of the study population, 55 (49.5%) patients had a PSI score ≥4 and 24 (21.6%) patients had a CURB-65 score ≥3. The receiver operating characteristic curve analysis showed that the optimal cutoff level, sensitivity, and specificity of TAPSE to distinguish the CH from the uncomplicated group were 18 mm, 73.3%, and 79.8%, respectively (AUC 0.78, 95% CI 0.64–0.91, p 0.001). The optimal cutoff of NT-proBNP levels to distinguish the CH from the uncomplicated group was 211 pg/mL, with a sensitivity and specificity of 86.7% and 75%, respectively (AUC 0.81, 95% CI 0.68–0.95, p <0.001). Univariate analyses showed that PSI score ≥4 (OR 18.78, 95% CI 2.37–148.63), CURB-65 score ≥3 (OR 11.71, 95% CI 3.47–39.43), and NT-proBNP ≥211 pg/mL (OR 18.78, 95% CI 2.37–148.63) were positively associated with CH, and TAPSE ≥18 (OR 10.45, 95% CI 3.01–36.32) was negatively associated with CH. The crude data of PSI score, NT-proBNP, and TAPSE are shown in Fig. 2(a), and CURB-65 score, NT-proBNP, and TAPSE are shown in Fig. 2(b).

Correlation analysis for NT-proBNP and TAPSE in patients with CH

The plasma concentration of NT-proBNP correlated with aortic strain (r -0.363, p <0.001), aortic distensibility (r -0.298, p 0.001), TAPSE (r -0.214, p 0.023), PSI score (r 0.276, p 0.003), and CURB-65 score (r 0.330, p <0.001). TAPSE was correlated with the presence of coronary artery disease (r -0.231, p 0.015), PSI score (r -0.216, p 0.023), serum troponin (r -0.193, p 0.043), and NT-proBNP levels.

Relation of NT-proBNP and TAPSE with outcomes

Of the 111 patients with CAP, 55 had NT-proBNP ≤211 pg/mL and TAPSE >18 mm, 44 had NT-proBNP >211 pg/mL or TAPSE ≤ 18 mm, and 12 had NT-proBNP >211 pg/mL and TAPSE ≤18 mm.

Patients with elevation of NT-proBNP and decreased TAPSE at presentation had a significantly higher probability of the composite outcome (60%) than patients with either elevated NT-proBNP or decreased TAPSE (40%) (Fig. 3). Patients with neither elevated NTproBNP nor decreased TAPSE had a 0% probability of CH.

Discussion

This study is the first to demonstrate a significant association between echocardiographic markers (TAPSE) and poor outcomes in patients with CAP. The addition of TAPSE to NT-proBNP provided incremental prognostic value, and patients with CAP who had concomitant elevations of NT-proBNP and impaired right ventricular systolic function as estimated by TAPSE were at particularly high risk for CH.

Although interactions between the pulmonary and cardiovascular systems are increasingly appreciated and the value of transthoracic echocardiography has been extensively studied in various lung diseases [25,26], its prognostic role in CAP has not been evaluated. Diseases of the respiratory system affect primarily the right side of the heart and echocardiography provides a rapid and non-invasive method to evaluate right ventricular functions. However, assessing right ventricular function by echocardiography is challenging because of complex geometry and the retrosternal position of the right ventricle, which can limit echocardiographic imaging windows [27]. Systolic displacement of the tricuspid annulus toward the right ventricle apex (longitudinal plane), referred to as TAPSE, closely correlates with right ventricle ejection fraction [27]. Importantly, TAPSE does not require geometric assumptions or right ventricle endocardial definition, and thus has been found to be highly reproducible and practical [27]. Normal values for TAPSE are 15–20 mm and decreased TAPSE portends a poor prognosis and is associated with longer hospital length of stay in patients with heart failure [15] and pulmonary hypertension [16]. Forfia and colleagues showed that patients with pulmonary hypertension and with a TAPSE <18 mm had dramatically reduced survival [28]. The value of TAPSE and right ventricle function were also studied in a few noncardiac or infectious illnesses [29–35]. Gajanana et al. showed that TAPSE <2.4 cm was associated with

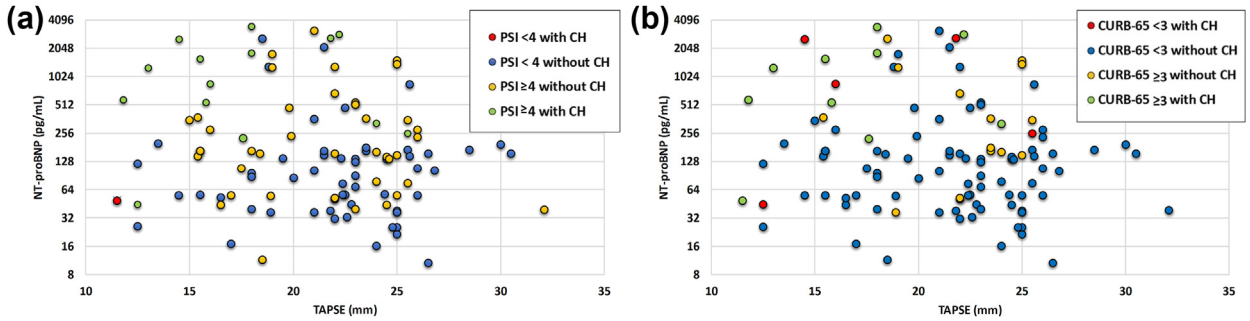

Fig. 2. (a) Association of pneumonia severity index (PSI) score, with N-terminal pro B-type natriuretic peptide (NT-proBNP) and tricuspid annular plane systolic excursion (TAPSE): crude analysis. (b) Association of CURB-65 (confusion, urea nitrogen, respiratory rate, blood pressure, age ≥65 years), with N-terminal pro B-type natriuretic peptide (NT-proBNP) and tricuspid annular plane systolic excursion (TAPSE): crude analysis.

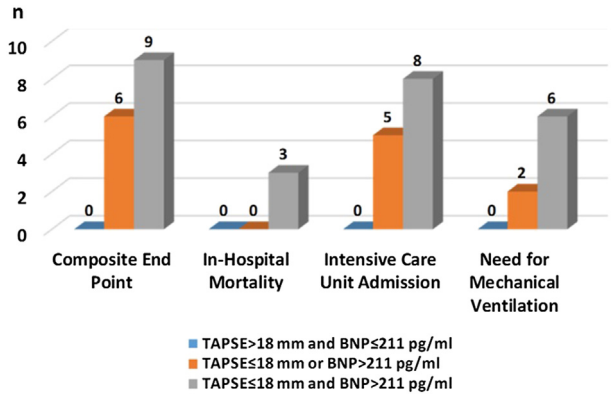

Fig. 3. Number of patients with composite and individual clinical outcomes according to the N-terminal pro B-type natriuretic peptide (NT-proBNP) levels and tricuspid annular plane systolic excursion (TAPSE).

increased length of stay and independently predicts in-hospital mortality in critically ill patients [29].

Demir et al. showed that TAPSE was decreased in hepatitis secondary to infection with the hepatitis C virus [30] or hepatitis B virus [31] compared with the healthy control group. Terzano and colleagues evaluated 75 patients hospitalized for chronic obstructive pulmonary disease exacerbation and demonstrated a relationship between TAPSE and hypoxaemia [32].

Orde et al. showed that right ventricle dysfunction was associated with high mortality in patients with severe sepsis or septic shock [33]. We showed recently that TAPSE was significantly lower in the adult patient group with CAP than in the control group [14]. The results of these studies suggest that systemic infectious diseases may influence the right ventricular function, which raises a question of the effect of acute illness and possible inflammation on the right ventricle.

Biomarkers are also useful tools in diagnosis, prognostics, and follow-up treatment of CAP. Recent studies have shown that cardiac complications are common in patients with CAP, are associated with more severe disease, and may predict prognosis [12]. As a result, cardiovascular biomarkers such as natriuretic peptides and troponins are found to be superior compared with inflammatory markers, especially for determination of long-term prognosis in CAP [12]. Chang and colleagues showed that elevated NT-proBNP is a strong predictor of mortality from CAP independent of clinical prognostic indicators [12]. The authors found that NT-proBNP >220 pg/mL had a sensitivity of 88% and a specificity of 71% for 30-day mortality. Mean platelet volume [34] and red blood cell distribution width levels [35] have also been shown to be valuable markers for predicting mortality and the severity of disease among patients with CAP. In our study, CAP patients with a CH had significantly higher NT-proBNP, troponin I, creatinine, and red blood cell distribution width but lower albumin compared with patients without CH. Plasma concentration of NT-proBNP correlated with aortic stiffness indices, TAPSE, PSI, and CURB-65 scores. Our data are in agreement with those reported by Christ-Crain et al., who demonstrated that BNP levels increased with rising disease severity as classified by the PSI in patients with CAP [36].

In our study, TAPSE was correlated with the presence of coronary artery disease, PSI score, serum troponin, and NT-proBNP levels. The results of our study demonstrated that not only NT-proBNP but also TAPSE objectively reflect severity of disease in patients with CAP (NT-proBNP was positively correlated and TAPSE was negatively correlated with the PSI), and none of the patients with NT-proBNP ≤211 pg/mL and TAPSE >18 mm at presentation had CH. Although the pathophysiological basis for elevated NT-proBNP and decreased TAPSE in patients with a complicated course of CAP is unknown, it suggests that cardiac involvement may be an underrecognised determinant of outcome in CAP and may require a different approach to treatment. Regardless of the underlying mechanism involved, our data suggest that the use of TAPSE as an objective prognostic marker may improve detection of patients at risk for complications in CAP.

Study limitations

This study was performed at single centre. Therefore, our results may not be relevant to all patients with CAP. Cardiac magnetic resonance imaging, which is accepted as the current gold-standard noninvasive measure of right ventricle function, was not used. TAPSE and NT-proBNP measurements were not systematically repeated during the follow-up period, and therefore the prognostic value of serial changes could not be assessed. A multivariate analysis could not be performed because of sparse data. Although our study showed that the TAPSE is associated with increased rates of adverse events, it is difficult to investigate the independent association of TAPSE or any factor with our outcome, as CH occurred only in 15 patients. Further prospective studies in a larger population with longer follow-up are needed to confirm our results.

Conclusions

In CAP patients, abnormalities in the structure and function of the right ventricle may be present at early stages of the disease. These abnormalities correlate with clinical scores and biomarkers, which seem to be particularly useful in clinical practice. Because NT-proBNP is a biomarker of subclinical myocardial injury and

TAPSE is an early and more easily quantifiable marker of subclinical right ventricular dysfunction, our findings suggest that markers reflecting distinct pathobiologic processes may provide complementary prognostic information in CAP. The addition of TAPSE to NT-proBNP provided incremental prognostic value, and patients with CAP who had elevation of NT-proBNP and decreased TAPSE were at particularly high risk for poor outcomes. Further research with more patients is needed to determine the prognostic significance of TAPSE in patients with CAP.

Transparency declaration

The authors declare that they have no conflicts of interest.

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