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Right Ventricular - Pulmonary Arterial Uncoupling in Patients with Acute Heart Failure and Reduced Ejection Fraction

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Abstract

This study investigated the TAPSE/PASP ratio, a measure of right ventricle-pulmonary artery coupling, as a predictor of short-term outcomes in heart failure patients with reduced ejection fraction.

Background: Acute heart failure is a serious condition with high readmission and mortality rates. Identifying patients at high risk can improve care. The right ventricle plays a key role, and the TAPSE/PASP ratio assessed by echocardiography is a promising tool. Right ventricular (RV) - pulmonary artery (PA) coupling has emerged as a comprehensive index of global RV performance. As echocardiography is the most conventional and feasible method for assessing cardiac morphologies and functions, many studies have evaluated several echocardiographic parameters through different modalities as reliable measurements of RV-PA coupling in comparison with invasive ones, of which the ratio between tricuspid annular systolic excursion (TAPSE) & pulmonary artery systolic pressure (PASP) has gain much attention in recent years.

Methods: This multicenter prospective comparative study studied 50 patients with acute heart failure. Researchers measured TAPSE/PASP ratio and tracked hospital stay, readmissions, and mortality.

Results: Lower TAPSE/PASP ratio correlated with longer hospital stays, more readmissions, and higher mortality. A cutoff value of 0.4 identified patients with worse outcomes (hospital stay and readmission) with high accuracy. Another cutoff of 0.28 predicted mortality with high accuracy.

Conclusion: TAPSE/PASP ratio appears to be a valuable tool for risk stratification and predicting outcomes in heart failure patients. This may help guide treatment decisions and improve patient care.

Keywords: Right ventricle; Pulmonary artery; Uncoupling; TAPSE/PASP; Acute heart failure

Abbreviations: TAPSE: Tricuspid Annular Systolic Excursion; PASP: Pulmonary Artery Systolic Pressure; RV: Right Ventricular; PA: Pulmonary Artery; HF: Heart Failure; AHF: Acute Heart Failure; LEVDD: Left Ventricular End Diastolic Dimension; LVESD: Left Ventricular End Systolic Dimension; LVEF: Left Ventricular Ejection Fraction; FAC: Fractional Area Change; AUC: Area Under Curve; IHD: Ischemic Heart Disease; HTN: Hypertension

Introduction

Heart failure (HF) is a syndrome characterized by recurrent episodes of hospitalizations that deeply affect patients' quality of life and account for large healthcare expenditures [1]. Acute heart failure refers (AHF) to rapid or gradual onset of symptoms and/or signs of HF, severe enough for the patient to seek urgent medical attention, leading to an unplanned hospital admission or an emergency department visit. Patients with AHF require urgent evaluation with subsequent initiation or intensification of treatment. AHF is a leading cause of hospitalizations in subjects aged >65 years and is associated with high mortality and rehospitalization rates [2]. The right ventricle is extremely sensitive to hemodynamic changes and increased impedance. In AHF, the development of pulmonary venous congestion and the increase of left ventricular filling pressures favors pulmonary vascular adverse remodeling and ultimately RV dysfunction, leading to the onset of symptoms and to a further deterioration of cardiac dynamics [3].

Different studies have shed light on both right ventricular dysfunction and pulmonary hypertension as important prognostic factors in patients with heart failure [4], whereas the relationship between them (best described as Coupling) has the most prognostic value. Right ventricular-pulmonary artery coupling can be defined as the relationship between RV contractility and RV afterload; The normal adult pulmonary vascular bed is a low-pressure, low-resistance and high compliance system capable of accommodating large increases in blood flow with minimal elevations of mean pulmonary artery pressure, the normal right ventricle is coupled to this low-pressure and high-compliance pulmonary circulation to ensure transfer of blood to the pulmonary arteries in an energy efficient fashion; As pulmonary hypertension develops, the vascular bed becomes a high-pressure, high resistance, and low compliance system leading to an additional load on the contracting ventricle; When RV contractility cannot rise anymore to match RV afterload, RV-PA uncoupling occurs. As echocardiography is the most conventional and feasible method for assessing cardiac morphologies and functions, many studies have evaluated several echocardiographic parameters through different modalities as reliable measurements of RV-PA coupling in comparison with invasive ones, of which the ratio between tricuspid annular systolic excursion (TAPSE) & pulmonary artery systolic pressure (PASP) has gain much attention in recent years [5].

It was first reported that TAPSE/PASP ratio assessed with echocardiography might be a useful clinical index of RV function. The ratio was thought to be a more accurate indicator of RV dysfunction severity than either TAPSE or PASP alone [6].

More recent studies concluded that TAPSE/PASP ratio is a straightforward measurement of RV-PA coupling based on its correlation with measurements through right heart catheterization [7]. This study aimed to study the short-term prognostic value of RV - PA uncoupling measured by TAPSE/PASP ratio in acute decompensated heart failure patients with reduced ejection fraction during hospitalization and its role in predicting short-term morbidity and mortality.

Study Design and Population

This multicenter prospective comparative study was conducted over 1 year period from August 2021 to August 2022 at Benha University hospital and Maadi military hospital. Informed consents were obtained from all participants & the study was approved by the ethics committee on research involving human subjects of Faculty of Medicine - Benha University. Our study was carried out on 50 patients clinically diagnosed with acute decompensated Heart Failure with left ventricular ejection fraction (LV EF) <40% on hospital admission.

The exclusion criteria were patients who are poorly echogenic, patients with significant valvular heart disease (severe Aortic or mitral stenosis and severe aortic or severe primary mitral regurgitation), patients with primary pulmonary hypertension, pulmonary hypertension due to chest disease (eg. COPD), pulmonary hypertension due to chronic thromboembolism, patients with recent acute coronary syndrome, patients with intracardiac devices, patients with debilitating diseases in addition to heart failure (end stage renal disease, liver cirrhosis, Cancer) and patients with marked cognitive impairment. All patients were subjected to:

i. **History taking:** Detailed personal history, past history of medical disease, drug history and family history were discussed with all participants.

ii. **Clinical examination:** Complete general and local examination on admission, including vital signs evaluation. A-General examination: All participants were subjected to complete physical examination including assessment of the general condition and vital signs as blood pressure and heart rate B- Cardiac examination: Heart sounds, Additional sounds, Cardiac murmurs.

iii. **Laboratory Investigations:** Complete blood count, plasma glucose level, serum creatinine, urea, serum electrolytes, coagulation profile, liver function tests, troponin, arterial blood gases.

iv. **Standard 12-leads ECG:** To detect Rate, rhythm, conduction abnormalities and ischemic changes.

v. **Resting Transthoracic Echocardiography (TTE):** Standard echocardiography with Doppler studies were performed using a Vivid S5 Dimension ultrasound framework (GE Healthcare, Waukesha, WI, USA).

All pictures and estimations were procured from standard perspectives and revised carefully. All patients had a baseline transthoracic echocardiogram within 24 hours of admission and upon discharge using 2D, M-mode and doppler imaging. Left ventricular end diastolic dimension (LVEDD), Left ventricular end systolic dimension (LVESD), Left ventricular ejection fraction (LVEF), left atrial dimension, LV diastolic function, right atrial dimensions, right ventricular dimensions, tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic excursion (PASP), right ventricular fractional area change (FAC), tricuspid lateral annular systolic velocity (RV S'). Values denoting RV dysfunction [8]: TAPSE < 16mm, RVFAC < 35% and RV s' < 9.5 cm.

Follow up: All patients were followed up during hospitalization. Follow up echocardiography before discharge using same parameters were obtained to assess RV-PA coupling after the proper treatment and its correlation with hospital stay duration and case progression, patients were followed for the next 30 days post discharge for short-term morbidity and mortality through telephone interviews or outpatient visits.

Sample Size Calculation

The minimum sample size required for sensitivity and specificity test was calculated by using PASS software (PASS 11 citation: Hintze J (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA). Based on the previous report by Saleiro and colleagues (2020), Kaplan Meier curves showed different event free survival

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among groups TAPSE/PSAP =0.33 vs <0.33mm/mmHg (69% vs 43%, Log Rank P=0.01) for all-cause mortality. Using Modified hypergeometric exact, proportion of outcome of 0.1, setting alpha error at 5% and power at 80%. The minimum required sample size for the study is determined to be 50 patients without accounting for dropout rate.

Statistical Analysis

An Excel spreadsheet was established for the entry of data. The analyses were be carried with SPSS software (Statistical Package for the Social Sciences, version 24, SSPS Inc, Chicago, IL, USA). Frequency tables with percentages were used for categorical variables and descriptive statistics (mean and standard deviation) were used for numerical variables. All statistical tests were two-sided. P values less than 0.05 were considered significant and P values less than 0.001 were considered highly significant. ROC analysis was done for TAPSE/PASP in predicting prognosis. Area Under Curve (AUC) with 95% confidence interval, best cutoff point, and diagnostic indices were calculated. Multivariate logistic regression analysis was done for predicting prognosis. The odds ratio and the 95% confidence interval were calculated.

Results & Discussion

Demographics and General Characteristics

The mean age in our study group was 63.62 ±5.06 years ranged between 54 to 73 and 66% of them were males, also 42% of patients were smokers. Regarding comorbidities: 50% of patients were diabetics (DM), 34% had history of ischemic heart disease (IHD) and 54% had history of hypertension (HTN). Regarding clinical data; the average HR was (108.7 ± 9.1) beat/min, the average RR was (24.8 ± 3.4) breath/min, and the average MAP was (77.4 ± 15.6) mmHg (Table 1).

Table 1: Socio-demographic data, risk factors and clinical data of all patients on admission,

Age (years)	Mean ±SD	63.6 ± 5
Sex	Males n (%)	33 (66%)
	Females n (%)	17 (34%)
Smoking	n (%)	21(42.0)
Diabetes mellitus	n (%)	25 (50%)
Hypertension	n (%)	27 (54%)
Ischemic heart disease	n (%)	17 (34%)
Heart rate (beat/min)	Mean ±SD	108.7 ± 9.1
Respiratory rate (breath/min)	Mean ±SD	24.8 ± 3.4
Mean arterial pressure (mmHg)	Mean ±SD	77.4 ± 15.6

Echocardiographic Data

Table 2: Echocardiographic data of all patients on admission and upon discharge.

		On Admission	Upon discharge
LVEDD (mm)	Mean ±SD	61.06 ± 2.36	61.14± 2.31
LVESD (mm)	Mean ±SD	43.16 ± 2.23	43.08 ± 2.21
LV EF (%)	Mean ±SD	29 ± 4.2	30 ± 4.1
RA size (cm)	Mean ±SD	45.08 ± 3.31	42.38 ± 2.61
RV 1 size (cm)	Mean ±SD	29.6 ± 7.20	28.74± 6.71
RV 2 size (cm)	Mean ±SD	34.04 ± 5.78	33.02 ± 5.81
RV 3 size (cm)	Mean ±SD	79.8 ± 7.45	78.17± 7.57
RV-FAC (%)	Mean ±SD	30.1 ± 4.23	32.47 ± 7.20
IVC diameter (cm)	Mean ±SD	18.94 ± 2.41	15.59± 1.51
RV S' (cm)	Mean ±SD	8.5 ± 2.04	9.68 ± 1.53
TAPSE (mm)	Mean ±SD	14.92 ± 2.85	15.31 ± 2.63
PASP (mmHg)	Mean ±SD	42.14 ± 8.94	37.38 ± 8.16
TAPSE/PASP Ratio	Mean ±SD	0.37 ± 0.11	0.43 ± 0.12

Abbreviations: LVESD: Left Ventricular End Systolic Volume. LVESD: Left Ventricular End Diastolic Volume. LV EF: Left ventricular Ejection Fraction. RA: Rt atrial. RV: Rt ventricle. FAC: Fractional area change. IVC: inferior vena cava. RV S': tricuspid lateral annular systolic velocity, TAPSE: tricuspid annular plane systolic excursion. PASP: pulmonary artery systolic pressure.

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Follow up Data

Average duration of hospital admission was 4.6 ± 1.6 days, 40% of cases reported re-hospitalization and 24% reported death during 30 day follow up, average time of death was 15 ± 7 days after discharge (Table 3).

Table 3: Duration of hospital stay and Follow-up of all patients.

Hospital admission duration (days)	Mean ±SD	4.6 ± 1.6
Re-hospitalization rate	n (%)	20 (40%)
Mortality rate	n (%)	12 (24%)
Time of mortality (day)	Mean ±SD	15 ± 7

Our study showed a statistically significant negative correlation between TAPSE/PASP Ratio on admission and Hospital admission duration ($P < 0.001$), Re-hospitalization ($P < 0.05$) and Mortality ($P < 0.001$) (Table 4).

Table 4: Correlation between TAPSE/PASP Ratio with admission and prognosis parameters of all selected patients.

	R	P
Hospital admission duration	-.885**	<0.0001
Re-hospitalization	-.420**	0.002
Mortality	-.754**	<0.0001

There was also a statistically significant negative correlation between TAPSE/PASP Ratio upon discharge and Hospital admission duration ($P < 0.001$), Re-hospitalization ($P < 0.001$) and Mortality ($P < 0.001$). (Table 5).

Table 5: Correlation between TAPSE/PASP Ratio with admission and prognosis parameters of all selected patients.

	R	P
Hospital admission duration	-.884**	<0.0001
Re-hospitalization	-.595**	<0.0001
Mortality	-.726**	<0.0001

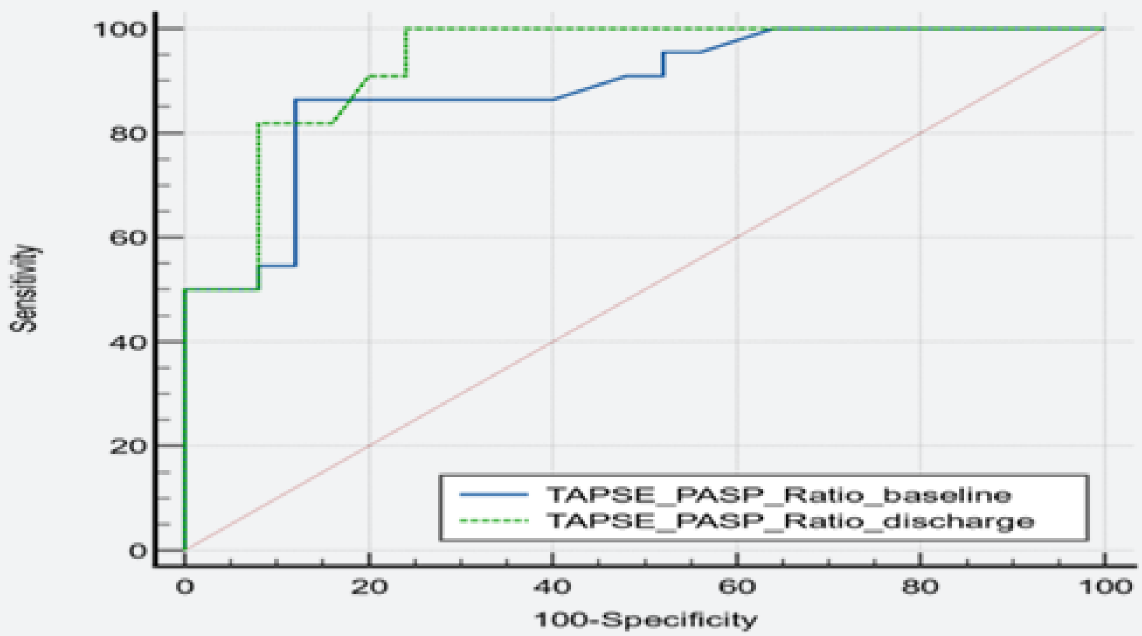

Figure 1: ROC curve of admission and discharge TAPSE/PASP Ratio in predicting Poor prognosis.

Table 6: Correlation between TAPSE/PASP Ratio with admission and prognosis parameters of all selected patients.

	AUC	Best Cut off point	Sensitivity (%)	Specificity (%)	P value
Admission TAPSE/PASP Ratio	0.901	≤ 0.40	88	88	<0.0001**

ROC curve analysis showed that Admission TAPSE/PASP Ratio at a cutoff point (≤ 0.40) predicted patients with poor prognosis (prolonged hospital admission and increased incidence of re-hospitalization) with sensitivity= 88% and specificity= 88% ($P \leq 0.0001$, AUC=0.948) (Table 6, Figure 1).

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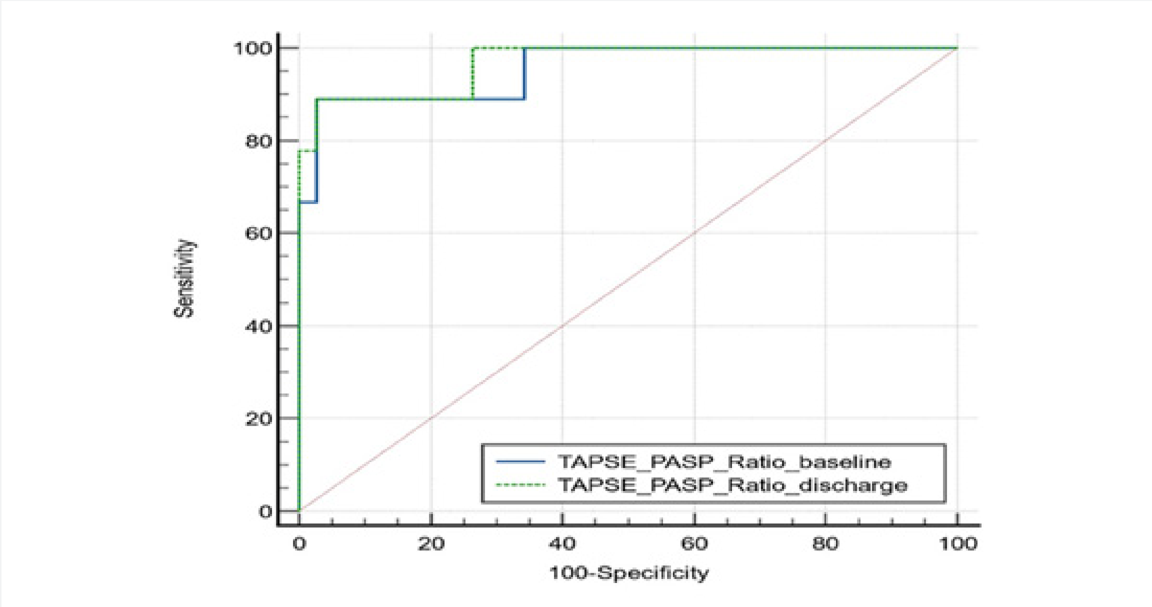

Figure 2: ROC curve of admission and Discharge TAPSE/PASP Ratio in predicting mortality.

ROC curve analysis showed that admission TAPSE/PASP Ratio at a cutoff point (≤ 0.28) predicted mortality, with sensitivity= 91% and specificity= 92% (P≤0.0001, AUC=0.958) (Table 7, Figure 2).

Table 7: Correlation between TAPSE/PASP Ratio with admission and prognosis parameters of all selected patients.

	AUC	Best Cut off point	Sensitivity (%)	Specificity (%)	P value
Admission TAPSE/PASP Ratio	0.958	≤ 0.28	91.67	92.11	<0.0001**

IN HF syndrome, development of right ventricular (RV) dilation and failure (RVF) are signs of accelerated disease progression that carry a two- to threefold increase in risk of cardiac death, irrespective of degree of left ventricular (LV) dysfunction [9]. TAPSE/PASP ratio is an easily obtained measure that provides a more comprehensive evaluation of the RV length/force relationship and has both pathophysiological and prognostic significance [10].

In our study, 50 % of the patients were diabetic, 34 % had IHD and 54% of them were hypertensive. In contrast with Bragança et al. [11] study which reported that a total prevalence of 42% diabetes, 80% hypertension and about half of patients (52%) had ischemic cardiomyopathy. In our study, on admission;, The mean EF in our study was 29%, in comparison with Guazzi et al. [6] study in which the mean EF was 33%, RV FAC baseline was 30 % in average while DTI s' baseline was 8.5, in contrast with Tello et al. [7] study which reported that average FAC was 21% and mean RV s' was 12.

In our study, on admission; the mean of TAPSE was 14.92 ± 2.85 while mean of PASP was 42.14 ± 8.94. The baseline TAPSE/PASP Ratio was 0.372 ± 0.11. On discharge: the mean of TAPSE was 15.32 ± 2.63 while mean of PASP was 37.38 ± 8.16. The TAPSE/PASP Ratio on discharge was 0.433 ± 0.12. It was concordant with Guazzi et al. [6] study in which mean TAPSE was 17.8 ± 2.9 mm and mean PASP was 39.6 ± 11.0 mmhg while mean TAPSE/PASP, mm/mmHg was 0.49 ± 0.18. It came in disagreement with Tello et al. [7] study where mean TAPSE was 18.1 ± 5.6 mm and mean PASP was 72.4 ± 24.5 mmhg while mean TAPSE/PASP, mm/mmHg was 0.25. The Mean of hospital stay in our study was 4.66 days ranged between 3 to 8 days. Regarding outcomes and follow-up, our study showed that 20 patients (40%) needed Re-hospitalization within 1 month from first admission. Regarding mortality rate during the period of follow-up, it was 12 patients (24%) and mean time of mortality was 15.17±6.9 days ranged between 6 to 27 days.

In our study, correlation between TAPSE/PASP Ratio with admission and prognosis of all patients showed that there was a statistically significant negative correlation between TAPSE/PASP Ratio and (Hospital admission duration, Re-hospitalization and Mortality). In our study, ROC curve analysis showed that admission TAPSE/PASP Ratio at a cutoff point (≤ 0.40) predicted patients with poor prognosis (prolonged hospital admission and increased incidence of re-hospitalization) with sensitivity= 88% and specificity = 88% (P≤0.0001, AUC=0.948), while admission TAPSE/PASP Ratio at a cutoff point (≤ 0.28) predicted

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mortality, with sensitivity= 91% and specificity= 92% (P≤0.0001, AUC=0.958).

It was in concordance with Trejo-Velasco et al. [12] study which concluded that, on Kaplan–Meier survival analysis, patients with TAPSE/PASP < 0.35 had a higher risk of suffering the primary combined endpoint, Log Rank 8.844, p = 0.003. Trejo-Velasco et al. [12] also reported that, the primary combined endpoint occurred more frequently among patients with lower TAPSE and TAPSE/PASP ratio.

These results also came in agreement with Popolo Rubbio et al. [13] study that concluded that TAPSE/PASP ratio ≤ 0.36, as an expression of the RV–PA uncoupling, is strongly associated with an increased risk of composite all-cause mortality and heart failure re-hospitalization. Popolo Rubbio et al. [13] also reported that, patients with TAPSE/PASP ≤ 0.36 presented higher incidence of 1-year all-cause mortality (32.2% vs. 8.1%; p ≤ 0.001), heart failure hospitalization (24.7% vs. 10.5%; p = 0.007) and of the combined primary endpoint (39.4% vs. 14.8%; p ≤ 0.001), if compared to patients with TAPSE/PASP > 0.36.

Bragança et al. [11] study reported that, the optimal cut-off points were 17.5 mm for TAPSE, 39 mmHg for PASP and 0.44 mm/mmHg for TAPSE/PASP. Among them, TAPSE/PASP ratio demonstrated the best discriminative ability (AUC of 0.76). The full diagnostic performance of the TAPSE/PASP ratio was the following: sensibility 76%, specificity 71%, positive predictive value 75%, negative predictive value 72%, positive likelihood ratio 2.6 and negative likelihood ratio 0.33.

Whereas Guazzi et al. [6] study reported that the ratio TAPSE/systolic pulmonary artery pressure (SPAP) improves the prognostic risk stratification in heart failure patients when compared to TAPSE alone and a ratio <0.36 mm/mmHg predicts higher mortality in such patients. While Tello et al. [7] study concluded that the TAPSE/PASP cutoff value for prediction of RV-arterial uncoupling was 0.31 [14,15].

Conclusion

TAPSE/PASP ratio appears as a good prognostic tool in acute heart failure patients with reduced ejection fraction that might improve risk stratification and outcome prediction.

Limitations

Small sample size, large exclusion criteria, short follow up duration.

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Author Contribution

Authors contributed equally in the study.

Conflicts of Interest

No conflicts of interest.

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