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Original Article

Predictive Power of N-terminal Prohormone of Brain Natriuretic Peptide on Admission and on Discharge for Short- and Long-term Clinical and Echocardiographic Outcomes in Patients With Pulmonary Thromboembolism

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ABSTRACT

Background: This prospective case-series study was conducted to determine the predictive power of the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) on short- and long-term outcomes in patients with pulmonary thromboembolism (PTE).

Methods: Ninety-two patients (age = 60 ± 1.97 y, 54.7% male) diagnosed with PTE were recruited. NT-proBNP levels and echocardiographic indices were measured and recorded. The primary endpoint was considered to be 3-month PTE-related deaths and long-term adverse outcomes including 1-year all-cause mortality, rehospitalization due to the recurrence of PTE, right ventricular dysfunction, and pulmonary hypertension.

Results: The serum NT-proBNP level and the right ventricular diameter were significantly higher in the patients with adverse outcomes than in the outcome-free patients. Several significant correlations were found between NT-proBNP levels and echocardiographic indices. During a mean follow-up time of 12 months, 1 patient suffered PTE relapse, 15 patients had right ventricular dysfunction and pulmonary hypertension, and 2 patients expired. Age was an independent value in the prediction of the adverse outcome (OR: 1.064, 95% CI: 1.01 to 1.11). Discharge NT-proBNP levels, calculated according to a multiple cutoff point strategy for heart failure, in the PTE patients with adverse outcomes was 2.36 fold that in the outcome-free patients. The optimal value for discharge NT-proBNP according to the receiver operating characteristic analysis was 327 pg/mL, with a sensitivity of 80% and a specificity of 43%.

Conclusions: NT-proBNP measurement during the course of PTE, especially on discharge, may have a role as an easy-to-use diagnostic tool for determining patients with poor prognoses. ***(Iranian Heart Journal 2020; 21(1): 45-54)***

KEYWORDS: N-terminal prohormone, Brain natriuretic peptide, Biomarkers, Pulmonary embolism

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Pulmonary thromboembolism (PTE) is a potentially fatal disorder, and its severity ranges from asymptomatic to multi-organ manifestations. [1-3] Hence, rapid and accurate diagnosis of patients, particularly to distinguish high-risk patients from low-risk ones, presents a challenge to emergency physicians. The most notable prognostic modalities currently available are imaging tools such as echocardiography and computed tomography angiography (CTA) and serum biomarkers such as troponins, plasma leptin concentrations, and heart-type fatty acid-binding proteins. [4-8]

N-terminal prohormone of brain natriuretic peptide (NT-proBNP) has been proposed as an additional tool for risk stratification. [9] NT-proBNP, released from myocytes in the ventricles of the heart, is frequently used in the diagnosis of congestive heart failure and in distinguishing between patients with dyspnea of cardiac or pulmonary origin. It has also been evaluated for the assessment and management of several other diseases such as sepsis, cirrhosis of the liver, and renal failure. [10]

Elevated NT-proBNP levels can identify patients with acute PTE at high risk of short-term death and adverse outcome events. Although evidence has shown that the NT-proBNP measurement in the primary phase has excellent power to predict the 30-day (short) outcome like pulmonary hypertension and right ventricular dysfunction in patients with PTE, [11 12] it has a low positive predictive value; accordingly, serial measurements in the hospital admission phase appear to be helpful. [13]

Currently, there is a paucity of data on the sequential measurement of NT-proBNP from admission to discharge and there are no known predictive models capable of forecasting poor long-term outcomes in patients suffering from PTE. [14] We, therefore, sought to determine the predictive power of the sequential measurement of NT-proBNP on admission and on discharge for short- and long-term clinical and echo-cardiographic outcomes in patients with PTE.

METHODS

This prospective case-series study was conducted on 92 consecutive patients with a diagnosis of acute PTE registered in the Pulmonary Embolism Database of Tehran Heart Center, affiliated with Tehran University of Medical Sciences, Tehran, Iran, between 2013 and 2016. The definitions of the diagnosis and management of PTE in our center have been published previously. [15]

The exclusion criteria were comprised of a history of previous PTE, PTE occurrence during patient admission due to another medical condition, and death during the first hospitalization due to PTE. Also excluded were patients with hemodynamic instability at presentation and delayed pulmonary computed tomography angiography (CTA) (48 hours after diagnosis).

In all the patients, PTE was defined as the illustration of partial or complete filling defects in the pulmonary circulation by pulmonary spiral CTA scan. According to pulmonary spiral CTA scans, PTE was classified as saddle PTE (if the thrombus was lodged at the level of the bifurcation of the pulmonary trunk and extended into both main pulmonary arteries), central PTE (if the thrombus involved the main branches through the segmental branches), and peripheral PTE (if the thrombus involved the segmental and sub-segmental branches).

Doppler and 2D echocardiographic examinations were conducted by experienced operators within 48 hours of admission, on discharge, and in each follow-up visit. All the quantifications were performed in accordance with the

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recommendations of the American Society of Echocardiography Committee. Right ventricular dysfunction was defined as a right ventricular diameter > 34 mm or a right-to-left ventricular ratio > 0.9, or the presence of wall motion abnormalities in the right ventricular free wall. Right ventricular systolic dysfunction was defined as a tricuspid annular plane systolic excursion < 16 mm or a pulsed Doppler peak velocity at the tricuspid annulus < 10 cm/s.

All the patients were cured in the acute phase with conventional therapeutic doses of unfractionated or low molecular-weight heparin. Thrombolytic therapy was used at the discretion of the treating cardiologist. The patients were discharged with warfarin and control of their international normalized ratio. Complete data on the study population's baseline demographic characteristics as well as clinical, laboratory, and imaging findings were acquired through face-to-face interviews and medical files. Upon admission, the levels of systolic blood pressure, heart rate, respiratory rate, O_2 saturation, and high-sensitivity cardiac troponin T (hs-cTnT) were measured.

Hemodynamic instability was defined as the presence of the following in the patients upon admission: need for cardiopulmonary resuscitation, systolic blood pressure < 90 mm Hg or a drop in systolic blood pressure > 40 mm Hg for 15 minutes with signs of end-organ hypoperfusion or need for catecholamine prescription to protect adequate organ perfusion, and systolic blood pressure < 90 mm Hg.

Within 48 hours of PTE diagnosis and on discharge, blood samples (2 cc) were taken from the patients. The samples were centrifuged at 5 °C at 3000 rpm for 10 minutes. The separated serum was thereafter stored at −20 °C until the NT-proBNP measurement. The levels of NT-proBNP were determined using an ELISA kit (USA). After discharge, the patients were contacted and asked to refer to our center for follow-up evaluations based on their availability time. In the case of death, the outcome data were obtained by contacting the deceased patient's relatives.

Follow-up was done by clinical examinations in outpatient clinics or telephone contacts with the patients or their relatives. The primary endpoint was considered to be 3-month PTE-related deaths; and because of our small sample size, in addition to 1-year all-cause mortality, other related outcomes such as rehospitalization due to the recurrence of PTE and echocardiographic indices including right ventricular dysfunction and pulmonary hypertension were considered to be long-term adverse outcomes.

This study was approved by our institutional review board, and all the patients gave informed consent for the use of their data for research purposes.

The continuous variables were expressed as the mean and the standard deviation and were compared between the patients with and without outcomes using the independent samples *t*-test. When the continuous data were nonparametric, they were expressed as the mean and the standard error and were compared between the groups via the nonparametric 2-independent samples (Mann–Whitney *U*) test. The categorical variables were displayed as frequencies and percentages and were compared between the patients with and without outcomes using the χ^2 or Fisher exact test, as appropriate.

Variables with a *P* value < 0.2 in the univariate analysis were chosen as candidates to enter the multivariable model. The multiple predictors of long-term outcomes were found through the application of a backward logistic regression model, with the removal and entry probabilities of 0.1 and 0.05. The effect of the covariates on the adverse outcomes was reported as an odds ratio (OR) with a 95%

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confidence interval (CI). The discrimination power of the model was determined by applying the area under the receiver operating characteristics (ROC) curve. IBM SPSS Statistics for Windows, version 22.0, was used to conduct the analyses.

RESULTS

Totally, 92 patients diagnosed with acute PTE were evaluated. During the first admission, 6 patients died and were, as a result, excluded. During a mean follow-up time of 12 months from the diagnosis of PTE, 13 patients were lost to follow-up (failure to return for the follow-up visits), 1 patient suffered PTE relapse, 15 (23%) patients sustained right ventricular dysfunction and pulmonary hypertension, and 2 patients expired due to PTE (1 patient immediately after discharge and the other after 14 months). Finally, 73 patients were analyzed in our study. The mean age of the study population, including 33 (40%) women, was 60 ± 1.97 years. All the patients were diagnosed by means of CTA. Only 1 patient needed fibrinolytic therapy. A previous history of diabetes was reported in 10 (13.7%) patients, hypertension in 26 (35.6%), and dyslipidemia in 13 (17.8%). Additionally, a previous history of HF was reported in only a single patient. All the baseline medical information of the study population is depicted in Table 1.

Upon admission, 5 (6.2%) patients had cancer (breast, gallbladder, ovary, prostate, and testis cancer 1 each). Immobility for more than 3 days was reported in 17 (21%) patients and previous deep vein thrombosis in 4 (4.9%).

On admission, the mean value of NT-proBNP was 4064.7 ± 577.3 pg/mL, the mean value of hs-cTnT was 68.2±8.8 ng/mL, the mean value of hemoglobin was 14.3±0.2 g/dL, and the mean value of creatinine was 1.01 ± 0.04 mg/dL. Additionally, the mean values of systolic blood pressure, heart rate, and O_2 saturation were 130.8 ± 2.1 mm Hg, 103.4 ± 2.1, and 92.6%, respectively. On discharge, NT-proBNP had a mean value of 1876.5 ± 358.1 pg/mL.

The change in the NT-proBNP level over time was evaluated: There was a decreasing trend of serum NT-proBNP during hospitalization, from admission to discharge, in the 2 study groups and there was a significant difference in the admission and discharge NT-proBNP levels between the 2 groups ($P < 0.05$) (Fig. 1).

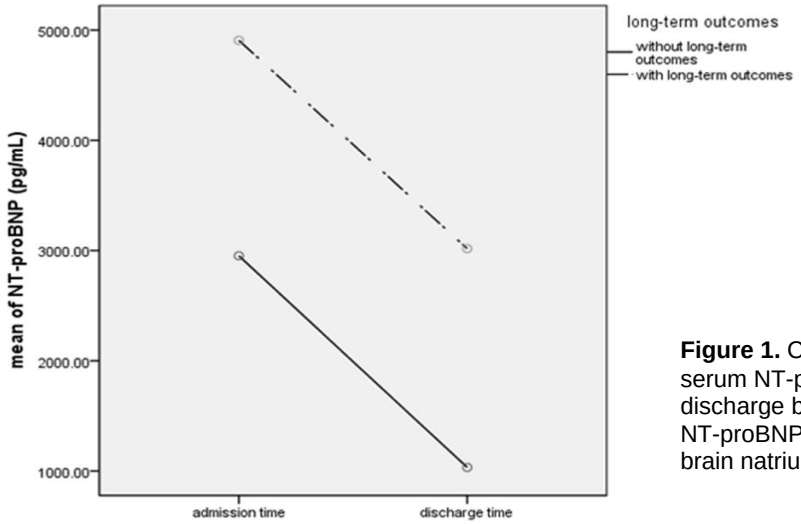

Figure 1. Comparison of the trend of serum NT-proBNP on admission and on discharge between the 2 study groups
NT-proBNP, N-terminal prohormone of brain natriuretic peptide

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Table 1. Demographic and clinical characteristics of the study patients

Variable	Total (N=73)	Without Outcomes, n=48	With Outcomes, n=25	*P* value	OR (95% CI)
Male	40(54.7)	26(54.1)	14(56)	0.881	1.077(0.407-2.848)
Age (y)	73	54.38±2.39	71.32±2.67	‹0.001	-
Comorbid Conditions					
Diabetes mellitus	10(13.6)	7(14.5)	3(12)	0.761	0.799 (0.188-3.399)
Hypertension	26(35.6)	16(33.3)	10(40)	0.572	1.333 (0.490-3.625)
Dyslipidemia	13(17.8)	7(14.5)	6(24)	0.318	1.850 (0.547-6.256)
Heart failure	1(1.3)	0(0)	1(4)	0.342	0.333 (0.240-0.462)
Risk Factors					
Immobility ≥3d	15(20.5)	7(14.5)	8(32)	0.801	2.756 (0.863-8.804)
Previous DVT	4(5.4)	3(6.2)	1(4)	0.689	0.625 (0.062-6.339)
Obesity	29(39.7)	18(37.5)	11(44)	0.590	1.310 (0.490-3.497)
Recent surgery	6(8.2)	4(8.3)	2(8)	0.961	0.957 (0.163-5.620)
Cancer	5(6.8)	4(8.3)	1(4)	0.487	0.458 (0.048-4.336)
Estrogen use	8(10.9)	8(16.6)	0(0)	0.031	0.615 (0.508-0.746)
Recent air travels	6(8.2)	4(8.3)	2(8)	0.961	0.957 (0.163-5.620)
Physical Examination					
Heart rate (b/min)	73	105.06±2.81	97.88±4.07	0.135	-
SBP (mm Hg)	73	132.17±3.32	127.56±2.57	0.613	-
RR (min)	73	21.93±0.93	25.25±1.43	0.020	-
O_2 saturation (%)	73	93.38±0.55	91.33±1.29	0.249	-
Sign of DVT	12(16.4)	7(14..5)	5(20)	0.371	1.813 (0.487-6.753)
High risk in simplified PESI score	44(60.2)	30(62.5)	14(56)	0.590	0.764 (0.286-2.040)
ECG Findings					
RBBB	14(19.1)	8(16.6)	6(24)	0.450	1.579 (0.480-5.196)
S1Q3T3	40(54.7)	26(54.1)	14(56)	0.881	1.077 (0.407-2.848)
Precordial T inversion in V_1	42(57.5)	24(50)	18(72)	0.071	2.571 (0.909-7.278)
Echocardiographic Findings					
RV dysfunction	629(84.9)	39(81.2)	23(92)	0.223	2.654 (0.527-13.363)
RV diameter	61(83.5)	37(77)	24(96)	0.039	7.135 (0.865-58.887)
Lab Findings					
Hemoglobin (g/dL)	73	14.45±0.33	14.16±0.49	0.577	-
White blood cell (mL)	73	11750.65±622.25	11248.33±517.99	0.897	-
Serum creatinine (mg/dL)	73	0.95±0.04	1.10±0.07	0.058	-
High sensitivity cardiac troponin T (ng/L)	73	78.47±12.12	46.02±6.27	0.374	-
D-Dimer (μg/L)	73	7.92±0.96	8.681.47	0.964	-
NT-proBNP (admission) (pg/mL)	73	2952.12±569.26	4906.72±1071.07	0.037	-
NT-proBNP (discharge) (pg/mL)	73	1032.69±247.39	3017.46±922.55	0.004	-
Spiral CTA Findings					
Pulmonary infarction	18(24.6)	10(20.8)	8(32)	0.294	1.788 (0.600-5.327)
Saddle embolism	15(20.5)	11(22.9)	4(16)	0.708	0.779 (0.211-2.8883)
Segmental artery embolism	5(6.8)	4(8.3)	1(4)	0.487	0.458 (0.048-4.336)
Pleural effusion	10(13.6)	6(12.5)	4(160	0.680	1.333 (0.339-5.243)

Continuous variables are displayed as the mean ± the standard errors and the categorical variables are presented as numbers (%).
DVT, Deep vein thrombosis; SBP, Systolic blood pressure; RR, Respiratory rate; RV, Right ventricle; RBBB, Right bundle branch block; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

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As can be seen in Table 1, of all the variables in the baseline paraclinical assessment, the serum NT-proBNP level, especially on discharge, and the right ventricular diameter were significantly higher in the patients with adverse outcomes than in the outcome-free patients. Furthermore, there were several significant correlations between the NT-proBNP level and echocardiographic indices (Table 2).

Table 2. Correlation between plasma NT-proBN at different time points and echocardiographic indices

Parameter	RV Diameter		RV Function		RV:LV Ratio	
	r	*P* value	*r*	*P* value	*r*	*P* value
NT-proBNP (admission)	0.293	0.009	-0.363	0.001	0.477	‹0.001
NT-proBNP (discharge)	0.273	0.015	-0.298	0.008	0.567	‹0.001
NT-proBNP (admission-discharge)	0.138	0.226	-0.198	0.085	0.140	0.237

RV, Right ventricle; LV, Left ventricle; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

The existing literature lacks a cutoff point for NT-proBNP in patients with PTE; we were, therefore, obliged to use the cutoff point of NT-proBNP in patients with heart failure in order to calculate the diagnostic markers. Table 3 shows the univariant comparisons between several parameters. As is depicted in Table 3, NT-proBNP on discharge, NT-proBNP–based heart failure, and age had significant differences between the patients with and without outcomes ($P < 0.05$) (Table 3).

NT-proBNP exhibited no predictive effect in the logistic regression equation, prompting us to enter the NT-proBNP calculated based on the multiple cutoff point strategy for heart failure in our logistic regression analysis. The results showed that age was an independent value in the prediction of the adverse outcome (OR: 1.064, 95% CI: 1.01 to 1.11) and discharge NT-proBNP calculated based on the multiple cutoff point strategy for heart failure in the PTE patients with adverse outcomes was 2.36 fold that in the outcome-free patients (Table 3).

Moreover, the area under the ROC curve analysis was used to identify the optimal plasma level of the discharge NT-proBNP cutoff value so as to distinguish patients with and without poor outcomes throughout the period of the study: The optimal value was 327 pg/mL. The value of the area under the ROC curve for the patients throughout the study was 0.707 (95% CI: 0.583 to 0.831), with a sensitivity of 80% and a specificity of 43% (Fig. 2).

Table 3. Prediction of the adverse outcomes in the patients with pulmonary thromboembolism

Variables Entered in the Model	Univariate Analysis		Multivariable Analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
NT-proBNP (admission)	1.009	0.095		
NT-proBNP (discharge)	1.026	0.027		
NT-proBNP difference (admission-discharge)	1.000	0.977		
NT-proBNP– based HF (discharge)	3.250	0.024	2.360	0.168
Age	1.078	‹0.001	1.064	0.007
Serum creatinine	3.379	0.095	1.684	0.566
Immobility ≥ 3 d	2.756	0.087	2.614	0.176

HF, Heart failure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide

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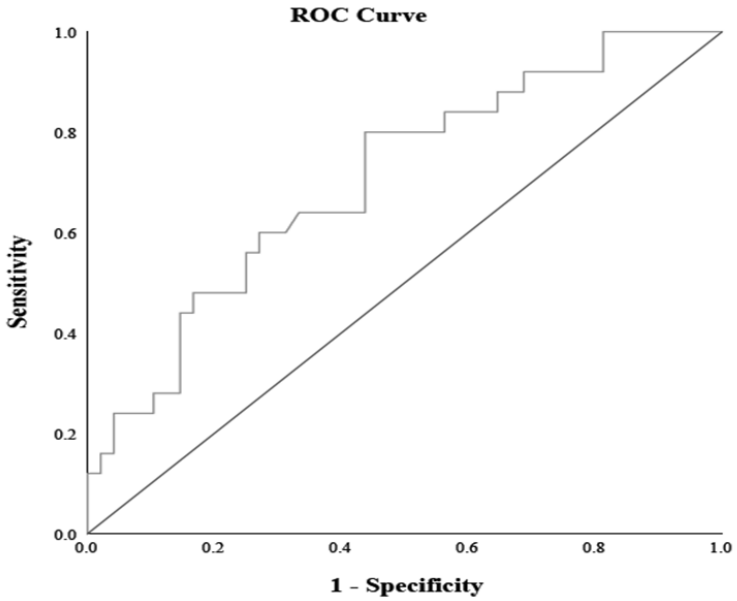

Figure 2. Area under the receiver operating characteristics (ROC) curve for serum NT-proBNP on discharge NT-proBNP, N-terminal prohormone of brain natriuretic peptide

DISCUSSION

Our study showed that in patients with adverse outcomes, the serum NT-proBNP level and the right ventricular diameter were significantly higher than those in outcome-free patients. There were several significant correlations between NT-proBNP levels and echocardiographic indices. We found that age was an independent value in the prediction of adverse outcomes and that discharge NT-proBNP calculated based on a multiple cutoff point strategy for heart failure in PTE patients with adverse outcomes was 2.36 fold that in outcome-free patients.

PTE is potentially an acute and fatal disease and requires emergency interventions if the patient's life is to be saved. Nonetheless, usually due to nonspecific symptoms, diagnosis is delayed and the golden time for treatment is lost. [16] Recent years have witnessed the emergence of several diagnostic modalities for the determination of patients with poor prognoses. Of course, it is not feasible to draw upon all these tools in practice, but NT-proBNP measurement during the course of PTE appears to be simple. [17-21]

Aside from patients with PTE, the level of NT-proBNP rises in other groups of patients with morbid conditions, including heart failure. [22-24] Similarly, our study showed that in patients with PTE, higher levels of NT-proBNP were significantly correlated with future adverse outcomes such as heart failure. [25, 26]

Interestingly, in our study, the mortality rate was low by comparison with previous studies. This variation may be due to a lack of significant difference in the baseline risk factors of PTE and the existing underlying disease between our 2 study groups. Another possible explanation is that we reported the death rate after the discharge time in our study, while previous studies have merely explained this rate within their patients' hospitalization period. [14, 27, 28]

In our univariate analysis, age and discharge NT-proBNP had significant correlations with the adverse outcomes (OR: 1.064, 95% CI: 1.01 to 1.11 and OR: 1.026 95% CI: 1.003 to 1.049, respectively). Whereas age is an unchangeable predictor, patients'

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discharge NT-proBNP is a suitable guide for appropriate follow-up interventions.

In our study, the discharge NT-proBNP cutoff point according to the ROC curve analysis was lower than the figures previously reported. This discrepancy may be because those investigations assessed NT-proBNP on admission, while we assessed it on discharge. In addition, NT-proBNP has a decreasing trend during the course of PTE. However, our study supports this notion that a low level of NT-proBNP is associated with having a good prognosis in the course of PTE. [10, 29]

We found a significant correlation between NT-proBNP levels and echocardiographic indices such as right ventricular dysfunction and the right-to-left ventricular ratio. It is worthy of note, however, that echocardiographic indices—in comparison with NT-proBNP levels—have low sensitivity for detecting poor prognoses in patients with PTE. Echocardiography should, therefore, be considered a suitable supplementary paraclinical tool in patients with PTE. [30-32]

First and foremost among the limitations of the present study is its small sample size. Another weakness of note is that we recruited only patients who were diagnosed with PTE in the emergency department and not those in whom PTE diagnosis was missed or those who expired before PTE diagnosis. That our study population was selected from a single-center PTE registry may limit the generalization of our results. Indeed, had we assessed a larger sample volume, some results that were significant in the univariate analysis might have been statistically significant in the logistic regression analysis.

CONCLUSIONS

Our study showed that higher serum NT-proBNP levels and abnormalities in echocardiographic indices were associated with adverse outcomes in patients with PTE. Although natriuretic peptides rise in several morbidity conditions such as heart failure, an increase in NT-proBNP should be deemed an alarm for all-cause mortality in patients with PTE. Thus, the NT-proBNP measurement during the course of PTE, especially on discharge, may have a role as an easy-to-use diagnostic tool for determining patients with poor prognoses.

Acknowledgments
Not applicable.

Conflict of Interest
The authors have no conflicts of interest.

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