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INTEGRATED ANALYSIS OF IMAGING AND SEROLOGICAL MARKERS FOR RISK STRATIFICATION IN ACUTE PULMONARY EMBOLISM

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Abstract:

Objectives: *To explore the association between pulmonary artery obstruction index and serological markers with risk stratification in acute pulmonary embolism(APE).*

Methods: *The computed tomography pulmonary angiography (CTPA) imaging of patients diagnosed with APE were retrospectively analyzed, and the relevant imaging parameters were measured and calculated. The serological examination results of APE patients were also collected. The relationship of parameters and risk stratification of APE was analyzed by Spearman rank correlation test. The prediction power of parameter with the highest correlation for each risk stratification of APE was tested by the receiver-operating characteristic (ROC) curve.*

Results: *A total of 62 consecutive patients with APE were categorized into high-risk group (20 cases, 32.26%) and low- and intermediate-risk group (42 cases, 67.74%) according to the guideline. The correlation analysis revealed that Mastora score($r=0.822, p < 0.001$) and BNP($r=0.754, p<0.001$) had strong correlation with risk stratification. Between the two groups, Mastora score(area under the curve 0.973, $p<0.01$) and BNP(area under the curve 0. 914,*

$p<0.01$) had the strongest prediction power for the high-risk group, respectively.

Conclusions: *Mastora score and BNP are associated with risk stratification in patients with acute pulmonary embolism.*

Key Words: *Acute pulmonary embolism, Computed tomography pulmonary angiography, Mastora score, BNP*

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1. BACKGROUND:

Acute pulmonary embolism (APE) is one of the common acute and critical cardiovascular diseases, and the important cause of death and disability. The total annual incidence in China is 8.7 per 100,000 population[1]. The mortality rate of people without timely treatment is as high as 25% ~ 30%, and early and reasonable treatment can reduce the mortality rate to 2% ~ 8%. The European Society of Cardiology (ESC) recommended that risk stratification, namely "high risk, intermediate risk, and low risk", replace the previous term "large area, sub-large area, and non-large area" to identify high-risk patients early in 2008 [2]. Reliable risk stratification is the basis of treatment strategy selection, but the method of risk stratification in the guidelines involves many clinical indicators, and there are still certain limitations in the rapid risk stratification of patients with APE in clinical practice.

Although the gold standard for the diagnosis of pulmonary embolism is still pulmonary angiography, it is invasive [3]. In recent years, computed tomography pulmonary angiography (CTPA) has become the preferred imaging method for suspected APE on account of its rapid acquisition, non-invasive[4], similar rate of failure to pulmonary angiography (approximately 5%)[5] and so on. Mastora and Qanadli et al. calculated the CT pulmonary embolism index based on CTPA showing the location of pulmonary embolism[6,7], which was confirmed to be correlated with the critical condition of APE patients [8]. In addition, right ventricular dysfunction (RVD) is a crucial indicator of risk stratification in APE. Gutte et al. found that BNP and D-dimer were related with remarkably increased levels in PE patients with RVD [9]. Therefore, the purpose of this research was to investigate the correlation of imaging and serological indicators with risk stratification of APE, and to determine whether they could be used as quantitative indicators to estimate the severity of patients with APE.

2. MATERIALS AND METHODS:

2.1 Study patients:

178 patients with suspected APE were collected in ZCH, China from January 2022 to December 2023, and 62 patients were confirmed with CTPA. Then, according to the Guidelines of APE (ESC 2014) [10], all patients were divided into two groups, namely high- risk group and low- and intermediate-risk group, and the flowchart was shown in Figure 1.

2.2 Study design and data collection:

Serological markers and imaging parameters of all patients with APE were included in the analysis of this study. Serological examinations contained brain natriuretic peptide (BNP), D- dimer (D-D), myoglobin (Myo), cardiac troponin-T (cTnT), activated partial thromboplastin time (APTT), thrombin time (TT), prothrombin time activity (PTA), prothrombin time (PT), fibrinogen (Fbg),protein S (PS) activity, protein C (PC) activity and blood type.

All patients underwent CTPA examination at APE onset. The CTPA images were independently evaluated by two radiologists with an experience of more than 10 years for CT diagnosis. All image observation and analysis were completed on the imaging workstation. If the two radiologists did not agree with each other, the senior radiologists were asked to re- evaluate. They observed and recorded the proximal location of the pulmonary embolus: main (main pulmonary trunk, left or right pulmonary artery), lobar, segmental, or subsegmental artery. The presence of pulmonary infarction, pleural effusion and pericardial effusion was observed as well. Measurement and calculation of the parameters included Mastora score(Figure 2), Qanadli score, the main pulmonary artery diameter (MPAd), the aorta diameter (Aod), the ratio of MPAd to Aod (MPAd/Aod)(Figure 3), the right ventricle maximum transverse diameter (RVd), the left ventricular maximum transverse diameter (LVd) and the ratio of RVd to LVd (RVd/LVd)(Figure 4).

Statistical analysis:

Statistical analysis were performed with R software (version 3.5.3) and SPSS software(version 20.0). The measurement data consistent with normal distribution were expressed as mean ± standard deviation, and the comparison between groups was performed by independent-sample t test. The composition ratio or rate of enumeration data was indicated, and chi-square test was used for comparison between groups. Spearman rank correlation coefficient was used to estimate the correlation between parameters and risk stratification. The parameter with the highest correlation and the two groups were subjected to the receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was counted. The difference was statistically significant with $p < 0.05$.

RESULTS:

2.3 Correlation Analysis:

62 APE patients including 30 males and 32 females (male/female =1/1.07) were enrolled in the study, and the mean age was 60.29±15.05 years. According to

the risk stratification, patients were divided into high-risk group (20 cases, 32.26%) and low-

and intermediate-risk group (42 cases, 67.74%). The correlation between imaging parameters and risk stratification of APE was shown in table 1, and we concluded that a significant positive correlation between Mastora score and risk stratification (r=0.822,p＜0.001).

The correlation between serological markers and risk stratification of APE was shown in table 2, and BNP was found to be significantly positively correlated with risk stratification (r=0.754, p＜0.001).

2.4 The predicted efficacy of parameters for high-risk group:

We selected Mastora score and BNP to perform the analysis of prediction efficiency for risk stratification, and found that the two parameters were showing a significant difference between the two groups. And the results were shown in Table 3.

The prediction efficiency of Mastora score for high-risk group: the specificity was 92.9%, the sensitivity was 95.0%, the AUC was 0.973 (p＜0. 001), and the cut-off value was 49.5 (Figure 5).

The prediction efficiency of BNP for high-risk group: the specificity was 92.9%, the sensitivity was 80.0%, and the AUC was 0.914 (p＜0. 001) , and the cut-off value was 363.75 (Figure 5).

Figure 1

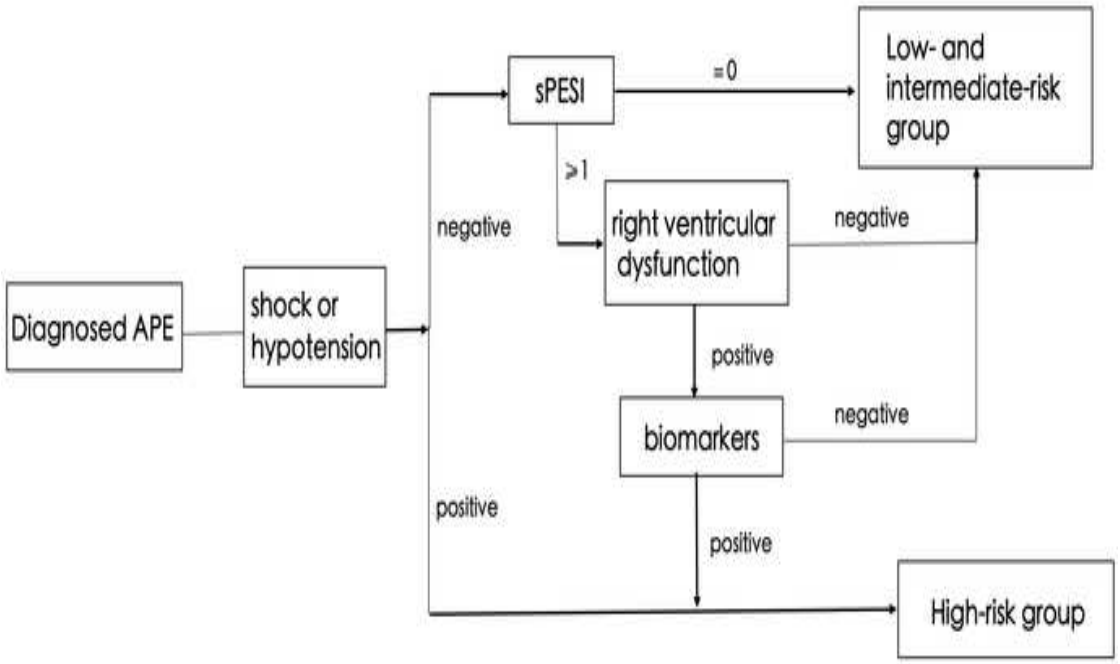

Figure1. Flowchart of APE grouping based on risk stratification

Shock or hypotension: systemic systolic blood pressure < 90mmHg (1mmHg = 0.133kpa) or > 40mmHg drop from the basic value lasting for more than 15 minutes, with the exclusion of hypotension caused by newly occurring arrhythmia, hypovolemia or infection;

sPESI: pulmonary embolism severity index score (age＞55—1 point, tumor—1 points, chronic heart failure/lung disease—1 points, pulse ≥11 beats/min—1 points, systolic blood pressure < 100mmHg—1 points, SpO2 < 90%—1 points); biomarkers: TnI > 0.4μg/L or TnT >0.1μg/L。

Figure 2

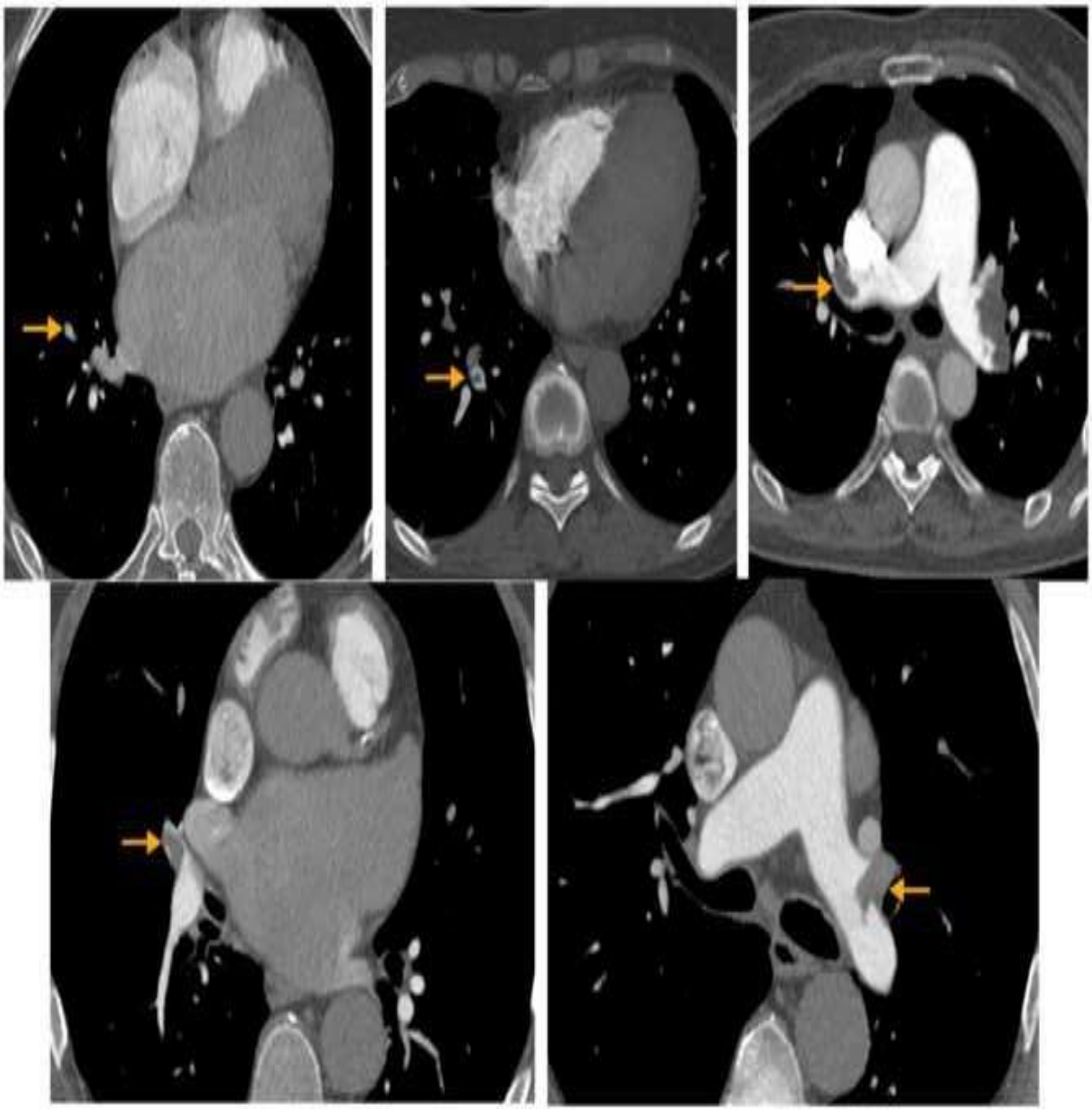

Figure2. Axial CTPA images show samples of point scales 1 (<25% pulmonary artery (PA) obstruction), 2 (25%-49% PA obstruction), 3(50%-74% PA obstruction), 4(75%-99% PA obstruction), and 5(total obstruction) in left and right pulmonary arteries.

Figure 3

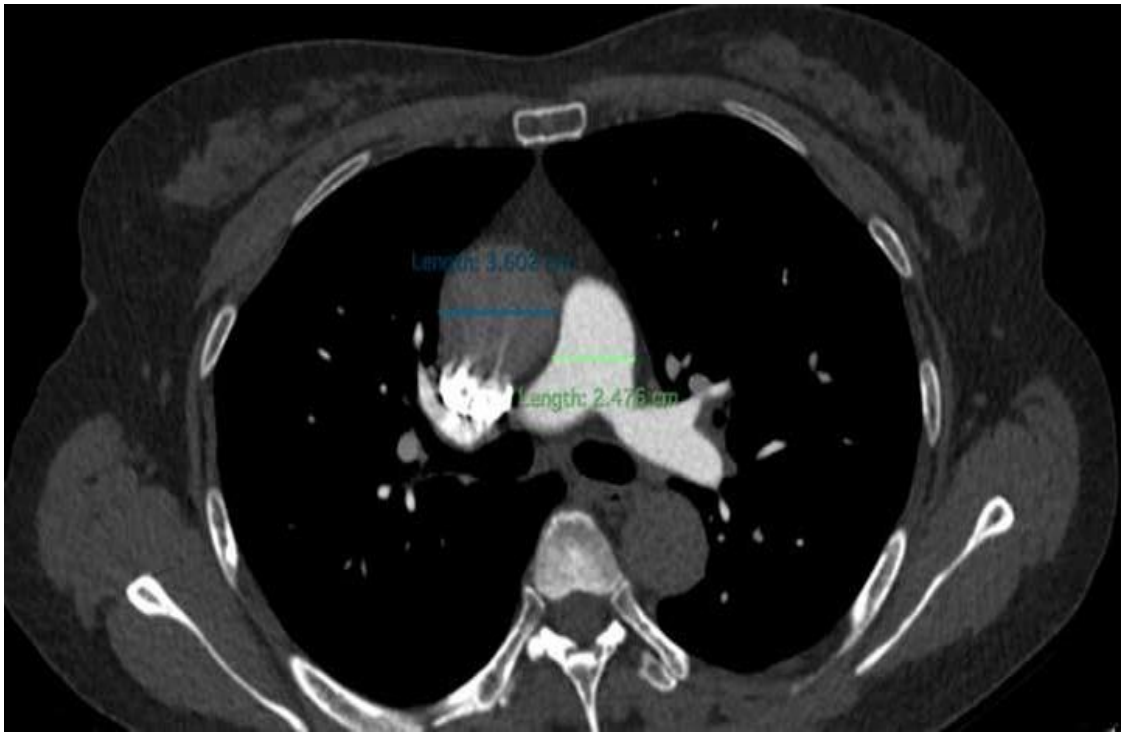

Figure3. Measurement of the main pulmonary artery diameter and the aorta diameter in CTPA images.

Figure 4

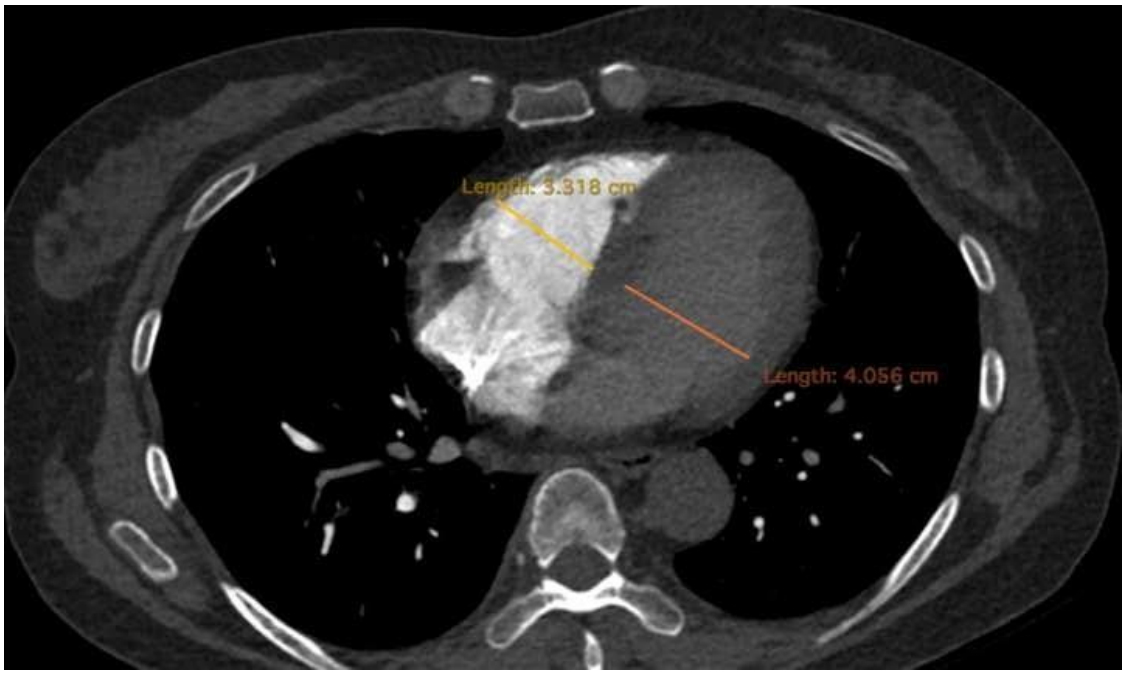

Figure 4. Measurement of the right and left ventricular maximum transverse diameter in CTPA images.

Figure 5 Click here to access/download;Figure;Figure5.tiff

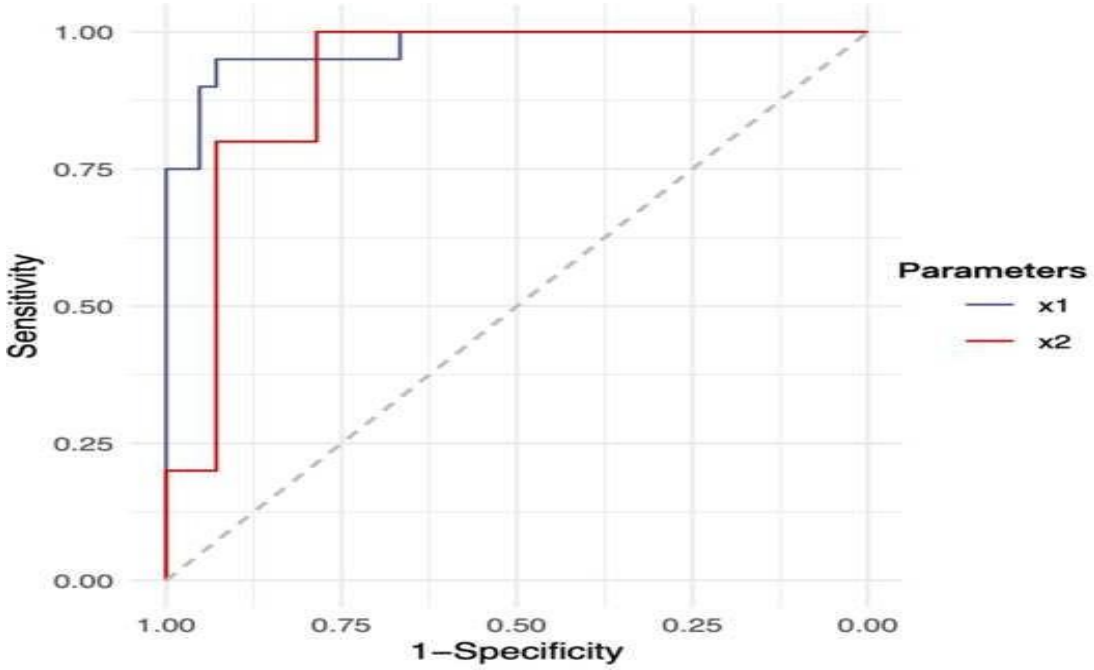

Figure 5. The predicted efficacy of parameters for high-risk group x1: Mastora score; x2: BNP

Table 1

Table 1 Correlation between imaging parameters and risk stratification of APE

Imaging parameters / risk stratification	*r*	*P* value
Mastora score	0.822	＜0.001
Qanadli score	0.753	＜0.001
Location of embolism	0.610	＜0.001
MPAd（mm）	0.259	0.042
Aod（mm）	0.065	0.614
MPAd/Aod	0.189	0.142
RVd（mm）	0.325	0.010
LVd（mm）	0.165	0.199
RVd/LVd	0.155	0.229
Pulmonary Infarction	-0.140	0.278
Pleural Effusion	0.106	0.412
Pericardial Effusion	0.054	0.679

MPAd: the main pulmonary artery diameter, Aod: the aorta diameter, MPAd/Aod ： the ratio of MPAd to Aod, LVd: the left ventricular maximum transverse diameter, RVd: the right ventricle maximum transverse diameter, RVd/LVd: the ratio of RVd to LVd.

Table 2

Table 2 Correlation analysis of serological markers with risk stratification of APE

Serological markers / risk stratification	*r*	*P* value
BNP (pg/ml）	0.754	＜0.001
cTnT（ng/ml）	0.640	＜0.001
PT（s）	0.139	0.281
PTA（%）	-0.134	0.298
Fbg（g/L）	-0.058	0.654
APTT（s）	0.409	0.001
TT（s）	0.246	0.054
D-D（mg/L）	0.466	＜0.001
PC（＜70%）	0.007	0.965
PS（＜55%）	-0.157	0.315
Myo（ng/ml）	0.202	0.174
cTnT（ng/ml）	0.640	＜0.001
BNP (pg/ml）	0.754	＜0.001
Blood Type	-0.283	0.227

BNP, brain natriuretic peptide; cTnT, cardiac troponin-T; APTT, activated partial thromboplastin time; PT, prothrombin time; PTA, prothrombin time activity; Fbg , fibrinogen; TT, thrombin time; D-D, D-dimer; PC, protein C; PS, protein S; Myo, myoglobin.

Table 3

Table 3 Comparison of parameters in different risk stratification

Parameters	High-risk group(n=20)	Low- intermediate-risk and group(n=42)	*P* value
Mastora score	71.10±15.68	19.21±18.18	＜0.001
BNP (pg/ml）	527.06±298.96	156.89±225.12	0.010

BNP, brain natriuretic peptide.

DISCUSSION:

For the correlation analysis of risk stratification in APE patients, the major findings of our study were as follows: Mastora score, Qanadli score, RVd, location of embolism, APTT, D-D, cTnT and BNP were related with risk stratification in APE patients, and Mastora score and BNP had significant positive correlation with it. ROC curves demonstrated that Mastora score and BNP were accurate for detection of risk stratification in APE.

In clinical practice, due to the lack of specificity of the symptoms of APE patients, it is easy to be misdiagnosed as other diseases. More than 95% of patients with APE are reported to be characterized by chest pain and dyspnea, which can easily be misdiagnosed as acute coronary syndrome and pulmonary disease in the early stage of the disease[11]. Becattini et al. found that up to 30% of APE patients may die within 30 days when hemodynamic instability exists [12]. Based on foreign statistics, PE ranks the third among the causes of death every year[13].

Thus, patients suspected of APE should be diagnosed with the least delay possible and its severity should be evaluated at the same time, so as to select the treatment strategy[14]. PESI score was added to the guidelines of APE (2014) to refine the risk stratification of APE, containing age, gender, basic concurrent disease and other indicators[10]. Therefore, it is difficult to quickly evaluate the risk stratification of patients with APE in clinical practice.

With the continuous development of CT diagnostic technology, CTPA can accurately detect thrombus in the subsegment and above pulmonary artery, and it is relatively non-invasive. Currently, as the first-line diagnostic method of pulmonary

embolism, CTPA can significantly improve the assessment of the severity of PE. Ghaye et al. suggested that MSCTPA could take the place of the "gold standard" status of echocardiography in the evaluation of right ventricular dysfunction (RVD) [15], because MSCTPA could not only efficiently diagnose APE, but also quantify the degree of PE by means of calculating CT pulmonary embolism index and measuring cardiovascular structure. In 2010, some researchers divided 73 APE patients into critical group and non-critical group in the light of clinical indexes, and reported that CT pulmonary embolism index was significantly higher in critical group than in non-critical group (43% vs 20%)[16]. In 2012, researchers found that increased CT pulmonary embolism index was a risk factor for poor prognosis in APE patients [17]. In 2020, Irmak et al. found that simplified Mastora score was correlated with risk stratification in APE patients[18]. And the above conclusions were consistent with the results of this study. In addition, thrombus vascular location was found to be correlated with risk stratification of APE in our research, which was also consistent with Irmak's findings[18].

We found that BNP had a significant correlation with risk stratification in patients with APE which hadn't been reported yet. According to the guidelines of APE (ESC 2014), RVD was an important indicator of risk stratification[10]. It was reported that BNP was related with remarkable increased level in APE patients with RVD, and the ROC curves shows that BNP has predictive power for RVD [9]. Therefore, BNP may indirectly reflect the risk stratification of patients with APE by reflecting RVD.

The Mastora score calculation method is simple, which could be calculated accurately without special software, and measurements of cardiac biomarkers are cheap and easy to obtain, so these indicators can be widely used in clinical practice. For patients with APE, the higher the Mastora score and the BNP level, the more risk stratification tends to be high-risk, and the risk stratification and the early mortality of patients go hand in hand. Therefore, Mastora score and BNP have to some extent reference significance for the clinical evaluation of APE.

CONCLUSIONS:

Mastora score and BNP were significantly associated with risk stratification in patients with acute pulmonary embolism, contributing to the identification of high-risk acute PE, timely and effective treatment, reduction of APE mortality and improved prognosis.

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Funding:

Not applicable.

Competing interests:

The authors have no conflicts of interest to declare.

Availability of data and materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

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