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Association of pulmonary artery obstruction index with elevated heart-type fatty acid binding protein and short-term mortality in patients with pulmonary embolism at intermediate risk

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PURPOSE

Heart-type fatty acid binding protein (H-FABP) is a sensitive marker of myocardial injury and predictor of worse prognosis in patients with pulmonary embolism (PE). Assessment of right ventricular dysfunction and pulmonary artery obstruction index (PAOI) with computed tomography (CT) has been reported as a predictor of mortality in PE. Therefore, we aimed to assess the correlation between H-FABP and CT angiographic PAOI in PE patients at intermediate risk.

MATERIALS AND METHODS

Sixty-one patients (28 males; mean age, 62±17 years) with diagnosis of PE were included in this study. CT was performed in all patients, and the following parameters were evaluated: right ventricle/left ventricle ratio (RV/LV), pulmonary artery axial diameter, superior vena cava axial diameter, and PAOI determined with Qanadli score. Blood samples were assessed for H-FABP and troponin levels. Patients were followed for 30 days after discharge.

RESULTS

Mean PAOI was 57±18%. Eleven patients died during the follow-up period due to PE (18% mortality rate). H-FABP was positive in 21 patients (35%). There was no difference in CT parameters between patients with positive H-FABP and negative H-FABP. In addition, CT parameters were similar between patients who survived and those who did not. RV/LV ratio correlated with PAOI score. Among the biomarkers, troponin levels correlated with both RV/LV ratio and PAOI. H-FABP was an independent predictor of mortality. PAOI and RV/LV ratio did not predict 30-day mortality.

CONCLUSION

Although H-FABP positivity confers a bad prognosis on PE patients at intermediate risk, PAOI did not predict mortality in this group.

Key words: • pulmonary embolism • heart-type fatty acid-binding protein • computed tomography • pulmonary artery obstruction index

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Despite important advances in the diagnosis and treatment of pulmonary embolism (PE), it remains a frequent cause of death. Risk stratification is very important, and is based on clinical features, echocardiography, and biomarkers (troponin I or T, brain natriuretic peptide, D-dimer, etc.) of myocardial dysfunction or injury. Intermediate risk PE is diagnosed if at least one right ventricular dysfunction or myocardial injury marker (troponin T or I) is positive (1). The management strategy in patients with PE at intermediate risk is still unclear.

Heart-type fatty acid binding protein (H-FABP) is an early, highly sensitive marker of myocardial injury that has been evaluated in patients with acute coronary syndrome (2). This marker was also assessed in PE patients and found to be a predictor of adverse outcome and mortality (3–5). In addition, H-FABP was well correlated with right ventricular dysfunction assessed with echocardiography (4).

Pulmonary contrast-enhanced computed tomography (CT) is now used as a first-line diagnostic strategy in patients suspected of PE (6). The CT obstruction index provides an objective and reproducible tool to quantify the obstruction severity of pulmonary arteries (7, 8). Whether pulmonary artery obstruction index (PAOI) assessed with CT predicts mortality in patients with acute PE remains controversial (9–13). The strong correlation between PAOI and troponin I has recently been emphasized by Shokoohi et al. (14) and Jeebun et al. (15). However, the data regarding a correlation of H-FABP and PAOI are scarce. Therefore, in this study we evaluated patients with PE at intermediate risk with positive H-FABP to determine if there is any correlation between H-FABP positivity and helical CT parameters (PAOI and ratio of the right ventricular to left ventricular [RV/LV] diameter).

Materials and methods

Study population

A total of 61 consecutive patients (38 females, 23 males; mean age, 62±17 years) with diagnosis of acute PE were prospectively included in this study. Acute PE was confirmed with CT scan. Intermediate risk PE was defined according to the new PE guideline by the European Society of Cardiology (1). Patients with cardiopulmonary shock, persistent hypotension, and contraindication to fibrinolysis were excluded from the study. To determine 30-day mortality, all patients who were discharged from our hospital were called and interviewed within 30 days of the CT examination.

Biomarker testing

All patients gave their consent for measurement of cardiac biomarkers. Initial troponin I, creatinine kinase of MB isoform (CK-MB), and

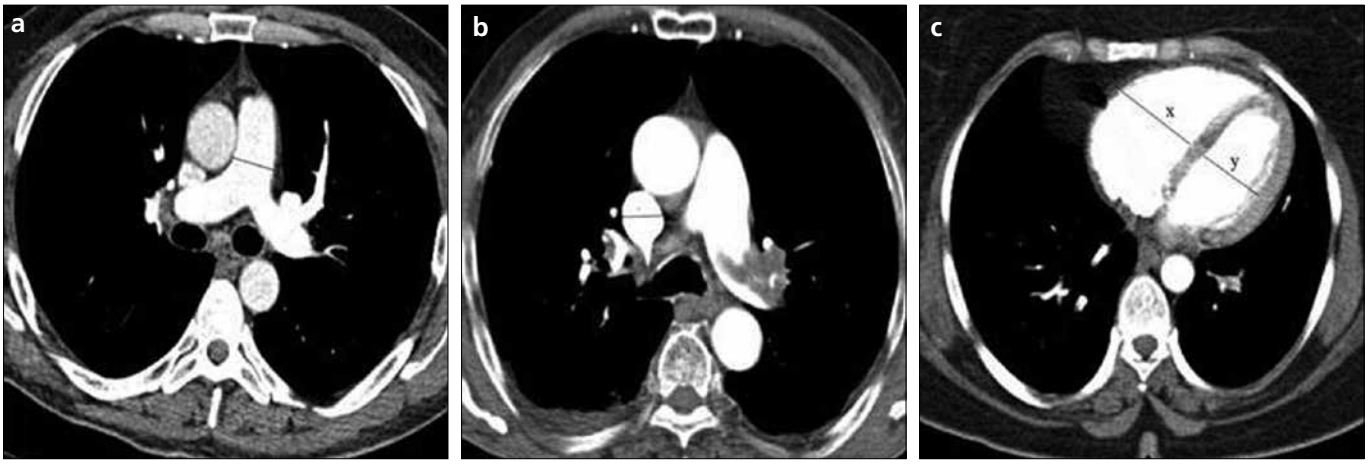

Figure 1. a–c. Diameters of common trunk of pulmonary artery **(a)** and superior vana cava **(b)** were measured on axial CT image. Right-to-left ventricular ratio **(c)** was also calculated on axial CT image (right-to-left ventricular ratio: x/y).

D-dimer levels were measured quantitatively upon admission into the study. For troponin I, a quantitative chemiluminiscence assay (DRG International Inc., Mountainside, New Jersey, USA; Cat No, EIA) was performed. Reported values in normal healthy adults are <0.04 ng/mL. An enzymatic immunological inhibition test for CK-MB isoenzyme (ADVIA Centaur CKMB, Deerfield, Illinois, USA) was performed. Normal values for CK-MB are <6.3 ng/mL. For D-dimers (Asserachrom DDi, Stago, Asnières, France), a quantitative enzyme-linked immunosorbent assay analysis was performed. The normal cut-off value was <0.45 µg/mL. Plasma concentrations of H-FABP were measured qualitatively using a HiSens h-FABP Card (HBI Co. Ltd., Anyang, Korea). The HiSens h-FABP Card is an immunochromatographic assay that includes an H-FABP-specific monoclonal antibody conjugated to colloidal gold particles, a second H-FABP-specific monoclonal antibody on the test line, and goat anti-mouse IgG antibody on the control line. The clinical cut-off value for H-FABP was 7 ng/mL, as previously established by several independent researchers and as proposed by the manufacturer (16, 17).

CT

CT pulmonary angiography (CTPA) evaluations were performed with a multidetector CT scanner (Siemens Somatom Sensation 64, Erlangen, Germany), following the CT protocol of our hospital for PE. CT scanning was performed without ECG gating and included the pulmonary parenchyma from apex to base. Scan parameters were as follows: 0.6 mm collimation, 1.5 mm slice thickness, 1.4 mm increment, 100 kV, 135 mAs, a pitch of 0.9, and a gantry rotation time of 0.33 s. Acquisitions were obtained after intravenous administration of 100 cc nonionic contrast material (iopromide, Ultravist, 300 mg/mL, Bayer Schering Pharma, Berlin, Germany) using an automatic injector via a vein in the arm at a flow rate of 4 mL/s. The automatic Care Bolus scan-triggering system was used, with the scan starting 4 s after the contrast medium reached the common pulmonary artery.

All the CTPA scans were evaluated by one radiologist (I.G.), according to methodology described in the literature (18, 19). CTPA studies were assessed for the following parameters:

1) RV/LV ratio was obtained by calculating the ratio between the diameters of the RV and LV short axes in the axial plane, measured from the endocardial margin of the free wall to the interventricular septum (Fig. 1a).
2) Maximum diameter of the pulmonary trunk was measured as the widest diameter perpendicular to the long axis of the main pulmonary artery at the pulmonary artery bifurcation level (Fig. 1b).
3) Diameter of the superior vena cava was measured 2.5 cm from its entrance into the right in axial plane (Fig. 1c).
4) PAOI was calculated according to Qanadli score (0%–100% obstruction), defined by the number of obstructed segmental arteries and corrected on the basis of the estimated degree of occlusion of each vessel (correction factor: 1, partial obstruction; 2, complete obstruction) (Fig. 2).

Qanadli score cut-off value for poor outcome and RV dysfunction was set at 40% vascular obstruction (7, 19). A previous study reported an 11.2-fold increased risk of death for PE patients with a PAOI of 40% or higher (9).

Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Sciences software (SPSS for Windows, version 15.0, SPSS Inc., Chicago, Illinois, USA). The data were expressed as the mean±standard deviation and/or median (interquartile range). The distribution of the variables was analyzed with the Kolmogorow-Smirnow test. Differences between parametric and non-parametric variables of two groups were assessed by Student t test and Mann-Whitney U test as appropriate. The relationship between the categorical variables was determined by the chi-square test. Pearson correlation analysis and Spearman rank order were used according to distribution of variables. The prognostic significance of CT parameters and cardiac biomarkers with regard to 30-day mortality was estimated with logistic regression analysis with the defined cut-off values. Kaplan-Meier analysis with log-rank test was performed to compare 30-day survival for H-FABP >7 ng/mL, PAOI >40%, and RV/LV >1. The study end-point was total mortality at 30 days of follow-up. A *P* value

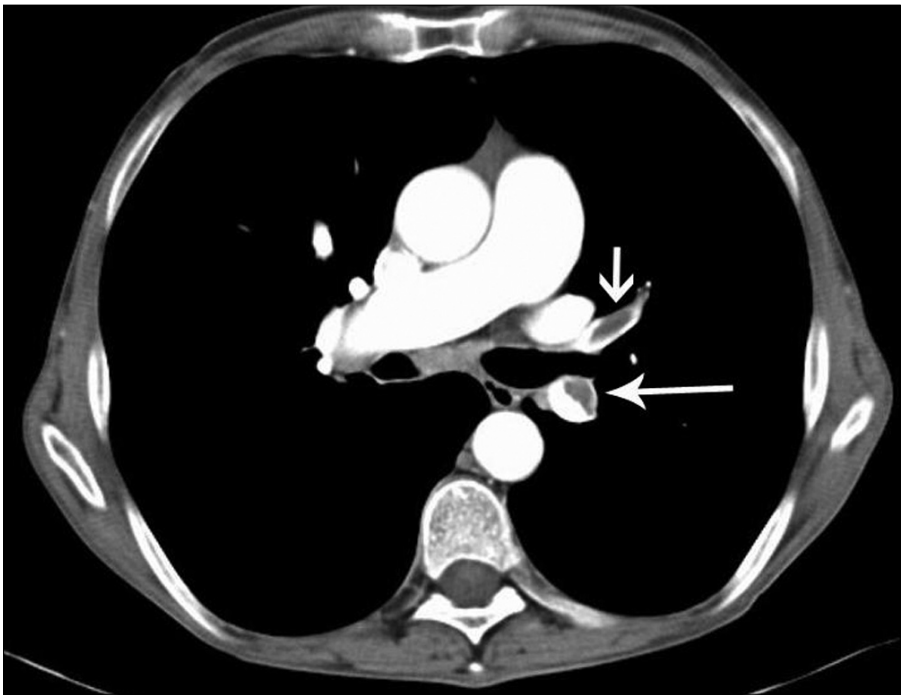

Figure 2. Transverse CT angiography images of a 56-year-old male patient with unilateral pulmonary embolism. Non-occlusive thrombus was seen in the left inferior lobar artery and lingular segment artery. Pulmonary artery obstruction index was calculated as 17.5% according to Qanadli obstruction index. The patient's cardiac biomarkers were as follows: troponin I, 0.13 ng/dL; H-FABP, negative. The patient was administered thrombolytic treatment, and clinical outcome was significantly improved. He was discharged five days after admission to the hospital.

under 0.05 was considered statistically significant.

Results

The demographic and clinical features of the study population are listed in Table 1. Twenty-seven patients (44%) were treated with thrombolytic therapy and 52 patients (85%) had heparin. Eleven patients (18%) died of PE within 30 days following CT.

H-FABP and CT parameters

The overall PAOI was 57±18%. H-FABP was positive in 21 patients (35%). There was no difference in CT parameters between patients with positive H-FABP and those with negative H-FABP (Table 2). Forty-eight patients (79%) had a PAOI >40%, and 47 patients (77%) had an RV/LV ratio >1. The mean RV/LV ratio was 1.22±0.26. In addition, CT parameters in patients who survived and those who did not survive were similar (Table 3).

Biomarkers and CT parameters

Multiple linear regression revealed a significant correlation between RV/LV ratio and PAOI (r=0.45, $P < 0.001$) (Table 4). In addition, SVC axial diameter also correlated with both RV/LV ratio and PAOI (r=0.30, $P = 0.02$, and r=0.32, $P = 0.01$, respectively). Among the biomarkers, weak but statistically significant correlations were noted between troponin I levels and both PAOI and RV/LV ratio (r=0.33, $P = 0.01$, and r=0.31, $P = 0.02$, respectively). CK-MB showed a weak correlation with PAOI (r=0.36, $P = 0.007$) (Table 4). Both SVC and PA trunk diameters were not significantly correlated with biomarkers.

Predictors of mortality

In a binary logistic regression analysis, we found that PAOI >40%, RV/LV >1, PA axial diameter >30 mm, and SVC >20 mm were not predictors of 30-day mortality (Table 5). Of the cardiac biomarkers, only H-FABP positivity was an independent predictor of mortality (Odds ratio=7.27, $P = 0.006$) (Table 5). H-FABP was significantly correlated with 30-day mortality ($P = 0.001$). However, RV/LV >1 and PAOI >40% did not show correlation with mortality within 30 days (Figs. 3 and 4).

Discussion

In this study, we found that PAOI and RV/LV ratio were not associated with elevated H-FABP. However, both PAOI and RV/LV ratio were correlated with troponin I levels. In addition, neither PAOI nor RV/LV ratio were predictors of 30-day mortality in patients with acute PE at intermediate risk.

Recent studies in patients with acute PE at intermediate risk have suggested that H-FABP levels on admission may predict the prognosis (4). Moreover, H-FABP levels were associated with the risk of in-hospital and 30-day mortality (3–5). Previous studies showed that H-FABP might be a useful marker for risk stratification of hemodynamically stable patients with acute PE (5).

The correlation of biomarkers with CT parameters has been previously investigated. The strong correlation between troponin I levels and both PAOI and RV/LV ratio has recently been emphasized by Shokoohi et al. (14) and Jeebun et al. (15). Consistent with these studies, we also found a significant but low correlation between troponin I levels and both PAOI and RV/LV ratio. In addition to troponin I, our results also demonstrated an association of H-FABP with CT parameters. The correlation of H-FABP with CT parameters was first investigated by Vuilleumier et al. (20) in non-massive pulmonary embolism. The authors found no statistically significant correlation between RV/LV ratio and both H-FABP and troponin I levels, and only a weak but significant correlation of brain natriuretic peptide with RV/LV ratio. However, they did not investigate the correlation of PAOI with H-FABP. To the best of our knowledge, ours is the first study investigating the association of PAOI with elevated H-FABP.

Whether PA obstruction scores (Mastora >49%, Qanadli >40%, Miller score >10) are predictors of death remains controversial. Van der Meer et al. (9) and Wu et al. (21) showed that obstruction scoring using the Qanadli system was a significant predictor of short-term outcome. Venkatash and Wang (12) also found that Qanadli score was a predictor of mortality in a univariate analysis; however using multivariate analysis, Qanadli score did not show significant correlation

Table 1. Demographic and clinical featrures of study population

Characteristics	Values
Age (years), mean±SD	62±17
Gender (male/female), n	23/38
Systolic blood pressure (mmHg), mean±SD	112±17
Diastolic blood pressure (mmHg), mean±SD	79±9
Heart rate (bpm), mean±SD	109±20
Biomarkers	
CK-MB (mg/dL), median (interquartile range)	3 (2.3–4.5)
Trp I (mg/dL), median (interquartile range)	0.12 (0.07–0.38)
D-dimer (mg/dL), median (interquartile range)	3.9 (0.23–4.0)
Comorbidities	
CAD, n (%)	4 (6)
Hypertension, n (%)	36 (59)
Diabetes, n (%)	9 (15)
Predisposants	
Surgery, n (%)	16 (26)
Immobilization, n (%)	44 (72)
DVT, n (%)	18 (29)
Treatment and clinical status	
Thrombolytic, n (%)	27 (44)
Heparin, n (%)	52 (85)
Warfarin, n (%)	61 (100)
Hospitalization duration (days), median (interquartile range)	9 (6–12)
Death, n (%)	11 (18)

CK-MB, creatinine kinase of MB isoform; Trp I, troponin I; CAD, coronary artery disease; DVT, deep vein trombosis.

Table 2. CT parameters according to H-FABP

	H-FABP (+) n=21	H-FABP (-) n=40	*P*
RV/LV ratio	1.22±0.26	1.21±0.26	0.95
SVC axial diameter (mm)	19±4.6	20±4.8	0.33
PA axial diameter (mm)	30±3.5	30±4.2	0.88
PAOI (%)	51±22	58±16	0.18
PAOI >40%	14 (66%)	34 (85%)	0.09
RV/LV >1.0	16 (76%)	31 (77%)	0.57

RV, right ventricle; LV, left ventricle; SVC, superior vena cava; PA, pulmonary artery; PAOI, pulmonary artery obstruction index; H-FABP, heart-type fatty acid binding protein.
Data are presented as mean±SD or n (%).

Table 3. CT parameters of survived and non-survived patients

	Survivors	Non-survivors	*P*
RV/LV ratio	1.25±0.25	1.13±0.26	0.12
SVC axial diameter (mm)	21±4	18±5	0.09
PA axial diameter (mm)	29±4	31±4	0.23
PAOI (%)	55±16	52±19	0.34

RV, right ventricle; LV, left ventricle; SVC, superior vena cava; PA, pulmonary artery; PAOI, pulmonary artery obstruction index.
Data are presented as mean±SD.

Table 4. Correlation of RV/LV ratio and PAOI with both CT parameters and cardiac biomarkers

	RV/LV ratio	PAOI
PAOI	r=0.45 $P < 0.001$	-
RV/LV ratio	-	r=0.45 $P < 0.001$
SVC axial diameter	r=0.30 $P = 0.02$	r=0.31 $P = 0.01$
CK-MB	r=0.12 $P = 0.24$	r=0.36 $P = 0.007$
Troponin I	r=0.31 $P = 0.02$	r=0.33 $P = 0.01$

RV, right ventricle; LV, left ventricle; SVC, superior vena cava; PA, pulmonary artery; PAOI, pulmonary artery obstruction index; CK-MB, creatinine kinase of MB isoform.

Table 5. Logistic regression analysis of CT parameters and cardiac biomarkers for 30-day mortality

	Odds ratio (95% confidence interval)	*P*
RV/LV >1	1.7 (0.08–36.5)	0.72
SVC axial diameter >20 mm	0.91 (0.78–1.06)	0.25
PA axial diameter >30 mm	1.89 (0.49–7.29)	0.35
PAOI >40%	0.81 (0.51–1.16)	0.31
H-FABP (+)	7.27 (1.78–29.7)	0.006
Trp I ≥0.04 ng/mL	1.11 (0.55–2.22)	0.77
CK-MB ≥6.5 ng/mL	0.97 (0.81–1.15)	0.72

RV, right ventricle; LV, left ventricle; SVC, superior vena cava; PA, pulmonary artery; PAOI, pulmonary artery obstruction index; H-FABP, heart-type fatty acid binding protein; Trp I, troponin I; CK-MB, creatinine kinase of MB isoform.

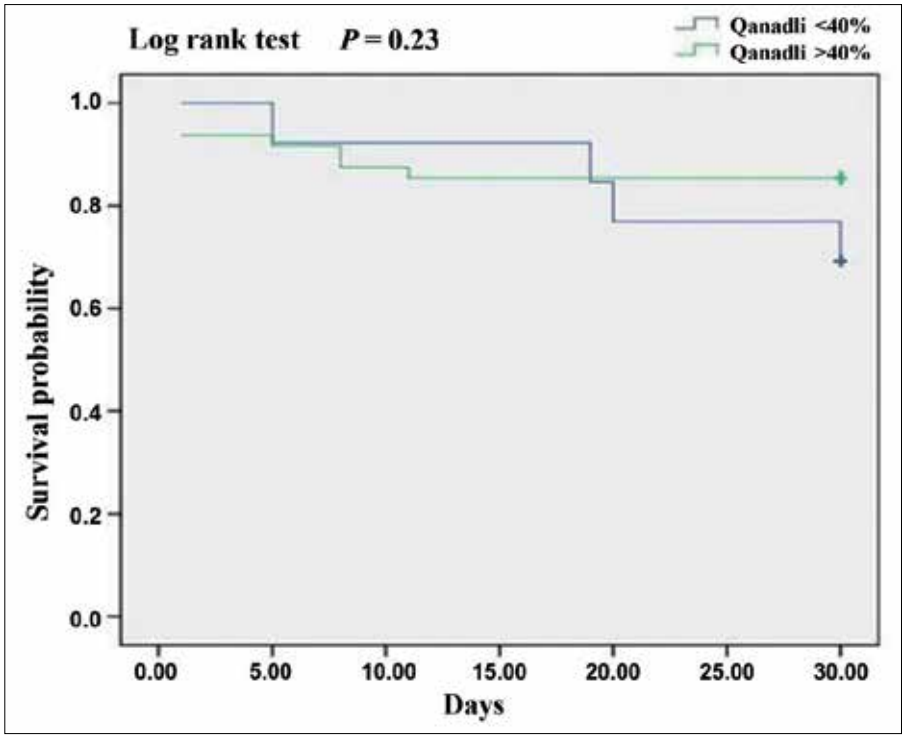

Figure 3. Kaplan-Meier curve for the end-point (30-day mortality) with respect to Qanadli.

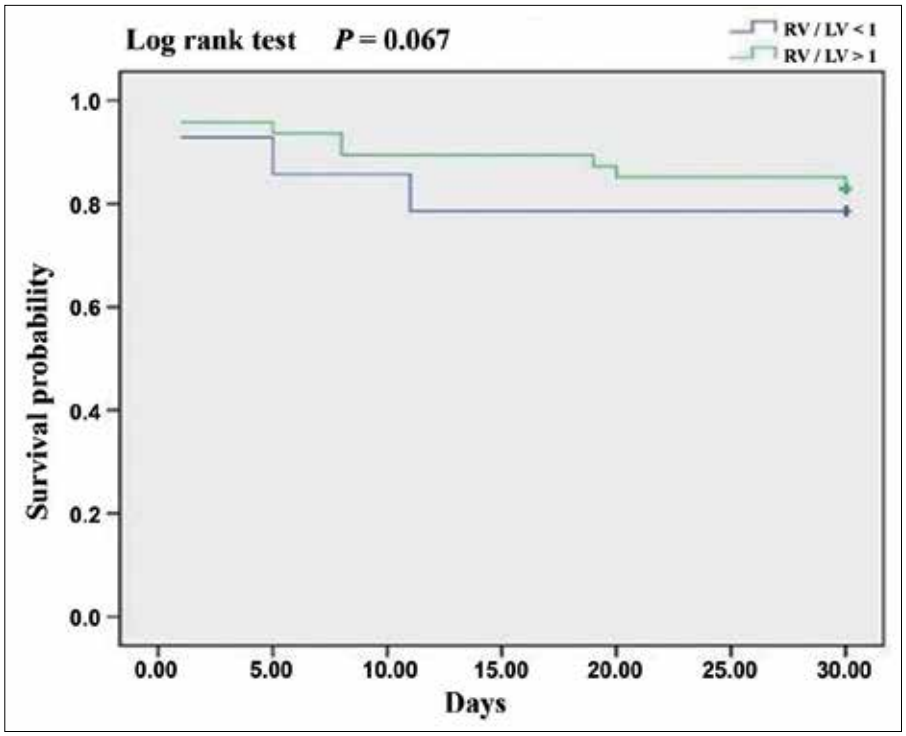

Figure 4. Kaplan-Meier curve for the end-point (30-day mortality) with respect to RV/LV.

with 30-day mortality. The median scores obtained by Wu et al. (21) and van der Meer et al. (9) (10% and 32%, respectively) were lower than those obtained in our study population (mean PAOI was 57%), which reflects differences in the populations studied. In the study performed by Bazeed et al. (22) that used a smaller sample size, PAOI was significantly higher in survivors compared to non-survivors. This study had some important limitations; the number of non-survivors was very low. In addition to the above-mentioned studies, Engelke et al. (23) also found that PA obstruction score was a significant predictor of short-term outcome; the authors in this study preferred Mastora score to Qanadli score. However, we had controversial results in the present study. Our study results are consistent with those of Araoz et al. (11), Ghaye et al. (10), Jeebun et al. (15), and Collomb et al. (13), who did not find any significant association between the PAOI determined with the Qanadli system and short-term death and outcome due to PE. The study performed by Araoz et al. (11) is the largest study in this field, and included 1193 patients with CT scans positive for PE. Recently, Apfaltrer et al. (24) also found that obstruction scores are not correlated to adverse clinical outcome in patients with acute PE. It has been postulated that PA obstruction scores can be an indicator of the severity of a current PE episode or treatment effectiveness, but cannot be used as a predictor of death (10, 11, 13). In patients with acute PE, PA obstruction scores may be valuable for identifying patients with RV dysfunction but appear limited for predicting adverse clinical outcome.

The RV/LV ratio has been considered to be correlated with the severity of PE (11). Whether RV/LV ratio predicts fatal outcome in patients with acute PE is controversial. According to Ghaye et al. (10) and van der Meer et al. (9), RV/LV ratio is a strong predictor of the severity of PE and patient outcome. This is in contrast to the studies of Araoz et al. (11) and Jeebun et al. (15), in which no association between the RV/LV ratio and death was reported. Similarly, in our study, RV/LV ratio did not predict mortality at 30-day follow-up. In addition, we found a significant correlation between RV/LV ratio and PAOI. This is consistent with findings reported in the literature, in which RV/LV ratio correlates with PAOI assessed with Qanadli score (9, 10, 25).

Some limitations of this study warrant discussion. First, although the study included a small sample size, study population consisted of patients with acute PE at intermediate risk. Second, the test performed for H-FABP measurement is qualitative, not quantitative, providing only positive or negative results. Third, this study is prospective with 30-day follow-up; long-term results, however, need to

be pursued. Fourth, we did not use an ECG-gated scanning technique for performing pulmonary CT. Non-ECG-gated pulmonary CT has limitations in accurately measuring ventricular chamber size. Fifth, transthoracic echocardiography was not performed to evaluate RV functions. The relationship between echocardiographic findings and CT parameters was outside of the scope of this study. Sixth, in contrast to the literature, the prevalence of thrombolytic usage was higher due to the policy of our clinic, and higher thrombolytic usage may alter the CT results. Last, CT parameters were evaluated by one radiologist. Measurement of CT parameters by two independent radiologists and analysis of reliability (inter- and intra-observer variability) are more accurate than evaluation by one radiologist.

In conclusion, scoring systems based on obstruction of pulmonary arterial circulation are relatively time-consuming and not easily applicable in routine practice. Our study suggests that although H-FABP predicts 30-day mortality, PAOI and RV/LV ratio do not predict 30-day mortality due to acute PE and are not correlated with elevated H-FABP levels. Therefore, we propose that H-FABP is more sensitive than CT parameters in predicting mortality.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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