

# Prediction of Mortality in Pulmonary Embolism Based on Left Atrial Volume Measured on CT Pulmonary Angiography



Galit Aviram, MD; Eugene Soikher, MD; Achiude Bendet, MD; Hezzy Shmueli, MD; Tomer Ziv-Baran, PhD; Yoav Amitai, MD; Limor Friedensohn, MD; Shlomo Berliner, MD, PhD; Ahuava Meilik, PhD; and Yan Topilsky, MD

**BACKGROUND:** Preliminary reports suggest that a small left atrium (LA) is associated with severe acute pulmonary embolism (PE). This study used data derived from volumetric analyses of computed tomographic pulmonary angiography (CTPA) to investigate whether a reduced LA volume can predict adverse outcome in a large series of patients with acute PE.

**METHODS:** We retrospectively analyzed 756 consecutive patients who received a diagnosis of acute PE by nongated CTPA between January 2007 and December 2010. Each CTPA was investigated with volumetric analysis software that automatically provides the volumes of the LA, right atrium, right ventricle, and left ventricle. A classification tree divided the cardiac chamber volumes and ratios into categories according to mortality. Cox regression assessed the association between these categories and 30-day mortality after adjustment for age, sex, and clinical background.

**RESULTS:** The final study group consisted of 636 patients who had successful volumetric segmentation and complete outcome data. Eighty-four patients (13.2%) died within 30 days of PE diagnosis. There was a higher mortality rate among patients with an LA volume  $\leq 62$  mL compared with those with an LA volume  $> 62$  mL (19.6% vs 8.9%, respectively; HR, 2.44;  $P < .001$ ), a left ventricle volume  $\leq 67$  mL (16.4% vs 8.3%; HR, 1.8;  $P = .024$ ) and a right atrium/LA volume ratio  $> 1.2$  (17% vs 9.4%; HR, 2.1;  $P = .002$ ). A reduced LA volume was the best predictor of adverse outcome.

**CONCLUSIONS:** Decreased LA volume is associated with higher mortality and is the first among the various cardiac compartments to predict mortality in patients with acute PE.

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**KEY WORDS:** computed tomography (CT); CT scan pulmonary; pulmonary embolism

**ABBREVIATIONS:** CTPA = computed tomographic pulmonary angiography; LA = left atrium; LV = left ventricle; PE = pulmonary embolism; RA = right atrium; RV = right ventricle

**AFFILIATIONS:** From the Departments of Radiology (Drs Aviram, Soikher, Bendet, and Amitai), Internal Medicine 'D' and 'E' (Drs Shmueli, Friedensohn, and Berliner), Cardiology (Dr Topilsky), and Clinical Performances Research Unit (Dr Meilik), Tel Aviv Sourasky Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; Department of Epidemiology and Preventive Medicine (Dr Ziv-Baran), School of Public Health, Sackler Faculty of Medicine, Tel Aviv University.

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**CORRESPONDENCE TO:** Galit Aviram, MD, Department of Radiology, Tel Aviv Sourasky Medical Center, Weizman St, Tel Aviv 64239, Israel; e-mail: [aviramgalit@hotmail.com](mailto:aviramgalit@hotmail.com)

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Computed tomography pulmonary angiography (CTPA) is currently the modality of choice for the diagnosis of acute pulmonary embolism (PE).<sup>1,2</sup> CTPA can also contribute to risk stratification of patients with PE by the assessment of right ventricular dysfunction, which presents as an increased ratio between the diameters of the right (RV) and left (LV) ventricles.<sup>1,3-8</sup> Reduced left atrial (LA) volume resulting from underfilling may accompany substantial obstruction of the pulmonary arteries, but the literature contains sparse reports describing its significance for risk assessment. Two small series of patients with acute PE<sup>9,10</sup> showed that a smaller LA area and a larger right atrial (RA) area, as measured on CTPA, are found among PE patients with higher pulmonary arterial clot load,<sup>9</sup> and that an

RA/LA area ratio  $>1.0$ , as measured by transthoracic echocardiography during a PE event, is associated with a threefold-increased risk of long-term mortality.<sup>10</sup>

A basic preliminary software system capable of analyzing the volumes of all four cardiac chambers of nongated CTPA was described in 2012 as a new technology for rapid risk stratification among a small series of patients with PE and control subjects without PE.<sup>11</sup> This system is fully automatic and able to provide the volumetric data within seconds following the diagnosis of PE. Our aim was to examine whether a small LA volume can predict adverse outcome, defined as mortality within 30 days, on a larger series of patients with acute PE.

## Materials and Methods

The study was conducted in a large, university-affiliated tertiary care 1,200-bed hospital. The institutional review board approved this retrospective analysis and waived the need for informed consent (Helsinki Committee, Division of Research and Development, Tel Aviv Sourasky Medical Center, project approval number: 0158-12-TLV).

### Study Population

The hospital's database was used to retrospectively identify the inpatients who underwent CTPA between January 1, 2007, and December 31, 2010. Patients were included if they received a diagnosis of acute PE on their CTPA. The chart records of these patients were then reviewed by two clinicians (H.S. and L.F.) who used the Integrated Radiological Information System database to retrieve clinical information that included sex and age, background and comorbid conditions, recent (during the preceding 3 months) events of cardiovascular disease, infection, operation, trauma, or hospitalization. Patients were excluded if their CTPA was inadequate (because of incomplete coverage of the heart in the Z-axis or inaccurate detection of the chambers' boundaries by the volumetric software) or if clinical follow-up information was unavailable. In the event of multiple scans, the results of the first one were entered into the analysis. Referral for CTPA studies was based on clinical suspicion of acute PE in patients with no contraindications to undergo them (eg, severe allergic reactions to iodine-containing contrast media, renal failure). Adverse clinical outcome was defined as death within 30 days after the diagnosis of acute PE. The date of mortality was collected from the database of the country's Ministry of Internal Affairs.

### CT Acquisition

All patients were scanned by a multidetector CT scanner (Mx8000 IDT or Brilliance; Philips Medical Systems) with 16 or 64 detector rows. The reconstructed slice thickness was 1 to 2 mm with an increment of 0.5 to 1 mm. Scans were acquired according to our routine nonelectrocardiographic-gated protocol with contrast injections of 70 to 100 mL of iodinated contrast material at a concentration of 300 mg iodine per milliliter (Ultravist, Schering) and at rates of 3 to 4 mL/s. To optimize visualization of the pulmonary arteries, an automated bolus-tracking technique was used with a region of interest placed within the main pulmonary artery. Five seconds after

reaching a threshold of 100 Hounsfield units at the region of interest, scanning began covering the chest from the lung bases to the thoracic inlet. All scans were obtained in a craniocaudal direction at end-of-inspiration during a single breath-hold.

### CT Assessment

Automated volumetric measurements of the RV, RA, LV, and LA were obtained using a new fully automatic algorithm (Comprehensive Cardiac Analysis, Extended Brilliance Workspace, Research Version Philips Healthcare) that adapts an anatomical model of the heart chambers to the CT image volume.<sup>11-14</sup> The output consists of a three-dimensional graphic display of the heart segmented into its main structures. We analyzed the volumes of the RV, RA, LV (excluding the myocardium), and LA. The volume of each cardiac chamber was automatically calculated as the product of a single voxel volume and the sum of all voxels included in it. This approach requires only that the reconstructed images of the entire volume of the chest be uploaded at once at the workstation. Importantly, no other human interaction was needed or performed. Loading and processing by the automated system took 20 to 40 seconds per study. The software allows the relevant segmentation structure to be color-coded and viewed simultaneously in both three and two dimensions superimposed on the reference image in the axial, coronal, sagittal, or cardiac views (short axis, vertical long axis, horizontal long axis). [Figure 1](#) presents an example of the software's output. Each structure was inspected visually on the reference images for conformity to the imaged cardiac anatomy to validate the correctness of the segmentation. Manual tools for the addition and subtraction of volumes are available, but they were not used in the present work to assess the completely automatic performance of the software. To assess whether automatic segmentation was done correctly, the CT scans were reviewed in consensus by two radiologists (E.S., G.A.) with 6 and 15 years of experience and who were unaware of the clinical history, the results of other imaging techniques, and the patient outcome. In the event that the automatic segmentation was visually assessed as being incorrect, the patient's data were excluded from the study. A previous version of this software had been validated on cardiac-gated scans,<sup>12</sup> and the current study is based on a newer version using an algorithm designed to improve the analysis of nongated CTPA studies. To evaluate the reproducibility of the software, we reloaded the images of 40 consecutive patients at a later date and compared the two measurements.



Figure 1 – Representative case of fully automated volumetric analysis of four cardiac chambers in a 59-year-old woman with acute pulmonary embolism who died 4 days following diagnosis. (A) Volumetric model of the four cardiac chambers. (B) Horizontal long axis reformation (four-chamber view). Left atrium = purple; left ventricle = pink; right atrium = yellow; right ventricle = orange. There are decreased left heart volumes: LA, 34 mL; LV, 50 mL; RA, 96 mL; RV, 143 mL. Note the complete filling defects resulting from pulmonary emboli that are seen in both the right and left lower lobe arteries (white arrows). The interatrial septum is shifted to the left (black arrow). LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

### Statistical Analysis

Categorical variables were reported as numbers (percentages), and continuous variables as means (SD) or medians (interquartile ranges). We used univariate Cox regression to evaluate the hazard ratios (HR) and the association between each variable (age, sex, comorbidities, the various cardiac chambers volumes, and the ratios between the RV/LV and RA/LA volumes) and mortality within 30 days of the PE diagnosis. Patients who survived 30 days following the diagnosis of PE were considered as censored. Classification tree methodology of  $\chi^2$  automatic interaction detection was used to separate each of the heart chamber volumes and their ratios into categories according to

the mortality status.<sup>15</sup> Then, each of these parameters was analyzed separately using multivariate Cox regression to evaluate the association with mortality while controlling for potential confounders. Age, sex, and any variable with a *P* value less than .2 in the univariate analysis were included in the multivariate analysis. A Kaplan-Meier plot was used to describe the mortality between categories, and the log-rank test was applied to compare between them. We also performed a  $\chi^2$  automatic interaction detection analysis, which included all the volumes and their ratios to identify the best predictor to classify patients according to outcome. A two-tailed *P* < .05 was considered statistically significant. Analyses were performed with SPSS, version 21.

## Results

Seven-hundred and fifty-six patients with acute PE met the inclusion criteria, and 120 (15.9%) patients were excluded: 77 (10.2%) because of inaccurate detection of the chambers' boundaries by the volumetric software, 25 (3.3%) because of an incomplete CT scan, and 18 (2.4%) because of unavailability of clinical follow-up information. The final study group, therefore, consisted of 636 patients (124 of whom had been included in a previous report).<sup>11</sup> The mean age of the patients was 67.5 years (SD, 17.5) and 44% of them were men. Eighty-four patients (13.2%) died within 30 days from the diagnosis of PE.

Baseline characteristics of the study cohort and comparison between the patients who died within 30 days and those who survived are presented in Table 1. The patients who died within 30 days from the diagnosis more commonly had active malignancy than the survivors (68.7% vs 29.2%, respectively; *P* < .001), diabetes mellitus (28.9% vs 18.3%; *P* = .023), and recent hospitalization (45.8% vs 30.8%; *P* = .007). There was no

difference in age, sex, or other comorbidities between the patients who died and the survivors.

Table 2 presents the association of each cardiac chamber volume and mortality within 30 days of PE diagnosis using univariate analysis. Patients who died within  $\leq 30$  days had smaller LA and LV volumes (ie, 57.5 vs 70.1 mL; *P* = .002, and 55.4 vs 62.6 mL; *P* = .013, respectively). The association between each chamber measurement and the mortality was further investigated by stratifying the patients using classification tree analysis. Following a multivariate Cox regression analysis, it emerged that decreased values of the left-sided chamber volumes as well as higher right-to-left atrial volumes ratio were indicative of mortality (Table 3). The 255 patients with an LA volume  $\leq 62$  mL had more than twofold-increased mortality than those with a volume higher than 62 mL (19.6% vs 8.9%; adjusted HR [HR<sub>adj</sub> = 2.44]; *P* < .001). Also, a higher mortality rate was demonstrated among the patients with LV volumes  $\leq 67$  mL compared with those having volumes >67 mL (16.4% vs 8.3%, respectively; HR<sub>adj</sub> = 1.8;

**TABLE 1 ]** Baseline Characteristics of the Study Cohort and Comparison Between Patients Who Died 30 Days Since Diagnosis of a Pulmonary Embolism and Those Who Survived

Variable	Study Population (N = 636)	Mortality ≤30 Days			
		No (n = 552)	Yes (n = 84)	HR (95% CI)	P
<b>Sex, n</b>					
Male	280 (44.0)	240/552 (43.5)	40/84 (47.6)	1.16 (0.75-1.78)	.505
Female	356 (56.0)	312/552 (56.5)	44/84 (52.4)	1	
Age, y median (IQR)	72 (57-81)	71 (56.3-81.0)	72 (60-82)	1.01 (0.99-1.02)	.096
Current smoker	58 (9.1)	49/548 (8.9)	9/82 (11.0)	1.23 (0.62-2.47)	.552
Past smoker	74 (11.6)	62/547 (11.3)	12/82 (14.6)	1.32 (0.71-2.43)	.378
Diabetes mellitus	124 (19.5)	100/547 (18.3)	24/83 (28.9)	1.73 (1.08-2.79)	.023
HTN	295 (46.4)	255/549 (46.4)	40/83 (48.2)	1.06 (0.69-1.64)	.778
COPD or asthma	64 (10.1)	54/546 (9.9)	10/83 (12.0)	1.23 (0.64-2.39)	.537
CHF	52 (8.2)	47/547 (8.6)	5/83 (6.0)	0.71 (0.29-1.74)	.448
Valvular	150 (23.6)	132/552 (23.9)	18/84 (21.4)	0.88 (0.52-1.49)	.636
IHD	113 (17.8)	98/547 (17.9)	15/83 (18.1)	1.002 (0.57-1.75)	.995
CVA or TIA	59 (9.3)	50/547 (9.1)	9/83 (10.8)	1.21 (0.61-2.42)	.586
Past malignancy	82 (12.9)	70/551 (12.7)	12/83 (14.5)	1.17 (0.64-2.16)	.613
Active malignancy	218 (34.3)	161/551 (29.2)	57/83 (68.7)	4.63 (2.91-7.36)	<.001
CVD event ≤3 months	15 (2.4)	14/547 (2.6)	1/83 (1.2)	0.49 (0.07-3.48)	.472
Infection or inflammation ≤3 months	103 (16.2)	86/547 (15.7)	17/83 (20.5)	1.36 (0.79-2.32)	.259
Surgery or trauma ≤3 months	189 (29.7)	168/547 (30.7)	21/83 (25.3)	0.77 (0.47-1.27)	.310
Hospitalization ≤3 months	207 (32.5)	169/548 (30.8)	38/83 (45.8)	1.82 (1.18-2.81)	.006
Angiography ≤3 months	10 (1.6)	9/547 (1.6)	1/83 (1.2)	0.78 (0.11-5.59)	.803

Data are presented as No. (%) unless otherwise indicated. CHF = congestive heart disease; CVA = cerebrovascular accident; CVD = cardiovascular disease; HTN = hypertension; HR = hazard ratio; IHD = ischemic heart disease; IQR = interquartile range; TIA = transient ischemic attack.

$P = .024$ ) and RA/LA volume ratios  $>1.2$  compared with those with ratios  $\leq 1.2$  (17% vs 9.4%, respectively;  $HR_{adj} = 2.1$ ;  $P = .002$ ). [Figure 2](#) depicts the Kaplan-Meier survival curves in relation to LA and LV volumes and the RA/LA volume ratios. Moreover, the classification tree

algorithm that included analysis of all the volume measurements and their ratios identified the LA volume as being the first splitting node without any additional subdivisions and, therefore, the best predictor of mortality. Assessment of the reproducibility of the

**TABLE 2 ]** Univariate Analysis of the Association Between the Volumes and Ratios of the Various Cardiac Compartments and Mortality Within 30 Days

Variable	30-Day Mortality			
	Yes Median (IQR)	No Median (IQR)	HR (95% CI)	P
LV volume	55.4 (46.0-67.8)	62.6 (49.0-78.4)	0.987 (0.978-0.997)	.013
RV volume	98.9 (80.0-119.8)	106.8 (83.0-130.8)	0.995 (0.989-1.002)	.152
LA volume	57.5 (45.4-74.8)	70.1 (54.1-86.6)	0.985 (0.975-0.994)	.002
RA volume	78.6 (63.3-102.0)	83.0 (64.5-107.8)	0.995 (0.989-1.002)	.150
RV/LV volume ratio	1.70 (1.41-2.19)	1.62 (1.32-2.08)	1.119 (0.904-1.384)	.261
RA/LA volume ratio	1.32 (1.06-1.64)	1.18 (0.93-1.49)	1.181 (0.894-1.561)	.258

Volumes are presented in millimeters. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. See [Table 1](#) legend for expansion of other abbreviation.

**TABLE 3 ]** The Association Between the Volumes and Ratios of the Various Cardiac Compartments and 30-Day Mortality as Categorized by Classification Tree Analysis Followed by Multivariate Cox Regression

Compartment	Volume	n/N (%)	30-Day Mortality		
			HR <sub>adj</sub>	95% CI	P
LA	≤62 mL	50/255 (19.6)	2.44	(1.52-3.9)	<.001
	>62 mL	34/381 (8.9)			
RA/LA ratio	>1.2	54/318 (17)	2.1	(1.32-3.37)	.002
	≤1.2	30/318 (9.4)			
LV	≤67 mL	63/384 (16.4)	1.8	(1.08-3.01)	.024
	>67 mL	21/252 (8.3)			

n = number of patients who died; N = number of patients in the group; % = mortality rate; HR<sub>adj</sub> = hazard ratio adjusted to age, sex, and any variable with a *P* value < .2 in the univariate analysis (eg, active malignancy, diabetes, recent hospitalization). See Table 2 legend for expansion of other abbreviations.

automatic volumetric measurements revealed that the automatic volumetric software always provided the same measurement (less than a difference of 1 mL).

## Discussion

Risk stratification in PE is traditionally based on echocardiography and CTPA-derived evidence of RV dysfunction.<sup>1</sup> The present work used a new tool for early risk stratification in patients with acute PE, transferring the focus from the RV to the LA. We have found that smaller LA and LV volumes as well as increased RA/LA volume ratios were shown to be associated with a significant increase in short-term mortality. Two of three previous meta-analyses that assessed the association between various increased RV/LV ratios as evidenced on CTPA and overall mortality reported a pooled OR of 2.08 (1.63-2.66)<sup>3</sup> and 1.8 (95% CI, 1.3-2.6),<sup>16</sup> whereas the third found no such association (OR, 1.54 [0.7-3.4]).<sup>17</sup> Because there are inconsistent reports regarding the association between CTPA-based increased RV/LV ratios and increased mortality, we reasoned that a different approach for risk assessment in acute PE might be valuable. Our results demonstrated that an LA volume ≤62 mL is associated with a significant increase in 30-day mortality with an HR of 2.44 (95% CI, 1.52-3.9). We applied a software analysis to extrapolate the LA and RA volumes from routine CTPA studies, which can continue to run automatically with the advantage of providing quantitative reproducible data without spending additional time for conducting further measurements.

The results of pathophysiological studies have suggested that there is an increase in pulmonary vascular resistance due to the anatomical obstruction caused by the emboli, the release of vasoconstricting agents, and

reflex hypoxemia during a major PE event.<sup>18</sup> The abrupt increase in pulmonary vascular resistance may result in RV dilatation and failure from pressure overload, which is considered the leading cause of death in severe PE. The decrease in stroke volume of the RV can lead to a decrease in pulmonary venous return with sudden underfilling of the LA, contributing to the decrease of LV preload, cardiac output, and systemic blood pressure and to coronary perfusion, which may eventually cause circulatory collapse.<sup>19,20</sup> In addition, RV dysfunction can cause not only impaired LV diastolic filling, but also enlargement of the RA, which is associated with increased RV end-diastolic pressure with concomitant increase in RA volume.

Because of the so-called “interdependence mechanism of the right and left cardiac chambers,”<sup>21,22(p382)</sup> and under pericardial restriction, an enlarging RA leads to compression and reduction in the size of the adjacent LA. Because both atrial walls are composed of thin membranous structures that are altered by minor changes of up to 5 mm Hg in intraatrial pressure, higher pulmonary pressures are needed to induce RV dilatation because the RV wall is muscular and stiffer than that of the RA.<sup>23</sup> Thus, an increase in RA volume and a decrease in LA volume resulting from the increased hemodynamic load imposed by the sudden increased pulmonary vascular resistance that accompanies PE may be more pronounced or even precede the changes at the ventricular level. This phenomenon was first described in three patients during massive PE.<sup>24</sup> Their CTPAs showed a reduction in LA volume during the acute event compared with the LA volume that was calculated from CT scans obtained earlier or following treatment. We are aware of only two echocardiography series that assessed atrial size in relation to PE severity: one of them

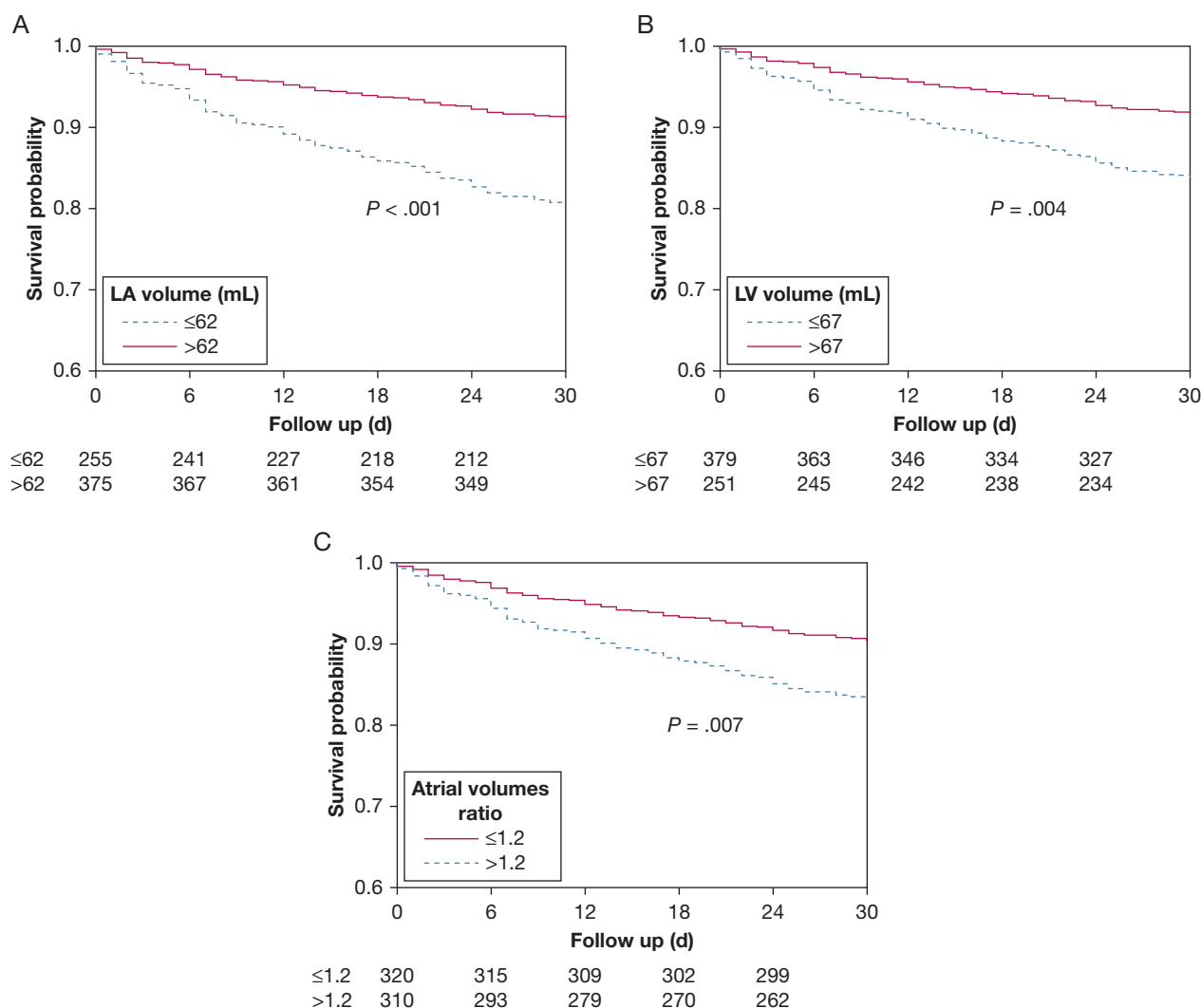


Figure 2 – Kaplan-Meier survival curves in relation to (A) LA volume, (B) LV volume, and (C) RA/LA volume ratio. See Figure 1 legend for expansion of abbreviations.

demonstrated that an increased ratio of right-to-left atrial end-systolic area correlated with obstruction of >30% of the pulmonary arterial tree<sup>21</sup>; the other, larger study<sup>10</sup> showed that an RA/LA area ratio >1.0 on echocardiography performed on the first day following the PE event is independently associated with a threefold increase in long-term mortality. Echocardiography, however, cannot be used for diagnosing PE because it has a limited ability to visualize pulmonary arterial clots that are not very large or centrally located<sup>25</sup> and its diagnostic ability is also operator- and patient-dependent.<sup>26</sup> CTPA, in contrast, is currently the leading modality for PE imaging, being capable of demonstrating even subsegmental and peripheral emboli.<sup>27</sup>

Manual measurements of the short and long axes as well as planimetric measurements of axial images of the RA

and LA on the CTPAs of 137 patients with PE revealed that reduced LA area, reduced LA/RA short axis diameter ratios, and increased RA/LA area ratios are found among patients with more severe PE, as expressed by their pulmonary arterial obstruction index.<sup>9</sup> The application of the automatic software for volumetric analysis was first described in a small group of 124 patients with acute PE who are also included in the present study.<sup>11</sup> In that series, we had used a preliminary version of the volumetric analysis software and reported that the patients with RA and RV volumes that fell in the upper tertile had HRs of 3.9 and 3.3, respectively, for adverse outcome (combined mortality or admission to the intensive care unit), compared with those in the lower tertile. The association between higher RA/LA volume ratio and adverse outcome is satisfactorily validated in the present series, which is significantly

larger. Of note, the RV/LV diameter ratios on the four-chamber view were not found to be associated with poor outcome in that small series.<sup>11</sup> The concept that a reduced LA volume may serve as a predictor of adverse outcome in PE is surprising in view of the fact that increased (rather than decreased) LA size is considered to be an important adverse prognostic factor of morbidity and mortality in the general population<sup>28,29</sup> as well as in patients with most cardiovascular diseases.<sup>30</sup>

The present work describes the novel concept of atrial evaluation for risk assessment in patients with PE. That approach also carries multiple advantages: (1) the atria are measured in three dimensions and not by planimetry, (2) the volumetric assessment is performed automatically by a software program and thus is not labor-intensive or operator-dependent, and (3) it applies the same CTPA images that were acquired for PE diagnosis, potentially leading to the achievement of expeditious risk assessment along with possible savings of additional time and costs for the echocardiography study.

### Study Limitations

One of our study's limitations is its use of nongated CT angiography for the assessment of cardiac volumes, an approach that may be associated with some blurring of myocardial borders because the obtained images represent a sort of averaging of systole and diastole. As such, the calculated volumes cannot be related to any particular phase of the cardiac cycle. Our purpose in the current study was to examine data obtained within routine clinical settings where nongated CT scans are performed. Another limitation is that the volumetric segmentation demonstrated by colors superimposed on

the two-dimensional images was imperfect in around 10% of the scans, leading to their exclusion from analysis. This problem can be solved by improved software accuracy, which can be expected in the very near future. In addition, the current work focused on using a quantitative and reproducible approach, which requires no human interaction; thus, there is no comparison between the volume and diameter measurements that can be obtained only manually. Finally, there is no real-time comparison with echocardiography, which could provide functional correlation and information on cardiac comorbidities. Also, because of the retrospective nature of this study, hemodynamic information on patients' status around the time they underwent CT was not available. As for the statistical analysis, given the number of deaths, use of a split-half approach for validating cutoffs for the volume variables likely was not feasible.

In conclusion, we used a new tool based on volumetric analysis of all four cardiac chambers obtained from routine nongated CTPA performed for PE diagnosis. We were able to show that a decreased LA volume is associated with a higher  $\leq 30$ -day mortality (19.6% vs 8.9%; HR, 2.44,  $P < .001$ ), and that it is the strongest predictor of mortality in patients with acute PE. Accordingly, the presence of an LA volume  $\leq 62$  mL during the diagnosis of PE by CTPA may serve as a potential early radiophysiological sign of an adverse prognosis. Application of an automatic volumetric assessment may allow improvement of care in patients with acute PE by expedition of risk assessment. Large-scale prospective studies are required for further evaluation of the possible advantages of the new approach described here.

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