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Early View

Original article

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Prognostic value of right atrial dilation in patients with pulmonary embolism

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Take home message:

RA dilation is a frequent finding, but its prognostic performance appeared inferior compared to other risk stratification markers. MR-proANP predicted an adverse outcome, but elevation did not appear to be caused by RA dilation to a relevant proportion.

Abstract

Aims: Right atrial (RA) dilation and stretch provide prognostic information in patients with cardiovascular diseases. We investigated the prevalence, confounding factors and prognostic relevance of RA dilation in patients with pulmonary embolism (PE).

Methods: Overall, 609 PE patients were consecutively included in a prospective single-centre registry between 09/2008 and 08/2017. Volumetric measurements of heart chambers were performed on routine non-electrocardiographic-gated computed tomography (CT) and plasma concentrations of mid-regional pro-atrial natriuretic peptide (MR-proANP) measured on admission. An in-hospital adverse outcome was defined as PE-related death, cardiopulmonary resuscitation, mechanical ventilation or catecholamine administration.

Results: Patients with an adverse outcome (11.2%) had larger RA volumes (median 120 [IQR 84-152] vs. 102 [78-134] ml; p=0.013), RA/LA volume ratios (1.7 [1.2-2.4] vs. 1.3 [1.1-1.7]; p<0.001) and MR-proANP levels (282 [157-481] vs. 129 [64-238] pmol/l; p<0.001) compared to patients with a favourable outcome. Overall, 499 patients (81.9%) had a RA/LA volume ratio ≥1.0 and a calculated cut-off value of 1.8 (AUC 0.64 [95%CI 0.56-0.71]) predicted an adverse outcome, both in unselected (OR 3.1, 95%CI 1.9-5.2) and normotensive patients (OR 2.7, 95%CI 1.3-5.6). MR-proANP ≥120 pmol/l was identified as an independent predictor of an adverse outcome, both in unselected (OR 4.6, 95%CI 2.3-9.3) and normotensive patients (OR 5.1, 95%CI 1.5-17.6).

Conclusions: RA dilation is a frequent finding in patients with PE. However, the prognostic performance of RA dilation appears inferior compared to established risk stratification markers. MR-proANP predicted an in-hospital adverse outcome, both in unselected and normotensive PE patients, integrating different prognostic relevant information from comorbidities.

Key words: computed tomography, risk stratification, right atrial dilation, RA/LA volume ratio, mid-regional pro-atrial natriuretic peptide (MR-proANP)

Introduction

Pulmonary embolism (PE) is the most serious manifestation of venous thromboembolism (VTE) and associated with relevant morbidity and mortality worldwide. (1,2) Risk stratification is mandatory to guide decision making on optimal management strategies. (3) Since it is broadly accepted that the extent of right ventricular (RV) dysfunction is the critical determinant of outcome in patients with acute PE, research aiming to optimize risk stratification has mainly focused on (bio-)markers indicating RV dysfunction or injury.

Considering the anatomy of the heart chambers with a thin right atrial (RA) wall and low resistance to the sudden increase of pulmonary artery pressure caused by embolization of a thrombus to the pulmonary vasculature, dilation of the RA and increase of RA volume may be expected to occur before RV dilation can be visualized or biochemically detected. (4) Right to left atrial (RA/LA) end-systolic area ratio assessed by transthoracic echocardiography (TTE) was shown to be associated with the extent of pulmonary artery obstruction on ventilation/perfusion lung scintigraphy (5), and a RA/LA area ratio >1.0 was independently associated with a three-fold increase in long-term mortality. (6) Furthermore, the RA/LA volume ratio on computed tomography pulmonary angiography (CTPA) was significantly larger in PE patients with insufficient contrast medium filling in pulmonary veins compared to those without (7), and patients with a RA/LA volume ratio >1.2 had a higher 30 day mortality rate. (8)

RA distention is not only easy to visualize by imaging modalities, but may also be detected biochemically. As a result of increased wall tension and stretch, mid-regional pro-atrial natriuretic peptide (MR-proANP) is secreted from the atria and a useful biomarker for the diagnosis of acute and chronic heart failure. (9) Interestingly, MR-proANP was more reliable for the detection of pulmonary hypertension due to left heart disease in patients with systemic sclerosis compared to the “ventricular” N-terminal pro-B-type natriuretic peptide

(NT-proBNP). (10) While the association of NT-proBNP with the presence and extent of RV dysfunction and the prognostic value of elevated NT-proBNP levels in patients with acute PE have been consistently demonstrated (11), the prognostic value of MR-proANP and association with RA dilation in acute PE is unknown.

In the present study we aimed to investigate whether a dilated RA (defined by the RA/LA volume ratio, in order to overcome sex- and body size-related physiological differences in atrial size) on diagnostic CTPA using volumetric analyses of the cardiac chambers predicts early adverse outcomes in a large series of patients with acute PE. Further, we investigated whether plasma concentrations of MR-proANP on admission are correlated with imaging findings and provide additive prognostic information.

Methods

Study design

Patients aged ≥18 years with objectively confirmed PE treated at the University Medical Center Goettingen, Germany were included in an ongoing non-interventional cohort study (Pulmonary Embolism Registry of Goettingen, PERGO). The study was conducted in accordance with the amended Declaration of Helsinki, the study protocol was approved by the local independent ethics committee of the University Medical Center Goettingen, Germany, and all patients gave written informed consent for participation in the study. All decisions related with the diagnostic or therapeutic management were made by the physicians caring for the patient and not influenced by the study protocol at any time. The study protocol has been described in detail before. (12)

For the present analysis, patients i) without CTPA for diagnosis of PE, ii) with insufficient quality of CTPA (e.g. inaccurate detection of the cardiac chambers' boundaries by the volumetric software, incomplete coverage of the heart or too little contrast enhancement) and iii) who died within two hours after hospital admission were excluded.

The primary study outcome was an in-hospital adverse outcome (defined as at least one of the following: PE-related death, cardiopulmonary resuscitation, mechanical ventilation or catecholamine administration); the secondary study outcome was in-hospital all-cause mortality. Death was determined to be PE-related if either confirmed by autopsy or following a clinically severe episode of acute PE in absence of an alternative diagnosis. All outcomes and causes of death were independently adjudicated by two of the authors (M.H.L. and K.K.) and disagreement was resolved by a third author (M.L.).

Volumetric and diameter measurements using CT

All patients were examined using Siemens Healthcare multidetector CT scanners (Siemens Sensation 16 [16 detector rows], Somatom Definition FLASH [128 detector rows], Somatom Definition AS+ [128 detector rows]). All CTPA scans were performed as a part of clinical routine for diagnostic confirmation of PE using a non-electrocardiographic (ECG)-gated protocol. Volumetric measurements of the cardiac chambers were obtained using a fully automated algorithm (Pulmonary Arterial Analysis, Extended Brilliance Workspace, Portal Version 7 Philips Healthcare). The output consists of a reconstructed color-coded three-dimensional graphic display of the heart (**Figure 1**). RA and LA volumes were automatically calculated as the product of a single voxel volume and the sum of all voxels. RV and left ventricular (LV) diameters were measured in axial views using the largest diameter of each ventricle and RV/LV diameter ratios calculated. All measurements were performed by a radiologist (M.H.L.) in consensus with an expert radiologist (G.A.) unaware of the patients' characteristics and outcome. A RA/LA volume ratio cut-off value of 1.2 was defined to predict in-hospital mortality. (8)

Biomarker measurement

Venous plasma samples were collected on admission, processed using standard operating procedures and immediately stored at -80°C. Plasma concentrations of MR-proANP, NT-proBNP and high-sensitivity troponin T (hsTnT) were measured in batches after a single thaw by the Institute of Clinical Chemistry of the University Medical Center Goettingen, Germany and *amedes MVZ wagnerstibbe*, Goettingen, Germany using commercially available assays (MR-proANP: BRAHMS GmbH, Thermo Fisher Scientific, Hennigsdorf/Berlin, Germany; NT-proBNP and hsTnT: Roche Diagnostics, Mannheim, Germany). Elevated biomarker levels were ad-hoc defined as NT-proBNP ≥600 pg/ml (11) and hsTnT ≥14 pg/ml (14)

(prognostic relevant cut-off values reported for patients with PE). Given the lack of a previous investigation of MR-proANP in patients PE, a threshold of ≥120 pmol/l was selected based on the "Biomarkers in Acute Heart Failure" (BACH) study (13).

Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov-Smirnov-test; variables not following a normal distribution are presented as median and interquartile range (IQR) and were compared using the Mann-Whitney U-Test. Categorical variables are presented as numbers and percentages and were compared using Fisher's exact test or chi^2 test, as appropriate. RA and LA volume and RA/LA volume ratio were correlated to continuous echocardiographic, laboratory and clinical parameters. Correlation coefficients were assessed by the Spearman-Rho rank test. Correlation with a r<-0.4 or >0.4 were considered clinically relevant. Receiver operating characteristics (ROC) analyses were used to investigate the prognostic performance of continuous measures (radiological, echocardiographic and laboratory parameters) and to determine patient-cohort optimal cut-off values by using Youden index quantification; results are reported as area under the curve (AUC) with corresponding 95% confidence interval (CI). The prognostic value of categorial parameters with regard to the primary and secondary study outcomes were investigated using univariate logistic regression analyses and results reported as Odds Ratios (OR) with corresponding 95% CI. To identify parameters associated with MR-proANP above the median concentrations of 142 pmol/l, univariate and multivariate (including all univariate predictors using stepwise forward selection) logistic regression analyses were performed. Subsequently, the independence of MR-proANP ≥120 pmol/l to predict an in-hospital adverse outcome was tested using a multivariate logistic regression model simultaneously including parameters (age ≥75 years, female sex, chronic heart failure, atrial fibrillation, coronary artery

disease, arterial hypertension, renal insufficiency) shown to independently predict MR-proANP elevation.

A two-sided significance level of α 0.05 was defined appropriate to indicate statistical significance. All statistical analyses were performed using the SPSS software (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

Overall, 718 PE patients were included in PERGO over a nine-year period (09/2008 to 09/2017). Of these, 114 patients (15.9%) were excluded for the following reasons: 47 patients (6.5%) because of missing CTPA scans and 62 (8.6%) because of insufficient quality of CTPA scans. Thus, the present study cohort consists of 609 patients (median age 69, IQR 56-77 years; 47.0% male). Baseline characteristic, comorbidities and clinical findings of the study patients are shown in **Table 1, left column**. Of note, 53 patients (8.7%) were classified as high risk using the algorithm suggested by the 2019 ESC guideline (3).

Representative images of volumetric analysis using CTPA are shown in **Figure 1**. In the overall cohort, the median RA and LA volume was 102 (IQR 78-134) and 71 (IQR 57-93) ml, respectively, and the median RA/LA volume ratio 1.37 (IQR 1.05-1.80). As shown in **Table 1s** of the **supplementary material**, patients with cardiovascular comorbidities but also male and elderly (≥75 years) patients had larger RA and LA volumes, respectively; cancer patients had a smaller RA and LA volume. While patients with cardiovascular comorbidities and cancer had a smaller RA/LA volume ratio, patients with more severe PE (e.g. indicated by tachycardia, syncope, elevation of laboratory biomarkers or higher ESC risk class) had a larger RA/LA volume ratio (**Table 1s**). Similar, as shown in **Table 2s,** patients with a RA/LA volume ratio <1.4 more frequently had cardiovascular comorbidities and cancer while patients with a RA/LA volume ratio ≥1.4 more frequently had more severe PE. The median RV/LV diameter ratio was 1.17 (IQR 0.98-1.51) and as many as 445 patients (73.1%) hat a RV/LV diameter ratio ≥1.0.

Plasma concentrations of MR-proANP were measured in 522 patients (85.7%; median 142, IQR 68-266, range 14-989 pmol/l), of NT-proBNP in 554 patients (91.0%; median 674, IQR 124-2,620, range 8-35,645 pg/ml) and of hsTnT in 568 patients (93.3%; median 27, IQR 10-65, range 3-3,094 pg/ml). The baseline characteristic, comorbidities and clinical findings

in study patients stratified according to the median MR-proANP concentration are shown in **Table 1, middle columns**. Older age and female sex, cardiovascular comorbidities as well as symptoms and laboratory biomarkers indicating more severe PE were associated with MR-proANP levels ≥142 pmol/l. The highest Odds Ratios for MR-proANP ≥142 pmol/l were observed for age ≥75 years, atrial fibrillation and renal insufficiency (**Table 1, right columns**); RA dilation assessed by CTPA or TTE was not associated with MR-proANP ≥142 pmol/l.

As shown in **Table 3s**, MR-proANP correlated with hsTnT (r=0.561), NT-proBNP (r=0.637) but also with age (r=0.623) and glomerular filtration rate (GFR; r=-0.495).

Prognostic performance of radiological, laboratory and clinical parameters

During the in-hospital stay, 68 patients (11.2%) had an adverse outcome (25 [37.3%] required cardiopulmonary resuscitation, 47 [70.1%] mechanical ventilation and 54 [79.4%] catecholamine administration) and 36 patients (5.9%) died; of those 26 (72.2%) due to PE. As expected, the highest rate of an adverse outcome was observed for patients classified as high risk (69.8%) followed by patients classified as intermediate-high (10.6%) and intermediate-low (4.8%) risk based on the algorithm suggested by the 2019 ESC guideline (3); none of the patients classified as low risk had an unfavourable clinical in-hospital course.

Patients with an in-hospital adverse outcome had larger RA volumes on CTPA (120, IQR 84-152 vs. 102, IQR 78-134 ml; p=0.013) and higher RA/LA volume ratios (1.66, IQR 1.19-2.35 vs. 1.33, IQR 1.05-1.74, p<0.001) compared to patients with a favourable clinical course. However, RA volume was only weakly associated with an in-hospital adverse outcome (AUC 0.59, 95% CI 0.52-0.67) while LA volume was not of prognostic value (AUC 0.44, 95% CI 0.36-0.53). Results remained unchanged if RA and LA volumes were corrected for body surface area (shown in the **supplementary material**). The AUC of the RA/LA

volume ratio with regard to an adverse outcome was 0.64 (95% CI 0.56-0.71; **Figure 2A**). As shown in **Table 2A**, increasing RA/LA volume ratios were associated with increasing specificity with regard to the prediction of an adverse outcome. While the pre-defined RA/LA volume ratio cut-off value of 1.2 was not associated with an increased risk, a calculated patient cohort-optimized cut-off value of 1.8 was associated with a 3.1-fold increased risk (95% CI 1.9-5.2) for an in-hospital adverse outcome. A RV/LV diameter ratio above the established cut-off value of 1.0 failed to predict an in-hospital adverse outcome.

Patients with an in-hospital adverse outcome had higher median biomarker concentrations compared to patients with a favourable clinical course (MR-proANP: 282, IQR 157-481 vs. 129, IQR 64-238 pmol/l, p<0.001; NT-proBNP: 1,538, IQR 440-3,629 vs. 556, IQR 114-2,461 pg/ml, p=0.001 and hsTnT: 58, IQR 27-101 vs. 24, IQR 8-57 pg/ml, p<0.001). The AUC of MR-proANP with regard to an adverse outcome (0.72 [95% CI 0.65-0.79]) was larger compared to that of NT-proBNP (0.62 [95% CI 0.55-0.70]) and hsTnT (0.69 [95% CI 0.63-0.76]; **Figure 2B**). Established laboratory (such as NT-proBNP ≥600 pg/ml and hsTnT ≥14 pg/ml) and clinical (such as chronic heart failure, renal insufficiency, syncope or tachycardia) parameters provided valuable prognostic information with regard to an in-hospital adverse outcome (**Table 2B**). MR-proANP ≥120 pmol/l was associated with a 4.6-fold increased risk (95% CI 2.3-9.3) for an in-hospital adverse outcome. Of note, if corrected for age, sex and comorbidities affecting MR-proANP concentrations (as described in the Methods), the prognostic value of MR-proANP remained independent (OR_{adj} 4.0, 95% CI 1.8-9.0).

The prognostic performance of radiological, echocardiographic, laboratory and clinical parameters with regard to in-hospital all-cause mortality is shown in **Table 4s** and with regard to an in-hospital adverse outcome in 556 (91.3%) normotensive patients in **Table 5s**.

Discussion

The present study findings in 609 consecutive PE patients included over a nine-year period (09/2008 to 09/2017) in a single-centre can be summarized as follows: i) patients with an in-hospital adverse outcome had larger RA volumes and RA/LA volume ratios on CTPA and higher MR-proANP concentrations compared to patients with a favourable clinical course, ii) a calculated patient-cohort optimized RA/LA volume ratio cut-off value of 1.8 was able to predict an in-hospital adverse outcome, both in unselected (OR 3.1, 95% CI 1.9-5.2) and normotensive patients (OR 2.7, 95% CI 1.3-5.6) and iii) MR-proANP ≥120 pmol/l was identified as independent predictor of an in-hospital adverse outcome, both in unselected (OR 4.6, 95% CI 2.3-9.3) and normotensive patients (OR 5.1, 95% CI 1.5-17.6).

Prognostic relevance of RA dilation in pulmonary embolism

Obstruction of the pulmonary vasculature by embolized thrombi leads to an increase of pulmonary artery pressure and pulmonary vascular resistance resulting in RV dilation and dysfunction. (3,15) As early as 1971, McIntyre and Sasahara reported that the degree of pulmonary embolic obstruction and mean pulmonary artery pressure correlate with mean RA pressure. (16) In a more recent study, investigating 1,640 consecutive patients who underwent TTE, increasing RV/RA pressure gradients were associated to an increase in RA dilation. (17) The RA/LA area ratio assessed by TTE correlated with the extent of pulmonary artery obstruction on ventilation/perfusion lung scintigraphy in 63 retrospectively studied PE patients (5) and a higher clot load in the pulmonary arteries was associated with a larger RA area and a smaller LA area on CTPA in a retrospective study of 137 PE patients. (4) In the present study, as many as 81.9% of patients had RA dilation (defined as RA/LA volume ratio ≥1.0) on CTPA. While patients with cardiovascular comorbidities and cancer had a smaller RA/LA volume ratio, patients with more severe PE (e.g. indicated by tachycardia, syncope,

elevation of laboratory biomarkers or higher ESC risk class) had a larger RA/LA volume ratio (**Table 1s**).

Recent studies indicate that RA dilation constitutes a prognostically relevant finding in patients with various cardiopulmonary disease. (18,19) For example, a RA/LA area ratio >1.0 on TTE was related to long-term all-cause mortality independently of LV ejection fraction in 289 elderly patients hospitalized for heart failure (20) and independently associated with a three-fold increased risk of long-term mortality in 193 patients with PE. (6) In a study investigating 636 PE patients, patients with a RA/LA volume ratio >1.2 on CTPA had a higher 30-day mortality rate. (8) In the present study, patients with an in-hospital adverse outcome had larger RA volumes and RA/LA volume ratios on CTPA and a calculated patient-cohort optimized RA/LA volume ratio cut-off value of 1.8 was able to predict an in-hospital adverse outcome, both in unselected (OR 3.1, 95% CI 1.9-5.2) and normotensive patients (OR 2.7, 95% CI 1.3-5.6), while the previously proposed cut-off value of 1.2 appeared too low to provide prognostic information. This difference might be attributed to differences in patient population, observation time and a larger number of patients with active cancer included in the study by Aviram and colleagues (34.3% compared to 17.6% in the present study), of whom 26.1% died during the first 30 days contributing to 67.9% of all deaths. (8) In comparison, in the present study, 72.2% of all deaths were due to PE. Although evidence appears to accumulate that a dilated RA may be of prognostic value in patients with acute PE, further studies are needed to investigate underlying mechanisms and to define its prognostic significance.

Prognostic relevance of MR-proANP

The major stimulus for ANP (and thus MR-proANP) release is increased atrial wall tension. (9) A number of studies have demonstrated that MR-proANP is a useful biomarker for the diagnosis of atrial fibrillation and heart failure. For example, in the Biomarkers in Acute Heart Failure (BACH) study including 1,641 patients, MR-proANP ≥120 pmol/l was as useful as NT-proBNP for a diagnosis of acute heart failure in dyspnoeic patients. (13) Further, MR-proANP was identified as predictor of long-term mortality in patients after acute myocardial infarction (21) and community patients. (22) The first study investigating ANP in patients with PE was published 30 years ago (23), followed by two small studies: Kiely and colleagues reported that ANP levels were higher in 17 patients with high probability of PE in ventilation/perfusion lung scan compared to 77 patients with low/intermediate probability and 20 patients with normal scans. (24) Gutte and colleagues reported that proANP levels were higher in 7 PE patients with RV dysfunction compared to 22 PE patients without RV dysfunction. (25) In the present study, patients with an in-hospital adverse outcome had higher MR-proANP concentrations compared to patients with a favourable clinical course and MR-proANP ≥120 pmol/l was identified as independent predictor of an in-hospital adverse outcome, both in unselected (OR 4.6, 95% CI 2.3-9.3) and normotensive patients (OR 5.1, 95% CI 1.5-17.6). However, older age, cardiovascular comorbidities (in particular atrial fibrillation) and renal insufficiency were associated with MR-proANP elevation ≥142 pmol/l. Despite the pathophysiological association between atrial wall distension and MR-proANP release, RA dilation assessed by CTPA or TTE was not able to predict elevated MR-proANP levels and only weak correlations for MR-proANP concentrations and RA volume on CTPA (r=0.369) were observed. In contrast, moderate correlations were found between MR-proANP concentrations and known risk factors such as age (r=0.623), GFR (r=-0.495) and NT-proBNP (r=0.637). Thus, the present study findings indicate that elevation of MR-proANP in patients with acute PE may only be explained to a small extent by the severity of the PE but rather appears to integrate different prognostic relevant information from comorbidities.

Limitations

Only 25.2% of study patients had an electronically stored TTE examination performed within 48 hours after diagnosis of PE in sufficient quality for reassessment; thus, study findings related to TTE must be interpreted with caution considering the small sample size. Therefore, we waive to perform advanced statistical analysis (such as multivariate models) and to discuss the findings in detail, which are presented in **supplementary material** only.

Volume measurements of RA and LA were performed in routine CTPA scans without ECG-gated information on the cardiac cycle. Thus, volumes were not assessed during end-systole only. Further, 17.7% of all CTPA scans required manual corrections of the automated volumetric measurements; however, manual changes were minimal (<5 ml per cardiac chamber) and did not result in differences in the prognostic performance.

Conclusion

We demonstrate that RA dilation assessed by volumetric analysis of the heart chambers on routine diagnostic CTPA is a frequent and prognostic relevant finding in both, unselected and normotensive patients with PE. However, the prognostic performance of RA dilation appeared inferior compared to other established risk stratification markers. Although MR-proANP elevation did not appear to be caused by RA dilation to a relevant proportion, MR-proANP ≥120 pmol/l was identified as predictor of an in-hospital adverse outcome, both in unselected and normotensive PE patients, integrating different prognostic relevant information from comorbidities.

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Conflict of interests

None of the authors reports a relationship with industry and other relevant entities – financial or otherwise – that might pose a conflict of interest in connection with the submitted article. The following authors report financial activities outside the submitted work:

Markus H. Lerchbaumer reports having received consultancy honoraria from Siemens Healthineers.

Matthias Ebner reports no conflicts of interest.

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Figure titles and legends

Figure 1. Representative case of volumetric analysis using CTPA

35-year old male patient without relevant comorbidities presenting with dyspnoea, haemoptysis and chest pain (heart rate 92 bpm, blood pressure 155/70 mmHg, respiratory rate 12/minute, oxygen saturation 99%) and normal biomarker plasma concentrations (MR-proANP 84 pmol/l, NT-proBNP 35 pg/ml and hsTnT <5 pg/ml). The patient was treated with low-molecular weight heparin followed by rivaroxaban and discharged after four days without suffering any relevant complications.

a) Central thrombus in the right (and left) pulmonary artery and thrombus in left segmental pulmonary artery (marked with arrows).

b, c) Automated reconstructed 4-chamber (b) and axial view (c) with colored overlay: RA 92 ml (yellow), LA 75 ml (purple), RA/LA volume ratio 1.23, RV 233 ml (orange), LV 203 ml (pink), myocardium (light blue).

d, e) Automated sagittal (d) and coronal (e) multiplanar reconstruction.

f) 3D volumetric model of the four cardiac chambers.

Figure 2. Prognostic performance of (A) radiological and (B) laboratory parameters with regard to an in-hospital adverse outcome in PE patients

a) AUC assessed by ROC analysis RA/LA volume ratio on CTPA.

b) AUC assessed by ROC analysis of MR-proANP (red), hsTnT (green) and NT-proBNP (grey).

Tables

Table 1. Baseline characteristic, comorbidities and clinical findings in PE patients (left column) stratified according to the median MR-proANP concentration (middle columns) and Odds ratios for predicting MR-proANP ≥142 pmol/l (right columns)

	All study patients (n=609)	MR-proANP <142 pmol/l (n=261)	MR-proANP ≥142 pmol/l (n=261)	p-value	OR (95% CI)	p-value
Age (years)	69 (56-77)	57 (43-70)	76 (69-82)	**<0.001**	age ≥75 years: 8.86 (5.75-13.66)	**<0.001**
Female sex	323 (53.0)	118/261 (45.2)	155/261 (59.4)	**0.001**	1.96 (1.32-2.91)	**0.001**
Comorbidities						
Active cancer	107/608 (17.6)	45/261 (17.2)	46/260 (17.7)	0.892	1.07 (0.64-1.78)	0.810
Chronic pulmonary disease	88/608 (14.4)	32/261 (12.3)	43/260 (16.5)	0.165	1.32 (0.76-2.30)	0.325
Chronic heart failure	88 (14.4)	14/261 (5.4)	57/261 (21.8)	**<0.001**	5.09 (2.56-10.15)	**<0.001**
Atrial fibrillation	64/603 (10.6)	9/258 (3.5)	45/260 (17.3)	**<0.001**	7.89 (3.02-20.62)	**<0.001**
Coronary artery disease	105 (17.2)	22/261 (8.4)	64/261 (24.5)	**<0.001**	3.23 (1.83-5.71)	**<0.001**
Arterial hypertension	370/609 (60.8)	121/261 (46.4)	196/2261 (75.1)	**<0.001**	3.54 (2.32-5.41)	**<0.001**
Renal insufficiency	187/601 (31.1)	30/260 (11.5)	128/261 (49.0)	**<0.001**	7.02 (4.16-11.82)	**<0.001**
Symptoms on admission						
Dyspnoea	477/605 (78.8)	199/261 (76.2)	204/257 (79.4)	0.392	1.10 (0.66-1.86)	0.708
Chest pain	279/603 (46.3)	139/261 (53.3)	100/256 (39.1)	**0.001**	0.58 (0.39-0.86)	**0.006**
Syncope	96/607 (15.8)	24/261 (9.2)	56/259 (21.6)	**<0.001**	2.89 (1.53-5.44)	**0.001**

Tachycardia (HR ≥100 bpm)	214/589 (36.3)	79/257 (30.7)	107/247 (43.3)	**0.003**	1.83 (1.21-2.78)	**0.004**
Hypoxia	162/523 (31.0)	45/220 (20.5)	95/230 (41.3)	**<0.001**	2.54 (1.59-4.15)	**<0.001**
Cardiogenic shock	51/608 (8.4)	12/261 (4.6)	32/260 (12.3)	**0.002**	5.71 (1.64-19.90)	**0.006**
Laboratory biomarkers						
hsTnT ≥14 pg/ml	367/568 (64.6)	101/257 (39.3)	227/257 (88.3)	**<0.001**	9.33 (5.60-15.55)	**<0.001**
NT-proBNP ≥600 pg/ml	286/554 (51.6)	72/257 (28.0)	197/260 (75.8)	**<0.001**	8.21 (5.23-12.89)	**<0.001**
ESC 2019 algorithm						
High risk	53/608 (8.7)	12/261 (4.6)	34/260 (13.1)	**0.001**	3.12 (1.58-6.18)	**0.001**
Intermediate-high risk	160/608 (26.3)	40/261 (15.3)	101/260 (38.8)	**<0.001**	3.51 (2.31-5.34)	**<0.001**
Intermediate-low risk	295/608 (48.4)	129/261 (49.4)	118/260 (45.4)	0.356	0.85 (0.60-1.20)	0.356
Low risk	100/608 (16.4)	80/261 (30.7)	7/260 (2.7)	**<0.001**	0.06 (0.03-0.14)	**<0.001**

Continuous variables are given as median (IQR), categorical variables are given as absolute/total numbers (n/N) and percentages in brackets.

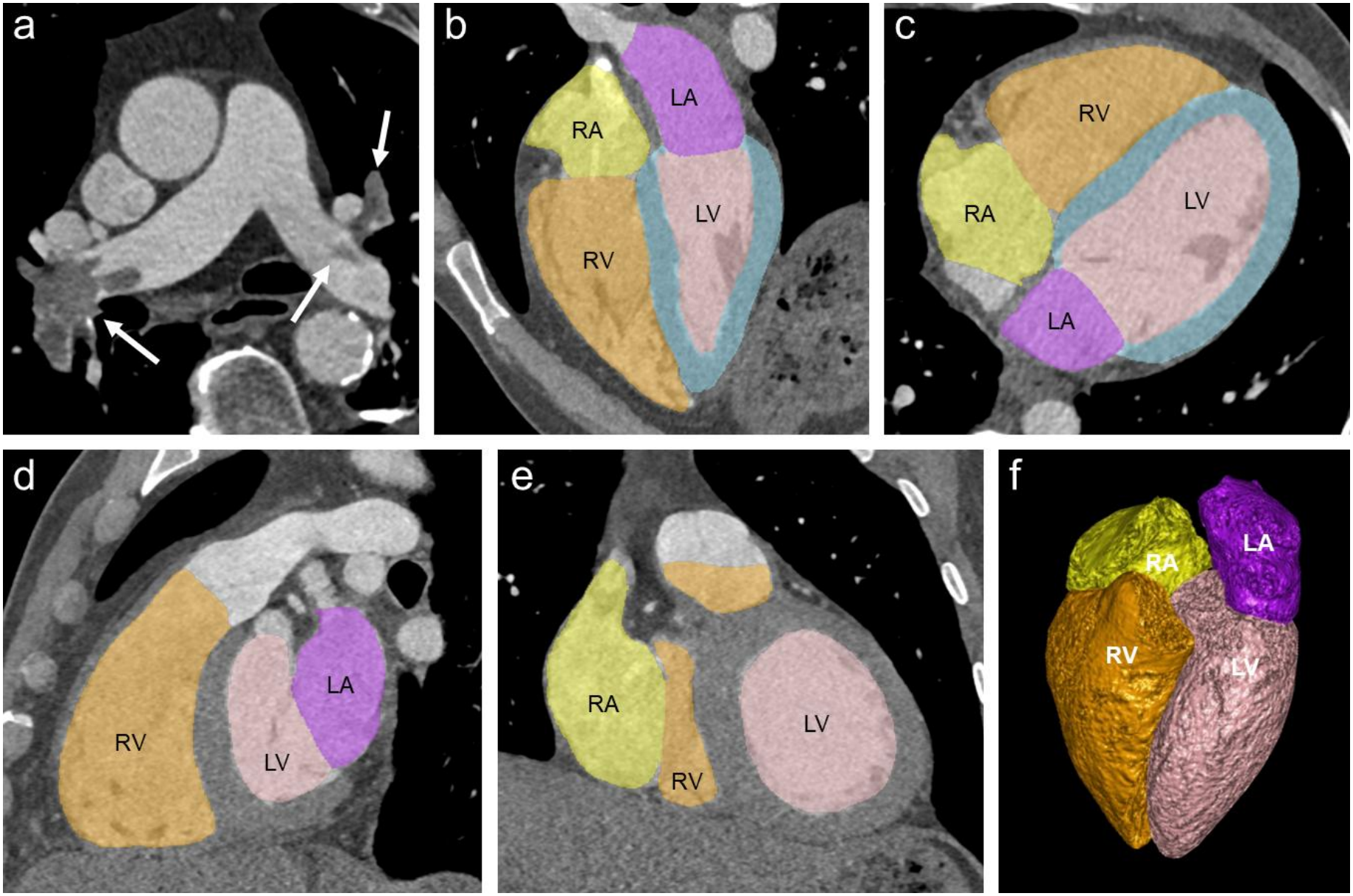
Table 2A and 2B. Prognostic performance of (A) RA/LA volume ratio using different cut-off values and (B) radiological, laboratory and clinical parameters with regard to an in-hospital adverse outcome in patients with PE

	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RA/LA volume ratio ≥1.0	60/499	1.71 (0.80-3.69)	0.172	88 (78-94)	19 (15-22)	12 (9-15)	93 (86-96)
RA/LA volume ratio ≥1.2	50/382	1.73 (1.00-3.05)	0.057	74 (62-83)	38 (34-43)	13 (10-17)	92 (88-95)
RA/LA volume ratio ≥1.4	43/286	2.10 (1.24-3.53)	**0.005**	63 (51-74)	55 (51-59)	15 (11-20)	92 (89-95)
RA/LA volume ratio ≥1.6	37/207	2.59 (1.56-4.32)	**<0.001**	54 (43-66)	68 (64-72)	18 (13-24)	92 (89-94)
RA/LA volume ratio ≥1.8	32/152	3.10 (1.85-5.21)	**<0.001**	47 (36-59)	78 (74-81)	21 (15-28)	92 (89-94)
RA/LA volume ratio ≥2.0	22/118	2.21 (1.27-3.84)	**0.005**	32 (22-44)	82 (79-85)	19 (13-27)	91 (88-93)
RA/LA volume ratio ≥2.2	18/91	2.30 (1.27-4.16)	**0.006**	26 (17-38)	86 (83-89)	20 (13-29)	90 (87-93)
RA/LA volume ratio ≥2.4	16/63	3.22 (1.71-6.08)	**<0.001**	24 (15-35)	91 (89-93)	25 (16-37)	90 (88-93)
RA/LA volume ratio ≥2.6	13/45	3.75 (1.86-7.56)	**<0.001**	19 (12-30)	94 (92-96)	29 (18-43)	90 (87-92)

	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RV/LV diameter ratio ≥1.0 on CTPA	56/445	1.85 (0.97-3.55)	0.064	82 (72-90)	28 (25-32)	13 (10-16)	93 (88-96)
Chronic heart failure	17/87	2.23 (1.22-4.08)	**0.009**	25 (16-36)	87 (84-90)	20 (13-29)	90 (87-92)
Renal insufficiency	41/187	4.00 (2.38-6.75)	**<0.001**	60 (48-71)	27 (24-31)	10 (7-13)	84 (78-89)
Syncope	24/96	3.61 (2.07-6.31)	**<0.001**	36 (25-48)	87 (83-89)	25 (17-35)	92 (89-94)
Tachycardia (HR ≥100 bpm)	29/214	1.87 (1.08-3.22)	**0.025**	50 (38-62)	65 (61-69)	14 (10-19)	92 (89-95)
hsTnT ≥14 pg/ml	55/365	4.92 (2.20-11.01)	**<0.001**	91 (80-97)	38 (34-42)	13 (10-17)	98 (94-99)
NT-proBNP ≥600 pg/ml	44/284	2.54 (1.43-4.53)	**0.001**	78 (64-88)	49 (45-54)	15 (11-20)	95 (91-97)
MR-proANP ≥120 pmol/l	50/289	4.63 (2.29-9.34)	**0.001**	88 (72-95)	48 (43-53)	13 (9-18)	98 (95-99)
ESC 2019 high risk*	37/53	39.01 (19.58-77.73)	**<0.001**	54 (43-66)	97 (95-98)	70 (56-80)	94 (92-96)

* high risk vs. not-high risk (stratified according the ESC 2019 guideline algorithm) (3)

n refers to number of patients with an in-hospital adverse outcome; N refers to the number of patients with positive finding.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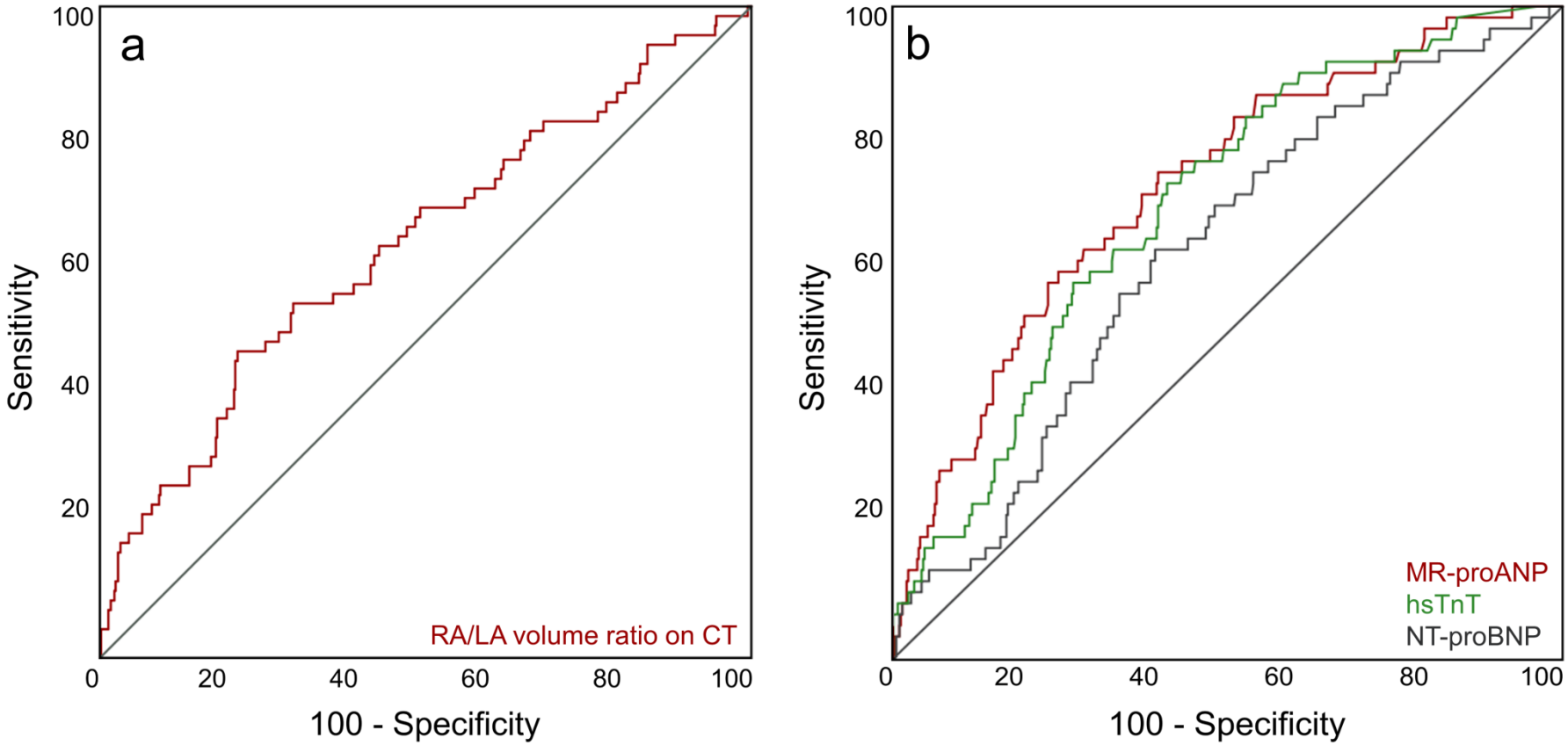
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Supplementary Material

Supplementary Methods

Transthoracic echocardiography

All transthoracic echocardiographic (TTE) examinations were performed as a part of routine clinical care. Only TTEs performed within 48 hours after diagnosis of PE were included in the present analysis. Electronically stored images were reassessed by two investigators (A.T. and L.H.) unaware of the patients' characteristics and outcome; disagreement was resolved by a third investigator (M.L.). End-systolic RA and LA area were assessed by planimetry in apical 4-chamber view. Prognostic relevant thresholds were defined as >18 cm² for RA area (1,2) and >1.0 for RA/LA area ratio (3).

Supplementary Results

Prognostic performance of RA and LA volume on CTPA corrected for BSA

Atrial volumes were corrected for body surface area (BSA) using Mosteller's formula: volume/(height x weight/3600)$^{1/2}$ in 575 patients (94.4%). Median RA volume$_{corr\ BSA}$ was 52 (IQR 41-67) ml/m^2 and LA volume$_{corr\ BSA}$ 36 (IQR 29-47) ml/m^2 with a median RA/LA volume ratio$_{corr\ BSA}$ of 1.36 (IQR 1.06-1.78). Patients with an in-hospital adverse outcome (n=55) had larger RA volumes$_{corr\ BSA}$ (61, IQR 48-78 vs. 52, IQR 41-66 ml/m^2, p=0.017), smaller LA volumes$_{corr\ BSA}$ (33, IQR 21-49 vs. 37, IQR 30-46 ml/m^2, p=0.042) and higher RA/LA volume ratio$_{corr\ BSA}$ (1.65, IQR 1.16-2.47 vs. 1.34, IQR 1.05-1.74, p=0.003) compared to patients with a favourable clinical course. Normotensive patients with an in-hospital adverse outcome (n=27) only had larger RA volumes$_{corr\ BSA}$ (71, IQR 43-82 vs. 51, IQR 41-65 ml/m², p=0.015) compared to those with a favourable clinical course (n=502).

Correction of atrial volumes for BSA let to a minimal (clinically and statistically irrelevant) improvement in the prognostic performance with regard to an in-hospital adverse outcome (RA volume$_{corr\ BSA}$ AUC 0.60, 95% CI 0.51-0.69, LA volume$_{corr\ BSA}$ AUC 0.42, 95% CI 0.32-0.51) and with regard to in-hospital all-cause mortality (RA volume$_{corr\ BSA}$ AUC 0.50, 95% CI 0.38-0.63, LA volume$_{corr\ BSA}$ AUC 0.43, 95% CI 0.29-0.57). RA/LA volume ratio$_{corr\ BSA}$ was associated with an adverse in-hospital outcome (AUC 0.62, 95% CI 0.54-0.71) and a calculated patient cohort-optimized RA/LA volume ratio$_{corr\ BSA}$ cut-off value of 1.9 was associated with a 3.13-fold increased risk (95% CI 1.77-5.54) for an adverse in-hospital outcome.

Prognostic performance of echocardiographic parameters

Electronically stored TTE examinations performed within 48 hours after PE diagnosis in sufficient quality for reassessment were available from 182 patients (25.2%). Median RA and LA area were 17.7 (IQR 14.6-20.7) cm² and 17.8 (IQR 15.2-20.9) cm^2, respectively, and the median RA/LA area ratio 0.93 (IQR 0.85-1.09). As shown in **Table 3s**, a moderate correlation was observed for RA volume on CTPA and RA area on TTE (r=0.583), LA volume on CTPA and LA area on TTE (r=0.441) and RA/LA volume ratio on CTPA and RA/LA area ratio on TTE (r=0.454).

Patients with an in-hospital adverse outcome had a larger RA area on TTE (21.0, IQR 18.3-22.6 vs. 17.4, IQR 14.5-20.6 cm^2, p=0.035) compared to patients with a favorable clinical course, while no difference in RA/LA area ratios was observed (1.03, IQR 0.93-1.17 vs. 0.93, IQR 0.85-1.08, p=0.105). The AUC of the RA area with regard to an adverse outcome was 0.69 (95% CI 0.53-0.75). A RA area >18 cm² (present in 9 of 86 patients [10.5%]) was associated with a sensitivity of 85 (95% CI 52-95)%, a specificity of 55 (95% CI 47-62)%, a positive predictive value (PPV) of 10 (95% CI 6-19)% and a negative

predictive value (PNV) of 98 (95% CI 93-99)%. Further, a RA area >18 cm² was associated with a 5.5-fold (95% CI 1.2-26.2) increased risk for an in-hospital adverse outcome while a RA/LA area ratio >1.0 did not provide prognostic information.

Prognostic performance of radiological, echocardiographic, laboratory and clinical parameters with regard to in-hospital all-cause mortality

During the in-hospital stay, 36 patients (5.9%) died. No differences in median atrial volumes were observed in non-survivors compared to survivors (RA volume: 103, IQR 78-146 vs. 102, IQR 78-134 ml, p=0.739; LA volume: 65, IQR 43-99 vs. 72, IQR 57-93 ml, p=0.268; RA/LA volume ratio: 1.54, IQR 1.13-2.00 vs. 1.35, IQR 1.06-1.77, p=0.209). Neither RA nor LA volume was associated with in-hospital all-cause mortality in unselected patients (AUC 0.52, 95% CI 0.42-0.63 and AUC 0.45, 95% CI 0.33-0.57, respectively) and normotensive patients (AUC 0.50, 95% CI 0.34-0.65 and AUC 0.53, 95% CI 0.38-0.68, respectively). The previously suggested RA/LA volume ratio cut-off value of 1.2 was not able to predict in-hospital all-cause mortality (**Table 4s**). Further, a RV/LV diameter ratio ≥1.0 failed to predict in-hospital all-cause mortality (OR 2.37, 95% CI 0.90-6.19).

On TTE, no difference was observed in median RA area (19.7, IQR 15.6-28.3 vs. 17.6, IQR 14.5-20.6 cm^2, p=0.272) and RA/LA area ratio (1.05, IQR 0.89-1.38 vs. 0.93, IQR 0.85-1.08, p=0.313) in patients who died during the in-hospital stay compared to survivors. Neither a RA area >18 cm² nor a RA/LA area ratio >1.0 was able to predict in-hospital all-cause mortality.

Furthermore, both, MR-proANP ≥120 pmol/l and NT-proBNP ≥600 pg/ml failed to predict in-hospital all-cause mortality. Only hsTnT ≥14 pg/ml was associated with an increased risk to die during the in-hospital stay (OR 7.55, 95% CI 1.77-32.18, p=0.006; **Table 4s**).

Prognostic performance of radiological, echocardiographic, laboratory and clinical parameters in normotensive PE patients

Of 553 (90.8%) normotensive patients, 31 (5.6%) had an in-hospital adverse outcome and 17 (4.9%) died: of those, 10 (58.8%) due to PE. Normotensive patients with an adverse outcome had larger RA volumes (127, IQR 74-153 vs. 102, IQR 78-133 ml, p=0.029) compared to patients with a favourable clinical course, while no differences were observed for LA volumes and RA/LA volume ratios. Thus, only RA volumes were weakly associated with an in-hospital adverse outcome (AUC 0.62, 95% CI 0.50-0.73). Although the RA/LA volume ratio failed to provide prognostic information if tested with ROC analysis (AUC 0.57, 95% CI 0.45-0.69), higher cut-off values were able to identify normotensive patients with increased risk of an in-hospital adverse outcome (**Table 5As**). The calculated patient cohort-optimized cut-off value of 1.8 was associated with a 2.7-fold increased risk (95% CI 1.3-5.6) for an in-hospital adverse outcome. A RV/LV diameter ratio ≥1.0 was not associated with an increased risk of an in-hospital adverse outcome (OR 1.40, 95% CI 0.45-4.30).

TTE examinations were available for 172 (31.1%) normotensive patients. No difference in RA area (18.5, IQR 15.6-20.9 vs. 17.4, IQR 14.5-20.5 cm^2, p=0.640) or RA/LA area ratio (1.12, IQR 0.89-1.26 vs. 0.93, IQR 0.85-1.08, p=0.209) was observed in patients with an in-hospital adverse outcome compared to patients with a favourable clinical course. Neither RA area >18 cm^2 nor RA/LA area ratio >1.0 provided prognostic information with regard to an in-hospital adverse outcome.

Normotensive patients with an in-hospital adverse outcome had higher median biomarker plasma concentrations compared to patients with a favourable clinical course (MR-proANP: 226, IQR 135-352 vs. 129, IQR 65-235 pmol/l, p=0.006; NT-proBNP: 2,693, IQR 1,233-4,132 vs. 627, IQR 119-2,496 pg/ml, p<0.001 and hsTnT: 60, IQR 23-84 vs. 23, IQR 8-

57 pg/ml, p=0.002). As shown in **Table 5Bs**, elevation of laboratory biomarkers and presence of clinical (such as chronic heart failure, renal insufficiency or tachycardia) parameters were associated with an elevated risk for an in-hospital adverse outcome.

Supplementary Tables

Table 1s. RA and LA volumes on CTPA in different patient subgroups

	RA volume (ml)			LA volume (ml)			RA/LA volume ratio		
Subgroup	**present**	**absent**	**p-value**	**present**	**absent**	**p-value**	**present**	**absent**	**p-value**
Age ≥75 years (n=209)	108 (84-140)	100 (76-129)	**0.008**	76 (61-104)	69 (55-89)	**<0.001**	1.34 (1.01-1.84)	1.37 (1.08-1.78)	0.247
Female (n=323)	97 (75-127)	110 (86-140)	**<0.001**	66 (53-87)	78 (62-97)	**<0.001**	1.39 (1.06-1.85)	1.31 (1.05-1.73)	0.375
Active cancer (n=107)	94 (69-123)	104 (81-136)	**<0.001**	66 (52-82)	73 (58-95)	**0.005**	1.21 (1.02-1.65)	1.39 (1.07-1.83)	**0.044**
Chronic pulmonary disease (n=88)	96 (75-128)	103 (78-134)	0.401	74 (60-96)	71 (56-93)	0.445	1.30 (1.02-1.75)	1.37 (1.07-1.82)	0.304
Chronic heart failure (n=88)	116 (89-160)	100 (76-130)	**<0.001**	95 (73-118)	70 (55-88)	**<0.001**	1.24 (1.01-1.59)	1.37 (1.07-1.83)	0.062
Atrial fibrillation (n=64)	139 (103-182)	100 (77-128)	**<0.001**	103 (81-140)	69 (55-88)	**<0.001**	1.25 (1.00-1.60)	1.38 (1.07-1.86)	**0.028**
Coronary artery disease (n=105)	114 (88-140)	100 (77-132)	**0.005**	90 (71-108)	69 (55-89)	**<0.001**	1.26 (0.99-1.62)	1.39 (1.07-1.86)	**0.024**
Hypertension (n=370)	108 (82-139)	97 (76-122)	**<0.001**	78 (61-100)	62 (52-80)	**<0.001**	1.27 (1.00-1.80)	1.44 (1.15-1.80)	**0.003**
Renal insufficiency (n=187)	113 (85-146)	100 (76-127)	**0.001**	74 (59-99)	70 (56-90)	0.074	1.38 (1.06-1.95)	1.35 (1.07-1.72)	0.252
Tachycardia (HR ≥100 bpm; n=214)	105 (74-137)	101 (80-132)	0.745	61 (50-83)	77 (62-96)	**<0.001**	1.54 (1.13-2.23)	1.27 (1.03-1.62)	**<0.001**
Syncope (n=96)	114 (91-137)	101 (76-133)	0.014	65 (51-98)	72 (58-92)	0.080	1.67 (1.16-2.32)	1.34 (1.03-1.70)	**<0.001**
hsTnT ≥14 pg/ml (n=367)	113 (88-143)	91 (73-112)	**<0.001**	70 (54-93)	74 (60-92)	0.165	1.53 (1.15-2.08)	1.19 (1.01-1.49)	**<0.001**
NT-proBNP ≥600 pg/ml (n=286)	119 (91-152)	94 (74-113)	**<0.001**	73 (56-99)	70 (56-87)	**0.038**	1.48 (1.19-2.04)	1.30 (1.03-1.65)	**<0.001**

Subgroup	RA volume (ml)			LA volume (ml)			RA/LA volume ratio		
	present	**absent**	**p-value**	**present**	**absent**	**p-value**	**present**	**absent**	**p-value**
MR-proANP ≥120 pmol/l (n=291)	118 (93-150)	92 (74-116)	**<0.001**	79 (60-103)	68 (55-84)	**<0.001**	1.40 (1.08-1.95)	1.37 (1.07-1.68)	0.107
ESC 2019 intermediate-high risk (n=160) *	132 (100-157)	97 (74-122)	**<0.001**	69 (53-94)	72 (58-93)	0.223	1.74 (1.33-2.27)	1.26 (1.01-1.63)	**<0.001**
ESC 2019 high-risk (n=53) †	114 (81-152)	102 (78-133)	0.061	64 (41-92)	72 (57-93)	0.017	1.85 (1.26-2.47)	1.33 (1.04-1.74)	**<0.001**

* intermediate-high risk vs. intermediate-low and low risk (stratified according the ESC 2019 guideline algorithm (4))

† high risk vs. not-high risk (stratified according the ESC 2019 guideline algorithm (4))

Abbreviations: RA denotes right atrial; LA, left atrial; CT, computed tomography; HR, heart rate; bpm, beats per minute; hsTnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; ESC, European Society of Cardiology.

Table 2s. Baseline characteristic, comorbidities and clinical findings in PE patients stratified according to the median RA/LA volume ratio on CT

	RA/LA volume ratio <1.4 (n=307)	**RA/LA volume ratio ≥1.4 (n=302)**	**p-value**
Age (years)	70 (57-78)	69 (52-76)	0.075
Female sex	153 (49.8)	170 (56.3)	0.294
BSA (m^2)	1.94 (1.77-1.94) n=288	1.94 (1.77-2.14) n=287	0.659
Comorbidities			
Active cancer	66 (21.5)	41/301 (13.6)	**0.011**
Chronic pulmonary disease	46/306 (15.0)	42 (13.9)	0.743
Chronic heart failure	51 (16.6)	37 (12.3)	0.126
Atrial fibrillation	39/302 (12.9)	25/301 (8.3)	0.060
Coronary artery disease	64 (21.2)	40 (13.2)	**0.010**
Arterial hypertension	207/307 (67.4)	163/302 (54.0)	**0.001**
Renal insufficiency	90/301 (29.9)	97/300 (32.3)	0.520
Symptoms on admission			
Dyspnoea	222/304 (73.0)	255/301 (84.7)	**<0.001**
Chest pain	143/303 (47.2)	136/300 (45.3)	0.647
Syncope	39/305 (12.8)	57 (18.9)	**0.040**
Tachycardia (HR ≥100 bpm)	81/298 (27.2)	133/291 (45.7)	**<0.001**
Hypoxia	54/263 (20.5)	108/260 (41.5)	**<0.001**
Cardiogenic shock	14/306 (4.6)	37 (12.3)	**0.001**
Laboratory biomarkers			
hsTnT ≥14 pg/ml	155/286 (54.2)	212/282 (75.2)	**<0.001**
NT-proBNP ≥600 pg/ml	125/273 (45.8)	161/281 (57.3)	**0.004**
MR-proANP ≥120 pmol/l	141/259 (54.4)	150/263 (57.0)	0.863
ESC 2019 algorithm			
High risk	16/306 (5.2)	37 (12.3)	**0.002**
Intermediate-high risk	44/306 (14.4)	116 (38.4)	**<0.001**

Intermediate-low risk	177/306 (57.8)	118 (39.1)	**<0.001**
Low risk	69/306 (22.5)	31 (10.3)	**<0.001**

Continuous variables are given as median (IQR), categorical variables are given as absolute/total numbers (n/N) and percentages in brackets.

Abbreviations: PE denotes pulmonary embolism; RA, right atrial; LA, left atrial; CT, computed tomography; BSA, body surface area; VTE, venous thromboembolism; HR, heart rate; bpm, beats per minute; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptides; sPESI, simplified Pulmonary Embolism Severity Index; ESC, European Society of Cardiology; IQR, interquartile range.

Table 3s. Correlation between RA and LA volumes on CTPA, MR-proANP and echocardiographic, laboratory and clinical parameters in PE patients

	RA volume (ml) on CTPA	**LA volume (ml) on CTPA**	**RA/LA volume ratio on CTPA**	**MR-proANP (pmol/l)**
Age (years)	0.131, p=0.001 (n=609)	0.233, p<0.001 (n=609)	-0.100, p=0.014 (n=609)	**0.623, p<0.001 (n=522)**
BSA (m^2)	0.238, p<0.001 (n=575)	0.184, p<0.001 (n=575)	0.069, p=0.100 (n=575)	-0.174, p<0.001 (n=491)
GFR (ml/min/1.73 m²)	-0.200, p<0.001 (n=598)	-0.095, p=0.020 (n=598)	-0.086, p=0.036 (n=598)	**-0.495, p<0.001 (n=518)**
Heart rate (bpm)	0.009, p=0.826 (n=589)	-0.269, p<0.001 (n=589)	0.229, p<0.001 (n=589)	0.146, p=0.001 (n=504)
hsTnT (pg/ml)	0.283, p<0.001 (n=568)	-0.040, p=0.339 (n=568)	0.281, p<0.001 (n=568)	**0.561, p<0.001 (n=514)**
NT-proBNP (pg/ml)	0.382, p<0.001 (n=554)	0.131, p=0.002 (n=554)	0.181, p<0.001 (n=554)	**0.637, p<0.001 (n=517)**
MR-proANP (pmol/l)	0.369, p<0.001 (n=522)	0.187, p<0.001 (n=522)	0.129, p=0.003 (n=522)	---
RA area (cm²) on TTE	**0.583, p<0.001 (n=182)**	0.197, p=0.008 (n=182)	0.288, p<0.001 (n=182)	0.236, p=0.003 (n=156)
LA area (cm²) on TTE	0.355, p<0.001 (n=182)	**0.441, p<0.001 (n=182)**	-0.076, p=0.309 (n=182)	0.204, p=0.010 (n=156)
RA/LA area ratio on TTE	0.273, p<0.001 (n=182)	-0.284, p<0.001 (n=182)	**0.454, p<0.001 (n=182)**	0.037, p=0.651 (n=156)

Data are provided as r (Spearman Rho) and corresponding p-value; n refers to the number of patients with available data. Correlations with r<0.4 or >0.4 are marked in bold.

Abbreviations: RA denotes right atrial, LA, left atrial; CTPA, computed tomography pulmonary angiography; MR-proANP, mid-regional pro-atrial natriuretic peptide; PE, pulmonary embolism; BSA, body surface area; GFR, glomerular filtration rate; bpm, beats per minute; hsTnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; TTE, transthoracic echocardiography.

Table 4s. Prognostic performance of radiological, echocardiographic, laboratory and clinical parameters with regard to in-hospital all-cause mortality in patients with PE

	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RA/LA volume ratio ≥1.2* on CT	23/382	1.04 (0.52-2.10)	0.913	64 (48-78)	37 (33-41)	6 (4-9)	94 (90-97)
RA/LA volume ratio ≥1.6† on CT	18/207	2.02 (1.03-3.96)	**0.042**	50 (34-66)	69 (65-73)	9 (6-14)	96 (93-97)
RV/LV diameter ratio ≥1.0 on CT	30/489	2.37 (0.90-6.19)	0.079	86 (71-94)	72 (68-76)	16 (12-22)	99 (97-99)
RA area >18 cm² on TTE	4/86	2.29 (0.41-12.84)	0.345	67 (30-90)	53 (46-61)	5 (2-11)	98 (93-99)
RA/LA area ratio >1.0 on TTE	3/64	1.88 (0.37-9.62)	0.446	50 (19-81)	65 (58-72)	5 (2-13)	97 (93-99)
Chronic heart failure	7/87	1.48 (0.63-3.49)	0.372	19 (10-35)	86 (83-89)	8 (4-16)	94 (92-96)
Renal insufficiency	21/187	3.59 (1.78-7.23)	**<0.001**	60 (44-74)	71 (67-74)	11 (7-17)	97 (94-98)
Syncope	11/96	2.61 (1.23-5.53)	**0.012**	31 (19-48)	85 (82-88)	11 (7-19)	95 (93-97)
Tachycardia (HR ≥100 bpm)	13/214	1.54 (0.72-3.31)	0.264	46 (30-64)	64 (60-68)	6 (4-10)	96 (93-98)
hsTnT ≥14 pg/ml	31/365	7.55 (1.77-32.18)	**0.006**	93 (77-98)	63 (59-67)	13 (9-18)	99 (98-100)
NT-proBNP ≥600 pg/ml	19/283	1.93 (0.77-4.82)	0.161	68 (47-84)	47 (43-52)	6 (4-10)	97 (93-98)
MR-proANP ≥120 pmol/l	25/288	2.58 (0.82-8.15)	0.105	75 (51-90)	46 (41-51)	5 (3-9)	98 (95-99)
ESC 2019 high risk‡	18/52	15.77 (7.53-33.03)	<0.001	50 (34-66)	94 (92-96)	35 (23-48)	97 (95-98)

* optimal cut-off value with regard to in-hospital mortality identified by Aviram et al. (5)

† cohort optimized cut-off value with regard to in-hospital mortality using Youden index quantification

‡ high risk vs. not-high risk (stratified according the ESC 2019 guideline algorithm (4))

n refers to number of patients who died within the in-hospital stay; N refers to the number of patients with positive finding.

Abbreviations: PE denotes pulmonary embolism; RA, right atrial; LA, left atrial; RV, right ventricular; LV, left ventricular; CTPA, computed tomography pulmonary angiography; TTE, transthoracic echocardiography; HR, heart rate; bpm, beats per minute; hsTnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; sPESI, simplified Pulmonary Embolism Severity Index; ESC, European Society of Cardiology.

Table 5As and 5Bs. Prognostic performance of (a) RA/LA volume ratio on CTPA using different cut-off values and (b) radiological, echocardiographic, laboratory and clinical parameters with regard to an in-hospital adverse outcome in normotensive PE patients

	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RA/LA volume ratio ≥1.0	25/450	0.96 (0.38-2.41)	0.932	81 (64-91)	19 (16-22)	6 (4-8)	94 (88-97)
RA/LA volume ratio ≥1.2*	19/339	1.00 (0.48-2.11)	0.991	61 (44-76)	39 (35-43)	6 (4-9)	94 (90-97)
RA/LA volume ratio ≥1.4	15/250	1.15 (0.56-2.37)	0.707	48 (32-65)	55 (51-59)	6 (4-10)	95 (92-97)
RA/LA volume ratio ≥1.6	14/176	1.84 (0.88-3.81)	0.104	45 (29-62)	69 (65-73)	8 (5-13)	96 (93-97)
RA/LA volume ratio ≥1.8†	13/125	2.65 (1.26-5.57)	**0.010**	42 (26-59)	79 (75-82)	10 (6-17)	96 (93-97)
RA/LA volume ratio ≥2.0	11/101	2.65 (1.22-5.71)	**0.013**	35 (21-53)	83 (79-86)	11 (6-18)	96 (93-97)
RA/LA volume ratio ≥2.2	8/75	2.37 (1.02-5.51)	**0.045**	26 (14-43)	87 (84-90)	11 (6-20)	95 (93-97)
RA/LA volume ratio ≥2.4	7/50	3.26 (1.33-7.99)	**0.010**	23 (11-40)	92 (89-94)	14 (7-26)	95 (93-97)
RA/LA volume ratio ≥2.6	6/34	4.24 (1.61-11.18)	**0.003**	19 (9-36)	95 (92-96)	18 (8-34)	95 (93-97)

	n/N	OR (95% CI)	p-value	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
RV/LV diameter ratio ≥1.0 on CT	25/442	1.40 (0.45-4.30)	0.563	81 (64-91)	20 (17-24)	6 (4-8)	95 (89-98)

RA area >18 cm² on TTE	4/78	2.49 (0.44-13.95)	0.301	67 (30-90)	55 (48-63)	5 (2-12)	98 (93-99)
Chronic heart failure	8/75	2.37 (1.02-5.51)	**0.045**	26 (14-43)	87 (84-90)	11 (6-20)	95 (93-97)
Renal insufficiency	14/155	2.15 (1.05-4.56)	**0.036**	45 (29-62)	73 (69-76)	9 (5-15)	96 (93-97)
Syncope	7/72	2.14 (0.88-5.19)	0.092	23 (12-41)	88 (84-90)	10 (5-19)	95 (93-97)
Tachycardia (HR ≥100 bpm)	17/195	4.37 (2.07-9.23)	**<0.001**	57 (39-73)	66 (61-69)	9 (6-14)	96 (94-98)
hsTnT ≥14 pg/ml	26/325	7.26 (1.69-31.16)	**0.008**	92 (75-98)	39 (34-43)	8 (5-11)	99 (96-100)
NT-proBNP ≥600 pg/ml	25/260	21.56 (2.88-161.51)	**0.003**	96 (79-99)	49 (45-54)	10 (7-14)	99 (97-100)
MR-proANP ≥120 pmol/l	21/252	5.05 (1.45-17.63)	**0.011**	84 (62-94)	49 (44-54)	8 (5-12)	98 (95-99)
ESC 2019 intermediate-high risk‡	17/160	3.23 (1.55-6.72)	**0.002**	55 (38-71)	73 (69-76)	11 (7-16)	96 (94-98)

* optimal cut-off value with regard to in-hospital mortality identified by Aviram et al. (5)

† cohort optimized cut-off value using Youden index quantification

‡ intermediate-high risk vs. intermediate-low and low risk (stratified according the ESC 2019 guideline algorithm (4))

n refers to number of patients with an in-hospital adverse outcome; N refers to the number of patients with positive finding.

Abbreviations: RA denotes right atrial; LA, left atrial; PE, pulmonary embolism; OR, Odds ratio; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; RV, right ventricular; LV, left ventricular; CTPA, computed tomography pulmonary angiography; TTE, transthoracic echocardiography; HR, heart rate; bpm, beats per minute; sPESI, simplified pulmonary embolism severity index; hsTnT, high sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MR-proANP, mid-regional pro-atrial natriuretic peptide; sPESI, simplified Pulmonary Embolism Severity Index; ESC, European Society of Cardiology.

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