Pulmonary embolism : diagnostic management and prognosis

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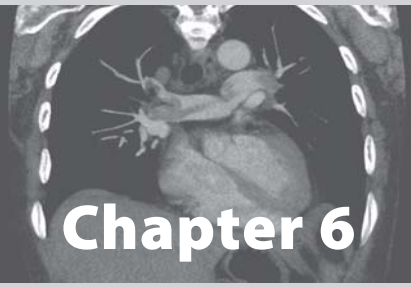

Chapter 6

Comparison of CT assessed right ventricular size and cardiac biomarkers for predicting short term clinical outcome in normotensive patients suspected for having acute pulmonary embolism

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ABSTRACT

Purpose

To compare the clinical utility of right ventricular enlargement assessed by multi-detector row computed tomography (CT) and elevation of cardiac biomarkers for predicting adverse outcome after acute pulmonary embolism (PE).

Methods

We included 113 consecutive normotensive patients with CT pulmonary angiography (CTPA) proven PE and 226 consecutive patients in whom PE was suspected but ruled out. The following predictors of complicated clinical course were studied: right/left ventricular ratios (RV/LV-ratios) on axial and reconstructed 4-chamber (4-CH) CT-views >1.0, D-dimer >3000 pg/mL FEU, Troponin-T >0.09 ng/mL and NT-pro-BNP >600 pg/mL.

Results

All predictors were associated with adverse outcome in patients with and without PE, with odds ratios of 3.7 (axial), 9.0 (4-CH), 3.5 (D-dimer), 6.3 (Troponin-T) and 31 (NT-pro-BNP) for patients with PE. Area under the receiver operator characteristic curve for PE patients of NT-pro-BNP was higher (0.85; 95% CI 0.73-0.97) than that of axial RV/LV-ratio (0.64, 95% CI 0.47-0.81; p=0.14), 4-CH RV/LV-ratio (0.64, 95% CI 0.48-0.81; p=0.15), D-dimer (0.64, 95% CI 0.46-0.82; p=0.048) and Troponin-T (0.62, 95% CI 0.41-0.82; p=0.037). 72% of patients had a NT-pro-BNP ≤600 pg/mL with a negative predictive value (NPV) of 99%. 4-CH RV/LV-ratio <1 had equally excellent NPV (98%), but less patients were categorized as having low risk for complications (43%; p<0.001).

Conclusion

NT-pro-BNP had the highest discriminative power and clinical utility as predictor of adverse events after PE in our study population. Future studies should confirm these findings and evaluate the safety of home-treatment based on low NT-pro-BNP levels or RV/LV-ratios.

INTRODUCTION

Mortality rates in hemodynamically stable patients with acute pulmonary embolism (PE) range from 2% to 6% and increase considerably to 30% or more in patients presenting with hemodynamic instability or shock.[1] For this latter patient category, invasive treatment regimes including thrombolysis, thrombosuction or surgical embolectomy might be life saving.[2,3] In contrast, outpatient treatment may be considered for hemodynamically stable patients with relatively mild disease.[2,4] It is however challenging to identify those patients who present in a hemodynamically stable state but who are at high risk for clinical deterioration and death in the first period after the diagnosis of PE and start of anticoagulation therapy. These patients might benefit from more intensive clinical surveillance or even thrombolysis, whereas outpatient treatment is contraindicated.[2,5-7]

One of the main causes of early death after PE is right ventricular failure.[1] Hence, it seems very plausible to use indicators of right ventricular function as predictors of short term clinical outcome after acute PE. Especially tests for the evaluation of ventricular function that are easy to obtain and widely available are of particular interest for clinical use, since these are likely to aid the physicians in performing rapid risk stratification and determining treatment strategy. Retrospective studies have previously shown that right ventricular enlargement on computed tomography pulmonary angiography (CTPA; Odds Ratio [OR] 4.0) and elevated levels of cardiac biomarkers such as NT-pro-BNP (OR 6.8) and Troponin (OR 7.0) are predictive for the occurrence of adverse events and early mortality after acute PE.[8-11] This is also true for highly elevated D-dimer levels as indicator of high embolus load (OR 7.3), which is associated with increased risk of right ventricular impairment.[12-14] Importantly, the ability of these different predictors to identify patients at risk for adverse clinical outcome has not yet been directly compared in a prospective outcome study. Furthermore, a recent paper demonstrated that results from previous studies should be interpreted and compared with caution because of the clinical and methodological diversity of these studies.[15]

Therefore, the purpose of this prospective cohort study was to compare the predictive accuracy and clinical utility of easy right ventricular function tests, i.e. CT-derived right-to-left ventricular diameter ratios (RV/LV-ratio) and NT-pro-BNP and Troponin-T, as well as D-dimer levels, for predicting adverse events in the short term clinical course of acute PE.

METHODS

Patients

Consecutive, hemodynamically stable in- and outpatients who presented to our hospital with suspected acute PE between September 1st 2005 and December 1st 2008, and with a strict indication for CTPA were included. This CTPA indication comprised patients with either a likely

clinical probability by the Wells Rule (>4 points total) or an abnormal D-dimer blood test (>500 ng/mL FEU).[16] Only patients with an unlikely probability in combination with a normal D-dimer test result did not undergo CTPA since PE can be safely ruled out in that patient category.[16] These latter patients could therefore not be included in this study. Patients diagnosed with acute PE by CTPA were initially treated with therapeutic unfractionated or low-molecular-weight heparin for at least 5 days, followed by vitamin K antagonists for a period of at least three months aiming at an INR of 2.0-3.0.[2] In case of severe PE or clinical deterioration, admission to the intensive care unit and/or administration of thrombolytic drugs was considered, according to the judgment of the attending clinician. Exclusion criteria for the study were: impossibility of follow-up, age younger than 18 years, pregnancy, known allergy to intravenous application of iodine contrast media or hemodynamic instability at initial presentation. This study was approved by the Institutional Review Board of our hospital and all patients provided written informed consent.

Endpoints

All patients were followed for 6 weeks. Follow-up consisted of a scheduled visit to our vascular medicine outpatient clinic for the patients with confirmed acute PE and a telephone interview for all patients in whom PE was ruled out by CTPA. The primary study outcome was the occurrence of one or more adverse clinical events in the first 6 weeks following study inclusion. Adverse events were defined as the occurrence of any of the following: all cause mortality, resuscitation after respiratory or cardiac arrest, admittance to intensive care unit, need for mechanical ventilation or use of inotropic agents, and administration of thrombolytic drugs.

Procedures

All patients underwent multi-detector row CTPA (Aquilion 64; Toshiba Medical Systems, Otawara, Japan) of the chest during breath-hold at inspiration. CTPA was performed after bolus injection of iodinated contrast agent (80-100 mL Xenetix 300, Guerbet, Aulnay-sous-Bois, France, or 60-80 mL Iomeron 400 mg/mL, Bracco, Milan, Italy) via antecubital vein injection with a flow rate of 4.0 mL/sec using an automatic injector (Stellant CT, MedRad, Pittsburgh, USA). Bolus tracking was performed by placing a region of interest in the pulmonary trunk. Image acquisition was automatically started 5 seconds after reaching a predefined threshold difference of 100 HU using SureStart (Toshiba Medical Systems, Otawara, Japan). Scan parameters were: rotation time 0.5 sec, pitch factor 53.0, tube voltage 100 kV and tube current depending on patient size and shape. Images were reconstructed with a slice thickness of 1.0 or 0.5 mm.

Analysis of RV/LV-ratios was performed on a post-processing workstation (Vitrea, version 2, Vital Images, Minnetonka, USA) in standard axial views and in reconstructed 4-chamber (4-CH) views (Figure 1) by one observer with two years of experience and supervised by a radiologist with 10 years of experience in thoracic CT imaging. The 4-CH view was reconstructed by using 2-dimensional multiplanar reformats of the original axial source data as was suggested by

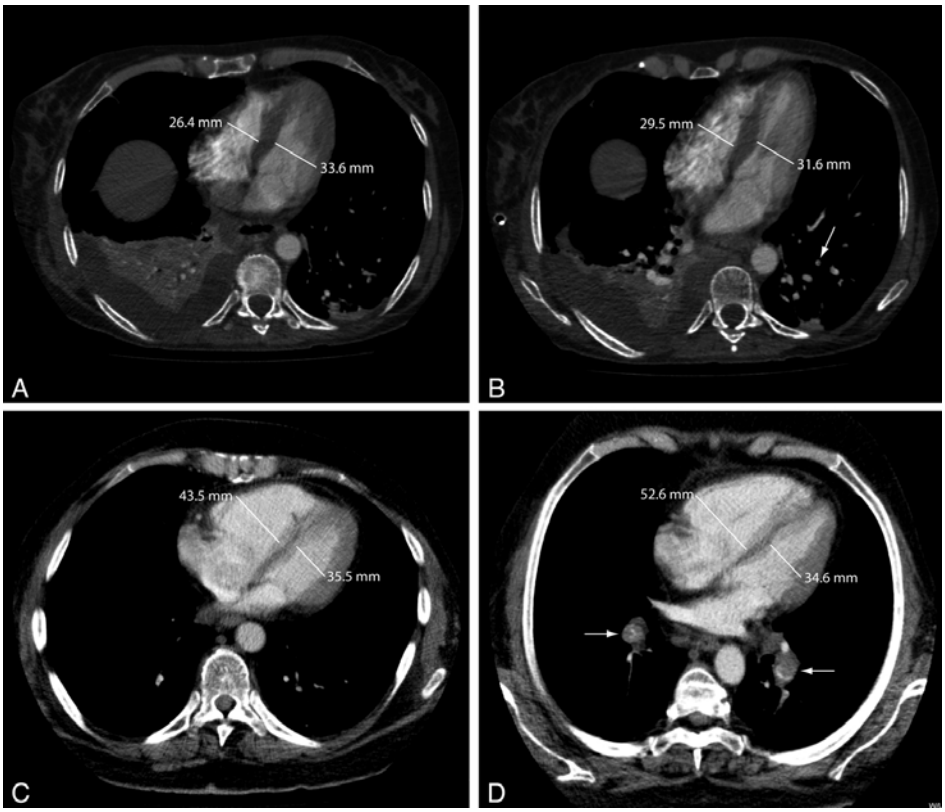

Figure 1. Measurement of right ventricular (RV) and left ventricular (LV) dimensions in axial (A, C) and reconstructed computed tomography 4-chamber views (B, D). A and B represent the same patient with acute pulmonary embolism (PE) and RV/LV-ratio ≤1.0. Note the right sided pleural effusion, bilateral atelectasis, and diaphragmatic hernia (A, B). Panels C and D represent a patient with acute PE and RV/LV-ratio >1.0. Large bilateral pulmonary artery emboli are present (D). Pulmonary emboli are marked by arrows (A-D).

Quiroz et al.[11] Right and left ventricular dimensions were measured by identifying the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis.[10,11] The RV/LV-ratio was then calculated. Right ventricular enlargement was considered present when the RV/LV-ratio was greater than 1.0.[10]

Venous plasma and serum samples were obtained on admission and were immediately stored at –80°C. After all patients were included, samples were analyzed in batches after a single thaw. Troponin-T and NT-pro-BNP levels were determined with the use of quantitative immunoassays (Elecsys 2010 analyzer, Roche Diagnostics, Mannheim, Germany). For Troponin-T, a reference value of 0.09 ng/mL was used to distinguish between normal and elevated levels as proposed by the manufacturer. For NT-pro-BNP, the prognostically relevant cut-off level was set at 600 pg/mL.[17] D-dimer levels were determined using a quantitative, automated immunoassay (STA LIA D-dimeer assay; Roche, Mannheim, Germany). D-dimer levels exceeding 3000 ng/mL FEU were defined to be a poor prognostic sign.[13]

The study was performed in blinded fashion: since both the CT measurements of ventricular function as well as the biomarker blood levels were assessed post-hoc, the treating physicians were unaware of these results, precluding information bias. Also, the researchers who measured the ventricular ratios and the biomarker levels were blinded for the clinical course of the study patients.

Statistics

The sample size calculation was primarily based on RV/LV-ratios with the following assumptions: a 20% risk on the primary study outcome in case of a RV/LV-ratio >1.0, a <3% risk in case of a RV/LV-ratio ≤1 and a 50% prevalence of RV/LV-ratio >1.0 in patients with acute PE.[1,8,10,11,18] To detect this risk difference with a power of 80% and a two-tailed alpha of 0.05, we needed 110 included subjects with PE.

For logistic and financial reasons, we determined before the start of the study that the measurements of ventricular function and biomarkers were to be performed in all patients with acute PE diagnosed within the study period, and in twice that number of patients in whom PE was ruled out by CTPA, but not in all of these latter patients. The cohort of patients without PE that was included in the following analyses consisted of consecutive patients from the start of the study until this double number was achieved.

First, we studied the association of right ventricular enlargement, biomarkers and acute PE by calculating ORs by logistic regression for elevated RV/LV-ratios and biomarker levels between patients with and without acute PE, adjusted for age, gender, active malignancy and presence of cardiopulmonary comorbidity. Second, we studied the association between RV/LV-ratios, biomarkers and adverse clinical outcome in patients with established PE as well as in those without PE separately. Also, we weighed the discriminatory ability of the predefined cut-off levels of the RV/LV-ratio and biomarkers for adverse clinical outcome by comparing the area under the curve (AUC) in receiver operator characteristic (ROC) analyses for patients with established acute PE only.[19] In addition, we used these ROC curves to evaluate whether the predefined cut-off points of our predictors were chosen optimally for predicting adverse outcome. Furthermore, we evaluated the clinical utility of RV/LV-ratios and biomarkers by assessing and comparing the specific test characteristics for predicting adverse clinical outcome for each predictor individually. These analyses were performed for all patients and for a selected cohort of outpatients only. Finally, we studied whether combing different tests would have additional predictive value and clinical applicability compared to the individual tests. Differences between categorical variables were studied using the Chi-Square test en continuous variables using an independent samples T-test. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis. A two-sided p-value <0.05 was considered to indicate a significant difference.

RESULTS

Patients

Within the study period, 113 of the included 439 patients were diagnosed with acute PE. All 113 patients with PE and the first 226 patients in whom PE was ruled out by CTPA were selected for further analysis. The baseline characteristics of these patients are depicted in Table 1. The mean age in the overall study population was 56 years. Patients with PE had a higher proportion of males (53% vs. 42%) and had more often previous venous thromboembolism (22% vs. 19%) and recent immobility, surgery, trauma or were in postpartum period (31% vs. 13%) than the patients without PE. The patients without PE had a higher prevalence of chronic obstructive pulmonary disease (COPD; 6.2% vs. 16%), left sided hart failure (4.4% vs. 7.5%) and were more often inpatients (18% vs. 25%).

Table 1. General characteristics of the study population.

	Patients with PE (n=113)	Patients without PE (n=226)
Age (years ±SD)	56 ±17	56 ±21
Male sex (n, %)	60 (53)	95 (42)
Previous PE or DVT (n, %)	25 (22)	43 (19)
Immobility, surgery, trauma, postpartum (n, %)	35 (31)*	29 (13)*
Known thrombophilia† (n, %)	3 (2.7)	10 (4.4)
Active malignancy (n, %)	24 (21)	56 (25)
COPD (n, %)	7 (6.2)*	36 (16)*
Left sided heart failure (n, %)	5 (4.4)	17 (7.5)
Inpatient (n, %)	20 (18)	57 (25)

†In our hospital, patients are not routinely screened for thrombophilia; *p<0.05 on Chi-Square test.
PE=pulmonary embolism, DVT=deep vein thrombosis, COPD=chronic obstructive pulmonary disease, SD=standard deviation, n=number.

Adverse events

Of the 113 patients with established acute PE, 10 had a complicated clinical course (8.9%; 95% CI 4.3-16%; Table 2). Four patients experienced clinical deterioration necessitating cardiopulmonary resuscitation within 12 days after diagnosis: of those, 2 died immediately, 1 died after 9 days of acute PE and severe cerebral hemorrhage, and one was successfully resuscitated and completed the follow-up period without further complications. One patient received thrombolytic therapy because of a large saddle embolus and one patient died after 10 days of hospital acquired pneumonia and PE. Three patients died of progressive cancer on days 15, 21 and 39 respectively. Finally, one patient suffered from acute PE after major abdominal surgery. After 10 days a large hepatic hematoma was discovered. Following this, this patient underwent new surgery and was admitted to the intensive care unit. She recovered completely without further complications. Overall, death was attributed to acute PE in 4 patients. None of the patients with acute PE was lost to follow-up.

Table 2. Characteristics of patients with adverse clinical events in the course of established acute pulmonary embolism.

Gender	Age (years)	In/out patient	Adverse event	RV/LV-ratio (axial view)	RV/LV-ratio (4-CH view)	D-dimer level (ng/mL FEU)	Troponin-T (ng/mL)	NT-pro-BNP (pg/mL)
Female	80	Out	day 1: unsuccessful resuscitation after saddle embolus, pulmonary embolism attributable death	3.1	3.2	>5000	<0.01	1964
Female	55	Out	day 1: thrombolysis because of large saddle embolus	1.5	1.5	>5000	0.03	5059
Female	83	Out	day 2: successful resuscitation followed by thrombolysis, mechanical ventilation and admittance to the ICU. Patient died at day 9 of pulmonary embolism and cerebral bleeding.	1.7	2.0	>5000	<0.01	6540
Male	70	Out	day 2: successful resuscitation	1.2	1.1	>5000	0.11	4245
Male	80	Out	day 10: patient died of severe pneumonia and pulmonary embolism	0.87	1.0	976	0.11	2979
Female	50	In	day 10: (PE occurred 1 day post major abdominal-surgery) re-operation and admittance to the ICU because of major bleeding.	1.2	1.3	4736	<0.01	2520
Female	80	Out	day 12: unsuccessful resuscitation, autopsy proven pulmonary embolism attributable death	1.4	1.5	1281	0.21	5026
Female	59	Out	day 15: patient died of progressive malignancy of unknown origin	0.94	1.04	>5000	0.10	1619
Male	47	In	day 21: patient died of progressive non-Hodgkin lymphoma	1.3	1.2	1332	<0.01	623
Male	68	Out	day 39: patient died of progressive prostate cancer	1.2	1.3	>5000	<0.01	151

Overall, death was attributed to pulmonary embolism in 4 patients. RV/LV-ratio=ventricular volume ratio, 4-CH=four chamber, PE=pulmonary embolism, ICU=intensive care unit.

Fifteen of the 226 patients without PE died during the follow-up period. Cause of death was malignancy in 11 patients and renal failure, pulmonary fibrosis, pneumonia and heart failure in the other patients respectively. In addition, 3 patients were admitted to the intensive care unit after heart surgery and one patient was lost to follow-up. Two patients in whom PE was initially ruled out had recurrent complaints and underwent a second CTPA. PE was established in one of these 2 patients. Patients with established PE were at slightly higher risk for complicated clinical course then patients in whom PE was ruled out: OR adjusted for age, gender, active malignancy and presence of cardiopulmonary comorbidity was 1.5 (95% CI 0.63-3.6).

RV/LV-ratios and biomarkers in patients with and without PE

RV/LV-ratio was higher in patient with PE than in patients without PE for both axial (1.1 vs. 0.89; p<0.001) as well as reconstructed 4-CH views (1.1 vs. 0.86; p<0.001). In addition, adjusted ORs for increased RV/LV-ratio were increased for patients with established acute PE for axial (OR 6.6, 95% CI 3.8-11) along with 4-CH views (OR 14, 95% CI 7.3-25). Adjusted OR for elevated levels of Troponin-T (3.6, 95% CI 1.3-10), NT-pro-BNP (1.5, 95% CI 0.87-2.7) and D-dimer (5.6, 95 %CI 3.1-9.9) were also increased for patients with PE. Thus, acute PE was independently associated with increased right ventricular dimensions and elevated biomarker levels.

RV/LV-ratio and biomarkers as predictors for adverse events

Blood levels of Troponin-T, D-dimer, NT-pro-BNP and RV/LV-ratios in both views were higher in the patients with acute PE who suffered adverse clinical events than in those with uncomplicated clinical course (Table 3). Following this, right ventricular enlargement and elevated biomarkers increased the risk of adverse events with adjusted ORs of 3.7 (95% CI 0.74-19), 9.0 (95% CI 1.1-79), 3.5 (95% CI 0.86-15), 6.3 (95% CI 1.3-31) and 31 (95% CI 3.6-257) for axial RV/LV-ratios, 4-CH RV/LV-ratios, D-dimer, Troponin-T and NT-pro-BNP respectively. Furthermore, we identified an increased risk for adverse events associated with right ventricular enlargement and elevated biomarkers in the patients in whom PE was ruled out, although less pronounced than in patients with PE, with adjusted ORs ranging from 2.0 to 3.8 (Table 3).

Table 3. Medians and interquartile range for ventricular volume ratio and biomarkers in patients with and without acute PE and with and without adverse clinical outcome.

	RV/LV-ratio (axial)	RV/LV-ratio (4-CH)	D-dimer level (ng/mL FEU)	Troponin-T (ng/mL)	NT-pro-BNP (pg/mL)
PE, uncomplicated clinical course (median, IQR)	1.0 (0.92-1.1)*	1.0 (0.90-1.1)**	2232 (1201-4656)*	0.0 (<0.01-<0.01)*	180 (45-387)**
PE, adverse clinical outcome (median, IQR)	1.3 (1.1-1.6)*	1.2 (1.1-1.4)**	>5000 (1319->5000)*	0.0 (<0.01-0.16)*	2068 (78-4400)**
Adjusted OR for adverse events†	3.7 (0.74-19)	9.0 (1.1-79)	3.5 (0.86-15)	6.3 (1.3-31)	31 (3.6-257)
PE ruled out by CT, uncomplicated clinical course (median, IQR)	0.90 (0.80-0.97)	0.85 (0.76-0.93)*	874 (595-1991)*	0.0 (<0.01-<0.01)	153 (54-522)*
PE ruled out by CT, adverse clinical outcome (median, IQR)	0.95 (0.82-1.1)	0.95 (0.79-1.0)*	2377 (1565-3194)*	0.0 <0.01-<0.01)	715 (76-5794)*
Adjusted OR for adverse events†	3.2 (1.1-9.4)	3.3 (1.1-9.8)	2.3 (0.74-7.4)	2.0 (0.22-18)	3.8 (1.4-10)

Mann-Whitney-U tests were performed between uncomplicated and complicated clinical course for patients with PE and without PE separately: *p<0.05, **p<0.01; †from predefined cut-off values. RV/LV-ratio=ventricular volume ratio, 4-CH=four chamber, CT=computed tomography, IQR=interquartile range.

Discriminatory ability and clinical utility of RV/LV-ratio and biomarkers for predicating adverse clinical outcome in patients with acute PE

ROC analyses revealed that from the 5 predictors of adverse events, NT-pro-BNP had higher AUC (0.85, 95% CI 0.73-0.97) compared to axial RV/LV-dimensions (0.64, 95% CI 0.47-0.81; p=0.014),

Table 4. Test characteristics of CT measured right ventricular enlargement and elevated biomarkers for predicting adverse clinical outcome in patients with acute PE.

	Increased RV/LV-ratio (>1.0, axial view)	Increased RV/LV-ratio (>1.0, 4-CH view)	Elevated D-dimer (>3000 ng/mL FEU)	Elevated Troponin-T (>0.09 ng/mL)	Elevated NT-pro-BNP (>600 pg/mL)
Sensitivity (%, 95% CI)	80 (44-96)	90 (56-99.8)	70 (35-93)	40 (12-74)	90 (56-99.8)
Specificity (%, 95% CI)	48 (38-58)	46 (36-57)	60 (50-70)	93 (86-97)	78 (70-84)
Proportion identified as high risk (%, 95% CI)	56 (46-66)	57 (47-67)	42 (33-52)	8.9 (4.4-16)	28 (20-38)
Proportion identified as low risk (%, 95% CI)	44 (34-54)	43 (33-53)	58 (48-67)	91 (84-97)	72 (62-80)
Negative predictive value (%, 95% CI)	96 (86-99.5)	98 (86-99.8)	95 (86-99)	93 (86-97)	99 (92-99.9)
Positive predictive value (%, 95% CI)	13 (5.7-24)	16 (7.8-28)	15 (6.5-28)	30 (8.1-65)	29 (15-48)

RV/LV-ratio=ventricular volume ratio, 4-CH=four chamber, CT=computed tomography, CI=confidence interval.

4-CH RV/LV-ratios (0.64, 95% CI 0.48-0.81; p=0.15), D-dimer (0.64, 95% CI 0.47-0.81; p=0.048) and Troponin-T (0.62, 95% CI 0.41-0.82; p=0.037). Of note, changing the thresholds of these 5 predictors did not improve the prognostic performance of any of them (data not shown).

The high discriminative power of NT-pro-BNP levels exceeding 600 pg/mL was underlined by a high sensitivity (90%, 95% CI 56-99.8) and specificity (78%, 95% CI 70-84) for adverse clinical outcome compared to the remaining 4 predictors (Table 4). RV/LV-ratio >1.0 on 4-CH view had equally high sensitivity (90%, 95% CI 56-99.8) but lower specificity (46%, 95% CI 36-57, p<0.001). Furthermore, although the specificity of elevated Troponin-T levels was higher (93%, 95% CI 86-97; p=0.004), this was accompanied by a significantly lower sensitivity (40%, 95% CI 12-74) than that of NT-pro-BNP (p=0.022).

None of the 5 predictors was able to identify patients at very high risk for adverse events, with low positive predictive values in the range of 14% to 30% (Table 4). On the other hand, negative predictive values were over 90% for all predictors and highest for NT-pro-BNP (99%, 95% CI 92-99.9) and RV/LV-ratio on 4-CH view (98%, 95% CI 86-99.8). Low Troponin-T (91%) and NT-pro-BNP levels (72%) categorized more patients as having a low risk on complications than normal RV/LV-ratio on axial (44%) and 4-CH view (43%; p<0.001 compared to low Troponin-T and NT-pro-BNP levels) and D-Dimer levels under 3000 ng/mL FEU (58%; p<0.01 compared to low Troponin-T levels and p=0.041 compared to low NT-pro-BNP levels). Elevated NT-pro-BNP levels in combination with LV/RV-ratio >1.0 on 4-CH views had a sensitivity of 80% (95% CI 44-96), a specificity of 88% (95% CI 0.78-93), a positive predicting value of 42% (95% CI 21-67) and a negative predicative value of 97% (95% CI 90-99.6), resulting in an AUC of 0.84 (95% CI 0.69-0.99). These test performances were not different from that of NT-pro-BNP alone.

Finally, we calculated the test characteristics of all 5 predictors of adverse clinical outcome for outpatients only. D-dimer levels below 3000 ng/mL FEU were found in 55% of the outpatients

with a negative predictive value of 96% (95% CI 90-99.5), low Troponin-T levels in 91% (negative predictive value 94%, 95% CI 87-98), low NT-pro-BNP levels in 77% (negative predictive value 99%, 95% CI 90-99.9), RV/LV-ratio <1.0 on axial view in 45% (negative predicative value 95%; 95% CI 82-99) and RV/LV-ratio <1.0 on 4-CH view in 44% of the out-patients (negative predictive value 97%, 95% CI 85-99.9).

DISCUSSION

This prospective cohort study has three important findings. First, acute PE is associated with an increased incidence of right ventricular enlargement and higher levels of cardiac biomarkers compared to patients in whom PE is ruled out by CTPA. Second, right ventricular enlargement and elevated levels of cardiac biomarkers predict adverse clinical events in both patients with PE as well as in those without PE. Finally, easy obtainable markers for right ventricular dysfunction such as RV/LV-ratios and cardiac biomarkers can be used for risk stratification, that is for identification of patients with PE who are at low risk for complications. Although all studied predictors had high negative predictive values for adverse events after acute PE, low levels of NT-pro-BNP were found to have superior clinical discriminatory ability and clinical utility compared to the other 4 predictors in our study population.

This clinical utility of the tests under study is determined by the ability of accurately distinguishing PE patients at high or low risk of early complications, thereby identifying a specific patient group that profits from customized, more aggressive treatment, i.e. more intensive clinical surveillance or thrombolysis, or less stringent treatment, i.e. outpatient treatment. ROC analysis showed that NT-pro-BNP levels over 600 pg/mL were found to have the highest AUC. Moreover, its negative predictive value was 99%, indicating a risk for adverse events lower than 1.0% for 72% of the patients with PE. The results from NT-pro-BNP analysis are usually available within the hour and since NT-pro-BNP has evolved to be an increasingly important diagnostic and prognostic tool for patients with heart failure, the assays are widely available. Increased RV/LV-ratio on 4-CH view had comparable excellent sensitivity and negative predictive value compared to elevated NT-pro-BNP levels. In addition, this is presumably the easiest and cheapest test of the two, since this can be performed in all standard CTPA scans, which have become the imaging test of choice for establishing the diagnosis of acute PE in recent years.[10,11,16] Measuring RV/LV-ratios does not require additional administration of contrast material or increased radiation dose, and takes only a few minutes of time. Nonetheless, RV/LV-ratios had significantly lower specificity than elevated levels of NT-pro-BNP and classified only 43% and 44% of the patients in the low risk category. Therefore, the accuracy and clinical utility of NT-pro-BNP for identification of PE patients with low risk of adverse events was superior to that of RV/LV-ratios. Markedly, risk stratification based on the combination of NT-pro-BNP levels as well as RV/LV-ratio on 4-CH views did not show better prognosis than NT-pro-BNP levels

alone. Finally, although high Troponin-T levels categorized 91% of the patients in the low-risk category, its negative predictive value was only 93% due to a lower sensitivity of 40%.

The underlying mechanism for increased right ventricular dimensions, decreased right ventricular function and acute PE has been well established.[1] Even so, to our knowledge this is the first prospective study describing the association of right ventricular enlargement and elevated cardiac biomarkers in patients with acute PE in contrast to patients in whom this diagnosis was suspected but ruled out. Furthermore, this is the first report directly comparing various cardiac biomarkers and RV/LV-ratios for predicting adverse outcome after acute PE.

What is the clinical applicability of our results? A recent meta-analysis[20] has shown that treatment with low molecular weight heparin is at least as effective and safe as treatment with unfractionated heparin for the initial treatment of non-massive PE, enabling start of treatment at an outpatient basis of these patients. This approach may imply great benefits such as saving costs and increasing patient satisfaction.[21] Reduction in iatrogenic problems might be a third beneficial effect.[22] Relatively small prospective outcome studies have demonstrated that outpatient treatment might be feasible, although these patients were selected for outpatient treatment based on clinical intuition, and not on explicit predefined criteria.[4,21] Identification of patients accessible for outpatient treatment based on well-defined, standardized selection criteria may help improving safety and more widespread acceptance of outpatient management. Our study demonstrates that from 5 easily obtainable tests of adverse clinical outcome, NT-pro-BNP is the best tool for selecting patients with a low risk for adverse outcome, who can be considered for outpatient treatment.

The main limitation of this study is that since the sample size of this study was primarily based on RV/LV-ratio on CTPA, the results observed for the other parameters might be underpowered, leading to wide confidence intervals. Furthermore, the fraction of males and the mean age of the patients with acute PE was slightly different compared to previous studies.[11,14,17,23,24] This could affect the generalizability of our study results and therefore, these should be accordingly interpreted. Nonetheless, we consider our data representative for several reasons. First, our study was of prospective design including consecutive patients with suspected acute PE, and by blinding both the attending physicians as well as the researchers, there was no information bias. Second, we had very low lost to follow-up rates: 0 of 113 patients with PE and 1 of 226 of the patients without PE. Third, we used predefined cut-off points for our predictors that were established by previous studies. Furthermore, post-hoc analyses in our data confirmed these thresholds to have the highest discriminatory ability (data not shown). Fourth, the ORs for adverse events regarding the 5 studied predictors calculated from our data are in accordance with the confidence intervals of those reported in previous studies.

Finally, although signs of right ventricular dysfunction on echocardiography are clearly associated with adverse events after PE[1,11,23,24], we have not incorporated echocardiography in our study design. The main reason for this decision was that in our hospital, as well as in many other hospitals, it is not possible to perform echocardiography as a clinical routine in all

patients diagnosed with acute PE. Additionally, the performance of RV/LV-ratios on 4-CH views has been demonstrated to be comparable to that of echocardiography.[11]

In summary, right ventricular enlargement and elevated cardiac biomarkers, that are independently associated with acute PE, are predictive for a complicated clinical course in patients with acute PE and also in patients who were suspected of this disease but in whom PE was ruled out by CTPA. These tests are especially valuable in identifying patients with low risk of adverse events after acute PE is diagnosed. NT-pro-BNP levels below 600 pg/mL have the highest clinical discriminatory ability and clinical utility as compared to D-dimer levels below 3000 ng/mL FEU, Troponin-T levels below 0.09 ng/mL and RV/LV-ratios less than 1.0 for both axial as well as 4-CH views in our study population. Future outcome studies should confirm these results and the safety of home-treatment based on low NT-pro-BNP levels and/or RV/LV-ratios.

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