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Early View

Original article

Prognostic value of cardiovascular parameters in CT Pulmonary Angiography in patients with acute pulmonary embolism

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Introduction

Pulmonary embolism (PE) is the third cardiovascular disease worldwide with mortality ranging up to 25%[1]. Calculating the risks of adverse outcome for a patient can guide therapeutic decision (home therapy, hospitalization, or thrombolysis)[2-4]. This risk can be based on clinical, biochemical and imaging parameters[5-7]. The detrimental consequences from PE are thought to be mainly associated with the development of right ventricular dysfunction (RVD), which could cause increase of cardiac biomarkers such as NT-proBNP[8]. The burden to the heart would lead to overall heart failure and subsequent death.

ESC guidelines categorize the risk of adverse outcome as high, intermediate or low. Risk calculations are based on sPESI, and are suggested to guide treatment accordingly[2]. For the large intermediate risk group, fine tuning can be done on the presence of RVD, categorizing patients to intermediate-high or intermediate-low risk as assessed by biomarkers or imaging[9]. In daily practice however, additional tests such as ultrasound or NT-proBNP are frequently not performed [10]. It would be ideal, if CT Pulmonary angiography (CTPA), the reference standard for the diagnosis of PE, could also be used to assess the prognosis [11]. So far, heterogeneity in study groups, definitions, and outcomes prohibits consensus on the prognostic performance of CTPA [12]. Two multicenter prospective studies have suggested that the right-to-left ventricular ratio can be used as a predictor for mortality. As these studies did not investigate other potential predictive parameters, the unique position of the right-to-left ventricular ratio can be questioned [13, 14]. Other reported radiological findings such as cardiovascular diameters, backflow or clot burden have been evaluated but findings on their value are inconsistent[15-20]. Consequently, it is unclear if one or more CTPA parameters can contribute to risk stratification in patients with acute PE.

To add strong evidence to the debate on the value of CTPA parameters in risk stratification we analysed imaging, clinical and follow-up data collected in a prospective multicenter trial in patients with acute PE [21]. Our focus was on the evaluation of the predictive effects of baseline CTPA parameters on short and long term clinical outcome.

Materials and Methods

Patients and study design

Patient data and images were collected in the context of a large international randomized clinical trial comparing two anticoagulant regimens in patients with venous thrombo-embolism (VTE). The results, design and methods of the Hokusai-VTE study have been described in detail previously (ClinicalTrials.gov identifier: NCT00986154)[21]. In short,

eligible patients were patients aged 18 years or older with acute, symptomatic venous thromboembolism (deep vein thrombosis and/or PE). Patients were excluded in case of contraindications to heparin or warfarin, severely impaired renal function or pregnancy. The institutional review board at each participating center approved the general study protocol, and all patients provided written informed consent.

Patients were enrolled between January 2010 and October 2012 at 439 centers in 37 countries. All data for the present analysis had been collected and assessed prospectively before the trial data lock. Follow-up was 12 months, covering both the in-hospital period as well as regular outpatient clinic controls, and patients on and off anticoagulant treatment. Adverse events were noted on separate forms, as well as whether this was PE related. An independent committee adjudicated all predefined outcomes.

For this additional study all patients with PE, either with or without DVT, were selected. Excluded were patients with DVT only, patients not evaluated by CTPA, or when images were not available in DICOM format or inaccessible for reading in the used image viewer (e.g. hard copy, corrupted discs).

Data collection

All clinical and radiological data were anonymized, and centrally registered with double data entry by an independent trial data management agency. Clinical data were retrieved from the original CRFs. In all patients NT-proBNP levels were measured at baseline.

CT-data were acquired from the local participating centers, using local settings and protocols. This means that a wide variety of CT-scanners were used, from basic until high-end CT. For quality evaluation a 5-point Likert scale was used, anchored at 1 (unacceptable), 2 (poor), 3 (satisfactory), 4 (good) and 5 (excellent quality). The enhancement of the pulmonary trunk was assessed by measuring a 1 cm region of interest (ROI) and expressed in Hounsfield Units (HU).

Anonymized patient images from the central database were evaluated by a radiologist (LB) with 12 years of experience in chest imaging supported by a dedicated research assistant. Both were unaware of patient details and clinical information. For image reading a commercially available image viewer was used (eFilm Workstation for Windows Version 3.4.0, Build 10, Merge Technologies Inc., Milwaukee, USA). Images were primarily read in axial sections with additional support of multiplanar reformatting (MPR). Standard pulmonary angiography, mediastinal and lung parenchyma window settings were used, with individual adaptation if deemed necessary. Data were registered on a specially designed CRF.

A random sample of 50 patients was used to evaluate the intra-observer variability for the main study parameters, as assessed by Cohen's k-statistic. Intra-observer agreement was graded according to Landis and Koch, with 0-20 indicating poor correlation, 20-40 moderate,

40-60 fair, 60-80 good, and 80-100 excellent correlation. No additional readers were engaged as intra-observer agreement for the selected parameters is reportedly high [22-24].

All continuous variables were noted in millimetres where applicable. The following parameters were assessed: transverse diameter of right ventricle, left ventricle (both on axial and reformatted short axis view), pulmonary trunk, ascending aorta, inferior and superior caval vein, azygos vein, right atrium, and heart and intrathoracic diameters. For the ventricular diameters, the largest cross-sectional distance between ventricular surfaces was taken. The right atrium was measured at its largest transverse diameter. Pulmonary trunk was measured at its largest transverse diameter, the ascending aorta at the level of the carina, the caval veins were measured 2 cm from their entrance into the right atrium, and the azygos vein at its most cranial part. For the heart volume and the intrathoracic distance, the largest transverse diameters from pericardial contours and costal margins were taken.

The right-to-left ventricular (RV/LV), right-to-left ventricular short axis (RV/LVsa), and pulmonary trunk-to-aorta (TP/Ao) ratios were calculated by dividing the values of respective transverse diameters. All obtained values were then dichotomized at earlier reported thresholds (RV/LV > 1.0; RV/LVsa > 0.9; TP/A0 > 1.0, TP > 29 mm; cardiothoracic ratio > 0.50).

Ordinal measures were: bowing of the interventricular septum (negative, neutral, positive); reflux of contrast medium in the inferior caval vein (no, only into the IVC, intrahepatic < 3 cm, and intrahepatic veins > 3 cm) and in the azygos vein (yes or no). Interventricular septum bowing was considered present when the septum was curved to the left ventricle, or flattened if the septum was straightened or bowed. Backflow was considered positive if reflux was into the intrahepatic veins; only into the inferior caval vein was considered negative. Azygos vein reflux was considered present if it reached the crossing with the right main stem bronchus.

Events were analysed focusing on 4 time points: early (1 week and 1 month) and late (on treatment, mostly 3-6 months, and 12 month) period. For right ventricular dysfunction the reference standard was an increased value of NT-proBNP ≥ 600 pg/ml at baseline[2].

Statistical analysis

Primary outcome for the study was mortality, secondary outcomes were recurrent VTE, hospitalization, bleeding and all adverse events. We calculated odds ratios with 95% confidence intervals (CI) to express the strength of the association between cardiovascular CTPA parameters and mortality, as well as other clinical outcomes. We also calculated estimates of sensitivity and specificity, PPV and NPV for mortality. Missing data were excluded from the analysis. No correction for multiple testing was performed. Significance of differences were evaluated with two-sided p-values; a p-value < 0.05 was considered to imply statistical significance. All statistics were performed in SPSS version 23 (SPSS Inc, Chicago Ill).

Results

In the RCT, 3,481 patients had PE, of which 3114 had been diagnosed using CTPA. After screening, 1164 of these were excluded because because images were presented on hard copies, jpeg or pdf only, no DICOM images were available, or because of a technically inadequate study as e.g. insufficient coverage of heart and chest (Figure 1). To address possible selection bias, we compared baseline characteristics of included and excluded patients and found no relevant differences. One year outcomes also were not different, as mortality and recurrent VTE was 3.0 and 2.6% for the included and 3.1% and 2.7% for the excluded group, respectively. Hence, data of 1950 patients were included in this evaluation. Of these, 1049 (54%) were male. Mean age was 57 years. A summary of their characteristics is shown in Table 1. PE was provoked in 1288 patients, 456 patients had PE with concomitant DVT. In 565 patients the NT-proBNP level was > 600 pg/ml.

Quality

Overall quality of the scans was good (3.7/5; SD=0.8). Mean Hounsfield Units in the pulmonary trunk was 325 (SD=118). Intra-observer agreement on a random sample from the complete database scored twice was excellent (kappa=0.9).

Frequencies

The median right-to-left-ventricle ratio on CTPA was 0.89 (SD=0.27); 621 patients (32%) had a ratio >1 (Tables 2 and 3). Compared to those without RVD on CT, in patients with RV/LV>1 NT-proBNP more often was raised. The median short axis right-to-left-ventricle ratio was 0.88, of which 890 (47%) were > 0.90.

In 538 (28%) patients the septum was flattened, septal bowing occurred in 153 patients (7.9%). The pulmonary trunk was enlarged in 634 patients (33%). A pulmonary trunk/aorta ratio > 1 was present in 408 patients (20.9%). Backflow of contrast medium into the hepatic veins occurred in 261 (15%), and into the azygos vein in 445 (23%) patients.

Short term outcomes

A summary of the investigated cardiovascular radiological parameters and their correlation with short and long term adverse events are displayed in Tables 4a and 4b (mortality) and 5 (only online: recurrent VTE, hospitalization, major bleeding and all adverse events).

During the first month 29 adverse events occurred, including 18 deaths, 12 recurrent VTEs, 13 bleedings. There were 26 hospitalizations.

Of all the radiological parameters evaluated, only pulmonary trunk diameter > 29 mm was significantly associated with mortality at 1 week (OR 4.18, CI=1.04-16.8; p=0.028, Table 2 and 3). The odds ratio at 1 month was lower and not statistically significant (OR 2.30, CI=0.97-5.45; p=0.051). All other parameters (RV/LV ratio, RV/LV short axis, septal bowing, pulmonary trunk/aorta ratio, cardiothoracic ratio and backflow to hepatic veins or azygos

vein) were not significantly associated with mortality. Of the 9 patients that died within the first week, 6 (66.7%) had an enlarged pulmonary trunk. In total 18 patients died within one month, an enlarged pulmonary trunk was present in half of these 18 patients. In patients who survived one week or subsequently one month an enlarged pulmonary trunk was present in 628 and 625 patients (32.4%, p = 0.028 respectively 32.4%, p=0.11).

An enlarged pulmonary trunk diameter was also associated with recurrent VTE (OR 5.22, CI=1.01-26.7; p=0.028) at 1 week. Here also the odds ratio was lower and not significant at 1 month (1.8, CI=0.6-5.3; p=0.051). None of the evaluated radiological parameters, apart from enlarged pulmonary trunk diameter was associated with hospitalization. Sensitivities were low for all the researched parameters, as were the specificities and positive predictive values; however, all parameters showed a high negative predictive value.

Long term outcomes

The median on treatment time was 215 days (IQR 178-358 days). During the complete 1 year period, 143 adverse events were registered in 131 patients. In total 58 patients died, 49 had recurrent VTE, 30 had a major bleeding and 90 were hospitalized.

An enlarged pulmonary trunk diameter was significantly associated with mortality during the on-treatment time as well as for the complete 12 months (p=0.004 resp. 0.001). A TP/Aorta ratio > 1.0 was also significantly associated with mortality during treatment (p=0.002; Table 4) but not for the complete period (p=0.055). Of the 11 patients with interstitial lung disease, 2 patients that had an enlarged pulmonary trunk died. In 43 patients with a history of pulmonary hypertension, 21 had an enlarged pulmonary trunk of which 2 died. All other evaluated cardiovascular parameters were not significantly associated with mortality or other adverse events.

Discussion

Our study showed that most of the investigated cardiovascular radiological parameters - including RV/LV ratio, septal bowing, cardiothoracic ratio and contrast medium backflow - have no prognostic value for short or long term mortality. The exception was an enlarged pulmonary trunk diameter, which on both short and long term was associated with increased mortality and the risk of recurrent VTE and hospitalization.

A strength of our study is that data were prospectively collected in a large international trial, and both imaging data and clinical outcomes were assessed blinded for treatment and outcome.

Our study also has limitations. Although in literature many parameters have been evaluated, we only analysed the most frequently used radiological parameters and cut off values as these would be most easily implementable, had we found any of these to be of value. As

reconstructed views yield comparative values but are more time-consuming, plain axial transverse images generally are preferred given the simplicity of analysis [25]. We evaluated observer agreement only for the main continuous variables, and not for the ordinal measurements. We also did not perform separate assessments for treatment allocation to edoxaban or enoxaparin followed by warfarin, as this subgroup analysis was done in the original dataset [21]. We did not perform a multivariable analysis, as we first aimed to assess the prognostic value of each parameter separately. Also, echocardiography can be a useful tool for short term mortality risk stratification [12]. As only 523 (26.8%) of the evaluated patients received this test, this was not analysed in the present study. We are aware that patients included in a randomized controlled trial do not necessarily reflect all those presenting in regular practice, and our results cannot be unconditionally generalized to those with exclusion criteria for the trial, such as hemodynamically unstable patients, patients with a limited life expectancy and pregnant women.

How do our findings fit into the current assessment of prognosis in patients with acute PE? We need better tools to identify high risk patients with a favourable risk-benefit ratio from thrombolysis, or, alternatively, to identify those who would benefit from close clinical monitoring in order to provide them with rescue thrombolysis. As the beneficial effect of thrombolysis primarily reflects the first days, an easily applicable modifier like an enlarged pulmonary trunk would probably facilitate such processes. In recent ESC guidelines primary categorization into low, intermediate or high risk is based on sPESI. In second instance either biomarkers, RV/LV ratio or echocardiography can be used for further stratification on RVD. However, no consensus exists on its usefulness, as well as on the threshold, as RVD values reported in the literatures are ranging from 0.9 until 1.8[26].

Several studies have reported that RVD on CTPA is an indicator of the risk of adverse events [13, 27]. Many studies however had a single center, retrospective design, with short follow up and surrogate outcomes. As such, they have intrinsic methodological limitations that weaken their validity and generalizability. The larger series have shown conflicting results, either confirming or denying that right-to-left ventricular ratio is associated with an increased mortality [14],[28, 29],[30].

A recent systematic review stated that although RVD assessed by CT showed an association with an increased risk of mortality in patients with hemodynamically stable PE, it resulted in only small increases in the ability to classify risk[31]. Although additional publications confirmed this finding [[31, 32], apparently, RV enlargement alone is not sufficient to indicate a poor short-term prognosis, and other factors should also be taken into consideration[33]. For the long-term persistent RV dysfunction seems common, reflecting on diminished exercise capacity and reduced quality of life [34]. One of the differences with the published cohorts is the fact that our study contains a population that was included in a randomized clinical trial rather than a prospective cohort study of consecutive patients, and thus could reflect different study populations. Our finding that right-to-left ventricular ratio

is not associated with an increased mortality could thus be an incentive to reconsider the risk stratification algorithm.

Reports on the other investigated outcomes –recurrent VTE, hospitalization, bleeding and adverse effects- are scarce, as most often they are used as a composite outcome, or focus on differences between treatment regimens[35].

Although an enlarged pulmonary trunk diameter is an established feature in the work up of chronic PE, for acute PE findings are contradictory, as an association with increased risk was not always observed in previous studies[36-40]. However, most of these studies were retrospective with limited number of patients. The assessment however is rather easy and not as time consuming as e.g. clot obstruction scores, and thus could be used easily in daily practice. Sensitivity for enlarged pulmonary trunk diameter may be low, but as specificity was high, we may be able to better identify specific risk groups. Its high negative predictive value indicates that it may be useful for identification of those patients that have a low risk for adverse events who will not need for aggressive therapy, and can be discharged home early. However, for prognostication towards high risk measures like admission to ICU or thrombolysis a multifactorial risk-benefit analysis would be necessary.

One intriguing point is the apparent discrepancy between the relative high number of RVD observed in the earlier published studies, and the fortunately relatively low mortality percentages. In other words: although many patients are categorized as high risk, be it from radiological, biochemical, or combined, this does not translate in the same manner in mortality and adverse events. From this point it should be logical to better investigate the role of radiological cardiovascular parameters in risk stratification, both separately, as well as in combination with other biomarkers. At present, in patients with an intermediate risk profile the ESC guidelines recommend to use an increased RV/LV-ratio either in CT or echocardiographic evaluation, after patients have been stratified by clinical parameters sPESI[2]. No statement has been made on the use of enlarged pulmonary trunk diameters. Our results on the PA diameter should be considered explorative findings, done in a trial population. The findings are promising with regard to predict poor prognosis/mortality but should be confirmed in consecutive cohorts. Measurement of PA is quicker to perform than a RV/LV ratio assessment, and hence easier to integrate/accept/adopt in daily practice. Incorporation of enlarged pulmonary trunk diameters is an attractive radiological marker to be further investigated in clinical management studies.

In conclusion, we found that several of the widely suggested radiological cardiovascular parameters did not show an association with short or long term adverse events like mortality, recurrent VTE, bleeding, hospitalization. Only an enlarged pulmonary trunk diameter was associated with an increased risk of mortality, recurrent VTE both on short as well as long term.

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Legend to Tables

Table 1

Baseline characteristics

Data are number (%) or median (IQR), unless otherwise specified. CHF – Chronic heart failure; DVT –Deep Vein Thrombosis; PE – Pulmonary Embolus; sPESI – simplified pulmonary embolism severity index; US – Ultrasound. . * - 523/1950 included and 496/1531 excluded patients (mm: mean , SD); ** sPESI- item on O_2 considered positive if patient needed oxygen administration

Table 2

CT Pulmonary Angiography diameters

Table 3

Frequency of abnormal cardiovascular radiological parameters

Table 4

Short and long term mortality

A. Odds ratio
B. Sensitivity, specificity, PPV, NPV

Appendix online

Table 5 Adverse events during short term (1 month) and long term (12 months)

A Short and long term recurrent VTE

B. Short and long term hospitalization

C. Short and long term bleeding

D. Short and long term total adverse events

Table 1 **Baseline characteristics**

	Included		Excluded	
	n	% (or SD)	n	% (or SD)
	1950	100	1531	100
Clinical				
Age (mean, SD)	57.0	16.6	57.5	16.5
Age > 65Y	714	36.6	560	36.6
Male	1049	53.8	793	51.8
Female	901	46.2	738	48.2
Weight (mean, SD)	84.5	20.1	79.8	19.9
Concomitant DVT	456	23.4	363	23.7
Smoking	854	43.8	635	41.5
Alcohol	754	38.7	446	29.1
US Right ventricular dimension *	37.2	28.2	31.8	22
Systolic Blood Pressure mmHg (mean, SD)	128	16.5	127	16.4
Diastolic Blood Pressure mmHg (mean, SD)	76	11	76	10.9
Heart Rate (mean, SD)	80	14	80	13.9
Respiratory Rate (mean, SD)	16	2.6	19.2	2
sPESI High Risk**	1051	53.9	990	64.8
Risk Factors				
Provoked PE	1288	66.1	959	62.6
Recent surgery, trauma, or immobilization	372	19.1	282	18.4
Sitting > 4 hours	185	9.5	121	7.9
Estrogen containing drugs use (Females)	196	21.8	103	6.7
Active cancer	56	2.9	34	2.2
Previous episodes of DVT/PE	415	21.3	305	19.9
Thrombophilic condition	94	4.8	59	3.9
Concomitant Disease History				
Hypertension	810	41.5	645	42.2
Diabetes	199	10.2	155	10.1
Cardiovascular Disease	314	16.1	274	17.9
CHF	35	1.8	62	4.1
Cerebrovascular Disease	73	3.7	65	4.3
Stroke	35	1.8	38	2.5
Renal Disease	129	6.6	132	8.6
Hepatic Disease	212	10.9	195	12.8
Pulmonary Disease	401	20.6	446	29.2
COPD	103	5.3	116	7.6
Interstitial Lung Disease	11	0.6	3	0.2
Pulmonary hypertension	43	2.2	56	3.7

Cancer	228	11.7	148	9.7

Table 2 **Radiological diameters**

	n	missing	mean	SD	Min	Max	IQR
RV axial plane	1950	0	38.3	7.8	17	67	33 - 43
LV axial plane	1950	0	41.5	7.1	18	69	37 - 48
RV short axis	1906	44	39.7	7.7	20	71	34 - 45
LV short axis	1906	44	42.6	6.7	22	73	38 - 47
Aorta	1949	1	32.3	4.9	18	52	29 - 35
Pulmonary Trunk	1949	1	27.7	4.6	15	52	25 - 31
Azygos	1947	3	8.3	2.3	2	20	7 - 10
SVC	1949	1	18.9	4.1	8	33	16 - 22
RV Wall Thickness	1950	0	1.5	0.8	1	8	1 - 2
RA	1950	0	49.0	9.1	24	88	43 - 55
IVC	1942	8	22.7	4.3	8	41	20 - 25
Heart	1950	0	128.6	14.9	85	228	119 - 138
Chest	1950	0	259.1	24.2	126	344	242 - 276
RV/LV Axial	1950	0	0.95	0.27	0.39	2.61	0.78 - 1.00
RV/LV short axis	1950	0	0.96	0.26	0.47	2.11	0.80 - 1.02
PT/Ao	1950	0	0.87	0.15	0.42	2.08	0.77 - 0.96
CTR	1950	0	0.50	0.06	0.34	0.97	0.46 - 0.54

Table 3 **Frequency of abnormal cardiovascular radiological parameters**

	n	missing	normal	%	abnormal	%
RV/LV > 1	1950	0	1329	68.2	621	31.8
RV/LVsa > 0.9	1914	36	1024	53.5	890	46.5
Septal Bowing	1949	1	1796	92.1	153	7.9
Septal Flattening	1949	1	1411	72.4	538	27.6
Aorta > 40 mm	1840	110	1800	97.8	40	2.2
Pulmonary Trunk > 29 mm	1949	1	1315	67.5	634	32.5
PT/Aorta > 1.0	1950	0	1542	79.1	408	20.9
Cardiothoracic ratio > 0,50	1833	117	897	48.9	936	51.1
Backflow IVC	1754	196	1105	63	649	37
Intrahepatic Contrast Reflux	1754	196	1493	85.1	261	14.9
Backflow azygos vein	1947	3	1502	77.1	445	22.9

Table 4A **Short and long term mortality**

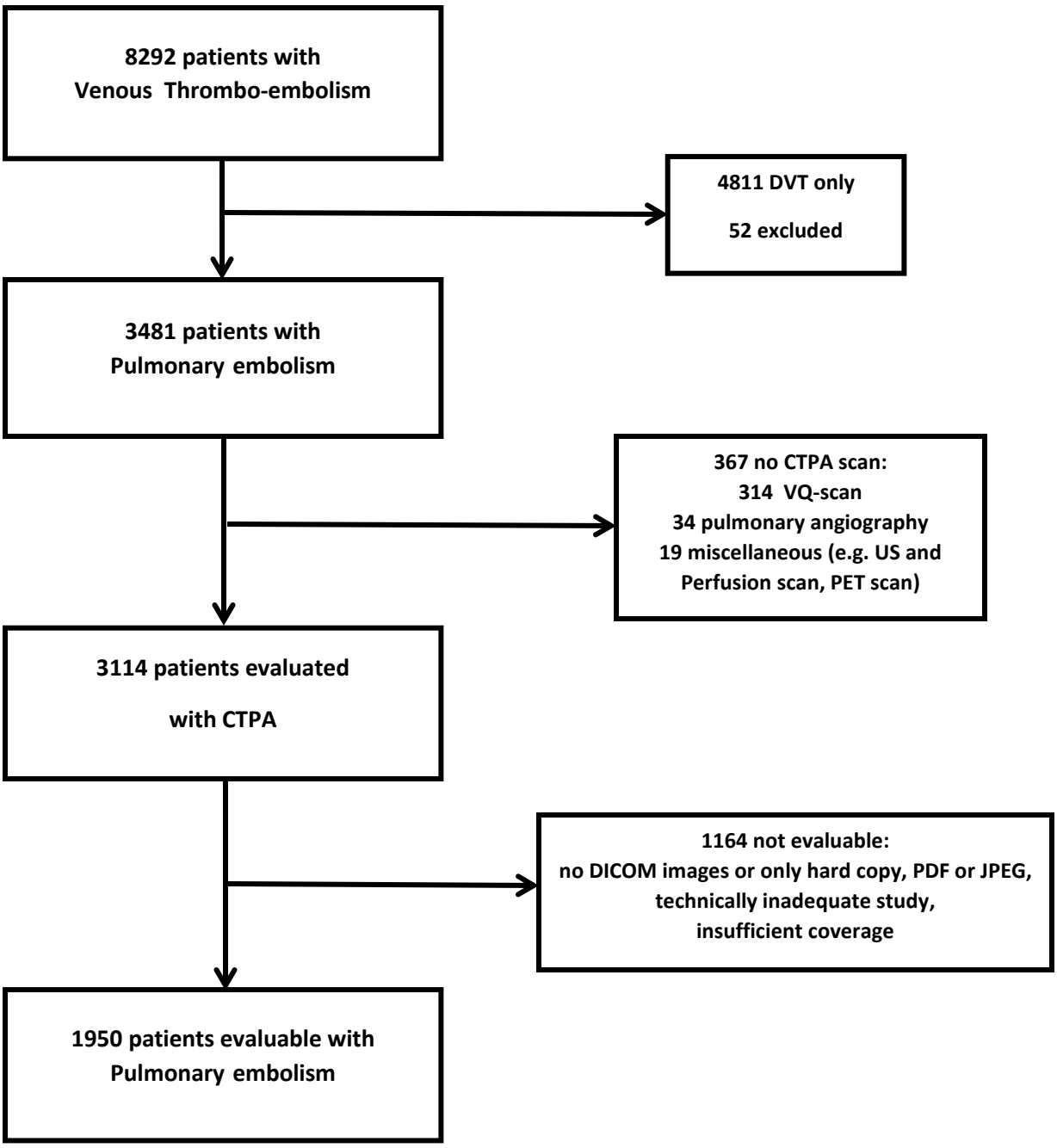
1 Week	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	6	66.7	3	33.3	1.07	0.27	4.29
RV/LVsa > 0,9	1914	4	44.4	5	55.6	1.44	0.39	5.38
Septal Bowing	1949	8	100.0	0	0.0			
Septal flattening	1949	5	62.5	3	37.5	1.58	0.38	6.62
Aorta > 40 mm	1840	9	100.0	0	0.0			
Pulmonary Trunk > 29 mm	1949	3	33.3	6	66.7	4.18	1.04	16.76
PT/Aorta > 1.0	1950	6	66.7	3	33.3	1.90	0.47	7.62
Cardiothoracic ratio > 0,50	1833	2	22.2	7	77.8	3.37	0.70	16.28
Backflow IVC	1754	5	62.5	3	37.5	1.02	0.24	4.29
Intrahepatic Reflux	1754	6	75.0	2	25.0	1.91	0.38	9.53
Backflow azygos vein	1947	7	77.8	2	22.2	0.96	0.20	4.66
1 Month	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	15	71.4	6	28.6	0.86	0.33	2.21
RV/LVsa > 0,9	1914	8	38.1	13	61.9	1.88	0.78	4.56
Septal Bowing	1949	20	100.0	0	0.0			
Septal flattening	1949	13	65.0	7	35.0	1.42	0.56	3.57
Aorta > 40 mm	1840	20	100.0	0	0.0			
Pulmonary Trunk > 29 mm	1949	10	47.6	11	52.4	2.30	0.97	5.45
PT/Aorta > 1.0	1950	14	66.7	7	33.3	1.91	0.76	4.75
Cardiothoracic ratio > 0,50	1833	7	33.3	14	66.7	1.93	0.78	4.81
Backflow IVC	1754	12	60.0	8	40.0	1.14	0.46	2.80
Intrahepatic Reflux	1754	15	75.0	5	25.0	1.92	0.69	5.34
Backflow azygos vein	1947	18	85.7	3	14.3	0.56	0.16	1.91
Complete On Treatment period	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	20	66.7	10	33.3	1.07	0.50	2.30
RV/LVsa > 0,9	1914	12	40.0	18	60.0	1.74	0.83	3.63
Septal Bowing	1949	29	100.0	0	0.0			
Septal flattening	1949	20	69.0	9	31.0	1.18	0.54	2.62
Aorta > 40 mm	1840	29	100.0	0	0.0	0.98	0.98	0.99
Pulmonary Trunk > 29 mm	1949	13	43.3	17	56.7	2.76	1.33	5.72

PT/Aorta > 1.0	1950	17	56.7	13	43.3	2.95	1.42	6.13
Cardiothoracic ratio > 0,50	1833	10	33.3	20	66.6	1.94	0.90	4.16
Backflow IVC	1754	17	60.7	11	39.3	1.10	0.51	2.37
Intrahepatic Reflux	1754	21	75.0	7	25.0	1.93	0.81	4.59
Backflow azygos vein	1947	26	86.7	4	13.3	0.52	0.18	1.48
1 Year Study period	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	42	72.4	16	27.6	0.81	0.45	1.45
RV/LVsa > 0,9	1914	28	48.3	30	51.7	1.24	0.74	2.09
Septal Bowing	1949	55	96.5	2	3.5	0.42	0.10	1.74
Septal flattening	1949	43	75.4	14	24.6	0.85	0.46	1.57
Aorta > 40 mm	1840	52	94.5	3	5.5	2.73	0.81	9.13
Pulmonary Trunk > 29 mm	1949	23	39.7	35	60.3	2.33	1.36	3.97
PT/Aorta > 1.0	1950	40	69.0	18	31.0	1.73	0.98	3.06
Cardiothoracic ratio > 0,50	1833	23	40.4	34	59.6	1.43	0.94	2.45
Backflow IVC	1754	28	54.9	23	45.1	1.41	0.81	2.48
Intrahepatic Reflux	1754	40	78.4	11	21.6	1.60	0.81	3.16
Backflow azygos vein	1947	51	87.9	7	12.1	0.46	0.21	1.01

Table 4B **Short and long term mortality**

1 Week	Sens	CI		Spec	CI		PPV	CI		NPV	CI	
RV/LV > 1	0.33	0.03	0.64	0.68	0.66	0.70	0.00	0.00	0.01	1.00	0.99	1.00
RV/LVsa > 0,9	0.56	0.23	0.88	0.54	0.51	0.56	0.01	0.00	0.01	1.00	0.99	1.00
Septal Bowing	0.00	0.00	0.00	0.92	0.91	0.93	0.00	0.00	0.00	1.00	0.99	1.00
Septal flattening	0.38	0.04	0.71	0.72	0.70	0.74	0.01	0.00	0.01	1.00	0.99	1.00
Aorta > 40 mm	0.00	0.00	0.00	0.98	0.97	0.98	0.00	0.00	0.00	1.00	0.99	1.00
Pulm. Trunk > 29 mm	0.67	0.36	0.97	0.68	0.66	0.70	0.01	0.00	0.02	1.00	1.00	1.00
PT/Aorta > 1.0	0.33	0.03	0.64	0.79	0.77	0.81	0.01	0.00	0.02	1.00	0.99	1.00
Cardiothor. ratio > 0,50	0.78	0.51	1.05	0.49	0.47	0.51	0.01	0.00	0.01	1.00	0.99	1.00
Backflow IVC	0.38	0.04	0.71	0.63	0.61	0.65	0.00	0.00	0.01	1.00	0.99	1.00
Intrahepatic Reflux	0.25	0.00	0.55	0.85	0.83	0.87	0.01	0.00	0.02	1.00	0.99	1.00
Backflow azygos vein	0.22	0.00	0.49	0.77	0.75	0.79	0.00	0.00	0.01	1.00	0.99	1.00
1 Month	Sens	CI		Spec	CI		PPV	CI		NPV	CI	
RV/LV > 1	0.29	0.09	0.48	0.68	0.66	0.70	0.01	0.00	0.02	0.99	0.98	0.99
RV/LVsa > 0,9	0.62	0.41	0.83	0.54	0.51	0.56	0.01	0.01	0.02	0.99	0.99	1.00
Septal Bowing	0.00	0.00	0.00	0.92	0.91	0.93	0.00	0.00	0.00	0.99	0.98	0.99
Septal flattening	0.35	0.14	0.56	0.72	0.70	0.74	0.01	0.00	0.02	0.99	0.99	1.00
Aorta > 40 mm	0.00	0.00	0.00	0.98	0.97	0.98	0.00	0.00	0.00	0.99	0.98	0.99

Pulm. Trunk > 29 mm	0.52	0.31	0.74	0.68	0.66	0.70	0.02	0.01	0.03	0.99	0.99	1.00
PT/Aorta > 1.0	0.33	0.13	0.53	0.79	0.77	0.81	0.02	0.00	0.03	0.99	0.99	1.00
Cardiothor. ratio > 0,50	0.67	0.47	0.87	0.49	0.47	0.51	0.01	0.01	0.02	0.99	0.99	1.00
Backflow IVC	0.40	0.19	0.61	0.63	0.61	0.65	0.01	0.00	0.02	0.99	0.98	1.00
Intrahepatic Reflux	0.25	0.06	0.44	0.85	0.84	0.87	0.02	0.00	0.04	0.99	0.98	1.00
Backflow azygos vein	0.14	0.00	0.29	0.77	0.75	0.79	0.01	0.00	0.01	0.99	0.98	0.99
On Treatment period	Sens	CI		Spec	CI		PPV	CI		NPV	CI	
RV/LV > 1	0.33	0.16	0.50	0.68	0.66	0.70	0.02	0.01	0.03	0.98	0.98	0.99
RV/LVsa > 0,9	0.60	0.42	0.78	0.54	0.51	0.56	0.02	0.01	0.03	0.99	0.98	0.99
Septal Bowing	0.00	0.00	0.00	0.92	0.91	0.93	0.00	0.00	0.00	0.98	0.98	0.99
Septal flattening	0.31	0.14	0.48	0.72	0.70	0.74	0.02	0.01	0.03	0.99	0.98	0.99
Aorta > 40 mm	0.00	0.00	0.00	0.98	0.97	0.98	0.00	0.00	0.00	0.98	0.98	0.99
Pulm. Trunk > 29 mm	0.57	0.39	0.74	0.68	0.66	0.70	0.03	0.01	0.04	0.99	0.98	1.00
PT/Aorta > 1.0	0.43	0.26	0.61	0.79	0.78	0.81	0.03	0.01	0.05	0.99	0.98	0.99
Cardiothor. ratio > 0,50	0.67	0.50	0.84	0.49	0.47	0.52	0.02	0.01	0.03	0.99	0.98	1.00
Backflow IVC	0.39	0.21	0.57	0.63	0.61	0.65	0.02	0.01	0.03	0.98	0.98	0.99
Intrahepatic Reflux	0.25	0.09	0.41	0.85	0.84	0.87	0.03	0.01	0.05	0.99	0.98	0.99
Backflow azygos vein	0.14	0.01	0.26	0.77	0.75	0.79	0.01	0.00	0.02	0.98	0.98	0.99
1 Year	Sens	CI		Spec	CI		PPV	CI		NPV	CI	
RV/LV > 1	0.28	0.16	0.39	0.68	0.66	0.70	0.03	0.01	0.04	0.97	0.96	0.98
RV/LVsa > 0,9	0.52	0.39	0.65	0.54	0.51	0.56	0.03	0.02	0.05	0.97	0.96	0.98
Septal Bowing	0.04	0.00	0.08	0.92	0.91	0.93	0.01	0.00	0.03	0.97	0.96	0.98
Septal flattening	0.25	0.13	0.36	0.72	0.70	0.74	0.03	0.01	0.04	0.97	0.96	0.98
Aorta > 40 mm	0.05	0.00	0.11	0.98	0.97	0.99	0.08	0.01	0.16	0.97	0.96	0.98
Pulm. Trunk > 29 mm	0.52	0.39	0.65	0.68	0.66	0.70	0.05	0.03	0.06	0.98	0.97	0.99
PT/Aorta > 1.0	0.31	0.19	0.43	0.79	0.78	0.81	0.04	0.02	0.06	0.97	0.97	0.98
Cardiothor. ratio > 0,50	0.60	0.47	0.72	0.49	0.47	0.52	0.04	0.02	0.05	0.97	0.96	0.98
Backflow IVC	0.45	0.31	0.59	0.63	0.61	0.66	0.04	0.02	0.05	0.97	0.97	0.98
Intrahepatic Reflux	0.22	0.10	0.33	0.85	0.84	0.87	0.04	0.02	0.07	0.97	0.97	0.98
Backflow azygos vein	0.12	0.04	0.20	0.78	0.76	0.80	0.02	0.00	0.03	0.97	0.96	0.98


8292 patients with
Venous Thrombo-embolism
4811 DVT only
52 excluded
3481 patients with
Pulmonary embolism
367 no CTPA scan:
314 VQ-scan
34 pulmonary angiography
19 miscellaneous (e.g. US and
Perfusion scan, PET scan)
3114 patients evaluated
with CTPA
1164 not evaluable:
no DICOM images or only hard copy, PDF or JPEG,
technically inadequate study,
insufficient coverage
1950 patients evaluable with
Pulmonary embolism

Appendix On line. 1 Month and 1 year recurrent VTE, hospitalization, major bleeding and adverse events

Recurrent VTE								
1 Month	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	7	53.8	6	46.2	1.84	0.62	5.51
RV/LVsa > 0,9	1914	5	38.5	8	61.5	1.85	0.60	5.67
Septal Bowing	1949	11	91.7	1	8.3	1.07	0.14	8.32
Septal flattening	1949	6	50.0	6	50.0	2.64	0.85	8.23
Aorta > 40 mm	1840	11	91.7	1	8.3	4.17	0.53	33.10
Pulmonary Trunk > 29 mm	1949	7	53.8	6	32.4	1.79	0.60	5.33
PT/Aorta > 1.0	1950	8	61.5	5	38.5	2.38	0.77	7.31
Cardiothoracic ratio > 0,50	1833	6	50.0	6	50.0	0.96	0.31	2.98
Backflow IVC	1754	7	63.6	4	36.4	0.97	0.28	3.34
Intrahepatic Reflux	1754	9	81.8	2	18.2	1.27	0.27	5.93
Backflow azygos vein	1947	12	92.3	1	7.7	0.28	0.04	2.16
1 Year	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	33	66.0	17	34.0	1.11	0.61	2.00
RV/LVsa > 0,9	1914	24	48.0	56	52.0	1.25	0.72	2.20
Septal Bowing	1949	45	91.8	4	8.2	1.05	0.37	2.94
Septal flattening	1949	35	71.4	14	28.6	1.05	0.56	1.97
Aorta > 40 mm	1840	45	95.7	2	4.3	2.05	0.48	8.77
Pulmonary Trunk > 29 mm	1949	35	70.0	15	30.0	0.89	0.48	1.64
PT/Aorta > 1.0	1950	41	82.0	9	18.0	0.83	0.40	1.71
Cardiothoracic ratio > 0,50	1833	25	51.0	24	49.0	0.92	0.52	1.62
Backflow IVC	1754	28	65.1	15	34.9	0.91	0.48	1.72
Intrahepatic Reflux	1754	34	79.1	9	20.9	1.53	0.73	3.23
Backflow azygos vein	1947	42	84.0	8	16.0	0.64	0.30	1.37
Hospitalisation								
1 Month	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	62	68.9	28	31.1	0.97	0.61	1.52

RV/LVsa > 0,9	1914	47	52.2	43	47.8	1.06	0.69	1.61
Septal Bowing	1949	81	91.0	8	9.0	1.17	0.55	2.46
Septal flattening	1949	65	73.0	24	27.0	0.97	0.60	1.56
Aorta > 40 mm	1840	82	96.5	3	3.5	1.70	0.51	5.63
Pulmonary Trunk > 29 mm	1949	54	60.0	36	40.0	1.41	0.91	2.17
PT/Aorta > 1.0	1950	67	74.4	23	25.6	1.32	0.81	2.14
Cardiothoracic ratio > 0,50	1833	41	46.1	48	53.9	1.13	0.74	1.73
Backflow IVC	1754	48	61.5	30	38.5	1.07	0.67	1.70
Intrahepatic Reflux	1754	66	84.6	12	15.4	1.04	0.56	1.96
Backflow azygos vein	1947	76	84.4	14	15.6	0.61	0.34	1.09
1 Year	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	62	68.9	28	31.1	0.97	0.61	1.52
RV/LVsa > 0,9	1914	47	52.2	43	47.8	1.06	0.69	1.61
Septal Bowing	1949	81	91.0	8	9.0	1.17	0.55	2.46
Septal flattening	1949	65	73.0	24	27.0	0.97	0.60	1.56
Aorta > 40 mm	1840	82	96.5	3	3.5	1.70	0.51	5.63
Pulmonary Trunk > 29 mm	1949	54	60.0	36	40.0	1.41	0.91	2.17
PT/Aorta > 1.0	1950	67	74.4	23	25.6	1.32	0.81	2.14
Cardiothoracic ratio > 0,50	1833	41	46.1	48	53.9	1.13	0.74	1.73
Backflow IVC	1754	48	61.5	30	38.5	1.07	0.67	1.70
Intrahepatic Reflux	1754	66	84.6	12	15.4	1.04	0.56	1.96
Backflow azygos vein	1947	76	84.4	14	15.9	0.61	0.34	1.09
Major bleeding								
1 Month	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	7	53.8	6	46.2	1.84	0.62	5.51
RV/LVsa > 0,9	1914	7	53.8	6	46.2	0.99	0.33	2.95
Septal Bowing	1949	12	92.3	1	7.7	0.98	0.13	7.57
Septal flattening	1949	9	69.2	4	30.8	1.17	0.36	3.81
Aorta > 40 mm	1840	13	100.0	0	0.0	*0.99*	*0.99*	*1.00*
Pulmonary Trunk > 29 mm	1949	6	46.2	7	53.8	2.44	0.82	7.28
PT/Aorta > 1.0	1950	7	53.8	6	46.2	3.27	1.09	9.79
Cardiothoracic ratio > 0,50	1833	3	23.1	10	76.9	3.22	0.88	11.73
Backflow IVC	1754	7	53.8	6	46.2	1.46	0.49	4.37
Intrahepatic Reflux	1754	9	69.2	4	30.8	2.57	0.78	8.40
Backflow azygos vein	1947	9	69.2	4	30.8	1.51	0.46	4.91
1 Year	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	18	60.0	12	40.0	1.43	0.69	3.00
RV/LVsa > 0,9	1914	15	51.7	14	48.3	1.08	0.52	2.24
Septal Bowing	1949	25	83.3	5	16.7	2.39	0.90	6.34
Septal flattening	1949	21	70.0	9	30.0	1.13	0.51	2.47

Aorta > 40 mm	1840	27	96.4	1	3.6	1.68	0.22	12.71
Pulmonary Trunk > 29 mm	1949	11	36.7	19	63.3	3.66	1.73	7.74
PT/Aorta > 1.0	1950	18	60.0	12	40.0	2.57	1.23	5.37
Cardiothoracic ratio > 0,50	1833	10	34.5	19	65.5	1.84	0.85	3.97
Backflow IVC	1754	16	57.1	12	42.9	1.28	0.60	2.73
Intrahepatic Reflux	1754	23	82.1	5	17.9	1.25	0.47	3.31
Backflow azygos vein	1947	24	80.0	6	20.0	0.84	0.34	2.07
All Adverse Events								
1 Month	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	92	69.7	40	30.3	0.93	0.63	1.36
RV/LVsa > 0,9	1914	66	50.4	65	49.6	1.14	0.80	1.63
Septal Bowing	1949	121	92.4	10	7.6	0.97	0.50	1.89
Septal flattening	1949	96	73.3	35	26.7	0.95	0.64	1.42
Aorta > 40 mm	1840	120	96.8	4	3.2	1.56	0.55	4.44
Pulmonary Trunk > 29 mm	1949	75	56.8	57	43.2	1.63	1.14	2.34
PT/Aorta > 1.0	1950	96	72.7	36	27.3	1.46	0.98	2.17
Cardiothoracic ratio > 0,50	1833	58	45.0	71	55.0	1.19	0.83	1.70
Backflow IVC	1754	71	61.2	45	38.8	1.09	0.74	1.60
Intrahepatic Reflux	1754	94	81.0	22	19.0	1.37	0.84	2.22
Backflow azygos vein	1947	110	83.3	22	16.7	0.66	0.41	1.05
1 Year	n	no	%	present	%	OR	CI	CI
RV/LV > 1	1950	92	69.7	40	30.3	0.93	0.63	1.36
RV/LVsa > 0,9	1914	66	50.4	65	19.6	1.14	0.80	1.63
Septal Bowing	1949	121	92.4	10	7.6	0.97	0.50	1.89
Septal flattening	1949	96	73.3	35	26.7	0.95	0.64	1.42
Aorta > 40 mm	1840	120	96.8	4	3.2	1.56	0.55	4.44
Pulmonary Trunk > 29 mm	1949	75	56.8	57	43.2	1.63	1.14	2.34
PT/Aorta > 1.0	1950	96	72.7	36	27.3	1.46	0.98	2.17
Cardiothoracic ratio > 0,50	1833	58	45.0	71	55.0	1.19	0.83	1.70
Backflow IVC	1754	71	61.2	45	38.8	1.09	0.74	1.60
Intrahepatic Reflux	1754	94	81.0	22	19.0	1.37	0.84	2.22
Backflow azygos vein	1947	110	83.3	22	16.7	0.66	0.41	1.05