Age-Dependency of Cardiac Troponin I in the Prediction of Right Ventricular Dysfunction in Normotensive Pulmonary Embolism

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Abstract

Aim: Right ventricular dysfunction (RVD) and cardiac troponin are important tools for accurate risk stratification in acute pulmonary embolism (PE). We aimed to investigate the impact of age on the effectiveness of cardiac Troponin I (cTnI) for predicting RVD and adverse outcomes in normotensive PE.

Methods: A retrospective analysis of normotensive PE patients (2006-2011) was performed. Patients were subdivided in age groups of <70 years and ≥70 years, and their data was compared with the Mann-Whitney-U test. A logistic regression model for the association between cTnI>0.1 ng/ml and RVD was constructed. Age-dependent ROC curves with AUC and cut-off values were calculated for cTnI to predict RVD and cTnI to predict adverse outcomes as a combination of in-hospital death, pneumonia (on the basis of lung infarction) and RVD.

Results: A total of 129 normotensive PE patients (59.7% women) were subdivided into groups of <70 years and ≥70 years (61 vs. 68 patients). The mean cTnI values of the <70 years and ≥70 years groups were similar (0.12±0.29 vs. 0.16±0.34 ng/ml, P=0.127). RVD was more frequent in the older group (82.4% vs. 55.7%, P=0.00106). In the logistic regression model, cTnI >0.1 ng/ml was associated with RVD (OR 4.00, CI95%: 1.23-13.04, P=0.0213). The AUC for cTnI predicting RVD was 0.76 in the younger age group and 0.84 in the older age group. The AUC for cTnI predicting adverse outcomes was 0.66 in the younger age group and 0.81 in the older age group. The cTnI cut-off values (0.005 vs. 0.015 ng/ml) for the identification of RVD and adverse outcomes (0.0050 vs. 0.0150 ng/ml) were slightly lower in younger than in older patients.

Conclusions: The effectiveness of cTnI at predicting RVD as well as adverse outcomes is better in normotensive PE patients aged 70 years and older than in those younger than 70 years.

ABBREVIATIONS

AHA: American Heart Association; AUC: area under the curve; cTn: Cardiac Troponin; cTnI: Cardiac Troponin I; CT: Computed tomography pulmonary angiogram; DVT: Deep vein thrombosis; ESC: European Society of Cardiology; PAP: Systolic pulmonary artery pressure; PE: Pulmonary embolism; ROC: Receiver operating characteristic; RVD: Right ventricular dysfunction; SD: Standard deviation; V/Q scan: Ventilation-perfusion scan; YI: Youden Index

INTRODUCTION

Pulmonary embolism (PE) is a common and potentially life-threatening event [1-8]. The outcome of an acute PE event is closely related to patients’ initial hemodynamic statuses and cardiac adaptations [4,9-12]. Normotensive PE patients are affected by lower mortality rates than those with hypotension or shock [4, 6]. Additionally, right ventricular dysfunction (RVD) or elevated cardiac Troponin (cTn) levels in hemodynamically stable PE patients appear to impair patients’ prognosis significantly [4, 8-10,13]. In the systematic review by Sanchez et al. [13], the pooled unadjusted relative risk of RVD for the prediction of short-term mortality in normotensive PE patients was 2.4 (95%CI 1.3-4.4) [13]. The meta-analysis by Bettacini et al. [8] showed that elevated cTn values were significantly associated with elevated short-term mortality in PE patients (OR 5.2; 95CI...
Normotensive PE patients with elevated cTn levels had 5.9-fold higher mortality rates than those with normal cTn values (OR 5.90, 95%CI, 2.68-12.95) [8].

We hypothesized that cTn levels would be more effective for predicting the prognosis of older PE patients than younger patients. cTn is a sensitive marker for myocardial injury and necrosis [8,14-22]. In addition to acute coronary syndrome, elevated cTn levels could be caused by several other diseases, such as heart failure, cardiomyopathy, myocarditis, tachycardia, exacerbation of chronic lung diseases and acute PE [9,10,14,16,17,19-21,23-26]. In acute coronary syndrome, exacerbation of chronic lung disease, dilative cardiomyopathy as well as PE elevated cTn levels are connected with increased mortality [3,9,16-19,21,23,25,27]. Because we should expect more comorbidities in older PE patients than in younger PE patients, cTn levels should also be more frequently elevated in older PE patients than in younger patients. We hypothesized that it does not matter which comorbidity that occurs in combination with the PE event causes the cTn elevation, as the cTn elevation alone predicts a poorer prognosis.

The aim of this study was to investigate the impact of age on the effectiveness and cut-off levels of cardiac Troponin I (cTnI) for the prediction of RVD as well as for adverse outcomes in normotensive PE patients aged <70 years and ≥70 years.

A cut-off age value of 70 years was chosen because several studies emphasized that an age of 70 years and older has a great impact on increased PE incidence [28], on diagnostic performance [29,30] and on the outcomes of acute PE [31].

**PATIENTS AND METHODS**

**Study design**

We performed a retrospective analysis of patients with a confirmed diagnosis of acute normotensive PE who were treated at the Internal Medicine Department between May 2006 and June 2011.

**Enrolled subjects**

The patients were identified by performing a search of the hospital information system database for the diagnostic code (ICD-10 Code) for PE: I26.

The patients were eligible for inclusion in this analysis if they had a confirmed acute PE and were treated at the Internal Medicine Department of the hospital; an accurate echocardiography examination of the acute phase existed; the PE patients were hemodynamically stable (systolic blood pressure ≥90 mmHg) according to the definition of the ESC guidelines [4,32] and AHA statement [33]; the patients were at least 18 years old, and the diagnosis of acute PE was confirmed by an identified filling defect in the pulmonary artery system in a computed tomography pulmonary angiogram (CT) of the chest or if a positive venous ultrasound/phlebography of an extremity was consistent with deep venous thrombosis (DVT) in patients with typical symptoms of PE (chest pain or dyspnea) and a positive D-Dimer value or a scintigraphic ventilation-perfusion (V/Q) scan was read as the patient had a high probability for PE.

All of the radiographic images were analysed by experienced radiologists. Patients who did not fulfil the above criteria were not included in this study.

Although 182 patients with confirmed PE were identified in the hospital's information system between May 2006 and June 2011, only 129 patients met the inclusion criteria.

**Study groups**

According to the patients' age at the time of the acute PE event, the normotensive PE patients were subdivided in two age groups with approximately equal numbers of patients: PE patients younger than 70 years (61 patients) and PE patients 70 years and older (68 patients).

**Study parameters**

For this analysis, we focused on parameters including the patients' ages, cTnI and the echocardiographic parameters of RVD. All of the parameters were retrospectively assessed.

**Definitions**

To define RVD in transthoracic echocardiography for this analysis, a combination of the RVD criteria of the ESC guidelines [4,32] and AHA statement [33] were used [4,9,13,32]: The criteria included RV dilatation (a quotient of the end diastolic lateral-septal RV diameter divided by the end diastolic left ventricular lateral-septal diameter >0.9), abnormal motion of the interventricular septum, RV hypokinesis, tricuspid regurgitation and elevated systolic pulmonary artery pressure (PAP) of more than 30 mmHg.

Myocardial necrosis was defined as an elevation of cTnI >0.1 ng/ml.

The adverse outcome was defined as the combined endpoint of in-hospital death, pneumonia as a complication of lung infarction related to PE (treated with antibiotics), and/or RVD.

**Statistical analysis**

The age groups were compared with the Mann-Whitney-U test. The age-dependent ROC curves and Youden-Index (YI) for both age groups were calculated to test the effectiveness of cTnI for predicting RVD in a clinical diagnostic setting as well as to test the effectiveness of cTnI for predicting the above defined combined adverse outcome in both age groups. The ROC curve calculations were performed for each age group. The Wilcoxon-Mann-Whitney test was used to test the deviation of the ROC curve from the angle bisector.

YI is frequently used with the ROC curve to measure the effectiveness of a diagnostic marker and enables the selection of an optimal cut-off value for the marker [34,35].

Furthermore, a logistic regression model was performed to test the coherence of cTnI levels >0.1 mg/ml and RVD adjusted for age and gender.

The commercial software BIAS® (version 1.0.04) was used.
for data processing and statistical computing.

RESULTS

Although 182 patients with acute and confirmed PE were identified in the hospital’s information system between May 2006 and June 2011, only 129 patients met the inclusion criteria. A total of 53 PE patients were not included in this analysis because of hemodynamic instability or the lack of an accurate echocardiography examination.

The majority of the included PE patients were female (59.7% women and 40.3% men). The PE diagnoses were confirmed in 84.5% of the patients with CT, in 9.5% with a scintigraphic V/Q scan and in 5.4% of the patients with a positive venous ultrasound/phlebography of an extremity consistent with DVT and a positive D-Dimer. The median age of the 129 PE patients was 70.0 years (60.7/81.0). Over half (69.8%) of the normotensive PE patients had a RVD in the transthoracal echocardiographic examination.

According to the median age of the included PE patients, the normotensive PE patients were subdivided into an age group of PE patients <70 years and an age group of PE patients ≥70 years (61 and 68 PE patients, respectively).

In the logistic regression model, cTnI values >0.1 ng/ml were significantly associated with RVD (OR 4.00, CI 95%: 1.23-13.04, P=0.0213) independent of age and gender.

The median age of the PE patients <70 years was 60.0 years (49.5/65.0), while that of patients ≥70 years was 80.0 years (75.0/82.0). The mean cTnI values of the PE patients <70 years and ≥70 years were similar (0.12±0.29 ng/ml vs. 0.16±0.34 ng/ml, P=0.127). While 25.5% of the younger PE patients had cTnI values >0.1 ng/ml, the percentage in the older age group (31.2%) was higher (P=0.499). RVD (82.4% vs. 55.7%, P=0.00106) and adverse outcomes (88.2% vs. 73.8%, P=0.0358) were more frequently found in PE patients aged 70 years and older (Table 1).

In the younger age group, analysis of the ROC curve revealed an AUC of 0.763 for cTnI predicting RVD, with an optimal cut-off value of 0.005 ng/ml and a P=0.000637 for differentiation. The percentages of the misclassification, sensitivity, specificity, and positive and negative predictive values were 23.1%, 83.8%, 72.3%, 66.7% and 87.1%, respectively (Figure 1).

The calculated ROC analysis for cTnI predicting adverse outcomes revealed an AUC of 0.662, with a cTnI cut-off value of 0.015 ng/ml and a P=0.00691 for the differentiation of the patients of the older age group. The percentages of the misclassification, sensitivity, specificity, and positive and negative predictive values were 31.3%, 70.6%, 67.2%, 64.3% and 73.2%, respectively (Figure 3).

The ROC analysis for cTnI predicting adverse outcomes found an AUC of 0.813 with a cTnI cut-off value of 0.0150 ng/ml and a P=0.00691 for the differentiation of the patients of the older age group.

### Table 1: The PE patients’ characteristics. PE patients were subdivided into two groups: PE patients younger than 70 years and those aged 70 years and older. The results are presented as the mean values with standard deviations or the median values with percentiles or relative percentages. The groups were compared with the Wilcoxon-Mann-Whitney-U test.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PE patients aged younger than 70 years</th>
<th>PE patients aged 70 years and older</th>
<th>P-value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>61 (47.3%)</td>
<td>68 (52.7%)</td>
<td></td>
</tr>
<tr>
<td>Age at event (years)</td>
<td>60.0 (49.5/65.0)</td>
<td>80.0 (75.0/82.0)</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>32 (52.5%)</td>
<td>45 (66.2%)</td>
<td>0.114</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT actually</td>
<td>44 (72.1%)</td>
<td>21 (69.1%)</td>
<td>0.709</td>
</tr>
<tr>
<td>Cancer disease actually or in patient's history</td>
<td>7 (11.5%)</td>
<td>14 (20.6%)</td>
<td>0.163</td>
</tr>
<tr>
<td>Lung infarction with pneumonia</td>
<td>24 (39.3%)</td>
<td>31 (45.6%)</td>
<td>0.476</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>0 (0%)</td>
<td>1 (1.5%)</td>
<td>0.344</td>
</tr>
<tr>
<td>Laboratory marker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Troponin I (ng/ml)</td>
<td>0.12±0.29 ng/ml</td>
<td>0.16±0.34 ng/ml</td>
<td>0.127</td>
</tr>
<tr>
<td>myocardial necrosis (cTnI &gt;0.1 ng/ml)</td>
<td>16 (25.5%)</td>
<td>21 (31.2%)</td>
<td>0.499</td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVD</td>
<td>34 (55.7%)</td>
<td>56 (82.4%)</td>
<td>0.00106</td>
</tr>
<tr>
<td>Combined outcome parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse outcome, defined as a combination of in-hospital death, pneumonia on the basis of lung infarction or RVD</td>
<td>45 (73.8%)</td>
<td>60 (88.2%)</td>
<td>0.0358</td>
</tr>
</tbody>
</table>
Figure 1 The ROC curve and Youden Index with optimal cut-off points for cardiac Troponin I predicting right ventricular dysfunction in the younger age group of normotensive PE patients aged <70 years.

Figure 2 The ROC curve and Youden Index with optimal cut-off points for cardiac Troponin I predicting right ventricular dysfunction in the older age group of normotensive PE patients aged ≥70 years.

age group. The percentages of the misclassification, sensitivity, specificity, and positive and negative predictive values were 22.0%, 74.3%, 83.1%, 85.7% and 70.4%, respectively (Figure 4).

DISCUSSION

Rapid risk stratification in acute PE is crucial for deciding appropriate therapy management [36-38]. Echocardiography, CT and cTn are important tools for accurate risk stratification in normotensive patients with acute PE [4, 7,10,33,39]. It is well known that the presence of RVD as well as elevated cTn levels in normotensive PE appears to significantly alter the patients' prognoses [8-10,13,14].

In two previously published analyses, we found an association between advanced age and increased PE severity in normotensive PE patients [40] and an elevated right ventricular load during an acute PE event, which was evident from RVD and elevated systolic pulmonary artery pressure (sPAP), in a study population with normotension and hemodynamically unstable patients [41]. These results confirm the importance of age as a cofactor for the initial risk stratification process and prognosis in acute PE.

To our knowledge, this is the first analysis about the impact of age on the effectiveness and cut-off levels of cTnI for the prediction of RVD and adverse outcomes in normotensive PE patients. Our study confirmed a strong association between elevated cTnI values >0.1 ng/ml and RVD in normotensive PE. This is consistent with the literature [42-44]. While older normotensive
PE patients more frequently developed an RVD and showed more prevalent adverse outcomes in an acute PE event; the percentage of elevated cTnI values was not significantly different between the younger and older PE patients. This finding was in contrast with our hypothesis of a presumably higher frequency of cTnI elevation in older PE patients who are assumed to have more comorbidities.

However, the effectiveness of cTnI for predicting RVD was higher in PE patients aged ≥70 years than in those aged less than 70 years, but the AUC for the effectiveness of this parameter was acceptable in both. The cut-off values were very low in both age groups. For the prediction of adverse outcomes, defined as a combination of in-hospital death, pneumonia (on the basis of lung infarction) or RVD, the effectiveness of cTnI was distinctly better in the older age group.

These calculated age-dependent AUC values for cTnI predicting a RVD of 0.76 for the younger and 0.84 for the older PE patients are both slightly higher than the non-age-dependent AUC values published by Henzler et al. [45] and Logeat et al. [46] of 0.70 and 0.72 for cTnI predicting RVD [45,46]. In a previous
analysis of the normotensive PE patients in our study, the AUC for cTnI predicting RVD independent of age was 0.80 [47].

The age-dependent cTnI cut-off levels for predicting RVD were low: >0.005 ng/ml in the younger age group and >0.015 ng/ml in the older age group. In a previous analysis of these normotensive PE patients, a cut-off level of >0.01 ng/ml independent of age was found [47]. In contrast, Henzler et al. [45] published a cTnI cut-off value of 0.07 ng/ml for predicting RVD in acute PE [45].

Our study results emphasize that the effectiveness of cTnI for predicting RVD and adverse outcomes is better in PE patients aged 70 years or older than in younger normotensive PE patients aged less than 70 years.

The results seem to indicate that the prognosis of older PE patients with elevated cTn is poorer than the prognosis of younger PE patients with elevated cTn. We suggest that the myocardial reserve of healthy muscle cells is larger in younger PE patients than in older patients. Therefore, the myocardial damage observed in elevated cTn levels is much more dangerous in older PE patients than in younger patients, and cTn elevations are more important in the risk stratification of older PE patients compared to younger patients.

Limitations and strengths

The limitations of this study are the small number of included patients and the retrospective study design. We are not able to draw conclusions regarding the outcomes after dismissal from the hospital. Moreover, we did not assess comorbidities, such as chronic lung disease, heart failure, coronary artery disease and diabetes, and therefore could not analyse the effect of these comorbidities on the prognosis and risk stratification process in acute PE patients. Despite these limitations, we were able to find answers to the main questions of the analysis.

ACKNOWLEDGMENTS

All of the authors contributed to the study conception, design, and data acquisition, analysis and interpretation.

REFERENCES