

ORIGINAL ARTICLE

Impact of cancer on the effectiveness of cardiac Troponin I to predict right ventricular dysfunction in acute pulmonary embolism

Karsten Keller^{1,2}, Martin Geyer¹, Johannes Beule³, Meike Coldewey^{1,2}, Jörn Oliver Balzer^{4,5*} & Wolfgang Dippold^{3*}

1 Department of Medicine II, University Medical Center Mainz, Johannes Gutenberg-University Mainz, Mainz, Germany

2 Center for thrombosis and hemostasis, University Medical Center Mainz, Johannes Gutenberg-University Mainz, Mainz, Germany

3 Department of internal medicine, St. Vincenz and Elisabeth Hospital Mainz (KKM), Mainz, Germany

4 Department of Radiology and Nuclear medicine, Catholic Clinic Mainz (KKM), Mainz, Germany

5 Department of Diagnostic and Interventional Radiology, University Clinic, Johann Wolfgang Goethe-University Frankfurt/Main, Mainz, Germany

Keywords

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Correspondence

Karsten Keller, Department of Medicine II, University Medical Center Mainz, Johannes Gutenberg-University Mainz, Langenbeckstr. 1, 55131 Mainz, Germany.

Tel: +49 6131 17 0

Fax: +49 6131 17 6672

Email: Karsten.Keller@unimedizin-mainz.de

*Both authors are co-shared last authors.

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Introduction

Cancer is connected with an increased risk of venous thromboembolism (VTE) and of its two VTE entities, pulmonary embolism (PE) and deep vein thrombosis (DVT).^{1,2} Cancer patients showed a four to seven-fold higher risk of developing a venous thromboembolic event in comparison to individuals without cancer.^{2–6} In addition, VTE is the second leading cause of death in patients with cancer, behind the cancer disease itself.² Therefore, VTE events impair the prognosis of cancer patients substantially.^{2,3,7–14}

We aimed to investigate the impact of cancer on the effectiveness of cardiac Troponin I (cTnI) to predict right ventricular dysfunction (RVD) in acute PE.

Abstract

Background: Deep vein thrombosis (DVT) and pulmonary embolism (PE) are connected with a poor outcome in cancer patients. We aimed to investigate the impact of cancer on the effectiveness of cardiac Troponin I (cTnI) to predict right ventricular dysfunction (RVD) in acute PE.

Methods: We retrospectively analyzed the data of 182 patients with confirmed PE. PE patients were subdivided into two groups: (i) with concomitant active cancer disease or history of cancer, and (ii) without known cancer. Receiver operating characteristic (ROC) curves with area under the curve (AUC) was calculated for cTnI predicting RVD and related cut-off levels for both groups.

Results: Thirty-seven PE patients (20.3%) had an active cancer disease or a history of cancer. In contrast, 145 (79.7%) of the included PE patients did not have a known cancer disease or a history of cancer. In the PE group with cancer, analysis of the ROC curve showed an AUC of 0.76 for cTnI predicting RVD with an optimal cut-off value of 0.04 ng/mL; the risk of misclassification was 25.0%. In the PE group without cancer, AUC was 0.81 for cTnI predicting RVD with an optimal cut-off value of 0.015 ng/mL; the risk of misclassification was 24.9%.

Conclusions: cTnI is effective for predicting RVD in PE patients with and without cancer. However, the effectiveness of cTnI to predict RVD was higher in PE patients without cancer than in those with cancer or a history of cancer.

Methods

Study design

A retrospective analysis of all PE patients who were treated at the internal medicine department between May 2006 and June 2011 was performed. We reviewed the medical records of 182 PE patients for anamnesis (symptoms and history), examinations (transthoracic two dimensional-echocardiography, computed tomography [CT], ventilation-perfusion [V/Q] scan, duplex ultrasound of the leg veins) and laboratory parameters.

In studies in Germany with a retrospective analysis of diagnostic standard data, no ethic statement is required.

Enrolled subjects

Patients were eligible for our analysis if they were at least 18 years old, treated in the internal medicine department of the hospital, and had a confirmed acute PE. PE patients were identified through a search on the hospital information system database for the diagnostic code of PE (ICD-10-Code I26).

PE diagnosis was confirmed if the patients had: a computed pulmonary angiogram of the chest with an identified filling defect in the pulmonary artery system; or a scintigraphic V/Q scan read as high probability for PE; or the patients showed a positive venous ultrasound or phlebography of an extremity consistent with DVT in patients with typical symptoms of PE (chest pain or dyspnoea) and positive D-dimer.

All of the radiographic images were analysed by experienced radiologists. If a PE diagnosis was not confirmed by these criteria, the patients were not included in this study.

Study groups

In this study, PE patients were subdivided into two groups:

- 1 PE group with cancer:** PE patients with concomitant active cancer disease or a history of cancer. Types of cancer were not differentiated.
- 2 PE group without cancer:** PE patients without concomitant known cancer or a history of cancer.

Laboratory examinations

Our analysis focused on cTnI level. Myocardial necrosis in acute PE was defined as an elevation of cTnI value >0.1 ng/mL.

Definition of right ventricular dysfunction

Right ventricular dysfunction was defined as a right ventricular (RV) enlargement corresponding to a quotient of the RV septal-lateral diameter divided by a left ventricular septal-lateral diameter of >0.9 in four chamber view in a CT or transthoracic echocardiography.¹⁵ Moreover, RVD was defined as RV hypokinesia and tricuspid regurgitation in echocardiography.¹⁵

Statistics

We compared the cTnI values of both groups with a Wilcoxon-Mann-Whitney-test. The receiver operating characteristic (ROC) curves with area under the curve (AUC) and Youden-Index (YI) with cut-off values were calculated to test the effectiveness of cTnI to predict a RVD in both groups. ROC curve and YI are frequently used tools to measure the

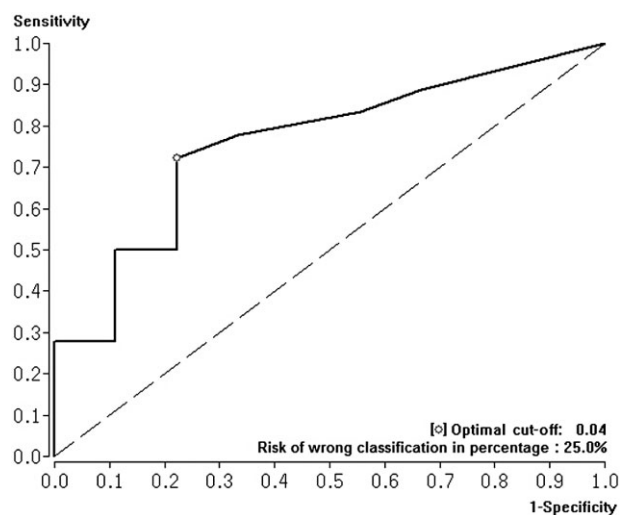


Figure 1 Receiver operating characteristic curve and Youden-Index with optimal cut-off point for cardiac Troponin I predicting right ventricular dysfunction in pulmonary embolism patients with active cancer or history of cancer.

effectiveness of diagnostic markers and enable the selection of an optimal cut-off value for this marker.^{16,17} In our study, the calculated YI cut-off value of cTnI was used to predict RVD in PE.

The commercial software BIAS (version 10.04, Epsilon-Verlag, Darmstadt; Dr. H. Ackerman, University Medical Center, Frankfurt, Germany) was used for data processing and statistical computing.

Results

A total of 182 PE patients (61.5% women) met the inclusion criteria and were included in this study. PE diagnosis was confirmed in 85.7% by CT, in 10.5% with V/Q scan, and in 3.8% by positive venous ultrasound or phlebography of an extremity consistent with DVT, in patients with typical symptoms of PE (chest pain or dyspnoea) and positive D-dimer value.

An active cancer disease or a history of cancer was reported in 37 PE patients (20.3%). In contrast, 145 (79.7%) of the included PE patients did not have a known cancer disease or a history of cancer.

The cTnI values were not significantly different between the PE patients with cancer or a history of cancer and in PE patients without a cancer diagnosis (0.15 ± 0.22 vs. 0.12 ± 0.29 , $P = 0.16$).

In the PE group with cancer, analysis of the ROC curve showed an AUC of 0.76 for cTnI predicting RVD with an optimal cut-off value of 0.04 ng/mL. The risk of an incorrect classification was 25%, sensitivity 74%, and specificity 76% (Fig 1).

In the PE group without cancer, the AUC was higher (0.81) with an optimal cut-off value of 0.015 ng/mL and compa-

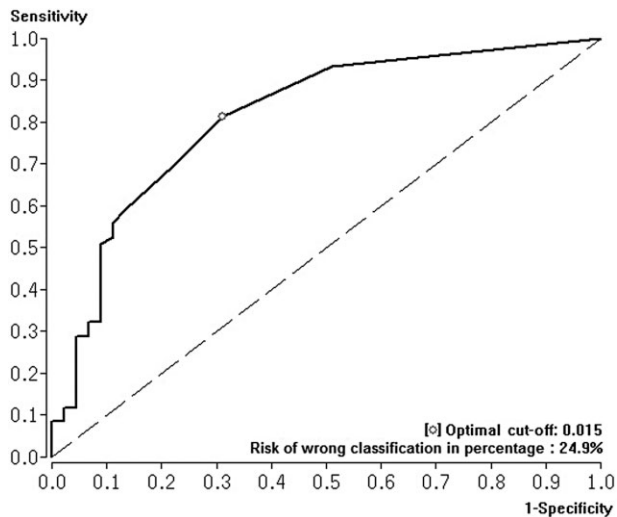


Figure 2 Receiver operating characteristic curve and Youden-Index with optimal cut-off point for cardiac Troponin I predicting right ventricular dysfunction in pulmonary embolism patients without known cancer or history of cancer.

rable risk of misclassification (25%). The sensitivity and specificity of the test was 79% and 72%, respectively (Fig 2).

Discussion

Cancer, as well as cancer related therapies, such as surgery, chemotherapy or supportive regimes, are well-known risk factors for both PE and DVT.^{1,3,6,7,9,10,18–24} PE events are more frequent among cancer patients than in individuals without cancer.^{25,26} Additionally, VTE events are strongly connected with poorer outcome and shorter survival in cancer patients.^{2,3,7–9,27–32}

To our knowledge, there have been no previous study results available about the impact of cancer on the effectiveness of cTnI to predict RVD in acute PE.

Apart from the impact of VTE on the prognosis of cancer patients, it is well known that RVD, as well as elevated (cTn) levels in PE patients, appears to alter patient outcome significantly.^{24,33–46} Both risk stratification markers, cTnI and RVD, are important for outcome prediction in acute PE.

Our study results reveal that cTnI is effective in predicting an RVD in PE patients with cancer, a history of cancer, and in PE patients without a cancer diagnosis. However, the effectiveness of cTnI to predict RVD was higher in PE patients without a cancer diagnosis than in those with cancer or a history of cancer. The AUC for cTnI to predict RVD was higher and the cut-off value to differentiate between PE patients with and without RVD was lower in PE patients without cancer than in PE patients with active cancer or a history of cancer.

In our study, the cTnI cut-off levels for predicting RVD in PE patients without cancer (>0.015 ng/mL), as well as in PE

patients with cancer (>0.04 ng/mL), were low, below the published cut-off value reported by Henzler *et al.* (>0.07 ng/mL).⁴⁷ Kucher *et al.* reported a cut-off value of 0.06 ng/mL for prediction of an adverse outcome.⁴⁸ Konstantinidis *et al.* (0.04 ng/mL and 0.07 ng/mL), Giannitsis *et al.* (0.10 ng/mL), and Janata *et al.* (0.09 ng/mL) described higher cut-off values for prediction of in-hospital death.^{37,49–51} In consensus with our results, Pruszczyk *et al.* and Ozsu *et al.* (each with 0.01 ng/mL) reported similar low cut-off values for prediction of in-hospital death and death in the first 30 days after a PE event.^{50,52–54}

Our study results revealed that the biomarker cTnI for prediction of RVD was effective in both groups. The AUC values in both PE patients with cancer (0.76) and without cancer (0.81) were beyond the published AUC values of Henzler *et al.* (0.70) and Logeart *et al.* (0.72).^{47,55} In contrast, Janata *et al.* reported a higher AUC (0.92) for cTnT predicting in-hospital death.⁵¹ Kucher *et al.* also reported a higher AUC (0.89) for cTnI predicting an adverse outcome than in our study for predicting RVD.⁴⁸ Henzler *et al.* reported a similar sensitivity and specificity to ours.⁴⁷

The main limitations of this study were the small sample size, the single center design, and the retrospective data assessment; therefore, follow-up examinations and strong outcome endpoint data after initial hospitalization are missing. Moreover, it is not known how many of the included PE patients without known active cancer or a history of cancer developed cancer after the PE event, which was not diagnosed up to their dismissal. It has been established that patients with acute VTE show an increased risk of occult malignancy.^{6,32,56–60}

Conclusions

cTnI is effective in predicting a RVD in PE patients with cancer, a history of cancer, or without a cancer diagnosis. However, the effectiveness of cTnI to predict RVD was higher in PE patients without a cancer diagnosis than in those with cancer or a history of cancer.

Disclosure

No authors report any conflict of interest.

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