Evaluation of Risk Stratification Markers and Models in Acute Pulmonary Embolism: Rationale and Design of the MARS-PE (Mainz Retrospective Study of Pulmonary Embolism) Study Programme

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ABSTRACT

An acute pulmonary embolism (PE) is a crucial event in patients' life and connected with serious morbidity and mortality. Regarding a high case-fatality rate, early and accurate risk-stratification is crucial. Risk for mortality and complications are closely related to hemodynamic stability and cardiac adaptations. The currently recommended risk-stratification approach is not overall simple to use and might delay the identification of those patients, who should be monitored more closely and may treated with more aggressive treatment strategies. Additionally, some risk-stratification criteria for the imaging procedures are still imprecise. Summarized, the search for the most effective risk-stratification tools is still ongoing and some diagnostic criteria might have to be refined.

In the MAinz Retrospective Study of Pulmonary Embolism (MARS-PE), overall 182 consecutive patients with confirmed PE were retrospectively included over a 5-year period. Clinical, echocardiographic, functional and laboratory parameters were assessed. The study was designed to provide answers to some of the mentioned relevant questions.

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INTRODUCTION

An acute pulmonary embolism (PE) is a crucial event in a patients' life accompanied by serious morbidity and death worldwide (1, 2). Annual PE incidence has been reported ranging between 23 and 69 cases per 100,000 people in the general population (3).

Clinical presentation of acute PE comprises a wide spectrum from asymptomatic incidental finding to typical symptoms such as chest pain, dyspnoea, hemoptysis, collapse, syncope that may accompanied by hypotension, right heart failure, right heart infarction, cardiogenic shock, resuscitation and sudden cardiac death (2, 4–6). Regarding a high case fatality rate ranging between 1% and 60% (4, 7), promptly, early and accurate risk stratification in respect to adverse outcome of patients with an acute PE event is crucial (2, 6, 8, 9).

Pathophysiologically, PE is caused by thrombotic material occluding the pulmonary arteries (10–12). If occlusion affects more than 30–50% of the pulmonary arterial bed, hemodynamically consequences of acute PE have to be expected. Right ventricle (RV) under normal conditions has a narrow range to handle an acute afterload increase. An abrupt afterload increase, seen in acute PE events, frequently results in RV overload with an elevated RV wall tension and right ventricular dysfunction (RVD) (10, 12–18). Depending on PE severity and intensity of right heart overload, RVD, coronary under-perfusion, decline of cardiac output, myocardial injury, cardiac shock, right heart failure and PE-related death could be the results (12–14, 16, 19, 20).

Risk for mortality and complications in acute PE events are closely related to (initial) hemodynamic stability as well as cardiac adaptations (12–17, 21–24). Therefore, a risk-related classification of acute PE severity has been recommended to guide risk-adjusted management of patients; the short-term adverse outcome of acute PE is dependent on PE severity status stratified by clinical findings during the acute phase, results of imaging procedures and biomarker measurements indicating for RVD, but also on the factors age and comorbidities (determining the reserve capacity of the cardio-pulmonary system) (2, 12). Haemodynamically unstable PE patients are classified as high-risk PE (2, 12) or massive PE (9), with high mortality rate (>15% in the first 30 days after PE event) (11, 12, 16, 21). Haemodynamically stable PE patients (non-high-risk or non-massive PE patients) can be subdivided into those with RVD and/or positive biomarkers, such as cardiac troponin (cTn) and/or brain natriuretic peptides (BNP), and those without both (11, 12). Haemodynamically stable PE patients with RVD or positive biomarker levels (submassive PE stadium) show an intermediate risk, with a short term mortality of 3–15% (10, 12, 16, 21). Haemodynamically stable PE patients without RVD and without an elevated biomarker levels (low-risk PE) reveal the best prognosis, with a short term mortality rate <2% (10–12, 14, 21). During the past years, recommendations for PE risk stratification were adapted, because it became obvious that laboratory biomarkers alone were not sufficient for risk stratification (12). Several risk stratification markers, algorithms and scores have been developed to identify those patients, who are at higher risk for the development of adverse events and especially mortality (2, 25).

Therefore, PE classification approach was refined and improved by the (simplified) Pulmonary Embolism Severity Index (PESI) implemented in the recommendations of the 2014 ESC guideline (2). Summarized, risk stratification comprises the factors age, gender, symptoms, clinical examination markers such as temperature, altered mental status, hypoxia, respiratory rate, blood pressure and heart rate, comorbidities, VTE risk factors, as well as biomarkers including especially markers of heart strain and myocardial injury and imaging procedures focusing on the adaptations of the heart and the burden of PE (2).

Several diagnostic tools and biomarkers are already in use for early risk stratification in non-high-risk PE patients. Especially, biomarker testing can improve inpatient management, enabling better outcomes in acute PE (21). cTn and BNP are well established markers for risk stratification in acute PE, and their elevations are closely connected with an increased mortality rate (11–18, 22, 24, 26–28). Besides these two biomarkers, several other biomarkers have been identified for prediction of poor outcome (9, 12, 21, 29).

More than 80% of the PE patients are normotensive (30, 31), and between 25% and 55% of the normotensive PE patients have an identified RVD in echocardiographic or computer-tomographic examinations (30, 32). RVD in hemodynamically stable PE patients appears to alter patients' prognosis significantly (30) and right ventricular failure (RVF) with RVD are the most common causes of death in the first 30 days after the PE index event (33). Therefore, morphologic adaptations of the heart identified in imaging procedures are important findings in risk stratification process. Especially, the prognostic value of echocardiography for risk stratification in hemodynamically stable PE patients was confirmed in several studies (30–36). Echocardiography is currently the mainstay examination for assessment of RVD in patients with PE (32, 37). Although several studies confirmed that RVD is connected with higher rates of death, recurrent PE events and complications (9, 12, 30, 32–34, 36), definitions of PE-induced RVD criteria vary markedly in different studies (30–32, 37) and recommendations for detection of RVD in the guidelines for the echocardiographic criteria for the assessment of RVD in acute PE are not precisely defined (2, 9, 12).

Another often used examination tool is the electrocardiography (ECG). In general, all patients with chest pain, dyspnoea, syncope or collapse should obtain an ECG in the emergency department immediately after first medical contact (38–40). This ECG is primarily used to exclude an acute ST-segment elevation myocardial infarction and arrhythmias (38, 39), but is also an important diagnostic tool in PE (40, 41).

Although this study focus on the in-hospital course of the PE patients and PE has traditionally been assumed as acute disease, also the long-term course of PE survivors can be complicated by recurrent venous thromboembolism events (VTE), development of post-thrombotic syndrome after accompanying deep venous thrombosis (DVT), chronic thromboembolic pulmonary hypertension (CTEPH), and treatment complications such as bleeding

events caused by anticoagulant therapy and might be accompanied by a higher risk for artherosclerotic events (42–45). Despite these established long-term sequelae, studies have consistently demonstrated, that approximately 1/2 of the patients suffer from functional limitations or decreased QoL and rare CTEPH seems to be only the most extreme expression (46).

UNANSWERED QUESTIONS IN THE ACUTE PHASE OF PE AND OBJECTIVES OF THIS STUDY

An acute PE is a frequent cause of death and serious disability (2). Risk of adverse outcome during the in-hospital phase varies widely depending on the clinical severity and presence of RVD and elevated biomarkers (2, 25).

The currently recommended risk stratification approach is in part not simple to use and might delay the resulting risk classification and identification of those patients, who should be monitored more closely and might undergo more aggressive treatment strategies such as systemic thrombolysis. Although it is widely easy to identify the high-risk PE patients, further risk classification in normotensive PE patients depends on imaging procedure, biomarkers and the sPESI or PESI according to the ESC guideline of the year 2014 (2). This approach for risk stratification in normotensive patients might delay the risk classification and is complicated for physicians in the emergency room with small time slots for each patient.

Additionally, some of the criteria, especially for the imaging procedures, remained imprecise.

Therefore, the search for the most effective risk stratification tools is still ongoing and diagnostic imaging criteria might have to be refined.

The MAinz Retrospective Study of Pulmonary Embolism (MARS-PE) study programme (Figure 1) for the evaluation of risk stratification process in acute PE enrolled consecutive patients with confirmed PE retrospectively over a 5-year period. Clinical, echocardiographic, functional and laboratory parameters were assessed. MARS-PE has been designed to provide answers to the above relevant remaining questions regarding morbidity and mortality after PE.
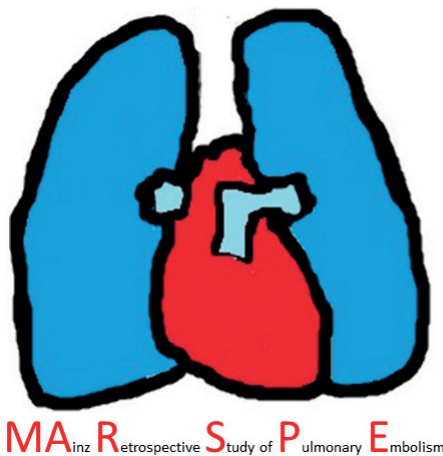

Fig. 1 MAinz Retrospective Study of Pulmonary Embolism (MARS-PE) Logo.

STUDY POPULATION

A total of 182 consecutive patients with acute, objectively diagnosed PE were retrospectively included in MARS-PE on the basis of the eligibility criteria listed in Table 1. The MARS-PE aimed to include PE all-comers with PE, irrespective of clinical severity, RVD, and size or extent of pulmonary emboli. All included patients were treated at the Department of Internal Medicine of the St. Vincenz and Elisabeth hospital of the Catholic Clinic Mainz (Mainz, Germany) between May 2006 and June 2011. The patients were found by a search of the hospital information system database for the diagnostic code of PE (ICD-Code: I26).

All CT, scintigraphic and phlebography images were analysed by experienced radiologists. If the diagnosis of PE was not confirmed by the criteria above, the patient was not included in this study.

Tab. 1 Eligibility criteria.

Inclusion Criteria	Exclusion Criteria
– Objectively confirmed diagnosis of acute PE by identified filling defect in the pulmonary artery system on a computed tomography pulmonary angiogram (CT) of the chest, a scintigraphic ventilation-perfusion (V/Q) scan read as high probability for PE or positive venous ultrasound/phlebography of an extremity consistent with deep venous thrombosis (DVT) in patients with typical symptoms of PE (chest pain or dyspnoea) and positive D-dimer – Age ≥18 years – Patients were treated in the Department of Internal Medicine in the St. Vincenz and Elisabeth hospital of the Catholic Clinic of Mainz, Mainz, Germany	– Patients in whom the diagnosis of PE was not confirmed by the examinations – Patients younger than 18 years old – Previous enrollment in this study

DEFINITIONS

MYOCARDIAL INJURY

According to the AHA scientific statement from 2011, myocardial necrosis was defined as a cardiac troponin I (cTnI) elevation >0.4 ng/ml (9).

RIGHT VENTRICULAR DYSFUNCTION (RVD)

RVD was defined according to the AHA scientific statement (9) as a quotient of right ventricular (RV) septal-lateral diameter / left ventricular (LV) septal-lateral diameter >0.9 in the four-chamber view on transthoracic echocardiography or CT (9). Moreover, the RVD was defined as RV hypokinesis and tricuspid regurgitation by echocardiography (9). For some analyses a sPAP > 30mmHg was additionally included in the RVD criteria.

HIGH-RISK PE SEVERITY STATUS

PE patients with a systolic blood pressure <90 mmHg at admission were classified as high-risk PE according to the definition from the recent and current ESC guidelines (2, 12) and the AHA scientific statement (9).

INTERMEDIATE-RISK (= SUBMASSIVE) PE SEVERITY STATUS

According to the recent, but at this time valid ESC guidelines from 2008 on the diagnosis and management of acute pulmonary embolism (12) and the AHA scientific statement for management of massive and submassive PE, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension from 2011 (9) the non-high-risk PE patients were subdivided in 2 groups with regard to RVD and cTnI level. PE patients with RVD or pathological cTnI levels were included in the submassive PE group with intermediate risk. Patients without RVD and without elevated troponin levels were classified as non-massive PE group with low risk.

STUDY PARAMETERS

The retrospective analysis of PE patients focused on anamnesis with medical history as well as clinical, laboratory, ultrasound, echocardiographic and CT examination results.

PATIENT OUTCOMES

We analyzed the study outcome parameters in all included PE patients or in those non-high-risk PE patients, who were hemodynamically stable (normotensive) and among these, especially in those normotensive patients with an accurate transthoracic echocardiography, as appropriate.

The proposed study endpoints comprised the following: i) all-cause in-hospital mortality as well the surrogate markers ii) RVD, iii) myocardial injury and iv) PE severity status according to the ESC guidelines from 2008 (12). The study endpoints of RVD, myocardial injury as well as the PE severity status according to the ESC guidelines from 2008 (12) are established surrogate markers of poorer outcome in the acute course after the PE event and therefore, were chosen as proposed study endpoint parameters.

STATISTICAL ANALYSIS

Descriptive statistics for the relevant baseline comparisons of the respective baseline-groups were provided with mean ± standard deviation, median and interquartile range (IQR), depending on Gaussian or skewed distribution, or absolute numbers and corresponding percentages. Baseline variables of the groups were compared using the Wilcoxon-Whitney U test, the Students' T-Test or in categorical variables with Fisher's exact or Chi² test, as appropriate.

We calculated uni-variate and (if necessary to test the independence) multi-variate logistic regression models to examine the associations between risk stratification markers and the study outcome markers.

Receiver operating characteristic (ROC) curves with areas under the curves (AUC) and Youden indices were calculated to test the effectiveness of markers to predict outcome parameters in acute PE. The Wilcoxon-Mann-Whitney test was used to test the deviation of the ROC curve from the angle bisector.

Although some of the statisticians recommend to calculate a post-hoc power analysis (47), we are in accordance with the majority of the statisticians of the opinion that a post hoc power analysis is inappropriate for the evaluation of study results (48, 49). Therefore, we did not calculate such a post-hoc power calculation.

The software SPSS® (version 22.0; SPSS Inc., Chicago, Illinois), R version 2.14.1 from R Development Core Team (2011) (R Foundation for Statistical Computing, Vienna, Austria) and the commercially available software BIAS® (version 10.04; epsilon press, Frankfurt, Germany) were used for computerized analysis. Only P values of <0.05 (two-sided) were considered to be statistically significant.

ETHICAL ASPECTS

The requirement for informed consent was waived as we used only anonymized retrospective data routinely collected during the health screening process. Studies in Germany involving a retrospective analysis of diagnostic standard data do not require an ethics statement.

The study was conducted in St. Vincenz and Elisabeth Hospital Mainz (KKM).

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