

BMJ Open Long-term outcomes in patients with acute pulmonary embolism after in-hospital treatment: study protocol of the prospective Lungenembolie Augsburg Studie (LEA study)

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ABSTRACT

Introduction Acute pulmonary embolism (PE) is a frequent life-threatening event and an important cause of hospitalisation, morbidity and mortality worldwide. Limited information on the long-term course of PE patients is available so far. The Lungenembolie Augsburg study will provide a view on the predisposing and PE-provoking factors, diagnostic procedures and short as well as long-term treatment options. Especially, the data on the long-term course of the disease—in combination with omics data obtained in biospecimens—will generate new knowledge regarding triggers, disease progression, treatment, long-term sequelae, prognosis and prevention of disease recurrence.

Methods and analysis In this prospective study, we will include about 1000 patients admitted to the university hospital of Augsburg, aged 18 years and older with a confirmed diagnosis of acute PE. At baseline, demographic information, symptoms on presentation, delay in diagnosis, predisposing and PE-provoking factors, comorbidity, quality of life, symptoms of anxiety and depression, information on invasive and non-invasive treatment procedures, complications and laboratory parameters will be collected. During the hospital stay, 30 mL blood will be collected from the patients, processed, aliquoted and frozen at -80°C . In a subgroup of patients, an eight-channel polygraphy will be carried out to assess sleep-disordered breathing. All study participants will be followed up for 60 months via postal questionnaires or telephone interviews after hospital discharge. Long-term survival, bleeding complications and PE recurrence during the follow-up are the primary study outcomes. To identify risk factors and determinants associated with these outcomes, confounder-adjusted Cox-regressions will be used for modelling and to estimate relative risks. Effect modification by age and sex will be examined.

Ethics and dissemination The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (Date of approval: 1 August 2017, Reference number: 17-378). Study results will be presented at national and international conferences and published in peer-reviewed scientific journals.

Strengths and limitations of this study

- This observational study will assess comprehensive information about the long-term course of patients after acute pulmonary embolism and on the health-care provided to these patients.
- Data are collected prospectively and systematically during the hospital stay and via postal questionnaires afterwards.
- The collection of biosamples in connection with socioeconomic, clinical, treatment and outcome data will allow further research regarding different patient subgroups to improve primary and secondary prevention strategies.
- A limitation of the study is that analyses are not based on randomised treatment assignments.
- Another potential weakness could be the lost to follow-up in the cohort, which may often lead to bias.

INTRODUCTION

Acute pulmonary embolism (PE) is a frequent life-threatening event, and mostly a consequence of deep vein thrombosis. It is the third most frequent cardiovascular syndrome after myocardial infarction and stroke^{1 2} and remains an important cause of hospitalisation, morbidity and mortality worldwide. In a prior study analysing WHO mortality data from 1998 to 2004, it could be shown that in most countries PE mortality decreased over time, but there was a continuous increase in Germany.³ Based on routine healthcare data, between 2005 and 2007, a total of 67 351, 69 234 and 71 223 PE cases International Classification of Diseases-10th revision-Germany (ICD-10: I26) were documented yearly as the main or secondary diagnosis in German hospitals, respectively.⁴ The incidence of the disease rises with age and due to the ageing Western societies, it can be expected that a

larger number of patients will be diagnosed with PE in the future.⁵ Patients with PE have a case fatality rate of 7%–11%, and approximately 10% of symptomatic PE cases are fatal within the first hour after symptom onset.^{6,7}

The treatment of acute PE is usually inpatient with anti-coagulants and possibly thrombolytic therapy. In patients in whom thrombolytic drugs are contraindicated, catheter-assisted thrombus removal or surgical pulmonary embolectomy may be considered.⁸ After discharge, treatment with anticoagulants is continued for at least three further months after the first episode of PE. In some conditions like PE recurrence, extended anticoagulant treatment is indicated. Nowadays non-vitamin K-dependent oral anticoagulants (NOACs) are established for the treatment and secondary prophylaxis of acute PE.⁹

While prior studies mainly focused on the short-term outcomes, there is limited information on the long-term course of patients after acute PE. However, some observational studies and randomised cohorts reported a high long-term mortality. For example, in a retrospective study including more than 1000 persons with PE, Ng *et al* found an all-cause mortality rate of about 35% after a follow-up of 4 years.¹⁰ A recent meta-analysis of publications on the long-term consequences of LE showed that patients have to expect an increased risk of death (11%) and disease recurrence (6%) after primary therapy.¹¹ Eighteen per cent had persistent right-ventricular dysfunction and 11% suffered from respiratory distress, which severely impairs performance in everyday life.¹¹ The quality of life of patients with acute PE was significantly reduced compared with the general population¹¹ and a more frequent onset of mental disorders such as depression, anxiety disorder and post-traumatic stress disorder was described as well.¹² It is unknown so far whether any particular treatment strategy can reduce these long-term outcomes and disease burden among patients with acute PE.

The Lungenembolie Augsburg (LEA) study will provide a view on the predisposing and provoking factors, comorbidity, diagnostic procedures, treatment options and the long-term course of PE. Furthermore, new knowledge regarding triggers, disease progression, treatment, long-term sequelae, prognosis and prevention of the disease will be generated by using information on omics data gained from different biological samples. The impact of predisposing factors for disease recurrence and comorbidities will be prospectively elucidated, helping to improve primary and secondary prevention strategies. In addition, the study will allow to assess subgroup differences regarding treatment effects and will contribute to our knowledge on patient outcomes such as long-term survival, bleeding complications and disease recurrence. Also, the evaluation of patient-oriented outcomes, such as quality of life and the burden of depression and anxiety disorders in PE patients, will be of advantage for the patients. Factors, which are associated with late recurrence of PE or long-term sequelae like chronic thromboembolic pulmonary hypertension (CTEPH), will be elucidated. This will help to identify patient subgroups

who could potentially benefit from a long-term anticoagulation therapy. Finally, with this observational study, knowledge about the safety and harm associated with the use of modern anticoagulation drugs in regular practice and in particular in cancer patients, who are usually not included in randomised control trials, will be generated. Thus, the study will provide a comprehensive view on the natural course of the disease and on the healthcare provided to patients with acute PE.

OBJECTIVES

Primary outcome

To estimate PE-related long-term survival, treatment-related bleeding complications, development of chronic thromboembolic pulmonary hypertension, and the frequency, circumstances and time points of PE recurrence. In particular, the association between inflammatory biomarkers (eg, high-sensitive C reactive protein (hs-CRP) and disease outcomes will be investigated.

Secondary outcomes

1. To identify subgroups of PE patients (eg, patients with persistent right-ventricular dysfunction, high risk of PE recurrence or bleeding, patients under NOAC treatment, etc) and to assess optimal treatment for these subgroups (in hospital and after discharge).
2. To examine the association between sleep-disordered breathing and nocturnal continuous positive airway pressure (CPAP) therapy and PE recurrence.
3. To evaluate the long-term health-related quality of life and the presence of anxiety and/or depression after PE.
4. To monitor the safety and harm associated with the use of specific treatments in hospital (eg, reperfusion treatment) and after discharge (secondary prevention, eg, the impact of direct oral anticoagulants).
5. To investigate the associations between metabolomics and proteomics and disease development as well as disease outcomes.
6. To determine the healthcare utilisation of patients with PE, and to determine differences in healthcare utilisation according to age, gender and socioeconomic status.
7. To evaluate the currently used risk stratification process for PE patients according to the European Society of Cardiology (ESC) guidelines, including the assessment of right ventricular dysfunction.

METHODS AND ANALYSIS

The study aims to include all consecutive patients with incident as well as recurrent confirmed acute PE (diagnosis based on multidetector CT pulmonary angiography or ventilation–perfusion lung scanning) of adults admitted to the university hospital Augsburg. The study began on 1 July 2017, and is expected to end on 31 December 2026 (recruitment phase and follow-up).

Participation in the study is voluntary, and irrespective of the management strategy and outcome. If a patient is willing to take part in the study, a written informed consent form has to be signed by him or her. In case a patient suffers from dementia or another disease with major restrictions, written informed consent will be signed by the responsible caregiver and a proxy interview will be conducted. The consent form is also provided in Turkish and Russian language, two very frequent population groups in the Augsburg region. All other patients with language difficulties will be asked whether a relative is available for translating the consent form and answering the questions. In the university hospital Augsburg, the majority of PE patients of the study region will be treated, yearly about 300 cases. Based on the experience in previous comparable studies, it is expected that about 80%–90% of the patients will take part in the study. Data collection procedures will be performed in accordance with the Declaration of Helsinki.

At the university hospital Augsburg trained study nurses prospectively record all confirmed cases with PE. In order to record all cases, an electronic list of suspected cases of PEs is compiled daily by the university hospital of Augsburg (inpatients and outpatients, also patients at the emergency department and intensive care unit). The study nurses then check and verify these suspected cases via the treating physicians. Patients with unsuspected PE on a regular CT are also included. There is a double read for all the tests for quality. The study nurses visit all patients to inform them about the study and to deliver the study documents. Patients will receive comprehensive and understandable information on the processes and consequences of the participation in the study.

Data collection at baseline hospital stay

Patient interview and chart review

After the patients have given informed consent, the study nurses will interview the study participants during their hospital stay using a standardised questionnaire. The interviews will cover demographic information, symptoms on presentation, delay in diagnosis, predisposing and PE-provoking factors, comorbidities (eg, carcinoma, pulmonary and cardiac comorbidities, diabetes mellitus, neuromuscular disease, sleep-disordered breathing, etc). The patients will be asked to fill in self-administered questionnaires, including the EuroQol (EQ-5D),¹³ and the Hospital Anxiety and Depression Scale.¹⁴ During the hospital stay, routinely collected clinical data will be assessed by chart review; this includes information on comorbidities, PE-provoking factors (eg, immobilisation, trauma, surgery, thrombophilia and carcinoma), medications prescribed prior to PE and at hospital discharge, diagnostic procedures, location of thrombotic material, presence of deep vein thrombosis, prior PE, clinical parameters for disease severity (eg, right ventricular dysfunction, myocardial injury, etc), laboratory parameters (routine parameters and biomarkers such as N-terminal pro-brain natriuretic peptide, troponin), invasive

and non-invasive treatment regimens as well as complications (eg, hypotension, cardiogenic shock, need of mechanical ventilation, rescue-thrombolysis, cardiac arrest, death, etc).

Substudy on sleep-disordered breathing

Recent research indicates that sleep-disordered breathing might be an independent risk factor for venous thromboembolism.¹⁵ However, it is still unknown if sleep-disordered breathing has any impact on the clinical course of PE or if nocturnal CPAP therapy can potentially prevent PE recurrence. Therefore, in a subgroup of patients, an eight-channel polygraphy (Mini Screen Plus, Heinen & Löwenstein, Bad Ems, Germany) will be carried out, measuring respiratory airflow, thoracic and abdominal breathing movements, pulse oximetry, pulse rate, snoring, body position and light. Polygraphy is a non-invasive, well-validated method for the diagnosis of sleep-disordered breathing, approved by health authorities and routinely performed at the university hospital Augsburg. The polygraphy measurements will be offered to all patients who are being treated for PE at the university hospital of Augsburg in 2019 and 2020 and who will consent to the examination. The measurements will be conducted during hospital stay, when the patients are on the general ward. The examination will not prolong the patients' hospital stay.

Collection of biomaterial

During the hospital stay, as soon as the patients are on the general ward, 30 mL blood will be collected from the patients in a fasting state. The blood samples will be processed and aliquoted into sample tubes at the Chair of Epidemiology, Ludwig-Maximilians Universität München, at UNIKA-T Augsburg. Thereafter, the aliquots will be frozen at -80°C and stored until laboratory analysis. Furthermore, from a subsample, that is patients with PE, who will be treated in the university hospital of Augsburg in 2020, 20 mL urine and a native as well as a stabilised stool sample will be collected and stored at -80°C .

It is planned to measure inflammatory markers (eg, hs-CRP), metabolomics and proteomics in blood samples. In urine and stool samples, metabolomics measurements (native stool samples) and 16S rRNA (V3/V4) microbiome sequencing (stabilised stool samples) will be conducted.

Follow-up of the PE patients

Morbidity follow-up and update of lifestyle and health factors

All study participants will regularly receive postal questionnaires or telephone interviews after hospital discharge (in the first year after 3, 6 and 12 months; thereafter every 12 months). The postal questionnaire will contain questions on disease symptoms, comorbidity, health-related quality of life (Pulmonary Embolism Quality of Life Questionnaire,¹⁶ EQ-5D,¹³ anxiety and depression (Hospital anxiety and depression scale¹⁴), dyspnoea, major bleeding complications, recurrent events and healthcare

utilisation (readmissions, visits to physicians, clinics and emergency departments). Information on diet (repeated 24 hours food list; Food-Frequency Questionnaire) and physical activity (German-Physical Activity Questionnaire PAQ-50+) will be gathered via standardised questionnaires. Data on current medication and treatment (eg, CPAP therapy) will be collected. Bleeding complications are classified as major if medical advice is needed. Recurrent PE is defined as the presence of any new pulmonary arterial clot obstruction after at least 3 months of sufficient anticoagulation therapy.

An overview of the data collected at baseline and follow-up is given in [table 1](#), and a study flow chart with enrolment and follow-up is depicted in [figure 1](#).

Mortality follow-up

Regular mortality follow-ups will be performed using information from the residents' registration offices in the study area. Causes of death will be extracted from the death certificates provided by the local health authorities in the study region and will be coded according to the ICD-10 (WHO).

Statistical analysis

After data cleaning, quality assurance and transformation of variables, descriptive statistics and explorative data analysis will be carried out to get an overview as well as basic information about the data. The formulated hypotheses and scientific questions will be examined according to a previously prepared statistical analysis plan.

Baseline characteristics will be presented as means \pm SD for normally distributed continuous variables and as median (IQR) for continuous variables without a normal distribution. Categorical variables will be expressed as percentages. Comparisons between two patient groups will be conducted using χ^2 -test or Fisher's exact test for categorical variables and the t-test for continuous variables.

Differences between at least three subgroups of PE patients, for example, related to their treatment and lifestyle factors (categorised variables), will be investigated using log-linear models and analysis of variance. If there are any differences, post hoc tests will be used for identifying them.

Primary outcome variables such as long-term survival, bleeding complications and PE recurrence will be available in a binary form as 'yes/no' variables. To identify risk factors and determinants associated with these outcome variables, confounder-adjusted Cox regression analysis will be used for modelling and to estimate relative risks. Effect modification by age and sex will be examined. To take account of competing risks of death when identifying predictors for individual outcomes such as bleeding complications or PE recurrence, competing risk analysis will be conducted.

Basically, for continuous outcomes, multiple linear regressions will be used, if the assumptions regarding the residuals and the predictors are fulfilled. If necessary,

the corresponding variables have to be transformed meanwhile.

All tests within the multivariable models will be conducted at an alpha level of 0.05. A correction of the significance level alpha will be made in case of multiple testing. All statistical analyses will be performed using SAS software 9.4 or R.

Sample size estimation

Every year, about 300 patients with acute PE receive in-hospital treatment at the university hospital Augsburg. Based on the experience from previous studies, it is expected that 80%–90% of the patients will take part in the study. Consequently, it is planned to recruit about 250 study participants every year; altogether about 1000 patients will be included within 4 years. To determine whether this cohort size will be sufficient to achieve 80% probability of detecting a statistically significant difference in primary outcome (mortality) regarding the hs-CRP values during hospital stay. On the basis of a previous meta-analysis,¹¹ the investigators expect a proportion of deaths of 11% within a median follow-up of 18 months. With an estimated effect estimate (HR) of 1.5, a variance of hs-CRP of 0.7 and a $\rho^2=0.36$, the inclusion of at least 969 patients will be able to detect a significant difference with a statistical power of 80% at a 5% significance level.

Dissemination

Written informed consent is obtained from the study participants. Patients who do not consent will not be included. The study results will be presented at national and international conferences and published in peer-reviewed scientific journals.

Patient and public involvement

Public and patients were not involved in development of the study design, in recruitment of study participants or the implementation of the study. However, the study results will be discussed using focus groups consisting of patients and healthcare providers.

DISCUSSION

The present manuscript describes the protocol for a prospective, observational cohort study designed to investigate the long-term course of patients treated for acute PE. Baseline data on lifestyle, predisposing factors, comorbidities, social variables, treatment procedures and complications are collected during hospital stay via face-to-face interviews and extracting data from the medical records. Follow-up data will be assessed using postal questionnaires and mortality surveys.

Limitations of the study will be the lost to follow-up and the occurrence of missing data. Furthermore, a selection bias could be a concern, because it can be assumed that very ill patients will rather not take part in the study. In addition, analyses are not based on randomised treatment assignments. Finally, in contrast to existing multicentre

Table 1 Data collected at baseline and during the follow-up

Patient-related characteristics	Baseline examination	Follow-up after 3 months	Follow-up after 6 months	Follow-up after 12 months	Follow-up after 24, 36, 48, 60 months
Age	X				
Sex	X				
Place of residence	X	X	X	X	X
Nationality	X				
Marital status	X				
Education	X				
Occupation	X	X	X	X	X
Smoking	X	X	X	X	X
Alcohol consumption	X	x	x	x	x
Female health (pregnancy, childbirth...)	X	x	x	x	x
(Prior) diseases	X	X	X	X	X
Prior treatments	X				
Family history of PE	X				
Symptoms of PE	X				
Start of PE symptoms	X				
(Prior) medication	X	X	X	X	X
Vital signs at hospital admission	X				
Physical activity	X	X	X	X	X
Treatment-related variables	X				
Date and time starting treatment prior admission	X				
Diagnostic procedures	X				
Date and time of diagnosis	X				
In-hospital treatment	X				
In-hospital complications	X				
Medication	X				
Treatment (eg, thrombolysis)	x				
Laboratory values	X				
General parameters					
Date and time of hospital admission	X				
Date hospital discharge	X				
Outcome parameters					
Health-related quality of life		X	X	X	X
Mental health		X	X	X	X
Healthcare utilisation		X	X	X	X
Medication		X	X	X	X
Treatment (eg, CPAP)		X	X	X	X
Relapse		X	X	X	X
Bleeding complications		X	X	X	X
Chronic thromboembolic pulmonary hypertension		X	X	X	X
Dietary intake	X	X	X	X	

CPAP, continuous positive airway pressure.

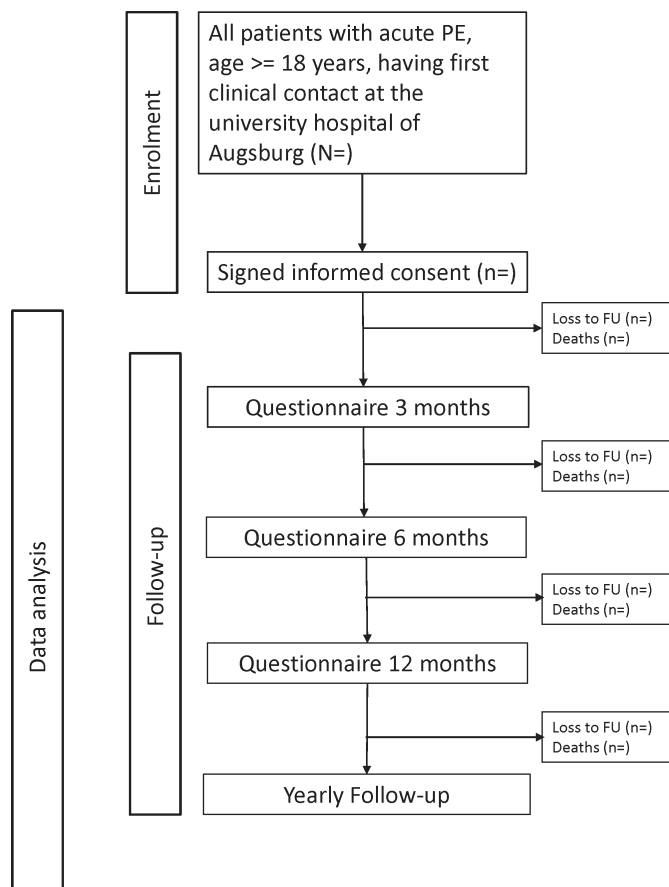


Figure 1 Study flow diagram with enrolment and follow-up. FU, follow-up; PE, pulmonary embolism.

venous thromboembolism registries,¹⁷ the present study is designed as a single centre study. The strengths of the study are the prospective long-term collection of data, the large sample size and the comprehensive collection of data from the study participants. Another strength is the personal interview of patients about the acute event and the collection of biomaterials.

The LEA study will provide a comprehensive view on the long-term course of the disease and on the healthcare provided to patients with PE. It will generate knowledge about factors that may have an influence on the outcome and disease burden of PE patients. Thus, the results of the study can help clinicians in treating and guiding these patients.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

- 1 Naess IA, Christiansen SC, Romundstad P, *et al*. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007;5:692–9.
- 2 Silverstein MD, Heit JA, Mohr DN, *et al*. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998;158:585–93.
- 3 Hoffmann B, Gross CR, Jöckel K-H, *et al*. Trends in mortality of pulmonary embolism – an international comparison. *Thromb Res* 2010;125:303–8.
- 4 Kröger K, Moerchel C, Moysidis T, *et al*. Incidence rate of pulmonary embolism in Germany: data from the federal statistical office. *J Thromb Thrombolysis* 2010;29:349–53.
- 5 ISTH Steering Committee for World Thrombosis Day. Thrombosis: a major contributor to global disease burden. *Thromb Res* 2014;134:931–8.
- 6 Stein PD, Beemath A, Olson RE. Trends in the incidence of pulmonary embolism and deep venous thrombosis in hospitalized patients. *Am J Cardiol* 2005;95:1525–6.
- 7 Kearon C. Natural history of venous thromboembolism. *Circulation* 2003;107:221–30.
- 8 Barco S, Konstantinides SV. Risk-adapted management of pulmonary embolism. *Thromb Res* 2017;151:S92–6.
- 9 Konstantinides SV, Torbicki A, Agnelli G, *et al*. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033–73.
- 10 Ng ACC, Chung T, Yong ASC, *et al*. Long-term cardiovascular and noncardiovascular mortality of 1023 patients with confirmed acute pulmonary embolism. *Circ Cardiovasc Qual Outcomes* 2011;4:122–8.
- 11 Sista AK, Miller LE, Kahn SR, *et al*. Persistent right ventricular dysfunction, functional capacity limitation, exercise intolerance, and quality of life impairment following pulmonary embolism: systematic review with meta-analysis. *Vasc Med* 2017;22:37–43.
- 12 Noble S, Lewis R, Whithers J, *et al*. Long-term psychological consequences of symptomatic pulmonary embolism: a qualitative study. *BMJ Open* 2014;4:e004561.
- 13 EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
- 14 Hermann-Lingen C, Buss U, Snaith RP, *et al*. *Hospital anxiety and depression scale – Deutsche version (HADS-D)*. Bern: Verlag Hans Huber, 2011.
- 15 Garcia-Ortega A, Mañas E, López-Reyes R, *et al*. Obstructive sleep apnoea and venous thromboembolism: pathophysiological links and clinical implications. *Eur Respir J* 2019;53.
- 16 Frey PM, Méan M, Limacher A, *et al*. Quality of life after pulmonary embolism: prospective validation of the German version of the PEmb-QoL questionnaire. *Thromb Res* 2015;135:1087–92.
- 17 Bickdeli B, Jimenez D, Haskins M, *et al*. Monreal M, and for the RIETE Investigators. rationale, design and methodology of the computerized registry of patients with venous thromboembolism (RIETE). *Thromb Haemost* 2018;118:214–24.