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RECOMMENDATIONS AND GUIDELINES

Definition of pulmonary embolism-related death and classification of the cause of death in venous thromboembolism studies: Communication from the SSC of the ISTH

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Abstract

Pulmonary embolism (PE)-related death is often a component of the primary outcome in venous thromboembolism (VTE) clinical studies. Definitions for PE-related death vary widely, which may lead to biased risk estimates of clinical outcomes, thereby affecting both internal and external validity of study results. We here provide a standardized definition of PE-related death and propose guidance for classification and reporting of the cause of death for clinical studies in VTE. The proposal was developed in a four-step process, including a systematic review of definitions used for PE-related death in previous studies, two subsequent surveys with VTE experts, and meetings held within the Scientific and Standardization Committee (SSC) working group until consensus on the proposal was reached. The proposed classification comprises three categories: Category A: PE-related death, category B: undetermined cause of death, and category C: cause of death other than PE. Category A includes A1: autopsy-confirmed PE in the absence of another more likely cause of death; A2:

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objectively confirmed PE before death in the absence of another more likely cause of death; and A3: PE is not objectively confirmed, but is most likely the main cause of death. Category B includes B1: cause of death is undetermined, despite available information; and B2: insufficient clinical information available to determine the cause of death. The use of the proposed definition will hopefully improve the accuracy of study outcomes, between-study comparisons, meta-analyses, and validity of future clinical VTE studies.

KEYWORDS

cause of death, classification, mortality, pulmonary embolism, venous thromboembolism

1 | INTRODUCTION

Pulmonary embolism (PE)-related death is often a component of the primary outcome (recurrent) venous thromboembolism (VTE) in clinical studies. Definitions and reporting of PE-related death vary widely.[1] The lack of a standardized definition of PE-related death, and differences in data collection and adjudication of death events may contribute to biased risk estimates of study outcomes, affecting both internal and external study validity. Depending on the sensitivity and specificity of the definition used for PE-related death, the number of death cases judged to be related to PE varies.[1] Death events falsely classified as being related to PE may "dilute" relative differences between treatment arms in clinical trials, possibly leading to type I or type II errors, depending on statistical comparison (ie, superiority versus non-inferiority study design). The current use of different definitions for PE-related death and the broad range of reported VTE case-fatality rates indicate the need for a standardized assessment of the cause of death. This communication from the Scientific and Standardization Committee (SSC) on Predictive and Diagnostic Variables in Thrombotic Disease provides a standardized definition of PE-related death and proposes guidance for classification and reporting of the cause of death in VTE studies.

2 | METHODS

The development process of the proposed definition for PE-related death and cause of death classification included (a) a systematic review as an initial assessment of the definitions used for PE-related death in recent studies,[1] (b) two subsequent surveys with VTE experts to evaluate the first and second version of the guidance proposal,[2] and (c) consensus meetings held within the SSC working group.

Methods and results of the systematic review on definitions and reporting of PE-related death in randomized controlled trials and cohort studies are described elsewhere.[1] In short, 83 studies published between January 2014 and April 2018, in which PE-related death was a component of the primary outcome, were included. Only 38 studies (46%) reported a definition for PE-related death, of which the most frequently used subcategories were: "autopsy-confirmed PE" (50%), "objectively confirmed PE before death" (55%), and "unexplained death" (58%).

The first version of the definition for PE-related death was developed based on the findings of the systematic review and was presented at the meeting of the SSC on Predictive and Diagnostic Variables in Thrombotic Disease at the 64th SSC Meeting of the International Society on Thrombosis and Haemostasis (ISTH) in Dublin, Ireland in July 2018. A real-time survey was held to obtain feedback of the expert attendees (N = 73) on the first version of the definition. The survey results were synthesized and reviewed by the working group to inform a second version of the guidance proposal.

International VTE experts and adjudicators of recent randomized controlled trials who were identified in the above-mentioned systematic review,[1] were invited to review the second version of the definition in an online survey.[2] A consensus meeting was held within the SSC working group to establish the final version of the guidance based on the results of the final survey. The subcommittee chairman and co-chairs have reviewed and approved the proposed definition and classification, which was presented at the annual ISTH meeting in Melbourne, Australia in July 2019.

3 | RECOMMENDATIONS

1. We recommend defining and classifying the cause of death in VTE studies as outlined in Table 1.
2. We recommend reporting absolute numbers of events for all subcategories outlined in Table 1.
3. We recommend specifying and ideally defining prevalent causes of death, other than PE, in the population of interest, in the study protocol.
4. We recommend classifying death events in patients with a terminal illness and a short life expectancy as having died from that illness, unless death circumstances clearly indicate that PE was the most likely immediate cause of death.
5. We suggest including only category A (PE-related death) in the primary analysis of PE-related death.

TABLE 1 Proposed classification of the cause of death in venous thromboembolism studies

A. Pulmonary embolism (PE)-related death
A1. Autopsy-confirmed PE in the absence of another more likely cause of death
A2. Objectively confirmed PE before death in the absence of another more likely cause of death
Definition of objectively confirmed PE includes ≥1 of the following situations in the last 48 hours* before death:
• PE diagnosed by imaging
• Objectively confirmed proximal deep vein thrombosis of the lower extremity in patients with clinical signs and symptoms of PE
A3. PE is not objectively confirmed, but is most likely the main cause of death
B. Undetermined cause of death
B1. Cause of death is undetermined, despite available information
B2. Insufficient clinical information available to determine the cause of death
C. Cause of death other than PE

*Longer time period may apply on a case-by-case basis.

4 | QUALIFYING REMARKS

All recommendations and suggestions made in this SSC communication apply to any clinical study in the field of VTE, irrespective of study design and population, and are supported by the majority of VTE experts who participated in the surveys as described in the Methods.[2] The following qualifying remarks explain the rationale for the proposed definition for PE-related death, classification of the cause of death, and primary analysis of PE-related death, including comments and concerns of the survey respondents. Clinical examples are provided in Table 2 to illustrate the application of the proposed criteria.

4.1 | A. Pulmonary embolism-related death

4.1.1 | A1. Autopsy-confirmed pulmonary embolism in the absence of a more likely cause of death

Classification of death as "autopsy-confirmed PE" is based on the pathologist's report. In case the pathologist did not define or report the cause of death, adjudication is based on the remaining criteria of the proposed classification or the adjudication committee's interpretation of the autopsy findings.

4.1.2 | A2. Objectively confirmed pulmonary embolism before death in the absence of a more likely cause of death

This category applies to objectively confirmed PE by imaging or imaging-confirmed proximal deep vein thrombosis (DVT) of the lower extremity in a patient with clinical signs or symptoms of PE in the last 48 hours before death. Imaging modalities directly visualizing the thrombus or ventilation/perfusion scintigraphy may be considered.

Previous studies have shown that in patients with symptoms of PE, objectively confirmed proximal lower limb DVT can be regarded as a surrogate for PE diagnosis.[3] In contrast, detection of distal DVT of the lower extremity is not specific enough to confirm PE, as in 36% of patients with suspected PE who are diagnosed with isolated distal DVT, PE is excluded upon computed tomography pulmonary angiography testing.[4] This does not disregard the fact that information on diagnosis of distal lower limb DVT or upper extremity DVT may be relevant for adjudication of the cause of death.

The timeframe of 48 hours before death was supported by most respondents in both surveys. Because clinical presentation and efficacy of therapeutic management may influence the risk of PE-related death, there are circumstances for which the proposed timeframe can be overruled by the adjudication committee on a case-by-case basis contingent upon initial presentation, therapeutic management, or response to treatment. Examples include, but are not limited to, death in patients with high-risk PE without clinical stabilization within the first 48 hours or death in patients who did not receive appropriate anticoagulant treatment following diagnosis.

4.1.3 | A3. Pulmonary embolism is not objectively confirmed, but is most likely the main cause of death

This category applies to cases in which PE is not objectively confirmed, but for which PE is most likely the main cause of death based on clinical information. Clinical judgment of the adjudication committee for this category is crucial and may be based on medical history, clinical examination, and relevant laboratory or indirect imaging findings that support classification of PE as the most likely cause of death. This could apply to a patient who presented with signs and symptoms strongly suggestive of PE (eg, chest pain and/or shortness of breath, tachycardia and symptoms of DVT) and in which no other cause of death, such as an acute coronary syndrome, sepsis, or another acute illness compatible with the clinical presentation, is deemed to be more likely than PE. A clinical example is described in Table 2.

4.2 | B. Undetermined cause of death

This category comprises two subcategories including B1: "Cause of death is undetermined, despite available information" and B2: "Insufficient clinical information available to determine the cause of death." Category B1 applies to cases in which the available information is inconclusive. For example, when a patient died in the hospital without any preceding signs or symptoms pointing toward a specific cause of death. This would also include those patients with symptoms that could correspond to a PE but were too vague to lead to the conclusion that PE was the most likely cause of death.

TABLE 2 Clinical vignettes to illustrate classification of the cause of death based on proposed criteria

A 56-year-old man is enrolled in a venous thromboembolism treatment study following a second episode of PE in the context of recent cancer surgery. The study nurse has received a message that the patient died after he missed the 3-month follow-up appointment.
Based on the information available, he would be classified in one of the following six categories.
Category A1: Autopsy-confirmed PE in the absence of another more likely cause of death
What if we knew that the ambulance was called for acute onset of shortness of breath and chest pain, 2 months after initiation of anticoagulation? The patient died before arrival at the emergency department. The autopsy report described PE as the immediate cause of death.
This death is classified in category A1. Death circumstances are in keeping with recurrent PE and PE is confirmed as the cause of death upon autopsy.
Category A2: Objectively confirmed PE before death in the absence of another more likely cause of death
What if we knew that the patient was admitted to the hospital and restarted on full-dose low-molecular-weight heparin after objective confirmation of a proximal left leg DVT. The patient died 6 hours later, after rapid worsening of hypoxemia.
This death is classified in category A2. Proximal DVT of the lower limb was confirmed shortly before death in a patient with clinical signs and symptoms of PE and in absence of a more likely other cause of death than PE.
Category A3: PE is not objectively confirmed, but is most likely the main cause of death
What if we knew that the patient was admitted for sudden onset of shortness of breath, 5 weeks after enrollment in the study? The medical records indicate that the postoperative course was uneventful, he received adjuvant chemotherapy, and that the dose of low-molecular-weight heparin was reduced 4 days prior to admission. Clinical examination upon admission showed an afebrile patient with tachycardia, hypoxia, and new left leg swelling. Blood work showed hemoglobin and creatinine clearance within normal limits but elevated D-dimer and troponin levels. The patient died 4 hours after presentation before further investigations could be performed.
This death is classified in category A3. Clinical presentation and medical history are suggestive of recurrent PE as the most likely main cause of death. Based upon the available information, there is no clear alternative cause of death to consider classification in category B1 or C.
Category B1: Cause of death is undetermined, despite available information
What if we knew the patient was admitted to intensive care unit after objective confirmation of recurrent PE and his course after initiation of appropriate anticoagulant therapy was complicated by bilateral pneumonia, major gastrointestinal bleeding, seizure, and delirium? The patient slowly improved but he then became somnolent 16 days after admission to the intensive care unit without preceding change in oxygen saturation or hemodynamic parameters. Computed tomography of the head was unremarkable. The patient died after rapid decline of consciousness.
This death is classified in category B1. Despite having detailed information on death circumstances, the cause of death remains undetermined. None of the mentioned acute illnesses including PE can be considered the most likely main cause of death.
Category B2: Insufficient clinical information available to determine the cause of death
What if the patient's family cannot be reached and the family physician cannot provide any additional information on death circumstances?
This death is classified in category B2 as no information is available on death circumstances.
Category C: Cause of death other than PE
What if we knew that initial ECG showed signs of anterolateral ST-segment myocardial infarction and bedside echocardiography revealed severe left ventricular systolic dysfunction? The patient died 4 hours after presentation following several episodes of ventricular tachycardia. Cardiac angiogram was not performed due to goals of care indicating that the patient prefers no invasive procedures or cardiopulmonary resuscitation.
This death is classified in category C. The additional information clearly indicates that myocardial infarction is more likely than PE as the cause of death.
What if we knew that shortness of breath progressed over the past 3 months? Computed tomography 2 weeks prior to admission showed progressive lung cancer with bilateral pleural effusion. The patient received palliative care and died 5 days after admission.
This death is classified in category C. Even though a recurrent PE cannot be excluded as immediate cause of death, the patient most likely died from progressive cancer on palliative treatment.

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Category B2 includes cases with no information available on the death circumstances. For example, when a patient died at home in the absence of any witnesses or if no information is available on the symptoms or signs in the hours/minutes preceding death (see Table 2 for clinical examples). To minimize the number of cases in this category, completeness of data collection on death events is crucial. Investigators should collect as much information as possible on the exact circumstances of death by a detailed assessment of the patient's medical record or by interviewing relatives or the primary care physician. The number of cases with no clinical information available (category B2) may be considered a study quality criterion and should therefore be reported separately.

Previously, cases with an undetermined cause (categories B1 and B2) were referred to as "PE cannot be ruled out" or as "sudden" or "unexplained" death. Commonly, a conservative approach has been used in VTE research, supported by regulatory agencies, in which these cases were all considered to be PE-related deaths.[1,5] However, we know from autopsy case series that only 3% to 6% of sudden or unexplained deaths are caused by PE.[6-8] This proportion may be higher in specific high-risk patient populations, such as those with a history of VTE. However, the committee concluded that also in these populations it would not be appropriate to classify all unexplained deaths as being related to PE. Therefore, we recommend to only classify death cases as being PE related in the case of objective confirmation (category A1 and A2) or when clinical information on death circumstances makes PE the most likely main cause of death (category A3).

4.3 | C. Cause of death other than pulmonary embolism

This category applies to causes of death other than PE, either objectively confirmed, or in the absence of objective confirmation, when a cause other than PE is considered the most likely main cause of death based on available clinical information. For example, a patient with known congestive heart failure presenting with acute shortness of breath and the clinical picture is consistent with decompensated heart failure (see Table 2 for clinical examples).

Importantly, patients with a terminal illness and a short life expectancy require a specific approach. Even though PE may contribute to death in such patients, they can be considered as having died from the terminal illness, unless death circumstances indicate clearly that PE was most likely the immediate cause of death and significantly shortened life expectancy. To better discriminate between death due to PE and other causes of death, we suggest that investigators predefine the most prevalent causes of death other than PE (eg, cancer, bleeding, cardiac, etc), as well as circumstances in which terminal illnesses may be regarded as having a short life expectancy, eg, cancer patients in the palliative care phase or patients referred to a hospice. This guidance does not provide a list with definitions for prevalent causes of death and terminal illnesses because these may vary by study population. However, it is highly encouraged to define these possible causes of death in the study protocol and in the charter for the event adjudication committee.

4.4 | Primary analysis

We suggest only including category A (PE-related death) in the primary analysis of PE-related death or composite endpoints including PE-related death. This approach implies that category B (undetermined cause of death) and category C (other cause of death) are excluded from this analysis. Thus far, cases for which the cause of death was undetermined were often designated to be PE-related death. Regulatory agencies have often required this definition for investigational trials of novel drugs, as a conservative approach for drug approval.[5] However, the optimal approach depends on study design and may differ for superiority and non-inferiority trials. Assuming that the majority of deaths for which the cause is undetermined are not related to PE, including category B (undetermined cause of death) in the primary analysis of PE-related death falsely inflates this clinical outcome. As PE-related death is often a component of the primary outcome (recurrent) VTE in randomized clinical trials, death cases with an undetermined cause would increase the primary outcome rate in both trial arms and thereby "dilute" relative differences between the groups. Our systematic review found that PE-related deaths account for 0 to 80% of all VTE events in recent clinical studies, suggesting a substantial risk of dilution in some studies.[1] In trials with a superiority design, "dilution" of the primary outcome by death cases with an undetermined cause may lead to a type II error (failure to reject the null hypothesis when it is false): a randomized controlled trial could be negative when in fact one of the two drugs was actually superior to the other. In contrast, in trials with a non-inferiority design it may lead to a type I error (rejection of the null hypothesis when it is true), falsely assuming non-inferiority when in fact a difference existed in the rate of actual VTE events. The same holds for studies with other designs. For example, in diagnostic studies, the failure rate of clinical decision rules or diagnostic tests could be overestimated due to an inflated proportion of VTE events during follow-up, thereby falsely refuting their safety.

Our suggestion regarding the primary analysis of PE-related death is based on the assumption that misclassification of PE-related death is reduced when including only category A and implies that data collection on death circumstances should be done meticulously to minimize the numbers of deaths with an undetermined cause (category B). This approach has been supported by 57.5% of respondents in the second survey with VTE experts, and another 32.5% of respondents were even more restrictive and would have preferred to only include category A1 and A2 in the primary analysis of death from PE. Only 5% would have preferred to include category A (A1, A2, and A3) and B1, and 5% category A and B.[2] In specific circumstances, such as drug approval studies with a superiority design, it may be reasonable to include category A (PE-related death) as well as category B (undetermined cause of death) or all-cause mortality in the primary analysis. In this situation, we suggest that authors provide the reason for such an approach. However, we advise against including category B (undetermined cause of death) in the primary analysis of PE-related death in non-inferiority trials, as it may mask relative differences.

5 | DISCUSSION

We here propose a definition of PE-related death and standardized classification and reporting of the cause of death in VTE studies. To enhance quality, generalizability, and acceptance of the proposed definition, its development was based on existing definitions for PE-related death identified in a systematic review,[1] and included feedback from key opinion leaders and experienced members of event adjudication committees in the field of VTE.[2] To further validate the proposed death cause classification, subsequent steps will include assessment of the interrater agreement and evaluation of the diagnostic accuracy of the criteria in an autopsy cohort study. In the absence of standardized criteria, studies suggested that the reproducibility of central outcome committee adjudications for PE-related death is insufficient.[9] We believe that our proposed definition will significantly improve the reproducibility of the adjudication process.

Ascertainment of the cause of death is often accompanied by uncertainty, particularly given that non-forensic autopsy rates declined over the past decades.[10,11] Although objective clinical parameters may guide classification of the cause of death, clinical interpretation by a central adjudication committee is always needed to determine the main cause of death, based on

all available information, including narration of events, signs and symptoms, and results of diagnostic testing. Because PE-related deaths are rarely objectively confirmed by imaging before death or by autopsy[1] and clinical signs and symptoms of PE are non-specific, discrimination between death due to PE and other causes remains challenging. However, cases for which there is no objective confirmation of PE, but for which PE is judged to be the most likely cause of death based on clinical information (category A3), are included in the outcome "PE-related death" to prevent underestimation of PE-related death rates.

Rigorous data collection on death circumstances is crucial to minimize the number of cases for which the cause of death remains undetermined. Relevant information could be obtained from the medical records of the patient, but also from relatives, the primary care physician, or other witnesses of the death circumstances. The proposed death cause categories specifically address the cases for which there is no clinical information available (category B2: insufficient clinical information available to determine the cause of death). The absolute number and proportion of death cases in this category may be considered a quality marker for completeness of data collection during follow-up and will provide a strong incentive for investigators to collect high-quality data. However, interpretation of this quality criterion has to be done cautiously because the feasibility of collecting information on death circumstances may vary based on study design and study population. Because the use of the proposed definition for PE-related death in future studies may result in lower absolute risks of PE-related death compared to past studies, which used a broader definition including unexplained death, reporting the absolute number of deaths for each subcategory is not only crucial for assessment of internal study validity but it also allows for comparison of absolute risk estimates between past and future studies.

The use of the proposed standardized definition of PE-related death and classification of the cause of death, as well as detailed data collection on death circumstances, will hopefully improve the accuracy of study outcomes, between-study comparisons, meta-analyses, and validity of future clinical VTE studies.

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CONFLICTS OF INTEREST

The authors state that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors contributed to concept, design, and conduct of the study, and writing of the manuscript. All authors approved the final version of the manuscript.

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