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TITLE

Development of a standardized definition of pulmonary embolism-related death: a cross-sectional survey of international thrombosis experts

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SHORT TITLE

Survey on definition of PE-related death

KEY WORDS

Cause of Death, Classification, Mortality, Pulmonary Embolism, Venous thromboembolism

ESSENTIALS

- Definitions for pulmonary embolism (PE)-related death vary widely.
- A cross-sectional survey on a standardized definition for PE-related death was performed.
- Acceptance of the proposed definition by the 40 thrombosis expert respondents was excellent.
- Suggestions for improvement were integrated in the final SSC definition of PE-related death.

ABSTRACT

Introduction: Pulmonary embolism (PE)-related death is often part of the primary outcome in venous thromboembolism (VTE) studies. The Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Haemostasis developed a definition for PE-related death and classification of the cause of death. The present survey evaluated a preliminary version of this definition and classification.

Methods: Sixty-nine VTE experts from 9 countries were invited for a cross-sectional online survey on January 15th, 2019, including multiple-choice and open-ended questions on a seven-subcategory classification of the cause of death. Descriptive statistics were used to describe the results; qualitative comments were summarized.

Results: Forty of 69 (58%) invitees completed the survey. All respondents agreed that guidance on classification of the cause of death in VTE studies is required. There was high agreement on the proposal (median overall score, 6; interquartile range, 6-7; scale from 1 [poor] to 7 [excellent]). All respondents approved the wording and content of the seven subcategories, except for 1 disagreeing vote for 2 subcategories (A3: 'PE is not objectively confirmed, but is most likely the main cause of death', and C1: 'Another cause of death is more likely than PE but has not been objectively confirmed'). Suggestions for improvement mainly concerned the extensiveness of the criteria and clinical situations described to define the cause of death.

Conclusion: Acceptance of the proposal was excellent. Suggestions for improvement were incorporated in the SSC communication on the definition of PE-related death and classification of the cause of death in VTE studies.

INTRODUCTION

Pulmonary embolism (PE) is a potentially fatal disease. As such, most venous thromboembolism (VTE) studies include PE-related death as part of their primary efficacy outcome (recurrent) VTE. However, in the absence of a standardized definition for PE-related death, current definitions for this outcome are heterogeneous and underreported [1]. The lack of standardization and reporting hinders comparison of study results and may hamper appraisal of the internal and external study validity.

In the current issue of the *Journal of Thrombosis and Haemostasis*, the International Society on Thrombosis and Haemostasis (ISTH) Scientific and Standardization Committee (SSC) on Predictive and Diagnostic Variables in Thrombotic Disease proposes a standardized definition for PE-related death and classification of the cause of death in clinical studies in the field of VTE (ref SSC communication). The definition was developed based on a systematic review of definitions for PE-related death used in recent VTE studies [1], and two subsequent surveys with VTE experts. The first was a real-time survey to seek feedback on a preliminary version of the definition at the 64th SSC Meeting of the ISTH in Dublin, Ireland in July 2018. The second survey, a web-based questionnaire, included a further developed definition for PE-related death and a classification for the cause of death in clinical VTE studies. The detailed results of this survey are presented here.

METHODS

An online survey was developed on a preliminary version of the definition for PE-related death and classification of the cause of death in VTE research. Preceding the invitation, the survey was pilot-tested by general internists and thrombosis specialists to minimize misinterpretation of questions and to ensure face validity and content validity. The survey included three main categories (A: 'PE-related death', B: 'undetermined cause of death', and C: 'cause of death other than PE'), consisting of seven subcategories to classify the cause of death (**Table 1**). Multiple-choice questions including a 5-point Likert scale were used to assess agreement regarding the wording and content of each of the proposed categories of the definition. Suggestions for improvement of each category as free text was optional. Additionally, respondents were asked which subcategories should be considered for the primary analysis and potential sensitivity analyses of the outcome PE-related death. The overall rating of the proposed definition was also assessed. Respondents were able to adjust given answers at any time before completion of the survey. No adaptive questioning was used. The objective of the study, the length of the survey, and the investigators conducting the study were described in an invitation letter, which included a web-link to the survey. Participation was voluntary and no consent was obtained, other than agreement to participate. There were no incentives for participation. SurveyMonkey (SurveyMonkey Inc.; San Mateo, California, USA; www.surveymonkey.com) was used to design, distribute, conduct, and analyze the survey. Data were stored on a personal account on SurveyMonkey.

The invitation email was sent to 69 VTE experts from 9 countries on January 15th, 2019. Two reminders were sent at 3-week intervals to those who did not complete the survey, and the survey was closed on March 18th, 2019. Invitees included key opinion leaders of the International Network of VENous Thromboembolism Clinical Research Networks (INVENT) and event adjudication committee members of recent randomized controlled trials with PE-related death as a component of the primary outcome which were identified in a systematic review of definitions for PE-related death in recent VTE studies [1].

Descriptive statistics were used to describe agreement for each subcategory. Proportions were calculated on the basis of the total number of respondents per question. Qualitative comments were summarized for all the subcategories.

This study adheres to reporting guidelines of survey research [2-4].

RESULTS AND DISCUSSION

Forty out of 69 (58%) invited VTE experts completed the survey. Respondents were from 9 different countries (Canada, the United States, the Netherlands, France, Switzerland, Italy, Germany, Norway, and Australia), and represented a diverse cohort of experienced researchers and clinicians trained in general internal medicine, hematology, pulmonology, vascular medicine, radiology, emergency medicine, intensive care medicine, and cardiology. Thirteen out of 16 multiple-choice questions were answered by all respondents; the remaining multiple-choice questions were answered by all but one respondent (98%). Per subcategory, 8 to 18 respondents suggested improvement of wording and content as free text.

All respondents agreed that guidance on adjudication of the cause of death in VTE studies, especially 'VTE-related death' or 'fatal PE', is required (87.5% strongly agreed, 12.5% agreed). All respondents approved the wording and content of the seven subcategories, except for 1 disagreeing vote for 2 subcategories (A3: 'PE is not objectively confirmed, but is most likely the main cause of death', and C1: 'Another cause of death is more likely than PE but has not been objectively confirmed') (**Table 2**). Most respondents (n=23; 58%) preferred to include subcategories A1, A2, and A3 (i.e., 'autopsy-confirmed PE in the absence of another more likely cause of death', 'objectively confirmed PE before death without a more obvious cause of death, and 'PE is not objectively confirmed, but is most likely the main cause of death') in the primary analysis of PE-related death (**Figure 1**), and 13 (33%) preferred to include only objectively confirmed PE (i.e., subcategories A1 and A2). The remaining 4 (10%) respondents preferred to include cases with an undetermined cause of death as well (subcategory B1 [i.e., cause of death is undetermined] or subcategories B1 and B2 [i.e., insufficient clinical information to determine the cause of death]). The vast majority (18 of 22; 81%) of the respondents who selected all 3 subcategories of category A ('PE-related death'; A1, A2, and A3) for the primary analysis of PE-related death, suggested to include both subcategories of category B ('undetermined cause of death'; B1 and B2) for the sensitivity analysis. On a scale from 1 to 7 (1 being poor, 7 being excellent), the

proposed definition for PE-related death and classification for the causes of death received an overall median rating of 6 (interquartile range, 6-7).

Based on suggestions from the respondents, the wording of all subcategories has been adjusted (**Table 1**). An additional comment was added to subcategory A1 (i.e., autopsy-confirmed PE), explaining that judgment is based on the cause of death in the autopsy report. If the cause of death is not reported, adjudication is based on the remaining criteria of the classification or on the adjudication committee's judgment regarding the autopsy results and available clinical information.

With regard to 'objectively confirmed PE before death' (subcategory A2), the majority of respondents supported the proposed maximum timeframe of 48 hours between imaging and death. It should be acknowledged that a longer timeframe may be more appropriate in certain circumstances, which are not limited to hemodynamic stabilization. Therefore, the explanation in the footnote of subcategory A2 was rephrased to read: 'a longer time period may apply on a case-by-case basis.'

Questions arose regarding which imaging modalities would allow for objective confirmation of PE as this was not defined in the proposed criteria, for example: *"What is acceptable for "imaging"? Is echocardiography okay?"*. The SSC working group suggests that imaging modalities directly visualizing the thrombus or ventilation/perfusion scintigraphy may be considered but further specification will not be provided as new imaging techniques may emerge over time.

Two respondents suggested to exclude the localization of a DVT as part of the criteria for objectively confirmed PE in a patient with symptoms of PE. *"Simply upper or lower limb DVT (no mention of size or proximity)."*; *"Presence of any kind of venous thrombosis may be reason to suspect PE, not just proximal."* While any confirmed DVT before death may be important to consider when adjudicating the cause of death, only proximal DVT of the lower extremity in a patient with clinical symptoms of PE can be considered a reliable surrogate for PE diagnosis [5]. In contrast, detection of distal DVT is not specific enough to confirm PE, because 36% of patients with suspected PE and confirmed distal DVT do not have a PE on computed tomography pulmonary angiography [6].

Several respondents suggested to merge subcategories A2 (i.e., objectively confirmed PE before death) and A3 (i.e., PE is not objectively confirmed, but is most likely the main cause of death), or subcategories A3 and B1 (i.e., cause of death is undetermined). While there is an obvious difference between objective confirmation of PE and suspected PE based on symptomatology (i.e., subcategories A2 and A3), the difference between subcategories A3 and B1 may be subtle in some cases. However, as a conservative approach, patients in whom PE is considered to be the most likely cause of death based on clinical signs or symptoms, in the absence of objective confirmation, should also be classified as having died from PE and not as 'undetermined cause of death' (category B).

Based on the respondents' suggestions, subcategories C1 (i.e., another cause of death is more likely than PE but has not been objectively confirmed) and C2 (i.e., confirmed cause of death other than PE) have been merged, as there is little interest and benefit in classifying and reporting those subcategories separately in VTE studies. Several respondents suggested to provide a list with prevalent causes of death including readily available definitions for other causes of death than PE: *"I suggest a limited list of other prevalent causes of death."; "There will need to be ready access to accepted criteria for attributing cause of death to other causes (e.g., myocardial infarction, stroke, accident, etc.)."* Even though, such a list would be desirable, relevant causes of death may vary depending on study population and developing definitions of other causes of death than PE was beyond the scope of this SSC guidance.

Most of the recent large randomized controlled trials included 'undetermined cause of death' as part of the primary analysis of the outcome 'PE-related death' [1]. Because the vast majority of unexplained death cases are not related to PE [7-9], this approach may falsely increase the number of deaths attributed to PE in both study arms, and thereby dilute relative differences in the outcome PE-related death. Therefore, most respondents suggested to only include category A (i.e., subcategory A1 [autopsy-confirmed PE], subcategory A2 [objectively confirmed PE before death] and subcategory A3 [PE is not objectively confirmed, but is most likely the main cause of death]), and exclude cases for which the cause of death remains undetermined (subcategories B1 and B2). Only 10% of

respondents suggested to include unexplained death (categories B1 and/or B2) as well. Surprisingly, one-third of respondents would only include subcategories A1 (i.e., autopsy-confirmed PE) and A2 (i.e., objectively confirmed PE before death). However, we believe that this approach is too exclusive as PE is hardly ever objectively confirmed as a cause of death [1]. Based on the suggestion from one respondent, the recommendation for a sensitivity analysis on subcategories of the cause of death has been removed from the SSC communication because this may not be a general requirement in VTE research and sensitivity analyses should be based on study question and design.

This study has potential limitations. First, the design of the survey and the presentation of the proposed criteria may have influenced the approval rate of the definition. However, answers to open-ended questions were in line with the responses regarding agreement of the proposed subcategories in multiple-choice questions, confirming the robustness of the results. Second, even though we used objective criteria to identify VTE experts, the selection of invitees may have biased the survey results. Finally, we cannot exclude that respondents differed from non-respondents. However, the response rate was comparable to previous response rates in surveys with physician experts [4].

In conclusion, this cross-sectional survey evaluated the acceptance of a proposed standardized definition for PE-related death, and classification of the cause of death with VTE experts. Overall, there was high agreement with regard to the proposed definition and the classification of causes of death. The majority of respondents agreed with the proposed primary analysis which includes only PE-related death, thereby excluding cases for which the cause of death is undetermined. Suggestions for improvement were incorporated in the SSC communication on the definition of PE-related death and classification of the cause of death in clinical VTE studies.

AUTOR CONTRIBUTIONS

All authors contributed to concept, design, and data analysis and interpretation. T. Tritschler and N. Kraaijpoel wrote the manuscript. All authors reviewed and revised the manuscript. All authors approved the final version of the manuscript.

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DISCLOSURES

The authors state that they have no conflict of interest.

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Table 1. Preliminary and final definition of pulmonary embolism-related death as proposed by the SSC from the ISTH.

Definition and classification as proposed in the survey	Revised and final definition endorsed by ISTH SSC
A) PE-related death	**A) PE-related death**
A1. Autopsy-confirmed PE in the absence of another more likely cause of death *Based on judgment of pathologist upon autopsy.*	A1. Autopsy-confirmed PE in the absence of another more likely cause of death
A2. Objectively confirmed PE before death without a more obvious cause of death *This includes the following situations in the last 48 hours* before death:* • *PE diagnosed by imaging.* • *Objectively confirmed proximal lower limb DVT in patients with symptoms of PE.*	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 DVT 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 *This includes the following situations in the last 48 hours* before death:* • *Patients who presented with signs or symptoms of PE or deep vein thrombosis without an objectively confirmed PE diagnosis, but without another cause of death that is more likely than PE.* • *Acute treatment such as thrombolysis given to a patient with suspected recurrent PE in the absence of an objective test*	A3. PE is not objectively confirmed, but is most likely the main cause of death

confirming recurrent PE diagnosis.	
B) Undetermined cause of death	**B) Undetermined cause of death**
B1. Cause of death is undetermined *This includes patients for which there is clinical information about the death circumstances, but without obvious signs or symptoms that indicate a specific cause of death.*	B1. Cause of death is undetermined, despite available information
B2. Insufficient clinical information to determine the cause of death	B2. Insufficient clinical information available to determine the cause of death
C) Cause of death other than PE	**C) Cause of death other than PE**
C1. Another cause of death is more likely than PE but has not been objectively confirmed *This includes patients without a confirmed cause of death who presented with signs or symptoms suggestive of a cause of death other than PE, or patients who were known to have a severe chronic medical condition with limited life expectancy (e.g., severe COPD, severe heart failure and metastatic cancer).*	
C2. Confirmed cause of death other than PE	
*Longer time period may apply if hemodynamic stabilization was never achieved between diagnosis and death.	*Longer time period may apply on a case-by-case basis.

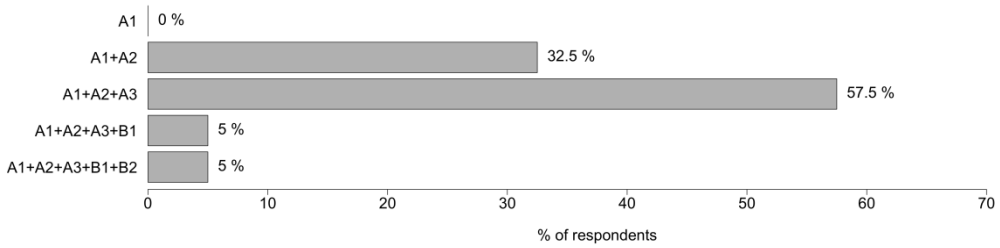
Table 2. Agreement of 40 venous thromboembolism experts with regard to wording and content of the proposed categories.

	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	No answer
A1. Autopsy-confirmed PE	30 (75%)	8 (20%)	2 (5%)	0	0	0
A2. Objectively confirmed PE before death	19 (47.5%)	17 (42.5%)	4 (10%)	0	0	0
A3. PE not objectively confirmed, but most likely main cause of death	8 (20%)	25 (62.5%)	6 (15%)	0	1 (2.5%)	0
B1. Cause of death is undetermined	16 (40%)	18 (45%)	6 (15%)	0	0	0
B2. Insufficient clinical information to determine cause of death	17 (43.6%)	19 (48.7%)	3 (7.7%)	0	0	1
C1. Another cause of death is more likely than PE but not objectively confirmed	16 (51%)	20 (51.3%)	2 (5.1%)	0	1 (2.6%)	1
C2. Confirmed cause of death other than PE	20 (50%)	20 (50%)	0	0	0	0

Abbreviation: PE, pulmonary embolism.

FIGURE LEGEND

Figure 1. Preference for primary analysis of pulmonary embolism-related death among 40 venous thromboembolism experts



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