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TITLE

ISTH definition of pulmonary embolism-related death and classification of the cause of death in venous thromboembolism studies: validation in an autopsy cohort

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RUNNING HEAD

Validation of ISTH definition of PE-related death

ESSENTIALS

- The ISTH's SSC recently proposed a new definition of pulmonary embolism (PE)-related death.
- We evaluated the accuracy and interrater reliability of the definition in an autopsy cohort.
- The definition had a high specificity, moderate sensitivity, and good interrater reliability.
- Our findings support the use of the ISTH definition of PE-related death in clinical VTE studies.

ABSTRACT

Background: The International Society on Thrombosis and Haemostasis (ISTH)'s Scientific and Standardization Committee (SSC) recently proposed a definition of pulmonary embolism (PE)-related death. We aimed to evaluate the accuracy and interrater reliability of the definition in an autopsy cohort.

Methods: We reviewed reports of 1,064 consecutive adult autopsies that were performed at the NewYork-Presbyterian Hospital from 01/2010 until 07/2019. We included all patients with autopsy-confirmed PE-related death (cases) during that time frame, combined with patients who died in 2018 from a cause other than PE (controls). Based on clinical summaries, two adjudicators independently adjudicated the cause of death in each patient using the ISTH classification for the cause of death, blinded to the case/control status and ratio. The primary outcome was autopsy-confirmed PE-related death. We determined the sensitivity and specificity of the ISTH definition to identify autopsy-confirmed PE-related death, and its interrater reliability using the percentage agreement and Cohen's kappa.

Results: A total of 126 patients who underwent autopsy were included in the analysis (median age, 68 years [range, 21-94], 60 [48%] women), of which 29 (23%) had died from PE as confirmed by autopsy. The ISTH definition's sensitivity and specificity for autopsy-confirmed PE-related death were 45% (95% CI, 26-64) and 99% (95% CI, 94-100), respectively. Interrater reliability for PE-related death was substantial (percentage agreement, 94% [95% CI, 89-97]; kappa, 0.73 [95% CI, 0.55-0.97]).

Conclusion: Adjudication of the cause of death using the ISTH definition resulted in very high specificity, moderate sensitivity, and good interrater reliability for PE-related death.

KEY WORDS

Cause of Death, Reproducibility of Results, Pulmonary Embolism, Validation Study, Venous Thromboembolism

INTRODUCTION

Determination of the cause of death in clinical studies can be challenging, particularly since non-forensic autopsy rates declined over the past decades [1,2]. Accurate adjudication of the cause of death is, however, of utmost importance in venous thromboembolism (VTE) studies, because pulmonary embolism (PE)-related death is often part of the primary outcome [3]. As such, inaccurate adjudication of the cause of death alters the number of primary outcome events and may thereby affect study results and validity.

Definitions of PE-related death in randomized controlled trials and cohort studies vary widely [3] and reproducibility of adjudications for the cause of death has been shown to be poor [4]. Therefore, the International Society on Thrombosis and Haemostasis (ISTH)'s Scientific and Standardization Committee (SSC) recently proposed a definition to better differentiate between PE-related death and other causes of death in VTE clinical studies [5]. The overall aim was to standardize the definition of PE-related death and to improve the reproducibility of adjudications of death events in VTE studies. In contrast to definitions that were used in many previous VTE studies [3], 'undetermined cause of death' (often referred to as 'unexplained death' or 'PE cannot be ruled out') is now a separate category, and is not included in the definition of the outcome 'PE-related death'. This approach was suggested by the ISTH's SSC, because the interrater reliability for adjudications of the cause of death in patients who die suddenly or unexpectedly is poor [4]. Furthermore, classifying 'unexplained deaths' as being related to PE, falsely increases the outcome 'PE-related death', since many unexplained deaths are not caused by PE [6-8]. Depending on study design, this may have different consequences on hypothesis testing and study findings [5].

The ISTH SSC's definition was developed using a mixed-methods approach, including a systematic review, two surveys of expert clinicians and researchers, and several consensus meetings of the SSC's working group [5,9]. The present retrospective autopsy cohort study aimed to validate the accuracy and interrater reliability of the ISTH SSC's classification for the cause of death and definition of PE-related death.

METHODS

Study design

We reviewed reports of 1,064 consecutive adult autopsies that were performed at the NewYork-Presbyterian Hospital/Weill Cornell Medical College, New York, United States between

January 2010 and July 2019. Autopsies were performed upon request of the treating physician or family members, i.e., not only in specific death circumstances (e.g., unexplained clinical findings) or consecutively. Since non-natural deaths are referred to the New York City Office of Chief Medical Examiner, the study included only patients that died due to a natural cause. A previous case-control study which included a small subset of the patients in the current cohort compared the cause of deaths in obese and non-obese individuals in whom an autopsy was performed at the NewYork-Presbyterian Hospital/Weill Cornell Medical College between January 2003 and September 2013 [10].

In the present study, we included all patients with PE-related death as confirmed by autopsy (cases), combined with patients who died in 2018 from a cause other than PE (controls). We included all non-PE-related deaths of an entire calendar year as controls to minimize selection bias and ensure inclusion of at least 3 controls per case.

Written consent for the autopsy was obtained by the spouse or legal next of kin as defined by New York State in accordance with the Decedent Estate Law (Public Health Law 4201 and article 205). No approval by the local Research Ethics Board was required given the retrospective design of the present study.

Post-mortem examination and determination of the cause of death

After fixation of tissue in formalin, routine sections of the heart and major coronary arteries, lung lobes, kidneys, adrenals, pancreas, liver, bone marrow, spleen, thymus, thyroid, lymph nodes, breasts, ovaries, uterus, testes, prostate, and any lesional tissue were obtained using the Letulle technique. Immunohistochemistry, special stains for microorganisms, bacterial cultures and other tests to detect microorganisms were performed if required. Reference ranges for organ measures were used [11].

The cause of death upon autopsy was determined by the pathologist based on the findings of the post-mortem examination and after detailed review of medical records including past medical history, laboratory investigations and imaging tests, and contacting the patient's clinical team to determine any specific concerns related to the death circumstances.

Adjudication of death events using the ISTH definition

Clinical summaries were extracted for each deceased patient from progress notes, the description of the medical history and clinical course prior to death in the autopsy report (no information from the post-mortem examination was included), laboratory values and imaging tests which were retrieved from the electronical health records and the autopsy study database. To avoid any bias in the information provided in the clinical summaries, we used only verbatim text from the source documents and presented the clinical summaries in a standardized fashion. Based on the clinical summaries, two experienced adjudicators (S.R.K. and D.G.) independently determined the cause of death in each patient using the ISTH definition and classification (Table 1) [5]. Patients with conflicting adjudications for the cause of death were independently assessed by a third experienced adjudicator (A.D.). The final classification of the cause of death was based on agreement of two adjudicators or, in case all three adjudicators classified the cause of death differently, through discussion among the three adjudicators. Adjudicators were blinded to the case-to-control ratio and the autopsy results. Clinical summaries were de-identified by the data extractors (T.T. and S.P.S.) including name, year of birth, and year of death to ensure anonymity and to avoid unblinding of adjudicators.

Adjudications were performed on an online adjudication platform (Venous Thrombosis Adjudication Platform – VERDICT) which was developed and is managed by the Canadian Venous Thromboembolism Research Network (CanVECTOR). The platform uses a standardized form for the

adjudication of the cause of death which was specifically developed based on the recommendations of the ISTH's SSC [5]. Death events were assigned in random order to the adjudicators. In addition to classification of the cause of death, adjudicators documented the certainty of their adjudication on a 5-point Likert scale (1 being very uncertain, 5 being very certain).

The ISTH classification of the cause of death in VTE studies includes three main categories: A) PE-related death; B) undetermined cause of death; and C) cause of death other than PE. Category A and category B are further divided into three and two subcategories, respectively (Table 1). As recommended by the ISTH, PE-related death included subcategory A2 (i.e., objectively confirmed PE before death in the absence of another more likely cause of death) and subcategory A3 (i.e., PE is not objectively confirmed, but is most likely the main cause of death). Inherent to the design of this study, death could not be classified as autopsy-confirmed PE (subcategory A1 of the ISTH classification). Causes of death other than PE (category C) were specified *a priori* and included 1) death related to cancer, defined as death caused by direct effects of a malignancy or death in a subject with progressive cancer who had a gradual decline in general condition or in whom palliative treatment only was decided; 2) cardiovascular death including death due to acute myocardial infarction, stroke, congestive heart failure, arrhythmia, cardiac surgery, systemic embolic disease other than PE, or other cardiovascular disease; 3) fatal bleeding defined as a bleeding event leading to death, such as intracranial hemorrhage with subsequent brain herniation; 4) death due to infection defined as death following septic shock or death cause by direct effects of an infection such as brain abscess with subsequent brain edema leading to death; 5) other known cause of death (e.g., renal failure); and 6) cause of death unknown but the cause of death was most likely other than PE [12]. If the cause of death could not be determined based on the available information, death was classified as subcategory B1 (i.e., cause of death is undetermined, despite available information) or subcategory B2 (i.e., insufficient clinical information available to determine the cause of death).

Statistical analysis

The primary outcome of the study was PE-related death as confirmed by autopsy. Descriptive statistics were used to summarize the cause of death as determined by autopsy and by each adjudicator. The accuracy of the ISTH classification of the cause of death for autopsy-confirmed PE-related death vs death not related to PE was evaluated by estimating the sensitivity, specificity, and positive and negative predictive values (see appendix for detailed definition of numerators and

denominators for sensitivity and specificity). The interrater reliability was determined by estimating the percentage agreement and Cohen's kappa and their 95% confidence intervals (CIs) using the Wilson method and bootstrapping with 2000 replications (percentile method). Kappa coefficients were interpreted as proposed by Landis and Koch: ≤0, poor; 0.01-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; and >0.8, almost perfect [13].

Descriptive statistics and the Wilcoxon rank sum test with continuity correction were used to summarize the certainty of adjudicator 1 and 2 on a 5-point Likert scale regarding their adjudications for patients with concordant and conflicting classifications.

Since previous VTE studies often incorporated unexplained deaths ('PE cannot be ruled out') in their primary definition of PE-related death [3], we performed a sensitivity analysis in which both category A (i.e., subcategory A2 ['objectively confirmed PE before death in the absence of another more likely cause of death'] and subcategory A3 ['PE is not objectively confirmed, but is most likely the main cause of death']) and category B (i.e., subcategory B1 ['cause of death is undetermined, despite available information'] and subcategory B2 ['insufficient clinical information available to determine the cause of death']) were considered to be related to PE (appendix).

All statistical analyses were performed in R, version 3.6.3. [14], using the *tidyverse* package for descriptive analysis, the *boot* package for bootstrapping, and the *irr* package for interrater reliability analysis.

RESULTS

Patient characteristics

A total of 126 patients were included in the analysis (median age, 68 years [range, 21-94 years], 60 [48%] women), of whom 29 (23%) died from PE as confirmed by autopsy (median age, 64 years [range, 28-87 years], 13 [45%] women). The most prevalent causes of death other than PE were infection (26%), cancer (17%), and cardiac death (13%).

Accuracy and interrater reliability of the ISTH classification for the cause of death

The adjudicators classified 14 of 126 (11%) deaths as PE-related (i.e., in subcategory A2 or A3), of which 13 (92%) were PE-related as confirmed by autopsy (Table 2). A total of 13 of 29 (45%) deaths from PE as confirmed by autopsy were correctly classified by the adjudicators. Of the 97 deaths not related to PE, the adjudicators correctly classified 96 as non-PE-related (99%). Overall,

17 of 126 (13%) deaths were misclassified when compared to the autopsy findings. Based on the adjudication results of the expert adjudicators, the ISTH definition's sensitivity, specificity, and positive and negative predictive values for autopsy-confirmed PE-related death were 45% (95% CI, 26-64), 99% (95% CI, 94-100), 93% (95% CI, 66-100), and 86% (95% CI, 78-92), respectively.

The interrater reliability for PE-related death was substantial (percentage agreement, 94% [95% CI, 89-97]; kappa, 0.73 [95% CI, 0.50-0.91]; Table 3). The certainty of adjudicator 1 regarding classification of the cause of death was higher in patients with concordant classifications (median, 3 points; interquartile range [IQR], 2-4 points) than in those with conflicting classifications (median, 2 points; IQR, 1-3 points) (Figure 1A, p=0.005). The certainty of adjudicator 2 was also higher for concordant classifications (median, 4 points; interquartile range [IQR], 2-4 points) than for conflicting classifications (median, 3 points; interquartile range [IQR], 2-4 points) (Figure 1B, p=0.03).

Sensitivity analysis

The adjudicators classified 35 deaths as category B ('undetermined cause of death'), of which 11 (31%) were PE-related as confirmed by autopsy. In a sensitivity analysis in which deaths adjudicated in both category A ('PE-related death) and category B ('undetermined cause of death') were considered to be PE-related, sensitivity, specificity, and positive and negative predictive values for PE-related death as confirmed by autopsy were 83% (95% CI, 64-94), 74% (95% CI, 64-83), 49% (95% CI, 34-64), and 94% (95% CI, 85-98), respectively. Overall, 30 of 126 (24%) deaths were misclassified by the adjudicators using the broader definition of PE-related death which included also deaths classified as having an undetermined cause. The interrater reliability for PE-related death as defined in the sensitivity analysis was moderate (percentage agreement, 71% [95% CI, 62-78]; kappa, 0.41 [95% CI, 0.24-0.57]).

DISCUSSION

In the present retrospective autopsy cohort study, two adjudicators independently determined the cause of death in 126 patients based on clinical summaries using the ISTH SSC's classification for cause of death in clinical VTE studies. The specificity of the ISTH's definition of PE-related death was very high (99%) and its sensitivity was moderate (45%). The interrater reliability for PE-related death as defined per the recommendation of the ISTH's SSC was substantial. Our findings also indicate that the increase in sensitivity (from 45 to 83%) of a broader definition of PE-related death

(i.e., including both PE-related death [category A] and undetermined cause of death [category B]) comes not only at the cost of specificity (decrease from 99 to 74%) but also interrater reliability (decrease of percentage agreement and kappa from 94 to 71% and 0.73 to 0.41, respectively), and increases the proportion of misclassified outcomes from 13 to 24%.

Accurate differentiation between PE-related and non-PE-related deaths in VTE studies is critical, because the number of PE-related death impacts the risk-benefit calculations that clinicians make about anticoagulant therapy or prophylaxis. Our results support the recommendations of the ISTH's SSC to differentiate between PE-related death, undetermined cause of death, and cause of death other than PE, and to include only category A ('PE-related death') and exclude category B (undetermined cause of death) from the primary analysis of the outcome PE-related death [5]. This approach was also preferred by 90% of thrombosis researchers in an online survey that was used to develop the ISTH classification [9].

When deciding on a study outcome and its definition, investigators need to consider the clinical importance of the outcome, as well as the reliability, sensitivity and specificity of the outcome's definition and assessment. Ideally, adjudicators can reliably determine the presence or absence of the outcome, and both specificity and sensitivity are high to correctly rule in or rule out the outcome. If such tests or definitions are unavailable, the optimal approach depends on the aim and design of a study [5], and the anticipated discrepancy of sensitivity and specificity when using a more specific or more sensitive definition. In this regard, our study provides important information: although missing PE-related deaths using a more specific definition is suboptimal, a broader definition does not guarantee to capture all PE-related deaths and leads to a significant dilution of the outcome PE-related death (decrease in specificity from 99% [95% CI, 94-100] to 74% [95% CI, 64-83]). Dilution of the outcome challenges the interpretation of study findings since it may mask relative differences in treatment effects [5], and can lead to a type I error (i.e., rejection of the null hypothesis when it is true) in trials with a non-inferiority design and a type II error (i.e., failure to reject the null hypothesis when it is false) in trials with a superiority design.

Although autopsy is considered the gold standard to determine the cause of death [15], it is rarely performed in VTE studies [3]. Adjudication of outcomes by a central committee may avoid introduction of detection bias and enhance within-study standardization, but only the use of a homogenous outcome definition across studies increases between-study standardization. However, to improve between-study comparisons and the validity of clinical VTE studies, the adjudication of

the cause of death does not only need to be standardized but also reproducible. Our findings indicate that the reproducibility of adjudications for PE-related death using the ISTH definition is good. Importantly, the results in the present study also support findings from a previous study [4], that a broader definition of PE-related death cannot be considered reliable in terms of reproducibility. This poor reproducibility is mainly due to the challenge in distinguishing deaths for which a PE (among other causes) can be considered as cause of death (i.e., category B, undetermined cause of death) from those that are most likely caused by a disease other than PE (i.e., category C). As per the recommendations of the ISTH's SSC, patients who most likely died from a cause other than PE should be classified as category C, even if PE as immediate cause of death cannot be excluded with certainty. However, the determination of adjudicators to dismiss the possibility of PE as cause of death differs, which we consider an important source for most conflicting adjudications in the present study. In autopsy case series, 3 to 6% of sudden or unexplained deaths were caused by PE [6-8]. Since adjudications for death cases for which the cause is undetermined are poorly reproducible and most unexplained deaths are not caused by PE, the inclusion of unexplained death in the primary analysis for the outcome PE-related death cannot be recommended.

The strengths of this study include the adjudication process which mimicked high-quality adjudications of a clinical trial by an independent adjudication committee that was blinded to the case-to-control ratio and the autopsy results, the use of a newly developed online adjudication platform, and the broad population of participants with a wide range of age, even distribution of sex and various causes of death other than PE. Furthermore, the study strictly followed a protocol for the adjudication process of death events and used a pre-specified statistical analysis plan.

This study also has limitations. First, this was a retrospective, single-center cohort study whose participants may not be representative for the population of certain VTE clinical studies. Importantly, the prevalence of PE-related death as well as the proportion of "sudden" or unexplained deaths may vary across studies and thereby influence the accuracy of the ISTH's definition of PE-related death. Patients with "sudden" or unexplained deaths are per definition more likely to be classified into category B ('undetermined cause of death') than patients with other death circumstances. Inherent to the study design, we were unable to determine the prevalence of PE-related death among patients with unexplained death. To increase the transparency of study findings and allow readers to evaluate their validity, it is therefore important to report not only the number of PE-related deaths but also the number of deaths for which the cause is undetermined. Second,

inherent to the patient population and study design, all patients had at least a short narrative on death circumstances. Therefore, only few deaths were classified in category B2 ('insufficient clinical information available to determine the cause of death') by the adjudicators and none of these as category B2 in the final consensus classification. However, we do not expect that this would have meaningfully influenced the results and their implications for future research, since high-quality clinical studies make every effort to obtain information on death circumstances to lower the risk of assessment bias. Third, in contrast to regular clinical VTE studies, autopsy results were not available for adjudications in our study. Albeit autopsies are rarely performed, providing autopsy results to adjudicators would likely lead to an increase in the sensitivity and specificity of the ISTH definition of PE-related death. Fourth, the inclusion period for cases was 2010-2019, while we only included deaths from 2018 as controls which may have led to differences between the two groups related to patient management, reporting of death circumstances and variability of causes of death other than PE. However, we believe that these potential differences might not meaningfully alter the inferences drawn from our findings. For example, there was no change in the frequency of leading natural causes of death in the United States between 2010 and 2016 that would lead to a relevant difference in causes of death other than PE in the present study [16]. Also, we selected all non-PE-related deaths of an entire calendar year as controls to minimize selection bias and include a broad sample of causes of death other than PE. Fifth, 10% of patients that died during the study period at the NewYork-Presbyterian Hospital underwent autopsy which indicates that our study included a selected patient population. Because autopsies are mostly performed in patients in whom the cause of death is uncertain, unexplained deaths are likely overrepresented in our study. However, as clinical information prior to death was detailed and available in all patients, and there was a broad variety of causes of death included in the study, we believe our results are generalizable. Finally, three experienced adjudicators who are experts in thrombosis medicine assessed the cause of death in this study. Whether adjudicators with different experience and training would achieve similar results is unknown.

In conclusion, adjudication of the cause of death using the ISTH's definition of PE-related death and classification for the cause of death in VTE studies resulted in very high specificity, moderate sensitivity, and good interrater reliability for PE-related death. These findings further support the use of the ISTH's definition of PE-related death in clinical VTE studies to improve between-study comparisons and enhance internal and external validity.

AUTHOR CONTRIBUTIONS

Study concept and design: T. Tritschler, N. Langlois, P. Girard, G. Le Gal. Data acquisition: T. Tritschler, S.P. Salvatore. Adjudication of death cases: S.R. Kahn, D. Garcia, A. Delluc. Data analysis: T. Tritschler. Drafting of the manuscript: T. Tritschler, N. Kraaijpoel, G. Le Gal. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the manuscript: All authors.

DISCLOSURES

All authors state that they have no conflicts of interest.

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Table 1. ISTH definition for PE-related death and classification of the cause of death in VTE studies

A) 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 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
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

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

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

Table 2. Adjudicators' final classification by autopsy result.

Adjudicators' final classification	All deaths (N=126)	Autopsy-confirmed PE-related death (n=29)	Autopsy-determined non-PE-related death (n=97)
Subcategory A2	6	6	0
Subcategory A3	8	7	1
Subcategory B1	35	11	24
Subcategory B2	0	0	0
Subcategory C	77	5	72

Abbreviations: PE, pulmonary embolism.

Table 3. Classification of the cause of death by adjudicator 1 (columns) and adjudicator 2 (rows).

Subcategory	**A2**	**A3**	**B1**	**B2**	**C**
A2. Objectively confirmed PE	5	-	-	-	-
A3. PE most likely the main cause of death	3	3	5	-	-
B1. Undetermined despite information	-	1	19	-	13
B2. Insufficient information	1	-	9	-	4
C. Cause of death other than PE	-	-	20	-	43

Abbreviations: PE, pulmonary embolism.

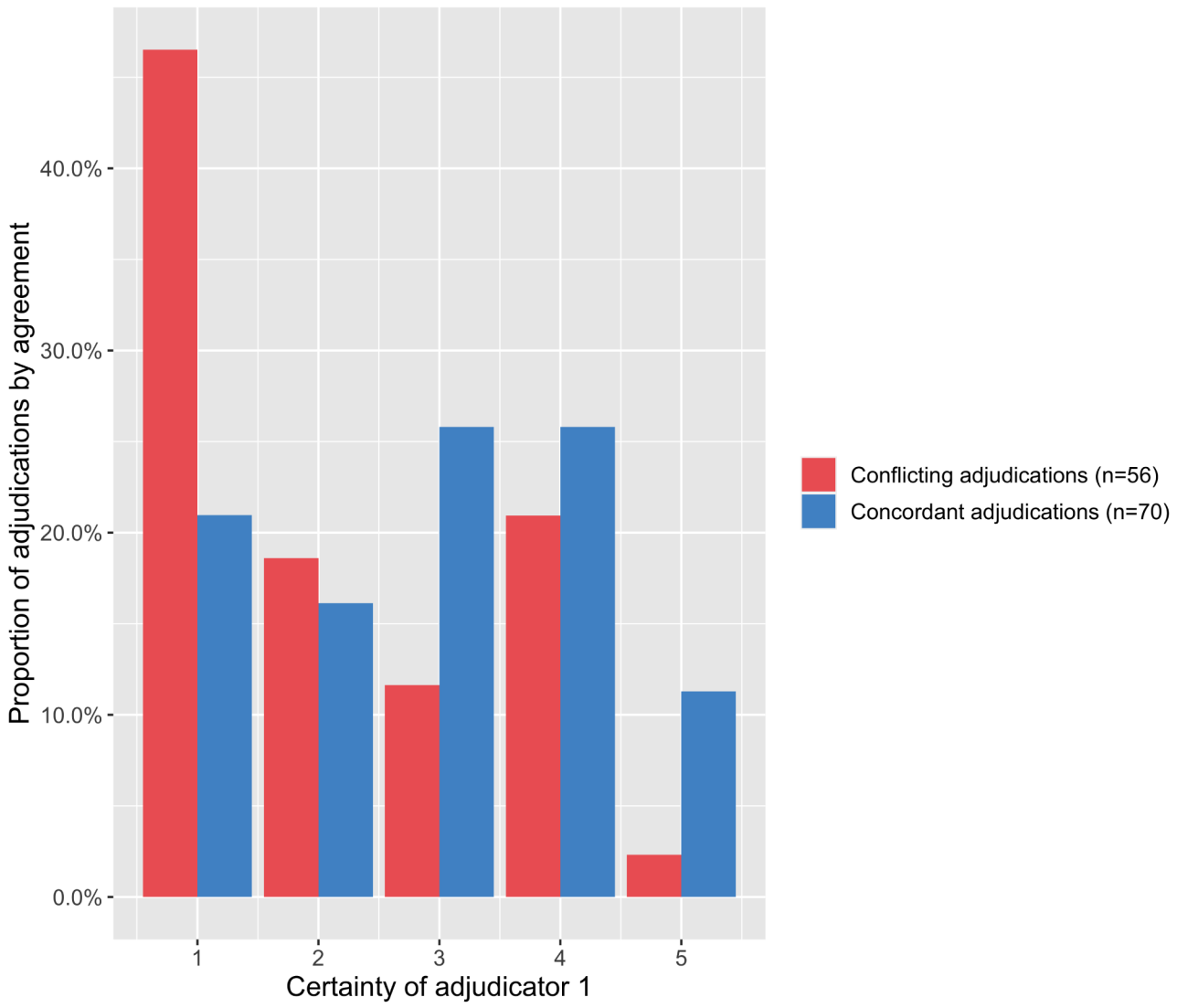
Subcategory A1 is not displayed, because the study design did not allow us to classify death events as autopsy-confirmed PE.

FIGURE LEGENDS

Figure 1. Certainty of the adjudicators regarding their classifications by interrater agreement.

Figure 1A. Adjudicator 1.

Figure 1B. Adjudicator 2.



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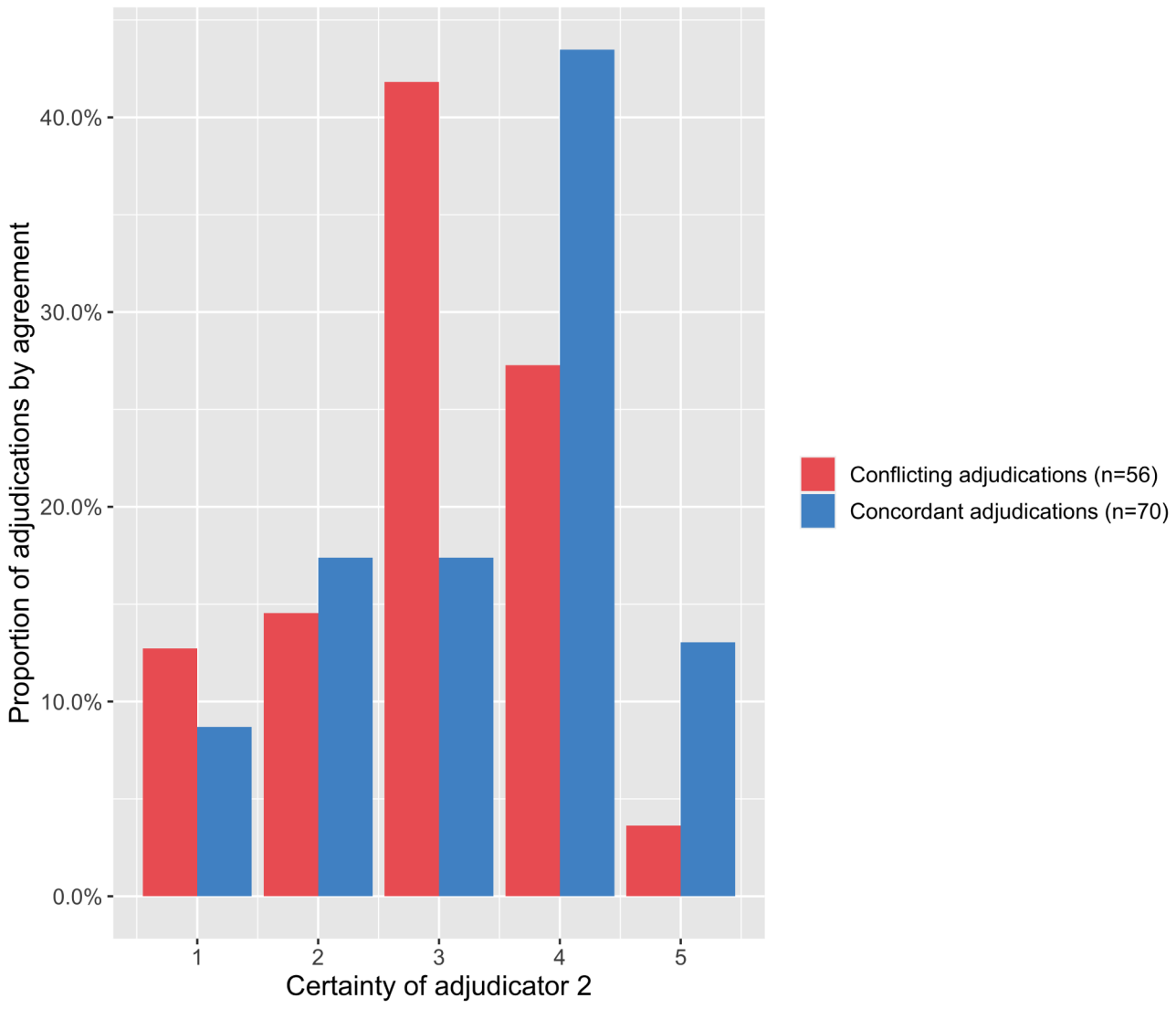

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