ORIGINAL ARTICLE

Defining, exploring the sources and expressing post-mortem diagnostic uncertainty

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Abstract

Background Diagnostic uncertainty is a well-recognized concept in clinical practice, encompassing both technical perspectives and the subjective perceptions of physicians. Post-mortem diagnostics (PMD), which involves all post-mortem investigations to assess diseases and injuries and determine the cause of death, shares this inherent uncertainty due to the complexity and multidisciplinary nature of autopsies.

Methods A comprehensive literature review was conducted to uncover relevant publications focusing on diagnostic uncertainty in PMD. An expert panel evaluated expressions and sources of diagnostic uncertainty to identify factors influencing PMD uncertainty.

Results Literature specifically addressing PMD uncertainty is sparse, though implicit and explicit references exist. This article illustrates the presence of uncertainty in PMD by drawing upon both literature and pathology practice. We introduce the definition of PMD uncertainty as "*the inability to determine the exact cause of death and/or the precise significance of certain autopsy findings*". PMD uncertainty can stem from a pathologist's subjective perception, but often results from several objective factors. Six factors inherent to the PMD setting were identified as contributing to this uncertainty. To systematically express the certainty of cause-of-death determinations, we developed a new Post-Mortem Diagnostic Certainty Scale (PMDCS) featuring eight categories, distinguishing between assignable and non-assignable causes of death.

Conclusion Understanding and applying the concept of PMD uncertainty will enhance comprehension of the importance of certain post-mortem findings and improve the accuracy of autopsy result interpretation. While eliminating PMD uncertainty entirely is not feasible, standardizing investigations can reduce uncertainty, and using the PMDCS can improve the clarity of autopsy reports.

Keywords Diagnostic uncertainty · Post-mortem diagnostics · Cause of death · Autopsy

Background

In the clinical setting, the concept of diagnostic uncertainty is relatively well-established, although no single definition has gained widespread acceptance yet. Ever since Sir William Osler stated long ago that *"Medicine is a science of uncertainty and an art of probability"*, various descriptions have emerged over the years, whether with or without strong philosophical influences [1]. Some authors, such as Mishel, Politi, Cousin and Seely, primarily describe diagnostic uncertainty from a technical or scientific perspective, suggesting that it arises in the first place from insufficient or inadequate knowledge and scientific data [2–5]. Others, including Penrod, Han, Greenhalgh, Sommers and Bhise, focus more on the subjective perception experienced by

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physicians rather than on objective measures [1, 6–9]. In 2017 Bhise et al. proposed, after conducting a systematic review, to define diagnostic uncertainty as "*the subjective perception of an inability to provide an accurate explanation of the patient's health problem*" [1]. Scientific knowledge on diagnostic uncertainty is becoming more clearly defined, although further research is needed to operationalize the definition [10]. Besides a shift towards accepting and embracing diagnostic uncertainty, insights into the importance of managing and communicating diagnostic uncertainty are growing [10–13].

Across most medical specialties, diagnostic uncertainty is a major factor contributing to the overuse of diagnostic testing and treatments, as well as the emergence of diagnostic errors, such as missed and delayed diagnoses [10, 14]. Despite its significance, discussions on the extent and repercussions of uncertainty in the diagnostic process remain rather uncommon at present [14].

Considering that diagnostic uncertainty is inherent in medical practice, it's reasonable to assume that post-mortem diagnostics (PMD) is also susceptible to it. PMD encompasses all investigations conducted after death to assess diseases, injuries, and determine the cause and manner of death. The autopsy, performed in either forensic or clinical settings, remains the primary method and therefore the cornerstone of PMD [15, 16]. Regardless of context, the autopsy is a complex procedure involving multiple observational and cognitive elements and is therefore prone to errors [17]. The extent to which clear and less clear autopsy findings can explain death generally depends on the pathologist's assessment and interpretation. As additional tests, including radiological imaging and laboratory analyses (such as toxicology, microbiology and biochemistry), as well as genetic testing, are frequently necessary to complete the diagnosis, PMD is increasingly recognized as a multidisciplinary field, which inherently adds to the complexity of the diagnostic process [15].

Methods

We conducted a comprehensive review of the literature published before April 2024 to identify relevant English-language publications addressing diagnostic uncertainty and post-mortem diagnostics. Our primary objective was to systematically screen for any reports of or references to post-mortem diagnostic uncertainty. Subsequently, reported expressions and well-known sources of clinical diagnostic uncertainty were evaluated by a Belgian-Dutch multicenter expert panel consisting of experienced specialists in post-mortem diagnostics, including four forensic pathologists, two clinical pathologists, and one expert in biomedical

quality assurance. This panel evaluated whether a translation and/or application to the postmortem setting was appropriate, thus identifying forms of expressions and various factors influencing postmortem diagnostic uncertainty. Furthermore, the panel was tasked with establishing a definition of PMD uncertainty.

Indications for the existence of PMD uncertainty

In literature

Based on our systematic screening of the literature, it is apparent that specific literature on PMD uncertainty is currently lacking. Nonetheless, references to PMD uncertainty, whether explicit or implicit, can be found. For example, some papers discuss difficulties and *uncertainties in death certification* [18, 19]. The College of American Pathologists (CAP) references the concept of *qualifying*, which includes words such as probable, presumed, unknown, unspecified, or undetermined in the cause-of-death statement to express a degree of uncertainty about its accuracy [20]. For the CAP, an *unqualified* cause-of-death statement connotes that the cause has been determined with a high degree of certainty about its accuracy [20]. Additionally, in the determination of the cause of death, Madea and Rothschild (2010) also distinguish between hard (linear type) and soft (more complex and multifactorial) causes, with the latter considered less certain [21].

The National Association of Medical Examiners (NAME) presented a general scheme of incremental '*degrees of certainty*' for manner of death classification based on the circumstances surrounding a particular cause of death, differentiating between 'Undetermined', 'Reasonable medical/investigative probability', 'Preponderance of medical/investigative evidence', 'Clear and convincing medical/investigative evidence', 'Beyond any reasonable doubt', and 'Beyond any doubt' [22]. The concept of a *reasonable degree of medical probability,* that indicates that a particular (post-mortem) diagnosis is more likely than not, is well established in some legal (criminal/civil) systems (e.g. United States) [23].

Furthermore, the existence of *autopsy findings of uncertain significance* in cases of sudden cardiac death has also been mentioned in literature [24]. The varying degrees of certainty (*certain, highly probable and uncertain*) regarding the cause-effect relationship between cardiovascular substrates and sudden death, as outlined in the 2008 and 2017 AECVP (Association for European Cardiovascular Pathology) guidelines for autopsy investigation, serve as a concrete reference for expressing uncertainty within the post-mortem diagnostic process [25, 26].

Table 1 Overview of the factors inherent to the post-mortem setting resulting in PMD Uncertainty

1) Lack of data
a. incomplete investigation
b. insufficient sampling
c. loss of data due to post-mortem changes and destructive forces
2) Unclear medical history, pre-mortem conditions and circumstances of the death
3) Lack of human post-mortem reference values
4) Lack of morphological abnormalities (the so-called negative autopsy)
5) Abundance of pathological findings, findings of unknown significance & multifactorial diseases
6) Lack of scientific breakthroughs and clarifications

In daily practice

Consistent with the existing insights into diagnostic uncertainty in the clinical setting, there are clear indications that pathologists are also confronted with uncertainty within the PMD process.

Analogous to surgical pathology reports, where studies indicate that expressions of uncertainty are found in up to 35% of diagnostic reports, similar direct and indirect expressions can be observed in autopsy practice [27]. The use of question marks in autopsy reports or the addition of words like 'probably', 'maybe', 'likely', 'suggestive of', 'suspicious for', 'consistent with', 'unclear' etc., indicate a certain level of uncertainty [28]. Mentioning rule-out diagnoses or a list of differential diagnoses can also be considered expressions of not being certain [28]. Although the use of probabilistic methods and likelihood ratios in post-mortem diagnostics until now is rare, it serves as another example of expressing uncertainty. Similar to the clinical setting, requesting multiple additional tests or stains could be seen as a more indirect manifestation of uncertainty [14]. Moreover, labeling descriptions as a diagnosis or the absence of an autopsy conclusion can also indicate PMD uncertainty. These seemingly inconspicuous expressions of uncertainty are important clues indicating that PMD is indeed not exempt from diagnostic uncertainty.

Just as it is not common practice in clinical pathology or cytology reports to express diagnostic uncertainty in a standardized manner, conveying PMD uncertainty systematically in reports is similarly uncommon. A prime example of this is the fact that the WHO death certificate format does not provide the opportunity to systematically express doubts about diagnoses or causes of death. The written cause of death and significant conditions contributing to death on the format, are the certifier's *best opinion* [29]. While the use of qualifiers such as 'probable' and 'presumed' is acceptable, the certifier is not expected to indicate the extent of investigation or describe a degree of (un)certainty [20]. Additionally, although some nosological codes permit the indication of unknown or uncertain causes of mortality, there is no provision in ICD-10 or ICD-11 to appropriately express the degree of (un)certainty about an established cause of death [30, 31].

Towards a definition of PMD uncertainty

Until now, literature has not provided a clear description of post-mortem diagnostic uncertainty, and no definition has been established thus far. Some concepts relating to diagnostic uncertainty in a clinical setting are applicable to the post-mortem diagnostic process. Obvious similarities with clinical uncertainty arise, for example, when confronted with incomplete data, lack of experience or inadequate knowledge. However, a major indisputable difference is inherent in the definition of PMD: it can only occur after death. Consequently, an important source of clinical diagnostic uncertainty, stemming from unpredictable disease evolutions or health conditions, is absent. In PMD, death itself is the absolute certainty. This undeniable outcome implies that a literal translation of the existing definitions of clinical diagnostic uncertainty to the post-mortem setting lacks relevance. In formulating a definition of PMD uncertainty, the specific characteristics of the post-mortem context must be taken into account.

Based on our current insights, PMD uncertainty can be defined as **"the inability to determine the exact cause of death and/or the precise significance of certain autopsy findings"**.

Sources of diagnostic uncertainty inherent to the post-mortem setting

PMD uncertainty could merely stem from the subjective perception of the pathologist or person involved in the PMD. Equally important is the recognition that PMD uncertainty often results from objective factors that are fundamentally inherent to the post-mortem setting. Six sources of uncertainty, stemming from these objective post-mortem factors, were identified (see Table 1).

1) Lack of data In the post-mortem setting, a lack of data is not uncommonly the result of incomplete investigations. Despite the introduction and implementation of specific autopsy guidelines and quality protocols over the years, there remains considerable variability in the thoroughness of post-mortem investigations. For instance, not all cases undergo a full autopsy involving the examination of all organs in all body cavities, along with a comprehensive histopathological analysis. Without conducting a brain autopsy or radiological imaging, it is impossible to definitively rule out unexpected intracranial haemorrhage. Similarly, diagnosing myocarditis without performing histopathological investigation is simply not feasible.

Insufficient sampling during autopsy could be another source of incomplete data. Without autopsy samples and without conducting additional toxicological analyses, one cannot diagnose a lethal drug intoxication. Likewise, performing post-mortem genetics is unthinkable without a sample stored after death.

Every corpse undergoes complex changes after death, influenced by various variables that affect the rate and extent of these alterations. In the post-mortem setting, the ability to make certain determinations is closely linked to factors such as the post-mortem interval and any exposure of the corpse to fire or other destructive forces. In cases of advanced decomposition, for example, some investigations become impractical or impossible. Unlike situations involving incomplete investigations or insufficient sampling, no one has control over these post-mortem changes and loss of data, which contribute to PMD uncertainty.

2) Unclear medical history, pre-mortem conditions and circumstances of the death The medical history of an individual, the progression of potential chronic and/or acute conditions and the symptoms before death are crucial for understanding and interpreting post-mortem findings. Cognitive bias and blindness can influence the interpretation of these findings[32]. A lack of pre-mortem clinical data (e.g., in cases of a sudden unexpected death) or the absence of information regarding the circumstances of death (including environmental factors and details of resuscitation attempts) further complicates the interpretation of autopsy findings, thereby increasing PMD uncertainty.

3) Lack of post-mortem reference values Medical imaging and laboratory tests, like all diagnostic tests, have a limited sensitivity and specificity, which diminishes certainty. Interpreting a result requires relevant reference values. Particularly notable in PMD is often the lack of reliable post-mortem reference values [33]. The extent to which the results of a post-mortem sample are representative is questionable due to the immeasurable impact of the post-mortem changes. Numerous (blood) tests used in the clinical setting (e.g., enzymes, inflammation markers, hormones) are therefore unsuitable in the post-mortem context. The absence of robust human post-mortem reference values often renders the distinction between lethal and non-lethal drug concentrations speculative, as evaluating post-mortem toxicological results is rarely straightforward [33].

4) Lack of morphological abnormalities Cardiac arrhythmias (including channelopathies such as LQTS, Brugada, CPVT), certain epilepsy syndromes, and some biochemical disorders capable of causing (sudden) death may present without any observable structural abnormalities. While post-mortem genetics are often indicated in these so-called negative autopsies, genetic testing certainly cannot clarify death in all these cases (yet) [34]. Consequently, conditions without detectable substrate remain a significant source of post-mortem diagnostic uncertainty.

5) Abundance of pathological findings, findings of unknown significance & multifactorial diseases The manifestation of a lethal disease often lacks clear pathognomonic findings, and even when such findings are present, they may not be discernible after death. Uncertainty about the causal relationship between pathological findings and death, as well as the distinction between pathological and normal variants, complicates the interpretation of post-mortem investigation results [24]. Not all findings that could explain death are necessarily its cause, and discovering an abnormality or anomaly does not always equate to finding the cause of death. Uncertainty arises when pathologists are confronted with autopsy findings of unknown significance, especially in cases of sudden death [35].

There is also uncertainty associated with determining the cause of death in patients with complex comorbid medical conditions or in elderly people with multiple pathologies [18]. When numerous morphological abnormalities exist, often with an unclear correlation between them, it becomes challenging to ascertain which findings are decisive and which are less significant. Additionally, diseases with a multifactorial etiology or with more than one possible underlying cause undoubtedly contribute to increased diagnostic uncertainty.

6) Lack of scientific breakthroughs and clarifications It is very clear that syndromes that are not yet fully clarified (e.g. Sudden Infant Death Syndrome) are a source of diagnostic uncertainty [36]. Despite all major advances in genetics, there is still a lot of ignorance about the precise causal effect or impact of some variants. For instance, over the last decade, 8.4% of variants in channelopathy-associated genes have changed pathogenicity status with a decline in overall diagnostic certainty [37].

Conveying (un)certainty in post-mortem findings.

In the post-mortem setting, expressing the degree of diagnostic uncertainty can provide valuable additional information regarding the cause of death and specific autopsy findings. However, effectively communicating the accuracy of these findings remains challenging due to the diverse factors contributing to uncertainty in PMD. Studies on communication in pathology reports reveal substantial variability in how uncertainty is conveyed, emphasizing the need for clear and unambiguous language [38].

To address these communication challenges, we have developed a *Post-Mortem Diagnostic Certainty Scale* (PMDCS), featuring eight categories (see Table 2). While this scale builds upon literature discussing incremental degrees of diagnostic certainty, its foundation is predominantly descriptive rather than semi-statistical [20, 39]. By categorizing diagnoses with specific certainty levels and distinguishing between assignable (category I to III) and non-assignable causes of death (category IV to VII), this scale facilitates a more nuanced understanding for all involved in interpreting autopsy findings. Category VIII indicates primarily that due to the lack of investigation, no clarity can be provided. Conducting further investigations into such deaths will very likely increase the level of certainty.

This PMDCS represents a first step in systematically expressing diagnostic uncertainty in PMD. By promoting transparency regarding the degree of certainty, the scale enhances clarity and consistency in autopsy reports and allows institutions to better evaluate and improve their procedures and methods.

Conclusion

By defining PMD Uncertainty as "*the inability to determine the exact cause of death and/or the precise significance of certain autopsy findings*", we introduce the concept of diagnostic uncertainty within the post-mortem diagnostic field. This article has acknowledged and clarified the existence of post-mortem diagnostic uncertainty and inventoried the objective factors inherent to the post-mortem setting that influence this uncertainty.

Understanding the sources of PMD uncertainty is crucial, as complete elimination is not feasible. The importance of standardized and comprehensive investigations, particularly in forensic and sudden unexpected death cases,

becomes more evident. Incomplete investigations can lead to less certain diagnoses, posing significant issues. In this context, implementing minimum autopsy standards within a quality system could be an important first step.

Ignoring the scope of PMD uncertainty may result in erroneous interpretations and false deductions, with far-reaching consequences for relatives, quality management, statistics, defendants, and others. Both those directly involved in PMD and stakeholders interested in more accurate post-mortem diagnoses, such as clinicians, researchers, healthcare agencies, and legal authorities, need to gain insight into the (un)certainty that lies within an autopsy diagnosis. Reducing diagnostic uncertainty by addressing the controllable sources will ensure more precise and complete diagnoses [14]. Highlighting PMD uncertainty during the diagnostic process conveys the value of post-mortem diagnoses.

The recognition and expression of diagnostic uncertainty in PMD is crucial for improving the accuracy and transparency of autopsy findings. Using a classification system like the *Post-Mortem Diagnostic Certainty Scale* (PMDCS) to express the (un)certainty of cause-of-death determinations could be a significant part of this approach. The PMDCS is a pioneering tool for systematically expressing diagnostic uncertainty in PMD, enhancing autopsy report clarity and enabling the refinement of institutional procedures.

Having a clear definition of PMD uncertainty and a scale for expressing it provides a foundation for future research, enabling more systematic studies and the development of targeted strategies to improve diagnostic accuracy. The insights provided in this article can serve as a starting point to refine the system, with continued investigation and validation improving its applicability and reliability across diverse post-mortem settings.

Keypoints

1. Post-Mortem Diagnostic uncertainty can be defined as "the inability to determine the exact cause of death and/or the precise significance of certain autopsy findings".
2. This study clarifies the existence of post-mortem diagnostic uncertainty and identifies six objective factors inherent to the PMD setting that contribute to this uncertainty.
3. Recognizing and systematically expressing PMD uncertainty aids in more accurate interpretations, supports quality improvement, and emphasizes the value of standardized post-mortem investigations.

Table 2 Post-Mortem Diagnostic Certainty Scale (PMDCS)

Category	Description	Example
I. Absolute Diagnostic Certainty	Assignable cause of death with findings corroborating this conclusion beyond any reasonable doubt. Pathological findings are inconsistent with continued life and the mechanism is obvious. No other explanations are possible	A gunshot wound to the head, sustained while alive, with an exit wound, extensive brain damage, and a bullet found at the scene, confirming the cause of death as a gunshot wound
II. High Diagnostic Certainty	Assignable cause of death with clear and convincing medical evidence. No contradictions in the explanation; minor elements to definitively rule out alternatives may be absent	Occluding coronary plaque rupture with significant, microscopically confirmed myocardial infarction and supporting symptoms such as chest pain and shortness of breath prior to death, leading to the conclusion that a heart attack is the cause of death
III. Moderate Diagnostic Certainty	Assignable cause of death with a preponderance of medical evidence suggesting one explanation is more likely than others	Extensive lung consolidation and positive bacterial cultures in a patient with a history of drug abuse and negative toxicological screening, suggesting pneumonia as the most likely cause of death
IV. Ambiguous Cause of Death	More than one meaningful finding, each with a reasonable degree of medical probability. No clear hierarchy to prioritize one explanation, indicating several plausible causes exist	Autopsy reveals significant ischemic cardiomyopathy and decompensated liver cirrhosis. Either condition could reasonably be considered the primary cause of death
V. Indeterminate Cause of Death with Abnormalities	Certain abnormalities are present, but their link to death remains unknown. Findings of uncertain significance	Autopsy reveals mild myocardial fibrosis and moderate coronary atherosclerosis with no clear evidence linking either to the immediate cause of death
VI. Indeterminate Cause of Death without Abnormalities	No clues to the cause of death after thorough investigation and review of all available information	PMD reveals no significant pathological findings or toxicological abnormalities in a seemingly healthy individual, leaving the cause of death indeterminate
VII. Undeterminable Cause of Death	Not determinable due to the condition of the remains or other insurmountable obstacles, making investigation impossible	A body recovered in an advanced state of decomposition where the remaining tissue has no discernible pathology; making it impossible to determine the cause of death
VIII. Unknown Cause of Death	Any explanation of the death is purely speculative due to the absence of investigation	A body discovered at home with no known medical history or contextual information. As of yet, no autopsy or other investigation has been conducted. Without further investigation, there are no clues to determine the cause of death

This table gives a concise description of each category of the Post-Mortem Diagnostic Certainty Scale (PMDCS) and provides concrete examples to illustrate each category, enhancing the understanding of the different degrees of certainty in determining the cause of death. Categories based on available pathological evidence and investigative findings range from absolute certainty to unknown causes. Categories I to III indicate a level of certainty for deaths where the postmortem findings are sufficiently conclusive, allowing the cause of death to be assigned. In contrast, categories IV to VII represent cases where the postmortem findings are essentially insufficiently conclusive, resulting in a non-assigned cause of death. Category VIII primarily indicates that due to the lack of investigation, no clarity can be provided

Declarations

Ethical approval
Ethical approval was not required for this study.
Conflict of interest
The authors have no competing interests to declare that are relevant to the content of this article. No funds, grants, or other support was received.

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