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ETHICS AND FORENSIC RADIOLOGY

Postmortem computed tomography angiography (PMCTA) and traditional autopsy in cases of sudden cardiac death due to coronary artery disease: a systematic review and meta-analysis

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Abstract

Introduction Several studies have been performed to assess the efficacy of postmortem computed tomography angiography (PMCTA) in solving cases of sudden cardiac death, even in comparison with the traditional autopsy. However, the results were often inconsistent and inconclusive. Therefore, a global discussion on the subject through a systematic review of the literature and a meta-analysis is necessary.

Methods A systematic search of PubMed was performed up to April 23, 2018. Studies exploring the role of PMCTA in cases of sudden cardiac death and the accuracy of this method in diagnosing the cause of death compared to traditional autopsy were included.

Results The overall sensitivity and specificity of the seven included studies, using conventional autopsy as a reference standard, were 92% and 95%, respectively. The positive and negative likelihood ratios were, respectively, 20.76 (95% CI 1.16–370.2) and 0.08 (95% CI 0.03–0.17), showing that PMCTA represents a strong indicator of the posttest probability of disease. The diagnostic odds ratio and the area under the curve were, respectively, 261.54 (95% CI 1.87–5760.53) and 0.93 (95% CI 0.90–0.95), indicating a high diagnostic power of the test.

Conclusion PMCTA demonstrated a high accuracy in the diagnosis of parietal and luminal coronary changes but was less effective in detecting myocardial ischemia and necrosis. Therefore, the only radiological investigation is often insufficient to determine the cause of sudden death and the conventional autopsy remains the gold standard. However, PMCTA can improve the performance of the autopsy, serving as an aid and guide in the sampling phase for histopathological investigations.

Keywords Postmortem computed tomography angiography · Traditional autopsy · Sudden cardiac death · Coronary artery disease

Introduction

Sudden cardiac death (SCD) has been defined as “a natural, unexpected fatal event occurring within 1 h from the onset of symptoms in an apparently healthy subject or in one whose disease was not so severe as to predict an abrupt outcome.” The incidence of SCD increases with age, in line with the increase in the incidence of the coronary artery disease which, according to numerous studies, represents the pathology most frequently involved in the determinism of sudden death (sudden coronary death) [1, 2].

Postmortem examination and autopsy represent reliable methods for determining the causes of SCD [3, 4]. However, due to ethical, religious, cultural, economic and organizational reasons, the number of autopsies performed

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is decreasing worldwide and the use of minimally invasive ancillary methods is considered preferable in some circumstances.

In view of these circumstances, postmortem cardiac imaging is assuming increasing importance in the study of myocardium and coronary arteries as an aid and guide in the execution of conventional autopsy and, sometimes, as an alternative [5, 6].

Currently, postmortem computed tomography (PMCT), postmortem computed tomography angiography (PMCTA), postmortem magnetic resonance (PMMR) and postmortem magnetic resonance angiography (PMMRA) have become established methods due to numerous studies that have documented the undeniable advantages in terms of acquisition times, costs and possibility to review the data acquired at any time [7–13].

A series of studies have been performed over the years to assess the efficacy of PMCTA in solving cases of sudden cardiac death, even in comparison with the traditional autopsy. However, the results are often inconsistent and inconclusive. Therefore, a global discussion on the subject through a systematic review of the literature and a meta-analysis is necessary.

This paper aims at analyzing the diagnostic accuracy of PMCTA in sudden cardiac death cases as well as evaluating the possibility to use this method as an alternative to postmortem examination and conventional autopsy in such cases.

Methods

The systematic review and the meta-analysis were conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement's criteria [14, 15].

Searching strategy

The study was performed using Boolean operators, MeSH terms and free-text terms to expand research and not to exclude potentially relevant articles.

Studies focusing on the role of PMCTA and traditional autopsy in cases of sudden cardiac death due to coronary artery disease were initially searched using PubMed, with the terms "((((((coronary artery disease[MeSH Terms]) OR cardiac death[MeSH Terms]) OR sudden cardiac death[MeSH Terms]))) AND (((((postmortem imaging) OR PMCTA) OR postmortem CTA) OR postmortem computed tomography angiography) OR non-invasive autopsy) OR minimally invasive autopsy) AND ((((conventional autopsy) OR traditional autopsy) OR autopsy) AND full text[sb] AND Humans[Mesh])."

"Full-text," "Humans" and "English" filters have been applied. No time restrictions have been applied. The last research was carried out on April 23, 2018. The PubMed section "similar articles" and the references of the selected articles were used to expand the research.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (1) population consisting of persons who died of suspected sudden cardiac death; (2) evaluation of the accuracy of PMCTA in diagnosing the cause of death and in detecting major or minor diagnostic findings; (3) comparison of the efficacy of PMCTA with the gold standard, the conventional autopsy; (4) availability of the entire panel of true positives (TP), false positives (FP), false negatives (FN) and true negatives (TN), or sufficient data to calculate them. Meanwhile, studies were excluded if they were: (1) case reports; (2) not original research, such as review articles; (3) studies conducted on fetuses.

Data extraction and assessment

Data from each included study were extracted using Microsoft Excel spreadsheets, including information on authors, journal, publishing years, nation, population selection criteria, sample size, gender, age, diagnostic technique under examination, reference standards, as well as results in terms of TP, FP, FN and TN.

The quality of the individual studies was determined through the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Study) tool, structured in four key domains: (1) patient selection; (2) index test; (3) reference standard; and (4) flow and timing. The risk of bias for each domain was considered low, high or unclear in cases where it was not deductible. The studies were considered at low risk of bias if the population selection criterion was clear, if the radiologist and forensic pathologist operated in double-blind, if they both had access to the same information about the case and if the interval between performing the imaging exam and the autopsy was less than 72 h. The studies were considered at moderate risk of bias in the presence of at least one of the following conditions: (1) unclear selection, (2) knowledge by the radiologist or the forensic pathologist of the other test results, (3) latency time between the two investigations exceeding 72 h. The studies were considered at high risk of bias in the presence of two or more of the previously indicated conditions.

Statistical analysis

The meta-analysis was conducted using Stata 13.0 (Stata Corporation, College Station, Texas, USA) [16–19]. The results in terms of TP, FP, FN and TN were used to calculate the sensitivity and specificity in each of the primary studies. The sensitivity and specificity values of the individual studies were graphically represented in a forest plot using the Meta-DiSc software (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain). The heterogeneity between the primary studies was evaluated through the Cochran Q test (Chi-square test) and the Higgins index (I^2). For the synthesis of the results on the PMCTA performances, two random effect models were used: the bivariate model and the HSROC (Hierarchical Summary Receiver Operating Characteristic) model.

Results

Included studies

By applying the search strategy mentioned above, we found a total of 793 studies in PubMed. A total of 767 articles were removed due to irrelevant titles or abstracts; most of them were researches regarding perinatal autopsy and postmortem MRI. After this elimination, 26 papers were eligible for full-text review. Finally, 7 studies were included in the meta-analysis, [20–26] while the others were excluded as they did not meet the eligibility criteria. The process of study inclusion is illustrated in Fig. 1.

The sample size ranged between 5 and 38 with a total of 127 subjects; the publication time was from 2010 to 2014. Three studies evaluated the diagnostic capacity of the PMCTA total body, associated with PMCT and/or biopsy. Four studies, on the other hand, investigated the role of selective coronary PMCTA. The reference standard was represented in all cases by conventional autopsy. The main characteristics of the seven included studies are listed in Table 1.

Risk of bias assessment

The quality of the studies was determined with the QUADAS-2 tool. The risk of bias was globally low or unclear in the four domains except for the reference standard; the latter was at high risk in two studies because the autopsy was performed by a pathologist aware of the results of radiological investigations. Therefore, four studies were considered at low risk of bias, one at low/undefined risk and two at moderate/undefined risk (Table 2).

Qualitative analysis (systematic review)

Bolliger et al. [20] evaluated the diagnostic accuracy of a minimally invasive approach (PMCT, PMCTA, CT-guided biopsy) in 20 cases of apparently natural death of which 11 of sudden coronary death. PMCTA and traditional investigations have agreed in all cases on the cause of death. In only one case, the minimally invasive approach underestimated

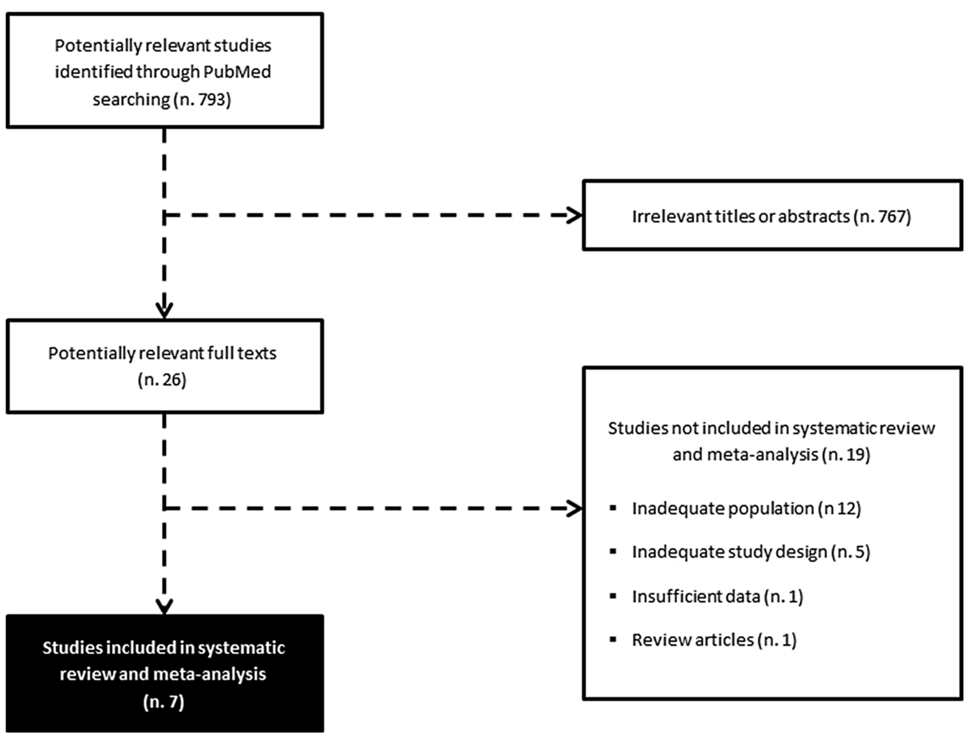


Fig. 1 Flow diagram of study selection process

Table 1 Features of the primary studies included

Authors	Journal and year of publication	Diagnostic test analyzed	Population			Results			
			Mean age (years)	M/F ratio	Sample size	TP	FP	EN	TN
Bolliger et al. [20]	American Journal of Röentgenology (2010)	Whole body PMCTA	56.4 (range 15–82)	16:4	20	11	0	0	9
Roberts et al. [21]	Clinical Radiology (2011)	Selective coronary PMCTA	77 (range 42–92)	8:2	10	8	1	0	1
Ross et al. [22]	Radiology (2012)	Whole body PMCTA	56 (range 15–80)	16:4	20	8	0	1	11
Midland et al. [23]	International Journal of Cardiovascular Imaging (2012)	Whole body PMCTA	52.3 (range 37–89)	21:2	23	20	1	2	0
Morgan et al. [24]	International Journal of Legal Medicine (2012)	Selective coronary PMCTA	– (range 67–86)	3:2	5	2	1	0	2
Inokuchi et al. [25]	Forensic Science Medicine and Pathology (2013)	Selective coronary PMCTA	–	–	38	18	0	2	13
Polacco et a1. [26]	International Journal of Legal Medicine (2014)	Selective coronary PMCTA	51 (range 33–75)	11:0	11	6	0	1	4

Table 2 Risk of bias assessment by QUADAS-2 tool

Studies	Patient selection	Index test	Reference standards	Flow and timing	Risk of bias
Bolliger et al.	Low	Unclear	Unclear	Unclear	Low/unclear
Roberts et al.	Low	Low	Low	Low	Low
Ross et al.	Low	Low	High	Unclear	Moderate/unclear
Midland et al.	Low	Low	Low	Low	Low
Morgan et al.	Low	Low	Low	Low	Low
Inokuchi et al.	Low	Low	High	Low	Moderate/unclear
Polacco et a1.	Low	Low	Low	Low	Low

the severity of ischemic heart disease because, despite the visualization of a coronary thrombotic occlusion, the necrotic area of interest had not been detected.

Roberts et al. [21] compared the diagnostic accuracy of selective coronary PMCTA and autopsy in 10 cases of sudden death. In 8 cases, there was complete agreement between the data obtained from the two tests, while in one case radiological investigations had overestimated the severity of a stenosis that was considered nonsignificant to autopsy. Finally, in one case there was a discrepancy between the two techniques, with a diagnosis of coronary stenosis and ischemic cardiopathy at PMCTA and a diagnosis of hypertensive heart disease and asthma at autopsy.

Ross et al. [22] have shown a concordance between conventional autopsy and PMCTA associated with CT-guided biopsy in 20 cases of sudden death after chest pain. In 8 of the 9 cases of sudden coronary death, the PMCTA had been able to highlight the alterations responsible for the death, while in one case, early myocardial infarction of the papillary muscles had been missed.

Michaud et al. [23] compared the results obtained with PMCT, PMCTA and conventional autopsy in 23 cases of sudden death associated with ischemic heart disease. PMCTA allowed an excellent visualization of the coronary arteries and a better evaluation of stenosis and occlusions. However, PMCTA has not been able to identify early-stage necrosis areas. Furthermore, a postmortem clot had been visualized as a complete perfusion defect resulting in a false positive.

Morgan et al. [24] investigated the sudden death of five subjects with selective coronary PMCTA. Regarding the detection of coronary disease, PMCTA and autopsy showed complete concordance in identifying at least one area of critical stenosis in each case; however, 18 discrepancies were recorded, including 5 major and 13 minor. PMCTA demonstrated poor accuracy in the evaluation of areas downstream of a critical stenosis, while it showed a greater diagnostic accuracy in the detection of coronary calcifications. Finally, PMCTA was unable to identify findings such as intraplaque hemorrhage and dissection with recanalization; however, the unidentified findings did not invalidate the judgment on the cause of death as they were at the level of correctly identified critical stenosis.

Inokuchi et al. [25] compared autopsy findings with those of selective coronary PMCTA in 38 cases of death apparently associated with ischemic heart disease. In 18 cases, both the autopsy and the PMCTA showed coronary lesions that only in 11 cases were causally related to death. In 2 cases, selective coronary PMCTA failed to detect the presence of a critical stenosis. In the remaining 18 cases, both methods did not show coronary disease.

Polacco et al. [26] investigated 11 cases of suspected SCD identifying 7 cases in which the cause of death was attributed to myocardial infarction; in 6 of these cases, the selective coronary PMCTA detected the ischemic area as an area of extravasation of the contrast medium. In 2 cases, the death was attributed to calcific aortic valve stenosis, while in the other two cases toxicological investigations were positive for lethal intoxication.

Statistical analysis (meta-analysis)

Sensitivity was homogeneously high in all studies with values ranging from 86 to 100% (mean value of 92%; CI 95% 0.84–0.97) and absent heterogeneity (p 0.67 at Cochran test; I^2 0%) (Fig. 2).

Specificity showed a wide variability ranging from 0 to 100% (mean value of 94%; CI 95% 0.83–0.99) and high heterogeneity (p 0.01 at the Cochran test; I^2 62.2%) (Fig. 3).

The summary point determined by the HSROC model showed values of 92% (CI 95% 0.84–0.96) for sensitivity and 95% (CI 95% 0.51–0.98) for specificity (Fig. 4). LR+ and LR− were, respectively, 20.76 (95% CI 1.16–370.2) and 0.08 (CI 95% 0.04–0.17); the dOR had a value of 261.54 (CI 95% 1.87–5760.53) (Table 3).

The area under the curve, analyzed using the bivariate model, showed a value of 0.93 (95% CI 0.90–0.95) (Fig. 5).

Discussion

Sudden cardiac death in adults is attributed in most cases to coronary artery disease and its complications, while non-ischemic cardiomyopathies or arrhythmic syndromes in the absence of coronary pathology are responsible for a minority of cases.

Fig. 2 Forest plot of sensitivity

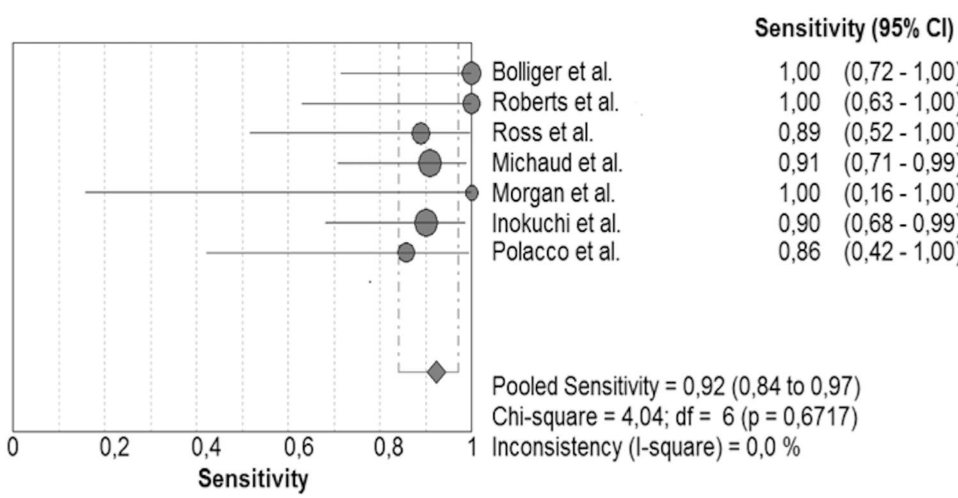
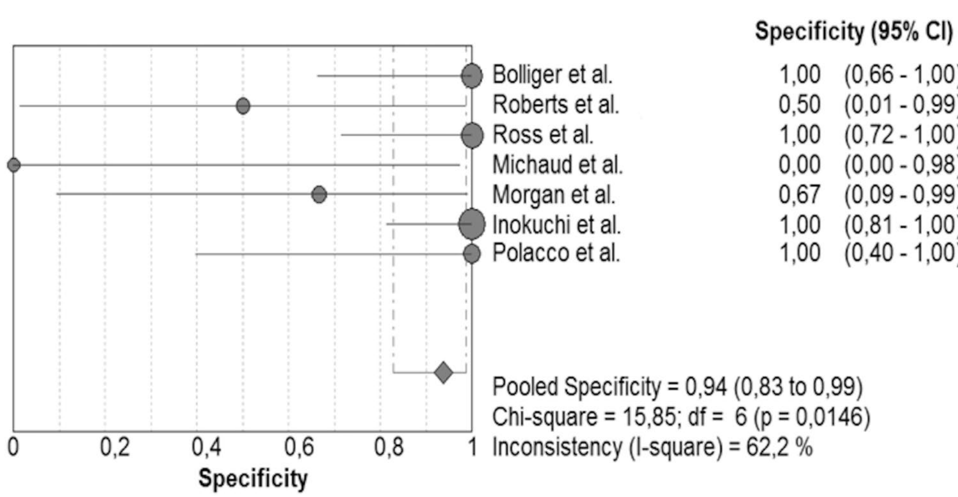


Fig. 3 Forest plot of specificity



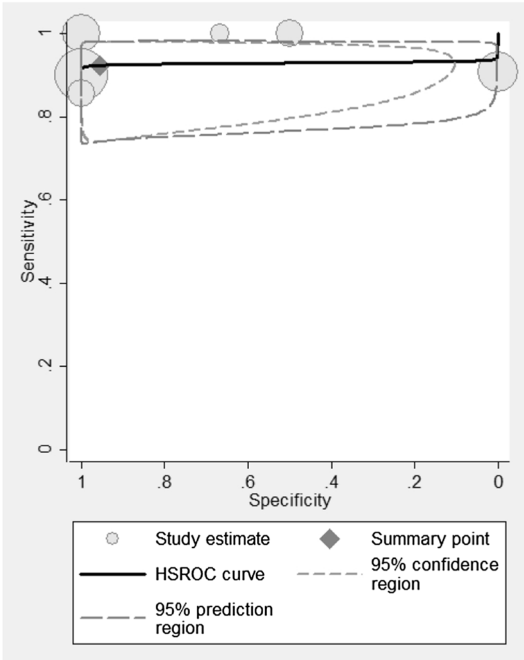


Fig. 4 HSROC model of sensitivity and specificity

Table 3 Metanalysis of the diagnostic accuracy conducted using the HSROC model

	Value	Standards error	95% CI
Sensitivity	0.92	0.3	0.84–0.96
Specificity	0.95	0.6	0.51–1
LR+	20.76	30.15	1.16–370.2
LR−	0.08	0.03	0.04–0.17
dOR	261.54	412.63	1.87–5760.53

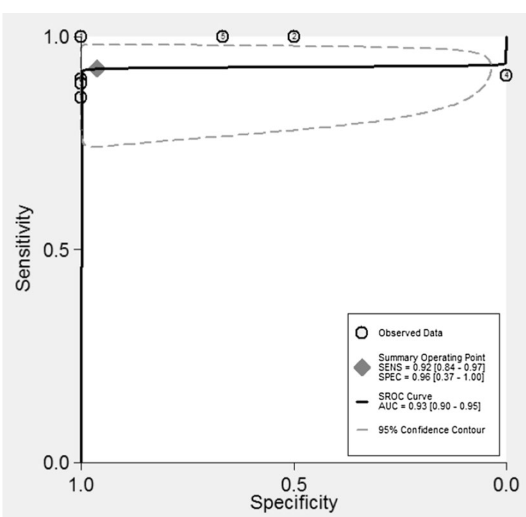


Fig. 5 Bivariat model of sensitivity and specificity

In conventional postmortem investigations, the diagnosis of coronary artery disease or ischemic heart disease is obtained after a complete autopsy followed by a gross examination of the heart and a microscopic examination with histological and immunohistochemical staining. Nevertheless, such investigations require the experience of the pathologist and the application of a rigorous methodological approach to the complex task represented by sudden cardiac death.

Postmortem imaging provides a decisive contribution to forensic pathology, its importance is widely recognized, and its use is increasingly common in forensic practice [27]. This consideration assumes remarkable significance in light of the importance of imaging methods in the approach to cases of sudden cardiac death [28, 29].

Computed tomography (CT) is the most widely used method in modern forensic radiology. Despite the extensive use of this type of investigation, the method presents two major limitations consisting of the low density of soft tissues and the poor visualization of vascular structures. In fact, in the included primary studies that required the execution of a scan without contrast medium before PMCTA, PMCT did not prove useful in the diagnosis of coronary heart disease, being able only to highlight findings such as cardiac tamponade or calcifications of coronary arteries.

Post-Mortem CT Angiography (PMCTA), on the other hand, is a minimally invasive procedure, able to show direct (coronary stenosis or occlusions) and indirect (contrastographic enhancement of the myocardium as a sign of ischemic necrosis) evidence of coronary artery disease with a much higher diagnostic accuracy than unenhanced PMCT [30, 31].

The main advantage of PMCTA is the possibility of visualizing myocardial bridging and alterations of luminal patency without altering the examined vascular structure, as it inevitably occurs during the conventional investigation. In fact, PMCTA studies the vessels throughout their course allowing to identify even small areas of critical stenosis that could be missed by the sections carried out during the autopsy. In addition, PMCTA has shown to be superior to autopsy in investigating the patency of coronary vessels as it is able to demonstrate through perfusion pressure the patency of calcific vessels that had been described as occluded at the autopsy.

Post Mortem CT Angiography also allows the study and three-dimensional evaluation of coronary artery bypass grafts and coronary stents, [32, 33] facilitating the forensic pathologist in the identification of findings difficult to highlight during autopsy due to the adhesion phenomena attributable to the surgical manipulation of the pericardium and heart. The injection of contrast medium finally allows a better assessment of pathological conditions of the myocardium such as traumatic tears or fibrotic areas.

The main limitation of PMCTA is the impossibility of providing data on the functional relevance of a stenosis, being an exclusively morphological imaging technique. The included primary studies have also shown that only a relatively low percentage of ischemic myocardial necrosis was detectable by PMCTA as a contrast enhancement area, documenting a sensitivity limit of this method compared to the histopathological evaluation or other imaging techniques such as PMMR. On the other hand, the tomographic scans are limited by the impossibility of visualizing the vessels downstream of the stenosis and by the difficulty in ascertaining the acute or chronic nature of the stenosis. A further doubt about the diagnostic efficacy of PMCTA could derive from the possibility of a thrombus displacement following coronary artery reperfusion, with consequent failure to visualize coronary occlusion; although the hypothesis cannot be refuted with certainty, several studies have reported as unlikely the possibility that a perfusion pressure lower than the in vivo one can determine the displacement of a thrombus.

The present systematic review and meta-analysis demonstrated the high accuracy of PMCTA in the diagnosis of sudden coronary death. Post Mortem CT Angiography represents a valid tool for the assessment of coronary arteries anatomy, for the detection of stenosis and occlusions, [34] as well as for the guide of sampling for histological examination. At the same time, however, this method has proved less effective in the visualization of myocardial ischemia and necrosis.

There are two major limitations concerning the present study. First, the meta-analysis was performed on a small number of primary studies, many of which had a small population and did not provide enough information to clearly determine the quality of the study. Second, there is a moderate heterogeneity between studies, probably due to the protocol used to perform PMCTA and to the population examined. Therefore, even if an HSROC model was used for data analysis, the results should be interpreted carefully.

For these reasons, to date, autopsy followed by histological examination remains the gold standard for the diagnosis of sudden coronary death. The current trend must be to combine PMCTA with a conventional autopsy to implement the diagnostic quality of postmortem investigations [35]. In fact, PMCTA is extremely useful in cases where a minimally invasive approach is required for several reasons or in cases where a guide to myocardial and coronary sampling is required during the autopsy.

In conclusion, in the field of cardiac pathology, postmortem coronary imaging is still insufficient to establish with certainty the cause of death and autopsy remains the gold standard. Currently, in fact, no radiological technique can replace the histological examination.

The value of this study is in the combination of data from several studies resulting in the evaluation of a larger cohort of subjects as well as in obtaining data more applicable to forensic practice. Nevertheless, further studies are still required to offer better evidence on the use of PMCTA as a routine investigation or as an aid to conventional autopsy.

The role of PMCTA in cases of sudden cardiac death is that of guidance and aid to traditional autopsy. In particular, this investigation can determine an increase in diagnostic performance and ensure a better evaluation of the coronary arteries as well as a more accurate coronary and myocardial sampling [36–40].

For these reasons, postmortem computed tomography angiography must be considered an ancillary method in determining the cause of sudden cardiac death, rather than an alternative to conventional investigations [41, 42].

Authors' contribution All authors contributed to manuscript drafting and critical discussion and approved the definitive version.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This article does not contain any studies with human participants or animals performed by any of the authors. All accepted principles of ethical and professional conduct have been followed.

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