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# BMJ Open

## Diagnosis of the cause of death without autopsy: can virtual autopsy with postmortem CT improve clinical diagnosis?

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Keywords:	Computed tomography < RADIOLOGY & IMAGING, cause of death, postmortem, autopsy, sensitivity, specificity

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8 3 **Diagnosis of the cause of death without autopsy: can virtual autopsy**  
9 **with postmortem CT improve clinical diagnosis?**  
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36 20 **Study design:** retrospective observational cohort study

37 21 **Word count:** 2958  
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34 **Key Words**

35 cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

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37 **List of abbreviations**

38 95% CI                      95% confidence interval

39 PMCT                      postmortem CT

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## Abstract

**Objective:** To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

**Design:** Retrospective observational cohort study. Inclusion criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion criteria: forensic cases, organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as the standard of reference, we compared the correctly identified causes of death, types of pathology and anatomical system involved before and after virtual autopsy using McNemar tests.

**Setting:** Tertiary referral center.

**Participants:** 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

**Intervention:** PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with or without brain autopsy.

**Primary and secondary outcome measures:** The number of correctly identified causes of death, types of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved.

**Results:** Using PMCT, the number of correctly identified immediate causes of death increased from 53% (95% CI 41 to 64) to 64% (53 to 75) ( $p=0.05$ ), type of pathology increased from 65% (54 to 76) to 83% (73 to 91) ( $p=0.001$ ) and the identification of the anatomical system increased from 65% (53 to 75) to 84% (74 to 92) ( $p=0.001$ ).

**Conclusion:** While postmortem CT cannot substitute for conventional autopsy, it can significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy would be desired but is turned down by the deceased's relatives.

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3 67 **Article summary**

4 68 **Strengths and limitations of this study**

5  
6 69 In light of decreased autopsy rates, this study investigated whether virtual autopsy with postmortem  
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8 70 CT improves clinical diagnosis of the immediate cause of death, with autopsy as the reference  
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10 71 standard, rather than only describing the diagnostic accuracy of postmortem CT.  
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14 73 In addition to scoring the type of pathology and anatomical system involved, the diagnostic accuracy  
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16 74 of a detailed immediate cause of death diagnosis was investigated.  
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21 76 Retrospective observational cohort study, with relative small sample sizes per type of pathology and  
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23 77 anatomical system.  
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27 79 Cause of death was not a categorical variable, so specificity for immediate cause of death diagnosis  
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29 80 could not be calculated.  
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3 81 **Contributors:** LJPS had full access to all of the data in the study and takes responsibility for the  
4 82 integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS  
5 83 and WMK interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised the study.  
6 84 LJPS, WMK and WMP contributed to the overall conception and design of the study. All authors  
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11 89 support from any organization for the submitted work, no financial relationships with any  
12 90 organizations that might have an interest in the submitted work in the previous three years, and no  
13 91 other relationships or activities that could appear to have influenced the submitted work.

14 92 **Ethical approval:** This study was approved by the local ethical committee in the form of a waiver in  
15 93 accordance with Dutch national law.

16 94 **Data sharing:** Details on how to obtain additional data from the study (eg, statistical code, datasets)  
17 95 are available from the corresponding author.

18 96 **Transparency:** The lead author affirms that this manuscript is an honest, accurate, and transparent  
19 97 account of the study being reported; that no important aspects of the study have been omitted; and  
20 98 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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## 107 Introduction

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109 Autopsies are regarded as the 'gold standard' in quality monitoring of health care. It is therefore

110 remarkable that in a time of heightened interest in patient safety, error prevention and healthcare

111 quality, worldwide autopsy rates continue to decline from roughly 40% in the nineteen sixties, to

112 below 10% nowadays<sup>1-7</sup>. Both religious and emotional objections against the invasiveness of

113 conventional autopsies, both by the relatives and the doctors, are considered as some of the reasons

114 for this decline. At present, determination of the cause of death relies heavily on clinical assessment.

115 Despite an increase in the use and improvement of diagnostic techniques in the last decades, major

116 error rates of approximately 25% for the primary cause of death have not substantially decreased<sup>8,9</sup>.

117 Accuracy rates of clinical diagnoses of the immediate cause of death are probably even lower<sup>10,11</sup>.

118 Therefore, there is a need to improve clinical diagnoses using techniques that are widely available

119 and acceptable, for example, postmortem CT (PMCT). Previous studies have shown that, as yet,

120 PMCT is insufficient to substitute for conventional autopsy<sup>12,13</sup>. This study investigates whether

121 virtual autopsy with PMCT improves clinical diagnosis of the immediate cause of death.



## 122 **Material and methods**

### 123 **Study design**

124 All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT  
125 and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic  
126 cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-  
127 abdomen autopsy, were excluded. Informed consent was obtained from the relatives for PMCT and  
128 autopsy. This retrospective study was approved by the local ethical committee in the form of a  
129 waiver in accordance with Dutch national law.

### 130 **PMCT and conventional autopsy**

131 PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few  
132 hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were  
133 Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion  
134 ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction  
135 interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation  
136 time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s.  
137 PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting,  
138 interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal  
139 settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single  
140 consensus report, all with minimal previous experience in interpreting PMCT images. Conventional  
141 autopsy consisted of thoracic-abdominal autopsy with or without examination of the brain, and  
142 included full macroscopic and microscopic inspection. Radiologists and pathologists were blinded to  
143 each other's results, and compiled a report based on their own findings and the clinical information  
144 present on the requisition form.

### 145 **Data collection**

146 For each cadaver the immediate cause of death, type of pathology and anatomical system involved,  
147 were collected in retrospect at three moments: before virtual autopsy, after virtual autopsy and

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2  
3 148 based on autopsy findings. The cause of death before virtual autopsy was based on clinical findings  
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5 149 only. The cause of death after virtual autopsy was based on both clinical findings and PMCT. If no  
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7 150 cause of death could be assigned at PMCT, the cause of death was based on clinical findings only.  
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9 151 Symptoms (for example, respiratory failure, sepsis etc.) and risk factors (atherosclerosis,  
10  
11 152 hypertension) were not considered as cause of death. Only when the primary source of sepsis (for  
12  
13 153 example pneumonia) was unknown, sepsis was diagnosed as cause of death. In cases of trauma, the  
14  
15 154 physical injury rather than the mechanism of trauma was assigned as cause of death.

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18 155 Type of pathology was scored according to the following categories; infection, hemorrhage,  
19  
20 156 perfusion disorder, other or not assigned. Perfusion disorders comprised all cardiac and vascular  
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22 157 perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial  
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24 158 infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with  
25  
26 159 hemopericardium were grouped in the hemorrhage category. The type of anatomical system was  
27  
28 160 scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and  
29  
30 161 subcategories used were derived from the classifications of anatomical regions and groups of  
31  
32 162 pathologies as used by Roberts and Wichmann et al.<sup>4,12</sup>.

### 33 34 35 36 163 **Statistical analysis**

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38 164 The number of correctly identified causes of death, type of pathology and anatomical system were  
39  
40 165 calculated with autopsy as the standard of reference. Sensitivity and specificity were calculated for  
41  
42 166 type of pathology and anatomical system subgroups. Cases where the outcome was not assigned  
43  
44 167 after autopsy were excluded from statistical analysis. McNemar tests (2-sided) were used to test for  
45  
46 168 significant differences before and after virtual autopsy. Logistic regression analysis was performed to  
47  
48 169 evaluate the influence of radiologists' experience. P values of 0.05 or less were considered  
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50 170 significant. IBM SPSS Statistics, version 22 was used.  
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## 171 Results

172 Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen  
173 autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on  
174 78 (4%) cadavers. One case was excluded due to organ donation prior to PMCT. A further nine out-  
175 of-hospital deaths on which PMCT and autopsy were performed, but who were not clinically  
176 examined in our hospital or by our emergency medical service, were included, leading to a total of 86  
177 cases (51 men, 35 women, with a mean age of 59 years). 54% of the deaths were after a resuscitation  
178 attempt. The mean postmortem interval between death and PMCT was 11 hours. In 69% there was  
179 no consent for brain autopsy and, in those cases, conventional autopsy consisted of a thorax-  
180 abdomen examination only.

181 An immediate cause of death was not found by autopsy in ten cadavers (12%). In 29 (34%) cadavers  
182 the immediate cause of death was not assigned before virtual autopsy, and not in seventeen (20%)  
183 cadavers after virtual autopsy. In two of the cases without an immediate autopsy cause of death, an  
184 intracerebral hemorrhage and a pulmonary embolism (Figure 1A), there was consensus between the  
185 clinicians and the radiologists as for the cause of death. In the first case, there was lack of consent to  
186 a brain autopsy and in the second case, the pulmonary embolism was not diagnosed at autopsy. In  
187 two other cases with unknown cause of death at autopsy, aspiration and heart failure were  
188 diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal  
189 focus and myocardial infarction were diagnosed by the clinicians. Both before and after PMCT, the  
190 cause of death was unknown in the remaining six cases.

### 191 The additional value of PMCT

192 The number of correctly identified causes of death before virtual autopsy was 53% (95% CI: 41-64%)  
193 and increased to 64% (95% CI 53-75%) after performing a PMCT scan. This improvement was  
194 statistically significant ( $p=0.05$ ). The potential value of PMCT increased further, when PMCT was used  
195 to indicate the type of pathology ( $p=0.001$ ) or anatomical system ( $p=0.001$ ) involved in the cause of  
196 death. The number of cases in which type of pathology was correctly identified increased from 65%

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3 197 (95% CI: 54-76) to 83% (95% CI: 73-91), and from 65% (95% CI: 53-75) to 84% (95% CI: 74-92) for  
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5 198 anatomical system (Table 1).

### 199 **Evaluation of cause of death, per type of pathology**

100 Table 2 shows all autopsy causes of death, classified by type of pathology and whether they were  
101 correctly appointed as cause of death before and after PMCT.

102 Pneumonia was the most common infectious cause of death. After PMCT, pneumonia was correctly  
103 diagnosed and assigned as the cause of death in 73%. In the other 27%, pneumonia was recognized,  
104 but not assigned as the cause of death. In two other patients, who had died from cerebral  
105 aspergillosis and heart failure, the ancillary pneumonia was incorrectly assigned as the cause of  
106 death on PMCT. Using PMCT, two cases of peritonitis (due to a misplaced gastrostomy button and  
107 ventriculoperitoneal drain) and one case of pancreatitis, which were clinically missed, were correctly  
108 diagnosed as cause of death. In one case, pneumonia was correctly diagnosed as cause of death after  
109 PMCT, where clinicians had incorrectly attributed death to interstitial lung disease.

110 In the group of perfusion disorders, all pulmonary embolisms were diagnosed at PMCT as cause of  
111 death. Furthermore, radiologists correctly diagnosed two arrhythmias, one heart failure and one  
112 volvulus which were initially missed as cause of death by the clinicians. Cardiac arrhythmia was  
113 suspected based on local hyperdensity of myocardial tissue corresponding to fibrosis and, in the  
114 other case, heart failure was based upon secondary characteristics, such as dilated atria and pleural  
115 effusion, in the absence of other significant findings. Myocardial infarction was correctly diagnosed  
116 as cause of death in 44% after PMCT. However, in 71% of these cases, radiologists did not appoint a  
117 cause of death, mostly due to absence of significant findings, and myocardial infarction as the cause  
118 of death was based on clinical findings only. In the other 29% (n=2), myocardial infarction was also  
119 suspected by the radiologists; in one case due to an intravascular hypodensity proximal of a coronary  
120 stent and in the other case due to the combination of significant coronary calcifications, enlarged  
121 right atrium, clinical history and absence of other significant findings.

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3 222 Using PMCT, hemorrhagic causes of death were correctly diagnosed in 85%. All five aortic dissections  
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5 223 were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic case,  
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7 224 radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed hemothorax  
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9 225 and a liver and kidney rupture (Figure 1B). In another traumatic case were death was attributed to  
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11 226 hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left coronary  
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13 227 artery (Figure 1C).

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16 228 In the category of other pathologies, PMCT showed an esophageal mass which was determined by  
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18 229 conventional autopsy as the primary tumor in a case with cerebral metastases where the primary  
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20 230 tumor was clinically unidentified. Two other cases of metastasized cancer (esophageal and breast)  
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22 231 were both before and after PMCT correctly diagnosed as cause of death. Three other cases with  
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24 232 cancer at time of death died from complications (septic cholecystitis, carotid artery bleeding and  
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26 233 endocarditis due to immunodeficiency).

#### 27 28 29 234 **Sensitivity and specificity for type of pathology and anatomical system subgroups**

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32 235 Based on type of pathology, the subgroup of perfusion disorders showed a significant improvement  
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34 236 ( $p=0.04$ ) in sensitivity from 56% to 76%, using PMCT (Table 3). When categorized based on  
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36 237 anatomical system, the cardiovascular subgroup showed a significant improvement ( $p=0.02$ ) in  
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38 238 sensitivity from 62% to 82%. There were no significant differences in specificity within the subgroups  
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40 239 before and after PMCT.

#### 41 42 43 240 **Performance of radiologists**

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46 241 Logistic regression analysis showed no trend in the number of correctly identified causes of death  
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48 242 ( $p=0.41$ ), type of pathology ( $p=0.81$ ) or anatomical system ( $p=0.41$ ) as diagnosed by the radiologists,  
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50 243 over the four years of initial experience in interpreting PMCT images.  
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## 244 Discussion

245 The number of correctly identified clinical diagnosis of the immediate cause of death increased from  
246 53% to 64% ( $p=0.05$ ) after performing PMCT, using conventional autopsy as the reference standard.  
247 Our analysis showed that the value of PMCT is variable per subcategory and depends on the cause of  
248 death. Where infections played a role, the added value of PMCT is moderate. Normal postmortem  
249 changes, such as the occurrence of pulmonary edema, could mask pneumonia (Figure 1D)<sup>14</sup>. In the  
250 subgroup of perfusion disorders, pulmonary embolisms, as diagnosed by radiologists, were not  
251 confirmed during autopsy in three of the six cases (Figure 1A). This could be due to difficulty to  
252 distinguish an ante-mortem thrombus from a post-mortem blood clot with PMCT, or the possibility  
253 that the embolus was lost during the autopsy procedure<sup>15-17</sup>. There were no false-negative findings  
254 for pulmonary embolisms as cause of death on PMCT. Furthermore, most causes of death in this  
255 subgroup were cardiac related. Clinicians are restricted in their ability to differentiate a cause of  
256 death, for example, cardiac malfunction, significant internal bleeding, aortic dissection or  
257 pneumothorax, due to the acute nature and time constraints of the situations (resuscitation setting)  
258 these patients present with. Cardiac causes of death are also difficult to diagnose with PMCT and by  
259 autopsy. For example, heart failure and cardiac arrhythmias are clinically diagnosed by means of  
260 dynamic examinations, such as echocardiography and electrocardiography. Postmortem  
261 angiography, now being developed and validated, can be effective in demonstrating any obstructing  
262 thrombi<sup>18</sup>. Autopsy can only detect a myocardial infarction in cases where patients have survived  
263 two to three hours post-infarction<sup>19</sup>. However, when secondary characteristics, such as dilated atria,  
264 or pulmonary edema are observed in the absence of other significant pathologies, both PMCT and  
265 autopsy can indicate a cardiac cause of death.

266 Table 1 shows increasing value of PMCT in identifying the type of pathology or anatomical system  
267 involved, indicating that even when the cause of death is inconclusive after PMCT, it is still a valuable  
268 tool in targeting the region of interest or excluding some of the differential diagnostic possibilities.  
269 This particularly applies to cardiac causes of death, as shown by the significant increase in sensitivity

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3 270 for perfusion disorders as type of pathology and the cardiovascular system as anatomical system  
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5 271 involved (Table 3). Clinical evaluation of the cause of death often indicates the failing system (for  
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7 272 example, respiratory failure) rather than the underlying illness or structural changes, whereas  
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9 273 radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how  
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11 274 confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.  
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14 275 Amongst non-invasive techniques, Blokker et al. conclude that PMCT and postmortem MRI yield the  
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16 276 highest diagnostic performance in adults, with PMCT performing somewhat better when only one of  
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18 277 the modalities is used<sup>12,13</sup>. PMCT is less expensive than a conventional autopsy, however, cost-  
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20 278 effective analyses have not been formulated. Images can be stored digitally (useful for legal or  
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22 279 educational purposes) and results can be audited and promptly reviewed by one or more  
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24 280 radiologists. Amongst minimally invasive methods, the highest performance is reported in studies  
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26 281 combining PMCT and CT-angiography. PMCT, enhanced with targeted coronary angiography, showed  
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28 282 a sensitivity of 92% for cause of death<sup>17</sup>. Two studies combining CT, CT-angiography and CT-guided  
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30 283 tissue biopsies achieved a pooled sensitivity of 91% for cause of death<sup>20,21</sup>.  
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34 284 To our knowledge this is the second study which has investigated the additional value of PMCT  
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36 285 compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in  
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38 286 sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths<sup>22</sup>. This is  
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40 287 somewhat higher than we found in our study, one reason could be the fact that less specific causes  
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42 288 of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT  
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44 289 compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some  
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46 290 use broadly defined categorizations and others use well-defined specific causes of death, or some  
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48 291 use the immediate cause of death and others the intermediate or underlying cause of death, or do  
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50 292 not state their definition of cause of death at all. Furthermore, most previous studies consisted of  
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52 293 small sample sizes (n<50) and used different study populations, different outcome parameters (for  
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54 294 example, cause of death, major or minor diagnoses) and different parameters of accuracy<sup>4,23-25</sup>. A

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3 295 large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32%  
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5 296 in determining the cause of death with PMCT compared to autopsy<sup>12</sup>. Another study showed a  
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7 297 sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in  
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9 298 101 cases<sup>26</sup>. This is in accordance with our results regarding the categorization of cause of death per  
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11 299 type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause  
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13 300 of death and 5/17=19% for a more specific description of the involved pathogenetic mechanism<sup>23</sup>.  
14  
15 301 Another study by Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both  
16  
17 302 definite and possible findings with PMCT as to cause of death<sup>24</sup>. The study by Puranik et al. supports  
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19 303 our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT<sup>25</sup>. A  
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21 304 sensitivity of 25% for cause of death was found in a population of seventeen young patients with  
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23 305 sudden cardiac death.  
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26 306 Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure  
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28 307 1D), are more confidently diagnosed with PMCT than autopsy<sup>12,27</sup>. Therefore, the presented  
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30 308 performance of PMCT will probably be underestimated in cases where pathologies are difficult to  
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32 309 confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no  
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34 310 longer be considered as the gold standard for all postmortem diagnoses, not only due to the  
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36 311 limitations of dissection, but also due to the decline in the number of autopsies performed, leading  
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38 312 to a decrease in pathologists' expertise. We would suggest a gold standard involving a  
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40 313 multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective  
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42 314 studies with larger sample sizes are required to investigate the additional value of PMCT in specific  
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44 315 subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques,  
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46 316 conventional autopsy will still be required in complex cases where clinical and radiological diagnosis  
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48 317 as to cause of death is inconclusive.  
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3 318 **Conclusion**

4 319 While virtual autopsy with postmortem CT cannot substitute for conventional autopsy, it can  
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6 320 significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone. Even in  
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8 321 cases where no immediate cause of death can be assigned after virtual autopsy, radiologists may  
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10 322 indicate a region of interest, so directing pathologists at autopsy. Future studies are needed to  
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12 323 investigate whether PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy  
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14 324 altogether.  
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## 393 **Figure legends**

### 394 **Figure 1. Examples of discrepant imaging and autopsy findings.**

395 **A.** A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia  
396 cicatrix correction with invagination complications. An ultrasound scan during resuscitation revealed  
397 pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2)  
398 pulmonary arteries. Autopsy did not assign a cause of death.

399 **B.** A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right  
400 side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a  
401 spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further  
402 findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-  
403 abdominal blood along the spleen.

404 **C.** A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical  
405 examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some  
406 other underlying pathology which may have caused the accident. During air ambulance transportation,  
407 ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1),  
408 probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not  
409 diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the  
410 pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

411 **D.** A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma.  
412 Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative  
413 disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of  
414 death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural  
415 fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings.  
416 Bronchopneumonia was not diagnosed at PMCT.

417 **Tables**

418

419 **Table 1. Number of correctly identified causes of death, types of pathology and anatomical system involved,**  
420 **before and after virtual autopsy with PMCT.**

	<b>Before PMCT (95% CI)</b>	<b>After PMCT (95% CI)</b>	<b>Significance (p-value)</b>
<b>Immediate cause of death</b> Identified at CA (n=76) <sup>a</sup>	53% (41-64%)	64% (53-75%)	0.05
<b>Type of pathology</b> Identified at CA (n=78) <sup>a</sup>	65% (54-76%)	83% (73-91%)	0.001
<b>Anatomical system</b> Identified at CA (n=77) <sup>a</sup>	65% (53-75%)	84% (74-92%)	0.001

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422

<sup>a</sup> Group sizes differ as autopsy was did not assign a cause of death in ten cases, a type of pathology in eight cases and anatomical system in nine cases.

423 **Table 2. Overview of all autopsy causes of death, classified by type pathology and whether they were**  
 424 **correctly diagnosed as the immediate cause of death before and after virtual autopsy. *Incorrect causes of***  
 425 ***death, as diagnosed after virtual autopsy, are stated in italics.***

	Correct COD, both before and after PMCT.	Incorrect COD before PMCT. Correct COD after PMCT.	Correct COD before PMCT. Incorrect COD after PMCT.	Incorrect COD, both before and after PMCT.
<b>Infections</b>	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i. <sup>b</sup> 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis <sup>a</sup> 1x diverticulitis and pancreatitis	1x endocarditis ( <i>pericarditis</i> ) 1x HSV hepatitis ( <i>urosepsis</i> ) 1x cerebral aspergillosis ( <i>pneumonia</i> )	4x pneumonia ( <i>1x COPD, 1x PTLN, 1x fibrotic lung disease, 1x not assigned</i> ) 1x endocarditis / pericarditis ( <i>fistula ureter vs. bowel</i> )
<b>Perfusion disorders</b>	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure ( <i>pneumonia</i> )	9x myocardial infarction ( <i>7x not appointed, 1x mediastinitis, 1x pulmonary embolism</i> ) 3x arrhythmia ( <i>1x pulmonary embolism, 1x myocardial infarction, 1x not assigned</i> ) 2x heart failure ( <i>1x pulmonary air embolism, 1x not assigned</i> ) 1x pulmonary veno- occlusive disease ( <i>not assigned</i> ) 1x bowel ischemia due to adhesions ( <i>infected aorta graft</i> )
<b>Hemorrhages</b>	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax ( <i>coronary artery air embolism</i> ) 1x liver and kidney rupture + hemothorax ( <i>spleen rupture + hemothorax</i> )
<b>Other</b>	1x breast cancer 1x esophageal cancer 1x anaphylaxis 1x (auto-)intoxication	1x esophageal cancer		

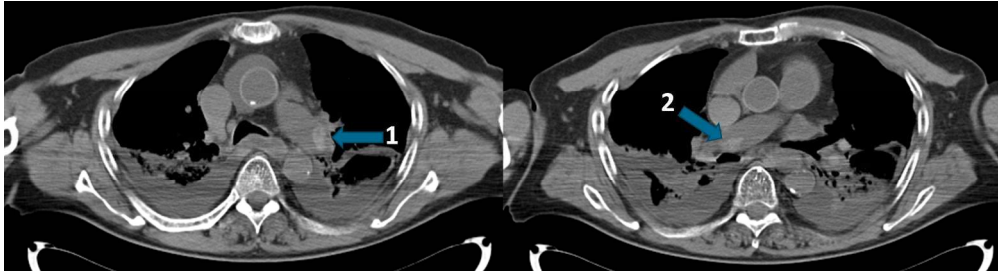
426 <sup>a</sup> Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced  
 427 ventriculoperitoneal drain in another case. <sup>b</sup> sepsis e causa ignota. COD: cause of death.

428 **Table 3. Sensitivity and specificity per subgroup of type of pathology and anatomical system, diagnosed**  
 429 **before and after virtual autopsy with PMCT.**

	Sensitivity			Specificity		
	Before PMCT	After PMCT	Sign <sup>a</sup>	Before PMCT	After PMCT	Sign <sup>a</sup>
<b>A. Type of pathology (n=78)<sup>c</sup></b>						
1. Infection (n=26)	69%	85%	NS <sup>b</sup>	96%	92%	NS <sup>b</sup>
2. Hemorrhage (n=13)	69%	92%	NS <sup>b</sup>	98%	100%	NS <sup>b</sup>
3. Perfusion disorder (n=34)	56%	76%	0.04	95%	93%	NS <sup>b</sup>
4. Other (n=5)	100%	100%	N/A <sup>d</sup>	99%	99%	NS <sup>b</sup>
<b>B. Anatomical system (n=77)<sup>c</sup></b>						
1. Pulmonary (n=18)	72%	89%	NS <sup>b</sup>	95%	95%	NS <sup>b</sup>
2. Cardiovascular (n=39)	62%	82%	0.02	100%	95%	NS <sup>b</sup>
3. Gastrointestinal (n=13)	54%	85%	NS <sup>b</sup>	98%	100%	NS <sup>b</sup>
4. Other (n=7)	86%	86%	NS <sup>b</sup>	97%	94%	NS <sup>b</sup>

430 <sup>a</sup> Significance (p-value). <sup>b</sup> NS: not significant. <sup>c</sup> Autopsy was not able to establish the type of pathology and  
 431 anatomical system involved in eight and nine deaths respectively. <sup>d</sup> Not applicable.

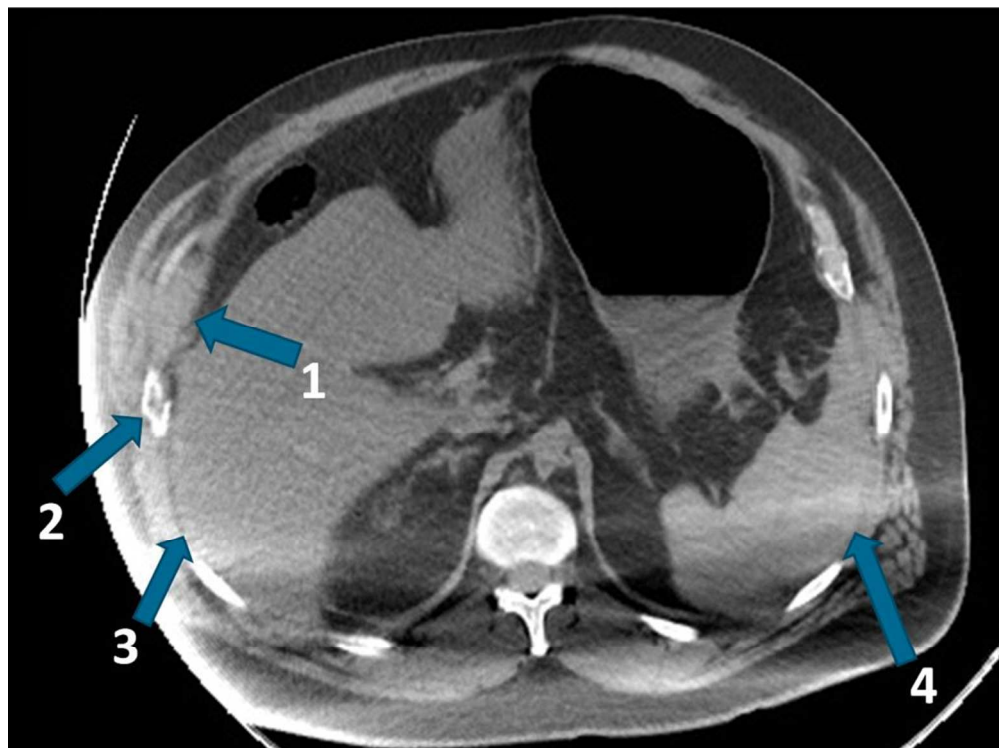




A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricial correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

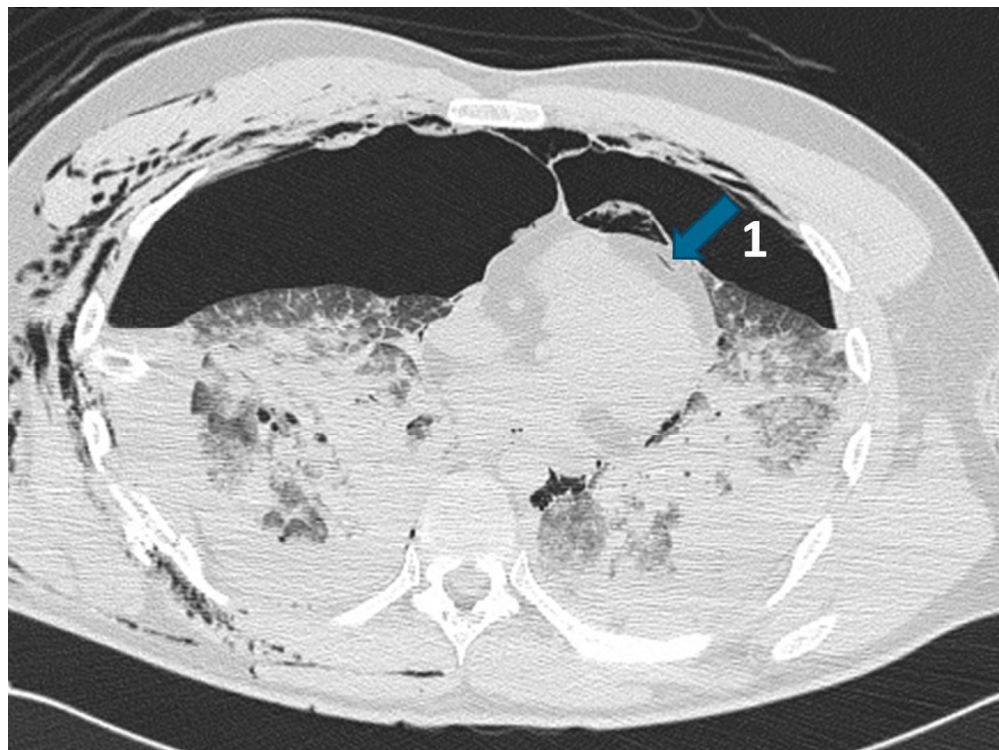
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peer review only



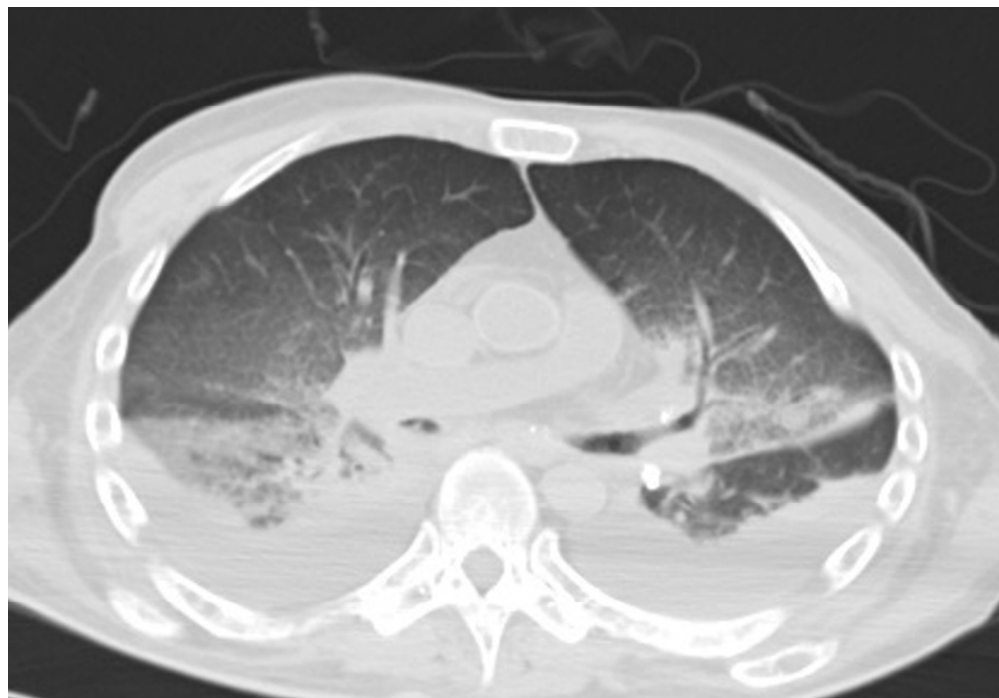
A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

268x200mm (96 x 96 DPI)



A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

380x284mm (96 x 96 DPI)



A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

241x166mm (96 x 96 DPI)

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Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
<b>ABSTRACT</b>			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
<b>INTRODUCTION</b>			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
<b>METHODS</b>			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
<i>Participants</i>	6	Eligibility criteria	5
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5
	9	Whether participants formed a consecutive, random or convenience series	5
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	5
	10b	Reference standard, in sufficient detail to allow replication	5
	11	Rationale for choosing the reference standard (if alternatives exist)	5
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	6
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	6
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	5
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	5
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	6
	15	How indeterminate index test or reference standard results were handled	6
	16	How missing data on the index test and reference standard were handled	6
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	6
	18	Intended sample size and how it was determined	
<b>RESULTS</b>			
<i>Participants</i>	19	Flow of participants, using a diagram	
	20	Baseline demographic and clinical characteristics of participants	7
	21a	Distribution of severity of disease in those with the target condition	
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	7
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	20,22
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	20,22
	25	Any adverse events from performing the index test or the reference standard	
<b>DISCUSSION</b>			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	11-13
	27	Implications for practice, including the intended use and clinical role of the index test	13
<b>OTHER INFORMATION</b>			
	28	Registration number and name of registry	
	29	Where the full study protocol can be accessed	
	30	Sources of funding and other support; role of funders	15

# STARD 2015

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## AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

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## EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

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## DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



# BMJ Open

## Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-018834.R1
Article Type:	Research
Date Submitted by the Author:	30-Oct-2017
Complete List of Authors:	Sonnemans, Lianne; Radboudumc, Radiology and Nuclear Medicine Kubat, Bela; Nederlands Forensisch Instituut, Pathology; Maastricht UMC+, Pathology Prokop, Mathias; Radboudumc, Radiology and Nuclear Medicine Klein, Willemijn; Radboudumc, Radiology and Nuclear Medicine; Maastricht UMC+, Radiology
<b>Primary Subject Heading</b>:	Radiology and imaging
Secondary Subject Heading:	Diagnostics, Pathology
Keywords:	Computed tomography < RADIOLOGY & IMAGING, cause of death, postmortem, autopsy, sensitivity, specificity

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Manuscripts

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9 4 **cause of death? A retrospective observational cohort study in a Dutch**  
10 5 **tertiary referral centre.**  
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33 19 Maastricht, The Netherlands  
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37 21 **Study design:** retrospective observational cohort study

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39 22 **Word count:** 3164  
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### 33 **Key Words**

34 cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

35

### 36 **List of abbreviations**

37 95% CI                      95% confidence interval

38 COD                        immediate cause of death

39 PMCT                      postmortem CT

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## Abstract

**Objective:** To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

**Design:** Retrospective observational cohort study. Inclusion criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion criteria: forensic cases, post mortal organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as the reference standard, we investigated the increase in sensitivity for immediate cause of death, type of pathology and anatomical system involved before and after virtual autopsy using McNemar tests.

**Setting:** Tertiary referral centre.

**Participants:** 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

**Intervention:** PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging.

Conventional autopsy consisted of thoraco-abdominal examination with or without brain autopsy.

**Primary and secondary outcome measures:** Sensitivity for the immediate cause of death, type of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved, before and after virtual autopsy.

**Results:** Using PMCT, the sensitivity for immediate cause of death increased from 53% (95% CI: 41 to 64) to 64% (53 to 75) ( $p=0.049$ ), for type of pathology from 65% (54 to 76) to 83% (73 to 91) ( $p=0.001$ ) and for anatomical system from 65% (53 to 75) to 84% (74 to 92) ( $p=0.001$ ).

**Conclusion:** While postmortem CT cannot substitute for conventional autopsy, it can significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy is not performed.

## 67 Article summary

### 68 Strengths and limitations of this study

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70 • This study investigated the diagnostic performance for clinical cause of death determination  
71 by use of postmortem CT and takes into account the added value over clinical diagnosis  
72 alone.

73 • The immediate cause of death (i.e. direct cause of death) was the main outcome rather than  
74 the primary cause of death (i.e. underlying cause of death or basic illness) as from a clinical  
75 point of view, diagnosis and treatment of the immediate cause of death is the most urgent.

76 • The sensitivity for clinical cause of death determination, with and without postmortem CT, is  
77 investigated on multiple levels of precision; both the determination of the immediate cause  
78 of death as well as the involved type of pathology and anatomical location were investigated.

79 • The retrospective design in a tertiary care centre has probably introduced a selection-bias  
80 towards patients with diagnostic difficulties or unresolved issues, resulting in an  
81 underestimation of the diagnostic performance compared to more general causes of death.

82 • Subgroups for type of pathology and anatomical system were relatively small due to the  
83 unexpected low consent rate for postmortem CT in general, as well as in cases with consent  
84 for conventional autopsy.

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3 86 **Contributors:** LJPS had full access to all of the data in the study and takes responsibility for the  
4 87 integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS,  
5 88 WMK, BK and WMP interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised  
6 89 the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All  
7 90 authors revised the manuscript for intellectual content.

8  
9  
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16 96 other relationships or activities that could appear to have influenced the submitted work.

17 97 **Ethical approval:** This study was approved by the local ethical committee in the form of a waiver in  
18 98 accordance with Dutch national law.

19 99 **Data sharing:** Details on how to obtain additional data from the study (eg, statistical code, datasets)  
20 100 are available from the corresponding author.

21 101 **Transparency:** The lead author affirms that this manuscript is an honest, accurate, and transparent  
22 102 account of the study being reported; that no important aspects of the study have been omitted; and  
23 103 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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31 111 [access-and-permission-reuse.](http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/copyright-open-access-and-permission-reuse)”  
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## 112 Introduction

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114 Autopsies are traditionally regarded as the 'gold standard' in quality monitoring of health care. It is  
115 therefore remarkable that in a time of heightened interest in improving patient safety, healthcare  
116 quality and error prevention, worldwide autopsy rates continue to decline from roughly 40% in the  
117 nineteen sixties, to below 10% nowadays.<sup>1-7</sup> Religious and emotional objections to the invasiveness  
118 of conventional autopsies, both by the relatives and the doctors, are considered as some of the  
119 reasons given for this decline. At present, determination of the cause of death relies heavily on  
120 clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the  
121 last decades, major error rates of approximately 25% have not substantially decreased.<sup>8-10</sup> According  
122 to the Goldman classification system, major errors are defined as clinically missed diagnoses related  
123 to the cause of death. In half of these cases this might have led to a change in therapy and prolonged  
124 survival, if known before death.<sup>8</sup> National mortality statistics are generally based on the primary  
125 cause of death (i.e. underlying cause or basic illness), which could be a longstanding, chronic  
126 disease.<sup>11</sup> However from an individual and clinical point of view, diagnosis and treatment of the  
127 immediate cause of death (i.e. direct cause of death) is the most urgent. Accuracy rates for  
128 immediate causes of death are probably lower than for underlying causes of death<sup>12,13</sup>, due to time  
129 constraints of the often acute situations these diagnoses present with. The high error rates  
130 emphasize the need to improve clinical diagnoses using techniques that are widely available and  
131 acceptable, for example, postmortem CT (PMCT). Previous studies have shown that as yet, PMCT is  
132 an insufficient substitute but can be used in adjunct to a conventional autopsy.<sup>14,15</sup> In order to  
133 provide answers and quality control also in cases without consent for conventional autopsy, we  
134 investigated whether virtual autopsy with PMCT improves clinical diagnosis of the immediate cause  
135 of death.

## 136 **Material and methods**

### 137 **Study design**

138 All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT  
139 and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic  
140 cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-  
141 abdomen autopsy, were excluded. Clinicians had to ask consent from relatives for both PMCT and  
142 conventional autopsy in all cases of death. This retrospective study was approved by the local ethical  
143 committee in the form of a waiver in accordance with Dutch national law.

### 144 **PMCT and conventional autopsy**

145 PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few  
146 hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were  
147 Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion  
148 ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction  
149 interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation  
150 time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s.  
151 PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting,  
152 interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal  
153 settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single  
154 consensus report. All radiologists had minimal previous experience in interpreting postmortem PMCT  
155 images, as postmortem imaging is a relatively new field of expertise. Conventional autopsy consisted  
156 of thoracic-abdominal autopsy with or without examination of the brain, and included full  
157 macroscopic and microscopic inspection. Radiologists and pathologists were blinded to each other's  
158 results, but had otherwise full access to the electronic patient files. Radiologists and pathologists  
159 compiled a report based on their own findings and clinical findings.

### 160 **Data collection**

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3 161 For each cadaver the immediate cause of death (i.e. direct cause of death), type of pathology and  
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5 162 anatomical system involved, were collected in retrospect at three moments: before virtual autopsy,  
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7 163 after virtual autopsy and based on autopsy findings. The cause of death before virtual autopsy was  
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9 164 based on clinical findings only. The cause of death after virtual autopsy was based on both clinical  
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11 165 findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was based on  
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13 166 clinical findings only. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors  
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15 167 (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary  
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17 168 source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In  
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19 169 cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of  
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21 170 death.

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24 171 Type of pathology was scored according to the following categories; infection, hemorrhage,  
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26 172 perfusion disorder, other or uncertain (i.e. not assigned). Perfusion disorders comprised all cardiac  
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28 173 and vascular perfusion disorders not due to infection, hemorrhage or neoplasm (for example,  
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30 174 myocardial infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections  
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32 175 with hemopericardium were grouped in the hemorrhage category. The type of anatomical system  
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34 176 was scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and  
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36 177 subcategories used were derived from the classifications of anatomical regions and groups of  
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38 178 pathologies as used by Roberts and Wichmann et al.<sup>4,14</sup>

### 179 **Statistical analysis**

180 Sensitivity and specificity were calculated with conventional autopsy as reference standard. Cases  
181 where the outcome (cause of death, type of pathology or anatomical system) was uncertain after  
182 autopsy were excluded from statistical analysis. McNemar tests (2-sided) were used to test for  
183 significant differences in sensitivity or specificity before and after virtual autopsy. Logistic regression  
184 analysis was performed to evaluate radiologists' improvement in reporting PMCT-scans over the four  
185 years of initial experience. Odds ratios were calculated for each year of experience in reporting

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186 PMCT-scans. P values of 0.05 or less were considered significant. IBM SPSS Statistics, version 22 was  
187 used.

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## 188 Results

189 Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen  
190 autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on  
191 78 (4%) cadavers. One case was excluded due to postmortem organ donation prior to PMCT. A  
192 further nine cases who deceased at home (n=7) or in another hospital (n=2) were brought to the  
193 hospital's mortuary for PMCT and autopsy examination. This led to a total of 86 included cases (51  
194 men, 35 women, with a median age of 62 (IQR: 47 to 74) years) (Table 1). 54% of the deaths were  
195 after a resuscitation attempt. The median postmortem interval between death and PMCT was 7.6  
196 (IQR: 3.1 to 18.8) hours. In 69% there was no consent for brain autopsy and, in those cases,  
197 conventional autopsy consisted of a thorax-abdomen examination only.

198 Conventional autopsy, as standard of reference, was not able to assign an immediate cause of death  
199 in ten cadavers (12%)(Figure 1). Therefore, these cases were excluded of sensitivity and specificity  
200 analyses for cause of death.

### 201 The additional value of PMCT

202 The number of correctly identified causes of death before virtual autopsy was 53% (95% CI: 41-64%)  
203 and increased to 64% (95% CI 53-75%) after performing a PMCT scan. This improvement was  
204 statistically significant (p=0.049). The additional value of PMCT increased further, when PMCT was  
205 used to indicate the type of pathology (p=0.001) or anatomical system (p=0.001) involved in the  
206 immediate cause of death. The number of cases in which type of pathology was correctly identified  
207 increased from 65% (95% CI: 54-76) to 83% (95% CI: 73-91), and from 65% (95% CI: 53-75) to 84%  
208 (95% CI: 74-92) for anatomical system (Table 2). 2-by-2 tables of the number of correctly diagnosed  
209 immediate causes of death, type of pathology and anatomical system before and after PMCT are  
210 presented in Table 3.

### 211 Evaluation of cause of death, per type of pathology

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3 212 Table 4 shows all autopsy causes of death classified by type of pathology and whether or not they  
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5 213 were correctly appointed as cause of death before and after PMCT.  
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8 214 Pneumonia was the most common infectious cause of death. It was correctly assigned as cause of  
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10 215 death in 11/15=73% after PMCT, compared to 10/15=67% before PMCT. In the other 27% (n=4),  
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12 216 pneumonia was recognized, but not assigned as cause of death. Vice versa, in two other patients who  
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14 217 had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly  
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16 218 assigned as cause of death on PMCT. Furthermore, two cases of peritonitis (due to a misplaced  
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18 219 gastrostomy button and ventriculoperitoneal drain) and one pancreatitis, which were clinically  
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20 220 missed (i.e. major errors) were correctly diagnosed at PMCT as cause of death.  
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23 221 In the group of perfusion disorders, all three pulmonary embolisms diagnosed at autopsy were also  
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25 222 assigned as cause of death at PMCT. In a further three cases, including one with pulmonary embolism  
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27 223 diagnosis on antemortem ultrasound (Figure 2), PMCT diagnosed pulmonary embolisms which were  
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29 224 not confirmed during autopsy. Moreover, radiologists correctly diagnosed two arrhythmias, one  
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31 225 heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac  
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33 226 arrhythmia was suspected based on left ventricular hypertrophy and aortic valve stenosis or local  
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35 227 hyperdensity of myocardial tissue corresponding to fibrosis in the absence of other significant  
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37 228 findings. In the other case, heart failure was also based upon secondary characteristics, such as  
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39 229 dilated atria and pleural effusion, in the absence of other significant findings. Myocardial infarction  
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41 230 was correctly diagnosed as cause of death in 7/16=44% after PMCT. However, in 5/7=71% of these  
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43 231 cases, myocardial infarction was not visible on PMCT and diagnosis of myocardial infarction was  
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45 232 based on the combination of clinical findings and absence of significant pathologies at PMCT. In the  
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47 233 two other cases, myocardial infarction was also suspected at imaging; once due to an intravascular  
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49 234 hypodensity proximal of a coronary stent, which might indicate a (fat) embolism, and once due to the  
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51 235 combination of significant coronary calcifications, enlarged right atrium, clinical history and absence  
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53 236 of other significant findings.  
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3 237 Using PMCT, hemorrhagic causes of death were correctly diagnosed in 11/13=85%. All five aortic  
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5 238 dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic  
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7 239 case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed  
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9 240 hemothorax and a liver and kidney rupture (Figure 3). In another traumatic case where death was  
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11 241 attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left  
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13 242 coronary artery (Figure 4).

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16 243 In the category of other pathologies, there were three patients who died from malignant disease.  
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18 244 The cause of death was correctly diagnosed before and after PMCT in two of these cases, one with  
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20 245 pleural carcinomatosis in breast cancer and one with respiratory failure due to cachexia in  
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22 246 metastasized esophageal cancer. In the other case, the patient died after an epileptic seizure due to  
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24 247 (unidentified) brain metastases. There were three other cases with cancer at time of death died, but  
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26 248 those patients died from complications (septic cholecystitis, carotid artery bleeding and  
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28 249 endocarditis due to immunodeficiency).

#### 30 31 250 **Sensitivity and specificity for type of pathology and anatomical system subgroups**

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34 251 Based on the type of pathology, the subgroup of perfusion disorders showed a significant  
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36 252 improvement ( $p=0.04$ ) in sensitivity from 19/34=56% to 26/34=76%, using PMCT (Table 5). When  
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38 253 categorized based on anatomical system, the cardiovascular subgroup showed a significant  
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40 254 improvement ( $p=0.02$ ) in sensitivity from 24/39=62% to 32/39=82%. There were no significant  
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42 255 differences in specificity within the subgroups before and after PMCT.

#### 43 44 45 256 **Performance of radiologists**

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48 257 Logistic regression analysis showed no significant improvement in radiologists' performance over the  
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50 258 four years of initial experience in reporting PMCT-scans. Odds ratios for each year of experience were  
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52 259 0.85 (95% CI: 0.56 to 1.27,  $p=0.41$ ) for correct assignment of the immediate cause of death, 0.95  
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54 260 (95% CI: 0.61 to 1.48,  $p=0.81$ ) for type of pathology and 0.82 (95% CI: 0.51 to 1.32,  $p=0.41$ ) for  
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56 261 anatomical system involved.

## 262 Discussion

263 The number of correctly identified clinical diagnoses of the immediate cause of death increased from  
264 53% to 64% ( $p=0.049$ ) after performing PMCT. Analyses showed that the value of PMCT is variable  
265 per subcategory and depends on the cause of death. Unfortunately, subgroups were a lot smaller  
266 than expected. The main reason for this was the unexpected low consent rate for PMCT in cases with  
267 consent for conventional autopsy. We did not investigate the reason for this low consent rate as  
268 motives for performing or not performing a PMCT-scan were not extensively documented. In case of  
269 death, clinicians had to ask consent for both PMCT and autopsy. Though some clinicians mentioned  
270 that they only requested for PMCT in case of refusal of conventional autopsy.

271 Pneumonia was the most common missed infectious cause of death, both before and after PMCT.  
272 Normal postmortem changes, such as the occurrence of pulmonary edema, could mask pneumonia  
273 (Figure 5).<sup>16</sup> In the subgroup of perfusion disorders, diagnosis of pulmonary embolism at unenhanced  
274 PMCT is challenging as it is notoriously difficult to distinguish an ante-mortem thrombus from a post-  
275 mortem blood clot.<sup>17-19</sup> This, or the possibility that the embolus was lost during the autopsy  
276 procedure, may explain why in three cases the pulmonary embolism was not confirmed during  
277 autopsy. Postmortem angiography, now being developed and validated, can be effective in  
278 demonstrating any obstructing thrombi.<sup>20</sup> Most causes of death in the subgroup of perfusion  
279 disorders were cardiac related. Clinicians are often restricted in their ability to differentiate a cause  
280 of death due to the acute nature and time constraints of the situations (resuscitation setting) these  
281 patients present with. On the contrary, cardiac arrhythmia and heart failure are impossible to  
282 diagnose by postmortem examinations only. Furthermore, an autopsy can only detect a myocardial  
283 infarction in cases where patients have survived two to three hours post-infarction.<sup>21</sup> Therefore,  
284 radiologists and pathologists had access to clinical information in order to assign the most probable  
285 cause of death based on postmortem findings and clinical findings as well. Accordingly, both PMCT  
286 and autopsy could indicate a cardiac cause of death, based on clinical findings and secondary  
287 characteristics in the absence of other significant pathologies.

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3 288 Table 1 and 5 show an increased additional value of PMCT when PMCT is used to identify the type of  
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5 289 pathology or anatomical system involved. This indicates that even when the cause of death is  
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7 290 uncertain after PMCT, it is still a valuable tool in targeting the region of interest or excluding some of  
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9 291 the differential diagnostic possibilities. By using PMCT, the sensitivity for type of pathology and  
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11 292 anatomical system increased by approximately 20% for all three main subgroups with the use of  
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13 293 PMCT (Table 5). Clinical evaluation of the cause of death often indicates the failing system (for  
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15 294 example, respiratory failure) rather than the underlying illness or structural changes, whereas  
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17 295 radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how  
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19 296 confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.  
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22 297 Amongst non-invasive techniques, Blokker et al. conclude that PMCT in combination with  
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24 298 postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing  
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26 299 somewhat better when only one of the modalities is used.<sup>14,15</sup> PMCT is less expensive than a  
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28 300 conventional autopsy, however, cost-effective analyses have not been formulated.<sup>22</sup> Images can be  
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30 301 stored digitally (useful for legal or educational purposes) and results can be audited and promptly  
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32 302 reviewed by one or more radiologists. Amongst minimally invasive methods, the highest  
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34 303 performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with  
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36 304 targeted coronary angiography, showed a sensitivity of 92% for cause of death.<sup>19</sup> Two studies  
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38 305 combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for  
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40 306 cause of death.<sup>23,24</sup>

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44 307 To our knowledge this is the second study which has investigated the additional value of unenhanced  
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46 308 PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in  
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48 309 sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths.<sup>25</sup> This is  
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50 310 somewhat higher than we found in our study, one reason could be the fact that less specific causes  
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52 311 of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT  
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54 312 compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some

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3 313 use broadly defined categorizations and others use well-defined specific causes of death, or some  
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5 314 use the immediate cause of death and others the intermediate or underlying cause of death, or do  
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7 315 not state their definition of cause of death at all. Furthermore, most previous studies consisted of  
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9 316 small sample sizes ( $n < 50$ ) and used different study populations, different outcome parameters (for  
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11 317 example, cause of death, major or minor diagnoses) and different parameters of accuracy.<sup>4,26-28</sup> A  
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13 318 large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32%  
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15 319 in determining the cause of death with PMCT compared to autopsy.<sup>14</sup> Another study showed a  
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17 320 sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in  
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19 321 101 cases.<sup>29</sup> This is in accordance with our results regarding the categorization of cause of death per  
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21 322 type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause  
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23 323 of death and a sensitivity of 5/17=19% for a more specific description of the involved pathogenetic  
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25 324 mechanism.<sup>26</sup> Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both  
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27 325 definite and possible findings with PMCT as to cause of death.<sup>27</sup> The study by Puranik et al. supports  
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29 326 our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT.<sup>28</sup> A  
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31 327 sensitivity of 25% for cause of death was found in a population of seventeen young patients with  
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33 328 sudden cardiac death.

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37 329 Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure  
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39 330 4), are more confidently diagnosed with PMCT than autopsy.<sup>14,30</sup> Therefore, the presented  
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41 331 performance of PMCT will probably be underestimated in cases where pathologies are difficult to  
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43 332 confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no  
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45 333 longer be considered as the gold standard for all postmortem diagnoses, not only due to the  
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47 334 limitations of dissection, but also due to the decline in the number of autopsies performed, leading  
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49 335 to a decrease in pathologists' expertise. We would suggest a gold standard involving a  
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51 336 multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective  
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53 337 studies with larger sample sizes are required to investigate the additional value of PMCT in specific  
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55 338 subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques,

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3 339 conventional autopsy will still be required in complex cases where clinical and radiological diagnosis  
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5 340 as to cause of death is inconclusive.  
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3 341 **Conclusion**

4 342 While virtual autopsy with postmortem CT cannot substitute for conventional autopsy, it can  
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6 343 significantly improve diagnosis of the immediate cause of death over clinical diagnosis alone. Even in  
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8 344 cases where no immediate cause of death can be assigned after virtual autopsy, radiologists may  
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10 345 indicate a region of interest, so directing pathologists at autopsy. Future studies are needed to  
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12 346 investigate whether PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy  
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14 347 altogether.  
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For peer review only



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## 431 **Figure legends**

432 **Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT**  
433 **and during conventional autopsy.**

434 <sup>a</sup> No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis  
435 for cause of death. <sup>b</sup> In four cases, where clinicians and radiologists were able to assign a cause of death,  
436 autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a  
437 case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at  
438 autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two  
439 other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the  
440 cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial  
441 infarction were diagnosed by the clinicians. COD: immediate cause of death.

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443 **Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem**  
444 **CT but were not confirmed during autopsy.**

445 A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricialis  
446 correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary  
447 embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary  
448 arteries. Autopsy did not assign a cause of death.

449 **Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.**

450 A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right side.  
451 Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen  
452 laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings:  
453 (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood  
454 along the spleen.

455 **Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.**

456 A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical  
457 examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some

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3 458 other underlying pathology which may have caused the accident. During air ambulance transportation,  
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5 459 ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1),  
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7 460 probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not  
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9 461 diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the  
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11 462 pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

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13 463 **Figure 5. Normal postmortem changes could mask underlying pathology**

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16 464 A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma.  
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18 465 Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative  
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20 466 disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of  
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22 467 death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural  
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24 468 fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings.  
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26 469 Bronchopneumonia was not diagnosed at PMCT.  
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## Tables

**Table 1. Patient characteristics**

	Study population (n=86), n (%)
<b>Sex</b>	
Male	51 (59%)
Female	35 (41%)
<b>Age, median (IQR)</b>	62 (47-74)
<b>Place of death</b>	
Emergency room	31 (36%)
Intensive care unit	30 (35%)
Clinical ward	18 (21%)
Out-of-hospital	7 (8%)
<b>CPR performed</b>	
Yes	46 (53%)
No	40 (47%)
<b>Brain autopsy performed</b>	
Yes	27 (31%)
No	59 (69%)
<b>Immediate cause of death</b>	
Infectious	26 (30%)
Perfusive disorder	32 (37%)
Hemorrhage	13 (15%)
Other	5 (6%)
Uncertain	10 (12%)

IQR: interquartile range. CPR: cardiopulmonary resuscitation.

**Table 2. Sensitivity for immediate cause of death, type of pathology and anatomical system involved, before and after virtual autopsy with PMCT.**

	Sensitivity before PMCT (95% CI)	Sensitivity after PMCT (95% CI)	Significance (p-value <sup>b</sup> )
<b>Immediate cause of death</b>			
Identified at CA (n=76) <sup>a</sup>	40/76=53% (41-64%)	49/76=64% (53-75%)	0.049
<b>Type of pathology</b>			
Identified at CA (n=78) <sup>a</sup>	51/78=65% (54-76%)	65/78=83% (73-91%)	0.001
<b>Anatomical system</b>			
Identified at CA (n=77) <sup>a</sup>	50/77=65% (53-75%)	47/65=84% (74-92%)	0.001

<sup>a</sup> Group sizes differ as conventional autopsy (CA) was not able to assign a cause of death in ten cases (Figure 1), a type of pathology in eight cases and anatomical system in nine cases. <sup>b</sup> p-values were calculated by use of McNemar tests.

**Table 3. Cross tabulations of correct and incorrect assigned immediate causes of death (A), type of pathology (B) and anatomical system (C), before and after PMCT**

A.		COD after PMCT		
		Correct	Incorrect	
COD before PMCT	Correct	36	4	40
	Incorrect	13	23	36
		49	27	76

B.		Type of pathology after PMCT		
		Correct	Incorrect	

Type of pathology before PMCT	Correct	50	1	51
	Incorrect	15	12	27
		65	13	78

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C.	Type of anatomical system after PMCT			
	Correct	Incorrect		
Type of anatomical system before PMCT	Correct	47	3	50
	Incorrect	18		27
		65	12	77

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COD: immediate cause of death.

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**Table 4. Overview of all causes of death diagnosed at autopsy, classified by type pathology and whether they were correctly diagnosed as the immediate cause of death before and after virtual autopsy.**

	Correct COD, both before and after PMCT.	Incorrect COD before PMCT. Correct COD after PMCT.	Correct COD before PMCT. Incorrect COD after PMCT.	Incorrect COD, both before and after PMCT.
<b>Infections</b>	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i. <sup>b</sup> 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis <sup>a</sup> 1x diverticulitis and pancreatitis	1x endocarditis 1x HSV hepatitis 1x cerebral aspergillosis	4x pneumonia 1x endocarditis / pericarditis
<b>Perfusion disorders</b>	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure	9x myocardial infarction 3x arrhythmia 2x heart failure 1x pulmonary veno- occlusive disease 1x bowel ischemia due to adhesions
<b>Hemorrhages</b>	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax 1x liver and kidney rupture + hemothorax
<b>Other</b>	1x pleural carcinomatosis 1x cachexia 1x anaphylaxis 1x (auto-)intoxication	1x epileptic seizure due to brain metastases		

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<sup>a</sup> Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced

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ventriculoperitoneal drain in another case. <sup>b</sup> sepsis e causa ignota. COD: immediate cause of death.

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**Table 5. Sensitivity and specificity for type of pathology and anatomical system per subgroup diagnosed before and after virtual autopsy with PMCT.**

	Sensitivity			Specificity		
	Before PMCT (95% CI)	After PMCT (95% CI)	p-value <sup>a</sup>	Before PMCT (95% CI)	After PMCT (95% CI)	p-value <sup>a</sup>
<b>A. Type of pathology (n=78)<sup>c</sup></b>						
1. Infection (n=26)	69% (48-86)	85% (65-96)	0.130.25	96% (87-100)	92% (81-98)	0.501.00
2. Hemorrhage (n=13)	69% (39-91)	92% (64-100)		98% (92-100)	100% (94-100)	
3. Perfusion disorder (n=34)	56% (38-73)	76% (59-89)	0.04	95% (85-99)	93% (81-99)	1.00
4. Other (n=5)	100% (48-100)	100% (48-100)	N/A <sup>c</sup>	99% (93-100%)	99% (93-100%)	1.00
<b>B. Anatomical system (n=77)<sup>c</sup></b>						
1. Pulmonary (n=18)	72% (47-90)	89% (65-99)	0.25	95% (86-99)	95% (86-99)	1.00
2. Cardiovascular (n=39)	62% (45-77)	82% (66-92)	0.02	100% (91-100)	95% (82-99)	0.50
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	0.22	98% (92-100)	100% (94-100)	1.00
4. Other (n=7)	86% (42-100)	86% (42-100)	1.00	97% (90-100)	94% (86-98)	0.50

501 <sup>a</sup> p-values were calculated by use of McNemar tests. <sup>b</sup> NS: not significant. <sup>c</sup> Autopsy was not able to establish  
 502 the type of pathology and anatomical system involved in eight and nine deaths respectively. <sup>d</sup> Not applicable.

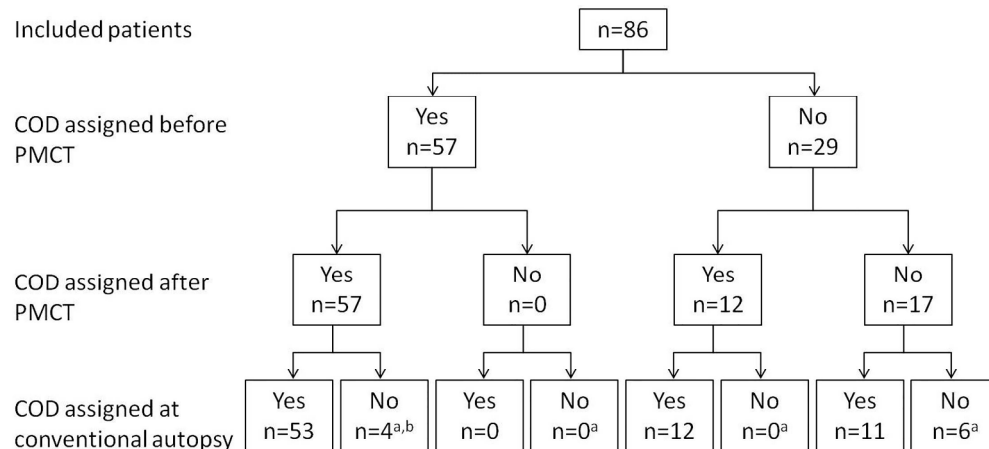


Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.

a No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. b In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

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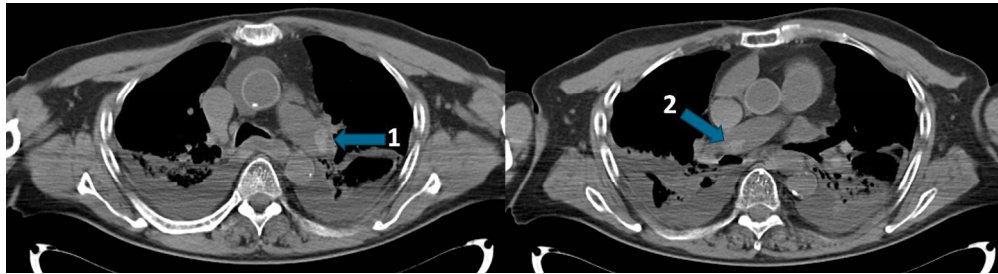


Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy.

A 70 year old man died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricialis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

757x203mm (300 x 300 DPI)

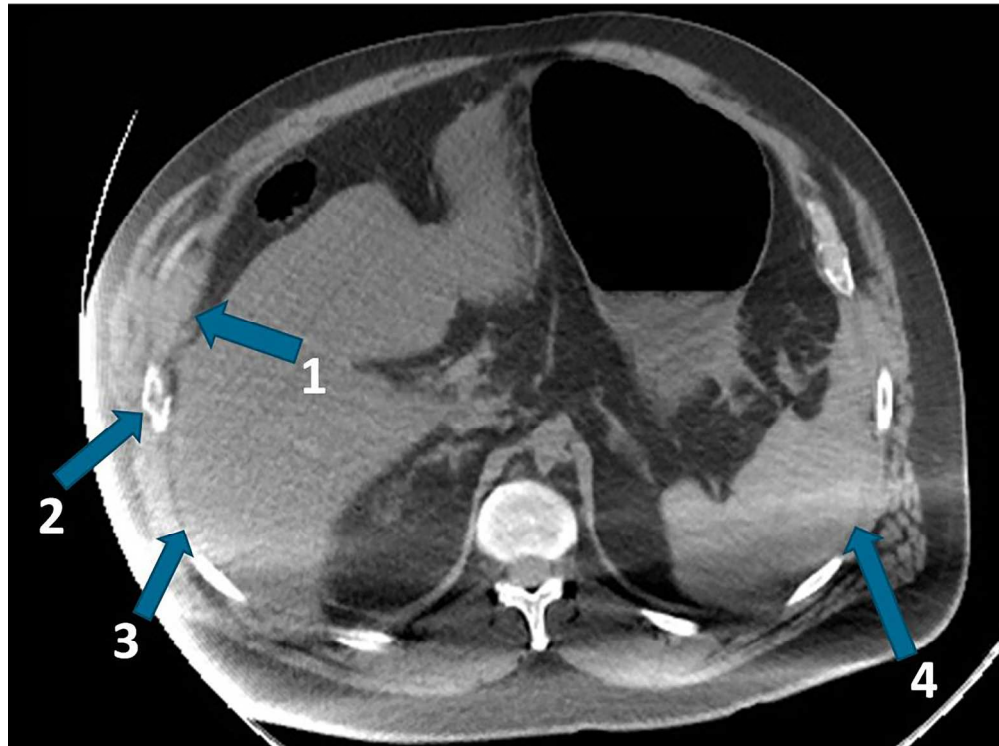


Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination. A 47 year old man died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

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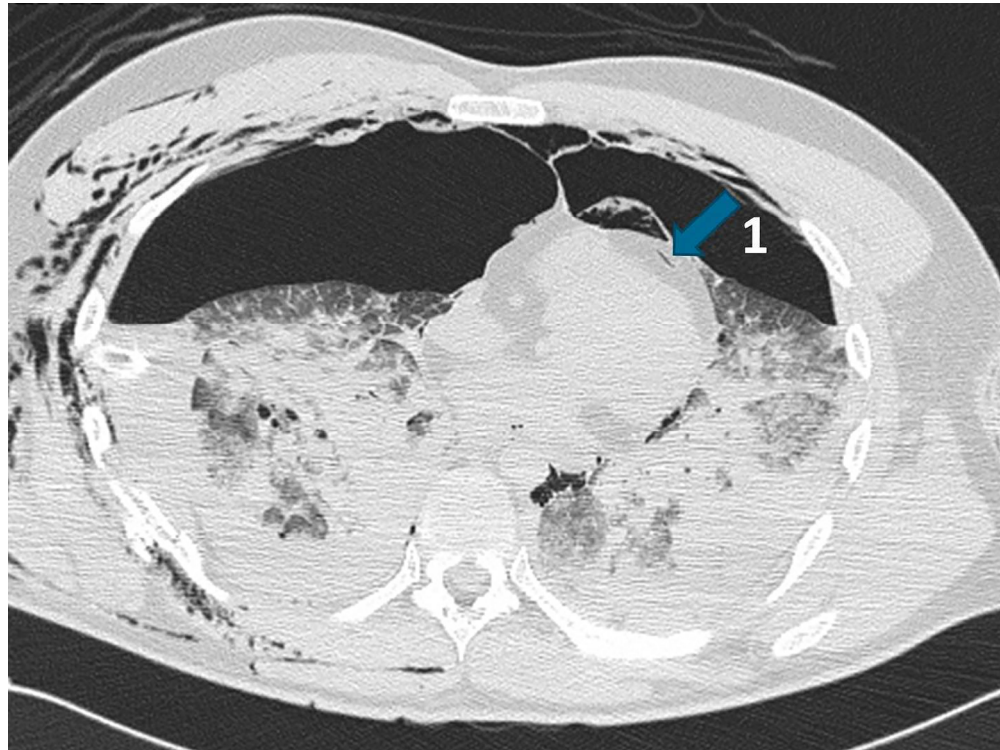


Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy. A 40 year old man died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

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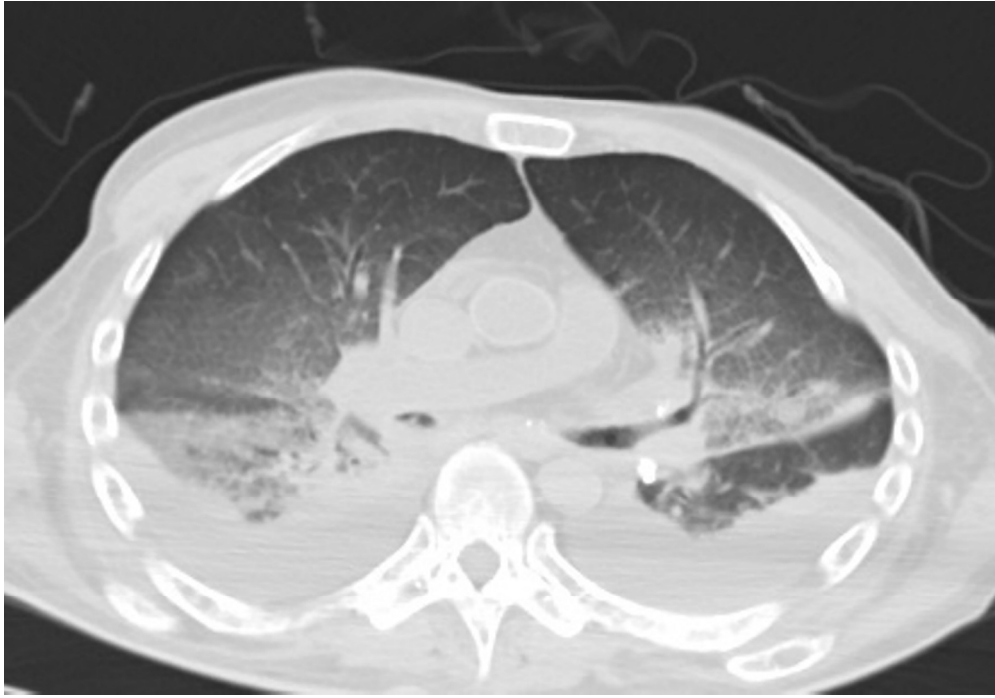


Figure 5. Normal postmortem changes could mask underlying pathology

A 60 year old man with a clinical history of allogeneic stem cell transplantation due to multiple myeloma.

Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings.

Bronchopneumonia was not diagnosed at PMCT.

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only

Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
<b>ABSTRACT</b>			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
<b>INTRODUCTION</b>			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
<b>METHODS</b>			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
<i>Participants</i>	6	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	7
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8
	18	Intended sample size and how it was determined	See supplementary file: 'response to editorial request'
<b>RESULTS</b>			
<i>Participants</i>	19	Flow of participants, using a diagram	Fig 1, page 20
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	NA
	22	Time interval and any clinical interventions between index test and reference standard	10
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3, page 22-23
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 2 + 5
	25	Any adverse events from performing the index test or the reference standard	
<b>DISCUSSION</b>			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	13-15
	27	Implications for practice, including the intended use and clinical role of the index test	13-15
<b>OTHER INFORMATION</b>			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	5
	30	Sources of funding and other support; role of funders	5

# STARD 2015

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## AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

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## EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

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## DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.



# BMJ Open

## Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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8 3 **Can virtual autopsy with postmortem CT improve clinical diagnosis of**  
9 4 **cause of death? A retrospective observational cohort study in a Dutch**  
10 5 **tertiary referral centre.**  
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37 21 **Study design:** retrospective observational cohort study

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33 **Key Words**

34 cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity

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36 **List of abbreviations**

37 COD                      immediate cause of death

38 PMCT                     postmortem CT

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## Abstract

**Objective:** To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

**Design:** Retrospective observational cohort study. Inclusion-criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion-criteria: forensic cases, post mortal organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as reference standard, we investigated the increase in sensitivity for immediate cause of death, type of pathology and anatomical system involved before and after virtual autopsy.

**Setting:** Tertiary referral centre.

**Participants:** 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

**Intervention:** PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with or without brain autopsy.

**Primary and secondary outcome measures:** Increase in sensitivity for the immediate cause of death, type of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved, before and after virtual autopsy.

**Results:** Using PMCT, the sensitivity for immediate cause of death increased with 12% (95% CI: -4 to 28) from 53% (41 to 64) to 64% (53 to 75), with 18% (4 to 32) from 65% (54 to 76) to 83% (73 to 91) for type of pathology and with 19% (6 to 33) from 65% (54 to 76) to 85% (75 to 92) for anatomical system.

**Conclusion:** While unenhanced postmortem CT is an insufficient substitute for conventional autopsy, it can improve diagnosis of cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy is not performed.

## 68 Article summary

### 69 Strengths and limitations of this study

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- 71 • This study investigated the diagnostic performance for clinical cause of death determination  
72 by use of postmortem CT and takes into account the added value over clinical diagnosis  
73 alone.
- 74 • The immediate cause of death (i.e. direct cause of death) was the main outcome rather than  
75 the primary cause of death (i.e. underlying cause of death or basic illness) as from a clinical  
76 point of view, diagnosis and treatment of the immediate cause of death is the most urgent.
- 77 • The sensitivity for clinical cause of death determination, with and without postmortem CT, is  
78 investigated on multiple levels of precision; the immediate cause of death as well as the  
79 involved type of pathology and anatomical location were investigated.
- 80 • The retrospective design in a tertiary care centre has probably introduced a selection-bias  
81 towards patients with diagnostic difficulties or unresolved issues, resulting in an  
82 underestimation of the diagnostic performance compared to more general causes of death.
- 83 • An unexpected low consent rate for postmortem CT in cases with consent for conventional  
84 autopsy resulted in a reduction of the statistical power of this study.

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3 86 **Contributors:** LJPS had full access to all of the data in the study and takes responsibility for the  
4 87 integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS,  
5 88 WMK, BK and WMP interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised  
6 89 the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All  
7 90 authors revised the manuscript for intellectual content.

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9  
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14 94 support from any organization for the submitted work, no financial relationships with any  
15 95 organizations that might have an interest in the submitted work in the previous three years, and no  
16 96 other relationships or activities that could appear to have influenced the submitted work.

17 97 **Ethical approval:** This study was approved by the local ethical committee in the form of a waiver in  
18 98 accordance with Dutch national law.

19 99 **Data sharing:** Details on how to obtain additional data from the study (eg, statistical code, datasets)  
20 100 are available from the corresponding author.

21 101 **Transparency:** The lead author affirms that this manuscript is an honest, accurate, and transparent  
22 102 account of the study being reported; that no important aspects of the study have been omitted; and  
23 103 that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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## 112 Introduction

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114 Autopsies are traditionally regarded as the 'gold standard' in quality monitoring of health care. It is  
115 therefore remarkable that in a time of heightened interest in improving patient safety, healthcare  
116 quality and error prevention, worldwide autopsy rates continue to decline from roughly 40% in the  
117 nineteen sixties, to below 10% nowadays.<sup>1-7</sup> Religious and emotional objections to the invasiveness  
118 of conventional autopsies, both by the relatives and the doctors, are considered as some of the  
119 reasons given for this decline. At present, determination of the cause of death relies heavily on  
120 clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the  
121 last decades, major error rates of approximately 25% have not substantially decreased.<sup>8-10</sup> According  
122 to the Goldman classification system, major errors are defined as clinically missed diagnoses related  
123 to the cause of death. In half of these cases this might have led to a change in therapy and prolonged  
124 survival, if known before death.<sup>8</sup>

125 National mortality statistics are generally based on the primary cause of death (i.e. underlying cause  
126 or basic illness), which could be a longstanding, chronic disease.<sup>11</sup> However from an individual and  
127 clinical point of view, diagnosis and treatment of the immediate cause of death (i.e. direct cause of  
128 death) is the most urgent. Accuracy rates for immediate causes of death are probably lower than for  
129 underlying causes of death<sup>12,13</sup>, due to time constraints of the often acute situations these diagnoses  
130 present with. The high error rates emphasize the need to improve clinical diagnoses using techniques  
131 that are widely available and acceptable, for example, postmortem CT (PMCT). Previous studies have  
132 shown that as yet, PMCT is an insufficient substitute but can be used in adjunct to conventional  
133 autopsy.<sup>14,15</sup> In order to provide answers and quality control also in cases without consent for  
134 conventional autopsy, we investigated whether virtual autopsy with PMCT improves clinical diagnosis  
135 of the immediate cause of death.

## 136 **Material and methods**

### 137 **Study design**

138 All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT  
139 and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic  
140 cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-  
141 abdomen autopsy, were excluded. Clinicians had to ask consent from relatives for both PMCT and  
142 conventional autopsy in all cases of death. This retrospective study was approved by the local ethical  
143 committee in the form of a waiver in accordance with Dutch national law.

### 144 **PMCT and conventional autopsy**

145 PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few  
146 hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were  
147 Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion  
148 ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction  
149 interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation  
150 time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s.  
151 PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting,  
152 interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal  
153 settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single  
154 consensus report. All radiologists had minimal previous experience in interpreting PMCT images, as  
155 postmortem imaging is a relatively new field of expertise. Conventional autopsy consisted of  
156 thoracic-abdominal autopsy with or without examination of the brain, and included full macroscopic  
157 and microscopic inspection. Radiologists and pathologists were blinded to each other's results, but  
158 had otherwise full access to electronic patient files. Radiologists and pathologists compiled a report  
159 based on their own findings and clinical findings.

### 160 **Data collection**

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3 161 For each cadaver the immediate cause of death (i.e. direct cause of death), type of pathology and  
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5 162 anatomical system involved, were collected in retrospect at three moments: before PMCT, after  
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7 163 PMCT and based on conventional autopsy findings. The cause of death before virtual autopsy was  
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9 164 based on clinical findings only. The cause of death after virtual autopsy was based on both clinical  
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11 165 findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was primarily  
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13 166 based on clinical findings. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors  
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15 167 (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary  
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17 168 source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In  
18  
19 169 cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of  
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21 170 death.

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24 171 Type of pathology was scored according to the following categories; infection, hemorrhage,  
25  
26 172 perfusion disorder, other or not assigned. Perfusion disorders comprised all cardiac and vascular  
27  
28 173 perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial  
29  
30 174 infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with  
31  
32 175 hemopericardium were grouped in the hemorrhage category. The type of anatomical system was  
33  
34 176 scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and  
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36 177 subcategories used were derived from the classification of anatomical regions and groups of  
37  
38 178 pathologies as used by Roberts and Wichmann et al.<sup>4,14</sup>

### 39 40 41 42 179 **Statistical analysis**

43  
44 180 Sensitivity and specificity were calculated with conventional autopsy as reference standard. 95%  
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46 181 confidence intervals (CI) of the differences in sensitivity or specificity before and after PMCT were  
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48 182 calculated. Cases where the cause of death, type of pathology or anatomical system could not be  
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50 183 established after conventional autopsy were excluded from statistical analysis. A sample size of  
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52 184  $n=113$  was required to demonstrate a difference of 15% in sensitivity with  $\alpha=0.05$  and  $\beta=0.10$ .  
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54 185 Logistic regression analysis was performed to evaluate radiologists' improvement in reporting PMCT-

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3 186 scans during the four year study period. Odds ratios were calculated for each additional year of  
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5 187 experience in reporting PMCT-scans. P values of 0.05 or less were considered significant. IBM SPSS  
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7 188 Statistics, version 22 was used.  
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## 189 Results

190 Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen  
191 autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on  
192 78 (4%) cadavers. One case was excluded due to postmortem organ donation prior to PMCT. A  
193 further nine cases who deceased at home (n=7) or in another hospital (n=2) were brought to the  
194 hospital's mortuary for PMCT and autopsy examination. This led to a total of 86 included cases (51  
195 men, 35 women, with a median age of 62 (IQR: 47 to 74) years) (Table 1). 54% of the deaths were  
196 after a resuscitation attempt. The median postmortem interval between death and PMCT was 7.6  
197 (IQR: 3.1 to 18.8) hours. In 69% there was no consent for brain autopsy and, in those cases,  
198 conventional autopsy consisted of a thorax-abdomen examination only. Conventional autopsy, as  
199 standard of reference, was not able to assign the immediate cause of death in ten cadavers (12%)  
200 (Figure 1). The type of pathology and anatomical system involved were both not assigned in eight  
201 cadavers. Therefore, analyses were based on the remaining 76 or 78 cadavers. Table 2 shows 2-by-2-  
202 tables of the number of correct diagnoses before and after PMCT.

### 203 Sensitivity for immediate cause of death

204 The overall sensitivity for immediate cause of death increased with 12% (-4 to 28) from 53% (41 to  
205 64) to 64% (53 to 75) after performing a PMCT-scan. Sensitivities specified per type of pathology or  
206 anatomical system are shown in Table 3. All autopsy causes of death, and whether or not they were  
207 correctly appointed before and after PMCT, are shown in Table 4.

208 Pneumonia was the most common infectious cause of death. It was correctly assigned as cause of  
209 death in 11/15=73% after PMCT, compared to 10/15=67% before PMCT. In the other 27% (n=4),  
210 pneumonia was recognized, but not assigned as cause of death. Vice versa, in two other patients  
211 who had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly  
212 assigned as cause of death on PMCT. Furthermore, two cases of peritonitis (due to a misplaced  
213 gastrostomy button and ventriculoperitoneal drain) and one pancreatitis, which were clinically  
214 missed (i.e. major errors) were correctly diagnosed at PMCT as cause of death.

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3 215 In the group of perfusion disorders, all three pulmonary embolisms diagnosed at autopsy were also  
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5 216 assigned as cause of death at PMCT. In a further three cases, including one with pulmonary embolism  
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7 217 diagnosis on antemortem ultrasound (Figure 2), PMCT diagnosed pulmonary embolisms which were  
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9 218 not confirmed during autopsy. Moreover, radiologists correctly diagnosed two arrhythmias, one  
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11 219 heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac  
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13 220 arrhythmia was suspected based on left ventricular hypertrophy and aortic valve stenosis or local  
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15 221 hyperdensity of myocardial tissue corresponding to fibrosis in the absence of other significant  
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17 222 findings. In the other case, heart failure was also based upon presence of secondary characteristics  
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19 223 (dilated atria and pleural effusion) in the absence of other significant findings. Myocardial infarction  
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21 224 was correctly diagnosed as cause of death in 7/16=44% after PMCT. However, in 5/7=71% of these  
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23 225 cases, the myocardial infarction was not directly visible on PMCT and was based on the combination  
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25 226 of clinical findings and absence of significant pathologies at PMCT. In the two other cases, imaging  
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27 227 was suspect for myocardial infarction; once due to an intravascular hypodensity proximal of a  
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29 228 coronary stent, which might indicate a (fat) embolism, and once due to the combination of significant  
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31 229 coronary calcifications, enlarged right atrium, clinical history and absence of other significant  
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33 230 findings.

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37 231 Using PMCT, hemorrhagic causes of death were correctly diagnosed in 11/13=85%. All five aortic  
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39 232 dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic  
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41 233 case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed  
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43 234 hemothorax and a liver and kidney rupture (Figure 3). In another traumatic case where death was  
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45 235 attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left  
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47 236 coronary artery (Figure 4).

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50 237 In the category of other pathologies, there were three patients who died from malignant disease.  
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52 238 The cause of death was correctly diagnosed before and after PMCT in two of these cases, one with  
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54 239 pleural carcinomatosis in breast cancer and one with respiratory failure due to cachexia in  
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3 240 metastasized esophageal cancer. In the other case, the patient died after an epileptic seizure due to  
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5 241 (unidentified) brain metastases. There were three other cases with cancer at time of death died, but  
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7 242 those patients died from complications (septic cholecystitis, carotid artery bleeding and endocarditis  
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9 243 due to immunodeficiency).

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12 244 **Sensitivity and specificity for type of pathology and anatomical system involved in the immediate**  
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14 245 **cause of death**

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16  
17 246 The overall sensitivity for type of pathology increased with 18% (4 to 32) from 65% (54 to 76) to 83%  
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19 247 (73 to 91) and with 19% (6 to 33) from 65% (54 to 76) to 85% (75 to 92) for the anatomical system  
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21 248 (Table 5). These improvements were statistically significant. In the subgroups of cardiovascular  
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23 249 causes and perfusion disorders as cause of death, where the sensitivity for immediate cause of death  
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25 250 was rather low, we observed (nearly) significant improvements of 21% (1 to 41) and 21% (-2 to 43)  
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27 251 for the identification of the involved anatomical system and type of pathology respectively. This  
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29 252 illustrates that PMCT can indicate a cardiovascular or perfusive cause of death, even in cases when  
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31 253 the exact cause of death within that subgroup cannot be differentiated. There were no significant  
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33 254 differences in specificity within the subgroups before and after PMCT.

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37 255 **Performance of radiologists**

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39 256 Logistic regression analysis showed no significant improvement in the performance of radiologists in  
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41 257 assigning the correct cause of death over the four-year study period. Odds ratios for each year of  
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43 258 additional experience in reporting PMCT-scans were 0.85 (95% CI: 0.56 to 1.27, p=0.41) for correct  
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45 259 assignment of the immediate cause of death, 0.95 (95% CI: 0.61 to 1.48, p=0.81) for type of  
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47 260 pathology and 0.82 (95% CI: 0.51 to 1.32, p=0.41) for anatomical system involved.

## 261 Discussion

262 The sensitivity for immediate cause of death increased from 53% to 64% after performing PMCT.

263 Analyses showed that the value of PMCT is variable per subcategory and depends on the cause of  
264 death. Unfortunately, subgroups were a lot smaller than expected, resulting in a lower statistical  
265 power and large confidence intervals. We had predicted to include 272 cases (4 years of inclusion \*  
266 average 80 thoraco-abdominal autopsies each year \* 0.85 PMCT consent rate). The main reason for  
267 the limited number of included patients was the unexpected low consent rate (78/304=26%) for  
268 PMCT in cases with consent for conventional autopsy. We did not investigate the reason for this low  
269 consent rate as motives for performing or not performing a PMCT-scan were not extensively  
270 documented. In case of death, clinicians had to ask consent for both PMCT and autopsy. Though  
271 some clinicians mentioned that they only requested for PMCT in case of refusal of conventional  
272 autopsy.

273 Pneumonia was the most common missed infectious cause of death, both before and after PMCT.

274 Resuscitation induced changes and normal postmortem changes, such as the occurrence of  
275 pulmonary edema, could mask pneumonia (Figure 5).<sup>16</sup> In the subgroup of perfusion disorders,  
276 diagnosis of pulmonary embolism at unenhanced PMCT is challenging as it is notoriously difficult to  
277 distinguish an ante-mortem thrombus from a post-mortem blood clot.<sup>17-19</sup> This, or the possibility that  
278 the embolus was lost during the autopsy procedure, may explain why in three cases the pulmonary  
279 embolism was not confirmed during autopsy. Postmortem angiography, now being developed and  
280 validated, can be effective in demonstrating any obstructing thrombi.<sup>20</sup> Most causes of death in the  
281 subgroup of perfusion disorders were cardiac related. Clinicians are often restricted in their ability to  
282 differentiate a cause of death due to the acute nature and time constraints of the situations  
283 (resuscitation setting) these patients present with. On the contrary, cardiac arrhythmia and heart  
284 failure are impossible to diagnose by postmortem examinations only. Furthermore, an autopsy can  
285 only detect a myocardial infarction in cases where patients have survived two to three hours post-  
286 infarction.<sup>21</sup> Therefore, radiologists and pathologists had access to clinical information in order to

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3 287 assign the most probable cause of death based on postmortem findings and clinical findings as well.  
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5 288 Accordingly, both PMCT and autopsy could indicate a cardiac cause of death, based on clinical  
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7 289 findings and secondary characteristics observed during postmortem examination in the absence of  
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9 290 other significant pathologies.

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12 291 Table 3 and 5 show an increase in overall sensitivity from 64% to 83-85% when PMCT is used for  
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14 292 identification of the type of pathology or anatomical system involved rather than for assigning the  
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16 293 exact immediate cause of death. This indicates that even when the cause of death is uncertain after  
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18 294 PMCT, it is still a valuable tool in targeting the region of interest or excluding some of the differential  
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20 295 diagnostic possibilities. Clinical evaluation of the cause of death often indicates the failing system (for  
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22 296 example, respiratory failure) rather than the underlying illness or structural changes, whereas  
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24 297 radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how  
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26 298 confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.

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29 299 Amongst non-invasive techniques, Blokker et al. conclude that PMCT in combination with  
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31 300 postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing  
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33 301 somewhat better when only one of the modalities is used.<sup>14,15</sup> PMCT is less expensive than a  
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35 302 conventional autopsy, however, cost-effective analyses have not been formulated.<sup>22</sup> Images can be  
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37 303 stored digitally (useful for legal or educational purposes) and results can be audited and promptly  
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39 304 reviewed by one or more radiologists. Amongst minimally invasive methods, the highest  
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41 305 performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with  
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43 306 targeted coronary angiography, showed a sensitivity of 92% for cause of death.<sup>19</sup> Two studies  
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45 307 combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for  
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47 308 cause of death.<sup>23,24</sup>

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51 309 To our knowledge this is the second study which has investigated the additional value of unenhanced  
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53 310 PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in  
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55 311 sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths.<sup>25</sup> This is

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3 312 somewhat higher than we found in our study, one reason could be the fact that less specific causes  
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5 313 of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT  
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7 314 compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some  
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9 315 use broadly defined categorizations and others use well-defined specific causes of death, or some  
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11 316 use the immediate cause of death and others the intermediate or underlying cause of death, or do  
12  
13 317 not state their definition of cause of death at all. Furthermore, most previous studies consisted of  
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15 318 small sample sizes ( $n < 50$ ) and used different study populations, different outcome parameters (for  
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17 319 example, cause of death, major or minor diagnoses) and different parameters of accuracy.<sup>4,26-28</sup> A  
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19 320 large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32%  
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21 321 in determining the cause of death with PMCT compared to autopsy.<sup>14</sup> Another study showed a  
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23 322 sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in  
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25 323 101 cases.<sup>29</sup> This is in accordance with our results regarding the categorization of cause of death per  
26  
27 324 type of pathology or anatomical system. Westphal et al. showed a sensitivity of  $18/27=67\%$  for cause  
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29 325 of death and a sensitivity of  $5/17=19\%$  for a more specific description of the involved pathogenetic  
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31 326 mechanism.<sup>26</sup> Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both  
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33 327 definite and possible findings with PMCT as to cause of death.<sup>27</sup> The study by Puranik et al. supports  
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35 328 our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT.<sup>28</sup> A  
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37 329 sensitivity of 25% for cause of death was found in a population of seventeen young patients with  
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39 330 sudden cardiac death.

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43 331 Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure  
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45 332 4), are more confidently diagnosed with PMCT than autopsy.<sup>14,30</sup> Therefore, the presented  
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47 333 performance of PMCT will probably be underestimated in cases where pathologies are difficult to  
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49 334 confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no  
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51 335 longer be considered as the gold standard for all postmortem diagnoses, not only due to the  
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53 336 limitations of dissection, but also due to the decline in the number of autopsies performed, leading  
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55 337 to a decrease in pathologists' expertise. We would suggest a gold standard involving a

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3 338 multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective  
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5 339 studies with larger sample sizes are required to investigate the additional value of PMCT in specific  
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7 340 subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques,  
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9 341 conventional autopsy will still be required in complex cases where clinical and radiological diagnosis  
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11 342 as to cause of death is inconclusive.  
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3 343 **Conclusion**

4 344 While virtual autopsy with postmortem CT is an insufficient substitute for conventional autopsy, it  
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6 345 can improve diagnosis of the cause of death over clinical diagnosis alone. Even in cases where no  
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8 346 immediate cause of death can be assigned after virtual autopsy, radiologists may indicate a region of  
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10 347 interest, so directing pathologists at autopsy. Future studies are needed to investigate whether  
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12 348 PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy altogether.  
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## 432 **Figure legends**

433 **Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT**  
434 **and during conventional autopsy.**

435 <sup>a</sup> No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis  
436 for cause of death. <sup>b</sup> In four cases, where clinicians and radiologists were able to assign a cause of death,  
437 autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a  
438 case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at  
439 autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two  
440 other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the  
441 cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial  
442 infarction were diagnosed by the clinicians. COD: immediate cause of death.

443  
444 **Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem**  
445 **CT but were not confirmed during autopsy.**

446 This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricialis  
447 correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary  
448 embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary  
449 arteries. Autopsy did not assign a cause of death.

450 **Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.**

451 This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial  
452 trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen  
453 laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings:  
454 (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood  
455 along the spleen.

456 **Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.**

457 This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical  
458 examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some

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3 459 other underlying pathology which may have caused the accident. During air ambulance transportation,  
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5 460 ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1),  
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7 461 probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not  
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9 462 diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the  
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11 463 pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

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13 464 **Figure 5. Normal postmortem changes could mask underlying pathology**

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16 465 This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical  
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18 466 examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder  
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20 467 (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and  
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22 468 did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and  
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24 469 interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was  
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26 470 not diagnosed at PMCT.

471 **Tables**

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473

**Table 1. Patient characteristics**

	Study population (n=86), n (%)
<b>Sex</b>	
Male	51 (59%)
Female	35 (41%)
<b>Age, median (IQR)</b>	62 (47-74)
<b>Place of death</b>	
Emergency room	31 (36%)
Intensive care unit	30 (35%)
Clinical ward	18 (21%)
Out-of-hospital	7 (8%)
<b>CPR performed</b>	
Yes	46 (53%)
No	40 (47%)
<b>Brain autopsy performed</b>	
Yes	27 (31%)
No	59 (69%)
<b>Immediate cause of death</b>	
Infectious	26 (30%)
Perfusive disorder	32 (37%)
Hemorrhage	13 (15%)
Other	5 (6%)
Uncertain	10 (12%)

474 IQR: interquartile range. CPR: cardiopulmonary resuscitation.

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477 **Table 2. Cross tabulations of correct and incorrect assigned immediate causes of death (A), type of pathology**  
478 **(B) and anatomical system (C), before and after PMCT**

A.		COD after PMCT		
		Correct	Incorrect	
COD before PMCT	Correct	36	4	40
	Incorrect	13	23	36
		49	27	76

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B.		Type of pathology after PMCT		
		Correct	Incorrect	
Type of pathology before PMCT	Correct	50	1	51
	Incorrect	15	12	27
		65	13	78

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C.		Type of anatomical system after PMCT		
		Correct	Incorrect	
Type of anatomical system before PMCT	Correct	48	3	51
	Incorrect	18	9	27
		66	12	78

483 COD: immediate cause of death.

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**Table 3. Sensitivity for immediate cause of death before and after virtual autopsy with PMCT.**

	Sensitivity		
	Before PMCT (95% CI)	After PMCT (95% CI)	Difference (95% CI)
<b>Immediate cause of death (n=76)<sup>a</sup></b>	<b>53% (41-64)</b>	<b>64% (53-75)</b>	<b>12% (-4-28)</b>
Per subgroup of type of pathology:			
1. Infection (n=26)	65% (44-83)	69% (48-86)	4% (-22-29)
2. Hemorrhage (n=13)	69% (39-91)	85% (55-98)	15% (-17-48)
3. Perfusion disorder (n=32)	31% (16-50)	47% (29-65)	16% (-8-40)
4. Other (n=5)	80% (28-99)	100% (48-100)	20% (-17-57)
Per subgroup of anatomical system:			
1. Pulmonary (n=18)	56% (31-78)	67% (41-87)	11% (-21-43)
2. Cardiovascular (n=37)	43% (27-61)	54% (37-71)	11% (-12-34)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (-5-66)
4. Other (n=8)	88% (47-100)	75% (35-97)	-13% (-50-25)

490 <sup>a</sup> Conventional autopsy was not able to establish a cause of death in ten cases.

491 **Table 4. Overview of all causes of death diagnosed at autopsy, classified by type pathology and whether they**  
 492 **were correctly diagnosed as the immediate cause of death before and after virtual autopsy.**

	<b>Correct COD, both before and after PMCT.</b>	<b>Incorrect COD before PMCT. Correct COD after PMCT.</b>	<b>Correct COD before PMCT. Incorrect COD after PMCT.</b>	<b>Incorrect COD, both before and after PMCT.</b>
<b>Infections</b>	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i. <sup>b</sup> 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis <sup>a</sup> 1x diverticulitis and pancreatitis	1x endocarditis 1x HSV hepatitis 1x cerebral aspergillosis	4x pneumonia 1x endocarditis / pericarditis
<b>Perfusion disorders</b>	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure	9x myocardial infarction 3x arrhythmia 2x heart failure 1x pulmonary veno- occlusive disease 1x bowel ischemia due to adhesions
<b>Hemorrhages</b>	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax 1x liver and kidney rupture + hemothorax
<b>Other</b>	1x pleural carcinomatosis 1x cachexia 1x anaphylaxis 1x (auto-)intoxication	1x epileptic seizure due to brain metastases		

493 <sup>a</sup> Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced  
 494 ventriculoperitoneal drain in another case. <sup>b</sup> sepsis e causa ignota. COD: immediate cause of death.

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500 **Table 5. Sensitivity and specificity for type of pathology and anatomical system diagnosed before and after virtual autopsy with PMCT.**

	Sensitivity			Specificity		
	Before PMCT (95% CI)	After PMCT (95% CI)	Difference (95% CI)	Before PMCT (95% CI)	After PMCT (95% CI)	Difference (95% CI)
<b>A. Type of pathology (n=78)<sup>a</sup></b>	<b>65% (54-76)</b>	<b>83% (73-91)</b>	<b>18% (4-32)</b>	<b>N/A<sup>b</sup></b>	<b>N/A<sup>b</sup></b>	
Per subgroup:						
1. Infection (n=26)	69% (48-86)	85% (65-96)	15% (-8-38)	96% (87-100)	92% (81-98)	-4% (-13-5)
2. Hemorrhage (n=13)	69% (39-91)	92% (64-100)	23% (-7-53)	98% (92-100)	100% (94-100)	2% (-2-5)
3. Perfusion disorder (n=34)	56% (38-73)	76% (59-89)	21% (-2-43)	95% (85-99)	93% (81-99)	-2% (-12-7)
4. Other (n=5)	100% (48-100)	100% (48-100)	0% (0-0)	99% (93-100%)	99% (93-100%)	0% (-4-4)
<b>B. Anatomical system (n=78)<sup>a</sup></b>	<b>65% (54-76)</b>	<b>85% (75-92)</b>	<b>19% (6-33)</b>	<b>N/A<sup>b</sup></b>	<b>N/A<sup>b</sup></b>	
Per subgroup:						
1. Pulmonary (n=18)	72% (47-90)	89% (65-99)	17% (-9-43)	95% (86-99)	95% (86-99)	0% (-8-8)
2. Cardiovascular (n=39)	62% (45-77)	82% (66-92)	21% (1-41)	100% (91-100)	95% (82-99)	-5% (-12-2)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (5-66)	98% (92-100)	100% (94-100)	2% (-2-5)
4. Other (n=8)	88% (48-100)	88% (48-100)	0% (-32-32)	97% (90-100)	94% (86-98)	-3% (-10-4)

<sup>a</sup> Autopsy was not able to establish the involved type of pathology and anatomical system in eight cases. <sup>b</sup> Not applicable.



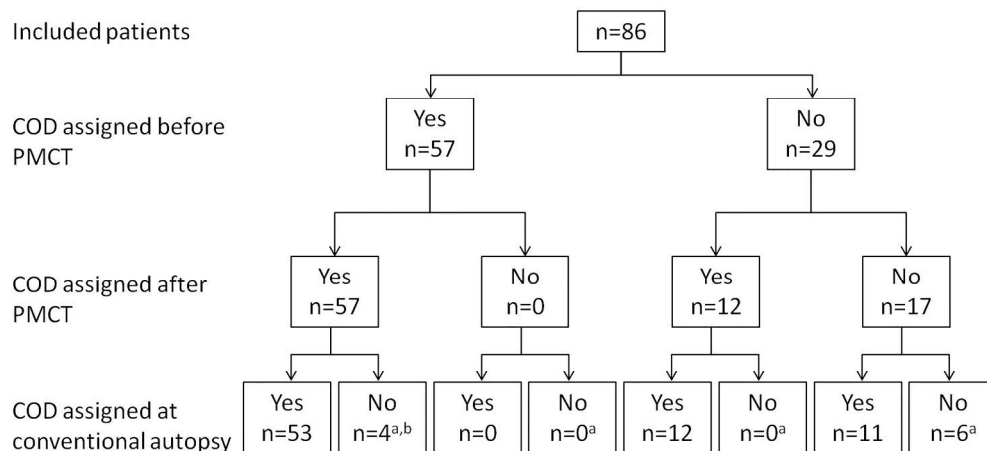


Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.

a No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. b In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

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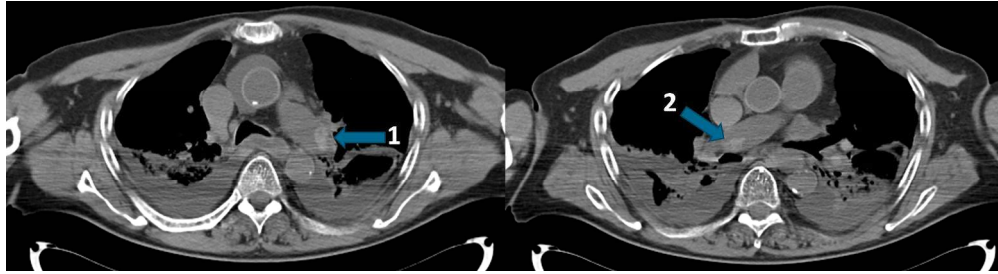


Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy. !! † This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

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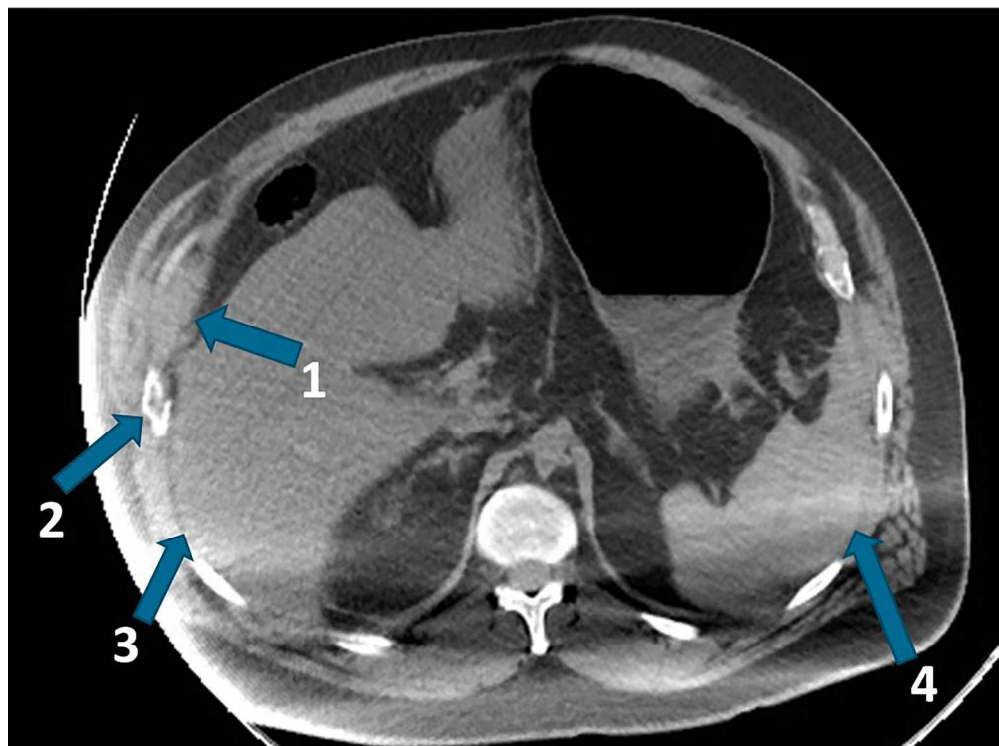


Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.!! † This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

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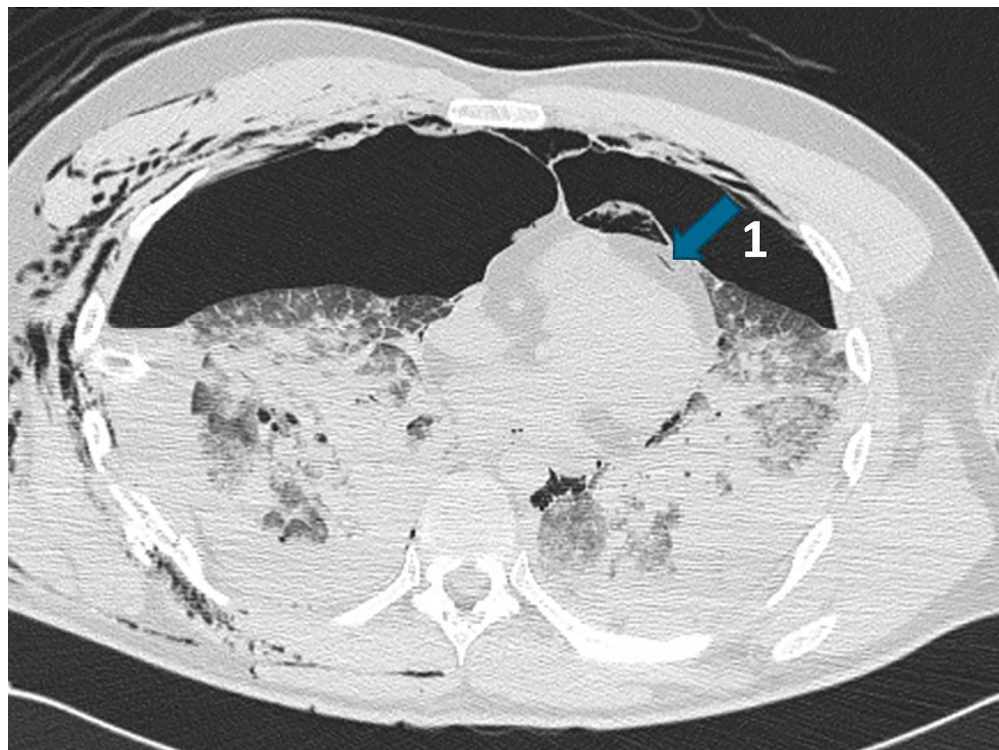


Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.

This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

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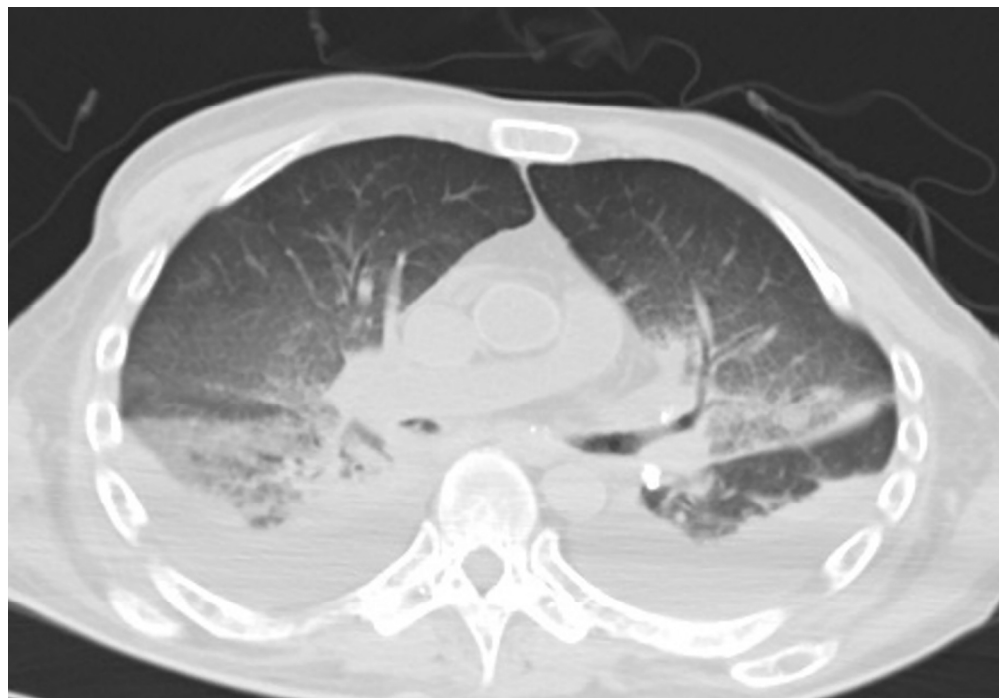


Figure 5. Normal postmortem changes could mask underlying pathology. This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

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Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
<b>ABSTRACT</b>			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
<b>INTRODUCTION</b>			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
<b>METHODS</b>			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
<i>Participants</i>	6	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	(6)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8
	18	Intended sample size and how it was determined	8 See supplementary file: 'response to editorial request'
<b>RESULTS</b>			
<i>Participants</i>	19	Flow of participants, using a diagram	Fig 1, page 20
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	10
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 23, page 22-23
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 23 + 5
	25	Any adverse events from performing the index test or the reference standard	
<b>DISCUSSION</b>			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	4, 13-165
	27	Implications for practice, including the intended use and clinical role of the index test	13-165
<b>OTHER INFORMATION</b>			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	5

For peer review only

# STARD 2015

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## AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

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## EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

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## DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.





# BMJ Open

## Can virtual autopsy with postmortem CT improve clinical diagnosis of cause of death? A retrospective observational cohort study in a Dutch tertiary referral centre.

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<b>Primary Subject Heading</b>:	Radiology and imaging
Secondary Subject Heading:	Diagnostics, Pathology
Keywords:	Computed tomography < RADIOLOGY & IMAGING, cause of death, postmortem, autopsy, sensitivity, specificity

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### 3 **Can virtual autopsy with postmortem CT improve clinical diagnosis of** 4 **cause of death? A retrospective observational cohort study in a Dutch** 5 **tertiary referral centre.**

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7

8 **LJP Sonnemans**<sup>1#</sup> PhD candidate in post-mortem radiology9 **B Kubat**<sup>2,3</sup> Pathologist10 **M Prokop**<sup>1</sup> Radiologist11 **WM Klein**<sup>1,4</sup> Radiologist

12

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20

21 **Study design:** retrospective observational cohort study22 **Word count:** 3225

23

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Field Code Changed

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1  
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33 **Key Words**

7  
8 34 cause of death, postmortem, computed tomography, autopsy, sensitivity, specificity  
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10 35

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12 36 **List of abbreviations**

13 37 COD immediate cause of death

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15 38 PMCT postmortem CT  
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## Abstract

**Objective:** To investigate whether virtual autopsy with postmortem CT (PMCT) improves clinical diagnosis of the immediate cause of death.

**Design:** Retrospective observational cohort study. Inclusion-criteria: in- and out-of-hospital deaths over the age of one year in whom virtual autopsy with PMCT and conventional autopsy were performed. Exclusion-criteria: forensic cases, post mortal organ donors and cases with incomplete scanning procedures. Cadavers were examined by virtual autopsy with PMCT prior to conventional autopsy. The clinically determined cause of death was recorded before virtual autopsy and was then adjusted with the findings of virtual autopsy. Using conventional autopsy as reference standard, we investigated the increase in sensitivity for immediate cause of death, type of pathology and anatomical system involved before and after virtual autopsy.

**Setting:** Tertiary referral centre.

**Participants:** 86 cadavers who underwent conventional and virtual autopsy between July 2012 and June 2016.

**Intervention:** PMCT consisted of brain, cervical spine and chest-abdomen-pelvis imaging. Conventional autopsy consisted of thoraco-abdominal examination with/without brain autopsy.

**Primary and secondary outcome measures:** Increase in sensitivity for the immediate cause of death, type of pathology (infection, hemorrhage, perfusion disorder, other or not assigned) and anatomical system (pulmonary, cardiovascular, gastrointestinal, other or not assigned) involved, before and after virtual autopsy.

**Results:** Using PMCT, the sensitivity for immediate cause of death increased with 12% (95% CI: 2 to 22) from 53% (41 to 64) to 64% (53 to 75), with 18% (9 to 27) from 65% (54 to 76) to 83% (73 to 91) for type of pathology and with 19% (9 to 30) from 65% (54 to 76) to 85% (75 to 92) for anatomical system.

**Conclusion:** While unenhanced postmortem CT is an insufficient substitute for conventional autopsy, it can improve diagnosis of cause of death over clinical diagnosis alone and should therefore be considered whenever autopsy is not performed.

## 68 Article summary

### 69 Strengths and limitations of this study

70

71 • This study investigated the diagnostic performance for clinical cause of death determination  
72 by use of postmortem CT and takes into account the added value over clinical diagnosis  
73 alone.

74 • The immediate cause of death (i.e. direct cause of death) was the main outcome rather than  
75 the primary cause of death (i.e. underlying cause of death or basic illness) as from a clinical  
76 point of view, diagnosis and treatment of the immediate cause of death is the most urgent.

77 • The sensitivity for clinical cause of death determination, with and without postmortem CT, is  
78 investigated on multiple levels of precision; the immediate cause of death as well as the  
79 involved type of pathology and anatomical location were investigated.

80 • The retrospective design in a tertiary care centre has probably introduced a selection-bias  
81 towards patients with diagnostic difficulties or unresolved issues, resulting in an  
82 underestimation of the diagnostic performance compared to more general causes of death.

83 • An unexpected low consent rate for postmortem CT in cases with consent for conventional  
84 autopsy resulted in a reduction of the statistical power of this study.

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**Contributors:** LJPS had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LJPS acquired and analyzed the data. LJPS, WMK, BK and WMP interpreted the data. LJPS drafted the manuscript. WMK and WMP supervised the study. LJPS, WMK and WMP contributed to the overall conception and design of the study. All authors revised the manuscript for intellectual content.

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**Competing interests:** All authors have completed the ICMJE uniform disclosure form and declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, and no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval:** This study was approved by the local ethical committee in the form of a waiver in accordance with Dutch national law.

**Data sharing:** Details on how to obtain additional data from the study (eg, statistical code, datasets) are available from the corresponding author.

**Transparency:** The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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## 112 Introduction

113  
114 Autopsies are traditionally regarded as the 'gold standard' in quality monitoring of health care. It is  
115 therefore remarkable that in a time of heightened interest in improving patient safety, healthcare  
116 quality and error prevention, worldwide autopsy rates continue to decline from roughly 40% in the  
117 nineteen sixties, to below 10% nowadays.<sup>1-7</sup> Religious and emotional objections to the invasiveness  
118 of conventional autopsies, both by the relatives and the doctors, are considered as some of the  
119 reasons given for this decline. At present, determination of the cause of death relies heavily on  
120 clinical assessment. Despite an increase in the use and improvement of diagnostic techniques in the  
121 last decades, major error rates of approximately 25% have not substantially decreased.<sup>8-10</sup> According  
122 to the Goldman classification system, major errors are defined as clinically missed diagnoses related  
123 to the cause of death. In half of these cases this might have led to a change in therapy and prolonged  
124 survival, if known before death.<sup>8</sup>

125 National mortality statistics are generally based on the primary cause of death (i.e. underlying cause  
126 or basic illness), which could be a longstanding, chronic disease.<sup>11</sup> However from an individual and  
127 clinical point of view, diagnosis and treatment of the immediate cause of death (i.e. direct cause of  
128 death) is the most urgent. Accuracy rates for immediate causes of death are probably lower than for  
129 underlying causes of death<sup>12,13</sup>, due to time constraints of the often acute situations these diagnoses  
130 present with. The high error rates emphasize the need to improve clinical diagnoses using techniques  
131 that are widely available and acceptable, for example, postmortem CT (PMCT). Previous studies have  
132 shown that as yet, PMCT is an insufficient substitute but can be used in adjunct to conventional  
133 autopsy.<sup>14,15</sup> In order to provide answers and quality control also in cases without consent for  
134 conventional autopsy, we investigated whether virtual autopsy with PMCT improves clinical diagnosis  
135 of the immediate cause of death.

## 136 **Material and methods**

### 137 **Study design**

138 All cadavers of in- and out-of-hospital deaths over the age of one year, who underwent both PMCT  
139 and conventional autopsy in our hospital, between July 2012 and June 2016, were included. Forensic  
140 cases, post mortal donors and cases with incomplete scanning procedures or without full thorax-  
141 abdomen autopsy, were excluded. Clinicians had to ask consent from relatives for both PMCT and  
142 conventional autopsy in all cases of death. This retrospective study was approved by the local ethical  
143 committee in the form of a waiver in accordance with Dutch national law.

### 144 **PMCT and conventional autopsy**

145 PMCT was performed as soon as possible after death and prior to autopsy. If scanning within a few  
146 hours was not possible, the cadaver was stored in the mortuary at 4°C. CT-scanners used were  
147 Siemens Somatom Sensation 16, Siemens Sensation 64 (Siemens Healthcare, Germany) and Aquilion  
148 ONE (Toshiba Medical Systems, Japan). All with a detector collimation of 1mm, reconstruction  
149 interval of 0.8mm and 120 kV. The Siemens scanners used a tube current of 400mA and 1s rotation  
150 time. The Toshiba scanner used Automatic Exposure Control (SD 17.5) with a rotation time of 0.5s.  
151 PMCT protocol consisted of a scan of the head and neck, in bone, soft tissue and cerebral setting,  
152 interpreted by a neuro-radiologist; a scan of thorax and abdomen in bone, lung and abdominal  
153 settings, interpreted by a specialist cardiothoracic and abdominal radiologist; summarized in a single  
154 consensus report. All radiologists had minimal previous experience in interpreting PMCT images, as  
155 postmortem imaging is a relatively new field of expertise. Conventional autopsy consisted of  
156 thoracic-abdominal autopsy with or without examination of the brain, and included full macroscopic  
157 and microscopic inspection. Radiologists and pathologists were blinded to each other's results, but  
158 had otherwise full access to electronic patient files. Radiologists and pathologists compiled a report  
159 based on their own findings and clinical findings.

### 160 **Data collection**



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6 161 For each cadaver the immediate cause of death (i.e. direct cause of death), type of pathology and  
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8 162 anatomical system involved, were collected in retrospect at three moments: before PMCT, after  
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10 163 PMCT and based on conventional autopsy findings. The cause of death before virtual autopsy was  
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12 164 based on clinical findings only. The cause of death after virtual autopsy was based on both clinical  
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14 165 findings and PMCT. If no cause of death could be assigned at PMCT, the cause of death was primarily  
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16 166 based on clinical findings. Symptoms (for example, respiratory failure, sepsis etc.) and risk factors  
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18 167 (atherosclerosis, hypertension) were not considered as cause of death. Only when the primary  
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20 168 source of sepsis (for example pneumonia) was unknown, sepsis was diagnosed as cause of death. In  
21  
22 169 cases of trauma, the physical injury rather than the mechanism of trauma was assigned as cause of  
23  
24 170 death.

25 171 Type of pathology was scored according to the following categories; infection, hemorrhage,  
26  
27 172 perfusion disorder, other or not assigned. Perfusion disorders comprised all cardiac and vascular  
28  
29 173 perfusion disorders not due to infection, hemorrhage or neoplasm (for example, myocardial  
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31 174 infarction, heart failure, pulmonary embolism, volvulus etc.). Type A aortic dissections with  
32  
33 175 hemopericardium were grouped in the hemorrhage category. The type of anatomical system was  
34  
35 176 scored as; pulmonary, cardiovascular, gastrointestinal, other or not assigned. This strategy and  
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37 177 subcategories used were derived from the classification of anatomical regions and groups of  
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39 178 pathologies as used by Roberts and Wichmann et al.<sup>4,14</sup>

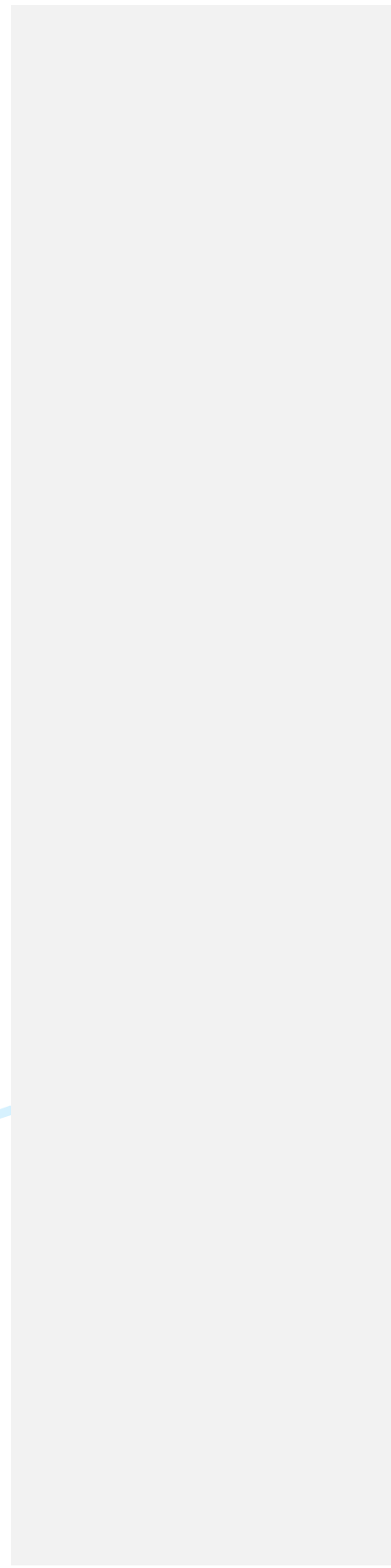
#### 40 179 **Statistical analysis**

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42 180 Sensitivity and specificity were calculated with conventional autopsy as reference standard. 95%  
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44 181 confidence intervals (CI) of the differences in sensitivity or specificity before and after PMCT were  
45  
46 182 calculated. Cases where the cause of death, type of pathology or anatomical system could not be  
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48 183 established after conventional autopsy were excluded from statistical analysis. A sample size of  
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50 184  $n=113$  was required to demonstrate a difference of 15% in sensitivity with  $\alpha=0.05$  and  $\beta=0.10$ .  
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52 185 Logistic regression analysis was performed to evaluate radiologists' improvement in reporting PMCT-

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186 scans during the four year study period. Odds ratios were calculated for each additional year of  
187 experience in reporting PMCT-scans. P values of 0.05 or less were considered significant. IBM SPSS  
188 Statistics, version 22 was used.

For peer review only



## 189 Results

190 Of 2155 clinically examined in- and out-of-hospital deaths in our hospital, a full thorax-abdomen  
191 autopsy was performed on 304 (14%) cadavers, a complete PMCT on 120 (6%) cadavers and both on  
192 78 (4%) cadavers. One case was excluded due to postmortem organ donation prior to PMCT. A  
193 further nine cases who deceased at home (n=7) or in another hospital (n=2) were brought to the  
194 hospital's mortuary for PMCT and autopsy examination. This led to a total of 86 included cases (51  
195 men, 35 women, with a median age of 62 (IQR: 47 to 74) years) (Table 1). 54% of the deaths were  
196 after a resuscitation attempt. The median postmortem interval between death and PMCT was 7.6  
197 (IQR: 3.1 to 18.8) hours. In 69% there was no consent for brain autopsy and, in those cases,  
198 conventional autopsy consisted of a thorax-abdomen examination only. Conventional autopsy, as  
199 standard of reference, was not able to assign the immediate cause of death in ten cadavers (12%)  
200 (Figure 1). The type of pathology and anatomical system involved were both not assigned in eight  
201 cadavers. Therefore, analyses were based on the remaining 76 or 78 cadavers. Table 2 shows 2-by-2-  
202 tables of the number of correct diagnoses before and after PMCT.

### 203 Sensitivity for immediate cause of death

204 The overall sensitivity for immediate cause of death increased with 12% (2 to 22) from 53% (41 to 64)  
205 to 64% (53 to 75) after performing a PMCT-scan. Sensitivities specified per type of pathology or  
206 anatomical system are shown in Table 3. All autopsy causes of death, and whether or not they were  
207 correctly appointed before and after PMCT, are shown in Table 4.

208 Pneumonia was the most common infectious cause of death. It was correctly assigned as cause of  
209 death in 11/15=73% after PMCT, compared to 10/15=67% before PMCT. In the other 27% (n=4),  
210 pneumonia was recognized, but not assigned as cause of death. Vice versa, in two other patients  
211 who had died from cerebral aspergillosis and heart failure, the ancillary pneumonia was incorrectly  
212 assigned as cause of death on PMCT. Furthermore, two cases of peritonitis (due to a misplaced  
213 gastrostomy button and ventriculoperitoneal drain) and one pancreatitis, which were clinically  
214 missed (i.e. major errors) were correctly diagnosed at PMCT as cause of death.

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6 215 In the group of perfusion disorders, all three pulmonary embolisms diagnosed at autopsy were also  
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8 216 assigned as cause of death at PMCT. In a further three cases, including one with pulmonary embolism  
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10 217 diagnosis on antemortem ultrasound (Figure 2), PMCT diagnosed pulmonary embolisms which were  
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12 218 not confirmed during autopsy. Moreover, radiologists correctly diagnosed two arrhythmias, one  
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14 219 heart failure and one volvulus which were initially missed as cause of death by the clinicians. Cardiac  
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16 220 arrhythmia was suspected based on left ventricular hypertrophy and aortic valve stenosis or local  
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18 221 hyperdensity of myocardial tissue corresponding to fibrosis in the absence of other significant  
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20 222 findings. In the other case, heart failure was also based upon presence of secondary characteristics  
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22 223 (dilated atria and pleural effusion) in the absence of other significant findings. Myocardial infarction  
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24 224 was correctly diagnosed as cause of death in 7/16=44% after PMCT. However, in 5/7=71% of these  
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26 225 cases, the myocardial infarction was not directly visible on PMCT and was based on the combination  
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28 226 of clinical findings and absence of significant pathologies at PMCT. In the two other cases, imaging  
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30 227 was suspect for myocardial infarction; once due to an intravascular hypodensity proximal of a  
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32 228 coronary stent, which might indicate a (fat) embolism, and once due to the combination of significant  
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34 229 coronary calcifications, enlarged right atrium, clinical history and absence of other significant  
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36 230 findings.

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38 231 Using PMCT, hemorrhagic causes of death were correctly diagnosed in 11/13=85%. All five aortic  
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40 232 dissections were correctly diagnosed on PMCT, including a clinically missed dissection. In a traumatic  
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42 233 case, radiologists diagnosed hemothorax and a spleen rupture where pathologists diagnosed  
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44 234 hemothorax and a liver and kidney rupture (Figure 3). In another traumatic case where death was  
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46 235 attributed to hemorrhagic shock due to hemothorax, radiologists diagnosed an air embolus in the left  
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48 236 coronary artery (Figure 4).

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50 237 In the category of other pathologies, there were three patients who died from malignant disease.  
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52 238 The cause of death was correctly diagnosed before and after PMCT in two of these cases, one with  
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54 239 pleural carcinomatosis in breast cancer and one with respiratory failure due to cachexia in

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6 240 metastasized esophageal cancer. In the other case, the patient died after an epileptic seizure due to  
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8 241 (unidentified) brain metastases. There were three other cases with cancer at time of death died, but  
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10 242 those patients died from complications (septic cholecystitis, carotid artery bleeding and endocarditis  
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12 243 due to immunodeficiency).

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14 244 **Sensitivity and specificity for type of pathology and anatomical system involved in the immediate**  
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16 245 **cause of death**

17  
18 246 The overall sensitivity for type of pathology increased with 18% (9 to 27) from 65% (54 to 76) to 83%  
19 247 (73 to 91) and with 19% (9 to 30) from 65% (54 to 76) to 85% (75 to 92) for the anatomical system  
20 248 (Table 5). These improvements were statistically significant. In the subgroups of cardiovascular  
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22 249 causes and perfusion disorders as cause of death, where the sensitivity for immediate cause of death  
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24 250 was rather low, we observed significant improvements of 21% (6 to 35) and 21% (5 to 36) for the  
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26 251 identification of the involved anatomical system and type of pathology respectively. This illustrates  
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28 252 that PMCT can indicate a cardiovascular or perfusive cause of death, even in cases when the exact  
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30 253 cause of death within that subgroup cannot be differentiated. There were no significant differences  
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32 254 in specificity within the subgroups before and after PMCT.

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36 255 **Performance of radiologists**

37 256 Logistic regression analysis showed no significant improvement in the performance of radiologists in  
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39 257 assigning the correct cause of death over the four-year study period. Odds ratios for each year of  
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41 258 additional experience in reporting PMCT-scans were 0.85 (95% CI: 0.56 to 1.27, p=0.41) for correct  
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43 259 assignment of the immediate cause of death, 0.95 (95% CI: 0.61 to 1.48, p=0.81) for type of  
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45 260 pathology and 0.82 (95% CI: 0.51 to 1.32, p=0.41) for anatomical system involved.

## 261 Discussion

262 The sensitivity for immediate cause of death increased from 53% to 64% after performing PMCT.

263 Analyses showed that the value of PMCT is variable per subcategory and depends on the cause of  
264 death. Unfortunately, subgroups were a lot smaller than expected, resulting in a lower statistical  
265 power and large confidence intervals. We had predicted to include 272 cases (4 years of inclusion \*  
266 average 80 thoraco-abdominal autopsies each year \* 0.85 PMCT consent rate). The main reason for  
267 the limited number of included patients was the unexpected low consent rate (78/304=26%) for  
268 PMCT in cases with consent for conventional autopsy. We did not investigate the reason for this low  
269 consent rate as motives for performing or not performing a PMCT-scan were not extensively  
270 documented. In case of death, clinicians had to ask consent for both PMCT and autopsy. Though  
271 some clinicians mentioned that they only requested for PMCT in case of refusal of conventional  
272 autopsy.

273 Pneumonia was the most common missed infectious cause of death, both before and after PMCT.

274 Resuscitation induced changes and normal postmortem changes, such as the occurrence of  
275 pulmonary edema, could mask pneumonia (Figure 5).<sup>16</sup> In the subgroup of perfusion disorders,  
276 diagnosis of pulmonary embolism at unenhanced PMCT is challenging as it is notoriously difficult to  
277 distinguish an ante-mortem thrombus from a post-mortem blood clot.<sup>17-19</sup> This, or the possibility that  
278 the embolus was lost during the autopsy procedure, may explain why in three cases the pulmonary  
279 embolism was not confirmed during autopsy. Postmortem angiography, now being developed and  
280 validated, can be effective in demonstrating any obstructing thrombi.<sup>20</sup> Most causes of death in the  
281 subgroup of perfusion disorders were cardiac related. Clinicians are often restricted in their ability to  
282 differentiate a cause of death due to the acute nature and time constraints of the situations  
283 (resuscitation setting) these patients present with. On the contrary, cardiac arrhythmia and heart  
284 failure are impossible to diagnose by postmortem examinations only. Furthermore, an autopsy can  
285 only detect a myocardial infarction in cases where patients have survived two to three hours post-  
286 infarction.<sup>21</sup> Therefore, radiologists and pathologists had access to clinical information in order to

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6 287 assign the most probable cause of death based on postmortem findings and clinical findings as well.

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8 288 Accordingly, both PMCT and autopsy could indicate a cardiac cause of death, based on clinical  
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10 289 findings and secondary characteristics observed during postmortem examination in the absence of  
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12 290 other significant pathologies.

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14 291 Table 3 and 5 show an increase in overall sensitivity from 64% to 83 or 85% when PMCT is used for  
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16 292 identification of the type of pathology or anatomical system involved rather than for assigning the  
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18 293 exact immediate cause of death. This indicates that even when the cause of death is uncertain after  
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20 294 PMCT, it is still a valuable tool in targeting the region of interest or excluding some of the differential  
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22 295 diagnostic possibilities. Clinical evaluation of the cause of death often indicates the failing system (for  
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24 296 example, respiratory failure) rather than the underlying illness or structural changes, whereas  
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26 297 radiologists appear to be more adept at ascertaining the involved anatomical system. Based on how  
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28 298 confident radiologists are of their findings, they can guide the pathologist to the region(s) of interest.

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30 299 Amongst non-invasive techniques, Blokker et al. conclude that PMCT in combination with  
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32 300 postmortem MRI yield the highest diagnostic performance in adults, with PMCT performing  
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34 301 somewhat better when only one of the modalities is used.<sup>14,15</sup> PMCT is less expensive than a  
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36 302 conventional autopsy, however, cost-effective analyses have not been formulated.<sup>22</sup> Images can be  
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38 303 stored digitally (useful for legal or educational purposes) and results can be audited and promptly  
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40 304 reviewed by one or more radiologists. Amongst minimally invasive methods, the highest  
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42 305 performance is reported in studies combining PMCT and CT-angiography. PMCT, enhanced with  
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44 306 targeted coronary angiography, showed a sensitivity of 92% for cause of death.<sup>19</sup> Two studies  
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46 307 combining CT, CT-angiography and CT-guided tissue biopsies achieved a pooled sensitivity of 91% for  
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48 308 cause of death.<sup>23,24</sup>

49 309 To our knowledge this is the second study which has investigated the additional value of unenhanced  
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51 310 PMCT compared to clinical diagnoses. The first study by Inai et al. showed a significant increase in  
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53 311 sensitivity from 46% to 74% for the immediate cause of death in 50 non-forensic deaths.<sup>25</sup> This is

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6 312 somewhat higher than we found in our study, one reason could be the fact that less specific causes  
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8 313 of death were used. Other previous studies have investigated the diagnostic accuracy of PMCT  
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10 314 compared to autopsy and not to clinical diagnoses. Those studies are difficult to compare, as some  
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12 315 use broadly defined categorizations and others use well-defined specific causes of death, or some  
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14 316 use the immediate cause of death and others the intermediate or underlying cause of death, or do  
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16 317 not state their definition of cause of death at all. Furthermore, most previous studies consisted of  
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18 318 small sample sizes ( $n < 50$ ) and used different study populations, different outcome parameters (for  
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20 319 example, cause of death, major or minor diagnoses) and different parameters of accuracy.<sup>4,26-28</sup> A  
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22 320 large prospective study of 182 adult deaths by Roberts et al. showed a major discrepancy rate of 32%  
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24 321 in determining the cause of death with PMCT compared to autopsy.<sup>14</sup> Another study showed a  
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26 322 sensitivity of 82% and a specificity of 97% for PMCT regarding the categorization of cause death in  
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28 323 101 cases.<sup>29</sup> This is in accordance with our results regarding the categorization of cause of death per  
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30 324 type of pathology or anatomical system. Westphal et al. showed a sensitivity of 18/27=67% for cause  
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32 325 of death and a sensitivity of 5/17=19% for a more specific description of the involved pathogenetic  
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34 326 mechanism.<sup>26</sup> Takahashi et al. found a sensitivity of 12% for definite findings and 53% for both  
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36 327 definite and possible findings with PMCT as to cause of death.<sup>27</sup> The study by Puranik et al. supports  
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38 328 our results regarding the difficulty in diagnosing cardiac causes of death with unenhanced PMCT.<sup>28</sup> A  
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40 329 sensitivity of 25% for cause of death was found in a population of seventeen young patients with  
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42 330 sudden cardiac death.

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44 331 Certain diagnoses, for example fractures or those related to the accumulation of gasses or air (Figure  
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46 332 4), are more confidently diagnosed with PMCT than autopsy.<sup>14,30</sup> Therefore, the presented  
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48 333 performance of PMCT will probably be underestimated in cases where pathologies are difficult to  
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50 334 confirm due to the limitations of autopsy. Generally, in our experience we find that autopsy can no  
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52 335 longer be considered as the gold standard for all postmortem diagnoses, not only due to the  
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54 336 limitations of dissection, but also due to the decline in the number of autopsies performed, leading  
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56 337 to a decrease in pathologists' expertise. We would suggest a gold standard involving a



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6 338 multidisciplinary consensus evaluation amongst clinicians, radiologists and pathologists. Prospective  
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8 339 studies with larger sample sizes are required to investigate the additional value of PMCT in specific  
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10 340 subgroups of causes of death. Even with the aid of improved non- or minimally invasive techniques,  
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12 341 conventional autopsy will still be required in complex cases where clinical and radiological diagnosis  
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14 342 as to cause of death is inconclusive.

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### 343 **Conclusion**

344 While virtual autopsy with postmortem CT is an insufficient substitute for conventional autopsy, it  
345 can improve diagnosis of the cause of death over clinical diagnosis alone. Even in cases where no  
346 immediate cause of death can be assigned after virtual autopsy, radiologists may indicate a region of  
347 interest, so directing pathologists at autopsy. Future studies are needed to investigate whether  
348 PMCT is able to reduce the invasiveness of autopsy or even avoid an autopsy altogether.

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## Figure legends

**Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.**

<sup>a</sup> No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. <sup>b</sup> In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

**Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy.**

This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricialis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

**Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.**

This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

**Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.**

This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some

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6 459 other underlying pathology which may have caused the accident. During air ambulance transportation,  
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8 460 ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1),  
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10 461 probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not  
11 462 diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the  
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13 463 pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.  
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15 464 **Figure 5. Normal postmortem changes could mask underlying pathology**

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17 465 This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical  
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19 466 examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder  
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21 467 (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and  
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23 468 did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and  
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25 469 interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was  
26 470 not diagnosed at PMCT.  
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## Tables

**Table 1. Patient characteristics**

	Study population (n=86), n (%)
<b>Sex</b>	
Male	51 (59%)
Female	35 (41%)
<b>Age, median (IQR)</b>	62 (47-74)
<b>Place of death</b>	
Emergency room	31 (36%)
Intensive care unit	30 (35%)
Clinical ward	18 (21%)
Out-of-hospital	7 (8%)
<b>CPR performed</b>	
Yes	46 (53%)
No	40 (47%)
<b>Brain autopsy performed</b>	
Yes	27 (31%)
No	59 (69%)
<b>Immediate cause of death</b>	
Infectious	26 (30%)
Perfusive disorder	32 (37%)
Hemorrhage	13 (15%)
Other	5 (6%)
Uncertain	10 (12%)

IQR: interquartile range. CPR: cardiopulmonary resuscitation.

**Table 2. Cross tabulations of correct and incorrect assigned immediate causes of death (A), type of pathology (B) and anatomical system (C), before and after PMCT**

A.		COD after PMCT		
		Correct	Incorrect	
COD before PMCT	Correct	36	4	40
	Incorrect	13	23	36
		49	27	76

B.		Type of pathology after PMCT		
		Correct	Incorrect	
Type of pathology before PMCT	Correct	50	1	51
	Incorrect	15	12	27
		65	13	78

C.		Type of anatomical system after PMCT		
		Correct	Incorrect	
Type of anatomical system before PMCT	Correct	48	3	51
	Incorrect	18	9	27
		66	12	78

COD: immediate cause of death.

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**Table 3. Sensitivity for immediate cause of death before and after virtual autopsy with PMCT.**

	Sensitivity		
	Before PMCT (95% CI)	After PMCT (95% CI)	Difference (95% CI)
<b>Immediate cause of death (n=76)<sup>a</sup></b>	<b>53% (41-64)</b>	<b>64% (53-75)</b>	<b>12% (2-22)</b>
Per subgroup of type of pathology:			
1. Infection (n=26)	65% (44-83)	69% (48-86)	4% (-16-24)
2. Hemorrhage (n=13)	69% (39-91)	85% (55-98)	15% (-4-35)
3. Perfusion disorder (n=32)	31% (16-50)	47% (29-65)	16% (0-31)
4. Other (n=5)	80% (28-99)	100% (48-100)	20% (-15-55)
Per subgroup of anatomical system:			
1. Pulmonary (n=18)	56% (31-78)	67% (41-87)	11% (-3-26)
2. Cardiovascular (n=37)	43% (27-61)	54% (37-71)	11% (-4-25)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (-2-64)
4. Other (n=8)	88% (47-100)	75% (35-97)	-13% (-35-10)

490 <sup>a</sup> Conventional autopsy was not able to establish a cause of death in ten cases.



491 **Table 4. Overview of all causes of death diagnosed at autopsy, classified by type pathology and whether they**  
 492 **were correctly diagnosed as the immediate cause of death before and after virtual autopsy.**

	Correct COD, both before and after PMCT.	Incorrect COD before PMCT. Correct COD after PMCT.	Correct COD before PMCT. Incorrect COD after PMCT.	Incorrect COD, both before and after PMCT.
<b>Infections</b>	10x pneumonia 1x infected liver cysts 1x sepsis e.c.i. <sup>b</sup> 1x pancreatitis 1x cholecystitis / cholangitis	1x pneumonia 2x peritonitis <sup>a</sup> 1x diverticulitis and pancreatitis	1x endocarditis 1x HSV hepatitis 1x cerebral aspergillosis	4x pneumonia 1x endocarditis / pericarditis
<b>Perfusion disorders</b>	7x myocardial infarction 1x heart failure 1x pulmonary embolism	2x pulmonary embolism 2x arrhythmia 1x volvulus 1x heart failure	1x heart failure	9x myocardial infarction 3x arrhythmia 2x heart failure 1x pulmonary veno-occlusive disease 1x bowel ischemia due to adhesions
<b>Hemorrhages</b>	4x type A aortic dissection 1x subarachnoidal hemorrhage 1x gastric hemorrhage 1x arteria carotis hemorrhage 1x arteria iliaca communis sinistra hemorrhage 1x hemorrhage from fistula; gastric tube vs. aorta	1x type A aortic dissection 1x hemothorax + intrapulmonary hemorrhage		1x hemothorax 1x liver and kidney rupture + hemothorax
<b>Other</b>	1x pleural carcinomatosis 1x cachexia 1x anaphylaxis 1x (auto-)intoxication	1x epileptic seizure due to brain metastases		

493 <sup>a</sup> Peritonitis was due to a misplaced gastrostomy button in one case, and due to a misplaced  
 494 ventriculoperitoneal drain in another case. <sup>b</sup> sepsis e causa ignota. COD: immediate cause of death.

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500 **Table 5. Sensitivity and specificity for type of pathology and anatomical system diagnosed before and after virtual autopsy with PMCT.**  
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	Sensitivity			Specificity		
	Before PMCT (95% CI)	After PMCT (95% CI)	Difference (95% CI)	Before PMCT (95% CI)	After PMCT (95% CI)	Difference (95% CI)
<b>A. Type of pathology (n=78)<sup>a</sup></b>	<b>65% (54-76)</b>	<b>83% (73-91)</b>	<b>18% (9-27)</b>	<b>N/A<sup>b</sup></b>	<b>N/A<sup>b</sup></b>	
Per subgroup:						
1. Infection (n=26)	69% (48-86)	85% (65-96)	15% (2-29)	96% (87-100)	92% (81-98)	-4% (-9-1)
2. Hemorrhage (n=13)	69% (39-91)	92% (64-100)	23% (0-46)	98% (92-100)	100% (94-100)	2% (-1-5)
3. Perfusion disorder (n=34)	56% (38-73)	76% (59-89)	21% (5-36)	95% (85-99)	93% (81-99)	-2% (-12-87)
4. Other (n=5)	100% (48-100)	100% (48-100)	0% (0-0)	99% (93-100%)	99% (93-100%)	0% (0-0)
<b>B. Anatomical system (n=78)<sup>a</sup></b>	<b>65% (54-76)</b>	<b>85% (75-92)</b>	<b>19% (9-30)</b>	<b>N/A<sup>b</sup></b>	<b>N/A<sup>b</sup></b>	
Per subgroup:						
1. Pulmonary (n=18)	72% (47-90)	89% (65-99)	17% (-1-34)	95% (86-99)	95% (86-99)	0% (-8-8)
2. Cardiovascular (n=39)	62% (45-77)	82% (66-92)	21% (6-35)	100% (91-100)	95% (82-99)	-5% (-12-2)
3. Gastrointestinal (n=13)	54% (25-81)	85% (55-98)	31% (-2-64)	98% (92-100)	100% (94-100)	2% (-1-5)
4. Other (n=8)	88% (48-100)	88% (48-100)	0% (-35-35)	97% (90-100)	94% (86-98)	-3% (-7-1)

503 <sup>a</sup> Autopsy was not able to establish the involved type of pathology and anatomical system in eight cases. <sup>b</sup> Not applicable.  
504

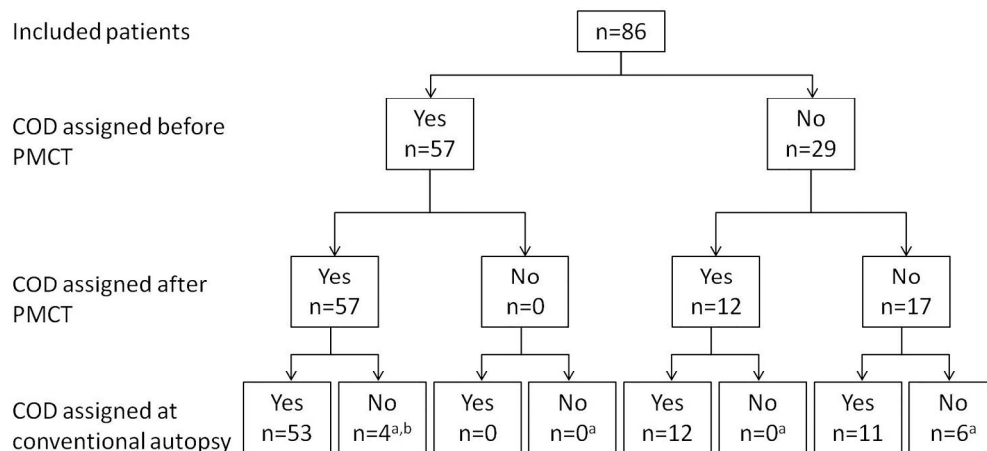


Figure 1. Flowchart of whether or not an immediate cause of death could be assigned before and after PMCT and during conventional autopsy.

a No cause of death could be assigned at autopsy in ten cases, and were excluded from the sensitivity analysis for cause of death. b In four cases, where clinicians and radiologists were able to assign a cause of death, autopsy did not reveal the cause of death. In one case this was due to lack of consent to a brain autopsy in a case with an intracerebral hemorrhage. In another case the pulmonary embolisms were not diagnosed at autopsy however identified with ultrasonography during resuscitation as well as on PMCT (Figure 2). In two other cases with unknown cause of death at autopsy, aspiration and cardiac failure were diagnosed as the cause of death after imaging, whereas previously sepsis with unknown abdominal focus and myocardial infarction were diagnosed by the clinicians. COD: immediate cause of death.

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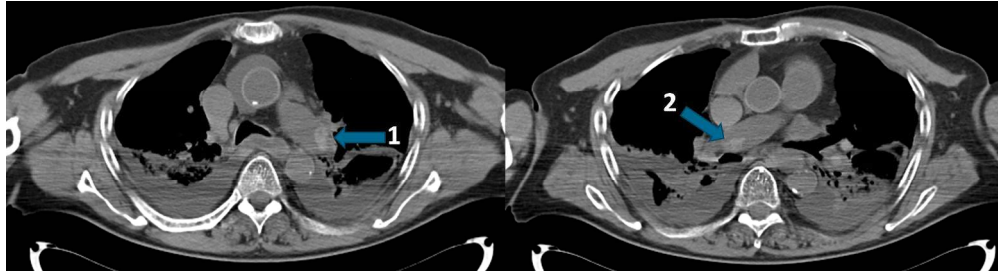


Figure 2. Example where pulmonary embolisms were diagnosed at antemortem ultrasound and postmortem CT but were not confirmed during autopsy. !! † This patient died after a resuscitation attempt, three days post re-laparotomy due to a hernia cicatricalis correction with invagination complications. An ultrasound scan during resuscitation revealed pulmonary embolisms. PMCT (postmortem interval of 2 hours) confirmed embolisms in the left (1) and right (2) pulmonary arteries. Autopsy did not assign a cause of death.

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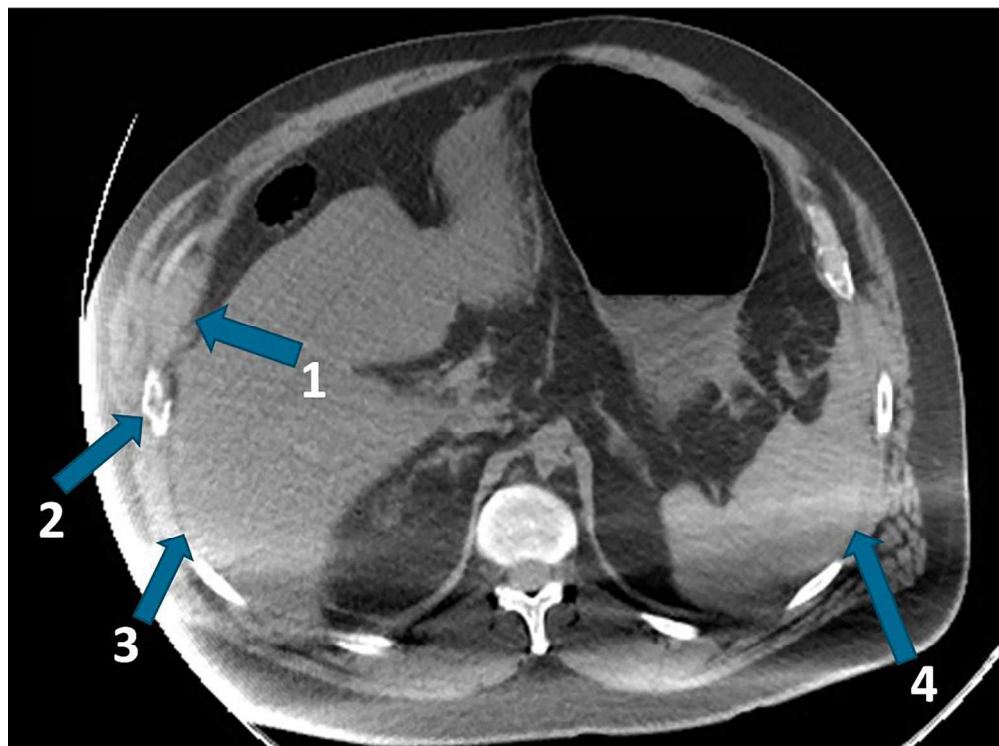


Figure 3. Example of discrepant diagnosis of the cause of traumatic exsanguination.!! † This patient died after a resuscitation attempt following a scooter accident with impact on the right side. Initial trauma screening revealed no significant pathologies. PMCT suggested exsanguinations due to a spleen laceration. Autopsy diagnosed exsanguinations due to lacerations of the liver and right kidney. Further findings: (1) abdominal wall hematoma, (2) rib fracture, (3) small rim of blood along the liver, (4) intra-abdominal blood along the spleen.

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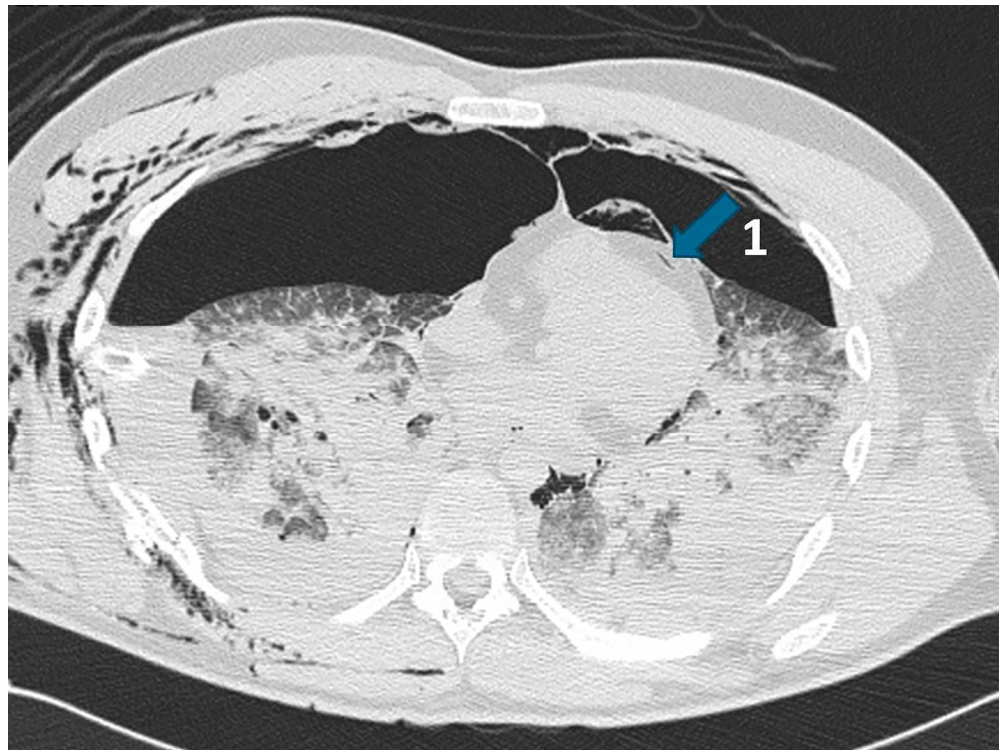


Figure 4. Example that gas related diagnoses can be more confidently diagnosed with PMCT than autopsy.

This patient died during a mid-transport resuscitation attempt following a car accident. Initial clinical examination found a hemothorax, however, it was unclear if the patient died due to blood loss or from some other underlying pathology which may have caused the accident. During air ambulance transportation, ventricular fibrillation occurred. PMCT showed an air embolus in the left anterior descending artery (1), probably due to extensive lung trauma and the decrease in atmospheric pressure during the flight. This was not diagnosed at autopsy, with death being attributed to a hemorrhagic shock due to hemothorax. Also, the pneumothorax, pneumopericardium and pneumomediastinum were not mentioned in the autopsy report.

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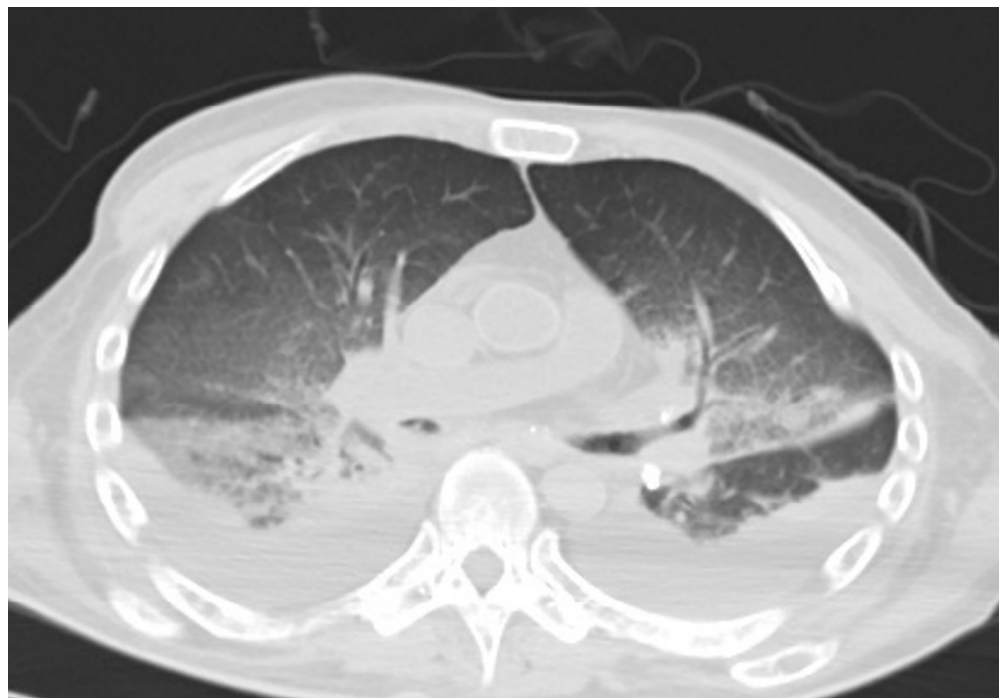


Figure 5. Normal postmortem changes could mask underlying pathology. This patient had a clinical history of allogeneic stem cell transplantation due to multiple myeloma. Clinical examination and antemortem MRI of the brain suggested a post-transplant lymphoproliferative disorder (PTLD). Autopsy diagnosed bronchopneumonia (left upper lobe and right lower lobe) as the cause of death and did not show PTLD, nor recurrence of multiple myeloma or other malignancy. PMCT showed pleural fluid and interstitial pulmonary edema, which were interpreted as normal postmortem findings. Bronchopneumonia was not diagnosed at PMCT.

333x231mm (300 x 300 DPI)

only

Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
<b>ABSTRACT</b>			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
<b>INTRODUCTION</b>			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	6
	4	Study objectives and hypotheses	6
<b>METHODS</b>			
<i>Study design</i>	5	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	7
<i>Participants</i>	6	Eligibility criteria	7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	7
	9	Whether participants formed a consecutive, random or convenience series	7
<i>Test methods</i>	10a	Index test, in sufficient detail to allow replication	7
	10b	Reference standard, in sufficient detail to allow replication	7
	11	Rationale for choosing the reference standard (if alternatives exist)	(6)
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	7
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	7
<i>Analysis</i>	14	Methods for estimating or comparing measures of diagnostic accuracy	8
	15	How indeterminate index test or reference standard results were handled	8
	16	How missing data on the index test and reference standard were handled	8
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8
	18	Intended sample size and how it was determined	8 See supplementary file: 'response to editorial request'
<b>RESULTS</b>			
<i>Participants</i>	19	Flow of participants, using a diagram	Fig 1, page 20
	20	Baseline demographic and clinical characteristics of participants	Table 1, page 22
	21a	Distribution of severity of disease in those with the target condition	NA
	21b	Distribution of alternative diagnoses in those without the target condition	
	22	Time interval and any clinical interventions between index test and reference standard	10
<i>Test results</i>	23	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 23, page 22-23
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Table 23 + 5
	25	Any adverse events from performing the index test or the reference standard	
<b>DISCUSSION</b>			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	4, 13-165
	27	Implications for practice, including the intended use and clinical role of the index test	13-165
<b>OTHER INFORMATION</b>			
	28	Registration number and name of registry	NA
	29	Where the full study protocol can be accessed	5



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# STARD 2015

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## AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

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## EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

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## DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.

