VIRTOPSY AS A BREAKTHROUGH IN NON-INVASIVE AUTOPSY: ITS PRINCIPLES AND POTENTIAL OF APPLICATION IN DEVELOPING COUNTRIES DURING THE COVID-19 PANDEMIC

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Abstract

Autopsy practice is often limited due to the risk of infection transmission and family objections. As an alternative, virtual autopsy (virtopsy) is proposed, which uses minimally invasive radiology techniques such as postmortem CT scan (PM-CT) and PM-MRI. However, there is a scarcity of literature comprehensively summarizing this topic. Therefore, this review article discusses the advantages and limitations of virtopsy in developing countries during the COVID-19 pandemic, along with ethical issues and a proposed algorithm for postmortem imaging. Virtopsy improves the sensitivity (93%) and specificity (83%) of diagnoses and offers several advantages, such as faster identification, good foreign body detection, three-dimensional reconstruction, and non-invasiveness. Limitations include difficulty in determining infection status and assessing internal organ characteristics, operator dependence, insufficient legal basis, and high costs. During the COVID-19 pandemic, this article compiles twenty-one studies from 2020 to 2022 that used virtopsy to investigate 191 cases of COVID-19 infection resulting in death. The studies were conducted in various countries, with only two developing countries [Brazil (n = 3) and India (n = 1)] reported to have used it. Most of the studies used PM-CT, while others used postmortem ultrasound, PM-MRI, and PM chest X-ray. Virtopsies were mostly performed within 24 hours. The age range of the deceased individuals investigated using virtopsy was between 11 and 99 years old, with males being predominant. Virtopsy was mostly used for triage or screening for conventional autopsy (CA) as well as adjuvant/complement to CA. In summary, virtopsy has potential benefits for developing countries during and after the COVID-19 pandemic, making it a valuable investment despite its limitations.

Keywords: Virtual Autopsy (Virtopsy), Computed Tomography, Imaging Modality, Magnetic Resonance Imaging, Non-Invasive Forensic Examination

Introduction

Despite the benefits of postmortem investigations, the use of conventional autopsy (CA) has significantly declined since the 20th century (1). The reduction in autopsy rates has become a global phenomenon. In the United States of America (USA), the rate of autopsies decreased from 17% in 1980 to 8.3% in 2003 (2, 3). Elsewhere, in Australia, the number of autopsies performed from 1992 to 2003 fell by 50% (2, 4). The rates of autopsies have decreased by 30% or more since 2005 in Germany, France, and Sweden (5). Unfortunately, limited information is available on the autopsy rate in developing nations. In Indonesia, where opposition to autopsies is prevalent, the autopsy rate has drastically decreased from 10.4% in 2011 to 6.9% in 2012, 4.2% in 2013, 5% in 2014, and 5.2% in 2015 (6). Autopsy rates have declined due to increased infection risk for clinicians handling deceased with infectious disease (e.g., HIV/AIDS) and during the COVID-19 pandemic, particularly in developing countries (7-9). COVID-19 patients' known cause of death led many hospitals to not perform autopsies, worsening already low rates and even making it harder for pathology and forensic residents to meet requirements (7). A study conducted in Rhode Island, USA, revealed that despite an increase in autopsy cases during the pandemic, the overall autopsy rate, which was already low, did not change significantly. The autopsy rate during the pandemic was 9.1%, which was not statistically different from the rate of 8.4% before the pandemic (10).

In developed countries, the decrease in autopsies is primarily attributed to the advancements in medical technology, which have led to a greater level of confidence in the antemortem diagnosis reducing the interest of clinician in performing CA to confirm diagnoses made during the patient's life. Meanwhile, in developing countries, the issue is more complex and caused by various constraints, including cost containment measures, physician discomfort, emotional objections, and family rejection (11-13). It is worth noting that this decline is not widely acknowledged, and there is limited research on its causes and consequences (14, 15). The decline in autopsies has led clinicians to find alternative techniques, such as virtual autopsy (virtopsy), which involves radiological and pathology diagnostic in forensic practice (16, 17). Virtopsy is presented as a non-invasive autopsy technique using computerised tomography (CT scan) and magnetic resonance imaging (MRI) modalities that can reconstruct corpses and trauma mechanisms (18, 19). It has been used successfully since 1896 to reveal deceased injury using radiological examinations (16, 17).

There is no available data on the prevalence of virtopsy versus CA during the COVID-19 pandemic, but it is anticipated to be on the rise as an alternative to CA. Post-mortem CT scans (PM-CT) have been increasingly recognised as an essential tool in COVID-19 cases, aiding in detecting disease markers both in the lungs and beyond (20). Virtopsy proved effective and dignified, allowing for faster release of the deceased to funeral homes and reducing contact between mortuary staff and the deceased (18, 19). However, despite the usefullness of virtopsy in forensic medicine, there are few comprehensive studies on its use in developing countries. Virtopsy is an appealing option for developing countries where cultural and religious beliefs, limited resources, and fear of stigmatisation often lead to the rejection of CAs (13, 21). Moreover, virtopsy comes from developed countries and thus should be proved further their benefits in the context of developing countries. While developing countries have more sufficient radiology infrastructure and personnel than underdeveloped countries, implementing virtopsy may require addressing unique cultural, ethical, and legal considerations (22-24). Therefore, this article aims to discuss the potential application of virtopsy as an autopsy method in developing countries. It highlights the advantages and limitations of virtopsy and proposes an algorithm for choosing postmortem imaging techniques in clinical settings. The review aims to encourage further research and pilot projects and to support virtopsy implementation in clinical practice and court in these regions. Ethical issues related to virtopsy are also discussed.

Materials and Methods

A literature search was conducted on seven databases, including Pubmed, EBSCOhost, ScienceDirect, Cochrane, and Scopus, from July 21 to August 3, 2022 (and updated in February 2023 for the topic of virtopsy use during the COVID-19 pandemic), following the evidence-based review method (25, 26). The primary search was conducted based on relevant keywords, including "virtopsy", "non-invasive autopsy", "COVID-19 pandemic", "developing countries", "radiological imaging", "postmortem examination", "cause of death", "challenges", "advantages", and "medical research".

Articles must meet the criteria for scientific evidence levels 1–5 (ranging from meta-analyses and systematic reviews to cross-sectional studies and case reports) and should be published within the last ten years. The validity, importance, and application screening analysis were carried out to see the article's suitability of the article's topic related to the use of virtopsy during the COVID-19 pandemic. The Joanna Briggs Institute (JBI) Critical Appraisal tools and Oxford Center for Evidence-Based Medicine (Oxford CEBM) checklist were adopted to assess the suitability of evidence for review (27-29).

The literature search was supplemented through Google Scholar and bibliographies of previously found articles. All literature was synthesised into a comprehensive review of evidence on virtopsy. No ethics approval was needed for this review since it relies on previously published studies that obtained informed consent and ethical clearance. Additionally, our study did not involve animals or humans (30, 31).

Results and Discussion

What is virtopsy and how does it work technically?

Virtopsy is a minimally invasive autopsy approach that has been initiated and developed to address declining autopsy rates in Europe. It is learned in the field of forensic radiology and has high correlation with conventional autopsies (32). This procedure utilises various radiology modalities, including post-mortem CT-scan (PM-CT) with or without angiography and multislice-CT (MSCT), post-mortem MRI (PM-MRI) with or without angiography and MR spectroscopy. It can also involve contrast injection and 3D photogrammetry-based optical surface scanning for injury assessment, identifying projectiles in gunshot victims, obtaining tissue samples using ultrasound-guided (PM-US) biopsies or robotic virtospies (33). Virtopsy can provide objective documentation and analysis to identify abnormalities or evidence on autopsy examination and guide disease prevention, control, and treatment strategies (34).

A virtopsy can determine the cause of death in situations where traditional autopsies are not possible or refused by the family (32). In details, such situations include cultural or religious beliefs that prohibit invasive procedures (11-13), suspected infectious diseases that could endanger medical personnel (7-9), and mass/natural disasters that render traditional autopsies impractical (35, 36). It allows for determining the cause of death without compromising the safety of medical personnel or disturbing the body. Although virtopsy is not commonly used in developing countries due to cost and infrastructure, its feasibility

and potential benefits should be considered despite high investment costs.

One technique in virtopsy using PM-CT that has garnered attention is multiphase angiography in various parts of the body. To perform this, a modified heart-lung machine is used to inject paraffin oil containing 6% Angiofil through femoral venous and arterial access, divided into three phases —the arterial, venous, and dynamic phases (37). In the arterial phase, according to Wichmann et al. (37), an amount of 1,200 mL of contrast medium is injected through the femoral artery at a rate of 800 mL/min, with a focus on the heart to increase sensitivity to pathological coronary vessel conditions (38). Around 1,600 mL of contrast medium is injected via retrograde injection through the femoral vein at an 800 mL/min rate, followed by CT of the venous system using the same variables as the arteries. In the dynamic phase, artificial circulation is created by injecting 200 mL of contrast at a rate of 500 mL/min into the arterial cannula, with vacuum administration in the venous cannula. Additional contrast medium, approximately 1,000 mL, may be required for bodies with a mass index greater than 30 kg/m^2 (37).

Requirements for imaging on virtopsy to replace conventional autopsies.

Virtopsy is a new technique that has the potential to replace CAs. To do so, it must demonstrate five important forensic medicine points. Firstly, it must be able to show atria mortis, which summarises the pathophysiology and mechanism of death, as outlined in Table 1 (32). Secondly, it must describe pathological and morphological findings of bone, tissue, and internal organs related to the manner of death, such as contusions and stab wounds. For example, CT scan can reveal hyoid horn fractures in hanging cases, while a T2-weighted fast spin-echo (SE)-MRI can detect hematomas and contusions as an intense enhancement in motor vehicle accidents consistent with the bruising and hematoma found by CAs. In cases of internal organ injuries, a sagittal view of the T2-weighted fast SE-MRI can visualise lesions on the heart muscle and chambers. The images show the penetration of the myocardium with hemopericardium and intracardial blood clots. Another technique, the T1-weighted fast SE-MRI will show blood clotting, hemopericardium, and descending aorta that collapses after blood loss (32).

Thirdly, it must present vital reactions chronologically to explain the sequence of injuries leading to death, especially in cases of violence. If the violence occurred before death, it could be characterised by evidence of intact circulation, such as ongoing and fatal bleeding, air and fat embolism, and subcutaneous emphysema, as well as signs of aspiration indicating persistent breathing (32).

Fourthly, virtopsy should be able to reconstruct injuries related to strength, biomechanics, and dynamics to better visualise the manner and cause of death in court or public. This aspect is essential to explain how external influences causing death give rise to atria mortis, pathological-morphological findings, and 'vital reactions.' For example, using MSCT or T2-weighted fast SE-MRI, virtopsy allows us to analyse the fracture patterns, time sequences, fracture sequences, and types of ammunition causing ballistic injuries. Therefore, the bullet penetration can be reconstructed well (32).

Table 1: Virtopsy appearance of various atria mortis (32, 37)

Organ system	Atria Mortis
Central nervous system	• Intracerebral haemorrhage • Intraventricular haemorrhage • Subdural hematoma • Epidural hematoma • Cerebrospinal fluid collapse • Fatal brain stem lesions • Secondary cerebral oedema • Increased intracranial pressure • Acute cerebral hypoxia due to strangulation
Cardiovascular system	• Changes in heart tissue due to ischemia • Myocardial hypertrophy • Coronary Sclerosis • Plaque rupture • Thrombosis • Massive swelling of the inferior vena cava • Right ventricular heart failure • Fatal bleeding
Respiratory system	• Lung contusion • Aspiration • Emphysema *aquosum* after drowning, showing patchy lobular lesions • Airless lungs in stillborn babies • Pulmonary embolism • Ventil pneumothorax

Finally, it should provide an easy-to-understand overview of the findings in court which can be achieved through two or three-dimensional reconstruction of imaging. These requirements can be met with the use of MSCT and MRI imaging, which provide a comprehensive and objective evaluation of medico-legal reports in courts, prosecutors, and the police. Virtopsy can provide a valuable alternative to traditional autopsies, and it has the potential to improve the accuracy and clarity of forensic medicine (32).

Existing studies on the accuracy of virtopsy

Studies on virtopsy's effectiveness have shown mixed results. In Germany, virtopsy confirmed 312 out of 336 antemortem diagnoses (93%), while CAs confirmed only 270 (80%) (37). Virtopsy with multiphase PM-CT angiography was more accurate for diagnosing cardiorespiratory-related deaths (37). Together, virtopsy and CAs provided 254 new diagnoses out of 590 confirmed diagnoses. Virtopsy identified 87% of the diagnoses, including 73 that were only

detectable by PM-CT angiography. Without this technique, 51 diagnoses may have been missed. Most of these missed diagnoses were related to cardiovascular diseases, such as coronary artery stenosis (n = 32), significant stenosis of the abdominal or leg arteries (n = 6), and pulmonary embolism (n = 3), as detailed in Table 2. In contrast, CAs could only identify 474 out of 590 (80%) cases (37).

Table 2: Several diagnoses of the cause of death among patients were identified from clinical records (antemortem), virtopsy with multiphase postmortem CT scan (PM-CT) angiography, and confirmed by conventional clinical autopsy (32, 37)

Diagnosis Classification	Antemortem Diagnosis from Clinical Records N (%)	Number of Confirmed Diagnosis by Virtopsy PM-CT Multiphase Angiography N (%)	Number of Diagnoses Confirmed by CA N (%)	Cumulative Number of Diagnosis made by All Methods N (%)
Cardiovascular*	114 (60)	176 (92)	179 (94)	191
Respiratory**	55 (57)	81 (84)	65 (67)	97
Cerebral***	8 (32)	21 (84)	22 (88)	25
Bleeding#	15 (42)	30 (83)	30 (83)	36
Neoplastic##	14 (67)	14 (67)	20 (95)	21
Infectious###	26 (87)	25 (83)	29 (97)	30
Other¶	104 (55)	168 (88)	129 (68)	190
Total	336 (57)	515 (87)	474 (80)	590

* Such as myocardial infarction and pericardial effusion
** Such as pleural effusion, pulmonary oedema, and pneumothorax
*** Such as hemorrhagic stroke and ischemic stroke
# Such as any bleeding except brain haemorrhage
Such as tumours and metastases
Such as pneumonia and endocarditis
¶ Such as rib fractures, postoperative complications, and nephrolithiasis
PM-CT: post-mortem CT
CA: conventional autopsy

In the Netherlands, a study found that PM-CT increased diagnostic specificity in victims compared to CA only, from 53% to 64%, and increased specificity of pathology type from 65% to 83% and anatomical structures from 65% to 85% (38). In Italy, Cirielli et al. (39) conducted a study on bodies with a presumed cause of death by trauma. They found that out of 23 bodies, only 8 required CAs to determine the exact cause of death (40). Similarly, another study in Italy found that virtopsy had similar to better confidence levels than CAs in assessing anatomic damage and estimating time to death (11).

Implementation of virtopsy during the COVID-19 pandemic

During the COVID-19 pandemic, modifications to reduce the risk of infection during autopsies have been recommended. These modifications include performing in situ examinations, reducing body manipulations, and avoiding embalming. However, these modifications may result in missing important information and misdiagnosing the cause of death. In situations where a full autopsy is necessary, the risk of infection for operators during the dissection of the body is a crucial concern (40). Despite the lack of current data on changes in CA trends during the COVID-19 pandemic, the outbreak of the pandemic in early 2020 enforced the need for safer alternatives to CAs (41). Additionally, the safety concerns stemming from the risk of infection have led to a significant decline in autopsy rates in the US. This decline not only affects the frequency of autopsies for medical and legal purposes but also their value as a learning tool (10, 42). To address these concerns, virtopsy has been suggested as a safer alternative to traditional autopsies. Forensic radiology with its virtopsy can help minimize the risk of COVID-19 transmission during autopsies by allowing for post-mortem evaluations without opening the body cavities.

Investigating the use of virtopsy during the COVID-19 pandemic is crucial for determining if a patient died with or due to COVID-19, which is linked to professional responsibility. Autopsies provide critical assessments of the severity of viral damage and organ failure in a patient's death (43). We have compiled a collection of twenty-one studies (Table 3) that employed virtopsy during the COVID-19 pandemic, including one case-control (43), four retrospective monocentric cross-sectional (44-47), six retrospective monocentric case series (48-53), one prospective monocentric case series (54), and nine case reports (55-63). Validity and applicability of all studies were assessed, as shown in **Supplementary Table 1–3**. These studies were of low-level evidence based on Oxford CEEBM due to the difficulty of conducting controlled trials during a pandemic. Despite this, each study was carried out consecutively.

Table 3: Summary of virtopsy implementation during the COVID-19 pandemic across different countries and regions worldwide

Authors, year, country	Number of cases	Male	Female	Age and its range (y.o)	Radiology modalities	Timeframe for performing virtopsy after death	Virtopsy's intended use in relation to CA	Measuring outcomes and benefits of implementation in detail
Case Control Studies								
De-Giorgio et al., 2021a, Italy (43)	13	2	11	Median: 89 (86-95)	PM-CT	48 h	Complete substitution	• PM-CT was used to confirm the post-mortem diagnosis of COVID-19 pneumonia, evaluating GGOs, consolidation, and pleural effusion for pulmonary abnormalities; • Whole-body CT scans were used for diagnosis in all subjects, with 100% of them showing GGO; • 9 out of 13 cases from a long-term care facility were diagnosed with severe COVID-19 pneumonia as the cause of death using PM-CT.
Retrospective Monocentric Cross-Sectional Studies								
Filograna et al., 2022, Italy (44)	8	5	3	Mean: 65 (36-89)	PM-CT	72 h	Initial autopsy (triage), adjuvant	• 6 out of 8 cases showed severe pulmonary signs of COVID-19 on histopathological analysis, with massive consolidation or bilateral diffuse mixed densities with a crazy-paving pattern; • The remaining 2 cases showed minor GGO mostly due to hypostasis; • In 6 out of 8 cases with severe pulmonary histopathological signs of lung COVID-19, autopsy confirmed cardiorespiratory failure as the cause of death; • Chest PM-CT findings were correlated with the severity of COVID-19 lung disease on histopathological examination;
Thomas et al., 2022, USA (45)	42	34	8	Mean: 49.6 (19-89)	PM-CT	24 h	Complete substitution	• 35 out of 42 individuals with official death certificates indicating death from COVID-19 had pulmonary PM-CT findings consistent with the disease; • PM-CT results suggest that 14.3% of the deceased individuals who were positive for COVID-19 may have died from a different cause; • 57% of individuals who died from COVID-19 had PM-CT results indicating vascular disease; • PM-CT can provide valuable additional information for forensic pathologists to determine the cause of death in individuals with SARS-CoV-2 infection.
Heinrich et al., 2020, Germany (62)	1	1	0	59	PM-CT	No data	Initial autopsy (triage), adjuvant	• Radiological assessment showed bilateral pleura effusions, ground-glass opacifications, and reticular consolidation in the lungs; • Internal examination revealed edematous and heavy lungs with deep-red discolorations, acute hemorrhagic tracheitis, and bronchitis; • Histopathology of the lungs revealed diffuse alveolar damage with hyaline membranes and mononuclear inflammatory cells; • Postmortem molecular genetic testing confirmed SARS-CoV-2 infection with high viral loads in the lung but no evidence of viral components in other organs or bodily fluids; • Other organs showed minimal signs of various conditions such as hepatomegaly, hepatic steatosis, renal cysts, advanced myocardial fibrosis, and unspecific immune response in the brainstem.

Table 3: Summary of virtopsy implementation during the COVID-19 pandemic across different countries and regions worldwide (continued)

Authors, year, country	Number of cases	Male	Female	Age and its range (y.o)	Radiology modalities	Timeframe for performing virtopsy after death	Virtopsy's intended use in relation to CA	Measuring outcomes and benefits of implementation in detail
O'Donnell et al., 2021, Australia (47)	39	24	15	Mean: 75 (15-95)	PM-CT	No data	Initial autopsy (triage), adjuvant	• The study examined PM-CT as a screening test for COVID-19; • 39 deceased with positive SARS-CoV-2 RT-PCR tested using routine whole-body CT scans, 12 underwent autopsy; • Lung histology consistent with COVID-19 pneumonia found in 9 of 12 autopsies, only 5 of 12 had typical clinical lung findings on PM-CT; • Pathologists may find it difficult to determine if SARS-CoV-2 caused or just associated with death as clinical lung findings not always visible on PM-CT; • PM-CT findings can vary in intensity, subtlety, and be obstructed by factors like agonal changes during dying.
Prospective Monocentric Case Series								
Coolen et al., 2020, Belgium (54)	19	14	5	Mean: 77 (49-94)	PM-CT PM-MRI	24 h	Complete substitution	• Parenchymal brain MRI abnormalities were observed in 4 of 19 decedents (21%); • The abnormalities included subcortical microbleeds, macrobleeds, edematous changes, and white matter changes; • Four others (21%) had asymmetrical olfactory bulbs, but no abnormalities were observed in the brainstem; • The study does not support the idea that respiratory distress in COVID-19 is caused by brainstem abnormalities; • It is possible that the virus affects the brainstem in ways that are not visible on MRI.
Retrospective Monocentric Case Series								
Martin et al., 2022, Brazil (48)	7	3	4	Mean: 44 (11-74)	PM-CT PM-US PM-MRI	No data	Complete substitution	• 7 COVID-19 deceased patients underwent virtopsy with brain MRI and CT images, and 6 of them had tissue sampling; • Various brain abnormalities were found in the imaging, including infarcts, brain hemorrhagic foci, subarachnoid hemorrhage, and signal abnormalities in different parts of the brain; • All 6 cases had reactive gliosis, congestion, cortical neuron eosinophilic degeneration, and axonal disruption in brain histological analysis; • Other findings included cerebral small vessel disease, perivascular hemosiderin deposits, alzheimer type II glia, and periventricular encephalitis foci.
De-Giorgio et al., 2021b, Italy (49)	9	0	9	Mean: 85 (71-99)	PM-CT	No data	Initial autopsy (triage), adjuvant	• The study analysed nine subjects from two nursing homes who were tested positive for COVID-19 and died; • The corpses exhibited uniform autopsy and histological features, including cherry-red hypostasis, internal visceral cherry-red coloration, pulmonary edema, and congestion accompanied by intraalveolar hemorrhages, and varying levels of atherosclerosis; • Carbon monoxide poisoning was identified as the cause of death in five cases, and COVID-19 was found to be a contributing cause in four cases; • Histological analyses and computed tomography examination were essential to classify the patients as dying with or due to COVID-19;

Table 3: Summary of virtopsy implementation during the COVID-19 pandemic across different countries and regions worldwide (continued)

Authors, year, country	Number of cases	Male	Female	Age and its range (y.o)	Radiology modalities	Timeframe for performing virtopsy after death	Virtopsy's intended use in relation to CA	Measuring outcomes and benefits of implementation in detail
								• CT imaging of COVID-19, including bilateral multi-lobar GGOs, was observed in all cases.
da Silva et al., 2021, Brazil (51)	5	0	5	Mean: 32 (11-67)	PM-CT and PM-US	24 h	Complete substitution	• PM-CT imaging showed disease progression until death in all five cases examined; • The main findings on PM-CT included consolidation of both lungs with GGOs and internal septal thickening in a crazy-paving pattern, indicating ARDS; • The study emphasized the importance of using premortem chest CT findings in conjunction with PM-CT findings for a more accurate interpretation of disease progression; • PM-CT can guide small tissue sample biopsies for important histopathologic analysis; • Despite the known limitations of PM-CT, the study concluded that it can be a useful tool in minimally invasive autopsies of fatal COVID-19 cases.
Kniep et al., 2021, Germany (50)	3	2	1	80, 89, and 90	PM-CT	48 h (two of cases were within 8 and 24 h)	Initial autopsy (triage), adjuvant	• PM-CT showed GGO, consolidation, nodules, and peripherally accentuated consolidations in the pulmonary lobes; • Difficulties in interpreting lungs in PM-CT include hypostasis, pleural effusions, and dorsal hypostasis appearing as milk glass opacity; • Fast post-mortem imaging is necessary to reduce the effects of hypostasis; • Autopsy confirmed COVID-19 pneumonia as the direct cause of death.
Williams et al., 2021, Canada (52)	5	5	0	Mean: 71 (51-77)	PM-CT	No data	Initial autopsy (triage), adjuvant	• PM-CT showed diffuse lung changes, ground glass-type opacifications, consolidation, and less involved lung parenchyma; • Histopathology revealed diffuse alveolar damage in varying stages of cellular evolution, confirming COVID-19 diagnosis; • PM-CT useful in cases of community deaths with limited medical history or social contacts; • Virtopsy allows pre-autopsy screening and appropriate precautions, and collection of respiratory specimens for virological studies.
Duarte-Neto et al., 2020, Brazil (53)	10	5	5	Median: 69 (33-83)	PM-US	No data	Complete substitution	• MIA-US showed extensive alveolar damage, fibrinous thrombi, and high density of alveolar megakaryocytes in all patients; • Thrombi were also found in other organs; • The severity of COVID-19 was associated with comorbidities, age, and sepsis, as well as tissue damage caused by the virus; • MIA-US is a safe and effective method for studying severe COVID-19.
Case Reports								
De-Giorgio et al., 2022, Italy (55)	1	0	1	42	PM-CT	24 h (perimortem) with the 2nd attempt was done in >72 h	Initial autopsy (triage), adjuvant	• The first PM-CT scan indicated COVID-19 with diffuse GGOs and interstitial markings in all lobes. The second scan was inconclusive due to postmortem changes, highlighting the limitation of PM-CT for late postmortem COVID-19 diagnosis;

Table 3: Summary of virtopsy implementation during the COVID-19 pandemic across different countries and regions worldwide (continued)

Authors, year, country	Number of cases	Male	Female	Age and its range (y.o)	Radiology modalities	Timeframe for performing virtopsy after death	Virtopsy's intended use in relation to CA	Measuring outcomes and benefits of implementation in detail
								• PM-CT findings of COVID-19 pneumonia are non-specific and can be masked by postmortem changes; • The unenhanced CT scan showed typical COVID-19 pneumonia findings, but not specific; • The PM-CT scan showed bilateral consolidation and effusion, but was unable to evaluate lung infectious diseases.
Vaishnav et al., 2022, India (56)	1	1	0	29	PM-CT	48 h	Complete substitution	• The risk of COVID-19 transmission has discouraged autopsies, creating ethical dilemmas in medicolegal cases. For example, in cases where a young person dies suddenly and foul play is suspected, forensic pathologists may be needed; • PM-CT appropriately determined the cause of death as cerebral edema with bilateral tonsillar herniation resulting from hypertensive intracerebral bleed.
Xie et al., 2022, Canada (57)	1	1	0	51	PM-CT	No data	Initial autopsy (triage), adjuvant	• CT imaging is more sensitive than RT-PCR in suspected COVID-19 cases with false negative results; • PM-CT is a powerful and safe screening tool for COVID-19 pneumonia, even in cases of double negative swabs; • The use of PM-CT for screening purposes is not limited by radiation risks and allows for targeted and safe autopsies; • PM-CT helps pathologists alter dissection approaches and minimizes the risk of pathogen exposure in COVID-19 cases.
Filograna et al., 2022, Italy (44)	8	5	3	Mean: 65 (36-89)	PM-CT	72 h	Initial autopsy (triage), adjuvant	• 6 out of 8 cases showed severe pulmonary signs of COVID-19 at histopathological analysis, with corresponding chest PM-CT findings of massive consolidation or bilateral diffuse mixed densities with a crazy-paving pattern. The remaining 2 cases had scant antideclive GGO due to hypostasis; • In 6 out of 8 cases, cardiorespiratory failure was confirmed as the cause of death in individuals with severe pulmonary histopathological signs of lung COVID-19. In the remaining 2 cases, lung alterations due to edema and some signs of SARS-CoV-2 infection were present, but COVID-19 was not attributed as the cause of death; • Chest PM-CT findings correlated with the severity of COVID-19 lung disease at histopathology examination.
Fitzek et al., 2020, Germany (59)	1	1	0	59	PM-CT	No data	Initial autopsy (triage), adjuvant	• PM-CT scan revealed bilateral pleural effusions, reticular consolidation, and ground-glass density nodules; • External post-mortem examination showed a slightly obese man in good health who received basic medical care; • Internal examination showed pneumonia superimposed by embalming, pulmonary edema, and hemorrhagic tracheobronchitis; • Cause of death suspected to be viral pneumonia and manner of death defined as natural;

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Authors, year, country	Number of cases	Male	Female	Age and its range (y.o)	Radiology modalities	Timeframe for performing virtopsy after death	Virtopsy's intended use in relation to CA	Measuring outcomes and benefits of implementation in detail
								• Lung histology revealed hyaline membranes, microthrombi, and protein-rich edema with low-grade lymphocyte infiltration, while moderate penetration of inflammatory cells was found in the intestinal wall. No other pathological findings were observed in other organs.
Barton et al., 2020, USA (60)	2	2	0	77 and 42	PM-chest-X-ray	No data	Initial autopsy (triage), adjuvant	• In Case 1, postmortem chest X-rays showed dense bilateral consolidations with diffuse alveolar damage and chronic inflammation found microscopically. T-lymphocytes were highlighted with immunohistochemical stains; • Case 2 displayed less consolidative diffuse opacities in both lungs with acute bronchopneumonia observed during autopsy. A pre-mortem CT scan showed bilateral ground-glass opacities, and a foreign particle was found in one of the airways microscopically.
Ducloyer et al., 2020, France (61)	1	1	0	75	PM-CT	24 h	Initial autopsy (triage), adjuvant	• The person died from untreated SARS-CoV-2 infection; • The use of PM-CT helped detect severe lung damage before autopsy in a natural death case; • Microscopic analysis showed severe lung damage, with diffuse alveolar damage, inflammation, and fibrosis as the main abnormalities.
Helmrich et al., 2020, USA (46)	14	11	3	Range 29-82	PM-CT	No data	Initial autopsy (triage), adjuvant	• Imaging findings of COVID-19 include mixed densities, traction bronchiectasis, crazy paving, and ill-defined rounded consolidations; • Traction bronchiectasis, ill-defined rounded consolidations, and reverse halo sign can distinguish COVID-19 from other postmortem changes; • PM-CT triage can help diagnose COVID-19 before autopsy examination.
Schweitzer et al., 2020, Switzerland (63)	1	1	0	50	PM-CT	24 h	Initial autopsy (triage), adjuvant	• The case reports an outpatient with rapidly progressing pulmonary symptoms and eventuallyeveloping ARDS; • Post-mortem CT can be useful in detecting COVID-19 related lung changes, but more specific tests may be needed for precise investigations; • Histological examination showed inflammation and binuclear lymphocytes; • Acute liver dystrophy and acute tubular necrosis were found in the kidneys; • The only notable pathology of the heart was coronary artery atherosclerosis.

ADC: apparent diffusion coefficient
ARDS: acute respiratory distress syndrome
CA: conventional autopsy
CT: computed tomography
DWI: diffusion-weighted imaging
GGOs: ground glass opacities
MIA-US: ultrasound- guided minimally invasive autopsy
PM-CT: post-mortem CT
RT-PCR: reverse transcription polymerase chain reaction

Based on the data extracted in Table 3, the search focused on the imaging appearances of lung and extrapulmonary disease in SARS-CoV-2 positive cases. We thoroughly examined 21 studies that included 191 cases of COVID-19 infection resulting in death and virtopsy. All the selected papers were limited to this area of research. The largest report came from the USA, which had 42 deceased with SARS-CoV-2 infection (45). The countries of publication included Italy (n = 5), the USA (n = 3), Brazil (n = 3), Germany (n = 3), Canada (n = 2), Belgium (n = 1), Australia (n = 1), France (n = 1), Switzerland (n = 1), and India (n = 1), with only two developing countries (Brazil and India) represented. Most of the studies used PM-CT (19 reports, n = 172 deceased), while 3 reports used PM-US (n = 22 deceased), 2 used PM-MRI (n = 26 deceased), and 1 used PM chest X-ray (n = 2 deceased).

The timing of the virtopsy in relation to the time of death is a crucial factor to consider. Most of the virtopsies were performed within 24 hours (n = 7), 48 hours (n = 3), and 72 hours (n = 1). However, 11 studies did not provide information about the timing of the virtopsy after death. It is important to note that postmortem intervals exceeding 72 hours can negatively impact accurate radiological evaluation due to significant postmortem changes, particularly the presence of gas within organs (58). The age range of deceased individuals investigated using virtopsy was between 11 and 99 years old. Old age is a prominent factor in the severity and risk of death from SARS-CoV-2 infection, and its distribution is higher in Italy compared to other countries (49). Males were predominant, with 113 deceased compared to 71 females. Virtopsy was used in 14 cases for triage or screening for conventional autopsy as well as adjuvant/complement to CA, while in 7 reports, virtopsy was used as a complete substitution for CA. During the COVID-19 pandemic, most cases used PM-CT and PM-MRI modalities. The use of virtopsy was 14 for triage or screening for CA as well as adjuvant/complement to CA, while 7 reports used virtopsy as a complete substitution for CA. Combining CT and CT-angiography has proven to be a sensitive tool for diagnosing the cause of death and can provide higher sensitivity than ordinary autopsy in detecting medico-legally essential findings. The use of PM-CT angiography is more effective than CT without angiography and CA in identifying important medical-legal findings. With the addition of CT angiography, the detection rate of new significant diagnoses increased from 71.4% to 92.9% (64).

Virtopsy using PM-CT is a useful and non-invasive method for analysing tissue and biological samples of suspected SARS-CoV-2 infected deaths, without posing a significant risk to operators. Preliminary information obtained from PM-CT can provide insight into potential COVID-19 lung disease, especially in the absence of pre-death clinical information and viral analysis results (63). However, interpreting the results of PM-CT scans can be challenging due to post-mortem artifacts that can diminish the usefulness of certain features in determining fatal COVID-19, but features such as traction bronchiectasis and ill-defined rounded opacities can indicate COVID-19 SA (46). Additionally, various factors such as hypostasis and autolysis can hinder PM-CT interpretation of lung pathology, but histology can confirm the cause of damage (47).

To diagnose fatal COVID-19 accurately, various correlations are required, including clinical, radiological, microbiological, and histopathological. Histopathological correlation is particularly crucial since it is unclear whether COVID-19 can cause non-lung-related complications, and further exploration is needed (52). A PM-CT scoring system was made to determine the sensitivity and specificity of features to distinguish between COVID and non-COVID deaths. Their scoring system has a sensitivity of 84.6% and specificity of 90.9% (43). Since COVID-19 may also cause abnormal coagulation due to severe endothelial injury, PM-CT angiography is a useful technique for detecting central and paracentral pulmonary embolism and other thrombotic or thromboembolic events, but peripheral pulmonary embolisms may be missed due to artifacts (65). PM-CT can be used routinely for screening purposes in post-mortem settings without the risk of radiation-related hazards. PM-CT-guided percutaneous biopsies can provide low-invasive investigations in deceased COVID-19 patients and reduce the risk of infection for operators compared to CAs (66).

Virtopsy with CT and MRI is effective but requires specialised facilities. Portable X-rays and ultrasound devices are cost-effective alternatives. In the USA (60), postmortem radiography using chest X-ray imaging was performed on two COVID-19 patients. Meanwhile, a portable ultrasound imaging has been used in remote areas of Africa during recent Ebola outbreaks (67). In the absence of high-tech virtopsy facilities, PM-US can be a cost-effective and safer alternative to extensive autopsies for COVID-19 cases (68). Lung ultrasound is a quick, sensitive, and non-invasive method that can detect several pulmonary diseases at the bedside, and “echopsy” is an ultrasound-guided collection of tissue samples that is regarded as a reliable and safer alternative to traditional autopsies. PM-US can be especially useful in low-resource settings during the COVID-19 pandemic to protect forensic personnel from exposure to the virus. Radiology, including ultrasound and fluoroscopy, can aid in detecting injuries and natural causes of death, with CT scans being the preferred method for diagnosing COVID-19 in post-mortem cases (69, 70).

Comparison of imaging modalities in virtual autopsy and their relevancy for COVID-19 cases prooving

The level of confidence in virtopsy depends on the modality used, which can consist of the following:

1. Postmortem ultrasound

Ultrasound is a non-invasive imaging technique increasingly used for virtopsy to avoid radiation contamination (71). PM-US is valuable in evaluating tumors, masses, pregnancy,

and cardiovascular pathology, including identifying atherosclerosis and thromboembolic disease (71). It is also useful in identifying changes in organ morphology and size, detecting fluid accumulation in body cavities, and guiding minimally invasive procedures. To obtain high-quality images, a delay of 1-2 hours after refrigeration is recommended, and different probes should be used for different areas. Although challenging for obese or postmortem gas-formed corpses, PM-US can help reduce the risk of infection and complications. A study found 83% agreement in cause of death and pathological findings between ultrasound and autopsy (echopsy) (72).

PM-US is often used in cases of fetal or perinatal death, which occur in approximately 1% of pregnancies, due to the lack of perinatal autopsies and demand for non-invasive methods (73, 74). While CA is valuable, legal formalities have reduced its rate. Non-invasive echopsy or virtual fetal autopsies have been suggested as alternatives, with fetal echopsy being a non-invasive USG-guided needle autopsy that confirms anomalies without parental consent, making it an effective research methodology (75). PM-US has reported sensitivity and specificity rates of 75% and 83.3%, respectively, for whole-body diagnoses. Accuracy rates for heart abnormalities are lower, ranging from 18.2-50% (68, 73, 76). PM-US can provide similar information as perinatal autopsy without additional imaging, but its diagnostic potential is reduced in small gestational aged fetuses, prolonged retention, and suspected cardiac anomalies. The CNS is the most common system discussed, with congenital disorders leading to pregnancy termination. Detecting complex cardiac anomalies is difficult due to lack of blood circulation and intra-cardiac gas. Renal, abdominal, skeletal, and soft tissue anomalies can also be detected. PM-US reviews associated structural anomalies rather than identifying specific anomalies (73).

Perinatal virtual autopsies using PM-US are valuable for confirming or ruling out antemortem diagnoses without invasive procedures, which can reduce distress for parents and provide important information for prenatal and genetic evaluations. It is necessary in cases of congenital malformations, recurrent fetal death, non-immune hydrops, IUGR, suspected infections, and unexplained events. Congenital malformations affect 8.3% of pregnancies, with the central nervous system, cardiovascular, musculoskeletal, and genitourinary systems being commonly affected (77). A pilot study showed that the fetal heart can be accurately imaged using PM-US, including atria, ventricles, and septum (78). Non-invasive imaging tools can serve as an audit for first-trimester anomalies. In a case report, fetal echopsy (PM-US) was used to diagnose abnormal connections between placental and cord vessels in monozygotic monoamniotic twins or triplets, which can result in the development of acardius myelancephalus and subsequently, twin-to-twin transfusion syndrome (TTTS). The use of USG allowed for a non-invasive approach to diagnose the condition, avoiding the need for invasive fetal autopsy (75).

Virtual autopsy using ultrasound has high sensitivity and specificity for detecting abnormalities in the brain, heart, lungs, and abdomen. A Belgian study found that it is feasible as early as 11 weeks' gestation (74). One study found that ultrasound findings were consistent with autopsy findings in 86.7% of cases (79), while another study found that autopsy confirmed the prenatal ultrasound findings in 50% of cases and changed the primary diagnosis in 9.09% of cases (80). In adults, PM-US can evaluate various pathological conditions in the body such as cardiac hypertrophy, liver metastasis, renal cysts, and intracranial hemorrhage in infants (72). In Brazil, ultrasound was used to guide tissue sampling in ten decedents with SARS-Cov2 infections, revealing positive signs such as pulmonary diffuse alveolar damage and myocardial fibrosis (53). PM-US has the potential to reduce autopsy costs, produce fewer aerosols, and avoid distress for parents in cases of congenital malformations and unexplained events (71).

Overall, ultrasound is a safe and affordable alternative to conventional autopsy that can enhance diagnostic accuracy and minimize risks. It has been used to identify pathological conditions and guide minimally invasive procedures, making it a valuable tool for studying infectious and non-infectious diseases (81). Ultrasound is also useful in limited resource settings and can provide forensic pathological insights into the corpse's internal structure. However, ultrasound images may not be feasible for highly decomposed bodies and have limitations in detecting soft-tissue abnormalities (77). Moreover, operator-dependent variability and the need for specific guidelines for PM-US examination restrict its use. Despite the potential benefits, virtopsy is replaced by more accurate modalities such as PM-CT and PM-MRI (74). While ultrasonography is not useful for determining the circumstances or causes of death, it may serve as a quick and easy screen for pneumothoraces before performing CA.

2. Postmortem CT scan

PM-CT is a commonly used imaging tool in forensic science for medico-legal death investigations and hospital-related death cases where autopsy is not available or allowed due to family objections. It is preferred for its ease of viewing tissue, identification of foreign substances, fractures, and accumulation of gases and fluids in the body. PM-CT also allows for three-dimensional reconstruction to clarify the mechanism of death and can be supported by angiography and tissue removal for postmortem biopsies (23, 82-83). Although PM-CT actually can be used in all cases, their benefits getting pay attention in COVID-19 cases in several prior studies reviewed (45, 53-54, 56, 60-61, 63). PM-CT is especially useful in COVID-19 cases as it can identify pulmonary changes with excellent contrast on non-enhanced CT scans (84). The most frequent findings include bilateral ground glass opacities (GGOs) with a crazy paving pattern and consolidations in either a diffuse or peripheral distribution (85). However, PM-CT is not specific enough to replace histopathological and microbiological analysis for determining the cause of death. Additionally,

early-stage pathology may not be detectable on PM-CT, and forced mechanical ventilation of cadaveric lungs may be necessary to enhance the detection of COVID-19-related lung alterations (62, 85).

Since SARS-COV-2 can harm other organs indirectly or directly, at this point, PM-CT imaging can detect most extrapulmonary CT changes related to the infection, such as brain damage, enlarged lymph nodes, and reduced liver density (86). Unenhanced PM-CT can also reveal intravascular coagulation and pulmonary thromboembolism in critically ill patients. Distension of the inferior vena cava on PM-CT may indicate pulmonary thromboembolism with 83% specificity and 54% sensitivity (87). PM-CT can be an alternative to autopsy for SARS-CoV-2 RT-PCR testing with proper clinical history due to safety concerns for mortuary staff and pathologists (47).

As a part of PM-CT, PM-CT angiography is useful in virtual autopsies to provide essential information about the vascular system in non-decomposed bodies. It can detect pulmonary thromboembolism and deep venous thrombosis in some cases but has limited ability to identify peripheral pulmonary embolism (88). PM-CT-guided biopsy is a minimally invasive technique that can provide tissue and fluid samples for further analysis in suspected COVID-19 cases. It has been successfully applied in post-mortem investigations of COVID-19 patients and can overcome some limitations of virtual autopsy techniques (66). While PM-CT angiography has its uses, histological analysis remains the preferred method for detecting microvascular thrombosis and embolism.

PM-CT is a less risky alternative to autopsy, especially during the pandemic. It can serve as a screening tool and reveal the cause of death and identify viral pneumonia as the cause of death with the landmark finding of peripheral milk glass opacity (50). PM-CT can also provide valuable information on lung disease and comorbidities without exposing operators to high-grade pathogens. The use of PM-CT has revealed that COVID-19 decedents commonly had comorbidities such as cardiac enlargement and vascular disease and were overweight or obese (45). However, PM-CT may not reliably detect moderate or asymptomatic cases. PM-CT can guide pathologists in investigating natural deaths and obtain appropriate samples for virology and histology. The findings highlight the potential of PM-CT to increase post-mortem analysis while preventing contamination (61).

3. Postmortem MRI

Postmortem MRI is a useful tool in clinical forensic investigations, allowing for non-ionizing radiation imaging of internal organs to identify soft tissue injuries and pathological conditions (23, 82-83). A Belgian study conducted brain MRI on 19 deceased individuals with COVID-19, which revealed subcortical macro- and micro-hemorrhages, edematous changes indicative of posterior reversible encephalopathy syndrome (PRES), nonspecific white matter changes, and asymmetric olfactory bulbs in some cases. This study found some abnormalities in the olfactory bulbs, which may be linked to anosmia. However, specific brainstem abnormalities were not found to support respiratory distress in COVID-19 (54). In Brazil, a study using brain MRI showed that intra-axial susceptibility abnormalities suggestive of microhemorrhage were the most common finding in COVID-19 patients, but these abnormalities are not specific to COVID-19 and can occur in other critically ill patients. Pathological analysis was found to be superior to imaging in detecting perivascular hemorrhages (48).

Despite the usefulness of postmortem MRI in demonstrating neurological pathology during the COVID-19 pandemic, understanding MRI results can be complicated due to several factors. These factors include changes that occur in the organ after death, a reduction in the apparent diffusion coefficient (ADC) throughout the organ that makes it difficult to interpret data from DWI scans, and the absence of blood flow, which makes it impossible to use certain types of tracers such as gadolinium, as well as endogenous tracers like arterial spin labeling, blood oxygen level-dependent signal, and time-of-flight angiography (54).

4. 3D Photogrammetry-Based Optical Surface Scanning

3D photogrammetry-based optical surface scanning involves scanning an object's surface from various angles and using a surface scanning application unit to form a real-colour 3D surface reconstruction with high accuracy down to less than 1 mm. This method is more effective in assessing surface tissue damage than postmortem CT scans and MRI (89-91).

A study in South Korea compared CT scans, MRI, and CA in determining the cause of death cases in five types of death cases, showing good consistency between radiological findings and conventional autopsies with high accuracy (92). CT scans are useful for diagnosing traumatic head injury, fatal bleeding, and pneumothorax, while MRI is preferred for diagnosing ischemic heart disease, tracking metal object route, and determining soft tissue lesions, degree of bleeding chronicity, and bone bruising (92). However, there is no comparison between 3D photogrammetry-based optical surface scanning and CT and MRI in virtopsy, as this method is designed for three-dimensional reconstruction of the body and injuries, which should be supported by other modalities (e.g., CT scan and MRI) with unique camera tools (23, 93).

In this evidence-based review, we proposed an algorithm for selecting the appropriate modality for postmortem imaging, taking into account the need for 3D reconstruction, biopsy, and CA in medical and court settings, As shown in Figure 1, this algorithm can facilitate the implementation of virtopsy in clinical practice, teaching, education, and research purposes for both in the forensic department and radiology division (94).

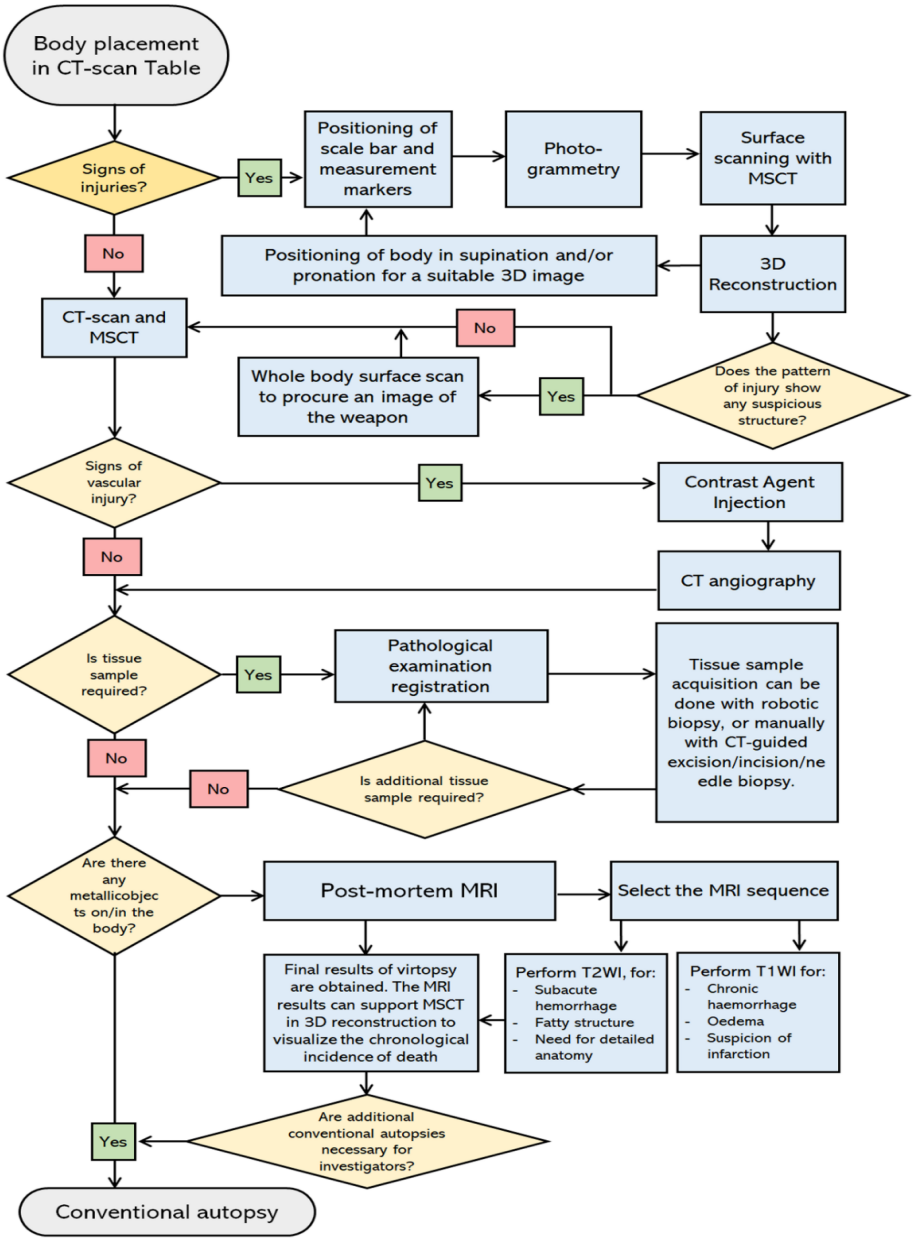

Figure 1: The flowchart for selecting imaging modalities in virtopsy, accompanied by an algorithm outlining the requirements for conventional 3D reconstruction, biopsy, and conventional autopsy.

According to the imaging modality selection flowchart, if there is a patterned injury, photogrammetric techniques should be used to capture a colour 3D documentation of the body surface from different positions. This data is then reconstructed into a 3D model using "virtual robot or virtobot" software. For suspected vascular injury or internal bleeding, CT scan angiography is the preferred method. If there are no ferromagnetic foreign bodies, such as metal fragments, detected by CT scan, then the body can be examined further with MRI for evaluation (94).

Benefits and limitations of virtopsy

Virtopsy offers several advantages over traditional post-mortem examinations. The first benefit of virtopsy is its efficiency and non-invasiveness, allowing for quick and accurate visualization of suspicious areas related to organ damage or foreign bodies. It allows for faster identification of the body and important anatomical structures such as bone and spinal degeneration, fractures, and calcifications in blood vessels. Virtopsy is particularly useful in developing countries where mass disasters are frequent. By quickly and accurately identifying anatomical structures, virtopsy expedites the identification process, which is crucial in such situations. This is especially important in areas with limited resources and infrastructure, where traditional post-mortem examinations may take longer or be less accurate (11, 23, 82-83).

Second, virtopsy is a valuable tool in developing countries with high rates of criminality, particularly in cases involving gunshot wounds. It can accurately locate foreign bodies

such as bullets and determine their path, position, and caliber, which is crucial for forensic investigations. CT scans can also measure the density of foreign bodies through Hounsfield unit (HU) measurements, providing additional information for criminal investigations. This technology is especially important in developing countries where resources for forensic investigation may be limited or unavailable, and where the accuracy of traditional post-mortem examinations may be insufficient for criminal investigations. (11, 23, 82-83).

The third advantage of virtopsy is particularly useful in the context of clinical forensics, as it can identify internal injuries that may not be visible during external examination. For instance, MRI can detect injuries in cases of strangulation, while other modalities like PM-CT can prevent damage to pathological conditions during internal autopsy examination (e.g., gas accumulations, pulmonary embolism, fragmented skull fractures) and thus do not interfere with pathological conditions that might be important for determining the cause of death (11, 23, 82-83).

In developing countries, the use of virtopsy can also provide significant advantages in forensic investigations. For instance, the ability to create three-dimensional reconstructions using MSCT or 3D photogrammetry-based optical surface scanning can help clinicians and investigators better understand pathological conditions and determine the cause of injury or death. Moreover, this technology can produce accurate forensic facial reconstructions, which can be crucial for identifying victims or perpetrators in medico-legal cases. The non-invasive nature of virtopsy also means that it can be performed without damaging the tissue, making it a valuable tool for forensic investigations in regions where resources are limited and access to CA procedures may be restricted (11, 23, 82-83).

Lastly, storing virtopsy results in a database is another significant advantage, particularly in the context of developing countries where resources may be limited. It reduces the need for exhumation and facilitates reassessments to identify missed abnormalities during internal examinations. The stored data can aid future investigations, especially when a case is brought back to court. This can be especially useful in developing countries where access to forensic experts may be limited, but the stored data can provide valuable information for ongoing investigations (11, 23, 82-83).

However, virtopsy also has several limitations. It cannot assess the color, texture, and odor of internal organs, nor provide direct information about a patient's infection status (82, 83). Additionally, normal findings can be mistaken for foreign bodies, such as accumulation of blood in livor mortis and the presence of maggots (23, 82-83). Moreover, vascular damage and decomposition can reduce the effectiveness of PM-CT angiography (83). Virtopsy is operator-dependent and requires specialized medical devices (83). Furthermore, the implementation of virtopsy may be hindered by legal and regulatory barriers, especially in developing countries where it may not be widely known or understood (83).

Application of virtopsy

Virtopsy has several applications, including triage, adjuvant, and an alternative to CA. As a useful triage tool, virtopsy can help determine whether a case requires a CA, especially in countries with limited forensic facilities (95). Radiologists can provide essential findings from virtopsy to forensic specialists to assess whether the available information is sufficient to determine the cause of death (94). Moreover, virtopsy can provide initial information for criminal investigation before proceeding with CA as requested by investigating police (64).

Another potential application of virtopsy is as an adjuvant to conventional autopsies. Virtopsy can simplify the task of forensic doctors by facilitating the discovery of important information and its relationship to the cause of death. This advantage is especially beneficial in developing countries where infection is a concern and physical contact with the body should be minimized. Some examples of the use of virtopsy as an autopsy adjuvant method include identifying fractures and reconstructing them, identifying emboli, calculating the amount and distribution of gas in the body, and identifying structural abnormalities of the vertebrae and spinal cord (92).

Finally, while some countries have used virtopsy as a complete substitute for CAs in disaster conditions, it is still unable to completely replace them in developing countries due to its limitations such as low-level accuracy in identifying damaged or broken bodies and degraded cadavers (96). Moreover, a lack of knowledge of forensic radiology can also lead to later discrepancies in the interpretation of findings. Further decomposition that damages the vascular mucosa may complicate contrast injection CT-scan angiography. In addition, the high cost of CT-scans and MRI equipment makes it challenging to provide separate imaging facilities, considering that imaging facilities for living patients should not be used for autopsy purposes and vice versa (92). Although there are challenges, virtopsy has been demonstrated to be a viable replacement for CA in several countries, especially during the COVID-19 pandemic. Table 3 data shows that virtopsy was primarily used for triage or screening for CA, as well as an adjuvant to CA. However, some reports indicate that virtopsy was used as a complete substitute for CA.

Implementation of virtopsy in various countries of the world

Virtopsy has been widely implemented in various countries, particularly in developed nations where radiology equipment is more readily available. Switzerland was the first to adopt virtopsy and has since implemented all procedures, using it mainly for health research and rare cases. However, virtopsy is accepted as reliable evidence in criminal trials in Switzerland. In Denmark, Sweden,

and France, CT scan virtopsy is used as an adjuvant to conventional autopsies (96). Germany uses virtopsy as a triage for CAs, and in some cases, PM-CT can replace CAs, particularly in sudden infant death syndrome cases. The UK uses virtopsy as triage in cases of suspicious death, pediatric and perinatal deaths, and high risk of infection, such as HIV. In Italy, virtopsy is also applied as triage, and in cases of mass deaths involving over ten victims, virtopsy replaces CAs (96). This advancement in technology is particularly useful during the current COVID-19 pandemic, where autopsies may still be required to determine the cause of death.

In Australia, spectroscopic MRI has been used to measure the time of death by examining metabolites in the brain related to postmortem decomposition. Postmortem angiography has also been used to visualise the cardiovascular system. CT-guided needle biopsy is frequently performed for histopathological analysis (97). In Japan, PM-CT is widely used for screening, triage, and an adjuvant purpose, with 89% of respondents in a study using PM-CT, possibly due to the abundance of CT-scan facilities (98).

No studies have yet investigated the use of virtopsy in underdeveloped nations due to the high cost and sophisticated resources required for non-invasive autopsy using radiology modalities. The use of virtopsy may be more limited in underdeveloped nations when compared to developing and developed countries (34). However, virtopsy procedures could benefit developing countries in Africa, South America, and Asia, including Indonesia, where the lack of funds and resources limits the availability of autopsies, pathologists, and forensic experts (99). In China, a report of three cases investigated using virtopsy resulted in similar conclusions to CAs for death by traffic accidents, but limited information for sudden cardiac death cases. Virtopsy excels in showing certain lesions, such as pneumatosis and fractures (100). The virtopsy protocol has also been used successfully in developing countries such as Brazil (48, 53) and India (56) between 2020 and 2022 to investigate disease in corpses and determine the cause of death during the COVID-19 pandemic (101).

Ethical, bioethical, social, cultural, religion, and medico-legal aspects of virtopsy

Although virtopsy is considered superior in forensic science and radiology, ethical and legal issues have hindered its development. In developing countries such as Indonesia, virtopsy is considered to not violate the applicable medical ethical framework (13). However, virtopsy requires special attention to the digital data's confidentiality. In addition, from an ethical point of view, virtopsy allows medical personnel to promote their professionalism and expertise in a multidisciplinary manner to play a joint role and cooperate in handling medico-legal cases. Medical personnel will get lessons learned to be wiser towards discoveries and respect the rights of patients, families, and other medical colleagues in applying virtopsy in daily practice. From the patient's perspective, the doctor must also provide information on this autopsy procedure to the patient's family, including alternative options (13).

Virtopsy in medico-legal practice has both benefits and disadvantages from bioethical standpoint including autonomy, beneficence, justice, and *non-maleficence*. From the 'autonomous' aspects, digital images require confidentiality similar to to medical records. The 'beneficence' aspect of virtopsy emphasises the advantages of this technology, which is non-invasive, acceptable for relatives of patients, and can be used for the common good in preventing infection transmission during the COVID-19 pandemic. From the 'justice' aspect, virtopsy must be appropriately analysed regarding the cost-effectiveness of in-hospital services because both living and dead patients need radiological modalities that must be allocated fairly. However, despite its benefit in proving death, virtopsy also has the danger of radiation emanating from the cadaver (102, 103). Thus, to uphold the principle of '*non-malifence*', policies related to potential radiation hazards that may persist until the body is buried should be given special attention, following the value of "*primum non nocere*" for personnels handling cadavers (13).

The current challenge of virtopsy is also about the way to integrate innovative methodologies to better comprehend diseases without offending traditional, ethical, religious, social, and cultural beliefs held by society. Many view CAs as destructive, and several religions have prohibitions against them. Jews, for example, strongly object to autopsies, while Hindus, Buddhists, and Christians may have milder objections (104). On the other hand, Muslim believe that invasive autopsies amount to pain in the deceased's soul, based on the principle that "breaking the bones of the dead is like breaking the bones of the living" (105, 106). In Islam, the need for burial waiting time not to exceed 24 hours discourages routine autopsies (104, 105, 107). Thus, on this matter, virtopsy is expected to be able to answer the challenge of patient refusal for previously mentioned reasons, so that the number of proven causes of death can increase.

Nevertheless, despite the allowance of imaging for forensic purposes, virtopsy still faces challenges in many countries, including Indonesia, where there is no legal basis for its use in court (96). There is also a lack of clear legal regulations surrounding data privacy, personal rights of victims, consent to action, methods, and storage of imaging documents (90, 108, 109). Therefore, in order to fully leverage the potential of virtopsy in advancing medical science, research, clinical practice, and legal courts, comprehensive analysis and clear legal regulations are necessary, particularly in developing countries during the COVID-19 pandemic. This challenge is not limited to Indonesia but is prevalent in many developing countries. Thus, proactive measures must be taken to address this issue, not only in the current pandemic, but also to anticipate similar contexts in the future.

Future prospects for implementing virtopsy in developing countries and in Indonesian context

Implementing virtopsy in developing countries particularly during the COVID-19 pandemic, holds promise due to the widespread rejection of traditional autopsy methods, limited resources, and fear of stigmatization. However, unique cultural, religious, ethical, and legal considerations must be taken into account. (13, 21, 110). In Zambia, the rejection rate for child autopsy was 75.4%, with reasons including time constraints, already issued death certificates, and cultural beliefs (111). Similarly, in Uganda, autopsies were not performed in 45% of HIV patients who died, with families refusing autopsies 36% of the time due to reasons such as lack of time and perceived lack of benefit (115). The acceptance rate of autopsies for general disease in Uganda was only 38% (112). Diagnostic discrepancies between clinical and post-mortem diagnoses are also prevalent in developing countries, including Southern Africa regions (113), with a 40% discrepancy rate found in maternal deaths in sub-Saharan Africa (114). Addressing these issues through the implementation of virtopsy could help increase diagnostic accuracy and improve healthcare outcomes in developing countries.

Developing countries, including Indonesia, are promising targets for implementing virtopsy implementation, as it has already shown potential in developed countries. Despite having more adequate infrastructure compared to underdeveloped countries, developing countries face unique challenges such as declining autopsy rates, cultural beliefs, and religious constraints that hinder the implementation of conventional autopsy methods (6). In addition, the burden of infectious diseases such as COVID-19 in these countries highlights the need for alternative autopsy methods like virtopsy. Indonesia, with its high population, lack of forensic specialists, and adequate radiology modalities, is a prime example of a developing country that could benefit from the implementation of virtopsy (115, 116).

Bringing more specific to the Indonesian context, in Indonesia, virtopsy has not been routinely carried out due to limited tools and the lack of collaboration between radiology and forensic medicine departments. The radiology facilities available are restricted to living patients and using them for autopsies is unethical. Moreover, virtopsy with PM-CT multiphase angiography requires a great logistical effort and technical skills, adding approximately $300 per case to the cost before the expense of the modified heart-lung machine is counted (96). Therefore, a cost-benefit analysis is necessary before developing virtopsy facilities in developing countries like Indonesia.

However, with a limited number of medical personnels in charge in autopsies, where there are only 300 forensic doctors available versus 1,646 radiologists for a population of 270 million, virtopsy can be beneficial to make an effective approach of autopsies, particularly in areas where hospitals lack forensic experts but have radiologists (117, 118). The data can be sent to a forensic expert to determine if CA is necessary, making virtopsy can later be applied in various forensic situations, including in traumatic injuries, suspicious causes of death, or COVID-19 pandemic circumstances (97). In countries with high rates of criminal deaths, natural disasters, and societal reluctance towards CA procedures, virtopsy can be a breakthrough for a future framework in hospitals with cooperation from legal and court matters.

Despite the benefits of virtopsy, the legal basis in Indonesia is unclear. However, as with autopsies, supporting examination such as postmortem imaging can be employed to demonstrate the cause of death (119, 120). The existing law allows laboratory investigations and biopsies of tissue organs and body fluids to prove the cause of death (119, 120). Ethical concerns surrounding patient's confidentiality and anonymity regarding radiography records must be addressed and managed in designated hospital storage (13). Additionally, the COVID-19 pandemic poses a significant risk to healthcare providers during the virtopsy process, and special measures must be implemented to prevent infection spread. Limited hospital resources due to the high number of COVID-19 cases may also prevent conducting virtopsy.

Conclusion

Virtopsy offers several benefits for developing countries during the COVID-19 pandemic. It is non-invasive, time-saving, and cost-effective method of determining the cause of death, and can be tailored to the specific cultural, ethical, and legal needs of the local population. It can be used as triage, adjuvant, or a complete substitute for conventional autopsies, and has been shown to increase the accuracy of diagnosing death, pathology, and anatomical structure involved. PM-CT imaging is most common modality used in virtopsy and a reliable diagnostic tool for determining causes of death in corpses and specifically good in identifying COVID-19 infection sign from CT appearance related chest changes with high accuracy.

Since forensic practitioners are at a higher risk of contracting COVID-19 during autopsies, virtopsy is a safer alternative for post-mortem evaluation. In cases where advanced virtopsy facilities are unavailable, portable X-ray and ultrasound machines are cost-effective alternatives. However, the limitations to virtopsy, such as difficulty of confirming true infection, assessing the colour, texture, and odour in internal organs, operator dependencies, legal basis, and implementation cost in developing countries. Further feasibility studies are necessary to address these issues. Despite its limitations, virtopsy could be a valuable investment for accurate diagnosis of the cause of death in developing countries during and after the COVID-19 pandemic.

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Competing interests

The authors declare that they have no competing interests.

Ethical Clearance

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Supplementary Table 1: An evaluation of the validity of case report studies related to the implementation of virtopsy during the COVID-19 pandemic

Studies	Reference	Clearly described patient's demographic characteristics	Patient's history clearly described and presented as a timeline	Current clinical condition of the patient on presentation clearly described	Diagnostic tests or assessment methods and the results clearly described	Intervention(s) or treatment procedure(s) clearly described	Post-intervention clinical condition clearly described*	Adverse events (harms) or unanticipated events identified and described	Case report provide takeaway lessons
DeGiorgio et al., 2022	(55)	🟡	🟡	🟡	🟡	🟡	🟢	🔴	🟢
Vaishnav et al., 2022	(56)	🟢	🟢	🟢	🟢	🟢	🔴	🔴	🟢
Xie et al., 2022	(57)	🟢	🟢	🟢	🟡	🟡	🟢	🔴	🟢
Filograna et al., 2022	(44)	🟢	🟢	🟢	🟡	🟢	🟢	🔴	🟢
Fitzek et al., 2020	(59)	🟡	🟢	🟡	🟡	🟡	🟢	🔴	🟢
Barton et al., 2020	(60)	🟢	🟢	🟢	🟡	🟢	🟢	🔴	🟢
Ducloyer et al., 2020	(61)	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢
Helmrich et al., 2020	(46)	🟢	🟢	🟢	🟡	🟡	🟢	🔴	🟢
Schweitzer et al., 2020	(63)	🟢	🟢	🟢	🟢	🟢	🟢	🔴	🟢

Notes: Yes (🟢), Unclear/Unsure (🟡), and No (🔴).**This parameter can be referred to the availability of pathological confirmation after radiological intervention*

Supplementary Table 2: An evaluation of the validity of case series and cross-sectional studies related to the implementation of virtopsy during the COVID-19 pandemic

Studies	Ref	Types of study	Clearly defined sample inclusion criteria	A detailed description of subjects and settings	Valid and reliable measurement of exposure	Standard criteria for disease/ injury measurement	Identification of confounding factors and dealing with	Valid and reliable measurement of outcome
De-Giorgio et al., 2021a	(43)	Case control	🟡	🟢	🟡	🟢	🔴	🟢
Filograna et al., 2022	(44)	Retrospective monocentric cross-sectional	🟢	🟢	🟡	🟢	🔴	🟢
Thomas et al., 2022	(45)	Retrospective monocentric cross-sectional	🟢	🟢	🟡	🟢	🔴	🟢
Heinrich et al., 2020	(62)	Retrospective monocentric cross-sectional	🟡	🟢	🟡	🟢	🔴	🟢
O'Donnell et al., 2021	(47)	Retrospective monocentric cross-sectional	🔴	🟢	🟡	🟢	🔴	🟢
Coolen et al., 2020	(54)	Prospective monocentric case series	🟢	🟢	🟡	🟢	🔴	🟢
Martin et al., 2022	(48)	Retrospective monocentric case series	🟢	🟢	🟡	🟡	🔴	🟡
De-Giorgio et al., 2021b	(49)	Retrospective monocentric case series	🟡	🟢	🟡	🟢	🔴	🟢
da Silva et al., 2021	(51)	Retrospective monocentric case series	🔴	🟢	🟡	🟡	🔴	🟢
Kniep et al., 2021	(50)	Retrospective monocentric case series	🔴	🟢	🟡	🟢	🔴	🟢
Williams et al., 2021	(52)	Retrospective monocentric case series	🔴	🟢	🟡	🟡	🔴	🟡
Duarte-Neto et al., 2020	(53)	Retrospective monocentric case series	🔴	🟢	🟡	🟢	🔴	🟢

Notes: Yes (🟢), Unclear/Unsure (🟡), and No (🔴).

Supplementary Table 3: An evaluation of the applicability of case report studies related to the implementation of virtopsy during the COVID-19 pandemic

Studies	The similarity of patients characteristics with the point of interest intervention	Valuable finding	Beneficial to the patient in this article's context
Case Control Studies			
De-Giorgio et al 2021a (43)	🟡	🟢	🟢
Retrospective Monocentric Cross-Sectional Studies			
De-Giorgio et al 2021a (43)	🟢	🟢	🟢
Filograna et al 2022 (44)	🟡	🟢	🟢
Thomas et al 2022 (45)	🟡	🟢	🟢
Heinrich et al 2020 (62)	🟡	🟢	🟢
Prospective Monocentric Case Series			
Coolen et al, 2020 (54)	🟡	🟢	🟢
Retrospective Monocentric Case Series			
Martin et al, 2022 (48)	🟢	🟢	🟢
De-Giorgio et al 2021b (49)	🟡	🟢	🟢
da Silva et al 2021 (51)	🟢	🟢	🟢
Kniep et al 2021 (50)	🟡	🟢	🟢
Williams et al 2021 (52)	🟡	🟢	🟢
Duarte-Neto et al 2020 (53)	🟢	🟢	🟢
Case Reports			
DeGiorgio, 2022 (55)	🟡	🟢	🟢
Vaishnav et al, 2022 (56)	🟢	🟢	🟢
Xie et al 2022 (57)	🟡	🟢	🟢
Filograna et al 2022 (44)	🟡	🟢	🟢
Fitzek et al 2020 (59)	🟡	🟢	🟢
Barton et al, 2020 (60)	🟡	🟢	🟢
Ducloyer et al, 2020 (61)	🟡	🟢	🟢
Helmrich et al 2020 (46)	🟡	🟢	🟢
Schweitzer et al 2020 (63)	🟡	🟢	🟢

Notes: Yes (🟢), Unclear/Unsure (🟡), and No (🔴).