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Clinical practice

Proposal for a harmonized protocol for COVID-19 screening and necropsy in forensic sciences facilities

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ABSTRACT

On 31 December 2019, health authorities in the People's Republic of China informed the World Health Organization of a then limited outbreak of interstitial viral pneumonia, identified at a laboratory in the city of Wuhan. In mid-April 2020 this outbreak of COVID-19 (as the disease has been called) has aggravated and spread worldwide, causing more than 200,000 deaths and affecting especially the United States, Spain, Italy, France and the United Kingdom. Despite the severity of the outbreak, the pathological findings have not been described in detail and there are very few guidelines or protocols for conducting autopsy studies on patients who have died from COVID-19. There are currently very few histopathological case series studies on this disease. In addition, some of these studies have been performed on biopsies or surgical resection pieces from patients in whom disease was subsequently demonstrated or through minimally invasive autopsy protocols. None of the studies offer a detailed necropsy protocol. This document proposes a protocol of action for the institutes of Forensic Medicine facing the current SARS-CoV2 pandemic, which combines protection of worker safety with optimization of tissue collection.

1. Introduction

In early January 2020 an RNA virus of the coronavirus family, SARS-CoV2, was identified as the causal agent of COVID-19.[1–4,6] Coronaviruses are non-segmented, enveloped RNA viruses belonging to the family *Coronaviridae* and the order Nidovirals, widely distributed in mammals.[7–9,25] Epidemics of severe acute respiratory syndrome (SARS-CoV)[10,11] and middle eastern respiratory syndrome (MERS-CoV)[12,14] have caused more than 10,000 cumulative cases in recent decades, with mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.[10–14] Despite the potentially high mortality of the ongoing outbreak, few necropsy studies have been performed,[16–20,69,73,78] with a relative lack of exhaustive search for extra-thoracic lesions.[75,78] Another limitation of these studies is the lack of clear autopsy protocols both for the pre-interventionist and.interventionist phases of the studies. As clinical necropsies are burdensome and time-consuming procedures (that overburdened hospitals in the hotspots of the pandemic may not afford) we suggest that forensic pathology institutes should step to the forefront and elaborate detailed protocols able to provide forensic diagnosis as well as recording any possible histopathological finding related to COVID-19. We expect that many judiciary cadavers, whether natural or non-natural, will test positive for COVID-19 independently of the ultimate cause of death. This fact may shed light over early pathological phenomena and serve as an invaluable source of human tissue for future research. Our proposal is based on three premises. 1) the normal functioning of the forensic pathology institutes worldwide should not be discontinued while prioritizing worker safety; therefore, immediate screening for COVID-19 infection in any cadaver admitted in a forensic pathology laboratory should be performed even if this means delaying the procedures until the results are ready[56–59,72,74] (a diagrammatic

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representation of the protocol is depicted in Table 1). 2) once a cadaver is known to be SARS-CoV2 +, a mixed autopsy protocol should be carried out, combining interventions directed to disclose the judiciary nature of the death with interventions aimed at a comprehensive tissue collection for COVID-19 research. 3) given the endothelial tropism[5,42,43,45,46] of the pathogen and the clinical reports about both rapid deterioration leading to death and neurological[46,47,49] manifestations of the disease, deaths with no obvious suspicion of criminality should be subjected to autopsy protocols akin to the ones employed in sudden death investigation[66,76,77] coupled with full examination of the encephalon. 4) Forensic facilities where screening is not possible or where worker's safety is not guaranteed may consider alternative measures to avoid both autopsy cancellation and worker exposure, in these cases we propose trans-carotid perfusion of 10 L of 3.7% formaldehyde[64,65] (at 0.5 ml/min) as an alternative.

2. COVID-19 as a systemic disease

Coronavirus SARS-CoV2 infection is mainly characterized by prolonged fever, cough, fatigue, dyspnea and anorexia, with myalgia, pharyngitis symptoms, digestive manifestations and prolonged headaches.[5,28,29] The laboratory findings, in addition to the elevation of traditional acute phase reactants, include a trend to eosinopenia, lymphopenia and thrombocytopenia together with D-dimer elevation.[30,31] Elevations of hepatic enzymes[5] and troponins[35] have been also observed in up to 12.5% of patients. Most of the deaths are associated with pulmonary involvement[25,26] and myocardial damage, suggested by the elevation of troponins.[26,27,28,29,39,97] Myocardial damage (reviewed by[5,33]),[34,97] is attributed to the presence of the ACE2 receptor used by the virus to enter the cell and includes acute coronary syndrome, heart failure, myocarditis, and malignant arrhythmias (up to 6% of patients and 17% of those with elevated troponins)[32]-.[36] There is also evidence of acute renal disease that has been attributed to ACE2 levels in the proximal convoluted tubule[37,38,78]

3. Histopathological findings in COVID-19 and related diseases

Reported histopathological findings have focused mainly in the lungs, where diffuse alveolar damage with exudate and hyaline membrane formation was invariably observed. This was accompanied by infiltration of the alveolar wall by macrophages and monocytes along with occasional alveolar multinucleated giant cells, eosinophils and neutrophils. Intense interstitial fibrosis was also present, not always of iatrogenic origin. The lymphocyte infiltrate was mostly CD4+.[15–19] Reactive proliferation of type II pneumocytes and frequent foci of epithelial desquamation have been found, both in the lung and upper respiratory tract, regardless of the presence of viral particles. No findings of potentially reversible processes such as mucus plugs, eosinophilia and/or organized pneumonia have been found,[17,19,97] which coincides with autopsy findings on victims of other similar outbreaks.[21] No histological evidence of myocarditis, encephalitis or viral hepatitis has been reported. However, a single study found direct kidney involvement.[78] Hemorrhagic and ischemic foci have been found in both the liver and heart (in addition to edema in various organs including the brain), which could be related to agonal phenomena.[17,19,69,73]

The necropsy findings in patients affected by MERS CoV largely overlap with those described in COVID-19[21,22,44], highlighting diffuse alveolar damage. Viral antigens are concentrated in type II pneumocytes and syncytial epithelial cells suggesting a direct cytopathic effect of coronaviruses on cells of the respiratory system. Renal glomerular sclerosis, thickening of the Bowman's capsule and arteriolosclerosis in the renal vessels were also found along with interstitial inflammatory infiltration and intratubular proteinaceous and granular casts. Lymph nodes with interfollicular proliferation of pleomorphic immunoblasts, intermingled with lymphocyte populations, were also identified. The bone marrow showed a normocellular aspect with preserved hematopoiesis and granulopoiesis, showing the changes typical of the acute phase reaction.[21]

In SARS patients of the 2003 outbreak, lung lesions were mainly desquamative alveolitis and bronchitis, with less noticeable thickening of the alveolar septa. As in MERS and COVID-19, there was evidence of diffuse alveolar damage with hyaline membranes and extensive intra-alveolar inflammatory exudate with signs of organization in patients with protracted course.[22] The most striking finding of the autopsies of patients with SARS was the extension of systemic vasculitis, with proliferation and apoptosis of endothelial cells accompanied by perivascular lymphoplasmacytic infiltration in heart, lung, liver, adrenal gland and skeletal muscle. These phenomena were accompanied by mixed and hyaline thrombi and fibrinoid necrosis of both vascular walls and spleen and lymph nodes. The perivascular inflammation also involved brain vessels, along with demyelination foci.[39]

4. Searching beyond the lungs: proposed modifications to the standard autopsy protocol in forensic pathology (Table 2)

The cardiovascular pathology associated with COVID-19 is of great interest.[29,30,41–43,45] Severe cases of COVID-19 suffer from disseminated intravascular coagulation[5] and vascular phenomena such as deep vein thrombosis and pulmonary thromboembolism are frequent in critical patients.[42,43] There are published case series that have demonstrated improvement in patients undergoing invasive mechanical ventilation after administration of tPA.[41] All these reports should raise the suspicion that the rapid clinical deterioration of many patients with COVID-19 is a vascular phenomenon. In other related epidemic diseases, similar vasculitis-like findings have been described.[40]

The involvement of the central nervous system has gone unnoticed in *post-mortem* studies, despite numerous clinical reports.[46–50] Neurotropism[50] is a known characteristic in various types of coronavirus which, after infecting the oropharyngeal mucosa, translocate to the central nervous system via the peripheral nerves.[50,67,68] Throughout the current COVID-19 pandemic, neurological manifestations of the disease have been described: the most frequently described are anosmia and ageusia,[70] although cases of ataxia,[49] decreased level of consciousness and loss of respiratory automatism have been also described.[47,49] Thus, many deaths occurring after a rapid aggravation of symptoms in previously stable patients should be treated from the forensic point of view as sudden deaths[77] and be subject to specific autopsy protocols,[66,76] which should also include a thorough brain examination.

Regarding the autopsy protocol, we propose an amendment to the standardized local protocol, e.g[63] encompassing the clinico-pathological data currently known. Fresh tissue for molecular studies and frozen tissue banking would be ideal, although a large number of molecular procedures can be performed on formalin fixed paraffin-embedded tissue. The central point is the *in toto* extraction of the thoracic organs. The cephalic end of the block should include at least the thyroid cartilage in order to collect a sample as large as possible from the respiratory tract. If safe, exudate samples should be collected at different levels of the respiratory tract and lung parenchyma and ventricular blood should be also sampled, along with thorough examination of the pericardial sac, its status and its content. Sections of each lung lobe are recommended to optimize fixation (consider sampling of lungs for COVID-19 confirmation at this step), as well as heart longitudinal sections along the cava-cava axis and two incomplete cross-sections of the myocardium, at 1 and 2 cm from the cardiac apex. This would allow adequate fixation of the tissue. After 48 h, sampling of the thoracic block should be completed. This would involve transection of the aortic arch and of the pulmonary vessels at the level of the pulmonary hilum, including search form thromboembolic events at the level of the pulmonary trunk. After this, the opening of the right atrium from the inferior vena cava to the apex of the auricle would be completed. The left atrium would then be opened cutting between the upper pulmonary veins (prolonged to the apex of the left auricle). Examination of the inner atrial aspect should

Table 1
Decision-making algorithm about the autopsy protocol. The pre-interventionist phase is essential; at admission (1) and after familiar anamnesis (2), all samples where a 24 h delay could be critically detrimental should be taken (3); this includes a nasal and oropharyngeal exudate to test for SARS-CoV2 by RT-PCR (4,5). The results of this test would determine further procedures. In cases where the deceased had influenza-like symptoms before death or in epidemiological hotspots, we suggest retesting to avoid the risk posed by any potential false negative result.*: consider blood sampling (2 × 5 ml EDTA) and serum for freezing **: if compatible history after family interview and negative RT-PCR, assess RT-PCR re-test or serology.

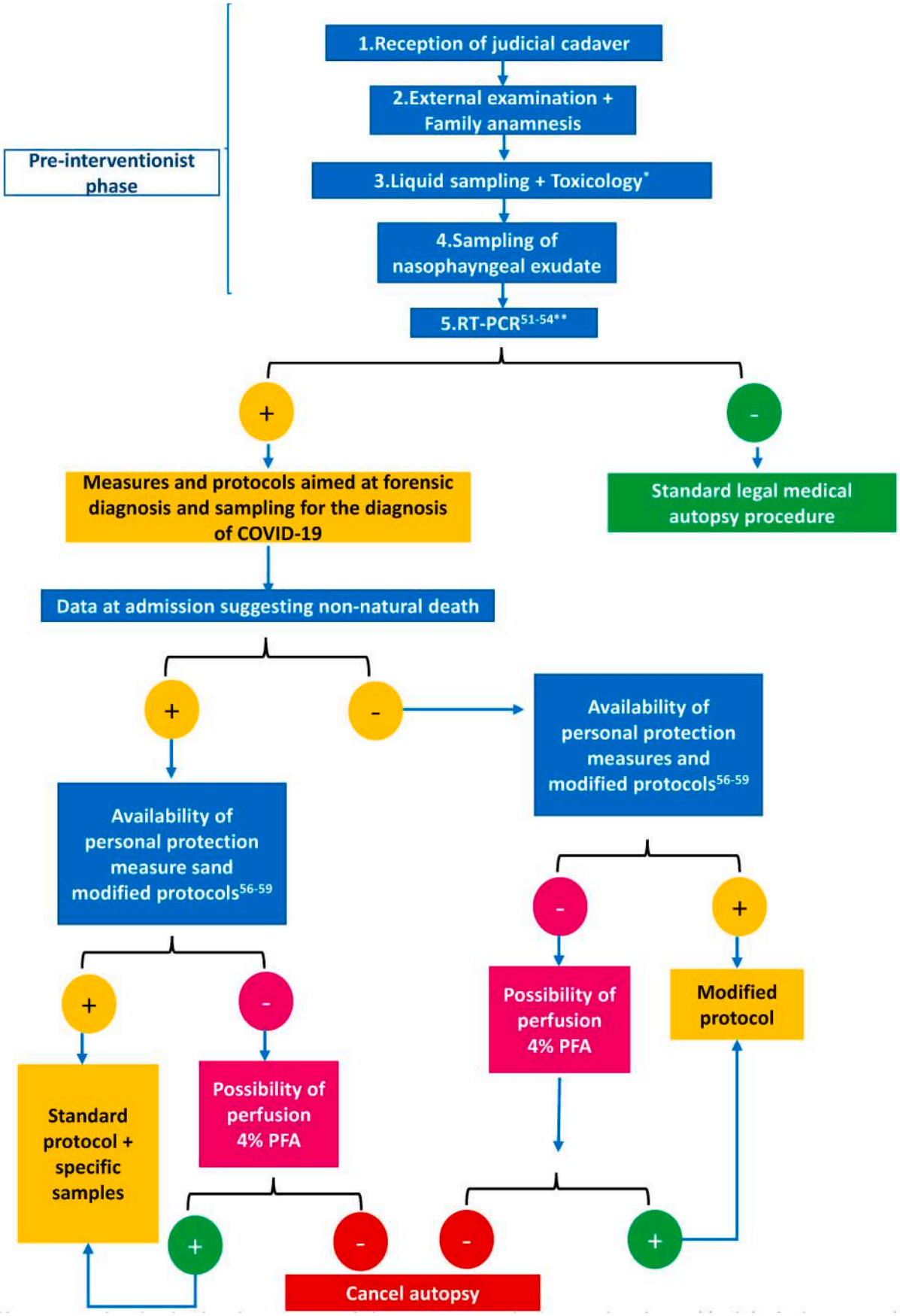
Pre-interventionist phase
1.Reception of judicial cadaver
2.External examination + Family anamnesis
3.Liquid sampling + Toxicology*
4.Sampling of nasophayngeal exudate
5.RT-PCR51-54**
+
-
Measures and protocols aimed at forensic diagnosis and sampling for the diagnosis of COVID-19
Standard legal medical autopsy procedure
Data at admission suggesting non-natural death
+
-
Availability of personal protection measures and modified protocols56-59
Availability of personal protection measure sand modified protocols56-59
-
+
+
-
Possibility of perfusion 4% PFA
Modified protocol
Standard protocol + specific samples
Possibility of perfusion 4% PFA
+
-
-
+
Cancel autopsy

Table 2
Proposed interventions and amendments to the current *in use* protocols, including the minimal set of tissue samples to be removed and examined with H-E staining or any other routine protocol and relevant references.

Intervention		Justification	Reference
1. Screening phase			
External examination, medical history		Assess most suitable protocol	[63]
Collection of liquid samples for toxicological study		Medical-legal study	[60–63]
Freezing two 5 ml vials of bood with EDTA and one of serum		Deferred study	[62]
RT-PCR		Screening COVID-19	[51,52,72]
Serology		Confirmation of screening in cases with doubtful medical history	[53,54,55,72]
Pre-fixation 4% PFA transcarotidea route		Worker safety	[20,23,24]
2. Interventionist phase			
Chest block extraction and delayed autopsy (24–48 h fixation 4% PFA)		Worker safety, clinical and autopsy findings	[1–3,5,9–21,20,23,24,64,65]
	Complete heart examination	Study of sudden death in the context of COVID-19	[1–3,9,26], clinical reports
	Coronary artery sampling	Study of sudden death in the context of COVID-19	[1–3,9,26], clinical reports
	Conduction system sampling	Study of sudden death in the context of COVID-19	[1–3,9,26], clinical reports
	Dissection of large vessels	Search for pulmonary thromboembolism. Study of sudden death in the context of COVID-19	[41–43,45]
	Dissection of large pulmonary vessels	Search for pulmonary thromboembolism. Study of sudden death in the context of COVID-19	[41–43,45]
	Lung sampling	Viral pneumonia study in the context of COVID-19	[9–19,44,69]
Limited management of the abdominal block		Worker safety, clinical findings	[1–3,5,71,20,23,24]
	Kidney extraction with pedicle	Kidney involvement by COVID-19	[5,30,31,38,40,78]
	Spleen extraction with pedicle	Splenic necrosis in the contex of COVID-19 infection	[21,22,44]
	Digestive tube wall sections	Digestive involvement by COVID-19	[71]
	Liver sampling	Liver involvement by COVID-19 and other coronaviruses	[5,21,22]
Brain extraction and delayed study after fixation in 10% PFA (2 weekss)		Neurological involvement by COVID-19	[46–49,67,68,70]
	Cross sections of craneal nerve I and olfactory tract	Anosmia	[46–49,70]
	Basal forebrain, anterior perforated substance, the insula, *limen insulae*, anterior temporal lobe	Anosmia	[46–49,70]
	Cortex sampling	Decreased level of consciousness	[46–49,70]
	Deep White matter, basal ganglia, thalamus	Vascular involvement in the contextof COVID-19, decreased level of consciousness	[46–49,70]
	Brainstem and	Loss of respiratory automatism, dysautonomia, arrhythmias	[46–49,67,70]
	Cerebellum sampling	Ataxia	[46–49,70]
	Craneal nerves, V, VII, IX, X	Ageusia, loss of respiratory automatism, clinical-radiological dissociation related to dyspnea	[46–49,67,70]

include sampling the cardiac conduction system. The aortic root would be inspected from a zenithal view; once identified the origin of the coronary arteries, they would be examined in their subepicardial path through cross sections every 0.3–0.4 cm. Finally, the dissection of the ventricles is completed with longitudinal sections in the direction of blood flow plus sampling of right, left and interventricular septum walls. Examination of the remaining thoracic aorta should focus on the study of the wall and the root of the bronchial arteries, if identifiable. Ideally, the continuation of the study of the pulmonary arteries would involve their dissection until their segmental levels to search for thrombo-embolic events.

Dissection of the abdominal block could be performed in a single operation and should include sampling of the liver parenchyma; subsequently, the omental bursa should be opened and the spleen and its vascular pedicle removed. Finally, the mesentery would be identified and sectioned until approximately the lower third of the abdomen, leaving the posterior parietal peritoneum exposed, allowing palpation of the kidneys and renal hilum. Both kidneys should be extracted with a vascular pedicle. In our opinion, a complete removal of the remaining abdominal and pelvic organs could not be necessary; the examination of the splanchnic block would include the collection of random samples of intestinal wall and mucosa.[71]

We consider the removal of the entire brain block to be essential. Skull opening should avoid the use of vibration saws because of the risk of aerosolization. If possible, samples of cerebrospinal fluids should be taken if omitted at admission, along with meninges. A V-shaped chisel excavation around the occipital protuberance allows the removal of a wedge of occipital bone and access the posterior fossa. Samples will be taken with special attention to the first cranial nerve and the olfactory tract. The entire brain should be removed and frontal, temporal, parietal, occipital cortices should be sampled along with basal ganglia, thalamus and deep white matter.

The brainstem must be separated from the brain by a cross-section through the midbrain and divided by the midline to obtain a sagittal section (sagittal half) of at least one of the halves. The remainder brainstem should be included in serially numbered cross-sections including the apparent origin of the cranial nerves V, VII, IX, X.[61–68,70] These nerves should be identified and included in specific cassettes. It is critical to identify and remove the vertebral arteries before transection of the spinal cord. Processing of the brain should be performed after two weeks of fixation by immersion in standard 3.7% formaldehyde on serial coronal sections.

5. General measures

General measures proposed are in line with the previously proposed ones for SARS-CoV2 and similar pathogens[56–59,60,64,65,74] and involve transportation and storage measures, autopsy handling recommendations, sanitation of the autopsy rooms, personal protection equipment and facility design (partially based on Aquila et al., 2020[79]). As previously stated, autopsy performance should avoid aerosol generating procedures as well as splashing and unsafe management of bony edges. Oscillation sewers should be either avoided or used along water discharge and attached to a vacuum extraction system.[79,80] All facility

surfaces must be disinfected by repeated cleaning with bleach/chlorine or 70% ethanol and waste should be directed to storing devices containing at least 400 mg/L chlorine.[80] The autopsy should be performed with the minimum amount of staff, allowing no additional people in the room. All workers should be provided with the recommended personal protective equipment, and the autopsy should be unambiguously cancelled if either this issue or proper waste handling cannot be guaranteed. Minimum personal protection should include disposable water-proof lab coats with long sleeves and elasticated cuffs, disposable gloves, safety glasses or any equivalent, boots and head and shoe protectors, as well as N95/FFP2 facemasks.[80,81,89] FFP3 facemasks should be used if aerosolization is expected.[80,81,83] Dressing, autopsy and undressing should be performed in non-communicated rooms allowing a clear-cut separation of "clean" and "contaminated" zones. Ideally, forensic facilities should be equipped with double access doors (if possible self-closing and with an interlocking mechanism), so that only one of them is open at any given moment. All surfaces must be waterproof and easy to clean. All existing openings must be hermetically sealed and provided with breakage-resistant glass. A foot operated sink and eyewash are also recommended. There must be a ventilation system that establishes a directional flow to the laboratory, and it must be constructed so that the air in the autopsy cannot invade areas of the building. The air should be filtered by a HEPA system, (already existing), reconditioned and recirculated inside the laboratory. An autoclave should be available inside the autopsy room to decontaminate the infected waste material before definitive disposal.[79–83] Contrary to personal protection equipment (which are a *sine qua non* requirement for autopsy procedure), we believe that partial deficits in facilities might be overcome by pre-perfusion with 4% formaldehyde.

6. Further implications of COVID-19 infection as a forensic diagnose

An active search for COVID-19 in cadavers submitted for judiciary autopsy will result in the discovery of previously unknown cases. Besides the scientifical interest of histopathological findings in early stages of the disease, this search poses interesting concerns regarding death certification fulfillment, forensic diagnose and informs and potential legal consequences. According to the WHO,[62] any case in which SARS-CoV2 infection is demonstrated through laboratory tests should be regarded as a confirmed case of COVID-19 and, as such, notified to the competent authority. Although deaths during a pandemic could be regarded somehow as a case of *force majeure* for many legal obligations[84] in the general public and trade law, the situation is different in cases where a COVID-19 infection could be considered a professional disease[85] or where the patients are under the tutelage of any public or private entity like care homes or prisons[86,87] as this disease is classified as preventable through adequate prophylaxis.[81,88,89] According to the Spanish legislation and the opinion of forensic experts, there is space for legal responsibility claims in professional environments where the infection can be traced to the lack of proper personal protection equipment,[85] disregarding the outcome.

In these cases there is a reversal of the burden of proof that operates in favor of the worker, falling on the company the obligation to show that it adopted the necessary measures to prevent and avoid the risk, the employer responding even in cases of carelessness of the worker as long as it is not reckless.[90–92]

Finally, the possible criminal liability that the company may incur is in the person of its administrators or persons in whom the employer has commissioned or delegated the implementation and execution of safety and hygiene measures, in accordance with the criminal types included in Articles 316[91] to 318[92] of the Spanish Penal Code.

Therefore, a positive RT-PCR for COVID-19 should be clearly stated in the forensic inform and the medical certification of death even in cases where the disease is not judged, after the forensic examination and autopsy, to have played a role in the pathogenic process leading to the decease (see below).

In the 7th June 2020, the WHO issued a technical note with guidelines regarding the medical certification and mortality coding during the pandemic.[98] Although the WHO provide clear examples where COVID-19 should be recorded as underlying cause of death, there is a major concern whether to term a death as caused by COVID-19 or simply as death with COVID-19 infection.[93] The Spanish medical associations acknowledges two main cases for death certification: a confirmed COVID-19 infection by RT-PCR should be termed "COVID-19 as underlying cause of death" and coded U07.1 according the WHO; conversely, a patient deceased after COVID-19-like symptoms in a suitable epidemiological context but with unconfirmed diagnosis would receive the diagnose of suspected COVID-19 as underlying deaths cause, coded U07.2 [93,94]. The protocol hereby proposed may uncover cases belonging to a third category that lays in the gray zone between both cases: confirmed cases where the cause of death might be attributable or not to COVID-19. In these cases, forensic clinical judgement should prevail regarding the definition of the underlying cause of death. We propose three different scenarios: a) Violent or traumatic death in COVID-19 confirmed cadavers (or natural causes otherwise clearly unrelated to the infection, e.g ruptured aneurism); b) Cases where the primary cause of death may bear a distant or still unknown relationship to the infection (e.g myocardial infarction, pulmonary thromboembolism or non-immediate deaths related to a traumatic event where the consequent clinical course may have been aggravated by the infection); c) Cases of unsuspected etiology at admission, COVID-19+, where autopsy findings include pulmonary edema, pleural effusion, thrombotic microangiopathy in pulmonary vessels, diffuse alveolar damage or any other feature of pulmonary disease caused by SARS-CoV2. In the first case, COVID-19 infection, albeit properly communicated for statistical and contact tracing purposes, should not be mentioned as the cause of death but clearly stated elsewhere in the forensic report. In the last case, COVID-19 is clearly the underlying cause of death (or *causa fundamental* according to Spanish terminology). In cases where infection may have conditioned the clinical course, we propose to classify the viral infection as "other significant condition contributing to death",[98] intermediate cause of death or any local equivalent.[93,94] Again, the clinical judgement should prevail in patients affected by vascular pathology (e.g pulmonary thromboembolism) where features strongly related to SARS-CoV2 like giant $CD61^{+}$ megakaryocytes[95,96] are found, at least until further research elucidates the relationship between SARS-CoV2 and fatal extrapulmonary phenomena. The protocol here described may contribute to clarify this issue.

7. Final perspective

Screening of COVID-19 at admission in forensic pathology facilities is essential for ensuring worker safety and allowing modifications of usual protocols that incorporate the clinical findings reported in this novel disease. Protocols should consider COVID-19 as a vascular, sudden death-prone disease with neurological involvement, apart from a respiratory infection. Thorough tissue sampling and sample banking are needed to understand early mechanisms of the disease, particularly in cases where COVID-19 is not the primary cause of death.

Author contribution

Emilio González-Arnay: Writing - original draft, wrote the manuscript, provided the original idea. Raquel Martín-Olivera: provided the original idea. Yamilet C. Quintero-Quintero: critically reviewed the manuscript. Ana I. Hernández-Guerra: critically reviewed the manuscript. All authors collaborated in the literature review.

Declaration of competing interest

Authors report no conflict of interest.

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