The trajectory of COVID-19 cardiopulmonary disease: insights from an autopsy study of community-based, pre-hospital deaths

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Shareable abstract (@ERSpublications)
Heterogeneous, overlapping and severe cardiopulmonary histopathological states occur following #COVID19 deaths in the community. Explanations for this were previously lacking and include unsensed hypoxaemia, rapid progression and psychosocial factors https://bit.ly/3CkEiij

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Abstract

Background *Post mortem* examination of lung and heart tissue has been vital to developing an understanding of COVID-19 pathophysiology; however studies to date have almost uniformly used tissue obtained from hospital-based deaths where individuals have been exposed to major medical and pharmacological interventions.

Methods In this study we investigated patterns of lung and heart injury from 46 community-based, pre-hospital COVID-19-attributable deaths who underwent autopsy.

Results The cohort comprised 22 females and 24 males, median age 64 years (range 19–91) at time of death with illness duration range 0–23 days. Comorbidities associated with poor outcomes in COVID-19 included obesity (body mass index >30 $kg \cdot m^{-2}$) in 19 out of 46 cases (41.3%). Diffuse alveolar damage in its early exudative phase was the most common pattern of lung injury; however significant heterogeneity was identified with bronchopneumonia, pulmonary oedema consistent with acute cardiac failure, pulmonary thromboembolism and microthrombosis also identified and often in overlapping patterns. Review of clinical records and next of kin accounts suggested a combination of unexpectedly low symptom burden, rapidly progressive disease and psychosocial factors may have contributed to a failure of hospital presentation prior to death.

Conclusions Identifying such advanced acute lung injury in community-based deaths is extremely unusual and raises the question why some with severe COVID-19 pneumonitis were not hospitalised. Multiple factors including low symptom burden, rapidly progressive disease trajectories and psychosocial factors provide possible explanations.

Introduction

Autopsies have been critical to our understanding of nascent disease pathophysiology for centuries, and the COVID-19 pandemic is no exception. True to its Ancient Greek etymology, "*autopsia*" allows the pathologist to "see for oneself" a temporal snapshot of diseased tissue at the time of death [1]. Peripheral blood sampling and radiological studies have informed much of our knowledge of COVID-19 pathophysiology to date, and although they are critical metrics, they provide mere inferences of the cellular responses and architectural injury hidden at the tissue level. The respiratory tract is the initial target of severe acute respiratory coronavirus 2 (SARS-CoV-2) and the most important site of disease progression [2]. Through autopsy series, diffuse alveolar damage (DAD), referring to a pattern of injury to pneumocytes and alveolar endothelial cells [3], has emerged as the dominant histological phenotype in

COVID-19 *post mortem* lung tissue (PMLT) obtained from the hospital setting [4] and can be found in two distinct phases: an early or exudative phase and a later proliferative and organising phase [4]. COVID-19 PMLT from hospital-based series is also extensively heterogeneous and often features superimposed bacterial bronchopneumonia, fungal infection, pulmonary features of acute cardiac failure and thrombosis [5–7].

The majority of published autopsy series have focused on hospital-based deaths with community-based series being scarce [8]. DAD was described in some early community-based case reports [9–11] and case series [8, 12–14]; however it is possible these do not cover the full clinicopathological spectrum in the community due to their small cohort numbers. Most importantly, in the pre-COVID-19 era, DAD was classically associated with the severe clinical trajectory of acute respiratory distress syndrome (ARDS) and significant symptom burden necessitating critical care support [15, 16]. DAD featuring in community-based autopsies has therefore bewildered pathologists, and explanations for why these people died at home rather than presenting to hospital are needed. During the COVID-19 pandemic, the phenomenon of "silent hypoxia" has been observed by clinicians, whereby severely low oxygen saturations, evidence of significant functional lung impairment, seems to be able to coexist with an incongruously low symptom burden [17]. In this study, we have integrated clinical, microbiological, macroscopic and histopathological data to provide a full picture of the pathological spectrum of cardiopulmonary disease in fatal COVID-19 cases in the community as well as chronicle symptomatic burden prior to death based on collateral accounts from next of kin.

Methods

A list was collated by the Newcastle upon Tyne NHS Foundation Trust Department of Cellular Pathology of all individuals referred for an HM Coroner's autopsy if they died in the community with proven or suspected COVID-19 before any hospital-based intervention, or if they died unexpectedly in the community and screening COVID-19 swabs were positive. Deaths included occurred between April 2020 and August 2021, corresponding to the first and second "waves" of COVID-19 in the UK. Autopsies were performed by a consultant pathologist following published risk reduction strategies [18]. Swabs of the nose, throat and/or lung parenchyma were taken for SARS-CoV-2 polymerase chain reaction (PCR) testing during autopsy. Only cases with positive SARS-CoV-2 PCR results were included in the study. Clinical metadata were collected routinely at autopsy and with the aid of collateral history from next of kin and included basic demographics, body mass index (BMI), symptoms prior to death, duration of illness and presence of comorbidities. Metadata was then extracted from available autopsy reports retrospectively and tabulated. Individuals were only included if it was determined that COVID-19 disease was the primary cause of death.

Macroscopic findings gathered included the significant pathological features on visual and tactile inspection and weights of the right and left lungs and the heart. Lung and heart samples were formalin fixed, paraffin-embedded, sectioned, mounted and stained for analysis. The microscopic slides were reviewed by pathologists with special expertise in cardiothoracic pathology. Their objective was to determine the dominant histological pattern of disease which, within the context of all other *post mortem* findings, was most likely to have caused death. Other pathologies that were thought to have played a non-dominant yet significant role in demise were reported as secondary pathologies. Considering the clinical, macroscopic and microscopic data, individuals were then classified into phenotypic groups by disease process.

Finally, based on the themes emerging from our analysis of clinical narratives, we hypothesised that a low symptom burden may have contributed to death in the community as individuals would be less likely to seek medical attention. We collated those in the cohort who had collateral history documented within the autopsy report clearly stating that prior to death the individual was 1) asymptomatic, or 2) had no lower respiratory tract symptoms (and only had extrapulmonary symptoms) or 3) a qualifier synonymous to "mild" was used to describe any lower respiratory tract symptoms present. All patients meeting these definitions were collated into a "low symptom burden" group for later analysis. To illustrate further which individuals might constitute this group, it would equally include an asymptomatic individual, a person with slight shortness of breath and a person with isolated myalgia. Respiratory symptoms included shortness of breath, cough, sputum production, haemoptysis, wheeze and chest pain or tightness. Common extrapulmonary symptoms were also collated including enteric symptoms (diarrhoea, vomiting, abdominal pain), fever and other systemic symptoms (such as myalgia, arthralgia, cutaneous exanthems).

Results

Cohort demographic and clinical data

Our study identified 46 individuals who died at home in North-East England in the first and second "waves" of the COVID-19 pandemic without admission to hospital during their period of illness, with

autopsies occurring between April 2020 and August 2021. All 46 were confirmed to be SARS-CoV-2 positive by PCR *post mortem* at autopsy. Age at death ranged from 19 to 91 years (table 1). 19 out of 46 (41.3%) were ⩽60 years old. Basic demographic information including prevalence of "COVID-19-relevant" comorbidities, symptoms and illness duration are summarised by table 1.

Lung findings

The lungs were generally heavier than normal reference weights [19] with the left lung median 754 g (range 320–1306 g) and 904 g for the right (range 445–1604 g). A median of seven blocks/case (range: 2–11) underwent histopathological evaluation. Pulmonary oedema and congestion were reported most frequently, featuring in 41 out of 46 cases (89.1%). Pneumonic consolidation featured in seven out of 46 (15.2%), focal haemorrhage in five out of 46 (10.9%) and pulmonary thromboembolism of medium-calibre arteries (1–10 mm diameter) and large-calibre arteries (>10 mm) in three out of 46 (6.5%). In five out of 46 cases (10.9%) a chronic respiratory condition was noted, including emphysema in four cases and pulmonary fibrosis in two cases (there was one case where both conditions were present).

Based on the clinical data, macroscopic findings and microscopic evaluation, the cases were grouped into four predominant disease phenotypes: 1) DAD; 2) acute (neutrophilic) bronchopneumonia (BRON); 3) pulmonary thromboembolism (PTE) of medium- and large-calibre arteries; and 4) pulmonary oedema due to presumed acute cardiac failure (PO-PACF) (figure 1). Since pulmonary oedema is a feature of the very early exudative phase of DAD, cases with pulmonary oedema without evidence of exudative/proliferative alveolar damage and within the context of concordant clinical and pathological findings were defined as PO-PACF.

DAD was the most frequent dominant histopathological phenotype, expressed in 26 out of 46 cases (56.5%), with 25 out of 26 in a predominantly exudative phase and just one case, who had had a 21-day illness duration, where the organising phase represented the dominant injury. BRON featured as a dominant phenotype in 11 out of 46 (23.9%), PO-PACF in seven out of 46 (15.2%) and PTE in two out of 46 (4.3%).

TABLE 1 Cohort demographics and clinical metadata (n=46)

Characteristics	Data (% cohort)
Age years	
Median	64
Range	19–91
Sex, female	22 (47.8)
Ethnicity	
White	43 (93.5)
BAME	3 (6.5)
Duration of illness days	
Range	0–23
Mean	5.9
Median	5
Symptoms (n=where symptoms known)	
Respiratory (n=37)	22 (59.5)
Fever (n=37)	8 (21.6)
Enteric (n=37)	4 (10.8)
Systemic (n=37)	20 (54.1)
Asymptomatic (n=37)	3 (8.1)
Nil or "mild" lower respiratory tract symptoms (n=37)	17 (45.9)
Comorbidities	
Pre-existing cardiac disease	14 (30.4)
Hypertension	12 (26.1)
Diabetes	8 (17.4)
COPD/asthma	10 (21.7)
Chronic kidney disease	8 (17.4)
Significant smoking history	8 (17.4)
Obesity	19 (41.3)
Dementia	6 (13)
1+ of above comorbidities	25 (54)

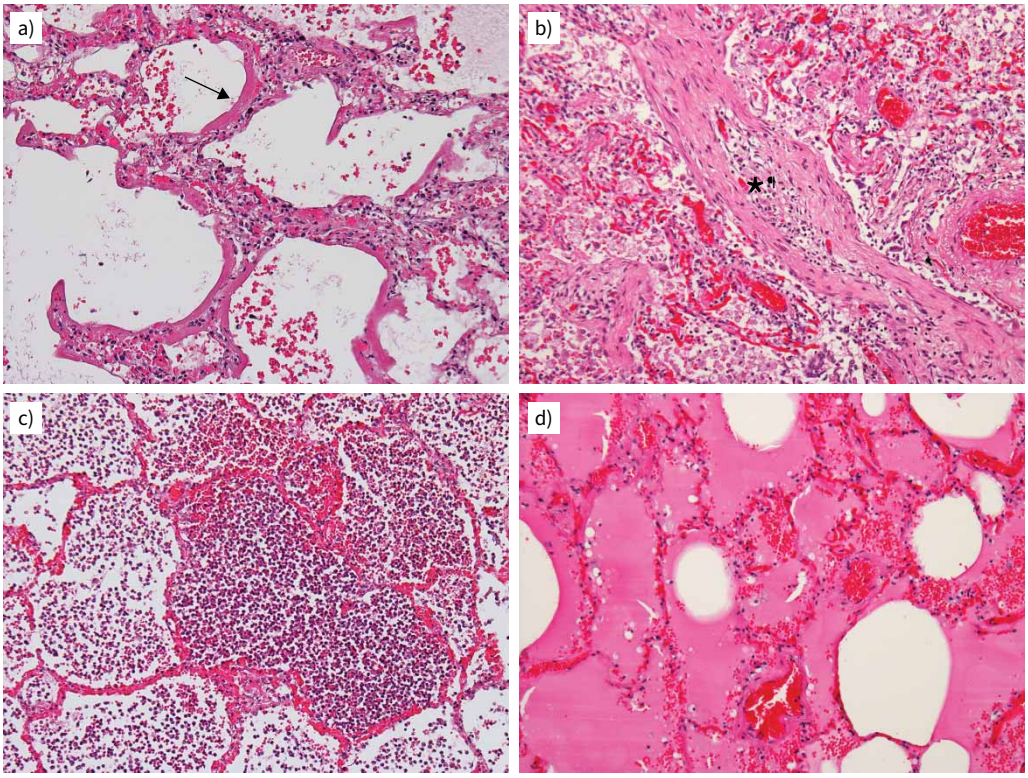

FIGURE 1 Haematoxylin and eosin (HE)-stained *post mortem* lung sections – dominant pathology phenotypes. a) Diffuse alveolar damage (DAD) exudative phase featuring hyaline membranes (arrow) and alveolar walls congested with infiltrating mononuclear cells and associated cellular debris and minimal alveolar haemorrhage (HE ×100). b) DAD organising phase featuring proliferating myofibroblasts (*) within the alveolar duct airspace along with substantial alveolar damage (HE ×100). c) Acute bronchopneumonia featuring prominent intra-alveolar neutrophilic inflammation (HE ×100). d) Pulmonary oedema, consistent with probable acute cardiac failure, characterised by a diffuse distribution of eosinophilic intra-alveolar space transudate along with alveolar capillary congestion and focal intra-alveolar haemorrhage (HE ×200).

There was a degree of overlap among these patterns of disease with 10 out of 46 (21.7%) revealing a secondary pathology (figure 2). The most common pathologies to overlap were DAD and BRON, seen in four out of 46 (8.7%).

Two other pathological features observed were microthrombi, which featured in 15 out of 46 cases (32.6%, figure 3), and alveolar/perivascular lymphohistiocytic infiltrates in nine out of 46 cases (19.6%). The microthrombi in small vessels were predominantly platelet-rich and occurred in the context of DAD in 12 out of 15 cases, but also occurred in two cases of BRON and in one case of PO-PACF. The lymphohistiocytic infiltrates were also seen chiefly in DAD in six out of nine cases but also in two cases of PTE and one case of BRON.

DAD: the major pathological phenotype in community-based COVID-19 PMLT

DAD was the dominant pathology in 26 out of 46 (56.5%) cases. 25 out of 26 (96.2%) were in the exudative phase of DAD and one out of 26 (3.8%) was in the organising phase. Microscopic lesions ranged from incipient and patchy to more developed and widespread. The DAD group consisted of 12 females and 14 males. Respiratory symptoms were only explicitly reported prior to death on the *post mortem* report for 11 out of 26 (42.3%) of these cases.

Cases with DAD as the primary pathology were significantly younger than those with other phenotypes (57.6 years *versus* 70.6 years, p=0.02, figure 4a). Duration of illness ranged from 0 to 21 days (median 4.5 days) and was not significantly different to those with other phenotypes where the range was 0–23 (median 7 days) (p=0.6, figure 4b). The DAD group had a comparable comorbidity burden to those with

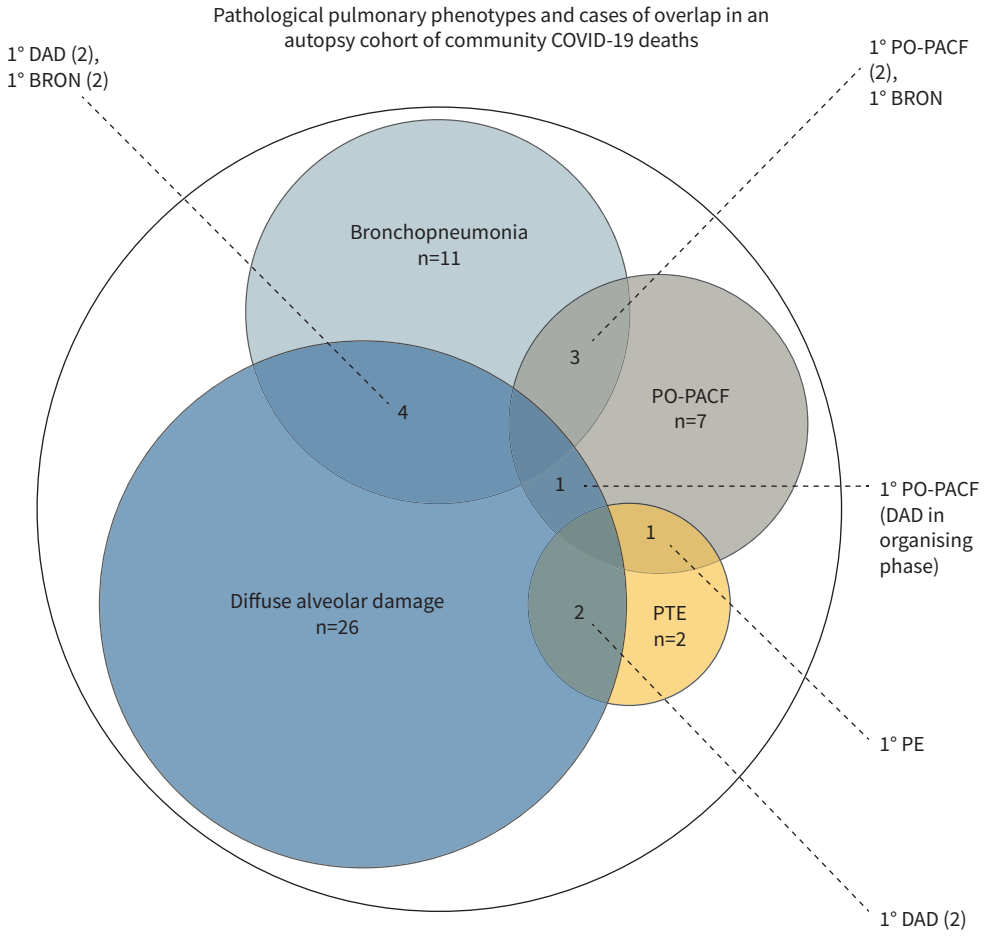

FIGURE 2 Pathological pulmonary phenotypes. Each circle represents total cases where this phenotype was predominant. Shared space between circles indicates all instances of overlap between pathology groups. In these cases, the primary pathology in each case is labelled as '1°' following dotted lines. Figure created in R. DAD: diffuse alveolar damage; BRON: bronchopneumonia; PO-PACF: pulmonary oedema–probable acute cardiac failure; PTE: pulmonary thromboembolism; 1°: primary pathology, indicated in cases of overlap between pathology types.

other dominant phenotypes. Of note, DAD cases had a significantly higher BMI than those with other phenotypes (35.7 $kg \cdot m^{-2}$ *versus* 24.35 $kg \cdot m^{-2}$, p=0.0002, figure 4c). Compared to other pathologies, cases with DAD had significantly greater mean heart weight (468 g *versus* 403 g, p=0.0439, figure 4d), right lung weight (986 g *versus* 740 g, p=0.002, figure 4e) and left lung weight (830 g *versus* 649 g, p=0.0079, figure 4f).

Other pathological phenotypes featuring in community-based COVID-19 PMLT

Bronchopneumonia was the dominant pathology phenotype in 11 out of 46 cases (23.9%). Five in this group were men, six were women. Respiratory symptoms were reported prior to death for six out of 11 (54.5%) cases. There were seven cases of PO-PACF, of whom two were female and five were male. Age ranged from 31–87 years (median=79). Illness duration ranged from 3 to 10 days (mean 7.2 days), indicating periods where symptomatic COVID-19 disease proceeded what appeared to be rapid deteriorations. Of interest, in two of these cases, microthrombi were present in small vessels within the myocardium but not in the lung parenchyma.

Pulmonary thromboembolism in medium- and large-calibre arteries was seen as the dominant histology in two out of 46 cases (4.3%). One was a 19-year-old female, the other an 87-year-old female. Pulmonary thromboembolism appeared as a secondary pathology in two cases, with DAD as the primary.

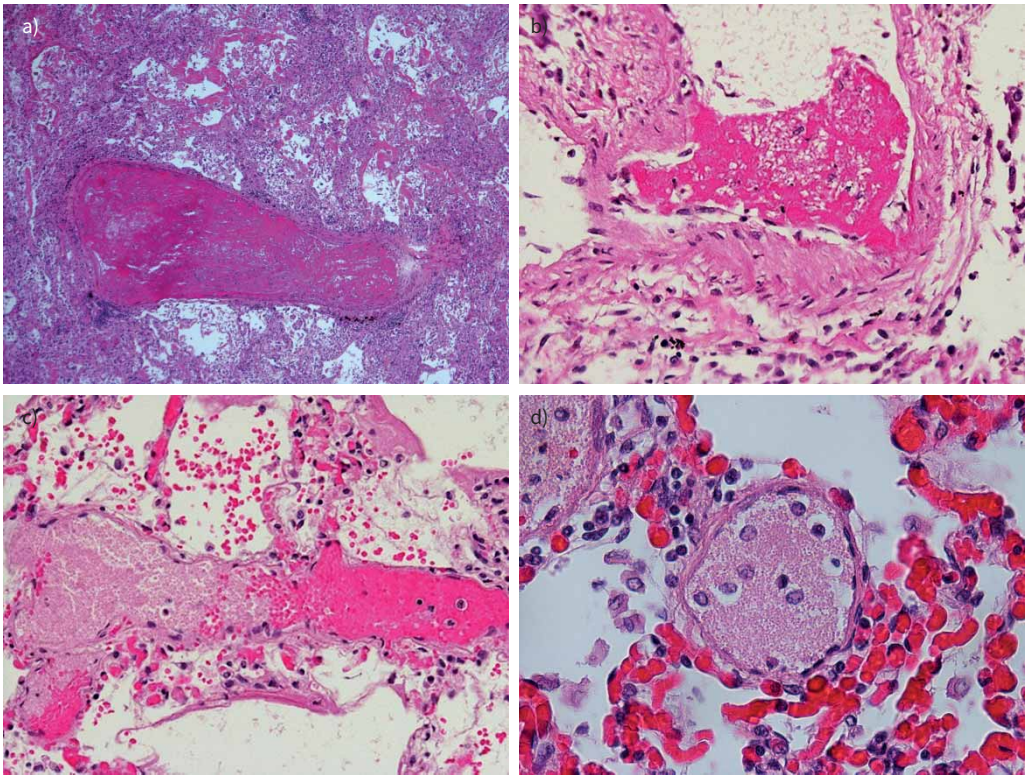

FIGURE 3 Haematoxylin and eosin-stained *post mortem* lung sections – thrombotic phenomena in lung tissue. a) Fibrin-rich pulmonary thromboembolism in medium-sized pre-acinar pulmonary artery, characterised by bright eosinophilic layered morphology, with surrounding lung parenchyma featuring exudative diffuse alveolar damage (HE ×40). b) Fibrin-rich pulmonary thrombi in intra-acinar pulmonary artery (HE ×200). c) Platelet-rich microthrombus causing dilatation of the vessel, with surrounding features of exudative DAD (HE ×200). d) Platelet-rich microthrombus causing expansion of small-sized intra-acinar pulmonary vessel (HE ×400).

Cardiac findings

Median heart weight was 427 g (range 230–700 g). The heart was described as "normal" in 13 out of 46 cases. In 14 cases, the heart was described as hypertrophic and in 12 out of 14 the heart weight was over 500 g. The expected normal heart weights are 365±71 g in men and 312±78 g in women [19].Ventricular dilatation was reported in seven cases. Severe coronary artery atheromatosis was reported in 10 cases, one of these had severe triple vessel atheromatosis, all others had involvement of one vessel including one case with critical stenosis. One heart showed a left ventricular posterior scar consistent with old acute myocardial infarction and another revealed acute myocardial infarction in the anterior ventricular wall.

A median of three (range: 0–6) full-thickness ventricular cardiac tissue blocks/case were examined. In one case of primary bronchopneumonia, cardiac microscopy revealed an acute infarction <48 h old (figure 5a,b). Thrombi in the heart were found in four cases. In one case, the thrombus was attached to the atrial side of the mitral valve and was predominantly composed of fibrin, with focal platelet-rich areas. The remaining three cases revealed microthrombi within small vessels (figure 5c,d).

Two cases revealed sparse lympho-histiocytic inflammatory foci without associated myocyte damage, but no cases with significant lymphocytic inflammatory infiltrates were seen.

The lung pathology phenotypes associated with cardiac pathologies are summarised in supplementary table S1. Notably, four cases of lung PO-PACF were associated with severe atheroma/thrombi and cardiomegaly (heart >500 g), while a fifth case appeared to be related to cocaine consumption.

Low symptom burden commonly features in those who died at home with COVID-19

20 out of 46 (43.5%) died with severe COVID-19-related lung disease with collateral evidence of a low symptom burden as defined above. Interestingly, 15 out of 20 (75%) of the low symptom burden cluster

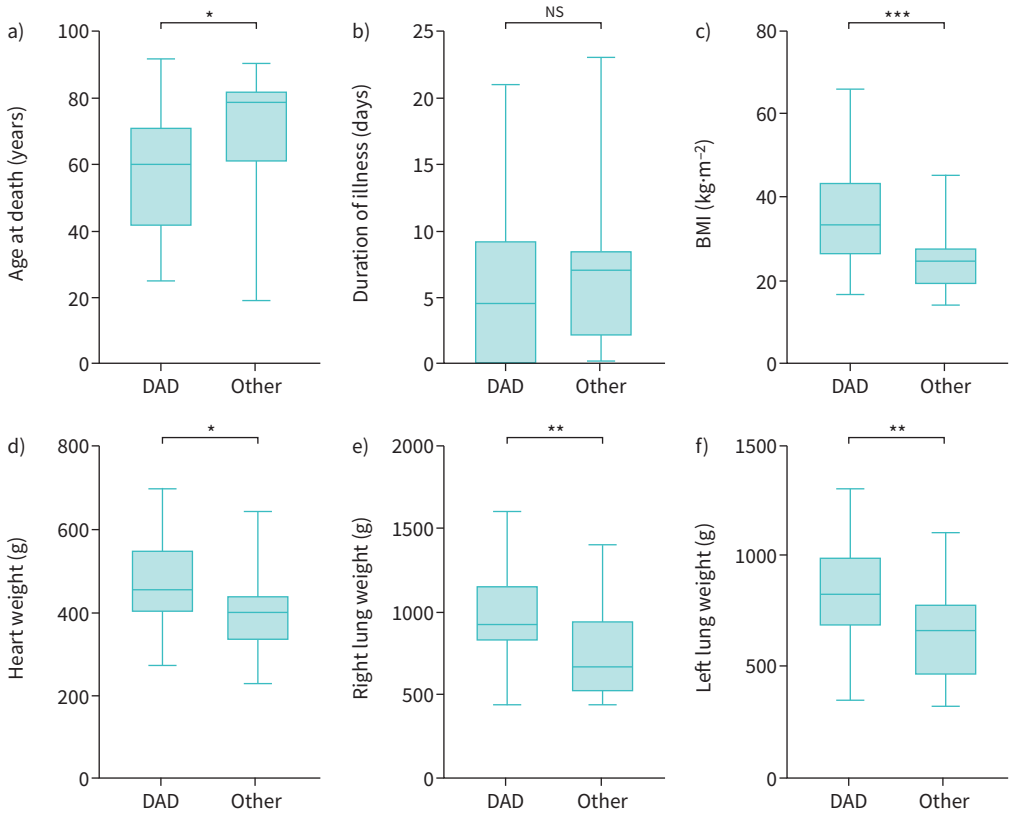

FIGURE 4 Comparative statistical analyses comparing diffuse alveolar damage (DAD) group with others with another dominant phenotype in a) age at death, b) duration of illness, c) body mass index (BMI), d) heart weight, e) right lung weight and f) left lung weight. NS: p>0.05; *: p⩽0.05; **: p⩽0.01; ***: p⩽0.001; ****: p⩽0.0001.

were in the DAD group. Psychosocial reasons for not presenting to hospital were cited in five cases. Four out of five of these cases had significant symptoms and would not have been considered to be in the "low symptom burden group". In two of these scenarios, first-responder emergency assistance was called for symptomatic COVID-19; however the individual died prior to ambulance arrival. In another two cases, ambulances were called by families due to concerns regarding symptomatic COVID-19; however on arrival the affected individual "declined going to hospital". In one instance, an individual sought advice from an urgent care service to be told their symptoms were too mild for hospital assessment. This patient was not included in the "low symptom burden" group as the qualifier "mild" was from the perspective of the urgent care service operative rather than the individual themselves or their family.

Discussion

This autopsy series offers unique insights into the natural history of COVID-19 in the absence of major pharmacological and medical interventions. Here we have described the clinical data, macroscopic findings and histopathology of a relatively young cohort of significant size compared to proceeding series [8–14] who died of the direct consequence of COVID-19 at home. Our key finding was that DAD was the most common pathological phenotype in community-based deaths, featuring in 56.5% of the cohort, consistent with similar case series [8–14]. The majority of the cohort were in the exudative phase of DAD with only one having progressed to a predominantly organising phase. This is in stark contrast to hospital-based series where the organising phase of DAD is more dominant. Although using different nomenclature, Li *et al.* (2021) [20] noted seven out of 30 (23%) of their cohort to be "organising predominant" and 12 out of 30 (40%) to be "fibrosing predominant". DAD in the community setting is an extremely unusual phenomenon [21]. DAD is the most common histological pattern in ARDS [15] and is usually associated with significant symptom burden, hospitalisation and intensive care requirements [15]. Katzenstein, one of the pathologists who originally described DAD [3], warned colleagues of caution when diagnosing DAD in patients not receiving mechanical ventilation [16]. This rule of thumb was applicable to community-based *post mortem* series prior to 2020; however the COVID-19 pandemic appears to have

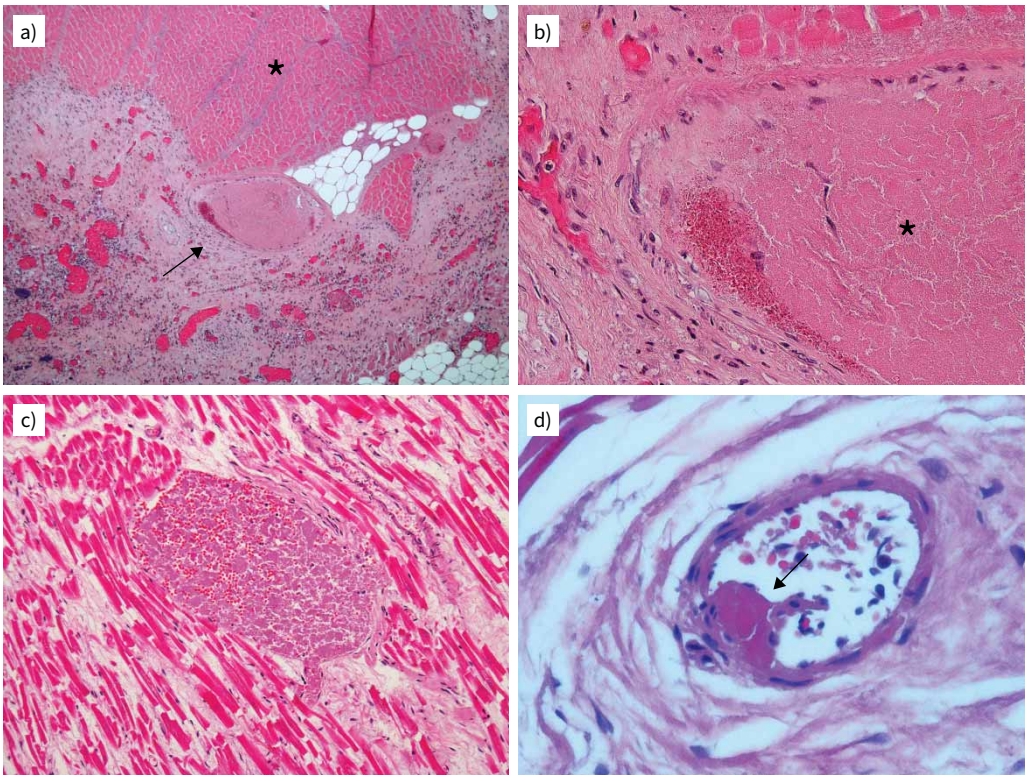

FIGURE 5 Haematoxylin and eosin-stained *post mortem* heart sections. a) Epicardial coronary artery blocked with thrombus formation (arrow), with associated recent (<48 h) acute myocardial infarction characterised by eosinophilic anucleated myocytes (*) (HE ×40). b) Same coronary arterial thrombus (*) at higher magnification, featuring its significantly platelet-rich composition (HE ×200). c) An intramyocardial coronary vessel (likely a vein) dilated due to a platelet-rich microthrombus, characterised by pale eosinophilic punctiform loose appearances (HE ×100). d) Fibrin-rich non-occlusive thrombus (arrow) attached to a small intramyocardial coronary artery wall, characterised by bright dark eosinophilic dense morphology and lack of platelet definition (HE ×400).

created a significant paradigm shift. COVID-19-associated DAD appears morphologically indistinct to DAD caused by other pathologies in histopathological analysis [22]; however subtle differences such as significantly increased pulmonary capillary microthrombi when compared to influenza DAD have been observed [23].

Hospital-based autopsy series have demonstrated significant heterogeneity of injury patterns in COVID-19 PMLT. Superimposed bronchopneumonia is common and can be bacterial [5] or fungal [24] in aetiology. Some patients have little to no lung involvement, with 11 out of 40 (27.5%) in one series having no specific acute lung injury features, typically dying of cardiac arrest and displaying pulmonary vascular congestion [6]. There is also a high incidence of pulmonary thromboembolism [25]. This heterogeneity has not, until now, been sufficiently reflected in community-based series. While DAD was our most common dominant pathology, this often "overlapped" with acute bronchopneumonia, acute cardiac failure and pulmonary thromboembolism. In other cases, these represented the dominant pathological picture.

Bronchopneumonia was the second most common dominant pathology pattern. Viral pneumonias such as influenza are well understood to predispose individuals to secondary bacterial infection through a range of mechanisms including architectural disruption and immune response alterations [26]. This also seems to be the case in COVID-19 [5], although the precise mechanisms underlying this emerging association require exploration.

Similarly, we documented seven cases with evidence of deterioration by acute cardiac failure. The pulmonary oedema seen in such cases represents a diagnostic challenge because it is itself an early feature of exudative DAD [3]. Therefore, to be confident enough that pulmonary oedema was likely associated

with acute cardiac failure, we combined cardiopulmonary macroscopic features and cardiac histology with an absence of hyaline membranes or alveolar damage in lung histology. This attempt to identify PO-PACF cases was deliberate since it is well known that COVID-19 infection might precipitate acute cardiac failure alone through hypoxic respiratory failure, cytokine and catecholamine dysregulation and unmasking of pre-existing cardiac conditions such as critical coronary occlusion and plaque destabilisation [5].

Consequently, it is important to consider lung findings alongside cardiac findings given the insults generated by SARS-CoV-2 on the entire cardiopulmonary unit. One large series of 2736 hospitalised COVID-19 patients found that myocardial injury was common (36%) but usually mild, and more frequent in patients with previous cardiovascular diseases [27]. In our cohort, 72% of the cases were considered to harbour a significant cardiac pathological abnormality, such as cardiomegaly, severe coronary artery atheromatosis, old and acute myocardial infarction and/or microthrombosis. Hence, because of this pathoclinical correlation, 15% of our cases were considered to have died of acute cardiac failure. Of interest, epicardial coronary arterial disease appears to be a risk factor, and cardiac failure may also be precipitated by cytokine storms, microthrombosis, myocarditis and hypoxaemia, perhaps in combination, leading to metabolic supply/demand mismatch [28]. Notably, Pellegrini *et al.* [29] differentiated between acute myocardial infarction (defined as area of necrosis $\geqslant 1$ cm^2) and focal myocyte necrosis (<1 cm^2), with the latter being more common (11 out of 14 cases) than the former (three out of 14 cases). Direct immune-mediated myocardial damage has been preliminarily investigated as well with Basso *et al.* [30] noting that only three out of 21 (14%) hearts had lymphocytic myocarditis and 18 out of 21 (86%) had increased interstitial macrophage infiltration by immunostaining, an element that was not investigated in our cohort.

The association between severe COVID-19, coagulopathy and thrombosis is an area of urgent pathophysiological investigation [31]. Pulmonary microthrombi were common in our cohort (15 out of 46 cases), and PTE was the primary pathology in two cases. COVID-19 is certainly also a systemic vascular disease given the significant endothelial dysfunction and endothelitis [23, 32], changes in platelet distribution and behaviour [33], and systemic coagulopathy that have been found [34, 35]. We can ascribe PTE as a direct cause of death in two patients and also as a concomitant severe phenomenon in two other patients who had DAD as their predominant pathology. Although the endothelial damage associated with SARS-CoV-2 may be one precipitant to thrombus formation, SARS-CoV-2 may cause coagulopathy through a variety of mechanisms including direct platelet infection, activation and aggregation [36].

Platelet-fibrin microthrombi are a common feature of COVID-19 autopsy series, present in 33 out of 38 (87%) in one series [4]. Thrombi are described as “white thrombi”, which are predominantly platelet-rich, and “red thrombi”, which are predominantly fibrin-rich [37]. In our cohort, the small-vessel microthrombi in the lungs were also predominantly platelet-rich, in agreement with findings from Rapkiewicz *et al.* [33]. Conversely, Pellegrini *et al.* [29] noted that cardiac microthrombi in COVID cases were significantly richer in fibrin when compared to their control non-COVID counterparts. Microthrombi occurred in the context of DAD in 12 cases, but also in two cases with bronchopneumonia and one case of acute cardiac failure without DAD, indicating these microthrombi may not be directly related to COVID-19 pneumonitis but to COVID-19-associated coagulopathy.

Classically, thrombi seen in the setting of non-COVID-related DAD tend to be “fibrin-rich” [16]. Extensive platelet-rich microthrombi used to be a rarity, with only a few cases reported in post-liver and post-lung transplant pathology [38, 39]. Therefore, platelet-rich microthrombi may also be particular to COVID-19. Indeed, Nishikawa *et al.* [40] showed excessive platelet aggregates in 90% of COVID-19 patients, these being linked with disease severity, mortality, severity of respiratory condition and vascular endothelial dysfunction. Interestingly, there were cases in this cohort with low D-dimers (cross-linked fibrin monomers), indicating platelet aggregation with relative absence of significant fibrin activity. Platelets, which express angiotensin converting enzyme 2 (ACE2) and TMPRESS2, can be functionally hyperactive when isolated from COVID-19 patients, and in *in vitro* and murine models, the SARS-CoV-2 spike protein has been shown to bind to platelets and enhance activation activities including aggregation and the release of coagulation and inflammatory factors [35].

By comparing DAD case demographics to all other dominant pathological lung phenotypes in our cohort, we found some notable differences including a younger age profile and obesity. Obese patients may be more likely to contract SARS-CoV-2, are more likely to have concurrent comorbidities, have reduced capacity to mount innate and adaptive immune responses including to vaccination, and have increased morbidity and mortality in COVID-19 [41]. Obesity was the most common comorbidity in our cohort, and we suspect that reduced respiratory reserve may have contributed to more rapid progression of pre-hospital deaths.

We hypothesised that a low symptom burden may have led to a failure of hospital presentation and found it to be a frequently represented narrative in community-based COVID-19 deaths. The low symptom group were asymptomatic or had mild or absent lower respiratory tract symptoms, yet clearly died with pathological features of significant COVID-19 lung disease. The majority of this group (15 out of 20, 75%) had DAD as their predominant lung pathology. To our knowledge, this is the first attempt at estimating the symptomatic burden of COVID-19 sufferers prior to death in the community setting. We suspect that this low symptom burden might be at least partially explained by the phenomenon of "silent hypoxaemia", whereby COVID-19-affected individuals might display pronounced arterial hypoxaemia due to severe lung pathology in the relative absence of dyspnoea [42]. Prevalence is estimated at 20–40% [17] with several possible underlying mechanisms postulated including direct viral effects on ACE2-expressing peripheral chemoreceptors [43], nasal mucosa [44] and central respiratory centres [45] as well as indirect modulatory effects *via* immune-mediated inflammatory mediators [46]. Relatively preserved carbon dioxide clearance may mask symptoms given respiratory centre sensitivity to hypercapnia rather than hypoxaemia [47]. Blunting of respiratory centres with age and diabetes [47] may contribute but does not offer an explanation in our cohort, which was relatively young with a low prevalence of diabetes (eight out of 47, 17%). Compared to "typical" ARDS, COVID-19 lungs demonstrate relatively preserved compliance [48] suggesting potential for preserved signalling *via* juxtacapillary J stretch mechanoreceptors [42]. Early exudative DAD, especially if incipient, as well as microthrombosis may underlie a large ventilation–perfusion mismatch but confer relatively preserved lung mechanics compared to congested, organising and fibrotic lungs associated with late DAD and bronchopneumonia. This would fit with our cohort where 96.2% of DAD cases were considered predominantly exudative DAD. Compliance is intricately linked with surfactant production, and it has been hypothesised that early preservation of its production may partly underlie silent hypoxaemia [49]. However, surfactant-producing Type II pneumocytes are the principal ACE2-expressing cells in the lungs [50], become virally infected [4] and do downregulate surfactant genes [51].

Other reasons cited that may have precluded hospital admission included psychosocial factors and healthcare resource factors. Fear of visiting hospital during the pandemic has been widely reported with deaths attributable to delayed presentation due to fear [52]. We can speculate that fear, stoicism and reluctance to further burden an overstretched healthcare system may have contributed. Concerningly, one individual sought advice from a medical advice service and was told they did not have enough symptoms for hospital assessment. Knowing that severe histological disease and a low symptom burden can coexist, clinicians may consider a lower threshold for face-to-face assessment in the future.

Limitations

Autopsy series are fundamentally limited in that they only reflect the final frame of disease progression. The clinical data obtained for this study were limited by the information provided from collateral history provided by next of kin and recorded in *post mortem* reports. Reporting of macroscopic features and tissue sampling were performed by pathologists with differing degrees of expertise in cardiopulmonary pathology. Sampling of organs for histological evaluation was not uniform across all cases, although we felt our high lung tissue block average was sufficient to draw robust conclusions in all cases. Our cardiac tissue block sampling was lower yet was still useful to understand the cardiac pathology in some cases but not universally. These limitations were mitigated with all clinical data and microscopic data reviewed by a consultant histopathologist with cardiothoracic expertise. Although all the autopsies fulfilling the inclusion criteria were included, the cohort reported in this study may have a selection bias towards unexpected and unexplained deaths, and as a result younger people with low reported symptom burden would be more likely to be selected for HM Coroner autopsy. We did not collect information pertaining to the socioeconomic circumstances of individuals, but given the NHS has universal free at the point of care coverage we suspect socioeconomic disadvantage plays a more limited role than it might in some other countries.

Conclusion

This study reveals that heterogeneous, overlapping and severe COVID-19 lung disease pathologies occur in the pre-hospital community-based setting. Published autopsy series are the virtual sepulchres of the COVID-19 era and their clinical narratives the "epitaphs" providing the context required to appropriately interpret tissue findings. DAD commonly featuring in community autopsies represents a paradigm shift of this era and one explanation might include unsensed hypoxaemia, a clinical phenomenon that should be put under the microscope.

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