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WHAT IS THE BURDEN OF ASPERGILLOSIS AND OTHER OPPORTUNISTIC FUNGAL INFECTIONS IN PATIENTS WITH SEVERE INFLUENZA AND COVID-19 IN THE ICU?

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Background Co-infection with *Aspergillus* previously described to cause significant morbidity and mortality in those with severe Influenza, has more recently been described in COVID-19. 'Influenza-Associated Pulmonary Aspergillosis' (IAPA) and 'COVID-Associated Pulmonary Aspergillosis' (CAPA) have been reported in up to 23% and 35% of severe disease, respectively. Establishing evidence of invasive Aspergillosis (IA) in these patients is challenging, requiring specific clinical, radiological and microbiological criteria. The burden of IAPA and CAPA in the ICU in our region is unknown.

Aims To identify the incidence of invasive Aspergillosis (IA) and other opportunistic fungal infection in those with severe Influenza and COVID-19 in a district general hospital, Fife, Scotland.

Methods Retrospective cohort review of ICU admissions with severe Influenza or COVID-19 from May 2017 - February 2021. IA was diagnosed using international definitions according to EORTC/MSG, AspICU and modified AspICU criteria.

Results 89 patients were identified with Influenza (27; median age 53.3 yrs, male 56%) and COVID-19 (62; median age 59.1 yrs, male 61%). No case satisfied criteria for definite IA, however, the majority of patients did not undergo all relevant tests; CT imaging features in 26/89 (29.2%), and fungal biomarkers in 3/89 (3.4%). Two patients demonstrated *Aspergillus* culture from respiratory samples but did not meet other criteria. Fungal infections were identified in 39/89 (44%), the majority *Candida* (37), mostly from ET secretions (54%). *Candida* was significantly higher in COVID-19 than in Influenza, including 2 patients with *Candidaemia*. Positive fungal culture was associated with increased length of stay (43d vs 20d), ICU bed days (26d vs 19d), but not mortality (33.3% vs 30.0%). Few patients (7.9%) received antifungal treatment, with possible explanations including unclear diagnosis, high costs, uncertain benefit. 54/89 (60.7%) demonstrated bacterial co-infection, including 31/89 (34.8%) with bacteraemia (COVID, 23; Influenza, 8).

Conclusions IAPA and CAPA were not identified in this 4-year cohort, although case finding was limited by inadequate diagnostics. Timely access to fungal biomarkers compromises diagnostic testing. The incidence is likely to be low, despite the significant study limitations. We recommend prospective systematic practice of investigations and improved fungal diagnostics to better understand the burden of Aspergillosis in these patients.

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COMPARISON OF INFLAMMATORY PROFILES BETWEEN COVID-19 AND OTHER ACUTE LOWER RESPIRATORY TRACT INFECTIONS: RESULTS FROM THE PREDICT-COVID19 STUDY

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Introduction COVID-19 has been reported to induce a 'cytokine storm' distinct from other acute respiratory tract infections (LRTIs). Understanding the similarities and differences in inflammatory profiles between SARS-CoV-2 infection and other respiratory infections may aid diagnosis, as well as the potential to repurpose therapies such as steroids and anti-IL-6 receptor antagonists for other respiratory infections.

Methods A prospective observational study of patients in 3 groups 1) PCR confirmed SARS-CoV-2 infection, 2) community-acquired pneumonia (CAP) without SARS-CoV-2, and 3) controls hospitalized for reasons other than infection. Patients were enrolled from a single centre in Dundee, UK. Patients were enrolled within 96 hours of hospital admission. 45 inflammatory biomarkers were measured in blood using the Olink target proteomic based biomarker panel. Additional markers were measured by ELISA/immunoassay and enzyme activity assay as appropriate. Discrimination between groups was evaluated using the area under the receiver operator characteristic curve (AUC).

Results 294 patients were included (COVID-19 n=176, CAP n=76, controls n=42), mean age 64 (SD±15.2) and 150 subjects were male (51.0%). Using ROC analysis the most discriminating biomarkers for COVID-19 compared to CAP were CXCL-10 (AUC 0.84 95%CI 0.78–0.90 p<0.001), CCL-8 (0.87 95%CI 0.82–0.92, p<0.001), CCL-7 (0.84 95%CI 0.78–0.89, p<0.001), CXCL-11 (0.80 95%CI 0.73–0.88, p<0.001). Further biomarkers included IL-18, IL-7, IL-10 and IL-33. The most discriminating biomarkers for COVID-19 compared to controls were CXCL-10 (0.89 95%CI 0.85–0.93, p<0.001), CCL-7 (0.88 95%CI 0.83–0.92, p<0.001), CCL-8 (0.87 95%CI 0.82–0.92, p<0.001). Further biomarkers included IL-10, CXCL-11 and IL-18. IL-4 was significantly lower in COVID-19 patients compared to controls (0.27 95%CI 0.16–0.38, p<0.001). No significant difference in IL-6 was seen between COVID-19 and CAP (median 21.9pg/ml vs 19.8pg/ml, p=0.59).

Conclusion Differential markers of inflammation were identified between COVID-19, CAP and control samples, indicating distinct immunological pathways. The identification of a similar IL-6 signature between COVID-19 and CAP indicates that IL-6 targeting therapies currently being used to treat COVID-19 may also be beneficial in the treatment of CAP.

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INFLUENZA AND COVID-19 PNEUMONIA: THE DIFFERENCE IS PULMONARY HYPERTENSION

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Purpose To describe the incidence of pulmonary artery thrombosis in COVID-19 versus influenza pneumonia using CT angiography and to assess whether it may increase the risk of pulmonary hypertension.

Materials and Methods Single and dual energy CT pulmonary angiography of age- and gender-matched patients with influenza and COVID-19 pneumonia, referred for extra-corporeal membrane oxygenation (ECMO) and/or mechanical ventilation from January 2016 to January 2021, were retrospectively evaluated. Two independent observers qualitatively and quantitatively assessed clot burden and Qanadli CT Obstruction Index. Two consensus observers calculated pulmonary artery volume

and right to left ventricular diameter ratio (Terarecon, California, USA) to diagnose pulmonary hypertension. Pulmonary infarct volume and perfused blood volume relative enhancement were also calculated (Syngo via, Siemens Healthineers, Forchheim, Germany). All radiologic parameters were correlated with clinical data. To assess if *in situ* thrombosis could be visualised on CT, isolated segmental and subsegmental filling defects were used as an imaging surrogate. For statistical analyses, Graphpad Prism9 and IBM SPSS v27.0 software were used.

Results The incidence of either central PE or DVT was equal between patients with COVID-19 and influenza pneumonia (20%). The incidence of isolated segmental and subsegmental filling defects was higher in COVID-19 but without statistical significance (44% vs 32%; $p=0.5607$). Right to left ventricular diameter and pulmonary artery to aorta ratios were higher in COVID-19 compared to influenza (1.01 vs 0.866 and 1.04 vs 0.904; $p=0.0071$ and $p=0.0023$, respectively).

Conclusion In a comparable group of patients with severe COVID-19 and influenza pneumonia, CT features of pulmonary hypertension are more often present in patients with COVID-19 pneumonia despite an equal clot burden on CT. This is not attributable to pulmonary thrombosis visible on CT and supports the hypothesis that micro- rather than macrovascular obstruction is the cause of severe hypoxia in COVID-19 pneumonia.

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ELEVATED D-DIMERS IN COVID-19 PATIENTS PREDICT PE BUT CAUTION IS NEEDED WITH HIGHER THRESHOLDS

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Introduction and Objectives COVID-19 is associated with a pro-inflammatory, hypercoagulable state, increasing the likelihood of developing pulmonary embolism (PE). Higher D-dimer levels have been noted in COVID-19 patients compared to the general population, which may lead to over-investigation by computed tomography pulmonary angiography (CTPA) if traditional thresholds (positive $\geq 0.5\text{mg/L}$) are used. We aimed to investigate whether a higher D-dimer threshold could be used.

Methods A retrospective observational study was performed at Barking Havering and Redbridge University Hospitals NHS Trust from April 2020 - March 2021. The study included a cohort of confirmed/suspected cases of COVID-19 requiring hospital admission. D-dimer level on admission, CTPA outcome and requirement for intensive care unit (ICU) admission were analysed to assess D-dimer as a predictor of PE and clinical outcome in COVID-19.

Results In 404 patients included, mean D-dimer was 3.03mg/L . 186 (46%) underwent CTPA, 32 (17%) of which detected PE. In those with PE, mean D-dimer was (8.62mg/L) , significantly higher than those without PE (2.55mg/L) ($P < 0.0001$). Patients admitted to ICU had a significantly higher D-dimer (4.35mg/L) than those who were not (2.69mg/L) ($P = 0.049$). Applying the traditional threshold of 0.5mg/L resulted in a sensitivity of 97% and specificity of 10% for detecting PE. Using higher thresholds of 1.0mg/L and 2.0mg/L

resulted in sensitivity of 87% and 71%, and specificity of 37% and 69%, respectively.

Conclusions Our data strongly suggests that higher D-dimer levels are associated with disease severity e.g. complication with PE and requirement for ICU admission. Caution is needed as higher thresholds of 2.0mg/L or greater, as suggested in previous studies,¹ would have resulted in an unacceptably low sensitivity in this cohort. Our study highlights the need for further work evaluating use of adjusted D-dimer thresholds in patients with acute COVID-19 to aid decision making and help balance the risks of radiation associated with CTPA and consequences associated with missed diagnosis of PE.

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PULMONARY VASCULAR DISEASE IN COVID-19: INSIGHTS FROM ARTIFICIAL INTELLIGENCE ANALYSIS IN A LARGE MULTICENTRE IMAGING DATABASE

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Aims and Objectives An increased incidence of pulmonary thrombosis (PT) and right ventricular (RV) dysfunction is reported in COVID-19. The clinical significance is not fully understood and there are few large, multicentre studies. The National Covid-19 Chest Imaging Database (NCCID) was analysed for prevalence of PT in COVID-19 patients; we hypothesised associations between macroscopic PT, severity of parenchymal disease, evidence of RV dysfunction on CT and mortality.

Methods NCCID is a multicentre UK-wide centralised database comprised of radiological images from hospitalised COVID-19 patients. 391 thoracic contrast CT scans from 14 centres across England and Wales performed between 2nd March 2020 - 10th September 2020 underwent automated post-processing software (IMBIO LLC.) to determine RV:LV diameter ratio. Scans were manually reported for PT and quantitatively scored for arterial obstruction and severity of parenchymal involvement using CT-Severity Scoring (CT-SS)[1]. Imaging metrics were analysed for association with PT and 30 day mortality.

Results Automated RV:LV analysis was successful in 90% (351/391) of scans. Mean age: 64, 53% (186/351) male. Mortality data was available for 325 patients: 22 died within 30 days of scan (6.7% (22/325)).

Macroscopic PT was present in 16% (56/351). Median Qanadli score was 6% (IQR 3%-17.5%), indicating low burden arterial obstruction. PT was not associated with mortality ($p=0.18$).

RV:LV >1 on CT was observed in 59% (206/351) (mean RV:LV 1.08). RV:LV was significantly higher in the presence of PT (mean RVLV 1.17 vs 1.06 $p=0.011$, $\chi^2(2) = 6.499$). RV:LV was not predictive of mortality (AUC 0.467, CI 0.358-0.576).

CT-SS significantly predicted mortality (AUC 0.787, $p < 0.0005$, CI 0.693-0.881). However there was no correlation between severity of parenchymal involvement and RV:LV