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O1209 MicroCT-derived biomarkers for longitudinal evaluation of sublethal influenza mouse models

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Background: Both seasonal and pandemic influenza infections can cause pulmonary complications, associated with important morbidity, mortality and health-care costs. Preclinical experimental influenza models are used to investigate the pathogenesis of viral pneumonia and the efficacy of novel antiviral and immunomodulatory drugs. Standard evaluation of disease in mouse models requires sacrifice, thereby limiting read-outs to a single time point. We therefore investigated the potential of microCT to follow-up influenza pneumonia longitudinally *in vivo*.

Materials/methods: We challenged C57BL/6N mice intranasally with 10 PFU of influenza A/Ishikawa/7/82 (n=14) or PBS (control, n=4). Body weight and clinical assessment were combined with lung imaging using small-animal µCT (SkyScan 1278, Bruker microCT) on a daily basis, starting one day prior to inoculation. We assessed six different imaging-derived lung biomarkers: total, aerated and non-aerated lung volume, and mean densities of these three volumes. Animals were sacrificed at various time points up to day 12 for evaluation of virus replication from lung homogenates by CCID-50 assay on MDCK cells, and for comparison of standard histology with imaging findings on day 6.

Results: Influenza inoculation results in heterogeneous lung lesions, ranging from hyperintense patches surrounding the airways, indicating local inflammation, to consolidation of entire lobes. Non-aerated lung volume, total lung volume and mean density of non-aerated lung volume increased significantly by day 6 ($p=0.0002$, $p=0.002$, $p=0.0001$ respectively), while the mean density of the aerated lung volume starts decreasing at day 2 up to day 5 post-inoculation, indicating airtrapping. Other imaging biomarkers did not show longitudinal changes upon influenza-inoculation. Though viral replication peaks at day 2 after inoculation, lung scan biomarkers and weight changes only become apparent in a later stage (at day 6) with persistence of lung lesions after recuperation of weight loss and viral clearance.

Conclusions: Low-dose µCT provides valuable visual insights and quantitative biomarkers for longitudinal follow-up of morbidity and dynamic disease processes with high temporal and spatial resolution in a sublethal influenza pneumonia mouse model. This non-invasive read-out has direct applications towards development of novel mouse models, and vaccine and drug screening *in vivo*.

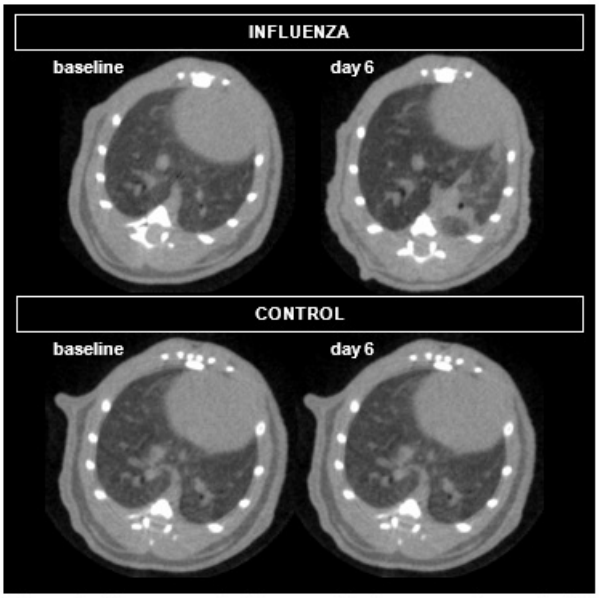

Figure 1: Representative images of influenza and control mice.