Harmonized Assessment and Quality Control of Quantitative Measures of Lung Structure on Pre-pandemic Cardiac and Lung Computed Tomography (CT) Scans for Large-scale Investigation of Risk of Long COVID-19: The Collaborative Cohort of Cohorts for COVID-19 Research (C4R)

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RATIONALE: Susceptibility to severe COVID-19 and long COVID may be influenced by pre-existing lung structure. ECG-gated, non-contrast cardiac CT scans, originally acquired for assessing coronary artery calcium, are available in multiple longitudinal cohort studies and have been previously validated against lung CT scans for densitometry; however, protocol variation across cohorts may hinder direct comparison. To address this, we developed a quality control (QC) rubric to grade cardiac CT scans for standardized quantitative lung measures across cohorts. **METHODS**: C4R assessed SARS-CoV-2 infection and outcomes in 14 NHLBI cohorts, of which 10 (six community-based and four longitudinal case-control studies) included CT scans (12,459 participants with lung and 13,752 with cardiac CTs). Logic rules were applied to categorize scans **(Table)**: Grade "A-B" scans had 2-3.5mm slice thickness, at least 20 axial slices, no lung cropping in axial view and lung and airway volumes greater than the cohort-specific 1st percentile. "C-D" scans had one lung obscured by cropping around the heart, so quantitative measures were restricted to the lung in complete view. "F-H" scans were deemed unusable, suffering from low slice count (<20), severe image cropping, low lung or airway volumes (< 1st %ile). Visual inspection was performed on a sample from each category to ensure accuracy. Percent of lung voxels in low attenuation areas < -950 HU (LAA_{950}), high attenuation areas (-600 to -250 HU, HAA) and 15th percentile HU value (perc15) were measured. Within-participant variability was quantified using the intraclass correlation coefficient (ICC). **RESULTS**: We performed QC on cardiac CT scans from an initial sample of 6,275 participants from three C4R cohorts (ARIC, CARDIA, MASALA), imaged with GE or Siemens scanners. Of these, 5,125 (81.7%) were graded "A-B", 496 (7.9%) were "C-D" and 654 (10.4%) were "F-H". The percentage of "F-H" scans varied widely across cohorts [<1% to 26%] due to image cropping. Among the 5,621 cardiac CT scans graded A-D, the mean±SD for LAA_{950}, HAA and perc15 respectively were 1.1±2.1%, 7.2±4.7% and -887±33 HU. Repeated imaging was available for 107 participants (time interval 5.1±0.7y). For paired scans in grades A-B (n=101/107), the within-participant correlation for LAA_{950}, HAA and perc15 were 0.91, 0.38 and 0.74 respectively. **CONCLUSION**: Initial application of QC to cardiac CT scans identified scans with high reproducibility, with the aim to provide valid quantitative lung metrics on over 20,000 highly characterized participants in C4R.

Table: Harmonized cardiac CT scan quality control grading labels for lung structure measures

QC Grade	A	B	C	D	E †	F	G	H
*Suitability for image analyses**	*Suitable*	*Suitable w. apical lung*	*Suitable for one lung*	*Suitable for one lung*	*Small lung or airway vol.*	*Unsuitable, few/thick slices*	*Unsuitable, cropped lungs*	*Unsuitable, combo of E-G*
Image criteria:								
Left lung volume**	>1st %ile	>1st %ile	>1st %ile	>1st %ile	Any volume ≤ 1st %ile	>1st %ile	>1st %ile	Any volume ≤ 1st %ile
Right lung volume**	>1st %ile	>1st %ile	>1st %ile	>1st %ile		>1st %ile	>1st %ile	
Airway volume**	>1st %ile	>1st %ile	>1st %ile	>1st %ile		>1st %ile	>1st %ile	
# Axial slices	≥ 20	≥ 20	≥ 20	≥ 20	≥ 20	**< 20**	≥ 20	≥ 0
Slice thickness (mm)	2-3.5	2-3.5	2-3.5	2-3.5	2-3.5	**> 3.5**	≥ 2	≥ 2
Length of Trachea (mm)[1]	**≤45**	**> 45**	≤45	**>45**	Any	Any	Any	Any
# lungs with full axial view	2	2	**1**	**1**	2	2	**0**	≥ 0
Manual Regrading: # or % checked scans‡								
	n=100	10%	10%	10%	**n=All†**	10%	10%	10%
Validity of qCT measure: LAA_{-950}, LAA_{-910}, %HAA, perc15								
	Valid	Valid	Valid(a)	Valid(a)	-	Invalid	Invalid	Invalid

Note. – Abbreviations: qCT, quantitative CT-derived lung structure measures; LAA_{-950}, percentage of lung voxels with value < - 950 HU; LAA_{-910}, percentage of lung voxels with value < - 910 HU; %HAA, percentage of lung voxels with value > - 600 HU and < -250 HU; perc15, 15th percentile HU value across lung voxels. *Suitability is in reference to lung analyses only. [1] 45mm=Max trachea length imaged on cardiac CT in MESA Exam 5. **Cohort dependent percentiles. Scans in 1st percentile comprised a mix of participants with small lung volumes and others with severe CT-artifact, evidence of lung surgeries, anatomic region of interest not captured. ‡Scans are selected at random for manual regrading. †Grade E is provisional, all scans are visually examined to assess suitability. (a) Measures are reported only for the lung with no axial cropping

This abstract is funded by: The American Lung Association. NIH/NHLBI OT2HL156812, R01-HL121700; The Atherosclerosis Risk in Communities study has been funded under Contract nos. (75N92022D00001, 75N92022D00002, 75N92022D00003, 75N92022D00004, 75N92022D00005) from the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), Department of Health and Human Services. CT scans to evaluate coronary artery calcium and extra-coronary calcium in ARIC were supported by R01HL136592.The Mediators of Atherosclerosis in South Asians Living in America (MASALA) was supported by R01HL093009 from the NHLBI, the National Center for Research Resources and the National Center for Advancing Translational Sciences, NIH, UCSF-CTSI Grant Numbers UL1RR024131, UL1TR001872. The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by contracts 75N92023D00002, 75N92023D00003, 75N92023D00004, 75N92023D00005, and 75N92023D00006 from the NHLBI.