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CXR-Age Gap: Deep Learning Biological Age Estimation from Chest X-Rays Predicts Mortality

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Background: Biological age diverges from chronological age and more strongly predicts mortality. Current biomarkers such as epigenetic clocks are expensive, slow, and inaccessible in routine care. Chest X-rays (CXR) are universal, cheap, and encode structural aging signatures. We hypothesized that the discrepancy between AI-predicted and true age from CXR (the CXR-Age Gap) captures biological aging and predicts mortality.

The aim: To develop a deep learning model estimating biological age from chest X-rays and evaluate whether the CXR-Age Gap independently predicts 30-day, 90-day, and 1-year all-cause mortality.

Materials and methods: We collected 404,812 frontal CXRs from five public datasets across three continents (MIMIC-CXR, CheXpert, PadChest, RexGradient, CASIA), paired with verified age, sex, and race. DenseNet-121 was trained in two stages: broad training on all images then fine-tuning on normal CXRs. An 80/20 split was strictly enforced. Logistic regression and Cox proportional hazards models assessed mortality associations, adjusting for age, sex, race, and comorbidities. AUC was compared between a clinical baseline and a model augmented with the gap.

Results: On 80,000 held-out images, MAE was 3.6 years and Pearson $r=0.85$. Mean gap was -0.2 years with no systematic bias. Each 5-year gap increase was associated with 22% higher adjusted odds of 30-day mortality, 25% for 90-day, and 18% higher hazard of 1-year mortality (all $p<0.001$). Adding the gap improved AUC from 0.79 to 0.83. Two-stage training outperformed normal-only (MAE 4.7) and all-data strategies (MAE 5.3).

Conclusions: The CXR-Age Gap is a clinically interpretable, universally accessible biomarker of biological aging derivable from routine imaging. It independently predicts short- and long-term mortality beyond established clinical variables, improving prognostic discrimination. Saliency mapping confirmed the model attends to anatomically meaningful aging structures — heart, mediastinum, pulmonary vasculature — without explicit supervision.

Keywords: biological age, chest X-ray, deep learning, mortality prediction, CXR-Age Gap, DenseNet-121