TH-PO566

Computational Assessment of Early Diabetic Nephropathy

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Background: Patients with diabetic nephropathy (DN) often have glomerular, tubular, interstitial, and vascular lesions on biopsy, though a recently proposed DN classification focuses on glomerular features. While it is important to quantify the extent of these histopathological manifestations across all stages of DN, we sought to investigate whether these findings can be identified in early DN patients.

Methods: A deep learning framework known as a feature pyramid network (FPN) was implemented to classify digitized renal biopsies as class I or II DN. PAS-stained whole slide images (WSIs) of cases with class I (n=23) or class II (n=77) DN were divided into training, validation, and test sets in 3:1:1 ratio. This process was repeated five times to achieve a 5-fold cross validation. The FPN expected two inputs, 224x224-pixel patches cropped from WSIs and 16x downsampled WSIs, to learn and combine features at two levels of magnification. Class activation maps (CAMs) were generated to visualize informative regions on the WSIs.

Results: Our FPN model achieved an accuracy of 0.8 and an F1 score of 0.6. On a representative set of test images, we found the majority (~84%) of patches identified by CAMs as highly informative for model prediction contained tubules or interstitium, not just glomerular regions (Fig. 1).

Conclusions: Our study identified several regions on the biopsy images as informative for prediction of class I vs II DN. Further analysis can elucidate the importance of various histopathological features of early stage DN.

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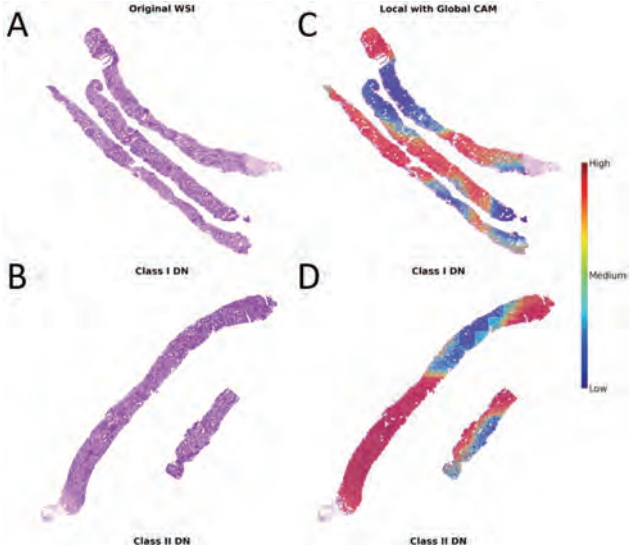

(A and B) Whole slide images and their class labels (Class I & II DN). (C and D) Class activation maps generated on the images, indicating the regions highly associated with the corresponding label. The warmer the color, the higher the probability of a region contributing to the DN class prediction.

TH-PO567

Machine-Learning-Quantified Lupus Nephritis Histological Features Correlate With NIH Activity and Chronicity Index Subscores

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Background: Histologic evaluation of renal biopsies is necessary for lupus nephritis (LN) diagnosis and treatment decisions; however, interobserver variability and poor quantitation limit the utility of histology-based metrics for precision medicine. To mitigate these challenges, we developed ML-based models to quantify histologic features in LN.

Methods: 374 hematoxylin and eosin (H&E)-stained whole-slide images (WSI) of non-LN kidney and LN biopsies were obtained, mainly from a LN cohort at the University of Geneva and a clinical trial of obinutuzumab (OBZ) in proliferative LN (NCT02550652). WSI were split into training (286; 76%) and validation (88; 24%) sets. Expert pathologist annotations trained deep convolutional neural networks, yielding two distinct segmentation models covering anatomic regions and histopathological features. Model performance was tested on a held-out set of 94 WSI. For each model, 20-30 image frames were annotated by 3-5 pathologists to derive ground truth consensus. Whole slide predictions on 73 baseline cases from the OBZ trial were correlated to manual revised NIH LN activity and chronicity index (CI) subscores and kidney function metrics using Spearman method.

Results: The model performed comparably to pathologists on both WSI and frames identifying tissue regions (e.g. cortex, $F1_{model}$=0.78; $F1_{pathologist}$=0.75) and tissue features (e.g. interstitial inflammation, $F1_{model}$=0.68; $F1_{pathologist}$=0.60). ML-quantified interstitial inflammation and sclerotic glomeruli regions correlated with the NIH activity index interstitial inflammation (r=0.638; p<0.0001) and CI glomerulosclerosis subscores (r=0.702; p<0.0001), respectively, as well as with eGFR, creatinine, and UPCR (r=0.32 - 0.47; p<0.01).

Conclusions: We developed ML models that quantify histologic features on LN H&E biopsies, revealing significant correlations with NIH disease index subscores and kidney function metrics. The findings demonstrate the feasibility of ML for quantifying LN histologic features. The utility of this approach in predicting treatment response is being evaluated.

Funding: Commercial Support - Genentech, PathAI

TH-PO568

Accurate and Regional Assessment of Tubular Diameter Predicts Progressive CKD After Radical Nephrectomy

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Background: Manual morphometry of near to normal adult kidneys demonstrated that larger glomerular volume but not cross-sectional tubular area predicts progressive CKD. We hypothesized that a more accurate and regional assessment of enlarged tubular size may be prognostic for progressive CKD.

Methods: Periodic Acid Schiff-stained sections from benign parenchyma from 1453 radical nephrectomies were scanned into whole slide images. The mean true diameter of circular or oval shaped (minor axis) tubules was determined separately for proximal and distal tubular profiles in the superficial, middle, and deep cortical regions. Cox models assessed the risk of CKD progression (defined as dialysis, kidney transplantation, or a 40% decline from postnephrectomy baseline eGFR) with proximal and distal tubular diameters at different depths. Cox models were unadjusted, and adjusted for age, sex, body mass index, hypertension, diabetes, eGFR, and proteinuria.

Results: Among 1453 patients (mean age, 64 years; postnephrectomy baseline eGFR, 50.9 ml/min per 1.73 m^2), 114 progressive CKD events, and 272 non-cancer deaths occurred during a median 3.4 years. As shown in the Table, larger proximal tubular diameter predicted CKD progression only in the superficial cortex; while larger distal tubular diameter predicted CKD progression in all cortical regions, though, more strongly in the superficial cortex. None of the tubular measures predicted non-cancer mortality.

Conclusions: Measurement of average proximal and distal tubular diameters separately at different depths was predictive of progressive CKD. Tubular hypertrophy of more distal nephron segments in the superficial cortex appears to be more prognostic of progressive CKD than deeper tubules and more proximal segments.

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Tubular measures as predictors of CKD progression from 4 months following a radical nephrectomy.

N=1453, 114 CKD events	Unadjusted		Adjusted for clinical characteristics*	
	HR (95% CI)	P value	HR (95% CI)	P value
Superficial				
Mean proximal tubular diameter	**1.33 (1.12, 1.59)**	**0.001**	**1.28 (1.05, 1.56)**	**0.01**
Mean distal tubular diameter	**1.59 (1.34, 1.88)**	**<0.0001**	**1.52 (1.26, 1.84)**	**<0.0001**
Middle				
Mean proximal tubular diameter	1.11 (0.93, 1.33)	0.26	1.11 (0.91, 1.34)	0.30
Mean distal tubular diameter	**1.41 (1.19, 1.66)**	**<0.0001**	**1.35 (1.12, 1.63)**	**0.002**
Deep				
Mean proximal tubular diameter	**1.21 (1.02, 1.45)**	**0.03**	1.15 (0.95, 1.40)	0.13
Mean distal tubular diameter	**1.37 (1.13, 1.64)**	**0.001**	**1.26 (1.02, 1.56)**	**0.03**

*Adjusted for age, sex, BMI, hypertension, diabetes, post-surgery baseline eGFR and proteinuria.