Validation of a Novel Cytologic Biomarker for Urothelial Carcinoma

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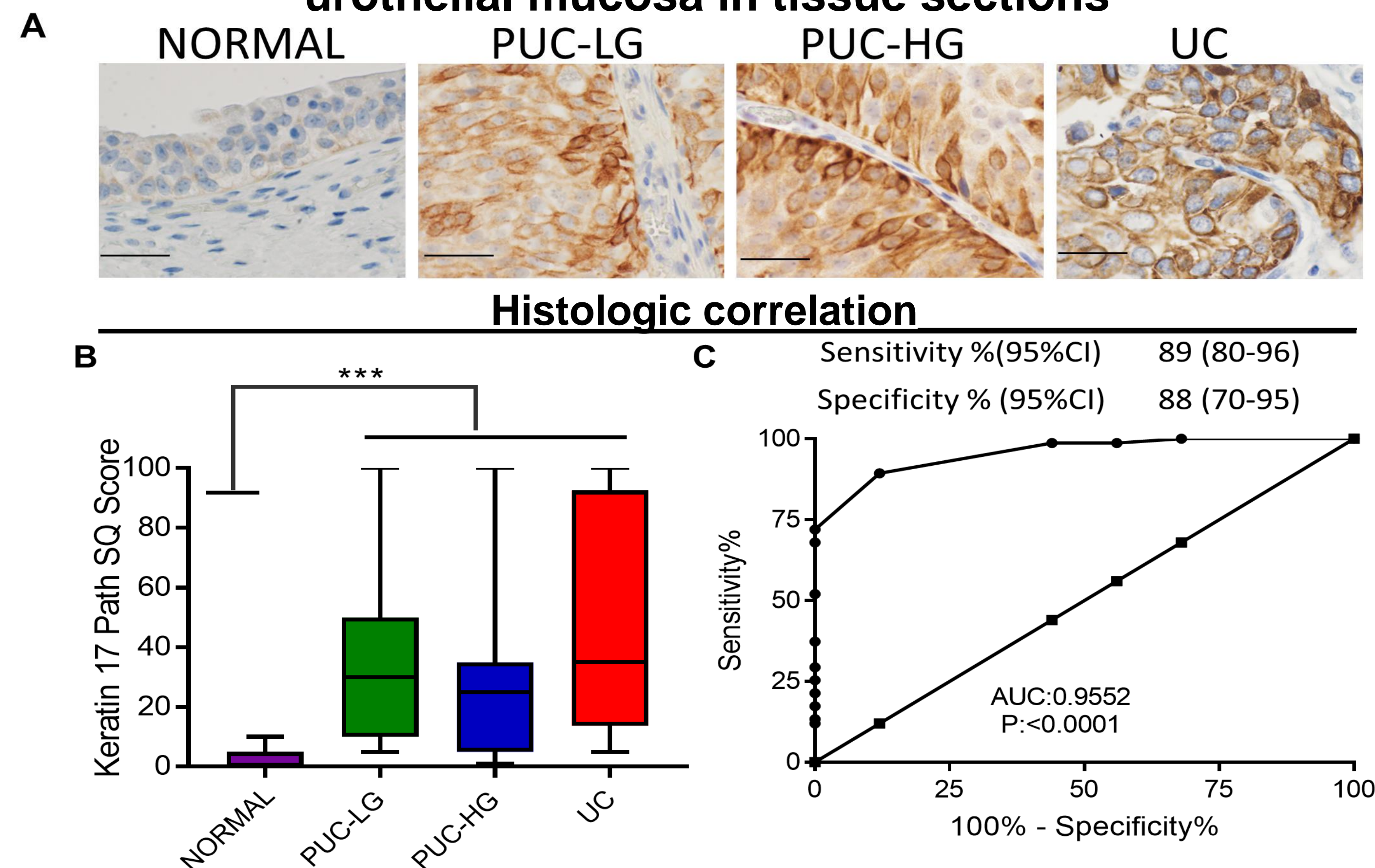
INTRODUCTION

Cytology and cystoscopy have limited sensitivity and specificity for the diagnosis of urothelial carcinoma (UC), due to inflammatory atypia, sampling errors, and other clinicopathologic factors that may obscure test results. Therefore, there remains an unmet clinical need to identify biomarkers to improve the diagnostic accuracy to detect UC.

Prior research from our laboratory established that Keratin17(K17) Immunocytochemistry (ICC) was sensitive and specific for UC in a preselected set of specimens with defined cytological diagnosis and clinical outcome data. The current study extends these preliminary finding to establish performance characteristics in a non selected, consecutive set of cases from a university hospital based cytopathology lab.

Keratin17 is highly expressed in urothelial carcinoma
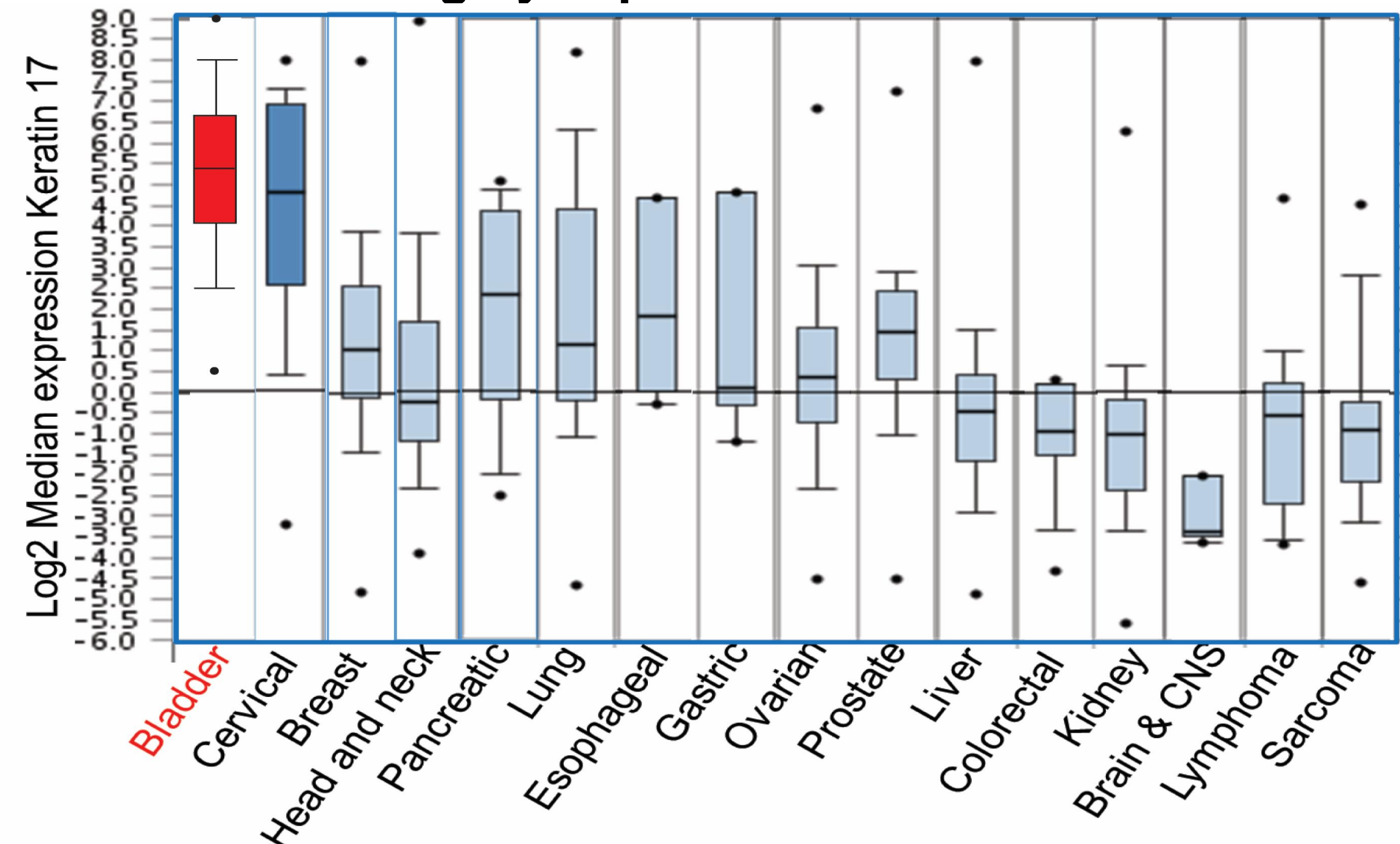
Keratin17 IHC is highly sensitive and specific to distinguish all primary categories of urothelial carcinoma from normal urothelial mucosa in tissue sections

NORMAL   PUC-LG   PUC-HG   UC

Histologic correlation

Sensitivity %(95%CI) 89 (80-96)
Specificity % (95%CI) 88 (70-95)

AUC:0.9552
P:<0.0001

(A) K17 ICC staining in representative cases from each diagnostic category. Normal: Benign urothelial mucosa; PUC-LG: Papillary urothelial carcinoma-low grade; PUC-HG: Papillary urothelial carcinoma-high grade; UC: Non-papillary invasive urothelial carcinoma. (B) K17 expression in each diagnostic category, PathSQ score, range and median. (C) Receiver operating characteristic (ROC) curves comparing benign mucosa versus urothelial neoplasia showing an AUC = 0.9552, at the PathSQ score of ≥ 10 distinguishes between neoplastic and benign lesions with a sensitivity (89%) and specificity (88%). *** p< 0.001

K17 ICC IS DIAGNOSTIC IN UC

Prior work from our lab established that K17 ICC detected malignant urothelial cells in urine cytology specimens in a preselected case (n=112) with a sensitivity of 100% and specificity of 96% which supporting our hypothesis that K17 could be a diagnostic biomarker for UC. (Babu *et al.*)

AIMS

To validate K17 immunocytochemical (ICC) test performance in a non- selected consecutive set of cases from a university based cytopathology laboratory setting.

METHODS
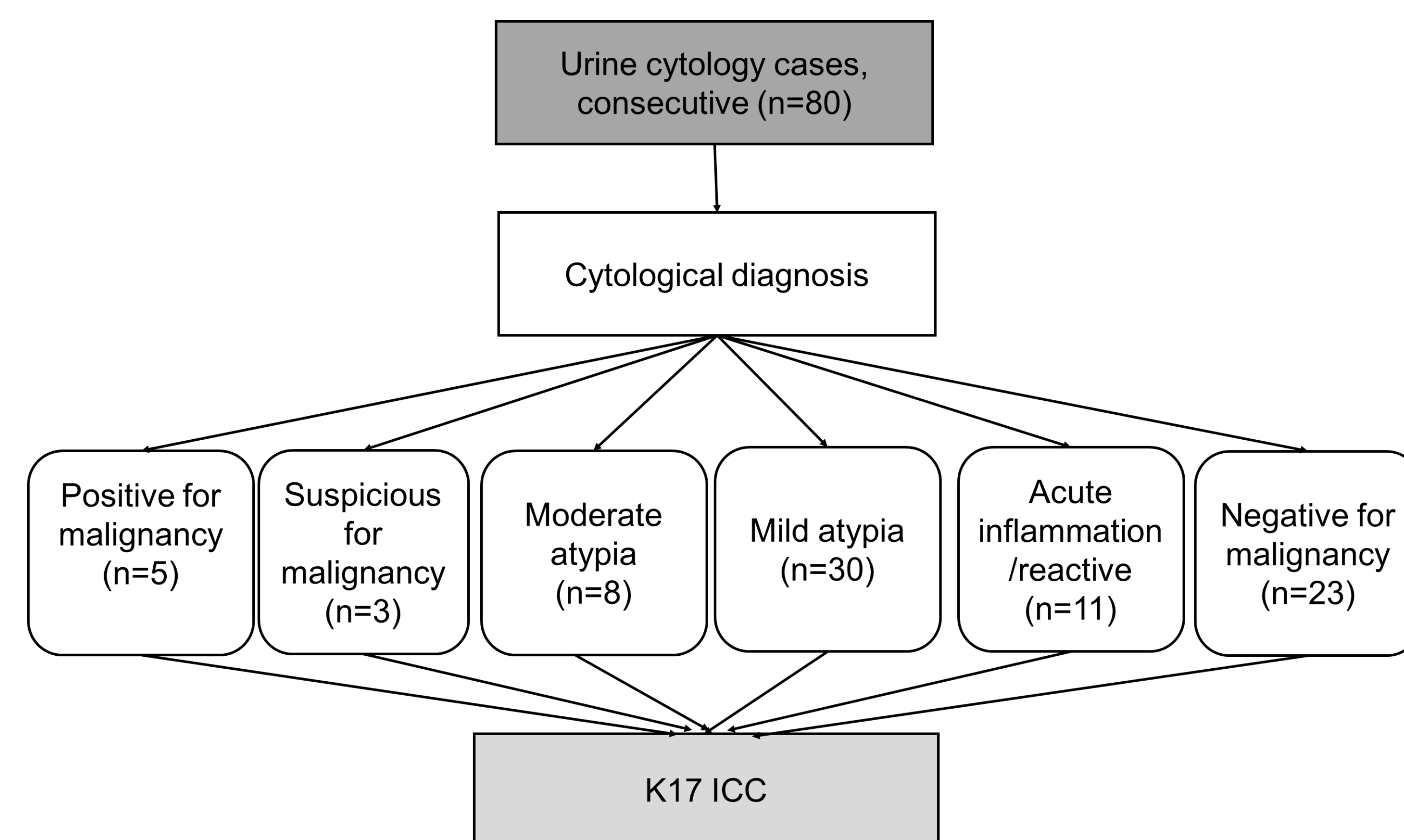
Cases included 80 consecutive ThinPrep CytoLyt-fixed urine specimens of patients were collected at Stony Brook Medicine in 2018. Of the 80 cases, 40/80 had a history of hematuria, 20/80 were submitted for surveillance of bladder cancer recurrence and 20/40 had other benign clinical conditions. K17 ICC was performed by indirect immunoperoxidase methods and K17 test results were scored solely based on the detection of immunoreactive urothelial cells , irrespective of the number of positive cells.

RESULTS

K17 is only detected in malignant urothelial cells in urine

BENIGN   **MALIGNANT**
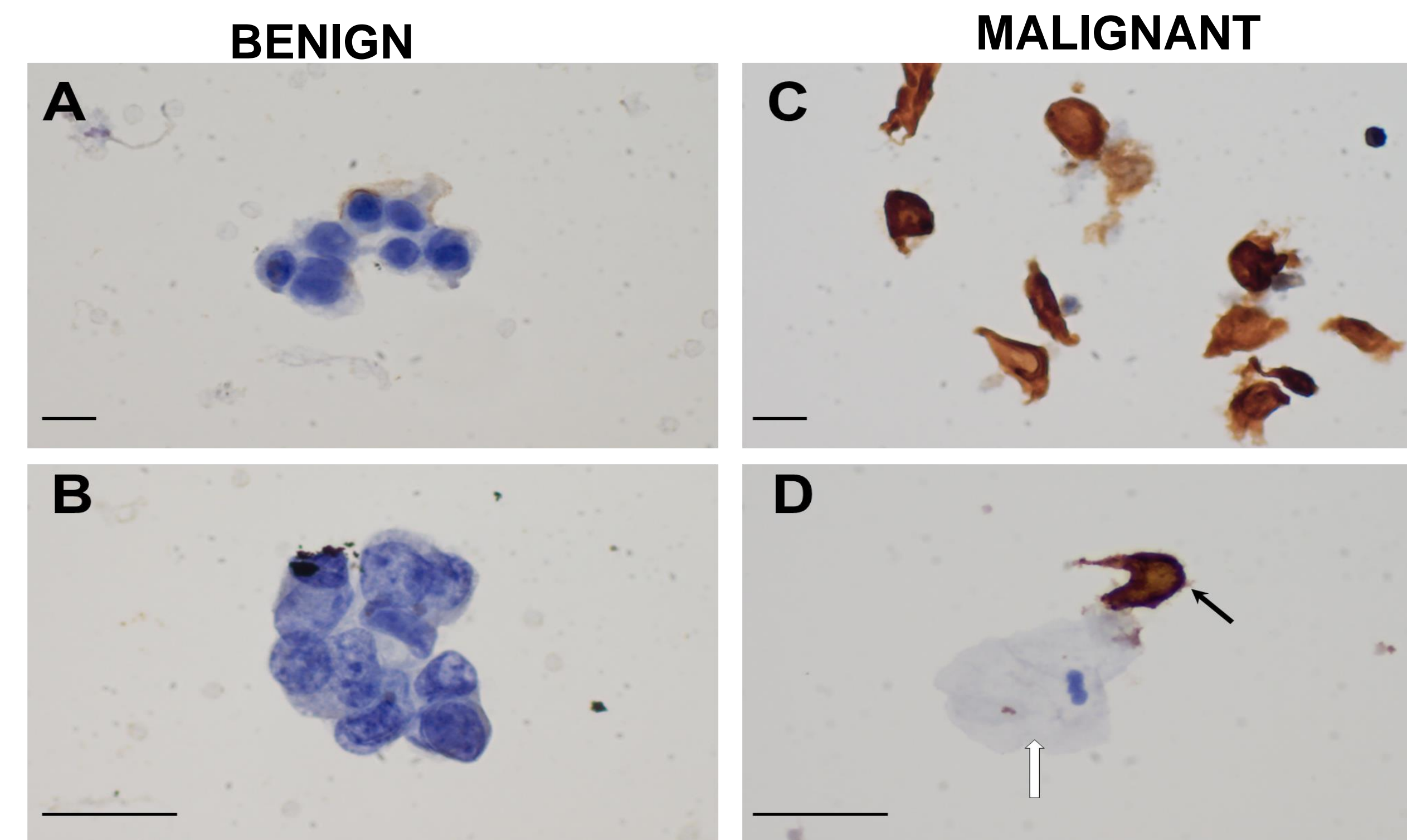
A. Benign urothelial cells; B Normal Urothelial cells; C. K17 positive urothelial cells; D. K17 positive urothelial cell (black arrow) adjacent to benign squamous cells (white arrow). Scale bar; 20µm (A&C), 50µm (B&D)

RESULTS

K17 ICC is a novel and highly sensitive and specific diagnostic test for underlying biopsy-confirmed UC

TEST	CYTOLOGY (n=69) % (95%CI)	K17 ICC (n=112) % (95%CI)
Sensitivity	41 (27-57)	100 (91-100)
Specificity	100 (91-100)	90 (77-96)
Positive Predictive Value	100 (80-100)	90 (78-96)
Negative predictive value	64 (51-75)	100 (90-100)

- At least 10 (10-100, median 30) immunoreactive urothelial cells/cases were detected in cytologically malignant urine specimens that had biopsy confirmed urothelial carcinomas.
- Among 39 cases with final clinicopathologic diagnosis, K17 ICC was positive in all 39 cases.
- K17 ICC was positive in 8/40 cases with history of hematuria (6 with gross hematuria and 2 with microscopic hematuria), non had previous diagnosis of bladder cancer and of these cases 6/8 had biopsy confirmed UC.
- K17 ICC was positive in 9/23 (39%) cases with negative urine cytology. Of these 9 cases, 4 cases had biopsy confirmed UC.
- K17 ICC was positive in 4/11 (36%) of cases with inflammatory/reactive changes. Of these 4 cases, 3 had biopsy confirmed UC.
- K17 ICC was positive in 14/30 (46%) of cases with mild atypia. Of these 14 cases, 12 had biopsy confirmed UC and 1 had PUNLMP.
- K17 ICC was positive in 16/16 (100%) of cases with moderate atypia (n=8), severe atypia (n=3), or UC (n=5), all with biopsy confirmed UC.

CONCLUSION

K17 ICC was highly sensitive and specific for UC in consecutive cases from an academic based cytopathology laboratory setting. Thus, K17 could serve as an adjunct to guide the clinical management of UC.

ACKNOWLEDGEMENTS & REFERENCES

References: Babu, *et al.* Keratin 17 is a sensitive and specific biomarker of urothelial neoplasia. Mod Pathol. 2018 (PMID: 30443013).

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DISCLOSURE OF CONFLICT OF INTEREST

The authors (Sruthi Babu, Lucia Roa-Peña, and Ina Chan) declare that they have no conflict of interest. Nam W. Kim and Sholeh Jahanfard are employees of KDx Diagnostics Inc. Kenneth R. Shroyer, Luisa F. Escobar-Hoyos, Nam W. Kim are co-Inventors for Keratin 17 as a biomarker for bladder cancer (US provisional Application No. 62/371,286; SSMP Docket: 33851P, International Publication number WO 2018/027091 A1)