A Multi-center Study Based on the Value of Erythrocyte Morphological Information in Detecting the Source of Hematuria in the EU 5600 Pro Automated Urine Analyzer and the Establishment of a Diagnostic Model for Renal Hemorrhage

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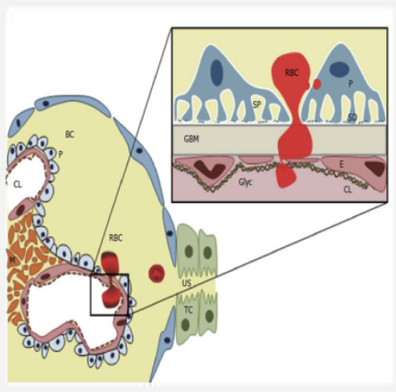
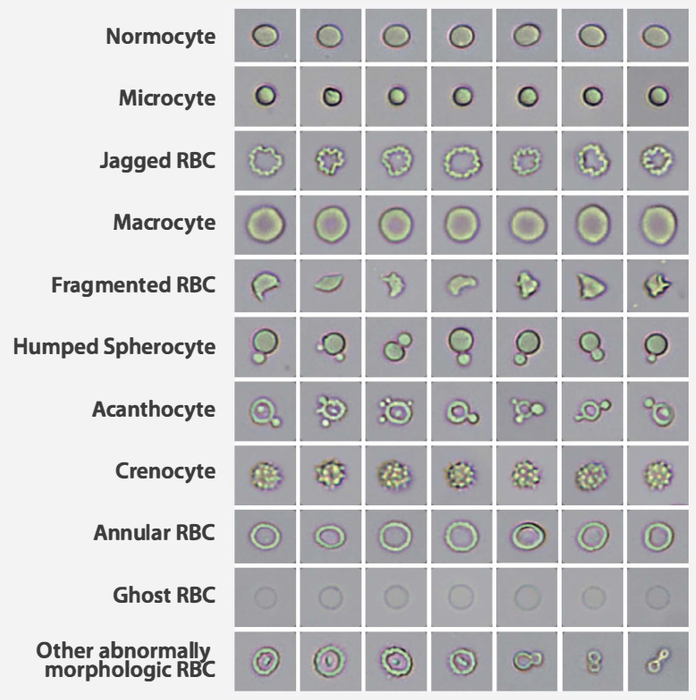
Introduction

- **Dysmorphic erythrocytes Overview: Dysmorphic erythrocytes** (RBC) suggest glomerular bleeding (kidney disease), while **isomorphic erythrocytes** (RBCs with regular size or shape) indicate bleeding originating from the tubuli or a lower site in the urinary tract, a general bleeding tendency, or contamination from vaginal bleeding.
- **Challenges:** Since the morphological analysis of urinary RBCs was proposed in the 1980s, the detection method is still based on the **manual method,** which makes it difficult to standardize the results and affects the accuracy of the results due to the differences in microscopic equipment, specimen preparation and observer's skills.
- **Study Aim:** In order to solve the many problems existing in the current RBC morphology examination and to **achieve automation and standardization,** a multicenter study was conducted to investigate the clinical value of RBC morphology in suggesting **the source of hematuria,** to determine the optimal diagnostic threshold for dysmorphic RBC rate and to establish an **auxiliary diagnostic model for renal hemorrhage**, with the Mindray urine analyzer



Yuste C, Gutierrez E, Sevillano AM, Rubio-Navarro A, Amaro-Villalobos JM, Ortiz A, et al. Pathogenesis of glomerular haematuria[J]. World journal of nephrology. 2015;4 (2):185-95



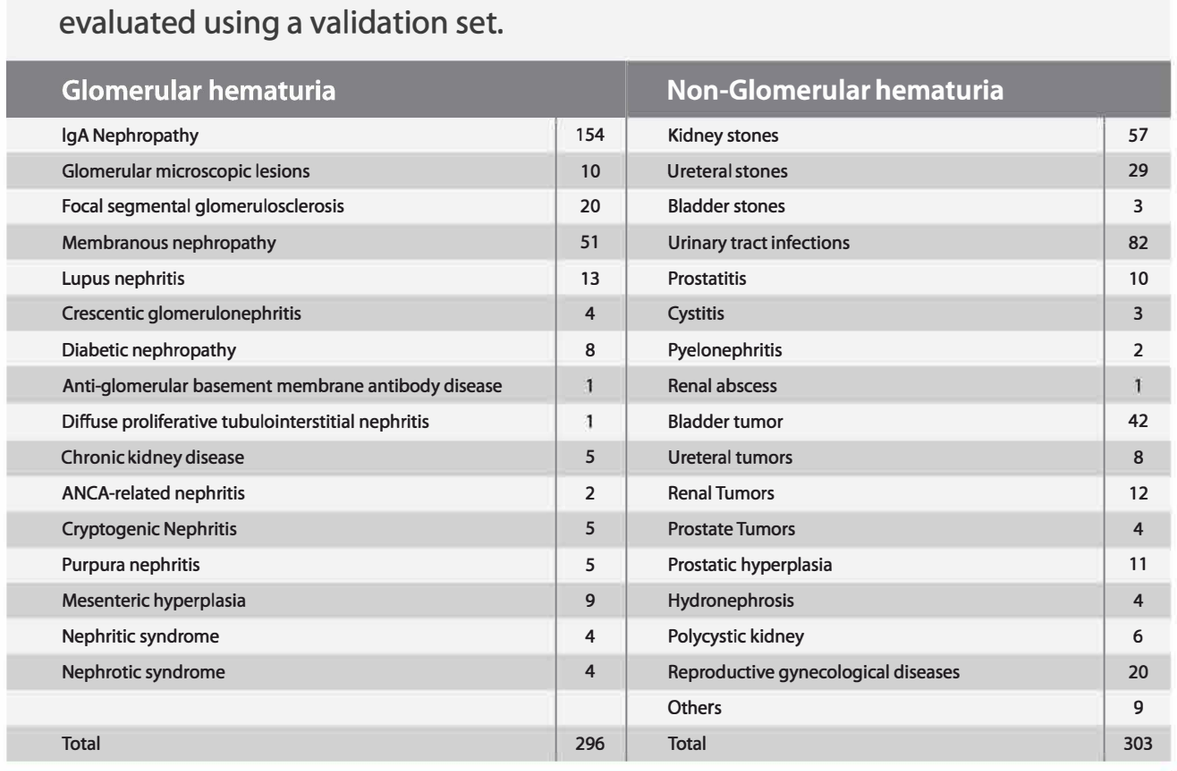
Methods

- **Sample Collection:** A total of 599 urine samples with RBC counts >25/uL were collected from patients across **eight hospitals,** including 296 cases diagnosed with glomerular disease via renal biopsy, and 303 cases diagnosed with non-glomerular disorders through imaging, cytology, or cystoscopy.
- **Dysmorphic RBC Rate Analysis:** RBC morphology results were assessed for diagnostic performance using receiver operating characteristic (ROC) analysis. **Parameters with the highest area under the curve (AUC) were selected as relevant features for glomerular hematuria.** Optimal thresholds for these RBC morphological categories were then determined.
- **Model Establishment:** A machine learning model was developed using parameters from both analyzers. Three machine learning algorithms—support vector machine **(SVM)**, logistic regression **(LR)**, and linear discriminant analysis **(LDA)**—were employed to build the models, and their performance was evaluated using a validation set.

Glomerular hematuria		Non-Glomerular hematuria	
IgA Nephropathy	154	Kidney stones	57
Glomerular microscopic lesions	10	Ureteral stones	29
Focal segmental glomerulosclerosis	20	Bladder stones	3
Membranous nephropathy	51	Urinary tract infections	82
Lupus nephritis	13	Prostatitis	10
Crescentic glomerulonephritis	4	Cystitis	3
Diabetic nephropathy	8	Pyelonephritis	2
Anti-glomerular basement membrane antibody disease	1	Renal abscess	1
Diffuse proliferative tubulointerstitial nephritis	1	Bladder tumor	42
Chronic kidney disease	5	Ureteral tumors	8
ANCA-related nephritis	2	Renal Tumors	12
Cryptogenic Nephritis	5	Prostate Tumors	4
Purpura nephritis	5	Prostatic hyperplasia	11
Mesenteric hyperplasia	9	Hydronephrosis	4
Nephritic syndrome	4	Polycystic kidney	6
Nephrotic syndrome	4	Reproductive gynecological diseases	20
		Others	9
Total	296	Total	303

Key RBC Types to Differentiate Glomerular Hematuria

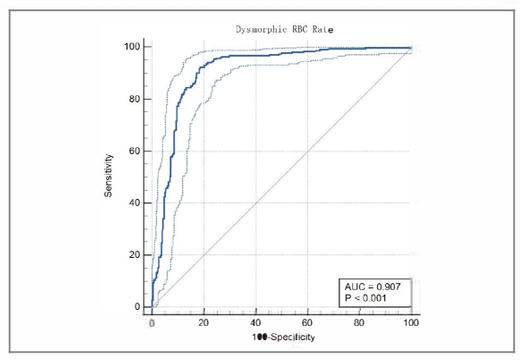
Four RBC morphological categories, **acanthocyte, jagged RBC,annular RBC and other abnormal RBCs,** showed the highest AUCs and were ultimately selected as parameters for the calculation of **dysmorphic RBC rate** for distinguishing glomerular from non-glomerular hematuria.



Parameter	ROC curve (AUC)	Significance level P(Area=0.5)
Normocyte	0.883	<0.001
Macrocyte	0.671	<0.001
Microcyte	0.666	<0.001
Acanthocyte	0.742	<0.001
Humped Spherocyte	0.532	0.154
Jagged RBC	0.821	<0.001
Crenocyte	0.602	<0.001
Fragmented RBC	0.507	0.61
Annular RBC	0.86	<0.001
Ghost RBC	0.758	<0.001
other abnormally morphologic RBC	0.875	<0.001

Optimal Threshold of Dysmorphic RBC Rate for Glomerular Hematuria Detection

The optimal threshold for the total dysmorphic RBC rate associated with glomerular hematuria was found to be **26%,** yielding a **sensitivity of 92.23%, specificity of 80.86%, and an AUC of 0.907.**



Area under the ROC curve (AUC)	
ROC curve (AUC)	0.907
Standard Error [a]	0.0131
95% Confidence interval [b]	0.881to 0.929
z statistic	31.014
Significance level P (Area=0.5)	<0.0001

Youden index	
index J	0.7375
Associated criterion	>0.26

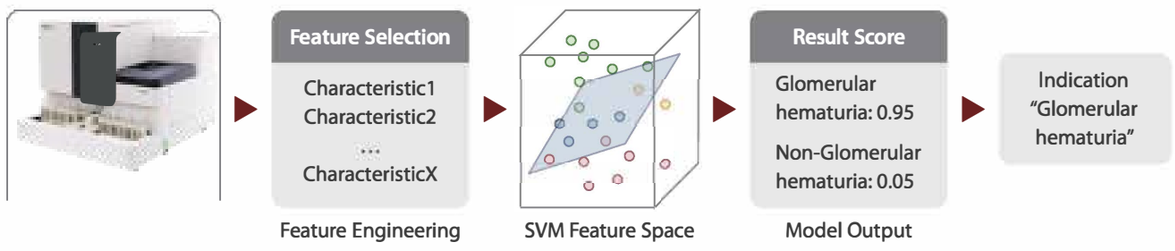
Dysmorphic RBC rate		Gold Standard		
		Positive	Negative	Total
EH-2090	Positive	273	58	331
	Negative	23	245	268
	Total	296	303	599

SVM Model Achieves High Accuracy in Diagnosing Glomerular Hematuria

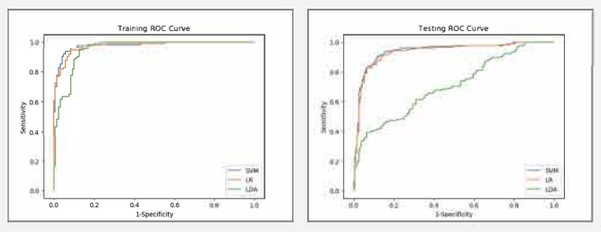
The **SVM model, constructed using normocytes, acanthocytes, jagged RBCs, crenocytes,** and **dry chemical protein test results,** showed the best diagnostic performance for glomerular bleeding:

Training set: Sensitivity 93.30%, Specificity 93.30%, AUC 0.978

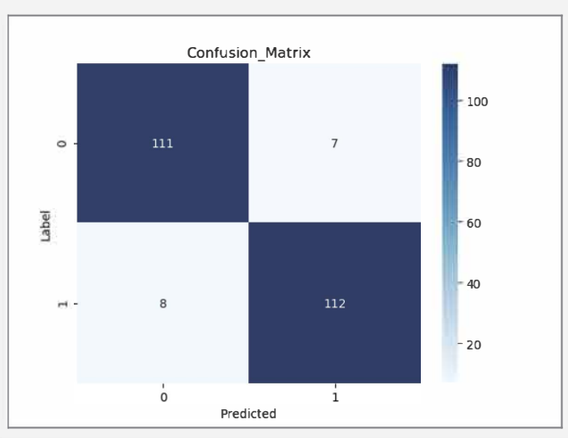
Validation set: Sensitivity 91.00%, Specificity 87.00%, AUC 0.938

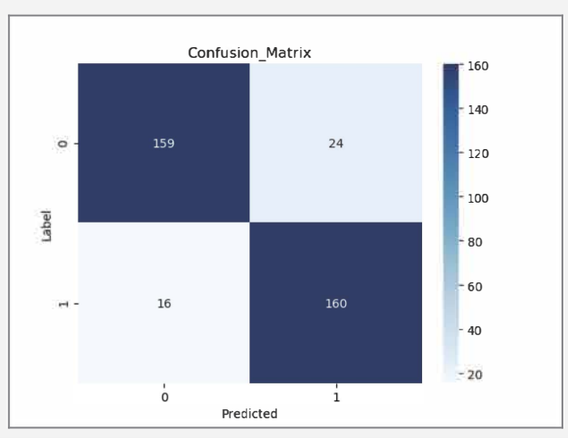


Training Set Validation Set



Model	Training Set	Validation Set
SVM	0.978	0.938
LR	0.975	0.935
LDA	0.952	0.703





Conclusion

- This study identified key RBC types to differentiate glomerular from non-glomerular hematuria, with an dysmorphic RBC threshold of 26%.
- The SVM-based model achieved high sensitivity and specificity, highlighting its potential to improve diagnostic accuracy and clinical decision-making in hematuria management.

Reference

Yuste C, Gutierrez E, Sevillano AM, Rubio-Navarro A, Amaro-Villalobos JM, Ortiz A, et al. Pathogenesis of glomerular haematuria[J]. World journal of nephrology. 2015;4(2):185-95.