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ORIGINAL ARTICLE

Urinalysis: diagnostic performance of urine dipstick compared to an automated microscopic method

Uroanálisis: desempeño diagnóstico de la tira reactiva comparada con un método microscópico automático

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Abstract

Introduction: *Urinalysis is one of the most important clinical laboratory tests because numerous pathologies can manifest or be suspected through this test. Although the previous reports mention that urinary microscopy is a fundamental part of urinalysis for diagnostic support of various conditions, there is a debate about the utility of this test section in a certain patient population. The aim of this study was to determine the diagnostic performance of the urinary dipstick analysis and the potential risks of false-negative (FN) results.* **Material and methods:** *This is a retrospective and observational study, and urinalysis information was obtained from non-hospitalized patients. The dipstick and microscopic analyses were performed using the Clinitek-ATLAS (index test) and iQ200-SPRINT (reference standard) devices. Dipstick or microscopy analyses were positive if ≥ 1 parameters were abnormal. A Bayesian hierarchal beta-binomial model was carried out for each performance parameter. Risk analysis was performed as proposed in the literature.* **Results:** *Five hundred and fifty-two patients were included in the study. The posterior median at group level was 94% (credible interval 95% [CrI 95%] 89.9-97%) for sensitivity (Se), 57.1% (CrI 95%, 50.1-64.1%) for specificity, and 5.8% (CrI 95%, 2.59-9.64%) for FN rate (FNR). The posterior probability Se > 90% was 95.9% at a group level. The risk analysis found only low-risk false-negative events.* **Conclusions:** *The performance of the dipstick analysis was appropriate, with a good certainty of Se > 90% and a FNR < 10% at the operator level. Omission of microscopic analysis can be a safe action in a patient with a negative dipstick since FNs with a clinical impact are not expected.*

Keywords: *Urinalysis. Urine dipstick. Urine microscopy. Risk analysis. Dipstick performance.*

Resumen

Introducción: *El uroanálisis es de las pruebas de laboratorio clínico más importantes ya que numerosas patologías pueden manifestarse mediante esta prueba. Aunque informes previos mencionan que la microscopía urinaria es parte fundamental del uroanálisis para apoyo diagnóstico de varias condiciones, existe debate sobre la utilidad de esta en determinadas poblaciones. El objetivo de este estudio fue determinar el rendimiento diagnóstico de la tira reactiva y riesgos potenciales de resultados falsos negativos.* **Material y métodos:** *Estudio retrospectivo y observacional. La información del uroanálisis se obtuvo de pacientes ambulatorios. Los análisis de tira reactiva y microscópico se realizaron en dispositivos Clinitek-ATLAS (prueba índice) e iQ200-SPRINT (estándar de referencia). Los análisis por tira reactiva o microscopía fueron positivos si*

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Date of reception: 08-07-2022
Date of acceptance: 03-10-2022
DOI: 10.24875/RMU.22000063

Available online: 05-01-2023
Medicina Universitaria. 2022;24(4):177-183
www.medicinauniversitaria.org

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≥ 1 parámetros estaban alterados. Se realizó un modelo beta-binomial jerárquico bayesiano para cada parámetro de rendimiento. El análisis de riesgo se realizó según lo propuesto en la literatura. **Resultados:** *Se incluyeron 552 pacientes. La mediana posterior a nivel grupo resultó 94% (intervalo credibilidad 95% [CrI 95%] 89.9-97%) para sensibilidad, 57.1% (CrI 95% 50.1-64.1%) para especificidad y 5.8% (CrI 95% 2.59-9.64%) para tasa de falsos negativos. La probabilidad posterior de sensibilidad > 90% fue del 95.9% a nivel grupal. El análisis de riesgo encontró solo falsos negativos de bajo riesgo.* **Conclusiones:** *El rendimiento de la tira reactiva fue adecuado, con buena certeza de sensibilidad > 90% y tasa de falsos negativos < 10% a nivel operador. La omisión del análisis microscópico puede ser una acción segura en pacientes con tira reactiva negativa, no se esperan falsos negativos con repercusión clínica.*

Palabras clave: *Uroanálisis. Tira reactiva urinaria. Microscopía urinaria. Análisis de riesgo. Desempeño de tira reactiva.*

Introduction

Urinalysis is one of the most important clinical laboratory tests. A diverse number of pathologies are diagnosed or suspected through this test (for example, the evaluation of renal function, urinary tract infections, microscopic hematuria, or as a screening test for bladder cancer[1]). However, it is not recommended as a routine test, except perhaps in women during pregnancy[2]. Conventionally, the test consists of a microscopic and a physicochemical analysis through the macroscopic inspection and the use of a chemical test strip. The latter, commonly known as a "urine dipstick" or "reagent strip," aims to detect the presence and semi-quantitatively calculate various chemical constituents, such as glucose, proteins, bilirubin, specific gravity, and pH, among others. The microscopic analysis aims to find formed elements in suspension, such as epithelial cells, leukocytes, erythrocytes, casts, and crystals. Both tests can be processed either manually by trained personnel or automatically with the help of a device specifically designed for that purpose.

Since 2000, the European Guidelines for Urinalysis have recommended to not routinely perform the microscopic analysis because it adds little value to negative dipstick results for erythrocytes, leukocytes, and proteins[3]. Some laboratories have adopted a reflex algorithm to perform a microscopic analysis conditioned on the dipstick result, but it is still a widespread practice to perform microscopy routinely. This could happen due to fear and anxiety produced by the possibility of omitting pathological findings in the analysis[4,5]. Several studies have estimated the diagnostic performance of dipstick results compared to microscopy, defining a positive dipstick and positive microscopy if one or more parameters are abnormal[4,6-10]. A sensitivity (Se) of 78-98.7%, specificity (Sp) of 36.3-74%, positive predictive value (PPV) of 24.1-76%, and negative predictive value (NPV) of 92-99% have been estimated for manual microscopy[6-10]. Se of 93%, Sp of 56.9%, PPV of 64.7%, and NPV of 90.5% were estimated for an automated analysis[4]. However, little attention has been given to the role of the operator. Studies only report performance by trained personnel without specifying the number of participants or if there is an apparent difference between them[4-10].

The aim of this study was to determine the diagnostic performance (Se, Sp, NPV, and PPV) and the false-negative rate (FNR) of the urinary dipstick analysis with respect to the automated microscopy examination at the operator level in non-hospitalized patients as well as to determine the total number of FN and the potential risks that would involve the omission of microscopic examination when presenting a negative result on the dipstick analysis.

Material and methods

Urine sample and general examination process

This was a retrospective and observational study approved by the Local Ethics Committee. Urinalysis information from non-hospitalized patients, midstream sample, and age ≥ 18 years from our institution's clinical laboratory database were obtained from September 1, 2021, to February 28, 2022. A sample of 552 patients was calculated (sample for a proportion in infinite population, proportion of 90%, and precision of 2.5%). We considered the Se as the main parameter of interest for diagnostic performance evaluation, which has been estimated to be around 90%[4,6-10] and a precision of 2.5% was found appropriate according to literature[11]. The dipstick analysis was performed with the Clinitek ATLAS (Siemens) device, evaluating 10 parameters (color, clarity, glucose, bilirubin, ketones, urobilinogen, pH, specific gravity, blood, leukocyte esterase (LE), nitrites (Nit), and protein). The microscopic urinary analysis was performed on an iQ200 SPRINT (Beckman and Coulter) device. If a parameter review alarm was

displayed, the microscopic fields (microphotographs) were reviewed and validated or reclassified as appropriate (based on the use of a digital image guide provided by the manufacturer). All procedures were performed by staff with a bachelor's degree in clinical biochemistry. The same operator on each sample performed both dipstick and microscopic analysis. Positive dipstick or positive microscopy was defined if one or more parameters met the threshold for positivity (Table 1)[1,2,12-24], giving each sample a classification for dipstick (positive or negative) and microscopic (positive or negative) analysis. The dipstick analysis was considered the index test and the microscopic analysis as the reference standard.

For the risk analysis, the criteria employed by Miler and Nikolac5 were used to assess de risk of omission of a microscopy test in a negative dipstick result. The proposed errors (FN causes), severity ("S1" minimal harm to the patient, "S2" need to repeat the test without additional harm to the patient, "S3" delayed treatment due to missing elements in the microscopy, and "S4" incorrect diagnosis with a probable state of threat to life or function), and classification of occurrence ("O1" frequency < 3%, "O2" frequency 3-10%, "O3" frequency > 10-25%, "O4" frequency > 25-50%, and "O5" frequency > 50%, defining the frequency as the number of errors per cause among total negative dipstick tests) were employed for this task. The risk matrix was made by combining severity and occurrence (4 × 5 matrix), classifying the cells into low, intermediate, and high risk in a similar way to Miler and Nikolac[5].

Table 1. Criteria for positivity on dipstick and microscopic analysis

Análisis	Parameter	Cutoff for positivity
Dipstick (dipstick is classified positive if ≥ 1 parameter meets cutoff value)	Protein[19-22]	≥ 1+ -30 mg/dL
	Blood[1,22-24]	≥ trace
	Leukocyte esterase[12,13,25]	≥ 1+
	Nitrite[12,13,26,26]	Positive
Microscopy (Microscopy is classified positive if ≥ 1 parameter meets cutoff value)	Erythrocyte[2,12]	≥ 6 cells/HPF
	Leukocyte[2,12,27]	≥ 3 cells/HPF
	Casts[2,28,29]	Any kind and quantity

HPF: high-power field.

Statistical analysis

Numerical variables were described as median and interquartile range (IQR), and categorical variables were described as percentage proportions. For the evaluation of the diagnostic performance (Se, Sp, PPV, NPV, and FNR) of the dipstick examination concerning the microscopic examination, a hierarchical beta-binomial model was carried out with reparametrization of the beta distribution as mean ($\mu = a/\eta$, $\eta = a + b$) in the second stage, with monitoring of the posterior distribution of μ and the proportion of performance according to the operator (p_i) for each performance parameter[25]. Informative literature-based hyperpriors were used[3,6-10] for μ_{Se}~Beta(18,2) [Se μ distributed in beta where a = 18, b = 2], μ_{Sp}~Beta(12,8), μ_{PPV}~Beta(10,10), μ_{NPV}~Beta(9,1) and μ_{FNR}~Beta(1,9). A hyperprior sample size of 100 (η) was used, with a shrinkage factor ~Uniform(0,1). The sampling of the posterior distributions was carried out using a Gibbs sampler, and the median and 95% credible interval (CrI 95%) were reported in percentages. Four Monte Carlo Markov Chains were performed for each diagnostic parameter, storing the 15th observation until reaching 5000 samples per chain (because of high autocorrelation). To evaluate the convergence of the chain, a potential scale reduction factor (PSRF) and cutoff of < 1.1 were used as the convergence criterion[26]. Effective sample size (ESS) was used for precision criteria, following the recommendation of ESS ≥ 10.000[26]. A seeded random number generator was used for each chain for reproducibility purposes.

An association test between gender and microscopy results (positive-negative) as well as the association between gender and false positives (FPs) in positive dipstick and gender and FNs in positive microscopy, considering the null hypothesis of independence and alternative of dependence equally probable, were done, and a multinomial joint sampling plan was considerated[27]. Bayes factor (BF_{10}, alternative hypothesis/null hypothesis) was reported following Jeffrey's guide for interpretation[28], and odds ratio (OR) was obtained if the results favored the alternative hypothesis.

The intention of using a hierarchical Bayesian model was to evaluate performance at the individual level, and since the sample size at this level was smaller in some operators, an individual and independent estimation of the performance by maximum likelihood could give us extreme and unreliable estimates, so the regularization provided by the hierarchical model was desirable for this particular problem. In addition to the above, we considered desirable the introduction of the prior knowledge based on the literature[25,29]. The JAGS (version 4.3.0),

Table 2. Description of urinalysis results

Dipstick	n (%)/ median (IQR)*	Microscopy	n (%)
Blood		Leukocyte/HPF	
0+	375 (67.9)	0-5	361 (65.4)
Trace	20 (3.6)	6-10	77 (13.9)
1+	41 (7.4)	11-20	42 (7.6)
2+	42 (7.6)	21-50	28 (5.1)
3+	74 (13.4)	≥ 51	44 (8)
LE		Erythrocyte/HPF	
0+	264 (47.8)	0-2	346 (62.7)
1+	99 (17.9)	3-5	86 (15.6)
2+	81 (14.7)	6-10	48 (8.7)
3+	60 (10.9)	11-20	29 (5.2)
4+	48 (8.7)	≥ 21	43 (7.8)
Nitrite		Casts	
Neg	504 (91)	Absent	518 (93.8)
Pos	48 (9)	Hyaline[a]	33 (6)
		Waxya	1 (0.2)
Protein mg/dL	0 (0-15)*		
Specific gravity g/mL	1.017 (1.012-1.023)*		

[a]all of them 1-2/low power field; *median and interquartile range (IQR).
HPF: high power field; LE: Leukocyte esterase.

R (version 4.0.5), and RStudio Desktop (version 1.4.1106) software were used for the statistical analysis ("base," "tidyverse," "runjags," "BayesFactor," and "coda" packages were used).

Results

Five hundred and fifty-two patients were included in the study, 304 females (55.1%) and 248 males (44.9%), with a median age of 51 years (IQR = 34-62). Table 2 shows the main findings in the patients. There were a total of seven operators; the experience of operators 1-7 was 33, 8, 4, 2, 21, 3, and 29 years, respectively. We found the total of true positives (TPs) = 267, FPs = 114, true negatives (TNs) = 156, and FNs = 15. The diagnostic performance for Se (TP/[TP + FN]), Sp (TN/[TN + FP]), PPV (TP/[TP + FP]), NPV (TN/[TN + FN]), and FNR (FN/[FN + TP]) is shown in table 3. The convergence of the chains was considered appropriate (PSRF < 1002 in all cases) as well as the precision (ESS > 10,000 in all cases).

The posterior probability that performance parameters at the individual and group level were equal to, or greater than the values found or recommended in the literature[3,4,6-10] is also reported, namely, P(Se ≥ 0.90)

Table 3. Diagnostic performance posterior probabilities of dipstick analysis (index text) with respect to microscopic analysis (reference standard)

Level	n_j	Se			Sp			FNR			PPV			NPV		
		Median	CrI 95%	P (Se ≥ 0.9)	Median	CrI 95%	P (Sp ≥ 0.6)	Median	CrI 95%	P (FNR < 0.1)	Median	CrI 95%	P (PPV ≥ 0.8)	Median	CrI 95%	P (PNV ≥ 0.9)
mu	NA	94	89.9-97	0.959	57.1	50.1-64.1	0.2	5.8	2.59-9.64	0.966	67.8	59.4-74.9	0	90.7	84.7-95.3	0.602
1	275	94.5	91.3-97.4	0.991	58	51.4-64.6	0.277	5.37	2.52-8.65	0.99	68.9	62.9-74.7	0	91.5	86.7-95.9	0.731
2	127	94.7	90.5-98.6	0.973	56.9	48.8-64.3	0.205	5.15	1.51-9.32	0.977	63.6	53.3-72	0	92.1	86.5-97.5	0.772
3	66	94.5	89.9-98.4	0.958	57.1	47.1-65.9	0.245	5.38	1.65-10	0.963	72	63.1-82.8	0.073	90.6	82.5-96	0.573
4	30	92.9	83.5-97.5	0.781	57.9	48.2-68.7	0.324	6.9	2.46-16	0.795	68.6	56.3-81.3	0.03	89.7	79.2-96	0.47
5	27	95	90.9-100	0.972	56.5	44.5-66.8	0.219	4.78	0-9.01	0.973	72.2	62.1-85.9	0.13	91.2	82.6-98.5	0.632
6	14	93.7	85.9-98.6	0.862	56.6	44.7-66.6	0.226	6.05	1.59-14.4	0.872	65.5	45.9-7.81	0.006	90.5	81.3-97.5	0.57
7	13	94.7	89.9-100	0.947	57.1	45.6-64.1	0.272	5.09	0-9.85	0.954	71.7	60.4-88.5	0.146	91.1	82.4-98.2	0.624

Parameters at the group (mu) and operator levels (1-7). The results were obtained through a beta-binomial hierarchal model (material and methods for details).
FNR: false negative rate; n_j: number of tests at the operator level; NA: not applicable; NPV: negative predictive value; P: posterior probability; Se: sensitivity; Sp: specificity; PPV: positive predictive value.

[Probability that posterior distribution of Se ≥ 0.90], P(Sp ≥ 0.60), P(PPV ≥ 0.80), P(NPV ≥ 0.90), and P(FNR < 0.10). The posterior Se median at the group level was 94% (CrI 95% 89.9-97%). The performance between operators was similar, and the probability of having a Se ≥ 90% was high (95.9% at group level), being 78.1% in the worst case (operator four); similarly, the posterior probability of NPV ≥ 90% was higher than 50% in all operators, except for operator four. Regarding the FNR, there is a high probability of complying with the recommendation of FNR < 10%, being 79.5% in the worst case (operator four) and ≥ 95% at the group level as well as in five operators.

Strong evidence was found for the association between gender and positive microscopy results, being higher in females (BF_{10} = 10.31, posterior probability OR median 1.64, CrI 95% 1.17-2.29, ESS > 10,000 PSRF < 1.01, using default priors). However, no association was found between sex and FP results given a positive dipstick analysis (BF_{10} = 0.25, neither for nor against the alternative hypothesis) nor between sex and FN results given a positive microscopy analysis (BF_{10} = 1.17, neither for nor against the alternative hypothesis). In other words, the prevalence of abnormal microscopy is related to gender, but gender does not influence the performance of the dipstick analysis.

Regarding the risk analysis, 15 patients with FN were found, one of them with a double cause (leukocyte 6-10/high-power field [HPF] and erythrocytes 3-5/HPF). The most frequent cause of FN was erythrocytes 3-5/HPF, with 11 events (including the patient with a double cause); in one case, it was not possible to obtain patient status data from the clinical record, and in the remaining cases, the microscopic result did not modify diagnostic or therapeutic behavior. There was one case of FN due to erythrocytes of 6-10/HPF. However, the patient was under follow-up due to psoriasis. The result also did not modify diagnostic or therapeutic behavior; urinary pH[2] (pH = 5) was identified as a probable cause of the FN result. In patients with FN results due to hyaline casts, data from the clinical record were not found in two of three patients. The remaining had a diagnosis of probable nephrolithiasis (1st time consultation). Still, the result did not modify diagnosis or treatment behavior. The patient with a double cause of FN result underwent follow-up consultation for infectious urethritis, and the result also did not modify diagnostic or therapeutic behavior. The severity and occurrence of FN results are summarized in table 4, and according to the risk analysis, the FN events observed in this study are considered low risk (Table 5).

Table 4. Causes of false negatives

FN cause	n	Severity	Occurrence
Hyaline cast 1-2/LPF	3	S1	O1 (1.75%)
Erythrocyte 3-5/HPF	11	S1	O2 (6.43%)
Erythrocyte 6-10/HPF	1	S3	O1 (0.58%)
Leukocyte 6-10/HPF	1	S2	O1 (0.58%)

FN: false negative; HPF: high-power field; LPF: low-power field.

Table 5. Risk matrix

	S1	S2	S3	S4
O5				
O4				
O3				
O2	Ery 3-5[a]			
O1	Hyal[b]	Leu[c]	Ery 6-10[d]	

[a]erythrocyte 3-5/HPF, [b]hyaline casts 1-2/LPF, [c]leukocyte 6-10/HPF, [d]erythrocyte 6-10/HPF. Color code is as follows: green, low risk; yellow, intermediate risk; red, high risk.
O: occurrence; S: severity.

In a *post hoc* analysis, the impact on time and costs of omitting negative dipstick microscopy analysis was evaluated. The average time for iQ200 was calculated as a weighted mean of the average time in samples with normal and altered microscopy given a negative reagent strip (calculated in the same way as Miler and Nicolac[5]), obtaining an estimated time of 0.73 min per sample. Considering a single morning shift (7.5 h) on weekdays (which is the shift in which most outpatient samples are processed), a median of 90 outpatient samples, and a proportion of 31% of samples with a negative test strip result, 28 samples would have been omitted for microscopic analysis, representing a saving of 20.44 min per morning shift. About the costs, taking an estimate of 0.69 USD/sample, in 1 week, a median of 450 urinalyses are performed, including all weekday morning shifts, representing the omission of 140 microscopic analyses and a median saving of 96.6 USD/week.

Discussion

The iQ200 methodology is based on the use of photomicrographs and a neural network algorithm for particle classification[30]. This device has been shown to have adequate intra-assay and interassay precision

(5% and 5.9%, respectively) for erythrocytes, leukocytes, and epithelial cells, not requiring centrifugation, decantation, and resuspension of the sample (which the manual method requires and is considered a potential source of variation). Nevertheless, problems have been described with the device's performance for parameters such as bacteria, crystals, yeasts, and casts[31]. During normal use of the iQ200, a "review and validation" step by the operator is required, allowing reclassification of particles whose classification by the algorithm is unreliable. These results mean that the operator's influence cannot be completely eliminated, despite being an automated method.

Chambliss et al.[4] reported a similar study, using the iQ200 as the reference standard. They found results of diagnostic performance like ours at the group level: Se (93% vs. median 94% in ours), Sp (56.9% vs. median 57.1% in ours), PPV (64.7% vs. median 67.8% in ours), PNV (90.5% vs. median 90.7% in ours), and FNR (3.2% vs. median 5.8% in ours). Some notable differences between both studies are the slightly lower prevalence of positive microscopy (45.9% vs. 50.9% in ours) and the fact that the population in their study included pediatric patients, emergency department patients, and hospitalized patients. Another difference is that in their study, they considered the presence of any amount of bacteria as a positive microscopy criterion, even though 92.9% of their FNs were for that reason. They also made a sub-analysis using urine culture as the reference standard and dipstick as the index test, finding an NPV of 93.7% for culture-confirmed urinary tract infections. In our case, we considered our approach of not including such criteria to be appropriate since there is evidence that parameters such as LE or nitrites have a good performance when trying to exclude urinary tract infection with high Se (LE: 48-86%, Nit: 46-50%, and Nit + LE: 68-88%) and NPV (LE: 82-91%, Nit: 70-88%, and LE + Nit: 78-98%)[2,12,13,32]. On the other hand, the presence of bacteria found by light microscopy in a random urine sample is not very sensitive and it is a poor predictor of urinary tract infection (Se 46-58% and PPV 54-88%)[2].

Considering the previous studies using manual methods[6-10], the diagnostic performance is similar for Se (78-98.7%) and Sp (36.3-74%). In our study, a posterior distribution of NPV was obtained with a median of 90.7% (CrI 95% 84.7-95.3%), which is lower than these studies (NPV 92-99%). However, they have a lower abnormal microscopy prevalence (17-42%)[6-10], which may explain the high NPV. Despite a high prevalence of positive microscopy in ours, a low FNR was obtained, with a high probability of being less than the recommended 10%, both at the group and individual levels. Another important point is that despite the heterogeneity in the experience of the operators (2-33 years), the performance was similar between them. The results here place Se > 90% with good certainty at the individual and group levels.

There are some limitations in the dipstick analysis, with special relevance to FN results in the blood (captopril, concentrated urine, proteinuria, and Vitamin C), LE (concentrated urine, ketonuria, proteinuria, antibiotics [cephalexin and nitrofurantoin], and Vitamin C), Nit (concentrated urine, non-nitrate-reducing bacteria, urine pH < 6, and Vitamin C), and proteins (acid or dilute urine)[2]. Nonetheless, with the risk analysis as described by Miler and Nikolac[5], no FNs with high risk for the patient were found in our study. Unfortunately, the diagnostic performance cannot be compared with Miler and Nikolac[5] as it is not reported. While Chambliss et al.[4] did not make a formal risk analysis, the causes of FN (excluding bacteria) were mainly erythrocytes < 4/HPF (96.6%) and leukocytes < 4/HPF (92.2%). Flexibility is required , if a patient has a condition (systemic disease or medication) that limits the Se of the dipstick analysis or the physician has a high suspicion, the need for microscopic analysis, regardless of the dipstick result, must be fulfilled.

The omission of negative dipstick microscopy could save us approximately 20.4 min per morning shift and approximately 96.6 USD/week, which is significant for our institution in the context of a developing country. The reduction in costs and time may vary depending on the methodology (microscopic analysis in the manual method has been estimated at 2.08 min[5]) and the prevalence of positive dipstick results. In other circumstances, the benefit may be greater.

The main weakness of our study is its retrospective nature, which prevents a quantitative or semi-quantitative evaluation of the degree of modification or reclassification of the results (both at the group and operator level), as well as the inability to assess the frequency of intervention by the operator.

Conclusions

The performance of the dipstick compared to the automated microscopy analysis is appropriate, with good certainty of Se > 90% and FNR < 10% at the operator level. Omission of microscopic analysis can be a safe action in a patient with a negative dipstick result and a low pre-test probability, as an FN that significantly modifies either diagnostic or therapeutic conduct is not expected.

Acknowledgments

The authors thank all the clinical laboratory staff for their invaluable work.

Funding

The authors declare that they have not received funding.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained approval from the ethics committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

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