

# Variables to Predict Nephrological Disease in General, and Glomerulonephritis in Particular, in Patients With Microhematuria

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## Abstract

**Background:** Microhematuria (MH) is a symptom frequently leading to uncertainty as to when a nephrology referral is appropriate. Because MH may be indicative of severe kidney disorders, prompt diagnosis and potential treatment initiation can be important. We aimed to identify further variables that point at a nephrological cause, in particular of glomerulonephritis (GN), when MH is diagnosed.

**Methods:** A retrospective analysis of data acquired from patients attending a nephrology office due to MH was performed. Demographic information and diagnostic tests were evaluated in order to identify factors that were associated with a nephrological cause.

**Results:** Patients with MH (n = 805) as indicated by a urine stick analysis were included. Of these, MH was confirmed by urine sediment analysis in 543 patients (67.5%). Of those, 48.3% had a nephrological cause, including 12.4% with GN and 2.9% with rapid progressive GN (RPGN). A urine dipstick finding of  $\geq 250$  erythrocytes per microliter, microalbuminuria and elevated leukocytes increased the probability of having a GN to 62.4%. Furthermore, the presence of microalbuminuria, GFR < 60 mL/min, history of hypertension and diabetes mellitus increased the probability for all nephrological causes to 95.4%.

**Conclusion:** There are a number of factors available that help to assess the need for a nephrology referral in patients with microhematuria.

**Keywords:** Microhematuria; Kidney disease; Diagnostic; General practice; Urinalysis

## Introduction

Microhematuria (MH) is commonly defined as the presence of at least three red blood cells per field of view under a high-power lens during analysis of a properly obtained urine specimen [1]. Usually asymptomatic, it is mostly an accidental finding that is considered to be of little importance unless patients are at an advanced age and are at risk of cancer [2]. Therefore, there is uncertainty as to the extent of workup needed [3-5].

The source of MH may be located anywhere along the urinary tract, with a wide variety of possible causes. These include benign reasons such as mild trauma or infections [6], but also malignancies [7]. Furthermore, a proportion of patients presenting with MH will have a nephrological condition that requires intervention in order to delay progression to end-stage renal disease (ESRD) and dialysis [1, 8]. The presence of dysmorphic red blood cells, proteinuria, cellular casts, and/or renal insufficiency indicates a need for further investigation to establish if there is a glomerular cause [1].

It is apparent from the literature that there is a high level of uncertainty surrounding the usefulness and accuracy of MH to predict serious nephrological disorders. This is particularly true among the majority of office-based physicians, which rarely have the means to perform urine sediment microscopy, and thus insufficient information to make a decision on the need for a nephrology referral [9, 10]. Clarification of this situation is essential for enabling accurate and rapid diagnosis.

We therefore carried out a retrospective evaluation of patients presenting with MH attending our nephrology office. The aim of the analysis was to identify factors that are routinely determined by the office-based physician and increase the likelihood of a nephrological cause of MH. Such information would improve the identification of patients that would benefit from early referral to a nephrologist, allowing for rapid diagnosis and initiation of appropriate treatment [8].

## Methods

### Study design

We carried out a retrospective analysis of data from patients

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**Table 1.** Patient Characteristics

	Mean ± SD (range) or n/N (%)
Epidemiology (N = 805)	
Age (years)	56.3 ± 18.1 (6 - 91)
Patients ≥ 40 years	665/805 (82.6%)
Sex (male)	389/805 (48.3%)
BMI (kg/m <sup>2</sup> )	27.8 ± 6.0 (12.6 - 64.7)
CV risk factors (N = 543)	
SBP (mm Hg)	144.7 ± 23.5 (90 - 227)
DBP (mm Hg)	82.4 ± 14.4 (50 - 145)
History of arterial hypertension	359/543 (66.1%)
Diabetes mellitus, type 1 or 2	86/543 (15.8%)
Hyperlipidemia	178/543 (32.8%)
Current smoker	132/543 (24.3%)
Kidney function (N = 543)	
eGFR (mL/min)	62.1 ± 34.1 (2 - 186)
eGFR < 90 mL/min	375/502 (74.1%)
eGFR < 60 mL/min	236/502 (47.1%)
Microalbuminuria > 20 mg/L	255/372 (68.5%)
Signs of urinary tract infection (N = 543)	
Leukocytes in urine test strip ≥ 25/μL	229/543 (42.2%)
Nitrite in urine	37/543 (6.8%)
Chronic infection of the urinary tract	53/543 (9.8%)

Epidemiological data were taken from the whole cohort (N = 805), whereas the other data (N = 543) were taken only from patients with confirmed MH (≥ 3 erythrocytes per high power field of view in urine sediment analysis). BMI: body mass index; CV: cardiovascular; SBP: systolic blood pressure; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate.

who presented at our nephrology office between 1998 and 2014. All patients with MH in a prior urine test strip analysis were included. No further inclusion or exclusion criteria were applied.

## Documentation

For all patients, demographic information was collected, along with the result of urine test strip analysis. Further data were recorded for those patients that tested positive for MH in the urine sediment analysis, being defined as ≥ 3 erythrocytes per visual field under a high power lens. A full medical history was taken, including the intake of relevant drugs (anticoagulation and NSAID), and additional diagnostic testing was documented. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula, and signs of a urinary tract infection (leukocyturia and nitrite) were recorded. Coagulation abnormalities (prothrombin time (PTT), Quick, international normalized ratio (INR), and thrombocytes) and systemic inflammation were evaluated.

The potential sources of the MH were taken from the patient files, which included the results of all diagnostic tests,

including the kidney biopsy if one had been performed.

The study was conducted according to the principles of the Declaration of Helsinki.

## Statistical analysis

Data were presented as means with standard deviations (SDs) and range or absolute values with percentages. Boosted regression was used to preselect variables affecting the likelihood of a nephrological cause (or glomerulonephritis (GN) specifically). The association analysis was based on patients with all necessary data available (n = 339 complete cases).

Logistic regression with Firth's penalised likelihood approach was used in order to reduce potential bias caused by low event rates. Univariate and multivariate effect estimates (OR) along with 95% confidence intervals (CIs) were given. Furthermore effect measures on the log OR were dichotomised to create a risk score. This model was then recalibrated based on the total risk score sums to get appropriate values for the probability of an event, with the area under the curve (AUC) as a goodness-of-fit measure. A P-value of < 0.05 was considered to be statistically significant. All analyses were performed us-

**Table 2.** Characteristics of Hematuria

	n/N (%)
Erythrocytes in urine stick analysis (per $\mu$ L)	
< 10	78/805 (9.7%)
$\geq$ 10 - 49	371/805 (46.1%)
$\geq$ 50 - 249	188/805 (23.4%)
$\geq$ 250	167/805 (20.8%)
Macroscopic hematuria	37/805 (4.6%)
Chronic hematuria	20/805 (2.5%)
Confirmed MH (urine sediment) <sup>†</sup>	543/805 (67.5%)

Data from the urine test strip analysis were collected at the first visit to the nephrologist (N = 805). <sup>†</sup>Confirmed hematuria is defined as patients that had  $\geq$  3 erythrocytes per high power field of view in urine sediment analysis.

using the software Statistica 12 (Statsoft, Hamburg, Germany) and R (R Foundation, Vienna, Austria).

## Results

### Patient characteristics and MH

A total of 805 patients that presented at the nephrology office due to an office-based physician diagnosis of MH were included in the study. The mean age of this population was 56.3  $\pm$  18.1 years (range: 6 - 91 years) (Table 1). At the time of the first nephrology visit, urine test strip analysis identified 90.3% of the 805 patients with  $\geq$  10 erythrocytes per microliter, and the remaining proportion with fewer than 10 erythrocytes per microliter. Macroscopic hematuria was documented for 4.6% of the 805 patients and chronic haematuria for 2.5% (Table 2).

MH was confirmed by urine sediment analysis in 543 (67.5%) patients. Thus, a total of 262 patients (32.5%) were determined to have transient MH or false positive urine test strip analysis (Table 2).

For the patients with MH confirmed by the urine sediment analysis, 66.1% (359/543) of patients had a history of arterial hypertension, 32.8% (178/543) hyperlipidemia and 15.8% (86/543) diabetes mellitus (type 1 or 2).

The eGFR was found to be below the normal value of 90 mL/min in 74.1% of the patients with 47.1% (236/502) having an eGFR value below 60 mL/min (Table 1).

### Underlying causes of MH

A potential nephrological cause of MH was identified for 48.3% (262/543) of patients (Table 3). The underlying disease was determined to be GN in 12.4% (68/543) of patients, with this diagnosed as RPGN in 2.9% (16/543). Interstitial nephritis, generally attributed to medication use, was found in 6.1% (33/543) of patients. High proportions of patients were found to have a first diagnosis of hypertensive (26.5%; 144/543) or

**Table 3.** Potential Sources of MH Identified in the Nephrology Office (Multiple Selections Are Possible)

	n/N (%)
Nephrological disease (all)	262/543 (48.3%)
Glomerulonephritis (all)	68/543 (12.4%)
Rapid progressive glomerulonephritis	16/543 (2.9%)
Interstitial nephritis	33/543 (6.1%)
Congenital kidney disease	15/543 (2.8%)
Diabetic nephropathy	51/543 (9.4%)
Hypertensive nephropathy	144/543 (26.5%)
Other kidney diseases*	16/543 (2.9%)
Urological source	113/543 (20.8%)
Infection of the urinary tract	55/543 (10.1%)
Pyelonephritis	10/543 (1.8%)
Coagulation abnormality <sup>#</sup>	64/541 (11.8%)
Vitamin K antagonist/NOAC use	44/543 (8.1%)
Anti-platelet drug use <sup>†</sup>	97/543 (17.9%)
NSAID use	66/543 (12.2%)
Systemic inflammation <sup>‡</sup>	124/543 (22.8%)
Number of potential sources of MH	
1	147/543 (27.1%)
2	127/543 (23.4%)
3	76/543 (14.0%)
4	19/543 (3.5%)
Unclear diagnosis, benign MH	174/543 (32.0%)

NOAC: non-vitamin-K oral anticoagulant; NSAID: non-steroidal anti-inflammatory drug. \*Includes multiple myeloma and renal amyloidosis; multiple myeloma; scleroderma; and suspected or non-proven glomerulonephritis. <sup>#</sup>Thrombocytopenia, increased INR, or elevated prothrombin time. <sup>†</sup>Includes aspirin, clopidogrel, dipyridamol, ticlopidine. <sup>‡</sup>CRP > 5 mg/L or ESR > 20 mm/h or leukocytes > 10/mL.

diabetic (9.4%; 51/543) nephropathy.

Only 27.1% (147/543) of patients had a single potential cause, with multiple reasons particularly common for the patients with renal diseases that are not normally associated with MH, such as hypertensive and diabetic nephropathy.

The most frequent concomitant cause of MH was urological (20.8%; 113/543), with 54.0% also presenting with a nephrological disorder. Further concomitant reasons were systemic inflammation (22.8%; 124/543), urinary tract infections (10.1%; 55/543) and coagulation abnormality (11.8%; 64/541), with 8.1% (44/543) being treated with anticoagulants or anti-platelet agents (17.9%; 97/543) (Table 3).

### Relationship between MH and a diagnosis of kidney disease

Kidney disease was diagnosed in 262 (48.3%) of the 543 patients that were found to have MH in the urine sediment analy-

**Table 4. Relationship Between MH and Renal Disease**

	Renal disease (all) (N = 262)			Glomerulonephritis (N = 68)		
	OR (95% CI), univariate	P-value	OR (95% CI), multivariate*	P-value	OR (95% CI), univariate	P-value
Erythrocytes in urine test strip analysis (per $\mu\text{L}$ )						
< 10	0.88 (0.54 - 1.42)	0.61	0.97 (0.45 - 2.07)	0.94	0.47 (0.15 - 1.06)	0.10
10 - 49	1.18 (0.82 - 1.71)	0.37	1.28 (0.68 - 2.47)	0.44	0.43 (0.20 - 0.80)	0.012
50 - 249	0.63 (0.42 - 0.92)	0.017	0.71 (0.38 - 1.27)	0.25	0.62 (0.31 - 1.14)	0.14
$\geq 250$	1.42 (0.98 - 2.07)	0.067	1.18 (0.63 - 2.22)	0.61	5.09 (2.44 - 7.00)	<0.001
Epidemiological data						
Age $\geq 40$ years	2.64 (1.69 - 4.27)	<0.001	0.55 (0.25 - 1.17)	0.13	0.74 (0.41 - 1.41)	0.32
Male sex	1.94 (1.38 - 2.74)	<0.001	1.22 (0.69 - 2.16)	0.48	3.24 (1.87 - 6.05)	<0.001
BMI > 30 kg/m <sup>2</sup>	1.91 (1.29 - 2.86)	0.001	1.81 (0.96 - 3.57)	0.072	0.68 (0.33 - 1.24)	0.23
Blood pressure						
History of hypertension	6.03 (4.03 - 9.30)	<0.001	4.10 (2.23 - 8.02)	<0.001	1.25 (0.73 - 2.25)	0.43
Hypertension (> 140/90 mm Hg)	2.73 (1.92 - 3.91)	<0.001	1.43 (0.78 - 2.67)	0.25	1.15 (0.69 - 1.94)	0.59
Kidney function						
eGFR < 90 mL/min	3.61 (2.34 - 5.66)	<0.001	1.91 (1.01 - 3.64)	0.047	1.25 (0.70 - 2.42)	0.47
eGFR < 60 mL/min	7.50 (5.07 - 11.3)	<0.001	5.38 (3.17 - 9.66)	<0.001	1.50 (0.90 - 2.54)	0.12
Microalbuminuria > 20 mg/L (=A2)	5.38 (3.45 - 8.63)	<0.001	3.90 (2.27 - 7.03)	<0.001	6.79 (2.93 - 21.8)	<0.001
Further risk factors						
Current smoker	0.79 (0.53 - 1.17)	0.25	1.55 (0.83 - 3.01)	0.17	0.80 (0.41 - 1.45)	0.48
Diabetes mellitus	5.43 (3.18 - 10.0)	<0.001	2.76 (1.24 - 7.06)	0.017	0.42 (0.13 - 1.04)	0.061
Systemic inflammation <sup>†</sup>						
CRP > 5 mg/L	2.32 (1.34 - 4.09)	0.003	1.14 (0.48 - 2.59)	0.76	1.84 (0.87 - 3.98)	0.11
Leukocytes > 10/nL	1.46 (0.93 - 2.33)	0.11	2.46 (1.18 - 5.56)	0.019	2.31 (1.28 - 4.02)	0.004

OR: odds ratio; BMI: body mass index; eGFR: estimated glomerular filtration rate; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate. A P-value of < 0.05 was considered to be significant. \*Variables entered in the multivariate analysis "Renal Disease (all)" were age > 40 years, male sex, BMI > 30 kg/m<sup>2</sup>, GFR < 90 mL/min, history of hypertension, diabetes mellitus type 1 and 2, microalbuminuria > 20 mg/L; other variables were not included owing to low numbers of patients. †Variables entered in the multivariate analysis "Glomerulonephritis" were erythrocytes in the urine test strip  $\geq 250/\mu\text{L}$ , age > 40 years, male sex, microalbuminuria > 20 mg/L, and severe systemic inflammation; other variables were not included owing to low numbers of patients. †Systemic inflammation: CRP > 5 mg/L or ESR > 20 mm/h or leukocytes > 10/nL. Severe systemic inflammation: CRP > 50 mg/L or ESR > 75/h or leukocytes > 15/nL.



sis. In univariate analysis, a patient age of  $\geq 40$  years was associated with a nephrological disease, as was male gender and a BMI of  $> 30 \text{ kg/m}^2$  (Table 4). In addition, a history of hypertension, blood pressure  $> 140/90 \text{ mmHg}$ , eGFR impairment, diabetes mellitus (type 1 and 2), and elevated systemic inflammation were associated with kidney disease in our cohort.

Factors associated with a patient that had a nephrological cause of MH were determined by selecting variables found to be statistically significant in multivariable logistic regression, while also being available in the daily physician office. The variables identified were a history of hypertension (OR: 3.98; 95% CI: 2.16 - 7.77;  $P < 0.001$ ), eGFR  $< 60 \text{ mL/min}$  (OR: 5.17; 95% CI: 3.05 - 9.21;  $P < 0.001$ ), the presence of microalbuminuria (OR: 3.76; 95% CI: 2.20 - 6.75;  $P < 0.001$ ), and diabetes mellitus (type 1 or 2; OR: 2.84; 95% CI: 1.29 - 7.24;  $P = 0.013$ ). The number of these indicators that are present can be regarded as a risk score for having a nephrological disease (AUC = 0.850), with an estimated probability of 95.4% whenever all four indicators are present (Fig. 1).

In the univariate analysis (328 complete cases), the likelihood of glomerulonephritis specifically was found to be higher for patients with a urine test strip results of  $\geq 250$  erythrocytes/ $\mu\text{L}$  (OR: 5.09; 95% CI: 2.44 - 7.01;  $P < 0.001$ ), those with microalbuminuria (OR: 6.79; 95% CI: 2.93 - 21.8;  $P < 0.001$ ), and those with elevated leukocytes ( $\geq 10/\mu\text{L}$ ; OR: 2.31; 95% CI: 1.28 - 4.02;  $P = 0.004$ ). The cut-off of  $\geq 10$  leukocytes/ $\mu\text{L}$  was chosen from the 80<sup>th</sup> percentile of the data as a cut-off value of  $\geq 11/\mu\text{L}$  yielded too few elevated cases (Table 4). The quantity of these three indicators that are present can be regarded as a risk score for having GN (AUC = 0.773), with an estimated probability of 62.8% in the case of all three indicators being present (Fig. 1).

## Discussion

In order to identify factors that may indicate the need for a referral to a nephrologist for an individual presenting with MH, we retrospectively analyzed data from patients attending our nephrology office. Certain factors were found to be associated with a greater likelihood of the presence of an underlying nephrological cause of the patient's MH. From the collated data, we calculated probabilities of nephrological disease in general and GN specifically, which could be used by an office-based physician when determining the necessity for a nephrology referral.

GN was a potential source of MH for 12.4% of patients, with 2.9% of these cases determined to be rapid progressive GN, a condition that can result in ESRD and a need for dialysis within a few weeks of its development. It is for these patients that a prompt consultation with a nephrologist is the most important. A urine test strip finding of  $\geq 250$  erythrocytes/ $\mu\text{L}$ , microalbuminuria, and elevated leukocyte count were all associated with GN, with a calculated probability of this condition being present of 62.8% if all three indicators were found. These could therefore be important parameters to indicate the presence of a serious nephrological disorder to the office-based physician, possibly even before a decrease in kid-

ney function/eGFR becomes apparent. All of these variables are readily available to the office-based physician.

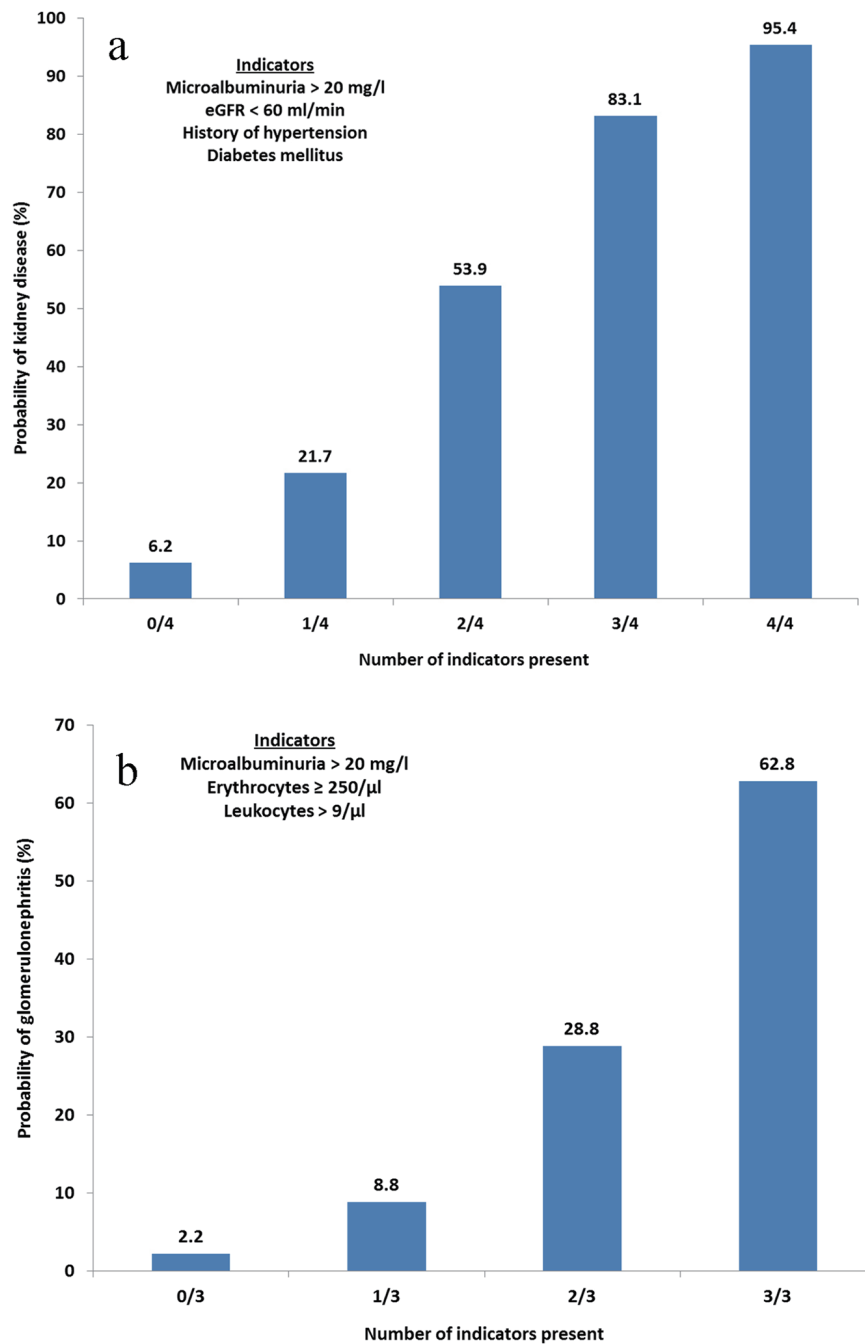
Interestingly, a high proportion of patients with MH were diagnosed as having hypertensive or diabetic nephropathy. These glomerulopathies are not normally associated with MH, thus, it is likely that these patients had an additional source. Indeed, approximately 40% of the patients included in our analysis had their MH attributed to more than one potential cause. This includes the use of anticoagulants or anti-platelet agents, infections and urological diseases. Therefore, although hypertensive or diabetic nephropathy is unlikely to be the sole cause of the MH, the presence of hypertension or diabetes should indicate to the office-based physicians that a nephrology referral may be warranted.

It should be noted that hypertensive nephropathy is over-represented in our cohort. While few of these patients had a kidney biopsy, Perkowska-Ptasinska et al. showed a low prevalence of hypertension-related lesions in the biopsies they performed on their nephrology patients, a high proportion of whom had hypertension [11]. Therefore, in patients presenting with MH and elevated blood pressure, other renal diseases have to be ruled out.

The presence of dysmorphic erythrocytes or cellular casts is a reliable indicator of a glomerular cause of the MH [12-14]. However, many nephrological conditions present with erythrocytes of unaltered morphology [15]. In addition, office-based physicians often do not have the facilities to perform urine sediment microscopy to make a decision regarding the need for a nephrology referral [10]. Thus, we decided to include all patients with a renal cause of MH, independent of its characteristics, in the statistical analysis and development of the probability scores. In order to aid the physician in their decision-making process, we statistically determined the individual risks associated with parameters that are routinely available in general clinical practice. Microalbuminuria, an eGFR below  $60 \text{ mL/min}$ , a history of hypertension, and the presence of diabetes mellitus type 1 or 2 were found to be highly associated with kidney disease. The probability of a nephrological disorder increased with the number of these indicators that were present, reaching approximately 95% when all four were found. Whilst we do not go so far as to recommend a cut-off point for a nephrology referral, this system provides useful guideline for the office-based physician. Validation of the model in a large cohort of patients displaying MH in a clinical practice setting may provide an estimation of an appropriate risk level at which a patient should be referred to a nephrologist.

## Limitations

One limitation to the present analysis is its retrospective nature. In addition, only patients with MH were included and there was no comparison to patients without MH. This analysis was based on the data of a single office rather than being a multi-center study. Furthermore, there are no data available from office-based physicians that may have seen these patients prior to the nephrology visit. Such information would have allowed for analysis of the appropriateness of current referral



**Figure 1.** (a) Probability of kidney disease based on clinical findings. Calculated probabilities of kidney disease based on factors found to be significant in the multivariate logistic regression. Any combination of indicators can be present. eGFR, estimated glomerular filtration rate. (b) Probability of glomerulonephritis based on clinical findings. Calculated probabilities of glomerulonephritis based on factors found to be significant in the multivariate logistic regression. Any combination of indicators can be present. Erythrocyte concentration determined by urine stick analysis.

practices and adherence to expert guidelines.

**Conclusions**

In a cohort of patients attending a nephrology clinic due to a

finding of MH, a number of factors were found to be associated with the presence of the condition, including hypertension, diabetes mellitus, microalbuminuria, and a reduced eGFR. Furthermore, a urine dipstick finding of ≥ 250 erythrocytes per microliter, microalbuminuria, and elevated leukocytes were independently associated with the presence of GN specifically.

In order to aid office-based physicians to determine when a nephrology referral is necessary for a patient with MH, we calculated probabilities of a nephrological disease being present, based on variables routinely available in clinical practice.

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## Conflicts of Interest

None.

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