Evaluation of Urinary and Serum Macrophage Migration Inhibition Factor in a group of Systemic Lupus Erythematosus Egyptian Patients

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Abstract

Objective: to evaluate the potential clinicopathological involvement of macrophage migration inhibitory factor (MIF) in systemic lupus erythematosus (SLE), and its relationship with lupus nephritis (LN) through measuring serum and urinary MIF levels. **Methods:** A cross-sectional case-control study was carried out on 30 SLE female patients and 30 healthy age-matched females as a control group. SLE activity was assessed by the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2k) and renal activity was evaluated with the renal-SLEDAI (rSLEDAI-2k). SLE damage was evaluated by the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index. Serum MIF (sMIF), urinary MIF (uMIF) levels were assayed and uMIF/creatinine ratio was estimated in all studied subjects. **Results:** SLE patients had significantly higher levels of sMIF, uMIF and uMIF/ creatinine ratio than the control group (p <0.001 for each). They were also significantly higher in SLE patients with lupus nephritis compared with those without lupus nephritis (p <0.001 for each) and in patients with active nephritis compared with inactive cases (p= 0.007, 0.001, 0.018, respectively). There were significant increase in sMIF, uMIF levels and uMIF/creatinine ratio in association with disease activity assessed by SLEDAI (p =0.005, 0.026, 0.049, respectively). Through regression analysis revealed that sMIF, uMIF, uMIF/creatinine ratio were found to be independent predictors for lupus nephritis development. **Conclusion:** This study showed that MIF is related to renal disease activity in SLE. Further prospective studies are required to verify whether MIF has a prognostic value in predicting clinical outcomes in SLE patients with different therapeutic regimens.

Keywords: Systemic lupus erythematosus; MIF; lupus nephritis; lupus biomarkers.

Introduction

Systemic lupus erythematosus (SLE) is a life-long multi-systemic autoimmune disease with partially understood pathogenesis. SLE patients have a high rate of morbidity and mortality, which is attributed to renal disease **(1)**. Up to 90% of SLE patients develop renal involvement at some point throughout the disease's course **(2)**. In more than 30% of cases, lupus nephritis (LN) develops synchronously. The most common cause of LN pathogenicity is cytokine overproduction, which leads to the formation of nephrotoxic autoantibodies and glomerular immune complex deposits **(3)**.

Renal biopsy is still the gold standard for determining LN activity, however serial renal biopsies are not applicable in clinical practice **(4).** Despite the revelation of numerous proinflammatory molecules as possible biomarkers for LN, an agreement on how to use these markers for LN remains elusive **(5).**

TNF superfamily cytokines weak inducers of apoptosis (TWEAK) induce mesangial cells, podocytes, and endothelial cells to generate pro-inflammatory chemokines such as macrophage migration inhibitory factor (MIF) and interleukin-10 (IL-10) that are critical in the pathophysiology of lupus nephritis **(6)**. MIF is a multifunctional protein that works as an innate immunity mediator and can also influence host inflammatory responses by regulating cellular processes such as T-cell proliferation and counteracting glucocorticoid immunosuppressive effects (GCs) **(3).** Serum MIF (sMIF) concentrations have been linked to SLE disease activity, damage ratings, and glucocorticoid dose **(7,8)**. Additionally, substantial levels of renal glomerular and tubular MIF expression have been reported in individuals with SLE and LN, implying that MIF could be found in the urine of LN patients **(9).** Urine concentrations of MIF (uMIF) have been reported previously in studies with relatively small group of patients with LN **(10, 11,12)** and reported the uMIF only as a potential overall disease biomarker **(5)**.

Thus, we aimed at evaluating the clinical significance of serum and urinary MIF concentrations in a group of Egyptian patients with SLE and assessing their clinical utility as non-invasive biomarker for LN development and activity.

Patients and Methods

Study design and population

This cross-sectional case-control study was conducted on 60 female subjects including 30

SLE patients who attended Rheumatology, Rehabilitation and Physical Medicine department, Benha University Hospital between October 2020 and January 2021.

All included SLE patients met the "Systemic Lupus International Collaborating Clinics" consortium designed classification criteria (SLICC'12)**(13)** . Any patient with chronic systemic disease not related to/associated with SLE (e.g., other autoimmune disorders, infections, tumors, diabetes mellitus, and hypertension) and patients with renal disease not related to SLE were excluded from the study. In addition, 30 apparently healthy age-matched female blood donors were selected to serve as a control group. The laboratory work was carried out in Clinical and Chemical Pathology department, Benha University Hospital .

The study was approved by the research ethics committee in faculty of medicine, Benha university in accordance with "The Code of Ethics of the World Medical Association" (Declaration of Helsinki). Informed written consent was obtained from each participant after being fully informed about the study purpose and procedures prior to enrollment.

Methods

Clinical evaluation

One expert rheumatologist evaluated the SLE cases using a structured chart, including disease manifestations, comorbidities, and current medications. Assessment of SLE activity was done using the Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2k)**(14)** .

The SLEDAI is an index designed to evaluate SLE activity in the previous 10 days, with 24 weighted clinic-laboratory parameters corresponding to 9 different organs/systems. The total SLEDAI-2K score ranges from 0 to 105, with higher scores for higher activities. Activity scores have been categorized into: no activity (SLEDAI= 0), mild activity (SLEDAI= 1 to 5), moderate activity (SLEDAI= 6 to 10), high activity (SLEDAI= 11 to 19), and very high activity (SLEDAI ≥20). Renal activity was evaluated with the renal-SLEDAI (rSLEDAI-2k)**(14)**, which represents the sum of the 4 renal domains of the SLEDAI: proteinuria, pyuria, hematuria, and casturia; each one is scored with 0 meaning absence or 4 points meaning presence.

The total rSLEDAI-2K score ranges from 0 to 16, with higher scores for higher lupus

nephritis activity. Active LN as renal SLEDAI-2K >0; non-renal disease activity will be measured using the SLEDAI-2K excluding renal domains **(15)**. Evaluation of SLE damage was explored using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) damage index **(16)**. SLE patients in our study were further sub-classified into; the renal-SLE group compared with the non-renal group, which consisted of SLE patients that did not meet any criteria of the rSLEDAI.

Laboratory evaluation

Peripheral venous blood was withdrawn from enrolled subjects. EDTA and citrated blood were used to perform the complete blood count (CBC) by Sysmex XS-500 I, Japan and erythrocyte sedimentation rate (ESR) by Westergren method. Serum was separated and used to assay C-reactive protein (CRP) by CRP-latix slide agglutination kit supplied by Spinreact, Spain, anti-nuclear antibodies (ANA), anti-double stranded DNA antibodies (anti-dsDNA) detected by IIF kit provided by Inova Diagnostics, USA, and complement components C3&C4 detected by simple radial immunodiffusion using Combi-plate (Far, Italy). Kidney and liver function tests were performed using Bio-System A25 autoanalyzer (Biosystems, Barcelona, Spain).

Fresh random urine sample was collected in a sterile container for complete urine analysis, urine creatinine and urine protein levels to assess urinary protein/creatinine ration (UPCR). The clear supernatant after centrifugation at 1500 rpm for 10 minutes was used to assay urinary MIF (uMIF) level . Urinary MIF was adjusted against creatinine concentration in the spot urine sample to estimate uMIF/creatinine ratio.

Serum and urinary MIF levels were measured by a quantitative sandwich enzyme immunoassay technique using a commercial ELIZA kit supplied by R&D system , USA **(5)**

Statistical methods

The collected data were tabulated and analyzed using IBM SPSS version 25.0.(Armonk, NY; IBM Corp), Shapiro test was done to test the normality of data distribution. Mean, standard deviation (± SD) was used to describe parametric numerical data, while median (range) was used for non-parametric numerical data. Student (t) test was used to compare between two study groups means, and one way analysis of variance (ANOVA) was used for the comparison of the multiple

subgroups' means. Mann Whitney (U) test was used to compare a non-parametric variable between two study groups, and the Kruskal-Wallis (KW) test was used to compare non-parametric variables in multiple study groups. Qualitative data were described as number (percent). Chi-Square (X^2) test, and Fisher's exact test (FET) were used to examine the relationship between them. The correlation coefficient (*r*) was used to define the strength of association and the direction of linear relationship between two quantitative variables. Receiver Operating Characteristic (ROC) curve analysis was used to evaluate the sensitivity and specificity of sMIF and uMIF levels that categorize cases into one of two groups. Finally, logistic regression analysis was used for prediction of risk factors of lupus nephritis, using generalized linear models. Odds ratio (OR) and 95% confidence interval (CI) were calculated. Significance of the obtained results was accepted at a *p* value <0.05 with 95%confidence interval.

Results

The present study included 60 age matched female subjects; 30 SLE diagnosed cases with a mean age 32.2±8.1 years and a disease duration ranged between 6 months and 15 years, and 30 apparently healthy subjects with a mean age 34±8.9 years (p= 0.415). All SLE cases had positive ANA, while 70% (21/30) had positive anti−dsDNA. The studied SLE patients presented with a wide spectrum of SLE clinical manifestations

The disease activity in patients was assessed by the SLEDAI index. Only one case (3.3%) had inactive disease, 43.3% (13/30) of cases had mild disease activity, 46.6% (14/30) had moderate activity and 6.6% (2/30) had high activity.19 (63.3%) cases from all studied SLE cases had lupus nephritis .12 cases (63.2%) of them had active nephritis while 7 cases (36.8%) were inactive. The rSLEDAI was used to assessed activity score among patients with active lupus nephritis (n=12); 50% (6/12) had score 4, 33.3% (4/12) had score 8 and 16.7% (2/12) had score 12. The SLEDAI was significantly higher in renal −SLE group than non−renal group (*p* =0.017). As regard the damage index; 60% of SLE patients had zero score, 36.7% had a score 1 and 3.3% had a score 2.

The results of our study revealed a significantly higher levels of serum creatinine, serum MIF, urinary protein/ creatinine ratio, urinary MIF and urinary MIF/ creatinine ratio, and a significant lower levels of hemoglobin and WBC count

between SLE cases group and control group (p <0.05 each) **(Table 1)**.

It was found that sMIF, uMIF levels and uMIF/creatinine ratio were significantly higher in SLE with lupus nephritis compared with patients without lupus nephritis manifestations (p <0.001 each). Also, there were significant trending increase in sMIF, uMIF levels and uMIF/creatinine ratio as regard disease activity assessed by SLEDAI index (p = 0.005, 0.026, 0.049, respectively) **(Fig. 2).** Moreover, higher sMIF, uMIF levels and uMIF/creatinine ratio were significantly associated with cases with active nephritis compared with inactive cases (p =0.007, 0.001, 0.018, respectively) **(Table 2).**

Both sMIF, uMIF levels and uMIF/creatinine ratio showed significant positive correlations with serum creatinine, proteinuria, SLEDAI index and renal SLEDAI index **(Table 3).**

Regarding the diagnostic performances of sMIF, uMIF levels and uMIF/creatinine ratio for discrimination between SLE cases and healthy controls; they showed 96.7%, 93.3% and 83.3% sensitivity and 100%, 100% and 96.7% specificity, with excellent AUCs of 0.999, 0.996 and 0.931 respectively. While, the diagnostic performances of sMIF, uMIF levels and uMIF/creatinine ratio in predicting lupus nephritis development; they showed 78.9%, 94.7% and 84.2% sensitivity and 100%, 90.9% and 100% specificity, with AUCs of 0.890, 0.981 and 0.928 respectively **(Fig. 3).**

In the regression analysis conducted to detect the predictors of lupus nephritis among SLE patients, it was found that sMIF, uMIF, uMIF/creatinine ratio were associated with LN prediction in univariable and multivariable analyses. Thus, they considered independent predictors for LN development **(Table 4).**

Table 1. Comparison of laboratory data between studied groups.

	Control N=30	**SLE N=30**	***p***
Hemoglobin (g/dL)	13±0.8	9.4±1.6	**<0.001**
WBC (x10^9/L)	6 (4.8−8.7)	3.4 (2.5−13.5)	**<0.001**
Platelets (x10^9/L)	225 (150−497)	212.5 (41−497)	0.059
Serum creatinine (mg/dl)	0.9±0.2	1.6±1.2	**0.011**
Serum Albumin (mg/dl)	4.2±0.4	3.7±0.6	**0.001**
sMIF (pg/ml)	1970 (1210−2700)	31720 (10900−82800)	**<0.001**
Urine creatinine (mg/dl)	50 (31.3−135)	52.5 (25−480)	**<0.001**
Urine protein (mg/dL)	7.5 (2−14)	22.6 (2.7−660)	**0.021**
UPCR	0.08 (0.02−0.١٣)	0.14 (0.02−6)	**<0.001**
uMIF (pg/ml)	3633.3 (1227−8700)	20445 (6150−78050)	**<0.001**
uMIF/creatinine ratio	47.4 (9.1−123.1)	439.6 (21.6−3026)	**<0.001**

Data represented either as mean ±SD or median (range)

Table 2. Comparisons of sMIF, uMIF, and uMIF/creatinine ratio between active and inactive nephritis.

LN	**sMIF (pg/ml)**	**uMIF (pg/ml)**	**uMIF/creatinine ratio**
Active (n=12)	53600 (32300−82800)	71325 (25200−78050)	1323.1 (260.8−3026)
Inactive (n=7)	25600 (21000−48200)	20340 (14050−29115)	522.9 (65.3−970.5)
p	**0.007**	**0.001**	**0.018**

Data represented either as mean ±SD or median (range)

Table 3. Correlations of sMIF, uMIF and uMIF/creatinine ratio with different parameters in SLE patients.

	sMIF (pg/ml)		**uMIF (pg/ml)**		**uMIF/creatinine ratio**	
	r	***p***	***r***	***p***	***r***	***p***
Serum creatinine (mg/dl)	0.391	**0.002**	0.459	**<0.001**	0.456	**<0.001**
Proteinuria	0.523	**<0.001**	0.525	**<0.001**	0.537	**<0.001**
SLEDAI index	0.6٦٤	**<0.001**	٠.595	**٠.001**	٠.457	**٠.011**
Renal SLEDAI index*	0.763	**<0.001**	0.824	**<0.001**	0.728	**<0.001**

r: correlation coefficient, * Correlations done only in cases with active nephritis.

Table 4. Regression analysis for prediction of lupus nephritis occurrence.

	Univariable		Multivariable	
	p	**OR (95% CI)**	***p***	**OR (95% CI)**
Serum creatinine (mg/dl)	0.108	0.995 (0.989−1.001)		
Proteinuria	0.062	1.248 (0.989−1.575)		
sMIF (pg/ml)	**0.020**	1.023 (1.012−1.087)	**0.023**	1.405 (1.158−1.534)
uMIF (pg/ml)	**0.011**	1.011 (1.005−1.061)	**0.029**	1.710 (1.503−2.028)
uMIF/creatinine ratio	**0.013**	1.006 (1.001−1.011)	**0.030**	1.186 (2.388−3.306)

OR: odds ratio, CI: confidence interval.

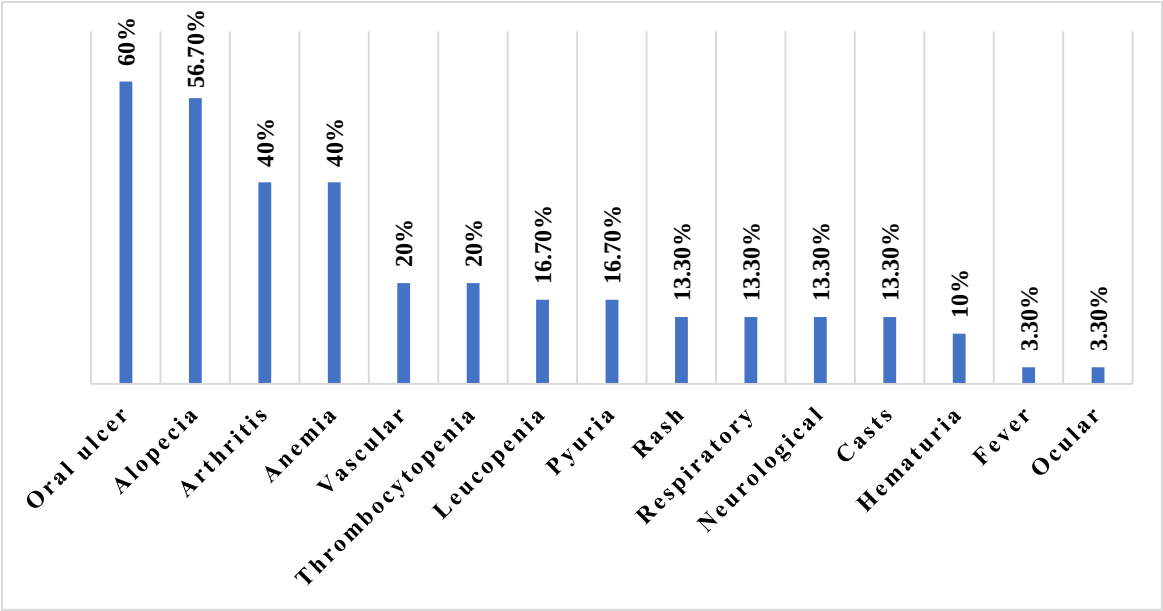

Figure (1): Frequencies of clinical manifestations in studied SLE cases.

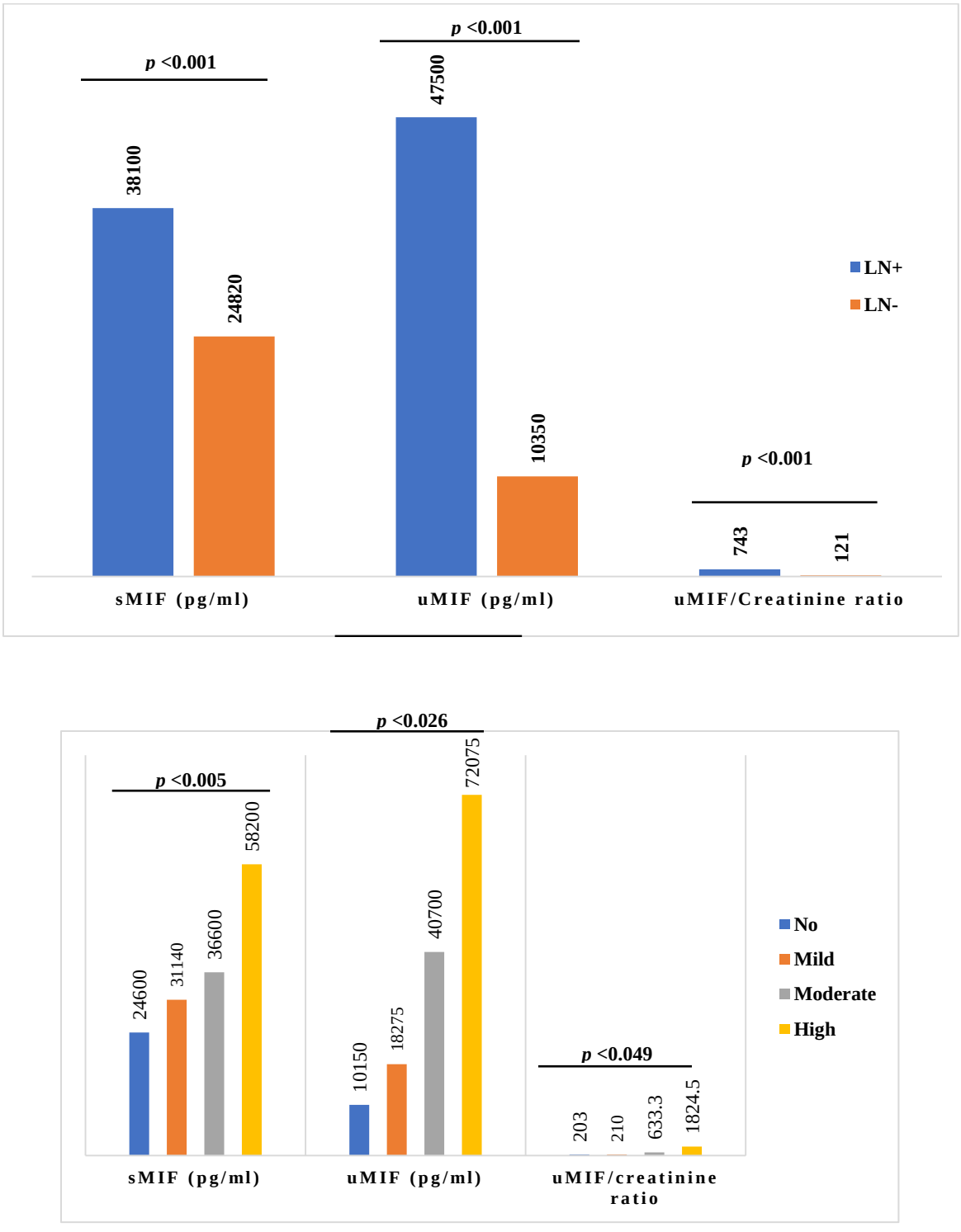

Figure (2): Comparison of sMIF, uMIF and uMIF/creatinine ratio in SLE patients according to lupus nephritis manifestations (upper chart) and disease activity by SLEDI-2K (lower chart)

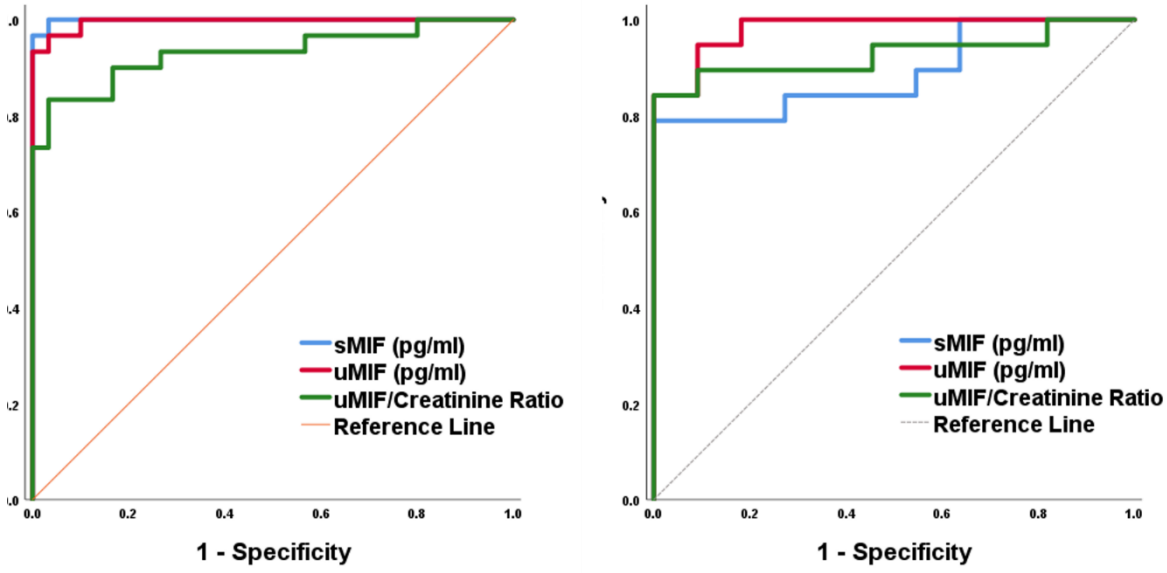

Figure (3): ROC curve for the performance of sMIF, uMIF and uMIF/creatinine ratio in discriminating SLE cases from healthy control (right curve), and in predicting LN development in SLE patients (left curve)

Discussion

Systemic lupus erythematosus (SLE) is a chronic, relapsing inflammatory disease characterized principally by involvement of the skin, joints, kidney and serosal membranes. It is of unknown etiology but is thought to represent a failure of the regulatory mechanisms of the immune system **(17)**. Kidney disease is one of the most serious manifestations of SLE and often develops concurrently or shortly following the onset of SLE and may have a protracted course with periods of remission and exacerbation **(15,18).** Despite the overall improvement in the care of SLE in the past two decades, up to 11% of patients still develop end stage renal failure 5 years after onset of renal affection **(19).**

Several studies have shown that biomarkers and their receptors are intimately involved in the pathophysiology of autoimmune diseases as RA and SLE **(20,21).** Over the past 2 decades, several novel biomarkers, such as serum and urinary cytokines, chemokines, adhesion molecules and growth factors, have been evaluated for monitoring therapeutic

response and detecting early renal flares in LN **(22).** Over the years, several studies have explored MIF levels in SLE and demonstrated that MIF level differs in SLE patients **(23).** Hence, our study was conducted to measure the serum and urinary levels of MIF in patients with SLE and find out their relation to the clinical disease activity.

This case-control study was conducted on 30 SLE female patients fulfilling SLICC criteria for the diagnosis of SLE **(13)** with a mean age of 32±8 years and a 5-year median disease duration, who were matched with 30 apparently healthy females with a mean age of 34±8 years.

In the present study, the patients' systemic disease activity, that was evaluated via SLEDAI-2k, was demonstrated as 43% mild activity, 47% moderate activity and 7% severe activity with a total median of 6 (range 6-12). All patients were ANA positive, with a 70% of them were having a positive anti-dsDNA. Regarding renal affection in our study, we found that almost 60% of patients with LN had an active disease (in the form of pyuria in 17%, hematuria in 10%, urinary casts in 13.3% and proteinuria in 40% of LN patients) with a median renal-SLEDAI-2k of 8.

Our data indicated that serum MIF levels were higher in SLE patients compared with healthy controls, consistent with other studies (7, 8, and 24). This could be explained by the high expression of MIF alleles that was found to be correlating with circulating MIF which was reported in several autoimmune diseases as SLE **(5)** and rheumatoid arthritis **(25)** as well as allergic conditions as atopic dermatitis **(26)**. MIF was proven to contribute to signals that break immune tolerance and sustained activation of immune response. It also reported that MIF expression was increased by monocyte in response to nucleic acid responsive TLR ligation that played a role in SLE pathogenesis. Ayoub and colleagues (2008) **(27)** had reported the potential actions of MIF in the pathogenesis of SLE including B- and T-cell activation and survival; macrophage activation and recruitment, TNF overexpression; expression of IL-6; and dysregulation of apoptosis .

To the best of our knowledge, we are the first to demonstrate a significant positive correlation between sMIF and LN. On the other hand, 2 previous reports showed that circulating MIF levels were more likely higher in their LN patients but statistically not significant **(11 & 8)**. Moreover, it was reported that MIF immunocytochemistry staining in the LN patients (7 cases) was

positively correlating with serum MIF levels (11). However, it was reported in a previous study (5) that there was no difference in sMIF observed between controls and a randomly chosen cases (60%) of their SLE group (details of this subset was not shown in their study. Also, a research done 2002 **(10)** reported no difference in sMIF levels between samples taken from normal subjects and patients with LN. However, their results should be interpreted with caution due to the small sample size. Recently, another research done in 2020 **(23)** reported higher level of sMIF in their SLE group with no difference between renal and non-renal SLE . One explanation for these discrepancies between the previous reports is that they did not provide detailed clinical features of their patients and the activity of LN. Further studies are required to clarify this issue.

Consistent with our uMIF results, several reports disclosed a significant increase in urine MIF concentration in LN **(5, 10, 11 & 12)** that was supported by other researchers **(26)** who showed that renal expression of MIF was increased in glomerulonephritis and correlated with leukocyte infiltration, glomerular injury and impaired kidney function.

According to the activity of renal disease as defined by the renal-SLEDAI-2k, MIF levels were 2-3 folds higher in patients with active nephritis than those with inactive nephritis. Additionally, significant positive correlations were found between MIF levels and serum creatinine, proteinuria and renal SLEDAI-2k indicating that MIF levels could potentially be used as an index of LN activity. Moreover, we reported a positive significant correlation between MIF levels and overall SLEDAI-2K, however, this correlation became insignificant after excluding the renal domains from SLEDAI score. This indicates that the difference in MIF levels detected between the entire SLE patients and controls was primarily owing to patients who had LN. However, a study disclosed that there was no difference in uMIF according to renal disease activity, despite having higher uMIF in patients with proteinuria (5). This could be explained by the relatively small sample of patients with active nephritis in their study (25%) (16/64). Additionally, 55% (35/64) of the research's SLE cohort (5) was receiving immunosuppressive therapy at time of the study, with which they reported a significantly lower uMIF levels as well. MIF production has been previously reported to be inhibited with immunosuppressive drugs (Pekarek et al., 1976**).** Likewise, in a study

done previously (24), it was reported that no correlation of sMIf with SLEDAI-2k and renal-SLEDAI-2k, despite having reported that sMIF levels were higher in their SLE patients and significantly correlating with proteinuria . This could be, also, explained by the higher doses of immunosuppressive therapy in their renal-SLE subgroup. The previous studies suggest that the relationship between the MIF and the presence of active LN is complex and might involve possible interactions with other molecules such as adiponectin or resistin **(24).**

Additionally, our results highlighted the close relation between serum and urinary MIF levels and LN. This was further supported by the non-statistically significant differences of MIF levels among different extra-renal clinical manifestation of SLE patients. In the same context, urinary MIF levels achieved excellent performance in discriminating LN form the rest of SLE cases in our study, higher than serum MIF levels, suggesting that the presence of MIF in the urine of these patients could reflect renal excretion, as well as a possible local production by tubular epithelium or glomerular infiltrated leucocytes. It is worth mentioning that many confounders can affect our results. Thus, we performed a multivariate regression analysis, including those variables that might affect the results. After this analysis, the risk of developing LN was 1.4 and 1.7 folds higher in SLE cases with higher sMIF and uMIF levels, respectively. These findings support that MIF levels may be considered as an independent predictor for LN, and a potential therapeutic target to prevent LN development and/or progression. Further studies are mandated to portray the mechanisms underlying the presence of MIF in the urine of SLE cases.

The precise clinical characteristics of the group of patients with SLE per the SLICC criteria is a strong point of this study. However, our study has several limitations. First, this is a single-center cohort, and a possible selection bias may therefore arise. Second, our results should be interpreted with caution owing to the relatively small sample size of patients with active nephritis (40%). Third, our results stemmed mainly from SLE patients with a long disease duration with median 5 years, ranged from 6 months up to 15 years and were previously treated with glucocorticoids and immunosuppressive drugs , thus a future study evaluating treatment naïve SLE patients with a recent diagnosis and measuring the MIF levels prior to starting treatment is recommended. Fourth, immunohistochemistry staining was not done in biopsy proven LN. Finally, owing to the

cross-sectional nature of our study, we were not able to monitor the chronological changes in the MIF levels with disease progression or remission.

We recommend, future prospective multicenter studies with larger sample size and clinical subgroups including renal and extra-renal manifestations supported by immunohistochemistry staining of tissue samples from involved organs to support our findings and verify whether MIF has a prognostic value in forecasting clinical endpoints in SLE patients with variable therapeutic interventions.

In conclusion, the results of present study in keeping with evidences from literature revealed that MIF was related to renal disease activity in SLE. Our findings are in agreement with rising evidence suggesting that each target organ affection in SLE may be coupled with the expression of various biomarkers. This has consequences for recognition of these biomarkers and hypothetically also for the selective targeted therapies.

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